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Large Animal Internal Medicine

FIFTH EDITION







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TO

Yibi, Chris, Bonnie, Kate, Everett, Alex, Mary-Lee, and Brianna for their love and support.

AND TO

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

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PREFACE



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Content

Large Animal Internal Medicine is an encyclopedic volume for the veterinary student or large animal veterinarian working with horses, cattle, sheep, or goats. Using the same popular format as the fourth edition, this edition provides the most current information available by utilizing more than 242 experts as authors. This edition contains additional pages of new color plates and more than 1210 figures, boxes, tables, color plates, and radiograph, ultrasound, computed tomography, and magnetic resonance images. A new section on ultrasound of the equine abdomen has been added. Many sections have been strengthened by the addition of outstanding new authors and new subjects, and chapters have been revised and improved with new references cited. Important new information regarding animal welfare is now included in Chapters 1 and 2. New genetic tests, which are rapidly developing, are described in Chapters 51 and 52. Many websites where important up-to-date information can be found are cited in this edition.

Since the last edition, rinderpest has been officially eradicated worldwide, the first disease of veterinary importance to achieve this milestone!

Problem-Oriented Approach to Disease Diagnosis

The catch-22 of most textbooks is that the clinician must know the diagnosis to locate and read about a specific disease. *Large Animal Internal Medicine* is a multiauthored text that allows the clinician to use the problem-oriented approach to the diagnosis of diseases of horses, cattle, sheep, and goats. More than 130 clinical signs or manifestations of disease are discussed. They are listed alphabetically on pages 21-22 (Part Two) and 221 (Part Three); this list can be used to locate a particular manifestation of disease. These same manifestations are listed by organ system at the beginning of Chapters 3-20. A favorite feature of the previous editions is the differential diagnosis boxes. These were largely created using Cornell's Consultant program, found at www.vet.cornell.edu/consultant. We have retained these invaluable diagnostic tools in this edition. Throughout Part Two, complete lists of common, less common, and uncommon diseases associated with manifestations or signs of disease are shown in these easy-to-find boxes (see p. xxiii for examples). The clinician is given an approach to each manifestation of disease and a method to work toward a diagnosis. The pathophysiology of a particular manifestation of disease is concisely summarized. Even if a final diagnosis is not reached, the animal with diarrhea, cough, or other problem can be treated symptomatically, a practice that is commonly used in the everyday world.

Similarly, abnormalities in laboratory test results are discussed in Part Four (p. 349), and complete lists of diseases associated with a given laboratory abnormality are found in easy-to-read boxes (see p. xxiv for an example). Interpretation of abnormalities in clinical chemistry, hematology, blood proteins, clotting tests, and bone marrow is made easy. For example, if the problem is elevated serum calcium, the causes of hypercalcemia are discussed concisely, and diseases associated with this abnormality are listed. The clinician can then proceed to a rational approach to the particular laboratory abnormality. Many readers have found the table for conversion from "American" units to SI units extremely useful.

Organization

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

PART ONE: History, Physical Examination, and Medical Records (with added material on welfare assessment)
PART TWO: Manifestations of Disease
PART THREE: Disorders and Management of the Neonate
PART FOUR: Collection of Samples and Interpretation of Laboratory Tests
PART FIVE: Disorders of the Organ Systems
PART SIX: Preventive and Therapeutic Strategies
PART SEVEN: Congenital, Hereditary, Immunologic, and Toxic Disorders

A neonatal disease section (Part Three), organized by presenting problem, discusses everything from prepartum care, to care of the newborn, to solving problems including everything from diarrhea to septicemia of foals, calves, lambs, and kids. To aid the clinician in arriving at the proper diagnosis, lists of diseases are given for each manifestation of neonatal disease. Chapters 51 and 52 deal with genetic disorders and genetic tests, most of which have only recently been developed. Differences in approach to diagnosis or treatment of neonates and adult animals are cross-referenced throughout the text.

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

Preventive and Therapeutic Strategies, Part Six, includes chapters with practical information on critical care and fluid therapy, antimicrobial therapy, infection control, prevention and detection of foreign animal diseases, vaccines and vaccination programs, and parasite control programs. Chapter 50 addresses nutrition of the sick animal and gives formulas for both enteral and parenteral support.

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

Definition and Etiology
Clinical Signs and Differential Diagnosis
Clinical Pathology
Pathophysiology
Epidemiology
Necropsy Findings

Treatment and Prognosis
Prevention and Control

Popular Features Retained

Color Inserts

Chapter 28, Collection and Analysis of Bone Marrow, includes color plates that show various bone marrow biopsies. Chapter 31, Diseases of the Respiratory System, features 12 color plates. Chapter 32, Diseases of the Alimentary Tract, includes color plates that feature endoscopic views of equine alimentary tract disorders. Chapter 39, Diseases of the Eye, contains color plates of ophthalmologic conditions that are best depicted in full color. Chapter 40, Diseases of the Skin, features new color plates of some dermatologic disorders, and Chapter 54, Disorders Caused by Toxicants, includes photographs that show several important toxic plants.

Printed Endsheets

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

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

New to This Edition

New Topics

The range of new topics is extraordinary. Every chapter has been thoroughly updated. A sampling of new topics includes information on assessing animal welfare, use of strong ion in making acid-base decisions, additional information on colostrum supplements and substitutes, antigen detection tests and polymerase chain reaction, and new aspects of critical care. The neonatal chapters have been reorganized and rewritten. The clinical pathology section includes four new experts as authors and is revised. The respiratory diseases chapter has added glanders and discussions of equine soft palate disorders, as well as a special section on disorders found in Australia and New Zealand. Also included are new discussions on legal requirements for use of pharmaceuticals in food animals, infection control methods for a large animal hospital, and the prevention of, detection of, and response to foreign animal diseases. New genetic tests and the labs that perform them, along with new findings on bluetongue and malignant catarrhal fever, have been added. Ultrasound images continue to be widely used, including a new section on the equine abdomen. National Research Council tables have been updated, and the neonatal sections are extensively revised. Also included are advances in vaccines, diagnosing and treating temporohyoid osteopathy and bone fragility disease in horses, and advances in endocrine and muscle disorders. The section on snakebite has been expanded and the toxicology chapter completely rewritten.

Index

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

Acknowledgments

The motivation for undertaking *Large Animal Internal Medicine* came, in large part, from having been influenced in my professional career by many teachers and colleagues with high standards. In particular I would like to acknowledge Alex Ardans, Humphrey Knight, Martin Drost, and Dick Mansmann. My gratitude to them and respect for them run deep. During my 35 years as a teacher, I had the good fortune of working with many talented, inquisitive, and dedicated colleagues, including Gary Carlson, Ian Mayhew, Lisle George, Sharon Spier, John Madigan, and Bob BonDurant, as well as countless others who helped me. Perhaps the individuals who have the greatest influence on a teacher are the students and residents who through their inquisitiveness keep us interested. Thanks to John House, Gilles Fecteau, Dave Van Metre, John Angelos, Mike McCloskey, and all the other great veterinarians I got to work with.

Many people worked hard to make *Large Animal Internal Medicine* the quality text that it is. More than 242 authors contributed in their area of expertise. This book would not be possible without them.

Special thanks to Whitney Noble, Penny Rudolph, Rhoda Bontrager, Brandi Graham, and all the others at Elsevier who worked so hard on this project.

Finally, I would like to acknowledge the love, support, and encouragement of my terrific family: Yibi, Chris, Alex, Bonnie, Kate, Everett, Mary-Lee, and Brianna.

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Causes of Icterus in Horses

Liver

Common Causes
Pyrrolizidine alkaloid toxicity
Serum-associated hepatitis
Acute hepatitis
Chronic active hepatitis
Cholangitis or cholangiohepatitis
Bile stones, other biliary obstruction
Fasting hyperbilirubinemia

Less Common Causes
Aflatoxicosis with liver failure
Tyzzer disease (foals)
Hepatic lipidosis
Hepatic abscess

Uncommon Causes
Black disease (infectious necrotic hepatitis)
Hemangioma, hemangiosarcoma, angiosarcoma
Cardiac neoplasm
Viral arteritis
Gastric or duodenal ulcers
Severe ascarid infection
Lymphosarcoma

Hemolytic Anemia

Common Causes
Immune-mediated hemolytic anemia
Equine granulocytic ehrlichiosis *(Anaplasma phagocytophilum,* formerly *Ehrlichia equi)*
Neonatal isoerythrolysis

Less Common Causes
Piroplasmosis (babesiosis)
Equine infectious anemia
Snake bite
Blood transfusion
Erythrocytosis

Uncommon Causes
Equine viral arteritis
Leptospirosis
Hemochromatosis
Bee or wasp sting
Sulfur toxicity
Trichloroethylene-extracted feed
Iron toxicity
Phosphorus toxicity
Herbicide toxicity
Phenothiazine toxicity
White snakeroot poisoning (tremetol)
Onions
Red maple *(Acer rubrum)*
Pentachlorophenol toxicity
Oak toxicity
Mycotoxicosis
Surra, *Trypanosoma evansi* (exotic)
Mal de caderas, *Trypanosoma equinum* (exotic)
Murrina de caderas, *Trypanosoma hippicum* (exotic)

Causes of Icterus in Ruminants

Liver

Common Causes
Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Fat cow syndrome (fatty liver)

Less Common Causes
Acute hepatitis
Liver flukes
Infectious necrotic hepatitis (black disease)
Liver abscess
Cholangiohepatitis

Uncommon Causes
Sarcocystosis
Hepatic neoplasia
Ruptured gallbladder
Cholelithiasis
Biliary obstruction
Nolina (beargrass) toxicity
Lantana, toxicity
Agave, toxicity
Wesselsbron disease (exotic) (B, O)

Hemolytic Anemia

Common Causes
Leptospirosis
Anaplasmosis
Bacillary hemoglobinuria *(Clostridium hemolyticum)*
Piroplasmosis, babesiosis (exotic)

Less Common Causes
Snake bite
Oak (acorn) toxicity
Immune-mediated hemolytic anemia
Transfusion reaction
Postparturient hemolytic anemia
Copper toxicity (especially sheep)
Neonatal isoerythrolysis
Yellow lamb disease (*Clostridium perfringens,* type A) (O)

Uncommon Causes
Anaplasma ovis
Eperythrozoonosis
Bee or wasp sting
Brassica species toxicity
Trichloroethylene-extracted feed toxicity
Iron toxicity
Onion poisoning
Zinc poisoning
Phosphorus poisoning
Mercury poisoning
Fireweed *(Kochia scoparia)* poisoning
Mycotic lupinosis
Mycotoxicosis
Theileriosis (East Coast fever) (exotic)

B, Bovine; *O,* ovine.

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Causes of Elevated Serum Enzymes

Elevation of Sorbitol Dehydrogenase (SDH)

Common Causes

Severe anoxia
Acute liver failure
Liver abscess
Secondary to damaged bowel
  Strangulating intestinal lesion
  Acute toxic enteritis
Chronic liver failure

Less Common Causes

Acute and severe anemia
General anesthesia
Anoxia

Elevation of γ-Glutamyltransferase (GGT)

Common Causes

Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Alkaline Phosphatase (ALP)

Common Causes

Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Creatine Kinase (CK)

Common Causes

Exertional rhabdomyolysis (azoturia, myositis, tying-up)
Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
Nutritional myodegeneration (selenium, vitamin E deficiency)
Post-endurance ride multisystemic disorder
Alert downer cow syndrome (muscle crush syndrome)
Malignant hyperthermia
Malignant edema
Prolonged recumbency with inability to rise

Uncommon Causes

Normal postexercise modest increase
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections

Elevation of Lactate Dehydrogenase (LDH)

Common Causes

Muscle disease
  Exertional rhabdomyolysis (azoturia, myositis, tying-up)
  Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
  Nutritional myodegeneration (selenium, vitamin E deficiency)
  Post-endurance ride multisystemic disorder
  Alert downer cow syndrome (muscle crush syndrome)
  Malignant hyperthermia
  Malignant edema
Liver disease
  Acute liver failure
  Chronic liver failure
  Cholangiohepatitis
  Cholelithiasis
In vitro hemolysis

Uncommon Causes

Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections
Fatty liver

Elevation of Aspartate Aminotransferase (AST)

Common Causes

Muscle disease
  Exertional rhabdomyolysis (azoturia, myositis, tying-up)
  Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
  Nutritional myodegeneration (selenium, vitamin E deficiency)
  Post-endurance ride multisystemic disorder
  Alert downer cow syndrome (muscle crush syndrome)
  Malignant hyperthermia
  Malignant edema
Liver disease
  Acute liver failure
  Chronic liver failure
  Cholangiohepatitis
  Cholelithiasis
  Liver flukes
  In vitro hemolysis

Uncommon Causes

Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections
Fatty liver



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USE OF *CONSULTANT* FOR DEVELOPMENT OF THIS TEXTBOOK

Maurice E. White

Each edition of *Large Animal Internal Medicine* has been facilitated by the online diagnostic system *Consultant*. *Consultant* comprises the thousands of diseases described in the veterinary literature; for each disease there is a brief description, references with links to journal articles, and clinical signs. *Consultant* is on the Web at http://www.vet.cornell.edu/consultant/consult.asp and since going online in January of 1997 has had millions of visitors and page views.

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

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

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

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PART ONE

History, Physical Examination, and Medical Records

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• CHAPTER 1

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Ruminant History, Physical Examination, Welfare Assessment, and Records

RONALD L. TERRA, *Consulting Editor*
JAMES P. REYNOLDS

Obtaining the History

The initial and often the most important step in the diagnostic approach to the sick ruminant is the physical examination. Before or perhaps throughout this process an anamnesis is obtained by asking questions of the owner or manager. The signalment can be derived by either observation or questioning the owner, and information related to the chief, or presenting, complaint should be determined, especially the duration, whether the onset was gradual or sudden, and any associated signs that may have been noted. For females, one must know when the last parturition occurred, and for dairy cows, what the production parameters were in the previous lactation, as well as in the current lactation. With dairy cows a drop in milk production is often the only sign noted by the owner. Weight can be either approximated, via heart-girth measurements, or determined exactly if facilities exist. What and how the animal is fed are questions to be asked. Does the animal refuse any or all of the feed offered? Is there more than one ration or feeding regimen for this particular operation? If so, are these same signs noted in animals exposed to different feeding practices? The examiner also obtains vaccination and worming history and inquires about pasture or housing practices to determine the influence that management factors have on the incidence of the disease. Previous diseases noted in the herd, therapeutic regimens used, and resolutions of previous problems are pertinent aspects. Finally, the examiner should note the treatment history of the patient. An example of a history questionnaire that can be used for ruminants is included (Fig. 1-1). Specific problems that are noted in the history or physical examination can be looked up on pages 21 and 22, and lists of differential diagnoses can be considered.

Examination

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

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

Visual Examination

As observations are made and a physical examination is performed, it is important to follow a systematic approach and to record findings. A checklist has been found to be extremely useful (Fig. 1-2). While observing the animal from a distance, the examiner should assess its posture, gait, behavior, and physical condition. Observation of the other members of the flock or herd helps to differentiate normal from abnormal characteristics under each particular management system because normal may vary from farm to farm and because what is considered "normal" for a farm by the owner or herdsman might actually be abnormal; this information is valuable for assessing the incidence of a disease or disorder that is caused by management. As more animals in more herds are observed, a background of knowledge is gained, allowing the practitioner to assess these management deficiencies more reliably.

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

Observe the animal for signs of abdominal splinting or arching of the back, as can be seen with peritonitis. This posture can also be noted with other disease processes when these produce pain in the ventral abdomen. Lateral curvature of the spine could indicate a congenital defect or a chronic spinal lesion. Carrying the tail up away

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VETERINARY MEDICAL TEACHING HOSPITAL
FOOD ANIMAL
INITIAL ENCOUNTER HISTORY

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

REFERRING VETERINARIAN: _____

OWNER: _____

PATIENT NAME OR TAG NUMBER: _____

DATE OF BIRTH: ___/___/___

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

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

PRESENTING COMPLAINT _____

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

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

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

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

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

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

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

PREVIOUS ILLNESSES: _____

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

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

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

PAST TREATMENTS, ADDITIONAL HISTORY: _____

_____

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FIG. 1-1 Example of an initial encounter history form for use in ruminants.

from the body is seen with conditions resulting in pain or irritation in the perineal region, vagina, or rectum. Standing with all four legs in the classic "saw-horse" stance with the neck and tail held erect is typical of tetanus. Abduction of the elbows is seen in disorders that cause thoracic pain. Lameness can be noted by observing unwillingness to bear weight fully on the affected limb, while either standing or walking. Loss of extensor or flexor capabilities of the joints is seen in nerve paralysis or paresis; it can also be caused by tendon and/or joint contractures, in which case joints are rigid. Walking as if all four feet are sore may indicate laminitis. With bright and alert recumbent animals, a thorough examination to rule out fractures or severe joint trauma is essential. Once these have been ruled out, inability to stand

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VETERINARY MEDICAL TEACHING HOSPITAL

FOOD ANIMAL

PHYSICAL EXAM DATA

Circle choice if abnormal
i.e., Ears: ☐ warm ☑ cold

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

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

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

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

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

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

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

TPR'S (Use additional page if necessary)

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

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

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

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

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

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

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

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

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

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

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

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

PERCUSSION OF CHEST: ☐ NORMAL ☐ DULL VENTRALLY ☐ OTHER

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

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

XIPHOID PAIN RESPONSE: ☐ NEGATIVE ☐ EQUIVOCAL ☐ POS GRUNT

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

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

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

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

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

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

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

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

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

OTHER ABNORMAL FINDINGS: _____

CLINICIAN: _____ **STUDENT:** _____

D1901 (1/84)

FIG. 1-2 Example of a data sheet for the recording of the pertinent findings from the physical examination.

may be indicative of generalized muscular paresis or paralysis. These can be of a primary nature, as with lesions within the spinal column causing cord compression, or secondary to mineral or electrolyte deficiencies (e.g., hypocalcemia, hypomagnesemia, hypokalemia).

To be able to judge the behavior of the animal as being normal or abnormal, the observer must call on a large amount of experience. Observing the animal from a distance allows assessment of eating and drinking behavior, as well as assessment of the subject as it is ruminating, urinating, and defecating. How the animal gets up or lies down and how it ambulates are important. Signs indicative of estrus or signs commonly seen with calving might be considered normal or abnormal, given the history and behavior of the animal during these

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

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

Physical Examination

With the animal properly restrained, the physical examination can now progress to specific palpation, auscultation, and percussion. Obtaining a sample of urine for urinalysis is of great value if incorporated into the physical examination; it is easy to perform with the use of dipsticks such as N-Multistix (Bayer AG, Leverkusen, Germany). Stroking the perineal region can aid in eliciting urination in the female bovine; however, even this is futile if the animal is apprehensive. Consequently, it is recommended that this be done first, while the patient is still fairly relaxed. In the male, elicitation of urination is slightly more difficult and requires massaging of the preputial orifice. Another method is to wash the outside of the prepuce with warm water, but this is less successful. In the female sheep and goat, stroking the perineal area can be attempted, but positive results are rarely achieved. A method that has been reported but which causes the animal great stress is to prevent it from breathing until urination is stimulated. In male or castrated male sheep and goats, gentle massage of the prepuce sometimes results in urination. If that fails, the breath-holding technique can be used. Because of the extreme stress associated with this induced hypoxic state, the author cautions against using this technique and further recommends that it not be attempted on patients that are severely compromised because of any disease process. (See Chapter 22 for further information on interpretation of the urinalysis.)

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

TABLE 1-1

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

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

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

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

Auscultation with concurrent percussion by snapping the finger against the thoracic and abdominal walls is the next procedure. Gas trapped within abdominal viscera elicits a "pinging" sound that can be heard with the stethoscope. Localization of these gas pings to certain areas within the abdomen is helpful in determining which alimentary structure is involved (Figs. 1-3 to 1-5). If the cecum is enlarged and gas filled, an abdominal ping can be heard. This can extend caudally to the tuber coxae and cranially through the paralumbar fossa and under the ribcage on the right side (see Fig. 1-3). The diameter of this area can be variable and range from 6 inches (15 cm) in a cecal displacement to 3 feet (1 m) horizontally in cecal torsions. Spiral colon pings are generally localized to the right dorsocranial paralumbar fossa and rarely extend farther forward than the tenth intercostal space. They tend to be round areas 10 inches (25 cm) or less in diameter centered high under the last rib (see Fig. 1-3) and are commonly found in sick cattle that are anorectic. These pings have no specific diagnostic significance. Gas pings associated with a right-sided displacement or torsion of the abomasum can extend as far cranially as the ninth intercostal space and caudally into the paralumbar fossa (see Fig. 1-4). The diameter of displacements is usually 18 inches (45 cm), whereas that of torsions can be up to 3 feet (1 m). In cases of abomasal volvulus, the animal is usually exhibiting other systemic signs such as increased heart rate, dehydration, depression, scleral injection, and mild colic. In simple right-sided

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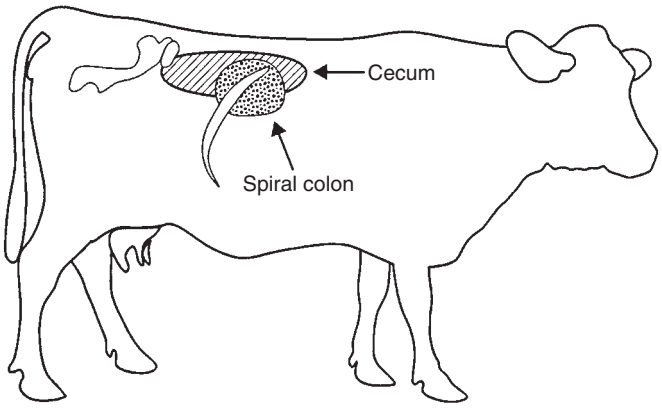


FIG. 1-3 Schematic representation of areas of gas pings elicited by percussion of the cecum and spiral colon.

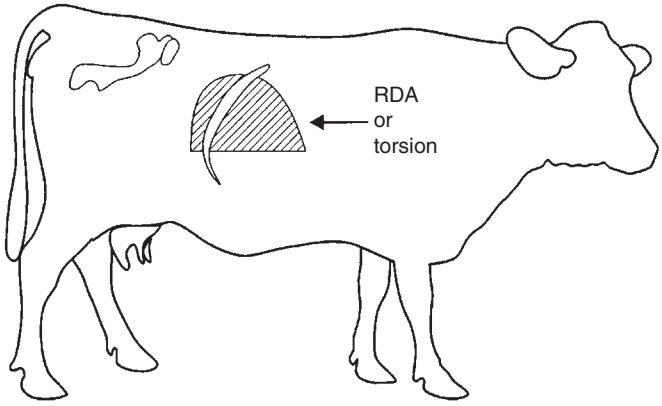


FIG. 1-4 Schematic representation of the area of the gas ping percussed in association with a right displaced abomasum *(RDA)* or abomasal torsion.

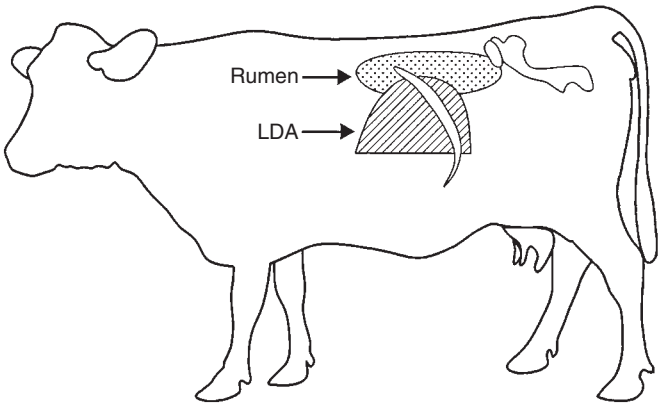


FIG. 1-5 Schematic representation of the area of the gas ping percussed in association with a left displaced abomasum *(LDA)* or gas ping in the rumen.

displacements or dilations of the abomasum, the only significant finding may be the small gas ping localized to the abomasum in a cow with depressed appetite and decreased milk production.

On the left side, gas pings can be noted as originating from the rumen, the peritoneum, or a left displaced abomasum (LDA). The auscultation of a gas ping that is primarily localized to the dorsal aspect of the paralumbar fossa and auscultable on both sides of the spinal column would be indicative of a pneumoperitoneum. The extent of these pings can be from the thoracolumbar junction caudally to the retroperitoneal space. Pings associated with ruminal tympany occupy the whole of the paralumbar fossa and can extend dorsally to the spinal column but generally do not extend over to the right side (see Fig. 1-5). LDA results in a gas ping that is localized, easily outlined, and approximately 12 to 18 inches (30 to 45 cm) in diameter. Caudal extent of the displacement is generally the thirteenth rib; however, it can extend into the paralumbar fossa, in which case the outline of the abomasum can be easily palpated. The LDA should ping over the eleventh rib on a line from the hip to the elbow (see Fig. 1-5). Rumen gas associated with a left-sided ping will rarely ping at this location. Identification of a fluid line within the displacement can aid in diagnosis and is accomplished by ballotting the left paralumbar fossa while auscultating the area of the gas ping concurrently, a process known as *succussion*. LDA often gives a pitch that changes in tone as it is percussed, as a result of movement of the rumen behind the abomasum. Often with LDA, intermittent gas bubbling or "sloshing fluid" sounds are heard. Rumen gas can be further differentiated from gas trapped in an LDA by rectal palpation of the rumen. One can also differentiate rumen gas from that trapped in an LDA by passage of a stomach tube into the rumen. Blowing into the rumen yields obviously auscultable sounds unless an LDA is present, in which case the sounds are muffled as the practitioner listens over the area of the ping. Performing a rumen or abomasal tap, the Liptac test, can further differentiate whether the ping originates from an LDA or the rumen. Fluid collected from an LDA would have a pH of less than 4, whereas that of the rumen should be 6 or higher.

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

The cardiac region of the thorax is auscultated next. Heart rate and rhythm are determined at this time. Rate varies among species, and age differences within species are noted. In general, older or larger animals have a slower heart rate. Table 1-2 lists the ranges of heart rate that are considered normal for the ruminant species, depending on age. Tachycardia can be seen in animals that have been stressed or excited, as in the process of restraint. However, with time the rate should return to within a more normal range. Any deviation from the normal heart rate in a quiet, relaxed animal implies a general disturbance of the normal health of the animal. Increased heart rate can be seen with fever, inflammation, pain, hypocalcemia, or metabolic disturbances that result in hypovolemia. Bradycardia is seen with conduction disorders within the heart muscle and with some metabolic disorders (uremia, hypokalemia). The most common causes of arrhythmias are atrial fibrillation in adult cattle and hyperkalemia in diarrhetic neonates. Location and intensity of the heart sounds are also important to note because muffling or displacement of the sounds can indicate space-occupying lesions within the thorax, pericardium, or mediastinum. With pericardial effusion the heart sounds are initially dull but develop splashy washing machine sounds as a gas-fluid interface develops. This often takes weeks. Normally the heart occupies a space on the ventral thorax between the third and sixth ribs. Most of the heart mass is located on the left side of the chest; thus the heart sounds should be louder on that side. However, if the heart is muffled on the left side and louder than normal on the right, one should consider the possibility of inflammation of the pericardium or lung lobes on the left side of the chest. Displacements of the heart sounds caudally are an indication of a space-occupying lesion in the anterior thorax or mediastinum, such as an abscess or neoplasm. Cranial displacements of the heart sounds would be noted

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TABLE 1-2

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

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

TABLE 1-3

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

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

with distention of the ruminoreticulum, eventration of abdominal viscera into the thorax through a diaphragmatic hernia, or other space-occupying lesions as noted previously. If any murmurs are noted on auscultation, an attempt should be made to localize the murmur to a specific heart valve. While the heart is auscultated, the pulse should also be palpated. The easiest point to find a pulse while the heart is being auscultated is at the vascular notch of the mandible where the facial artery is easily palpated. Pulse deficits in conjunction with an increase in heart rate are seen in atrial fibrillation and premature ventricular contractions. The heart rhythm is also noted. Dropped beats, gallop rhythm, and sinus arrhythmias should be compared with other clinical signs to determine importance.

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

The thorax is then auscultated and percussed. Respiratory rate (Table 1-3) and pattern are determined at this time, and the lungs are auscultated. If increased inspiratory or expiratory effort is noted, it should be correlated with auscultatory and percussive findings in an effort to determine lung pathology. Normal ruminant lung sounds vary greatly among species. In calves, sheep, and goats the relatively thin chest wall allows one to hear inspiratory sounds ventrally and over the large airways, whereas expiratory sounds are minimal (except in sheep, where they are frequently audible because of the large amount of mucus in sheep airways). In larger cattle, only very faint inspiratory sounds are normally heard. Lung sounds can be classified as normal or harsh (tubular) or as wheezes or crackles. These sounds can vary over the different areas of the thorax or can be found singularly over the entire lung field. Significant pulmonary pathology may be present in ruminants *without* any auscultable abnormalities. Total absence of lung sounds ventrally indicates pleural effusion or pulmonary abscessation with loss of airways. When ventral consolidation of the lung occurs, airway sounds are transmitted well and easily heard ventrally as pipestem sounds similar to those heard over the trachea, whereas percussion reveals a marked increase in ventral lung density. The trachea should also be auscultated. Inspiratory dyspnea and stridor are usually the result of extrathoracic obstructions to airflow (nose, pharynx, larynx, extrathoracic trachea). Pneumothorax can also result in loss of auscultable airway sounds, which may be absent dorsally or entirely over the entire side if the lung has collapsed completely.

Place the middle finger in the intercostal space and slap the finger with the opposite hand or use a tablespoon and rubber hammer to accomplish percussion of the chest wall to determine the ventral lung border. Percussion is most useful in goats and calves. In sheep the wool precludes effective use of the technique, and in adult cattle the chest wall is often too thick to effectively evaluate changes in percussion tones. The chest is percussed in a dorsal-to-ventral direction, moving caudal to cranial on the chest wall. A change in resonance is noted when the ventral border is reached; a line demarcating this change in resonance is the junction of the diaphragm to the thoracic wall. In the ruminant this line should be described by joining a point at the junction of the eleventh rib and the epaxial musculature dorsally to a point at the middle of the ninth rib, then cranially to the point of the olecranon. The cranioventral portion of the percussed thorax is dull because of the heart field (≈3 inches [7.5 cm] above the olecranon in adult cattle; 1 to 2 inches [2.5 to 5 cm] in calves, sheep, and goats). Finding an increased area of dullness in the cranioventral lung field associated with harsh lung sounds would be an indication of lung consolidation as seen in *Pasteurella* pneumonia. Pulmonary emphysema (atypical interstitial pneumonia) should be considered when the lung field is larger than expected, the animal is dyspneic, and airway sounds are minimal, whereas a ventral border that is markedly elevated and in a straight line could be an indication of pleural effusion. In this case auscultation would reveal decreased lung sounds ventrally and possibly the presence of pleural friction rubs. Acoustic percussion of the lung field can extend into the chest only to a depth of 2 to 2½ inches (5 to 6 cm); therefore lesions within the thoracic cavity that lie deeper than this cannot be percussed.

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

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

If the animal is lame or has postural abnormalities, the feet and legs are palpated next. If the animal is uncooperative, it may be necessary to sedate and/or cast it. If sedation is necessary, it should be performed at the end of the physical examination. Care should be exercised for obvious reasons. The examination consists of comparing one foreleg with the other and then comparing both with the expected norm. The same procedure is followed for the hind legs. Abnormalities in the shape of the claw may be hereditary or may be caused by nutritional deficiencies, poor leg conformation, poor housing, or as a sequela to laminitis. The coronary bands should be palpated for evidence of pain or increased heat. An attempt should be made to pick up all four feet individually and observe the soles and interdigital regions for necrotic areas, areas of bruising or swelling, draining tracts, or presence of foreign bodies. The fetlock, carpal and tarsal, stifle, and elbow joints are all easily accessible and should be examined for swelling, tenderness, edema, heat, instability, and crepitation. Each joint should be tested over its full range of motion, and any elicitation of pain should be noted. Physical findings should be consolidated into a decision as to whether the joint problems are infectious or traumatic. Sheep or goats with acute polyarthritis most commonly have mycoplasma or chlamydial infection. Chronic joint pain in goats (often with soft tissue thickening and enlargement caused by synovitis) is frequently attributable to caprine arthritis encephalomyelitis. Conformation of the legs should be analyzed because this could contribute to a joint or foot problem. The pelvic girdle does not lend itself to extensive examination; however, one can note symmetry or asymmetry and further evaluate during the rectal examination. Fractures of the tuber coxae, subluxation of the sacroiliac junction, acetabular fractures, fractures of the head or neck of the femur, and dislocation of the coxofemoral joint may all be diagnosed by evidence gained during palpation and observation of the pelvic area. The dislocated or fractured limb is frequently shorter than the normal opposite limb. The tail can also be examined for evidence of fractures, paresis, or paralysis.

The perineal region is examined by noting the external condition of the genitals and rectum. Anal sphincter tone can be assessed, and the presence of vaginal discharge can be noted. In males the testicles, spermatic cord, and epididymis should be palpated for the presence of nodules or areas of fibrosis. The testicular circumference can be measured and compared with what is expected for age and breed. These measurements are noted in Tables 1-4 and 1-5. The perineal part of the penis can be palpated for the presence of hematoma or swelling and pain (cellulitis or abscess). In the female the supramammary lymph nodes can be felt at the attachment of the udder to the perineum. Enlargement of these nodes occurs with mastitis or lymphosarcoma. The udder is palpated for the presence of fibrotic areas, commonly seen secondary to staphylococcal mastitis or associated with *Trueperella pyogenes* (formerly *Arcanobacterium [Actinomyces] pyogenes*) abscesses. The presence of a swollen quarter or quarters with pain and heat may be associated with mastitis caused by gram-negative bacteria. Cold damp areas of skin on the udder that are discolored, necrotic, and possibly sloughing are evidence of gangrenous mastitis. In lactating animals, milk should be present in each quarter and some of this milk should be expressed for examination. The milk should be of normal color and consistency and should not have any appreciable smell. The presence of leukocytic flakes or clots (garget) is an indication that the udder is mounting an inflammatory response. This response can be measured qualitatively by using the California Mastitis Test (CMT). One should also collect individual quarter samples from those quarters showing garget or those that test positive on the CMT for bacterial culture and sensitivity.

TABLE 1-4

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

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

TABLE 1-5

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

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

The next step is to evaluate the head and neck regions. The head should be symmetric in appearance, and any asymmetry should be evaluated to determine whether the deviation is caused by a neuromuscular or skeletal defect. Facial nerve paralysis results in one type of asymmetry, whereas a frontal sinusitis with concurrent displacement of the frontal bone appears differently. Discharges from the eyes, ears, nose, or mouth are noted and correlated with other physical findings. The oral cavity is examined by grasping the tongue with the hand and extending it out through the interdental space. Muscular tone of the tongue is evaluated at this time. The normal animal will resist extraction of the tongue and will quickly retract the tongue into the oral cavity when released. Increased ease of extraction and delayed retraction are indicative of diseases resulting in flaccid paralysis or paresis of skeletal muscle (e.g., as seen in botulism). The tongue and oral mucosa are examined for the presence of erosions, ulcerations, foreign bodies, or areas of necrosis. The dental arcade is evaluated for age of animal, absence of teeth, loose teeth, or necrotizing gingivitis. The color of the mucous membranes is noted. Icterus, pallor, hyperemia, cyanosis, excessive reddening, or brown "mud-colored" mucous membranes can all be noted, depending on the underlying disorder. Mucous membrane color is best evaluated in the eyes and/or vulva because of the presence of pigments in the oral mucosa of many ruminants. The smell of the breath is noted and, if fetid, might be an indication of a retropharyngeal abscess caused by trauma, lung abscess, or gangrenous pneumonia. If the breath is foul, deep palpation within the oral cavity for an abscess or necrotic area is indicated.

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

The eyes are examined next. The sclera and mucous membranes are evaluated in much the same manner as the oral and nasal mucous membranes. The corneas are examined for the presence of opacities, discolorations, ulcerations, and lacerations. The position and size of the corneal opacities or ulcerations can be helpful in determining the cause. Foreign bodies such as plant awns and seeds beneath the third eyelid often cause opacity of the medial aspect of the cornea. Infectious bovine keratoconjunctivitis (pinkeye) is usually localized to

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the central cornea and causes severe corneal ulceration. When the mucosal diseases cause corneal opacities, they generally do so at the junction of the cornea and sclera and usually do not ulcerate the cornea. The anterior chamber should be examined for the presence of hyphema or hypopyon. These can sometimes be seen in animals with severe bacteremia, especially in neonates with failure of passive transfer. The animal should be evaluated for the presence of a menace reflex (absent in normal neonates for up to 2 weeks), and the pupillary light responses should be observed. Nystagmus and strabismus should be characterized, if present, because the direction is important in localizing the lesion. Nystagmus or strabismus or a deficit noted in the pupillary light reflex or menace reflex is indicative of underlying neurologic or ophthalmologic disease.

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

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

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

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

The final step in the physical examination is rectal palpation. This cannot be accomplished in small ruminants, so this section is directed primarily toward the bovine. The pelvic area is evaluated for the presence of retroperitoneal abscesses or fractures of the pelvic bones. The left kidney can be palpated for overall size and shape, which is normally lobulated in cattle, and the kidney can be gently squeezed to determine if pain is evident. The rumen should be palpated and the findings compared with those noted on percussion and auscultation. If there is any evidence of intraabdominal gas pings, an attempt should be made to palpate the suspected organ. This can provide information that may be helpful in determining therapeutic or diagnostic directions. The rectal palpation can reveal the presence of masses that were not palpable externally, such as fat necrosis or tumors. Adhesions and evidence of peritonitis can also be palpated rectally, and attempts should be made to localize them to a specific area of the abdomen to establish potential cause. The preiliac (or internal iliac) lymph nodes are located by sweeping the hand along the craniodorsal face of the ilium. These nodes normally have the size and shape of a walnut. Enlargements are noted with lymphosarcoma, peritonitis, and severe limb inflammation. The lymph nodes of the aortic bifurcation are small and not easily palpated. Their ability to be palpated would be evidence of abnormal enlargement. Palpation of the genital tract is directed toward establishing size, shape, and presence of abnormalities. These contents could be normal, as with a pregnant animal bearing a fetus, or abnormal, as seen with a pyometra. If it is determined that a cow is not pregnant, the ovaries and oviducts should be palpated for structures and abnormalities. In the bull, particular attention should be paid to the prostate, seminal vesicles, and bulbourethral gland.

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

Medical Record

The information gathered by means of the physical examination (see Fig. 1-2) is compiled and correlated with the data obtained during the history (see Fig. 1-1). A problem list should be formulated through the physical examination and anamnesis, leading to the development of a specific diagnostic plan, a differential diagnosis list, and a proposed course of therapy (Fig. 1-6). Prognosis can also be assessed with the information now in the examiner's hands. Accurate recording of the abnormalities noted during the examination should become part of the medical record and can prove valuable in following the course of the case. In addition, with each complete and accurate physical examination performed, the practitioner becomes more skilled in the procedure, adapting it to fit his or her needs, and using his or her time more efficiently. With the number of diagnostic tests available to the profession today, the information gained from the physical examination will allow the examiner to pick the tests that are specific for those disorders suspected, which saves the practitioner time and the client money.

Diagnostic Tests That Can Be Applied in the Field

Laboratory procedures can be performed in the field, the results of which would prove beneficial in the development of a diagnostic plan. These include the CMT, partial urinalysis (dipsticks), ruminal pH determination, and milk or blood progesterone tests. In

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DIAGNOSTIC AND TREATMENT SHEET

FARM OWNER _____ **DATE** _____

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

PHYSICAL EXAM

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

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

TREATMENT

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

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

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

1. _____

2. _____

3. _____

4. _____

WITHDRAWAL INFORMATION

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

DOCTOR: _____

FIG. 1-6 Example of a diagnostic and treatment sheet. *(Courtesy Lander Veterinary Clinic, Turlock, Calif.)*

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addition, some serum chemistries can be performed cowside with the use of the i-Stat Serum Chemistry Analyzer (i-Stat Corporation, Princeton, NJ).

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

Assessing the Welfare of the Individual Animal or the Herd

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

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

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

The welfare status of an animal is assessed by determining whether the Five Freedoms of Animal Welfare (Box 1-1) are being met. The Five Freedoms[6,7] categorize the basic elements of animal welfare and therefore allow determination of the state of an animal in each area. An animal has poor or compromised welfare if any of the Five Freedoms is not being met.

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

BOX 1-1

Five Freedoms of Animal Welfare

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

Assessing Welfare

The tools used to assess welfare in the field are mainly observation of animals for physical outcomes and behaviors. A basic tenet of welfare is that housing should be clean, dry, and comfortable. The animals will show if that is the case: if the housing and lying areas are clean, then the areas they lie in are clean. If the housing and resting areas are comfortable, the animals will not have skin or leg lesions or abrasions from hard surfaces. Behaviors associated with compromised welfare include aggression, cannibalism, depression, and stereotypies. Stereotypies are what animals display to compensate for inabilities to express innate behaviors or for boredom. They include biting other animals, excessive licking or chewing, tongue rolling, and banging on enclosures. Scoring systems[8,9] have been developed or adapted to quantitatively assess four aspects of welfare (Table 1-6): body condition score, hygiene score, leg lesion score, and locomotion score. A total score of 4 is perfect, while 4-9 scores are acceptable, and 10-17 scores are unacceptable.

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

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

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

In conclusion, evaluation or assessment of the welfare of an animal or a group of animals is similar. The most generic version of a welfare assessment is the FARM program (http://nationaldairyfarm

TABLE 1-6

Animal Scoring Systems Used to Evaluate the Welfare of Dairy Cattle

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

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.com/animal-care-resources.html). It includes the FARM (Farmers Assuring Responsible Management) manual that details most of the points discussed. The practitioner must understand what normal, or good, welfare is, and then through systematic evaluation of each of the Five Freedoms determine if the animal's welfare is normal/acceptable for that species or is compromised.

Insurance, Interstate, and Prepurchase Health Examinations

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

The prepurchase examination is similar to the insurance examination. The physical examination form (see Fig. 1-2) can be used to record findings. The prepurchase examination could be performed on the highly pedigreed female that is being consigned to sale, but it is more often performed on the male scheduled for use as an artificial insemination stud. Occasionally one could be asked to examine an animal under consideration for purchase. Experience indicates that the veterinarian should be employed by the potential buyer in these cases. This arrangement avoids any potential accusations of conflict of interest on the part of the examining veterinarian. A complete blood count and a chemistry panel should be run. Generally it is prudent to certify that the animal is healthy and to test for tuberculosis, brucellosis, and bovine leukosis (using agar gel immunodiffusion). Additional laboratory tests for anaplasmosis and bluetongue may be indicated. Often an animal being consigned to sale or one going into artificial insemination service is required to meet federal regulations for interstate shipment. This information can be obtained from the federal veterinarian in charge in your area or from the office of the state veterinarian in the state of destination.

A problem arises when the number of animals submitted for interstate health examination is large. Economic and temporal constraints usually preclude complete examination of all the animals presented. At such times the visual examination described earlier can prove helpful in determining which animals are to be singled out for the more complete physical examination. The examination of individuals is less complete than for prepurchase or insurance examinations because such factors as fertility are not at issue when filling out an interstate health certificate. Choosing animals with abnormalities in behavior, physical condition, gait, or posture allows the practitioner to concentrate on those that have the most potential to be diseased. Also, one can be fairly confident that if all the animals appear normal on the general examination, they are healthy and would be suitable for interstate shipment as long as the results of the intradermal tuberculosis test and required serologic tests prove negative. To sign an interstate health certificate, a veterinarian must be accredited and licensed in a state. It is essential that a veterinarian signing an interstate health certificate have examined the livestock sufficiently and diligently enough to be confident that no infectious or contagious diseases are present in the consigned group. A call should be placed to the office of the state veterinarian in the state of destination to be sure that all current requirements are fulfilled before shipment is scheduled.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 2

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

T. DOUGLAS BYARS and KATHLEEN CASEY GONDA, *Consulting Editors*

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

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

Physical Examination Record

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

Equine Insurance

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

History

The medical history should be directed to the clinical problem. The "herd health" of the stable or farm can be assessed briefly as depicted by the vaccination and parasite control program and visually by the condition of other horses residing on the premises. The patient's individual problems should be determined according to such factors as clinical history of onset, feed and water consumption, fevers, and

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decrease in performance. In essence, the clinician must effectively zero in on the problems at hand, which may affect multiple body systems.

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

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

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

Physical Examination

The extent of the physical examination will be subject to the condition of the patient, the environment where the examination is conducted (field vs. hospital), the equipment at hand, and the ancillary personnel available for restraint and procedural purposes. In a hospital setting the clinician should have immediate access to most of the equipment and diagnostic instrumentation listed in Box 2-1. The physical examination sheet should provide a systematic list of the organ systems being evaluated. Vital signs (temperature, pulse, and respiratory rate) should be documented in the "calm" animal, if possible (Table 2-1). Abnormal findings are described in an appropriate space provided, usually below the body systems checklist. Using the same numeral for each body system throughout the examination process and in problem identification is useful for future caseload recall, especially if a computer is used and codes can be applied to clinical findings and diagnosis. At the completion of the physical examination, the major problems identified are listed, and appropriate laboratory tests can be requested. The final diagnosis is seldom determined at the time of the initial examination; however, the final diagnosis represents the final assessment and should be filled in at the appropriate time (e.g., hospital discharge).

A general evaluation of the equine patient should be made from afar. This is particularly important for neonates at the side of their dams. The initial observations of body condition, posture, weakness, lethargy, incoordination, lameness, and musculoskeletal asymmetry are more easily observed a slight distance away from the patient. The integumentary system can usually be quickly evaluated as to the type, distribution, and number of lesions and site and layer of involvement. However, subtle lesions of petechia and ecchymosis cannot be visualized in the integument because the hair coat and pigment hide lesions that are obvious in other species, such as purpura of nonpigmented humans and pigs. In these instances the mucous membranes must be examined as an extension of the integumentary system. If obvious multiple lesions of the skin are present, documentation is usually expedited by photographing or drawing a picture of the horse and indicating the distribution on the drawing including both sides (see Chapter 11). Gross generalized distortions (e.g., anasarca) may be viewed as lesions of possibly more than one body system (integumentary and circulatory).

Abnormalities in demeanor and mentation can be assessed by watching the horse's initial response to the environment and again once the physical examination and interaction with the patient begins. Whatever the approach, the physical examination should be systematic and orderly, so as not to miss subtle features in the face of obvious abnormalities. In general, most examinations start at the head, so as not to startle the horse or foal and to prevent possible injury to the veterinarian who may be unfamiliar with the horse's temperament or previous handling experience. Evaluation of facial symmetry and cranial nerve function can be accomplished with minimal handling or manipulation. The eyes can be examined by a rapid visual assessment using a penlight. The cornea and cranial and caudal lens capsules can be evaluated by horizontally moving the penlight and noting the crossing light reflexes. Pupillary constriction

BOX 2-1

Recommended Examination Room Equipment and Ancillary Services

Examination Room Equipment

Records (examination sheet, request forms, and euthanasia forms)
Thermometer
Clock with second hand
Stethoscope
Twitch
Rectal sleeves, sterile examination gloves and lubricants
Nasogastric tubes in various diameters/lengths
Hand pump
Hoof knife and testers
Ophthalmoscope/Otoscope
Dental speculum
Endoscope (1-, 2-, and 3-meter lengths)
Electrocardiogram (ECG) machine
Ultrasound (linear or sector scanner)*
Sphygmomanometer and Doppler (tail or limb)
High-volume fluid pump
Refrigerator
Incubator
O_2 tank and foal mask
Culture swabs, transport media, blood culture bottles

Ancillary Services

Radiology and imaging services
Ultrasound consultation
Laboratory services

TABLE 2-1

Vital Signs in Normal Horses and Foals

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

*Heart and respiratory rates vary depending on level of excitement and autonomic stimulation.

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to light and the "menace" response should be observed, although these reflexes may be significantly slower or absent in the neonate. An ophthalmoscope retinal examination should be performed whenever the eyes represent the primary complaint, and fluorescein dye should be used for the detection of corneal ulcers before the installation of other ophthalmic agents. Blindfolding of one eye at a time may aid in the assessment of unilateral blindness and should be conducted in a safe area with "blunt" devices contrived as an obstacle course.

Evaluation of the circulatory system starts with assessment of heart rate, rhythm, and any presence of murmurs. Mucous membrane color, capillary refill time, scleral injection, palpable changes in the temperature of the ears and extremities, jugular pulsation, and pitting subcutaneous edema are the most common obvious circulatory physical examination parameters. The heart should be auscultated bilaterally, and murmurs graded according to intensity (I to VI or I to V), character, the valve site, and phase of the cardiac cycle. Cardiac arrhythmias usually necessitate an electrocardiogram (ECG), except in the case of type II atrioventricular block, a normal finding commonly observed in clinically asymptomatic horses. Type II heart block in normal horses can usually be obliterated by exciting the horse with a threatening gesture or trotting the horse a few steps to increase the heart rate. In addition to electrocardiography, transcutaneous ultrasound examination of the heart and pericardium and transrectal evaluation of the caudal aorta and iliac arteries for intraabdominal thrombotic lesions can be used.[3] If procedural assessments of blood pressure are necessary, a manometer for central venous pressure or a sphygmomanometer with Doppler ultrasound is used on the base of the tail in foals[4] and adults.[5]

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

Percussion of the thorax is a reliable clinical tool and should be performed in cases of suspected abscess, tumor, or pleural effusion. A pleximeter and tablespoon are the only tools required, although some clinicians are adept at direct finger percussion of the chest. In foals, percussion can be performed by placing a stethoscope on one side of the chest and reaching over the back of the foal to manually percuss the opposite side. Fractured ribs may be recognized in the neonatal foal as palpable asymmetry or a bony crepitus ("clicks"), often with edema of the sternum or elbow coinciding with the fractured side. Horses with pleuropneumonia may exhibit a reluctance to move (pleurodynia) similar to that seen in horses with laminitis, which is a possible sequela to endotoxemia caused by gram-negative bacterial pneumonia.[7]

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

A systematic approach should always be used when examining the horse for gastrointestinal disease. Although the majority of emergencies and referrals are related to colic or acute intestinal disease, the clinician should resist the temptation to focus only on the abdomen, so that important clinical signs relating to other problems are not missed (e.g., gastric ulceration, botulism). If a clinical complaint involving the abdomen is present or in suspected cases of intestinal displacement, obstruction, or volvulus, the gastrointestinal system is initially examined with bilateral auscultation of intestinal sounds by dividing the abdomen into four quadrants. Intestinal borborygmi vary by location and in the cecum and ascending colon propulsive contractions tend to occur in waves, with periods of quiescence, over several minutes. In general, small intestinal sounds are the least dramatic, heard in the area of the left flank. In addition, the abdomen should be auscultated ventrally for sounds similar to "ocean waves" or sand pouring on itself, indicative of the presence of sand within the gastrointestinal tract.[9] The presence of increased (hypermotile), reduced, or absent borborygmi (ileus) should be considered important features of the physical examination. It is helpful to document the activity or lack thereof in each of the four abdominal quadrants, especially in hospitalized patients where different clinicians may be monitoring the patient over several days. In cases in which the gastrointestinal tract is the site of the primary lesion, checking for gastric reflux and performing a rectal examination are required elements. Although only about 40% of the gastrointestinal tract can be reached by palpation, it is a valuable technique that can quickly identify surgical cases and affect survival.[10] Clinicians should strive to become adept at rectal palpation and regard the procedure as a premier diagnostic skill while respecting the risks involved for the patient and veterinarian.

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

The use of long endoscopes (e.g., 2 to 3 m) is valuable in the visual assessment of the esophagus and stomach with lesions such as esophageal stricture and gastric ulceration. For a diagnostic endoscopic

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examination of the stomach, it is recommended that the patient be muzzled or held off feed for at least 10 hours to allow complete visualization of the stomach.[12]

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

The urogenital system can be examined by manual palpation, rectal palpation, vaginoscopic (speculum examination) viewing, endoscopy, and ultrasound. The caudal portion of the left kidney is easily palpated in most horses. Uterine and catheterized samples should be obtained (e.g., cultures, urinalysis) before any contaminating invasive procedures (e.g., rectal palpation) are performed and before fluid therapy is initiated. Sphincter tone may be subjectively or objectively (urethral pressure profile) assessed in horses with urinary incontinence or stranguria. Horses with incontinence often demonstrate "scalding" of the perineum, and hind legs and foals with a patent urachus may dribble urine from a moist umbilical stump.

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

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

For the internist, evaluation of the musculoskeletal system usually involves a rudimentary examination of the site and appearance of the disease processes. Primary lameness is more commonly evaluated by clinicians familiar with diagnostic nerve blocks, arthrocentesis methods (e.g., septic arthritis in foals), and radiographic findings. It should be noted that acute (caused by fracture) or chronic lameness can coexist with primary neurologic disorders (e.g., equine protozoal myeloencephalitis). Therefore, when warranted, the patient should receive a cursory neurologic evaluation (see Chapter 8) in conjunction with the musculoskeletal examination. Conversely, all horses presented with systemic illness (pneumonia, colitis) should also be evaluated for signs of laminitis in all four feet because this complication is often the limiting factor for the horse's survival. Visual inspection of the hoof wall and sole may indicate previous laminitic episodes and should be documented because this may increase the patient's risk and lower the threshold for repeat episodes. Careful palpation of the lower limbs may indicate increased intensity of digital pulses or changes in the coronary band that may be related to the "sinker" syndrome (distal phalangeal displacement).[13] If laminitis is present as a complicating factor, the clinician should be able to add to the clinical prognosis by using Obel grading (1 to 4).

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

Use of Ancillary Equipment in the Examination Procedure

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

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

Medical Record

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

Medical Record Filing

Two major systems of medical record filing exist: numeric and name filing. Numeric systems offer consistency of the record and avoid the confusion of patients with similar names. The problem of name similarity is primarily confined to the nonregistered breeds of horses. Breed registration requires name approval to avoid duplication, among other undesirable designations. Again, for record-keeping purposes, clinic or ambulatory records for unnamed young horses are best designated by the dam's name and the foal's year of birth (e.g., Curious '06) and filed by month and year of examination. A "master" admission log should be maintained for record retrieval purposes,

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especially when a patient has been seen on multiple occasions. Color coding, along with numbering of the file folders, may be helpful in record retrieval. Computers offer the advantage that records can be retrieved through any one of a number of recall parameters (e.g., problem, client).

Computer-Generated Medical Records

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

Computers offer the advantages of legibility, quick data retrieval, and immense archiving capacity. The need for rapid transfer of medical information from doctor to doctor or doctor to referral facility is being met by advances in computer software and Internet access. Thus the current trend in human and veterinary medicine is the development and implementation of an electronic medical record (EMR) that is entirely computer generated. An EMR permits one or more individuals, simultaneously, to access laboratory results, imaging studies, and other pertinent patient information.[15] For the equine practitioner, the availability of real-time ultrasound imaging and digital radiography has revolutionized the production and transmission of high-quality diagnostic images, via computer, within moments after they have been taken. This has greatly increased the quality of medicine and efficiency of patient care, allowing general practitioners rapid access to the opinions of specialists at sites distant from the patient. Over time, acceptance of the EMR may result in the complete dissolution of the paper-based medical record.

Several software systems have been designed specifically for equine hospitals and include adaptations for ambulatory "off-site" data entry and retrieval (Mobile Data Software, Inc., Mesa, Ariz; Sound-Eklin, Carlsbad, Calif; IDEXX Laboratories, Westbrook, Me). In addition to patient information, other applications such as client invoicing, inventory management, and payroll are included in these software packages.

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

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

Record Keeping for Special Purposes

The Drug Enforcement Administration (DEA) requires veterinary practices to maintain detailed inventory records for scheduled drugs. Drug inventory and use must be documented in a record book kept accessible to the area contained behind two locks where the scheduled drugs are stored. Records must be documented to either a clinic area where a minimal volume of drug can be kept (e.g., a single vial of diazepam) or for patient use. Use should identify the patient, volume used/wasted, date, and authorized person who obtained the drug. The drug use should be further documented in the PMR so as to account for the volume having been depleted from the inventory. A monthly or bimonthly accounting suitable for inspection should be conducted from the storage inventory and patient files to accurately account for scheduled drug use. This same accounting and inventory system applies to ambulatory vehicles.

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

Recognizing Abuse and Neglect in Equine Patients

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

What *Is* Equine Welfare?

Defining what constitutes acceptable welfare practice continues to be an evolving process that has yet to be conclusively agreed upon among investigators.[17] Previous to the past decade, the emphasis focused on food animal confinement systems with the improvements in welfare correlating positively with increased production. The modern concept of welfare attempts to merge scientific knowledge with the emotional state or "experience," which has led to a greater emphasis on quality-of-life assessments.[18] Evaluating the health and welfare of horses can be a complex undertaking when one considers the number of contradictory ideas and opinions relating to husbandry and training practices. To circumvent these differences, surveys[19] and sophisticated methodologies[20] have been developed as tools to examine socio-emotional issues such as welfare. Cruelty may be intentionally imposed or take the form of neglect due to ignorance, financial hardship, or poverty. Poor husbandry, unrecognized

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clinical and subclinical disease, improperly directed performance training, and work-related activities are examples of unintentional abuse and neglect that can also negatively affect a horse's quality of life.

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

Spotting Cruelty or Neglect

Millions of horses and donkeys around the world live in the poorest, most underdeveloped countries, where their primary use is work related—transporting goods, working in factories, on farms, or as the sole source of transportation for their owners. Veterinary care and education in animal husbandry practices are often lacking or nonexistent, and sources of quality forage in many areas further affect general health and survival. Signs of abuse and neglect are usually obvious to even the untrained eye, as evidenced by open wounds, chronic sores, overt lameness, and a skeletal appearance. In a study by Pritchard and colleagues,[21] which examined nearly 5000 working donkeys, horses, and mules residing in Afghanistan, Egypt, India, Jordan, and Pakistan, 70% had a body condition score of 2 or less (scale of 1-5) and nearly 90% of the 2071 horses examined had obvious lameness or gait abnormalities, associated with limb and/or hoof deformities.

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

UNEQUIVOCAL CRUELTY OR NEGLECT. All practicing veterinarians will likely be confronted with some form of cruelty or neglect during their careers. Aside from being exposed to these issues in their own practices, veterinarians may be invited to render second opinions or act as agents for humane organizations or local authorities investigating cases of welfare. In the case of the latter, a veterinarian may act as both caregiver and advocate for the horse(s) in question. The decision regarding when to intervene with clients may be complicated by several obstacles including the relationship with the owner or trainer, the veterinarian's employment status, and personal convictions. Depending on the magnitude of the abuse or neglect, sharing concerns and providing a plan to owners must be carefully thought out to prevent embarrassment or alienation. By showing empathy for the horse and owner, most clients are willing to be compliant and eager to share the responsibility of improving the situation. To provide the best plan of action, it is imperative that practitioners show flexibility and understanding with regard to the owner's particular situation. In cases where a veterinarian is merely an employee without ownership in the practice, a practice manager or owner may attempt to pressure a colleague against proceeding with a welfare claim for more practical reasons such as the loss of an influential client or one who may contribute significantly to the financial interests of the practice. In certain cases, state or local laws and ordinances may apply and it is the veterinarian's responsibility to be aware of such statutes, to not only protect his or her own interests but also remain in compliance. The American Veterinary Medical Association Model Veterinary Practice Act[22] guarantees immunity from liability in welfare cases, and most state and local laws ensure the protection of veterinarians who report cases of neglect or cruelty in good faith. In either case, evidence including accurate medical records, diagnostic tests, and photographic documentation is necessary to support a case of abuse and protect the veterinarian against liability claims. This becomes particularly important when it is necessary to proceed with a case before a regulating body or those that progress toward criminal indictment. It is of the utmost importance that veterinarians choosing to assist in welfare cases understand the legal process, are experienced in equine medicine, and are confident in their skills to collect and provide clear and "irrefutable evidence" to the courts.[23] Because considerable variation may be present within groups of equally neglected horses, practitioners should have in place organized methodology to approach cases of neglect or abuse so that subtle features are not missed. Observation of behavior and general condition should include careful physical palpation to determine the magnitude of muscle mass and identify the presence of scars or lacerations that may be obscured by profuse or matted coats. Photos of the animals and areas of concern may prove useful.

Beyond an intensive physical examination and body condition assessment, additional diagnostic tests may be warranted and serve to support claims of subclinical, clinical, chronic, or terminal diseases such as gastric ulceration, pituitary pars intermedia dysfunction (PPID), laminitis, and neoplasia, respectively. The minimum database includes a complete blood count, chemistry profile, and fecal analysis. Several body condition scoring systems have been developed to determine body condition in horses and donkeys.[23] All are comparatively similar for horses but vary enough in the scoring number and description, such that all clinicians in a practice should agree to use the same numeric system to avoid any ambiguity that may occur with an already subjective assessment. Box 2-2 illustrates an example of a nine-point scoring system for horses. Because donkeys accumulate fat preferentially over localized areas, scoring systems developed for horses should not be used to assess body condition in donkeys and mules.[24] The Donkey Sanctuary (www.thedonkeysanctuary.org.uk) has developed a body condition score chart specifically for donkeys.

IMPACT OF HUSBANDRY ON WELL-BEING AND BEHAVIOR. Regional (rural Western states vs. Eastern cities), cultural (Amish), political (animal rights activists), and religious differences strongly affect how societies and individuals view the treatment of horses and other animals. Husbandry practices vary widely and are also affected by location, property size, financial commitment, and an individual's personal background and exposure. Irregularities can impact the health and behavior of horses, leading to boredom, stall vices, training problems, and stereotypic behaviors. Problems usually result

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BOX 2-2

Body Condition Scoring*†

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

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

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

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

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

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

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

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

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

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

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

from misguided information or anthropomorphism, as most owners love their horses and do not set out to cause them harm. Paradoxically, veterinarians are often confronted with overzealous or ignorant owners who "over-care" for their horses and unnecessarily keep them covered in heavy blankets and hoods, ill-fitting tail sets, and tight leg bandages or well-meaning owners who simply overfeed and oversupplement their horses. These benign-appearing practices may seem harmless, but should be monitored by the veterinarian because they can affect the horse's behavior, health, and well-being and can lead to systemic disease such as laminitis secondary to obesity; localized disease (bacterial/fungal skin infections, blanket sores); and physical discomfort (overheating, pruritus).

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

Modern feeding practices such as time grazing, forage and concentrate selection, quantities fed, and feeding intervals are not in line with the horse's natural behavioral and gastrointestinal requirements. Ideally, horses kept in confinement should have access to pasture or turnout for extended periods and be allowed to socially interact with other horses, as this has been shown to reduce stress[26-28] and behavioral problems,[26-31] improve musculoskeletal health,[30,32] reduce the occurrence of gastric ulceration[29] and certain types of colic,[31,33] and improve quality of life.[18]

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

WELFARE AND TRAINING PRACTICES. Not every horse has the talent or mentality to excel at the discipline the owner has chosen, but many owners are unable to make this determination or refuse to accept such reality and will search for "shortcuts" designed to force the horse to succeed. Countless methods, training devices, and frightening contraptions have been developed over centuries to teach certain disciplines. Tying a horse's head in a fixed position for extended periods[34] and the use of severe bits, electric shock prods, and topical blisters are examples seen in modern training barns. Additionally, surgical cosmetic alterations, systemic drugs or topical irritants, silicone injections, and alcohol tail blocks may be used in some breeds to enhance certain physical "breed" characteristics or change the horses' conformation to fit a show ring ideal. Physical and in some cases psychological effects resulting from such abusive practices can confound physical examination findings and delay diagnosis and timely intervention. This may be of particular concern for someone hired as an official horse show veterinarian who is inexperienced or unfamiliar with training practices related to a particular

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breed or discipline and is presented with an affected horse on emergency. For example, the ideal Western pleasure horse should carry the head and neck in a low, fixed, relaxed position while performing required gaits in the show ring. In order to maintain this unnatural head position[35] for the duration of the class, trainers suspend or "hang" the horse's head high above the withers for hours before the entered class. As a result, the neck muscles of these horses become fatigued and sore to the point that they will refuse to lift their heads above a horizontal plane, appearing compliant and well-disciplined during the class. Clever pharmaceutical intervention is also used by some to affect the horse's vision, particularly in an indoor show ring. Ophthalmic atropine is used occasionally in English show horses to alter the gait, head and neck carriage, and how they "look" through the bridle. The resulting mydriasis can last for days to weeks.[36] Depending on the presenting complaint, it is clear from only two isolated examples how secondary signs from undisclosed intervention may lead to confusion on initial physical examination.

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

Musculoskeletal disease and lameness are common client complaints in equine practice. Numerous elements can contribute to lameness including misadventure, overexertion, inappropriate footing, poor conditioning, abusive or inappropriate training techniques, lunging, poor riding skills, poor hoof care, and improper shoeing. These should always be evaluated when attempting to determine the cause of an injury or change in temperament. Poorly fitting tack, unbalanced or heavy-handed riders, and inappropriate use of training aids (spurs or whips) can result in avoidance or physical damage to the horse. To make a complete assessment, it is often advantageous to observe the horse under tack to determine what factors may be causing or contributing to musculoskeletal or behavior issues. Unsuccessfully managed lameness can result in chronic pain, spread to other areas such as the back,[30] and limit the horse's value and potential welfare. Practitioners should stress the importance of rest and rehabilitation after injury and carefully monitor the client's use and potential abuse of antiinflammatory drugs, over-the-counter medications, and supplements.

Veterinarian's Responsibility to Patient Welfare

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

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

Veterinarians should strive to do the following:

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

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

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PART TWO

Manifestations of Disease

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• CHAPTER 3

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Pain

SUZANNE T. MILLMAN and JOHANN (HANS) F. COETZEE, *Consulting Editors*

Addressing pain is a key expectation for animal welfare in the eyes of the public, and large animal practitioners have an important role in educating clients to recognize and respond to livestock pain. Pain is a subjective experience. Hence one cannot truly know what another being (human or animal) experiences. Subjective experiences are challenging in medicine but not unique to veterinary practice. Some techniques used in human medicine, particularly for nonverbal and preverbal patients, can be applied to animals.

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

Diagnosing Pain in Livestock

Pain processing includes sensation and perception. Sensation refers to the lower-level neurologic and biochemical components (nociception), whereas higher cognitive processing such as interpretation is associated with perception. A modification to the International Association for the Study of Pain definition of pain was suggested for application to animals: "an aversive sensory experience caused by actual or potential injury that elicits progressive motor and vegetative reactions, results in learned avoidance behavior, and may modify species-specific behavior including social behavior."[7] Three functions of nociception are (1) warning the animal of actual damage to its tissues, (2) predicting when tissue damage is likely to occur, and (3) warning conspecifics of the presence of danger. Pain responses vary according to species, ontogeny, and type of the insult. Basic motor responses such as withdrawal occur in response to acute pain stimuli and are associated with protection from further tissue damage. However, simple withdrawal responses can occur consciously or unconsciously, in awake and in anesthetized animals. More organized behavioral responses involving higher cognitive processing include aggression or escape attempts.

Increased pulse, respiratory rate and tidal volume, pupil dilation, and other physiological responses occur during pain but are nonspecific indicators because these responses also occur during arousal, such as during fear and excitement. Conversely, pain behaviors occur when pain is present versus absent and are absent or decrease when animals are provided with appropriate analgesia treatments versus placebo treatments, such as saline. These pain behaviors can be measured objectively or subjectively. Subjective assessments traditionally have been the most practical for clinical application, but advances in technology provide opportunities for objective assessments outside the laboratory.

Clinical Scoring of Visual and Behavioral Indicators of Pain

Pain assessment in veterinary practice has typically relied on subjective global pain scales, with clinicians or animal caretakers providing proxy assessments for the animals in their care. Intangible measures such as demeanor, attitude, or lethargy are often cited for clinical scoring of pain but are poorly defined. Hence challenges are likely to occur with interobserver and intraobserver reliability and interpretation. Subjective scoring systems may be improved when descriptions, photographic images (Fig. 3-1), or video clips of behaviors are provided for training clinicians and animal caretakers. A website developed by Dr. Joyce Kent and Dr. Vince Molony, Royal (Dick) School of Veterinary Studies, provides an excellent resource with photographs and video clips of pain responses in several livestock species to common clinical situations ("Guidelines for the Recognition & Assessment of Animal Pain," http://www.link.vet.ed.ac.uk/animalpain/Default.htm).

Validation of subjective scoring systems for animal subjects is emerging and is a positive step in the evolution of pain research. A standardized facial grimace scale has been validated for assessing pain in mice, including five distinct components, three of which are also observed in the human facial pain grimace.[8] Livestock may display similar facial grimace components such as orbital tightening and ear position. Because changes in posture are subtle and often characteristic of particular types of pain, it is wise to standardize the visual assessment of the animal, scoring sequentially from head to tail (Table 3-1). Furthermore, changes in motivation and motor patterns are also characteristic of the type and location of pain and should be scored systematically (Table 3-2). Effective pain scoring protocols are critical for evaluating the effectiveness of interventions and determining humane end points when alleviation of pain cannot be achieved. Scoring of affective states such as depression can be refined with transparency regarding the responses recorded and use of specific tests to evoke behavioral responses (Table 3-3). Subjective pain scoring is most refined in terms of lameness and locomotion scoring, with excellent training resources available for bovine and equine practitioners and caretakers. Locomotion scoring systems that provide detailed descriptions of the observable changes in gait and allow observers to score components of the gait separately have been validated for identifying cows with severe hoof lesions[9] and cows that have received a local anesthetic.[10]

Pain behavior responses can also be measured objectively, particularly in experimental applications where detailed observations are collected during live observations or more frequently from video recordings. In ethology, the science of animal behavior, a key component of research methodology is development of an appropriate ethogram, which consists of a list of definitions for mutually exclusive behaviors.[11] For transparency and to avoid inherent bias associated with interpretation, definitions that focus on motor patterns or movements that an animal performs are preferred over those described in terms of an underlying motivation. Pain behaviors can

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FIG. 3-1 Humans report severe abdominal pain associated with infection with *Cryptosporidium parvum*. Similarly, when compared with healthy calves **(A),** calves infected with *C. parvum* **(B)** display a dull eye, ear rotation, lower head carriage, and back arch postures characteristic of abdominal pain. *(Courtesy Dr. Cynthia Todd, University of Guelph.)*

TABLE 3-1

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

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

*Standing with crossed fore limbs results in weight transferred from the inner claw to the outer claw.

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

TABLE 3-2

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

Behavior	Abdominal Pain	Lameness Pain
Redirected and pain avoidance behaviors	Bruxism (teeth grinding) Wound licking Wound scratching Self-mutilation (equine) Rolling (equine) "Looking"—nose to flank Pawing, stamping (fore) Kicking, stamping (hind) Abnormal gait Crawling on knees Tail flicking	Abnormal gait Crawling on knees Difficulty turning
Activity	Statue standing* Increased lying Increased standing inactive Hyperactivity, restlessness Frequent standing/lying transitions Reduced grooming Reduced exploration	Increased standing inactive Increased lying Reduced standing/lying transitions Abnormal standing/lying transitions Reduced exploration
Feeding	Anorexia (acute) Reduced feeding duration Intermittent eating Intermittent drinking Playing with water Cessation of rumination	Reduced feeding duration
Social interactions	Aggression Social isolation Reduced play	Reduced play
Vocalizations	Distress calls Groaning Grunting Snorting Sneezing (goats)	

*Standing immobile in a fixed, rigid posture.

then be quantified in terms of frequency and duration of occurrence. Experiments can also be designed to provoke behavior, and quantified in terms of latency to respond and thresholds of stimulus required for response. Although pain-specific behaviors are relatively straightforward to observe and quantify when detailed definitions are provided, manual collection of behavior data is labor intensive and difficult to record because they occur at low frequencies even when the animal is undisturbed by activity in the barn.

New technologies such as accelerometers for frequency and duration of activity and resting behavior are emerging for automated data collection (Fig. 3-2), and they show promise for detecting behavioral changes associated with lameness.[12] Accelerometers are increasingly

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TABLE 3-3

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

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



FIG. 3-2 Accelerometers quantify activity when affixed to the limb and may provide useful data for identifying lame cows. The output includes duration and frequency of standing and lying bouts and number of steps. For some devices, output is integrated into dairy management software to alert the stockperson when changes in activity patterns occur. *(Courtesy Dr. Janet Higginson Cutler, University of Guelph.)*



FIG. 3-3 Mechanical nociception threshold test using pressure algometry to test pain sensitivity at a sole ulcer lesion. Cattle tolerate less pressure before displaying an avoidance (hoof withdrawal) response when the pressure algometer tip is applied to the sole ulcer compared with normal sole. *(Courtesy Dr. Janet Higginson Cutler, University of Guelph.)*

being incorporated into dairy management software programs, with changes in activity flagged for further investigation by the stockperson. In addition to specific pain responses, general pain responses are associated with changes in motivation during painful conditions. During acutely painful procedures, livestock typically struggle or attempt to escape. Escape attempts can be quantified using exit velocity, determined by the latency for the animal to break an infrared beam, by strain gauges measuring the force the animal exerts on the restraint chute, or by software analysis of head movements captured with video images.[13]

Similarly, in some livestock species distress calls are performed during painful procedures and can be discriminated from other vocalizations such as contact calls by the increase in rate, pitch, and volume.[14] Distress calls given during painful procedures are greater in intensity than other vocalizations such as short calls at lower fundamental frequencies that are emitted from cattle when isolated.[15] However, vocalizations may not be a robust measure of pain for cattle because they rarely vocalize, and propensity to vocalize is associated with breed, perhaps due to variations in excitability.[16] Conversely, goats are expressive vocally, despite also being a prey species.

Nociceptive Threshold Tests

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

Pressure algometry is an example of a mechanical nociception test that has proven useful for assessing pain in livestock (Fig. 3-3). This tool measures the amount of force applied to a surface, and painful thresholds are determined using a withdrawal response. When applied around the horn buds, calves display significantly lower nociception thresholds following disbudding when compared with pressure tolerated on the day before surgery. Furthermore, calves display less pressure sensitivity when treated with a nonsteroidal antiinflammatory drug versus a placebo solution.[17] Pressure algometry data suggest that the duration of postsurgical pain is greater than estimates using neuroendocrine markers because significantly lower nociception thresholds are observed for 3 days following surgery relative to baseline values.[18] Pressure algometry appears to be a robust tool, with potential for clinical application because it is cheap and easy to use and differences in response are often large.

Thermal nociception threshold is quantified by the amount of time (latency) for an avoidance response to a radiant or laser thermal stimulus. A CO_2 laser thermal stimulator was found to provoke a foot lift or kicking withdrawal response when skin temperature reached 45° to 55° C, and because CO_2 laser stimulators use a monochromatic, long wavelength infrared source of radiation, absorption is not affected by pigmentation of the skin.[19] Standard operating procedures for all thermal nociception tests require the skin surface to be free of hair, manure, and moisture, and safety precautions such as maximum duration of stimulus application must be followed to avoid tissue damage on different skin surfaces.[20] A ceiling value of 20 seconds was successfully used as a safety precaution when a radiant thermal nociception stimulus (constant 80% beam intensity, 200C) was used

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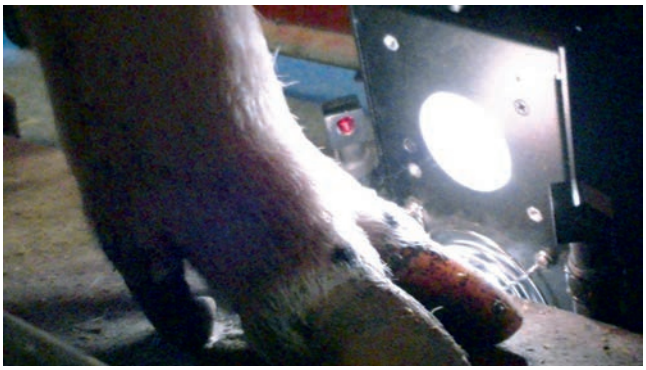


FIG. 3-4 Thermal nociception threshold test using a radiant thermal stimulus to test pain sensitivity at the coronary band on a lame sow. Effective analgesia is evident by increased tolerance of the thermal stimulus and corresponding greater latency for an avoidance (leg withdrawal) response. *(Courtesy Ms. Kathleen Tapper, Iowa State University.)*

during a lameness study in sows (Fig. 3-4). However, these same criteria were insufficient when the thermal test was used in a disbudding study, resulting in blisters on two calves.[18]

Pain Aversion Tests

Classical pain tests that quantify reflexive nociceptive withdrawal responses to mechanical or thermal stimuli provide information about the sensory-discriminatory aspects of pain, but not the affective (emotional) components. Evidence indicates that some species such as chickens and sheep choose to self-medicate to avoid painful conditions. Conditioned avoidance tests are based on an animal's ability to recall an association of a stimulus such as a location or a person with a previous aversive experience. Conditioned place avoidance is commonly observed where livestock have previously experienced painful interventions such as branding, dehorning, or castration. Similarly, cattle may associate the appearance or odor of the veterinary practitioner with previous aversive experience, resulting in difficulties with handling. However, it is often difficult to tease apart aversion arising due to experiences associated with pain versus fear. This is especially problematic with extensively managed livestock that are unfamiliar with handlers and equipment. In several species, electrical stimulation results in startle and withdrawal reflexive behaviors, as well as higher pain processes associated with aggression and avoidance behaviors. However, it is used in livestock to facilitate movement (electric prods), for restraint (electroimmobilization), and for semen collection (electroejaculation). Aversiveness of electroimmobilization is evident by conditioned aversion responses by livestock, resulting in reluctance to move through handling chutes or avoidance of particular handlers.[21] These results have been used to advise against the practice of electroimmobilization, such as animal welfare policies of the American Veterinary Medical Association and Canadian Veterinary Medical Association.

Pharmacologic Interventions to Treat Livestock Pain

Negative public perception of pain associated with routine animal management practices such as dehorning and castration is mounting, with increasing call for the development of practices to relieve pain and suffering in livestock. Preemptive analgesia can be applied in advance of the painful stimulus, thereby reducing sensitization of the nervous system to subsequent stimuli that could amplify pain. Agents that could be used to provide preemptive analgesia include local anesthetics, nonsteroidal antiinflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl-D-aspartate (NMDA) receptor antagonists. However, less than 20% of U.S. veterinarians currently report using analgesia routinely at the time of dehorning and castration.[22]

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

Hyperalgesia has been reported to persist in dairy cattle and lame sheep for at least 28 days after the causal lesion has resolved.[23,24] Consequently, chronic pain associated with lameness is considered one of the most significant welfare concerns in dairy cows. Inflammatory pain associated with lameness responds modestly to treatment with NSAIDs,[25,26] but neuropathic pain (due to nerve damage or neuronal dysfunction) is considered refractory to the effects of NSAIDs and many opioid analgesics. Therefore there is a need to identify novel drugs and drug targets for alleviating chronic pain of neuropathic origin in animals.

Challenges Associated with Providing Analgesia in Food Animals

Several challenges are associated with providing effective analgesia in food animals in the United States. First, there are currently no analgesic drugs specifically approved for the alleviation of pain in livestock. Therefore use of any drug for pain relief constitutes extralabel drug use (ELDU).[27] Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), ELDU is permitted for relief of suffering in cattle provided specific conditions are met. These conditions include that (1) ELDU is allowed only by or under the supervision of a veterinarian, (2) ELDU is allowed only for U.S. Food and Drug Administration (FDA)-approved animal and human drugs, (3) ELDU is only permitted when the health of the animal is threatened and not for production purposes, (4) ELDU in feed is prohibited, and (5) ELDU is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore use of an analgesic to alleviate pain associated with castration in calves in the United States would be required by law to comply with these regulations.

A second challenge to providing effective analgesia in cattle is that there is often a delay between the time of drug administration and the onset of analgesic activity. For example, local anesthetics require 2 to 5 minutes before a maximal effect is achieved. This may slow animal processing as producers must wait for local anesthesia to take effect. This delay may serve as a disincentive for them to provide routine preemptive analgesia. Furthermore, the requirement for large numbers of animals to be processed quickly may result in procedures being initiated before optimal analgesia is achieved. A third challenge is that the route or method of analgesic drug administration may require specialized training and expertise or may be hazardous to the operator. For example, the NSAID flunixin meglumine is only approved for intravenous (IV) administration in the United States.[27] Therefore, administration requires the animal to be adequately restrained and the operator to be proficient in IV administration. Similar issues are encountered with epidural analgesic drug administration and administration of local anesthesia into the scrotum. The latter procedure is also considered especially hazardous by many livestock handlers. In addition, the majority of analgesic drugs that are available in the United States have a short elimination half-life necessitating frequent administration in order to be effective.[27] This increases the stress on the individual animal and increases labor and drug costs.

In addition to the regulatory considerations discussed previously, certain drug classes such as the opioid and NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement Administration (DEA). Therefore administration of these compounds to provide preemptive analgesia is restricted to use by licensed veterinarians. Finally, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures, especially because there is no perceived economic benefit for doing so. It may also be difficult for producers and veterinarians to determine if analgesic compounds are effective because cattle may not show overt signs of pain and

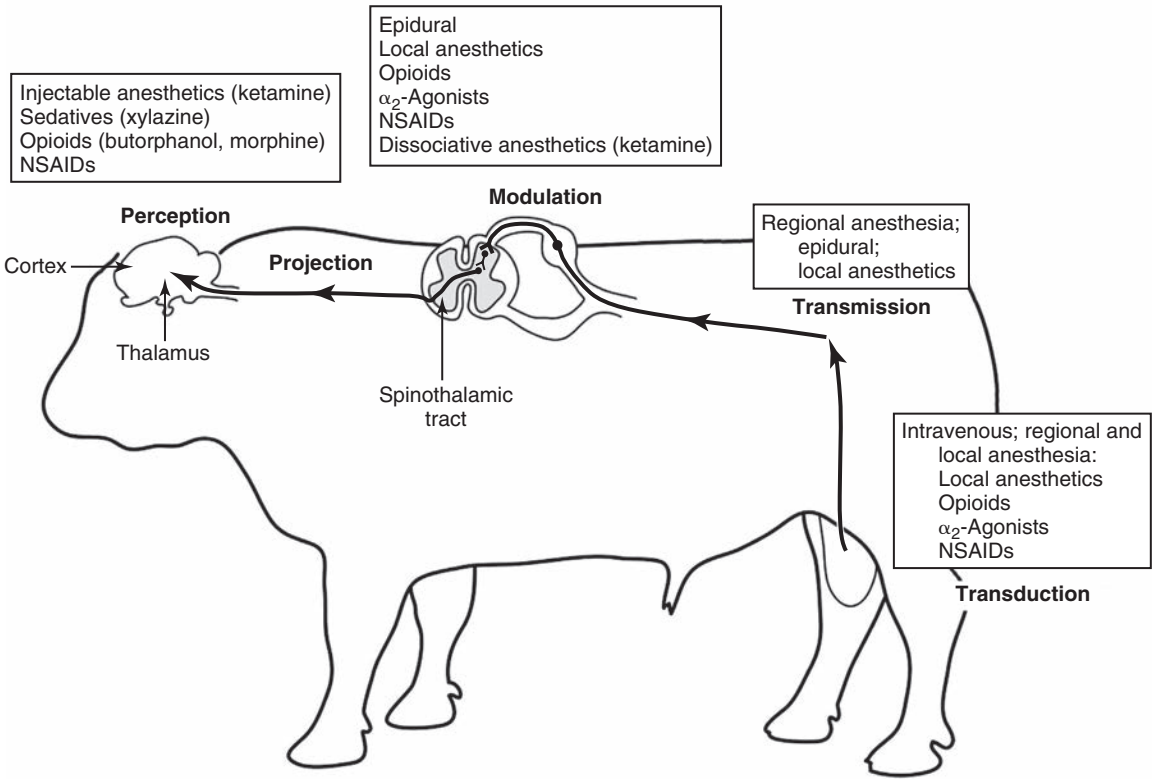


FIG. 3-5 A schematic representation of the nociceptive pathway in cattle indicating the anatomic location of target receptors for analgesic drug activity. *(Courtesy Ms. Mal Hoover, Kansas State University.)*

distress. Thus determining the need for analgesia and the dose, route, duration, and frequency of drug administration in cattle can be especially challenging.

Analgesic Compounds and Their Effect in Cattle

Pain perception involves the transduction of chemical signals at the site of injury into electrical energy (Fig. 3-5). This is followed by transmission of the electrical signal via nerve fibers up the spinothalamic tracts, where modulation may occur in the dorsal horn. Finally, the impulse is projected to the brain where pain perception occurs. The initial response to a noxious stimulus is typically brief, well localized, and somewhat proportional to the intensity of the insult. The second phase of the response is prolonged, diffuse, and often associated with hypersensitivity around the point where the initial stimulus was applied. This effect may lead to persistent postinjury changes in the central nervous system (CNS), resulting in pain hypersensitivity or central sensitization ("wind-up"). These effects lead to hyperalgesia (increased pain from previously painful stimuli) and allodynia (a previously nonpainful stimulus now produces pain).

Surgery-induced pain and central sensitization consist of two phases: an immediate incisional phase and a prolonged inflammatory phase that arises primarily due to tissue damage. The goal of administering analgesic compounds before castration is to mitigate both the incisional and inflammatory phase of the pain response. Effective analgesia therefore requires a multimodal approach using compounds that act on different receptor targets along the nociceptive pathway (see Fig. 3-1). This can be achieved through a combination of local anesthesia, NSAIDs, and sedative-analgesic combinations of opioids, α2-agonists, and NMDA receptor antagonists.

Local Anesthesia

Local anesthetics are the most commonly prescribed preemptive analgesic drugs used in food animal practice.[28] These compounds produce reversible loss of sensation in a localized area without causing loss of consciousness. Local anesthetics enter and block open sodium channels of nerve cells and prevent generation and propagation of nerve impulses. Repeatedly stimulated nerve cells are therefore more susceptible to the effects of local anesthetics. Furthermore, unmyelinated nerve fibers that transmit pain signals are preferentially blocked by local anesthetics compared with myelinated fibers that are responsible for pressure sensation and motor activity. The quality of local anesthesia in an acidic environment such as infected tissues is often poor because these compounds are weak bases that must dissociate in an alkaline environment to exert their effect. Lidocaine has a fairly rapid onset of activity (2 to 5 minutes) and an intermediate duration of action (90 minutes). Local anesthetic administration into the epidural space has also been shown to provide regional analgesia of the perineal region, commencing 5 minutes after administration of 0.2 mg/kg lidocaine and lasting 10 to 115 minutes.[28]

Compounds That Potentiate Local Anesthesia

MAGNESIUM SULFATE ($MgSO_4$). Magnesium sulfate has been combined with lidocaine to potentiate the local anesthetic effects.[29] Magnesium competitively antagonizes NMDA receptors and their associated ion channels in the same manner as ketamine, thus reducing central sensitization caused by peripheral nociceptive stimulation. It was recently reported that the combination of lidocaine with magnesium sulfate produced epidural analgesia of longer duration than lidocaine with distilled water. In this experiment, local anesthesia with 2% lidocaine solution administered at 0.22 mg/kg was potentiated with 1 mL of 10% magnesium sulfate solution. Magnesium also reportedly has antinociceptive effects in animals and humans after systemic administration.[30] These effects are considered to be associated with the inhibition of calcium influx into the cell and antagonism of NMDA receptors. Further studies with respect to the safety and efficacy of magnesium augmentation of local anesthesia are necessary before this technique can be recommended.

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

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TABLE 3-4

Nonsteroidal Antiinflammatory Compounds Available for Use in Cattle

Drug	Approved Species	Indications	Dose (Cattle)	T½	Withhold Period
Flunixin meglumine	Cattle, horses, and pigs	NSAID—antipyretic, antiinflammatory	1.1-2.2 mg/kg IV q12h or q24h for up to 3 days	3-8 hr	Meat 4 days Milk 36 hr
Phenylbutazone	Horses and dogs	NSAID—antiinflammatory	4 mg/kg IV ONLY!	40-55 hr	Not approved in cattle in the United States
Ketoprofen	Horses and dogs	NSAID—antiinflammatory	3 mg/kg IV, IM	0.42 hr	Not approved in cattle in the United States
Aspirin	No FDA approval Horses and cattle	NSAID—reduction of fever Relief of minor muscle aches and joint pain	50-100 m g/kg PO Oral F < 20%	0.5 hr (IV salicylate)	No formal FDA approval Not for use in lactating cattle
Carprofen	EU approval in cattle Dogs	NSAID—adjunctive therapy of acute respiratory disease and mastitis	1.4 mg/kg body weight IV or SC	Age dependent <10 weeks: 49.7 ± 3.9 hr (R–) and 37.4 ± 2.4 hr (S+) Adult cows; 30.7 ± 2.3 hr	Not approved in cattle in the United States
Meloxicam	EU and Canadian approval in cattle Dogs and cats	NSAID—adjunctive therapy of acute respiratory disease; diarrhea and acute mastitis (Europe)	0.5 IV, SC 0.5-1 mg/kg PO	27 hr (range 19.97-43.29 hr)	Not approved in cattle in the United States

EU, European Union; *IM,* intramuscular; *IV,* intravenous; *NSAID,* nonsteroidal antiinflammatory; *PO,* oral; *SC,* subcutaneous.

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

Alternatives to Local Anesthesia

Ethanol injection demyelinates nerve fibers and may be a promising long-acting local anesthetic for use at the time of disbudding.[18] When ethanol was administered as a corneal nerve block before disbudding, calves failed to display increased pain sensitivity in response to pressure algometry relative to their baseline values. Furthermore, ethanol-treated calves differed significantly from calves treated with the local anesthetic lidocaine at 1 hour postdisbudding, when the lidocaine is assumed to be wearing off. Ethanol blocks appeared to desensitize the site of cautery dehorning for longer than 83 hours, at which time the experiment concluded. In this experiment, 2 mL of 100% ethanol was injected at the site of the corneal nerve block. However, more than half the calves subjected to ethanol anesthesia required a second injection to achieve complete loss of sensation in one or both horns. Further studies with respect to the safety and efficacy of ethanol blocks for local anesthesia are necessary before this technique can be recommended.

Nonsteroidal Antiinflammatory Drugs

NSAIDs produce analgesia and antiinflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclooxygenase (COX) in the peripheral tissues and CNS. COX exists in two isoforms. COX-1 is constitutively expressed in both the peripheral nervous system and CNS, although expression is enhanced by pain and inflammatory mediators. COX-2 is ubiquitous in the CNS but only becomes the major enzyme for PG synthesis after induction by factors released during cell damage and death. It takes 2 to 8 hours for maximal COX-2 mRNA expression to occur in the peripheral tissues; therefore initial release of PG is primarily due to COX-1. PG in the peripheral tissues lowers the activation threshold of sensory neurons and may initiate nociceptive activity. PG also works in concert with substance P, histamine, calcitonin gene-related peptide (CGRP), and bradykinin to lower the firing threshold of sensory nerves and produce inflammation. Therefore NSAIDs that inhibit COX-1 may have a more immediate impact on pain by inhibiting PG production in the periphery than COX-2–selective compounds. However, NSAIDs that inhibit COX-1 may be associated with increased risk for adverse gastrointestinal and renal effects.

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

The dose and pharmacokinetic parameters of commonly used NSAIDs in the United States are summarized in Table 3-4.

FLUNIXIN MEGLUMINE. Flunixin is a highly substituted derivative of nicotinic acid. Currently flunixin meglumine is the only NSAID approved for use in cattle in the United States.[27] The plasma elimination half-life of flunixin is reported to be 3 to 8 hours. Following a single IV dose of 2.2 mg per kg of body weight (mg/kg), plasma concentrations decreased from 16.16 ± 5.28 µg/mL to 1.22 ± 0.16 µg/mL in 2 hours and reached 0.5 ± 0.02 µg/mL by 30 hours.[31] A peak concentration (Cmax) of 0.9 ± 0.05 mcg/mL occurred at 3.5 ± 1.0 hours (Tmax) after a single oral dose of 2.2 mg/kg with an estimated half-life of 6.2 hours and bioavailability of 60%. Therefore once-daily administration is likely required to maintain effective plasma drug concentrations. Although this drug class is recognized as having analgesic properties, flunixin is only indicated for control of fever associated with respiratory disease or mastitis, as well as fever and inflammation associated with endotoxemia, rather than for control of pain. Studies demonstrating the analgesic effects of flunixin administered alone at the approved dose of 2.2 mg/kg are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for IV administration, which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that the intramuscular (IM) administration of flunixin may result in significant myonecrosis and tissue residues.[27]

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PHENYLBUTAZONE. Phenylbutazone is not approved for use in cattle in the United States, although it has been used in veterinary medicine for more than 50 years.[32] The pharmacokinetics of phenylbutazone is characterized by a slow clearance and longer terminal half-life compared with other NSAIDs. The oral bioavailability of phenylbutazone ranges from 54% to 69% with peak plasma concentrations achieved in 8.9 to 10.5 hours.[33] Phenylbutazone has been associated with rare but fatal blood dyscrasias including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and deaths in humans. In light of these potential adverse effects associated with exposure to phenylbutazone, the FDA has issued an order prohibiting the extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older. There is also a zero tolerance for phenylbutazone residues in edible tissues from any class of animal. Use of phenylbutazone as an analgesic in food animals is therefore strongly discouraged.[27]

KETOPROFEN. Ketoprofen is a member of the propionic acid class of NSAIDs. Ketoprofen has a short plasma elimination half-life of 0.42 hours in adult cattle, making it less attractive for use as a preemptive analgesic.[34] Although it has been demonstrated that concentrations of ketoprofen are higher in inflammatory exudates than plasma, 80% of a parenteral dose is reportedly eliminated in the urine within 24 hours of administration.[35] Therefore multiple doses of ketoprofen will likely be required to maintain adequate analgesic concentrations.

Ketoprofen is approved in the European Union and Canada for the alleviation of inflammation and pain associated with arthritis and traumatic musculoskeletal injuries and as an adjunctive therapy for the alleviation of fever, pain, and inflammation associated with acute clinical mastitis.[35] The recommended dose in cattle is 3 mg per kg of body weight by IM or IV injection, every 24 hours for up to 3 days. Ketoprofen is commonly used in small animal and equine medicine in the United States; however, there are currently no approved formulations for use in livestock.[27]

SALICYLIC ACID DERIVATIVES. Salicylic acid derivatives including aspirin (acetylsalicylic acid) and sodium salicylate were the first NSAIDs to be used in modern medicine and are still widely used for their analgesic, antipyretic, and antiinflammatory properties. Although the veterinary forms of aspirin are extensively marketed with label indications for the treatment of fever, inflammation, and pain relief, these have never been approved by the FDA Center for Veterinary Medicine for these indications.[36] Therefore the legality of using salicylic acid derivatives in cattle is questionable because these are technically compounded products.

Aspirin elimination half-lives after oral administration range from approximately 4 hours after oral administration in cattle to approximately 38 hours in cats.[36] The slow absorption rate after oral administration demonstrated in adult dairy cows is evident in the difference between elimination half-times for IV sodium salicylate (0.54 ± 0.04 hr)[37] and oral acetylsalicylic acid (3.70 ± 0.44 hr).[38] The elimination half-life is longer after oral administration of aspirin because the rumen acts as a slow-release reservoir for aspirin absorption. The low volume of distribution (0.24 ± 0.02 L/kg) is indicative of limited distribution to tissues. It is noteworthy that salicylic acid derivatives are not associated with clotting deficits in cattle.

CARPROFEN. Carprofen is a member of the propionic acid class of NSAIDs.[39] The relative antiinflammatory, analgesic, and antipyretic activity of carprofen is reported to be greater than phenylbutazone or aspirin in calves.[40] Carprofen is approved in the European Union as an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle. The recommended dose for subcutaneous or intravenous administration is 1.4 mg/kg body weight. Carprofen is commonly used in small animal medicine in the United States; however, there are currently no approved formulations for use in livestock.[27]

MELOXICAM. Meloxicam is an NSAID of the oxicam class that is approved in the European Union for adjunctive therapy of acute respiratory disease, diarrhea, and acute mastitis when administered at 0.5 mg/kg IM or subcutaneous (SC).[41] It has been shown that 0.5 mg/kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for longer compared with calves receiving only local anesthesia before cautery dehorning.[17] Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves over 24 hours postdehorning. It was recently reported that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with administration of a cornual nerve block alone.[42] The authors also observed that meloxicam administered at 0.5 mg/kg IV before dehorning in 16-week-old calves reduced plasma substance P concentrations and improved weight gain over 10 days compared with untreated controls.[43] These reports demonstrate that administration of meloxicam before dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

Meloxicam (20 mg/mL) is approved for use in cattle in several European countries with a 15-day meat withdrawal time and a 5-day milk withdrawal time following administration of 0.5 mg/kg IM or SC.[41] An oral meloxicam suspension (1.5 mg/mL) and injectable formulation (5 mg/mL) are approved in the United States for the control of pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/mL) is approved for the control of postoperative pain and inflammation in cats. The pharmacokinetics of meloxicam after oral and IV administration to cattle have recently been described.[44] A mean peak plasma concentration (Cmax) of 3.10 μg/mL (range 2.64 to 3.79 μg/mL) was recorded at 11.64 hours (range 10 to 12 hours) with a half-life ($T_{½\lambda z}$) of 27.54 hours (range 19.97 to 43.29 hours) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (range 0.64 to 1.66). These findings indicate that oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves. Several inexpensive generic tablet formulations containing meloxicam (7.5 and 15 mg) have recently been approved for relief of signs and symptoms of osteoarthritis in human medicine. In the absence of FDA-approved analgesic compounds in food animals, use of oral meloxicam tablets for alleviation of pain in cattle could be considered under AMDUCA.

Sedative-Analgesic Drugs

Opioids, α2-agonists, and NMDA receptor antagonists are the most commonly used sedative analgesic compounds in veterinary medicine. These compounds may act synergistically and are therefore increasingly coadministered. A recent survey of Canadian veterinarians found that respondents who did use an analgesic at the time of castration used xylazine (>50% of respondents) more frequently than lidocaine (<30% of respondents).[3] Administration of local anesthetics into the testicles is considered by some to be dangerous and time consuming with unpredictable efficacy, especially when circumstances do not allow sufficient time for maximal anesthesia to take effect.[3] Sedative-analgesic compounds may replace the need for intratesticular anesthetic injection and thus enhance animal well-being and operator safety. A subanesthetic combination of xylazine administered at 0.02 to 0.05 mg/kg and ketamine at 0.04 to 0.1 mg/kg given IV or IM ("Ketamine Stun") is reported to provide mild sedation without recumbency in cattle.[45,46] Butorphanol (0.01 mg/kg) or morphine (0.05 mg/kg) may be included for enhanced analgesic effects.[45]

OPIOID ANALGESICS. The analgesic effects of opioids are associated with binding to spinal and supraspinal mu (μ), kappa (κ), and sigma (σ) receptors. Drug binding decreases propagation of the nociceptive signal by activating receptor-linked potassium channels and inhibiting voltage-gated calcium channels. In addition to producing analgesia, μ receptor activation is associated with respiratory depression, decreased gastrointestinal motility, increased appetite, sedation,

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euphoria, and nausea. Therefore partial and mixed receptor opioids have been developed with fewer adverse effects and, in some cases, a lower abuse potential than pure μ agonists. There are currently no narcotic analgesics approved for use in cattle in the United States. Opioids are designated as Schedule 3 drugs in the United States and are subject to regulation by the U.S. Drug Enforcement Agency (DEA).

Butorphanol is a κ-opioid receptor agonist and either a partial μ agonist or antagonist. The potency of butorphanol is reported to be five to seven times that of morphine, although some authors dispute this. The efficacy of butorphanol is limited to mild and moderate pain but is one of the most common narcotic analgesics used in veterinary medicine. The half-life of butorphanol in dairy cows administered 0.25 mg/kg IV was 82 minutes.[47] Peak plasma concentration for butorphanol of 7.07 ± 0.55 ng/mL was observed at 9.5 ± 0.50 minutes after coadministration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, and 0.1 mg/kg ketamine IM immediately before dehorning and castration with a plasma elimination half-life of 71.28 ± 7.64 minutes.[48] In dogs a plasma concentration of 45 ng/mL is considered an effective analgesic concentration, but this has not been confirmed in cattle.

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

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

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

Xylazine epidural has been shown to produce greater perineal analgesia than xylazine given intramuscularly.[49] Xylazine epidural has been proposed as a method of providing sedation and analgesia to facilitate castration in mature bulls.[50] The onset of analgesia following administration of xylazine alone was found to be significantly longer (11.7 ± 1 minute) than the combination of xylazine and lidocaine (5.1 ± 0.9 minutes) and lidocaine alone (4.8 ± 1.0 minutes).[51] The combination of lidocaine and xylazine produced analgesia of significantly longer duration (302.8 ± 11.0 minutes) than xylazine alone (252.9 ± 18.9 minutes) or lidocaine alone (81.8 ± 11.8 minutes). Xylazine induced mild to moderate sedation and ataxia. Ataxia was also noted in cattle receiving lidocaine alone.

***N*-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS.** Ketamine is an NMDA-receptor antagonist that produces analgesia and dissociative anesthetic effects when administered at a dose of 2 to 4 mg/kg IV to calves.[52] Ketamine and its active metabolite, norketamine, also bind μ and κ opioid receptors producing analgesia. Data from rats suggest that norketamine contributes to the analgesic effect of ketamine, with a potency that is one third of the parent drug.

Subanesthetic ketamine administered at 0.1 to 1 mg/kg as an IV bolus is effective in managing acute postoperative pain in human medicine. In humans, plasma ketamine concentrations above 4 to 5 μmol/L (1000 ng/mL) are required to produce anesthetic effects, whereas analgesic effects are associated with plasma concentrations below 1 μmol/L (275 ng/mL) or one tenth to one fifth of the anesthetic dose. Plasma ketamine concentrations ranging from 40 to 150 ng/mL were associated with analgesia in humans. The authors' group previously demonstrated that mean plasma ketamine and norketamine concentrations in cattle decreased to below 40 ng/mL and 10 ng/mL after 30 and 60 minutes, respectively, after administration of a subanesthetic combination of xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg).[53] NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement Agency (DEA).

Future Prospects for Treating Chronic Pain and Central Sensitization in Cattle

GABAPENTIN. Gabapentin (1-[aminomethyl] cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analogue originally developed for the treatment of spastic disorders and epilepsy. Studies have reported that gabapentin is also effective for the management of chronic pain of inflammatory neuropathic origin. Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α_2-δ subunit of voltage-gated calcium channels acting presynaptically to decrease the release of excitatory neurotransmitters. Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations. It has also been reported that gabapentin can interact synergistically with NSAIDs to produce antihyperalgesic effects. The authors report a mean peak plasma gabapentin concentration (Cmax) of 3.40 μg/mL (range 1.70 to 4.60 μg/mL) at 7.20 hours (range 6 to 10 hours) after oral gabapentin administration to calves at 15 mg/kg.[54] An elimination half-life ($T_{½}\lambda z$) of 7.9 hours (range 6.9 to 12.4 hours) was recorded. Oral administration of gabapentin at 15 mg/kg may be associated with plasma concentrations of greater than 2 μg/mL for up to 15 hours. The pharmacokinetics of gabapentin suggests that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle.

Summary

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

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Alterations in Body Temperature

MARIE-EVE FECTEAU, *Consulting Editor*
SUSAN L. WHITE

■ MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

Hyperthermia, 31
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Control of Body Temperature

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

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

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

Conditions of Increased Body Temperature (Hyperthermia)

Body temperature disorders in which the core body temperature set point is unaltered can occur from increased heat production, absorption of heat, or impairment of heat loss. Central nervous system (CNS) disorders that disturb the hypothalamic regulatory center, certain drugs, and metabolic disorders may also cause temperature changes. Regardless of the triggering cause, hyperthermia should be considered a medical emergency and severely hyperthermic patients require immediate total body cooling as temperatures above 107° F (41.6° C) may lead to permanent organ damage or death. Cooling options for the hyperthermic patient include surface cooling techniques (clip hair, apply water to skin, fan, ice packs over areas with large vessels [neck, axilla, inguinal region]); internal cooling techniques (rectal administration of cool isotonic fluids, gastric lavage); and administration of intravenous isotonic fluids.

Drugs with Effect on Body Temperature Regulation

Phenothiazine tranquilizers are a recognized cause of loss of ability to control body temperature.[4] Conversely, α_2-agonist sedatives (xylazine and detomidine) have been shown to induce tachypnea and decrease body temperature in febrile horses.[5] The potential mechanism for the antipyrexic effect of α_2-agonist drugs may be related to their ability to decrease prostaglandin E_2 production by the hypothalamus.[5-6] Erythromycin may induce hyperthermia during hot weather, particularly in foals.[7-8] This side effect has been attributed to a reaction to erythromycin itself or to an alteration of the foal's thermoregulatory system by mechanisms not yet described.[8]

Malignant Hyperthermia

Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscles that presents as a hypermetabolic response to potent volatile anesthetic gases such as halothane, sevoflurane, desflurane, and the depolarizing muscle relaxant succinylcholine and, rarely, in humans, to stresses such as vigorous exercise and heat.[9] The classical signs of MH include marked hyperthermia, tachycardia, tachypnea, increased end-expired carbon dioxide production, increased oxygen consumption, acidosis, hyperkalemia, and muscle rigidity.[9] The

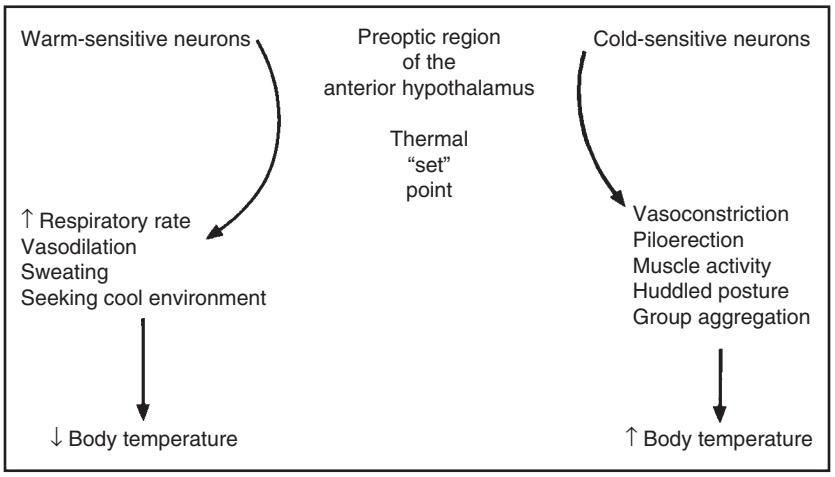


FIG. 4-1 Regulation of body temperature.

pathophysiology of MH involves an uncontrolled release of intracellular calcium from skeletal muscles' sarcoplasmic reticulum, resulting in activation of muscle contraction, oxygen consumption, carbon dioxide production, adenosine triphosphate (ATP) breakdown, and heat.[9] Although MH is most common in humans and pigs, it has been reported in horses.[10-13] Of note, MH has also been reported in potbellied pigs.[14] Mutation of the ryanodine receptor 1 gene, which is essential in skeletal muscle excitation-contraction coupling, is the basis of MH in humans, pigs, and dogs.[15] Mutation of this gene (autosomal dominant) has been documented in Quarter Horses with MH.[16] In all species, MH typically leads to death if it is not recognized and treated early.

Exercise

During sustained exercise, heat production may exceed the ability of heat loss mechanisms, leading to a stable increase in core body temperature proportional to the intensity and duration of exercise. The elevation in temperature often persists for several hours after exercise, but temperature returns to normal with rest as heat loss mechanisms remain activated. Body temperature increases of greater than 2° C (4° F) above normal during exercise, especially if reached early in exercise, are usually the result of severe environmental conditions and/or failure in heat loss mechanisms. In one study looking at the effect of age on thermoregulation during exercise, old horses reached higher body temperatures faster and had greater sweat losses when compared with young horses.[17] Peripheral cooling to augment heat loss should be used to lower body temperature because increases in temperature caused by exercise are unaffected by antipyretic drugs.[18-19]

The intense muscular activity associated with generalized tonic-clonic seizures may, like vigorous exercise, cause a rise in body temperature. If central heat regulatory systems are unaffected by the disease process, body temperatures return to normal no longer than 48 hours after the last seizure.[20] Elevated temperatures that persist for longer periods should prompt investigation into other causes for the increased temperature. Similarly, hyperkalemic periodic paralysis of horses has also been associated with episodes of hyperthermia.[21]

Heat Stroke

When animals are exposed to high ambient temperatures, intense solar radiation, and/or high humidity so that heat load increases at a rate faster than heat can be dissipated, heat stroke may develop. Heat stroke is more common in ruminants because of their inability to sweat and thus their diminished evaporative ability for heat loss. Sheep with fleece and large dense cattle are especially prone to heat stroke when denied access to shade or adequate water and/or when physical activity is imposed on them. Rectal temperature will often exceed 107° F (41.5° C), and central body temperature may exceed 112° F (44.5° C). Heat stress is a recognized condition of llamas and alpacas that are exposed to high ambient temperature and high humidity.[22] Clinical findings include hyperthermia (often >105° F), signs of respiratory distress, tachycardia, recumbency, increased muscle enzymes, and hypoproteinemia.[22] Horses continuously exercised in high heat and humidity may also develop heat stroke. Evaporative heat loss from sweating is the most important means of heat loss as metabolic heat production increases during exercise, especially as ambient temperature and humidity increase.[23] Efficiency of evaporative heat loss diminishes when temperature and humidity are high and there is a significant radiation component resulting from strong sunshine.[24] Horses' susceptibility to heat stroke is enhanced if dehydration and electrolyte imbalances occur because of large losses of sweat (see also Exhaustion in Endurance Horses, Chapter 42). Adrenaline and noradrenaline may play a role in the adaptation of horses to thermal stress.[25]

As rectal temperature increases above 107° F (41.5° C), the homeostatic mechanisms of temperature regulation fail; peripheral vasoconstriction, decreased blood pressure, and decreased cardiac output occur. The animals are lethargic and have weak, flaccid muscles; prostration and shock occur rapidly. Disseminated intravascular coagulation, liver damage, renal failure, and myocardial necrosis are frequent complications.

Anhidrosis

Up to 25% of horses in hot, humid environments lose their ability to sweat and subsequently suffer from hyperthermia as a result of impairment of heat loss.[26] In a more recent study that included more than 4500 horses from 500 Florida farms, the prevalence of anhidrosis was 11% at the farm level and 2% at the animal level.[27] Horses in training have been reported to have a higher frequency of anhidrosis, as are horses shipped to hot environments from more temperate regions; however, horses indigenous to hot, humid areas that perform less rigorously or not at all may also develop anhidrosis.[28,29] In addition to hyperthermia, clinical signs are poor performance, total or partial loss of ability to sweat, increased respiratory rates (three to five times normal), and dry, thin hair coats with areas of alopecia (see also Anhidrosis, Chapter 41).

Ergopeptine Alkaloid Toxicosis

Tall fescue infected with the endophyte *Neotyphodium coenophialum* contains vasoactive ergopeptine alkaloids that cause vasoconstriction and reduced blood flow to the skin of ruminants.[30] These alkaloids also induce bronchoconstriction and pulmonary vasoconstriction, which further compromise ruminants' ability to lose heat, especially during hot environmental conditions.[30] Affected animals have a poor appetite and other indications of poor performance recognized as part of the syndrome of fescue toxicosis, or "summer slump."[30] A

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BOX 4-1

Drugs Associated with Fever

Frequently

Penicillins
Sulfonamides
Erythromycin
Antihistamines
Procainamide
Quinidine
Amphotericin B

Occasionally

Cephalosporins
Cimetidine
Ranitidine
Iodides
Rifampin
Ranitidine
Levamisole
Furazolidone

Rarely

Chloramphenicol
Tetracyclines
Phenothiazines
Salicylates
Herbal remedies
Others

BOX 4-2

Toxins Associated with Fever in the Horse

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

Plant Toxins

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

related endophyte infesting perennial ryegrass has been found to produce a similar hyperthermic condition in the western United States.[31] *Claviceps purpurea* infestations of annual or perennial ryegrass and of cereal grain heads have also been reported to produce a similar hyperthermic syndrome, which may lead to heat prostration and death when ambient temperatures are high.[32-34]

Cattle affected by any of these ergopeptine alkaloids have few to no clinical signs when environmental conditions are cool and heat loss mechanisms are not challenged. It is not yet known, however, if all of the effects of the alkaloids are peripheral or if they may also act within the CNS.[30]

Diseases of the Nervous System

CNS disorders that damage areas of the hypothalamus associated with temperature regulation may lead to either decreases or increases in body temperature, although hypothermia is most common. Hemorrhage, space-occupying masses (abscesses, tumors), infectious or inflammatory diseases, and degenerative disorders have all been implicated in hyperthermia. Hyperthermia is a common occurrence in humans with brain or spinal cord injury.[35] Central hyperthermia is usually characterized by lack of diurnal variation, absence of sweating, resistance to antipyretic drugs, and excessive response to external cooling.[3,4]

Certain toxins and drugs may act to increase body temperature by causing an increase in metabolic work (Boxes 4-1 to 4-3). Chlorophenols and nitrophenols, used as herbicides and wood preservatives, cause uncoupling of oxidative phosphorylation within mitochondria and lead to rapid extreme rises in body temperature.[36] Chronic and/or low-level exposure to these compounds may manifest clinically as hyperthermia.

BOX 4-3

Toxins Associated with Fever in Ruminants

Arsenic
Selenium
Mercury
Zinc
Crude oil, kerosine, coal oil
Organochlorine, chlorinated hydrocarbons
Iodine
Paraquat
Dinitrophenol
Propylene glycol
Trichloroethylene-extracted feeds
Halothane toxicity (C)

Plant Toxins

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

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

Fever

True fever differs from other hyperthermic states in that the desired core body temperature or set point is elevated.[1] This new, higher set point is vigorously defended by the same mechanisms that maintain body temperature in health. Initiation of the febrile state can occur by a variety of infectious, inflammatory, immunologic, neoplastic, or injurious conditions. In the classic model of fever these stimuli cause the production of multifunctional pyrogenic cytokines by a wide variety of cells, but primarily by fixed or circulating monocytes and macrophages (Fig. 4-2).[37] Currently at least 11 cytokines have been shown to induce the febrile response in humans and animals. Of these cytokines, interleukin 1 (IL-1α, IL-1β) and tumor necrosis factor alpha (TNF-α) are the most potent. Pyrogenic cytokines reach the POAH via the circulation and induce the production of arachidonic acid and its metabolism to prostaglandin E_2 (PGE_2), by the cyclooxygenase (COX)-2 pathway. This process will eventually result in a higher "set point" within the hypothalamic thermoregulatory center[37,38] (see Fig. 4-2). COX inhibitors, specifically COX-2 inhibitors, effectively reduce the febrile temperature to normal but have no effect on normal body temperature.[3,38] In addition, pyrogenic cytokines stimulate the activation and proliferation of T lymphocytes and of antibody-producing B lymphocytes, which, in turn, produce additional cytokines that both enhance and inhibit further production of pyrogenic cytokines.[39,40] Finally, pyrogenic cytokines, particularly IL-1 and TNF-α, cause membrane perturbation in a variety of body tissues, with a resultant increase in phospholipases and the production of arachidonic acid. Subsequent production of mediators is dependent on the metabolic pathways for arachidonic acid in the target tissue. Prostaglandins induced by pyrogenic cytokines have been shown to stimulate the muscle catabolism associated with fever and to induce collagenase synthesis from synovial cells.[41] These processes contribute to the muscle and joint pain associated with fevers that are relieved by COX inhibitors. Local tissue responses to IL-1β and TNF-α may stimulate afferent neural impulses that are responsible for many of the behavioral changes (increased sleep, decreased appetite, and loss of social behavior) associated with fever.

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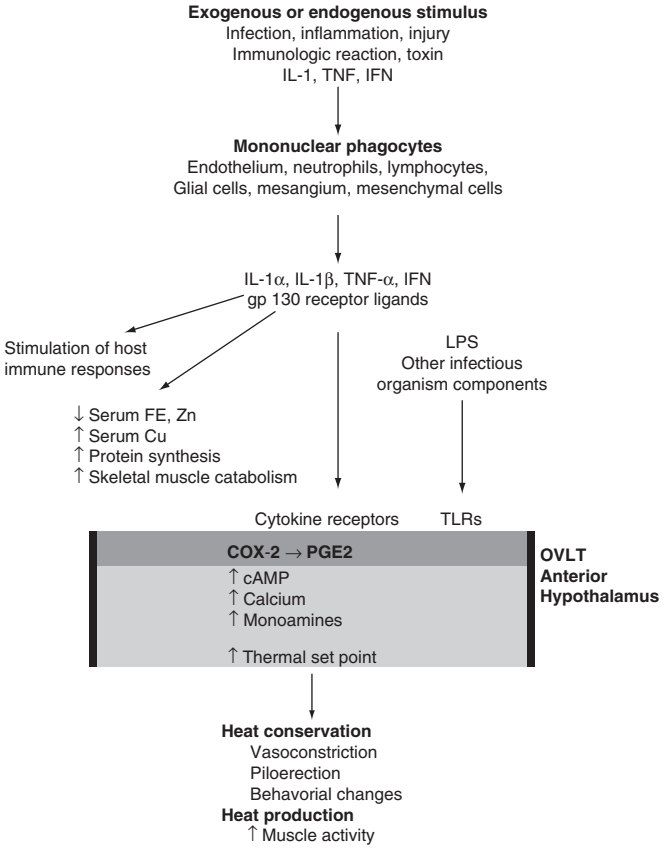


FIG. 4-2 Pathogenesis of fever. *OVLT,* Organum vasculosum laminae terminalis endothelium; *TLRs,* toll-like receptors.

This model, however, does not fully explain the presence of fever because specific blockade of IL-1 or TNF-α activity does not diminish the febrile response to lipopolysaccharide (LPS) or other microbial products in experimental studies or in patients with natural infections. Microbial products from a variety of agents bind to toll-like receptors (TLRs) on the surface of cells. Toll-like receptors and IL-1 receptors share the same signaling areas and, along with other pyrogenic cytokines, a common pathway to activate nuclear factor (NF)-κB. Activated NF-κB in turn results in expression of COX-2 or COX-3 and PGE_2 synthesis. Mice deficient in COX-2 and injected with LPS, IL-1, TNF-α, or IL-6 either intravenously or within the CNS do not develop a fever.[38] Thus the induction of COX-2 and the subsequent production of PGE_2 provide a common pathway for divergent pyrogens to produce the febrile response (see Fig. 4-2).

There is an apparent role for the vagal nerve in the production of the febrile response. Studies in laboratory animals in which the hepatic branch of the vagus nerve is severed have shown diminution of the febrile response to a relatively low dose of intraperitoneally injected LPS but not intramuscularly administered LPS or high-dose intraperitoneally injected LPS. Local production of cytokines may stimulate primary hepatic vagal receptors that, via vagal afferent fibers and A1/A2 noradrenergic cell groups in the brainstem, release noradrenaline, which subsequently induces the production of PGE_2 and fever.[42] Transection of the visceral vagal afferents has been shown to attenuate febrile behavioral responses, but not the associated temperature elevation, to high-dose intraperitoneal LPS injection in rats.[43]

In addition to a rise in body temperature, the febrile state is accompanied by a variety of metabolic, hematologic, and immunologic changes. IL-6 and IL-11, induced by IL-1α, IL-1β, and TNF-α, induce the synthesis of fibrinogen, C-reactive protein, haptoglobin, ceruloplasmin, and certain macroglobulins, known collectively as *acute phase proteins,* by hepatocytes.[38] In addition, these cytokines mediate the accompanying hypoferremia, hypozincemia, and hypercupremia of the acute phase response.

Physiologic control of the febrile response is multifactorial and prevents extreme elevations in body temperature that are incompatible with life in most instances. TNF-α inhibits further production of itself. IL-1 and other inhibitory cytokines stimulate the production of IL-1 receptor agonist, which prevents further binding of IL-1. In addition, one of the receptors on cell surfaces for IL-1 (type II receptor) does not result in cell signaling and is thought to serve as a "decoy" receptor to decrease the concentration of IL-1.[44] IL-10, induced by pyrogenic cytokines, inhibits IL-1, TNF, and IL-6 production and suppresses the production of IL-2 and IFN-γ by T-helper cells.[44,45] Circulating pyrogenic cytokines may be bound to carrier molecules that reduce or prevent the interaction with receptors. For example, IL-1β has been shown to bind to α_2-macroglobulin, a protein increased during the acute phase response.[3] Glucocorticoids inhibit the transcription of numerous genes encoding the pyrogenic cytokines IL-1β, Il-6, and TNF-α. Within the brain both arginine vasopressin (AVP) and alpha melanocyte stimulating hormone (αMSH) act as potent antipyretic agents. Receptors for AVP, which acts as a neurotransmitter within the brain, are found lateral to the PAOH and decrease fever in both natural and experimentally induced fever, whereas injection of AVP receptor antagonist elevates fever and delays defervescence.[46,47] αMSH binds to local melanocortin receptors within the brain and on cell receptors of immune cells to decrease fever and inflammation. When administered systemically to humans, αMSH is 20,000 times more potent on a molar basis than acetaminophen in decreasing fever from endogenous pyrogens.[47] In the brain, nitric oxide (NO) participates in regulation of body temperature by activating soluble guanylate cyclase and increasing cyclic guanosine monophosphate (cGMP) levels. Intracerebral ventricular injection of NO donors depresses fever in rats, whereas inhibition of NO synthesis within the CNS enhances fever.[44]

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

Beneficial Effects of Fever

It should be emphasized that fever is not an illness but is, in fact, a physiologic mechanism that has beneficial effects in fighting infection. Body temperature elevation in pyrogenic-mediated fevers, in contrast to hyperthermic states, rarely exceeds 5°F (2.5°C) above normal. Although the severity of some viral infections is decreased at these temperatures, most pathogens are not affected by a modest rise in temperature. Studies on bacterial infections in fish, lizards, rabbits, and humans, however, have shown an increase in survival correlated with the presence of fever.[3,48,49] One well-studied effect of fever on bacterial proliferation is the effect of hypoferremia. Bacteria, which require iron for multiplication, are inhibited by the reduced availability of iron during the acute phase reaction. This response is augmented by the increased susceptibility of bacteria to low iron at higher temperatures.[50,51] Certain neoplastic cells are inhibited during fever, although it is likely that inhibition of neoplastic cell division results from augmentation of immune responses.[52]

Literature on the effect of fever is conflicting owing to the multiple variables present in in vivo studies and the application of heat in temperature ranges exceeding those of natural fevers in in vitro studies. Enhancement of host defenses, however, appears to be the primary beneficial effect of fever. Fever or heat applied in in vitro studies within the physiologic range of natural fevers has a beneficial effect on multiple processes of the adaptive immune response. Neutrophils and monocytes have increased motility and emigration, enhanced phagocytosis, increased oxygen radical production, and enhanced killing of intracellular bacteria. IFN production increases, and its antiviral, antitumor, antiproliferative, and natural killer (NK) cell—stimulating properties are enhanced. Increased T-cell proliferative responses to nonspecific mitogens IL-1 and IL-2 and enhanced

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T-helper cell activation, expression, recruitment, and cytotoxicity have all been correlated with fever. Enhancement of B cells, with a subsequent increase in production of antibodies, and enhanced expression of Fc receptors occur during fever.[53]

Activity of pyrogenic cytokines is also influenced by temperatures achieved during fever. For example, in a mouse-endotoxin model, fever enhanced the early expression of TNF-α but limited the duration of its expression. Production of IL-1β was delayed, whereas that of IL-6 (which downregulates production of TNF-α and IL-1β) was enhanced, preventing the simultaneous expression of TNF-α and IL-1β and the potential harmful effects of their simultaneous expression.[54] Other studies have demonstrated that the effect of fever on various cytokines is specific for each cytokine and specific to body compartments. Thus fever is an important component of the coordinated and specific cytokine response of the host to various inflammatory stimuli.[3,41,53]

Adverse Effects of Fever

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

Fever is one of the earliest and most prominent manifestations of the acute phase reaction. Veterinarians have used the clinical thermometer to aid in diagnosis and to monitor the progress of illness in animals since 1770. With the increased knowledge of the pathogenesis of fever has come a better appreciation for the diverse causes of the febrile state. In ruminants and horses, however, infectious disease remains the most common reason for development of fever (Boxes 4-4 and 4-5). Careful evaluation for the presence of infectious disease is always indicated, especially when the onset of a fever is abrupt; the temperature is higher than 39.4° C (103° F); and the fever is accompanied by depression, variable loss of appetite, serous nasal exudate, epiphora, enlargement of lymph nodes, or diarrhea and a decreased or increased leukocyte count. Other causes of fever are neoplasia (Boxes 4-6 and 4-7), immune-mediated diseases (Boxes 4-8 and 4-9), noninfectious inflammation (Boxes 4-10 and 4-11), and certain drugs.

BOX 4-4

Infectious Causes of Fever in Horses

Common Causes

Upper respiratory viral diseases
Strangles, *Streptococci equi*
Pneumonia, bacterial or viral
Pleuropneumonia
Gastrointestinal parasitic infections
Enteritis, *Clostridium difficile, Lawsonia,* or of unknown causes
Salmonellosis
Equine monocytic ehrlichiosis (Potomac horse fever)
Proximal duodenitis-jejunitis
Rotavirus diarrhea (foals)
Endotoxemia from gastrointestinal disorders
Septicemia, septic arthritis, osteomyelitis (foals)
Urachal abscess (foals)
Metritis (mares)
Peritonitis
Tetanus
Traumatic tenosynovitis, cellulitis
Localized occult abscesses (thorax, abdomen, upper respiratory system)
Tumors (see list in Box 4-6)

Less Common Causes

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

Uncommon Causes

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

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

Fevers of Unknown Origin

Most febrile illnesses encountered in large animal practice are caused by infectious diseases that are readily diagnosed by careful evaluation of history and physical examination or are of short duration, run their course, and progress to complete recovery within 2 weeks without a specific etiologic diagnosis having been made. Some febrile conditions, however, continue for weeks or months, accompanied only by nonspecific signs of depression, variable anorexia, and weight loss, while the diagnosis remains obscure. Patients with prolonged febrile episodes of 3 weeks' duration or longer in which a diagnosis has not been made after a week of routine diagnostic efforts or after 3 days of hospitalization and diagnostic tests are considered to have fever of unknown origin (FUO). The majority of cases that meet the definition of FUO have infectious causes. Neoplastic diseases, immune-mediated vasculitides, and autoimmune diseases are the next most common causes. Adverse drug reactions and other miscellaneous diagnoses are the least common documented causes of FUO. Most cases of FUO are caused by common diseases with an unusual presentation; an ordered, problem-oriented approach to diagnosis will render a diagnosis in 90% of cases.[55,56] The following steps are suggested (Fig. 4-3).

Document Fever

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

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BOX 4-5

Infectious Causes of Fever in Ruminants

Common Causes

Mastitis
Metritis
Pneumonia: viral, mycoplasma, bacterial
Traumatic reticuloperitonitis (B)
Peritonitis (from other causes, e.g., ruptured abomasal ulcer, uterine tear)
Septicemia, osteomyelitis, infectious arthritis, omphalophlebitis (neonates)
Toxemia from gastrointestinal disorders
Enteritis
Abscesses
- Liver
- Pharyngeal/retropharyngeal
- Internal lymph nodes (C, O)
- Associated with foot

Endocarditis
Pericarditis (B)
Listerosis
Tetanus
Bovine viral diarrhea (BVD), mucosal disease (B)
Foot rot
Otitis media, interna *(Mycoplasma bovis)* (B)
Clostridial infections
- Blackleg *(Clostridium chauvoei)*
- *Clostridium perfringens* types D, A (C, O)

Contagious ecthyma (C, O)
Histophilus somni infection (thromboembolic meningoencephalomyelitis)
Mycoplasma species arthritis, septicemia (C)
Mycoplasma bovis (B)
Verminous pneumonia (B)

Less Common Causes

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

Uncommon Causes

Neoplasms (see list in Box 4-7)
Infectious necrotic hepatitis *(Clostridium novyi)*
Sarcocystosis (B)
Tuberculosis (B)
Systemic candidiasis, aspergillosis
Eperythrozoonosis
Brainstem, pituitary abscess
Systemic toxoplasmosis (C, O)
Tularemia
Pseudorabies
Brucellosis
Ovine progressive pneumonia
Chlamydial sporadic bovine encephalomyelitis

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

BOX 4-6

Neoplastic Causes of Fever in Horses

Common Causes

Metastatic melanomas
Lymphosarcoma
Squamous cell carcinoma
Fibrosarcoma

Less Common Causes

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

Uncommon Causes

Hemangiosarcoma
Mesothelioma
Pheochromocytoma
Osteosarcoma
Myeloma of the gastrointestinal tract

BOX 4-7

Neoplastic Causes of Fever in Ruminants

Common Causes

Lymphosarcoma

Less Common Causes

Adenocarcinoma
Metastatic melanoma (C)
Liver neoplasia
Mesothelioma

Uncommon Causes

Skeletal neoplasia
Malignant neuroblastoma

C, Caprine.

BOX 4-8

Immunologic Causes of Fever in Horses

Common Causes

Purpura hemorrhagica
Urticaria
Drug-induced fever

Less Common Causes

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

Uncommon Causes

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

IgM, Immunoglobulin M.

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BOX 4-9

Immunologic Causes of Fever in Ruminants

Common Causes

Drug allergies
Urticaria (milk allergy in cattle)

Less Common Cause

Neonatal isoerythrolysis (B)

Uncommon Cause

Pemphigus foliaceus (C)

B, Bovine; *C,* caprine.

BOX 4-10

Noninfectious Inflammatory and Miscellaneous Causes of Fever in Horses

Hepatic disorders
Hyperlipidemia, equine hepatic lipidosis
Acute hepatic necrosis (Theiler disease)
Chronic active hepatitis
Cholelithiasis
Hyperkalemic periodic paralysis
Foreign bodies
Nasal, oral, pharyngeal, tracheal, bronchial
Thrombophlebitis
Ocular trauma, recurrent uveitis
Burns, smoke inhalation
Snake bite
Acute renal failure
Idiopathic interstitial pneumonia

BOX 4-11

Noninfectious Inflammatory and Miscellaneous Causes of Fever in the Ruminant

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

B, Bovine.

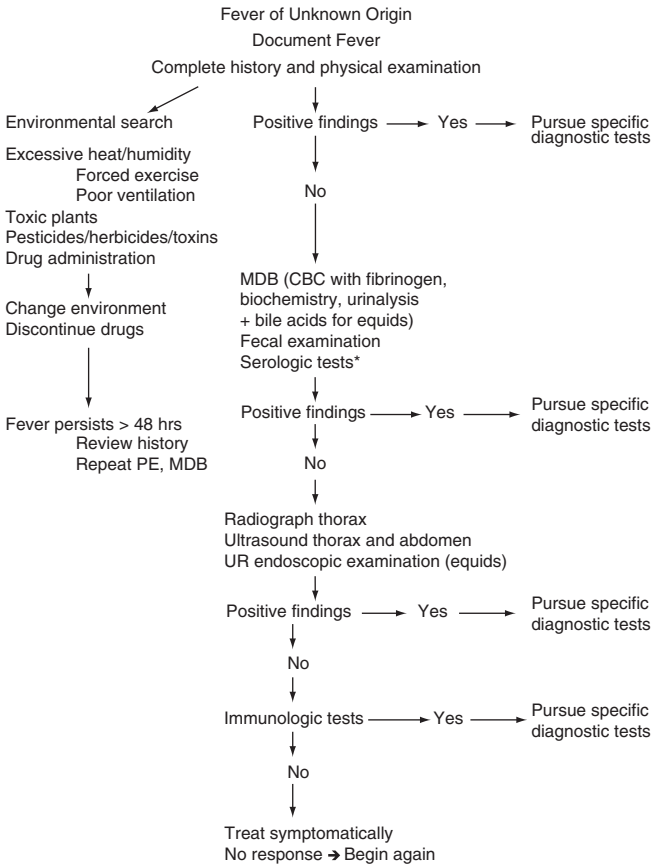


FIG. 4-3 Approach to fever of unknown origin (FUO). *CBC,* Complete blood count; *EIA,* equine infectious anemia; *MDB,* minimum database; *PE,* physical examination; *UR,* upper respiratory.

morning, but approximately 10% of cases will have a reverse pattern. Intermittent fever is most commonly associated with pyrogenic infections, although it may occur in neoplasia, especially if tissue necrosis and inflammation are concurrent. *Remittent fevers* are characterized by a period of days in which elevated temperatures occur, followed by several days of normal temperature, only to have the cycle repeat again. Brucellosis in ruminants, equine infectious anemia (EIA) in horses, and blood-borne protozoal diseases such as babesiosis may exhibit this type of pattern. *Sustained fevers* are characterized by a consistently raised temperature without variation and appear as a "flat line" on a temperature chart. Fevers caused by drug administration and certain toxins may be of this type, especially if the patient does not exhibit any other signs of illness.[3] Any pharmacologic agents being administered to the patient should be discontinued. Defervescence of fever from drug administration should occur in 48 hours.

Consideration of Epidemiology

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

Physical Examination

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

1. Horses
   a. Complete visual or manual oral examination; percussion of sinuses; endoscopic examination of upper airway structures and of the trachea and bronchi (if length of the endoscope allows)
   b. Complete ophthalmic examination
   c. Thorough auscultation of cardiopulmonary system at rest, with rebreathing bag, and following exercise; evaluation of peripheral perfusion before and after exercise

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d. Palpation of external lymph nodes, ballottement, and deep palpation of external abdomen for pain
e. Rectal examination
f. Fecal odor, consistency, volume; frequency of defecation
g. Evaluation of external genitalia and mammary gland
h. Evaluation of musculoskeletal conformation and gait analysis for lameness

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

Diagnostic Aids (Table 4-1)

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

Serum protein and albumin determinations characterize either hypoproteinemia or hyperproteinemia. Serum protein electrophoresis and immunoelectrophoresis further classify deficiencies or increased production of proteins. Serum enzyme determinations and bile acid concentration for liver evaluation are also warranted.

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

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

Serologic evaluation for infectious diseases common in the geographic area and/or patient population should be performed. Single serologic determinations are usually of value only in those diseases in which one positive titer is significant and when the disease is characterized by persistent infection such as EIA, brucellosis, or Johne's disease. In many instances vaccination history and/or accompanying clinical signs must be correlated with titer determinations.

TABLE 4-1

Fever of Unknown Origin: Diagnostic Procedures

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

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

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Paired samples for toxoplasmosis, babesiosis, and various mycotic diseases (especially coccidioidomycosis) are indicated when the diagnosis remains obscure. Serologic determination of antibody titers to the SeM protein of *S. equi* can aid in the diagnosis of internal abscessation.[57] The synergistic hemolysis inhibition (SHI) test may be helpful in the diagnosis of *Corynebacterium pseudotuberculosis* infections in horses and small ruminants.[58-60] Virus isolation, PCR, and/or immunohistochemistry, particularly in persistent bovine viral diarrhea (BVD)–infected cattle, may be helpful.

Evidence of gastrointestinal protein loss, intermittent/chronic diarrhea, and weight loss warrants fecal cultures and rectal biopsy for ruling out salmonella or infiltrative bowel disease in horses, whereas such signs in adult dairy cattle warrant ruling out abomasal lymphosarcoma as the cause.

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

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

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

Nuclear imaging and imaging using autologous WBCs labeled with technetium-99m or indium-111 are increasingly used in human and small animal medicine.[61] These procedures may be helpful in localizing abscesses, particularly osteoarticular infections. These modalities may prove to be of benefit for large animals as the modalities' availability increases. As a note, the use of nuclear imaging in food-producing animals is strongly discouraged.

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

Hypothermia

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

Animals with severe hypothermia should be warmed gradually over 24 hours, with careful monitoring of body temperature and the cardiovascular system. Maintenance of adequate systemic perfusion is the most important means of preventing cardiac failure.[62,63] Acidosis and potassium imbalances are common and may fluctuate rapidly. Consequently, repeated measurements, especially when a patient's clinical condition worsens in the process of warming, are often necessary. Appropriate crystalloid fluids, warmed to body temperature, are usually necessary throughout the warming process. Evaluation of blood glucose and concurrent dextrose therapy, especially in neonates, should also be performed.

Warmed humidified oxygen therapy both as an aid in treatment of hypoxia and as a means of warming is helpful. Gastric (rumen) or rectal lavage with warmed fluids may also be used. However, care should be taken in rapid rewarming because an imbalance in the basal metabolic rate (which is temperature dependent) and systemic perfusion may result in life-threatening cardiac dysrhythmias and worsening of metabolic acidosis and hypoxia. Hypothermia attenuates the inflammatory response by a multiplicity of effects on cytokines and other key signaling mechanisms.[64] Thus the adverse metabolic effects of disease are slowed at low body temperatures, and, as body temperature elevates, signs of systemic disease become apparent.[65] In hypothermic animals in shock, particularly neonates, severe anoxic changes in the bowel wall may result in severe diarrhea, sloughing of mucosa, or clostridial growth in the bowel.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 5

Alterations in Respiratory Function

W. DAVID WILSON and JEFFREY LAKRITZ, *Consulting Editors*

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MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Cough

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

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

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

NEURAL PATHWAYS INVOLVED IN THE COUGH REFLEX. Coughing is an involuntary reflex; however, this reflex may be voluntarily initiated or suppressed.[2,3] The reflex pathways involve sensory receptors present within the airway epithelia, from the larynx to the respiratory bronchioles, with nerve fibers conducting afferent impulses within vagal, glossopharyngeal, trigeminal, and phrenic nerves.[1,3,4,5] The receptors, mainly irritant receptors, are particularly numerous within the proximal airways (trachea and bronchi), especially around the hilus of the lung and bifurcation of the bronchi.[1,4] Other receptors capable of activating the cough reflex are found within lung parenchyma, the pleura, and elsewhere. Brainstem neuronal pathways for the cough reflex in the horse are not well characterized; however, in other species, afferent signals to the medulla oblongata are received and efferent fibers pass back down to the respiratory system within the vagal, phrenic, intercostal, and lumbar nerves and motor portions of the trigeminal, facial, hypoglossal, and accessory nerves to supply striated and smooth muscles of the larynx, tracheobronchial tree, diaphragm, intercostal muscles, abdominal muscles, and secretory glands of the respiratory tract.[1,5-7]

Irritant receptors are stimulated by mechanical deformation induced by compressing the trachea, by bronchoconstriction, inert dusts such as carbon, irritant gases such as ammonia, inflammatory conditions, and by biological mediators such as histamine, prostaglandins, or bradykinins (Boxes 5-1 and 5-2).[2,4] Sensitivity to mechanical stimulation varies along the airway, and in horses the upper airway cough receptors appear to be less active than observed in many other species.[8] For example, a stomach tube inadvertently passed into the trachea frequently does not induce coughing until it reaches the carina. Similarly, endoscopic examinations often reveal large pools of exudate within the trachea of horses with limited history of coughing.[6] Foals with *Rhodococcus equi* pneumonia often develop a tracheal rattle, reflecting accumulation of exudates within the trachea, but may not cough. Repeated stimulation of irritant receptors over several hours does not appear to diminish sensitivity but may lead to changes in threshold.[4]

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

Mechanics of Coughing

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

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BOX 5-1

Causes of Coughing in Horses

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

Toxic Causes

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

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

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

Dynamic compression also increases the resistance to airflow.[4] Once dynamic compression of peripheral (smaller) airways occurs, further increases in expiratory effort cause greater narrowing of the airway; thus the flow rate that can be generated at a given lung

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BOX 5-2

Causes of Coughing in Ruminants

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

Toxic Causes

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

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

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

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

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

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

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

Coughing is a prominent feature of cardiac disease in many species, although cardiac diseases are not often encountered in large domestic animals. Failure of the left side of the heart as a result of congenital defects, valvular stenosis or incompetence, conduction disturbances, myocardial disorders, or restrictive pericardial disease causes an increase in pressure in the pulmonary venous return from the lung. This results in transudation of fluid from the pulmonary capillaries into the pulmonary parenchyma and airspaces (cardiogenic pulmonary edema) and causes swelling of the mucosal lining of small airways.[2] These changes stimulate cough receptors and initiate the cough reflex. Coughing that occurs secondary to cardiac disease is usually chronic, although acute-onset coughing may be observed with ruptured mitral chordae tendineae and bacterial endocarditis.[16]

Approach to Diagnosis of Coughing

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

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

When evaluating the potential for contagious diseases or those related to common environmental conditions, the vaccination status of the affected animal and herdmates and the presence of similar clinical signs in other in-contact animals sharing common facilities or common airspaces should be determined. In nursing animals the vaccination status of the dam is important. A history of other signs such as anorexia, nasal discharge, weight loss, exercise intolerance, stridor, lymphadenopathy, facial swelling, diarrhea, colic, and edema may provide important clues to the cause of the current problem. Weight loss occurs in many acute and chronic diseases, both infectious and noninfectious. Anorexia may indicate that eating is too painful for an animal, for example, because of a painful nasopharyngeal lesion or because the animal is devoting so much effort to breathing that it will not eat.

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

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

Important historical features of the cough include the time and speed of onset; frequency; duration (chronic if longer than 1 month); relation to feeding, housing, or weather; relation to exercise and timing during exercise; improvement, deterioration, or other change since onset; and the presence of and similarity to previous episodes

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of coughing or respiratory disease. Many coughs are exacerbated by exercise because exercise places greater stress on the respiratory tract. The resulting rapid airflow improves mobilization of secretions and also irritates the airway directly. Coughs that occur during eating suggest specific or nonspecific sensitivity to molds, pollen, or other dusts in feed; inflammatory conditions of the larynx or pharyngeal region; laryngeal or pharyngeal problems, including complications of surgery, that interfere with swallowing or guarding of the lower airway; or esophageal obstruction (choke). The effort required to cough and associated pain may also give clues to the cause of the cough.

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

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

The larynx, trachea, lungs, and heart should be carefully *auscultated,* as should both sides of the chest, in a quiet environment with the animal at rest and after the rate and depth of respiration have been increased by application of a rebreathing bag, by temporary occlusion of the nostrils, or by light exercise (see Cyanosis, p. 63). Auscultation of the trachea and larynx should be performed at an early point in the examination, before a rebreathing bag is applied, in order to assess the potential for upper airway obstruction during the examination of the thorax. Auscultation permits detection of turbulent airflow, increased or decreased bronchovesicular sounds, wheezes, crackles, pleural friction rubs, or pleural fluid splashes, all of which indicate disease of the airways, pulmonary parenchyma, or pleura. Wheezes and crackles reflect airway narrowing and dynamic airway collapse, respectively, and are both evidence of small airway disease.[16] A small (12 L) or medium-size (52 L) plastic trash bag makes an adequate rebreathing bag; a plastic rectal sleeve is satisfactory for foals or calves if the opening is stretched so that it does not occlude the nostrils. The response to application of a rebreathing bag should also be noted. Most horses tolerate this procedure well and breathe more deeply, whereas animals with chest pain often do not. Normal horses do not cough when the bag is applied unless they have been eating recently, whereas horses with airway irritation caused by pneumonia or other conditions often cough paroxysmally in response to application of a rebreathing bag. The time taken to regain the normal respiratory rate and character after removal of the bag provides a reasonable, qualitative indicator of ventilatory reserve. Normal animals recover quickly, within a few breaths, whereas respiration may be altered for several minutes in animals with significant lung disease.

The chest wall should be *palpated* to detect pleural friction rubs or lesions such as rib fractures, and the symmetry of chest expansion should be determined. Young calves with chest deformation (unilateral or bilateral) and severe inspiratory and expiratory respiratory distress should be evaluated for fractured ribs that are causing tracheal compression/stenosis (see Chapter 31; p. 566 for horses and p. 581 for more on ruminants). Temporary tracheostomy does not relieve this respiratory embarrassment. Unilateral chest pain (pleurodynia) often reduces chest excursion on the affected side. Both sides of the chest should be *percussed* systematically to detect changes in resonance and chest pain. The caudoventral percussion border in the normal horse traces from the level of the tuber coxae at the seventeenth intercostal space (the horse normally has 18 pairs of ribs) to the level of the tuber ischii at the fifteenth intercostal space to the midthorax at the thirteenth intercostal space to the level of the point of the shoulder at the eleventh intercostal space; it continues as a curving line to a point 1 to 3 inches above the olecranon. The normal caudoventral percussion boundary in cattle and small ruminants traces from the eleventh intercostal space at the level of the lateral edge of the epaxial musculature to the ninth rib at a level halfway between the costochondral junction and the lateral edge of the epaxial musculature to the fifth rib at the olecranon (cattle, goats, and sheep normally have 13 pairs of ribs). Percussion is an important diagnostic tool in all large animals, but it is most useful in foals, calves, and goats. The precise percussion boundaries, degree of resonance, and auscultation findings are influenced by age, size, body condition, fitness, and hair coat, as well as by disease processes; a gas-filled abdominal viscus can also confuse interpretation. Hyporesonance (dullness) may indicate pulmonary consolidation, large mass lesions, cardiomegaly, pleural effusion, or other pleural disease. Free pleural fluid usually causes an abrupt change from normal resonance above a horizontal fluid line to hyporesonance below this line. Hyperinflation or pneumothorax may cause hyperresonance with or without expansion of the normal percussion boundaries. A painful response to percussion may indicate pleuritis or some other inflammatory process involving the parietal pleura. Painful responses may be dramatic and potentially injurious to the examiner.

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

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

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

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

TRACHEAL ASPIRATION. Tracheal aspiration with cytologic studies and quantitative or semiquantitative aerobic and anaerobic culture, or PCR testing, of collected samples is indicated in the evaluation of patients suspected of having disease of the lungs or pleura, particularly if an infectious cause is likely. Tracheal wash samples collected using the percutaneous transtracheal technique are preferred for bacterial culture because they are not contaminated by oropharyngeal organisms.[20,21] Collection of samples by introduction of a sterile catheter through the biopsy channel of a presterilized endoscope inserted within a sterile sheath, or by introduction of a double-sheathed catheter via the biopsy channel, is acceptable and less subject to complications than is the transtracheal technique, but samples obtained transendoscopically may be contaminated with *Pseudomonas* species and anaerobic bacteria despite use of a guarded technique.[21] If tracheal aspiration is to be performed percutaneously, the procedure should precede endoscopic examination of the lower airways to avoid contamination. Culture may fail to reveal the primary bacterial pathogen, especially in animals that have been treated with antibiotics. The diagnostic value of tracheal wash samples can be improved by discontinuing antibiotic therapy for at least 24 hours before collecting samples, rapidly processing samples, using antibiotic removal devices and selective culture media and, if necessary, repeating sampling. Culture results should be evaluated in relation to the clinical signs, clinical experience (especially on the farm of origin of the patient), results of cytologic evaluation, and response to treatment. The trachea is not a sterile environment; therefore culture of small numbers of bacteria without cytologic evidence of infection is of questionable significance.

BRONCHOALVEOLAR LAVAGE. Samples collected by BAL are less useful than those collected by tracheal aspiration for evaluating infectious lower airway diseases and focal pulmonary conditions because the technique samples secretions from only a limited area of the caudodorsal lung on one side and is subject to contamination during introduction of the BAL tube through the nasopharynx. However, BAL yields better samples for cytologic assessment and is therefore preferred for evaluation of patients with generalized, noninfectious lower airway diseases such as RAO or silicosis.[18] BAL samples can be collected under endoscopic guidance by means of catheters introduced through the biopsy channel of a suitable endoscope (<9 mm in diameter and longer than 180 cm) or by using commercially available BAL tubes. The advantage of collection via endoscopy is that specific areas of the lung can be sampled, although

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gaining access to the cranial lung lobes is difficult with any method. Differential cell counts in BAL fluid of normal horses vary depending on age, environment, activity, and other factors. In young horses (<6 years of age), the distribution of macrophages, lymphocytes, neutrophils, mast cells, and eosinophils is on average 65%, 30%, 3%, 0.5%, and 0%, respectively.[22] In horses older than 6 years of age, the neutrophil population may reach 15% in normal horses, with a corresponding decrease in the proportion of lymphocytes and macrophages.[22] The percentage of neutrophils in normal calves is generally within the range of 5% to 20% depending on calf age, type, health status, and sampling method.[23,24]

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

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

BLOOD GAS ANALYSIS. Blood gas analysis on arterial blood to determine oxygen (O_2) and carbon dioxide (CO_2) tensions is indicated in the evaluation and monitoring of patients in which a history or clinical signs of coughing are accompanied by signs of respiratory distress or cyanosis (see Respiratory Distress, p. 56, and Cyanosis, p. 63).

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

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

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

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

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

BIOPSY. Biopsy, with histologic evaluation of samples, is indicated to diagnose certain mass lesions such as neoplasms, cysts, polyps, fungal granulomas, or foreign body granulomas in or surrounding the airway. Masses in the airway can be biopsied through the biopsy channel of an endoscope, but these samples inevitably are small. Biopsies can also be collected at the time of exploratory or corrective surgery from lesions in the upper airway. Lung biopsies can be collected blindly, using Tru-Cut, Biopty, or similar instruments, preferably from the peripheral areas of the lung to reduce the likelihood of serious hemorrhage (see Chapter 31). Focal lesions can be visualized ultrasonographically or radiographically during the

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percutaneous biopsy procedure to improve the likelihood of obtaining diagnostic specimens. Lung biopsy is most useful for diagnosing diffuse nonseptic conditions such as pneumoconiosis. The inherent risks associated with the procedure indicate that percutaneous lung biopsy should be reserved for circumstances in which the animal is not showing signs of marked respiratory distress, uncontrollable coughing, or bleeding disorders and a high likelihood exists that the procedure will yield significant diagnostic information. Open lung biopsy is possible, albeit rarely indicated.

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

ALLERGEN TESTING. Intradermal allergen testing (IDT), a radioallergosorbent test (RAST), ELISA tests for immunoglobulin E (IgE) on serum, and inhaled challenge have been advocated for the evaluation of horses suspected of having allergic respiratory disease based on exacerbation of signs in certain environments or with certain feeding practices. Whereas there are anecdotal reports that horses with RAO have been hyposensitized successfully using allergens selected on the basis of these allergen tests, the authors are unaware of documentation in well-controlled studies. In addition, a recent study showed that compared with normal nonatopic horses, RAO-affected horses did not have a significantly greater number of positive reactions in intradermal skin tests (IDT) against any allergen group (molds, grasses, weeds, trees, and insects), leading the authors to conclude that reactions to individual allergens in IDTs should not be used to determine that horses have clinically relevant hypersensitivity.[29] Many normal horses show sensitivity to individual mold spores and other allergens, and there is poor correlation between the dermal and pulmonary reactivities to mold antigens.[13] Furthermore, when compared with the results of IDT, RAST and ELISA serum allergy tests have been shown to have low sensitivity in detecting allergen sensitivity.[30] Whereas the use of recombinant allergens rather than crude mold extracts in ELISA tests substantially improves sensitivity in detecting levels of allergen-specific IgE,[31] and significantly more RAO-affected horses than normal horses have high allergen-specific IgE levels, the degree of overlap of results precludes use for diagnostic purposes.[32] The crude trial-and-error approach of adding or removing potential allergens from the environment is sometimes helpful diagnostically and therapeutically in RAO cases in which an allergic cause is suspected. Feeding of pellets instead of hay and using shredded paper, peat moss, or wood shavings instead of straw bedding are common examples of this approach (see the section on RAO in Chapter 31). Allergen testing or serologic evaluation of adult cattle with historical evidence of recurrent, seasonal, respiratory disease (extrinsic allergic alveolitis) have not proven diagnostic of specific allergen-induced disease; rather, results merely suggest prior exposure to molds (see Chapter 31).

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

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

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

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

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

Cough without fever is typically found in RAO, abnormalities of the larynx or pharynx, parasitic pneumonia, exercise-induced pulmonary hemorrhage (EIPH), tracheobronchial foreign body, tracheal collapse, and airway-oriented neoplasia (e.g., bronchial carcinoma).[37]

Horses with chronic interstitial pneumonia such as silicosis or granulomatous pneumonia are usually afebrile but may have mild to moderate fever.[1]

Nasal Discharge

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

Definition Nasal discharge, which is any nongaseous material that exits the respiratory tract through the external nares, is described according to its *physical characteristics* (serous, mucoid, purulent, hemorrhagic [sanguineous], or a combination of these types or feed material); *acuteness of onset* (sudden or insidious); *origin* (unilateral or bilateral); *volume* (profuse or scant); and *association with activity* (spontaneous or intermittent).[38-40]

Pathophysiology

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

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

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

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

Inflammation, irritation, and other pathologic states affecting the trachea and bronchi increase the production of mucous and serous secretions in the tracheobronchial tree[41] (Boxes 5-3 and 5-4). Initially the accompanying nasal discharge is mucoid (clear, colorless, thin, and elastic in consistency), but with chronicity and secondary bacterial invasion, neutrophils and other inflammatory cells accumulate in the tracheobronchial secretions and the nasal discharge becomes purulent, progressing from cloudy to opaque and then to viscous with a whitish cream color (Boxes 5-5 and 5-6).

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

BOX 5-3

Causes of Serous and Mucoid Nasal Discharge in Horses

Common Causes

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

Less Common Causes

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

Uncommon Causes

Nasal fungal infection (rhinophycomycosis), aspergillosis
Nasal amyloidosis
Coccidioidomycosis
Restrictive pulmonary disease, pneumoconiosis
Trauma to the skull or upper airway
Tuberculosis
Tularemia
Guttural pouch neoplasia
Chlamydia psittaci pneumonia
Nocardiosis
Cryptococcosis
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, pythiosis
Lungworm infection (*Dictyocaulus arnfieldi*)
Ascarid migration
Cyst (pharyngeal, subepiglottal)
Progressive ethmoidal hematoma
Lymphosarcoma, lymphoma, leukemia
Halicephalobus (Micronema) deletrix granuloma
Pulmonary edema
Pulmonary aspergillosis
Stachybotryotoxicosis
Trichloroethylene-extracted feed toxicity
Pentachlorophenol toxicity
Organophosphate, carbamate toxicity
Ammonia toxicity
St. George disease (*Pimelea* species poisoning) (exotic)
Trypanosoma evansi, surra (exotic)
Trypanosoma equinum, mal de caderas (exotic)
Trypanosoma hippicum, murrina de caderas (exotic)
Besnoitiosis, globidiosis (exotic)
African horse sickness (exotic)
Getahvirus (exotic)
Glanders (exotic)
Louping ill (exotic)

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BOX 5-4

Causes of Serous or Mucoid Nasal Discharge in Ruminants

Common Causes

Debilitating illnesses that reduce lingual nose cleaning in cattle (B)
Mannheimia hemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)
Histophilus somni pneumonia (B)
Nose bots *(Oestrus ovis)* (O, C)
Lungworm infection, verminous pneumonia
Atypical interstitial pneumonia (B)
Infectious bovine rhinotracheitis (IBR; BHV-1) (B, C)
Bovine respiratory syncytial virus (B)
Parainfluenza virus type 3
Mycoplasma species pneumonia
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)
Caprine arthritis-encephalomyelitis (CAE) pneumonia (C)
Early bacterial pneumonia
Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)
Abscess (oral, pharyngeal, retropharyngeal)
Esophageal obstruction, foreign body, choke
Septicemia (neonates)

Less Common Causes

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

Uncommon Causes

Familial allergic rhinitis (B)
Bovine nasal granuloma, atopic rhinitis, summer snuffles (B)
Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis
Nasal actinobacillosis (B)
Sarcocystosis (B)
Tularemia (O)
Phycomycosis, pythiosis (B)
Pulmonary aspergillosis
Bronchobiliary fistula (yellow froth) (B)
Zygomycosis, mucormycosis (B)
Pneumocystis carinii (renamed *P. jiroveci* in humans) pneumonia
Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)
Buss disease, chlamydial sporadic bovine encephalomyelitis (B)
Winter dysentery (B)
Immunodeficiency states
Pregnancy toxemia (B)
Border disease (hairy shaker) (O, C)
Lymphosarcoma
Johne's disease
Listeriosis (C)
Tetanus
Rinderpest (exotic)
Theileriosis, East Coast fever (exotic)
Contagious bovine pleuropneumonia (exotic) (B)
African bovine malignant catarrhal fever, early (exotic) (B)
Virulent sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)
Contagious caprine pleuropneumonia (exotic) (C)
Rift Valley fever (exotic)
St. George disease (*Pimelea* species poisoning) (exotic)
Trypanosoma evansi, surra (exotic) (B)
Trypanosomiasis, nagana (exotic)
Jembrana disease (exotic) (B)
Sweating sickness (exotic) (B, O)
Cestrum poisoning (exotic)
Stinkweed poisoning (exotic) (B)
Endemic ethmoid carcinoma (exotic) (B)
Ephemeral fever (exotic) (B)
Lumpy skin disease (exotic) (B)
Nasal schistosomiasis (exotic)
Besnoitiosis, globidiosis (exotic)
Louping ill (exotic)
Theilezia rhodensis (exotic)
Cotyledon species poisoning, Krimpsiekte (exotic) (O, C)
Gedoelstia hasleri nasal bots (exotic) (O, C)
Nairobi sheep disease (exotic) (O, C)
Schistosoma nasale (exotic) (B)

Toxic Causes

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

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

accumulate in the trachea and pharynx, drain into the nasal passages, and exit from the nares.

Hemorrhagic (sanguinous) nasal discharge, or epistaxis, occurs secondary to trauma, coagulopathies, and erosive or invasive conditions that insult the richly vascular nasal mucosa or secondary to conditions that invade regional blood vessels such as occurs when the internal carotid artery is eroded by a mycotic plaque in horses with guttural pouch mycosis. Pulmonary disorders such as infarctive pneumonia in horses and pulmonary thromboembolism secondary to posterior vena cava thrombosis in cattle may also induce epistaxis (see Epistaxis, p. 53).[38-40]

Foul odor (ozena) accompanying nasal discharge suggests an anaerobic infection, a necrotizing condition (e.g., fungal infection, neoplasia, turbinate necrosis, or necrotizing pneumonia), foreign body, or communication between the oral and nasal cavities (e.g., maxillary sinusitis secondary to tooth root infection in the horse).[40]

Food or water may drain from the external nares when there is communication between the oral and nasal cavities (e.g., cleft palate);

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BOX 5-5

Causes of Purulent Nasal Discharge in Horses

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

BOX 5-6

Causes of Purulent Nasal Discharge in Ruminants

Common Causes

Debilitating illnesses that reduce lingual nose cleaning in cattle
Post-viral bacterial infection of the respiratory tract
Mannheimia hemolytica or *Pasteurella multocida* pneumonia
Histophilus somni pneumonia (B)
Necrotic laryngitis, calf diphtheria (B)
Lungworm infection, verminous pneumonia
Mycoplasma species pneumonia
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)
Chronic bacterial pneumonia with consolidation or abscessation (*Arcanobacterium pyogenes* and other bacteria)
Esophageal obstruction, foreign body, choke
Nose bots (*Oestrus ovis*) (O, C)
Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)
Abscess (oral, pharyngeal, retropharyngeal)
Septicemia (neonates)

Less Common Causes

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

Uncommon Causes

Ovine nasal granuloma, atopic rhinitis, summer snuffles (B)
Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis
Nasal actinobacillosis (B)
Bovine salmonellosis (B)
Sarcocystosis (B)
Tularemia (O)
Tuberculosis
Phycomycosis, pythiosis (B)
Pulmonary aspergillosis
Bronchobiliary fistula (yellow froth) (B)
Zygomycosis, mucormycosis (B)
Pneumocystis carinii (renamed *P. jiroveci* in humans) pneumonia
Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)
Immune deficiency states
Lymphosarcoma

Toxic and Exotic Causes

See Box 5-4, p. 49.

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

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

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

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

ORIGIN OF NASAL SECRETIONS. Unilateral nasal discharge generally originates from structures located rostral to the caudal end of the nasal septum. Bilateral nasal discharge results from disease

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processes affecting structures caudal to the caudal end of the nasal septum or from conditions involving the nasal passages or paranasal sinuses bilaterally.[39,40] A discharge that appears from one nostril on some days and from the opposite nostril on others generally indicates a lesion or disease process caudal to the nasal septum.[40] The paired guttural pouches of the horse drain separately through ostia located dorsolaterally in the wall of the nasopharynx. Exudate draining from the guttural pouches may appear unilaterally at the ipsilateral nostril if the volume of drainage is small, but moderate to profuse guttural pouch drainage appears as a bilateral nasal discharge.[40]

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

Approach to Diagnosis of Nasal Discharge

Because many conditions, particularly those involving the lower respiratory tract, are associated with both nasal discharge and cough, the diagnostic approach used for large animal patients presented for evaluation of nasal discharge is similar to that used for large animals presented for evaluation of cough (see Cough, p. 40). Only those components of the history and diagnostic evaluation that differ substantially from those used in patients with cough are described in depth in this section.

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

The association of discharge with certain activities such as initiation of exercise, when the animal is first disturbed in the morning, or when it is eating with its head lowered can provide useful clues to the origin or cause. It should be determined if the animal is showing other signs of respiratory disease (e.g., cough, respiratory distress, or exercise intolerance), dental disease (e.g., quidding or slow eating), or systemic disease (e.g., weight loss, depression, anorexia, fever, or lymphadenopathy).

It should also be determined if in-contact animals have exhibited nasal discharge or other signs of respiratory disease. The vaccination status of affected and in-contact animals should be ascertained. Recent transportation, surgery, or weaning should be noted as supportive of stress, and a history of contact with other animals at sales, shows, or other events should be established. Environmental quality and the overall management of the affected animal and the herd should be assessed (see Cough, p. 40). Progression or improvement in the signs, attempted therapy, and response to current or previous treatments should also be ascertained.

PHYSICAL EXAMINATION. Physical examination of an animal showing nasal discharge should be complete and include inspection from a distance and close examination using *auscultation, palpation,* and *percussion* techniques (see Physical Examination, p. 44, and Cough, p. 40). The character and volume of the nasal discharge should be noted. Particular attention should be paid to whether:

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

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

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

Further diagnostic evaluation of nasal discharge may include a complete blood count with determination of the fibrinogen concentration, a serum biochemistry profile, endoscopy of the upper and lower airways and the esophagus, nasal or nasopharyngeal swabbing for molecular diagnostic testing or virus isolation, virus serologic testing, tracheal aspiration, BAL, ultrasonography, thoracocentesis, radiography, blood gas analysis, nuclear scintigraphy, fecal examination, pulmonary function testing, and lung biopsy. For further information on diagnostic procedures not discussed in the following sections, see Cough, page 40.

ENDOSCOPIC EXAMINATION. Endoscopic examination of the upper and lower airways is a useful ancillary diagnostic procedure in all animals with nasal discharge. The nasal passages; the conchae (turbinates) including the ethmoidal conchae; the nasal septum; and the pharynx, larynx, and trachea should be examined through both nostrils. The presence, nature, and origin of exudates and the presence of anatomic or functional abnormalities or mass lesions should be noted. Although it is not possible to introduce standard, 8- to 12-mm–diameter endoscopes into the paranasal sinuses via the nasal passages, drainage from the sinuses may be detected by examining the middle meatus.[40] Examination of the middle meatus may also reveal turbinate necrosis or mass lesions (e.g., tumors, fungal granulomas, nasal foreign bodies). Lesions such as progressive hematomas (expanding mass lesions of variable size on the ethmoid turbinates) can be visualized by advancing the endoscope slightly, after deflecting its tip dorsally through the common meatus, from a position in the caudal part of the ventral meatus just rostral to the choana. In the horse the pharyngeal openings of the guttural pouches, which are located dorsolaterally on the wall of the pharynx, should be inspected for drainage. The interior of both guttural pouches can be examined for exudate, blood, mycotic plaques, and other proliferative lesions by advancing the endoscope through the pharyngeal openings of each guttural pouch. This procedure is facilitated by first introducing a biopsy instrument or similar guidewire into the guttural pouch via the biopsy channel of the endoscope.

Bronchoscopic examination may prove useful for identifying the bronchus of origin of pulmonary exudates and for facilitating appropriate BAL. In horses with intermittent bilateral nasal discharge, it may be helpful to repeat the endoscopic examination after exercise, which often mobilizes secretions from the lower respiratory tract and causes them to pool in the horizontal trachea. Endoscopic examination of the esophagus is indicated in patients with a history of dysphagia or return of ingesta through the nose (Boxes 5-7 and 5-8).

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BOX 5-7

Causes of Ingesta in Nasal Discharge in Horses

Common Causes

Esophageal obstruction, choke
Cleft palate, palatal hypoplasia (neonate)
Pharyngitis
Strangles (*Streptococcus equi* infection)
Dorsal displacement of the soft palate
Guttural pouch infection, mycosis, neoplasia
Glossopharyngeal nerve damage
Botulism, shaker foal
Retropharyngeal abscess

Less Common Causes

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

Uncommon Causes

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

BOX 5-8

Causes of Ingesta in Nasal Discharge in Ruminants

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

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

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

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

ULTRASOUND EXAMINATION. Ultrasound examination of externally visible lesions such as possible retropharyngeal abscesses or distended guttural pouches assists in characterization of lesions and collection of samples by aspiration or biopsy. Thoracic ultrasound is indicated when lower airway, pleural, or cardiac disease is the suspected cause of nasal discharge.

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

CENTESIS. Centesis of affected paranasal sinuses helps localize the source of exudates and provides samples for cytologic examination and culture in patients with chronic unilateral nasal discharge in which sinus percussion or radiographic examination (or both) suggests the presence of a sinus lesion. In the normal horse the rostral and caudal maxillary sinuses are separated by a thin osseous septum. This septum is often eroded in horses with septic sinusitis; therefore the caudal maxillary sinus is typically entered first. If no exudate can be aspirated, either directly or after lavaging the sinus, and if increased purulent drainage from the ipsilateral nostril is not accomplished during lavage, centesis of the rostral maxillary sinus is performed and the procedure repeated. If the aspirated material is not malodorous and if there is no evidence of dental disease, there is a reasonable likelihood that primary (nondental) sinusitis is present. In the horse the rostral maxillary sinus can be entered at a site 2.5 cm dorsal and

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2 to 3 cm caudal to the rostral end of the facial crest. The caudal maxillary sinus is entered at a point 2.5 cm dorsal to the facial crest and 2 cm rostral to the medial canthus of the eye. After shaving and surgical preparation of the skin and subcutaneous placement of a small volume of local anesthetic, a stab incision is created through the skin and extended down to the periosteum. A small hole is then drilled through the bone with a Steinmann pin in a handheld chuck or a 14-gauge needle. A 14-gauge cannula is introduced into the sinus and, if necessary, a No. 5 French catheter can be inserted through the cannula to facilitate sample collection and lavage (see Diseases of the Paranasal Sinuses, Chapter 31; p. 559 for horses and p. 578 for ruminants).

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

Epistaxis and Hemoptysis

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

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

Pathophysiology Blood at the external nares originates from one or more of the following structures: nasal cavity, paranasal sinuses, guttural pouch (auditory tube diverticulum), oral cavity, pharynx, larynx, trachea, or lungs.[47] These respiratory structures may be affected by a primary disease process or may be one of many mucosal surfaces involved in a bleeding diathesis (Boxes 5-9 and 5-10). The actual disease condition, the affected structure, and the large animal species involved determine whether epistaxis is profuse or scant, unilateral or bilateral, induced by exercise, accompanied by hemoptysis, and/or associated with concurrent abnormal nasal discharge.

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

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

BOX 5-9

Causes of Epistaxis in Horses

Common Causes

Exercise-induced pulmonary hemorrhage (EIPH)
Guttural pouch mycosis
Progressive ethmoidal hematoma
Nasal trauma
Pharyngeal or retropharyngeal trauma or abscess
Nasal polyps
Tumors (nose, paranasal sinuses)
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Purpura hemorrhagica

Less Common Causes

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

Uncommon Causes

Nasal amyloidosis
Rectus capitis ventralis rupture
Black disease *(Clostridium novyi)*
Snakebite
Retrobulbar neoplasia
Chronic hepatitis or cholangitis
Acute renal failure
Cardiac neoplasia
Laryngeal hemiplegia
Phycomycosis, pythiosis, zygomycosis
Thrombasthenia-like syndrome
Besnoitiosis, globidiosis (exotic)
Dacryohemorrhea (exotic)

Toxic Causes

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

PATHOLOGIC CONDITIONS OF THE GUTTURAL POUCHES OF THE HORSE. Spontaneous epistaxis that occurs at rest in a mature horse warrants consideration of the guttural pouch as the source of hemorrhage.[50] In the case of guttural pouch mycosis, epistaxis is typically caused by fungal erosion of the internal carotid artery in the roof of the medial compartment of the guttural pouch.[50-52] The horse initially experiences several episodes of minor hemorrhage characterized by a small amount of fresh blood at the external nares; this may be preceded by a unilateral catarrhal nasal discharge and

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BOX 5-10

Causes of Epistaxis in Ruminants

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

Toxic Causes

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

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

followed by a seromucous nasal discharge. Ultimately, massive arterial bleeding associated with erosion of the internal carotid artery manifests as large volumes of blood gushing from both nostrils.[51] Epistaxis caused by bleeding from the guttural pouch is typically most pronounced on the ipsilateral side, but nasal bleeding is usually bilateral in this condition, especially if hemorrhage is profuse, because the nasopharynx drains into both nasal passages.[52]

BOX 5-11

Causes of Hemoptysis in Ruminants

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

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

Exercise-induced pulmonary hemorrhage (EIPH), a syndrome experienced by 40% to 75% of Thoroughbred racehorses and by horses of other breeds engaged in strenuous activity, is characterized by hemorrhage into the tracheobronchial tree during competitive exercise.[47,53,54] Although pulmonary hemorrhage can be identified by endoscopic examination of the trachea immediately after exercise in these horses, EIPH manifests as frank epistaxis at the external nares in only a small percentage of cases.[53] Bleeding at the nares may range from a slight orange-tinged serous nasal discharge to a constant trickle of fresh blood that persists for several hours after exercise.[47,54] The exact source of hemorrhage in horses with EIPH has not been identified, but it is known that affected horses have proliferation of the bronchial arterial blood supply to the lungs.[55] Fatal massive epistaxis, an infrequent sequela to exercise, has been attributed to tearing of the lung in association with pleural adhesions or focal shear stress.[56] Other less common causes of postexercise pulmonary hemorrhage in horses include pulmonary abscesses or pleuropneumonia with pulmonary infarction; in these cases the odor of the breath may be fetid, and hemorrhage may occur spontaneously (without exercise), which aids in the differentiation of these conditions from EIPH.[47,57]

CVCT (also known as *pulmonary embolic aneurysm* or *pulmonary thromboembolism*) is the disease most likely to be associated with epistaxis and hemoptysis in cattle (Box 5-11).[58] This sporadic, fatal condition of feedlot cattle is the result of a four-step sequence of events that culminates with the rupture of a pulmonary artery aneurysm into a bronchus. Initially, affected cattle exhibit tachypnea, lethargy, painful cough, melena, and anemia. Terminally the disease is characterized by discharge of bright, foamy red blood from the nose and mouth, severe respiratory distress, and widespread pulmonary crackles.[58]

Pulmonary edema present in the terminal stages of left-sided heart failure may also be responsible for bilateral serosanguineous discharge at the external nares of large animals.[47]

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

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

Approach to Diagnosis of Epistaxis and Hemoptysis

HISTORY. History taking should closely follow that described for animals with nasal discharge and should include duration of ownership, time of first appearance of blood at the nares, number of times the animal has bled, volume and color of blood, presence of blood at one or both nostrils, association of epistaxis with exercise, swallowing motions or cough after exercise, concurrent hemoptysis, other signs of respiratory tract disease (e.g., stridor, cough, nasal discharge, respiratory distress), evidence of involvement of cranial nerves (e.g., feed particles at the nares, drooping of the lip or ear), possibility of recent trauma (e.g., nasogastric intubation or head injury), and exposure to toxic plants (e.g., bracken fern or sweet clover).

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

EVALUATION OF THE HEAD AND RESPIRATORY SYSTEM. A complete evaluation of the head and respiratory system should also be carried out. The nasal bones and flat bones overlying the maxillary and frontal sinuses should be examined for asymmetry or deformation; the eyes should be evaluated for exophthalmos or epiphora; the nasal mucosae should be inspected with a light source to demonstrate erosive, ulcerative, or mass lesions; and the sinuses should be percussed to detect altered resonance or pain. On continuing the examination, the following should be evaluated: symmetry and amount of airflow through the nostrils and the effect of occluding each nostril independently; odor at the nose or mouth; presence of stridor; and the effect of applying pressure to the larynx or trachea. The oral cavity should be carefully inspected in animals in which epistaxis is accompanied by a necrotic breath odor. Special attention should be paid to the maxillary cheek teeth of horses and the base of the tongue and the oropharynx of all large animals. Structures in the external pharyngeal region (mandibular lymph nodes, Viborg triangle, retropharyngeal lymph nodes, parotid salivary gland) should be observed and palpated for swelling, heat, or pain, and the trachea should be observed and palpated where exposed to detect any abnormalities. The larynx, trachea, and lungs should be carefully auscultated at rest and after application of a rebreathing bag for abnormally loud breath sounds, crackles, or wheezes, which may implicate pulmonary disease as the cause of epistaxis. Careful cardiac auscultation should be carried out to detect murmurs or dysrhythmias, which may be associated with left-sided heart failure and pulmonary edema. The chest wall should be palpated to detect rib fractures or pleural friction rubs, and the thorax should be percussed bilaterally to demonstrate large mass lesions, pleural effusion, or pleurodynia.

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

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

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

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

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

TRACHEAL ASPIRATION, BRONCHOALVEOLAR LAVAGE, AND THORACOCENTESIS. Percutaneous transtracheal aspiration or endoscopic tracheal aspiration, BAL, or thoracocentesis with cytologic studies and culture of collected samples is indicated when pulmonary or pleural diseases are thought to be responsible for hemorrhage into the respiratory tract[20,21,62-64] (see discussion of Cough, pp. 45 and 46). The presence of hemosiderophages in tracheobronchial aspirates or BAL fluid is generally considered indicative of previous pulmonary hemorrhage[53]; however, mucopolysaccharides engulfed by alveolar macrophages can bind plasma iron in the absence of pulmonary hemorrhage to form an iron pigment resembling hemosiderin.[64]

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

ULTRASOUND EXAMINATION. See discussion of Cough, page 40.

PARACENTESIS. Paracentesis of the maxillary sinuses[20] can be performed if percussion and inspection indicate that a lesion in the maxillary sinus may be the cause of epistaxis (see Nasal Discharge, p. 48).

PLEUROSCOPIC EXAMINATION. Pleuroscopic examination[65] is rarely indicated in the evaluation of epistaxis and should be limited to cases in which a disease process involving the pleura (e.g., pleural neoplasia, pleuropneumonia with pulmonary infarctions) is strongly suspected on the basis of the results of other diagnostic tests and a diagnosis cannot be reached by less invasive approaches (see Cough, p. 40).

Tachypnea

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

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

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

Pathophysiology Respiratory rate, depth, and rhythmicity are regulated by respiratory centers in the brainstem. Central chemoreceptors responding to increased levels of CO_2 (decreased cerebrospinal fluid pH) and peripheral chemoreceptors (carotid and aortic bodies) responding to hypoxemia (PaO_2 below 60 mm Hg), increases in $PaCO_2$, and decreases in pH initiate increases in the respiratory rate. Mechanoreceptors in the lungs and joints also influence ventilation. Lung inflation stimulates stretch receptors in the airways, which decreases the inspiratory effort, whereas mechanoreceptors in the joints are thought to be partly responsible for the increases in ventilation that occur during exercise. Pulmonary chemoreceptors that influence the respiratory cycle include irritant receptors in the airways, which are stimulated by dust and histamine, and J receptors, which apparently detect levels of interstitial fluid and are thought to be responsible for the respiratory pattern observed in animals with pulmonary edema.

Tachypnea is classified as physiologic when it occurs in the absence of underlying disease and as pathologic when it is a manifestation of respiratory distress. Physiologic tachypnea is associated with pain, exertion, heat, fever, anxiety, and other stresses (Boxes 5-12 and 5-13). Factors predisposing to pathologic tachypnea are the same as those that cause respiratory distress: inadequate oxygenation of the blood (i.e., a need for additional oxygen); compensation for metabolic acidosis; excessive environmental heat; disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions) if they disrupt the control of breathing; disorders that cause dysfunction of motor nerves and/or weakness of respiratory muscles (e.g., botulism, hypocalcemia); and painful conditions involving the respiratory sensory nerves, muscles, pleurae, and ribs (e.g., chest trauma, pleural infection, or neoplasia)[66] (see Respiratory Distress later).

Approach to Diagnosis of Tachypnea

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

Respiratory Distress (Dyspnea)

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

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

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

Manifestations of respiratory distress include elevated respiratory rate (see Tachypnea, p. 56), extended head and neck position, mouth breathing (ruminants), nostril flaring (horses, sheep, and goats), abnormal respiratory noise (stridor or stertor), exercise intolerance, exaggerated intercostal or abdominal effort (or both), a double expiratory lift and a "heave line" (expiratory respiratory distress), abducted elbows, anxious expression, and inactivity. Animals in severe respiratory distress may show cyanosis (see p. 63) and (especially those with severe RAO) may exert so much effort to breathe that the whole body rocks, the anus pumps in and out, and the animal does not move or eat because this diverts its energies from respiration.[67]

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

- Inadequate oxygenation of blood (i.e., a need for additional oxygen)
- Compensation for metabolic acidosis
- Excessive environmental heat
- Disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions)
- Disorders that cause dysfunction of motor nerves or weakness of respiratory muscles (e.g., botulism, hypocalcemia)

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BOX 5-12

Causes of Tachypnea in Horses*

Common Respiratory Causes

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

Common Nonrespiratory Causes

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

Less Common Respiratory Causes

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

Less Common Nonrespiratory Causes

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

Uncommon Respiratory Causes

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

Uncommon Nonrespiratory Causes

Lactation tetany
Hydroallantois or hydrops
Nutritional myodegeneration (foals)
Methemoglobin reductase deficiency
Acute hepatic insufficiency
Electrocution
Cardiac neoplasia
Embryonal mediastinal cyst

Toxic Causes

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

*All causes of respiratory distress (see p. 59) are also causes of tachypnea.

- Painful conditions involving the respiratory sensory nerves, muscles, pleura, and ribs (e.g., chest trauma, pleural infection, neoplasia)

Inadequate oxygenation of blood leads to arterial hypoxemia (low partial pressure of oxygen in arterial blood [Pa_{O_2}]). This can be caused by a low partial pressure of inspired oxygen (PI_{O_2}), such as occurs at high altitude; by disorders that interrupt the transfer of oxygen from the environment to the blood (e.g., upper and lower airway obstruction, pulmonary disease associated with alveolar flooding or collapse, and pulmonary or intracardiac right-to-left shunting of blood); or by a decrease in the oxygen-carrying capacity of the blood, such as occurs in anemia, methemoglobinemia, and carboxyhemoglobinemia.[66] Primary or secondary disease conditions that affect the respiratory and cardiovascular systems induce arterial hypoxemia by causing alveolar hypoventilation, ventilation-perfusion mismatch, diffusion limitation, right-to-left shunting of blood, or combinations of these abnormalities (see Cyanosis, p. 63).[11,66]

Compensation for metabolic acidosis involves "blowing off" carbon dioxide, which may increase both the rate and depth of respiration.[66] The resulting hyperventilation causes a decline in the

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BOX 5-13

Causes of Tachypnea in Ruminants

Common Respiratory Causes

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

Common Nonrespiratory Causes

Hyperthermia (fever, heatstroke, rapid rise in ambient temperature, other)
Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, musculoskeletal injury, other)
Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)
Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)
Shock (hypovolemic, cardiac, septic)
Anemia (iron deficiency, postparturient hemoglobinuria, blood loss, other)
Distended abdominal viscus (ruminal bloat, other)
Anaphylaxis
Blood transfusion reaction
White muscle disease

Less Common Respiratory Causes

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

Less Common Nonrespiratory Causes

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

Uncommon Respiratory Causes

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

Uncommon Nonrespiratory Causes

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

Toxic Causes

Sodium fluoroacetate
Strychnine
Sulfur
Propylene glycol
Urea or nonprotein nitrogen
Water deprivation or salt toxicity
Potassium
Nitrates
Bromide
Iron
Selenium
Organophosphate
Organochlorine or chlorinated hydrocarbon
Larkspur (*Delphinium* species)
Japanese yew (*Taxus cuspidata*)
Sneezeweed (*Helenium autumnale*)
Hairy vetch (*Vicia villosa*)
Whitehead (*Sphenosciadium capitellatum*)
White snakeroot (*Eupatorium rugosum*)

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

Note: Tachypnea is a rather nonspecific sign and is associated with toxicity caused by a large number of plant species; only a few are listed in this box. See also Box 5-15, p. 60.

partial pressure of arterial carbon dioxide ($PaCO_2$) in the face of clinical signs of respiratory distress.

Animals dissipate a considerable amount of heat through the respiratory tract. In ruminants, but not in horses, heat dissipation is further aided by the animals' ability to mouth breathe and pant to increase evaporative cooling of blood passing through the tongue and other structures in the oral cavity and oropharynx. The need to dissipate heat when exposed to high environmental temperatures induces labored breathing (Boxes 5-14 and 5-15). Apparent respiratory distress also occurs when the weather is not excessively hot but the temperature has risen rapidly, such as occurs when cattle in cold climates are brought indoors in the winter. When the environmental temperature has been consistently low, cattle in feedlots may also experience respiratory distress if the temperature suddenly rises from 4.4° to 10° C (40° to 50° F).

Observation of the nature of the respiratory distress may give important clues as to the functional characterization, and perhaps cause, of the underlying disease process. Obstructive diseases

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BOX 5-14

Causes of Respiratory Distress in Horses

Common Respiratory Causes

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

Common Nonrespiratory Causes

Cardiac disease (e.g., congestive cardiac failure, mitral insufficiency, other cardiac diseases)
Shock (septic, cardiogenic, hypovolemic, acute blood loss)
Endotoxemia
Anemia (e.g., neonatal isoerythrolysis, autoimmune hemolytic anemia, blood loss, other causes of acute anemia)
Pain (e.g., abdominal crisis, laminitis, myopathy, fracture, other lameness)
Hyperthermia (e.g., fever, postexhaustion syndrome, anhidrosis, heatstroke, erythromycin associated)

Less Common Respiratory Causes

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

Less Common Nonrespiratory Causes

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

Uncommon Respiratory Causes

Stenotic external nares
Cutaneous, nasal amyloidosis
Cutaneous, nasal habronemiasis (summer sore)
Failure of closure of the false nostril
Abnormalities of the nasal septum
Choanal (posterior nares) atresia or stenosis (foals)
Nasopharyngeal cicatrix
Laryngopalatal dislocation (dorsal displacement of soft palate), soft palate hypoplasia
Rostral displacement of the palatopharyngeal folds
Pharyngeal hematoma
Laryngeal paralysis
Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal)
Chondroma of the arytenoid cartilage
Laryngeal spasm
Hypertrophic ossification of the laryngeal cartilages, laryngeal chondropathy
Neoplasia of the upper airway
Tracheal stenosis, stricture, collapse, rupture
Phycomycosis, pythiosis
Pneumoconiosis (e.g., silicosis)
Interstitial pneumonia (restrictive pulmonary disease)
Pulmonary thromboembolism
Pneumocystis carinii (renamed *P. jiroveci* in humans) pneumonia
Pulmonary lobar hypertrophy (foals)
Infarctive lobar pneumonia
Chlamydia psittaci pneumonia
Pulmonary nocardiosis
Pulmonary tuberculosis
Pulmonary aspergillosis
Besnoitiosis *(Besnoitia besnoiti* and *Besnoitia jellisoni)*
Pulmonary neoplasia (primary or metastatic)
Pleural neoplasia (mesothelioma, lymphosarcoma)
Embryonic cyst (mediastinal, branchial, cervical, thyroglossal duct)
Hendra virus infection (exotic)

Uncommon Nonrespiratory Causes

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

Toxic Causes

Vitamin D
Lead
Organophosphate-associated laryngeal paralysis
Monensin, lasalocid, salinomycin
Propylene glycol
Iron
Dinitrophenol
Selenium
Bromide
Sodium fluoroacetate
Strychnine
Ammonia
Theobromine, chocolate

Continued

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BOX 5-14

Causes of Respiratory Distress in Horses—cont'd

Cantharidin (blister beetle)
α-Naphthyl thiourea (ANTU)
Red maple *(Acer rubrum)*
Water hemlock (*Cicuta* species)
Oleander *(Nerium oleander)*
Japanese yew *(Taxus cuspidata)*
Larkspur (*Delphinium* species)
Ryegrass (*Lolium* species)
White snakeroot *(Eupatorium rugosum)*
Crofton weed *(Eupatorium adenophorum)*
Pyrrolizidine alkaloid
Locoweeds (*Astragalus* species, *Oxytropis* species)
Avocado *(Persea americana)*
Hoary alyssum *(Berteroa incana)*
Coffee senna seed *(Cassia occidentalis)*
Rubber vine *(Cryptostegia grandiflora)*
Birdsville disease (*Indigofera* species) (exotic)
Trachyandra paralysis (exotic)

BOX 5-15

Causes of Respiratory Distress in Ruminants

Common Respiratory Causes

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

Common Nonrespiratory Causes

Hyperthermia (fever, heatstroke, rapid rise in ambient temperature, other)
Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, other)
Distended abdominal viscus
Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)
Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)
Hypovolemic, cardiac, or septic shock
Fluid or electrolyte loss (acute diarrhea, gastrointestinal obstruction, other)
Endotoxemia (coliform mastitis, metritis, enteritis, salmonellosis, septicemia, other)
Neonatal septicemia
Anemia (iron deficiency, postparturient hemoglobinuria, hemolytic, anaplasmosis, eperythrozoonosis, other)
White muscle disease (nutritional myodegeneration)
Anaphylaxis or allergy, milk allergy

Less Common Respiratory Causes

Pulmonary embolus from posterior vena cava thrombosis (B)
Parainfluenza virus type 3
Adenovirus (B, O)
Nasal trauma
Tumors of the nose, paranasal sinuses, oral cavity
Nasal granulomas (fungal granuloma, atopic rhinitis)
Congenital cystic nasal conchae
Nose bots *(Oestrus ovis)*
Sinusitis (maxillary, frontal, postdehorning)
Laryngeal trauma or abscess
Trauma (oral, pharyngeal, retropharyngeal), abscess, hematoma
Tracheal stenosis, collapse, stricture
Bovine rhinovirus (B)
Bovine malignant catarrhal fever (B)
Bovine herpesvirus DN-599 (B)
Ascaris suum migration (calves) (B)
Thoracic trauma, rib fracture
Pneumothorax
Pleuritis or pleural effusion
Caprine arthritis-encephalitis (CAE) pneumonia (C)
Sheep pulmonary adenomatosis virus (Jaagsiekte) (O)
Smoke inhalation
Foreign body (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial)
Caprine herpesvirus (C)
Bluetongue
Peste des petits ruminants (C, O) (exotic)
Congenital cardiac anomalies (ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, transposition of the great vessels, other anomalies)
Acquired cardiac failure (bacterial endocarditis, valvular incompetence, valvular stenosis, cardiomyopathy, pericarditis, other causes)
Central nervous system disease (trauma, meningoencephalitis, encephalomalacia, abscess, louping ill, pseudorabies, other causes)
Esophageal obstruction, foreign body, laceration, rupture, megaesophagus
Clostridial diseases (Black disease, enterotoxemia, tetanus, blackleg, bacillary hemoglobinuria, others)
Anthrax
Complications of fluid therapy (pulmonary edema)
Water deprivation (salt poisoning) (B)
Blood transfusion reaction
Anaphylaxis
Burn, thermal injury, electrocution
Systemic toxoplasmosis (C, O)
Tick paralysis (C, O)
Bladder rupture
Bee or wasp sting, snakebite
Photosensitization

Uncommon Respiratory Causes

Actinobacillosis (wooden tongue)
Actinomycosis (lumpy jaw)
Diaphragmatic hernia
Pleural mesothelioma
Pneumocystis carinii (renamed *P. jiroveci* in humans) pneumonia
Pulmonary aspergillosis
Pulmonary neoplasia
Pulmonary tuberculosis
Chlamydia psittaci pneumonia
Cyst (branchial, cervical, salivary, thyroglossal duct)
Bronchobiliary fistula
Contagious bovine pleuropneumonia (exotic) (B)
Endemic ethmoid carcinoma (exotic) (B)
Theileria annulata and *Theileria hirci* (exotic) (B)
Heartwater *(Cowdria ruminantium)* (exotic)

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BOX 5-15

Causes of Respiratory Distress in Ruminants—cont'd

Uncommon Nonrespiratory Causes

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

Toxic Causes

Sodium fluoroacetate
Strychnine
Sulfur (B, O)
Propylene glycol (B)
Oxalate, ethylene glycol (B, O)
Urea or nonprotein nitrogen
Potassium (B)
Nitrates
Bromide (B, C)
Lead
Mercury (C)
Iron (B, C)
Selenium
Arsenic
Organophosphate or carbamate
Organochlorine or chlorinated hydrocarbon
Permethrin
Gossypol
Ergot *(Claviceps purpura)*
Phosphate fertilizer (B, O)
Vitamin D_3 (B)
Warfarin, dicumarol, diphacinone
Metaldehyde
Formaldehyde
Ammonia
Hydrogen sulfide
Monensin, salinomycin
Dinitrophenol (B, O)
Copper (acute oral toxicity)
Insect fogger pneumonitis (B)
Aflatoxicosis (C)
Levamisole (C, O)
Polychlorinated biphenyl (PCB) (B)
Xylazine-induced pulmonary edema (O)
Carbolic dips (O)
Cyanogenic plants (arrow grass, Johnson grass, common sorghum, Sudan grass, chokecherry, acacia, other plants)
Avocado *(Persia americana)*
Moldy sweet clover (*Melilotus* species)
Moldy sweet potato *(Ipomoea batatas)* (B)
Brassica species
Ryegrass (*Lolium* species) (B, O)
Larkspur (*Delphinium* species)
Japanese yew *(Taxus cuspidata)*
Hairy vetch *(Vicia villosa)* (B)
Whitehead *(Sphenosciadium capitellatum)* (B)
White snakeroot *(Eupatorium rugosum)* (B, O)
Chinese tallow *(Sapium sebiferum)* (B)
Purple mint *(Perilla frutescens)* (B)
Oleander *(Nerium oleander)*
Nightshade (*Solanum* species) (B)
Cocklebur (*Xanthium* species) (B, O)
Locoweeds (*Astragalus* species, *Oxytropis* species) (B, O)
Foxglove *(Digitalis purpurea)* (B)
Water hemlock (*Cicuta* species)
Milkweed (*Asclepias* species) (B, O)
Hepatotoxic plants (*Senecio* species, *Amsinckia* species, others containing pyrrolizidine alkaloid)
Fescue summer poisoning (B)
Rubberweed (*Hymenoxys* species)
Sneezeweed *(Helenium autumnale)*
False hellebore (*Veratrum* species) (B, O)
Rhododendron (*Andromeda* species) (B, O)
Algae
Lupines (*Lupinus* species) (B, O)
Prickly paddy melon *(Cucumis myriocarpus)*

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

Note: Respiratory distress is a sign associated with toxicity caused by a large number of plant species. Not all have been listed here.

involving the intrathoracic airways (e.g., RAO in horses and farmer's lung in cattle) are more likely to cause flow limitation during expiration because of dynamic airway narrowing or collapse (see Cough, p. 40).[11,68,69] This results in expiratory respiratory distress and a pattern of respiration in which the expiratory phase occupies an increased proportion of the respiratory cycle as the patient attempts to expel air from the lungs.[68] In the extrathoracic airways, dynamic collapse occurs during inspiration because intraluminal pressures are subatmospheric at this time.[11,68,69] Therefore patients with upper airway obstructions, especially of the nonfixed type (e.g., laryngeal hemiplegia), generally show inspiratory respiratory distress and may have a prolonged inspiratory phase.[11,68] Fixed airway obstructions of either the upper or lower airway (e.g., intraluminal mass, bronchoconstriction) are present during both phases of respiration and may lead to both inspiratory and expiratory distress.[11] However, the distress is likely to be accentuated during a particular phase of respiration, depending on the anatomic site of the obstruction (i.e., fixed upper airway obstructions cause more distress during inspiration, and fixed lower airway obstructions cause more distress during expiration). Restrictive diseases (e.g., pleural effusion, pneumoconiosis) inhibit expansion of the lungs and therefore generally lead to inspiratory respiratory distress.[11] Because an animal with restrictive disease has reduced compliance and must perform more respiratory work than normal to expand its lungs, a common strategy for maintaining adequate ventilation is to increase the respiratory rate and lower the tidal volume (i.e., rapid, shallow breathing).[11] Animals with obstructive diseases generally have a normal or even increased tidal volume.[11]

In many instances, respiratory distress is not apparent at rest but occurs in association with exercise. Under these circumstances the animal's capacity to exercise is impaired, and the owner may complain of exercise intolerance (see Exercise Intolerance and Poor Performance in Horses, p. 70).

Approach to Diagnosis of Respiratory Distress

HISTORY. After ruling out environmental causes of respiratory distress (e.g., heat stress, high humidity, moving from outside into a heated barn in the winter, handling stress, or relocation to high altitude) and attending to the immediate needs of the patient, a careful history should be taken that includes the following factors: time and speed of onset of the clinical signs of respiratory distress; progression of clinical signs; whether this is the first episode of respiratory distress or whether the animal is subject to recurrent attacks; whether signs are present at rest or only after exercise; the

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relationship of signs to environmental conditions and the response to environmental change; recent administration of pharmacologic or biological agents; the presence of an audible respiratory noise; or other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, facial paralysis, or retropharyngeal swelling). A history of recent trauma or exposure to potentially toxic substances such as lead-containing paints, nitrate-accumulating plants or urea (ruminants), or carbon monoxide should be elicited. The animal's appetite and attitude and signs of disease in other systems (e.g., diarrhea) should be determined. In neonates the circumstances surrounding gestation and parturition should be ascertained because prematurity, dysmaturity, congenital infection, birth trauma (e.g., rib fracture) related to dystocia, prolonged parturition, and aspiration of amniotic fluid and meconium are all important causes of respiratory distress. However, it should be noted that tachypnea, with respiratory rates of 60 to 80 breaths/min, is normal in foals during the first 30 minutes after birth as they "blow off" carbon dioxide.

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

The mucous membranes should be examined carefully for cyanosis, pallor, cherry red color, hemorrhages, congestion, or injection. The capillary refill time should be determined, and the peripheral pulse rate, rhythm, and character should be assessed. Other signs of heart failure (e.g., jugular distention or pulsation and peripheral edema) and signs of dehydration (e.g., delayed jugular filling, dry mucous membranes, and altered skin turgor) should be noted. The larynx, trachea, and lungs should be carefully *auscultated* at rest and after the rate and depth of respiration have been increased, if it is safe to do so, by application of a rebreathing bag, by occlusion of the nostrils, or by exercising the animal, so that turbulent airflow and abnormal lung sounds may be detected. The heart should be auscultated to detect murmurs, cardiac dysrhythmias, muffling of heart sounds, or other abnormalities. The chest wall should be carefully *palpated* to detect rib fractures and other lesions; and both sides of the chest should be *percussed* to detect large mass lesions, lung consolidation, pleural effusion, hyperinflation, pneumothorax, or a painful response, which may indicate pleuritis. A thorough oral examination is important, and in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx (see Nasal Discharge, p. 48).

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

Further diagnostic evaluation of respiratory distress may include a complete blood count with fibrinogen concentration; blood gas analysis; serum biochemistry determinations; endoscopy of the upper and lower airways and esophagus; nasal or nasopharyngeal swabbing or scraping; virus identification, isolation, and serologic testing; bronchodilator response testing; tracheal aspiration; BAL; ultrasound examination of the chest and of suspected mass lesions that impinge on the upper airway; thoracocentesis; radiography of the nasal passages, paranasal sinuses, pharynx, guttural pouches, larynx, trachea, and chest; fecal examination for lungworms and other parasites; CT scanning of the upper airway; nuclear scintigraphy; pulmonary function testing; and biopsy of externally visible or palpable lesions or those identified by ultrasound, endoscopy, or radiography as described for the evaluation of cough and nasal discharge (see Cough, p. 40, and Nasal Discharge, p. 48). The examiner should exercise discretion in the selection of diagnostic tests for animals with respiratory distress because procedures such as BAL or endoscopy may prove to be excessively stressful and exacerbate the distress, with potentially fatal consequences.

COMPLETE BLOOD COUNT. A complete blood count including fibrinogen and plasma protein concentrations helps evaluate the role of hemoconcentration, anemia, or leukocytosis and hyperfibrinogenemia, which may accompany pneumonia and other inflammatory conditions.

ENDOSCOPIC EXAMINATION. Endoscopic examination of the upper and lower airways is particularly helpful in evaluating patients suspected of having obstructive disease[70] (see Cough, p. 40; Nasal Discharge, p. 48; and Stridor, p. 66). Endoscopic examination of the esophagus is indicated in patients with a history of bloat, dysphagia, or return of ingesta through the nose in addition to respiratory distress (see Nasal Discharge, p. 48, and Stridor, p. 66).

BLOOD GAS ANALYSIS. Blood gas analysis and acid-base determinations should be performed on arterial blood to determine O_2 and CO_2 tensions so that the contribution of hypoxemia or acidosis to the signs of respiratory distress can be ascertained. In foals and calves, arterial samples are usually obtained from the great metatarsal artery or the brachial artery as it crosses the medial aspect of the foreleg.[71] The auricular artery is also convenient in calves. The femoral artery can be used in neonates but is less convenient because it tends to roll. The facial artery can be used in adult horses, and the auricular or coccygeal artery can be used in mature ruminants.[72] During the sampling process the patient should be quiet and not struggling, which can decrease the $PaCO_2$.[73] Local subcutaneous infiltration of 2% lidocaine without epinephrine over the artery being sampled minimizes needless struggling and facilitates sample collection. A heparinized syringe and a 22- to 26-gauge needle can be used. Any air bubbles should be removed after sample collection and the needle properly sealed. If the sample is kept on ice, the pH will remain unchanged for 3½ hours and the blood gases for 6 hours.[74] The animal's temperature should be recorded at the time of sample collection so that it can be used in the calculation of actual blood gas concentrations.

The normal PaO_2 for the horse is 83.6 ± 1.7 mm Hg, and the normal $PaCO_2$ is 42.2 ± 0.8 mm Hg.[75] Hypoxemia is defined as a PaO_2 below 80 mm Hg.[75] Cyanosis is usually not evident until the PaO_2 is much lower than this (usually below 40 mm Hg).[75] Hypercarbia, or hypercapnia, is a condition of increased $PaCO_2$ (above 44 mm Hg).[75] Because CO_2 diffuses readily, considerable ventilatory dysfunction can occur before the $PaCO_2$ rises; therefore severe hypoxemia can occur with a normal $PaCO_2$. An elevated $PaCO_2$ generally indicates that hypoventilation or a severe pulmonic pathologic condition is present. Because venous blood samples reflect tissue metabolism, they are not considered adequate for evaluating pulmonary function. However, a partial pressure of carbon dioxide in venous blood

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($PvCO_2$) above 60 mm Hg usually reflects arterial hypercapnia, and a partial pressure of oxygen in venous blood (PvO_2) below 20 mm Hg usually indicates arterial hypoxemia.[74]

Venous admixture is the term used to denote the ways that blood can pass from the right side to the left side of the circulation without being properly oxygenated and represents the efficiency with which the lung oxygenates blood. The magnitude of venous admixture (efficiency of oxygenation) can be assessed by calculating the PaO_2/FiO_2 ratio or the alveolar-arterial PO_2 gradient. The PaO_2/FiO_2 ratio is normally 500. PaO_2/FiO_2 ratios between 300 and 400 reflect significant lung injury, values below 300 reflect profoundly inefficient lung function such as occurs with acute lung injury, and values below 200 reflect severe life-threatening lung disease typical of acute respiratory distress syndrome (ARDS). The alveolar-arterial (A-a) PO_2 gradient difference is the difference between calculated alveolar PO_2 and the measured arterial PO_2. Alveolar PO_2 = Inspired PO_2 − $PaCO_2$ (1.1), where inspired PO_2 = barometric pressure × 21% and 1.1 = 1/RQ, where RQ is the respiratory quotient and has an assumed value of 0.9. The A-a PO_2 difference is typically about 10 mm Hg in a normal horse breathing 21% oxygen (room air) at sea level and about 100 mm Hg when breathing 100% oxygen. The "120 rule" is a simplified version of the alveolar gas equation that can be applied to a patient breathing 21% oxygen at near sea level. The measured PaO_2 and $PaCO_2$ should add up to 140 ± 10. If the sum is less than 120, the patient has venous admixture; and the lower the value, the worse the admixture.

INSUFFLATION OF 100% OXYGEN. Insufflation of 100% oxygen causes a significant increase in PaO_2 if hypoxemia is caused by hypoventilation or ventilation-perfusion mismatch, whereas little or no improvement in PaO_2 occurs if hypoxemia is caused by anatomic or physiologic right-to-left shunting.[11] Therefore measuring PaO_2 5 minutes after insufflation of 100% oxygen can help in determining the pathophysiologic processes contributing to arterial hypoxemia. In full-term neonates and adults the PaO_2 should exceed 200 mm Hg after 5 minutes of oxygen administration.[73] Continued cyanosis or inability to raise the PaO_2 above 100 mm Hg is highly suggestive of a right-to-left shunt.

DETECTION OF ABNORMAL HEMOGLOBIN. Blood samples should be evaluated for abnormal hemoglobin (e.g., methemoglobin) if exposure to nitrates or other intoxications is suspected (see Cyanosis, p. 63).

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

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

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

Cyanosis

Jeanne Lofstedt • W. David Wilson • Jeffrey Lakritz

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

Pathophysiology Oxygen is carried in blood in two forms, dissolved and in combination with hemoglobin (Hb). The amount of dissolved oxygen present in arterial blood is relatively small and is proportional to the PaO_2. Oxygen transport to tissues is facilitated by the ability of hemoglobin in erythrocytes to combine in a reversible manner with oxygen. When erythrocytes pass through the pulmonary circulation, oxygen binds to hemoglobin, forming oxyhemoglobin (HbO_2). As oxyhemoglobin passes through systemic capillaries, oxygen diffuses into tissues, and hemoglobin is once again formed.

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

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

Cyanosis develops when the oxygen saturation of hemoglobin is below 80%. With a normal oxygen-hemoglobin dissociation curve, the PaO_2 is usually below 40 mm Hg before cyanosis is noted in the patient.[77] The hemoglobin concentration of blood must be near normal for cyanosis to be clinically evident[78]; therefore patients with severe anemia and concomitant marked arterial oxygen desaturation may not show cyanosis. In contrast, patients with marked polycythemia may be cyanotic at higher arterial oxygen saturation than patients with normal hematocrit values.

Classification

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

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

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TABLE 5-1

Pathophysiologic Classification of Central Cyanosis and Examples of Associated Conditions

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

CENTRAL CYANOSIS. Central cyanosis results from either inadequate oxygenation of arterial blood or from the presence of an abnormal hemoglobin derivative and is characterized by cyanosis of mucous membranes (Table 5-1). Causes of inadequate oxygenation of arterial blood are respiratory disease or congenital cardiac anomalies causing right-to-left shunting (Boxes 5-16 and 5-17). Acquired abnormalities of hemoglobin function can be induced by a number of chemicals. Exposure to these chemicals results in the formation of methemoglobin or sulfhemoglobin, neither of which is capable of binding oxygen. Nitrites and nitrates are powerful reducing agents that produce methemoglobinemia by directly oxidizing hemoglobin to methemoglobin. Nitrate poisoning is most commonly associated with the incorporation of nitrate-accumulating plants (e.g., pigweed *[Amaranthus retroflexus]*, lamb's-quarters *[Chenopodium album]*, and mintweed *[Salvia reflexa]*) in livestock forage. Nitrate intoxication is usually seen only in ruminants because rumen microorganisms reduce nitrate to the more toxic nitrite ion. Congenital defects in hemoglobin function have been reported in humans and may occur in large domestic animals. Examples of such defects are nicotinamide adenine dinucleotide methemoglobin reductase deficiency and familial methemoglobinemia.

Conditions That Predispose to Hypoxemia and Central Cyanosis

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

ALVEOLAR HYPOVENTILATION. Alveolar hypoventilation is defined as a reduced volume of inspired air reaching the alveoli per unit time. Alveolar hypoventilation is always associated with an increased $PaCO_2$. Conditions associated with alveolar hypoventilation are drug-induced respiratory depression (morphine, barbiturates), brainstem disease (encephalitis, trauma, hemorrhage, neoplasia), and transection of the cervical spinal cord. All these conditions prevent proper generation and transmission of signals from the respiratory center to respiratory muscles. Other possible causes of alveolar hypoventilation are abnormal respiratory muscle function (diaphragmatic hernia, botulism), thoracic cage abnormalities (rib fracture), increased airway resistance (e.g., stenotic nares, laryngeal stricture or paresis, foreign body obstruction, bronchitis, bronchiectasis), and pleural space disease (inflammatory or neoplastic effusions, pneumothorax, hydrothorax, chylothorax, pyothorax, hemothorax).

BOX 5-16

Causes of Central Cyanosis in Horses

Common Causes

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

Less Common Causes

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

Uncommon Causes

Pulmonary lobar hypertrophy (foals)
Embryonal mediastinal cyst
Pulmonary tuberculosis, nocardiosis
Pneumocystis carinii (renamed *P. jiroveci* in humans) pneumonia
Air embolism
Pulmonary neoplasia
Transposition of great vessels
Tricuspid atresia
Aortic, pulmonary artery rupture
Interruption of aortic arch
Common ventricle with separate pulmonary outflow chamber
Multiple cardiac anomalies
Methemoglobin reductase deficiency
Lactation tetany
Clostridial diseases
Malignant hyperthermia

Toxic Causes

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

*Nitrate accumulator, which causes methemoglobinemia.

IMPAIRED DIFFUSION. Impaired diffusion, a second cause of hypoxemia, results from increased thickness of the blood-gas barrier. Equilibrium between alveolar oxygen and pulmonary blood oxygen is not reached because of increases in distance or resistance of barriers through which oxygen must pass to bind to hemoglobin. Because

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BOX 5-17

Causes of Central Cyanosis in Ruminants

Common Causes

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

Less Common Causes

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

Uncommon Causes

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

Toxic Causes

Strychnine
Arsenic
Metaldehyde
Hydrogen sulfide
Organochlorine, chlorinated hydrocarbon
Organophosphate, carbamate
Acute selenium toxicosis
Nitrate, nitrite
Perennial broomweed *(Gutierrezia microcephala)*
Oleander *(Nerium oleander)*
Whitehead *(Sphenosciadium capitellatum)*
Milkweed (*Asclepias* species) (O)
Rhododendron (*Andromeda* species)
Fireweed *(Kochia scoparia)*
Canary grass (*Phalaris* species)
Kikuyu poisoning (exotic) (B, O)
Albizia poisoning (exotic) (B, O)
Euphorbia, Sarcostemma poisoning (exotic) (B, O)
Acacia poisoning (exotic) (B, O)
Wild onion *(Allium validum)** [O]
Variegated thistle *(Silybum marianum)**
Redroot pigweed *(Amaranthus retroflexus)*
Sudan grass *(Sorghum vulgare var. sudanensis)**
Winged thistle *(Carduus tenuiflorus)**
Mintweed *(Salvia reflexa)**
Lamb's-quarters *(Chenopodium album)**
Many pasture grasses fed during optimum growth conditions*
Locoweeds (*Astragalus* species, *Oxytropis* species)*

*Nitrate accumulator, which causes methemoglobinemia.

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

carbon dioxide diffuses more readily than oxygen, the $PaCO_2$ is not usually increased in conditions that cause impaired diffusion. In fact, $PaCO_2$ may actually be reduced because of compensatory hyperventilation stimulated by hypoxemia. Conditions that may result in impaired diffusion are pneumonia, pulmonary edema, atelectasis, pulmonary contusions, and pulmonary neoplasms.

VENTILATION-PERFUSION MISMATCH. Ventilation-perfusion mismatch occurs eventually in all generalized pulmonary diseases and is the predominant mechanism by which hypoxemia develops in respiratory conditions. Overall gas exchange is impaired by uneven ventilation and blood flow. Lung areas that are overperfused in relation to ventilation (low ventilation/perfusion ratio) contribute disproportionate amounts of blood with a low PaO_2 to the systemic circulation. Examples of respiratory diseases that can cause low ventilation/perfusion ratios include bronchitis, bronchoconstriction, airway closure, pulmonary atelectasis or consolidation, and local restriction of lung movement. In the case of pulmonary embolization or decreased pulmonary arterial pressure, ventilation may exceed perfusion (high ventilation/perfusion ratio) and result in pathologic dead space. Pulmonary mechanisms can partly compensate for ventilation-perfusion inequalities. Alveolar hypoxia may lead to reflex pulmonary arterial constriction, which redirects blood flow to alveoli that are adequately ventilated. Airway hypocapnia can stimulate bronchoconstriction, resulting in redirection of airflow to better-perfused alveoli.

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

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Approach to Diagnosis of Cyanosis

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

PHYSICAL EXAMINATION. A thorough physical examination should include visual *inspection* to detect abnormalities in the respiratory pattern (e.g., tachypnea, respiratory distress, stridor) and careful *auscultation* of the larynx, trachea, and lungs to provide information that helps further define the cause of respiratory dysfunction. Rebreathing bags (12- to 52-L capacity for adult horses and cattle, 6- to 12-L capacity for calves, foals, and small ruminants) cause temporary buildup of CO_2, stimulating the respiratory center, prompting deep breathing immediately after the bag is removed and the animal is allowed to inspire room air. Loud breath sounds, pulmonary crackles and wheezes, or pleural friction rubs may suggest cyanosis in association with pathologic respiratory conditions. Loud cardiac murmurs accompanied by precordial thrills point to congenital heart disease as the cause of cyanosis.

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

ENDOSCOPIC EXAMINATION. An endoscopic examination should be performed if upper airway obstruction or malformation is suspected (see Cough, p. 40; Nasal Discharge, p. 48; and Respiratory Distress, p. 56).

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

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

ARTERIAL BLOOD GAS ANALYSIS. Arterial blood gas analysis is indicated to determine O_2 and CO_2 tension (see Respiratory Distress, p. 56).

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

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

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

Abnormal Respiratory Noise (Stridor)

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

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

Pathophysiology The extrathoracic airway of the horse consists of segments that are relatively rigid (e.g., nasal passages, extrathoracic trachea) and others (e.g., nostrils, soft palate, larynx) that not only are elastic but also have valvelike actions that are further capable of modifying the cross-sectional area and therefore resistance to airflow.[68,80] Pressures in the extrathoracic airways are subatmospheric during inspiration,[68,70,80] which causes the less rigidly supported parts of the upper airway to narrow (dynamic narrowing or collapse) during inspiration.[68-70,80,82] A major function of the upper airway muscles and other supporting structures is to prevent this dynamic narrowing or collapse during periods of high inspiratory gas flow.[68] Disease in these structures or a more rostral obstructing lesion that causes a greater negative pressure during inspiration may make them incapable of resisting axial displacement.[68,70] The increased resistance to flow induced by static or dynamic obstructions increases the driving pressure and therefore the work needed to move a given volume of air.[80]

Approximately 80% of the total airway resistance to gas flow at rest and during exercise is located in the upper airway rostral to the thoracic inlet.[70] Nasal resistance, most of which is caused by resistance just within the external nares, comprises more than 50% of the total upper airway resistance in the horse.[69,81] In most species including ruminants, this resistance can be bypassed by mouth breathing to accommodate the high airflow rates that accompany strenuous exercise. The horse, in contrast, is limited to nasal breathing even during exercise[69,70,82,83] because the larynx is firmly maintained in the nasopharynx by the tight seal formed around it by the muscular palatopharyngeal ring (intrapharyngeal osteum), except during swallowing.[83,84] Therefore mechanisms other than mouth breathing are necessary to reduce the energy cost of breathing in the horse.[68,81,83] These mechanisms include dilation of the distensible external nares by actively pulling the alar folds laterally, vasoconstriction in the erectile nasal vascular tissues to reduce congestion in the nasal mucosa, straightening of the respiratory tract, and dilation of the larynx by abduction of the vocal folds.[68,70,80-83,85,86]

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

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

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

Stridor is best heard during inspiration in most cases because the usual source of origin, the upper airway, is subject to dynamic narrowing during the inspiratory phase of the respiratory cycle.[68,69,81] In particular, nonfixed obstructions such as the paretic vocal folds of horses with idiopathic laryngeal hemiplegia (ILH) cause obstruction to airflow and turbulence only when dynamically drawn into the airway by the high inspiratory airflow rates that accompany fast exercise. Other obstructions such as arytenoid chondritis are fixed and obstruct airflow during both inspiration and expiration, which frequently results in audible stridor during both phases of respiration.

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

Because food animals are not normally expected to perform fast exercise, signs of stridor are usually present at rest when the animals are presented to veterinarians for examination. Stridor in resting animals usually indicates moderate to severe upper airway obstruction of a fixed nature. In ruminants the epiglottis is relatively short and blunt, and the palatopharyngeal ring allows the laryngopalatal dislocation necessary for mouth breathing. In conditions that give rise to respiratory distress and mouth breathing, the turbulence produced is often sufficient to induce abnormal (grunting) expiratory sounds, which may be classified as expiratory stridor. The external nares of cattle are much less compliant than those of sheep, goats, and horses, which prevents dynamic collapse during inspiration; thus conditions such as paresis of the nares that cause stridor in sheep, goats, and horses do not cause stridor in cattle (Boxes 5-18 and 5-19).

Approach to Diagnosis of Stridor

HISTORY. The procedure for taking a history should follow that used in the evaluation of cough and nasal discharge (see Cough, p. 40, and Nasal Discharge, p. 48). The history should also include the duration of ownership; time of onset of the clinical signs of stridor; progression of clinical signs; presence or absence of the noise at rest; relation of noise to fitness; relation of noise to speed, duration, and direction of work; relation of noise to head position during work; association of noise with poor performance or exercise intolerance; and other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, retropharyngeal swelling).

PHYSICAL EXAMINATION. A physical examination of the entire respiratory tract at rest should be performed as described for cough (see p. 40) and respiratory distress (see p. 56). In addition, the presence or absence of stridor at rest should be ascertained by listening at the nostrils, and digital pressure should be applied to the retropharyngeal region and to the larynx during palpation of these areas to evaluate whether stridor or pain (or both) can be induced easily or exacerbated. The dorsal surface of the larynx should be palpated with the fingertips with the horse relaxed and its head and neck in an extended position. This permits comparison of the prominence of the muscular process of the arytenoid cartilages and the thickness of the cricoarytenoideus dorsalis (CAD) muscle, both of which are affected in horses with atrophy of the CAD in association with ILH. Air turbulence, flattening, swelling, and pain should be assessed during palpation of the extrathoracic airway. The larynx, trachea, and lungs should be carefully auscultated, and the chest should be percussed. A thorough oral examination should be completed, particularly in ruminants; in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx through the oral cavity.

FIELD EXERCISE TESTING.[84] In performance horses most examinations are carried out because the horse makes a noise only when worked, because of exercise intolerance or poor performance, or as part of a prepurchase examination. Unless a high-speed treadmill is available, the exercise testing should be completed under saddle with a competent rider, preferably with an intensity of work that matches the horse's normal activity.[70,83] It is less satisfactory but often necessary to work the horse on a lunge line, in which case it should be lunged in both directions.[83]

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

A satisfactory exercise test should include at least 5 minutes of work at the canter, after which the horse should immediately be brought over to the observer so that the character and sequence of abnormal sounds that persist can be determined. All horses that have been worked adequately make a loud expiratory blowing sound at this time. Turbulence of airflow in the larynx may be audible with a stethoscope.[84] Inducing adduction of the vocal fold, particularly on the right side, by application of gentle pressure in a rostromedial direction to the muscular process of the arytenoid cartilage often accentuates an inspiratory noise in horses with laryngeal hemiplegia. Noises originating from unilateral lesions in the nasal passages are easily localized because the sound can be eliminated by alternately blocking off airflow through each nostril with the hand. Temporary occlusion of both nostrils simultaneously may provoke laryngopalatal dislocation and a loud gurgling sound in a susceptible horse.[83,84] The presence of nasal discharge or blood at the nostrils should be noted, and the time required for the heart and respiratory rates to return to preexercise values should be interpreted in light of the severity of the exercise test.[83]

INTERPRETATION OF ABNORMAL SOUNDS. A normal horse makes no audible respiratory sound at rest and when exercised at a canter or slow gallop makes only a blowing expiratory sound.[70,83,84] In unfit horses, particularly overweight ones, an inspiratory sound is also frequently audible. This sound can be quite loud, and it may be difficult to differentiate from sounds caused by abnormalities of the respiratory tract.[82,83] Thus evaluation of the horse's "wind" is best carried out when the horse is in fit condition for its intended use. It

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BOX 5-18

Causes of Stridor in Horses

Common Causes

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

Less Common Causes

Arytenoid chondroma, chondropathy
Pharyngeal paresis
Botulism, shaker foal
Dynamic collapse of the pharynx
Subepiglottal, pharyngeal cyst
Subepiglottal abscess
Epiglottal retroversion
Guttural pouch tympany
Guttural pouch neoplasia
Rostral displacement of the palatopharyngeal arch
Nasal fungal infection (e.g., aspergillosis, rhinophycomycosis)
Nasal polyp
Nasal foreign body
Nasal trauma
Nasal tumor
Nasopharyngeal cicatrix
Progressive ethmoidal hematoma
Sinusitis (sinus empyema)
Sinus cyst
Sinus tumor
Atheroma
Laryngeal trauma
Tracheal collapse (scabbard trachea)
Tracheal stricture, stenosis
Tracheal chondroma
Tracheal rupture, perforation
Stenotic nares
Laryngeal edema
Purpura hemorrhagica
Anaphylaxis or acute drug reaction
Chronic lead poisoning
Choanal (posterior nares) atresia, hypoplasia (foals)
Fracture of laryngeal cartilages
Laryngeal granuloma, scar tissue
Equine influenza
Exercise-induced pulmonary hemorrhage (EIPH)
Jugular thrombosis
Hyperkalemic periodic paralysis (HYPP)

Uncommon Causes

Amyloidosis (cutaneous, nasal)
Lymphosarcoma, lymphoma
Bee or wasp sting
Snakebite
Thyroid adenoma, adenocarcinoma
Vesicular stomatitis
Retrobulbar neoplasia
Dystrophic myodegeneration (white muscle disease)
Neoplasia (oral, mandibular, maxillary, laryngeal, pharyngeal, tracheal)
Coccidioidomycosis
Inhalation pneumonia, smoke inhalation
Burns (thermal, chemical)
Congestive cardiac failure
Cutaneous habronemiasis
Unilateral ventral displacement of the roof of the nasopharynx
Epiglottiditis
Hyoid bone injuries
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, cryptococcal rhinitis, equine nasal granuloma
Goiter
Hypertrophic ossification of the laryngeal cartilages
Abnormalities of the nasal septum
Intramural esophageal cyst
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Hyperparathyroidism
Phycomycosis, pythiosis
Anaerobic abscesses (e.g., *Clostridium perfringens*)
Besnoitiosis, globidiosis (exotic)
Glanders (exotic)

Toxic Causes

Organophosphate-induced laryngeal paralysis
Lead-induced laryngeal paresis
Reserpine

takes at least 1 month for an older horse that has been turned out to pasture to regain a satisfactory level of fitness to perform a meaningful wind examination. Many normal horses produce a harsh expiratory "high blowing sound" of variable pitch, which results from resonance in the cavity of the false nostril during expiration.[83,84,90] If the source of the stridor remains in doubt, temporary suturing of the alar fold dorsal to the nostril can help localize noises suspected of being caused by vibration of the alar fold.

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

The sounds generated by horses with laryngeal chondritis, severe proliferative pharyngeal lymphoid hyperplasia, epiglottic entrapment, and tracheal stenosis can be similar to those caused by ILH.[83,84] Laryngopalatal dislocation (dorsal displacement of the soft palate) gives rise to a transient, vibrant, gurgling sound.[69,83,84] In many instances a severe exercise test is required to induce this condition; thus this sound may be heard only during a race.[70,83,84] It is thought that the condition may occur when pharyngeal stimulation causes swallowing during fast exercise.[84] Instead of the horse completing the process and regaining the laryngopalatal seal consistent with the respiratory position of the larynx in the nasopharynx, the tip of the epiglottis disengages from the rostroventral aspect of the palatopharyngeal ring (the caudal free border of the soft palate), resulting in the entire epiglottis slipping ventral to the soft palate. At the subsequent inspiration the palatopharyngeal arch tends to be drawn into the rima glottis, and at expiration it is driven toward the roof of the pharynx by the air stream. The palatopharyngeal arch acts as an airway obstruction, and the tissue vibration and resulting turbulence

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BOX 5-19

Causes of Stridor in Ruminants

Common Causes

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

Less Common Causes

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

Uncommon Causes

Tuberculosis (B)
Congenital cystic nasal conchae (B)
Choanal atresia (O)
Salivary cyst, mucocele, ranula, trauma (C)
Photosensitization in Southdown and Corriedale sheep (O)
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma (B, C)
Phycomycosis, pythiosis (B)
Goiter, iodine deficiency
Hyperparathyroidism (B, C)
Enzootic ataxia, swayback (C, O)
Besnoitiosis, globidiosis (exotic)
Endemic ethmoid hematoma (exotic) (B)
African bovine malignant catarrhal fever (exotic) (B)
Lumpy skin disease (exotic) (B)
Nasal schistosomiasis (exotic)
Virulent sheep and goat pox (exotic) (C, O)
Peste des petits ruminants (exotic) (C, O)
Gedoelstia hasleri nasal bots (exotic) (C, O)

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

generate a sound of varying pitch and intensity, often described as gurgling followed by swallowing.[84] The horse often slows suddenly or stops when this event occurs, and the jockey often reports that the horse stopped after "choking" or "swallowing its tongue." If repeated swallowing is successful in relocating the normal laryngopalatal respiratory arrangement, the horse often continues to race after slowing or stopping.[70]

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

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

Interpretation of stridor in yearlings presented for sale is difficult because these animals are rarely fit and it is usually possible to exercise them only at a canter on a lunge line. It has been shown that resentment of restraint under such circumstances can significantly alter the linking of locomotion and respiration, which complicates recognition of the respiratory phasing of noise production.[86] In addition, there is not always a close correlation between noise production, endoscopically visible abnormalities, and signs of exercise intolerance even in fit adult horses.[70,83]

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

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

Interpretation of the findings of the endoscopic examination of the pharynx and larynx is by no means straightforward. The results can be influenced by the day the examination was done, the use of sedation, the side through which the endoscope was passed, and the observer's interpretation.[101] The appearance of laryngeal symmetry or asymmetry in resting horses varies considerably and therefore is of limited clinical usefulness unless complete hemiparalysis is present. Many horses have asynchronous or asymmetric laryngeal movement at rest but not during exercise, whereas other horses have a normal-appearing larynx at rest but suffer dynamic collapse during exercise. Interpretation of findings is improved by use of an objective grading system, which includes assessment of the ratio of the areas of the left and right half of the rima glottis and by correlating findings at rest with those observed on video endoscopy performed during maximal exercise.[93] For evaluation of the larynx at rest, full abduction of the vocal folds should be induced by exercise or by temporary occlusion of the nostrils.[83] Contralateral adductory laryngeal movement should be stimulated by slapping the horse just behind the withers (slap test).[94] To induce the horse to swallow, the tip of the epiglottis should be touched with the endoscope, or water should be flushed through the endoscope. These maneuvers help to establish whether movement of the arytenoid cartilages is synchronous and symmetric and

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increase the predictive value of endoscopic observations, allowing laryngeal function to be graded as follows.[93]

- Grade 1: Synchronous, full adduction and abduction of the left and right arytenoid cartilages (considered normal).
- Grade 2: Asynchronous movement such as hesitation, fluttering, or adductor weakness of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction of the left arytenoid cartilage, inducible by nasal occlusion or swallowing. Grade 2 findings are considered a normal variation and are not usually associated with dynamic airway collapse during exercise.
- Grade 3: Asynchronous movement of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction is not inducible by nasal occlusion or induction of swallowing. The true functional significance of grade 3 findings can be determined only by performing endoscopic examination during maximal exercise, a procedure that has led to subclassification of grade 3 findings.[95] Some grade 3 horses (grade 3A) are able to achieve full abduction during exercise, whereas others maintain a partly abducted position similar to the resting position (grade 3B) or experience dynamic collapse (grade 3C).[95]
- Grade 4: Marked asymmetry of the larynx at rest and no substantial movement of the left arytenoid cartilage during any phase of respiration. These horses have complete left laryngeal hemiplegia, are true "roarers," and consistently experience dynamic collapse on inspiration during strenuous exercise.[93]

Performing an endoscopic examination during exercise over ground or on a high-speed treadmill makes it possible for a stationary observer to gain a good dynamic appreciation of the significance of upper airway abnormalities (i.e., dynamic endoscopy)[95-99] (see Exercise Intolerance and Poor Performance in Horses, p. 70). Dynamic changes in airway lumen diameter occur quickly during treadmill endoscopy and may be difficult to visualize; therefore the endoscopic examination should be videotaped for later playback in slow motion and freeze-frame.[99] Racehorses should be exercised maximally and to exhaustion because some abnormalities are apparent only at maximal exercise toward the end of a race when pharyngeal or laryngeal muscles become fatigued and are no longer able to resist the transmural pressure gradient, which tends to induce dynamic collapse of the upper airway during inspiration.[95-99] Endoscopic identification of an upper respiratory tract abnormality in a resting horse does not necessarily mean that it is inducing a problem during exercise, and, conversely, the absence of an upper respiratory tract abnormality at rest does not rule out the possibility of intermittent airway obstruction during strenuous exercise. For example, dorsal displacement of the soft palate, epiglottic entrapment, dorsal displacement of the epiglottis, dynamic collapse of the left arytenoid cartilage or vocal fold (or both), and unilateral or bilateral ventral displacement of the roof of the pharynx (dynamic pharyngeal collapse) have been observed during treadmill exercise in horses with an endoscopically normal upper airway at rest.[95-99]

RADIOGRAPHIC EXAMINATION. Radiographic examination of the nasal passages, paranasal sinuses, pharynx, retropharyngeal area (including guttural pouches), larynx, and proximal trachea is indicated to confirm anatomic or functional problems or space-occupying lesions not definitively diagnosed by clinical examination and endoscopy (see Nasal Discharge, p. 48, and Respiratory Distress, p. 56). Radiography is particularly useful for visualizing subepiglottic masses such as cysts or abscesses and for evaluating the epiglottis of the horse when it is obscured from endoscopic view by dorsal displacement of the soft palate or other space-occupying lesions. An accurate assessment of epiglottic length can also be made from standardized true lateral radiographs of the larynx by measuring the distance from the body of the thyroid cartilage to the tip of the epiglottis (thyroepiglottic length).[100] The mean ± SD (standard deviation) thyroepiglottic length in normal Thoroughbreds is reported to be 8.76 ± 0.44 cm.[100] Significantly shortened thyroepiglottic lengths have been recorded in Thoroughbreds with dorsal displacement of the soft palate (laryngopalatal dislocation) and in those with entrapment of the epiglottis in the aryepiglottic folds.[100] Tracheal diseases such as chondroma or dynamic collapse may be visualized on radiographs of the trachea, particularly those made during the inspiratory phase.

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

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

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

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

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

Exercise Intolerance and Poor Performance in Horses

Stephanie J. Valberg • W. David Wilson

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

Exercise Responses

As horses accelerate during exercise, motor units within active muscles fire in a coordinated fashion to produce the power necessary to drive the animal forward. Initially, slow-twitch type 1 muscle fibers are recruited, followed at increasing speed by recruitment of oxidative fast-twitch type 2A fibers and finally the fastest and most powerful muscle fibers, type 2B (also called *2X*). The increased demand for adenosine triphosphate (ATP) to support muscle contractions during exercise can be met initially by small intracellular stores of creatine

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phosphate, but within seconds oxidative or glycolytic metabolism (or both) is activated. At submaximal speeds the major factors contributing to fatigue are motivation, total depletion of fuel reserves (glycogen), fluid and electrolyte losses, and hyperthermia.[101] Nociceptive input from muscle receptors to the brain may be a primary motivator to discontinue exercise in many horses, as in people.[102] Training increases the oxidative and endurance capacity of skeletal muscle by increasing the volume of mitochondria and the capillary density surrounding muscle fibers.[103] This delays the onset of fatigue by increasing the availability and metabolism of plasma free fatty acids and glucose, thus sparing muscle glycogen. Training also fine-tunes the motor unit recruitment pattern to provide the most efficient and coordinated pattern of movement.

When a horse accelerates toward a maximum speed, a peak in the total amount of oxygen consumed is realized (VO_{2max}). Additional energy to produce speeds beyond VO_{2max} must be supplied by anaerobic glycolysis with lactic acidosis as a consequence. The term *anaerobic threshold* has been used to describe the speed at which this exponential rise in lactate begins to occur. Fatigue with maximum (fast) exercise occurs when muscle pH falls so low that glycolysis and excitation contraction coupling are inhibited and muscle ATP concentrations fall.[104,105] Muscle [ATP] begins to decrease after muscle lactate exceeds 40 to 80 mmol/kg of dry muscle and muscle pH falls below 6.8. Muscle glycogen stores are not a limiting factor with maximum exercise.[106] Training over time increases the mitochondrial volume and the ratio of type 2A to type 2B muscle fibers.[103,107] As a result, the onset of anaerobic metabolism is delayed until a higher speed is reached and horses are able to maintain a higher speed over a given distance.

The cardiovascular system plays a central role in the oxygenation of blood by the lungs, in the delivery of oxygen and other energy substrates to exercising muscles, and in the removal of metabolic products from those muscles. Cardiac output increases with exercise in horses, largely as a function of an increase in heart rate.[108] As exercise begins, the heart rate quickly increases and then reaches a steady state within minutes at a submaximal speed. With increasing exercise intensity the heart rate shows a linear relationship with speed up to a maximum rate of 210 to 230 beats/min. The mean systemic arterial pressure does not change with submaximal exercise but rises with maximum exercise. Mean pulmonary arterial pressures increase with speed as the heart rate increases, reaching remarkably high levels that are four times resting values.[109] The oxygen-carrying capacity of the blood also rises with increasing speed through splenic contraction and a more than 50% increase in blood hemoglobin.[110] The increase in blood viscosity that occurs with splenic contraction is believed to contribute to the increase in blood pressure with exercise. Among the adaptive cardiovascular responses to training are a lowered heart rate and blood pressure at the same exercise intensity[11]; increased red cell volume[92]; and increased capillarization of muscle.[103]

After an initial abrupt rise, the respiratory rate increases linearly with the speed of trotting until, at a canter or gallop, respiration is linked to stride frequency on a 1:1 basis.[87,89] This leaves less time available for completing a respiratory cycle at faster speeds. To counter this, inspiratory and expiratory airflow velocities must increase to maintain or increase minute volume. As airflow rates increase, increased turbulence and an increased tendency for dynamic narrowing of the airways causes an increased resistance to flow and increases the work (energy cost) of breathing.[70,81] A finite maximum flow rate is eventually achieved, beyond which the expiratory muscles and the physical characteristics of the respiratory tract do not permit further increases in flow rate.[81] In addition, a maximum stride frequency is reached, restricting the maximum respiratory rate to 140 to 150 breaths/min.[87,89] It has been suggested that beyond the finite maximum flow rate, the animal is forced to hypoventilate, which may result in arterial hypoxemia during fast exercise.[112] The limitation placed on oxygen diffusion by blood hyperviscosity and the short transit time of blood through the pulmonary capillary bed at rapid heart rates also likely contribute to arterial hypoxemia.[113] The arterial hypoxemia and incomplete saturation of hemoglobin that occur during strenuous exercise do not necessarily limit delivery of oxygen to the tissues, however, because the decline in blood oxygen tension is offset by the increase in the total blood hemoglobin oxygen content resulting from splenic contraction. This fact and the horse's ability to sustain at least a sixfold increase in cardiac output between rest and the point of maximum oxygen uptake (VO_{2max})[114] are the major factors that contribute to the enormous aerobic capacity of the horse.

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

Approach to Diagnosis of Exercise Intolerance and Poor Performance

Top athletes arise from both a genetic background that emphasizes athletic ability and environmental influences that capitalize on this inherent potential. A coordinated, energy-efficient gait, muscular power and endurance, a large capacity for oxygen transport, and several intangible factors such as the horse's mental toughness and competitive spirit and the rider's skill all contribute to successful performance. *Poor performance* most often results from inadequate training, a lack of genetic potential, or both or from a congenital or acquired dysfunction of the locomotor, cardiovascular, or respiratory systems. The term *exercise intolerance* is often used to describe this inability to perform up to an expected or previously attained intensity of exercise.

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

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

CLINICAL EXAMINATION. Overt clinical diseases that cause exercise intolerance at moderate speeds usually can be diagnosed with a good history, physical examination, and selected ancillary diagnostic techniques. The diagnostic procedures and specific diseases that can be identified at rest are detailed in subsequent chapters in this book (particularly Chapters 30, 31, 37, 38, 41, and 42).

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Problems that are subclinical at rest provide a greater diagnostic challenge. When testing procedures at rest fail to identify the cause of exercise intolerance, various types of ancillary diagnostic procedures including exercise tests may be used to further define the problem. Because the respiratory, cardiovascular, musculoskeletal, and hematopoietic systems are all important for competitive performance and because diseases in these systems are the most likely causes of exercise intolerance, these systems should receive particular attention in the detailed clinical examination of the horse at rest.

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

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

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

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

EVALUATION OF THE RESPIRATORY TRACT. Standard parameters of a routine examination including rectal temperature, respiratory rate, respiratory character, mucous membrane color, and capillary refill time should be carefully evaluated at rest. The presence of nasal discharge, cough, edema, jugular distention or pulsation, or other signs suggesting local or systemic disease should be noted. The larynx, muscular process of the arytenoid cartilages, retropharyngeal area, and trachea should be palpated for size and symmetry. The heart and lungs should be carefully auscultated and percussed at rest, and auscultation of the lungs should be repeated as the horse is induced to breathe more deeply by application of a rebreathing bag. When stridor is part of the history, the upper respiratory tract should receive particular attention in the diagnostic evaluation. Not only must the character of the noise be determined, but the extent of work the patient can tolerate before exhibiting diminished performance must be established, because this helps in the interpretation of abnormalities seen on the endoscopic examination (see Stridor, p. 66). Often the onset and intensity of the stridor coincide with a decrease in work capacity that is typical of certain obstructive airway diseases. Endoscopy, including treadmill endoscopy if facilities permit, and radiography form an important part of the diagnostic evaluation of horses with upper airway abnormalities[122] (see Respiratory Distress, p. 56, and Stridor, p. 66). The most common abnormalities of the upper airway that cause poor performance include dorsal displacement of the soft palate, dynamic pharyngeal collapse, dynamic collapse of the left arytenoid cartilage in association with ILH, epiglottic entrapment, pharyngitis, and collapse of the alar folds.[97,99] Diminished performance in horses with mild or subclinical viral infection is probably mediated at least partly by abnormalities in the respiratory tract.[123] If no abnormalities are detected at rest, functional disturbances of airflow may occur during maximum exercise, and these disorders can best be identified by examining the upper airway using video endoscopy either on a treadmill during exercise or using over-the-ground video endoscopy units. Slow-motion playback must be used because many abnormalities occur rapidly with each respiratory cycle. In particular, dorsal displacement of the soft palate and the extent of dynamic laryngeal obstruction with ILH can be more fully evaluated with videoendoscopy during exercise.[97,99,122,124] Over-the-ground videoendoscopy has the distinct advantage of allowing the horses to be examined under the exact conditions under which the problem occurs. The presence of inspiratory or expiratory obstruction can be further evaluated during treadmill exercise by introducing transducers via the nostrils to measure airway pressures at the level of the pharynx and trachea.[99,122] During a treadmill exercise test, samples for blood gas analysis can be drawn from extension tubing connected to an 18-gauge, 2-inch catheter inserted into the transverse facial artery.

Further diagnostic evaluation of the lower airways is indicated in horses with an abnormal respiratory rate or character, cough, nasal discharge, abnormal lung sounds, prolonged recovery after application of a rebreathing bag, or a history of EIPH, cough, or respiratory distress with exercise. Horses in which excess mucus or exudate can be demonstrated in the trachea during endoscopy performed after exercise are also candidates for further evaluation. Applicable tests include a complete blood count, tracheal wash or BAL, endoscopy, radiography, and ultrasound examination (see Cough, p. 40, and Stridor, p. 66). Tracheal wash samples collected after exercise are more likely to identify lower airway disease than those collected before exercise.[125] Respiratory viral infection, EIPH, bronchiolitis, hyperreactive airways, and RAO are all conditions that may not be apparent at rest but that constitute significant causes of exercise intolerance.

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EVALUATION OF THE CARDIOVASCULAR SYSTEM. A full evaluation of the mucous membranes, capillary refill time, pulse rate, pulse character and rhythm, heart rate and rhythm, and auscultatory findings is an important part of the evaluation of the performance horse. Failure to maintain cardiac output because of an inability to regulate either heart rate or stroke volume is the mechanism through which cardiac diseases induce exercise intolerance. Many cardiac dysrhythmias and valvular dysfunctions are readily apparent on auscultation of the resting horse. However, the contribution of mild abnormalities to exercise intolerance may require exercise testing. In addition, some arrhythmias and valvular or myocardial dysfunctions can be detected only during or shortly after exercise. Thus resting and exercising electrocardiography and echocardiography before and immediately after exercise are indicated.[99,122] The heart rate can be monitored during exercise using either telemetric electrocardiography or commercial heart rate monitors. Electrocardiograms (ECGs) provide the additional benefit of evaluating both heart rate and rhythm. Supraventricular tachyarrhythmias, the most important of which is atrial fibrillation (AF) in horses, can lead to heart rates exceeding 240 beats/min at submaximal exercise.[126] Under these circumstances, cardiac output may be limited by the decreased time available for diastolic perfusion of the myocardium; the absence of atrial contraction; and the reduced time for passive ventricular filling, leading to reduced stroke volume. Many horses with AF maintain efficient circulation at rest and during light exercise but are intolerant to strenuous exercise because they are unable to increase cardiac output sufficiently at rapid heart rates.[127] Some horses show transient paroxysmal AF during exercise but not at rest.[127] These are often easiest to observe in ECG tracings obtained within 60 seconds after an exercise test. Conversion to sinus rhythm, either spontaneously with quinidine sulfate or with electroconversion,[128] usually leads to a return to normal performance in horses with AF.[129,130] The ability to maintain cardiac output can be compromised by other cardiac arrhythmias such as ventricular tachycardia and ventricular premature depolarization.[99,131] The frequency of premature depolarization can increase with exercise, and the timing of resultant abnormal extra systoles can reduce cardiac output even at submaximal heart rates.[131] Intraatrial block, second-degree atrioventricular (AV) block, and intraventricular block have also been documented in exercise-intolerant, poorly performing horses.[132,133] Horses with cardiac arrhythmias may show abnormal elevations in lactate concentration in response to exercise, indicating a lowered anaerobic threshold, which contributes to exercise intolerance.[111]

Electrocardiography is believed by some veterinarians to be of value in identifying myocarditis. T wave abnormalities (positive and peaked T waves, in contrast to the normal diphasic T waves) in multiple leads on resting ECG traces have been found in a high percentage of horses with a history of fading during the final portion of a race.[132] T waves are highly labile, affected by training status, and the mechanism by which abnormal T waves are generated is uncertain. However, T wave changes have been identified in some horses with myocarditis confirmed at necropsy.[119,133,134] Myocarditis may be more definitively documented by evaluating cardiac troponin I.[135] A positive correlation has been demonstrated between heart size and racing performance.[133] Electrocardiography has been used to assess performance potential by heart score measurement. The heart score represents the mean QRS duration in leads 1, 2, and 3 expressed in milliseconds and has been strongly correlated with heart weight and prize money won by racehorses.[119,133] The physiologic basis for heart score remains in dispute, and expertise is required to standardize leads and measure QRS complexes.

An *echocardiogram* provides essential information in many cases in which clinical evidence of valvular or myocardial dysfunction is present. The pericardium, the size of the heart chambers, the presence of congenital defects, the function of valvular leaflets, and myocardial contractility all can be assessed (see Chapter 30). Decreased myocardial contractility, regurgitant leaks caused by valvular incompetence, left-to-right shunts, and increases in afterload such as occur in aortic stenosis result in systolic dysfunction and a drop in cardiac output.[136] A pulsed, continuous, or color flow Doppler technique may be necessary to determine the size and significance of any disturbances to flow. Cardiac conditions such as effusive pericarditis and myocardial fibrosis and peripheral vascular conditions that inhibit venous return may interfere with ventricular filling during diastole, resulting in decreased end-diastolic volume, stroke volume, and cardiac output.[136] Measurement of fractional shortening before and immediately after treadmill exercise, when pulse rates are above 100 beats/min, permits documentation of resting and exercise-induced myocardial dysfunction.[99] Contrast angiographic studies may be indicated if congenital or acquired cardiac outflow problems are suspected. Nuclear angiocardiography is also useful for evaluating myocardial contractility, cardiac chamber enlargement, outflow problems, and other abnormalities. Hemodynamic studies, which measure pulmonary capillary wedge pressure, pulmonary driving pressure, and pressure in the right side of the heart and pulmonary artery, have proven useful in detecting early cardiac and pulmonary failure in poorly performing trotting horses. These studies involve the introduction of flow directional balloon-tipped catheters through the jugular vein into awake horses.[137]

EVALUATION OF THE SKELETAL SYSTEM. A lameness examination including appropriate flexion tests and other stress tests should be completed to help rule out musculoskeletal problems. If lameness is observed, appropriate diagnostic nerve blocks, radiographs, scintigraphy, rectal examination of the bony pelvis and aortoiliofemoral arterial pulses, or ultrasound examinations are indicated to help localize the lameness and determine its cause, significance, and prognosis. Some lameness problems that are evident only at high speed may best be evaluated using treadmill exercise. For example, aortoiliofemoral thrombosis reduces peripheral perfusion but often causes only progressive hindlimb lameness with exercise. Foot balance should be carefully assessed at rest and, if possible, during exercise, because gait changes and subtle lameness related to foot imbalance can adversely affect performance. Dynamic evaluation of hoof balance can be accomplished by examining videotapes recorded from behind the horse while it is exercising on a high-speed treadmill or by trotting the horse over force plates embedded in a firm level surface.[138]

Subtle lameness can increase the metabolic cost of locomotion by inducing changes in gait and coordination, which accelerate the onset of fatigue. In the same fashion, some horses may have an inefficient gait that reduces their performance capacity. Video imaging systems and gait analysis may play an increasingly important role in identifying these individuals in the future.

EVALUATION OF THE MUSCULAR SYSTEM. Primary skeletal muscular limitations on performance may occur as the result of painful conditions such as exertional rhabdomyolysis or weakness due to defects in energy generation or loss of muscle mass. In resting samples high serum AST may indicate chronic rhabdomyolysis. Measurement of serum CK 4 to 6 hours after an exercise test is most useful in detecting horses with chronic or subclinical forms of exertional rhabdomyolysis. Serum muscle enzyme concentrations measured in blood samples collected immediately after exercise are often normal, but in horses with chronic exertional rhabdomyolysis significant abnormal elevations may be seen when CK peaks at 4 to 6 hours after completion of exercise. In the past it has been recommended that the exercise test be conducted at a speed and duration of exercise similar to that expected of the horse in competition. However, it has been shown that a 15- to 30-minute test at a slow trot more frequently produces abnormal elevations in serum CK (more than twofold to threefold) in susceptible horses.[139] Standardbreds and Thoroughbreds with histories of recent episodes of recurrent exertional rhabdomyolysis and horses with type 1 polysaccharide storage myopathy (PSSM) often show a greater than twofold increase over normal resting values in response to an exercise test.[139] Horses with type 2 PSSM may show exercise intolerance after 10 to 15 minutes under

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saddle, reluctance to pick up and maintain a canter, or an inability to collect and maintain self-carriage under saddle.

Muscle biopsy is a relatively simple procedure that can prove useful for characterizing the nature of an identified exertional myopathy. However, the procedure is not widely used in the diagnostic assessment of poor performance because the evaluation of samples requires considerable histochemical expertise. Percutaneous techniques using a 6-mm–diameter needle (Bergstrom biopsy needle, Mortenson, Copenhagen, Denmark) and local anesthetic are routinely used. The middle gluteal muscle is most often sampled because it is relatively accessible and active at all intensities of exercise.[103,107,140] In adult horses a biopsy is collected at a depth of 2½ to 3 inches from a site 8 inches from the tuber coxae along a straight line connecting the point of the tuber coxae with the base of the tail. Open surgical biopsies are most easily obtained from the semimembranosus or semitendinosus muscle at a site approximately 3 inches below the tuber ischii. After the skin has been shaved and aseptically prepared, lidocaine is injected under the skin. A 2-inch–long incision is made through the skin and fascia, and two parallel incisions, 1 inch long and ½ inch apart, are made vertically in the muscle. The muscle is grasped in one place, to prevent handling artifacts, and the biopsy is first transected proximally, freed to a depth of ¼ inch, and then transected distally. The disadvantage of open surgical biopsies is the recovery period of 1 week that is often required, whereas when the needle biopsy is used horses can immediately begin to exercise. Muscle samples should be sent to a laboratory, where they will be frozen in isopentane that has first been chilled in liquid nitrogen. Commonly used histologic and histochemical stains include adenosine triphosphatase (ATPase) after alkaline and acid preincubations, nicotinamide dinucleotide diaphorase (NADH), periodic acid–Schiff (PAS), and hematoxylin and eosin.

An estimate of the state of training can be made by determining the percentage of type 1, type 2A, and type 2B (or type 2X) muscle fibers, as well as the oxidative capacity of skeletal muscle in these small muscle samples. In general, horses suited for short-distance, fast exercise have a greater proportion of fast-twitch fibers in the middle gluteal muscles than horses suited for longer distance events, which have a higher proportion of slow-twitch type 1 fibers.[140] However, there are many successful athletes that do not follow this pattern. The proportion of type 1 to type 2 fibers is thought to be genetically based and cannot be manipulated to a great extent by training, whereas age and training increase the proportion of oxidative fast-twitch type 2A fibers relative to type 2B fibers.[103,107,139] Histochemical assessment of NADH staining or quantitative measurement of enzymes such as citrate synthase in biopsy samples frozen rapidly in liquid nitrogen may provide a guide to the state of aerobic fitness.[136] The use of muscle biopsies in horses with poor performance has also aided in the identification of oxidative enzyme defects in Arabian horses and glycogen storage disorders in Quarter Horses that can markedly affect performance.[140,141]

Standardized Exercise Testing

Exercise intolerance is ultimately a neuromuscular phenomenon resulting from extreme metabolic stress at the level of the muscle fibers.[104] Under many circumstances premature muscle fatigue occurs secondary to disorders that affect oxygen transport (cardiopulmonary systems) or mechanical efficiency (lameness) (Box 5-20). Standardized treadmill exercise tests are often required to assess the function of these systems at high speeds to determine the primary cause of poor performance and to measure the metabolic response of skeletal muscle relative to work intensity. In a substantial number of cases, poor performance results from related or unrelated disorders in more than one body system, such as dynamic airway obstruction and cardiac dysrhythmia in the same horse.[99]

TREADMILL TESTS. Horses often need to be acclimated to a treadmill before representative exercise testing can be performed. Standardbred horses are typically exercised while wearing their usual racing tack, whereas horses of other breeds are typically exercised in a halter or bridle with a lead rope attached to each side. Most horses exercise comfortably on a treadmill after two to four training sessions at speeds that include all gaits to be tested. Breaking into a canter is an important skill to train horses to perform on the treadmill. During one of the training sessions, endoscopy of the upper airway can be performed to evaluate upper airway function during maximal speeds. Two types of standardized exercise tests can be used: a high-speed test, in which horses are accelerated to maximal speed for their normal racing distance, or an incremental test, in which speed is increased every 1 or 2 minutes until fatigue is reached. The incremental exercise test is used most commonly because it includes both submaximal and maximal intensities and is readily reproducible. Many exercise tests are performed with the treadmill set at a 6% to 10% slope to minimize the possibility of injury at top speeds and to ensure that maximum exercise intensity is reached.

Several measurements are possible during treadmill exercise testing. In its simplest form, the heart rate can be monitored after 1 minute at each intensity of exercise using a heart rate monitor, although recording of an ECG during exercise provides additional information about exercise-associated dysrhythmias.[99] Blood samples can also be drawn from a jugular catheter during the final 15 seconds at each speed. A linear relationship between heart rate and speed is expected, with a plateau forming at the maximum heart rate. The maximum heart rate does not change with training, but the speed at which the maximum heart rate is reached should increase with training. As an alternative, a linear regression can be used to determine the horse's speed at a heart rate of 200 beats/min (V_{200}). V_{200} is close to the anaerobic threshold, may predict aerobic capacity, increases with increasing fitness, and has a high individual predictability that allows for early and valid detection of clinical disorders that limit performance.[111,119,142] The speed at which horses reach a maximum heart rate has been proposed as a better measure than V_{200} because it is an absolute rather than a relative measure; however, measurement of maximum heart rate requires a more strenuous exercise test. Parameters such as the velocity at which the whole blood lactate value reaches 4 mmol/L (V_{LA4}) and the heart rate at which blood lactate reaches 4 mmol/L (HR_{LA4}) can be calculated to evaluate the anaerobic threshold.[111,142] The rate of lactate accumulation may also provide valuable information.

Lactate concentrations can be determined in either whole blood or plasma. Recent studies suggest whole blood lactate may provide a more accurate reflection of lactate accumulation than plasma lactate[143] because red blood cells actively take up lactate and buffer it, and the type and number of red blood cell lactate transporters differ markedly among horses.

The value of V_{200}, V_{LA4}, HR_{LA4}, and other parameters is that they provide standards against which improvement or deterioration in fitness can be assessed and individual horses can be objectively compared.[111,119,142] Hematocrit can also be easily determined from blood samples obtained at each speed to provide a rough estimate of the number of circulating red blood cells. Blood samples drawn before and 4 hours after exercise for measurement of CK activity can be used to screen for subclinical exertional rhabdomyolysis.

Further evaluation of the oxygen transport system can be obtained in laboratories where the sophisticated open-flow gas-collection system necessary to measure oxygen consumption ($\dot{V}O_2$) is available. During the incremental exercise test, a plateau in oxygen consumption eventually is reached, representing maximum oxygen uptake. $\dot{V}O_2$ can be used at submaximal speeds to calculate the oxygen cost of locomotion, and $\dot{V}O_{2max}$, a key indicator of aerobic capacity, can be determined. The cardiopulmonary system can be further evaluated during exercise by measuring arterial blood gases from the transverse facial artery using an 18-gauge indwelling catheter.[142] An accurate measure of the total red blood cell volume in a horse can be determined using an Evans blue dye dilution technique immediately after maximal exercise.

FIELD TESTS. Standardization of field exercise tests is difficult because weather, track conditions, and other factors influence the

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BOX 5-20

Causes of Exercise Intolerance That Are Inapparent at Rest

Respiratory Causes

Obstructive Upper Airway Diseases

Common Causes

Laryngopalatal dislocation (dorsal displacement of the soft palate)
Dynamic pharyngeal collapse
Dynamic collapse of the left arytenoid cartilage in association with idiopathic laryngeal hemiplegia
Chronic pharyngeal lymphoid hyperplasia
Epiglottic entrapment
Axial deviation of the aryepiglottic folds
Arytenoid chondritis
Paranasal sinus empyema
Paranasal sinus cysts
Guttural pouch infection

Uncommon Causes

Dynamic collapse of the alar folds
Nasal polyps
Progressive ethmoid hematoma
Subepiglottic cysts
Epiglottic retroversion
Chondroma of the arytenoid cartilages
Fractured laryngeal cartilages
Nasopharyngeal cicatrix

Congenital

Choanal (posterior nares) atresia or stenosis
Excessive alar folds
Stenotic nares
Abnormalities of the nasal septum
Rostral displacement of the palatopharyngeal arch
Tracheal stenosis, stricture, collapse

Lower Airway Diseases

Common Causes

Inflammatory lower airway disease
Exercise-induced pulmonary hemorrhage (EIPH)
Recurrent airway obstruction (RAO or COPD)
Equine herpesvirus types 1 and 4 (EHV-1 and EHV-4)
Other viral infections (influenza, rhinitis A and B viruses, adenovirus, reovirus)
Bacterial pneumonia
Pleuropneumonia, pleuritis

Uncommon Causes

Pulmonary abscess
Pneumoconiosis (e.g., silicosis)
Interstitial pneumonia
Diaphragmatic hernia

Cardiovascular Causes

Common Causes

Atrial fibrillation
Ventricular premature contractions
Ventricular tachycardia
Mitral insufficiency
Aortic insufficiency
Resting or exercise-induced myocardial dysfunction and reduced fractional shortening
Pericarditis
Aortoiliofemoral arteriosclerosis or thrombosis

Uncommon Causes

Ventricular septal defects
Monensin toxicity
Heart block (intraatrial, second- and third-degree atrioventricular and intraventricular)
Endocarditis
Congestive cardiac failure
Ruptured chordae tendinea
Cor pulmonale
Congenital defects

Musculoskeletal Causes

Exertional rhabdomyolysis
Lameness involving limbs, sacroiliac joint, back
Focal muscle strain

Metabolic and Systemic Causes

Anemia
Fluid and electrolyte imbalances
Anhidrosis
Heat exhaustion
Neoplasia
Liver disease (pyrrolizidine alkaloid)

General Causes

Obesity
Poorly trained horse
Poor genetic potential
Administration of illicit medications (doping)

amount of work performed. The simplest form of exercise test involves timing a horse exercising maximally over a fixed distance and evaluating heart rate recovery rates at specific time points after exercise. Additional information can be obtained by measuring heart rate during exercise using a heart rate monitor or telemetric ECG.[119] As fitness improves, the heart rate for a given speed of exercise should be lower. Incremental field exercise tests have been used most successfully in Standardbred horses in which the heart rate and blood lactates were measured after several heats at predetermined increases in pace. At speeds above 450 m/min, lactate begins to accumulate in the blood during exercise; the precise kinetics of accumulation depends on the horse's fitness and exercise capacity. Fitness responses include a lower heart rate and lactate concentration for the same exercise speed. The value of these measurements is only as good as the standardization of the testing procedures used.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 6

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Alterations in Cardiovascular and Hemolymphatic Systems

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MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Peripheral Edema, Pleural Effusion, and Ascites

Edema is an abnormal accumulation of extracellular fluid in the interstitial spaces of the tissues or in body cavities that can be generalized or localized. If the fluid accumulation occurs in the pleural cavity, it is referred to as *pleural effusion* or *hydrothorax;* if the fluid accumulation is in the abdominal cavity, it is referred to as *peritoneal effusion* or *ascites*.

Fluid accumulates more easily in those parts of the body where the connective tissue structure is relatively loose. The accumulated fluid tends to gravitate to the dependent areas of the body. In the cow, generalized edema is detected externally by swelling of the submandibular tissue, the brisket, the ventral abdomen, and occasionally the limbs (Fig. 6-1). External manifestation of generalized edema in the horse is frequently in the pectoral region between the frontlimbs, along the ventral abdomen, in the prepuce in stallions and geldings (Fig. 6-2), in the limbs, and sometimes in the head. Stocking up, or limb edema restricted to the lower limbs, is commonly detected in stabled horses with no underlying disease. Large amounts of fluid may accumulate before clinical signs become evident. External evidence of pulmonary edema (i.e., a frothy, possibly blood-tinged fluid in the nares or expectorated) is rarely detected in large animals (Fig. 6-3). There are numerous causes of edema, including congestive heart failure (CHF) (Boxes 6-1 and 6-2). Edema is a late sign of CHF; other subtle signs of failure may be present before edema appears.

Mechanisms of Edema

Edema is caused by an alteration in the equilibrium between capillary permeability and the forces that govern fluid movements at the capillary level. These forces are as follows:

1. Intravascular hydrostatic pressure
2. Interstitial fluid hydrostatic pressure, which exerts a counterpressure to keep fluid within the capillary
3. Intravascular colloid oncotic pressure exerted by plasma proteins, which favors the resorption of interstitial fluid; the major determinant of colloid osmotic pressure in the capillary is albumin
4. Interstitial fluid colloid osmotic pressure exerted by some proteins in the interstitial fluid, which resists resorption of fluid from the interstitial space
5. Vascular surface area capable of fluid transport
6. Vascular permeability to proteins and water

Activation of complement and liberation of cytotoxic agents such as oxygen radicals, leukotrienes, hydrogen peroxide, platelet-activating factor, and lysosomal enzymes contribute to the endothelial and epithelial damage, causing permeability edema. Subsequent increase in colloid osmotic pressure causes fluid accumulation in the interstitial space. The most common causes of increased capillary permeability are trauma, infection, endotoxemia, and hypersensitivity (allergic) vasculitis. Topical administration of counterirritants can also cause local increase in capillary permeability. Equine purpura hemorrhagica, the most common vasculitic disease in horses, may in its mildest form have symptoms of mucosal petechiae and plaques of edema or, in severe cases, serum exudation from and necrosis of skin surfaces.

Increased hydrostatic pressure can cause either localized or generalized edema. In horses and ruminants the most common causes of increased hydrostatic pressure are CHF, venous thrombosis, liver disease causing obstruction of the portal venous system, lymphadenopathy, a cranial mediastinal mass, compression bandages, limb immobilization, and topical administration of counterirritants. CHF occurs when there is concomitant pulmonary and systemic vascular congestion. The compensatory salt and water retention increases ventricular diastolic, venous, and capillary pressures, which can result in the formation of generalized edema. Arteriolar vasodilation, caused by release of tissue mediators of inflammation or increased venous pressure resulting from obstruction to venous outflow, can also elevate capillary hydrostatic pressure and result in edema formation.

When the plasma protein concentration decreases from normal to values less than 5 g/dL or albumin concentration is less than 1.5 g/dL, generalized edema may occur. Hypoproteinemia can result from (1) decreased production of plasma proteins with starvation, liver disease, or severe heart failure, or (2) augmented loss of plasma

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proteins resulting from kidney disease, protein-losing enteropathies (Johne's disease, chronic inflammatory bowel disease), peritonitis, or pleuritis. Hemodilution as a result of overzealous administration of fluids or decreased elimination of fluid can cause edema. Failure to excrete adequate water to maintain fluid balance can result from decreased glomerular filtration as a result of kidney disease or heart failure.

Increased tissue colloid osmotic pressure is rarely a cause of edema in horses and ruminants. Interstitial fluid has a lower plasma protein concentration than plasma. When capillary permeability is increased or when abnormal protein-like material is present in the interstitial space, edema can develop by this mechanism. The latter may occur with infection or after administration of topical counterirritants.



FIG. 6-1 Cow with brisket, ventral, and udder edema.



FIG. 6-2 Gelding with ventral and preputial edema.

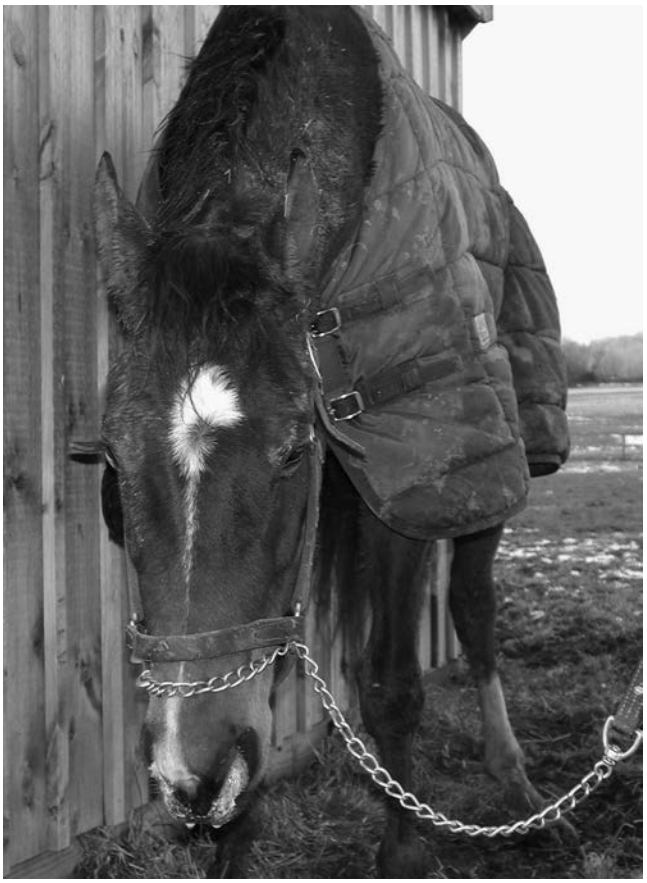


FIG. 6-3 Gelding with acute fulminant pulmonary edema.

BOX 6-1

Causes of Peripheral Edema, Pleural Effusion, and Ascites in Horses

Common Causes

Chronic heart failure
Mitral or tricuspid regurgitation
Aortic regurgitation
Vegetative endocarditis
Congenital heart defects
Cardiomyopathy
Vitamin E, selenium deficiency
Pericarditis
Pleuritis
Neoplasia: lymphosarcoma
Hypoproteinemia
Liver disease
Gastrointestinal malabsorption: inflammatory bowel disease, neoplasia, parasitism
Peritoneal or pleural effusion
Vasculitis
Equine infectious anemia
Purpura hemorrhagica
Equine granulocytic ehrlichiosis (*Anaplasma phagocytophilum*)
Equine viral arteritis
Thrombophlebitis
Lymphatic obstruction
Ulcerative lymphangitis
Lymphadenitis (*Corynebacterium pseudotuberculosis* abscesses)
Trauma

Uncommon Causes

Aortic cardiac fistula
Heart base tumor other than lymphosarcoma
Cranial mediastinal mass
Neoplasia: plasma cell myeloma, squamous cell carcinoma, fibrosarcoma
Starvation
Kidney disease: glomerulonephritis, amyloidosis
Ionophore toxicity
Copper deficiency
Counterirritant application
Hemodilution
Pregnancy
Ruptured bladder
Cassia occidentalis toxicity

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BOX 6-2

Causes of Peripheral Edema, Pleural Effusion, and Ascites in Ruminants

Common Causes

Chronic heart failure
Mitral or tricuspid regurgitation
Vegetative endocarditis
High-altitude disease (brisket disease)
Congenital heart defects
Cor pulmonale
Vitamin E, selenium deficiency
Pericarditis (traumatic reticulopericarditis)
Pleuritis
Heart base tumor: lymphosarcoma
Hypoproteinemia
Liver disease
Kidney disease: amyloidosis, glomerulonephritis
Gastrointestinal malabsorption: lymphosarcoma, Johne's disease, parasitism
Peritoneal or pleural effusion
Lymphatic obstruction (*Corynebacterium pseudotuberculosis*, lymphosarcoma)
Thrombophlebitis
Urolithiasis: ruptured urethra or bladder

Uncommon Causes

Eperythrozoon wenyoni (B)
Idiopathic pericardial effusion
Cardiomyopathy
Starvation
Hemodilution
Ionophore toxicity
Copper deficiency
Infectious myocarditis
Vasculitis
Trauma
Pregnancy
Caudal vena caval thrombosis
Anaplasmosis
Gossypol toxicity
Cassia occidentalis
Phalaris species toxicity
Oxytropis (locoweed) toxicity

B, Bovine.

Lymphedema occurs when lymphatics are absent or obstructed. Congenital absence of lymphatics is extremely rare. Obstruction to lymphatic drainage can be caused by tumor, local inflammation (lymphangitis or lymphadenitis), or elevated central venous pressure as in heart failure.

Approach to Diagnosis of Peripheral Edema, Pleural Effusion, and Ascites

1. Take history. Note especially history of deworming program, diet, and vitamin or mineral supplements. Determine onset, progression, and duration of the problem and whether other animals are affected. Ask about history of fever, signs of respiratory disease or difficulty, appetite, consistency of feces, and previous medications. Establish the function of the animal and whether there have been changes in performance capability. Compare growth and activity level to that of peers.
2. Perform a physical examination and record vital signs. Determine whether edema is localized or generalized. Palpate external lymph nodes. Palpate edematous areas to determine whether there is heat, pain, or fluid exudation. Edema is typically cool, nonpainful, and pitting, leaving an indentation when a finger is pushed against it. Carefully auscultate heart and lungs. Note abnormalities in cardiac rhythm, murmurs, or other sounds associated with the cardiac cycle. Palpate a peripheral pulse; observe mucous membranes for color, capillary refill time, and petechiae. Observe the jugular vein for distention and pulsations. Evaluate peripheral veins, including the mammary vein, for distention and pulsations. Perform a rectal examination to determine whether internal lymph nodes are enlarged. Palpate the aorta and iliac arteries for pulse strength and fremitus.
3. Obtain whole blood for the following:
   a. Complete blood count (CBC) (includes fibrinogen and plasma protein concentration)
   b. Selenium concentrations if cardiomyopathy is suspected
   c. *Anaplasma phagocytophilum* (formerly *Anaplasma equi* or *Ehrlichia equi*) morula in granulocytes or *Anaplasma* DNA by polymerase chain reaction if edema, petechial hemorrhages, fever, icterus, or muscle stiffness is present
4. Test serum or plasma for the following:
   a. Total protein and albumin concentrations; measure or calculate globulin fraction
   b. Tests for kidney function as follows: serum urea nitrogen (SUN) and creatinine concentrations, serum electrolyte (Ca, P, Na, K, Cl) concentrations, fractional excretion of electrolytes (see Chapter 34 for method), complete urinalysis; serum concentrations of Na may be decreased, and SUN may also be elevated in chronic heart failure
   c. Liver enzyme concentrations and liver function (aspartate aminotransferase [AST], sorbitol dehydrogenase [SDH], alkaline phosphatase, γ-glutamyltransferase [GGT], bilirubin, and bile acid concentrations); values may be elevated in CHF
   d. Check for antibodies to equine infectious anemia virus by agar gel immunodiffusion (AGID) or Coggins test
   e. Check for antibodies against *Streptococcus equi* M protein if signs are compatible with purpura hemorrhagica
   f. Determine titers to equine viral arteritis by serum neutralization if there is ocular inflammation, nasal discharge, abortion, or fever with edema
   g. *A. phagocytophilum* antibodies as demonstrated by immunofluorescence if physical examination reveals icterus and fever with edema
   h. Vitamin E levels if cardiomyopathy suspected
5. Perform two-dimensional (2D), M-mode, and Doppler echocardiography if there is a cardiac murmur that is not localized to the left heart base, that radiates, is greater than 2/6 intensity, or is of significant duration.
6. Analyze fluid to rule out peritonitis, pleuritis, and pericarditis; if physical examination and CBC findings are compatible, examine:
   a. Pleural fluid
   b. Pericardial fluid
   c. Peritoneal fluid
7. Isolate virus from nasopharyngeal swabs, buffy coat, or semen for equine viral arteritis if clinical signs are compatible.
8. Oral D-xylose or glucose absorption test should be done in horses if there is hypoproteinemia and if starvation, renal disease, hepatic disease, pleuritis, peritonitis, infectious gastrointestinal disease, and hemodilution have been ruled out; these tests are not useful in ruminants unless intraabomasal instillation of D-xylose or glucose is accomplished.

Cardiac Arrhythmias

Cardiac arrhythmias are abnormalities in the normal heart rate, rhythm, or conduction pattern. Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. In the normal heart the impulse is generated in the sinus node because it has the highest rate of spontaneous depolarization. Atrial contraction is followed shortly by ventricular contraction. There is variability in reported normal ranges for heart rate in the large adult animal species, but there is general acceptance of the following ranges:

- Horses: 26 to 50 beats/min; 60 to 80 beats/min in foals
- Cattle: 49 to 84 beats/min
- Sheep and goats: 70 to 90 beats/min

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Arrhythmias are more common in horses than in other domestic animal species. Up to 25% of horses that have no other signs of heart disease have cardiac arrhythmias during routine examination or electrocardiography.[1] During continuous 24-hour electrocardiography, 44% of normal horses had second-degree atrioventricular (AV) block, 10% had sinus arrhythmia, 3% had sinoatrial (SA) block, 27% had occasional supraventricular extrasystoles, and 15% had occasional ventricular arrhythmias.[2] Cardiac arrhythmias may be present in 40% of horses that have other signs of cardiac disease.[1] Unlike other species, the horse has arrhythmias at rest that are considered benign or functional. Benign, physiologic, or functional arrhythmias are usually bradyarrhythmias and are thought to be the result of increased vagal tone. These arrhythmias disappear at high heart rates (exercise or excitement) or with the administration of atropine (0.02 to 0.05 mg/kg subcutaneously [SC] or intramuscularly [IM]) or glycopyrrolate (0.003 to 0.006 mg/kg SC or IM). Some examples of benign or functional arrhythmias are as follows:

- Second-degree AV block
- Sinus arrhythmia
- Sinus bradycardia
- SA block
- SA arrest

Other arrhythmias are usually considered to be pathologic, even if there are no other overt signs of cardiac disease. Some examples of pathologic arrhythmias are:

- Atrial fibrillation
- Frequent atrial and ventricular premature depolarizations
- Supraventricular or ventricular tachycardia
- Advanced second-degree or third-degree (complete) AV block

The most effective method of identifying the specific arrhythmia is by performing an electrocardiogram (ECG). Arrhythmias that are transient or intermittent may not be detected with resting electrocardiography. Radiotelemetry or continuous 24-hour ECG recordings are useful to characterize the type, frequency, and severity of arrhythmias. Exercising electrocardiography may identify arrhythmias that are absent or clinically insignificant at rest but that may impair performance.

In general, cattle do not have benign arrhythmias like horses, but they are frequently found to have sinus bradycardia and sinus arrhythmia associated with lack of feed intake. These arrhythmias were previously thought to be abnormal and associated with vagal indigestion but have been shown to occur in normal cattle held off feed for 12 to 48 hours.[3] Cattle with gastrointestinal disease seem to have increased susceptibility to cardiac arrhythmias, especially atrial premature depolarizations and fibrillation. Although the reason for the susceptibility is not established, abnormal electrolyte concentrations, acid-base disturbances, and aberrations in autonomic nervous system balance have been proposed.[4,5] Sinus arrhythmia in goats is considered to be a benign arrhythmia and is present in many normal animals. Normal camelids also frequently have sinus arrhythmia.

Mechanisms of Cardiac Arrhythmias

Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. A variety of mechanisms can cause abnormal impulse generation or conduction (Boxes 6-3 and 6-4). Abnormal impulse generation occurs because of localized changes in ionic currents that flow across the membranes of single cells or groups of cells. Abnormal impulse generation can be seen as automaticity (normal and abnormal) or triggered activity.

Automaticity, the ability to initiate action potentials spontaneously, is a property of cells in the sinus node, some parts of the atria, the AV junction, and the His-Purkinje system. Cardiac disease can be responsible for the development of automaticity in cells that normally do not have this property. Normal automaticity develops when the membrane potential slowly falls (i.e., becomes less negative) during diastole. When the membrane reaches its threshold potential, an impulse is initiated. The most common clinical arrhythmias that are thought to be caused by the automaticity mechanism are sinus tachycardia and sinus bradycardia, which are the result of alterations in autonomic nervous system tone. Enhanced automaticity in another area of the heart that is capable of automaticity (spontaneous depolarization) may be responsible for atrial or ventricular premature beats. It is not clear what clinical arrhythmias are caused by triggered activity.

Under certain circumstances, conduction abnormalities allow a propagating impulse, which has already excited the heart, to persist and reexcite the atria or ventricles after the end of the refractory period. This can occur in an ordered or random fashion. Random reentry occurs over reentrant pathways that continuously change in size and location with time, whereas ordered reentry occurs over a relatively fixed reentrant pathway. Impulse propagation may be slow enough that reentrant circuits can be established in small areas of myocardium. In large animals the size of the myocardial circuit is large enough that relatively mild alterations in impulse propagation

BOX 6-3

Causes of Cardiac Arrhythmias in Horses

Common Causes

Excitement
Autonomic imbalance
Fever
Sepsis
Toxemia
Hypoxemia
Colic
Metabolic imbalance
Electrolyte abnormalities
Congenital defects
Myocarditis
Valvular disease

Uncommon Causes

Ionophore toxicity
Anesthesia
Other drugs
Pericarditis
Cardiomyopathy
Cardiac or heart base tumor
Aortic root rupture
Severe hemorrhage
Dynamic upper airway obstruction
Rattlesnake envenomation

BOX 6-4

Causes of Cardiac Arrhythmias in Ruminants

Common Causes

Gastrointestinal disease
Lymphosarcoma
Valvular heart disease
Myocardial diseases
Brisket disease
Pericarditis
Cor pulmonale caused by pulmonary hypertension
Excitement
Foot rot
Fever
Sepsis
Toxemia
Metabolic imbalance
Electrolyte abnormalities
Myocarditis

Uncommon Causes

Ionophore toxicity
Anesthesia
Hypoxemia
Cardiomyopathy
Autonomic imbalance

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may make reentry feasible and may account for the relatively greater frequency of arrhythmias in these species. Although it is not possible to precisely define the mechanism of clinical arrhythmias, it is believed that atrial and ventricular fibrillation may be caused by random reentry.

Under clinical conditions, cardiac arrhythmias may be associated with disturbances in electrolyte concentrations, especially potassium and calcium; in acid-base balance; and in autonomic nervous system balance. These conditions can precipitate cellular changes conducive to the development of arrhythmias by any of the previously mentioned mechanisms.

Approach to Diagnosis of Cardiac Arrhythmias

It is important to distinguish between abnormal arrhythmias that are primary and those that are secondary. Most abnormal arrhythmias of horses and cattle are tachyarrhythmias. Primary arrhythmias are caused by pathologic conditions of the heart (myocarditis, valvular disease, conduction system abnormalities, and pericarditis). Secondary arrhythmias develop in the absence of heart disease and can be caused by excitement, fever, sepsis, hypoxemia, metabolic or electrolyte imbalances, gastrointestinal disturbances, anesthesia, ionophores, other drugs, or toxemia. The treatment and prognosis for the two types of arrhythmias can be very different, and examination and laboratory tests are used to assist in making the distinction.

1. Take history. Determine the diet, feed additives, or medication (including furosemide, bicarbonate, or other prerace medications); note whether there has been exercise intolerance, syncope, fever, coughing, or edema; inquire about gastrointestinal problems, diarrhea, or colic; inquire about access to cattle or chicken feed or supplements and about previous respiratory tract infections in this animal or stablemates.
2. Perform a physical examination to determine whether there is primary cardiac disease. Record the animal's vital signs. Determine whether this is a bradyarrhythmia or tachyarrhythmia. Careful auscultation should note which heart sounds are present and should characterize the arrhythmia. There may be irregularities in the basic rhythm, added sounds, or long pauses; classification of heart rate by regularity of rhythm can distinguish one arrhythmia from another (see Chapter 30). Note whether a pulse deficit is present by simultaneous auscultation and palpation of the peripheral arterial pulse; note the strength of the peripheral arterial pulse; observe the jugular vein for pulsations and distention; examine peripheral veins for distention; and examine mucous membrane color and capillary refill time. Careful auscultation of the lungs with and without a rebreathing bag should be performed.
3. Record an ECG. The base-apex lead can be used to screen for arrhythmias; it is attached using positive, negative, and ground leads as follows:
   a. Positive lead is attached to skin over the left fifth intercostal space at the point of maximal intensity (PMI) of the apex beat; using lead I, this is the left arm electrode; using lead II or lead III, it is the left leg electrode.
   b. Negative lead is attached to the skin of the right jugular furrow two thirds of the distance from the ramus of the mandible to the thoracic inlet; using lead I or lead II, this is the right arm; using lead III, it is the left arm. ECG interpretation is discussed in Chapter 30.
4. If there is a cardiac murmur, perform an echocardiogram (including 2D, M-mode, and Doppler). Look for evidence of ventricular dysfunction, myocardial failure, chamber dilation, tumor, valvular abnormalities such as endocarditis, congenital defects, aortic cardiac fistula, and pericardial effusion.
5. Obtain feed for analysis if ionophore (monensin, lasalocid, salinomycin) exposure is suspected.
6. Obtain blood for the following:
   a. CBC
   b. Selenium concentrations if cardiomyopathy suspected
   c. Blood gas determinations and acid-base status
7. Test serum or plasma for the following:
   a. Electrolyte (Na, K, Cl, Ca, Mg, P) concentrations
   b. Vitamin E (α-tocopherol) concentration
   c. Cardiac troponin-I (cTnI)[6] if myocardial inflammation, injury, or necrosis is suspected
8. Test urine for the following:
   a. Electrolyte (Na, K, Cl) concentrations
   b. Creatinine determination
9. Calculate fractional excretion of potassium in the urine. This will be variable, depending on the diet, but a low value indicates the need for supplementation.
10. Treat the arrhythmia if:
    a. Patient is hemodynamically unstable (e.g., poor cardiac output, weak peripheral pulses, cold extremities, syncopal)
    b. There is ventricular tachycardia with a rapid rate (heart rate >120 beats/min)
    c. There are multifocal ventricular ectopic beats
    d. A QRS is detected in the preceding T wave (R on T)
    e. There is advanced second-degree or complete (third-degree) AV block
    f. The primary problem is cured or the condition is stabilized, and the patient is symptomatic with the cardiac arrhythmia

Cardiac Murmurs

Throughout the cardiovascular system, blood has a laminar or streamlined flow, except in the heart and sometimes in the aorta. Occasionally conditions occur that cause turbulent flow that is sufficient to cause resonance in adjacent structures. This resonance may be heard as a murmur when a critical level of turbulence is reached (Boxes 6-5 and 6-6). The factors that determine whether blood flow is laminar or turbulent are related by the Reynolds number, which is the ratio of the inertial to viscous forces. When the Reynolds number exceeds a critical value (about 2000 in large vessels), turbulence occurs. Increased flow velocity or reduced blood viscosity (e.g., anemia) predisposes to murmur development. The characteristics of the murmur depend on the velocity of the blood flow and the nature of the structures that are caused to vibrate.

It is useful to characterize murmurs with regard to timing in the cardiac cycle (systolic, diastolic, or continuous), duration in the cardiac cycle (early, mid, late, holo-, pan-), intensity (loudness), shape and quality or frequency, PMI, and radiation of the murmur. Systolic murmurs occur any time between the first and second heart sound. Diastolic murmurs occur between the second and first heart sounds. Continuous murmurs occur throughout the cardiac cycle (Fig. 6-4). The intensity of murmurs is frequently graded on a scale of 1 to 6[7]:

- *Grade 1* is a soft murmur heard only after minutes of careful listening.

BOX 6-5

Causes of Cardiac Murmurs in Horses

Common Causes

Valvular disease: degenerative, infective, dilation
Congenital defects
Anemia
Excitement
Fever
Functional murmur
Exercise

Uncommon Causes

Aortic cardiac fistula
Cardiomyopathy
Pericarditis
Cranial mediastinal abscess

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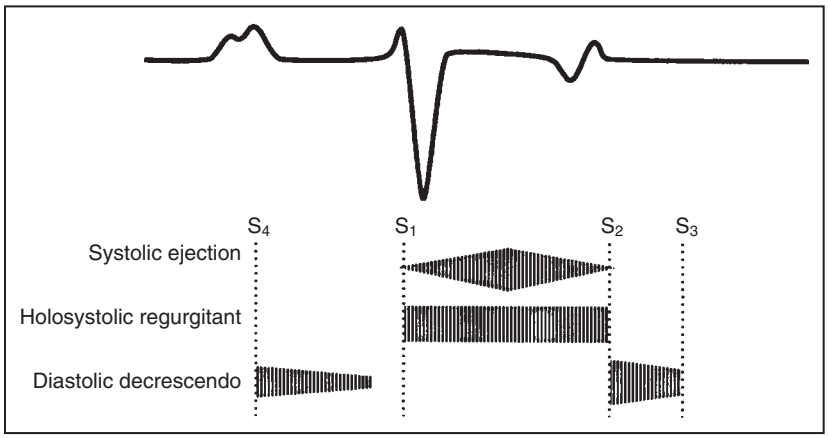


FIG. 6-4 Phonocardiographic characteristics of systolic ejection, holosystolic (pansystolic) regurgitant, and diastolic decrescendo cardiac murmurs.

BOX 6-6

Causes of Cardiac Murmurs in Ruminants

Common Causes

Anemia
Excitement
Fever
Functional murmur
Valvular disease: infective, degenerative, dilation
Congenital defects
Lymphosarcoma
Pericarditis (usually traumatic reticulopericarditis)

Uncommon Causes

Cardiomyopathy
Myocarditis

BOX 6-7

Possible Causes of Ejection and Regurgitant Systolic Cardiac Murmurs

Ejection

Innocent murmur
Anemia
Fever
Aortic stenosis
Pulmonic stenosis
Atrial septal defect
Ventricular septal defect
Tetralogy of Fallot

Regurgitant

Mitral regurgitation
Tricuspid regurgitation
Ventricular septal defect
Tetralogy of Fallot

- *Grade 2* is a soft murmur heard immediately on auscultation.
- *Grade 3* is a murmur of moderate intensity.
- *Grade 4* is a loud murmur associated with a palpable thrill.
- *Grade 5* is a loud murmur with a palpable thrill and is not heard when the stethoscope is removed from the chest wall.
- *Grade 6* is a loud murmur with a palpable thrill and is audible with the entire stethoscope chest piece held away from the chest wall.

The PMI of a murmur usually corresponds to the location of one of the heart valves. Murmurs associated with the mitral valve will frequently be heard best in the left fifth intercostal space just dorsal to the level of the elbow. These murmurs usually radiate dorsally or toward the aortic valve area. Pulmonic valve and aortic valve murmurs are best heard at the base of the heart. For this area to be accessed, the hand is moved under the left triceps muscle to the third and fourth intercostal spaces just below the level of the shoulder. Aortic valve murmurs are located just dorsal and caudal to the pulmonic valve. Murmurs associated with the tricuspid valve are frequently located in the right third or fourth intercostal space between the shoulder and elbow.

Most systolic murmurs fall into one of two categories: ejection or regurgitant (see Fig. 6-4). Systolic ejection murmurs are caused by obstructed, increased, or turbulent blood flow across normal or damaged semilunar valves. Valvular obstruction is rare in large animals, but functional ejection murmurs are commonly found in healthy horses. The PMI of the functional murmur is typically at the pulmonic or aortic valve or just dorsal to them over the great vessels. It is a crescendo-decrescendo murmur that is audible in early to mid systole. The diagnostic considerations for systolic ejection murmurs are given in Box 6-7. The innocent or functional murmur may be distinguished from a pathologic murmur by being of lower and variable intensity, peaking in early to mid systole, ending well before the second heart sound, and having no radiation. The physiologic systolic ejection murmur may disappear or become louder after exercise. Diagnostic considerations for systolic regurgitant murmurs are listed in Box 6-7.

Regurgitant murmurs can be variable in duration and may occur in early, mid, or late systole or can be pansystolic or holosystolic. Location of the PMI and the direction of radiation of the systolic murmur distinguish mitral or tricuspid regurgitation from a ventricular septal defect (VSD). Systolic clicks are rare in horses and cattle but may indicate abnormalities of the chordae tendineae, AV valve prolapse, or dilation of the aorta. The presence of a musical murmur indicates vibration of a cardiac structure such as rupture of one of the chordae tendineae or a torn valve leaflet.

Diastolic murmurs can occur between S_4 and S_1 (atrial systolic murmurs), between S_2 and S_3 (ventricular filling murmurs), or from S_2 to S_1 (aortic regurgitation or rarely, pulmonic regurgitation). Both the atrial systolic and ventricular filling murmurs are usually functional, can be heard over the left or right hemithorax, and can vary in intensity. They may have a musical or "squeaky" quality. The aortic regurgitation murmur is typically a decrescendo murmur with its PMI over the aortic valve that begins immediately after S_2 (see Fig. 6-4). Some aortic regurgitation murmurs can be harsh or musical, associated with high-frequency vibrations of an aortic valve leaflet, and they may be audible over the right thorax.

Continuous murmurs are uncommon in horses and ruminants. Patent ductus arteriosus, a finding in normal foals for a short time after delivery, can be heard in the left third intercostal space. This murmur can be continuous, but more frequently only a residual systolic murmur is audible.[8] Continuous machinery murmurs are most frequently reported in adult horses with an aortic cardiac fistula secondary to rupture of the aortic root or of a sinus of Valsalva aneurysm. A continuous "washing machine" murmur/rub, which is most

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easily heard over the left cardiac area, is associated with traumatic pericarditis in cattle and is caused by the accumulation of fluid, gas, and fibrin within the pericardium. Acquired systolic and diastolic murmurs in adult horses or cattle are usually the result of separate murmurs but can sometimes be confused.

Approach to Diagnosis of Cardiac Murmurs

1. Take a history. Note the age, onset, duration, and progression of the condition. Determine exercise capability, growth, and attitude; inquire about previous fever, illness, or medications.
2. Perform a physical examination. Record the animal's vital signs. Determine timing, duration, intensity, location of PMI, shape, and radiation of murmur. Palpate peripheral arterial pulse and observe jugular vein for distention and pulsations. Carefully auscultate the lungs at rest and during deep inspiration.
3. Obtain blood for CBC (includes fibrinogen and total plasma protein concentration).
4. Test serum or plasma for the following:
   a. Electrolyte concentrations
   b. Bovine leukosis virus (BLV), AGID status (cows)
   c. Cardiac troponin I[6] if myocardial inflammation, injury, or necrosis is suspected
5. Record an ECG.
6. Perform an echocardiogram to look for valve abnormalities, abnormalities of the aortic root, congenital defects, chamber enlargement, and wall motion abnormalities; use pulsed wave and color flow Doppler echocardiography to localize the shunt, regurgitant blood flow, or stenosis (rare); use color flow and continuous wave Doppler echocardiography to estimate the severity of the jet associated with a shunt, valvular regurgitation, or stenosis (rare); estimate pulmonary artery pressure by applying the Bernoulli equation to tricuspid or pulmonic regurgitant jet velocities, if present; and use contrast echocardiography for examination of congenital defects and detection of an aortic cardiac fistula and some valvular insufficiency.
7. Take radiographs or perform thoracic ultrasonography to find evidence of pulmonary edema or pleural effusion.
8. Catheterize the right heart to determine pulmonary artery and wedge pressures, which may complement data obtained noninvasively with Doppler echocardiography.

Muffled Heart Sounds

Auscultation of heart sounds requires that the vibrations generated by the heart be transmitted through the tissues of the thorax to the outer chest wall with sufficient amplitude to be heard. Blood transmits sound well, whereas lung tissue strongly attenuates sound waves. The chest wall itself causes attenuation of the sound that is most significant at the interface between bone and muscle. Therefore physical factors in a normal patient, such as a large, thick chest or obesity, can cause heart sounds to be muffled. If the environment for auscultation is conducive to hearing heart sounds, other factors such as stethoscope quality may cause muffling of heart sounds in a normal patient. One should strive to have a stethoscope with comfortably fitting earpieces; thicker and shorter tubing; a rigid diaphragm to hear S_1, S_2, and higher-frequency sounds; and a bell piece for auscultation of S_3, S_4, low-frequency sounds, and murmurs.

Heart sounds are muffled primarily because of displacement of the heart from the thoracic wall by fluid (pericardial effusion), a soft tissue mass (abscess or tumor), or air (pneumothorax, pneumomediastinum, or emphysema) (Boxes 6-8 and 6-9). Rarely is muffling of heart sounds attributed to weak cardiac contractions alone, although this may be a finding in recumbent cows with marked hypocalcemia.

BOX 6-8

Causes of Muffled Heart Sounds in Horses

Common Causes

Obesity
Large or thick chest wall
Pericarditis or pericardial effusion
Neoplasia: lymphosarcoma
Abscess
Chronic heart failure

Uncommon Causes

Pulmonary emphysema
Pneumothorax
Neoplasia: squamous cell carcinoma, fibrosarcoma

BOX 6-9

Causes of Muffled Heart Sounds in Ruminants

Common Causes

Obesity
Large or thick chest wall
Pericarditis (traumatic reticulopericarditis)
Neoplasia: lymphosarcoma
Abscess
Chronic heart failure
Emphysema

Uncommon Cause

Pneumothorax

Approach to Diagnosis of Muffled Heart Sounds

1. Take a history. Inquire about any change in attitude, appetite, diet, or posture; determine whether a magnet has been administered to cattle; note any history of fever, weight loss, respiratory disease, colic, or diseases of other body systems and the deworming history; determine whether cattle are known to be BLV positive.
2. Perform a physical examination and determine vital signs. Carefully auscultate the lungs to establish whether there is ventral dullness or evidence of increased or added sounds from pulmonary parenchymal compression; carefully auscultate the heart for pericardial friction rubs; determine whether there are signs of CHF (jugular venous distention, peripheral edema); percuss the thorax to determine whether there is emphysema, pleural fluid, or pneumothorax; note that pleural fluid in the absence of pericardial effusion causes radiating heart sounds but absence of airway sounds; determine whether there is thoracic and/or abdominal pain; and in cattle, check for the presence of a reticular magnet using a compass or stud finder.
3. Obtain blood for the following:
   a. CBC
   b. Fibrinogen concentration
   c. Plasma or serum protein concentration
   d. Liver enzymes and tests for liver function (AST, SDH, alkaline phosphatase, GGT, bilirubin, and bile acid concentration)
   e. Tests for kidney function (urinalysis, creatinine, blood urea nitrogen [BUN], Na, K, Cl, P concentrations and fractional excretion of Na, Cl, P)
4. Test serum for BLV serology and for equine influenza, viral arteritis, and herpes virus.
5. Take radiographs of the thorax to determine whether there is pulmonary parenchymal and/or pleural or pericardial disease.
6. Perform an ECG.
7. Perform a thoracic ultrasound examination/echocardiogram to determine if there is pericardial or pleural fluid, a cardiac mass, or a mass in the cranial mediastinum compressing the heart. Determine the location and type of fluid present.
8. Analyze pericardial or pleural fluid, and perform culture and sensitivity testing if indicated.

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Cardiovascular Exercise Intolerance, Weakness, and Syncope

Exercise intolerance, weakness, or syncope can be a clinical sign associated with disease in many body systems. Exercise intolerance can be manifested as sudden deceleration or stopping, failure to perform at an expected level, a sudden change in the level of performance or production, lowered enthusiasm for work, cough on exertion, evidence of respiratory distress, or excessive sweating. Weakness can be manifested as recumbency, difficulty in rising from recumbency, muscle tremors or fasciculations, reluctance to move, or toe dragging. Syncope is a sudden collapse and loss of consciousness (fainting).

Mechanisms of Cardiovascular Exercise Intolerance, Weakness, and Collapse

The clinical signs of exercise intolerance, weakness, or collapse can be caused by cardiovascular disease (Boxes 6-10 and 6-11). They are the result of failure to maintain cardiac output, caused by inability to regulate either heart rate or stroke volume. A normal horse increases cardiac output at submaximum heart rates (<210 beats/min in horses) primarily by tachycardia. At maximum heart rates (≈210 to 240 beats/min in horses), subsequent increments in cardiac output occur by increased stroke volume.[9] The maximum heart rate for cattle and small ruminants has not been published.

Supraventricular cardiac arrhythmias, primarily atrial fibrillation in horses, can lead to heart rates greater than 240 beats/min with submaximal exercise.[10,11] Heart rates exceeding the maximum rate may limit cardiac output by decreasing the time for diastolic perfusion of the myocardium or by limiting stroke volume because the short diastolic intervals leave inadequate time for ventricular filling. The ability to maintain cardiac output can also be compromised by other cardiac arrhythmias such as ventricular premature systoles. The frequency of extrasystoles can increase with exercise, and the timing of the abnormal beats can reduce cardiac output even at submaximal heart rates.[12] Horses with cardiac arrhythmias can have abnormal elevations in lactate concentration in response to exercise, indicating a lower anaerobic threshold and leading to exercise intolerance.[13,14]

BOX 6-10

Causes of Exercise Intolerance, Weakness, and Syncope in Horses*

Common Causes

Myocardial disease
Cardiac arrhythmias
Aortic or pulmonary artery rupture
Aortoiliac-femoral arteriosclerosis or thrombosis
Congenital heart defects
Chronic heart failure
Pericardial disease
Hyperkalemic periodic paralysis
Central nervous system disturbances resulting in loss of consciousness

*See Chapters 8 and 13 for additional noncardiac causes.

BOX 6-11

Causes of Exercise Intolerance, Weakness, and Syncope in Ruminants*

Common Causes

Myocardial disease
Cardiac arrhythmias
Congenital heart defects
Chronic heart failure

*See Chapters 8 and 13 for additional noncardiac causes.

Cardiac output maintenance may also be compromised in animals by diseases affecting myocardial contractility or diseases that result in increased end-systolic volume despite a submaximal heart rate.[15] Diseases that result in decreased venous return (peripheral vascular disease) can also reduce cardiac output and cause signs of exercise intolerance, weakness, or collapse.

Exercise intolerance or weakness can also be caused by painful peripheral vascular conditions or conditions causing peripheral hypoxia or lactic acid accumulation. In horses such conditions may exist with aortoiliac thrombosis. Sudden episodes of weakness and collapse without change in consciousness are associated with hyperkalemic period paralysis in horses (see Chapter 42).

Collapse may be associated with epilepsy or other central nervous system (CNS) disturbance. If cardiovascular and pulmonary function appears normal, the nervous system should be examined in detail (see Chapter 8). Collapse at rest may also be caused by sleep disorders/deprivation or poorly defined mechanisms such as girth tightening. Collapse during exercise is most commonly caused by cardiovascular disease, whereas collapse at rest is usually associated with neurologic disease.

Approach to Diagnosis of Exercise Intolerance, Weakness, and Collapse

1. Note signalment and take history. Establish onset of problem, previous performance history, activity level, and whether there is loss of consciousness when clinical signs are observed. Determine whether there is coughing, dyspnea, or excessive sweating associated with stress or exercise. Determining whether the weakness or collapse primarily occurs with exercise or at rest will direct further workup.
2. Perform a physical examination and record vital signs. Of particular importance are heart rate at rest, peripheral arterial pulse characteristics, presence of pulse deficits, mucous membrane color, and appearance of jugular venous pulses. Lungs should be auscultated for evidence of pulmonary edema or pleural effusion. The chest should be percussed. Rectal examination should be performed to evaluate aortic and iliac arterial pulses; metatarsal artery pulses and saphenous vein refill should be evaluated.
3. Perform neurologic and lameness evaluations. Perform a rectal ultrasound examination if aortoiliac thrombosis is suspected, to document the disease and assess its severity.
4. Perform an echocardiogram (2D, M-mode, and Doppler) to evaluate the size of heart chambers; to look for congenital defects, acquired valvular heart disease, and pericardial disease; and to evaluate myocardial contractility and ventricular wall motion.
5. Record an ECG at rest. Record a continuous 24-hour ECG to determine the frequency of arrhythmias detected on the resting ECG or to look for infrequent or paroxysmal arrhythmias not detected at rest.
6. Simultaneous video monitoring and continuous ECG recording can help determine if episodes of collapse are associated with cardiac rhythm disturbances. Video surveillance can also help characterize the nature of the collapse episodes and aid in differentiation of seizure activity from sleep disorders or deprivation.[16]
7. If collapse is associated with exercise and a definitive diagnosis cannot be made with resting diagnostics, an exercising stress test should be performed. Diagnostics may include resting and exercising upper airway endoscopy, an exercising ECG preferably with real-time monitoring, stress echocardiogram before and immediately after exercise, resting and exercising lactic acid and arterial blood gas concentrations, resting and postexercise creatine kinase, and cTnI concentrations and a postexercise bronchoalveolar lavage. Clinicians should be prepared to discontinue the test, treat life-threatening arrhythmias, and/or establish a patent airway (tracheostomy) in horses with a history suggestive of ventricular arrhythmias or upper airway obstruction, particularly pharyngeal collapse.

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Venous Distention and Pulsations

The jugular venous pulsations observed in the neck are primarily a reflection of right atrial and right ventricular activity. There may be some small contribution from carotid arterial impact.[17] The jugular venous pulse reflects the right atrial or central venous pressure, which is influenced by blood volume, right ventricular cardiac output, and right atrial contractility (Boxes 6-12 and 6-13). Jugular venous pulsations are observed in normal animals, but the pulse seldom radiates more than one third of the distance from the thoracic inlet to the ramus of the mandible when the head is held in a normal, upright position.

Mechanisms of Venous Distention and Pulsations

The normal jugular venous pulse consists of three positive and two negative deflections (Fig. 6-5). The first and dominant positive wave is the A wave, produced by atrial contraction. During atrial relaxation the pressure declines until ventricular systole. The second positive deflection is the C wave, which is produced by the bulging of the tricuspid valve leaflets into the right atrium during early (isovolumetric) right ventricular systole. Carotid arterial impact on the jugular vein may also contribute to the C wave.[17] As the ventricle contracts, the plane of the tricuspid valve is pulled toward the apex of the heart and the atrial pressure declines, producing the X descent. The X descent is terminated by the V wave, which is associated with venous return, subsequent atrial filling, and a closed tricuspid valve. At the end of ventricular systole, the atrial pressure falls again as a result of tricuspid valve opening and rapid right ventricular filling. This is the Y descent. The Y descent is terminated as the pressure gradually rises with right-sided heart filling.

Abnormal pulsations occur with increased resistance to right ventricular filling, regardless of the cause. Distention and pulsations in the jugular vein are usually associated with an elevated right ventricular pressure such as occurs in right-sided heart failure, constrictive pericarditis, or, more rarely, cardiomyopathy. Prominent jugular pulsations are noted with tricuspid regurgitation and certain cardiac arrhythmias, especially those arrhythmias associated with atrial contraction against a closed AV valve. The carotid arterial pulse can mimic jugular venous pulsations. To distinguish among the causes of jugular venous pulsations, lightly compress but do not occlude the jugular vein at the thoracic inlet. The jugular vein will distend enough to eliminate carotid arterial pulsations. If pulsations are still present, tricuspid regurgitation, atrial arrhythmias, or right-sided heart failure should be considered. If the jugular vein is compressed near the ramus of the mandible and massaged toward the thoracic inlet, refilling is indicative of tricuspid regurgitation. Jugular venous distention without pulsations can occur with compression of the cranial vena cava from a cranial thoracic or mediastinal mass or from occlusion of the jugular vein with a thrombus.

Approach to Diagnosis of Venous Distention and Pulsations

1. Take history. Note especially history of respiratory disease, exposure to high altitude and locoweed, or ingestion of potential cardiotoxins. Determine whether other animals have been similarly

BOX 6-12

Causes of Jugular Venous Distention and Pulsation in Horses

Common Causes

Right-sided heart failure
Left-sided heart failure with pulmonary hypertension
Cardiomyopathy
Atrial fibrillation
Tricuspid regurgitation
Cranial mediastinal mass
Lymphosarcoma
Abscess
Jugular venous phlebitis and thrombosis

Uncommon Causes

Ionophore toxicity
Pericarditis
Myocarditis
Ventricular tachycardia
Squamous cell carcinoma
Fibrosarcoma
Cor pulmonale
Chronic obstructive pulmonary disease
Overhydration

BOX 6-13

Causes of Jugular Venous Distention and Pulsation in Ruminants

Common Causes

Right-sided heart failure
Left-sided heart failure with pulmonary hypertension
Vitamin E or selenium deficiency (white muscle disease)
Cardiomyopathy
Tricuspid regurgitation
Pericarditis
Jugular venous phlebitis and thrombosis
Heart base tumor: lymphosarcoma
Heart base abscess
Cor pulmonale caused by chronic pneumonia
Brisket disease

Uncommon Causes

Ionophore toxicity
Overhydration
Cranial mediastinal mass

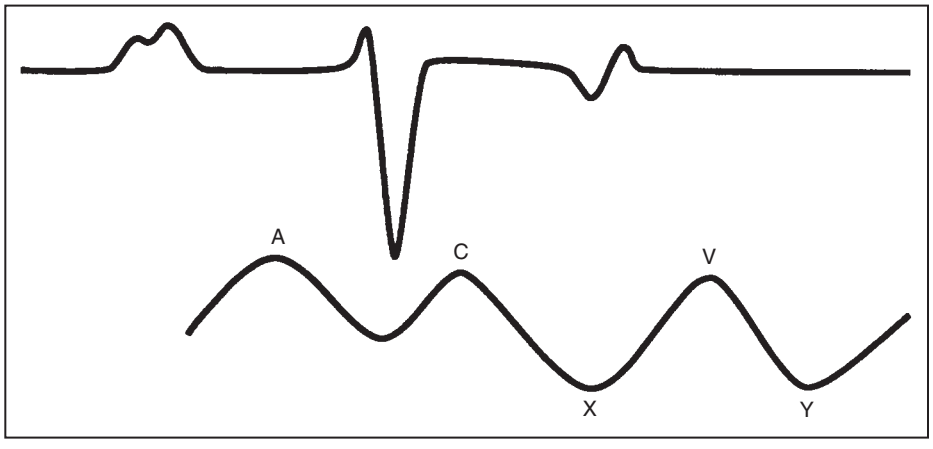


FIG. 6-5 Schematic illustration of a venous (jugular or atrial) pressure curve and its relationship to events of the electrocardiogram. *A,* Positive wave produced by atrial contraction; *C,* second positive deflection caused by bulging of the tricuspid valve during isovolumetric systole; *X,* first negative wave produced by the plane of the atrioventricular valve being pulled toward the apex of the heart during systole; *V,* positive pressure wave caused by venous return; *Y,* negative wave produced by AV valve opening.

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affected, whether the BLV status of affected cattle is known, and whether a magnet has been administered.
2. Perform a physical examination. Determine whether there is tachypnea or tachycardia. Carefully auscultate for abnormal heart sounds, rhythm, or intensity of sounds; note whether jugular veins are patent. Look for jugular venous pulsations as described previously.
3. Obtain blood for the following:
   a. CBC
   b. Fibrinogen concentration
   c. Total protein concentration
   d. BLV status (bovine) and serology for equine influenza, viral arteritis, and herpes virus
   e. Vitamin E (serum) and selenium concentrations if cardiomyopathy suspected
4. Take radiographs of the thorax and abdomen to establish whether there is respiratory disease, a magnet, or a penetrating foreign body.
5. Record an ECG when there is an arrhythmia to look for atrial premature depolarizations.
6. Perform an echocardiogram to examine the following:
   a. Right ventricular size and function
   b. Right atrium, for abnormal size or structures
   c. Tricuspid valve
   d. Pulmonary artery diameter looking for evidence of pulmonary hypertension
   e. Left atrial size
   f. Left ventricular size and function
   g. Pericardium
   h. Interventricular septal thickness and motion
7. Perform Doppler echocardiogram to look for:
   a. Tricuspid regurgitation
   b. Pulmonic regurgitation
   c. If tricuspid or pulmonic regurgitation is detected, check for concurrent mitral and aortic regurgitation. Use velocity of tricuspid and/or pulmonic regurgitation to calculate/estimate pulmonary artery pressure.
8. Perform ultrasound examination of the cranial thorax and cranial mediastinum.
9. Jugular venous catheterization may be useful to determine right atrial (central venous), right ventricular, and pulmonary arterial pressures.

Painful Peripheral Swellings

Close inspection of the skin and extremities of patients can reveal evidence of peripheral vascular or lymphatic system disease. These diseases can be manifested by diffuse swelling, localized swelling (papules, nodules, macules, or wheals), or subcutaneous edema of the extremities. Frequently there is necrosis, ulceration of the skin, and exudation as the disease progresses. Animals may be lame or dyspneic, have heat in the involved area, or exhibit a painful response to palpation of the area (Boxes 6-14 and 6-15), which helps to differentiate these conditions from nonpainful peripheral edema.

Approach to Diagnosis of Painful Peripheral Swellings

1. Take history. Establish whether there is a history of a wound or trauma to the area or previous drainage; inquire about previous infections, particularly those referable to the respiratory system, in this animal or others; determine vaccination, deworming, and drug administration history.
2. Perform a physical examination. Determine vital signs. Note whether the animal is febrile; examine extremities for wounds, dilated lymphatic channels, ulcers, focal swellings, and edema; determine the temperature and sensitivity of the swollen area; examine mucous membranes for color and presence of hemorrhages; perform a rectal examination and palpate aortic quadrifurcation in horses for vessel size, firmness, pain, fremitus, and strength of pulse; evaluate these vessels before and after exercise, if indicated; test saphenous refill by holding off the saphenous vein distally over the hock, stripping the vein proximally, and releasing the pressure over the vein at the level of the hock.
3. Obtain blood for the following:
   a. CBC (includes examination of red blood cells, neutrophils, and eosinophils for inclusion bodies or morula and determination of platelet count)

BOX 6-14

Causes of Painful Peripheral Swellings in Horses

Common Causes

Thrombophlebitis
Abscess (*Corynebacterium pseudotuberculosis* in western United States)
Cellulitis
Hypersensitivity vasculitis (complicated by skin necrosis and secondary infection)
Equine viral arteritis
Equine granulocytic ehrlichiosis (*Anaplasma phagocytophilum,* formerly *Anaplasma equi* or *Ehrlichia equi*)
Equine infectious anemia
Purpura hemorrhagica
Clostridium species myositis
Septic tenosynovitis
Bursitis
Muscle disruption/hematoma
Fracture
Insect bite
Application of topical counterirritants, firing, or soring

Uncommon Causes

Frostbite
Piroplasmosis
Ulcerative lymphangitis
Epizootic lymphangitis
Glanders
Sporotrichosis
Immune vasculitis
Aortoiliac thrombosis
Sporadic lymphangitis
Congenital lymph node and lymphatic dysgenesis
Hemangiosarcoma
Snakebite

BOX 6-15

Causes of Painful Peripheral Swellings in Ruminants

Common Causes

Thrombophlebitis
Abscess
Clostridial myositis
Malignant edema
Blackleg
Muscle disruption/trauma/hematoma
Carpal hygroma
Fescue foot
Ergotism
Cellulitis (injection site or wound)
Fracture
Insect bite
Frostbite

Uncommon Causes

Disseminated hemangiosarcoma
Heartwater disease (*Ehrlichia ruminantium,* exotic)
Snakebite
Septic tenosynovitis
Bursitis

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b. Fibrinogen concentration
c. Total protein concentration
d. Coombs or direct immunofluorescence test
e. Appropriate tests for equine ehrlichiosis (immunofluorescence assay), piroplasmosis (complement fixation), or viral arteritis (serum neutralization), if indicated

4. Take radiographs of swollen extremities, if appropriate.
5. Perform an ultrasound examination of the swelling, if appropriate. Perform transrectal ultrasound examination of terminal aorta and iliac arteries of horse if palpation suggests thrombus.
6. Obtain Gram stain and bacterial and fungal culture of ulcerated area or exudate.
7. Perform a biopsy of granulomas and submit for histopathology and culture and sensitivity testing, if appropriate.
8. Analyze and culture fluid obtained from dilated lymphatic channels or localized edematous areas.
9. Analyze urine to look for hemoglobinuria or hematuria.
10. Test feces for fecal occult blood.

Enlarged Lymph Nodes

Diffuse or single lymph node enlargement occurs with infectious (bacterial, viral, fungal) conditions, neoplasia, and, rarely, immune-mediated causes in large animals (Boxes 6-16 and 6-17). Lymphadenopathy may cause obstruction to lymphatic drainage, leading to peripheral edema, pleural effusion, or ascites. The peripheral lymph nodes that are most readily accessible for examination are the submandibular (horses), superficial cervical (ruminants), and superficial inguinal (ruminants) lymph nodes. When there is generalized lymphadenopathy, internal lymph nodes may be enlarged, causing clinical signs such as dyspnea, esophageal obstruction, diarrhea, or other signs of organ dysfunction.

Approach to Diagnosis of Enlarged Lymph Nodes

1. Take history. Note especially history of weight loss, inappetence, depression, lethargy, or lymph node enlargement; inquire about previous illness or wounds; for cattle, determine whether there is a history of lymphosarcoma in the family or herd and whether the cow has a positive BLV test result; for sheep and goats, determine whether there is a history of *Corynebacterium pseudotuberculosis* abscesses in the flock or herd.
2. Perform a physical examination. Determine vital signs. Examine peripheral lymph nodes or other swellings, perform a rectal examination to palpate accessible internal lymph nodes, and, when appropriate, examine the uterus in cattle; check mucous membranes for pallor or icterus; determine whether there is jugular venous distention or pulsations or whether there is evidence of pleural or pericardial effusion or ascites.
3. Obtain blood for the following:
   a. CBC to examine for anemia or leukemic changes; note inclusions, morula, or abnormal appearance of cells
   b. Serum chemistry profile to determine if there are signs of other organ dysfunction (e.g., gastrointestinal [hypoproteinemia], liver, or kidney)
4. Test feces for occult blood, if indicated.
5. Perform ultrasonographic examination of the lymph node or swelling.
6. Obtain lymph node or swelling aspirate and biopsy sample for culture and histopathologic examination.
7. Obtain a bone marrow sample for cytologic examination.

BOX 6-16

Causes of Enlarged Lymph Nodes in Horses

Common Causes

Strangles
Lymphosarcoma
Upper respiratory infection
Corynebacterium pseudotuberculosis lymphadenitis

Uncommon Causes

Ulcerative lymphangitis
Epizootic lymphangitis
Sporadic lymphangitis
Glanders
Granulomatous lymphadenitis
Plasma cell myeloma
Tuberculosis
Hemolytic uremic-like syndrome

BOX 6-17

Causes of Enlarged Lymph Nodes in Ruminants

Common Causes

Caseous lymphadenitis (*Corynebacterium pseudotuberculosis*)
Lymphosarcoma (including bovine leukosis virus)
Abscess or cellulitis of area drained

Uncommon Causes

Tuberculosis
Sporadic bovine encephalomyelitis
Malignant catarrhal fever

Abnormal Peripheral Pulse

Palpation of the arterial pulse is an important aspect of the examination of the patient with cardiovascular disease. Arterial pulse strength and contour (how fast pressure rises and falls) are the objectives of the examination and are determined by the cardiac output, heart rate, and vascular impedance. The arterial pressure pulse begins with the opening of the aortic valve and ventricular ejection and rises rapidly in early systole. The pulse pressure reaches a peak and then declines as ventricular ejection slows. During isovolumic relaxation (before AV valve opening), there is a transient reversal of flow in the arterial system, and an incisura or dicrotic notch (Fig. 6-6) is inscribed on the descending limb of the pressure curve. Following the incisura, there is a small positive wave that is attributed to elastic recoil of the aorta and the aortic valve and the summation of reflected waves from more distal arteries.[15] After the positive wave, the pulse pressure declines because there is peripheral runoff of blood in diastole. The incisura and secondary positive wave are not usually palpable. Palpation of peripheral arteries (facial, transverse facial, and digital arteries

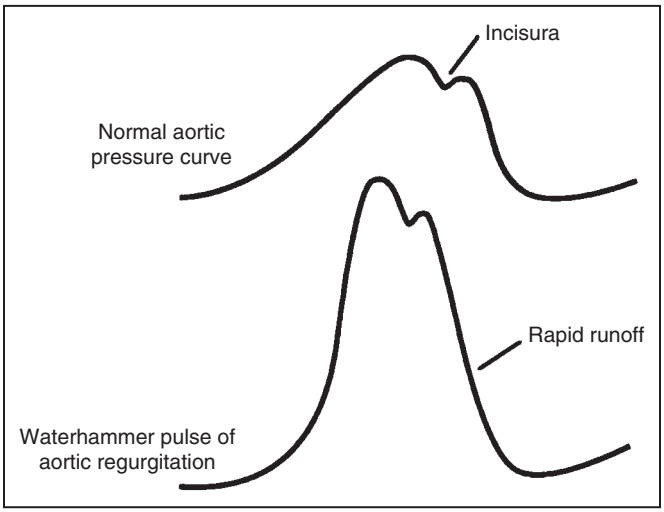


FIG. 6-6 Schematic illustration of the normal arterial pressure pulse. The incisura that occurs during the descending limb is caused by a transient reversal in flow during isovolumic relaxation. Compared with the normal arterial pressure pulse, the waterhammer pulse of aortic regurgitation builds rapidly and has a rapid runoff.

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BOX 6-18

Causes of Abnormal Peripheral Pulse in Horses

Common Causes

Dehydration
Shock
Toxemia
Congestive heart failure
Electrolyte imbalances
Acid-base disorders
Hypertension
Hypotension
Exercise
Fever
Laminitis
Aortic regurgitation
Cardiac arrhythmias

Uncommon Cause

Aortic cardiac fistula
Peripheral arteriovenous shunt
Patent ductus arteriosus

BOX 6-19

Causes of Abnormal Peripheral Pulse in Ruminants

Common Causes

Dehydration
Shock
Toxemia
Congestive heart failure
Electrolyte imbalances
Acid-base disorders
Fever
Cardiac arrhythmias

Uncommon Causes

Patent ductus arteriosus
Aortic regurgitation
Peripheral arteriovenous shunt

in the horse and median and coccygeal arteries in ruminants) normally reveals a smooth, rapid upstroke, a dome-shaped summit, and a downstroke that is slightly more prolonged than the upstroke.

Pressure values and pulse wave configurations are altered as the pressure waves are transmitted through the peripheral arterial tree. With increasing distance from the heart, the dicrotic notch and second positive wave disappear, the systolic pressure gets higher (loss of distensibility in the distal arteries and summation of reflected pulse waves from the distal vascular bed), and the diastolic pressure gets lower. The difference between the systolic and diastolic pressure determines pulse pressure and can be evaluated by an impression of pulse strength. Pulse pressure increases as one moves to more peripheral arterial sites. The mean arterial pressure changes little but decreases slightly as one moves downstream in the arterial system from the pressure source. Systolic blood pressure, as measured indirectly at the tail or on a limb, is higher than that measured in the ascending aorta. In smaller arterial beds (e.g., arteries of the ear), the pulse wave is gradually dampened and pulsatile characteristics are lost on the capillaries and small veins.

Mechanisms of Abnormal Peripheral Pulse

Hyperkinetic arterial pulses occur in patients with increased cardiac output (e.g., fever, exercise, excitement), increased stroke volume, or bradycardia (Boxes 6-18 and 6-19). It may also occur when there is rapid runoff of blood in the arterial system, as occurs with aortic valve regurgitation, patent ductus arteriosus, or aortic cardiac fistulas. In aortic valve regurgitation the rapidly rising, hyperdynamic pulse is caused by increased stroke volume (regurgitated blood in the left ventricle), followed by a rapid runoff of pressure later in systole as a result of regurgitation (see Fig. 6-6).

Hypokinetic pulses are present in patients with diminished stroke volume caused by hypovolemia, left ventricular failure, or, rarely, in large animals, mitral or aortic valve stenosis.

Abnormal peripheral pulses are detected in patients with cardiac arrhythmias. With premature ventricular contractions (PVCs), the compensatory pause that occurs after the PVC allows a longer period of time for ventricular filling, which results in a greater end-diastolic volume, increased contractile force, and a stronger pulse in the beat that follows the PVC. The strength of the peripheral pulse is variable in arrhythmias such as atrial fibrillation because the irregular rhythm is associated with variable time for ventricular filling. Certain arrhythmias, particularly tachyarrhythmias, allow inadequate ventricular filling to generate a peripheral arterial pulse, and a pulse deficit is palpated. This is particularly likely with ventricular tachycardia at high heart rates.

Approach to Diagnosis of Abnormal Peripheral Pulse

1. Take history. Note changes in appetite, attitude, milk production, or ability to exercise; determine whether there have been signs of previous illness and duration and progression of the problem.
2. Perform a physical examination. Determine vital signs. Note whether there is a cardiac arrhythmia, murmur, or other evidence of heart disease (e.g., jugular venous distention or pulsation, edema). Palpate the pulse in multiple sites and bilaterally to rule out occlusive arterial disease; check patient's hydration.
3. Obtain blood for the following:
   a. CBC; look for evidence of toxemia or anemia
   b. Blood gases to determine acid-base balance
   c. Electrolyte concentration, especially Ca and K
4. Record an ECG to characterize any arrhythmia.
5. Determine blood pressure. The site for indirect blood pressure measurement in the standing animal is the tail over the coccygeal artery; a limb can be used in a recumbent animal. Take the mean of several (minimum of three) readings in which the blood pressure cuff is gradually inflated and deflated at approximately 2 to 4 mm Hg/sec; values obtained should be corrected for the difference in height between the site measured and the heart, which is considered to be at the level of the shoulder; the difference in height (centimeters) between the heart and the site of pressure measurement is multiplied by 0.77 (constant used to convert centimeters of blood to millimeters of mercury). In standing horses, approximately 27 mm Hg is added to the indirectly measured coccygeal artery pressure to give the corrected value[18]; no correction factor is necessary if the measurement is made in a recumbent animal. An appropriately sized blood pressure cuff is considered to be one fourth of the tail circumference[19]; in horses a 4.5- to 5.6-cm cuff has been recommended for electronic oscillometric devices, and a 10.6-cm cuff is used for ultrasonic flowmeters.[18] Values for normal horses by blood flow detection methods are 79/49 to 145/106 mm Hg (uncorrected for the height of the tail).[17]
6. Blood pressure can be evaluated by Doppler scan, or measurements can be recorded by direct cardiac catheterization (see Chapter 30).
7. Perform an echocardiogram to evaluate size of chambers, myocardial function, presence of valvular or pericardial disease, or congenital defects.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 7

Alterations in Alimentary and Hepatic Function

BRADFORD P. SMITH and K. GARY MAGDESIAN

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MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

Diarrhea, 88
Colic (abdominal pain), 94
Melena, 97
Blood, fibrin, and/or mucus in feces (dysentery), 98
Abdominal distention and constipation, 98
Regurgitation and vomiting, 100
Dysphagia, 101
Oral vesicles, erosions, ulcers, or growths, 103
Dental abnormalities, 104
Icterus (jaundice), 105

Diarrhea

K. Gary Magdesian • Bradford P. Smith

Diarrhea is an increase in the frequency, fluidity, or volume of feces. Diarrhea may be a sign of a primary gastrointestinal (GI) disease or a nonspecific response to sepsis, toxemia, or disease of another organ system.

Under normal circumstances a large volume of essentially isotonic fluid enters the proximal GI tract daily. Most of this fluid is resorbed, and only a small percentage is ultimately passed with the feces. The fluid comes from dietary intake and from endogenous secretions of the upper digestive tract. The total daily volume exchanged exceeds that of the animal's total extracellular fluid volume. Normally absorption just exceeds secretion; therefore small changes in rate of absorption or secretion can result in diarrhea. In the horse most water resorption occurs in the cecum and large colon, and diarrhea in the horse (other than neonates) usually involves some abnormality in the lumen or wall of the large intestine.

Normal fecal color is tan, brown, or greenish, depending on diet. The adult horse normally produces 11 to 13 kg of fecal material per day (20 to 28 g/kg of body weight per day) while on a diet of grass hay and 3 lb of oats.[1] Fecal output is as high as 20 kg/day in horses fed a mixture of alfalfa and orchard grass ad libitum.[2] Horses with chronic watery diarrhea can produce up to 214 g/kg of body weight per day, 1 which is over 90 L of diarrhea in a 450-kg horse. Cattle normally produce 15 to 28 kg of feces per day with a water content of about 75% to 85% on a diet of grass hay.[3] Fluidity of cattle feces can increase markedly in animals on lush green feed. Sheep and goat feces contain only 50% to 60% water.[3] Fluid feces in the cow and unformed feces in the horse, goat, and sheep are nonspecific signs that often accompany sepsis or illness other than a primary gastrointestinal disease.

Animals with chronic diarrhea rarely develop severe dehydration because they compensate for increased fecal water losses by increasing water consumption by an equivalent amount. Normal water consumption in the horse on a hay diet in a mild ambient temperature environment is about 24 to 30 L/day, whereas cattle consume 30 to 60 L/day based on 10 kg of dry matter feed intake. Water and feed intake do not increase linearly with increasing body size, but by multiplying body weight in kilograms to the 0.75th power (BW $Kg^{0.75}$) by a base factor (≈200 mL for water). Thus a 500-kg horse requires 21 L of water. The effect of temperature on water intake is dramatic and is not linear; as ambient temperatures rise close to 37° C (98° F), water intake per kilogram of dry matter increases much more rapidly than at lower temperatures. Exercise and loss through sweat, particularly in the horse, can dramatically increase salt and water requirements.

Mechanisms of Diarrhea (Box 7-1)

The following six major mechanisms produce diarrhea:

- Decreased or damaged absorptive surface area (malabsorption)
- Increased numbers of osmotically active particles within the intestinal lumen
- Increased volume of secretion of solutes and water
- Abnormal intestinal motility resulting in decreased transit time, as with systemic inflammatory response syndrome (SIRS)
- Increased blood-to-lumen pressure as in heart failure or acute or chronic inflammatory bowel diseases
- Gastrointestinal inflammation, as occurs with peritonitis

The common net result is an increase in fecal water.

Decreased surface area is mainly a result of villous blunting (atrophy) and/or microvillous damage in the small intestine, which lead to malabsorption. Both occur to some degree with most enteric diseases, and regeneration of surface area from crypt cells with healing is accompanied by a gradual decrease in the volume of diarrhea. Diseases in which this is a major mechanism include neonatal diseases such as rotavirus and coronavirus enteritis,[4] cryptosporidiosis, acute inflammatory disease such as salmonellosis, and chronic diseases such as Johne's disease and other granulomatous bowel diseases. The finding of villous atrophy is so nonspecific that it is not diagnostic in itself. It can also occur in advanced cases of secondary copper deficiency (molybdenosis) with diarrhea. Loss of villous epithelial cells can result in maldigestion because these cells produce

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BOX 7-1

Mechanisms of Diarrhea

Malabsorption (villous atrophy)
Osmotic overload
Secretory
Abnormal motility
Increased blood-to-lumen hydraulic pressure
Inflammation
Decreased transit time

important enzymes such as lactase. Many neonates with enteritis develop temporary lactose intolerance as a result, especially with rotaviral and clostridial infections. Damaged surface area occurs in such diseases as salmonellosis, where the mucosa of the large colon and cecum may be severely disrupted.

Inflammation can be accompanied by increased mucous production and increases in size of membrane pores, through which tissue fluids and serum proteins leak into the lumen. This is associated with increased capillary and lymphatic hydraulic pressures. Both acute (salmonellosis) and chronic (Johne's) inflammatory bowel diseases are protein-losing enteropathies. Low plasma protein concentrations, particularly low albumin, are often found (unless hypovolemia and hemoconcentration are present). Bowel inflammation often results in transudation and exudation of serum proteins, blood, and/or mucus, resulting in dysentery (bloody diarrhea). In addition to salmonellosis, dysentery may also commonly be seen with enterotoxemia caused by *Clostridium perfringens,* types A, B, or C; *Clostridium difficile; Lawsonia intracellularis*[5]; attaching effacing *Escherichia coli; Campylobacter jejuni;* coccidiosis; malignant catarrhal fever (MCF); arsenic toxicity; and oak toxicity. Inflammation results in malabsorption, maldigestion, osmotic effects, and, in acute disease, changes in intestinal motility. Because most water absorption in the horse occurs in the cecum and colon, inflammatory typhlitis and colitis are the major causes of diarrhea in the adult horse (Boxes 7-2 and 7-3). The neonatal foal commonly develops small intestinal enteritis.

Irritation of the bowel with a foreign body such as sand may result in either low-grade recurrent colic or diarrhea. Weight loss may also be evident with a large amount of sand. Sand accumulation in the large bowel of the horse may be suspected when there is evidence of a significant amount of sand in the feces or when sand can be auscultated with a stethoscope over the ventral abdomen. Irritation probably causes diarrhea through creation of an inflammatory response and altered motility.

Osmotic diarrhea results from any disease causing maldigestion and/or malabsorption. Any osmotically active solute can produce diarrhea in normal animals if given in quantities sufficient to surpass the intestinal capacity for digestion or absorption. Disaccharides are natural examples. Osmotic cathartics such as dioctyl sodium sulfosuccinate (DSS) hold water in the intestine and act as fecal softeners. Magnesium phosphates and sulfates and other divalent and trivalent cations and anions are poorly absorbed and thus are effective laxatives and cathartics.

Osmotic diarrhea can be associated with ingestion of osmotically active and poorly absorbed solutes, overloading of the intestine with carbohydrates or lipids beyond the amount that can be digested and absorbed, sudden dietary changes resulting in marked shifts in gut flora and resulting bacterial action on ingested substrate (e.g., grain overload), or bowel disease in which surface area is diminished or digestion interfered with in some manner. Lactase deficiency, secondary to rotavirus or *C. difficile* infections, may result in osmotic diarrhea in foals.[6] This results in increased concentration of undigested and/or unabsorbed nutrients entering the lower bowel, increased bacterial fermentation, and an increase in the concentration of osmotically active particles. Unfavorable electrochemical gradients prevent resorption of water. Mucosal digestive enzyme levels are often decreased with any disease involving the small intestine, resulting in maldigestion. When osmotic diarrhea is suspected in mature animals, dietary modification to basic roughage should be tried as part of the nonspecific therapy. Sodium and potassium are normally present in roughly equal amounts in feces and (with small concentrations of ammonium) make up the vast majority of cations in the feces. Concentrations of sodium and potassium in feces and osmotically active nonelectrolytes influence fecal water. In general, osmotic diarrheas diminish when the animal is fasted. When the offending substance is reintroduced, diarrhea occurs.

BOX 7-2

Causes of Diarrhea in Horses*

Common Causes

Colitis or typhlitis
Salmonellosis
Enteritis, unknown cause
Potomac fever (equine monocytic ehrlichiosis)
Endotoxemia or gram-negative sepsis
Overfeeding or sudden change in diet
Clostridium difficile
Parasites (ascarids, large and small strongyles)

Less Common Causes

Eosinophilic gastroenteritis
Renal failure, uremia
Necrotizing enterocolitis
Heart failure
Enterotoxemia (*Clostridium perfringens,* mainly type A)
Lawsonia intracellularis (mainly foals and weanlings), proliferative enteropathy
Intestinal lymphosarcoma
Cathartics or laxatives
Parasympathomimetics
Chronic granulomatous bowel disease
Proximal enteritis
Peritonitis
Intussusception
Sand, gravel, or enterolith in gut lumen
Gut stenosis
Antibiotic use
Gastroduodenal ulcers
Rhodococcus equi, gut infection (mainly foals)
Cryptosporidiosis (mainly foals)
Giardiasis (mainly foals)
Toxins or poisonous plants (see Box 7-3)

Uncommon Causes

Hepatic failure
Cholelithiasis
Vascular aneurysm
Combined immunodeficiency
Agammaglobulinemia
Lactose intolerance (mainly foals)
Campylobacter jejuni (mainly foals)
Colorectal polyps
Anaphylaxis
Vitamin A deficiency
Tularemia
Snake bite, insect or spider sting or bite
Histoplasmosis
Hydroallantois
Hyperlipidemia
Internal abdominal abscess
Pheochromocytoma
Viral arteritis
Sarcoidosis
Addison disease
Malignancy
Grass sickness (exotic)
Glanders (exotic)
Besnoitiosis (globidiosis) (exotic)

*See Chapter 17 for information on neonates.

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BOX 7-3

Toxic Causes of Diarrhea in Horses*

Phenylbutazone toxicity
Blister beetle toxicity (cantharidin)
Salt poisoning
Selenium toxicity
Slaframine toxicity (slobber factor)
Amitraz toxicity
Propylene glycol toxicity
Dioctyl sodium sulfosuccinate (DSS) toxicity
Sulfur toxicity
Phosphorus toxicity
Nicotine, Black Leaf 40 toxicity
Reserpine toxicity
Arsenic toxicity
Mercury toxicity
Monensin, lasalocid, or salinomycin toxicity
Organophosphate toxicity
Iron

Plant Toxins

Oleander poisoning
Japanese yew *(Taxus cuspidata)* poisoning
Castor bean poisoning
Avocado poisoning
Thorn apple *(Datura stramonium)* toxicity
Potato poisoning
Heath *(Ericaceae)* poisoning
Algae poisoning
Acorn or oak poisoning
Hypericum (St. John's wort, Klamath weed) poisoning
Agrostemma githago (corn cockle) poisoning
Mycotoxicosis
Pimelea poisoning (St. George disease) (exotic)
Monkshood
Buttercup
Death camas
Datura
Foxglove
Hoary alyssum

*See additional lists at www.vet.cornell.edu/consultant.

Secretory diarrheas are most important in neonates[4] (e.g., enteropathogenic *E. coli*), but many strains of *Salmonella* that are associated with colitis in large animals may also produce enterotoxins that stimulate secretion. Enterotoxins act by stimulating cyclic adenosine monophosphate (AMP) or other intracellular messengers to promote secretion of chloride, sodium, and other electrolytes into the gut lumen. Water is carried with these electrolytes and osmotically retained. The hallmark of secretory diarrheas is the large volume of feces produced.

Examples of secretory diarrheas are enterotoxigenic *E. coli,* many strains of *Salmonella,* and *C. perfringens. Salmonella* and other invasive microorganisms produce inflammation that may induce prostaglandin-mediated secretion as well. Secretion may occur with viral diarrhea by a different mechanism, as damaged mature (absorbing) villous cells are replaced by immature (secreting) crypt cells.[7] An example of viral secretory enteritis is rotavirus.

Decreased intestinal transit time, associated with increased peristalsis and/or decreased segmentation, appears to occur in many bowel diseases because of bowel irritation. Peritonitis is a major cause of bowel inflammation and should always be explored as a contributing cause of diarrhea, especially when fecal output volume is scant. Abnormal motor patterns have been demonstrated to occur with many infectious diarrheas and may be a bowel response to irritation and/or increased intraluminal volume. Elimination of gut contents thus appears to be a normal gut defense mechanism against infection and should not be pharmacologically alleviated in acute infectious diarrheas. Primary motility disorders of animals are not well recognized; diarrhea associated with nervous or excited animals may be the best example of this type. In general, fecal volume associated with motility disorders is not great.

Increased hydraulic or hydrostatic pressure, from the blood to the intestinal lumen, also decreases net fluid absorption. These can result from decreased oncotic pressure (hypoalbuminemia), increased capillary hydrostatic pressure (heart failure or portal hypertension as with liver disease), or decreased lymphatic drainage associated with inflamed or blocked lymph vessels or nodes (lymphosarcoma). These mechanisms are most commonly associated with chronic diarrhea, but acute inflammation can also result in diarrhea associated with this mechanism.

Two or more of these mechanisms are probably at work in most diarrheal diseases. Therapy of diarrhea is therefore nonspecific and supportive, except when the actual causative agent can be identified and is treatable. Diagnosis of a specific causative agent is most important when diarrhea is caused by an infectious agent, so that appropriate therapeutic steps can be taken before chronicity develops, spread of disease can be prevented, and an accurate prognosis can be made.

In mature horses, small intestinal diseases such as granulomatous bowel disease or duodenitis/proximal jejunitis (anterior enteritis) may not be associated with diarrhea and diseases of the stomach almost never cause diarrhea. Most significant diarrheal disease in adult horses involves the large colon because this is the principal site of water absorption. The exception to this is the neonatal foal, in which primarily small intestinal diseases such as rotavirus infection and cryptosporidiosis may cause severe diarrhea.

The frequency of defecation is usually increased when diarrhea is present, and defecation frequency is highest when the colon or rectum is irritated. When these areas are involved, tenesmus (straining) may result. Tenesmus can also occur with hepatic failure in ruminants and in horses and ruminants with rectal tears or strictures, vaginitis, retained placenta, dystocia, intussusception, urolithiasis, perirectal abscesses, rabies, and diseases involving the nervous system when there is retention of feces or urine. Severe rectal irritation can lead to straining and rectal prolapse.

In ruminants, abnormalities such as grain overload (toxic indigestion) resulting in ruminal osmotic changes can produce diarrhea, as can changes in abomasal pH such as occur with type II ostertagiasis. Diarrhea in ruminants is frequently caused by forestomach problems (Boxes 7-4 and 7-5). The colon and remainder of the distal bowel are involved in diseases such as salmonellosis. Gram-negative infections and resulting endotoxemia, found in conditions such as coliform mastitis and septic metritis, are relatively common causes of nonspecific diarrhea. Foals with septicemia also commonly develop nonspecific diarrhea associated with SIRS. Diarrhea may be (1) a manifestation of a primary disease (bovine viral diarrhea [BVD]; Johne's disease; *C. difficile,* salmonellosis); (2) one of the signs of a generalized disease (MCF, uremia); or (3) secondary to toxemia (coliform mastitis, septic metritis, septicemia, salmonellosis).

Nonspecific Fluid Therapy for Diarrhea

Dehydration, electrolyte losses, and acid-base abnormalities can occur rapidly when diarrhea is present. Treatment to correct these problems is an important component of nonspecific therapy in animals with diarrhea. Often the cause of diarrhea remains undetermined, yet correction of hypovolemia, dehydration, and acid-base and electrolyte abnormalities can result in a return to normal systemic function, particularly if the diarrhea is acute and severe. Fluids and electrolytes can be given orally or parenterally. Oral fluids can be given rapidly and inexpensively but only if dysmotility is not present. Oral fluids should be isotonic or hypotonic. The degree of dehydration should be estimated as a percentage of body weight. Mild dehydration is usually considered less than 5%; moderate, 5% to 8%; and severe, over 8%. Thus a severely dehydrated 450-kg patient with an estimated 10% dehydration (weakness, cold extremities, sunken eyes, decreased urine output, decreased elastic skin rebound, weak pulse, rapid heart rate) may require up to 45 L of fluids over time. Boluses of 10 to 20 mL/kg of isotonic crystalloid can be administered until signs of shock abate or plateau.

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BOX 7-4

Causes of Diarrhea in Ruminants (Except Neonates; see Chapter 20 for Neonates)

Common Causes

Parasitism, worms
Coccidiosis
Salmonellosis
Colitis or typhlitis
Enteritis, unknown cause
Indigestion (spoiled feed, overfeeding, or sudden change)
Displaced abomasum (B)
Abomasal torsion (B)
Peritonitis
Intussusception
Sepsis or toxemia
Johne's disease
Enterotoxemia
Grain overload (rumen acidosis)
Bovine viral diarrhea (B)
Winter dysentery (B)
Liver failure
Malignant catarrhal fever (B)
Molybdenosis or copper deficiency
Heart failure
Uremia, renal failure
Xylazine, following large doses
Cathartics or laxatives
Parasympathomimetics
Toxins or poisonous plants (see Box 7-5)

Less Common Causes

Amyloidosis
Giardiasis (mainly calves)
Intestinal obstruction, partial
Intestinal neoplasia
Traumatic reticuloperitonitis (hardware)
Vagal indigestion
Selenium deficiency (white muscle disease)
Cecal dilation (B)
Liver abscess
Brisket disease (high-altitude disease) (B)
Sarcocystosis (B)
Bluetongue (O)
Bovine leukosis (BLV) (B)
Hemorrhagic bowel syndrome (B)

Uncommon Causes

Fat necrosis (B)
Abomasal impaction
Duodenal ulcers
Systemic candidiasis
Vitamin A deficiency
Volvulus, root of mesentery
Water intoxication (B)
Cholelithiasis
Cobalt deficiency
Zinc deficiency (baldy calf) (B)
Hydrops allantois (B)
Lethal trait A 46, keratogenesis imperfecta (parakeratosis) (B)
Zygomycosis, mucormycosis
Pregnancy toxemia
Bacillary hemoglobinuria
Rumen flukes, paramphistomosis
Pancreatic adenocarcinoma
Bee or wasp sting
Pseudorabies
Hemochromatosis of Salers cattle (B)
Rift Valley fever (exotic)
Rinderpest (exotic)*
Schistosomiasis (exotic)
Theileriosis (East Coast fever) (exotic)
Wesselsbron disease (exotic) (B, O)
Heartwater (exotic)

*Rinderpest was a cause of diarrhea in ruminants until 2011, when it was eradicated worldwide.
B, Bovine; *O,* ovine.

BOX 7-5

Toxic Causes of Diarrhea in Ruminants*

Arsenic poisoning
Sulfur poisoning
Salt poisoning
Propylene glycol
Levamisole
Monensin, salinomycin, lasalocid (ionophores)
Polybrominated biphenyl
Sodium bicarbonate
Aflatoxin
Herbicide
Zinc
Lead
Phosphorus toxicity
Nicotine (Black Leaf 40) toxicity
Copper
Chlorpyrifos (Dursban)
Organophosphates
Phosphate fertilizer
Lincomycin
Trichothecene (T-2 toxin)
Plant toxins
Oak (acorn poisoning)
Senna occidentalis (coffee weed)
Selenium accumulators
Slaframine (blackpatch-diseased legumes, slobber factor)
Mycotoxicoses
Helenium (sneezeweed, bitterweed)
Solanum (nightshade)
Pyrrolizidine alkaloid (*Senecio, Crotalaria, Amsinckia* species)
Brassica (mustards, crucifers, cress)
Oleander poisoning
Japanese yew *(Taxus cuspidata)* poisoning
Whitehead *(Sphenosciadium capitellatum)*
Pokeweed *(Phytolacca americana)*
Mushroom
Inkweed *(Drymaria pachyphylla)*
Tung tree (aleurites)
Chinese tallow tree
Kalanchoe (crassulaceae)
Fungal toxicity
Sesbania (rattlebox)
Gutierrezia (broomweed, snakeweed)
Hypericum (St. John's wort; Klamath weed) poisoning
Agrostemma githago (corn cockle) poisoning
Monkshood
Buttercup
Castor bean (ricin)
Foxglove (digitalis)
Larkspur

*See additional lists at www.vet.cornell.edu/consultant.

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The optimal means of determining electrolyte status is to analyze a plasma or serum sample before initiating fluid therapy. Electrolyte requirements can be estimated; with diarrhea, mixed water and electrolyte losses occur, so sodium-containing fluids are usually required to replace lost sodium and improve blood volume (see also Critical Care and Fluid Therapy, Chapter 44). Unless the acid-base status can be measured, the safest sodium-containing fluids are balanced polyionic fluids such as PlasmaLyte A, PlasmaLyte 148, or lactated Ringer solution. Normal saline is a satisfactory alternative in most cases, but the relatively high concentration of chloride ions in saline can aggravate a preexisting metabolic acidosis through raising chloride concentration, producing a hyperchloremic metabolic acidosis (HCMA). In calves with severe metabolic acidosis, use of fluids containing sodium bicarbonate is indicated. In horses, it is best not to include large quantities of sodium bicarbonate in fluids unless there is good evidence that a severe strong ion metabolic acidosis exists (such as hyperchloremia). Flow rates for administering isotonic intravenous fluids should be monitored, with close attention to perfusion parameters, in order to avoid fluid overload, pulmonary edema, and excessive diuresis. When the patient is shocky, flow rates close to 20 mL/kg/h or faster may be required for administration of isotonic crystalloid fluids, but in general rates below 10 mL/kg/h are desirable, especially once hypovolemic shock has been addressed. Hypertonic saline (7% NaCl) may be given rapidly intravenously at a dose of 4 to 5 mL/kg. When a colloid fluid is required to combat low plasma protein concentrations, hetastarch or plasma can be used. Hetastarch is available as 6% hetastarch in a balanced electrolyte or normal saline solution. A dose of 10 mL/kg should not be exceeded for hetastarch because of development of dose-dependent coagulopathies. The use of hetastarch in human critical care has recently been questioned. A meta-analysis has suggested an increase in renal disease and mortality in patients treated with hetastarch.[7a] How this applies to large animals is unknown, but creatinine should be monitored closely. See Neonatal Diarrhea, Chapters 17 (neonatal foals) and 20 (neonatal ruminants); Fluid and Electrolyte Balance, Chapter 22; and Fluid Therapy, Chapter 44 for more details on fluids and acid-base balance.

Approach to Diagnosis of Diarrhea in the Horse (for Neonates, see Chapter 17)

1. Take history. Especially note change in diet, deworming program, housing and management, and whether diarrhea is acute or chronic. Note appetite, whether animal is drinking an adequate volume of water, and whether salt is available. Note whether it is a single or multiple case, if there are concurrent diseases, or if other medications or exposure to toxins is involved. Most antimicrobials have been associated with diarrhea in horses at times, but especially lincomycin, tetracyclines, and erythromycin. Antimicrobials should be discontinued if diarrhea develops during administration. Most pathogenic bacterial and protozoal agents rely on altered intestinal microflora to proliferate in the gut and cause diarrhea. Note whether nonsteroidal antiinflammatory agents were used before the development of diarrhea. Many causes of diarrhea can be eliminated from consideration on the basis of history. Find out about housing and whether animals have access to pasture or natural water sources or are stall confined. For example, Potomac horse fever would be considered in horses with access to water sources in endemic areas.
2. Perform physical examination. Take vital signs (these are often normal in chronic cases). Perform rectal examination unless an infectious contagious agent is suspected, especially if diarrhea is scant in volume. Note body condition score (see Chapter 9). Systemic signs of toxemia, SIRS, hypovolemia, and dehydration often accompany acute colitis, salmonellosis, equine monocytic ehrlichiosis (Potomac horse fever), clostridiosis, and many other acute diseases.
3. Examine feces. Perform gross inspection; note whether blood or fibrin is present (see list of causes of dysentery).
   a. Gram stain of feces. A predominance of gram-positive rods may indicate an anaerobic overgrowth such as occurs with *C. difficile* infections, although this is not highly sensitive or specific. Perform microscopic examination for ova and protozoa, especially for chronic cases.
   b. Perform multiple cultures for *Salmonella, C. difficile,*[8] and *C. perfringens* if onset is acute, if animal is febrile, or if feces contain fibrin and mucus. A commercial polymerase chain reaction (PCR) test can be used as an aid to evaluate for the presence of salmonellosis.[9] Cultures for *C. difficile* should be performed on selective media (cycloserine-cefoxitin-fructose agar). Recently *Brachyspira pilosicoli* has been isolated from the feces of weanlings with chronic diarrhea.[10] This warrants further investigation as a cause of diarrhea and failure to thrive in young horses. Fecal PCR and serology for *L. intracellularis* should be performed on young horses with hypoproteinemia, unthriftiness, and variable diarrhea.
   c. An evaluation for *C. difficile* and *C. perfringens* toxins (with fecal enzyme-linked immunosorbent assays [ELISAs] or a stool cytotoxin assay for *C. difficile*) should be made if the diarrhea is temporally associated with antibiotic administration. Several ELISA kits are available for identification of toxins A (enterotoxin) and B (cytotoxin) of *C. difficile* in feces. A stool cytotoxin cell culture is available for toxin B.[11,12] Toxin B cell culture testing is considered the gold standard.[13]
   d. Isolates of *C. perfringens* should be examined for the ability to produce alpha, beta, epsilon, and beta 2–toxins because certain strains may be associated with gastrointestinal disease.[14,15] Type C *C. perfringens* isolates have been associated with the most severe disease in horses and foals. Gene sequences for these toxins are found by PCR once the isolates are cultured. In addition, a commercial fecal ELISA is now available for detection of alpha-toxin, beta-toxin, and epsilon-toxin in feces directly at the California Animal Health and Food Safety Laboratory (San Bernardino). This allows diagnosis of *C. perfringens,* types A (alpha toxin) and C (alpha and beta toxins).
   e. Fecal occult blood (if positive, see list of causes of melena and blood in feces).
   f. Fecal osmolality, sodium, and potassium concentrations (optional). Electrolyte concentration in feces is roughly twice the sodium plus potassium. When this value is much lower than the measured osmolality of the feces, the difference is an osmolar gap caused by osmotically active nonelectrolytes, and osmotic diarrhea is confirmed.
   g. Check for sand by placing some feces in a bucket of water, mixing thoroughly, and decanting the water. If a radiographic unit with the appropriate power capability is available, abdominal radiographs should be taken to detect the presence and amount of sand. Ultrasound of the ventral abdomen can be used to diagnose the presence of sand, although this requires considerable expertise.
   h. A PCR test for feces is available at University of Minnesota Diagnostic Laboratory at www.vdl.umn.edu and the University of California Molecular Laboratory at www.vetmed.ucdavis.edu/vme/taqmanservice/ (see Chapter 29 for complete list) for detection of *L. intracellularis,* organisms in weanlings and yearlings with diarrhea, weight loss, general malaise, and hypoalbuminemia.[16] Also see serum test described later.
   i. *Rhodococcus equi* can cause diarrhea in 3-week to 6-month-old foals. Diagnostic tests include cultures of transtracheal aspirates, abdominal fluid cytology and culture, abdominal ultrasonography, and ruling out other etiologies of diarrhea. Fecal PCR techniques are also available.[17]
   j. If all other cultures are negative and an infectious cause of diarrhea is suspected, the feces should be cultured for *Aeromonas* species and *C. perfringens* (see earlier).[18,19]
4. Obtain blood for the following database:
   a. Complete blood count (CBC; includes fibrinogen and plasma protein concentrations). Increased fibrinogen concentration indicates inflammation. Decreased protein concentrations

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indicate protein-losing enteropathy. Thrombocytopenia may indicate a coagulopathy. Neutropenia with or without a toxic, left shift (immature neutrophilia) is often present with infectious and inflammatory causes of acute colitis, indicating SIRS. Increases in packed cell volume (PCV) and red cell mass are often present, indicating hemoconcentration and/or splenic contraction in horses.

b. Acid-base analysis should be performed if the condition is acute and the horse is dehydrated or toxic. Although acid-base values are not useful diagnostically in terms of specific etiology, they allow for initiation of proper acid base and electrolyte supportive therapy.

5. Test serum for the following:
   a. Electrolyte (Na, K, Cl, Mg, Ca, HCO_3) concentrations.
   b. Serum creatinine and blood urea nitrogen (BUN) concentrations—prerenal azotemia is common as a result of dehydration; check again after rehydration. Acute renal failure is also common. Serum chemistries should be evaluated for liver and other organ disease.
   c. Albumin and globulin concentrations; hypoalbuminemia is seen with chronic protein-losing enteropathies such as inflammatory bowel disease (e.g., granulomatous enteritis), phenylbutazone toxicity (right dorsal colitis), and acute colitis conditions (such as salmonellosis).
   d. Specific immunoglobulin (Ig) A, IgM, and IgG concentrations; immunodeficient individuals may have chronic diarrhea. Specific immunoglobulin concentrations may be altered with lymphoma or multiple myeloma. Elevated globulins may indicate the presence of chronic disease.
   e. PCR for *Neorickettsia risticii* (Potomac horse fever) in whole blood and feces samples. Paired sera for *Neorickettsia risticii* titer following acute diarrhea with fever can also be performed.
   f. Clotting times (prothrombin time [PT] and partial thromboplastin time [PTT] or activated clotting time [ACT]) should be monitored as indicators of coagulopathies such as disseminated intravascular coagulation (DIC) in horses with acute typhlocolitis. Antithrombin III levels can be monitored for the risk of thromboses, particularly in horses with hypoproteinemia.
6. Perform abdominocentesis, especially if signs of colic are present. Evaluate cytology, protein, and fibrinogen values in chronic cases to rule out peritonitis, tumors, and mesenteric abscess.
7. Perform function and absorption tests in chronic diarrhea cases, especially when weight loss is present.
   a. Oral glucose or xylose small intestine absorption tests (see Chapter 32) for chronic cases, particularly if a high index of suspicion of malabsorption exists because of hypoalbuminemia. If tests indicate malabsorption, either biopsy the gut (duodenum through duodenoscopy or rectum) or assess the response to treatment following larvicidal anthelmintic treatment.
   b. Perform liver function tests such as measurement of serum bile acid concentrations if liver involvement is suspected as a result of increased liver enzyme concentrations and/or hypoalbuminemia. Liver enzymes are increased in many cases of enterocolitis and in these cases do not necessarily indicate primary liver disease (see Chapter 33). Secondary liver disease may occur secondary to endotoxemia or altered hemodynamics, as well as cholangiohepatitis.
8. Examine tissue.
   a. Rectal or intestinal (duodenal) biopsy for microscopic examination and fluorescent antibody for immune-mediated diseases (also culture for *Salmonella*). Rectal histopathology is particularly useful in horses with hypoalbuminemia or weight loss.[20]
   b. Detection of *C. perfringens* beta 2–toxin from types A or C by immunohistochemistry of gut mucosa is diagnostic on biopsy or postmortem specimens.[21]
   c. Liver biopsy if indication of significant or persistent liver disease, especially in chronic cases.
9. Toxicology.
   a. Blood lead, liver lead, and liver arsenic concentrations can be measured if toxicity is suspected.[22]
   b. High-pressure liquid chromatography or gas chromatography-mass spectrometry can be used to detect cantharidin (blister beetle toxin) in urine or gastrointestinal contents.[23]
   c. Urine, serum, and gastrointestinal contents can be evaluated for the presence of oleandrin toxins using thin-layer chromatography. Oleander toxicity should be suspected in animals with diarrhea, colic, arrhythmias, and renal disease.[24]
10. Evaluate response to treatment with undiagnosed chronic diarrhea.
    a. Alter diet to simple grass hay. Alternatively, a complete pelleted diet can be tried, especially if right dorsal colitis or maldigestion/malabsorption is suspected. Psyllium mucilloid (4 oz), and 1 to 2 cups of corn oil can be added to the daily diets of horses with right dorsal colitis.[25,26]
    b. Stop nonsteroidal drugs such as phenylbutazone if toxicity is a possible cause.
    c. If no protozoa are seen in fecal samples, attempt transfaunation with fecal (or colon or cecum if available) contents from a healthy animal.
    d. Attempt to classify by rectal biopsy; many changes are nonspecific.
       (1) Mononuclear cell infiltrate (lymphocytic or granulomatous enteritis): Administer 0.04-0.06 mg/kg dexamethasone per day, tapering down to 0.02 mg/kg in 1 week; if response is favorable, continue with 1-1.5 mg/kg prednisolone PO per day, taper over 2 months.

           Eosinophilic infiltrate: Administer larvicidal anthelmintic dose of fenbendazole plus corticosteroids as earlier.
    e. Transfusion with plasma (1 to 2 mL/kg) in young horses 2 to 12 months of age that may need some additional proteins, antithrombin, or immunoglobulin. Synthetic colloids such as hetastarch can be used in animals with reduced colloid osmotic pressure (hypoalbuminemia); check especially if edema is present. Hetastarch has been used at 10 mL/kg, and this dose should not be exceeded daily because of risks of dose-dependent coagulopathies.[27]
    f. Horses with Potomac horse fever often respond favorably to systemic treatment with tetracycline.
    g. Metronidazole (15 mg/kg PO q 8 h) can be used empirically, especially if an anaerobic overgrowth is suspected, or when the diarrhea is secondary to antibiotic use.[28]

Approach to Diagnosis of Diarrhea in Ruminants (for Neonates, see Chapter 20)

1. Take history. Especially note diet, appetite, previous deworming and vaccinations, and whether it is an individual or herd problem. In animals younger than 1 year of age, *Coccidia, Ostertagia,* or other helminths should be strongly considered. Determine if onset is acute or chronic. If chronic, first consider diseases such as parasitism, Johne's disease, copper deficiency (molybdenosis), selenium deficiency, liver failure, and other diseases of individual cows such as bovine leukosis virus (BLV), amyloidosis, heart failure, or uremia.
2. Perform physical examination. Especially note weight loss, fever, systemic signs, rumen activity, and oral lesions. Perform rectal examination. In most acute-onset diseases, vital signs are abnormal and systemic involvement or oral lesions (especially with BVD) may be obvious.
3. Examine feces.
   a. Gross inspection
   b. Microscopic examination for ova and parasites

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c. Culture for *Salmonella* if animal is febrile or feces appear inflammatory (fibrin or mucus)
d. Check for fecal occult blood
e. Culture of *Mycobacterium avium* subsp. paratuberculosis, if weight loss is a problem (especially if a herd problem in animals older than 2 years of age)

4. Take rectal scrapings of mucous if weight loss and chronic diarrhea are present.
   a. Make thin smear on glass slide for acid-fast staining for *M. avium* subsp. paratuberculosis. Examine under oil immersion lens.
5. Obtain blood for the following:
   a. Plasma proteins
   b. Fibrinogen
   c. In acute cases, electrolytes and acid-base status
   d. If a herd problem, copper and selenium status
6. Test serum for the following:
   a. BUN
   b. Liver enzymes (γ-glutamyltransferase [GGT] and sorbitol dehydrogenase [SDH])
   c. Albumin and globulin values
   d. Agar gel immunodiffusion (AGID) for BLV (single animals); request gp51 and p24 antibody status
   e. If Johne's disease is suspected, perform ELISA test
7. Perform paracentesis. Paracentesis rules out gross peritonitis, but many false-negatives are possible as a result of focal or fibrinous peritonitis.
8. Perform urinalysis for protein to rule out consideration of amyloidosis or other multisystemic immune-mediated disease. Because ruminants normally have a urine pH of 8 or higher, most dipstick tests will give a trace or a 1+ positive reading for urine protein even when the animal's urine is normal.
9. Examine tissue. Perform rectal, intestinal, or mesenteric lymph node biopsy for acid-fast stain for Johne's disease, for culture for *Salmonella,* and for presence of lymphosarcoma.
10. Perform feed analysis (herd problem only); check copper, molybdenum, and selenium levels.
    a. Toxins suspected (e.g., mercury, arsenic)
11. Tap abomasum for increased pH; rule out type II ostertagiasis.
12. Perform necropsy (herd problem only).
    a. Pick severely affected individual to examine thoroughly.

Colic

K. Gary Magdesian • Bradford P. Smith

Colic is defined as the manifestation of visceral abdominal pain. Colic may be the result of nongastrointestinal pain such as urinary tract obstruction (Boxes 7-6 and 7-7). This section discusses colic of gastrointestinal origin. Pain may be acute, chronic, or recurrent. Gas distention or recognizable organic problems such as displacements are most frequently associated with acute colic. Five basic causes of colic in large animals are as follows:

- Distention of gut with fluid, gas, or ingesta
- Pulling on the root of the mesentery (mesenteric tension)
- Ischemia or infarction
- Deep ulcers in the stomach or bowel
- Peritoneal pain (peritonitis)

Signs of colic in the horse include restlessness, lying down and getting up, groaning, grunting, rolling, sweating, kicking at the abdomen, or suddenly dropping to the ground in pain. Anorexia and depression often accompany these signs. Horses may develop hypovolemic or endotoxic shock characterized by tachycardia with weak pulse quality and prolonged capillary refill time, cold extremities, and bright red (vasodilatory phase) followed by dark or pale (vasoconstrictive phase or low cardiac output state) mucous membranes if the problem is severe and affects cardiovascular integrity.

Evidence of shock is usually present only when the disease condition is severe and involves ischemic or infarctive disease (volvulus,

BOX 7-6

Gastrointestinal Causes of Colic in Horses*

Common Causes

Accumulation of intestinal, cecal, or colonic gas
Hypermotility and intestinal spasms
Feed impaction, constipation
Meconium impaction (newborn)
Gastric ulcers (foal)

Less Common Causes

Thromboembolism
Intestinal foreign body (sand; enterolith; phytobezoar)
Volvulus of small intestine
Pedunculated lipoma with bowel strangulation
Hernia, inguinal, epiploic, umbilical, diaphragmatic
Nephrosplenic ligament bowel entrapment
Ascarid impaction
Massive strongyle infection
Gastric dilation
Anterior enteritis (duodenitis or proximal jejunitis)
Enteritis, impending or active
Peritonitis
Parasympathomimetic drugs
Irritant cathartics
Necrotizing enterocolitis
Psychogenic colic
Rectal tear
Volvulus or displacement of large bowel
Rupture of stomach or intestine
Ileus
Intussusception

Uncommon Causes

Abdominal adhesions
Intramural hematomas of stomach or intestine
Stenosis or stricture of bowel lumen
Botulism
Tetanus
Potomac fever
Exhaustion
Anaphylaxis
Rhodococcus equi, gut abscesses
Cribbing or wind sucking
Abdominal fibroma
Segmental ischemic necrosis following mesocolic tearing
Equine viral arteritis
Anthrax with bleeding
Malignant edema (*Clostridium* species)
Malignant mesothelioma
Gastric or intestinal tumor
Atropine
Vitamin K3 deficiency (moldy sweet clover)

Toxins

(See also toxins listed under Diarrhea)
Cantharidin toxicity
Dioxin
Trichloroethylene-extracted feed toxicity
Warfarin (dicumarol)
Herbicides
Lead
Nitrophenyl urea (vacor)
Phenylbutazone or other nonsteroidal antiinflammatory drugs
Poison plants (many of those that produce diarrhea also produce colic; see plant toxins listed under Diarrhea)
African horse sickness (exotic)
Grass sickness (exotic)

*See additional lists at www.vet.cornell.edu/consultant.

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BOX 7-7

Causes of Colic in Ruminants*

Common Causes

Increased intestinal gas
Intussusception
Torsion or volvulus of the mesenteric root
Peritonitis
Intestinal foreign body or obstruction
Urolithiasis
Ruptured bladder
Acute pyelonephritis
Abomasal torsion
Abomasal ulcer
Cecal dilation or volvulus
Severe bloat

Less Common Causes

Cystitis or urinary tract disease
Abomasal bloat (neonates)
Uterine torsion or rupture
Hernia
Parturition, impending
Hypermotility and spasms of gut
Feed impaction
Right displaced abomasum
Acute traumatic reticulitis, abomasitis, or duodenitis
Acute liver disease
Vagal indigestion
Hemorrhagic bowel syndrome
Atresia coli (neonates)

Uncommon Causes

Rabies
Rectal tear
Rectal prolapse
Diaphragmatic hernia
Grain overload
Water intoxication
Winter dysentery
Ovarian abscess
Fat necrosis
Cholelithiasis
Intestinal adhesions
Enterotoxemia
Ileus
Intestinal strangulation
Inversion of uterine horn
Malignant edema
Malignant mesothelioma
Ruptured uterine artery
Intestinal neoplasia
Aortic, iliac, or femoral thrombosis
Anaphylaxis
Renal cysts
Ruptured prepubic tendon
Vaginal laceration
Torsion of descending colon
Rinderpest (exotic)†

Toxins

Plant poisonings (many of those that cause diarrhea also produce colic; see plant toxins listed under Diarrhea)

*See additional lists at www.vet.cornell.edu/consultant.
†Rinderpest was a cause of colic in ruminants until 2011, when it was eradicated worldwide.

torsion, thromboembolism) or advanced visceral distention (extreme flatulence, impaction, or dilation). Foreign bodies such as sand or enteroliths in the large colon may result in low-grade recurrent colic. When an enterolith is passed into the transverse colon where it obstructs the bowel, signs of complete obstruction and acute colic ensue. These signs are manifestations of visceral pain, mediated by the sympathetic nervous system. External palpation and pushing on the abdomen of adult horses does not usually elicit pain unless the affected inflamed or dilated viscus is contacted.

In contrast, parietal pain associated with peritonitis is sometimes responsive to external palpation. Whereas the animal with visceral pain shows active signs of colic, the animal with parietal pain is usually reluctant to move and has a splinted abdomen. Acute peritonitis occurs within minutes after rupture of the stomach or perforation of an ulcer as a result of immediate irritation of serosal surfaces by the acid contents, whereas with rupture of the colon or rectum it may take several hours or more before peritonitis is clinically apparent.

Ruminants exhibit colic less frequently than horses, probably because of a higher threshold for pain and because dietary shifts principally affect the rumen; thus intestinal gas pains occur less frequently. Colic with visceral pain (including urinary tract) is manifested by grinding the teeth (odontoprisis or bruxism), grunting or groaning, treading with the hind feet, kicking at the abdomen, restlessness, repeatedly lying down and getting up, anorexia, and depression. With parietal pain caused by peritonitis, ruminants demonstrate abdominal pain by arching the back, splinting, and exhibiting pain on deep palpation of the area. These signs are seen most commonly with traumatic reticuloperitonitis and abomasal ulcers; rarely are these diseases associated with the colic signs described previously.

Diagnosis and Management of Colic in the Horse (for Neonates, see Chapter 17)

1. Take history. Because colic is a common problem in horses, mild to moderate degrees of abdominal pain are often initially treated symptomatically with analgesics and/or laxatives before major diagnostic efforts are undertaken. Most colic of mild to moderate severity responds favorably to symptomatic treatment. In general, severe pain or pain that is unresponsive to analgesics indicates a more serious condition for which more aggressive medical management or surgical correction may be indicated. Recurrent mild-to-moderate colic may be an indication of a more serious problem such as bowel entrapment or displacement, thromboembolism, internal abscess, enterolith, sand or other foreign body, tumor, gastric ulcer, hypobiotic cyathostomiasis, *Strongylus vulgaris* larval migration, heavy burden of ascarids, abdominal adhesions, strictured bowel, or urinary tract disease.
2. Perform physical examination. Intestinal causes of colic can often be differentiated from colic associated with other organ systems (Box 7-8) by physical examination findings and laboratory data. Although extraintestinal origins of acute colic are relatively uncommon in the horse, they include abdominal abscesses, tumors, cholelithiasis or cholestatic disease, and genitourinary tract disease and can be recurrent. It is important to note the presence or absence of normal intestinal borborygmi and whether or not feces are being passed in determining whether the problem is extraintestinal. Careful auscultation of the thorax should be performed to evaluate for the presence of diaphragmatic hernias or pleural disease. The testicles should be palpated on all stallions to screen for scrotal hernias or testicular torsions. Rectal examination findings often help to determine anatomic location within gut or other site. Abdominal tumors, abscesses, and other masses may be palpable. Although mild to moderate chronic intermittent colic may be of extraintestinal or intestinal origin, most cases of severe unremitting colic indicate gut involvement, often with anatomic displacement or ischemia.
3. Ultrasound and radiology. Ultrasound may help in locating masses, adhesions, or enlarged liver (see Abdominal Ultrasonography, Chapter 32). It may also be helpful in the diagnosis of gastrointestinal disease including nephrosplenic entrapment of the large colon and small intestinal distention. Detection of sand from the ventral abdomen may be possible. Ultrasound can be particularly useful in foals and small ruminants because of their size. Radiology can also be useful in detecting enteroliths or sand

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BOX 7-8

Extraintestinal Causes of Colic in Horses

Common Causes

Mesenteric abscess
Ovarian tumor, abscess, or hematoma
Parturition
Acute hepatitis (massive necrosis) or hepatic lipidosis
Diaphragmatic hernia
Ruptured bladder (foal)
Uterine torsion

Less Common Causes

Urinary tract or renal disease, including urolithiasis
Pleuritis or pericarditis (referred pain)
Retained placenta
Uterine rupture or retroflexion
Spermatic cord thrombosis or torsion

Uncommon Causes

Perirectal abscess
Pheochromocytoma
Purpura hemorrhagica
Biliary atresia
Vaginal or vulvar tear
Cholelithiasis
White muscle disease
Atypical myopathy
Rabies
Rupture of prepubic tendon
Splenitis, splenic abscess, splenomegaly
Cauda equina neuritis with retention of feces or urine

in adult horses and in some gastrointestinal conditions of foals, provided powerful units are available. Rarely is radiology useful in diagnosing the cause of colic in ruminants, except for urethrographs in sheep and goats to locate a urethral stone.

4. Examine feces. Gross examination of feces should be performed. The presence of sand can often be detected by mixing feces with water in a bucket, then pouring off the water and looking for sediment. If no feces are passed, a more serious condition is usually indicated, particularly if intestinal sounds are absent.
5. Use laboratory aids. Laboratory aids of immediate benefit in diagnosis and management include measurement of PCV and plasma protein concentration to aid in assessing hydration and vascular integrity and an abdominal paracentesis to evaluate abdominal fluid grossly and microscopically. Pain and excitement alone can increase the PCV, but there is a correlation of increased PCV (>55%) in colics with nonsurvival. Plasma proteins are not increased acutely unless blood volume is decreased through shifts in compartmental distribution of body fluids. In colic cases these fluid shifts usually mean that an increased and abnormal amount of extracellular fluid is in the gut lumen, a "third space" where it is not available for maintaining blood volume. Blood lactate concentration measurement has become routine in evaluation of horses with acute abdominal disease. It is useful in monitoring as an end point to fluid therapy. Some studies have suggested a prognostic role of lactate in horses with colic, although there is marked variability. An increase in peritoneal lactate concentration over time has been predictive of strangulating lesions in horses with colic.[29] Abdominal fluid is normally present in small volume (a few drops to 50 mL); is clear and colorless to yellow; and has a total protein concentration below 2.5 g/dL, specific gravity less than 1.015, little or no fibrinogen (<100 mg/dL), and fewer than 5000 white blood cells (WBCs) per microliter. Increases in these parameters or increased numbers of neutrophils in peritoneal fluid often indicate inflammation on serosal surfaces. Comparisons of abdominal fluid glucose with serum glucose (>50 mg/dL difference is abnormal) and evaluation of abdominal fluid pH, lactate (as compared with blood lactate), and lactate dehydrogenase (LDH) concentrations can aid in the diagnosis of septic peritonitis.[30] Grossly, fluid changes to cloudy yellow, then to blood-tinged with fibrin clots, and finally to black in color as bowel necrosis and hemolysis of extravasated red blood cells (RBCs) occur. Increased levels of peritoneal fluid protein concentrations are consistently found in anterior enteritis (duodenitis and proximal jejunitis) and often disproportionate to the increase in white blood cell concentration and therefore provide a useful differential aid, although this finding is nonspecific and observed with other conditions, such as in cantharidin poisoning. Increased protein levels are present in peritonitis but accompanied by increased numbers of neutrophils. If peritoneal fluid is grossly contaminated with feed material, rupture of a viscus should be considered. Another peritoneal tap in a different location should be undertaken if the possibility of bowel penetration during paracentesis cannot be ruled out. It is not necessary to have abnormal peritoneal fluid before consideration of surgical correction of colic is contemplated. Recently, abdominal fluid lactate has been shown to be predictive of intestinal ischemia secondary to strangulating obstruction and may aid in early detection of intestinal strangulation, rupture, and septic peritonitis.[31] Many chemical analyses (e.g., lactate) of blood or peritoneal fluid have been recommended as an aid in prognosis and gauging severity of tissue damage. Plasma fibrinogen, as well as peripheral leukocyte counts, can aid in the differentiation of enterocolitis or anterior enteritis from strangulating lesions. Serum electrolyte concentrations and acid-base status are important from a therapeutic standpoint. Serum biochemistries, including liver enzymes, creatinine, and BUN, are important in evaluating for liver and renal compromise. Hyperglobulinemia may be indicative of chronic disease.
6. Evaluate response to treatment. The approach to diagnosis of colic signs is often tied in with management because if the animal's pain cannot be alleviated, surgical intervention and specific diagnosis of displacements, torsions or volvulus, internal hernias, masses, and adhesions are the next steps. The initial diagnosis considers the history of deworming and feeding. The findings of the physical examination, including rectal examination and evaluation of the degree of pain, determine whether additional laboratory workup is indicated. In many cases with mild to moderate pain and no evidence of shock, standard treatment is parenteral administration of an analgesic agent (see Chapter 3) and oral administration of a mild laxative such as mineral oil (4 to 8 mL/kg). When a nasogastric tube is passed, the stomach should be checked for reflux and decompressed as needed. The pH of the gastric reflux may indicate primary gastric dilation if acidic, or small intestinal blockage or ileus if alkaline. Dark brown, foul-smelling, and alkaline reflux is often associated with anterior enteritis (duodenitis and proximal jejunitis). If a significant amount of reflux is present, oral medications should be withheld. If cardiovascular function is impaired (poor mucous membrane color and capillary refill, weak pulse, cold extremities, impending shock), balanced, polyionic, and isotonic crystalloid fluids should be given intravenously at a rate of 10 to 20 mL/kg boluses until signs of shock abate or plateau. In addition, 4 mL/kg hypertonic saline can be administered as a rapid but transient treatment of shock. Large amounts of painful gas auscultable in the right flank can be tapped and drawn off with cecal trocharization, although the risk for peritonitis should be considered and this technique should be reserved when surgical exploration is not an option or is delayed. The principles of colic management include (1) control of pain, (2) relief of distention, (3) relief of obstruction, and (4) treatment of shock.
7. Perform exploratory surgery. In making a decision concerning management of colic, it is important to separate impending enteritis and peritonitis from bowel disease requiring surgical intervention. Anterior or proximal enteritis can result in prolonged moderate pain and requires constant or frequently

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repeated analgesic administration and gastric decompression of the foul-smelling, dark reddish-to-brownish stomach contents. However, pain often subsides and is replaced with depression after gastric decompression in horses with anterior enteritis, whereas horses with strangulating lesions often remain in pain. The presence of fever or decreased total WBC count (with neutropenia) may be an indication of impending or ongoing enteritis, in which case surgery may not be indicated.

Surgery is indicated in the following situations:

a. Pain is severe and intractable or nonresponsive/poorly responsive to analgesics.
b. Pulse is weak and rate is over 70 beats/min, and oleander or other cardiotoxicity is ruled out.
c. Perfusion is poor, as evidenced by cold extremities, mucous membranes are off color, and capillary refill is poor.
d. No gut sounds are auscultated (a lack of fecal production).
e. Bowel is markedly distended.
f. Large volumes of yellowish alkaline gastric reflux are present.
g. Abdominocentesis indicates damaged bowel (blood tinged, increased protein, increased WBCs). When proximal enteritis remains a possibility, surgery should be avoided.

Surgery may be contraindicated in the following situations:

a. Fever
b. Neutropenia or marked neutrophilia
c. Severe icterus or marked enzyme abnormalities indicating primary liver disease
d. Foul-smelling, brownish-red gastric reflux characteristic of proximal enteritis (duodenitis/jejunitis), especially when removal of reflux results in discontinuation of signs of pain
e. Evidence of an extraintestinal cause not amenable to surgical correction (such as severe pyelonephritis)
f. Colitis or diarrhea
g. Abnormal behavior or neurologic signs (look for neurologic diseases and blood ammonia concentrations)

Diagnosis and Management of Colic in Ruminants

1. Take history. Colic in neonates is most often associated with increased abomasal or intestinal gas and is discussed in Chapter 20. Perforating ulcers are not uncommon as a cause of colic in calves 1 to 6 months of age. It should be determined whether the onset of colic was acute or whether the colic is chronically recurrent. Few diseases cause recurrent colic in ruminants. Urolithiasis is the most common cause of colic in male or neutered male goats and sheep and occurs under varied dietary and environmental conditions. Urolithiasis in cattle occurs most frequently in bulls or steers eating high-grain diets, but silicate stones can occur in very young animals and animals on pasture diet.
2. Perform a physical examination. Take vital signs; with torsion or severe peritonitis, shock signs such as rapid heart rate (>90 beats/min), cold extremities, and weakness may be seen. Tympany can be detected by simultaneous auscultation and percussion. Such causes of colic as cecal dilation, bloat, free gas in the peritoneal cavity, and severe abomasal dilation can be diagnosed in this way (see Figs. 1-3 to 1-5). Rectal examination detects such abnormalities as gas in the cecum, uterine abnormalities, urinary tract disease, and intussusception. Observe animal urinating to rule out obstructive urolithiasis. Ultrasound examination of the abdomen is also useful (see Abdominal Ultrasonography, Chapter 32).
3. Examine feces. Observe grossly; intussusception usually has scant dark red (almost black) feces. Black tarry feces may also be seen with bleeding abomasal ulcer of some duration. Scant feces are seen with cecal dilation or displacement.
4. Check preputial hairs and urethral process for sediment and stones. Grit on the preputial hairs is often associated with urolithiasis. Observe animal urinating and check urine for abnormalities. Rule out pyelonephritis. Radiology and ultrasound can be useful in sheep and goats when urolithiasis is a consideration. Ultrasound can detect a distended bladder, and stones may sometimes be detected. Radiology (lateral view) may detect a stone in the urethra or stones in the bladder. A contrast urethrogram may also be diagnostic.
5. Perform paracentesis to look for peritonitis caused by perforated abomasal ulcer, serosal devitalization, intussusception, or ruptured bladder. Interpret as earlier for horses, except that normal peritoneal fluid protein concentration can go as high as 5 g/dL in ruminants.
6. Other laboratory aids such as CBC and clinical chemistries are seldom diagnostic in ruminant colic. If grossly abnormal, they may be grounds for formulating a poor prognosis. Intussusception may be associated with neutrophilia (as well as dark feces and colic) in cases where peritonitis is occurring.
7. Symptomatic treatment of colic includes analgesics and, if heart rate is over 90 beats/min, intravenous fluid therapy with a sodium-containing fluid. Take blood sample for electrolytes and acid-base status before initiating fluid therapy.
8. Surgical exploration is indicated if colic is persistent, abdominal distention occurs, the heart rate is over 100 beats/min, feces are scant (especially those that are dark red and indicative of intussusception), there are pings indicating abomasal or cecal displacement or torsion, or the peritoneal fluid indicates bowel devitalization (blood-tinged fluid with elevated protein and WBCs). If surgical exploration is indicated, an important consideration is whether the animal will remain standing under local anesthesia during surgery. It is often best to perform abdominal surgery on animals with colic in left lateral or dorsal recumbency, aided by sedation and restraint, to avoid sudden collapse when painful surgical manipulations are performed. If the left lateral position is selected, use padding to raise the hip and shoulder so that the abdominal viscera can sit in a depression.

Melena

Bradford P. Smith

Melena (dark, tarry feces) is caused by blood in the lumen of the stomach or proximal intestinal tract, resulting in black (digested) blood appearing in the feces (Boxes 7-9 and 7-10). Usually blood is a result of a bleeding ulcer in the stomach or abomasum but may also result from ingestion, oral or pharyngeal bleeding, or coughing up

BOX 7-9

Causes of Melena in Horses

Common Causes

Gastric or duodenal ulcer
Gastric squamous cell carcinoma
Coughing up and swallowing blood

Less Common Causes

Phenylbutazone toxicity (nonsteroidal antiinflammatory drugs)
Purpura hemorrhagica
Gastroenteritis with bleeding
Warfarin toxicity or other coagulation disorder
Colonic hematomas
Disseminated intravascular coagulation with mucosal hemorrhage
Anterior or proximal enteritis (duodenitis or proximal jejunitis)
Arsenic toxicity
Hepatic failure with hemolysis
Nonsteroidal antiinflammatory drug (NSAID) toxicity

Uncommon Causes

Lupus erythematosus
Factor VIII deficiency, hemophilia A
Histoplasmosis
Hemangiosarcoma
Snake bite

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blood that is then swallowed. In ruminants the presence of dark red feces from an intussusception is the main differential to be considered. Blood must stay in the intestinal tract for hours before the hemoglobin is altered and turns black. Small amounts of hemoglobin can be detected by using one of the tests for occult blood. In general, fairly large volumes of blood (1 to 2 L) are required to produce a positive fecal occult blood test in the horse (Carlson G, personal communication, 1990). A 24- to 48-hour time period is necessary for orally administered blood to reach the rectum in the horse. In ruminants, smaller volumes of blood are necessary to produce a positive fecal occult test, and a faster transit time is expected (Carlson G, personal communication, 1990).

In approaching a diagnosis, rule out pulmonary, oral, or pharyngeal bleeding. Bleeding of gastrointestinal origin can be determined to be caused by mucosal disease or full-thickness bowel disease (such as an intussusception or neoplasia) by examining peritoneal fluid for abnormalities. Abnormalities in peritoneal fluid are usually present in the case of serosal involvement. Bleeding abomasal ulcers are probably the leading cause of melena in ruminants. They can be silent except for the dark feces and weakness if severe anemia develops. In older horses, gastric squamous cell carcinoma is a frequent cause of gastric hemorrhage. Significant bleeding is much less common in foals and calves with gastric ulcers, and melena is rare in foals and calves with gastric ulcers.

Consideration should be given to whether or not the melena is the result of clotting abnormalities associated with such diseases as DIC or warfarin poisoning. In cattle with colic and dark red-to-black feces, intussusception should be considered likely.

When severe anemia develops, there is evidence of blood loss because the decrease in PCV and RBCs is accompanied by a decrease in plasma proteins. Nonspecific therapy for melena consists principally of blood transfusions in life-threatening cases. Sudden, massive gastric or abomasal bleeding may result in anemia and collapse before melena has appeared.

In the foal, gastric ulcers may be treated with histamine-2 (H2) blockers such as ranitidine or cimetidine. These drugs are probably less effective in ruminants. Their benefit in ruminants with abomasal ulcers is not well understood at present. Drugs such as the hydrogen pump blocker omeprazole are useful and potent gastric pH effectors. Therapy with protectants such as sucralfate (which coats the ulcer) is a viable and clinically useful therapy in the horse. In ruminants, orally administered protectants and antacids are so diluted by the time they reach the abomasum that they are probably of limited benefit.

BOX 7-10

Causes of Melena in Ruminants

Common Causes

Abomasal ulcer
Intussusception

Less Common Causes

Lung abscess with ruptured blood vessel
Oak toxicity
Coccidiosis
Gastroenteritis with bleeding
Arsenic toxicity
Ingestion of blood after parturition
Intestinal parasites
Toxicity from nonsteroidal antiinflammatory drugs
Abomasal torsion or volvulus
Hemorrhagic bowel syndrome

Uncommon Causes

Duodenal ulcers
Hemophilia A, factor VIII deficiency
Bacillary hemoglobinuria
Sulfur toxicity
Warfarin poisoning or other coagulation disorder
Snake bite
Bovine viral diarrhea
Malignant catarrhal fever
Winter dysentery
Narthecium asiaticum maxim poisoning (exotic)

Blood, Fibrin, and/or Mucus in Feces (Dysentery)

Bradford P. Smith

Bloody diarrhea is termed *dysentery.* The presence of fresh blood or clots in the feces is termed *hematochezia,* and is the result of bleeding into the distal intestinal tract. Occasionally blood from the female reproductive tract may appear in or on the feces. Fibrin indicates severe inflammatory bowel disease. Fibrin appears as casts, chunks of yellow-gray material, or mucosa-like sheets. Mucus in feces increases with inflammatory bowel diseases such as salmonellosis. It is often seen when fecal volume is small in animals that are anorectic, in which case the feces are often coated with mucus. This mucous coating can become obvious in the horse and is not a sign of bowel disease in this case.

Frank blood in feces without diarrhea and other evidence of gastrointestinal dysfunction or systemic illness may be a result of a bleeding disorder, a traumatic foreign body, rectal examination trauma, sadistic rectal trauma, or rectal trauma in a mare from a stallion penetrating the rectum (Boxes 7-11 and 7-12). Many of the diseases listed as causes of melena may also result in gastrointestinal hemorrhage and are therefore listed in both places. If the bleeding is in the distal gastrointestinal tract, fresh blood may be seen in the feces. With diseases midway down the tract, such as intussusception, fecal material is dark red and may appear black until a sample is examined closely and spread on a white surface.

Abdominal Distention and Constipation

Bradford P. Smith

Abdominal distention may be caused by feed, fluid, gas, feces, or a neoplasm (Boxes 7-13 and 7-14). Pregnancy or extreme obesity may also result in an enlarged abdomen. The physical examination should determine which of these is the most likely cause. Often in ruminants the distention can be seen as primarily left sided, right sided, or bilateral. For example, bloat in ruminants results in a characteristic high left-sided gas distention. It may be primary or associated with

BOX 7-11

Causes of Blood, Fibrin, or Mucus in Feces of the Horse

Common Causes

Foreign body
Rectal tear or trauma
Intussusception
Blister beetle (cantharidin) toxicity
Colitis, unknown cause
Salmonellosis

Less Common Causes

Purpura hemorrhagica
Small strongyle infection (cyathostomiasis)
Colorectal polyps
Eosinophilic gastroenteritis
Acorn or oak poisoning
Arsenic toxicity
Organophosphate toxicity
Warfarin poisoning or other coagulation disorder
Mycotoxicoses
Besnoitiosis (globidiosis) (exotic)

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BOX 7-12

Causes of Blood, Fibrin, or Mucus in Feces of Ruminants

Common Causes

Foreign body
Intussusception
Coccidiosis
Salmonellosis

Less Common Causes

Rectal tear or trauma
Rectal examination trauma
Volvulus, root of mesentery
Malignant catarrhal fever
Enterotoxemia
Bovine viral diarrhea
Arsenic toxicity
Abomasal torsion
Warfarin poisoning or other coagulation disorder
Castor bean *(Ricinus)* poisoning
Tung tree *(Aleurites)* poisoning
Solanum (nightshade, potato) poisoning
Sesbania (rattlebox) poisoning
Bracken fern

BOX 7-13

Causes of Abdominal Distention and Constipation in Horses

Common Causes

Ileus
Intestinal foreign body such as enterolith (see Colic)
Peritonitis
Intestinal obstruction, impaction, or gas (see Colic)
Necrotizing enterocolitis (foals)
Torsion or volvulus of gut (see Colic)
Sudden decrease in exercise

Less Common Causes

Pregnancy
Pelvic mass (abscess, tumor)
Cecal tympany (see Colic)
Hernia, obstructive (see Colic)
Intussusception (see Colic)

Uncommon Causes

Anticholinergics
Opiates
Intrinsic colonic nerve dysfunction
Anorectal pain
Perineal hernia
Hypokalemia
Tetanus
Hypocalcemic tetany
Intramural hematomas on gut
Propylene glycol toxicity
Grass sickness (exotic)

BOX 7-14

Causes of Abdominal Distention and Constipation in Ruminants

Common Causes

Pregnancy
Obesity
Vagal indigestion
Grain overload
Bloat
Ileus
Cecal volvulus or dilation with ileus
Peritonitis, traumatic or other cause
Fat necrosis involving rectum or colon
Ruptured bladder (uroperitoneum)
Intestinal obstruction
Pelvic mass (abscess, tumor)
Hypocalcemia
Omasal obstruction or foreign body

Less Common Causes

Anticholinergics
Intussusception
Abomasal volvulus
Abomasal impaction
Tetanus
Abomasal bloat (calf)
Necrotizing enterocolitis (calf)

Uncommon Causes

Hydrops
Ascites
Torsion of descending colon
Internal herniation, especially diaphragmatic hernia involving reticulum
Displacement of intestine to left of rumen
Stenosis of duodenum
Adhesions of intestine
Bovine leucosis
Intestinal volvulus
Atresia of anus, colon, rectum, or intestine
Abomasal adenocarcinoma
Omental bursitis
Perforated abomasal ulcer
Zinc toxicity
Crude oil toxicity
Diesel fuel toxicity
Propylene glycol toxicity
Larkspur poisoning

vagal indigestion, tetanus, or hypocalcemia. With vagal indigestion the rumen becomes enlarged and fluid filled, often giving a pear shape to the abdomen as it is viewed from the rear, or a pear shape on the right and an apple shape on the left ("papple" shape) if some degree of bloat is also present. Hypocalcemia and hypokalemia contribute to ileus and may result in constipation and abdominal enlargement. In sheep, abomasal impaction and enlargement associated with abomasal emptying defects can result in an enlarged abdomen with decreased food intake. When a mass (most commonly an abscess, a tumor, or a fat necrosis [cattle only]) obstructs fecal passage, abdominal enlargement can become severe. With obstructive disease, some degree of colic is almost always present. Ruptured bladder results in a large fluid-filled abdomen, but constipation is not an obvious sign.

The most common causes of decreased fecal output in ruminants and horses are decreased feed intake and dehydration. In such cases the animal will appear gaunt or have a relatively empty abdomen or rumen. Horse feces in cases of prolonged transit are often covered with a layer of tenacious, thick, yellow mucus. When a functional obstruction (ileus, vagal indigestion) or physical obstruction (impaction, foreign body, displaced intestine, fat necrosis) occurs as a cause of constipation, the abdomen is more likely to appear normally full or to become distended. Rectal examination is of great help in determining whether a mass or an obstruction exists because loops of distended small bowel can sometimes be palpated in the latter case.

Radiographs and ultrasound may be valuable to help determine the cause of abdominal distention in foals, calves, and small ruminants. Increased gastrointestinal gas may result in abdominal distention. Abomasal bloat and necrotizing enterocolitis in young animals may best be confirmed with lateral abdominal radiographs.

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Dehydration may also result in dry feces but not in abdominal enlargement. When constipation is present and feces are drier than normal, rehydration and correction of hypocalcemia, hypokalemia, and any existing acid-base abnormalities are important parts of correction of the constipation. Other nonspecific therapies for functional constipation include laxatives, cathartics, and cholinergic drugs. When treating constipation, which is usually a secondary problem, it is important to simultaneously attempt to diagnose the primary disease.

In ruminants, when abdominal distention involves the rumen or is caused by pregnancy or obesity, colic is absent. When abdominal distention is the result of obstruction from the pylorus distal, colic is usually present. Abdominal distention and constipation are frequently accompanied by colic in the horse, regardless of anatomic site involved (review the approach to colic).

Regurgitation and Vomiting

Bradford P. Smith

Regurgitation is the reflux of esophageal, gastric, or rumen contents into the mouth or nose. This may be caused by malfunction of the esophagus or in ruminants as part of the normal physiology for rechewing ingested plant fiber (Boxes 7-15 and 7-16). Vomiting is a coordinated, centrally (medulla) mediated event, usually preceded by nausea (inappetence), increased salivation, or retching. In vomiting the abdominal musculature contracts, the diaphragm is pushed caudally, and the cardia relaxes. The medullary vomiting center can be stimulated by visceral afferent stimuli or through the chemoreceptor trigger zone. Most toxins and drugs that cause vomiting act by directly affecting the chemoreceptor trigger zone. Other than with toxins, most cases of feed returning to the mouth in large animals are examples of regurgitation rather than true vomiting. Vomiting is unusual in both ruminants and horses.

BOX 7-15

Causes of Regurgitation and Vomiting in Horses

Common Causes

Choke
Damaged esophagus, foreign body, or diverticulum
Foreign body in pharynx, trachea, or nose
Guttural pouch infection and pharyngeal paresis with nerve involvement
Gastric dilation
Gastric rupture

Less Common Causes

Snake bite
Tetanus
Tick paralysis
Anterior enteritis (duodenitis or proximal jejunitis)
Gastric stenosis, ulcers
Hydrocephalus, meningitis, encephalitis
Central nervous system trauma
Polyneuritis
Peritonitis
Persistent right aortic arch
Grass sickness (exotic)

Toxins

Phosphorus
α-Naphthyl thiourea (ANTU)
Cyanide
Herbicides
Arsenic
Lead
Nitrophenyl urea (vacor)
Organochlorine

Plant Toxins

Oleander
Castor bean
Death camas (*Zigandenus* species)
Algae
Heath *(Ericaceae)*

BOX 7-16

Causes of Regurgitation and Vomiting in Ruminants

Common Causes

Esophageal trauma or foreign body
Oral or pharyngeal foreign body, abscess, or trauma
Salt toxicity (water deprivation-access)
Tumor, papilloma, or other mass in rumen or esophagus
Toxins and poisonous plants

Less Common Causes

Megaesophagus
Hiatal or diaphragmatic hernia
Esophageal diverticulum
Esophageal reaction to *Hypoderma lineatum* (B)
Hydrocephalus
Meningitis, meningoencephalitis
Central nervous system trauma
Hypomagnesemia

Uncommon Causes

Intestinal neoplasia
Traumatic reticulitis
Tick paralysis
Tetanus
Bluetongue (O)
Peritonitis
Persistent right aortic arch
Pseudorabies
Rift Valley fever (exotic)

Toxins

Methanol or ethanol
Acute oral copper
Phosphorus
Arsenic
Nitrates
Crude oil
Diesel fuel
Snake bite

Plant Toxins

Solanum species
Melia (chinaberry)
Larkspur *(Delphinium)*
Cyanogenic plants
Nitrate accumulators
Death camas (*Zigandenus* species)
Castor bean
Oleander
Cocklebur
Tremorgenic toxins
Heath *(Ericaceae)*
Helenium (sneezeweed, bitterweed)
Hymenoxys (rubberweed, bitterweed)
Veratrum (hellabore)
Amianthium (stagger grass)
Haplopappus (burroweed)
Psilostrophe (paper flowers) (O)
Agrostemma githago (corn cockle)
Kalmia (laurel)
Kikuyu grass, *Pennisetum clandestinum* (exotic)
Ibaraki disease (exotic)
Geigeria (exotic)
Yellow-wood (exotic)

B, Bovine; *O,* ovine.

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Although regurgitation is a normal phenomenon in ruminants, it is unusual to find excessive regurgitation as a sign of disease. Physical blockage of ruminoreticular outflow by a foreign body, warts, actinobacillosis, granulomas, or diaphragmatic hernia can cause rumen distention and excessive regurgitation after eating. An esophageal foreign body can cause irritation and result in regurgitation. Animals with facial paralysis may drool feed and saliva on the affected side; this should be differentiated from animals with excessive or abnormal regurgitation. Vomiting or forced regurgitation in ruminants is rare and is seen principally with the toxins listed.

Horses have such a marked tone at the cardiac sphincter that vomiting occurs only when extreme intragastric pressures develop, usually in small intestinal obstructive diseases or proximal enteritis. Vomiting in the horse thus often occurs with gastric rupture or terminally with shock. Stomach contents are usually pH 5 or below. Because it is a terminal event, vomiting in the horse is often grounds for rendering a poor prognosis. Abdominocentesis should be performed on a horse after vomiting to rule out gastric rupture. To avoid this sequence of events, decompression using a nasogastric tube should be performed in any horse with evidence of gastric distention (see approach to colic). Regurgitation and vomiting in horses most commonly occur from the nose rather than into the mouth because of the anatomy of the soft palate. With choke (esophageal obstruction), esophageal regurgitation from the nares consists of mixed feed and saliva.

In foals a few weeks to several months of age, milk returning from the nares is often associated with gastric ulceration, along with signs of colic, lying in dorsal recumbency, hypersalivation, and champing movements of the mouth. In advanced cases with duodenal ulcers, pyloric outflow can be obstructed by scarring, resulting in more pronounced signs. Foals 1 to 6 months of age are most susceptible to gastric ulceration.

Occasionally, neonatal foals without cleft palate have some mild degree of dysphagia with milk regurgitation from the nose for the first 24 to 48 hours of life, which spontaneously corrects. The cause of this is unknown, but it would appear to be a failure of normal swallowing events to be sufficiently strong or coordinated in the newborn. The major ruleout in these cases is cleft palate.

Approach to Diagnosis of Regurgitation and Vomiting

Evaluation of regurgitation or vomiting should include a history to determine possible exposure to toxins or poison plants, which is most likely when multiple animals are affected. Age of the animal limits some considerations; young animals are more prone to meningitis and central nervous system (CNS) trauma, and congenital problems such as esophageal diverticula and persistent right aortic arch are found only in neonates and may not manifest as choke or regurgitation until solid food intake is increased.

The physical examination can determine whether the problem is vomiting or regurgitation. In ruminants, regurgitation often occurs as a result of distention and overfilling of the rumen, resulting in an obviously distended abdomen. Painful pharyngeal lesions can also cause pharyngeal paresis, which results in gagging and regurgitating. In horses the most common causes of feed coming from the nares are spontaneous choke and pharyngeal paresis associated with guttural pouch lesions (see section on dysphagia).

Physical examination should also include passing a stomach tube to determine whether any impediment to passage of ingesta is present (Box 7-17). Endoscopy is useful to visualize esophageal defects. Many endoscopes currently in use are not long enough to reach the stomach of the adult horse. Endoscopy of the rumen is rarely diagnostic because it is almost impossible to empty it adequately to allow for visualization of a lesion. Ultrasound of the cervical esophagus may also be useful.

In horses and small ruminants radiography, particularly barium contrast studies, can be useful in detecting esophageal abnormalities. In foals, prolonged gastric emptying time may be diagnosed from contrast studies. Normal emptying and movement of contrast media into small bowel occur in less than 2 hours; contrast media reach the large bowel by 3 hours. Radiography may also be useful in detecting diaphragmatic hernia.

BOX 7-17

Useful Techniques in Diagnosing Cause of Regurgitation

- Passing of stomach tube
- Endoscopy of pharynx, guttural pouches, esophagus, and stomach
- Ultrasound examination of the cervical esophagus may be helpful
- Radiographs; plain films of pharynx, guttural pouches, esophagus, and stomach
- Radiographs, barium swallows, checking gastric emptying time in horse

The most significant complications of regurgitation and vomiting include aspiration pneumonia, dehydration, and electrolyte imbalances. The marked hypochloremic alkalosis common to most monogastrics is rare in horses and occurs in ruminants mainly with internal vomiting (one type of vagal indigestion) associated with reflux of abomasal contents back into the rumen.

Vomiting, like diarrhea, is often an attempt by the body to rid itself of a noxious or toxic substance. Antiemetics are therefore rarely indicated in vomiting of central origin and rarely effective in regurgitation in large animals.

Dysphagia (Including Feed from Nares and Excessive Salivation)

Bradford P. Smith

Dysphagia is used here to refer to abnormalities of prehension, mastication, or swallowing. It is associated with diseases of the mouth, lips, pharynx, esophagus, mandible, or masseter muscles or, in the case of neurologic problems, with central or peripheral lesions resulting in malfunction in these areas. Diseases resulting in erosions, ulcers, swellings, crusts, or growths in or on the lips, mouth, or pharynx are discussed under a separate heading. Painful causes of dysphagia such as dental problems require differentiation from oral lesions such as ulcers.

The causes of dysphagia can be divided into three clinical categories: (1) pain induced, (2) neurologic, and (3) obstructive (Boxes 7-18 and 7-19). A fourth category is mechanical interference with prehension and swallowing, but this usually manifests in a manner resembling the manifestation of painful lesions. Particularly in horses, worn, missing, capped, abscessed, overgrown, or broken teeth often result in mechanical interference with chewing, resulting in half-chewed feed being dropped from the mouth (quidding). Observation of the animal as it attempts to eat and a good physical examination including oral inspection and passage of a stomach tube to rule out choke are essential in determining the cause of dysphagia. Use of a fiberoptic endoscope to visualize the pharynx, guttural pouches, and esophagus may be helpful. Plain film radiographs and barium swallows may also be indicated to see functional abnormalities in the pharynx and esophagus during swallowing and to rule out fractures of the hyoid or mandible. Ultrasound should also be employed.

Pain is probably the most frequent cause of dysphagia in ruminants and horses. Oral lesions, oral foreign bodies, and poor teeth result in decreased feed intake, in increased salivation, and often in dropping feed from the mouth while attempting to chew. Dental problems are relatively common in sheep and goats. In cattle, pharyngeal injuries from balling guns and paste wormers can result in severe pharyngeal cellulitis, which is manifested by an extended head, ptyalism, foul breath, and a painful, externally palpable pharyngeal swelling. Mandibular fractures must be ruled out by careful examination because even nondisplaced unilateral mandibular fractures can result in weak jaw tone, reluctance to eat, and drooling.

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BOX 7-18

Causes of Dysphagia in Horses

Pain

Tooth root abscess or periodontal disease
Worn, missing, capped, overgrown, or broken teeth
Foreign body in mouth, pharynx, nose
Oral vesicles, erosions, ulcers, or growths
Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia
Esophageal choke, trauma
Strangles
Rupture of rectus capitus ventralis muscle
Snake bite
Oral, mandibular, or maxillary fracture, neoplasia, or granulomas
White muscle disease
Epiglottiditis, epiglottic cysts
Trauma or excessive traction to tongue
Hyoid bone injury
Nasal mass (granuloma)

Obstruction

Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia
Esophageal choke, trauma, megaesophagus
Strangles
Rostral displacement of palatopharyngeal arch
Damaged or abnormal esophagus
Cleft palate
Dorsal displacement of soft palate
Epiglottiditis, epiglottic cysts
Nasal mass (granuloma)
Lymphosarcoma
Purpura hemorrhagica

Neurologic, Neuromuscular

Yellow star thistle (nigropallidal encephalomalacia)
Guttural pouch mycosis, infection, or tympany
Megaesophagus
Botulism
Lead toxicity
Rabies
Snake bite
Tetanus
Tick paralysis
Encephalitis, meningitis
Encephalopathy, hepatic
White muscle disease
Cerebrospinal nematodiasis
Electrocution
Transit or lactation tetany
Lymphosarcoma
Myeloproliferative disease
Myotonia
Otitis interna and media
Pontomedullary, brainstem neoplasia, pituitary abscess, trauma, neoplasm
Postanesthetic myasthenia
Herbicide toxicity
White snakeroot (tremetol) toxicity
Moldy corn poisoning
Locoweed *(Astragalus, Oxytropis)* toxicity
West Nile fever
Borna disease, Near East encephalitis (exotic)
Grass sickness (exotic)

BOX 7-19

Causes of Dysphagia in Ruminants

Pain

Oral vesicles, erosions, ulcers, growths (see following section)
Foreign body
Pharyngeal abscesses, cellulitis, or tumor
Traumatic or irritant stomatitis
Snake bite
White muscle disease
Actinobacillosis
Actinomycosis
Worn, missing, overgrown, or broken teeth
Periodontal disease or tooth root abscesses
Oral, maxillary, or mandibular neoplasia
Fractured mandible or maxilla
Stomatitis
Necrotic laryngitis (calf diphtheria)
Ruptured or damaged esophagus

Obstruction

Foreign body
Pharyngeal abscess, cellulitis, or tumor
Choke
Snake bite
Actinobacillosis
Oral, maxillary, or mandibular neoplasia
Megaesophagus
Hiatal or diaphragmatic hernia
Cleft palate
Bovine leukosis

Neuromuscular

Listeriosis
Rabies
Tetanus
Botulism
Tick paralysis
Encephalitis, encephalopathy
Brain abscess
White muscle disease
Megaesophagus
Paresis of masseter muscles (mandibular branch of trigeminal)
Bovine leukosis
GM1 gangliosidosis in Friesian cattle
Meningitis
Encephalitis or encephalopathy
Atlantoaxial subluxation or occipitoatlantoaxial malformation
Hypocalcemia
Otitis media and interna
Pontomedullary brainstem neoplasia, trauma, infection, inflammation
Pituitary abscess
Pseudorabies
White snakeroot (tremetol) poisoning
Fireweed *(Kochia scoparia)* poisoning
Locoweed *(Astragalus, Oxytropis)* poisoning
Mercury poisoning
Kikuyu grass *(Pennisetum clandestinum)* poisoning (exotic)
Ibaraki disease (exotic) (B)
Geigeria poisoning (exotic)
Ephemeral fever (exotic) (B)

B, Bovine.

When dysphagia is associated with loss of large amounts of saliva, metabolic acid-base and electrolyte disorders may develop. Cattle and sheep have saliva high in sodium (136 to 201 mEq/L) and bicarbonate (108 mEq/L), with potassium and chloride values in the 14 to 15 mEq/L range.[32,33] As a result, losses of large amounts of saliva can result in hypovolemia and severe metabolic acidosis. In contrast, horses have relatively high levels of salivary chloride (48 to 82 mEq/L) with relatively low salivary bicarbonate (44 to 52 mEq/L). Equine salivary potassium is 14 to 18 mEq/L, and sodium 54 to 90 mEq/L.[34,35] As a result, horses with esophageal fistulas that have lost saliva have a transient metabolic alkalosis.[34]

In the horse a common cause of acute dysphagia is choke (esophageal obstruction), followed in frequency by pharyngeal paresis (neurologic) resulting from lesions in the guttural pouch that affect the pharyngeal nerves. Feed coming from the nose is the most obvious sign of both of these conditions. In choked horses, as a result of the

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length and position of the soft palate, feed comes mainly from the nares rather than coming back into the mouth. Choke and other obstructive diseases can be easily identified by using a nasogastric tube, whereas pharyngeal paresis may be associated with a number of neurologic or neuromuscular conditions, such as botulism or guttural pouch mycosis, which require careful differentiation. The most frequent serious problem associated with choke or pharyngeal paresis is inhalation (aspiration, foreign body) pneumonia. Mineral oil or other material that is particularly damaging if it gains entry into the lung should never be used in choke for this reason. In any animal with dysphagia, care must be taken to prevent aspiration pneumonia and to evaluate the thorax periodically.

Animals with facial paralysis often drool from the affected side and may pack feed into the cheek on the affected side. Listeriosis in ruminants is frequently associated with facial paralysis. In horses facial paralysis is usually caused by halter trauma or a blow to the head.

Oral Vesicles, Erosions, Ulcers, or Growths

Bradford P. Smith

Oral lesions are found with many conditions (Boxes 7-20 and 7-21). In general, they result in some degree of dysphagia or reluctance to eat because of pain. The lesions include vesicles, erosions, ulcers, crusts, or growths in or on the lips, tongue, gums, palate, or pharynx. Oral lesions are often associated with champing and increased amounts of saliva being observed on the lips or running from the mouth. When the volume of saliva is increased, the condition is called *ptyalism* and the animal may be observed swallowing repeatedly. Pseudoptyalism refers to a normal volume of saliva that, because it is not swallowed, is visible to the observer and may be confused with dysphagia (see previous section).

The approach to determining the cause of oral lesions is based on first determining whether the cause is likely to be an infectious disease (Table 7-1). Essentially all these infectious diseases are associated with a fever, although it is short-lived and moderate in the case of bovine papular stomatitis (BPS) and actinobacillosis. Papular stomatitis rarely causes illness and is usually an incidental finding in calves with a different clinical problem, although BPS can cause severe lesions and illness. Most of the infectious diseases are associated with additional lesions or symptoms. They can be conveniently grouped into those causing diarrhea and those not usually associated with diarrhea. Of those not associated with diarrhea in North America, BPS, actinobacillosis, and vesicular stomatitis (VS) are most common in cattle; VS in horses; bluetongue in sheep; and contagious ecthyma (CE) in sheep and goats. CE can be readily differentiated from bluetongue because it involves primarily lips and gums and is proliferative, whereas bluetongue involves the tongue and dental pad most severely, is erosive, and is associated with other signs of generalized vasculitis. Laboratory diagnosis in acute cases of VS is done by working with state and federal veterinarians. Because VS is highly contagious and similar in clinical appearance to foot-and-mouth disease, quarantine and proper diagnosis are essential. Bluetongue is diagnosed by serology (AGID), PCR, and virus isolation. CE can be diagnosed serologically, by fluorescent antibody on the impression smear or biopsy of a lesion, and by isolation. Asymptomatic seroconversion to bluetongue is common where *Culicoides* vectors are active. Congenital defects can result from bluetongue infection of the fetus in sheep, goats, and cattle.

The two most common North American infectious diseases associated with oral lesions and diarrhea in cattle are bovine viral diarrhea/mucosal disease (BVD/MD) and malignant catarrhal fever (MCF). MCF can usually be differentiated because it most commonly occurs sporadically in single animals and has signs of generalized vasculitis such as bilateral corneal opacity, mucopurulent nasal discharge, enlarged lymph nodes, and high fever. Dysentery is common in MCF, and some animals exhibit CNS signs or have thickened and cracking skin. Laboratory diagnosis in acute cases of BVD (see Bovine Viral Diarrhea, Chapter 32) involves fluorescent antibody testing of slides made from ear notch biopsies, lesion swabs, buffy

BOX 7-20

Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Horses

Common Causes

Vesicular stomatitis
Phenylbutazone toxicity
Yellow bristle grass *(Setaria lutescens* or *Setaria glauca)* ulcers
Other plant awn stomatitis
Oral foreign body

Less Common Causes

Irritant or caustic chemical stomatitis
Periodontal gingivitis
Blister beetle (cantharidin) toxicity
Uremia
Drug eruption
Oral neoplasia

BOX 7-21

Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Ruminants

Common Causes

Bluetongue (O)
Contagious ecthyma (Orf virus) (O, C)
Bovine viral diarrhea/mucosal disease (B)
Bovine papular stomatitis (B)
Traumatic or irritant stomatitis
Bristle grass *(Setaria lutescens* or *Setaria glauca)* ulcers
Other plant awn stomatitis
Oral foreign body
Actinobacillosis (woody tongue)
Vesicular stomatitis

Less Common Causes

Actinomycosis (lumpy jaw)
Cheek abscess
Periodontal gingivitis
Oak or acorn toxicity
Malignant catarrhal fever (B)
Irritant or caustic chemicals

Uncommon Causes

Caprine herpesvirus (C)
Blister beetle (cantharidin toxicity)
Necrotic stomatitis
Epidermolysis bullosa
Familial acantholysis (B)
Oral neoplasia
Epitheliogenesis imperfecta
Hereditary zinc deficiency (baldy calf) (B)
Electrical injury
Bovine herpes 2 mammillitis (B)
Elaeophorosis (O)
Chlorinated naphthalene toxicity (B)
Thallium toxicity (O)
Giant hogweed *(Heracleum mantegazzianum)* toxicity
Lead toxicity
Mycotoxicoses
Ibaraki disease (exotic) (B)
Lumpy skin disease (exotic) (B)
Sweating sickness (exotic) (B)
Sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)

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

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TABLE 7-1

Infectious Diseases Associated with Oral Lesions in Cattle, Sheep, Goats, and Horses

Disease	Natural Species	Oral Lesions	Other Lesions
Vesicular stomatitis (VS)	Cattle Horse Sheep (rare)	Vesicles for short time, then large ulcers; tongue usually severely involved	Teats and feet may be involved
Bluetongue	Sheep Goat (rare) Cattle (rare)	Large oral ulcers; dental pad and tongue most affected; generalized vasculitis	Coronitis, muscle degeneration, lameness, pulmonary edema, edema of face and ears
Contagious ecthyma (CE; Orf)*	Sheep Goat	Proliferative scabby lesion on lips to fleshy growth on gums	Occasionally on teats of nursing dams
Bovine papular stomatitis*	Cattle	Round, dark red, raised papules on muzzle and on hard palate	Occasionally in esophagus
Foot-and-mouth (exotic)	Cattle Sheep Goat	Vesicles for short time, then large ulcers	Teats and coronary bands often involved
Bovine viral diarrhea/mucosal disease (BVD/MD)	Cattle	Ulcers in mouth, particularly on hard palate; erosive stomatitis	May have skin lesions; a few have corneal edema or enlarged lymph nodes; pneumonia and lesions in esophagus and gastrointestinal tract common; severe diarrhea
Malignant catarrhal fever (MCF)	Cattle	Erosive stomatitis with ulcers; generalized vasculitis	Purulent nasal discharge, corneal edema, enlarged lymph nodes, ± cracking skin, ± central nervous system signs; severe diarrhea; high fever
Rinderpest (exotic)†	Cattle Sheep Goat	Erosive stomatitis	Blepharospasm, severe intestinal involvement, and diarrhea
Alimentary form of infectious bovine rhinotracheitis (IBR) in calves	Cattle	Gray pinpoint pustules on soft palate and occasionally in nares; minimal oral lesions	Rhinotracheitis, conjunctivitis, pneumonia

*Infectious to humans.

†Rinderpest was eradicated worldwide in 2011.

coat, or tissue. Virus isolation from swabs, serum, or blood or a rise in serum titer from acute to convalescent samples is also diagnostic. Asymptomatic seroconversion is also common, and infection of the fetus may result in congenital anomalies, including cerebellar hypoplasia in cattle.

In animals without fever and other signs of systemic involvement, irritants and caustic chemicals should be considered as possible causes of oral lesions. Horses and young calves are susceptible to severe ulceration when consuming hay contaminated with yellow bristle grass, which is armed with barbed bristles.[36] Horses sometimes develop gingivitis or oral ulcers associated with dry plant awns called foxtails, which become embedded into the gums around teeth. Foals and ponies are most susceptible to phenylbutazone toxicity, which can produce oral ulceration. In cattle the surfaces of masses produced by actinobacillosis and actinomycosis sometimes ulcerate. Many cattle without significant disease have one or more small ulcers of traumatic origin from plant awns on the hard palate and in the cleft (sulcus lingualis) where the base and shaft of the tongue meet.

BOX 7-22

Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Horses

Periodontal disease
Chronic fluoride toxicity
Dental decay
Fractured teeth
Osteomalacia, osteodystrophy
Halicephalobus (Micronema) deletrix, granulomas of mandible or maxilla
Skeletal neoplasia of mandible or maxilla
Hyperparathyroidism
Tooth root abscess with osteomyelitis, secondary to open infundibulum
Ameloblastoma (odontoma)
Dental stain (black walnut hull ingestion or other compound)

Dental Abnormalities

Bradford P. Smith

Chronic fluorosis is a cause of a variety of dental abnormalities in young animals with developing teeth (Boxes 7-22 and 7-23). Although cattle are most frequently involved, all large animals are susceptible. The teeth may appear mottled, striated, chalky, or hypoplastic or may have defective calcification. In severe cases teeth may be yellow, brown, or black and have multiple caries. Animals of any age may also develop bone lesions associated with chronic fluorosis.

Porphyria is a rare congenital condition of cattle transmitted by a simple autosomal-recessive gene. The teeth often appear pink because of the presence of porphyrins and fluoresce pink, purple, or red when exposed to ultraviolet light. Affected calves often develop photosensitization and anemia. This condition must be differentiated from superficial staining caused by ingestion of black walnut hulls or other compounds with staining properties. Cattle fed sweet potato cannery waste develop dental erosions and tooth discoloration.

Excessive or uneven wear or loss of teeth is often seen in horses and ruminants as they age. Tooth wear, particularly of incisors, is more rapid in animals on sandy range. Periodontal disease can cause premature loss of teeth (broken mouth) and tends to be most common in sheep in some geographic areas; the cause of this is unknown.[37]

The most common dental disease in horses has been described as periodontal disease.[38] In horses fractured teeth or teeth with a small tract into the root through an open infundibulum often result in

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BOX 7-23

Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Ruminants

Chronic fluoride toxicity
Bovine erythropoietic porphyria
Fractured teeth
Osteogenesis imperfecta in Holstein Friesians
Osteomalacia, osteodystrophy
Actinomycosis
Skeletal neoplasia of mandible or maxilla
Lymphosarcoma (goat and sheep)
Periodontal disease
Broken mouth (old worn teeth)
Tooth root abscess with osteomyelitis
Ingestion of black walnut hulls or other dental stain
Ingestion of sweet potato cannery waste (B)

tooth root abscesses. This dental decay is a result of hypoplasia of the cementum of the enamel lakes and occurs most frequently in the second and third lower cheek teeth and third and fourth upper cheek teeth.[39] These can cause sinusitis and foul-smelling unilateral nasal discharge if upper cheek teeth are involved or draining tracts to the exterior skin surface if lower cheek teeth are involved.

Most of the other causes of dental abnormalities listed here are bone abnormalities that cause secondary loss of teeth. See dental sections of Chapter 32 for more details.

Icterus (Jaundice)

Bradford P. Smith

Icterus and *jaundice* are synonymous terms referring to the expression of a yellow coloration in the sclera and mucous membranes resulting from increased amounts of bilirubin in tissues and increased serum bilirubin levels (Boxes 7-24 and 7-25). Bilirubin especially stains elastic tissues and is thus most visible in the sclera and vulva. Icterus usually indicates decreased excretion of bilirubin with liver or biliary tract diseases or increased production of bilirubin with hemolytic anemia.

The accumulation of conjugated bilirubin results in more pronounced jaundice than does a similar amount of unconjugated bilirubin, with the result that the most pronounced jaundice is usually seen with hepatic or biliary obstructive disease. Laboratory examination of serum for relative amounts of unconjugated (indirect reacting) and conjugated (direct reacting) bilirubin is essential in determining the cause of the icterus. Generally, mainly unconjugated bilirubin levels are elevated with hemolytic anemia. Anorectic horses may have a plasma unconjugated bilirubin of 5 or 6 mg/dL without any evidence of hemolytic anemia or liver disease. Anorectic ruminants also experience a rise in plasma unconjugated bilirubin, often to a level between 0.5 and 2 mg/dL.

In determining the cause of icterus, laboratory tests including PCV, RBC count, and the liver enzymes SDH and GGT should be determined. In horses, alkaline phosphatase (AP) may also be useful, although it is not liver specific.

When active hepatocellular damage is occurring, SDH, which is liver specific, and aspartate aminotransferase (AST [SGOT]), which is not liver specific, are found in serum in elevated levels. GGT and AP are more indicative of biliary tract disease or proliferation and tend to rise more slowly but also to remain elevated for a longer period than SDH, which has a short half-life. Elevated levels of GGT or AP are often associated with chronic liver disease, cholangitis, cholelithiasis, or liver flukes. It is possible to have liver disease without icterus. Production and elimination of bilirubin are often equal in chronic liver disease, but acute liver disease or liver failure is usually associated with icterus. Although liver function tests such as BSP half-time can be run to determine the extent of liver damage, in most cases a liver biopsy must be taken for histopathologic examination to make a specific etiologic diagnosis of the cause of liver disease.

Liver abscesses rarely result in icterus because they rarely damage a sufficient percentage of liver to impair bilirubin clearance. They do cause multifocal hepatic damage and therefore are often associated with increased levels of SDH and AST when in the acute stages of formation.

BOX 7-24

Causes of Icterus in Horses

Liver

Common Causes

Pyrrolizidine alkaloid toxicity
Serum-associated hepatitis
Acute hepatitis
Chronic active hepatitis
Cholangitis or cholangiohepatitis
Bile stones, other biliary obstruction
Fasting hyperbilirubinemia

Less Common Causes

Aflatoxicosis with liver failure
Tyzzer disease (foals)
Hepatic lipidosis
Hepatic abscess

Uncommon Causes

Black disease (infectious necrotic hepatitis)
Hemangioma, hemangiosarcoma, angiosarcoma
Cardiac neoplasm
Viral arteritis
Gastric or duodenal ulcers
Severe ascarid infection
Lymphosarcoma

Hemolytic Anemia

Common Causes

Immune-mediated hemolytic anemia
Equine granulocytic ehrlichiosis (*Anaplasma phagocytophilum*, formerly *Ehrlichia equi*)
Neonatal isoerythrolysis

Less Common Causes

Piroplasmosis (babesiosis)
Equine infectious anemia
Snake bite
Blood transfusion
Erythrocytosis

Uncommon Causes

Equine viral arteritis
Leptospirosis
Hemochromatosis
Bee or wasp sting
Sulfur toxicity
Trichloroethylene-extracted feed
Iron toxicity
Phosphorus toxicity
Herbicide toxicity
Phenothiazine toxicity
White snakeroot poisoning (tremetol)
Onions
Red maple (*Acer rubrum*)
Pentachlorophenol toxicity
Oak toxicity
Mycotoxicosis
Surra, *Trypanosoma evansi* (exotic)
Mal de caderas, *Trypanosoma equinum* (exotic)
Murrina de caderas, *Trypanosoma hippicum* (exotic)

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BOX 7-25

Causes of Icterus in Ruminants

Liver

Common Causes

Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Fat cow syndrome (fatty liver)

Less Common Causes

Acute hepatitis
Liver flukes
Infectious necrotic hepatitis (black disease)
Liver abscess
Cholangiohepatitis

Uncommon Causes

Sarcocystosis
Hepatic neoplasia
Ruptured gallbladder
Cholelithiasis
Biliary obstruction
Nolina (beargrass) toxicity
Lantana, toxicity
Agave, toxicity
Wesselsbron disease (exotic) (B, O)

Hemolytic Anemia

Common Causes

Leptospirosis
Anaplasmosis
Bacillary hemoglobinuria *(Clostridium hemolyticum)*
Piroplasmosis, babesiosis (exotic)

Less Common Causes

Snake bite
Oak (acorn) toxicity
Immune-mediated hemolytic anemia
Transfusion reaction
Postparturient hemolytic anemia
Copper toxicity (especially sheep)
Neonatal isoerythrolysis
Yellow lamb disease (*Clostridium perfringens,* type A) (O)

Uncommon Causes

Anaplasma ovis
Eperythrozoonosis
Bee or wasp sting
Brassica species toxicity
Trichloroethylene-extracted feed toxicity
Iron toxicity
Onion poisoning
Zinc poisoning
Phosphorus poisoning
Mercury poisoning
Fireweed *(Kochia scoparia)* poisoning
Mycotic lupinosis
Mycotoxicosis
Theileriosis (East Coast fever) (exotic)

B, Bovine; *O,* ovine.

Hemolytic anemia is characterized by destruction of RBCs either intravascularly or in the reticuloendothelial organs. This increased destruction results in production of bilirubin more rapidly than it can be removed by the liver, resulting in icterus. The specific cause of hemolytic anemia may sometimes be evident, as when autoagglutination is seen (autoimmune hemolytic anemia). *Anaplasma* bodies are visible in stained RBCs of cattle, or *Anaplasma phagocytophilum* (formerly *Ehrlichia equi*) blue cytoplasmic inclusion bodies are seen in stained neutrophils from horses.

In mature sheep, the most common cause of severe icterus is copper toxicity. In lambs, yellow lamb disease caused by *C. perfringens,* type A is a leading cause.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 8

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Localization and Differentiation of Neurologic Diseases

DAVID C. VAN METRE and ROBERT J. MACKAY, *Consulting Editors**

■ MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

Ataxia, 112-114, 127
Behavior, abnormal, 110-112, 121
Blindness, amaurosis, hemianopsia, 118, 122-124, 126
Coma, semicoma, 112, 121
Circling, 113, 120, 124
Conscious proprioceptive deficit, 113-114
Deafness, 126
Depressed mentation, 110-112, 121
Facial analgesia, anesthesia, 119, 126
Facial paralysis, 119-121, 126
Flaccid tail and anus, 130
Head pressing, 111, 121
Head tilt, 114, 124-126
Hemianopsia, blindness, 118, 122-124
Hypermetria, 125-126, 128
Hyperreflexia, 116, 128
Hyporeflexia, 116, 128, 130
Incontinence, urinary, 128, 130
Jaw weakness, 119, 126
Menace, loss of, 117, 118, 122-124, 126
Muscular rigidity or flaccidity, 128-130
Muscle atrophy, 115, 117, 129
Narcolepsy, 112, 123
Nystagmus, 119, 124-126
Opisthotonos, 113, 125
Paralysis, 127-130
Paresis and ataxia, 127
Ptosis, 119, 120, 126
Roaring, snoring, dysphonia, 120, 126
Seizures (convulsions), 112, 121-122
Spasticity, 115, 125
Strabismus, 118-119, 120, 126
Tremors, intention, 125, 126
Vocalization, abnormal, 121, 126

■ TERMINOLOGY AND DESCRIPTION OF CLINICAL SIGNS OF NEUROLOGIC DISEASE (SEE TABLE 8-1)

Telencephalon (cerebrum, basal ganglia) and diencephalon (thalamus)
Changes in behavior
Changes in the level of consciousness
Dullness, obtundation
Stupor
Coma
Excitement, mania
Seizures (convulsions)
Narcolepsy
Vision disturbance
Blindness in both visual fields (amaurosis)
Blindness in the contralateral visual field (hemianopsia)
Menace reflex deficit
Change in pupil size: small to pinpoint pupils
Circling (toward the side of the lesion)
Head turn (toward the side of the lesion)
Gait usually normal
Abnormal postural reactions (contralateral)
Decreased or absent conscious proprioception
Noticeable ataxia, paresis (weakness), and paralysis are uncommon
Abnormal spinal reflexes
Normal to increased (hyperreflexic) myotatic reflexes
Altered muscle tone
Normal to increased muscle tone (spasticity)
Urinary incontinence (upper motor neuron)
Tremors

Mesencephalon (midbrain)
Changes in the level of consciousness
Dullness (depression)
Stupor
Coma
Narcolepsy
Abnormal posture
Opisthotonos
Decerebrate posture
Abnormal visual or ocular function
Blindness in both visual fields (amaurosis)
Blindness in the contralateral visual field (hemianopsia)
Change in pupil size
Small pupils in early, mild lesions
Dilated, nonresponsive pupils in severe lesions
Menace reflex deficit (ipsilateral)
Anisocoria (asymmetric lesions)
Circling (toward side of lesion—ipsiversive)
Head turn (toward side of lesion—ipsiversive)
Abnormalities of gait (usually contralateral to lesion)
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes
Normal to increased (hyperreflexic) myotatic reflexes
Altered muscle tone
Spasticity
Urinary incontinence (upper motor neuron)

Metencephalon (pons, cerebellum)
Abnormal posture
Head tilt
Decerebellate posture
Circling (usually away from side of lesion—paradoxic signs)
Head turn (usually away from side of lesion—paradoxic signs)
Nystagmus (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)
Abnormalities of gait
Ataxia
Dysmetria—typically, hypermetria
Abnormal spinal reflexes (occasional)
Normal to increased myotatic reflexes (hyperreflexia)

*Contributions to previous editions by Lisle George and Mary Smith are acknowledged.

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Altered muscle tone
Normal to increased muscle tone on the opposite side of the body (contralateral spasticity)
Normal to decreased muscle tone on the same side of the body (ipsilateral hypotonus)
Urinary incontinence (upper motor neuron) (rare)

Medulla oblongata
Changes in the level of consciousness
Dullness, obtundation
Abnormal posture
Head tilt (toward side of lesion—ipsiversive)
Circling (toward side of lesion—ipsiversive)
Head turn occasionally (toward side of lesion)
Strabismus—variable
Nystagmus—spontaneous, abnormal (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)
Dysphagia
Facial analgesia
Facial paresis or paralysis
Menace reflex deficit
Jaw weakness
Roaring, snoring, dysphonia
Tongue weakness, deviation, or paralysis
Abnormalities of gait—ipsilateral
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes
Normal to increased (hyperreflexic) myotatic reflexes
Altered muscle tone
Normal to increased muscle tone
Urinary incontinence (upper motor neuron)

Spinal cord C1-C5
Abnormalities of gait in thoracic and pelvic limbs—ipsilateral
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes—ipsilateral
Hyperreflexia in both thoracic and pelvic limbs
Decreased to absent caudal cervical and auricular reflexes
Decreased to absent slap test (horses)
Altered muscle tone
Normal to increased muscle tone
Urinary incontinence (upper motor neuron)

Spinal cord C6-T2
Abnormalities of gait in thoracic and pelvic limbs—ipsilateral
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes—ipsilateral
Hyporeflexia in thoracic limbs
Hyperreflexia in pelvic limbs
Decreased to absent caudal cervical and auricular reflexes
Decreased to absent slap test (thoracolaryngeal reflex, horses)
Absent panniculus reflex
Horner syndrome (ipsilateral)
Altered muscle tone
Decreased muscle tone in thoracic limbs
Normal to increased muscle tone in pelvic limbs
Urinary incontinence (upper motor neuron)

Spinal cord T3-L2
Abnormalities of gait in pelvic limbs only—ipsilateral
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes—ipsilateral
Hyperreflexia in pelvic limbs only
Decreased panniculus reflex caudal to lesion
Altered muscle tone—ipsilateral
Normal to increased muscle tone in pelvic limbs
Urinary incontinence (upper motor neuron)

Spinal cord L3-S3
Abnormalities of gait in pelvic limbs only—ipsilateral
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes—ipsilateral
Hyporeflexia in pelvic limbs only
Altered muscle tone
Decreased muscle tone in pelvic limbs
Flaccidity of the tail
Urinary incontinence (lower motor neuron)
Fecal incontinence (lower motor neuron)
Peripheral nerve and muscle
Abnormalities of gait
Paresis to paralysis
Decreased or absent conscious proprioception
Ataxia
Paresis (weakness)
Paralysis
Abnormal spinal reflexes—ipsilateral
Hyporeflexia
Altered muscle tone
Decreased muscle tone
Muscle atrophy
Flaccidity of the tail
Urinary incontinence (lower motor neuron)
Fecal incontinence (lower motor neuron)

The clinical signs of neurologic disease depend on the location of the disease process within the nervous system (Table 8-1). Widely varying disease entities may produce similar or identical clinical signs. Seizures, for example, may be the result of metabolic, toxic, traumatic, neoplastic, or other causes. Definitive diagnosis of neurologic disease, therefore, cannot be made on the basis of clinical signs alone. Localization of lesions within the nervous system by meticulous physical and neurologic examination is the first and key step in developing a differential diagnosis list and a rational diagnostic and therapeutic plan.

Diagnosis of Neurologic Diseases

Signalment

The species, breed, age, and pedigree of an animal are important considerations in the differential diagnosis of neurologic disease. Many diseases are species specific, particularly in the case of infectious and genetic diseases. Some diseases are not only species specific but also have higher incidence in certain breeds of that species. An example of this is juvenile idiopathic epilepsy, which has been observed in several breeds of horses but has its highest incidence in Arabian foals.[1] Examples of the numerous other breed-related neurologic diseases of large animals are cerebellar abiotrophy (Arabian foals), progressive ataxia (Charolais), demyelinating myelopathy (Limousins), neuraxial edema (polled Herefords), and many others.[2-10] Atlantoaxial malformations most commonly occur in Arabian foals and Holstein calves but can occur in other breeds.[11,12]

Disease susceptibility also may be linked to age. Acute lead poisoning, for example, occurs most commonly in calves, whereas adult cattle tend to develop the subacute form of the disease.[13]

Some diseases are found in the neonate at birth. A large number of congenital disorders of the central nervous system (CNS) can affect domestic livestock. These diseases have a variable clinical course, depending on the nature of the disorder. Congenital disorders of myelin metabolism worsen with age, whereas other developmental conditions may remain stable throughout the animal's life.[14-19] Examples of these disorders that have genetic tests available are listed in Chapter 52.

History

Many disorders of the CNS produce characteristic patterns of onset and progression. Some CNS diseases occur acutely, developing the full range of clinical signs within hours. If the disease is not fatal, the signs either stabilize by 24 hours and remain constant thereafter or improve. Diseases that may display this clinical course include traumatic injuries and some types of toxic, infectious, and metabolic diseases. Diseases with degenerative, neoplastic, and certain viral causes may develop more slowly, requiring days to weeks for development of characteristic clinical signs.[2,20,21]

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TABLE 8-1

Localization of Central Nervous System Lesions According to Major Signs Encountered

Sign or Problem Encountered	Lesion Location
Changes in Gait and Locomotion	
Ataxia	Spinocerebellar tracts, spinal cord, and brainstem; vestibular system; cerebellum
Conscious proprioceptive deficit	Fasciculus gracilis and fasciculus cuneatus and connections, spinal cord, brainstem, forebrain
Knuckling	Usually LMN, ventral horn gray matter, spinal cord; occasionally UMN, spinal cord, brainstem
Abduction or adduction	Spinocerebellar tracts, spinal cord, brainstem, cerebellum
Abnormal postural placement	Spinocerebellar tracts, spinal cord, and brainstem; gracilis and fasciculus cuneatus and connections, spinal cord and brain
Hypermetria	Cerebellum, cerebellar peduncles, spinocerebellar tracts
Circling, or falling to one side	Forebrain, vestibular nuclei and connections, cerebellum
Paraplegia	UMN, from T2 to S2, or LMN, L3 to S2
Hemiplegia	Ipsilateral brainstem or spinal cord, cranial to T3
Changes in Sensorium and Behavior	
Coma or semicoma	ARAS; diffuse forebrain
Obtundation	ARAS; forebrain
Seizures	Forebrain
Head pressing, compulsive walking	Forebrain
Aggression or rage	Forebrain
Inappropriate sexuality	Forebrain
Hyperphagia or hypophagia	Hypothalamus
Diabetes insipidus	Hypothalamus
Head shaking	Unknown, probably peripheral trigeminal neuralgia
Changes in Head Posture	
Stiff neck	Meninges, cervical spine
Head tilt	Vestibular nuclei and connections (medulla oblongata, cerebellum)
Head tremor	Cerebellum, basal ganglia
Opisthotonos	Cerebellum (rostral vermis), rostral brainstem, cerebrum, cranial nerve VIII
Cranial Nerve Dysfunction	
Blindness	Cerebral cortex, internal capsule, optic tracts, optic chiasm, optic nerve, eye
Anisocoria	Cervical spinal cord (tectotegmentospinal tract), cranial thoracic nerve roots, vagosympathetic trunk, midbrain (oculomotor nerve nucleus), cranial cervical ganglion, ciliary ganglion, oculomotor nerve, optic nerve
Mydriasis	Oculomotor nerve, midbrain, optic nerve, eye
Miosis	Vagosympathetic trunk, ciliary ganglia, tectum, brainstem, cervical spinal cord
Ptosis	Facial nerve, vagosympathetic trunk, cranial cervical ganglion, midbrain, oculomotor nerve, cervical spinal cord (tectotegmentospinal tract)
Strabismus	
Ventrolateral	Cerebellum, vestibular nucleus, oculomotor nerve
Dorsomedial	Trochlear nerve
Medial	Abducent nerve
Nystagmus	
Horizontal	Nerve VIII (peripheral)
Vertical or rotatory	Vestibular nuclei, peripheral vestibular receptor, cerebellum, vestibulocochlear nerve
Jaw drop	Trigeminal motor nucleus (pons), trigeminal nerve
Flaccid tongue	Hypoglossal nucleus (medulla oblongata), hypoglossal nerve, lingual muscle
Facial paralysis	Facial nucleus (medulla oblongata), facial nerve, facial muscles
Facial analgesia	Trigeminal nerve (sensory component), pons, forebrain
Dry eye	Cranial nerve VII before exiting petrous temporal bone
Changes in Reflexes	
Patellar	L3-L6 spinal cord, femoral nerve, quadriceps femoris muscle
Flexors (thoracic limbs)	C5-T2 spinal cord segments, radial, ulnar, musculocutaneous and median nerves, and innervated muscles
Flexors (pelvic limbs)	L6-S2 spinal cord segments (pelvic limbs); sciatic, peroneal, and tibial nerves; flexor muscles of the limbs
Triceps	C6-T1 spinal cord segments, radial nerve, triceps muscle
Cutaneous trunci	C8-T1 spinal cord segments, lateral thoracic nerve, white matter of thoracic spinal cord
Anal	S1-S5 sacral spinal cord segments, pudendal nerve
Cervicofacial	Dorsal columns of cervical spinal cord segments; facial nucleus (medulla oblongata), nerve, facial nucleus, muscles of ear; connections between cervical plexus and facial nerve
Dysuria (dribbling urine)	Spinal cord, S1-S5, sacral nerves, bladder wall

ARAS, Ascending reticular activating system; *LMN,* lower motor neuron; *UMN,* upper motor neuron.

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TABLE 8-2

Dietary Deficiencies Associated with Neurologic Disorders of Livestock

Dietary Deficiency	Disease Produced	Neurologic Sign
Copper	Demyelination, pathologic fractures of vertebrae	Ataxia, recumbency
Vitamin E	Demyelination	Ataxia, recumbency
Vitamin A	Encephalopathy	Convulsions, blindness
Magnesium	Grass tetany, transport tetany, milk tremors	Convulsions, tremors, ataxia
Potassium	Weakness	Postpartum recumbency
Calcium or phosphorus	Milk fever, pathologic vertebral fractures, tetany	Weakness, ataxia, recumbency, tetany
Vitamin E or selenium	Nutritional myodegeneration	Weakness, ataxia, recumbency, sudden death

Diet

The diet of patients with neurologic disease should be evaluated[20-25] (Table 8-2). Equine motor neuron disease is seen mainly in horses that are housed without access to pasture and whose diet is deficient in vitamin E.[26] Copper deficiency occurs in ruminants pastured in areas with shale or volcanic soils, which are either deficient in copper or contain high concentrations of molybdenum and sulfur; demyelination of the spinal cord in newborn small ruminants may result, as can vertebral fractures in calves. Dietary deficiency of calcium in rapidly growing weaned calves also results in vertebral and long bone fractures. Overfeeding of protein and energy, as well as imbalance of certain trace minerals, has been linked to cervical vertebral stenotic myelopathy in horses (wobbler).[27,28]

Environment

Examination of the patient's environment may provide valuable information about the cause of CNS disease. Outbreaks of botulism and listeriosis have been associated with ingestion of rotting vegetation around haystacks, silos, and feed bunks.[29,30] Plant poisonings are common in livestock, and identification of neurotoxic plants is important whenever multiple animals are affected simultaneously[30-32] (Table 8-3). Nonplant neurotoxicants of livestock include lead, ethylene glycol, organic mercurials, chlorinated hydrocarbons, organophosphates, salt, sulfur, petroleum distillates, and many others. Dose of the neurotoxicant may be important, with different clinical signs appearing depending on the level of exposure. For example, ingestion of high concentrations of organophosphates or carbamates produces marked ataxia, coma, muscle tremors, salivation, and miotic pupils. When low doses of organophosphates are ingested chronically, however, the result is an axonopathy of spinal cord and medullary neurons, resulting in pelvic limb paresis and ataxia, which may progress to tetraparesis and recumbency.[33] Therapeutic and dietary interventions also may result in toxicoses when improperly administered. Overdosing of cattle with propylene glycol produces profound ataxia, depression, and coma.[34] Ingestion of urea or ammoniated feedstuff produces hyperesthesia, excitability, coma, and convulsions. High concentrations of salt in drinking water or, more commonly, lack of fresh water or interruption of the water supply followed by unlimited access to water can result in laminar necrosis of the cerebral cortex or eosinophilic meningitis.[33] The clinical signs are those of forebrain dysfunction, including blindness, dullness, seizures, coma, and death.[35-37] Geographic area also may be important in the differential diagnosis of neurologic disease. Certain infectious diseases may be more common in particular areas of the country or even regions within a single state where the conditions for disease vectors are optimal.[38] The travel history of the animal must be considered, as well as the animal's location at the time clinical signs appeared. Travel also may result in increased contact with other animals and greater risk of exposure to infectious diseases. Intermingling of horses from different premises is a potential risk for equine herpesvirus-1 myeloencephalopathy (EHM).[39]

Vaccination and Disease History

When a neurologic problem is evaluated, the vaccination history and previous herd or individual disease problems should be noted. Some vaccines are highly protective, such as those for rabies and tetanus. Neurologic disease may be a secondary complication of disease in another organ system. Foals and calves with severe diarrhea, for example, may convulse secondary to hypokalemia, hypernatremia, hyponatremia, or hypoglycemia. Preexisting diseases in the population should be determined. For example, outbreaks of EHM are sometimes preceded by respiratory disease or abortions in herdmates.[39] Thromboembolic meningoencephalitis of cattle often follows an outbreak of respiratory disease within the herd. Historical evidence of limited colostral intake may be important in the diagnosis of bacterial meningitis of neonates. Bloody diarrhea often precedes the onset of nervous coccidiosis of calves.[40]

Gestational Stage

Hypomagnesemia, eclampsia (hypocalcemia), hypokalemia, hypophosphatemia, and nervous ketosis are common causes of recumbency, convulsions, and tremors in adult livestock. These diseases usually occur between the beginning of the last trimester and the first 2 months after parturition.

Nervous System Examination

General Comments

A thorough physical examination should always precede or be performed concurrently with the neurologic examination. In some instances disease of organ systems other than the nervous system may take precedence for diagnosis and treatment. Such may be the case with animals in shock or suffering from other life-threatening cardiovascular or respiratory disturbances.

The neurologic examination should be carried out in a systematic fashion. The exact order of the examination is not important in itself, but procedures that may cause discomfort or pain such as palpation of the spine should be left until last. A common system used by many neurologists is to start at the head and progress to the tail.[41] Some clinicians prefer to examine the animal standing in the stall initially and then observe the gait. Because large animals are less amenable to handling than the typical cat or dog, another system for the neurologic examination is to begin with procedures that require minimal handling of the animal, such as observation of mental status, posture, and gait, and proceed to those that require greater manipulation: examination of the cranial nerves, assessment of spinal reflexes, and so on.

Neurologic examination alone rarely leads to definitive diagnosis but rather helps to answer the questions "Does the animal have neurologic disease?" and "What is the location of the neurologic lesion?" Once these questions are answered, a list of differential diagnoses can be made in light of other information such as the signalment of the animal and the history of the current problem. The diagnostic plan is based on the location of the lesion and the most likely differential diagnoses.

Mentation and Behavior

Initial examination should be done from a distance. The examiner observes the animal's mental state and whether its responses to its

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TABLE 8-3

Selected Poisonous Plants Producing Neurologic Signs (also see Chapter 54)

Plant Poisoning	Clinical Signs
Blue green algae *(Aphanizomenon, Anabaena flos-aquae)*	Sudden death, tremors, salivation, miosis, bradycardia
Bracken fern *(Pteridium aquilinum)*	Ataxia, weight loss, strip sweating (horses only)
Buckeye (*Aesculus* species)	Incoordination, twitching, sluggishness
Catsear *(Hypochaeris radicata)*	Hyperflexion of the hock during movement (stringhalt)
Cheesewood *(Malva)*	Tremors, worsened by forced exercise, hyperflexion of the hock during movement (stringhalt)
Creeping indigo *(Indigofera spicata)* and Birdsville indigo *(Indigofera linnae)*	Ataxia, obtundation, blepharospasm, corneal edema, lingual ulcers, seizures
Dandelion *(Taraxacum officinale)*	Hyperflexion of the hock during movement (stringhalt)
Death camus (*Zigadenus* species)	Trembling, uncontrolled running, recumbency, opisthotonos, convulsions, vomiting, salivation
Dutchman's breeches *(Dicentra)*	Trembling, uncontrolled running, recumbency, opisthotonos
Fiddleneck *(Amsinckia intermedia)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Horse tail *(Equisetum arvense)*	Ataxia, weight loss, strip sweating (horses only)
Laburnum *(Laburnum anagyroides)*	Excitement, incoordination, convulsions, death
Larkspur *(Delphinium)*	Ataxia, collapse, recumbency, inability to lift head, tremors of face, flank, and hip; vomiting
Locoweed (*Astragalus* species)	Ataxia, weight loss, recumbency, hyperesthesia
Lupine *(Lupinus)*	Tremors, hyperexcitability, depression
Milkweed (*Asclepias* species)	Tremors, salivation, ataxia
Monkshood *(Aconitum)*	Restlessness, salivation, paresthesia, irregular heartbeat, recumbency, coma
Nightshades (*Atropa* species, *Solanum* species)	Tremors, ataxia, recumbency, convulsions
Poison hemlock *(Conium maculatum)*	Tremors, vomiting, ataxia, sudden death, abortions, pupillary dilation, bradycardia, coma
Rape *(Brassica napus)*	Blindness, ataxia, aggressiveness
Rattlebox *(Crotalaria spectabilis)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Rayless goldenrod *(Haplopappus heterophyllus)*	Lassitude, obtundation, arched back, stiff-legged gait, tremors, weakness, collapse
Russian knapweed *(Rhaponticum repens; Acroptilon repens)*	Facial rigidity and dystonia, lack of prehension, ataxia, depression (horses only)
Tansy ragwort *(Senecio jacobea)* and common groundsel *(Senecio vulgaris)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Tobacco (*Nicotiana* species)	Tremors, salivation, ataxia, convulsions, birth defects
Water hemlock *(Cicuta maculata)*	Tremors, vomiting, ataxia, sudden death, convulsions, odontoprisis, pupillary dilation, abortions, bloat
White snakeroot *(Eupatorium rugosum)*	Tremors, salivation, convulsions
Yellow star thistle *(Centaurea solstitialis)*	Facial rigidity and dystonia, lack of prehension, ataxia, depression (horses only)

surroundings are appropriate. This is done ideally in the animal's usual environment, where it would be expected to be calmest. When this is not possible, the influence of factors such as the stress and excitement of previous travel and the animal's natural fear of unfamiliar surroundings, sounds, and smells must be taken into account. The reports from the animal's usual handler may be informative, if he or she is a good observer and has an understanding of normal behavior in animals. Compare the patient's interaction with its environment to a summary of its previous behavior and to the activities of the herdmates. All livestock should recognize and fear strangers and should show awareness of the examiner's position. Normal animals change the posture of the head, ears, and eyes as the examiner moves. Depending on previous conditioning, normal behavior may include cautionary moves, avoidance, belligerence, or affection. Animals with decreased mental alertness (obtunded, dull, depressed) have reduced responses to examination, lassitude, lack of recognition, unwillingness to rise or lift the head from the ground, lack of appetite, drooped ears, stupor, or coma (Fig. 8-1). Systemic illness also may cause dull mentation; thorough physical examination and, perhaps, diagnostic tests including a complete blood count and serum chemistry are important in determining whether systemic disease is present.

Changes in behavior are consequences of diseases affecting the forebrain: the cerebrum or the relay areas of the diencephalon. Abnormal behavior caused by forebrain dysfunction can be termed *dementia*. Some common examples of dementia include head-pressing, compulsive walking (often around the inside of an



FIG. 8-1 Dull mentation in a horse with cerebral toxicosis caused by sage toxicity (*Salvia* species).

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enclosure), frequent yawning, loss or absence of innate behaviors such as udder seeking by neonates and mutual affinity of dams and offspring, and loss of learned behaviors such as the ability to be led by a lead rope and halter. Hyperexcitability, rage, mania, exaggerated fear, or frantic motor activities are suggestive of a lesion of the limbic system of the forebrain, an assembly of interconnected neurons in the brain that is involved in emotional responses and patterns of behavior. Animals so affected may strike or kick at inappropriate times, demolish their stalls, bellow, show belligerence, or, if recumbent, struggle violently. The age, species, previous management system, and even the breed of animal are important considerations in the assessment of behavior. Bulls and stallions exhibit behavior that is very different from that of steers and geldings. Beef cattle behave differently than dairy cattle do. Animals that are handled regularly show fewer and milder fearful or aggressive responses than do animals that are handled rarely.

The source of mental alertness is the ascending reticular activating system (ARAS) of the brainstem, which repetitively signals the forebrain to maintain consciousness. For this purpose, the ARAS integrates inputs to the brain of all sensory modalities. The portion of the ARAS within the midbrain is functionally the most important with progressively less input caudally and rostrally in the brainstem. The ARAS is important in maintaining the animal's level of consciousness and arousal. The relationship between the cerebral cortex and the ARAS is sometimes described as follows: The cerebral cortex determines the *content* of consciousness, and the ARAS determines the *level* of consciousness. Diseases affecting the ARAS tend to produce profound depression of consciousness, particularly if the midbrain segment of this system is affected. In this case, other signs of midbrain disease such as pupillary dilation and loss of the oculocephalic reflexes (see later) are often observed. The forebrain is the "seat of consciousness": Conscious perception of both external stimuli (e.g., vision, hearing, touch) and internal stimuli (e.g., abdominal pain) depends on its integrity. In general, level of consciousness is *not* substantially altered by forebrain diseases unless the injury is diffuse and severe.

A seizure (convulsion, ictus) is a manifestation of forebrain dysfunction characterized by involuntary somatic and autonomic motor activities and/or loss of consciousness. Seizures may be generalized or focal (partial). Generalized seizures are characterized by recumbency, loss of consciousness, flailing or galloping motions of the limbs, elimination of feces and urine, and nystagmus. Localized involuntary movements with or without obvious alterations of consciousness characterize focal seizures. Alternatively, focal seizures may result in episodes of abnormal or bizarre behavior or momentary lapses of consciousness without collapse or significant motor activity. A third form of seizure is focal with secondary generalization. The onset of the seizure is focal within the forebrain, but seizure activity subsequently spreads throughout the brain, resulting in a generalized seizure. Animals with this form of seizure activity exhibit initial focal signs such as head turning, bellowing, and focal tremors followed by loss of consciousness and generalized signs of involuntary motor activity, as described previously. Rarely, seizures in large animals may be preceded by an aura, a period in which the animal exhibits anxiety or restless behavior shortly before the onset of the seizure itself. A postictal phase, a period of time subsequent to the seizure during which the animal is obtunded or, occasionally, restless and anxious, is usual after seizures in most animals. The postictal phase usually lasts a few minutes to hours but may last as long as several days. The postictal phase may be the only stage of the seizure observed by the animal's handler. Thus seizures should be considered as a possible cause in any animal with a history of episodes of abnormal behavior. The typical history is that the animal is found in a dull or excited state, without the handler observing the onset of this change of behavior. Additional signs of postictal forebrain dysfunction may include blindness, absent menace responses, and insensitivity to cutaneous noxious stimulation. Additional supporting evidence includes physical injuries such as scrapes and cuts that may have been incurred during the seizure.

Abnormalities of forebrain dysfunction are the ultimate cause of seizure activity. During a seizure, neurons in the cerebral cortex exhibit spontaneous electrical activity, beginning either focally or simultaneously throughout the cortex, resulting in the clinical manifestations of focal or generalized seizures. Causes of seizures are legion, including alterations in the neuronal environment resulting from metabolic disturbances or toxicities and the effects of structural brain diseases such as congenital or developmental disorders, traumatic injuries, neoplasia, and inflammatory conditions. Diagnosis of seizures and other states of altered mentation must include a thorough physical examination and screening for metabolic diseases such as electrolyte imbalances and hepatic or renal failure.

Abnormalities in the neurologic examination found between seizures (interictal period) support a diagnosis of primary brain disease and are an indication for diagnostic procedures such as cerebrospinal fluid (CSF) tap. Some toxins cause additional systemic signs such as neuromuscular involvement (tremors, weakness) or parenchymal organ failure (icterus, uremia). Such signs, combined with clinical history and inspection of the environment, will help to direct specific tests for toxins.

Narcolepsy is a condition reported in cattle and horses wherein the normal mechanisms of sleep are disturbed.[42-45] Although sudden onset of sleep is one manifestation of narcolepsy, the acute onset of cataplexy—complete paralysis of striated muscles—is usually a more prominent clinical feature. Animals may be observed to suddenly collapse to the ground or to buckle at the knees. Cardiac and respiratory muscles are not affected. Narcoleptic attacks may be difficult to distinguish from seizures but are not accompanied by the involuntary motor activity that characterizes most generalized seizures. In some cases, traumatic injuries to the head, face, and limbs can result.

Gait

Gait should be evaluated by moving the animal in a straight line, moving it in a tight circle, backing up, and moving it over obstacles such as a curb. Having the patient walk up and down a slope with varying steepness and with the head elevated may reveal subtler abnormalities. The examination may need to be modified depending on the species of the patient, amenability to handling, and consideration of safety concerns.

Quadrupeds begin walking by protracting the pelvic limb, followed by the thoracic limb of the same side, then the opposite pelvic limb, and finally the opposite thoracic limb. Gait on a level surface requires integrity of the musculature, motor and sensory components of the peripheral nerves, local spinal reflexes, ascending and descending pathways in the spinal cord, and centers within the brainstem. Dysfunction of ascending pathways (spinocerebellar tracts) results in mild to severe proprioceptive disturbances when standing or walking, which are exacerbated by turning the animal in a circle or stepping it on and off a curb. Animals with cerebral disease are usually able to perform simple motor activities such as walking along a straight path without obvious deficits but may exhibit decreased proprioception when they are required to perform complex motor activities such as walking on slopes or negotiating obstacles such as curbs or ground poles.

Subtle gait deficits may be elicited by walking and then trotting the patient, or walking or trotting the patient briskly and then stopping suddenly. While a helper is walking the animal in a straight line on a level surface, the examiner should take hold of the tail on the same side and pull the animal firmly to one side during the stance phase of the stride. The normal animal will move toward the pull but should not stumble or fall. If the tension on the tail is maintained, strength can be assessed. Animals with lesions anywhere within the ascending or descending pathways controlling gait may be weak and/or show decreased proprioception in the form of stumbling, tripping, or crossing the limbs. The same test can be performed in the patient at rest. Resistance to lateral pressure at rest is provided by the antigravity myotatic reflex. Because this reflex uses peripheral nerves and spinal cord segments of the lumbosacral intumescence, inability to resist the tail-pull test at rest is suggestive of lower motor neuron

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(spinal cord gray matter, nerve roots, or peripheral nerves) of the L3 to S2 spinal cord segments on the side being tested. Circling the patient in a wide circle and then a tight circle also may elicit deficits, such as knuckling, stumbling, interference between feet, pivoting on one foot, or wide movements in the outside limb (circumduction), that are not observed when the animal is walked in a straight line. Assessment of gait is facilitated when animals are halterbroken and can be led. This is not the case in many ruminants, so the clinician must rely more on observing the animal in its usual environment or in a confined area such as a pen. A handler may drive animals that are not halterbroken, but this should be done with due consideration of animal and handler safety.

A grading system for gait deficits has been described elsewhere,[46] as follows:

Grade 0: Normal gait
Grade 1: Very subtle deficits, observed by only an experienced clinician
Grade 2: Deficits apparent to an inexperienced clinician
Grade 3: Deficits apparent to laypersons
Grade 4: Severe deficits including stumbling, knuckling at the fetlock, falling
Grade 5: Recumbency and inability to rise

Proprioception is the sense of body position in space. Proprioceptive information is collected by receptors in the skin, joints, muscles, and vestibular system. General proprioceptive pathways run mainly in the lateral (spinocerebellar) and dorsal (conscious perception) funiculi of the spinal cord, relaying information to centers in the brainstem, cerebellum, and cerebral cortex. The vestibular system and pathways in the spinal cord to the vestibular centers in the medulla oblongata and cerebellum also help to control proprioception. Abnormalities of proprioception include stumbling, adduction or abduction of the limbs, circumduction, and interference between limbs (Fig. 8-2). Animals with proprioceptive deficits often slap down the feet hard, rather like the gait of a person walking down stairs in the dark, unsure of where the next step is. Walking the animal off a curb or step or down a slope exaggerates this appearance. When spun in a tight circle, normal animals lift the inside forefoot as the weight shifts. The outside rear leg is put down within a line demarcated by the lateral margin of the trunk. When spun in a tight circle, patients with abnormal proprioception may pivot on the inner hindfoot rather than lifting it and replacing it into a normal position. The outside foot may circumduct widely, knuckle, or buckle, and the inside foot may step on the outside foot. Animals with abnormal proprioception worsen when they are required to climb hills or lift the foot over a curb or are walked with the head elevated. The gait of noncompliant cattle may be assessed by observation of maneuvers through corrals, alleys, or a squeeze chute.

Having the animal walk backward also tests proprioception. The normal subject should be able to do so in a smooth, coordinated fashion, with conjugate movement of diagonally opposite limbs.

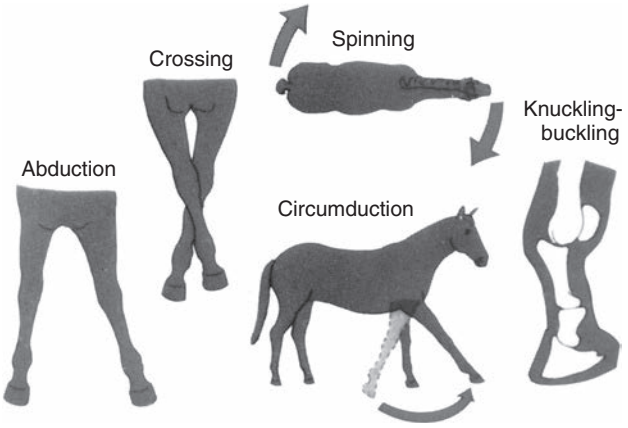


FIG. 8-2 Examples of conscious proprioceptive deficits in a horse. The signs of proprioceptive deficits in ruminants are similar.

Animals with lesions of upper motor neurons in the descending motor pathways may exhibit abnormalities such as foot dragging and weakness, sometimes to the point of "dog-sitting"; others may be reluctant to move straight backward and will try avoidance maneuvers such as circling to one side or the other in order to avoid it. Such tactics should raise the index of suspicion of a neurologic deficit. Care should be taken when backing an animal with severe neurologic deficits because some animals could fall backward during the procedure. Animals that are uncooperative or that have been little handled may exhibit reluctance to walk backward that is not caused by neurologic disease. Observing the patient's general level of cooperation and having a behavioral history will help the examiner determine whether the problem is caused by neurologic disease or the animal's lack of compliance.

Cerebellar disease causes errors in the rate, range, and force of voluntary movements; there is generalized ataxia with a rolling, drunken gait. Protraction of the limbs is delayed and limb movements are exaggerated, characterized either by excessive flexion during protraction, a condition known as *hypermetria,* or by *hypometria,* characterized by reduced joint flexion. There are often coarse bobbing movements of the head when the patient is walking; an intention tremor (most notable in the head) occurs when the animal initiates purposeful movements, such as reaching out to take food. Intention tremors may disappear when the animal is relaxed or recumbent. Cerebellar diseases may also result in opisthotonos or seizure-like fits.

Spontaneous circling is seen in diseases of the vestibular system and forebrain. Circling varies from a mild tendency to move in one direction to spinning and staggering in tight circles. Circling most often occurs *toward* the side of the lesion, except in paradoxic vestibular disease (caused by lesions in the vestibular components of the cerebellum) and with some asymmetric forebrain lesions, in which the animal circles *away* from the side of the lesion. Localization of the neurologic lesion in animals that circle is made on the basis of other neurologic abnormalities such as dementia, seizures, and central blindness (forebrain disease) or proprioceptive deficits, head tilt, spontaneous nystagmus, obtundation, and other cranial nerve deficits (vestibular disease).

Conscious Proprioception and Postural Reactions

The integrity of conscious proprioceptive pathways may be tested by means of the postural reactions. Normal animals stand at rest with the limbs in line with the abaxial boundaries of the trunk. When the limbs are moved, normal alert animals do not permit the limbs to be placed outside of the body axis or across midline. After the examiner places the limbs in an abnormal position, the neurologically intact animal returns to a normal stance within a few seconds. Animals with conscious proprioceptive deficits allow the limb to remain in the abnormal position for longer than the usual period of time. This can vary from animals in which replacement of the limb into a normal position is slightly slowed to animals that do not try to replace the limb at all. The examiner should cross one of the animal's limbs over the opposite limb or abduct one limb; the normal response is for the limb to be placed back into the resting position. Normal animals often strongly resist attempts to place the limbs in abnormal positions. It should be noted that normal animals are extremely variable in their responses to this maneuver, so undue reliance should not be placed on its results, particularly if there are no other signs of ataxia. Animals with proprioceptive deficits may spontaneously place the limbs in abnormal positions: excessively adducted, abducted, or even crossed. Abnormalities of proprioception alone are poorly localizing signs, although a couple of generalities may be stated. Unilateral lesions rostral to the medulla oblongata produce mild to moderate proprioceptive and postural deficits in the *contralateral* limbs. Unilateral lesions in the medulla oblongata or spinal cord produce more severe proprioceptive and postural deficits in the *ipsilateral* limbs. Lesions of the cerebellum rarely result in postural deficits.

Additional postural reactions such as hopping, hemiwalking, and wheelbarrowing can be tested in small ruminants, calves, and some

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foals. Hopping is tested in the thoracic limbs by lifting the pelvic limbs a few inches off the ground by means of a hand and arm placed around the abdomen, flexing one thoracic limb slightly, and moving the animal away from the side of the flexed thoracic limb so that it has to hop laterally on the thoracic limb still in contact with the ground. It is easiest if the examiner stands in one place and turns clockwise when testing the animal's right thoracic limb and counterclockwise when testing the left thoracic limb. Hopping in the pelvic limbs can be tested similarly, supporting both thoracic limbs off the ground with an arm around the chest. Hemiwalking is done by supporting both limbs on one side of the body in a slightly flexed position and pushing the animal toward the opposite side so that it must walk laterally on the two limbs still in contact with the ground. Both hopping and hemiwalking should be done with care not to push the patient over. Adult horses can be made to hop on one thoracic limb by picking up the opposite limb and firmly pushing the head and shoulders laterally. Hopping and hemiwalking involve the same ascending and descending motor tracts involved in gait on a level surface but also require input from the forebrain. These maneuvers are abnormal on the ipsilateral side in animals with lesions in the skeletal muscles, peripheral nerves, spinal cord, and medulla oblongata and on the contralateral side in animals with lesions in the midbrain or forebrain. Animals with forebrain lesions have normal gait on a level surface but subtle deficits in hemiwalking and hopping.

Abnormalities of Posture and the Righting Response

Posture refers to the position of the body and head in space, in relationship to gravity and to each other. Animals adopt slightly different postures when on a sloped or uneven surface compared with posture on a level surface. However, sustained asymmetric postures such as head tilt (Fig. 8-3), in which one ear is closer to the ground than the other, and head turn (Fig. 8-4), in which the nose is turned back toward the trunk, are abnormal. Circling often accompanies head tilt and head turn in asymmetric vestibular disease, and all tend to be toward the direction of the lesion. The exception to this rule occurs in paradoxic vestibular syndrome, in which head tilt and circling occur in a direction away from the side of the lesion.

The righting response is most easily tested in small ruminants and in recumbent large animals (Fig. 8-5). The response is initiated by receptors in the eyes and vestibular labyrinths and by proprioceptive receptors in the joints, tendons, and muscles. Information regarding limb position and balance is relayed ultimately to the cerebral cortex. Descending impulses are initiated in the motor cortex and relayed via the brainstem, cerebellum, and spinal cord to the appendicular musculature. The normal response to stimulation is to lift the head, assume sternal recumbency, and rise. The normal horse rises on the thoracic limbs first, whereas the normal ruminant rises on the pelvic limbs first. Animals that are in lateral recumbency and unable to lift the head from the ground may have lesions in the peripheral or brainstem vestibular centers or in the cervical spinal cord cranial to the C4 spinal cord segment. Unilateral lesions in this area result in an inability to lift the head from the ground when the lesion side is up. When the lesion side is down, the animal can raise the head slightly. Animals with incomplete lesions of the C7 to T2 spinal cord segments are able to lift the head and neck but cannot rotate the thorax into a prone position, and they may remain recumbent. Animals with lesions of the thoracolumbar and lumbosacral spinal cord (T3 to S3 spinal cord segments) can usually lift the head and neck, arise on the thoracic limbs, and assume a dog-sitting position.

Spinal Reflexes

The spinal reflexes are stereotyped responses to specific stimuli. They include the myotatic or tendon reflexes, the cutaneous trunci reflex (incorrectly called the "panniculus reflex"), the perineal reflex, and several others. As their names imply, spinal reflexes depend on the integrity of local spinal cord segments, dorsal and ventral nerve roots, and peripheral nerves, neuromuscular junctions, and muscles. Lesions of descending pathways in the spinal cord that are located cranial to the spinal components of the peripheral nerves to the limbs being tested result in *normal to increased* spinal reflexes and are commonly referred to as *upper motor neuron lesions*. Lesions in the gray matter of the spinal cord segments at the level of the reflex arc, the ventral roots, or peripheral motor nerves cause *diminished* spinal reflexes and are commonly referred to as *lower motor neuron lesions*.



FIG. 8-3 Head tilt caused by vestibular dysfunction in a horse that sustained head trauma.

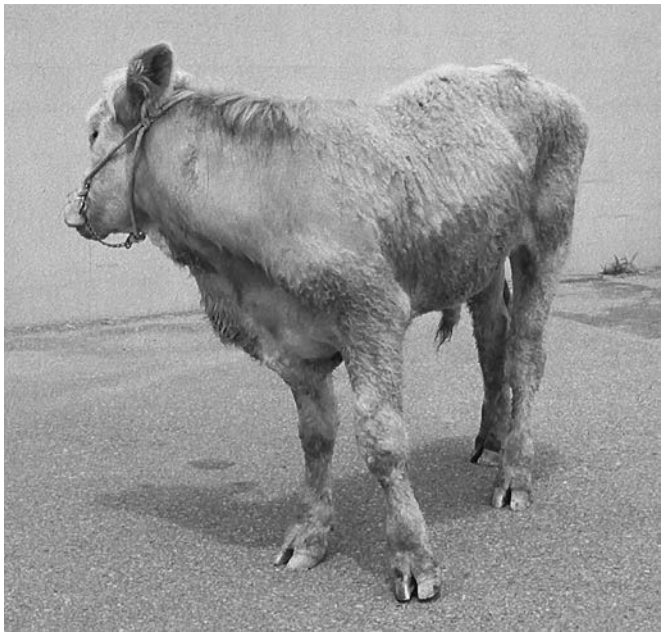


FIG. 8-4 Head turn in a steer with polioencephalomalacia.

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It is appropriate at this point to define the terms *upper motor neuron* and *lower motor neuron.* Upper motor neurons are nerve cells contained completely within the CNS with cell bodies in the brain and axons that terminate at synapses within the brain or spinal cord. Disease affecting upper motor neurons results in normal to increased spinal reflexes, variable severity of weakness, and variably increased muscle tone (spasticity). The nerve cell bodies of somatic lower motor neurons lie in the nuclei of cranial nerves in the brainstem or in the ventral horn gray matter of the spinal cord. The axons exit the CNS, course within the peripheral or cranial nerves, and terminate at neuromuscular junctions. Diseases affecting lower motor neurons result in decreased spinal reflexes, ataxia, moderate to severe weakness, decreased muscle tone (flaccidity), and rapid, pronounced atrophy of the denervated muscles.

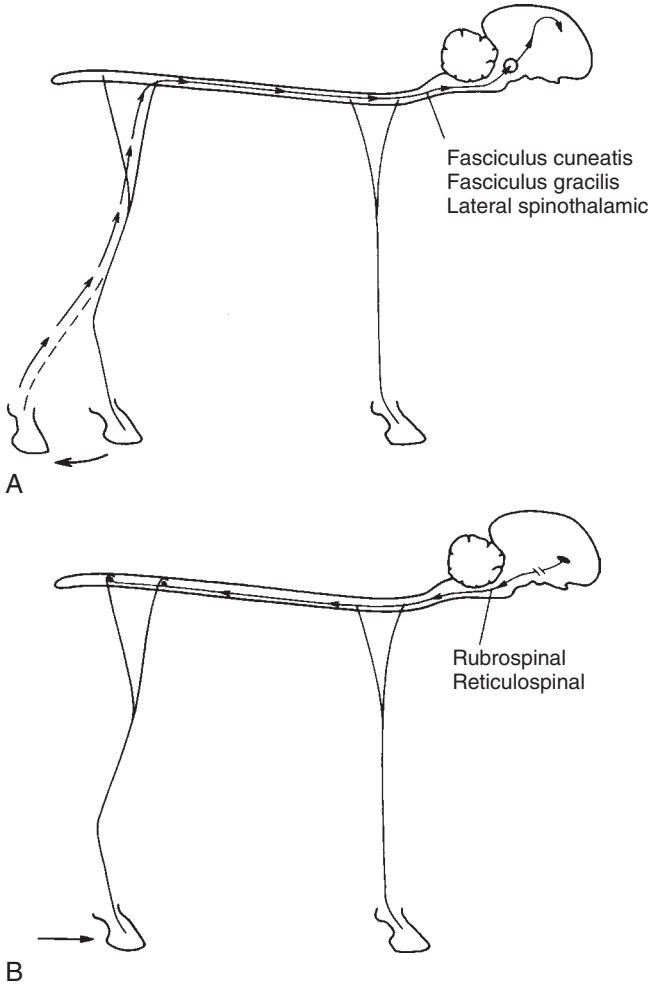


FIG. 8-5 **A,** Afferent pathways responsible for providing proprioceptive information to the brainstem and higher centers. **B,** Efferent pathways responsible for providing motor activities to the motor neurons.

Myotatic Reflexes

Myotatic or tendon reflexes are tested by sharply striking the tendon of a specific muscle (or sometimes the muscle itself) and evaluating the strength of the reflex contraction. The afferent component of the reflex arc involves the muscle spindles, which are stretch detectors, sensory fibers in the peripheral nerve, the dorsal nerve root and its ganglion, and the connection from the sensory nerve fiber to the lower motor neuron in the ventral horn of the same spinal cord segment (Fig. 8-6). The efferent component of the reflex arc involves the lower motor neuron, ventral nerve root, motor fibers in the peripheral nerve, the neuromuscular junction, and the muscle being tested. Lesions in the spinal cord cranial to the level of the reflex arc and lesions of the brain result in *normal to increased* myotatic reflexes after a period of several days. Lesions in either the afferent or efferent components of the reflex arc result in *decreased to absent* myotatic reflexes.

In adult horses and many adult cattle, myotatic reflexes can be tested only in recumbent animals. Some cattle can be cast with ropes for this purpose, and young animals and small ruminants can be placed in lateral recumbency for testing. These reflexes should be tested only in the limbs that are uppermost when the animal is lying on one side. The animal must be turned over to test the limbs on the opposite side; however, reflexes are often diminished in limbs that have been laid upon for prolonged periods of time (hours). In adult horses and cattle, only patellar reflexes can be reliably tested. The reflex responses are assigned a qualitative clinical score as follows:

0—No reflex activity
1—Hypoactive
2—Normal
3—Hyperactive
4—Hyperactive and clonic

Clonus is a phenomenon observed with severe upper motor neuron lesions: the response of the muscle being tested is a series of rapid, repeated contractions rather than a single contraction. The innervation of the limbs is listed in Tables 8-4 and 8-5.

THORACIC LIMB MYOTATIC REFLEXES

Triceps Reflex. Hold the limb moderately flexed at the elbow, and percuss the triceps tendon just above the olecranon using a heavy instrument. The normal response is a contraction of the triceps muscle, leading to retraction of the upper limb and extension of the elbow. The triceps reflex measures the integrity of the radial nerve and the C7 to T1 spinal segments.

TABLE 8-4

Innervation of the Thoracic Limbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
C7	Suprascapular	Supraspinatus, infraspinatus
C6, C7	Subscapular	Subscapularis
C7, C8, T1	Pectoral	Subscapularis, pectoral muscles
C6*, C7, C8	Musculocutaneous	Biceps brachii, coracobrachialis, brachialis
C8, T1, T2	Median	Flexor carpi radialis, deep digital flexor, superficial digital flexor
C8*, T1, T2	Ulnar	Flexor carpi ulnaris, deep digital flexor, superficial digital flexor
C7, C8, T1	Radial	Triceps, extensor carpi radialis, ulnaris lateralis, lateral and common digital extensors
C6†, C7, C8	Axillary	Deltoideus, teres minor, subscapularis, cleidobrachialis
C7, C8	Long thoracic	Serratus ventralis
C8, T1, T2†	Thoracodorsal	Latissimus dorsi
C8, T1	Lateral thoracic	Cutaneous trunci

*Contributes innervation in the ruminant only.

†Contributes innervation in the horse only.

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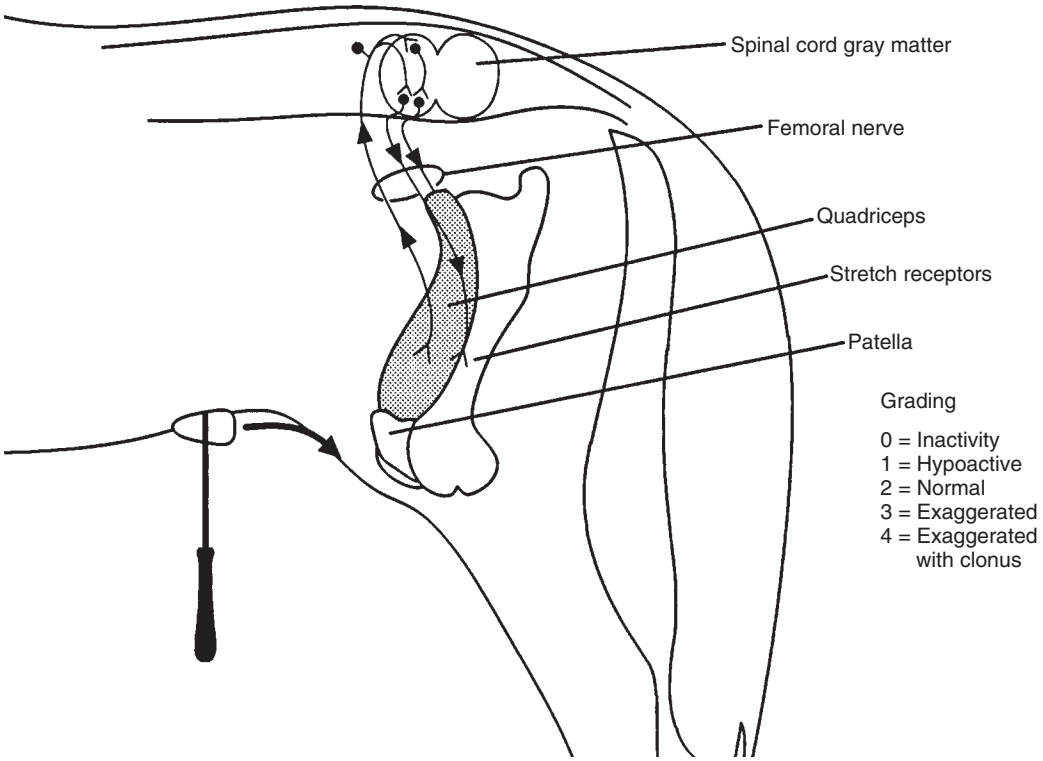


FIG. 8-6 Pathways governing patellar tendon reflex.

TABLE 8-5

Innervation of the Pelvic Limbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
L3*, L4, L5, L6†	Femoral	Quadriceps
L5*, L6, S1	Cranial gluteal	Gluteals, tensor fascia lata
S1-S5	Caudal gluteal, pudendal	Biceps femoris, middle and superficial gluteals
L5*, L6, S1, S2	Sciatic, peroneal	Lateral digital extensor, long digital extensor, short digital extensor, cranial tibial
L5*, L6, S1, S2	Tibial	Gastrocnemius, popliteus, superficial and deep digital flexor, interosseus
L5*, L6, S1, S2	Pudendal	Retractor penis
S3-Cd5	Caudal rectal	Rectum, anal sphincter, bladder

*Contributes innervation in the horse only.

†Contributes innervation in the ruminant only.

Biceps Reflex. Hold the limb moderately extended at the elbow and place the supporting hand over the attachment of the biceps muscle on the dorsomedial aspect of the limb at the level of the elbow joint. Percuss the biceps tendon or the taut biceps muscle with a heavy instrument. Contraction of the muscle may be perceived visually or by palpation. A slight flexion of the elbow and extension of the carpus is normal. The test measures the function of the musculocutaneous nerve and spinal cord segments C6 to C8 in ruminants and C7 and C8 in horses.

Lesions cranial to C6 result, within several days from the time of injury, in general hyperreflexia of both thoracic limbs and pelvic limbs. Lesions located in spinal segments C5 to T2 result in immediate hyporeflexia to areflexia of the thoracic limbs and, within several days, hyperreflexia of the pelvic limbs.

PELVIC LIMB MYOTATIC REFLEXES

Patellar Reflex. Flex the stifle moderately, and sharply percuss the middle patellar ligament with a heavy instrument. The normal reflex is a sharp contraction of the quadriceps femoris muscle resulting in extension of the stifle and a forward jerk of the lower part of the limb. The patellar reflex measures the function of the femoral nerve, the quadriceps femoris muscle, and L3 to L5 and L4 to L6 spinal cord segments in horses and cattle, respectively.

Cranial Tibial Reflex. The cranial tibial reflex is elicited by flexing the hock and sharply striking the belly of the cranial tibial muscle. The reflex consists of a slight extension of the digit. The cranial tibial reflex is mediated through the peroneal and sciatic nerves and spinal cord segments L5 to S2 or L6 to S2 in the horse and the ruminant, respectively. Lesions of the spinal cord anterior to L3 segments result in hyperreflexia, whereas lesions of L3 to L6 spinal segments result in hyporeflexia or areflexia.

FLEXOR (WITHDRAWAL) REFLEXES. The flexor reflexes are elicited on the upside front and hind limb in the recumbent large animal. For safety, the examiner should be positioned on the dorsal side of the animal, or well cranial to the limb being tested. A painful stimulus is applied to the uppermost foot or distal limb. The normal response consists of two phases: (1) rapid reflex limb flexion, and (2) slower conscious perception of and response to the stimulus, characterized by attempts to assume sternal recumbency, vocalization, ear and eye movements, and/ or kicking. The thoracic limb flexor reflex tests the integrity of the axillary, median, and musculocutaneous nerves and spinal cord segments C5 through T2, as well as the flexor muscles of the limb. The pelvic limb flexor reflex is mediated by means of the sciatic, peroneal, and tibial nerves and the pelvic limb flexor muscles and spinal cord segments L6 to S2.

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Spinal cord and peripheral nerve lesions may be localized further by testing the integrity of the sensory innervation of the skin of the limbs. Areas of decreased or absent cutaneous sensation reflect lesions of the peripheral nerves innervating those regions of the skin or of the spinal cord segments in which those sensory nerves terminate. The skin over the trunk and much of the limbs is innervated by more than one peripheral nerve. Some areas of the limbs derive sensory innervation from a single peripheral nerve. These areas are termed the *autonomous zones* for those peripheral nerves. Damage to a peripheral nerve innervating the skin of a limb therefore will result in decreased to absent cutaneous sensation in the autonomous zone for that nerve. This information can be used to localize lesions. Decrease or loss of sensation to an entire limb or to limbs on both sides of the body suggest a lesion affecting several local spinal cord segments, or a transverse spinal cord lesion rostral to the affected limbs.

Other Spinal Reflexes

PERINEAL REFLEX. The perineal reflex is elicited by pinching the mucocutaneous junction of the anus. The normal reflex includes tightening of the sphincter muscle and contraction of the ventral tail muscles. Conscious perception of the stimulus produces avoidance or protective responses that may range from a slight movement of the pelvic limbs and pelvis to a violent kick. The reflex is mediated by the pudendal nerve and spinal cord segments S1 to S5. Lesions in the nerve or in the sacral spinal cord result in a dilated, atonic rectal sphincter that fails to respond to noxious stimuli. Additional signs of sacral spinal cord injury may include fecal impaction in the rectum and a dilated urinary bladder. The bladder is full of urine and dribbles whenever digital pressure is applied through the rectum or vagina. The perineum remains wet and may become irritated from constant contact with urine.

CUTANEOUS TRUNCI REFLEX. The cutaneous trunci reflex (also known incorrectly as the "panniculus") is a shrugging or flinching of the skin over the thorax when it is stimulated by light touch or by pinching. Tap the skin with an extended thumb (in adult horses) or with a hemostat. The normal reflex response is a skin twitch often followed by a conscious avoidance maneuver such as moving away from the stimulus. The afferent part of the cutaneous trunci reflex is mediated by the segmental spinal nerves and dorsal nerve roots in the territory of the reflex. The tracts ascend in the dorsal funiculi of the spinal cord and synapse on efferent neurons in spinal segments C8 to T1 in ruminants and C8 to T2 in horses. The efferent axons exit in the ventral roots and form the lateral thoracic nerve, which innervates the cutaneous trunci muscle. The degree of reflex responsiveness varies among the large animal species. Sheep, goats, and many cattle possess a poor cutaneous trunci reflex. Horses and Zebu cattle have a well-developed reflex.

CERVICAL REFLEXES. Two reflexes have been described in the cervical area of the horse.[47] The cervical reflex is tested by tapping or pinching the skin of the cervical region over the brachiocephalicus muscle and behind the second cervical vertebra. The expected response is contraction of the brachiocephalicus muscle and twitching of the skin. The pathway is believed to involve the cervical segmental spinal nerves and the local spinal cord segments. The cervicofacial reflex is elicited in horses by tapping the skin as described for the cervical reflex. As the skin is stimulated in normal horses, the ear reflexively twitches rostrally and ventrally, and the commissure of the lip retracts. This test measures the integrity of the dorsal funiculi of cervical spinal cord segments and the facial nerve in the medulla oblongata. The diagnostic usefulness of this test in ruminants is unknown.

Both reflexes may be abnormal in animals with lesions affecting the cervical spinal cord, such as cervical vertebral stenotic myelopathy in horses. The cervicofacial reflex also may be diminished or absent in animals with caudal brainstem lesions involving the facial nerve or with peripheral facial nerve lesions.

"SLAP" TEST (LARYNGEAL ADDUCTOR REFLEX). A sharp slap applied in the saddle region on one side of a horse's thorax results in adduction of the vocal folds of the larynx on the opposite side.[48] Standing on one side of the animal, the examiner curls his or her fingers around the dorsolateral aspect of the larynx on the opposite side. A slap is applied to the saddle region on the side on which the examiner is standing. The response is palpated as a small movement of the arytenoid cartilage felt under the fingertips on the opposite side of the larynx. The pathway for the reflex is only partially understood. Sensory information from the skin and/or pleural stretch receptors is relayed to the spinal cord in the segmental spinal nerves. The ascending pathways cross the spinal cord and run cranially in the spinal cord to the origin of the vagus nerve in the medulla oblongata. The efferent part of the reflex runs in the cervical vagosympathetic trunk and thence to the recurrent laryngeal nerve, which branches from the vagus in the cranial thorax. The recurrent laryngeal nerve courses cranially alongside the trachea to the larynx. Reduced or absent laryngeal adductor reflexes are found in animals that have lesions of the cervical spinal cord but also in those with caudal brainstem lesions, vagus nerve lesions, and lesions of the left recurrent laryngeal nerve (some of which are clinical "roarers"). The test's accuracy may be limited. In one study there was poor correlation when predicting the presence or absence of cervical spinal cord or brainstem disease.[49] Interpretation of the results depends on the experience of the examiner. The laryngeal adduction elicited in this test can also be observed endoscopically.

Muscle Mass and Tone

Normal mass and tone of the musculature depends on an intact nerve supply. Primary diseases of muscle and loss of use of a limb secondary to orthopedic disease are often associated with mild to moderate muscle atrophy that develops over weeks to months. Atrophy caused by denervation, however, is more severe and rapid in onset. Visible loss of mass of specific muscles or groups of muscles is most likely caused by damage to the nerve supply to those muscles, either by direct injury to peripheral nerves or injury to the cell bodies of those nerves in the ventral horn of the gray matter of the spinal cord (Fig. 8-7). Knowledge of the central origins of the nerves to the limbs and the course of those nerves in the periphery can be used to specifically localize neurologic lesions (see Tables 8-4 and 8-5). Electromyography and nerve conduction testing can further be used to help identify muscle denervation and peripheral neuropathies (see Chapter 35).

Muscle tone can be evaluated in the recumbent animal by passively flexing the limbs. Evaluation is not accurate in the standing animal or in animals supported in slings because of resistance from taut bands of connective tissue. In normal animals repeated flexion is accompanied by an increase in the tone in the flexed limb. The limbs of animals with a lower motor neuron deficit remain flaccid.

The tone of the thoracic limbs is controlled through spinal cord segments C6 to T2 and the radial, musculocutaneous, median, ulnar, axillary, and long thoracic nerves. The motor tone of the pelvic limbs is controlled through spinal cord segments L3 to S2 and the femoral, cranial and caudal gluteal, and sciatic nerves. The lower motor neurons to the anus originate in spinal cord segments S1 to S5, via the pudendal nerve. The tail is innervated by the coccygeal segmental spinal nerves.

Examination of Cranial Nerves

Examination of the cranial nerves is most easily carried out by examining the functions of groups of nerves that innervate particular regions of the head rather than performing the examination in a strictly numeric order. For example, examination of vision and other ocular functions such as the menace response, pupillary light reflexes, and physiologic nystagmus reveals the integrity of several cranial nerves, not only II, III, IV, and VI but also V (sensory to the cornea), VII (motor to the eyelids), and VIII (providing vestibular input to control the functions of III, IV, and VI), as well as centers within the brain.

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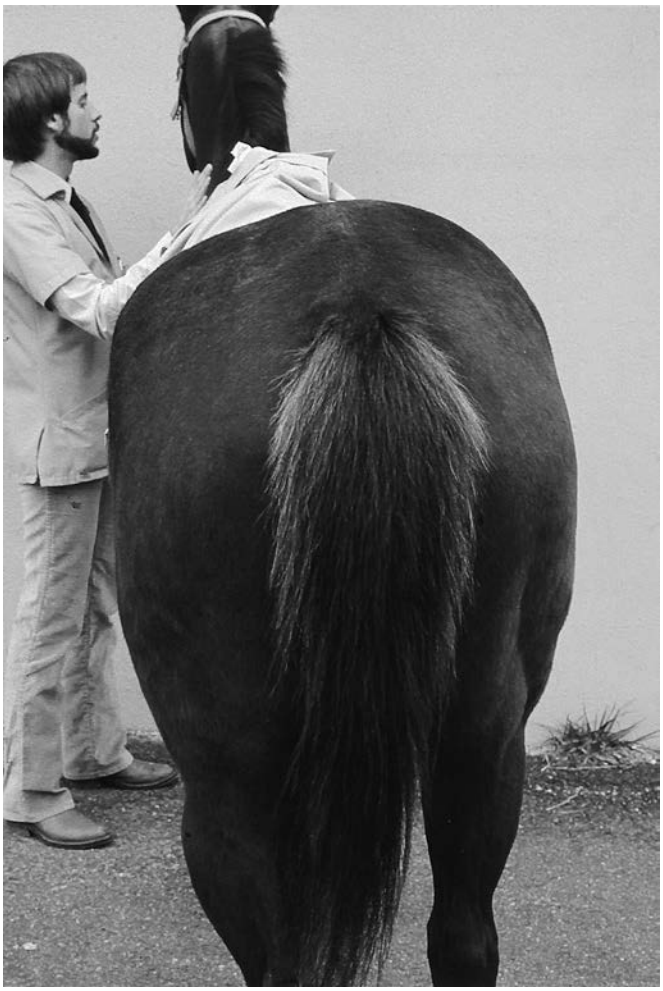


FIG. 8-7 Muscle atrophy in the gluteal muscles in a horse with equine protozoal myeloencephalitis.

CRANIAL NERVE I—OLFACTORY NERVE. Reliable and specific testing of the sense of smell is difficult in animals. Large animals require an intact sense of smell to eat properly, so it can be inferred that animals with good appetites possess an adequate sense of smell. Having a blindfolded animal track food moved from side to side in front of the nose may be helpful. Irritating substances such as ammonia should not be used for evaluation of olfactory nerve function; such compounds stimulate nociceptors in the nasal mucosa, which are the dendrites of the maxillary nerve (cranial nerve V), rather than stimulating olfactory receptors innervated by the olfactory nerve. Loss of the sense of smell is more likely to be caused by disease within the nasal passages than by a primary neurologic disease.

CRANIAL NERVE II—OPTIC NERVE. Vision and light perception are the functions of cranial nerve II, the optic nerve. Observing the animal's response to its environment provides a good initial assessment. Does it respond to visual cues such as movement or does it walk into objects? Noise may cause the animal to turn its head toward the sound, so the observer must be careful to distinguish such responses from those made in response to visual cues. A maze can be set up using straw bales or other objects, and the animal gently driven through the maze. Normal animals will avoid colliding with objects. Animals that are severely obtunded, however, may walk into objects even when they can see. Thorough evaluation of the complete neurologic examination is necessary to distinguish this from true blindness.

The menace response measures the integrity of the entire visual pathway. The afferent pathway runs from the retina via the optic nerves and internal capsule to the visual areas in the occipital lobe of the cerebrum. Information from the visual cortex is processed and relayed to the ipsilateral motor cortex. The efferent pathway of the menace response runs from the motor cortex via the pons to the nucleus of the facial nerve in the medulla oblongata and thence via the facial nerve to the orbicularis oculi muscle. It is not known whether or not this pathway passes through the cerebellum, but it is clear that the ipsilateral cerebellar cortex is required for a competent menace response. The menace test is performed by rapidly advancing the hand toward the eye and observing a closure of the eyelid. In addition to the closure of the eyelid, some animals display a generalized avoidance response characterized by coordinated movement of the head and neck away from the stimulus. The opposite eye may be covered to ensure that only one eye is being stimulated. Care must be taken not to touch the face or eyelashes or create air currents near the face. Separate menacing gestures must be directed from both the nasal and temporal aspects, in order to cover the entire visual arc. The menace response measures the integrity of the retina, optic nerve, optic chiasm, optic tracts, thalamus, internal capsule, and occipital cortex. There is approximately 90% crossing over of optic nerve fibers in the optic chiasm of livestock. Unilateral lesions central to the optic chiasm—in the optic tract, internal capsule, thalamus, or occipital lobe—cause loss of vision in the opposite eye, with apparently normal vision in the ipsilateral eye. It should be noted that normal neonatal animals may not display a response to a menace gesture because this is a learned response.

Menace deficit may be the result of facial nerve paralysis. In such cases the animal does not blink but shows avoidance of the stimulus by pulling the head away. Facial nerve deficits will be apparent in these animals by their inability to close the eyelids in response to cutaneous stimulation around the lid margins (palpebral reflex) and by other signs such as drooping of the lip and ear on the same side. Animals with cerebellar disease may also display a menace deficit yet possess normal vision. Menace deficits resulting from facial nerve or cerebellar disease may be differentiated from deficits in other areas by maze testing. Animals with cerebellar or facial nerve disease retain visual acuity and maneuver through the course successfully. In addition to the optic pathways, the test measures the integrative pathways in the frontal and parietal lobes of the brain, the motor neurons, and the proprioceptive pathways (Table 8-6). Myasthenic diseases (e.g., botulism, hypocalcemia, hypomagnesemia) result in bilaterally decreased menace and palpebral responses but do not produce blindness.

The pupillary light reflex measures the integrity of the retina, optic nerves, optic chiasm, pretectal and oculomotor nuclei in the midbrain, oculomotor nerve, ciliary ganglia, and constrictor pupillae muscle. The test is performed by shining a bright light into each eye and observing constriction of the pupil in the ipsilateral eye (direct reflex) and the contralateral eye (indirect reflex). Lowering the ambient light level may facilitate this test by causing the pupils to dilate. The reflex in large animals is considerably slower than those observed in cats and dogs. A "swinging light" test has been recommended in large animals to reduce the dazzle and startle responses elicited by suddenly shining a bright light into the eyes.[46] From a position directly in front of the animal, a strong light is slowly swung from one eye to the other while bringing the light closer and closer to the head and observing the responses in each pupil. The effects on the pupillary light reflex of lesions at various levels along the visual pathway are shown in Table 8-6.

Unilateral lesions in the forebrain may result in blindness of the opposite eye. With forebrain lesions, the pupillary light reflexes are usually normal. If the forebrain disease is accompanied by increased intracranial pressure, the oculomotor nerve or nucleus may be compressed in the midbrain, resulting in ipsilateral mydriasis.

CRANIAL NERVES III, IV, AND VI—OCULOMOTOR, TROCHLEAR, AND ABDUCENT NERVES. The position of the globe in the orbit is governed by the activities of the oculomotor, trochlear, and

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TABLE 8-6

Guide to Neuroophthalmologic Lesion Location

Lesion Location	Menace Response		Pupillary Light Reflex		
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Maze Test*
Unilateral retina, optic nerve	Absent	Present	Absent (direct), slightly dilated	Normal	Abnormal
Bilateral retina, optic nerve, optic chiasm	Absent	Absent	Fixed	Fixed	Abnormal
Unilateral oculomotor nerve	Absent	Present	Dilated nonresponsive	Normal	Normal
Unilateral occipital cortex	Present	Absent	Normal†	Normal†	Abnormal
Bilateral occipital cortex	Absent	Absent	Normal†	Normal†	Abnormal
Bilateral vagosympathetic trunk	Present	Present	Miotic	Normal	Normal
Bilateral cerebellar cortex	Absent	Absent	Normal	Normal	Normal‡

*In unilateral cases, assumes that contralateral eye is blindfolded.

†Assuming that no cortical swelling has occurred.

‡Animals walk abnormally but recognize and generally avoid obstacles.

abducent nerves. Dysfunctions of these nerves result in deviation of the globe that is constant in all head positions. Loss of oculomotor nerve function results in ventrolateral strabismus. Trochlear nerve dysfunction results in rotation of the dorsal aspect of the globe away from the midline (dorsomedial strabismus). Loss of abducent nerve function results in medial strabismus and inability to retract the globe, which is best demonstrated by closing the eyelid and then pushing on the globe through the eyelid. The normal reflex is a retraction of the globe.

Competent function of the oculomotor, trochlear, and abducent nerves is also required for the oculocephalic reflexes. When the head is turned from side to side in a horizontal plane, physiologic horizontal nystagmus is observed, with the fast phase of the nystagmus in the direction of head movement. The sensory receptors for this reflex lie within the semicircular canals of the inner ear, and they detect angular acceleration of the head. Input from the semicircular canals is transferred to the vestibular centers in the medulla oblongata and the cerebellum and then via the medial longitudinal fasciculus and reticular formation to the nuclei of cranial nerves III, IV, and VI. Lesions of the peripheral or central components of the vestibular system can also result in abnormal eye position (strabismus) and movement (nystagmus), described in more detail later. With peripheral or central vestibular lesions, however, eye position typically changes when the head and neck are moved, in contrast to the constant deviation of the globe seen with direct lesions to the oculomotor, trochlear, and abducent nerves.

The oculomotor nerve is motor to the levator palpebrae superioris muscle, the most important of the muscles responsible for elevation of the upper eyelid. Lesions of the nerve cause ptosis (drooping of the upper eyelid) in addition to the signs described previously. Ptosis can also be induced by lesions of the sympathetic nerve supply to the eye because of paralysis of the superior tarsal (Mueller's) muscle and, in the horse only, by lesions of the facial nerve, which innervates the levator anguli oculi medialis muscle (see later).[50]

CRANIAL NERVE V—TRIGEMINAL NERVE. The trigeminal nerve is sensory to the face and motor to the muscles of mastication. The sensory functions of the trigeminal nerve are tested by lightly stimulating the forehead, upper and lower jaws, and muzzle using the tip of a closed hemostat or a finger. The normal response is one of avoidance using neck, facial, and appendicular musculature; the animal usually pulls the head away and blinks simultaneously. Some areas such as the cheeks, forehead, and chin are normally less sensitive, whereas the periorbital region, nasal planum, nasal septum, and lips are sensitive. The test evaluates the function of the sensory part of the trigeminal nerve, the trigeminal ganglion, the nucleus and spinal tract of the trigeminal nerve, the pontine sensory tract nucleus of cranial nerve V, the thalamus, and the sensorimotor cortex. After the trigeminal nerve enters the lateral aspect of the pons, axons both ascend and descend through the medulla as the spinal tract of the trigeminal nerve. Ascending information ultimately reaches the sensorimotor cortex via the thalamus, where it is consciously perceived. Descending information projects to the nucleus of the facial nerve in the medulla and also into the first cervical spinal segment. Unilateral loss of facial perception of touch most commonly results from damage to the peripheral portion of the trigeminal nerve, the trigeminal ganglion in the petrosal bone of the skull, or the contralateral forebrain (i.e., thalamus or cerebrum). Lesions affecting the spinal tract of the trigeminal nerve in the medulla and midbrain would likely be fatal, because they also would affect adjacent respiratory and cardiovascular centers in the brainstem. Patients with bilateral facial hypalgesia most often have bilateral forebrain disease.

The palpebral reflex is elicited by lightly touching the periorbital area (both above and below the eye) and observing a brisk closure of the eyelid. This reflex reflects the sensory function of the trigeminal nerve and the motor function of the facial nerve and orbicularis oculi muscle. Simultaneous loss of the menace response and the palpebral reflex suggests a lesion in the facial nerve or the orbicularis oculi muscle. Loss of the palpebral reflex with normal menace responses suggests a lesion in the trigeminal nerve or ganglion. Loss of menace response with preservation of the palpebral reflex and pupillary light reflex suggests the presence of either contralateral forebrain disease or ipsilateral cerebellar cortical disease.

The jaw should be opened to assess the strength of the masticatory muscles. This measures both the sensory (proprioceptive) fibers of the trigeminal nerve and the motor component of the nerve. Bilateral lesions of the motor component of the trigeminal nerve result in a dropped jaw. Affected animals may protrude the tongue but can retract it normally when stimulated. Animals with dropped jaws may drool because they cannot hold saliva within the oral cavity. Unilateral lesions of the trigeminal nerve produce asymmetric jaw closure, with deviation of the mandible away from the affected side, and neurogenic atrophy of the visible masticatory muscles (i.e., masseter and temporalis).

CRANIAL NERVE VII—FACIAL NERVE. The motor nucleus of cranial nerve VII (the facial nerve) originates in the middle and ventral part of the medulla oblongata. The motor fibers are distributed to muscles of facial expression. Just as the motor fibers are exiting from the lateral aspect of the brainstem they merge with axons from the parasympathetic facial nucleus. These autonomic fibers innervate the lacrimal and salivary glands and separate from the motor component of the facial nerve as it traverses the petrous temporal bone. Lesions of CN VII located between the brainstem and this separation usually result in "dry eye." More distal lesions, however, have no effect on tear production. The tone of the facial musculature is examined by palpation of the ears, lips, eyelids, and muzzle. Clinical signs of facial nerve dysfunction include drooped ear and lips, drooling saliva, and retention of food in the cheek pouch on the denervated side (Fig. 8-8). Closure of the eyelids is weak in partial facial nerve lesions and absent in severe lesions. Despite this,

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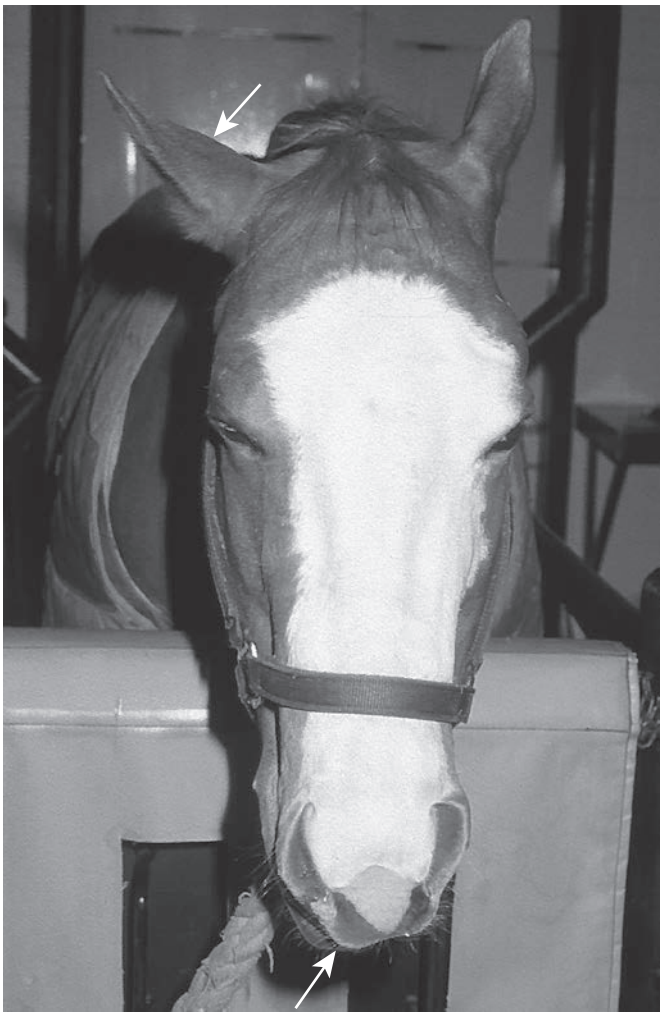


FIG. 8-8 Acute right facial paralysis in a horse with guttural pouch mycosis. Note the drooped right ear and deviation of the muzzle toward the left side *(arrows)*.

there is slight drooping of the upper eyelid (ptosis) because of paralysis of the levator anguli oculi medialis muscle, which contributes to eyelid retraction. In species with a soft muzzle (e.g., horses, sheep, goats), there is a marked deviation of the nasal filtrum *away* from the side with the lesion after unilateral loss of facial nerve function. The filtrum of affected cattle is not deviated because of the large amount of fibrous tissue in the planum nasale. In *chronic* facial paralysis the face may be deviated *toward* the affected side because of atrophy and contracture of the denervated musculature of the face. In horses, neurogenic atrophy of the parotidoauricularis muscle is evident as a groove behind the vertical ramus of the mandible.

CRANIAL NERVE VIII—VESTIBULOCOCHLEAR NERVE

Vestibular System. The function of the vestibular system, which is composed of the sensory structures in the inner ear (semicircular canals, utriculus, saccule), the vestibular portion of cranial nerve VIII, and the central components of the vestibular system in the medulla oblongata and cerebellum, is tested by assessment of gait, extensor tone, head posture, and eye movements. Signs of vestibular dysfunction include a staggering gait, circling, falling, rolling, head tilt, and spontaneous nystagmus. Lesions can be classified as peripheral or central. Diseases affecting the inner ear or cranial nerve VIII result in signs of peripheral vestibular disease. Lesions affecting vestibular structures in the medulla oblongata result in central vestibular signs, and lesions affecting vestibular structures in the cerebellum result in paradoxic vestibular signs. Blindfolding affected patients results in a worsening of clinical signs because of elimination of visual compensatory mechanisms. Recumbent animals with vestibular lesions tend to lie with the side of the vestibular lesion downward. When turned, these animals spontaneously rotate back to the lesion-down position and may strongly resist attempts to turn them over. Animals with unilateral vestibular disorders typically have ventral strabismus in the ipsilateral eye and dorsal strabismus in the contralateral eye. Bilateral, symmetric lesions of the vestibular system are rare. Bilateral vestibular dysfunction does not cause head tilt, nystagmus, or strabismus. Affected animals are reluctant to move. They stand with a basewide posture, with the head held low, and fall easily when forced to move.

CRANIAL NERVES IX, X, AND XI—GLOSSOPHARYNGEAL, VAGUS, AND SPINAL ACCESSORY NERVES. Cranial nerves IX, X, and XI originate in the nucleus ambiguus, a column of motor neurons in the medulla oblongata. They provide motor control to the muscles of the neck, pharynx, and palate. The vagus nerve contains efferent fibers that stimulate the secretions of glands of the visceral and respiratory mucosa and control forestomach motility in ruminants. The glossopharyngeal and accessory nerves carry afferent fibers from the mucosa of the tongue, larynx, and pharynx.

The signs of glossopharyngeal and vagus nerve dysfunction include dysphonia (roaring, snoring); dysphagia; and regurgitation. Animals with pharyngeal paralysis regurgitate food and saliva from the nose. Roaring is a characteristic stridor emanating from the larynx. The abnormal sound may only be heard during exercise. Functional examination of these nerves should include auscultation of the larynx for stridor, observation of the animal as it swallows, passage of a nasogastric tube to evaluate deglutition, endoscopic examination to evaluate pharyngeal and laryngeal movements, and palpation of the larynx for muscle atrophy. The slap test, described earlier, is a test for function of the vagal innervation of the larynx via the recurrent laryngeal nerve. Specific descriptions of the endoscopic appearance of pharyngeal paralysis and roaring are presented elsewhere (see Chapter 31).

Signs of spinal accessory nerve dysfunction are extremely rare and include atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles.

SYMPATHETIC INNERVATION OF THE HEAD—HORNER SYNDROME. Preganglionic sympathetic motor fibers that innervate structures of the head originate from the first three thoracic spinal cord segments. These fibers ascend the neck in the vagosympathetic trunk to the cranial cervical ganglion under the tympanic bulla, where they synapse with postganglionic sympathetic fibers. The postganglionic fibers are distributed to the smooth muscles of the head via the ciliary nerves, passing through the petrous temporal bone area. Lesions anywhere along the course of the preganglionic or postganglionic sympathetic nerves, in spinal cord segments T1 to T3 or, rarely, in the upper motor neuron component of the sympathetic pathway in the cervical spinal cord or brainstem (tectotegmentospinal tract) cause a characteristic constellation of clinical signs known as *Horner syndrome*. Signs include miosis, ptosis, and increased warmth on the ipsilateral side of the face. In cattle there is a loss of sweating on the ipsilateral half of the planum nasale, whereas in horses there is excessive sweating on the affected side of the head and upper neck. Miosis is produced by lack of sympathetic tone to the affected pupil. Diseases that could produce Horner syndrome in large animals include lesions of the T1 to T3 spinal cord segments, mediastinal or thoracic abscesses or neoplasia, trauma or infection involving the cervical sympathetic trunk, esophageal perforations, guttural pouch mycosis in horses, otitis media and interna, and retrobulbar abscesses. Lesions of the midbrain may produce miotic pupils without other signs of Horner syndrome. This is a common sign in cattle with polioencephalomalacia and lead poisoning.

CRANIAL NERVE XII—HYPOGLOSSAL NERVE. The hypoglossal nerve supplies motor innervation to the muscles of the tongue and the geniohyoideus muscle. The nucleus is located in the caudal

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medulla oblongata. Hypoglossal nerve function is tested by pulling the tongue out of the mouth. Normal animals should have forceful resistance to passive manipulation of the tongue. Lesions of the hypoglossal nerve result in flaccidity and atrophy of the tongue. Acute lesions result in deviation of the tongue away from the side of the lesion; with time the tongue may deviate toward the affected side because of muscle atrophy and contracture.

Other Aspects of Physical Examination of the Patient with Neurologic Disease

Diagnosis of a neurologic disease can often be facilitated by the observation of physical abnormalities in other systems. When one examines animals with limb ataxia or tetraparesis, the head, neck, and back should be gently manipulated while the spine is palpated for pain, crepitation, or swelling. These findings could indicate the presence of a fracture, malformation, or luxation of one or more cervical vertebrae, vertebral osteomyelitis, diskospondylitis, or osteoarthritis of intervertebral joints. Do not manipulate the neck when there is evidence of acute cervical vertebral trauma. Swelling, bruising, or hair loss on the skin around the head or bleeding from the ears or nose could signify cranial trauma. Hair loss and dermatitis around the perineum and medial thigh may indicate urinary incontinence. In neonates a hairless patch over the dorsum of the spine or skull could indicate a meningomyelocele or meningoencephalocele. Crepitation over coxofemoral or stifle joints of recumbent cattle could indicate a luxation or fracture. The pelvic limb and pelvis should be examined in all recumbent large animals to detect displacement of the hip joint into the obturator foramen or fractures through the shaft of the ilium. All joints should be passively manipulated to detect dislocations or fractures. The heart should be auscultated for murmurs that could suggest left-sided endocarditis because such lesions can shower bacteria into the meninges. Odors on the breath such as ammonia, ketones, or petroleum distillates could provide clues about possible toxic causes. The ocular fundus should be examined ophthalmoscopically to detect retinal hemorrhages (trauma), papilledema (increased intracranial pressure), or vasculitis.

Examination of the Neonate

Most of the physical diagnostic techniques described in the preceding paragraph for the adult may be applied to examination of the neonate. Most spinal reflexes of livestock are well developed after birth. In the normal foal younger than 3 weeks of age, the limbs are hypertonic and hyperreflexic, with occasional myoclonus occurring after percussion of the patellar or triceps tendons. This hyperreflexia is most pronounced in the pelvic limbs. A lack of menace response for up to 2 weeks after delivery is expected because the menace response must be learned. When restrained the newborn foal relaxes into a trance-like state, periodically awakening and struggling violently before becoming passive again.

Bottle-reared calves aggressively attempt to suck while being examined, including vigorously head-butting the handler. Beef calves attempt to escape restraint and do not attempt to suck. See Chapters 17 for more on foals and Chapter 20 for more on neonatal ruminants.

Localization of Central Nervous System Lesions

Localization of a CNS lesion on the basis of clinical signs is vital because many specific diseases are restricted to particular regions of the CNS. Lesions can be localized to one of seven regions of the CNS: forebrain, midbrain, cerebellum, medulla oblongata, spinal cord, peripheral nerve (either cranial nerves or spinal nerves), and muscle. Once the clinician has located the anatomic site of a neurologic lesion, a list of rule-out diagnoses may be formulated. Additional tests including CSF analysis, radiography, magnetic resonance imaging (MRI), computed tomography (CT), serology, electroencephalography, brainstem auditory evoked response (BAER), and myelography can be performed to further characterize the disease.

Localization of Neurologic Diseases by Major Clinical Signs

Abnormal Mentation and Behavior and Seizures

Decreased mental alertness (dullness, obtundation, stupor, coma) is the most common change of mental status in animals with neurologic disease, although increased responsiveness to external stimuli (anxiety, mania, aggression) sometimes occurs. Altered mentation results from lesions in the ARAS or after diffuse severe forebrain disease. Diseases affecting the ARAS tend to produce severe changes in mentation (stupor, coma), whereas those affecting the forebrain tend to produce mild obtundation with concurrent behavioral abnormalities (i.e., dementia). In order of worsening severity, decreased mental status in animals can be categorized as follows.

LETHARGY. Animals respond to normal stimuli but are duller than normal.

STUPOR. Animals appear to be asleep and will respond only to vigorous and painful stimuli. Responses are blunted even to these stimuli. Semicoma is a severe form of stupor wherein patients are too obtunded to remain standing.

COMA. Animals are unconscious and will not respond even to the most painful stimuli. Animals in coma are recumbent.

DEMENTIA. Animals with dementia exhibit abnormal reactions and responses to their environments, including to inanimate objects, humans, and other animals within those environments. Signs are extremely variable, from head-pressing and yawning to compulsive walking, bellowing, rearing, self-mutilation, and aggression.

SEIZURES, COLLAPSE. Episodic abnormalities of behavior or consciousness are usually the result of seizure activity, narcolepsy or cataplexy, or syncopal attacks caused by cardiovascular or respiratory dysfunction. Intermittent toxicities or fluctuating metabolic abnormalities such as occasionally occur with hepatic encephalopathy may also cause episodic changes in mentation and behavior. Animals with a history of episodic collapse should undergo a thorough physical examination to determine whether disease of the cardiovascular system (e.g., cardiac arrhythmias, intermittent hemorrhage) or respiratory system (e.g., laryngeal paralysis) is present. Animals that have seizures usually have a period of abnormal behavior after the seizure (postictal phase of the seizure), whereas those with narcolepsy, cataplexy, or non-neurologic causes of collapse usually do not.

Diffuse forebrain disease often results from metabolic, toxic, or infectious diseases. Increased intracranial pressure, the consequence of early acquired hydrocephalus, mass lesions within the cranial vault, inflammatory diseases, or cerebral edema, tends to produce signs of diffuse forebrain dysfunction, which can range from mild to severe. Mild to moderate forebrain dysfunction usually results in an animal with decreased mental awareness or, more rarely, excitement and overreaction. Diffuse disease does not result in circling, and gait on a level surface may appear normal, or almost so. Gait may be abnormal, however, when the animal is challenged to ascend or descend slopes, step over objects on the ground, step onto and off curbs, circle, or back up. Postural and proprioceptive reflexes and reactions similarly may be abnormal. When an animal is walking at normal speed on a level surface, local reflexes in the spinal cord and regulatory information from the red and reticular nuclei in the brainstem control simple gait patterns. Movements that require visual input or complex limb and body integration of movements are initiated in motor centers of the cerebral cortex and regulated by the cerebellum. The combination of normal gait on a level surface with obvious proprioceptive and postural deficits should immediately alert the examiner to the likelihood of forebrain disease.

Vision and the menace response may be defective (see Blindness, later). Pupillary light reflexes and oculocephalic reflexes are usually

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normal in animals with forebrain disease. Responses to noxious tactile stimuli, especially around the head, are reduced.

The hypothalamus regulates primitive functions such as eating, drinking, cardiovascular function, and sexual behavior. Lesions of the hypothalamus may cause behavioral changes ranging from profound depression, rage, and inappropriate sexual activities to unusual affection, as well as polydipsia, polyuria, bradycardia, and abnormal appetite (pica).

Seizures are the physical manifestations of spontaneous paroxysmal electrical activity arising in the forebrain. When seizure activity is limited to a small area of the cerebral cortex, the seizure is focal, resulting in localized abnormal motor activity such as muscular twitching in the face or in one limb or episodes of lateralizing abnormal behavior. More commonly the seizure is generalized or starts focally and becomes generalized to the entire cerebral cortex. Generalized seizures cause loss of consciousness, collapse, and generalized tonic-clonic motor activity. The presence of seizures indicates forebrain dysfunction, but the initiating cause may lie elsewhere in the brain; the origin may even be extracranial. *Epilepsy* is a term that means repeated seizures of any cause, although it is often used to indicate seizures of unknown cause. The nature of the seizure, whether focal or generalized, is not a reliable indicator of the underlying cause. Congenital, familial, or idiopathic epilepsy syndromes such as benign epilepsy of Arabian foals are usually characterized by generalized seizures. Partial or focal seizures more commonly indicate an acquired cause. Animals with seizures should undergo a complete physical examination, together with diagnostic testing for suspected toxins and underlying metabolic diseases, as well as a thorough neurologic examination to localize any interictal neurologic signs. Further diagnostics such as CSF analysis and MRI are performed as indicated after this initial workup.

When forebrain disease is unilateral or asymmetric, asymmetry of clinical signs becomes apparent. Circling often occurs, ranging from a tendency to drift toward one side to obvious and compulsive circling around the inside of an enclosure. It is usually possible to stop the circling, although the animal may be reluctant to turn in the opposite direction. Proprioceptive and postural reaction deficits may be present in the limbs on the side of the body opposite to the lesion (contralateral) and vary in severity with the severity of the underlying neurologic disease. The head and neck may be turned to one side (usually toward the side of the lesion), but the head tilt characteristic of vestibular disease is not seen. The absence of signs such as head tilt, nystagmus, and strabismus, together with the presence of contralateral proprioceptive and postural reaction deficits, distinguishes forebrain lesions from those affecting the vestibular system.

Specific diseases associated with the forebrain of ruminants and horses are given in Tables 8-7 and 8-8, respectively.

Blindness and Ocular Abnormalities

Blindness may be the result of lesions in the eye, optic nerve, optic chiasm, optic tracts, or central projections of the visual pathways. Ophthalmic examination, including fundic examination, should be part of the routine physical examination. Animals presented with the complaint of blindness should receive a more detailed ophthalmic examination to determine whether or not primary ocular disease is the cause of the problem (see Chapter 39). Sophisticated diagnostics such as electroretinography (ERG) may be indicated in some animals. When no ocular disease can be found to account for blindness, a lesion in the nervous system is likely to be responsible. Observing the animal's ability to negotiate its environment, particularly in unfamiliar surroundings, and testing the menace responses are the primary methods of determining visual function. Further testing can be performed by setting up a maze of objects for the animal to negotiate, by using different light levels and assessing vision in bright versus dim light, and by blindfolding each eye in turn when unilateral deficits are suspected. About 90% of optic nerve fibers (i.e., axons of retinal ganglion cells) cross to the opposite side of the brain in the optic chiasm of ungulates; thus central representation of vision in these species is predominantly *contralateral*. Fibers that remain uncrossed originate from the temporal extreme of the retina. Lesions in the visual apparatus distal to the optic chiasm (i.e., lesions of the globe, the retina, or the optic nerve) produce ipsilateral visual deficits. Lesions proximal/central to the optic chiasm produce lesions in the opposite visual field.

The following discussion refers to severe or complete lesions because these are most easily understood and described. Partial

TABLE 8-7

Diseases of Ruminants That May Produce Forebrain Signs

Disease	Predominant Clinical Signs	Species Affected
Ammoniated feed toxicosis	Trembling, fear, uncontrolled running, crashing through objects, coma, convulsion	Cow
Babesiosis (exotic)	Odontoprisis, ataxia, conscious proprioceptive deficits, coma, convulsions	Cow
Border disease	Ataxia, tremors, bunny-hopping	Sheep, goat
Borna disease (exotic)	Head tremors, hyperesthesia, ataxia, anorexia, compulsive walking, coma, convulsions	Cow, sheep, goat
Bovine spongiform encephalopathy	Aggression, weight loss, milk production, ataxia, recumbency, coma	Cow
Brain abscess, meningitis	Recumbency, opisthotonos, blindness, hyperesthesia, stiff neck, proprioceptive deficit, ataxia, head pressing, depression, coma	Cow, sheep, goat
Brain tumor	Obtundation, facial paresis or paralysis, facial analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia	Cow
Caprine arthritis-encephalitis	Obtundation, ataxia, head pressing, convulsions, coma	Goat
Ceroid lipofuscinosis	Blindness, ataxia, weight loss, coma, convulsions	Cow
Citrullinemia	Recumbency, coma, convulsions, death by 4 days of age	Cow
Coenurus cerebralis	Blindness, circling, ataxia, conscious proprioceptive deficit, head tilt, recumbency, coma, convulsions	Sheep
Ethylene glycol poisoning	Obtundation, somnolence, blindness, ataxia, facial analgesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Globoid cell leukodystrophy	Ataxia, proprioceptive deficits, hyperreflexia, depression, coma	Sheep
Grass staggers	Tremor, ataxia that worsens with excitement or exercise	Cow, sheep, goat
Heartwater (exotic)	Hyperesthesia, behavioral changes, muscular fasciculations, hypermetria, ataxia, head pressing	Cow, sheep, goat
Hepatic encephalopathy	Hyperexcitability, aggression, rage, odontoprisis, ataxia, head pressing, coma, convulsions, semicoma, blindness, tenesmus, rectal prolapse	Cow, sheep, goat

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TABLE 8-7

Diseases of Ruminants That May Produce Forebrain Signs—cont'd

Disease	Predominant Clinical Signs	Species Affected
Hydrocephalus, hydranencephaly, microcephaly, anencephaly	Blindness, ataxia, proprioceptive deficit, ventrolateral strabismus, failure to suckle, dysphonia	Cow, sheep, goat
Hypocalcemia	Cow, doe: weakness, ataxia, inappetance, bloat, proprioceptive deficit, cool extremities, weak pulse, bizarre head posture, dysuria	Cow, goat
Hypoglycemia	Coma, semicoma, convulsions, blindness, hyperesthesia, cold extremities	Cow, sheep, goat
Hypomagnesemia	Stiffness, hyperexcitability, recumbency, ataxia, muscle tremors	Cow
Idiopathic epilepsy	Intermittent psychomotor seizures	Cow, goat
Infectious bovine rhinotracheitis	Fever, bellowing, coma, convulsions, somnolence, hyperexcitability, hyperesthesia, proprioceptive deficit, recumbency	Cow
Insecticide poisoning (organophosphate carbamate)	Salivation, vaginal discharge, diarrhea, tremors, coma, convulsions, diarrhea, ataxia, recumbency	Cow, sheep, goat
Lead poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial analgesia, weak tongue, anisocoria (late), head pressing, opisthotonos, odontoprisis, convulsions, decerebrate rigidity	Cow, sheep, goat
Louping ill (exotic)	Fever, anorexia, obtundation, constipation, muscular tremors, head tremors, hypermetria, ataxia, proprioceptive deficits, hyperexcitability, incoordination, rabbit-hopping gait, recumbency, convulsions, coma	Sheep, cow
Maedi-visna	Obtundation, ataxia, head pressing, convulsions, coma	Sheep
Malignant catarrhal fever	Aggression, rage, ataxia, depression, head pressing, blindness, nystagmus, bellowing, mucosal and skin erosions, lymphadenopathy, diarrhea	Cow
Narcolepsy	Sleep state, recumbency, loss of consciousness, loss of motor activity, rapid eye movement	Cow
Nervous coccidiosis	Diarrhea, recumbency, obtundation, somnolence, blindness, ataxia, compulsive walking, head pressing	Cow
Nervous ketosis	Aggressiveness, tremors, ataxia, paresthesia, recumbency, ataxia, hyperesthesia, bellowing	Cow
Nitrofurazone poisoning	Obtundation, proprioceptive deficit, recumbency, convulsions, coma	Cow, sheep, goat
Nitrofurazone toxicosis	Hyperirritability, compulsive running, muscular tremors, blindness, convulsions	Cow
Organochlorine poisoning	Tremors, hyperesthesia, recumbency, coma, convulsions	Cow, sheep, goat
Plant poisonings	Convulsions, blindness, ataxia, compulsive walking, head pressing, odontoprisis, hyperexcitability, salivation, proprioceptive deficit, sudden death, vomiting, fetal malformations	Cow, sheep, goat
Polioencephalomalacia	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial analgesia, weak tongue, anisocoria (late), dorsomedial strabismus, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat
Propylene glycol poisoning	Depression, bloat, ataxia, recumbency, ataxia	Cow, sheep, goat
Propylene glycol toxicosis	Ataxia, obtundation, bloat, characteristic garlic-like odor	Cow, sheep, goat
Pseudorabies	Obtundation, ataxia, hyperesthesia, paresthesia, self-mutilation, aggressiveness, fear, head pressing, compulsive walking, hypersexuality, salivation, coma, convulsions, recumbency, conscious proprioceptive deficit	Cow, sheep, goat
Rabies	Obtundation, excitement, aggressiveness, hyperesthesia, analgesia, anesthesia, proprioceptive deficits, recumbency, compulsive walking, head pressing, tenesmus, hypersexuality, salivation	Cow, sheep, goat
Salt poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial analgesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, decerebrate rigidity	Cow, sheep, goat
Sarcocystis	Fever, weight loss, tremors, weakness, diarrhea, loss of hair on the tail switch, abortions	Cow
Sarcocystis species infection	Seizures, blindness, opisthotonos, nystagmus, ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency	Cow
Scrapie	Chewing, licking, wool break, depression, weight loss, ataxia, reduced menace, hypertonicity, hyperreflexia, proprioceptive deficit, recumbency, coma	Sheep, goat
Sporadic bovine encephalomyelitis	Blindness, circling, ataxia, proprioceptive deficits, pleural friction rubs, pericardial friction rubs, abdominal tenderness	Cow
Theileriosis (central nervous system form, exotic)	Depression, hypersensitivity, ataxia, circling, paralysis, convulsions	Cow
Trauma, hematoma, brain edema	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial analgesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, blood from ears or nose, decerebrate rigidity	Cow, sheep, goat
Trypanosomiasis (exotic)	Ataxia, somnolence, circling, head pressing	Cow
Urea poisoning	Muscle tremor, bloat, salivation, incoordination, struggling, ataxia, proprioceptive deficit, recumbency, bellowing, coma, convulsion	Cow
Vitamin A deficiency	Obtundation, somnolence, blindness with fixed pupils, ataxia, facial analgesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cow, sheep, goat

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TABLE 8-8

Diseases of the Horse That Produce Forebrain Disease

Disease	Predominant Clinical Signs
Brain abscess, meningitis	Head pressing, blindness, conscious proprioceptive deficit, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking
Brain tumor	Depression, facial paresis or paralysis, facial analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia
Hepatoencephalopathy, gastrointestinal hyperammonemia	Aggression, rage, hyperexcitability, odontoprisis, ataxia, head pressing, convulsions, obtundation, coma, semicoma, blindness, fear, red urine (hemolysis), icterus
Hydrocephalus	Coma, semicoma, blindness, somnolence, head pressing, dysphonia, ataxia, weak tongue
Idiopathic epilepsy	Intermittent psychomotor seizures, normal interictal periods
Leukoencephalomalacia	Recumbency, ataxia, aggression, obtundation, coma, semicoma, head pressing, circling, compulsive walking, mydriasis, tenesmus, fear, continual chewing
Rabies	Recumbency, ataxia, aggression, depression, coma, semicoma, head pressing, circling, compulsive walking, mydriasis, tenesmus, fear, continual chewing
Trauma, hematoma	Head pressing, blindness, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking, blood from ear or nose
Verminous encephalitis	Head tilt, hyperexcitability, odontoprisis, ataxia, head pressing, circling, coma, semicoma, blindness, anisocoria, convulsion, tongue dystonia
Viral encephalomyelitis (nonrabies) Eastern equine encephalomyelitis Western equine encephalomyelitis Venezuelan equine encephalomyelitis Borna disease	Head pressing, blindness, ataxia, circling, depression, coma, convulsions, recumbency, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking

lesions will produce similar but milder signs (e.g., reduced visual acuity rather than complete blindness). Absent or reduced menace response can be caused by lesions of the facial nerve (cranial nerve VII), the cerebellum, or the forebrain. Animals with facial nerve lesions can see, but palpebral reflexes cannot be elicited. Animals with cerebellar disease can see and have normal palpebral reflexes. Forebrain disease causes defective menace responses with intact pupillary light and palpebral reflexes. Localization of lesions causing blindness is summarized in Table 8-6.

Pupillary size and movement of the globes are affected by cranial nerves II, III, IV, and VI and the sympathetic innervation of the eye. Clinical signs of diseases affecting these nerves are described earlier.

Circling

Circling is a sign of lateralized disease in the forebrain or vestibular system. Circling associated with forebrain disease is usually toward the side of the lesion. Animals that circle secondary to cerebral disease often also keep the head and neck turned toward the side of the lesion. Whereas gait may appear normal on a level surface, there are proprioceptive and postural reaction deficits on the side of the body contralateral to the lesion. Head tilt and spontaneous nystagmus are not observed. Physiologic nystagmus is normal. The severity of circling seen with lateralized cerebral disease is variable, from a subtle tendency to marked compulsive circling.

Head Tilt and Nystagmus

The presence of a head tilt, wherein the head is rotated so that one ear is held closer to the ground than the other, indicates dysfunction of the vestibular system. Head tilt is usually accompanied by spontaneous or positional (abnormal) nystagmus and a variety of other clinical signs. Vestibular disease can be classified as peripheral or central. Peripheral vestibular disease occurs with lesions of the vestibular apparatus of the inner ear (utricle, saccule, semicircular canals) or vestibulocochlear nerve (cranial nerve VIII) or, theoretically, when there is involvement of vestibular afferents from the proximal part of the neck. Animals with peripheral vestibular lesions have normal mentation but may be extremely disoriented, making assessment of mentation difficult. The head tilt (i.e., the lower ear) in animals with peripheral vestibular disease is toward the side of the lesion. Unilateral peripheral vestibular dysfunction causes decreased extensor tone in the limbs ipsilateral to the lesion and increased extensor tone in the contralateral limbs, resulting in the clinical signs of leaning, falling, curling, and rolling toward the affected side. Asymmetric peripheral vestibular lesions produce horizontal or rotatory conjugate nystagmus, with the fast phase directed *away* from the side of the lesion. The direction of the nystagmus in relation to the head is unchanged no matter what the position of the head. Physiologic nystagmus may be absent or decreased, particularly when the head is moved in a horizontal plane toward the side of the lesion. The facial nerve is closely associated with the vestibulocochlear nerve within the skull, and there may be facial paralysis along with peripheral vestibular disease when the facial nerve is also damaged by the underlying cause such as may occur in skull trauma, temporohyoid osteoarthropathy of horses, or severe otitis media or interna. Rarely, involvement of the postganglionic sympathetic nerve to the eye as it courses through the petrous temporal bone results in ipsilateral Horner syndrome (ptosis, miosis, facial sweating in horses, reduced sweating on the nasal planum in cattle).

Lesions within the vestibular centers in the medulla oblongata and cerebellum also cause signs of vestibular dysfunction. Head tilt in central vestibular disease is usually toward the side of the lesion but may be in the opposite direction when the underlying disease involves the cerebellum (i.e., paradoxic vestibular syndrome). Similarly, nystagmus may be horizontal or rotatory as in peripheral vestibular disease but also may be vertical, diagonal, or different in each eye (disconjugate nystagmus); may change in direction when the position of the head is changed (positional nystagmus); or may be horizontal or rotatory with the fast phase toward the side of the lesion (paradoxic vestibular syndrome). Signs of involvement of the motor and sensory tracts to and from the limbs as they course through the medulla usually accompany central vestibular disease. Proprioceptive and postural reaction deficits are present in the ipsilateral limbs, together with mild hyperreflexia. Obtundation and signs of other cranial nerve dysfunctions may accompany central vestibular disease and can be used diagnostically to distinguish central from peripheral lesions.

Animals with either peripheral or central vestibular lesions tend to lean against walls and may fall when forced to perform a complex motor maneuver. They may adopt recumbency with the lesion side directed down and have poor righting responses, particularly from lesion-side-down recumbency. When positioned so that the lesion side is directed up, they often will roll to a lesion-down position.

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Blindfolding the patient eliminates visual compensatory mechanisms and therefore increases the severity of the clinical signs (Romberg test). Blindfolding may help reveal subtle dysfunction but should be done with caution. Animals with vestibular disease occasionally may have slight ventral strabismus in the ipsilateral eye and slight dorsal strabismus in the contralateral eye. These deviations are exaggerated when the head is held in the median plane and the chin is lifted. This *vestibular* strabismus can be differentiated from the ventrolateral *true* strabismus seen with lesions of the oculomotor nerve because the former changes when the head is rotated, whereas the latter does not.

Animals with bilateral vestibular lesions do not have strabismus, head tilt, or nystagmus. The animal stands with the legs basewide and may fall to either side when head position is rapidly altered. Affected animals may show a coarse side-to-side head tremor. Bilateral vestibular lesions are usually peripheral and are rarely encountered in clinical practice. Central lesions extensive enough to cause bilateral vestibular disease are likely to be fatal.

Incoordination, Hypermetria, Hypometria, Dysmetria, and Intention Tremor

Clinical signs that occur in animals with cerebellar disorders include hypermetria, hypometria, intention tremor, and truncal ataxia (excessive body sway during movement along a straight path). Conscious proprioceptive fibers do not pass through the cerebellum. Consequently, postural placement of the limbs is normal. Animals with cerebellar disease move the limbs with imprecise and variable rate, range, and force. There is a slight delay in lifting the limb from the ground. At the peak of protraction the limbs are lifted too high and too far anteriorly. The legs then hit the ground with excessive force. During the exaggerated protraction, thoracic limbs may flex excessively, termed *hypermetria,* or may appear stiff because of reduced flexion, termed *hypometria* or *spasticity.* The animal may violently thrust the outside pelvic limb backward and laterally when turned. The thoracic limbs and the pelvic limbs occasionally collide during the turn (interference). At rest the animal stands with the legs abducted, in a basewide stance. This is not a conscious proprioceptive deficit, however, because the animal consciously returns the limbs to the basewide posture if the leg position is manually corrected. There is intention tremor, most marked in the head. When the animal attempts to reposition the head, it overshoots the intended position, corrects, and then overshoots again. The sequence of overcompensation and overcorrection results in a coarse oscillation or bobbing of the head. The head tremor is most conspicuous when the animal is alert, especially when eating. Intention tremor disappears when the animal is recumbent and the musculature is relaxed. In animals with cerebellar disorders, the extensor muscles of the limbs may be hypertonic, and spinal reflexes occasionally are exaggerated. Lesions of the rostral cerebellum can result in opisthotonos. Animals with cerebellar cortical disease may lack a menace response but retain their vision and can negotiate around obstacles. Animals with pure cerebellar dysfunction remain bright, alert, and responsive to external stimuli. Animals with severe lesions of the cerebellum may be recumbent and unable to rise and show opisthotonos. Cerebellar disease is often bilaterally symmetric, but lateralized lesions cause signs on the ipsilateral side of the body. Diseases that cause spasticity or tremors in livestock are listed in Table 8-9.

Involvement of the vestibular components of the cerebellum (caudal cerebellar peduncle, flocculonodular lobe, and fastigial

TABLE 8-9

Diseases of Spasticity or Tremors in Horses and Ruminants

Disease	Clinical Manifestations	Affected Species
Cerebellar hypoplasia Bovine viral diarrhea Bluetongue Akabane Border disease Wesselsbron disease Hereditary	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, sheep, goats
Cerebellar abiotrophy	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, horses, goats
Grass staggers	Hypermetria, hyperreflexia, truncal ataxia, head tremors, basewide stance, recumbency, ptyalism, hyperexcitability, hyperesthesia	
Bermuda staggers		Cattle, horses
Paspalum staggers		Horses
Perennial ryegrass staggers		Cattle, sheep, goats, horses
Other fungal tremorgens		Cattle, sheep, goats, horses
Annual ryegrass toxicity		Cattle, sheep, goats, horses
Kikuyu grass		Cattle, sheep
Phalaris (canarygrass)		Sheep
Hypomagnesemia	Hypermetria, hyperreflexia, truncal ataxia, recumbency, hyperesthesia, menace deficit, opisthotonos, aggressiveness, hypertonia	Cattle, horses
Lysosomal storage disease	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos, blindness, aggressiveness	Cattle, goats
Locoism and *Swainsona* poisoning	Ataxia, obtundation, intentional head tremor, loss of herd instinct, maniacal behavior, flaccidity of the nose and lips, basewide stance	All species
Aspergillus clavatus toxicosis	Ataxia, weakness, muscle tremors, hypersalivation, altered behavior, recumbency, opisthotonos, death	Cattle, sheep
Hereditary neuraxial edema	Recumbency, head tremor, good appetite, hyperesthesia, nystagmus, strabismus, muscular fasciculations	Cattle
Bovine familial convulsions and ataxia	Tetaniform seizures, ataxia, hypermetria, hyperreflexia, head tremors, truncal ataxia	Cattle
Maple syrup urine disease	Obtundation, recumbency, opisthotonos, stimulus-induced tetanic spasms, convulsions, generalized decrease of spinal reflexes	Cattle
Solanum spp. storage disease	Head tremors, hypermetria, hypertonia, hyperesthesia, weight loss, opisthotonos, recumbency, and convulsions	Cattle, goats

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nucleus) results in signs of paradoxic vestibular syndrome, described earlier.

Abnormalities of Cranial Nerve Function

The normal functions of the cranial nerves are described earlier, in the discussion of the neurologic examination. Cranial nerve dysfunction may be central or peripheral in type, depending on whether the neurologic lesion lies within the central components of the cranial nerves within the brain or in the peripheral portions of the nerves. Clinical signs of cranial nerve dysfunction are ipsilateral to the lesions that cause them.

BLINDNESS, STRABISMUS, OCULAR PARESIS OR PARALYSIS, ABNORMALITIES OF PUPIL SIZE OR PUPILLARY LIGHT REFLEXES. Lesions involving cranial nerves II, III, IV, and VI are described earlier, in the discussion of blindness and other visual dysfunctions.

FACIAL HYPALGESIA OR ANALGESIA, DEVIATED OR DROPPED JAW. Loss of or reduced sensory perception on the face, including the inside of the mouth, the nasal planum, the nasal septum, the cornea, and the lower jaw area occurs with lesions of the trigeminal nerve. It is important to distinguish this from the signs of contralateral forebrain disease. Unilateral loss of facial sensation may result from damage to the peripheral portion of the trigeminal nerve or the trigeminal ganglion in the petrosal bone of the skull, or its connections in the pons or from contralateral forebrain disease. Bilateral facial hypalgesia is most likely caused by diffuse forebrain dysfunction rather than trigeminal nerve disease. The mandibular branch of the trigeminal nerve also carries motor innervation to the muscles of mastication from the pontine motor nucleus of the trigeminal nerve. Bilateral involvement of the motor component of the nerve results in a dropped jaw and inability to prehend and chew food, together with drooling saliva. The muscles of mastication atrophy rapidly over a few weeks, most obviously in the masseter and temporalis muscles. Unilateral disease causes atrophy of the denervated muscles, and mild jaw weakness may be appreciated, but the animal can still eat and close the jaw. Usually the mandible is deviated away from the side of the trigeminal nerve lesion. Central lesions in the trigeminal nerve may also involve adjacent structures in the brainstem, such as the facial nerve, the vestibular system, and the long motor and sensory tracts to and from the limbs.

FACIAL PARESIS OR PARALYSIS. Lesions of the facial nerve result in ipsilateral atonia or hypotonia of the facial muscles. The clinical signs of facial nerve paralysis in all large animals include ptosis, dropped ear, and absence of the menace response and palpebral reflex. There is accumulation of food in the cheek pouch and commissure of the lips on the ipsilateral side. Affected animals frequently drool saliva from the lip commissure on the affected side. The animal is unable to open the nostril on the affected side during inspiration. The muzzle of the horse, goat, and sheep deviates away from the direction of the neurologic lesion. Deviation of the muzzle is not seen in cattle because of the normal rigidity of the planum nasale. If the neurologic lesion is located between the medulla oblongata and the stylomastoid foramen, the ipsilateral eye may be dry because of loss of innervation from the parasympathetic nucleus of cranial nerve VII. Lesions of the central components of the facial nerve in the medulla oblongata also destroy upper motor neurons, proprioceptive tracts, and reticular activating system (RAS) neurons, resulting in limb weakness, ataxia, and sometimes obtundation. Lesions of the peripheral component of cranial nerve VII cause facial atonia or hypotonia but do not produce obtundation or ataxia.

HEAD TILT, SPONTANEOUS NYSTAGMUS, DEAFNESS. Lesions involving cranial nerve VIII, the vestibulocochlear nerve, produce signs of vestibular dysfunction, as described previously. Deafness may also be a consequence of vestibulocochlear nerve disease. Bilateral deafness has been reported in Paint horses,[51] where it may be a heritable defect associated with the gene for white coat color, similar to the situation that exists in a number of breeds of dogs with white or merle coat color. Deafness can also result from severe aural disease. Although bilateral deafness is fairly easy to recognize clinically, unilateral deafness may be less obvious. Inability to localize sound occurs when animals have unilateral deafness and may be suspected when animals alert to sound but do not turn toward the sound. Auditory evoked potentials can be used to determine the integrity of the auditory pathway in the inner ear and medulla oblongata.[51,52]

DYSPHAGIA, DYSPHONIA, STRIDOR. Lesions in the nuclei of cranial nerves IX, X, and XI in the medulla oblongata produce dysphonia, inspiratory dyspnea, dysphagia, and neurogenic atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles. The inspiratory dyspnea is characterized by roaring and stridor. Roaring is a stridor that is made during peak inspiratory flow in horses with idiopathic left recurrent laryngeal neuropathy. It is caused by paralysis of the left cricoarytenoideus dorsalis muscle, resulting in failure to abduct the arytenoid cartilages during inspiration. Additional evidence of paralysis of cranial nerves IX and X may be obtained by endoscopic examination of the pharynx. Other signs of paralysis of cranial nerves IX and X include failure to abduct the vocal folds, collapse of the pharynx, dorsal displacement of the soft palate, and inability to swallow a nasogastric tube. Animals with peripheral nerve deficits remain alert and appetant and do not show conscious proprioceptive deficits, whereas animals with centrally located lesions may be depressed and inappetant and may have ataxia and limb weakness. Animals with bilateral lesions in the peripheral nerves are unable to open the glottis during inspiration and display extreme respiratory distress. Peripheral lesions of the accessory nerve that have been present for longer than 1 month may produce neurogenic atrophy of the trapezius, brachiocephalicus, and sternocephalicus muscles. This is frequently accompanied by aspiration pneumonia. Lesions of the visceral efferent component of cranial nerve X in ruminants produce vagal indigestion, which is characterized by ruminal distention with fluid, ruminal tympany, abomasal stasis, and sometimes a hypochloremic, hypokalemic metabolic alkalosis. This is an important disease of the ruminant gastrointestinal tract. Hypoglossal nerve lesions produce a weak or flaccid tongue. In animals with unilateral lesions, the tongue deviates away from the side with the lesion and is flaccid when it is manually extended from the mouth. After prolonged denervation (2 weeks or more) the ipsilateral side of the tongue atrophies and the tongues deviates toward the affected side. Horses with lesions in the forebrain may also fail to retract the tongue normally; however, the lingual musculature is normal, the tone is variable, and the animal can retract the tongue if it receives sufficient stimulation. In comparison, the tongue tone is consistently weak in cases of hypoglossal paralysis.

Signs of cranial nerve dysfunction, together with the central origins or projections of the nerves, are summarized in Table 8-10. Diseases that involve the brainstem and cranial nerves are summarized in Table 8-11.

Lesions of the medulla oblongata can produce severe obtundation, somnolence, or coma as a result of ARAS dysfunction in addition to signs of vestibular dysfunction and functional deficits in cranial nerves V to XII. These effects on consciousness are strong with lesions in the rostral medulla and progressively weaker in parts closer to the foramen magnum. Other clinical signs of medullary lesions include ipsilateral paresis and proprioceptive deficits. The spinal reflexes of the ipsilateral limbs are exaggerated, and the extensor muscle tone is increased. Further details are given later in the discussion of quadriparesis and hemiparesis.

Measurement of Brainstem Function Using Auditory Evoked Potentials

The integrity of the vestibulocochlear apparatus can be examined using brainstem auditory evoked potentials.[51-54] This method examines the averaged brain waveform that is generated after an auditory click in the ear. Ablation of the entire cochlear apparatus and

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TABLE 8-10

Clinical Signs of Cranial Nerve Dysfunction

Cranial Nerve	Central Origin or Projection	Clinical Signs of Dysfunction	Comments
I—Olfactory	Olfactory bulb, limbic system (behavior and emotion centers), cerebral cortex	Loss of sense of smell (anosmia)	Olfactory nerve lesions are rare and difficult to detect clinically.
II—Optic	Optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, occipital cortex	Blindness	See text for additional comments (blindness).
III—Oculomotor	Midbrain somatic and parasympathetic nuclei	Ventrolateral strabismus, ptosis (somatic component); dilated, nonresponsive pupil (parasympathetic component)	
IV—Trochlear	Midbrain	Dorsomedial strabismus	Trochlear nerve lesions are rare and usually accompanied by other signs of midbrain dysfunction.
V—Trigeminal	Pons (motor nucleus), medulla, and rostral cervical spinal cord (sensory tract)	Dropped jaw in bilateral motor paralysis; deviated jaw in unilateral paralysis; decrease or loss of sensation to most of the structures of the head and face in sensory nerve disease	Rabies is an important differential diagnosis in animals with a dropped jaw.
VI—Abducent	Rostral medulla oblongata	Medial strabismus (paralysis of the lateral rectus muscle)	
VII—Facial	Medulla oblongata (rostral to middle); motor, sensory, and parasympathetic components	Facial paralysis (motor component); loss of sense of taste to rostral two thirds of the tongue; decreased tear production (dry eye) and decreased salivation (parasympathetic components)	The facial nerve is particularly susceptible to damage in its peripheral course because of its proximity to the middle ear and to the guttural pouch in horses and its superficial location on the face.
VIII—Vestibulocochlear	Medulla oblongata (middle)	Decreased hearing or deafness; vestibular signs (head tilt, nystagmus, falling, rolling)	See description of vestibular disease in text.
IX, X, XI—Glossopharyngeal, vagus, accessory	Medulla oblongata (nucleus ambiguus in middle to caudal medulla and rostral cervical spinal cord)	Dysphagia (IX and X), laryngeal paresis to paralysis (X), atrophy of sternocephalicus, brachiocephalicus, and trapezius muscles (XI)	Rabies is an important differential diagnosis in animals with dysphagia or choke.
XII—Hypoglossal	Medulla oblongata (caudal)	Paralysis of the tongue	Acute unilateral lesions result in the tongue being deviated away from the side of the lesion. In chronic disease, atrophy and contracture of the affected side of the tongue result in deviation toward the affected side.

vestibular nerve, as might occur with otitis interna, results in a loss or attenuation of waveform activity after the click stimulus. Injury to the brainstem vestibular nuclei or pons results in specific losses of certain waveforms.

Paresis and Ataxia in Two or Four Limbs

Quadriparesis and hemiparesis are seen with lesions affecting the mid to caudal brainstem (midbrain, pons, medulla oblongata) or the cervical spinal cord (C1 to T2 spinal cord segments). Quadriparesis can also be seen in generalized peripheral nerve or muscle disease, discussed later. Paraparesis results from disease lesions of the spinal cord affecting segments T3 to S2 or the peripheral nerves to the pelvic limbs. Disease of the forebrain does not produce appreciable paresis and ataxia when the animal is walking in a straight line on a level surface, but these signs may become apparent in the limbs contralateral to the lesion when the animal is asked to circle, back, step over obstacles, or walk on a slope. Localization of the lesion when signs of paresis and ataxia are present depends on the assessment of muscle mass and tone, spinal reflexes, and evaluation of brainstem function; the last is determined by the presence or absence of signs such as altered mentation and cranial nerve deficits.

Quadriparesis and ataxia with normal muscle mass and tone and normal to increased spinal reflexes can be explained by a lesion of the descending and ascending tracts in the brainstem or spinal cord segments C1 to C5. Note that such a finding does not exclude multifocal lesions within the same areas of the CNS. Presence of clinical signs of brain disease indicates that the lesion (if singular) is in the brainstem, as described earlier. Lesions in the midbrain cause contralateral postural and proprioceptive deficits, whereas those in the medulla oblongata cause ipsilateral signs. Cerebellar disease causes head, neck, truncal, and limb ataxia, without limb weakness. Lesions of the forebrain (thalamus and cerebrum) cause minimal to no paresis or ataxia when the animal moves on a level surface, but contralateral subtle proprioceptive and postural reaction deficits are present. Altered mentation and other signs of forebrain disease such as compulsive circling or central blindness are expected. Animals with spinal cord disease have normal mentation. The clinical signs shown by such patients depend on the location of the lesion and the relative amount of damage to gray (cell bodies) and white (myelinated spinal cord tracts) matter. Loss of white matter affects upper motor neurons and proprioceptive and other sensory pathways, whereas gray matter damage produces lower motor neuron deficits. The sensory losses manifest as either proprioceptive deficits or loss of cutaneous sensation. Spinal cord diseases may be localized to one of the following five regions: high cervical (C1 to C5), cervicothoracic (C6 to T2), thoracolumbar (T3 to L2), lumbosacral (L3 to S2), and sacrococcygeal (S3 to Cd5) regions. Tables 8-4 and 8-5 list the peripheral nerves and the spinal segments that innervate them.

Cervical Spinal Cord

Animals with incomplete section of the cervical region of the spinal cord display hemiparesis or tetraparesis. The clinical signs include

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TABLE 8-11

Diseases of the Brainstem and Cranial Nerves

Disease	Location	Clinical Signs and Laboratory Findings
Nonrabies viral encephalomyelitis, rabies, malignant catarrhal fever (cattle only)	Multifocal brainstem, particularly medulla oblongata	Head tilt, nystagmus, circling, ataxia, tongue paralysis, anisocoria, dilated nonresponsive pupils, strabismus, lingual paralysis, dysphonia, dysphagia; CSF may show pleocytosis (mainly mononuclear cells) and high protein concentration
Listeriosis (ruminants, horses [rare])	Multifocal brainstem, particularly basal ganglia, metencephalon, and medulla oblongata	Circling, head tilt, facial paralysis, stridor, stertor, dysphagia, obtundation, coma, convulsions, ataxia; CSF shows pleocytosis (mainly mononuclear) and a high protein concentration
Thromboembolic meningoencephalomyelitis (cattle)	Multifocal brainstem	Circling, nystagmus, head tilt, strabismus, tongue paralysis, dysphagia, facial paralysis, coma, convulsions, obtundation; xanthochromic CSF with increased neutrophils and protein concentration
Peripheral vestibular disease	Petrous temporal bone, membranous labyrinths, vestibulocochlear nerve, often accompanied by facial nerve paralysis	Head tilt, circling, or leaning toward lesion side; ventrolateral strabismus on ipsilateral side; dorsomedial strabismus on contralateral side; nystagmus (usually horizontal and constant)
Verminous encephalitis	Multifocal brainstem, most commonly thalamus	Circling, nystagmus, head tilt, strabismus, tongue paralysis, facial paralysis, obtundation, coma, convulsions, depression, proprioceptive deficit, bradycardia, salivation, head pressing, blindness; high protein concentration and increased nucleated cell count in CSF
West Nile virus	Multifocal brainstem	Fasciculations of neck and facial muscles in addition to the other signs
Equine protozoal myeloencephalitis	Multifocal brainstem and cerebrum	Seizures, head tilt, facial paralysis, circling, nystagmus, dysphagia, facial paralysis, blindness, ataxia, paresis, hyporeflexia, hyperreflexia
Space-occupying mass Tumor, abscess	Cerebellopontine angle; cranial nerves V, VII, and VIII	Head tilt, strabismus, proprioceptive deficit, facial analgesia, jaw drop, obtundation, coma, strabismus, nystagmus, hyperreflexia, hypertonia, falling or circling toward affected side, blindness on contralateral side, tongue paralysis, hemianopsia, bradycardia, coma, convulsion
Horner syndrome	T1 to T3 motor neurons (gray matter), spinal roots, vagosympathetic trunk, sympathetic UMN of spinal cord (tectotegmentospinal), periorbita	Miosis, lack of nasal sweat (cattle only), ipsilateral facial swelling (horses only)
Guttural pouch mycosis (horses)	Guttural pouch	Dysphagia, head shyness, head shaking, roaring, dysphonia, protrusion of the tongue from the mouth, epistaxis, head tilt, nystagmus, facial sweating, shivering, Horner syndrome, colic, facial paralysis

CSF, Cerebrospinal fluid; *UMN,* upper motor neuron; *WBCs,* white blood cells.

knuckling, stumbling, failure to lift the inside feet when turned in a tight circle, circumduction of the outside pelvic limb during circling, interference, hypometria or hypermetria, abnormal postural placement responses, crossing over midline when turned, and excessive truncal sway. Animals with more severe lesions of the cervical spinal cord become recumbent and are unable to lift the head from the ground. There is an asymmetric righting response in animals with unilateral lesions. They can raise the head and neck to a variable distance only when lying with the lesion side facing down. Within several days of the time of spinal cord injury, muscle tone and spinal reflexes in the limbs of recumbent animals are exaggerated. The urinary bladder is distended. Affected animals have difficulty posturing and urinating, and afterward the bladder contains a large amount of residual urine and sediment. Animals with complete spinal cord transection anterior to C5 die suddenly from respiratory failure as a result of paralysis of the intercostal muscles and diaphragm.

Lesions from C6 to T2 spinal segments (i.e., brachial intumescence) result in proprioceptive deficits in all four limbs and tetraparesis or tetraplegia (recumbency). There is flaccidity and hyporeflexia of the thoracic limbs and hypertonia and hyperreflexia of the pelvic limbs. Unilateral lesions result in ipsilateral signs. Lesions of C6 to T2 segments involving white but not gray matter do not produce thoracic limb hypotonia. Perception of painful stimuli over all four limbs may be reduced. Flexor reflexes in the thoracic limbs may be depressed but are normal in the pelvic limbs. The righting responses of the head and neck are normal, but the animal may have difficulty rolling onto its sternum from a laterally recumbent position. Voluntary control of urination is poor or absent, posturing for urination is difficult, and the urinary bladder is distended and has a large residual volume. After 2 weeks or more, lesions of the gray matter of the spinal cord or the peripheral nerves may result in neurogenic atrophy of one or more muscle groups of the thoracic limbs. Gray matter lesions of T1 to T3 spinal segments may cause Horner syndrome, which is characterized by miosis and ptosis in all species. Unilateral facial sweating occurs in horses; lack of sweating on the planum nasale occurs in cattle. Differentiation of high (C1 to C5) and low (C6 to T2) cervical spinal cord lesions may be difficult in horses, especially when signs are fairly mild.

Lesions of the thoracolumbar region (T3 to L3 inclusive) cause paraparesis and ataxia in the pelvic limbs but usually do not affect the thoracic limbs. There may be knuckling, stumbling, abduction, adduction, interference, excessive truncal sway, circumduction of the outside limb, and failure to lift the inside foot when pivoted in a tight turn. With complete lesions, the animal becomes recumbent but intermittently assumes a dog-sitting position, with the thoracic limbs extended and weight bearing and the pelvic limbs flexed. Muscle tone and spinal reflexes are exaggerated in the pelvic limbs. The urinary bladder is distended and, because of poor coordination of bladder

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TABLE 8-12

Diseases of the Spinal Cord, Peripheral Nerve, and Motor End Plate of Large Animals

Disease	Signs	Species Affected
Occipitoatlantoaxial malformation	Ataxia, spasticity, hyperreflexia, crepitation or pain with neck flexion, head tilt, torticollis, ataxia, visible swelling or asymmetry	All species
Fractures and dislocations	Tetraparesis, tetraplegia, paraparesis, paraplegia, hyperreflexia, stiff neck, recumbency, ataxia, acute death, crepitation, pain, swelling	All species
Cervical spinal abscesses	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, sudden death, crepitation, pain, swelling	All species
Cervical vertebral stenotic myelopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, strip sweating	Horse
Spinal tumor (lymphosarcoma, neurofibroma)	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	All species
Equine herpesvirus myeloencephalopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia, flaccid anus, flaccid tail, dysuria, distended bladder, impacted rectum, urine scalding	Horse
Copper deficiency	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	Sheep, goat
Cauda equina neuritis	Pruritus in perineum, hair loss in perineum, analgesia in perineum, flaccid tail, flaccid anus, paraphimosis, dysuria, facial palsy, head tilt, leaning, nystagmus	Horse
Ischemic myelopathy (fibrocartilaginous embolism)	Paraplegia, tetraplegia, flaccid tail, flaccid anus, areflexia at site of lesion, hyperreflexia distal to site of lesion, ataxia	Horse, sheep
Postanesthetic myelopathy	Paraparesis to paraplegia, ataxia, hypalgesia, scoliosis	Horse, cattle
Caprine arthritis-encephalitis virus	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	Goat
Segmental myelitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, strip sweating, hyporeflexia, areflexia, lower motor neuron deficit, facial nerve paralysis, jaw drop	Horse
Developmental defects (spina bifida, Arnold-Chiari syndrome, syringomyelia, hemivertebrae, spinal cysts)	Paraplegia, paraparesis, tetraplegia, tetraparesis, hypotonia, atonia, neurogenic atrophy, torticollis, scoliosis, kyphoscoliosis, misshapen tail, absence of skin over dorsal midline	All species
Verminous encephalitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia, head tilt, hyporeflexia, areflexia, hyperreflexia, hypertonia, hypotonia	All species
Tetanus	Stiffness, normal reflexes, flashing third eyelid, trismus, bloat, convulsions, coma, raised tailhead	All species
Botulism	Flaccidity, ataxia, dysphagia, hyporeflexia, pupillary dilation, facial hypotonia, flaccid tail, flaccid anus	All species
Progressive ataxia	Ataxia, recumbency	Charolais cattle
Locoism	Ataxia, recumbency, bizarre behavior	All species
Dying back axonopathies	Hypermetria, hyperreflexia, ataxia, flaccid tail, anus, fecal and urine retention, urine scalding, recumbency	All species
Else heel (spastic paresis)	Affected pelvic limb is hyperextended and swings in pendulum fashion; tailhead is elevated	Cow
Bovine spastic syndrome	Episodic hyperextension of the pelvic limb, extension of the limb behind the cow, head and neck extension	Cow
Peripheral nerve injuries	Areflexia, hypotonia, hyporeflexia, atonia, anesthesia, analgesia of a specific area of limbs or trunk, inability to support weight, normal function of limbs distal to denervated site	All species
Ionophore toxicosis (salinomycin, lasalocid, monensin)	Tetraparesis, tetraplegia, ataxia, colic, cardiac dysrhythmia, sudden death	All species
Periodic hyperkalemia (called HYPP)	Episodic tremors, weakness, spasticity during episodes, recumbency	Horse
Myotonia congenital	Episodic weakness, spasticity during episodes	All species
Bromide intoxication	Weakness, ataxia, stumbling, ataxia, closed eyelids, drooped head and neck, paraphimosis	Horse
Coyotillo poisoning	Progressive weakness, hypermetria, areflexia	Goat
Neosporosis	Recumbency, ataxia, neurogenic atrophy	Calf
Cycad palm poisoning	Posterior paresis, elevated tailhead, paraparesis, paraplegia	Cow
Acquired torticollis	Abnormally positioned head and neck	All species
Sorghum toxicosis	Ataxia, paraparesis, paraplegia, rabbit-hopping gait, ataxia, recumbency, weight loss	Horse, cow
Stringhalt	Normal at rest, involuntary hyperflexion of the hock and stifle	Horse
Tick paralysis	Progressive generalized paresis, ataxia, recumbency, flaccid tail, flaccid anus, weak facial muscles	All species

filling with detrusor and sphincter tone (dyssynergia), residual volume is large. The tone of the urethral sphincter is normal. Rarely, animals with severe spinal cord lesions between T2 and L2 display transient hypertonia of the thoracic limbs (Schiff-Sherrington syndrome).[55] This condition is caused by interference with inhibitory fibers ascending from the lumbar segments in the dorsal funiculi to the lower motor neurons of the thoracic limbs.[55] These fibers synapse on the lower motor neurons of the brachial intumescence. Hypertonia from this deficit may be differentiated from cervical cord lesions by the lack of conscious proprioceptive deficits in the thoracic limbs of animals with thoracolumbar lesions.

The lumbosacral region (L3 to S2) of the spinal cord contains lower motor neuron efferents to and general proprioceptive afferents from the pelvic limbs. Lesions in this area result in paraparesis

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or paraplegia. Affected animals are ataxic and have conscious proprioceptive deficits of the pelvic limbs. Patients with complete spinal cord lesions of L3 to S2 exhibit flaccid paraplegia, which is accompanied by hyporeflexia or areflexia of the pelvic limbs. With prolonged denervation, there is neurogenic atrophy of the pelvic limb musculature.

Lesions located between L3 and L6 spinal cord segments result in urinary bladder distention and maintenance of a large residual volume. The sphincter tone is intact, but urine is not voided unless the intravesicular pressure exceeds that of the sphincter. These animals usually have contact dermatitis of the perineum and preputial area because of urine scalding. Lesions located around the S1 and S2 segments result in bladder distention and flaccidity. Urine may drip continuously from the urethral orifice. The rate of flow may be increased by manually pressing on the bladder during a rectal examination.

Lesions of the sacrococcygeal (S3 to Cd5) spinal cord segments or cauda equina produce flaccidity and muscular atrophy of the tail and anus and, in males, penile paralysis (paraphimosis). Lesions in this area also result in desensitization of the tail, penis, vulva, rectum, anus, and perineum. The urethral sphincter is dilated, and urine constantly drips from the urethral orifice. The animal does not evacuate the bladder and is unable to defecate, resulting in a large dilated urinary bladder and distention of the rectum with feces (obstipation).

If the entire neurologic lesion is located caudal to S2, ataxia or limb weakness is not seen. The combination of flaccidity of the tail and anus and the constant urine leakage produces contact dermatitis of the perineum and pelvic limbs. Perineal scalding is characteristic of lesions of the cauda equina. Specific diseases of the spinal cord, peripheral nerves, and motor end plate are listed in Table 8-12.

Muscle Atrophy, Reduced Muscle Tone, Flaccid Paresis, Focal Analgesia

Reduced muscle tone, muscle atrophy, and flaccid paresis are characteristic of peripheral nerve, muscle, or neuromuscular diseases. Signs may be localized to a single limb, as in the case of traumatic peripheral nerve injury; generalized, as in botulism and many myopathies; or multifocal, as in equine protozoal myeloencephalitis and other diseases that attack multiple areas of the CNS. Details of neuromuscular diseases and the use of ancillary diagnostic testing to localize peripheral nerve, muscle, and neuromuscular disease are described in Chapter 35. Muscle disorders are discussed in Chapter 42.

Peripheral nerve lesions, whether of the central components of the nerves in the spinal cord and brainstem or along their peripheral course in the limbs and head, can also result in focal hypalgesia or anesthesia. Knowledge of the autonomous zones for the peripheral nerves innervating the limbs can be used to localize such peripheral nerve lesions.[56]

Urinary Incontinence and Urine Retention

The clinical signs of urinary bladder denervation are variable and depend on the lesion location. Lesions of the sacral segments of the spinal cord produce a flaccid bladder, which distends with a large residual volume. Spontaneous urine leakage occurs continuously through the paralyzed atonic urethral sphincter. Additional urine flow occurs when the abdominal pressure is increased. Lesions of the brainstem or spinal cord anterior to S1 produce reflex dyssynergia, a disturbance in coordination of micturition, wherein the facilitatory influence of the bladder stretch receptor (afferents) maintains tonic activity on the efferents of the urethral sphincter. The lack of inhibition of these reflexes from the upper motor neuron pathways produces hypertonicity of the urethral sphincters and results in an impediment to urine flow. There is a high intravesicular pressure and a large postvoiding urine volume. The urine escapes paroxysmally only when the intravesicular pressure exceeds the sphincter pressure. After approximately 1 month of denervation, local spinal reflexes between the sacral afferent and efferent neurons develop in the S1 to S5 segments, and incomplete voiding occurs. In these cases the residual volume remains large, and the normal urination posture is not attained.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 9

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Alterations in Body Weight or Size

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JOHN MAAS

■ MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Slowed growth and below-normal weight gain usually happen at the same time, although occasionally they develop separately. By definition a decrease in growth and weight gain is limited to the growing animal. Similar pathogenic mechanisms cause weight loss or an emaciated condition in an adult patient. This arbitrary age division allows the clinician to consider possible causes that are more or less common for a given age group.

Potential growth and weight gain are genetically determined. They differ according to species, breed, and sex, and marked differences in potential growth exist within a breed. The potential for growth in ruminants is greater in the offspring of multiparous females than in those from primiparous females. The normal or minimum growth and weight gain rates for common breeds of the various large animal species are outlined in the section on assessment of growth and weight gains.

Mechanisms of Decreased Growth and Decreased Weight Gain

Major pathogenic mechanisms that result in decreased growth and decreased weight gain include the following:

- Inadequate dietary intake of essential nutrients
- Infections or inflammation
- Parasitism
- Genetic errors in metabolism or physiologic function
- Concurrent toxicosis
- Environmental causes
- Multiple causes

Inadequate intake of one or more essential nutrients is an important cause of decreased growth. In many cases growing animals are not provided with a sufficient volume of feed to meet their nutrient requirements. Young animals rely on a highly digestible diet that provides energy and essential nutrients for growth. Even animals fed an appropriate volume of a poor-quality milk replacer could suffer from poor growth. Milk replacers formulated with sources of protein, fat, vitamins, and minerals that have limited nutrient digestibility may induce a state of energy, protein, vitamin, or mineral malnutrition. For some young animals, poor-quality forage is the only feed available. Weaned foals and ruminants rely on forages and cereal grains to provide essential nutrients. Hay that has been harvested at a late stage of growth usually has a lower nutrient digestibility compared with young forages. Diets low in digestible energy or protein or both reduce total daily intake in ruminants (Table 9-1) because of the increased turnover time ($T_{1/2}$) in the gastrointestinal tract and subsequent decreased throughput. This compounds the problems caused by an inadequate intake of digestible nutrients. The digestibility of forages is even lower for horses than for ruminants.

Protein-calorie malnutrition (PCM) is the most common clinical cause of decreased growth and decreased weight gain in young animals. It is characterized by smaller size and lower weight than the normal minimums for age, breed, and sex. Inadequate intake of digestible energy and protein (or essential fatty acids in the neonate primarily adapted to a milk diet) results in inadequate levels of amino acids, fats, and carbohydrates for normal metabolism and growth. Diets that lack any of the other essential nutrients (essential fatty acids, vitamins, macrominerals, or trace minerals) can also decrease growth. Deficiencies of calcium, phosphorus, and magnesium result in improper skeletal formation. Deficiencies in other macrominerals (e.g., sodium, chloride, potassium), trace minerals (e.g., copper, zinc, manganese, cobalt, iron), and vitamins (e.g., A, D, E, thiamin) cause biochemical dysfunctions that lead to inefficient metabolism and growth. Large animal patients that grow slowly as a result of inadequate diets often have normal or increased appetites until they are terminally ill. Physical findings and clinicopathologic data from animals with PCM are often within the normal range until the disease process is well advanced.

Infections or inflammatory processes are important causes of decreased growth and decreased weight gain in young horses and ruminants. The decrease in growth can be of short duration followed by recovery and compensatory gain (cryptosporidiosis) or can persist (chronic bronchopneumonia). Infections or inflammatory processes can also result in nutrient malabsorption (chronic salmonellosis, acute rotavirus diarrhea, equine proliferative enteropathy), anorexia (pharyngeal abscesses, systemic disease), increased nitrogen turnover, and direct protein losses (gastrointestinal disease). Both energy and protein requirements may be increased as a result of infection and inflammation.

Parasitism often affects young horses and ruminants and results in decreased growth and decreased weight gain by increasing nutrient requirements, increasing nutrient losses, and/or decreasing nutrient absorption. The animal's metabolic rate and nutrient requirements may also increase as a result of inflammatory and immune reactions that arise secondary to parasitism.

Genetic diseases (α-mannosidosis, dwarfism) result in decreased growth through generalized errors in the genetic code or interference with strategic reactions in one or more metabolic pathways. Congenital cardiac malformations (tetralogy of Fallot, interventricular septal defect) create physiologic inefficiencies that require energy beyond the body's ability to supply it. Congenital renal disease (agenesis, dysplasia, hypoplasia, polycystic kidney disease) affects homeostatic

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TABLE 9-1

Maximum Dry Matter Intake (DMI) Related to Forage Quality for Cattle

Forage Quality	Maximum DMI/Day (% Body Weight)	Maximum DMI for 500 kg/ Cow/Day (kg)
Poor	1-1.5	5-7.5
Oat straw		
Corn stover		
Average	2	10
Meadow grass hay		
Excellent	2.5	12.5
Alfalfa hay (25% crude fiber)		
Corn silage		

From Maas J. 1987. Relationship between nutrition and reproduction in beef cattle. Vet Clin North Am 3:634.

mechanisms that regulate electrolyte and acid-base balance, results in the production of uremic toxins, and often results in partial anorexia and PCM. Digestive tract malformations including cleft palate, megaesophagus, and brachygnathism can reduce nutrient ingestion and impair growth.

Toxicities, although rare in growing animals, result in decreased weight gain by interfering with metabolic pathways (e.g., ammonia toxicity, zinc-induced copper deficiency with abnormal skeletal development in foals), by causing loss of body reserves (e.g., thiamin deficiency in horses, bone marrow hypoplasia and associated bleeding diatheses in ruminants associated with bracken fern toxicity), by inducing anorexia, or by a combination of mechanisms. The pathogenic mechanisms of many toxins are not yet known.

Environmental factors including extreme heat or cold or high humidity result in decreased growth and decreased weight gain. Extremely cold conditions increase an animal's daily energy requirements. During extremely hot weather feed intake often decreases, which may contribute to decreased growth. Often, environmental conditions influence the development of disease, resulting in a subsequent increase in nutrient requirements in a growing animal (e.g., calves with PCM housed in poorly ventilated or overly humid conditions become much more susceptible to infectious pneumonia).

In many cases a combination of these diverse factors may influence the growth and weight gain of young animals. A period of increased growth rate and weight gain, called *compensatory gain,* often occurs after a period of restricted growth once adequate dietary energy and protein are available. In growing foals, compensatory gain should be closely monitored to prevent rapid growth and abnormal skeletal development, which could lead to developmental orthopedic disease.

Boxes 9-1 and 9-2 list many of the possible causes of decreased growth and decreased weight gain in horses and ruminants, respectively.

Approach to the Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Horses

1. Take a general history and a diet history.
   a. General history
      i. Foal factors: What is the patient's age? Was the foal born prematurely? Were any congenital defects identified during the initial examination of the foal after birth? Did the foal have any complications from sepsis? What is the vaccination history of the mare and the foal? Has the foal shown any evidence of systemic illness (diarrhea, nasal discharge, cough, pyrexia)?
      ii. Environmental factors: How is the foal housed? What type of protection is provided from adverse weather conditions? Has the foal experienced any extreme weather conditions (cold, heat, humidity)? Does the foal have access to a pasture or dry lot? Are there any toxins in the foal's environment? What is the stocking density of the herd? Is the foal exposed to a high parasite load in the environment? What is the foal's deworming history? Have there been previous problems with gastrointestinal parasitism on the farm? Does the farm have a history of

BOX 9-1

Causes of Decreased Growth and Decreased Weight Gain in Horses

Common Causes

Protein-calorie malnutrition (PCM), inadequate nutrient intake
Extreme environmental factors (cold, heat)
Diarrhea (*Clostridia* species, *Salmonella* species, rotavirus, sand enteropathy, other causes)
Parasitism (*Parascaris equorum,* small strongyles, large strongyles, tapeworms, threadworms, bots)
Gastric ulcers
Bacterial pneumonia (*Rhodococcus equi, Streptococcus zooepidemicus,* other)
Viral pneumonia (equine herpesvirus, equine influenza)
Lameness (e.g., physitis, osteochondritis dissecans, contracted tendons, osteomyelitis)
Prematurity, dysmaturity

Less Common Causes

Jaw pain (fracture, dental abnormality)
Esophageal stricture, megaesophagus (idiopathic, acquired)
Campylobacter jejuni
Cryptosporidium parvum
Equine proliferative enteropathy
Fungal pneumonia
Congenital cardiac and great vessel anomalies
Endocarditis
Ventricular septal defect
Abdominal abscess
Peritonitis
Osteodystrophy
Goiter
Calcium deficiency
Copper deficiency
Phosphorus deficiency
Selenium deficiency
Zinc deficiency
Vitamin A deficiency

Uncommon Causes

Hydrocephalus
Biliary atresia
Hepatic portosystemic shunt
Congenital renal abnormalities (hypoplasia, dysplasia, agenesis, polycystic kidney disease)
Wound myiasis
Agammaglobulinemia
Fell Pony syndrome
Selective IgM deficiency
Severe combined immunodeficiency
Transient hypogammaglobulinemia
Congenital hypothyroidism
Gonadal dysgenesis, intersex (XO, XXY)
Thiamine deficiency
Vitamin D deficiency

Toxins

Ammonia toxicity
Fluorosis
Phenylbutazone, flunixin meglumine, and other nonsteroidal antiinflammatory drugs
Lead toxicity
Zinc toxicity

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BOX 9-2

Causes of Decreased Growth and Decreased Weight Gain in Ruminants

Common Causes

Protein-calorie malnutrition (PCM)
Extreme environmental factors (cold, heat)
Diarrhea (Enterotoxigenic *Escherichia coli,* attaching and effacing *E. coli, Shiga* toxin-producing *E. coli, Salmonella,* bovine virus diarrhea, coronavirus, rotavirus infection, *Cryptosporidium parvum,* coccidiosis, other causes)
Ostertagiasis I and II
Parasitism (flukes, gastrointestinal worms, lungworms)
Bacterial bronchopneumonia
Viral bronchopneumonia
Hepatic abscessation
Sarcoptic mange
Lameness (sole abscess, foot rot, laminitis, foot warts, osteomyelitis)
Agammaglobulinemia (failure of passive transfer) in neonates
Copper deficiency (molybdenosis)
Selenium deficiency

Less Common Causes

Hydrocephalus
Pharyngeal abscess, injury
Severe bovine papular stomatitis
Abomasal ulcers
Giardiasis
Cardiac or great vessel anomalies
Peritonitis
Urachal or bladder abscess
Arthrogryposis
Osteodystrophy, rickets
Immune-mediated anemia
Neonatal isoerythrolysis
Sarcocystosis
Myiasis
Tick infestation
Goiter
Cobalt deficiency
Thiamine deficiency
Vitamin A deficiency
Zinc deficiency

Uncommon Causes

Brisket disease
Osteogenesis imperfecta in Friesians
Calf lymphosarcoma
Congenital porphyria
Granulocytopathy
Epidermolysis bullosa
Mucormycosis
Zygomycosis
α-Mannosidosis
Generalized glycogenosis (GM1 gangliosidosis, type II glycogenosis)
Gonadal dysgenesis, intersex
Hypersensitivity to soy protein
Phosphorus deficiency

Toxins

Aflatoxicosis
Ammonia (urea) toxicity
Fluorosis
Herbicide toxicity
Iodine toxicity
Selenium toxicity
Zinc toxicity

Plant Toxins

Bracken fern *(Pteridium aquilinum)*
Cassia spp.
Fescue toxicity
Oxalate toxicity
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., and others)
White leadtree *(Leucaena leucocephala)*

Exotic Diseases

Babesiosis *(Babesia bigemina, Babesia bovis)*
Schistosomiasis
Trypanosomiasis (*Trypanosoma* spp.)

infectious disease agents (*Rhodococcus equi, Streptococcus equi* subsp. *equi, Clostridium difficile*)? Are there any sick horses on the same farm? If so, what age cohort is sick?

b. Diet history
   i. Foal: If the foal is nursing, is the mare at an ideal body weight? Is the mare producing a sufficient amount of milk for the foal? If the foal is an orphan, what type of milk replacer is the owner using? What is the daily energy and protein intake of the foal? Is the owner mixing the milk replacer properly? Does the foal have access to a creep feed? What is the owner using as a creep feed? How much of the creep feed does the foal consume daily?
   ii. Weanling: When was the foal weaned? Does the foal compete with other foals for feed? Has the owner changed the foal's diet recently? If yes, what changes were made? Does the foal have a good appetite? Has the foal's appetite changed recently?
      (1) Forage: What type of forage is fed to the foal? Does the foal have access to pasture? How long is the foal turned out in the pasture? What is the nutritional quality of the hay or pasture? Is there gross evidence of dirt, mold, or weed contamination in the hay? Has a hay analysis been performed? If so, what is the digestibility of the hay? How much hay is offered to the foal (in weight) daily? How much forage (in weight) does the foal eat each day?
      (2) Supplemental Feeds and Grain: What type of supplemental feed or grain is fed to the foal? Is the feed of high quality and appropriate for a growing foal? What is the nutrient composition of the supplemental feed? How much of the supplemental feed or grain (in weight) does the foal eat each day?
      (3) Vitamins and Minerals: Is the foal offered a vitamin and mineral supplement? Is the vitamin and mineral supplement appropriate for a growing foal? Is the vitamin and mineral supplement offered free choice? How much of the supplement (in weight) does the foal eat each day? Could any nutrients be consumed in a toxic amount? Has the owner provided any supplemental parenteral vitamins or minerals to the foal?

2. Perform a physical examination.
   a. What is the body weight of the foal (measured by using either a scale or weight tape if the foal is 3 months of age or older)? What is the body condition score (BCS) of the foal (see Table 9-22)? Is the foal small, thin, or underweight according to growth charts (Table 9-2; Figs. 9-1 and 9-2)?
   b. Does the foal have evidence of a congenital abnormality (cardiac, renal, gastrointestinal, oral)?
   c. Does the foal show any signs of infectious disease (current or resolved)?
   d. Does the foal have any musculoskeletal abnormalities?

3. Examine the feces. What is the consistency of the feces? Refer to Chapter 17 for the diagnosis and management of neonatal diarrhea; refer to Chapter 7 if the foal is older and has evidence of diarrhea. Is there evidence of sand in the manure? Perform a fecal egg count. If the foal has a positive fecal egg count, follow the parasite control program recommendations in Chapter 49. If a negative fecal egg count is reported but parasitic infestation is still suspected, repeat the test in 2 to 3 weeks or follow the deworming protocols in Chapter 49. Evaluate the feces for occult blood. If the foal has a positive fecal occult blood test, review the medical management for melena in Chapter 7.
4. Perform blood analyses.
   a. Perform a complete blood count (CBC) and include a plasma protein and fibrinogen concentration. If the foal is anemic, determine the cause of the anemia following the guidelines in Chapter 24. If the foal's CBC indicates inflammation, review Chapters 25 and 26 and select appropriate ancillary diagnostic tests to identify the source of the infection or inflammation.
   b. Perform a serum biochemical analysis. Evaluate the results for evidence of systemic disease. Serum albumin is usually within normal limits with PCM until the condition is terminal. Serum glucose is usually normal, but it may be decreased in neonatal foals with sepsis. Serum glucose may be elevated in stressed animals. Serum urea nitrogen and creatinine concentrations are elevated in foals with renal disease. Serum urea nitrogen decreases in cases of chronic protein malnutrition.
   c. If the foal has evidence of systemic disease, perform ancillary diagnostic tests to identify the source of the illness and then manage the case with appropriate medical or surgical intervention.
5. Analyze the diet and improve the feeding program.
   a. Determine whether the energy, protein, mineral, and vitamin content of the diet meets the requirements of the growing foal (Table 9-3). Use the Nutrient Requirements of Horses free companion computer program as a reference for all essential nutrients (www.nap.edu, search word "horse").
      i. Dietary protein and essential amino acids are especially important in young growing horses. Lysine is the first, and threonine is the second limiting amino acid in the equine. Growing foals should consume 4.3% of their crude protein requirement as lysine (multiply the crude protein requirement by 4.3%).[6] Growing foals should also consume at least 0.5% threonine dry matter (DM) in their diet. Soybean meal and alfalfa hay contain approximately 3.3% and 0.9% lysine (DM), respectively. Cereal grains are poor sources of lysine.
      ii. Milk replacer: If the foal is consuming a milk replacer, review the guaranteed analysis and ingredient list of the product. Review the mixing instructions with the owner or farm manager. Develop a feeding program appropriate for the foal's age.
      iii. Forage: Determine the nutrient content of forage or pasture with an analysis. Forage sampling instructions and forage analysis companies are listed in Boxes 9-3 and 9-4. University extension services often provide a forage analysis service. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu) and nutrient tables from the

TABLE 9-2

Weight as a Percentage of Mature Body Weight in Horses

Age (Months)	Ponies[4] (%)	Light Horses[1-3,5] (%)	Draft Horses (%)
6	55	46	40
12	75	67	57
18	84	80	75

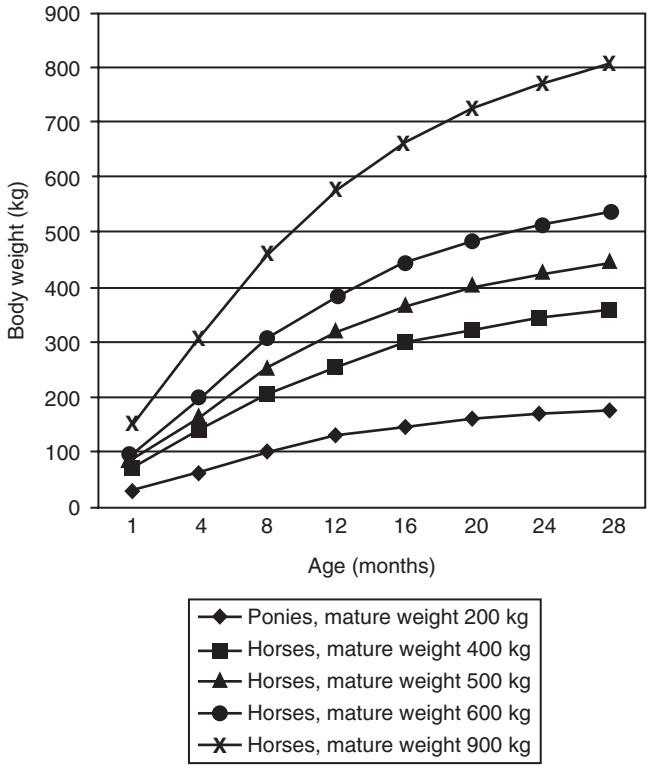


FIG. 9-1 Estimated weight gain of horses of various mature body weights. *(Modified from National Research Council [NRC]. 2007. Nutrient requirements of horses. National Academies Press, Washington, DC.)*

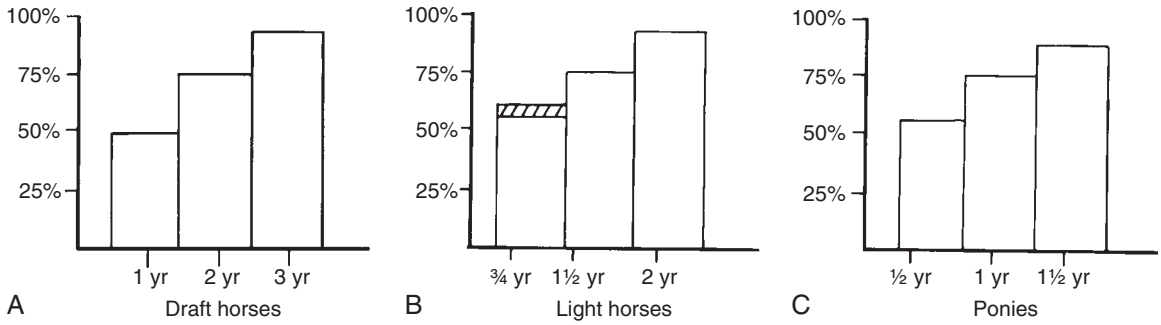


FIG. 9-2 **A** to **C,** Body weight as a percentage of mature body weight for horses at a given age. *(**A** modified from Crampton WW. 1923. J Agric Hortic 26:172; **B** modified from Lewis LD. 1982. Feeding and care of the horse. Lea & Febiger, Philadelphia, PA; **C** modified from Hintz HF. 1979. Factors affecting the growth rate of horses. Horse Short Course Proceedings. Texas A&M Animal Agriculture Conference, College Station, TX.)*

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TABLE 9-3

Daily Nutrient Requirements for Growth in Equines of Various Mature Body Weights

Mature Body Weight (kg/lb)	Category	Weight (kg)	Weight (lb)	Daily Gain (kg)	Daily Gain (lb)	Digestible Energy (Mcal)	Crude Protein (g)	Lysine (g)	Calcium (g)	Phosphorus (g)
Ponies 200 kg (440 lb)	Nursing foal (4 mo old)	67	147	0.34	0.75	5.3	268	11.5	15.6	8.7
	Weanling (6 mo old)	86	189	0.29	0.64	6.2	270	11.6	15.5	8.6
	Yearling (12 mo old)	128	282	0.18	0.40	7.5	338	14.5	15.1	8.4
	Long yearling (18 mo old)	155	341	0.11	0.242	7.7	320	13.7	14.8	8.2
	2-year-old (24 mo old)	172	378	0.07	0.154	7.5	308	13.2	14.7	8.1
Horses 400 kg (880 lb)	Nursing foal (4 mo old)	135	297	0.67	1.47	10.6	535	23.0	31.3	17.4
	Weanling (6 mo old)	173	381	0.58	1.28	12.4	541	23.3	30.9	17.2
	Yearling (12 mo old)	257	565	0.36	0.79	15.0	677	29.1	30.1	16.7
	Long yearling (18 mo old)	310	682	0.23	0.51	15.4	639	27.5	29.6	16.5
	2-year-old (24 mo old)	343	755	0.14	0.31	15.0	616	26.5	29.3	16.3
Horses 500 kg (1100 lb)	Nursing foal (4 mo old)	168	370	0.84	1.85	13.3	669	28.8	39.1	21.7
	Weanling (6 mo old)	216	475	0.72	1.58	15.5	676	29.1	38.6	21.5
	Yearling (12 mo old)	321	706	0.45	1.0	18.8	846	36.4	37.7	20.9
	Long yearling (18 mo old)	387	851	0.29	0.64	19.2	799	34.4	37.0	20.6
	2-year-old (24 mo old)	429	944	0.18	0.40	18.7	770	33.1	36.7	20.4
Horses 600 kg (1320 lb)	Nursing foal (4 mo old)	202	444	1.01	2.22	15.9	803	34.5	46.9	26.1
	Weanling (6 mo old)	259	570	0.87	1.91	18.6	811	34.9	46.4	25.8
	Yearling (12 mo old)	385	847	0.54	1.19	22.5	1015	43.6	45.2	25.1
	Long yearling (18 mo old)	465	1023	0.34	0.75	23.1	959	41.2	44.5	24.7
	2-year-old (24 mo old)	515	1133	0.22	0.48	22.4	924	39.7	44.0	24.4
Horses 900 kg (1980 lb)	Nursing foal (4 mo old)	303	667	1.52	3.34	23.9	1204	51.8	70.3	39.1
	Weanling (6 mo old)	389	856	1.30	2.86	28.0	1217	52.3	69.5	38.7
	Yearling (12 mo old)	578	1272	0.82	1.80	33.8	1522	65.5	67.8	37.7
	Long yearling (18 mo old)	697	1533	0.51	1.12	34.6	1438	61.8	66.7	37.1
	2-year-old (24 mo old)	773	1701	0.32	0.70	33.7	1386	59.6	66.0	36.7

Modified from National Research Council (NRC). 2007. Nutrient requirements of horses. National Academies Press, Washington, DC.

BOX 9-3

Forage and Large Animal Feed Sampling Instructions

Sampling Pasture

1. Collect pasture samples from a 1-foot-square area. Sample only the same type of forage that the horses are grazing. Sample 10 to 20 sites.
2. Using scissors, cut the pasture to within 1 inch of the ground. Do not collect soil-contaminated pasture. Cut all samples to a length of 1 inch, and place all samples into a clean bucket.
3. After sampling is complete, mix the samples well and place the forage into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date of sampling, the collection site, and the owner's name.
4. If the sugar and starch content of the sample is of special interest, the sample should be frozen and shipped on ice to the analysis company.

Sampling Hay Using a Core Hay Sampler

1. Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.
2. Use the core hay sampler with a ratchet brace or drill to collect two samples from each bale. Square bales should be sampled from the long end of the bale. Round bales should be sampled along a horizontal line at the curve of the bale. Place all samples into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name.

Sampling Hay by Hand

1. Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.
2. Open the bale, and divide the bale in thirds. Collect a handful of hay from the center of the bale at each site (two samples per bale). Include everything that you have grabbed (including weeds and other plants) in the sample. Cut all samples to a length of 1 inch, and place all samples into a clean bucket. Thoroughly mix the cut hay samples, place the forage into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name. Ensure that all parts of the sample (leaves and stems) are included in the final sample.

Sampling Grain or Pelleted Feed

1. Analysis of two to four samples from 10 bags is recommended to obtain a representative sample of feed. Only one type of feed should be submitted for analysis in the same container. If more than one type of grain or pelleted feed is analyzed, each should be placed into a separate, labeled plastic bag.
2. Open a bag or a bin, and obtain a 2- to 4-oz sample from two to four locations in the bag or bin. A sample should be obtained from the bottom of the bin or bag to ensure that a sample of the settled feed is analyzed. When multiple bags or bins are sampled, samples from each bin or bag should be placed into a clean plastic bucket. Once all sampling has been completed, the feed sample should be mixed well, and approximately 1 lb of the feed should be placed into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date, type of feed, and owner's name.

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BOX 9-4

Feed Analysis Companies

Submission forms are available online.

1. Equi-Analytical Laboratories
   730 Warren Road
   Ithaca, NY 14850
   (877) 819-4110
   www.equi-analytical.com
2. Cumberland Valley Analytical Services
   Mailing address: P.O. Box 669
   Maugansville, MD 21767
   UPS/FedEx: 14515 Industry Drive
   Hagerstown, MD 21742
   (800) 282-7522
   www.foragelab.com
3. Eurofins
   2200 Rittenhouse Street, Suite 150
   Des Moines, IA 50321
   (515) 265-1461
   www.eurofinsus.com

Equi-Analytical Laboratories forage laboratory database (www.equi-analytical.com) can be referenced to estimate the concentration of different nutrients in common forages and supplemental feeds. Use the daily nutrient requirements (see Table 9-3) to recommend the type and amount of forage the foal should consume on the basis of the nutrient content of the forage.

iv. Commercial feeds and grain mixes: The guaranteed analysis on the feed tag label provides the nutrient content of certain ingredients. Contact commercial feed companies for the energy content of their product. Make recommendations about the appropriate use of commercial equine feeds, grain, or grain mixes to complement the forage-based ration for growing foals on the basis of the clinical health of the foal.

v. Vitamins and minerals: Ensure that the ration meets the vitamin and mineral requirements of the foal and that proper mineral ratios are maintained in the ration. Supplement the ration if necessary.

b. If the foal or weanling has a nutrient deficiency, the problem should be corrected by a change in the ration or through appropriate parenteral supplementation.

c. If the diet history indicates that nutrients for maintenance and growth have been available and steadily consumed, the search for another cause of decreased growth and decreased weight gain should continue.

6. Perform ancillary diagnostic tests. If the cause of the decreased growth and/or poor weight gain has not been determined, additional diagnostic tests should be performed. Possible tests include, but are not limited to, ultrasound, radiographs, serum or whole blood trace mineral analysis, and carbohydrate absorption tests (oral D-glucose, D-xylose).

Approach to the Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Ruminants

1. Take a general history and a diet history.
   a. General history
      i. What is the age of the animal? When was a decrease in growth observed? How many animals in the herd are affected? What are the ages of the affected animals? Has the herd had historical problems with growth of the young?
      ii. Identify the problem as acute, subacute, or chronic.
      iii. Check for signs or history of previous infectious disease in the herd.
      iv. Determine the parasite control procedures for the animal or herd.
      v. Examine the environment, including feed preparation areas and equipment, for possible toxic substances (e.g., zinc from galvanized buckets). Ensure cleanliness of bottles and equipment used with nursing animals.
   b. Diet history
      i. Obtain an accurate diet history, including diet information when milk or a milk replacer is being fed (birth to 2 or 3 months of age). Note the age and condition of the dam if patient was suckled before weaning. An accurate postweaning dietary history is essential. Suckled animals are developed ruminants at weaning, but hand-reared animals (dairy calves, bummer lambs, and dairy kids) are usually not fully developed ruminants at the time they are weaned from milk.
      ii. Inspect all forages and concentrates for quality, signs of spoilage, or abnormal color or odor. Has an analysis been performed on the forage or feed? Is the feed formulated appropriately for a young growing animal? Is the feed stored appropriately?
      iii. Because ruminants are often fed in groups, note whether all animals have adequate space to eat simultaneously.
2. Perform a physical examination.
   a. Determine the patient's age and weight. Is the patient growing appropriately on the basis of age and weight charts (Figs. 9-3 to 9-6)?
   b. Does the animal show any signs of infectious or parasitic disease?
   c. Does the animal show any signs of congenital abnormalities?
3. Examine the feces. Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestation. Perform a fecal occult blood test; if the result is positive or if there is evidence of diarrhea, see the section on melena or diarrhea in Chapter 7. If diarrhea is noted in neonatal calves, refer to Chapter 20 for diagnostic and therapeutic management.
4. Perform blood analysis.
   a. Perform a CBC, including plasma protein and fibrinogen. Calculate the erythrocytic indices, and document and characterize the anemia if present. If a herd problem exists in a selenium-deficient region, measure the whole blood selenium concentration or glutathione peroxidase activity.
   b. Perform a serum biochemical analysis. Serum albumin is decreased late in PCM. Albumin is normally lower in neonates (≈1 g/dL less) than in adults. The blood urea nitrogen (BUN) level is often low in ruminants as a result of urea recycling through saliva. Total serum calcium may be decreased with hypoalbuminemia (ionized serum calcium remains normal), anorexia, or hypocalcemic syndromes (milk fever). Serum phosphorus may be increased during severe starvation or decreased with anorexia. Hypophosphatemia may be the result of dietary deficiency or *Brassica* feeding, or it may be associated with copper deficiency. Measure serum (plasma) copper if a herd problem exists in a copper-deficient region (or a region with excess molybdenum or sulfate or both). Copper (serum or plasma) concentrations below 0.5 µg/mL (ppm) indicate deficiency. The concentration of copper in the liver is even more indicative of status. Serum glucose may be increased with stress or decreased or normal near death.
5. Analyze the diet and improve the feeding program. Compare nutrient intake with the requirements for maintenance and growth of the various ruminant species (Tables 9-4 through 9-11). If the neonate is being fed a milk diet, evaluate the quality of the product and ensure that the animal's intake meets the dietary requirements (see Tables 9-4 and 9-5). Requirements for other breeds and life stages can be found in the nutrient requirement textbooks for dairy cattle, beef cattle, and small ruminants. Ensure that the milk replacer is mixed properly. If the ruminant is consuming a grain mix or forage, ensure that the quantity and the quality of the feed are adequate to allow sufficient intake in developed ruminants (see Table 9-1). Forage sampling

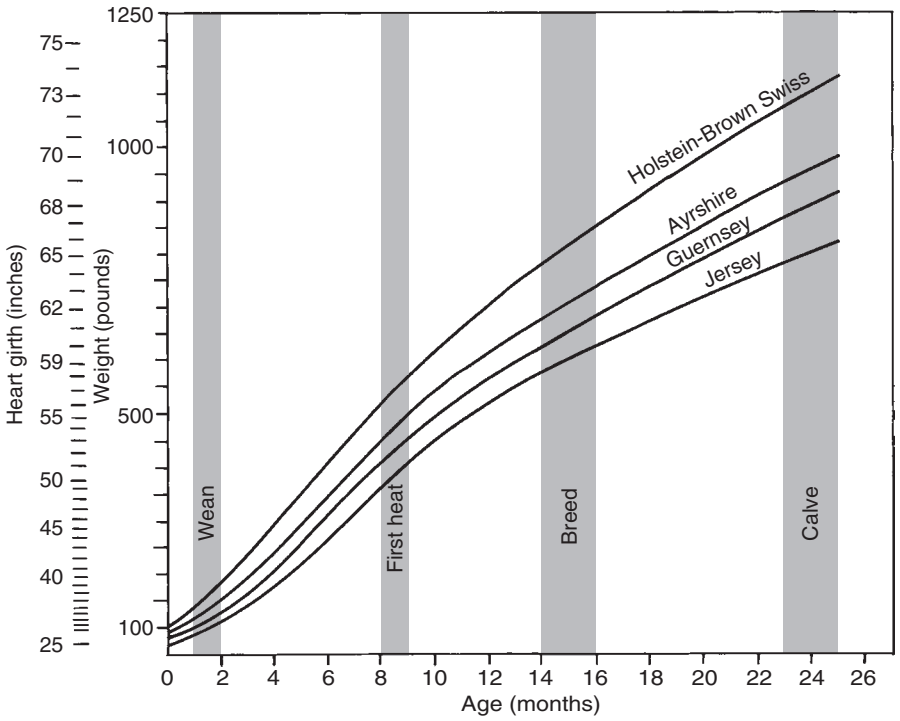


FIG. 9-3 Minimum growth curve for dairy heifers. *(From Sniffen CJ. 1984. Feed Manage 35:37.)*

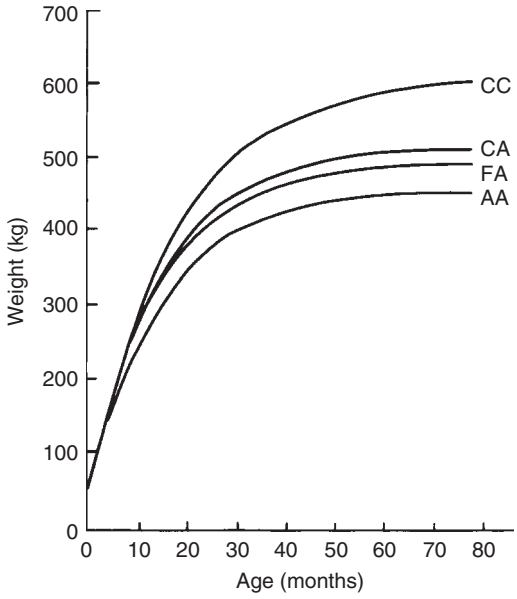


FIG. 9-4 Estimated growth curves for beef cows of various breeds. *AA,* Angus; *CC,* Charolais; *CA,* Charolais × Angus; *FA,* Holstein × Angus. *(Modified from Nadarajah K, Marlowe TJ, Notter DR. 1984. Growth patterns of Angus, Charolais, Charolais X Angus and Holstein X Angus cows from birth to maturity. J Anim Sci 59:957.)*

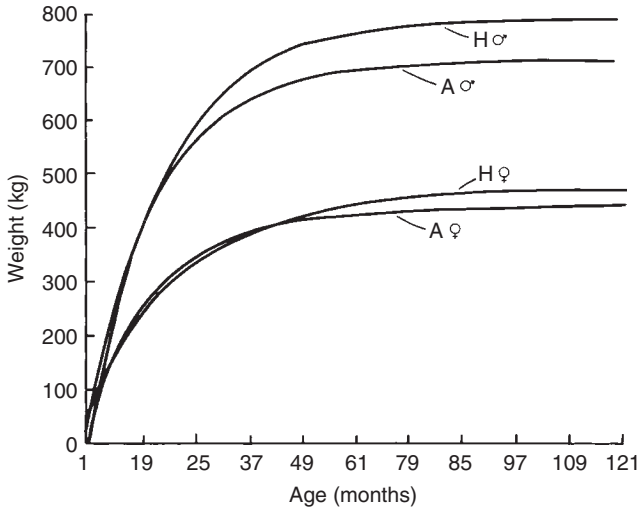


FIG. 9-5 Mean growth curves of Angus *(A)* and Hereford *(H),* males (♂) and females (♀). *(Modified from Brown JE, Brown CJ, Butts WT. 1972. A discussion of the genetic aspects of weight, mature weight and rate of maturing in Hereford and Angus cattle. J Anim Sci 34:525.)*

instructions are listed in Box 9-3. If anorexia is present, look for more specific signs of a primary disease process. If the diet supplies adequate nutrients for maintenance and growth, consider decreased growth and decreased weight gain to be caused by a primary disease condition.

Weight Loss

The clinical problem of weight loss suggests that an individual large animal patient or a herd has lost weight over a known period of time. It may also suggest that the patient has reached a subnormal adult weight and size (see section on decreased growth and decreased weight gain, earlier). Late pregnancy, early lactation, and intense exercise are normal physiologic conditions commonly accompanied by mild to moderate weight loss. Late pregnancy can be associated with decreased body condition without actual weight loss, because weight is gained with the conceptus. During pregnancy and lactation the loss of body condition may be mild, resulting in a low normal BCS, or the loss may be severe and can threaten the health of both the dam and neonate.

Weight loss in adult animals is most commonly associated with one or more of the following circumstances (other causes are listed in Boxes 9-5 and 9-6):

- Anorexia
- Increased nutrient demands
- PCM
- Micronutrient deficiencies
- Parasitism

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Anorexia usually occurs secondary to a primary disease. Increased nutrient requirements are associated with normal physiologic conditions (e.g., pregnancy, lactation, exercise, cold weather) and with pathologic processes (e.g., sepsis, trauma, parasitism, burns). Mild to severe PCM is often associated with inadequate feed quality (see Table 9-1) or quantity but can also be caused by increased energy requirements resulting from adverse environmental conditions. Weight loss can also occur with a deficiency of essential micronutrients such as copper, cobalt (vitamin B_{12}), or vitamin A. Parasitism should always be on the differential list in an animal that has lost weight.

Mechanisms of Weight Loss

Anorexia is the loss of appetite or lack of desire for food; it may be complete or partial. It is a primary mechanism for weight loss of short or intermediate duration. Weight loss results from decreased nutrient intake. When partial anorexia occurs over a long period, the weight loss may be subtle and go unrecognized. Acute, complete anorexia results in more dramatic rapid weight loss.

In domestic species, anorexia is usually associated with a primary disease condition and is regulated by cytokines, including interleukin (IL-1) and tumor necrosis factor alpha (TNF-α), released during an inflammatory response. Resolution of the primary disease process usually results in a return to voluntary food consumption. Anorexia must be differentiated from dysphagia by observation. The distinction between the conditions that cause anorexia and those that control hunger and satiety is not clear; however, many diseases that cause anorexia also result in dehydration, electrolyte imbalances, and/or acid-base disorders.

In addition to causing anorexia, many disease processes cause an increase in the nutrient requirements for basal metabolism. Nutrient requirements for maintenance, growth, pregnancy, lactation, and exercise have been well defined for many large animal species. Nutrient requirements in disease have not been adequately evaluated in large animals, and most information is currently extrapolated from humans, laboratory animals, and small animal species. In human patients, published estimates indicate that requirements for energy and protein increase approximately 10% after elective surgery, 20% with fractures, 30% to 60% with severe infection or sepsis, 40% with peritonitis, and 50% to 110% with major burns.[7,8] In humans, the resting energy expenditure is estimated to increase by 14% for each degree Celsius increase in body temperature.[9] Extrapolation of these data directly to equine and ruminant patients is probably not possible; however, the figures do indicate the degree of change in

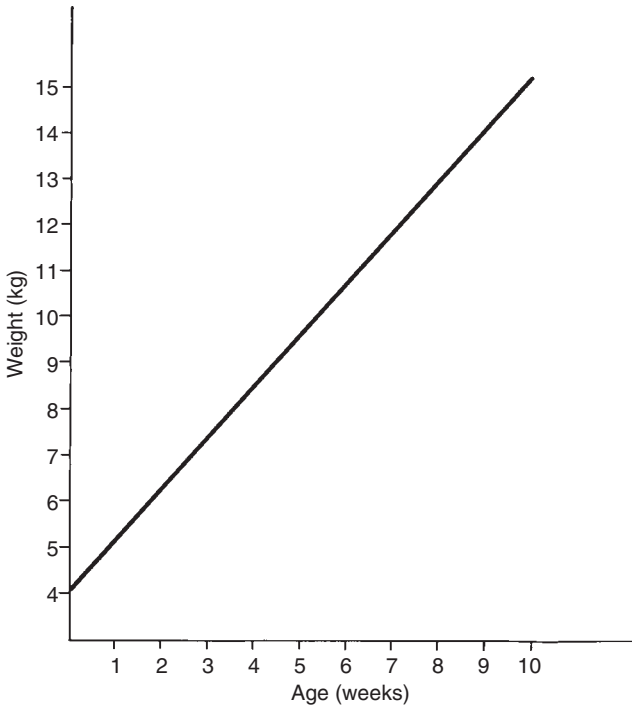


FIG. 9-6 Growth curve for young goats. *(Modified from Morand-Fehr P, Hervieu J, Bas P, et al. 1982. Proc Third Int Conf Goat Prod Dis 3:96.)*

TABLE 9-4

Daily Energy and Protein Requirements for 50-kg Calves on a Milk Diet

	Digestible Energy Requirements	Digestible Protein Requirements
Maintenance	45-55 kcal/kg body weight	0.5 g/kg body weight
Gain	300 kcal/100 g gain in body weight*	22 g/100 g of weight gain†
0.5 kg daily gain	1500 kcal	
1 kg daily gain	3000 kcal	

*A 50-kg calf gaining 0.75 kg/day would have a daily energy requirement of 5000 kcal of digestible energy (2750 kcal maintenance + 2250 kcal/0.75 kg of gain).

†A 50-kg calf gaining 0.75 kg/day would have a daily protein requirement of 190 g of digestible protein (25 g of maintenance + 165 g of gain).

TABLE 9-5

Net Energy (NE) Requirements of Young Lambs on Milk-Replacer Diets*

	Body Weight in Kilograms (Pounds)				
Average Daily Gain (g)	5 (11)	7.5 (16.5)	10 (22)	12.5 (27.6)	15 (33)
NE_m Required, kcal/day					
	358	487	603	712	817
NE_g Required, kcal/day					
100	127	172	214	253	290
150	193	262	325	383	440
200	261	353	438	518	594
250	330	447	555	355	751
300	401	543	674	796	913
350	473	641	796	940	1078
400	547	742	921	1088	1247

From Chiou PWS, Jordan RM. 1973. Ewe milk replacer diets for young lambs. IV. Protein and energy requirements of young lambs. J Anim Sci 37:581.

*Protein requirements for young lambs on a milk-replacer diet are approximately 20 g, 40 g, and 60 g for weight gains of 0, 100, and 200 g/day, respectively.

NE_g, Net energy of gain; NE_m, net energy of maintenance.

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TABLE 9-6

Daily Nutrient Requirements for Growth of Dairy Calves

Body Weight (kg)	Body Weight (lb)	Breed	Age (wk)	Daily Gain (kg)	Digestible Energy (Mcal/day)	Metabolizable Energy (Mcal/day)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
Heifers and Bulls Fed Only Milk									
25	55	Small	1	0.2	1.56	1.50	70	6	4
30	66	Small	3	0.4	2.31	2.22	124	7	4
45	99	Large	1	0.2	2.30	2.21	81	8	5
50	110	Large	3	0.6	3.86	3.70	185	9	6
Growing Heifers and Bulls Fed Mixed Diets									
50	110	Large	3	0.5	5.42	5.20	198	10	6
Growing Dairy Heifers									
100	220	Small	26	0.5	8.35	8.00	360	16	6
200	440	Small	54	0.5	14.06	13.5	586	20	13
300	660	Small	83	0.5	18.74	18.00	746	23	17
Growing Dairy Bulls									
100	220	Small	26	0.5	8.35	8.0	361	16	8
200	440	Large	24	0.5	13.66	13.1	602	20	13
300	660	Large	38	0.5	18.56	17.8	777	24	18

Modified from National Research Council (NRC). 1978. Nutrient requirements of dairy cattle. National Academy of Sciences, NRC, Washington, DC, and from NRC. 2001. Nutrient requirements of dairy cattle. National Academy of Sciences, NRC, Washington, DC.

TABLE 9-7

Net Energy (NE) Requirements for Growth of Beef Cattle (Mcal/day)

Daily Gain (kg)	Body Weight (kg); (NE_m Required)			
	200 (4.1)	250 (4.84)	300 (5.55)	350 (6.23)
Medium-Frame Steer Calves NE_g Required				
0.5	1.27	1.50	1.72	1.93
1.0	2.72	3.21	3.68	4.13
1.5	4.24	5.01	5.74	6.45
Daily Gain (kg)	**Body Weight (kg); (NE_m Required)**			
	300 (6.38)	400 (7.92)	500 (9.36)	600 (10.7)
Growing Bulls NE_g Required				
0.5	1.72	2.13	2.52	2.89
1.0	3.68	4.56	5.39	6.18
1.5	5.74	7.12	8.42	9.65

Modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy of Sciences, NRC, Washington, DC.

NE_g, Net energy of gain; NE_m, net energy of maintenance.

TABLE 9-8

Protein Requirements for Growth of Beef Cattle*

Daily Gain (kg)	Body Weight in Kilograms			
	200	250	300	350
Medium-Frame Steer Calves				
0.5	356	394	432	464
1	501	539	577	605
1.5	643	679	716	739

Modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy Press, Washington, DC.

*Metabolizable protein g/day.

TABLE 9-9

Calcium (Ca) and Phosphorus (P) Requirements for Growth of Beef Cattle (g/day)

Daily Gain (kg)	Mineral	Body Weight in Kilograms			
		200	250	300	350
Medium-Frame Steer Calves					
0.5	Ca	20	21	21	22
	P	11	11	12	12
1	Ca	33	33	32	32
	P	16	16	16	16
1.5	Ca	45	44	42	41
	P	21	21	20	20

Modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy Press, Washington, DC.

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TABLE 9-10

Daily Nutrient Requirements of Sheep (Growing Lambs, Growing Rams, and Yearlings)

Body Weight (kg)	Body Weight (lb)	Daily Body Weight Gain (g)	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
Growing Lambs and Yearlings; Late Maturing; 4 Mo Old/8 Mo Old							
20	44	100	1.09/1.41	300/390	51/49	2.3/2.2	1.5/1.5
		150	1.50/1.81	410/500	70/65	3.1/3.0	2.2/2.1
		200	1.42/1.99	390/550	78/75	3.7/3.5	2.5/2.6
		300	1.74/2.69	480/750	104/105	5.1/5.0	3.5/3.8
40	88	250	2.53/3.10	700/860	115/108	5.0/4.7	3.7/3.6
		300	2.94/3.53	820/980	134/124	5.9/5.5	4.4/4.3
		400	2.78/3.9	770/1080	150/144	7.0/6.7	5.1/5.2
		500	3.35/4.62	930/1280	182/174	8.6/8.2	6.3/6.4
60	132	250	2.74/4.44	760/1230	122/140	5.1/5.7	3.8/4.6
		300	3.15/3.95	870/1100	141/134	6.0/5.7	4.5/4.5
		400	3.98/4.82	1100/1340	179/167	7.8/7.3	5.9/5.8
		500	3.57/5.69	990/1580	190/199	8.7/8.9	6.4/7.2
		600	4.15/5.83	1150/1620	222/214	10.3/9.9	7.6/7.8
80	176	150	2.08/3.58	580/990	92/109	3.4/4.0	2.5/3.2
		200	2.50/4.21	690/1170	111/130	4.3/4.9	3.2/4.0
		300	3.34/5.48	930/1520	149/171	6.1/6.8	4.6/5.6
		400	4.19/5.24	1160/1450	186/176	7.9/7.5	6.0/6.0
		500	5.03/6.13	1390/1700	224/209	9.7/9.1	7.5/7.3
Growing Rams; Late Maturing; 4 Mo Old/8 Mo Old							
20	44	100	1.14/1.5	320/420	52/50	2.3/2.2	1.5/1.5
		150	1.18/1.91	330/530	62/66	2.9/3.0	1.9/2.2
		200	1.47/2.09	410/580	78/76	3.7/3.6	2.5/2.6
		300	1.79/2.8	500/780	105/106	5.1/5.1	3.5/3.8
40	88	250	2.62/3.28	730/910	116/110	5.1/4.8	3.7/3.7
		300	3.03/3.71	840/1030	135/126	6.0/5.6	4.5/4.4
		400	2.87/4.08	800/1130	151/146	7.0/6.8	5.1/5.2
		500	3.45/4.81	960/1340	184/176	8.6/8.3	6.3/6.5
60	132	250	2.85/3.76	790/1040	124/120	5.2/5.0	3.9/3.9
		300	3.27/4.2	910/1160	143/137	6.1/5.8	4.6/4.6
		400	4.11/5.08	1140/1410	181/170	7.9/7.4	6.0/5.9
		500	3.7/5.34	1020/1480	191/187	8.7/8.5	6.4/6.7
		600	4.28/6.1	1190/1690	224/217	10.3/10	7.7/7.9
80	176	150	2.22/3.87	620/1070	94/114	3.5/4.1	2.5/3.3
		200	2.65/4.51	730/1250	113/134	4.4/5.1	3.3/4.2
		300	3.49/5.81	970/1610	151/176	6.2/7.0	4.7/5.8
		400	4.34/5.56	1200/1540	189/180	8.0/7.6	6.1/6.1
		500	5.19/6.47	1440/1790	227/214	9.8/9.2	7.6/7.5

Modified from National Research Council (NRC). 2007. Nutrient requirements of small ruminants. National Academies Press, Washington, DC.

nutrient requirements as a result of disease. The stress of many disease processes results in an increase in serum cortisol and glucagon. The decreased insulin/glucagon ratio alters the production of glucose and results in hyperglycemia because of enhanced hepatic gluconeogenesis. An increase in sympathetic activity appears to regulate fat oxidation, the increased release of fatty acids from cellular lipid stores, and the development of hypertriglyceridemia in many patients with sepsis. Protein degradation and a negative nitrogen balance are also hallmarks of the acute response to infection. Weight loss resulting from protein and lipid catabolism is often observed in large animal patients with sepsis, owing to altered metabolic activity and nutrient requirements.

In conditions such as burns, peritonitis, pleuritis, colitis, and granulomatous bowel disease, nutrients (particularly proteins) are lost. In many disease conditions, concurrent anorexia and increased nutrient requirements greatly increase the risk of PCM and weight loss. Certain conditions such as Johne's disease in ruminants and granulomatous enteritis in horses are also associated with a malabsorption or malassimilation syndrome. In these types of diseases, nutrients are not efficiently digested and absorbed; anorexia may be absent, and dietary intake may appear normal, but weight loss still occurs.

PCM continues to be a persistent problem in domestic animals. Inadequate ingestion of energy and protein obviously results in weight loss, but PCM and associated weight loss can occur through several other mechanisms. The most direct cause is that the animals receive an inadequate volume of feed to meet their dietary requirements. This can occur as frank underfeeding of all animals or as a consequence of inadequate feeding facilities that create competition among animals for available feed. The latter circumstance occurs most dramatically when animals of varying ages are mixed; the younger animals with the highest requirements are often pushed away by older, dominant individuals.

The quality of the diet, particularly dietary forages such as hay and pasture, is an important factor in the development of PCM and total nutrient intake. Table 9-1 lists guidelines for estimating the maximum daily intake by cattle. It is evident that as forage quality (digestibility) decreases, maximum daily intake decreases because poor-quality feed must remain in the rumen for an increased period of time before it is sufficiently digested to allow passage through the reticuloomasal orifice. Maximum dry matter intake (DMI) as a percentage of body weight is somewhat higher in small ruminants than in cattle. However, the energy requirement per kilogram of body weight is higher in small ruminants than in cattle. Similar estimates

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TABLE 9-11

Daily Nutrient Requirements of Goats (Growing Goat Kids)

Body Weight (kg)	Body Weight (lb)	Daily Body Weight Gain (g)	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
10	22	0	0.72/0.61	200/170	17/17	0.9/1.0	0.5/0.6
		25	0.86/0.75	240/210	25/27	1.6/1.5	0.8/0.8
		100	1.27/1.16	350/320	46/58	3.5/3.5	1.6/1.5
		150	1.55/1.44	430/400	61/78	4.8/4.8	2.2/2.1
		200	1.82/1.71	510/470	75/98	6.2/6.1	2.7/2.7
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
20	44	0	1.21/1.02	340/280	29/29	1.4/1.3	1.0/0.9
		25	1.35/1.16	370/320	36/39	2.2/2.0	1.4/1.2
		100	1.76/1.57	490/440	58/69	4.0/3.9	2.0/1.9
		150	2.04/1.85	570/510	73/90	5.1/5.2	2.4/2.6
		200	2.31/2.13	640/590	87/110	6.4/6.3	3.0/2.9
		250	2.59/2.4	720/670	102/130	7.7/7.6	3.5/3.4
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
30	66	0	1.64/1.38	460/380	39/39	1.8/1.6	1.4/1.2
		25	1.78/1.52	490/420	47/49	2.5/2.3	1.7/1.5
		100	2.19/1.94	610/540	68/80	4.2/4.5	2.3/2.5
		150	2.47/2.21	680/610	83/100	5.6/5.4	2.9/2.8
		200	2.74/2.49	760/690	97/120	7.0/6.8	3.5/3.4
		250	3.02/2.76	840/770	112/140	7.9/8.2	3.7/4.0
		300	3.30/3.04	910/840	126/161	9.3/9.1	4.3/4.2
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
40	88	0	2.04/1.72	560/480	49/49	2.1/1.8	1.7/1.4
		25	2.17/1.86	600/510	56/59	2.8/2.6	2.0/1.8
		100	2.59/2.27	720/630	78/89	5.0/4.7	3.0/2.8
		150	2.86/2.55	790/710	92/109	5.8/6.2	3.1/3.5
		200	3.14/2.82	870/780	107/130	7.2/7.0	3.7/3.6
		250	3.42/3.10	950/860	121/150	8.6/8.4	4.4/4.2
		300	3.69/3.37	1020/940	136/170	10.0/9.8	5.0/4.8

Modified from National Research Council (NRC). 2007. Nutrient requirements of small ruminants. National Academies Press, Washington, DC.

BOX 9-5

Causes of Weight Loss in Horses

Common Causes

Protein-calorie malnutrition (PCM)
Dental disease
Jaw abnormalities
Gastric ulcers
Right dorsal colitis
Parasitism (small strongyles, large strongyles, tapeworms, bots)
Sand enteropathy
Pneumonia (bacterial, viral)
Pleuritis, pleuropneumonia, pulmonary abscessation
Recurrent airway obstruction
Internal abdominal abscess
Peritonitis
Streptococcus equi (lymph node abscessation, pulmonary or mesenteric abscessation)
Acute renal failure
Chronic renal failure
Pituitary pars intermedia dysfunction
Neoplasia (alimentary tract)

Less Common Causes

Equine herpes myeloencephalopathy
Equine motor neuron disease
Oral foreign body
Guttural pouch infection
Otitis media, interna
Paranasal sinus infection
Esophageal abnormalities (esophagitis, diverticula)
Vesicular stomatitis
Gastric impaction
Gastric squamous cell carcinoma
Duodenal ulcers
Inflammatory bowel disease (basophilic enterocolitis, eosinophilic enterocolitis, granulomatous enteritis, lymphocytic-plasmacytic enteritis, multisystemic eosinophilic epitheliotropic enterocolitis)
Chronic colonic impaction
Idiopathic diarrhea
Giardiasis
Fungal pneumonia
Pneumoconiosis (silicosis)
Tuberculosis
Cholelithiasis
Chronic hepatitis
Toxic hepatopathy
Atrial fibrillation
Cardiac or great vessel anomalies
Congestive heart failure
Endocarditis, pericarditis
Splenic rupture, abscess
Amyloidosis
Glomerulonephritis

Continued

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BOX 9-5

Causes of Weight Loss in Horses—cont'd

Less Common Causes—cont'd

Pyelonephritis
Renal neoplasia
Renal tubular acidosis
Urinary bladder neoplasia
Urolithiasis
Infectious arthritis
Osteomyelitis
Granulosa cell tumor
Lymphoma, lymphosarcoma
Malignant melanoma
Autoimmune anemia or thrombocytopenia
Purpura hemorrhagica
Coccidioidomycosis
Cryptococcosis
Nocardiosis
Agammaglobulinemia
Equine adenovirus
Equine infectious anemia
Equine viral arteritis
Anhidrosis

Uncommon Causes

Botulism
Micronema deletrix, infection of the central nervous system
Nigropallidal encephalomalacia
Nutritional rhabdomyolysis
Rabies
Rectus capitus ventralis muscle rupture
Spinal abscessation
Prognathia, brachygnathia
Pyloric stenosis
Basophilic enterocolitis
Colonic fistula
Ileal hypertrophy
Strongylus vulgaris, thromboembolism
Micropolyspora faeni, hypersensitivity pneumonitis
Pleural mesothelioma
Rhodococcus equi, infection
Tuberculosis
Mammary carcinoma
Malignant mesothelioma
Ovarian adenoma
Pancreatic neoplasia
Pulmonary neoplasia
Skeletal or vertebral neoplasia
Testicular neoplasia
Portal vein shunt
Liver fluke
Theiler's disease-associated virus (TDAV)
Enzootic cystitis
Polycystic disease
Diabetes mellitus
Hyperparathyroidism
Pheochromocytoma
Steatitis
Brucellosis
Multiple cartilaginous exostoses
Bullous pemphigoid
Eosinophilic dermatitis
Fungal granuloma
Horsefly-deerfly infestation
Lupus erythematosus
Panniculitis
Pemphigus foliaceous
Seborrhea
Wound myiasis
Babesiosis
Erythrocytosis
Histoplasmosis
Myeloproliferative disease
Phycomycosis
Tularemia
Goiter
Phosphorus deficiency
Thiamine deficiency
Vitamin A deficiency

Toxins

4-Aminopyridine
Aflatoxicosis
Arsenic toxicity
Dioxin
Fluorosis
Mercury toxicity
Pentachlorophenol
Phenylbutazone, flunixin meglumine, and other nonsteroidal antiinflammatory drugs
Selenium toxicity
Vitamin D calcinosis
Vitamin K_3 toxicity
Zinc toxicity

Plant Toxins

Crofton weed *(Ageratina adenophora)*
Plant calcinosis (*Cestrum diurnum, Trisetum flavescens,* others)
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., others)
Red maple leaf *(Acer rubrum)*
Jimsonweed (*Datura* spp.)
White snakeroot *(Eupatorium rugosum)*
Yellow star thistle *(Centaurea solstitialis),* Russian knapweed *(Centaurea repens)*

Exotic Diseases

Besnoitiosis *(Besnoitia bennetti)*
Burkholderia pseudomallei
Dourine *(Trypanosoma equiperdum)*
Equine dysautonomia (grass sickness)
Glanders *(Burkholderia mallei)*
Mal de caderas *(Trypanosoma equinum)*
Nagana (*Trypanosoma* spp.)
Stachybotryotoxicosis
Surra *(Trypanosoma evansi)*
Trombiculiasis
Trypanosoma hippicum

for maximum DMI in horses related to forage quality are not available. Horses do not have a pregastric fermentation organ (rumen) and can ingest slightly more of the same quality forage than cattle. Low-quality forages are often the cause of PCM, even when an unlimited quantity is available. The best way to determine the nutrient content of forage, grain, and pelleted feeds is to have the feed analyzed by a forage laboratory. Feed analysis instructions are provided in Box 9-3. Feed tag labels or forage databases can be referenced if an analysis is not performed.

Environmental factors can have a major influence on nutrient requirements and can increase the subsequent risk for PCM and weight loss. The most important environmental factor is the ambient temperature. Nutrient requirements for maintenance change with a decreasing ambient temperature as follows:

- *Adult horses:* Estimated increase in digestible energy (DE) requirements by 2.5% for every degree Celsius below the lower critical temperature (LCT). The LCT for adult horses ranges from 5° C to −15° C, depending on the horse's adaptation to the environment.

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BOX 9-6

Causes of Weight Loss in Ruminants

Common Causes

Protein-calorie malnutrition (PCM)
Dental abnormalities
Pharyngeal, retropharyngeal abscess
Actinobacillosis
Actinomycosis
Diarrhea (Enterotoxigenic *Escherichia coli, Salmonella,* bovine virus diarrhea, coronavirus, rotavirus infection, *Cryptosporidium parvum,* coccidiosis, winter dysentery [B], other causes)
Johne's disease (paratuberculosis)
Parasitism (lungworms, gastrointestinal parasites)
Abomasal ulcer
Displaced abomasum
Ruminal lactic acidosis
Vagal indigestion
Intussusception
Bacterial pneumonia, pulmonary abscessation
Infectious bovine rhinotracheitis
Traumatic reticuloperitonitis, pericarditis
Hepatic abscess
Liver fluke infestation
Ketosis
Fat necrosis (B)
Pregnancy toxemia
Leptospirosis
Pyelonephritis, cystitis
Urolithiasis
Mammary abscess
Mastitis, coliform or staphylococcal
Anaplasmosis (B)
Bovine leukosis
Septic arthritis
Foot rot
Pedal osteomyelitis
Sole abscess
Lice or ked infestation
Sarcoptic mange
Wound myiasis
Copper deficiency
Selenium deficiency
Bluetongue (O)

Less Common Causes

Coenurosis (gid)
Listeriosis
Rabies
Sarcocystis
Mandible, maxilla fracture
Loss of teeth, periodontal disease
Lingual injury, abscess
Otitis media, externa
Sinusitis
Esophageal malfunctions
Omasal impaction
Abomasal impaction
Colonic obstruction
Aspiration pneumonia
Micropolyspora faeni, hypersensitivity pneumonitis
Pleuritis
Tuberculosis
Brisket disease
Cardiac or great vessel anomalies
Endocarditis
Vena caval thrombosis
Thymic lymphosarcoma (B)
Malignant catarrhal fever
Ulcerative stomatitis
Vesicular stomatitis
Neoplasia
Acute renal failure
Glomerulonephritis
Hydronephrosis, urachal abscess, bladder abscess
Postparturient hemoglobinuria
Renal amyloidosis
Congenital porphyria
Eperythrozoonosis
Sarcocystosis (B)
Dermatophilosis
Papular stomatitis (B)
Psoroptic mange
Goiter
Cobalt deficiency
Sodium chloride deficiency
Thiamine deficiency
Water deprivation, salt toxicity

Uncommon Causes

Bovine spongiform encephalopathy
Sporadic bovine encephalomyelitis
Omental bursitis (B)
Bronchobiliary fistula (B)
Pulmonary listeriosis
Endocardial fibroelastosis (B)
Cholelithiasis
Portal vein anomaly
Neoplasia (other than bovine leukemia virus)
Diabetes mellitus
Ulcerative posthitis, vulvitis (B)
Local and systemic mycoses
Systemic candidiasis
Mycoplasma, arthritis
Epidermolysis bullosa (B, O)
Familial acantholysis
Fungal granuloma
Polycythemia (B)
Granulocytopathy
Idiopathic granulocytopenia or thrombocytopenia
GM1 gangliosidosis
Hypersensitivity to soy or milk replacer
α-Mannosidosis (B)
Bovine hereditary zinc deficiency (lethal trait A-46)
Generalized glycogenosis (B)
Phosphorus deficiency
Vitamin A deficiency
Zinc deficiency

Toxins

4-Aminopyridine
Aflatoxicosis
Arsenic
Chlorpyrifos
Cobalt
Crude oil
Diesel fuel
Ergotism
Ethylene glycol
Fluorosis
Furazolidone
Herbicides
Kerosine
Lead toxicity
Mercury toxicity
Polybrominated biphenyls
Selenium toxicity
Sodium chloride toxicity
Trichothecene (T-2)
Vitamin D_3 toxicity
Zinc toxicity
Stachybotryotoxicosis (exotic)

Continued

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BOX 9-6

Causes of Weight Loss in Ruminants—cont'd

Plant Toxins

Acorn, oak (*Quercus* spp.)
Bermuda grass (prussic acid)
Bracken fern (*Pteridium aquilinum*)
Cocklebur (*Xanthium* spp.)
Fescue (B)
Fireweed (*Kochia scoparia*)
Geigeria spp. (exotic)
Gossypol (cottonseed) (*Gossypium* spp.)
Grass staggers (*Phalaris* spp.)
Hairy vetch (*Vicia villosa*)
Leucaena leucocephala (exotic)
Locoweed (*Oxytropis, Astragalus*)
Mushroom (*Amanita* spp.)
Perennial broomweed (*Gutierrezia sarothrae*)
Pimelea spp. (exotic)
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., and others)
Sneezeweed (*Helenium hoopesii*)
Tung tree (*Aleurites fordii* Hemsl.)
White snakeroot (*Eupatorium rugosum*)
Yellow-wood (*Terminalia oblongata* spp. *oblongata*) (exotic)

Exotic Diseases

African bovine malignant catarrhal fever
Babesiosis (*Babesia bigemina, Babesia bovis*)
Besnoitiosis (*Besnoitia besnoiti*)
Bovine petechial fever (*Ehrlichia ondiri*) (B)
Burkholderia pseudomallei
Contagious bovine pleuropneumonia (*Mycoplasma mycoides mycoides*) (B)
East Coast fever (theileriosis)
Echinococcosis
Foot-and-mouth disease (*Aphtae epizooticae*)
Ibaraki disease (B)
Ovine encephalomyelitis (O)
Schistosomiasis
Surra (*Trypanosoma evansi*)
Trypanosomiasis (*Trypanosoma* spp.)

B, Bovine; *O,* ovine.

In cold temperatures, when the hair coat is wet, the maintenance DE requirement may be increased by as much as 50%.[10]

- *Beef cattle:* 1% increase in maintenance energy requirements (total digestible nutrients [TDN], net energy of maintenance [NE_m], digestible energy [DE], and metabolizable energy [ME]) for each 1° C drop below 20° C (68° F).
- *Dairy cattle (lactating):* 25% increase in energy requirements (TDN, net energy of lactation [NE_L]) as ambient temperature drops from 20° C (68° F) to −10° C (14° F).
- *Sheep with 10-cm wool:* 1% increase in energy requirements (TDN, ME, DE) for each 1° C drop below lower critical temperature (approximately −10° C).

There are also additive effects of wind and rain that increase energy requirements in large animal species. As nutrient requirements increase, the dietary intake must also increase to prevent weight loss associated with PCM. Horses in inclement weather may not be able to consume enough forage to meet their increased energy requirements, and for these animals, dietary fat and limited grain supplementation may be required.

Deficiencies of micronutrients (trace minerals, B vitamins) often result in inefficiencies in basic biochemical pathways. These inefficiencies, if marked, can be associated with weight loss. Genetic errors in metabolism can cause similar disturbances, but these usually manifest as decreased growth and even death in young animals.

Parasitism is a common cause of weight loss in adult domestic animals. The mechanisms by which parasite infestation can result in weight loss include a loss of body fluid and tissues resulting in increased nutrient requirements, competition for nutrients in the gastrointestinal tract, malassimilation and malabsorption, inflammation resulting in increased nutrient requirements, micronutrient deficiencies, and organ or vascular damage from migrating parasite larvae. Anorexia may also develop in the advanced stages of severe parasitism.

Approach to the Diagnosis and Management of Weight Loss in Adult Horses

Use the flow sheet in Fig. 9-7 to aid in decision making.

1. Take a general history and a diet history.
   a. General history
      i. Is the weight loss affecting one animal or many animals? If many horses are affected, what is the age range of the affected animals? How long has the caretaker noticed the weight loss? Has the diet been changed to manage the weight loss? What is the change in BCS of the horse(s)? How much weight has been lost? Is this an estimate of weight loss, or have the horse(s) been monitored on a scale or with a weight tape? Weight loss is often suspected but not documented in the initial complaint or history. Acute weight loss of 5% to 10% is significant. If a weight tape will not fit around the girth of the horse or if the horse has a BCS of 1 to 3, a rough estimate of body weight can be made using measurements of the length and girth of the horse.[11-12] Length is measured from the tuber ischium to the point of the shoulder, and girth is measured at the withers, behind the elbows, at the end of expiration.

$$\text{Body weight (kg)} = \frac{\text{Chest girth (cm)}^2 \times \text{Length (cm)}}{11{,}877}$$

The weight of miniature horses should be obtained using a small animal clinic scale. If a scale is not available to weigh a miniature horse, then the following equation can be used to estimate the weight of the miniature horse.[13]

$$\text{Body weight (kg)} = \frac{(3.7 \times \text{Chest girth in cm}) + (2 \times \text{Length in cm}) - 348.5}{2.2}$$

      ii. Is there any past or current clinical disease in the horse or herd? If so, when was the disease first diagnosed? How many animals were affected? What type of treatment was administered? Was the diet changed during this period of time? Question the caretaker closely about any clinical signs of diarrhea, coughing, dysphagia, or polyuria. What is the deworming history of the horse and herd? Has the deworming protocol been changed lately?
   b. Diet history
      i. Type of feed. Obtain an *accurate* dietary history including the type and amount of feed offered (in pounds, ounces) and the amount of feed refused by the horse(s). It is essential that feeds are weighed accurately. What type and volume of forage is available? Inspect the pasture and all feeds for gross quality, evidence of spoilage, abnormal color or odor, presence of weeds and mold, and quantity of feed the owner has at the facility. Has an analysis been performed on the forage (pasture grass and/or hay)? If yes, obtain a copy of the analysis for the patient record. How much time does the horse have to graze in a pasture? What

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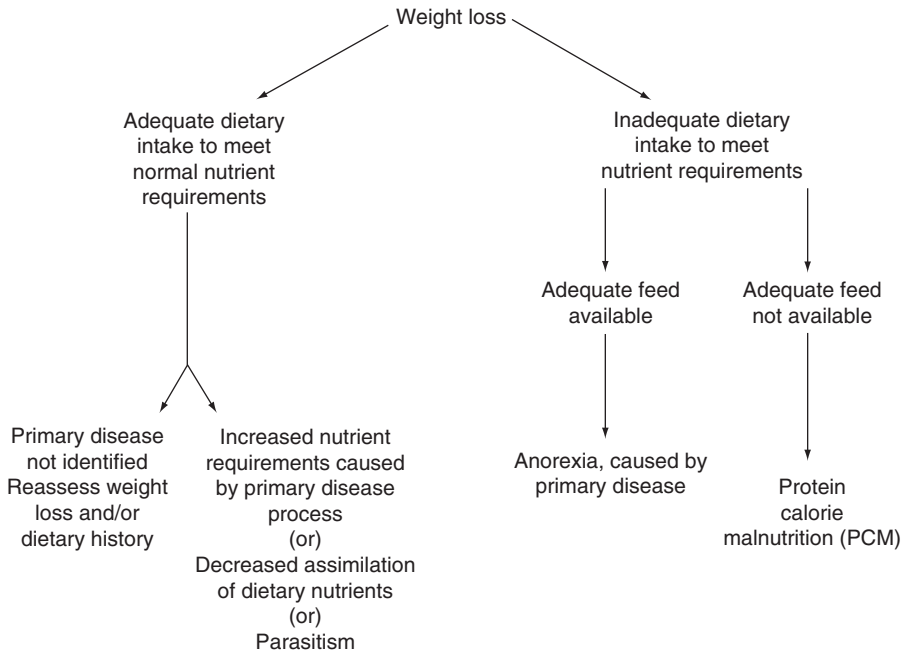


FIG. 9-7 Flow sheet for classifying conditions associated with weight loss.

type of grass is available in the pasture? Is the pasture overgrazed? Are there any plant toxins in the pasture or environment? Have there been any changes in the type of forage offered to the horse(s)? Hay quality is often not consistent between shipments. If grain or other supplemental feeds are used, what volume is fed and consumed by the horse(s)? Are any diet supplements fed to the horse? If so, what amount is fed? Does the horse have access to a salt or trace mineral block? How long has this diet been fed? Nutrient requirements of adult ponies and horses are listed in Table 9-12 and can also be calculated using the Nutrient Requirements of Horses free companion computer program (www.nap.edu, search word "horse").

ii. Feeding management. How often are the horses fed? What type of feeder is used? Are mats placed under the feeders to reduce sand and dirt ingestion? Is there competition among the horses for food? Are there any toxic substances in the horse's environment? What is the water source for the horses? How many water sources are available? Is the water clean?

2. Perform a physical examination.
   a. Observe the horse while it is eating. Can the horse prehend, masticate, and swallow food normally? Is the horse dysphagic? Does the horse have a good appetite? Is the horse hungry? Are there any signs of neurologic disease?
   b. Examine the patient closely to identify signs of concurrent disease (e.g., pyrexia, diarrhea, melena, dysphagia, abnormal dentition, icterus, nasal discharge, cough, dyspnea, tachycardia, cardiac murmur, dysuria).
   c. What is the horse's body weight (scale or weight tape) and BCS (see Table 9-22)?
3. Examine the feces. What is the consistency of the feces? If the horse has evidence of diarrhea, review the section on diarrhea in Chapter 7. How long are the fibers in the feces? Perform a glove test. Is there evidence of sand in the feces? Horses can have a significant volume of sand in the large intestine while having negative fecal sand test results. Perform a fecal egg count. An enzyme-linked immunosorbent assay (ELISA) may be useful in diagnosing a tapeworm infection. Follow the parasite control program in Chapter 49 if the horse has evidence of fecal parasites or if a parasite infection is suspected despite a negative fecal egg count. Perform a fecal occult blood test; if the result is positive, see the section on melena in Chapter 7.
4. Perform blood analyses.
   a. Perform a CBC, including plasma protein and fibrinogen. Examine the results closely for indication of an inflammatory process (e.g., leukocytosis, neutrophilia, leukopenia, neutropenia, hyperfibrinogenemia, decreased plasma protein/fibrinogen ratio [below 10]). Calculate the erythrocytic indices, and characterize anemia, if present.
   b. Perform a serum biochemical analysis. The serum albumin half-life is approximately 19 days in horses. Hypoalbuminemia may be associated with colitis, internal abscessation, PCM, liver disease, renal disease, and granulomatous bowel disease, among other conditions. Albumin is often within normal limits in PCM until the patient is near death. Globulin (particularly γ-globulins) may be increased with inflammation, and the albumin/globulin ratio may be decreased. The glucose concentration is usually normal or elevated as a result of stress and may also be elevated in horses with pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome. Hyperlipidemia (serum triglyceride between 100 and 500 mg/dL) is commonly associated with early anorexia and can be present in horses with PPID. Hyperlipemia (serum triglyceride above 500 mg/dL) is a serious condition associated with prolonged anorexia and hepatic lipidosis and is often found in miniature horses, ponies, and donkeys under severe physiologic stress (PCM and lactation). Unconjugated bilirubin levels can rise to 6 or 7 mg/dL with anorexia or decreased food intake. An elevated γ-glutamyltransferase (GGT) (above 25 IU/L) may indicate hepatic disease. Horses with PCM may have a low serum urea nitrogen if the protein malnutrition is prolonged and severe.
5. Analyze the diet and improve the feeding program.
   a. Determine if the energy, protein, mineral, and vitamin content of the diet meets the nutrient requirements of the horse at their current metabolic state and activity level (see Table 9-12). Include pertinent environmental and management factors in the nutrient requirement calculations. The quality of the feeds should be assessed.
      i. Forage. Determine the nutrient content of forage or pasture with an analysis (see Boxes 9-3 and 9-4). A university extension service often can assist with a forage

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TABLE 9-12

Daily Nutrient Requirements of Ponies and Horses of Mature Body Weight

Category	Digestible Energy (Mcal)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
Mature Ponies, 200 kg (440 lb) of Mature Body Weight				
Maintenance, average activity	6.7	252	8	5.6
Mares, last 90 days of gestation	7.7-8.6	319-357	14.4	10.5
Lactation, first 3 mo	12.7-12.2	614-587	23.6-22.4	15.3-14.4
Mature Horses, 400 kg (880 lb) of Mature Body Weight				
Maintenance, average activity	13.3	504	16	11.2
Mares, last 90 days of gestation	15.4-17.1	637-714	28.8	21
Lactation, first 3 mo	25.4-24.5	1228-1174	47.3-44.7	30.6-28.8
Mature Horses, 500 kg (1100 lb) of Mature Body Weight				
Maintenance, average activity	16.7	630	20	14
Mares, last 90 days of gestation	19.2-21.4	797-893	36	26.3
Lactation, first 3 mo	31.7-30.6	1535-1468	59.1-55.9	38.3-36
Mature Horses, 600 kg (1320 lb) of Mature Body Weight				
Maintenance, average activity	20	756	24	16.8
Mares, last 90 days of gestation	23.1-25.7	956-1072	43.2	31.5
Lactation, first 3 m	38.1-36.7	1842-1761	70.9-67.1	45.9-43.2
Mature Horses, 900 kg (1980 lb) of Mature Body Weight				
Maintenance, average activity	30	1134	36	25.2
Mares, last 90 days of gestation	34.6-38.5	1434-1607	64.8	47.3
Lactation, first 3 mo	54.4-52.4	2763-2642	106.4-100.6	68.9-64.9

Modified from National Research Council (NRC). 2007. Nutrient requirements of horses. National Academies Press, Washington, DC.

analysis. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu) or nutrient tables from the Equi-Analytical Laboratories forage laboratory database (www.equi-analytical.com) can be used to estimate the concentration of different nutrients in common forages and supplemental feeds.

ii. Grain, commercial feeds, and other supplemental feeds. Review the feed tag label to determine the nutrient concentration of protein and other essential nutrients. Contact commercial feed companies for the energy content of their products. Use nutrient databases to estimate the nutrient content of other feeds.

iii. Vitamins, minerals, and other dietary supplements. Review all products used on the horse(s). Ensure adequacy of all essential nutrients. Are there any nutrient toxicities? Are all products necessary? If botanical ingredients are fed, are there any nutrient-drug interactions or contraindications in feeding the botanicals?

b. If the horse has a dietary deficiency, the problem should be corrected by a change in the diet or through appropriate supplementation. Contact an equine clinical nutritionist for guidance on ration formulation.

c. If the dietary history indicates that adequate nutrients for maintenance, or the appropriate life stage, or performance have been steadily consumed, continue to search for another cause of the weight loss.

6. Perform ancillary diagnostic tests. If the weight loss is not caused by inadequate or poor-quality feed, additional diagnostic tests should be performed. Possible tests include but are not limited to ultrasound, gastric endoscopy, radiographs, serum or whole blood trace mineral analysis, serum insulin concentration, carbohydrate absorption tests (oral D-glucose, D-xylose [see Chapter 32]), and appropriate organ biopsy.

Approach to the Diagnosis and Management of Weight Loss in Adult Ruminants

1. Take a general history and a diet history.
   a. General history: Question the caretaker closely about any clinical signs that might indicate a primary disease (e.g., diarrhea, coughing, dysphagia, polyuria, depression, agalactia). Note if body condition is less than desired. Quantitate the weight loss or BCS if possible. Acute weight loss of 5% to 10% is quite significant. Carefully note the production level of the animal or herd (e.g., pregnancy [single, twins, triplets], lactation [level of milk production]). Evaluate the parasite control program. Does the herd have a history of chronic or recurrent disease (Johne's disease, bovine virus diarrhea, ruminal lactic acidosis, laminitis, mastitis, pneumonia)?
   b. Diet history: Obtain an *accurate* dietary history, particularly when signs of a primary disease are absent. Inspect all forages, concentrates, and feed additives for quality, signs of spoilage, abnormal color or odor, and quantity on hand. Be sure the feeding system allows for adequate consumption by all animals and that competition for feedstuffs does not occur. Check to see if the feeding program was changed before the onset of observed weight loss or loss of body condition. The history should include the *weight* of each feedstuff and supplement fed and consumed per day. The maximum DMI can be estimated according to feed quality for cattle (see Table 9-1). Determine or estimate the nutrient analysis of the feedstuffs being fed. Examine the environment for possible toxic plants or substances.
2. Perform a physical examination. Examine patients carefully for signs of concurrent disease (e.g., diarrhea, decreased ruminal motility, pyrexia, dysphagia, abnormal dentition, melena, icterus, mastitis, metritis, dyspnea, tachycardia). Is the patient hungry? Weigh the patient (or use a heart-girth measurement) and note the BCS (see Tables 9-19 through 9-21). Observe the patient for signs of muscle wasting and the presence or absence of

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subcutaneous fat. Test the milk with nitroprusside powder (a positive reaction indicates an acetoacetate concentrate above 5 mg/dL and is diagnostic of ketonlactia and ketonemia), or measure the ketone concentration in the urine. Measure the ruminal pH (pH above 7 is indicative of anorexia). Examine the skin for evidence of lice or keds.

3. Examine the feces. Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestations. If the feces test positive for occult blood or are very dark, see the section on melena in Chapter 7. If there is evidence of or apparent diarrhea, see the section on diarrhea in Chapter 7.
4. Perform blood analysis.
   a. Perform a CBC, including plasma protein and fibrinogen. Interpret for evidence of inflammation. Calculate the erythrocytic indices, and characterize the anemia if present. Analyze for blood selenium concentration or glutathione peroxidase activity if a herd problem of weight loss exists in a selenium-deficient region.
   b. Perform a serum chemistry analysis. The serum albumin half-life is approximately 16½ days in cattle and 14 days in sheep and goats. Hypoalbuminemia is associated with internal abscessation, PCM, liver disease, renal disease, and Johne's disease, among other conditions. In the first two of these conditions, albumin is often normal until the patient is near death, whereas with protein-losing renal or gastrointestinal disease or with failure to make albumin in severe hepatic disease, hypoalbuminemia is often seen by the time noticeable weight loss occurs. Globulins, particularly γ-globulins, may be increased with inflammation, and the albumin/globulin ratio may be decreased. The serum glucose concentration is usually not helpful in determining the cause or causes of weight loss. An elevated serum GGT (above 25 IU/L) may indicate hepatic disease or, in rare cases, pancreatic disease. Serum BUN is often low with PCM in ruminants because of salivary urea recycling. Serum (total) calcium may be decreased with hypoalbuminemia, anorexia, or hypocalcemic syndromes. Serum phosphorus may be increased during severe starvation or Johne's disease or decreased with anorexia. The serum (plasma) copper concentration may be decreased if a herd problem of copper deficiency exists. Weight loss is particularly associated with copper deficiency when diarrhea is present in a region known to be copper deficient or in a region with excess dietary molybdenum or sulfates or both. A low serum copper concentration (below 0.5 μg/mL or ppm) indicates deficiency. Ketonlactia (above 5 mg/dL), indicated by a positive reaction (blue or purple) of milk with nitroprusside, may be associated with anorexia in ketosis or other conditions. Plasma β-hydroxybutyrate (BHB) concentrations have been reported to be a useful tool in diagnosing *inadequate caloric intake* in pregnant sheep.[14] Plasma BHB concentrations should be less than 0.8 mmol/L in pregnant ewes consuming adequate energy.[14]
5. Analyze the diet and improve the feeding program. Is the feed quantity and quality adequate to allow sufficient intake of nutrients (see Table 9-1)? Compare the nutrient intake from the diet with the requirements for the appropriate species (Tables 9-13 through 9-18). Consider any important environmental and management factors in the daily nutrient requirements. Review nutrient analysis profiles on the feeds and total mixed ration (TMR) ingredients. Is the TMR mixed properly? Are grain rations mixed properly? Is too much grain being fed to the animal or herd? Analyze the pasture, forage, or concentrate rations (see Box 9-3). Make appropriate recommendations to optimize the ration. Determine if the patient or patients have a normal appetite. Is anorexia present? If the dietary history and analysis indicate that adequate nutrients have been steadily consumed, the search for a primary cause for the weight loss should be resumed.
6. Perform ancillary diagnostic tests.
   a. If the weight loss is not related to the diet, additional diagnostic tests should be performed on the animal or on a number of animals in the herd. Possible tests include but are not limited to trace mineral analyses, ultrasound, and appropriate organ biopsy.
   b. Pathologic findings of affected ruminants often provide evidence of the effects of a systemic disease or of chronic malnutrition. Ruminants with PCM exhibit serous atrophy of fat in the coronary grooves of the heart and bone marrow at necropsy. Subcutaneous, abdominal, and perirenal fat are not present.

Obesity

Mechanisms of Obesity

Obesity is a common problem in domestic large animal species, especially in horses, and in ruminants raised as companion animals. In ruminants, obesity increases the risk of metabolic disease, reproductive failure, and health complications during late pregnancy and lactation. The risk of obstructive urolithiasis increases in overweight goats and sheep. In horses, obesity is related to a variety of diseases

TABLE 9-13

Daily Nutrient Requirements for Dairy Cattle

Body Weight (kg)	Body Weight (lb)	NE_L (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
Maintenance of Mature Lactating Cows						
400	880	7.16	3.15	373	15	13
500	1100	8.46	3.72	432	18	15
600	1320	9.7	4.27	489	21	17
650	1430	10.3	4.53	515	22	18
700	1540	10.89	4.79	542	24	19
Maintenance Plus Last 2 Mo of Gestation of Mature Dry Cows						
400	880	9.3	4.1	702	26	18
500	1100	11	4.84	821	31	22
600	1320	12.61	5.55	931	37	26
650	1430	13.39	5.9	984	39	28
700	1540	14.15	6.23	1035	42	30

Modified from National Research Council (NRC). 2001. Nutrient requirements of dairy cattle. National Academy of Sciences, NRC, Washington, DC.

NE_L, Net energy of lactation. Maintenance requirements can also be calculated by the following formula: Maintenance $NE_L = 0.080$ Mcal/kg $BW^{0.75}$.

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TABLE 9-14

Daily Nutrient Requirements for Lactating Dairy Cows at Various Production Levels

Daily Milk Production (3.5% Butterfat) (kg)	(lb)	NE_L (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
400 kg of Body Weight						
20	44	21	9.23	2	67	48
30	66	28	12.27	2.83	96	66
40	88	34.80	15.31	3.65	116	83
500 kg of Body Weight						
20	44	22.26	9.80	2.07	70	50
30	66	29	12.84	2.9	96	68
40	88	36	15.88	3.71	119	85
600 kg of Body Weight						
20	44	23.5	10.35	2.2	73	52
30	66	30.4	13.39	2.95	99	70
40	88	37.3	16.43	3.77	125	87
700 kg of Body Weight						
20	44	24.69	10.87	2.2	59	54
30	66	31.59	13.91	3	77	72
40	88	38.49	16.95	3.82	94	89

Modified from National Research Council (NRC). 2001. Nutrient requirements of dairy cattle. National Academy of Sciences, NRC, Washington, DC.

NE_L, Net energy of lactation. The energy requirement for milk production when only the butterfat content of the milk is known by the following formula: NE_L (Mcal/kg milk) + 0.360 + (0.0969 [fat%]).

TABLE 9-15

Daily Nutrient Requirements for Mature Beef Cows

Reproductive Status	Daily Gain (kg)	Digestible Energy (Mcal/day)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
Mature 500-kg (1100-lb) Beef Cow					
Nonpregnant, maintenance	0	18.9	0.63	17	17
Pregnant, third trimester	0.4*	22.4	0.73	25	20
Lactating, 20 lb milk per day	0	29	1.18	38	27
Mature 600-kg (1320-lb) Beef Cow					
Nonpregnant, maintenance	0	21.6	0.69	20	20
Pregnant, third trimester	0.4*	25.1	0.83	28	23
Lactating, 20 lb milk per day	0	33	1.35	43	31

Modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy Press, Washington, DC.

*This gain represents only the growth of the fetus.

TABLE 9-16

Daily Nutrient Requirements for Bulls: Maintenance and Regaining Body Condition

Weight (kg)	Daily Gain (kg)	(lb)	Digestible Energy (Mcal/day)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
650	0.6	1.3	32.6	0.96	27	24
700	0.6	1.3	34.3	1	29	26
800	0*	0	27.7	0.88	27	27
800	0.2	0.4	31.2	0.96	27	27

Modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy Press, Washington, DC.

*Maintenance only, no gain.

including insulin resistance, equine metabolic syndrome, laminitis, and colic associated with strangulating lipomas. Obese horses and ponies that have increased metabolic energy demands (late pregnancy, lactation) that are rapidly losing weight or that are anorexic are particularly susceptible to hyperlipidemia and hyperlipemia.

Obesity results from the consumption of more calories than are required by an animal based on their lifestage and level of activity. Individual animals and certain breeds appear to be predisposed to obesity even if they are fed to meet their maintenance energy requirements. Obesity frequently occurs in horses fed high-energy feeds

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TABLE 9-17

Daily Nutrient Requirements of Sheep

Body Weight (kg)	Body Weight (lb)	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
Maintenance, Mature Ewes						
60	132	2.01	560	53	2.2	1.8
80	176	2.49	690	66	2.6	2.2
100	220	2.94	820	78	3.0	2.7
120	264	3.37	940	90	3.3	3.1
Breeding, Mature Ewes						
60	132	2.21	610	62	2.6	2.1
80	176	2.74	760	77	3.1	2.7
100	220	3.24	900	92	3.6	3.2
120	264	3.71	1030	106	4.0	3.7
Early Gestation, Mature Ewes, Twin Lambs; BW = 3.4-6.6 kg						
60	132	2.89	800	87	5.9	4.2
80	176	3.52	980	105	7.0	5.1
100	220	4.10	1140	123	7.9	5.9
120	264	4.66	1290	139	8.7	6.6
Late Gestation, Mature Ewes, Twin Lambs; BW = 3.4-6.6 kg						
60	132	3.94	1090	116	8.1	4.8
80	176	4.75	1320	139	9.4	5.8
100	220	5.48	1520	173	11.3	7.7
120	264	6.19	1720	196	12.5	8.6
Early Lactation, Mature Ewes, Twin Lambs; Milk Yield = 1.18-2.21 kg/day						
60	132	4.31	1200	189	7.3	6.3
80	176	5.15	1430	222	8.5	7.4
100	220	5.92	1640	253	9.5	8.5
120	264	6.63	1840	296	11.3	10.7
Early Lactation, Mature Ewes, Parlor Production; Milk Yield = 2.37-3.97 kg/day						
60	132	6.14	1700	291	11.4	9.4
80	176	7.26	2010	351	13.8	12.0
100	220	8.27	2290	396	15.5	13.5
120	264	9.22	2560	438	17.0	14.9
Maintenance, Rams						
100	220	3.38	940	86	3.3	3.1
125	275	4.00	1110	102	3.8	3.7
150	330	4.58	1270	118	4.3	4.3
200	440	5.69	1580	148	5.2	5.3

Modified from National Research Council (NRC). 2007. Nutrient requirements of small ruminants. National Academies Press, Washington, DC.

including grain and energy-dense commercial feeds and in horses grazing highly digestible pasture. Even horses that are only fed hay may gain weight if they consume an excess amount of energy. Purebred or pet sheep and goats (particularly wethers) tend to be overfed. In dairy cattle, obesity occurs when cattle are fed well above requirements for maintenance and milk production. Poor reproductive performance is often associated with the initiation of obesity in ruminants and is also a common sequela to obesity. Feeding for high milk production for lengthy periods in production groups predisposes infertile cows to become fat cows. Dry cows with access to high-energy diets are also predisposed to fat cow syndrome. The systemic complications associated with fat cow syndrome (fatty liver), as well as its diagnosis and treatment, are described in Chapter 33.

Diagnosis of Obesity in Horses and Ruminants

Obesity is diagnosed by measuring the animal's body weight and assigning a subjective BCS number on the basis of muscle mass and external fat deposits. The clinical description of obesity provided by the BCS system is straightforward (Tables 9-19 to 9-22). Overweight and obese animals have an elevated BCS (7 to 9/9 for horses; 8 to 9/9 for beef cattle; 4 to 5/5 for dairy cattle, sheep, and goats). Palpation of the back, gluteal area, and ribs should be included in the physical examination of sheep and camelids with long wool or fiber and of horses with a long winter hair coat so that a BCS can be determined. In some animals, external signs of fat deposition may be subtle. In horses, a BCS greater than 5-6/9 does not accurately predict the total body fat mass of the animal in a linear fashion as may be expected using the linear BCS system.[15] Instead, body fat shows an exponential increase in horses with moderate to obese BCS.[15] Other measurements of body fat deposition including abdominal girth and fat depth (subcutaneous and retroperitoneal) measured by ultrasound may provide a better assessment of obesity in horses when the BCS is greater than 5.[15-16] Assessment of the back fat in cattle can also be evaluated with an ultrasound examination.

In some animals, obesity can be mistaken for the normal physiologic condition of pregnancy. In other cases, obesity could be mistaken for a distended abdomen from acute pathologic disease conditions including uroabdomen and peritonitis. A CBC and serum

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TABLE 9-18

Daily Nutrient Requirements of Milk and Meat Goats

Body Weight (kg)	Body Weight (lb)	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
Maintenance, Mature Does (Dairy/Nondairy)						
20	44	1.13/0.96	310/260	27/24	**1.3/1.2**	0.9/0.8
40	88	1.91/1.61	530/450	45/41	**1.9/1.7**	1.5/1.3
60	132	2.58/2.18	720/600	61/55	**2.4/2.1**	2.0/1.7
80	176	3.2/2.7	890/750	75/68	**2.8/2.5**	2.4/2.0
Late Gestation, Mature Does (Dairy/Nondairy), Twin Kids; BW = 2.6/2.11-4.8 kg						
20	44	1.96/1.78	540/490	70/69	**5.0/4.9**	2.4/2.3
40	88	3.07/2.77	850/770	111/107	**5.8/5.6**	3.2/3.0
60	132	4.05/3.64	1120/1010	143/139	**6.4/6.1**	3.7/3.5
80	176	4.93/4.43	1370/1230	172/179	**6.9/7.2**	4.3/4.6
Early Lactation, Mature Does (Dairy), Twin Kids; Milk Yield = 2.06-3.22 kg/day						
40	88	3.77	1050	178	**9.5**	5.9
60	132	4.98	1380	230	**10.3**	6.7
80	176	6.09	1690	275	**11.1**	7.5
Early Lactation, Mature Does (Dairy), Parlor Production; Milk Yield = 5.82-8.04 kg/day						
50	110	7.62	2110	398	**19.7**	11.4
70	154	9.54	2640	487	**20.7**	12.3
90	198	11.27	3130	566	**21.5**	13.1
Early Lactation, Mature Does (Nondairy), Twin Kids; Milk Yield = 0.91-2.08 kg/day						
20	44	1.59	444	73	**7.6**	4.1
40	88	2.53	700	118	**8.6**	5.0
60	132	3.34	930	152	**9.2**	5.6
80	176	4.04	1120	181	**9.7**	6.1
Maintenance, Mature Bucks (Dairy/Nondairy)						
50	110	2.59/2.18	720/610	58/52	**2.4/2.1**	2.0/1.7
75	165	3.51/2.96	970/820	78/70	**3.0/2.7**	2.6/2.2
100	220	4.36/3.67	1210/1020	97/87	**3.7/3.2**	3.2/2.7
125	275	5.15/4.34	1430/1200	114/103	**4.2/3.7**	3.8/3.2
150	330	5.91/4.98	1640/1380	131/118	**4.8/4.1**	4.3/3.7
Prebreeding, Mature Bucks (Dairy/Nondairy)						
50	110	2.85/2.40	790/670	63/57	**2.6/2.2**	2.1/1.8
75	165	3.86/3.26	1070/900	86/77	**3.3/2.9**	2.9/2.4
100	220	4.79/4.04	1330/1120	106/96	**4.0/3.4**	3.5/3.0
125	275	5.67/4.78	1570/1320	126/113	**4.6/4.0**	4.1/3.5
150	330	6.50/5.48	1800/1520	144/130	**5.2/4.5**	4.7/4.0

Modified from National Research Council (NRC). 2007. Nutrient requirements of small ruminants. National Academies Press, Washington, DC.

biochemical analysis can identify many subclinical diseases in an obese animal. A full physical examination should always be performed on a large animal patient before a weight loss ration is fed.

Treatment of Obesity

Overweight and obese horses and ruminants should lose weight to improve their health, extend life span, and to improve production efficiency. In many cases a reduction in energy intake can be achieved by simply eliminating excess calories in the ration. Animals that fail to lose weight after 1 to 2 months after removing high-calorie feeds often require a more aggressive weight loss program with a therapeutic ration and a gradual implementation of an exercise program. Voluntary activity in animals that are turned out in pasture is rarely high enough to promote weight loss. Obese laminitic horses present a difficult challenge because exercise may not be practical, and weight loss must rely solely on dietary energy restriction.

Horses and companion ruminants that require a managed weight loss program should have the energy content of their diet evaluated by the veterinarian. The actual energy intake should be compared against the energy requirement for the animal's current lifestage (see Tables 9-12 to 9-18). The animal's current calorie intake should be reduced by 10% to 20% at the start of the weight loss program. Dietary protein should not be restricted. Supplemental feeds and treats should be reduced or eliminated from the diet. A forage analysis can be used to select feeds that are low in nonstructural carbohydrates.

Feeding straw to horses increases the risk of impaction colic and other gastrointestinal complications and should be avoided. A vitamin and mineral supplement should be fed with a weight loss ration to ensure all nutrient requirements are met. To prevent boredom and improve the regulation of glucose, small amounts of forage should be fed in multiple small meals throughout the day. Horses can be fed hay in a hay bag, in doubled hay nets, in a NibbleNet, or with a mechanical feeder (Stable Grazer, The Grazer Hay Feeding Machine) as long as the horse can safely tolerate this equipment in its stall. The target weight loss goal is between 0.5% and 1% body weight each week. A weight tape should be used to assess the horse's weight if a scale is not available. Abdominal girth

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TABLE 9-19

Body Conditioning Scoring System for Beef Cattle

Group	Score	Definition
Thin condition	1	Emaciated (body fat = 3.8%) Cow is extremely emaciated with no detectable fat over spinous processes, transverse processes, hipbones, or ribs. Tailhead and ribs project quite prominently. Minimal fat and muscle mass observed.
	2	Very thin (body fat = 7.5%) Cow still appears somewhat emaciated, but tailhead and ribs are less prominent. Individual spinous processes are still rather sharp to the touch, but some tissue exists along spine. Some muscling visible in hindquarters.
	3	Thin (body fat = 11.3%) Ribs are still individually identifiable but not quite as sharp to the touch. There is obvious palpable fat along spine and over tailhead and some tissue cover over dorsal part of ribs.
Borderline condition	4	Borderline (body fat = 15.1%) Individual ribs are no longer visually obvious. Spinous processes can be identified individually on palpation but feel rounded rather than sharp. There is some fat cover over ribs, transverse processes, and hipbones.
Optimum moderate condition	5	Moderate (body fat = 18.9%) Cow has generally good overall appearance. On palpation, fat cover over ribs feels spongy, and areas on either side of tailhead now have palpable fat cover.
	6	Good (body fat = 22.6%) Optimum moderate condition. Firm pressure must be applied to feel spinous processes. High degree of fat cover is palpable over ribs and around tailhead.
	7	Very good (body fat = 26.4%) Cow appears fleshy and obviously carries considerable fat. There is a very spongy fat cover over ribs and over and around tailhead. "Rounds" or "pones" of fat are beginning to be obvious. There is some fat around vulva and in crotch.
Fat condition	8	Fat (body fat = 30.1%) Cow is very fleshy and overconditioned. Spinous processes are almost impossible to palpate. There are large fat deposits over ribs, around tailhead, and below vulva. "Rounds" or "pones" of fat are obvious.
	9	Very fat (body fat = 33.9%) Cow is obviously obese. Tailhead and hips are buried in fatty tissue, and "rounds" or "pones" of fat protrude. Bone structure is no longer visible and barely palpable. Animal's mobility may even be impaired by large fatty deposits.

From Spitzer JC. 1986. Influences of nutrition on reproduction in beef cattle. In Morrow DA (ed), Current therapy in theriogenology. Saunders, Philadelphia, PA, and modified from National Research Council (NRC). 1996. Nutrient requirements of beef cattle, ed 7. National Academy Press, Washington, DC.

TABLE 9-20

Body Conditioning Scoring System for Dairy Cattle

Score	Description
1	Individual spinous processes have limited flesh covering and are prominent; the ends are sharp to the touch, and together the processes form a definite overhanging shelf effect to the loin region. Individual vertebrae of the chine, loin, and rump regions are prominent and distinct. Hooks and pin bones are sharp with negligible flesh covering, and severe depressions between hooks and pin bones are noted. The area below the tailhead and between the pin bones is severely depressed, causing the bone structure of the area to appear extremely sharp. (Body fat = 3.77%)
2	Individual spinous processes are visually discernible but not prominent. The ends of processes are sharp to the touch, although they have greater flesh covering, and the processes do not have a distinct overhanging shelf effect. Individual vertebrae of chine, loin, and rump regions are not visually distinct but are readily distinguishable by palpation. Hooks and pin bones are prominent, but the depression between them is less severe. The area below the tailhead and between the pin bones is depressed, but the bone structure is not devoid of flesh covering. (Body fat = 11.3%)
3	Spinous processes are discernible by applying slight pressure. Together the processes appear smooth, and the overhanging shelf effect is not noticeable. Vertebrae of the chine, loin, and rump regions appear as rounded ridges, and hooks and pin bones are rounded and smooth. The area between the pin bones and around the tailhead appears smooth, with no sign of fat deposition. (Body fat = 18.84%)
4	Individual spinous processes can be distinguished only by firm palpation, and together the processes appear flat or rounded with no overhanging shelf effect. The ridge formed by the vertebral column of the chine region is rounded and smooth, but loin and rump regions appear flat. Hooks are rounded, and the span between the hooks is flat. The area around the tailhead and pin bones is rounded, with evidence of subcutaneous fat deposition. (Body fat = 26.38%)
5	Bone structure of the vertebral column, spinous processes, hooks, and pin bones is not visually apparent, and evidence of subcutaneous fat deposition is prominent. The tailhead appears to be buried in fatty tissue. (Body fat = 33.9%)

From Wildman EE, Jones GM, Wagner PE, et al. 1982. A dairy cow body condition scoring system and its relationship to selected production characteristics. J Dairy Sci 65:495, and modified from National Research Council (NRC). 2001. Nutrient requirements of dairy cattle. National Academy of Sciences, NRC, Washington, DC.

measurements, ultrasonographic evaluation of subcutaneous fat at the 12th intercostal space, and BCS measurements can be made to monitor weight loss every month.[15-16]

Owner compliance is essential during a weight loss program for horses and companion large animals. Owners should be encouraged to keep a journal of their animal's ration, body weight, and BCS. Horse owners can also monitor the horse's abdominal circumference, measured around the widest part of the abdomen.[16] Digital photos can help document physical changes over time. Excessive, rapid weight loss should be avoided. Weight loss programs should be

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TABLE 9-21

Body Condition Scoring System for Sheep

Score	Description
0	Animal is extremely emaciated and at the point of death. No muscular or fatty tissue can be detected between the skin and the bone.
1	The spinous processes are prominent and sharp. The transverse processes are also sharp; the fingers pass easily under the ends, and it is possible to feel between each process. The eye muscle areas are shallow with no fat cover.
2	The spinous processes still feel prominent but also smooth, and individual processes can be felt only as fine corrugations. The transverse processes are smooth and rounded, and the fingers can be passed under the ends with a little pressure. The eye muscle areas are of moderate depth but have little fat cover.
3	The spinous processes are detected only as small elevations; they are smooth and rounded, and individual bones can be felt only with pressure. The transverse processes are smooth and well covered, and firm pressure is required to feel over the ends. The eye muscle areas are full and have a moderate degree of fat cover.
4	With pressure the spinous processes can just be detected as a hard line between the fat-covered muscle areas. The ends of the transverse processes cannot be felt. The eye muscle areas are full and have a thick covering of fat.
5	The spinous processes cannot be detected even with firm pressure, and there is a depression between the layers of fat where the spinous processes would normally be felt. The transverse processes cannot be detected. The eye muscle areas are very full and have a very thick fat cover. Large deposits of fat may be seen over the rump and tail.

From Russel A. 1984. Body condition scoring of sheep. In Pract 6:91.

TABLE 9-22

Body Condition Scoring System for Horses

Score	Description
1	Poor. Animal is extremely emaciated. Spinous processes, ribs, tailhead, tuber coxae, and tuber ischii project prominently. Bone structure of the withers, shoulders, and neck is noticeable. No fatty tissue can be felt.
2	Very thin. Animal is emaciated. There is a slight fat covering over the base of the spinous processes; the transverse processes of the lumbar vertebrae feel rounded. Spinous processes, ribs, tailhead, tuber coxae, and tuber ischii are prominent. Bone structure of the withers, shoulders, and neck is faintly discernible.
3	Thin. Fat buildup is present about halfway on the spinous processes; the transverse processes cannot be felt. There is a slight fat cover over the ribs. Spinous processes and ribs are easily discernible. Tailhead is prominent, but individual vertebrae cannot be visually identified. Tuber coxae appear rounded but are easily discernible; tuber ischii are not distinguishable. Bone structure of the withers, shoulders, and neck is accentuated.
4	Moderately thin. Negative crease can be seen along the back. Faint outline of ribs is discernible. Tailhead prominence depends on conformation; fat can be felt around tailhead. Tuber coxae are not discernible. Withers, shoulders, and neck are not obviously thin.
5	Moderate. Back is level. Ribs cannot be visually distinguished but can be felt easily. Fat around tailhead is somewhat spongy. Withers appear rounded over spinous processes, and shoulders and neck blend smoothly into the body.
6	Moderately fleshy. Slight crease may be seen down the back. Fat over ribs is spongy, and fat around tailhead is soft. Fat is beginning to be deposited along withers, behind shoulders, and along neck.
7	Fleshy. Crease may be seen down the back. Individual ribs can be felt, but there is noticeable filling of fat between ribs. Fat around tailhead is soft. Fat is deposited along withers, behind shoulders, and along neck.
8	Fat. Crease is seen down the back. Ribs are difficult to feel. Fat around tailhead is very soft. Areas along withers and behind shoulders are filled with fat, and neck is noticeably thickened. Fat is deposited along inner thighs.
9	Extremely fat. Obvious crease is seen down the back. Patchy fat appears over ribs. Bulging fat is seen around tailhead along withers, behind shoulders, and along neck. Fat along inner thighs may cause thighs to rub together. Flank is filled with fat.

From Henneke GD, Potter GD, Kreider JL, et al. 1983. Relationship between condition score, physical measurements and body fat percentage in mares. Equine Vet J 15:371.

approached with caution in animals that are either pregnant or lactating. Once the animal has achieved the ideal body weight and BCS, it should be placed on a maintenance ration and exercise program that will ensure the ideal weight is maintained.

In a production management setting the ration should be evaluated and revised to reduce calories while maintaining sufficient energy intake to maximize reproduction or milk production. Care should be taken to ensure the animals consume an adequate concentration of vitamins and minerals to meet their requirements when they are fed an energy-restricted ration.

Pica

Pica (geophagia) is defined as a depraved or abnormal appetite. It is usually associated with animals that chew or eat wood (fences, trees, buildings), dirt, bones, or other inanimate objects not usually considered feedstuffs. The mechanism or mechanisms of pica are not yet understood. Pica has been associated with PCM, parasitism, obesity, and deficiencies of phosphorus, salt, protein (kwashiorkor), and micronutrients. Diagnosis is by observation or history or both. The main emphasis must be placed on identification and resolution of the primary problem. Pica must be differentiated from abnormal behavior associated with central nervous system diseases, bovine ketosis, and equine behavioral abnormalities associated with boredom.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 10

Alterations in Urinary Function

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■ MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED*

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Anuria and oliguria, 159
Uremia, 160

Dysuria, Stranguria, and Incontinence

Dysuria is defined as difficult or painful urination. *Stranguria* is defined as straining to urinate, with the normal rate of voiding and urine egress being decreased and the effort required to void increased. Because these signs are often difficult to distinguish from each other and often present concurrently, they are considered together in this section. The most common causes of dysuria and stranguria are urethral obstruction, inflammation of the urethra and/or the bladder, and neurologic conditions that prevent normal emptying of the bladder. Adhesions between the bladder and other structures in the abdominal or pelvic cavities can create mechanical interference with bladder emptying, resulting in dysuria and stranguria.

The horse voids urine actively and forcefully. Both male and female adult horses may briefly groan and strain slightly during normal urination. This should not be misinterpreted as dysuria or stranguria. In other large animal species, urination is more passive and straining or groaning normally is not observed. Conditions in which a horse may spuriously appear to have dysuria include lower urinary tract disease, abdominal pain, peritonitis, pleuritis, severe musculoskeletal disease, or neurologic disease. With any of these conditions, the horse may attempt to posture and urinate but may not be able to sufficiently increase intraabdominal pressure to allow complete voiding.

Signs of dysuria and stranguria include treading, repetitive switching or flagging of the tail, pollakiuria (frequent voiding of small amounts of urine), flatulence during voiding, and retention of the urination posture for several seconds after voiding has ceased. Urine scalding of the perineal region or rear legs may be noted in either ruminants or horses with dysuria or stranguria. Vocalization during urination may accompany dysuria. While straining to void, the affected animal may show forceful contractions of the abdominal musculature. Male horses and ruminants that are experiencing dysuria or stranguria typically stand with the back slightly extended (mild lordosis), with the front legs held farther ahead of the body and the hind feet positioned farther behind the body than normal (Fig. 10-1).

Dysuria or stranguria in large animals may be confused with tenesmus, or straining to defecate. This is most frequently a dilemma in neonatal foals with a ruptured bladder or meconium impaction. However, with tenesmus the rear feet of the foal are positioned slightly more anteriorly than with stranguria or dysuria. Stranguria may be severe enough in some cases to induce secondary rectal prolapse; therefore, when examining an animal with rectal prolapse, the clinician must establish whether or not the underlying cause might be urinary tract disease. Conversely, animals with tenesmus may strain to defecate with sufficient force to void small amounts of urine, and the observer may mistakenly attribute the problem to primary urinary tract disease.

Urinary *incontinence* is defined as the involuntary voiding of urine. It is most frequently indicative of impaired neuromuscular control of urination. Concurrent fecal incontinence is commonly found if disease or trauma to the sacral segments of the spinal cord is present. Urinary incontinence may also occur with severe cases of lower urinary tract trauma and inflammation. In young animals, congenital abnormalities such as ectopic ureter must be considered in the differential diagnosis for urinary incontinence.

Approach to Diagnosis of Dysuria, Stranguria, and Incontinence

Initially, the signalment, dietary and environmental history, onset of signs, duration, progression, and response to treatment should be established. Urethral calculi should be considered in castrated ruminants on high-grain diets. A history of one or more horses showing clinical signs of spinal cord disease, respiratory disease, stranguria, or urinary incontinence should immediately lead the practitioner to consider equine herpesvirus-1 myelitis in the differential. A history of dysuria or stranguria that develops after parturition usually indicates an injury to the lower urinary tract; such injuries can increase the female's risk of subsequent urinary tract infection. For safety's sake, the clinician should consider the potential for rabies as a primary cause before initiating the examination. A full physical examination should be performed because abnormal urination may be a sign of disease in other body systems, such as those characterized by diffuse muscular weakness. Common causes of dysuria, stranguria, and urinary incontinence are shown in Box 10-1.

When possible, the animal should be observed urinating, and a sample of urine should be collected for dipstick urinalysis, measurement of specific gravity, and sediment examination; urine can be collected in a separate, sterile container for culture, if indicated. Urination can be induced in female cattle by gently rubbing the perineum immediately ventral to the vulva. In male cattle, the examiner may induce urination by placing a finger into the preputial cavity and gently rubbing the preputial mucosa. In ewes, urination can be induced by holding off the nose until the ewe struggles; urination typically occurs at this point. Obviously, this procedure should not be performed on ewes in shock or those with poor cardiac or respiratory function. In horses, goats, and male sheep, the examiner simply

*A detailed discussion of interpretation of urinalysis is covered in Chapter 22.

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FIG. 10-1 Lordosis and stranguria in a steer with urethral obstruction.

BOX 10-1

Causes of Dysuria, Stranguria, and Urinary Incontinence in Horses and Ruminants

Adhesions of the bladder
Balanitis/posthitis/vulvitis/vaginitis
Bracken fern intoxication (R)
Botulism
Cantharidin (blister beetle) toxicosis (E)
Ectopic ureter
Equine dysautonomia (grass sickness) (E)
Equine herpesvirus-1 myelitis (E)
Equine neonatal maladjustment (E)
Estrogen-responsive dysuria (E)
Everted bladder
Habronemiasis (E)
Hemorrhage into the urinary tract
Hendra virus (E, Australia and Southeast Asia)
Laminitis
Myopathy
Neoplasia of the urinary tract
Painful conditions of the abdominal organs or abdominal wall
Painful conditions of the thoracic organs or thoracic wall
Parturition
Penile, vaginal, urethral, or preputial trauma
Penile masses or encircling hair rings
Pelvic entrapment of the bladder
Pelvic, sacral, or vertebral fracture
Polyneuritis equi
Prolapsed bladder
Prolonged recumbency
Rabies
Rectovaginal fistula
Ruptured urethra, bladder, or ureter
Seminal vesiculitis
Smegma accumulation (E)
Sorghum intoxication
Squamous cell carcinoma (penis, prepuce, or vulva)
Tetanus
Ulcerative posthitis and vulvovaginitis (pizzle rot) (R)
Urachal infection or abscesses
Urinary calculi (urolithiasis)
Urinary tract infection
Vaginal prolapse
Vertebral or spinal malformation

E, Found only in horses; *R,* found only in ruminants.

has to wait until the animal is ready to void, although urination may be encouraged by placing the animal in a freshly bedded stall. Recumbent animals will often void soon after standing. Normal equine urine is turbid owing to the presence of mucus and calcium-based crystals.

The male's preputial hairs and the female's perineal region should be closely inspected for the presence of blood, exudate, or crystalline debris. Sedation and/or epidural anesthesia may be necessary to induce sufficient relaxation of the retractor penis muscles to enable examination of the penis. In prepubescent ruminants, the frenulum often prevents complete exteriorization of the penis for examination of the urethral orifice; general anesthesia may be necessary to induce sufficient relaxation. In bulls and steers, transrectal massage of the pelvic segment of the urethra may stimulate penile relaxation to enable penile visualization. The glans penis and urethral orifice should be carefully examined for masses such as papillomas, evidence of trauma, encircling hair rings, and embedded foreign bodies (e.g., grass awns). Penile examination is of particular importance in the dysuric or stranguric small ruminant because urinary calculi frequently become lodged in the urethral process (see Urolithiasis, Ruminants, Chapter 34).

An accumulation of smegma, composed of mucus and cellular debris, may cause preputial swelling and dysuria in adult male horses. Smegma can usually be found as a hard, waxy mass in the urethral diverticulum. Preputial swelling without overt urinary dysfunction may be seen in equine Cushing syndrome (see Equine Pituitary Pars Intermedia Dysfunction, Chapter 41).[1]

In the male the penis and the urethra should be palpated percutaneously from the perineum distally to the sheath. Swelling, pain, abnormal urethral pulsations, and calculi lodged in the urethra may be detected. Urethral calculi are most commonly lodged just below the anus in male horses, and these can occasionally be palpated on the midline of the perineum. Marked swelling along the prepuce and ventral body wall in a bull or steer with active or recent dysuria/stranguria can indicate urethral rupture.

The vulva, caudal vagina, and urethral orifice should be visualized and palpated in females. Sacrocaudal epidural anesthesia may facilitate examination if painful lesions are present. In females of breeding age, the cervix should be visualized or palpated and the uterus evaluated by palpation or ultrasonography because the pollakiuria and apparent dysuria that may occur at the onset of parturition may be the primary complaint of a novice observer. Previous dystocia can result in sufficient soft tissue trauma, laceration, swelling, and pelvic neuropraxia to induce dysuria or stranguria. The ventrum of the tail, perineum, udder, and hindlimbs should be examined for adherent blood or exudate originating from the female's reproductive or urinary tract.

In adult horses and cattle, rectal palpation should be performed when dysuria and stranguria are present. Before examination the clinician should take careful note of the tail and anal tone of the animal; reduction of either or both may indicate underlying neurologic or muscular disease. Introduction of the examiner's hand and wrist into the rectum is usually sufficient for palpation of the pelvic segment of the urethra and bladder trigone. The caudal extent of the pelvic cavity should be carefully palpated for masses that might mechanically interfere with voiding. The bladder is typically located on the midline at the level of the pubic brim. Its presence in the caudal pelvic cavity, particularly in the standing animal, may suggest pelvic entrapment of the bladder.

Bladder distention is commonly found in persistently recumbent horses and cattle, and on rectal examination the bladder is often positioned farther caudally than in standing animals. In the horse, bladder distention may also be found with abdominal or thoracic pain. Apparently, the abdominal pressure necessary to empty the bladder incites sufficient pain of diseased structures to cause reluctance to void. Musculoskeletal and neurologic disease may also result in bladder distention. These other possibilities should be carefully investigated when bladder distention is detected, yet no primary disease is found in the urinary tract.

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A careful rectal examination of the bladder and the proximal urethra of the horse might allow identification of urethral or cystic calculi. Most cystic calculi in the horse are singular and located in the trigone of the bladder and are palpable with the examiner's arm inserted to the level of the wrist. If there is a large amount of urine in the bladder, the stone may not be palpable; in such cases, transrectal ultrasound examination may enable visualization of the stone. Sabulous calculi may be found in horses with stranguria or urinary incontinence, and on rectal examination the clinician may interpret the palpation findings as a bladder tumor or large stone.[2] Detection of calculi in the bladder or urethra should prompt the clinician to consider the possibility of concurrent nephrolithiasis.

If bladder dysfunction is not caused by structural abnormalities, trauma, or infectious disease, a thorough neurologic examination should be conducted. If neurologic dysfunction is suspected, an attempt should be made to determine whether the primary lesion is affecting the detrusor muscle or the urethral sphincter muscles of the bladder. This determination is often helpful in localizing the lesion and is important when selecting treatment.

When bladder paralysis is caused by upper motor neuron (UMN) dysfunction, signs of UMN dysfunction may be evident in the rear limbs. The animal frequently postures and strains to urinate but voids only a small amount of urine because the striated urethral muscles are disinhibited from higher centers and their resultant increased tone impedes urine outflow from the bladder. Frequent, small-volume urine egress from the distended bladder occurs when the animal responds to the urge to void or when the bladder undergoes reflex contraction.

With severe disease of the sacral spinal cord or sacral nerve plexus, lower motor neuron (LMN) input to the detrusor muscle is impaired or absent. Urinary incontinence is often the predominant clinical sign (e.g., cauda equina neuritis in horses or lymphoma in cattle). The bladder is usually moderately to severely distended, and urine can be expressed easily if pressure is applied to the bladder during rectal examination. With LMN dysfunction urine may also be voided as the animal walks. Voluntary or involuntary voiding is often incomplete, leading to retention of urine in the bladder. This, in turn, increases the patient's risk of urinary tract infection and, in horses, sabulous calculi accumulation in the bladder. Other neurologic signs involving the sacral and coccygeal nerves may be apparent, such as decreased tail and anal tone and atrophy of the gluteal or tailhead musculature. Ataxia or weakness of the rear limbs may or may not be present with an LMN bladder. Urethral and bladder pressure profiles can be determined to better assess the location of the lesion.[3-5]

In small ruminants and neonates, transabdominal palpation is useful for evaluation of the urinary tract. In these animals a distended bladder can usually be palpated by simultaneously placing one hand on each side of the caudal ventral abdomen at the level of the pelvic brim and pressing the fingers of each hand toward the abdominal midline. If the bladder has been ruptured, it will be difficult to identify by palpation but ascites due to uroperitoneum can be detected. Digital rectal examination of the pelvic segment of the urethra can be performed in neonatal cattle and horses and in small ruminants. The umbilicus should be carefully palpated in neonates with dysuria or stranguria because urachal abscesses and adhesions to the bladder may impair voiding. An infected urachus will occasionally communicate with the bladder lumen, creating concurrent septic cystitis.

Ectopic ureter(s) should be considered in young animals with persistent urinary incontinence; stranguria and dysuria are less common primary complaints. In affected females, vaginal urine pooling is often present. Vaginoscopic or cystoscopic examination can be performed, but the opening of the ectopic ureter can be difficult to locate during routine examination. Intravenous urography is typically required to locate the ectopic structure(s). As for all congenital defects, a careful assessment for defects in other organs should be performed in confirmed cases.

If physical examination and urinalysis do not reveal the source of dysuria, stranguria, or incontinence, ultrasonographic evaluation of the urogenital tract should be performed. An endoscope can be used for visualization of the vaginal vault and preputial cavity and penis; air insufflation can be used to expand the walls and achieve a clear view of these structures. When advanced retrograde into the urethra, the urethral wall, bladder, and ureteral openings can be visualized. In neonates and small ruminants, plain abdominal radiographs, positive contrast urethrocystography, and intravenous urography are additional options.

Hematuria and Pigmenturia

Hematuria is defined as blood in the urine. It may appear as occult blood detected during urinalysis, as uniformly red-colored urine throughout urination, or as blood clots passed at any phase of urination. If large clots are present, obstruction of the urinary tract may occur, resulting in concurrent stranguria and dysuria. *Pigmenturia* is defined as the presence of abnormal pigment in the urine; in large animals such pigments are usually limited to hemoglobin or myoglobin. Hemoglobin, myoglobin, and blood all cause a positive reaction for blood and protein on an orthotoluidine-based urine dipstick test. Certain oxidizing disinfectants can also trigger a positive reaction for blood on these strips. In addition, contamination of the urine with blood from the reproductive organs can result in hematuria, as can admixture of fecal blood with voided urine in females. Blood from penile or preputial injuries can contaminate the urine of males.

When clots of blood are visible in the urine, the presence of hematuria is confirmed. Also, when scattered spots of color change are evident on the blood reagent pad of the urine dipstick, the reaction pattern reflects the presence of small aggregates of red cells deposited on the pad. Otherwise, differentiation of hematuria from hemoglobinuria and myoglobinuria requires that the discolored urine be centrifuged and the sediment examined. Hematuria is characterized by red-, pink-, or brown-colored urine that clears partially or entirely after centrifugation, resulting in a pigmented sediment pellet. With hematuria, red cells or red cell "ghosts" (red cells devoid of pigment) are visible on microscopic examination of urine sediment.

Urine containing hemoglobin is clear to dark red in color, depending on the concentration of hemoglobin in the sample. If visibly discolored, the urine sample with hemoglobinuria does not clear when centrifuged. Animals with hemoglobinuria may be experiencing intravascular hemolysis, which leads to passage of hemoglobin from the plasma into the tubular fluid of the nephrons. The serum or plasma of these animals may be pink in color. Mucous membrane pallor or icterus may be evident, and tachycardia and tachypnea are present when red cell destruction is rapid and extensive. The packed cell volume may be decreased at the time of initial examination, or it may decrease progressively over 12 to 24 hours of monitoring. Release of hemoglobin from red blood cells in the vasculature may result in elevation of the plasma and serum total protein concentration. The clinician should note that hemoglobin is potentially nephrotoxic; renal function and hydration should be monitored in such cases. Sediment findings vary according to the underlying disease, and hyaline or cellular casts may be seen if pigment nephropathy is present.

Urine containing myoglobin may be of normal color; if present in high concentrations in a sample, it imparts a dark red to brown color to the urine (Fig. 10-2). If visibly discolored, urine containing myoglobin does not clear when centrifuged. Sediment findings are variable but can include hyaline or cellular casts if pigment nephropathy is present. Myoglobin can be differentiated from hemoglobin in urine through ammonium sulfate precipitation, electrophoresis, or spectroscopy. Animals with myoglobinuria have muscle necrosis or injury, which leads to release of myoglobin from damaged muscle cells into the plasma and renal tubular fluid. Extensive muscle trauma (e.g., dog attacks, trailer accidents) or primary myopathies can induce myoglobinuria. Affected animals may show abnormal stance or gait or other evidence of muscle swelling, pain, or weakness. The serum activity of the enzymes creatine phosphokinase (CPK), aspartate

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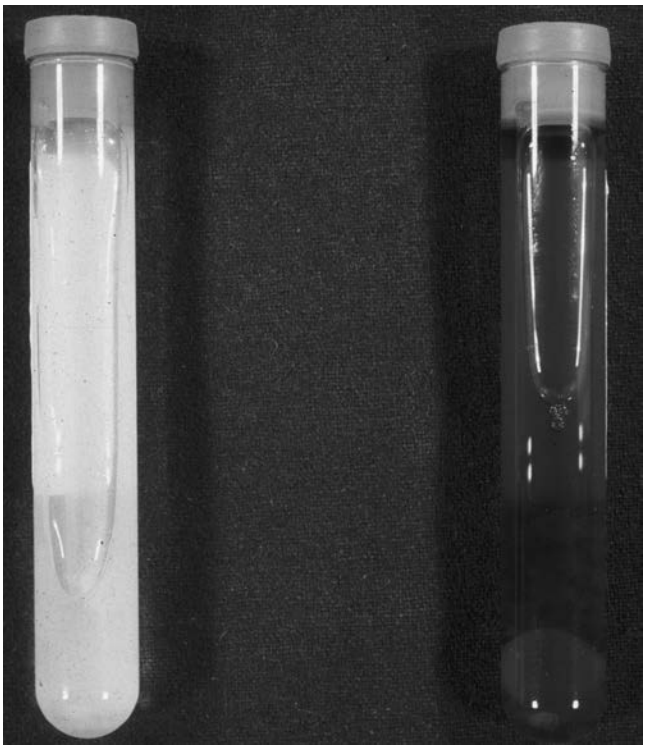


FIG. 10-2 Normal equine urine *(left)* and urine with severe myoglobinuria *(right)*. Urine containing myoglobin is not always so markedly discolored. *(Photo courtesy Paul S. Morley.)*

aminotransferase (AST), and lactate dehydrogenase (LDH) is variably increased, depending on the duration and severity of muscle injury. As for hemoglobin, the persistence of myoglobin in the tubular fluid of the nephrons can induce tubular necrosis.

Approach to Diagnosis of Hematuria and Pigmenturia

Geldings and stallions may develop spontaneous hematuria associated with a vascular fistula or cavernosal rupture in the most proximal urethra.[6,7] The history should include data on recent infectious diseases, exercise, diet, and treatment. Hematuria after exercise may indicate the presence of erosions in the urinary tract mucosa, anomalous vascular structures, or mucosal trauma from uroliths. Ingestion of certain toxins (e.g., cantharidin, bracken fern) can create hematuria. Hemoglobinuria can result from exposure to hemolytic toxins such as red maple leaves, copper, onions, and certain bacterial hemolysins. Intravenous infusion of markedly hypotonic or hypertonic fluids, such as water or undiluted dimethyl sulfoxide (DMSO) solution, respectively, can result in intravenous hemolysis and hemoglobinuria. In dehydrated animals, ingestion of large volumes of water can reduce intravascular osmolality to the point of causing hemolysis, with resultant hemoglobinuria.

A full physical examination should be conducted. Hemolysis should be investigated through examination of the serum or plasma, serum total protein measurement, and/or a complete blood count. A urine sample should be obtained for full urinalysis, centrifugation, and sediment examination. The patient with potential hematuria should be carefully examined for clinical signs suggestive of impaired coagulation. Severe vulvitis often develops in female horses and ruminants with diarrhea as a result of prolonged contact of the vulvar mucosa with fecal contents. A trace reaction for blood is often evident in the urine of these animals; however, the possibility of hemorrhage from tubular injury caused by hypovolemia should be considered as well. Common causes of hematuria and pigmenturia are listed in Box 10-2.

BOX 10-2

Causes of Hematuria and Pigmenturia in Horses and Ruminants

Hematuria

Aberrant parasite migration within the urinary tract
Admixture of fecal blood with urine
Admixture of blood from the reproductive organs with urine (e.g., metritis, orchitis, seminal vesiculitis)
Bleeding diatheses (e.g., warfarin, disseminated intravascular coagulation [DIC])
Cantharidin (blister beetle) poisoning (E)
Contamination of urine with oxidant disinfectants
Enzootic hematuria (R)
Exercise-induced hematuria (E)
Habronemiasis (E)
Leptospirosis
Neoplasia of the urogenital tract
Penile, vaginal, preputial, or urethral trauma
Penile masses or encircling hair rings
Renal papillary necrosis (e.g., related to nonsteroidal antiinflammatory drugs [NSAIDs])
Urinary calculi (urolithiasis)
Urinary tract infection
Vascular anomaly, corpus cavernosum rupture (proximal dorsal urethral hemorrhage in males) (E)

Hemoglobinuria

Burns (severe)
Clostridium hemolyticum infection (redwater) (R)
Copper intoxication
Excess water intake, water intoxication
Hepatic failure
Intravenous (IV) hypotonic fluid administration (e.g., 0.45% saline or water)
IV hypertonic fluid administration (e.g., dimethyl sulfoxide [DMSO])
Leptospirosis
Onion and *Brassica* species (rapeseed, kale, mustard, etc.) intoxication
Neonatal isoerythrolysis
Postparturient hemoglobinuria (combined phosphorus/selenium and/or copper deficiency) (R)
Red maple intoxication (E)

Myoglobinuria

Clostridial myonecrosis
Compartmental syndrome/downer myopathy
Exertional/capture rhabdomyolysis
Hereditary/congenital myopathies
Infarctive purpura hemorrhagica (E)
Muscle trauma
Myopathy associated with streptococcal infections (E)
Nutritional myodegeneration
Postanesthetic myoneuropathy
Toxic myopathies (e.g., *Cassia* species, ionophores, gossypol)
Viral myopathies (influenza, equine herpesvirus [EHV], bluetongue)

E, Found only in horses; *R,* found only in ruminants.

Lesions of the urethra most often produce hematuria at the beginning of urination. Hematuria that originates from the bladder is most likely to be seen or appear more pronounced at the end of urination. Hemorrhage originating from the upper urinary tract is likely to be more pronounced at the end of urination. It should be noted, however, that it is not always possible to accurately localize the source of urinary tract hemorrhage by the timing of the appearance of blood in the voided sample. If the urine discoloration appears uniform throughout urination and no clots are obvious, the veterinarian must first determine that the discoloration is hematuria and not hemoglobinuria, bilirubinuria, or myoglobinuria. This can be accomplished by routine dipstick urinalysis; urine sediment

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examination; assessment of the patient's packed cell volume, plasma protein concentration, and serum muscle enzyme activities; and visualization of the color of the plasma and mucous membranes.

Hematuria often accompanies pyuria and bacteriuria in urinary tract infection. If hematuria is confirmed and urinary tract infection or genital or perineal trauma is *not* the cause, rectal examination may reveal calculi or tumors in the proximal urethra or bladder. Endoscopic examination of the urethra and bladder is necessary if the lesion cannot be detected during rectal or physical examination.

During endoscopic examination of the urethra and bladder, if the source of hemorrhage is not apparent, the openings of the ureters and the color of the urine coming from both of them should be visualized. This is best performed after suctioning urine from the bladder and then distending the bladder with air, taking care that bubbling of the urine does not occur. The ureteral opening can be seen dorsally as the scope is first introduced into the bladder. The two openings can be visualized simultaneously by passing the scope farther into the bladder and retroflexing the scope caudally until the entire trigone area is visualized. If hemorrhage is seen to originate from one or both ureteral openings, the next diagnostic step is ultrasound examination of the kidneys and ureters because the hemorrhage has now been localized to the upper urinary tract.

When myoglobinuria is present, the potential for exposure to gossypol and ionophores should be investigated. Certain viral and bacterial infections, such as streptococcal infections in horses, can induce myopathy and myoglobinuria. A recent history of heavy exertion or abnormally high ambient temperature (heat stroke) may exist in cases of myopathy with myoglobinuria. The potential for nutritional myodegeneration from vitamin E and/or selenium deficiency should be considered in light of the animal's diet and the regional soil selenium content. A previous history of recurrent exercise intolerance or muscle dysfunction may be evident in certain inherited, idiopathic, or diet-associated cases of rhabdomyolysis. Prolonged recumbency, as occurs under general anesthesia, can induce sufficient pressure myopathy to cause myoglobinuria. Rarely, idiosyncratic responses to medications can induce hemolysis or muscle injury, resulting in hemoglobinuria and myoglobinuria, respectively.

Pyuria

Pyuria is defined as gross or microscopic evidence of inflammatory cells and debris in the urine. Dysuria, stranguria, pollakiuria, crystalluria, urine scalding of the perineum, or hematuria may accompany the pyuria. Pyuria may result from septic or nonseptic inflammatory disease. Causes of pyuria are listed in Box 10-3. The normal turbidity of equine urine (Fig. 10-3) should be considered when appraising the horse for pyuria.

BOX 10-3

Causes of Pyuria in Horses and Ruminants

Admixture of exudate from the reproductive tract of males or females
Ectopic ureter
Encircling hair rings of the penis
Leptospirosis
Nephritis
Penile, preputial, or urethral trauma or neoplasia
Rectovaginal fistula
Ulcerative posthitis and vulvovaginitis (small ruminants)
Urinary calculi
Urinary tract infection (urethritis, cystitis, ureteritis, and/or pyelonephritis)
Urinary tract neoplasia
Viral infections of the genitalia
Vulvar, vaginal, or urethral trauma or neoplasia

Approach to Diagnosis of Pyuria

The history should be taken, and a complete examination of the entire urinary tract should be performed, including rectal palpation or transabdominal palpation of the bladder. Although cystitis may be characterized by a thickened bladder wall, this is often difficult to detect during rectal palpation and ultrasonographic examination may be necessary. In males the accessory sex glands should be carefully examined because exudate from these structures may be admixed with urine. Predisposing factors such as urinary calculi, dystocia, abnormal urethral or genital structure, and neurologic diseases should always be considered.

Pyuria is confirmed by obtaining a midstream or catheterized urine sample (or both) and quantitating the number of white blood cells and bacteria in the urine sediment. Evaluation of urine sediment within 30 to 60 minutes of collection enables preservation of the greatest cytologic detail. Pyuria is confirmed by the presence of more than 10 white blood cells per high-power microscopic field of a midstream-voided or catheterized sample. When bacterial infection is the cause, there are typically more than 20 organisms visible per high-power field. The cytologic features of urine sediment are greatly influenced by the method of collection, rigor of aseptic technique, and degree of contamination of the prepuce, vulva, and urethral orifice. Catheterization can be used to obtain urine from the bladder of most male and female horses and female ruminants. In male ruminants the urethral recess (diverticulum) prevents retrograde catheterization of the bladder, and collection of a midstream sample is usually the sole option. Cystocentesis of a large animal with a urinary tract infection carries the risk of induction of septic peritonitis.

Quantitative cultures of the samples should be performed soon after collection in order to prevent false increases in the colony count that can occur from bacterial proliferation in the sample during storage. The results of quantitative culture are greatly influenced by the method of collection and the degree of contamination of the prepuce and vulva. In specimens collected by midstream free catch, bacterial counts greater than 1×10^4 bacteria per milliliter of urine are indicative of urinary tract infection if compatible dipstick and sediment examination findings are present. Normal male and female horses have fewer than 20,000 colony-forming units (CFUs)/mL of urine on a free catch sample and fewer than 500 CFUs/mL on a catheterized sample.[8] A culture that yields a large number of a variety of bacterial species may reflect heavy contamination of the vulva or penis, fecal admixture, a urinary tract infection involving multiple bacterial species (although this is rare), or delay before culture was initiated.

Once pyuria is confirmed, the clinician should next determine the location or origin of the pyuria, the cause, and any predisposing conditions. In females the reproductive tract should be evaluated to confirm that it is not the source of the exudate because mixing of urine and exudate in the urethra and vestibule may result in a spurious diagnosis of pyuria. Similarly, trauma or inflammation of the glans penis or prepuce can result in admixture of exudate with urine,

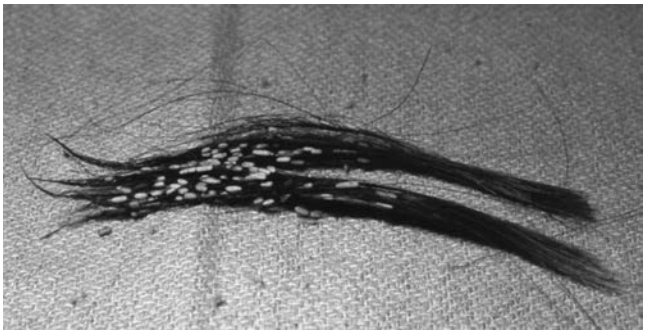


FIG. 10-3 Crystals adherent to the preputial hairs of a steer with urolithiasis. The crystals were analyzed and found to be composed of struvite (magnesium ammonium phosphate).

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as often occurs in cases of ulcerative posthitis in rams and bucks. Endoscopic examination of the vaginal vault or preputial cavity may be helpful, using air insufflation to aid in visualization of the mucosa. Inflammatory diseases of the urethra and bladder usually produce obvious clinical signs of dysuria but minimal to no signs of systemic disease. Low-grade fever may be present in occasional cases of cystitis, but affected animals rarely appear to be systemically ill.

If the pyuria originates from the upper urinary tract (ureters and kidneys), the animal is usually persistently or intermittently febrile and shows systemic signs of disease. Inflammation of the ureter(s) and kidney(s) may result in colic. The rectal examination may reveal enlargement of one or both ureters, pain on palpation, and possibly an enlargement or abnormal shape (or both) of the left kidney. If grossly enlarged, the right kidney can occasionally be palpated per rectum in the horse or cow. In cows and heifers, vaginal palpation may reveal thickening and pain of one or both ureters, which are more readily identified during vaginal palpation than during rectal palpation. Changes suggestive of inflammation are often present on the complete blood count. Casts of exudate, blood, protein, or cellular debris may be seen in the urine sediment in cases of pyelonephritis. An ultrasonographic examination of both kidneys and ureters should be performed in all animals with evidence of upper urinary tract infection. The technique for ultrasound examination of the urinary tract is described in Ruminant Abdominal Ultrasonography, Urinary Bladder and Ureters, Chapter 32.

If *Leptospira interrogans pomona* is suspected as a cause of pyuria, urine sediment should be placed on a microscope slide, air dried, and examined by fluorescent antibody for *Leptospira* antigen.[9] Polymerase chain reaction testing for this organism can be performed on urine sediment; in cattle, greater sensitivity may be achieved by obtaining a urine sample after administration of furosemide.[10]

Crystalluria

Crystalluria is defined as the presence of crystals in the urine. Calcium carbonate and calcium phosphate crystals are abundant in normal equine urine. These, along with mucus, impart a turbid, slightly opaque quality to normal equine urine. Herbivore urine is normally alkaline, which reduces the solubility of certain calcium- and phosphate-based compounds in urine, inducing crystal development. Therefore calcium phosphate, calcium carbonate, or calcium oxalate crystals may be present in highly concentrated ruminant urine. In such cases, crystalluria should be considered an incidental finding if the animal is healthy and free from signs of urinary tract disease. However, in male ruminants, heavy or persistent crystalluria may indicate the potential risk of urolithiasis because the combination of highly concentrated urine and urinary mineral precipitation is considered instrumental in calculogenesis. A precautionary review of diet, salt intake, and water management may be indicated in such cases.

Crystalluria presents a medical problem when crystals enlarge through precipitation, causing microscopic or gross traumatic injury to the urinary epithelium and urinary tract obstruction. When crystals coalesce and enlarge to form calculi (uroliths), the calculi may remain occult or cause disease through trauma to and obstruction of the urinary tract. As a result, the clinician usually detects crystalluria in these animals during the diagnostic workup for hematuria, dysuria, stranguria, pyuria, or signs of urinary tract obstruction. It is critical to note that the *absence* of crystalluria does not indicate that the urinary tract is free of calculi or renal mineralization, just as the presence of crystalluria does not necessarily indicate disease.[11-14] Causes of crystalluria are listed in Box 10-4.

Approach to Diagnosis of Crystalluria

Toxins such as oxalic acid and ethylene glycol can induce calcium oxalate crystalluria, so animal access to oxalate-containing plants and storage areas or garages should be investigated. Administration of high doses of parenteral vitamin C can also induce calcium oxalate deposition in the urinary tract. Previous urinary tract surgery, dystocia, or genital trauma may not directly contribute to crystalluria per se, but abnormal structure of the urinary tract, suture material inadvertently placed in the tract, or loss of uroepithelial integrity can promote crystal precipitation into calculi.

BOX 10-4

Causes of Crystalluria in Horses and Ruminants

Alkaline urine
Calcium-based crystalluria of horses (normal)
Concentrated urine
Ethylene glycol intoxication
Oxalate intoxication
Urolithiasis
Urinary tract infection
Vitamin C intoxication

The hairs surrounding the preputial orifice or vulva should be carefully examined for visible crystals that cling to the hair (see Fig. 10-3). Animals with dysuria and stranguria or incontinence may have crystals adherent to the hair of the hindlegs or tail as well. The presence of adherent crystals on hair indicates that crystalluria is heavy, and in males, given that urolithiasis is the most important diagnosis to investigate, the clinician should determine whether or not the urinary tract is patent in such instances.

Urinary tract infection can induce microscopic crystalluria, visible crystal and exudate accumulation on the external genitalia, or, more rarely, calculus formation. Urease-producing bacteria may increase the pH of urine to the point of inducing precipitation of certain minerals suspended in the urine into calculi. In addition, exudation into the infected urinary tract also provides nidi for deposition of urinary minerals. The approach to urinary tract infections is discussed in the previous sections on dysuria, stranguria, and pyuria.

Polyuria

Polyuria can be defined as the passage of abnormally large amounts of urine. This may be a normal response when excessive fluid, electrolytes, or both are presented to the tubules of a healthy kidney. It may also occur with renal failure when tubular function is impaired or when enough individual nephrons have been lost that the remaining ones are presented with excess fluid and/or solute. Polyuria is also present in central or neurogenic diabetes insipidus (caused by insufficient secretion of antidiuretic hormone [ADH]), nephrogenic diabetes insipidus (caused by diminished effect of ADH on receptors in the kidney), renal medullary washout (caused by an insufficient interstitial concentration gradient), excessive drinking (polydipsia), liver failure, and certain electrolyte abnormalities. Polyuria may also be evident after urinary tract obstructions have been relieved, a phenomenon termed *postobstructive diuresis*. Causes of polyuria are listed in Box 10-5.

Approach to Diagnosis of Polyuria

Evaluation of an animal with polyuria should begin with an inquiry about any history of recent disease, drug administration (e.g., diuretics, corticosteroids, xylazine), fluid therapy, change in diet, change in water quality or availability, or known laboratory evidence of renal disease. The next step is to collect a urine sample to measure the osmolality or specific gravity (UspG). If the osmolality is close to the isosthenuric range (UspG of 1.008 to 1.014), and the concentration remains similar to the plasma concentration in the face of dehydration, primary renal disease should be considered as a cause. This is typically confirmed by measuring the serum creatinine concentration, although radionuclide clearance studies and/or 12- or 24-hour urinary creatinine clearance can also be performed. If evidence of renal failure is not evident on these tests, a water deprivation test may be necessary to determine the tubules' ability to concentrate urine. This test should be performed in a normovolemic patient with careful

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BOX 10-5

Causes of Anuria, Oliguria, and Polyuria in Horses and Ruminants

Anuria and Oliguria

Acute or chronic renal failure (multiple causes)
Blood loss
Cardiac failure
Dehydration
Rupture of the urethra, bladder, or ureter(s)
Septic/toxic shock
Urinary tract obstruction (e.g., urinary calculi)

***Apparent* Anuria or Oliguria**

Bladder paralysis/atony
Botulism
Dysautonomia (grass sickness) (E)
Ectopic ureter(s)
Encephalopathies
Painful diseases of the abdomen or abdominal wall
Painful diseases of the thorax or thoracic wall
Prolonged recumbency
Neonatal maladjustment syndrome
Patent urachus
Ruminal acidosis/grain overload
Severe spinal cord disease

Polyuria

Acute or chronic renal failure (multiple causes)
Cantharidin intoxication
Diabetes insipidus (central or nephrogenic)
Diabetes mellitus
Drugs: diuretics, xylazine, corticosteroids
Encephalopathies
Excessive intravenous fluid therapy
Excessive water/salt ingestion
Hepatic failure
Hypercalcemia (including iatrogenic)
Hyperglycemia (including iatrogenic)
Medullary washout
Organophosphate intoxication
Postobstructive diuresis
Psychogenic polydipsia
Renal amyloidosis
Salt deficiency
Vitamin D intoxication

monitoring of patient status during the test because the mild dehydration induced during this test may exacerbate preexisting, occult renal disease.

As an alternative to the water deprivation test in identifying tubular disease and dysfunction as the cause of polyuria, the fractional clearance (fractional excretion) of sodium in the urine can be measured. This test is performed on simultaneously collected urine and serum samples by measuring the creatinine and sodium in both the serum and the urine. The fractional clearance (Fc_{Na}) of sodium is then determined by the following formula:

$$Fc_{Na}(\%) = \frac{[Na_u]}{[Na_p]} \times \frac{[Cr_p]}{[Cr_u]} \times 100$$

where Na_u is the urine sodium concentration, Na_p is the plasma creatinine concentration, Cr_u is the urine creatinine concentration, and Cr_p is the plasma creatinine concentration. A fractional sodium clearance value above 1% in adult horses is suggestive of primary tubular disease,[15] particularly if the animal's diet and physiologic state are such that avid sodium conservation is expected. Fractional clearance of sodium values of up to 4% have been measured in healthy, lactating dairy cattle.[16] Thus for this test to be valid, salt intake must be normal and the animal must not be given diuretics, parenteral fluids, or fluids administered orally other than what is ingested voluntarily by the animal. Further, due consideration of the animal's diet and physiologic state must be given.

If the UspG or osmolality is less than that of the plasma (1.007), diabetes insipidus, psychogenic polydipsia, and renal medullary washout should be considered. Diabetes insipidus, although rare, has been reported in the horse and may be the result of inadequate secretion of vasopressin (neurogenic diabetes insipidus) or inadequate response to vasopressin in the kidney (nephrogenic diabetes insipidus).[17] However, the patient may simply be ingesting large amounts of water in response to exercise or a high ambient temperature, so interpretation of low UspG requires due consideration of the animal's physiologic state.

Anuria and Oliguria

Anuria is defined as the absence of urine production, and *oliguria* is defined as scant or subnormal urine production. Unless the patient's history includes a careful record of urine output, these two disease conditions are often difficult to distinguish at the onset of the evaluation. Furthermore, the difficulties associated with maintaining urine collection devices in large animals make an accurate measurement of urine production difficult in many cases.

The volume of urine produced by healthy large animals varies tremendously according to breed, age, physiologic status, level of exercise, diet, and a multitude of environmental factors. Altman (1961) determined normal urine output for the large animal species to be as follows: horses, 3 to 18 mL/kg/day; cattle, 17 to 45 mL/kg/day; and sheep and goats, 10 to 40 mL/kg/day.[18] Anuria and oliguria frequently become apparent to the clinician when an azotemic animal is diagnosed with a primary disease in which renal function is commonly threatened (e.g., severe diarrhea) and urine output after initiation of fluid therapy is noted to be subnormal or absent.

If urine collection and measurement cannot be performed, the adult animal with potential anuria or oliguria can be closely watched or placed in a stall with minimal bedding or fine, fresh bedding (e.g., sawdust) in order to facilitate detection of urine on the stall floor. When indicated, fluid therapy should be initiated and expectations for urine output predicted on the basis of the rate and route of fluid administration. Animals with painful thoracic or abdominal disease may refrain from urination, and the clinician must remember to evaluate *bladder filling* and not just the volume of urine voided. Recumbent, obtunded foals, particularly males, may not reliably void urine; monitoring bladder fill by ultrasound or directly monitoring urine output by placement of an indwelling urinary catheter is recommended. Urachal leakage of urine must be considered in neonates with suspected anuria or oliguria because these animals may be observed to void less frequently than normal. Animals with encephalopathies (again, rabies warrants mention) or severe spinal cord disease may not be capable of voluntary voiding.

When evidence for anuria mounts, the clinician must determine if the urinary tract is patent and rule out the presence of rupture of the bladder, urethra, or ureters. Repeat physical examination and ultrasound of the upper and lower urinary tract and abdominal cavity is warranted in such instances. Obstructive diseases of the lower urinary tract are typically accompanied by signs of colic and stranguria. However, these signs will not be present if the patient has a preexisting rent in the urinary tract or if the animal is severely obtunded from uremia.

Oliguria is a physiologic adaptation to dehydration and can be expected in animals with prerenal azotemia. Assessment of the urine specific gravity is critical in determining the presence of renal failure in such cases. If urine cannot be collected from the dehydrated animal, fluid therapy should be initiated and the azotemia monitored. Oliguria is a relatively common feature of acute renal failure, particularly if the disease process involves obstruction of the nephron lumen with crystals, cellular debris, or proteinaceous casts. However, the volume of urine produced by the large animal in renal failure can vary greatly according to the patient's hydration status, diet, and the inciting cause. In short, urine production can be normal, increased,

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or decreased in renal failure. Renal failure is covered in detail in Chapter 34. Causes of anuria and oliguria are listed in Box 10-5.

Uremia

Uremia is defined as the constellation of clinical signs, impaired metabolic processes, and alteration of the function of multiple organs that occurs as a result of failure to excrete waste products from the body via the urine. Uremia may be the result of either acute or chronic renal failure, retention of urine in the body as a result of urinary tract leakage (e.g., bladder rupture), or both. Various retained toxins are associated with the uremic process, including urea, guanidine, phenolic compounds, and phosphorus.[19,20] The predominant clinical signs of uremia seen in large animals are depression and anorexia. Weight loss, gastrointestinal ulcers, polyuria, polydipsia, melena, and diarrhea are other noticeable effects. Oral erosions or ulcers, gingivitis, diffuse stomatitis, dental tartar, and halitosis may be evident on examination of the oral cavity. Coagulopathy and platelet dysfunction make uremic patients prone to gastrointestinal hemorrhage and impaired clotting during surgery. Pulmonary edema and uremic encephalopathy may develop in rare cases.

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• CHAPTER 11

Alterations in the Skin

STEPHEN D. WHITE, *Consulting Editor**

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MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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General Approach to Diseases That Alter the Skin

It is important to remember that the skin has a limited repertoire with regard to its presentation; many diseases with various causes may manifest with similar lesions. However, certain patterns of response to disease are also recognized. In order to manage skin problems successfully, the veterinarian must use a systematic approach by obtaining a complete history, performing a thorough physical examination, and, when appropriate, using one or more simple diagnostic techniques.[1] The following sections discuss the materials and methods necessary to perform techniques commonly used to diagnose large animal skin disease.

History

To obtain a differential diagnosis list, the questions listed on the sample history form (Fig. 11-1) should be answered. Often it is helpful to repeat the questions to the owners at a later time or to give them a history form to complete at their leisure, which allows them greater opportunity to remember details relevant to the skin disease. The goals should be to determine the initial features of the skin disease, how the problem has progressed, and what factors have influenced its progression to the present state.

Physical Examination

The diagrams and terms listed on the sample form (Fig. 11-2) may serve as a useful guide for recording the physical findings. The animal's overall condition should be assessed, and a general physical examination should be performed to determine if the disease is limited to the skin or if systemic signs of disease are also present. The distribution, morphology (e.g., papules, nodules, wheals, patches of alopecia), and size of skin lesions should be noted. The mucous membranes also should be examined, and the skin surface palpated to determine features not readily noted visually (e.g., crusts beneath the hair, dryness, ability to epilate hairs, and presence of peripheral lymphadenopathy).

The practitioner's goal should be to describe accurately the animal's clinical appearance in a written record for future reference.

Diagnostic Techniques

For most of the techniques that follow, a good-quality microscope equipped with ×4, ×10, ×40, and ×100 (oil immersion) objectives is recommended.

SKIN SCRAPINGS. Skin scrapings are used primarily to demonstrate microscopic ectoparasites, specifically mites. Scraping is a quick, simple, inexpensive diagnostic technique that is more useful in ruminants than in horses because equine mite infestations are relatively uncommon. The materials needed to perform a skin scraping are a sterile container, mineral oil, a medical-grade spatula (Fisherbrand Microspatula with Flat-Ended Blade, catalogue no. 21-401-20, Fisher Scientific, Pittsburgh; www.fisherscientific.com), glass slides, and cover slips. Although a No. 10 scalpel blade may be used, a medical-grade spatula will not cut the skin in cases of sudden movement of the animal yet is just fine enough to be able to scrape deep enough to find *Demodex* species mites, if indicated. If the hair coat is thick, a small area should be clipped before scraping. Multiple superficial scrapings that cover large surface areas should be performed, as well as several scrapings covering a small area that are deep enough to create capillary oozing. The collected material should be placed in a container until it can be examined microscopically. Some of the sample can then be placed on a glass slide and finely dispersed in enough mineral oil to provide a confluent layer without air bubbles beneath a cover slip. The slide should be scanned systematically with the ×10 objective. If something of importance is noted, the ×40 objective can be used to examine the specimen in more detail.

DERMATOPHYTE CULTURE. The materials necessary to perform a dermatophyte culture include dermatophyte test medium, mosquito forceps, a medical-grade spatula, and sterile empty containers such as evacuated blood collection tubes. The forceps should be sterile, and each lesion to be sampled should be wiped gently with either water or isopropyl alcohol (there is some controversy as to which is better; I use water out of concern that the alcohol may inhibit fungal growth on the culture medium) to remove as many bacterial and fungal contaminants as possible and allowed to dry. Multiple small, scaling, and slightly crusted lesions should be sampled; the samples should be stored in individual containers. Broken hairs, scales, and crusts from the periphery of the lesions are collected (because dermatophytes cause peripherally expanding lesions). A spatula may be useful for scraping scales and debris from the skin surface. The forceps are used to pluck broken hairs.

If the clinician's practice performs its own fungal cultures, the samples should be removed from the containers with a sterile forceps in a clean working area and gently pressed onto, but not buried beneath, the culture medium. The top of the culture dish or vial should be loosely replaced to allow sufficient ventilation for the culture to grow. Most dermatophytes grow at room temperature, except for some strains of *Trichophyton verrucosum* that require

*Contributions to portions of this chapter in previous editions by Anne G. Evans are acknowledged.

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DERMATOLOGY HISTORY FORM

Owner_____ Date_____

Animal's name_____ Case #_____

Age of animal_____

Age when purchased_____ Age when skin problem started_____

Where on the body did the problem start?_____

What did the skin problem look like initially?_____

How has it spread or changed?_____

What season did the problem start?_____

Is the problem seasonal or year round?_____

If seasonal, what seasons is the disease present?_____

Does the animal itch?_____ If so, where?_____

Do any animals contacting the affected animal have skin problems?_____

Do any people in contact with the animal have skin problems?_____

Is fly control used?_____ If so, describe_____

_____

Do any relatives of this animal have skin problems?_____ If yes, explain_____

_____

List injectable, oral, or topical medications that have been used before and after onset of the disorder_____

_____

_____

Which medications were of benefit?_____

_____

Which medications aggravated the condition?_____

_____

Describe the environment where the animal is kept, including bedding_____

_____

_____

_____

What is the animal fed?_____

_____

Any additional information you feel is relevant to the skin disease_____

_____

_____

FIG. 11-1 Sample dermatologic history form.

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DERMATOLOGY PHYSICAL EXAMINATION FORM

Date_____

Distribution of lesions:

_____

_____

_____

Primary lesions (circle):

Macule	Patch	Papule
Pustule	Vesicle	Bulla
Wheal	Nodule	Tumor

Secondary lesions (circle):

Scale	Erosion	Excoriation
Fissure	Ulcer	Lichenification
Erythema	Alopecia	Hyperpigmentation
Crust	Comedone	

Pruritus_____ Epilation_____

Skin thickness_____ Skin tone_____

Hair coat_____ External parasites_____

Diagnostic workup:

Skin scrapings_____

KOH preparation_____

Dermatophyte culture_____

Acetate tape prep_____

Dermatophilus prep _____

Histopathology_____

Immunofluorescence_____

Microfilarial prep_____

Bacterial culture & sensitivity_____

Differential diagnosis:_____

Initial therapy:_____

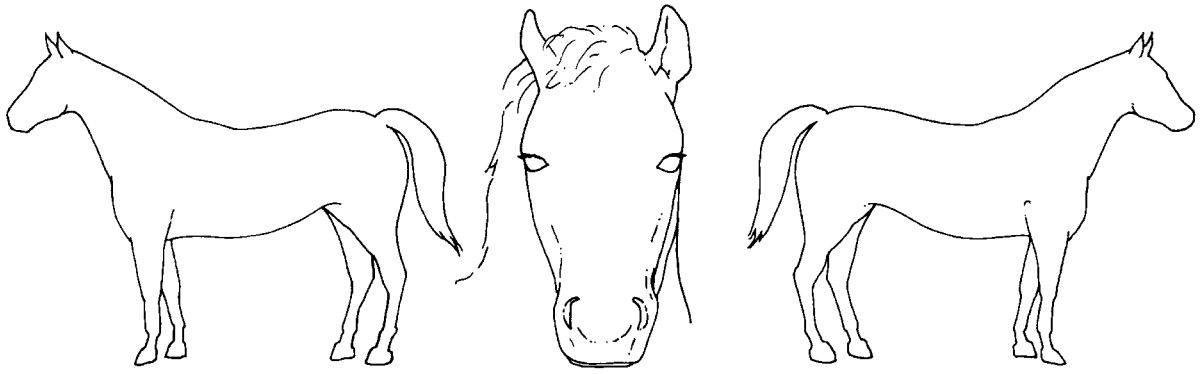


FIG. 11-2 Sample dermatologic physical examination form.

incubation at 37° C (98.6° F). The colony usually first appears in 5 to 7 days, although all cultures should be allowed to incubate for 3 weeks before a negative result is declared.

Dermatophyte test medium is an amber-colored Sabouraud's dextrose agar containing phenol red, a pH indicator, and several antibacterial and antifungal agents to inhibit growth of contaminant organisms. Dermatophytes preferentially use the protein in the medium as they begin to grow, producing alkaline metabolites that cause the medium to turn red. The dermatophyte colony is typically a white to beige, powdery to fluffy growth; the colonies are never dark colored. Most saprophytic (contaminant) fungi metabolize the carbohydrates first, producing acidic metabolites that do not change the color of the medium. It should be stressed that after the carbohydrate source has been depleted, saprophytes use the proteins and produce a red color change.

Positive identification of a dermatophyte is made in most instances if a white to beige, powdery to fluffy colony begins to appear on the medium at the same time or within 24 hours of the appearance of a

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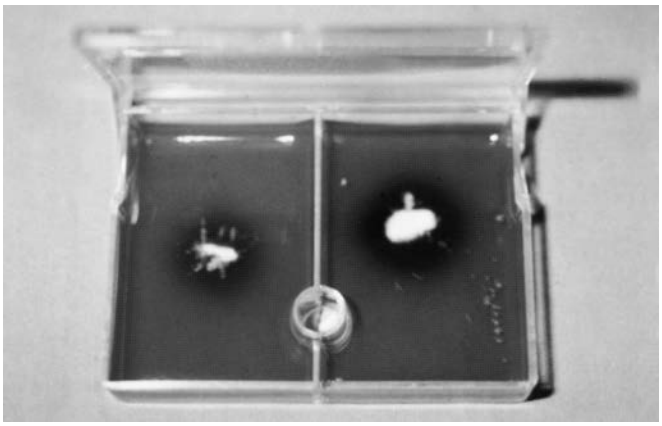


FIG. 11-3 Positive result on dermatophyte culture. Growth of light-colored colony and simultaneous red color change are shown on dermatophyte test medium (right half of culture plate). Growth of dermatophyte on rapid-sporulating medium is shown on left half of culture plate.

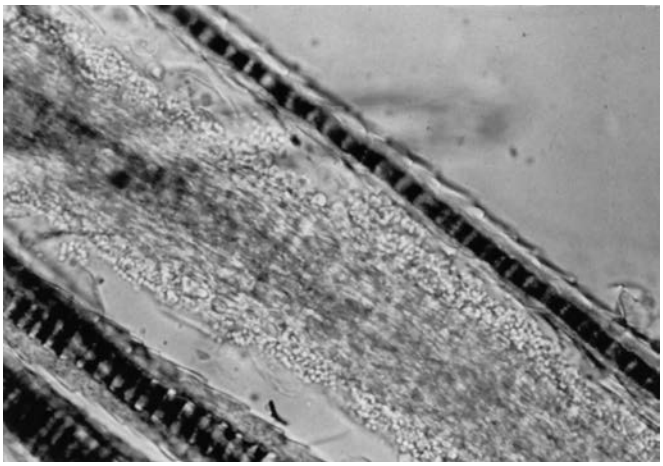


FIG. 11-4 Positive result on potassium hydroxide (KOH) preparation. Note the small, spheric fungal elements (arthroconidia) on the hair shaft.

red color change in the medium (Fig. 11-3). An infrequently encountered exception to this rule is growth of the saprophyte *Scopulariopsis brevicaulis,* a tan to light brown, smooth or mealy colony that produces a concurrent red color change in the medium. It is essential to check the cultures daily to determine if the red color change and colony growth occur nearly simultaneously. If any doubt exists about the type of colony growth, the sample should be submitted to a diagnostic laboratory for specific identification.

POTASSIUM HYDROXIDE PREPARATION. A potassium hydroxide (KOH) preparation may permit immediate diagnosis of dermatophytosis. However, examination of KOH preparations requires considerable experience because fungal elements may be easily overlooked (false-negative result) and numerous artifacts such as fibers, cholesterol crystals, or oil droplets may be mistaken for fungal elements (false-positive result). It is always advisable to perform a dermatophyte culture in conjunction with a KOH preparation.

The materials necessary to perform a KOH preparation include mosquito forceps, a medical-grade spatula, a sterile empty container, glass microscope slides, cover slips, a Bunsen burner, and clearing solution. As with a dermatophyte culture, it is important to sample several lesions to increase the chances of obtaining a diagnostic sample. Hairs and scales are collected from the periphery of the lesions with the mosquito forceps and the spatula. The samples are stored in the sterile container until a microscopic examination can be performed. A drop of the KOH clearing solution is placed on a glass slide, hairs and scales are added to the solution, and a cover slip is placed over the material. The slide should be scanned systematically with the ×10 objective for abnormal-appearing hairs with a fuzzy internal structure. If these features are noted, a higher-powered objective should be used for more detailed examination. A positive result with a KOH preparation demonstrates hyphae, which are usually uniform in width and septate. Beadlike chains of arthroconidia may be seen as well (Fig. 11-4).

The purpose of the clearing solution is to dissolve the hard keratin and bleach the melanin of the hair shaft so that the fungal hyphae and arthroconidia can be identified more readily. Care should be taken not to spill any clearing solution on the microscope because it can damage the lenses. Several types of clearing solutions are available. If 15% KOH is used, the slide should be heated for 15 to 20 seconds to facilitate clearing before examination. As an alternative, the preparation can be allowed to stand at room temperature for 30 minutes before viewing.

ACETATE TAPE PREPARATION. Acetate tape preparations for parasites are used primarily to diagnose infection with *Oxyuris equi,* although they may also be used to diagnose *Chorioptes* species. The

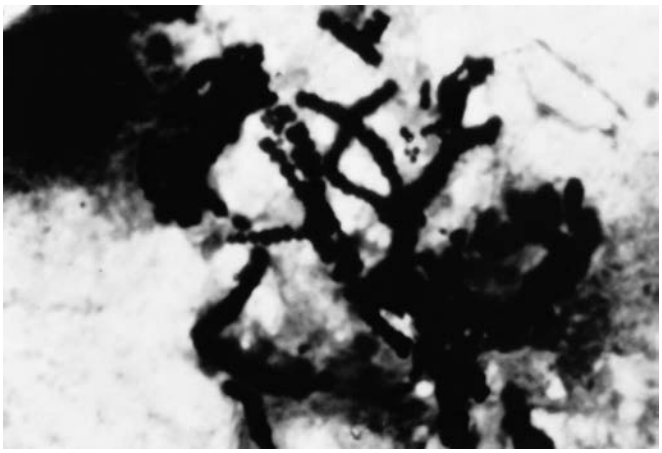


FIG. 11-5 Positive result on *Dermatophilus* preparation. *Dermatophilus congolensis* is a large, gram-positive, filamentous bacterium that divides horizontally and longitudinally, forming parallel rows of cocci (zoospores) that are commonly described as "railroad tracks."

materials required to perform an acetate tape preparation include acetate (nonfrosted) tape, mineral oil, and glass microscope slides. A piece of the tape is pressed over several areas in the anal and perianal region when looking for *O. equi* or over an affected region that has been lightly clipped when looking for *Chorioptes* species. The tape is then placed with the adhesive side down on a line of mineral oil that was placed lengthwise on a glass microscope slide. The purpose of the oil is to help clear the debris and facilitate examination of the preparation for parasites. The preparation is scanned with the ×10 objective for organisms.

DERMATOPHILUS PREPARATION. This test is used as an aid in identification of *Dermatophilus congolensis.* Crusts should be removed from the patient and the excess hair carefully trimmed from the crusts with a small pair of scissors. The crusts are minced with the scissors and mixed with several drops of saline on a glass slide. After the crusts have softened in the saline for several minutes, they should be crushed with the tip of an applicator stick. The excess debris is removed, and the slide is allowed to air dry. The slide should then be heat fixed; stained with Gram, Giemsa, or Wright stain; and examined for the characteristic bacteria. *D. congolensis* organisms are gram-positive, branching, filamentous bacteria that divide horizontally and longitudinally, forming parallel rows of cocci (zoospores) that are commonly described as resembling "railroad tracks" (Fig. 11-5).

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CYTOLOGIC STUDIES. Cytologic studies are of value when dealing with crusts, scales, pustules, vesicles, nodules, or tumors. They can quickly indicate the presence of infectious organisms and provide a rough assessment of the spectrum of cell types present in a lesion (e.g., neoplastic, acantholytic, or inflammatory). The surface of the lesion should be gently shaved (if necessary); particular care must be taken not to rupture fragile pustules and vesicles or remove crusts. Crusts and scales may be evaluated by performing a superficial scrape with a spatula, placing the material on a dry (i.e., no mineral oil) microscope slide, heat fixing, and then staining with Gram, Giemsa, or Wright stain. Alternatively, acetate tape may be used to collect the material, and instead of placing the tape on a slide that has mineral oil (as is done when looking for parasites), the tape is placed on a slide on which several drops of the "blue" solution from the Wright stain have been placed. With either of these methods, the slide is scanned for areas of sufficient stain with the ×4 objective and then examined using the ×100 objective with immersion oil.

Cytologic evaluation of intact pustules and vesicles is best accomplished by gently opening an intact lesion with the tip of a sterile No. 15 scalpel blade or 25-gauge needle and smearing the contents on the surface of a glass slide. The slide should be air dried, heat fixed, stained with one of the previously mentioned stains, and examined. Nodules, tumors, and swellings are best evaluated by fine-needle aspiration. A 25- or 22-gauge needle on a 12-mL syringe is introduced into the mass, and negative pressure is applied. Several passes through the mass at different angles should be performed. After negative pressure has been released, the needle is removed from the mass. The needle is then removed from the syringe, the syringe is filled with air, and the needle is reattached. Alternatively, just the needle is introduced into the mass in several places and then attached to a syringe filled with air. The contents of the needle are pushed out onto glass slides, which are subsequently dried, fixed, and stained as described previously.

BIOPSY FOR ROUTINE HISTOPATHOLOGIC EXAMINATION. The following materials are necessary to perform a skin biopsy:

- 6-mm and 4-mm biopsy punches
- No. 15 scalpel blade
- Sharp scissors
- Curved mosquito forceps
- Needle holders
- No. 2-0 or 3-0 nonabsorbable suture
- 2% lidocaine
- 3-mL syringe with a 22- to 25-gauge needle
- Tongue depressor or cardboard
- Gauze
- 10% buffered formalin

It is important *not* to surgically prepare a lesion that is going to be biopsied for histopathologic examination. Shaving and scrubbing remove crusts and epithelial tissue that may be important in reaching a diagnosis. Cutaneous infections caused by biopsies taken in this manner are extremely uncommon. If the clinician is concerned about infections, surgically prepare the site *after* the biopsy has been taken, before suturing.

Local anesthesia is sufficient for obtaining most skin biopsies. A 22- to 25-gauge needle is inserted at the margin of the lesion until the bevel is buried in the subcutaneous tissue beneath the lesion. The 2% lidocaine (0.5 to 1 mL) is injected, allowing 1 to 2 minutes for the anesthetic to take effect. Infiltration of the dermal or epidermal tissue with lidocaine should be avoided because this causes artifactual changes in the specimen.

Four techniques can be used to biopsy skin: the excisional, wedge, punch, and elliptic techniques. When the lesion to be sampled is a single nodule, the ideal biopsy technique is excisional because the lesion can be eliminated at the same time the histologic diagnosis is made. If the lesion is a tumor and too large to be excised, a generous wedge biopsy should be performed, which ideally extends from the margin to the center and includes the full depth of the lesion.

Most lesions can be sampled with a 6-mm biopsy punch. A disposable biopsy punch (Baker's Biopsy Punch, Chester A. Baker Laboratories, Miami, Fla.) can usually be used to obtain two or three biopsies before its edge is dulled and it must be discarded. The punch is placed directly over the lesion and rotated in a continuous circular motion while pressure is applied until the blade of the punch is in the subcutaneous tissue. If the punch has cut to a sufficient depth, when it is removed the tissue sample is free of the adjacent dermis and remains only loosely attached to the underlying subcutaneous tissue by a thread of connective tissue. A small pair of curved mosquito forceps is used to gently grasp the subcutaneous part of the biopsy and elevate it from the surrounding tissue. The specimen is then cut free with a pair of sharp scissors. It is important to avoid handling the epidermal and dermal parts of the sample during this procedure to minimize artifactual changes in the tissue sample. The sample is *gently* blotted to remove any surface hemorrhage and immediately placed in 10% buffered formalin for fixation. The site from which the sample was taken may then be cleaned with an antiseptic solution and closed with either two simple interrupted sutures or a cruciate stitch using No. 2-0 or 3-0 nonabsorbable sutures.

Although punch biopsies are convenient and easy to use, they are not appropriate for vesicular, bullous, and ulcerative lesions (unless the first two are small enough to be completely enclosed within the biopsy punch). For these lesions the method of choice is a surgical elliptical biopsy. The biopsy of vesicular and bullous lesions should encompass the entire lesion. Biopsy of samples of ulcerations should include abnormal tissue, the leading edge of the lesion, and normal tissue. Because an ulcer lacks epithelial tissue, the leading edge where epithelium remains may be the most rewarding in providing a histologic diagnosis. Thus the skin is biopsied so that the long axis of the ellipse crosses perpendicular to the leading edge of the ulcer (Fig. 11-6). It is important to mount surgical elliptical biopsies before placing them in formalin or they will curl during fixation, resulting in distortion of the histologic features during sectioning. To mount the specimen, the subcutaneous surface is placed on a small piece of a wooden tongue depressor or cardboard while gentle pressure is applied to the tissue so that it adheres to the surface. Then the specimen is placed in the formalin.

Ideally biopsy specimens should be submitted to a veterinary histopathologist with special interest and training in dermatopathology. Submission of adequately biopsied specimens of properly chosen lesions is the clinician's responsibility. To further increase the chances of securing clinically valuable information from the biopsy samples, the clinician must also provide the pathologist with a concise history of the skin problem, physical findings, a description of the morphology and location of the lesions (and if possible, images of the lesions),

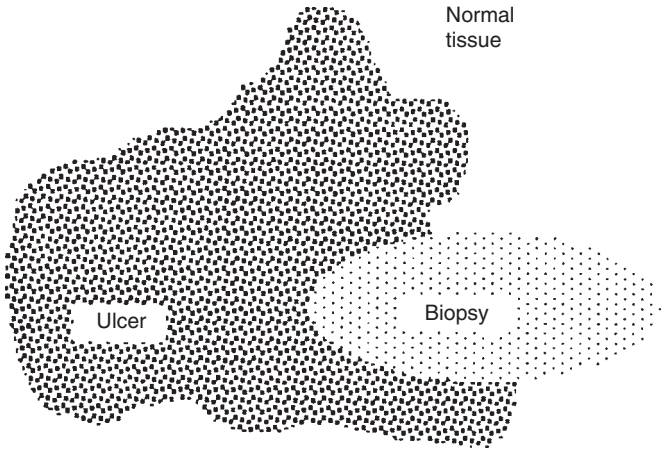


FIG. 11-6 An ulcerative lesion should be biopsied in an elliptical fashion, using a No. 15 scalpel blade, so that the long axis of the ellipse crosses perpendicular to the leading edge of the lesion.

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and a list of differential diagnoses. When the suspected clinical diagnoses are provided, the pathologist's efforts can be directed specifically toward confirming or ruling out those diagnoses.

BIOPSY FOR IMMUNOPATHOLOGY. Immunopathology may be used as an adjunct to conventional histologic testing when the clinician suspects that the patient has an immune-mediated skin disease. The two methods used are direct immunofluorescence, which requires a special medium for fixation (Michel's fixative), and immunoperoxidase techniques, which may be performed on the paraffin block prepared for the histopathologic study (i.e., the formalinized tissue section). The materials and the technique for biopsy for immunopathology are essentially identical to those for a routine histologic examination. Administration of corticosteroid medications within 3 weeks of testing may be associated with false-negative test results. It is advisable to bisect biopsy samples along their long axis, submitting half for direct immunopathology and half for histopathologic examination. It should be borne in mind that histopathology of the lesions, rather than immunopathology, is often the more accurate of the two methods in the diagnosis of autoimmune diseases; thus if faced with the choice (because of financial reasons or paucity of lesions) the clinician should always choose the former.

MICROFILARIAL PREPARATION. The microfilarial preparation technique is applicable to the diagnosis of cutaneous onchocerciasis in horses, stephanofilariasis in cattle, and elaeophorosis and parelaphostrongylosis of sheep and goats. After selecting the lesion to be sampled, a 6-mm punch biopsy is used to obtain the tissue sample in the same manner as for the histopathologic biopsy. The tissue should be split, and half preserved in 10% buffered formalin for routine histologic studies. The other half is placed on a dampened gauze sponge in a tightly closed container until the preparation can be performed. A small piece of the tissue that includes the dermis is placed on a glass slide and minced with a razor blade; a few drops of nonbacteriostatic saline are added. Bacteriostatic saline should not be used, because it kills the microfilaria and thus makes their identification more difficult. The specimen is incubated at room temperature for 15 minutes. The slide is then scanned with the ×4 objective along the margins of the tissue debris while the clinician searches for indication of motion in the saline. If the characteristic whiplash movement of the parasite is noted, a higher-powered objective should be used. If the preparation result is negative, a small amount of water is added to a Petri dish, the glass slide is rested on two wooden sticks above the water, and the cover is replaced on the dish. The preparation should be incubated for several hours or overnight and reexamined. The Petri dish helps prevent the sample from drying out.

BACTERIAL CULTURE. The method of bacterial culture depends on the type of lesion. All haired lesions should be gently shaved. Nodules and tumors should be cultured by aseptically excising the lesion or by obtaining a generous wedge of the tissue. To prevent culture contamination by surface bacteria, the nodules should be gently shaved, washed with an antiseptic soap, and dried with a sterile gauze pad. A perilesional injection of 2% lidocaine is used to anesthetize the tissue. The sample is placed in a transport medium and sent to a microbiology laboratory for culture. A papular eruption (rash) is best cultured by obtaining a sterile 6-mm punch biopsy of skin. Crusts may be lifted up and the underside cultured via a sterile culturette. Ulcerative lesions should not be cultured because any bacteria isolated are more likely to be opportunistic rather than primary pathogens. If the lesions are fluctuant (vesicles, pustules), the overlying skin can be opened gently with a No. 15 blade and some of the contents of the lesion transferred with the blade to the tip of a sterile culture swab. Although some older literature recommends not using sterile culturettes directly on the skin surface, due to concerns that nonpathogenic bacteria from the skin surface may be cultured,[1] the author has used this method of culturing papular eruptions or scale when a biopsy is not feasible.

SUBCUTANEOUS AND DEEP FUNGAL CULTURE. Subcutaneous and deep fungal cultures should be performed on nodules, tumors, and swellings. The technique is identical to that described for bacterial culture of these lesions.

Pruritus

Definition

Pruritus is an unpleasant sensation that provokes the desire to scratch. It is designated a primary cutaneous sensation, along with heat, cold, pain, and touch. There are two broad categories of pruritus. Physiologic or spontaneous itch is a sharp, well-defined, pruritic sensation that is sufficiently intense to prompt scratching but that does not result in significant irritation of the skin; this is a frequent daily occurrence in normal individuals. Pathologic itch is the less well-defined pruritus that occurs in a variety of primary and secondary skin disorders and in systemic diseases. It is an intense cutaneous discomfort that provokes vigorous scratching.[2]

Mechanisms of Pruritus

The investigation of the mechanism of pruritus has been primarily in laboratory animals and humans. It is presumed that much of this knowledge is applicable to other animal species. Pruritus is a distinct sensory quality transmitted from an arborizing network of nerve endings situated at or near the dermoepidermal junction. The sensation is carried to the spinal cord through small, unmyelinated C fibers. The fibers enter the dorsal root of the spinal cord and ascend in the ventrolateral spinothalamic tract through the posterior ventral nucleus of the thalamus to the sensory cortex. The pruritic sensation may be modified in the sensory cortex by behavioral factors or competing stimuli.[3,4]

Many physical and chemical stimuli can evoke pruritus, and many substances have been implicated as mediating pruritus in humans. Examples of these mediators, which are assumed to have importance in domestic animals as well, include the following[4]:

- *Histamine.* Histamine has been regarded as the classic mediator of pruritus. Histamine is present in mast cells in the dermis and in blood basophils. An intradermal injection of histamine produces pruritus within 20 to 50 seconds. Because many pruritic disorders respond poorly to antihistamines given either therapeutically or prophylactically, histamine is not believed to be the sole mediator of pruritus.
- *Endopeptidases.* Examples include trypsin, papain, and kallikrein.
- *Prostaglandins (E series* and *endoperoxidases).* Prostaglandins induce pruritus by potentiating the release of proteases from keratinocytes and leukocytes and by lowering the threshold and increasing the duration of histamine-induced pruritus.
- *Endogenous opioid peptides.* Opiates may potentiate preexisting pruritus. The opiate antagonist naloxone hydrochloride has an attenuating effect on the histamine-induced component of pruritus.
- *Substance P.* Substance P is a neurotransmitter found in the central and peripheral nervous systems. When introduced intradermally, it elicits a pruritic response.

Many factors can potentiate existing pruritus. Neurologic factors such as boredom and fatigue can potentiate a pathologic itch and possibly transform a physiologic itch into a pathologic itch. Local axonal reflexes can potentiate pruritus; that is, if a second stimulus is applied to an area close to one that is pruritic, the second stimulus, irrespective of its type, is perceived as an itch. In addition, skin with chronic dermatitis has limited perception of stimuli, and any stimulus applied to the affected region may be perceived as either a burning sensation or an itch. This phenomenon is known as "conversion itch." Secondary bacterial infections, vasodilatation, and inflammation result in a local increase in proteases that potentiate pruritus.[3]

Pruritus can be diminished by several nonpharmacologic mechanisms, the most common being application of competing stimuli. Pruritus is a minor sensation compared with the other primary

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BOX 11-1

Most Common Causes of Pruritus in Horses and Ruminants

Ectoparasites

Culicoides species (horses)
Other flying insects
Lice
Psoroptes cuniculi (goats)
Psoroptes ovis (sheep)
Sarcoptes scabiei (ruminants)
Chorioptes species (horses and cattle)

Hypersensitivity (Horses)

Atopic dermatitis

Infectious

Staphylococcal pyoderma (horses)
Dermatophytes

sensations of heat, cold, touch, and pain; thus local application of a competing stimulus to a pruritic area often suppresses the pruritic sensation. Scratching is an example of a competing stimulus. Scratching may relieve pruritus by disturbing the rhythm of afferent impulses traveling toward the central nervous system. An alternative theory is that scratching may cause transient damage to nerve fibers that convey the pruritic sensation. Unfortunately the effect is short-lived because the epidermal damage induced by scratching causes the release of epidermal proteases that may later increase the degree of pruritus. Centrally acting factors such as diversions or distractions can also diminish the perception of pruritus by providing competing stimuli directly to the cortex rather than locally to the skin.[3]

Approach to the Diagnosis of Pruritus

Pruritus is the most common sign of cutaneous disease. Most often in large animals it is caused by ectoparasites or a hypersensitivity reaction, or both (e.g., *Culicoides* hypersensitivity), but it may also be caused by cutaneous bacterial or fungal infections (e.g., dermatophytes, *Malassezia* species) (Box 11-1). Because pruritus may be a feature of a more generalized disease process, it is important to take the patient's general health into account. Hypersensitivity reactions, which are commonly pruritic, may or may not be limited to the skin. For example, anaphylaxis is a life-threatening hypersensitivity reaction that may manifest as pruritus in its early stages. Other pruritic skin diseases include immune-mediated diseases such as atopic dermatitis or pemphigus foliaceus; direct irritation by chemicals; and photoactivated dermatoses. It is helpful to formulate a differential diagnosis by considering each of these broad categories of diseases and using historic information, other cutaneous signs, and appropriate diagnostic tests to narrow the list of differential diagnoses.

The following steps are a guide to the diagnosis of pruritus in the horse and ruminant:

1. History and physical examination (see Fig. 11-1).
   a. Determine if the pruritus is a seasonal or year-round problem. A seasonally recurrent pruritic disease tends to suggest either seasonal exposure to a parasite (e.g., lice in the winter, flies in the summer) or a seasonal environmental allergen (e.g., pollens) as the cause. Determine the level of fly exposure for the animal that is pruritic in the warmer months.
   b. Determine if the pruritus is generalized or localized and, if localized, what areas of the body are affected. For example, photoactivated dermatoses are limited to the white-haired regions.
   c. Determine if contact animals of the same and/or different species are affected or unaffected. The presence of multiple pruritic animals is suggestive of a contagious disease (e.g., dermatophytes, ectoparasites) or a disease of common exposure *(Culicoides)*. A single pruritic animal among a group of unaffected animals is more likely to be experiencing a hypersensitivity reaction (drug or environmental).
   d. Determine what topical and systemic medications were given to the animal both before and after the onset of the problem. Medications given before onset may be the cause of the pruritus, and those given after onset may interfere with the results of diagnostic tests.
   e. Determine whether all the cutaneous lesions can be attributed to self-trauma or if primary cutaneous changes are present (e.g., wheals, nodules, pigmentary changes).
   f. Determine whether, on close inspection, the coat shows evidence of small but grossly visible parasites such as lice or their eggs.
2. The most useful diagnostic tests are skin scrapings, acetate tape preparations, dermatophyte culture plus KOH preparation, *Dermatophilus* preparation, microfilarial preparation, biopsy for routine histopathologic examination, and intradermal testing (see Chapter 40).

Nodules, Tumors, and Swellings

Definition

A nodule is a circumscribed, solid elevation larger than 1 cm in diameter that does not deform when palpated. Nodules extend into the deeper layers of the skin and are usually the result of cellular infiltrates in the dermis or subcutis. *Tumor* is a less precise term that usually refers to a neoplastic, nodular enlargement of the skin or subcutaneous tissue.[3] The term *tumor* is most commonly used to describe large nodular neoplasms. In addition to nodules and tumors, swellings include elevated lesions that pit with pressure (wheals) and fluctuant lesions (cysts and abscesses).

Mechanisms of Nodule, Tumor, and Swelling Formation

Nodular lesions can be subdivided into inflammatory and neoplastic lesions. Inflammatory nodules are composed of a massive mixed cellular infiltrate involving the dermis, the subcutis, or both. The inflammatory infiltrate may contain variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils. Cellular infiltration is usually stimulated by the presence of foreign material, and the nature of that material influences the composition of the inflammatory infiltrate. The foreign material may be infectious (parasite, bacteria, or fungi) or noninfectious (fibrin, crystalline material, or other inert substances). Grossly visible nodules develop as the masses of inflammatory cells accumulate in the tissues to phagocytize or "wall off" the foreign material. As the lesion enlarges, the dermis and subcutis are obliterated by the inflammatory infiltrate and the overlying epidermis may become atrophic, resulting in ulceration of the nodule's surface.

Most cutaneous and subcutaneous neoplasms form nodular lesions. Cutaneous and subcutaneous neoplasms may either arise from a cell type of the epidermis, dermis, or subcutis or less commonly metastasize from another tissue of origin. Cytologically and histologically, neoplasms are composed of a uniform population of pleomorphic cells with variable atypia. Neoplasms may stimulate a secondary inflammatory reaction.

Swellings include solid lesions such as nodules and tumors, as well as urticaria, cysts, and abscesses. Urticarial lesions (wheals, hives) are often transient, localized, inflammatory lesions caused by a vascular reaction in the dermis in which vasodilatation results in fluid transudation with or without erythema. The fluid is not compartmentalized but dispersed evenly throughout the dermal tissue. The result is an elevated lesion that, unlike a nodule, pits with pressure and often dissipates within minutes to hours as the fluid is resorbed. Typically a sparse, perivascular infiltrate that is usually lymphocytic is seen, although the infiltrate may be dense and intermingled with eosinophils. Urticaria is usually well circumscribed, although with confluence the edema may assume geometric shapes.

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BOX 11-2

Most Common Causes of Nodules, Tumors, or Swellings in Horses and Ruminants

Horses

Infectious

Corynebacterium pseudotuberculosis
Habronema species
Sporotrichosis

Neoplasia

Sarcoid
Squamous cell carcinoma
Melanoma

Sterile, Nonneoplastic

Eosinophilic granuloma
Exuberant granulation tissue (proud flesh)
Urticaria (hives)

Ruminants

Infectious

C. pseudotuberculosis
Hypoderma species (warbles)
Sporotrichosis
Actinobacillosis
Actinomycosis

Neoplasia

Squamous cell carcinoma
Fibroma or fibrosarcoma
Epidermal inclusion cysts

Sterile, Nonneoplastic

Urticaria (hives)

A cyst (Latin for *sac*) is an epithelium-lined cavity containing fluid or semisolid material.[3] A cyst usually presents as an elevated, smooth, well-circumscribed, fluctuant mass. Cutaneous cysts are usually lined by adnexal epithelium (hair follicle, sebaceous or apocrine epithelium) and are filled with cornified cellular debris and sebaceous or apocrine secretions.

An abscess is a localized, fluid-filled, fluctuant lesion; if large enough, it may be balloted. It results from a dermal or subcutaneous accumulation of the debris of dead cells and tissue elements liquefied by the proteolytic and histolytic enzymes elaborated by polymorphonuclear cells (e.g., pus). Abscesses most commonly result from localized infection, although they occasionally result from septicemia or may be sterile.

Approach to the Diagnosis of Nodules, Tumors, and Swellings

Nodules, tumors, and swellings may arise from a variety of cutaneous disorders and, in rare cases, as signs of a systemic disease. The major categories of diseases that should be considered when forming a differential diagnosis include hypersensitivity reactions, infectious diseases, sterile inflammatory diseases, and neoplasia (Box 11-2). The primary systemic diseases that should be considered are amyloidosis, lymphosarcoma, and anaphylaxis.

The following steps are a guide to the diagnosis of nodules, tumors, and swellings in horses and ruminants:

1. History (see Fig. 11-1). Pay particular attention to:
   a. Signalment. Older animals are at greater risk for cutaneous neoplasia (e.g., gray horses and melanomas). However, neoplasia is not restricted to older animals; equine sarcoids are frequently recognized in horses as young as 3 years of age.
   b. Number and progression of lesions. If one or only a few lesions are present, hypersensitivity to arthropod bites should be considered, particularly if there is rapid onset of the lesion. Rapid onset of generalized lesions such as urticaria suggests a differential diagnosis of drug, flying insect, environmental (pollen), or (rarely) food allergies.
   c. A recent history of systemic illness, which might suggest that the lesion is a bacterial abscess.
2. Physical examination (see Fig. 11-2). In particular:
   a. Determine by palpation if the cutaneous lesions are nodules or swellings.
   b. Inspect the lesion or lesions closely for evidence of cutaneous parasitism (ticks, breathing pores associated with *Hypoderma* larvae, yellow granules associated with cutaneous habronemiasis).
   c. Determine if the lesions are painful or pruritic (e.g., evidence of excoriations).
3. Perform fine-needle aspiration for cytologic studies.
4. Perform biopsy for histopathologic examination.
5. Perform bacterial culture and sensitivity.
6. Perform subcutaneous and deep fungal cultures.
7. Perform dermatophyte culture and KOH preparation.

Ulcerations and Erosions

Definition

An ulcer is a cutaneous defect that results from a complete loss of the epidermis and usually part of the underlying dermis.[3] Ulcers often heal with scarring that is caused by destruction of dermal collagen. An erosion is a cutaneous defect that results from a partial loss of the epidermis that does not penetrate beneath the basal laminar zone. Because an erosion does not involve the dermis, it heals without leaving a scar. Because the epidermis is a cutaneous barrier to invading microorganisms, ulcers and erosions are often secondarily infected.

Mechanisms of Ulcer and Erosion Formation

Ulcers and erosions are secondary lesions. Primary lesions develop spontaneously and are a direct reflection of underlying disease. Secondary lesions evolve from primary lesions or are artifacts induced by excoriation or external trauma. Primary lesions that may lead to the formation of ulcers and erosions include fluid-filled lesions such as pustules and vesicles. Rupture of these fragile lesions results in epidermal destruction and erosion or ulcer formation. Swellings such as abscesses and cysts may also rupture, resulting in ulceration, but these primary lesions are more stable and often remain intact. Nodules and tumors may become secondarily eroded or ulcerated. As the nodule or tumor enlarges, the mass exerts pressure on the overlying epidermis, leading to epidermal atrophy and ultimately a break in epidermal confluence, resulting in ulceration and erosion. The most common cause of ulceration and erosion is pruritus, which induces excoriation and hence epidermal destruction. Ulcers and erosions may also result from external trauma such as epidermal destruction arising from mechanical, thermal, or chemical causes (Box 11-3).

Approach to the Diagnosis of Ulcerations and Erosions

To diagnose the cause of an ulcer or erosion, the clinician must first determine the primary lesion that resulted in ulceration and erosion. Ulcers and erosions occurring secondary to pustules and vesicles, to swellings such as abscesses and cysts, to nodules and tumors, to pruritus, and to external trauma must be differentiated. The list of differential diagnoses relevant to each of these groups of primary lesions is then considered.

The following steps are a guide to the diagnosis of ulcerations and erosions in horses and ruminants:

1. History (see Fig. 11-2)
   a. Determine if the animal is pruritic.
   b. Determine if the animal has been subjected to external trauma (mechanical, thermal, or chemical).

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BOX 11-3

Most Common Causes of Ulcerations and Erosions in Horses and Ruminants

Immune-Mediated

Adverse drug reaction
Contact irritant or hypersensitivity
Photosensitivity
Purpura hemorrhagica (horses)
Vasculitis

Infectious

Dermatophilus congolensis
Habronema species (horses)
Viral diseases (in ruminants; e.g., infectious bovine rhinotracheitis, vesicular stomatitis, bovine herpes mammillitis)

Neoplasia

Squamous cell carcinoma

c. Determine what topical and systemic medications were given to or used on the patient before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest a drug hypersensitivity.

2. Physical examination (see Fig. 11-2)
   a. Examine the oral cavity and mucocutaneous junctions for lesions. Oral or mucocutaneous lesions (or both) in the horse might suggest accidental ingestion of a vesicant, or the rare diagnosis of bullous pemphigoid or pemphigus vulgaris. In a ruminant these lesions are often seen with viral infections.
   b. Look for evidence of excoriation, suggesting that the ulcerations and erosions have occurred secondary to pruritus.
   c. Look for evidence of primary lesions such as pustules, vesicles, nodules, tumors, or swellings, which may have preceded the ulcerations and erosions.
3. Biopsy for routine histopathologic examination
4. Biopsy for direct immunofluorescence testing

Papules, Pustules, and Vesicles

Definition

A papule is a solid, circumscribed, elevated lesion up to 1 cm in diameter. Papules are essentially small nodules that do not extend beneath the dermis. A pustule is a fluctuant, circumscribed, elevated accumulation of pus (inflammatory cells and often necrotic debris) up to 1 cm in diameter (e.g., a small abscess). Pustules are frequently associated with infectious diseases, although sterile pustular diseases (such as pemphigus foliaceus) exist. A vesicle is a fluid-filled, acellular, circumscribed, elevated lesion up to 1 cm in diameter. A bulla is a vesicle that is larger than 1 cm in diameter. All these lesions can be either follicular or nonfollicular in orientation, depending on the underlying cause. Pustules and vesicles are rarely seen clinically because of their fragility and hence their susceptibility to rupture. Because papules are solid lesions, they are more stable and therefore more commonly encountered.

Mechanisms of Papule, Pustule, and Vesicle Formation

Papules usually form as a result of an infiltrate in the dermis, either cellular or noncellular. Cellular infiltrates may include inflammatory or neoplastic cells, although neoplastic papular lesions are relatively uncommon in large animals. Inflammatory infiltrates may be mixed, containing variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils, or one cell type may predominate. The composition of the inflammatory cells is influenced by the underlying cause of the papule, and the possible causes are extensive. Noncellular papular infiltrates include substances such as edema fluid, amyloid, and proliferative collagen, although these are relatively rare.

Pustules form as the result of an intraepidermal, subcorneal, or, less commonly, subepidermal accumulation of inflammatory cells. Infiltration of inflammatory cells, particularly polymorphonuclear leukocytes, leads to the release of proteolytic enzymes that liquefy tissue elements and result in the formation of a fluctuant lesion. Eosinophils, acantholytic cells, and infectious organisms may also be noted in a pustule, depending on the underlying cause. The stimulus leading to pustule formation is most commonly infectious, although pustules can result from noninfectious causes such as hypersensitivity reactions and autoimmune disease.

Vesicles form either at the dermoepidermal junction (subepidermal) or in the epidermis (intraepidermal) as a result of malformation or destruction of the basement membrane zone, or confluence of intercellular edema (spongiosis). Clinically these types of vesicles are indistinguishable. Vesicles form as the result of certain viral diseases, during severe inflammatory reactions (allergic contact dermatitis), or with cutaneous physical damage (mechanical, chemical, or thermal). In pemphigus foliaceus or pemphigus vulgaris, autoantibodies bind to transmembrane proteins between the epidermal cells, causing disruption of epidermal intercellular attachments. The result is intraepidermal cleft formation that leads to vesiculation. In bullous pemphigoid, complement-activating antibodies bind to antigens in the basement membrane zone, causing degranulation of mast cells, chemotaxis of neutrophils and eosinophils, and release of tissue-destructive enzymes that injure the basement membrane zone. The result is loss of dermoepidermal adherence and vesicle formation.[3] Vesicles are transient, fragile lesions and therefore are rarely recognized clinically. If they are not destroyed by surface trauma, rapid infiltration by inflammatory cells often transforms a vesicle into a pustule.

Approach to Diagnosis of Papules, Pustules, and Vesicles

Although papules, pustules, and vesicles may look somewhat similar on a cursory physical examination, the clinician must differentiate among the three and determine which of the lesions are present. Examination with a hand lens may help. The differential diagnoses relevant to papules, pustules, and vesicles are not necessarily the same (Box 11-4). In all cases it is important to determine if disease is limited to the skin or if the animal's general health is compromised as well.

Papular lesions have the most extensive differential diagnoses:

- *Hypersensitivity reactions.* Parasitic hypersensitivities are the most common (e.g., *Culicoides* hypersensitivity), although drug and (rarely) food hypersensitivities should also be considered. Many hypersensitivity reactions are pruritic.
- *Parasites.* Some species simply irritate the skin with their bites (e.g., horn fly [*Haematobia irritans*]) without inducing a hypersensitivity reaction.
- *Infectious diseases (bacterial, fungal, and viral).* Typically papules caused by infections have a follicular orientation.
- *Certain neoplastic diseases (papillomas or sarcoids).*
- *Uncommon causes* including autoimmune diseases such as pemphigus foliaceus, and diseases of uncertain cause such as equine sarcoidosis.

Pustules are most commonly associated with bacterial infections, although fungi and, in rare cases, parasites (*Demodex* species) can cause pustule formation. Sterile pustular diseases are less frequently seen (drug eruptions, sterile eosinophilic folliculitis of cattle)[5] but should be included in the differential diagnoses. Vesicles are rapidly infiltrated by inflammatory cells and transformed into pustules. Diseases commonly associated with vesicles include viral diseases of ruminants, autoimmune diseases, contact dermatoses, and burns.

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BOX 11-4

Most Common Causes of Papules, Pustules, and Vesicles in Horses and Ruminants

Horses

Hypersensitivity—Usually Papules

Culicoides species
Other flying insects

Infectious—Papules or Pustules

Staphylococcal pyoderma
Dermatophilus congolensis

Immune-Mediated

Pemphigus foliaceus—papules or pustules
Bullous pemphigoid—vesicles

Ruminants

Ectoparasites—Usually Papules

Sarcoptes scabiei
Psoroptes cuniculi (goats)
Lice

Infectious

Viral diseases (e.g., vesicular stomatitis)—vesicles
Staphylococcal pyoderma (goats)—pustules or papules

The following steps are a guide to the diagnosis of papules, pustules, and vesicles in horses and ruminants:

1. History (see Fig. 11-1)
   a. In particular, determine whether the lesions are pruritic, painful, or asymptomatic.
   b. Determine if contact animals of the same and/or different species are affected or unaffected. If contact animals are affected, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral (contagious ecthyma), or parasitic (*Culicoides* hypersensitivity).
   c. Trace the temporal course of development. Rapid onset of lesions may suggest a hypersensitivity reaction.
   d. Check for seasonality. A seasonal problem suggests a parasitic or hypersensitivity (pollens) cause. Lice are a problem in the winter, trombiculidiasis tends to occur in the fall, and most of the flying insects are present in the spring, summer, and early fall.
   e. Determine what topical and systemic medications were given to or used on the animal before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest drug hypersensitivity.
   f. Determine if the animal has been subjected to external trauma (thermal or chemical).
2. Physical examination (see Fig. 11-2)
   a. Gently palpate the lesions to determine if they are solid (papules) or fluctuant (pustules or vesicles).
   b. Note if the lesions have a follicular orientation, suggesting an infectious cause.
   c. Check for lesions involving the oral cavity and mucocutaneous junctions.
   d. Look for evidence of excoriation, suggesting that pruritus is a feature of the disease.
   e. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.
   f. Inspect contact animals for evidence of disease.
3. Skin scrapings of papular lesions
4. Cytologic studies
5. Dermatophyte culture and KOH preparation
6. *Dermatophilus* preparation
7. Bacterial culture and sensitivity
8. Microfilarial preparation
9. Biopsy for routine histopathologic examination
10. Biopsy for direct immunofluorescence testing

Scaling and Crusting

Definition

Scale is a visible accumulation of fragments of the horny layer of the skin (stratum corneum); it represents the final product of epidermal keratinization.[3] The process of forming the stratum corneum is termed *cornification.* Histologically scale is recognized as hyperkeratosis and can be subdivided into parakeratosis (cornification with nuclear retention) or orthokeratosis (cornification without nuclear retention). In some conditions parakeratosis and orthokeratosis may be present together. Grossly the scale varies in appearance. The color may be white, silver, yellow, brown, or gray. The consistency may be like that of bran flakes or powdery, coarse, greasy, or dry. Scale can be either loose or adherent to the skin or hair shafts.

Crusts are composed of variable amounts of serum, cells (leukocytes, erythrocytes, keratinocytes), fibrin, infectious agents (bacteria and fungi), debris, and/or medications. They often cover erosions or ulcerations. Heaped-up crusts are referred to as *vegetations.* On the basis of their histologic composition, crusts may be subdivided into cellular, serocellular, serous, and hemorrhagic types.

Mechanisms of Scale and Crust Formation

Scaling results from increased desquamation (exfoliation) of the stratum corneum. Exfoliation is the final stage of keratinization, the process by which the permanent population of cells of the basal layer of the epidermis divides, undergoes specific patterns of differentiation, and progresses toward the surface, where it is shed.[3,5] Excessive exfoliation and scale formation occur when the rate of keratinization is accelerated; when trauma to the surface of the epidermis (chemical, mechanical, or thermal) loosens the stratum corneum; or when the structures sustaining epidermal intercellular cohesion (such as transmembrane proteins) are destroyed, resulting in a loss of cohesion between epidermal cells.

Because crusts are composed primarily of serum and cells, their presence on the skin surface implies that vascular and epidermal permeability has increased to permit their formation. Serum and inflammatory cells are released into the tissues from the dermal vasculature and then cross the epidermis to the skin surface either through erosions or ulcerations or by permeating between the intercellular spaces. The exudate dries on the skin surface, in combination with any medication or debris that was already present on the hair or skin, to form the visible crust. Desquamating keratinocytes may be swept up in the exudate and become part of the crusts. Bacteria frequently invade crusts after they have formed and will be noted on histologic examination, even though they may not be a factor in the pathogenesis. Fungal organisms, when present, are more likely to be important to the pathogenesis of the underlying disease process.

Approach to Diagnosis of Scaling and Crusting

The most important factor in determining the underlying cause of scale or crust formation in either a horse or a ruminant is to determine if the patient is pruritic and if some or all of the lesions are induced by self-trauma. If pruritus is a feature, the approach to diagnosis of pruritus should be used because all pruritic diseases can cause scale and crust formation. If the patient is not pruritic, the most important differential diagnoses include infectious diseases (particularly dermatophilosis and dermatophytosis), nutritional disorders, toxicities, autoimmune disease (pemphigus foliaceus), cutaneous filariasis, photosensitization, irritant contact reactions or burns, and diseases of uncertain cause (e.g., in equine patients, sarcoidosis, aural plaques, and primary seborrhea) (Box 11-5).[3,6] Viral diseases are important nonpruritic causes of scaling and crusting in ruminants, although they are usually associated with ulceration and erosion with involvement of the oral cavity and mucocutaneous regions.

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BOX 11-5

Most Common Causes of Scaling and Crusting in Horses and Ruminants

Ectoparasites

Sarcoptes scabiei (ruminants)
Psoroptes cuniculi (goats)
Psoroptes ovis (sheep)
Lice
Chorioptes species (horses and cattle)

Infectious

Dermatophilus congolensis
Staphylococcal pyoderma
Dermatophytosis

Immune-Mediated

Pemphigus foliaceus (horses and goats)
Photosensitization (horses)

Nutritional

Zinc deficiency (ruminants)

The following steps are a guide to the diagnosis of scaling and crusting in horses and ruminants:

1. History (see Fig. 11-1)
   a. In particular, determine if the patient is pruritic.
   b. Determine if contact animals of the same and/or different species are affected. If they are, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral, or parasitic.
2. Physical examination (see Fig. 11-2)
   a. Look for evidence of excoriation, suggesting that pruritus is a feature.
   b. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.
   c. Inspect contact animals for evidence of disease, suggesting a contagious cause.
3. Skin scrapings
4. Acetate tape preparations
5. Dermatophyte culture and KOH preparation
6. *Dermatophilus* preparation
7. Biopsy for routine histopathologic examination (careful histologic examination of scale and crusts is essential to the search for the underlying cause of their formation)
8. Microfilarial preparation
9. Biopsy for direct immunofluorescence testing
10. Bacterial culture and sensitivity

Abnormal Coat Length and Density

Definition

Abnormalities in coat length and density can be subdivided into decreased coat length and density (alopecia, hypotrichosis) and increased coat length and density (hirsutism, hypertrichosis). Hirsutism, or excessive body hair, is far less common than alopecia, which is an absence of hair from areas where hair is normally present. Alopecias are usually classified as scarring (cicatricial) or nonscarring (noncicatricial). In cicatricial alopecias the hair follicles are destroyed, and hair loss is permanent because neogenesis of the hair follicle does not occur in an adult mammal. In nonscarring alopecias the hair follicles are retained; therefore the potential for regrowth remains. Both alopecia and hirsutism may be complete or partial, diffuse or focal, and congenital or acquired.

Mechanisms of Development of Abnormal Coat Length and Density

A basic understanding of the dynamics of hair structure and development is essential to an understanding of the mechanisms associated with pathologic changes in coat length and density.

The hair follicle and the sebaceous and apocrine glands are epidermal appendages. The hair follicle forms during fetal development as a downgrowth of epidermal cells toward a group of mesenchymal cells that ultimately become the dermal papillae. The sebaceous and apocrine glands begin as buds of epithelium from the sides of the developing hair follicle.

Hair is composed of keratin and is the product of the hair follicle. The hair shaft is the part of the hair that emerges from the skin surface. The hair root is the part of the hair in the follicle. The hair bulb is a knob of epidermal cells that attaches the follicle to the dermal papilla. Both the hair follicle and the shaft have distinct layers. There are two types of hair follicles: simple and compound. A simple hair follicle produces a single hair. A compound hair follicle produces multiple hairs with bundles of hairs sharing a common skin opening and a single follicle down to the level of the sebaceous gland. Below the sebaceous gland the follicle branches so that each hair has its own hair bulb. Horses and cattle have only simple follicles. Goats and sheep have a mixture of simple and compound hair follicles (Fig. 11-7).[3,5]

The normal hair growth cycle is divided into repeating stages: anagen, catagen, telogen, and exogen, with the size and shape of the follicle changing during each stage (Fig. 11-8). The amount of time a follicle spends in each phase varies with the species, breed, individual, and body region. In addition, it is influenced by factors such as photoperiod, stress, and disease. Anagen is the active phase of hair growth. Catagen is the transition stage from the growing to the resting state. Catagen is short, and the hair quickly enters the telogen phase, in which hair growth stops. As the follicle reenters anagen, a new hair grows up beside the old and dislodges it (exogen). The signal that stimulates progression from telogen to anagen is unknown.

Coat abnormalities may result from a multitude of endogenous and exogenous factors that can modify the normal pattern of hair growth and development.

The length, density, and texture of the coat of a normal animal are determined genetically, and a variety of hereditary defects result in coat abnormalities. These defects may cause changes in hair length, density, or quality. Coat quality may be abnormal at birth or may become apparent sometime before 6 months of age. A given defect may alter the number of follicles present in the skin, or the number of follicles present may be normal but there may be genetic alterations in the way the hair is produced. Altered hair production may manifest as an increased or a decreased growth rate or as structural deformities that result in weak hair shafts that break easily.

Nutritional imbalances can affect growth and maintenance of the coat in various ways, depending on the species. Nutritional deficiencies may result in a shift of greater numbers of follicles into telogen, thus increasing shedding. Dietary carbohydrate and protein deficiencies reduce the length, diameter, and strength of hair. Supplementing the diet with carbohydrate and protein releases protein for keratin formation, provides energy to use protein, and maintains mitotic activity in the hair matrix. Fatty acid deficiencies affect lipid production in the skin, leading to a dry coat with increased fragility. A variety of vitamin and mineral deficiencies may also result in poor hair growth or quality.

Inflammatory skin diseases frequently result in hair loss. Infectious inflammatory processes such as dermatophytosis and pyoderma are usually directed specifically at the hair or hair follicle. Inflammatory processes directed elsewhere may still affect the hair follicle by sweeping it up as an "innocent bystander."

Hormonal effects on hair growth are complex. Thyroid hormones, corticosteroids, sex hormones, melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), growth

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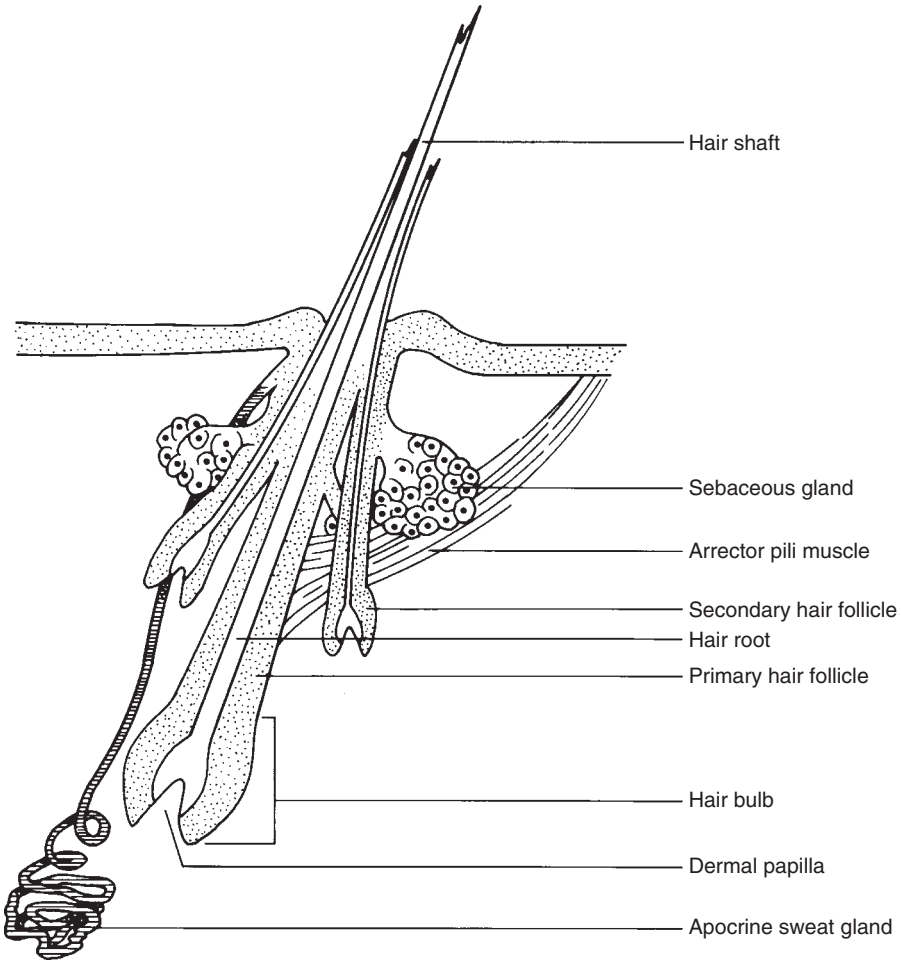


FIG. 11-7 Longitudinal section of a compound hair follicle.

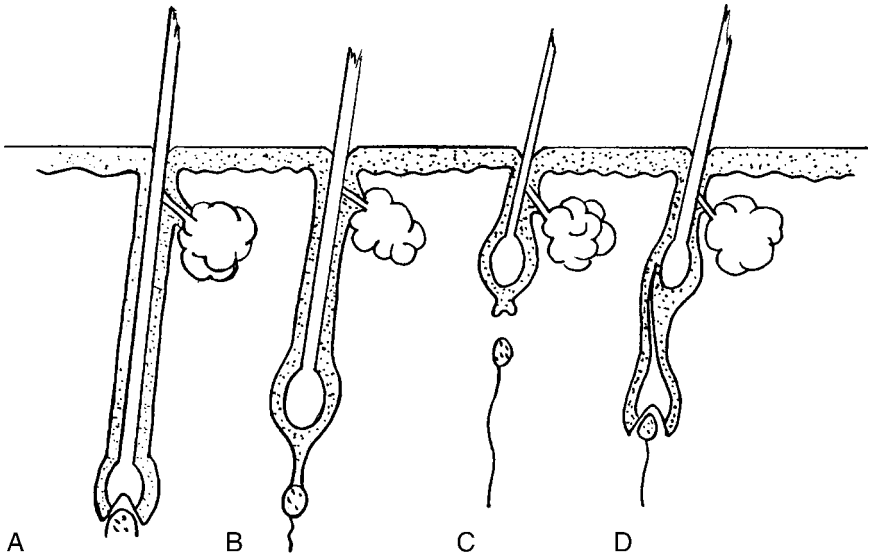


FIG. 11-8 Stages of the hair growth cycle. **A,** Anagen. **B,** Catagen. **C,** Telogen. **D,** Early anagen/exogen.

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hormone, and prolactin all affect hair growth. The effect of a single hormone may be modified in the presence of other hormones, and the importance or effect of any one hormone on hair growth may differ from species to species. Hormonal variations affect the hair coat quality and length by altering the period of time that hair follicles spend in any given part of the cycle, by influencing the rate of hair growth, and by inducing follicular atrophy. External factors such as changes in the photoperiod influence hair growth by altering hormonal levels.

Trauma to the skin is a frequent secondary cause of hair loss. Self-trauma induced by pruritus is the most common cause of alopecia. Hairs may be lost either from trauma to the hair shaft, resulting in breakage, or from trauma to the dermis, resulting in destruction of the hair follicle. In the former case, the hair regrows once the source of trauma has been removed. In the latter case, hair loss is permanent.

A variety of factors can result in hair loss by causing an abrupt shift of hairs into the telogen phase. Recognized causes of telogen effluvium include stress from high fever or severe illness and parturition.

Approach to Diagnosis of Abnormal Coat Length and Density

The differential diagnosis of abnormalities resulting in *increased* coat length and density is relatively limited and does not provide much of a diagnostic dilemma for the clinician. In the horse increased coat length and density is an acquired abnormality associated with equine hyperadrenocorticism.[3] In ruminants defects are congenital and are either the result of an in utero infection (border disease) or a breed-specific hereditary defect.[5]

The differential diagnoses of *decreased* coat length and density are extensive. The initial step is to determine if the alopecia is congenital, implying a hereditary defect, or acquired. If the abnormality is acquired, the clinician must determine if it is a primary alopecia or secondary to another cutaneous abnormality such as pruritus or ulceration. If alopecia is the result of another primary cutaneous abnormality, the clinician should focus on the differential associated with that primary abnormality. Finally, to help provide a prognosis for hair regrowth, the clinician should biopsy to determine if the alopecia is scarring (cicatricial) or nonscarring (noncicatricial). Regardless of the underlying cause and its resolution, hair will not regrow with a cicatricial alopecia because by definition the hair follicle has been destroyed. In a noncicatricial alopecia the potential for hair regrowth remains if the underlying cause for hair loss can be identified and resolved (Box 11-6).

The following steps are a guide to the diagnosis of decreased coat length and density in horses and ruminants:

1. History (see Fig. 11-1)
   a. Determine whether the lesions are congenital or acquired. If they are congenital, determine if any related animals are affected and if the lesions have progressed since birth.
   b. If the alopecia is acquired, determine if the animal is pruritic and if other cutaneous lesions have been observed.
   c. Determine if the animal's diet is nutritionally complete.
   d. Determine if the animal has been exposed to any toxic substances.
   e. Determine if contact animals of the same and/or different species are affected. If contact animals are affected, a contagious problem such as dermatophytosis or dermatophilosis should be considered. Because feed and environment are also shared, dietary deficiencies and toxicities should be included in the differential diagnosis.
   f. Determine what medications have been given systemically or applied topically to the patient. Use of certain topical agents, along with a history of an inflammatory stage preceding or coincident with the alopecia, may suggest a diagnosis of contact dermatitis. Administration of systemic medications may suggest that the cause is a drug hypersensitivity.
   g. Determine if the animal has been subjected to any stresses that might provoke a telogen effluvium.
2. Physical examination (see Fig. 11-2)
   a. Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting hair loss related to a dietary deficiency? Is it febrile or suffering from a severe systemic disease, suggesting a telogen effluvium?
   b. Can the hairs be epilated readily from the coat? If not, hair loss may be caused by trauma (self-induced or external). If so, underlying nutritional, hormonal, or stress-related causes of alopecia are more likely.
   c. Look for evidence of excoriation, suggesting that self-trauma is the cause of the hair loss.
   d. Determine whether the lesions are generalized or localized, either to particular areas of the body or to certain hair colors (e.g., black hair follicle dystrophy). Note if the hair loss has a symmetric pattern.
   e. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.
   f. Inspect contact animals for evidence of disease.
3. Microscopic examination of the ends of affected hairs (squared or broken ends suggest that the hair loss is traumatically induced; tapered ends suggest an abnormality in the hair follicle, growth cycle, or an inflammatory process such as dermatophytosis)
4. Skin scrapings
5. Acetate tape preparations
6. Dermatophyte culture and KOH preparation
7. Microfilarial preparation
8. Biopsy for routine histopathologic examination (sagittal sections should be evaluated to determine the proportion of hairs in the various phases; for the presence or absence of inflammation and infectious organisms; and for evidence of scarring, which suggests a poor prognosis for hair regrowth; cross-sections of the biopsy specimen should be evaluated in noninflammatory alopecias to determine the number of hair follicles present per given area)

The following steps are a guide to the diagnosis of increased coat length and density in horses and ruminants:

1. Horses demonstrating increased coat length and density should be evaluated with appropriate laboratory tests for hyperadrenocorticism.
2. Lambs with increased coat length and density should be evaluated for evidence of border disease.
3. Cattle with increased coat length and density probably have hereditary hypertrichosis.

BOX 11-6

Most Common Causes of Abnormal Coat Length and Density in Horses and Ruminants

Alopecia*

Dermatophytosis
Staphylococcal pyoderma (horses)
Alopecia areata (horses, cattle)
Drug reaction
Congenital hypotrichosis (cattle)
Onchocerciasis (horses)

Increased Coat Length

Pars intermedia pituitary dysfunction (horses)
Congenital hypertrichosis

*Alopecia without pruritus, crusts, or other clinical signs.

Abnormal Pigmentation

Definition

The following terms are used when discussing pigmentation and pigmentary abnormalities.[3]

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- *Melanin* is a brown-black, light-absorbing, insoluble pigment formed in many organisms by specialized cells called *melanocytes*.
- *Hyperpigmentation* is an excessive tissue deposition of pigment, usually melanin.
- *Hypopigmentation* refers to less than normal pigmentation and can be congenital or acquired.
- *Leukoderma (hypomelanosis)* is a partial or total acquired loss of melanin pigment from the skin. The term *vitiligo* also refers to an acquired loss of melanin from the skin but is often reserved for a specific type of leukoderma found in humans.
- *Leukotrichia* is an acquired loss of pigment from the hair.
- *Albinism* is a congenital lack of pigment in all tissues.

Mechanisms of Pigmentation Abnormalities

Cutaneous pigmentation results from the interaction of melanocytes and keratinocytes. The degree of "baseline" pigmentation observed in an animal is genetically controlled. Melanocytes are of neural crest origin and migrate from this site during embryologic development. They are present in nearly all tissues but occur in the highest numbers in the epidermis, mucous membrane epithelium, dermis, hair follicles, leptomeninges, uveal tract, and retina. Epidermal melanocytes are found in the basal cell layer, and each melanocyte is presumed to supply melanin to 10 to 20 keratinocytes. Melanin is usually found in the deeper layers of the epidermis, although darkly pigmented animals may have melanin throughout the epidermal layers.

Melanocytes produce membrane-bound organelles called *melanosomes* that fuse with vesicles containing the enzyme tyrosinase. Melanin, a black-brown pigment, is produced from tyrosine in the presence of tyrosinase and copper. It is deposited on the protein matrix in the melanosomes. Once melanosomes are fully melanized, they disperse to the periphery of the dendrites of the epidermal melanocytes and the dendritic tips are phagocytized by keratinocytes. Melanin is also synthesized and transferred to cells of the hair shaft during the anagen phase.[3]

In general, mechanisms associated with pathologic pigmentary disturbances in large animals are poorly understood. Hyperpigmentation results from increased amounts of melanin in the epidermis or dermis or both. The melanin may be present in melanocytes, keratinocytes, or melanophages (dermal macrophages that have phagocytized melanin pigment). Hyperpigmentation is an uncommon problem in horses because most normally have darkly pigmented skin. Hyperpigmentation may be reversible: with removal of the pigment-promoting stimulus, it tends to decline over time to the baseline level.

MSH may stimulate hyperpigmentation. MSH acts by affecting the levels of cyclic adenosine monophosphate (cAMP), resulting in increased tyrosinase activity. MSH also causes increased dispersion of melanosomes into melanocyte dendritic processes, where they are phagocytized by keratinocytes. Increased levels of ACTH, estrogens, progesterones, and androgens may also have effects on pigmentation, although the importance and mode of action in large animals is not clear.

Inflammation from a variety of causes and persistent cutaneous trauma from friction induce hyperpigmentation. Stimuli that may be factors in large animals include physical cutaneous damage (trauma, friction), chemicals (primary irritants, allergic sensitizers, photosensitizers), infectious agents, and nutritional disturbances.

Hypopigmentation is the result of a decreased amount of melanin in the epidermis or dermis (or both) and may be congenital or acquired (depigmentation). Possible mechanisms include decreased melanin production (defects in melanocyte migration during embryogenesis or disorders of melanin synthesis), decreased dispersion of melanin granules (defective transfer of melanin to keratinocytes), and increased loss of melanin (accelerated desquamation of epidermal melanin, epidermal pigment loss caused by disruption of the basement membrane with resultant pigmentary incontinence, or immunologic destruction of melanin or melanocytes).

Several congenital genetic abnormalities that result in partial or total hypopigmentation have been identified in large animals. Albinism is a recessive condition in which a normal complement of melanocytes is present but a biochemical defect results in lack of ability to synthesize tyrosinase, so melanin is not produced. There is complete lack of melanin in all tissues in a true albino. Pseudoalbinism, in which there is ocular pigmentation, may be more common. Other genetic disorders include abnormal melanosome production and abnormalities in melanocyte development and migration from the neural crest (piebaldism).[3,5]

Acquired hypopigmentation (leukoderma) may be caused by several factors, including genetic abnormalities, trauma, inflammation, dietary imbalances, hormonal influences, and immunologic disorders. In some cases acquired hypopigmentation is idiopathic. Juvenile Arabian leukoderma appears to have a genetic basis because of the predilection for the Arabian breed and the occurrence of the disease in young animals.[6] Trauma and inflammation are the most common factors associated with depigmentation, particularly in the horse. The intensity of the inflammatory reaction may bear little relation to the degree of postinflammatory leukoderma. Dietary abnormalities, particularly molybdenum toxicity and copper deficiency, are associated with faded or washed out coat color in food animals. Severe protein deficiency, such as occurs in kwashiorkor in humans, can lead to deficient melanin pigmentation. Melatonin is a hormone produced by the pineal gland that antagonizes MSH, thus causing decreased pigmentation, although an association with pathologic hypopigmentation in large animals has not been documented. Immunologic destruction of melanocytes has been documented in humans and is suspected of being a factor in acquired hypopigmentation in the dog but has not yet been documented in large animals. Idiopathic leukodermas are noted in all species.

Leukotrichia is the result of decreased amounts of melanin in the hair shaft. In most cases the pathogenesis is speculative, and the actual factors are unknown. Melanocytes in the hair bulbs can be affected independently of melanocytes in the epidermis, and leukotrichia without a coexistent leukoderma is common. Leukoderma, however, is usually accompanied by leukotrichia; thus when the two conditions are seen in combination, their pathogenesis is the same. Several leukotrichias that occur independently of leukoderma appear to be genetically induced because of breed predilections (e.g., reticulated leukotrichia of Quarter Horses). In addition, viral infection is suspected as one of the causes of hyperesthetic leukotrichia of horses.

Approach to Diagnosis of Pigmentation Abnormalities

The initial approach to diagnosis of pigmentary abnormalities is to determine whether the defect is congenital or acquired. Congenital pigmentary abnormalities are almost always caused by a genetic defect, whereas acquired abnormalities most commonly do not have a hereditary basis. If the abnormality is acquired, the clinician must determine if it is a primary pigmentary abnormality or if it is associated with some other pathologic change such as inflammation or trauma. If associated changes are a feature of the disease, differential diagnosis should focus on the initial pathologic changes (Box 11-7).

BOX 11-7

Most Common Causes of Abnormal Pigmentation in Horses and Ruminants

Loss of Pigmentation

Burns and other trauma
Idiopathic leukotrichia and leukoderma (horses)
Copper deficiency (ruminants)

Increase in Pigmentation

Pruritus
Melanoma

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The following steps are a guide to the diagnosis of pigmentation abnormalities in horses and ruminants:

1. History (see Fig. 11-1)
   a. If the pigmentary change is congenital, determine if related animals are affected and if the lesions have progressed or regressed since birth. Take note of the patient's signalment and determine if that breed has been documented to have congenital pigmentary abnormalities.
   b. If the pigmentary change is acquired, determine if the animal has been subjected to cutaneous trauma that could result in posttraumatic pigmentary change. Determine if other cutaneous lesions in addition to the pigmentary changes have been observed (e.g., inflammation, ulceration).
   c. Determine if the animal's diet is nutritionally complete and balanced.
   d. Determine if the animal has been exposed to any toxic substances.
   e. Determine if contact animals of the same or different species are affected. Because feed and environment are shared, if contact animals are affected, dietary imbalances and toxicities should be included in the differential diagnosis.
   f. If the affected animal is a horse, determine what parasiticidal agents have been administered and if they are effective in the treatment or prevention of onchocerciasis.
2. Physical examination (see Fig. 11-2)
   a. Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting a pigmentary change secondary to a dietary deficiency or toxicity?
   b. If the patient's problem is hypopigmentation, examine the coat closely to determine if leukoderma, leukotrichia, or both are present.
   c. Look for evidence of other cutaneous lesions (inflammation, ulceration) that could result in postinflammatory pigmentary changes.
3. Microfilarial preparation
4. Biopsy for routine histopathologic examination (affected, unaffected, and marginally affected areas should all be biopsied and labeled appropriately for histologic comparison).

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• CHAPTER 12

Alterations in Sexual Function

MATS H.T. TROEDSSON and BRUCE W. CHRISTENSEN, *Consulting Editors*

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Alterations in Male Sexual Function

Stallions, bulls, rams, and bucks intended to be used as breeding animals need to have (1) normal genital organs, (2) the libido necessary to tease females and gain an erection, (3) the physical ability to mount and intromit the penis into the female's vagina, and (4) an adequate number of morphologically normal, motile spermatozoa in each ejaculate to be considered as satisfactory breeders under natural service conditions. Digression from normal sexual function in males is usually recognized clinically by changes in sexual behavior, abnormalities or diseases of the genital organs, or a decreased pregnancy rate in dams bred. Subfertile males may be responsible for significant economic loss in the livestock industry.

Mechanisms of Altered Male Sexual Function

Sexual function may be altered by any of four major mechanisms: general physical abnormalities, abnormalities of the genital organs, decreased libido, and poor semen quality (Boxes 12-1 and 12-2).

The male must be mobile enough, especially in a pasture breeding program, to locate, tease, mount, and breed estrual females successfully. Musculoskeletal abnormalities may limit reproductive ability or desire. Hindlimb conformation defects in bulls and rams, degenerative joint disease involving the hock in stallions, and foot problems in rams are examples of conditions that may cause enough discomfort to interfere with the normal breeding process or prevent normal mobility, impairing reproductive performance.[1-3]

Congenital or acquired abnormalities of the genital organs, including the penis, prepuce, scrotum, testicles, spermatic cords, or accessory sex glands, can lead to altered sexual function or infertility. Congenital abnormalities such as persistent penile frenulum and penile deviations in bulls may prevent normal intromission.[4] Acquired lesions such as a penile hematoma caused by rupture of the tunica albuginea of bulls at time of service may limit sexual function by causing paraphimosis, adhesions, or sensory nerve damage.[5]

Libido is an essential component of breeding performance but may be difficult to measure during a breeding soundness examination and cannot be evaluated if semen is collected by electroejaculation. Libido has been demonstrated to be an inherited behavioral trait in bulls.[6]

Semen volume, concentration of spermatozoa, percentage of progressive motility, and percentage of morphologically normal spermatozoa are semen parameters commonly measured during a breeding soundness examination. Abnormalities of semen quality associated with decreased fertility in bulls include spermatozoa morphology and, to a lesser degree, motility.[2,4,7]

Approach to Diagnosis of Altered Male Sexual Function

A complete breeding soundness examination and history should be obtained, including number of females bred each year, conception rates, breeding methods (natural service or artificial insemination), and results of previous breeding soundness examinations (Box 12-3). A medical or health history, including medications, vaccinations, and previous illnesses, should be obtained. The animal should be given a general physical examination. Hindlimb conformation and the presence of degenerative joint disease, laminitis, foot abscesses, abnormal foot wear, corkscrew claw defect, weak pasterns, postleggedness, sickle hock, interdigital fibromas (bulls), foot rot, ulcerative dermatitis and pizzle rot (rams), and caprine arthritis-encephalitis (CAE) (bucks) should be noted. An ophthalmologic examination should be done to ensure that the animal has adequate vision and that no significant pathologic condition is present. A special emphasis is placed on identification of squamous cell carcinoma and pinkeye *(Moraxella bovis)* and corneal lesions in bulls. Range animals showing weight loss and a decline in reproductive performance should be given an oral examination, and the parasite control program should be evaluated.

The external genital organs should be examined carefully. The penis of the stallion is easiest to examine after an erection is obtained by teasing to an estrual female. In ruminants manual palpation of the penis per rectum or by use of an electroejaculator is suitable in many cases. The penis should be normal in size and shape and free of lesions. In bulls, deviations or other abnormal configurations such as corkscrew penis may occur with use of an electroejaculator and therefore cannot be considered abnormal.[5] Rams and bucks should be carefully examined for abnormalities of the urethral process, including the presence of calculi.[8] The lesions most often observed on the penises of stallions are squamous cell carcinoma and cutaneous habronemiasis.[9,10]

The prepuce should also be examined for lesions. Strictures of the preputial orifice may increase the risk of phimosis or paraphimosis. Bulls of the *Bos indicus* breeds often have a pendulous prepuce that is predisposed to traumatic injury, abscessation, stricture formation, and eversion.[5,11] Ulcerative posthitis (pizzle rot) caused by *Corynebacterium renale* in rams on a high-protein diet is the most common lesion of the prepuce in rams.[12]

The scrotum, testicles, and spermatic cords should be examined for size, consistency, symmetry, and presence of lesions. Two scrotal testicles should be present, each smooth, resilient on palpation, and freely movable. Testes volume and consequently the amount of testicular parenchyma present are highly correlated with daily sperm production in all species. Each gram of testicular tissue should produce 15 to 20 million sperm per day. In ruminants, scrotal

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BOX 12-1

Causes of Altered Sexual Function in Stallions

Abnormalities of the Penis

Balanoposthitis
Paraphimosis
Phimosis
Trauma
Hematoma, seroma
Abscess
Urolithiasis
Equine coital exanthema
Tumor (squamous cell carcinoma)
Cutaneous habronemiasis (equine summer sores)
Improper use of stallion rings

Abnormalities of the Prepuce

Trauma
Foreign body
Preputial stenosis
Balanoposthitis
Tumor (squamous cell carcinoma, sarcoid)
Hematoma
Abscess
Cutaneous habronemiasis
Varicosities of the preputial vein
Equine viral arteritis

Abnormalities of the Testicles, Spermatic Cord, and Scrotum

Testicular hypoplasia, atrophy
Testicular degeneration
Segmental aplasia
Testicular, scrotal neoplasia
Thrombosis of the spermatic cord
Torsion of the spermatic cord
Orchitis, epididymitis
Sperm, parasitic granuloma
Trauma
Hematoma, hematocele
Inguinal, scrotal hernia
Androgen, anabolic steroid effects
Cryptorchidism
Pseudohermaphrodism
Actinomycosis
Chemical irritation of the scrotum
Equine viral arteritis

Lack of Libido

Malnutrition, protein-calorie starvation
Testicular neoplasia
Lameness
Trauma, foreign body of the prepuce
Overuse
Equine coital exanthema
Iodine deficiency
Penile trauma, hematoma, abscess
Psychological impotence

Infertility

Segmental aplasia of the reproductive tract
Vesicular gland adenitis
Malnutrition, protein-calorie starvation
Testicular degeneration
Testicular hypoplasia, atrophy
Testicular neoplasia
Thrombosis of the spermatic cord
Torsion of the spermatic cord
Urolithiasis
Vitamin A deficiency
Hemospermia
Lameness
Iatrogenic causes, including artificial insemination-associated infertility
Bacterial contamination of the semen
Brucellosis
Trauma, foreign body of the prepuce
Balanoposthitis
Paraphimosis
Orchitis, epididymitis
Sperm, parasitic granuloma
Androgen, anabolic steroid use
Testicular trauma, hematoma, hematocele
Chromosomal abnormalities
Hermaphrodism, pseudohermaphrodism
Cryptorchidism
Ejaculation failure
Frostbite
Abnormalities of spermatogenesis
Sperm storage dysfunction
Iodine deficiency
Heat stress, heat stroke
Inguinal, scrotal hernia
Psychological impotence

circumference has been determined to be highly correlated with testes weight or volume. Yearling beef bulls should have a scrotal circumference of 30 cm or more, depending on the animal's age and breed.[7] In stallions, measurements of total scrotal width or, more accurately, testicular volume have been evaluated and correlated to potential daily sperm production. Mature stallions should have a scrotal width of at least 8 cm. Testicular volume in stallions can be determined by the following steps[13]:

1. Measure the length (L), width (W), and height (H) of each testicle.
2. Volume of each testicle can be determined using the formula:

$$\text{Testicular volume } (\text{cm}^3) = 0.5233 \, \text{L} \times \text{W} \times \text{H}$$

3. Add the volume of each testicle to obtain total testicular volume.
4. Expected daily sperm production (DSP) (in billions of sperm per day) can be calculated using the formula:

$$\text{Expected DSP} = 0.024 \, (\text{Total testicular volume in cm}^3) - 1.26$$

The epididymides should be palpated for position, size, and presence of lesions. The most common palpable abnormality in rams is epididymitis caused by infection with *Brucella ovis, Actinobacillus seminis,* or *Histophilus ovis.*[8,12,14] A definitive diagnosis is obtained by isolation of bacterial organisms in the semen and serologic testing.

Diseases of the accessory sex glands are diagnosed most frequently in bulls. Vesicular gland adenitis is clinically recognized by the presence of leukocytes in the semen and enlargement, induration, and loss of lobulation noted during palpation and ultrasonographic examination of the glands per rectum.[15,16]

Libido and the ability to mate should be assessed after the physical examination. The male should be teased to a female in estrus. Interest in and interactions with the female and ability to gain an erection, mount, intromit the penis into the vagina (or into an artificial vagina), and ejaculate are noted. Libido and mating ability cannot be evaluated when using an electroejaculator to collect semen from ruminants. Tests for "serving capacity" have been described for bulls.

The evaluation of semen quality is a major part of the breeding soundness examination. Semen from stallions is collected into an artificial vagina. Semen from ruminants may be collected into an artificial vagina or obtained by use of an electroejaculator. Semen collected by electroejaculation usually has a higher volume and a lower concentration of spermatozoa than semen collected by an artificial vagina. Semen quality in ruminants is scored primarily on the

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BOX 12-2

Causes of Altered Male Sexual Function in Ruminants

Abnormalities of the Penis

Penile deviation (B)
Balanoposthitis
Paraphimosis
Phimosis
Penile-preputial adhesions (B)
Penile hair ring (B)
Penile trauma, hematoma, abscess
Urethral calculi
Ruptured urethra
Persistent penile frenulum (B)
Papillomatosis
Infectious bovine pustular vulvovaginitis (B)
Herpes vulvovaginitis (C)
Ovine ulcerative dermatosis (O)

Abnormalities of the Prepuce

Abscess, cellulitis
Balanoposthitis
Trauma
Foreign body
Preputial stenosis
Prolapsed prepuce
Ulcerative posthitis (pizzle rot)
Ovine ulcerative dermatosis (O)

Abnormalities of the Testicles, Spermatic Cords, and Scrotum

Scrotal abscess (O)
Orchitis, epididymitis
Segmental granuloma, spermatocele
Testicular degeneration
Testicular hypoplasia, atrophy
Varicocele
Zinc deficiency
Testicular tumors
Brucellosis (B, O)
Testicular trauma, hematoma, hematocele
Inguinal, scrotal hernia
Cryptorchidism
Actinomycosis
Intersex in polled goats (C)
Pseudohermaphrodism (C)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

Lack of Libido

Malnutrition, protein-calorie starvation
Ulcerative posthitis
Vertebral osteophytosis, spondylosis (B)
Zinc deficiency
Lameness
Trauma, foreign body of the prepuce
Prolapsed prepuce (B, O)
Loss of penile sensation (B)
Penile hair ring (B)
Corpus cavernosum vascular shunts (B)
Iodine deficiency
Psychological impotence
Penile trauma, hematoma, abscess
Persistent penile frenulum (B)
Epididymitis, orchitis (O, C)
Intersex in polled goats (C)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Obesity
Spondylosis (B)

Infertility

Testicular degeneration
Orchitis, epididymitis
Trauma, foreign body of the prepuce
Paraphimosis
Heat stress, heat stroke
Penile trauma, hematoma, abscess
Segmental aplasia
Vesicular gland adenitis
Sperm granuloma, spermatocele
Malnutrition, protein-calorie starvation
Testicular hypoplasia, atrophy
Ulcerative posthitis (pizzle rot)
Urolithiasis
Varicocele
Vitamin A deficiency
Zinc deficiency
Manganese deficiency
Iodine deficiency
Hemospermia
Lameness
Iatrogenic, including artificial insemination–associated infertility
Balanoposthitis
Testicular trauma, hematoma, hematocele
Cryptorchidism
Dermatophilosis
Frostbite
Inguinal, scrotal hernia
Psychological impotence
Hermaphrodism, pseudohermaphrodism
Short retractor penis muscle in Dutch Friesian bulls (B)
Abscess of scrotum (O)
Prolapsed prepuce (B, O)
Penile deviation (B)
Penile-preputial adhesions (B)
Vertebral osteophytosis, spondylosis (B)
Testicular tumors (B, O)
Bulls born co-twin with freemartins (B)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Infectious bovine rhinotracheitis–contaminated semen (B)
Infectious bovine rhinotracheitis–associated dermatitis (B)
Bovine virus diarrhea–contaminated semen (B)
Chromosomal abnormalities (B, O)
Loss of penile sensation (B)
Penile hair ring (B)
Bovine herpesvirus type 1
Corpus cavernosum vascular shunt (B)
Urethral fistula (B)
Cold weather–associated infertility (B)
Papillomatosis, warts (B)
Abnormalities of spermatogenesis
Micropenis, penile hypoplasia (B)
Persistent penile frenulum (B)
Ovine ulcerative dermatosis (O)
Congenital phimosis (O)
Overuse
Chorioptic mange (O, C)
Hexachlorophene toxicity
Gynecomastia (C)

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

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BOX 12-3

Outline of a Breeding Soundness Examination for Diagnosis of Male Infertility

1. Species, breed
2. Age
3. Month of evaluation
4. Breeding history
5. Physical examination
   a. General
   b. External genital organs
      (1) Penis
      (2) Prepuce
      (3) Testes
      (4) Scrotum
      (5) Epididymides
6. Libido
7. Mating ability
8. Semen evaluation
   a. Motility
   b. Concentration
   c. Morphology
   d. Volume
9. Microbiologic culture
10. Serologic tests

BOX 12-4

Causes of Cyclic Irregularity in Mares

Common Causes

Transition season
Erroneous heat detection
Diestrus ovulation
Intrauterine therapy
Diestral endometrial biopsy
Pneumovagina
Endometritis
Pubertal cycles
Early embryonic death
Spontaneous corpus luteum prolongation
Endophyte-infested fescue
Cervical dilation

Less Common Causes

Urovagina
Rectovaginal fistula
Ovarian tumors
Pyometra
Persistent follicles
Split heats
Endotoxemia
Hemorrhagic anovulatory follicles
Old age
Use of Deslorelin implant

Uncommon Causes

Contagious equine metritis
Corpus luteum inadequacy
Anabolic steroids
Progesterone therapy
Phosphorus deficiency
Sex chromosome anomalies
Administration of oxytocin during days 7 to 14 of the estrous cycle

basis of motility and morphology.[7] Evaluation of semen from stallions should include determination of volume, concentration, motility, and morphology. The motility of the spermatozoa should be evaluated microscopically on raw and extended semen immediately after collection. In ruminants, bright-field microscopy at ×40 to ×125 magnification is used to detect mass motion or swirling to evaluate gross motility. Changes in sperm concentration, progressive motility, or speed of progression of spermatozoa will decrease or eliminate the swirling effect. Phase contrast microscopy at ×200 to ×500 is used to evaluate motility of individual spermatozoa. Computer-assisted semen analysis (CASA) is commonly used at larger reproduction facilities.

Concentration can be measured by use of a hemocytometer or a calibrated spectrophotometer. Morphology can be evaluated microscopically, using stained semen samples (e.g., eosin-nigrosin stain) or phase-contrast microscopy.

Ejaculates from stallions may be collected once daily for 5 to 10 days until daily sperm output (DSO) is achieved to fully evaluate potential fertility.[17] However, this is time-consuming, labor-intensive, and expensive. Consequently, most stallions are evaluated by the collection of two ejaculates 1 hour apart, with the total number of progressively motile, morphologically normal spermatozoa in the second ejaculate most critically evaluated.

The age of the stallion or male ruminant being evaluated for potential fertility may influence the semen parameters, measurements of the testicular size, mating ability, and libido. Puberty is attained in the stallion at 18 months, in the bull at 9 to 12 months, and in the ram and buck at 7 to 8 months.[18] Semen parameters and testicular size continue to increase until sexual maturity is reached. The season of the year in which the fertility evaluation is done may affect semen parameters in the stallion, ram, and buck.

Microbiological samples should be routinely collected when evaluating infertility in the stallion and when evaluating high-risk populations of bulls. Smegma samples should be collected from the prepuce of bulls and cultured for *Trichomonas foetus* and *Campylobacter fetus.* Swabs from the preejaculate and postejaculate urethra, semen, fossa glandis, and prepuce of stallions should be cultured for potentially pathogenic bacterial organisms, especially *Taylorella equigenitalis, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.*[9] The semen of rams should be cultured for *B. ovis, A. seminis,* and *H. ovis.*[8,12,14] Serologic testing for exposure to equine arteritis virus (EAV), the causative agent of equine viral arteritis (EVA), is important for breeding stallions. Determination of negative serologic status should be required before vaccination against the virus may be performed.

Other tests that are occasionally performed to evaluate male reproductive function, health, or pathology include hormone analysis, chemical evaluation of seminal plasma, transmission electron microscopy of semen, karyotype, sperm chromatin structure assay, urethral endoscopy (stallion), and testicular biopsy.

After summarizing the results of the entire breeding soundness evaluation, stallions and male ruminants may be categorized into classifications such as satisfactory, questionable, or unsatisfactory. In bulls a fourth category of "decision deferred" may be used for young prepubertal bulls or mature bulls that have recently experienced a transient disturbance in spermatogenesis.

It must be emphasized that the breeding soundness examination is a measure of potential fertility.[19] True fertility can be determined only by the results of breeding trials or by conception and live birth-rates in dams bred.

Cyclic Irregularity

Claudia Klein

Cyclic irregularities become evident in the display of irregular estrous cycles (i.e., an abnormal interval from one estrus to the subsequent estrus). Irregular estrous cycles can be physiologic such as during the transition period in seasonal breeders, can be pathologic such as a sequel to endometritis, or may be an artifact such as failure in estrus detection (Box 12-4).

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BOX 12-5

Causes of Cyclic Irregularity in Ruminants

Common Causes

Erroneous heat detection
Endometritis
Intrauterine therapy
Cystic ovaries
Heat stress
Leptospirosis
Infectious bovine rhinotracheitis (IBR) (B)
Bovine virus diarrhea (BVD) (B)
Campylobacteriosis
Trichomoniasis
Embryonic death after maternal recognition of pregnancy

Uncommon Causes

IBR- or BVD-infected semen
Bluetongue-infected semen
Zearalenone toxicity
Ovarian neoplasia
Corpus luteum inadequacy
Copper deficiency (O, C)
Molybdenum deficiency (O, C)
Iodine deficiency
Phytoestrogen toxicity
Segmental aplasia of the uterus

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

Cattle

Irregular estrous cycles in the cow may result from a number of factors (Box 12-5). Detection of heat in cattle is challenging given that the average duration of estrus is 18 hours and in many cows may be appreciably shorter. Failure to detect heat in intensively managed herds bred by artificial insemination is common and is one of the most important management factors contributing to a perceived abnormal estrus interval.[20] Missed heats should be expected if the heat intervals approximate multiples of 21 days, the normal cycle length. Errors in estrus detection are further indicated when (1) more than 10% of the interestrus intervals are 3 to 17 days or 25 to 35 days long, (2) more than 5% of the cows have two artificial inseminations within 3 days, or (3) cows are calving early or are further in gestation than predicted from the last breeding when examined for pregnancy. Seventy percent of cows should have an interestrus interval of fewer than 30 days, and 60% should be in the range of 18 to 24 days. The ratio of 18- to 24-day cycles to 38- to 46-day cycles should be 5:1.[21] Evaluation of heat detection methods is important in artificial insemination programs. Cows need to be observed at least twice daily for signs of estrous behavior. Heat detection aids such as tailhead chalking (will be rubbed off), adhesive heat pads (will change color), and pedometry (record an increase in activity) are indispensable tools for efficient estrus detection. Especially pedometry can detect estrus accurately, is least labor intensive, and through a software program generates daily lists of cattle with increased activity.[22]

Silent heat, which is the lack of cycling cows to express estrous behavior (silent ovulation), occurs most commonly in the immediate postpartum period. More than 50% of cattle display a silent heat on their first ovulation postpartum with the incidence declining thereafter.[23] This may be related to insufficient progesterone priming of the behavior center for optimum expression of estrus. Lameness or general disease impairing an animals' ability to move will mask signs of heat independently from its reproductive status. Silent heat can be diagnosed only through rectal palpation of the ovaries or the use of progesterone assay in milk or plasma.

While the cow cycles normally in the face of failure in heat detection or silent heat, true, irregular cyclicity does occur. Endometritis, through the release of prostaglandin, can result in premature lysis of the corpus luteum (CL) and therefore a shortened diestrus phase.[24] Cystic ovarian follicles, either in the form of follicular or luteal cysts, interfere with regular cyclic ovarian activity. This condition is mainly observed in high-yielding dairy cows during the first months postpartum. Estrogen-producing follicular cysts may result in nymphomania, a state of persistent or frequent heats. Progesterone-producing luteal cysts result in absence of estrous behavior and prolonged interestrus interval.[25] Early embryonic death occurring after the time period of maternal recognition of pregnancy will prevent lysis of the CL, and the cow will undergo a prolonged interestrus interval due to the action of progesterone.[26] A less common cause for prolonged diestrus is segmental aplasia of the uterine tract.[27] If ovulation occurs ipsilateral to a missing uterine horn, the CL will persist due to the lack of exposure to prostaglandin.

Mares

Irregular estrous cycles in the mare are most commonly encountered during the transitional period and are considered physiologic then. Follicles will initiate growth during the transition from winter anestrus to spring reproductive activity, resulting in estrous behavior. Due to inadequate gonadotropin, support follicles may fail to ovulate and eventually regress after a varying period of time leading to irregular estrus intervals.[28] Mares that have been artificially induced to develop a follicle and ovulate during seasonal anestrus using GnRH or recombinant FSH usually do not display regular estrous cyclicity following the artificially induced ovulation till the onset of breeding season. Likewise, mares foaling during the nonbreeding season may display foal heat, which may be followed by a variable period of anestrus. Mares older than 20 years of age may experience irregular estrous cycles independent of the time of the year, and it is not unusual for mares older than 25 years of age to stop cycling altogether. During the regular breeding season, prolonged interestrus intervals may occur in association with diestrous ovulations.[29] Follicles developing during diestrus may either regress or, less commonly, ovulate. If this ovulation occurs on or after day 10 of diestrus, the newly resulting CL will be refractory to the actions of prostaglandin released from the endometrium around day 14 of the cycle. This becomes evident in a prolonged interestrus interval. Prolonged diestrus may also be observed following early embryonic death occurring after the time of maternal recognition of pregnancy. If a pregnancy is lost following formation of endometrial cups, the mare may not display regular cyclic activity during the remainder of that breeding season. Ovulation failures such as hemorrhagic luteinized follicles or anovulatory persistent follicles interfere with regular cyclicity. Anovulatory hemorrhagic follicles that luteinize may persist for more than a month without treatment, which is reflected in a prolonged diestrus phase. Anovulatory persistent follicles may or may not interfere with cyclic activity. Some mares will develop a new dominant follicle despite the presence of this abnormal structure, whereas other mares will not show signs of heat as long as these structures are present.[30] Persistent estrous or stallion-like behavior is commonly described as a sequel to the presence of a granulosa cell tumor.[31] Following unilateral ovariectomy mares usually return to regular cyclicity within 6 months following surgery. Endometrial irritation such as endometritis or uterine lavage can result in shortened intervals between heats due to the release of prostaglandin.[32] A less commonly encountered cause of irregular cyclicity in mares is chromosomal abnormalities such as XO genotype.[33] Iatrogenic causes of irregular cyclicity are the accidental administration of prostaglandin (shortened luteal phase) or the twice-daily administration of oxytocin during days 7 to 14 (prolonged luteal phase).[34]

Sheep and Goat

The first ovulation at the beginning of the breeding season is often not accompanied by overt signs of estrus due to the absence of progesterone priming. The corpora lutea arising from these ovulations often regress prematurely, again because of the inadequate progesterone priming. A pathologic cause of irregular or prolonged estrous cycles is the consumption of phytoestrogens from plants such as clover and alfalfa, which may lead to signs of irregular and prolonged estrous cycles.

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BOX 12-6

Causes of Anestrus in Mares

Common Causes

Season (fall, winter)
Poor heat detection
Corpus luteum persistence
Diestrus ovulation
Pregnancy
Early embryonic death after recognition of pregnancy
Fetal death after endometrial cup formation
Psychological impediments
Maternal behavior

Less Common Causes

Ovarian tumors
Pituitary tumors
Pyometra
Weight loss
Chronic disease
Lactation
Old age

Uncommon Causes

Gonadal dysgenesis
Intersex conditions
Progesterone therapy
Nonsteroidal antiinflammatory drugs (NSAIDs)
Phosphorus deficiency
Ovarian hypoplasia
Anabolic steroids
Zearalenone toxicity
Chromosomal abnormalities
Persistent endometrial cups
GnRH immunization
Deslorelin implants

BOX 12-7

Causes of Anestrus in Ruminants

Common Cause

Season (C, O)
Pregnancy
Poor heat detection
Luteal cysts (B, C)
Pyometra
Poor nutrition, energy
Heat stress
Foot and leg problems
Poor footing (B)
Nursing beef cows and ewes (B, O)
Lactation (O)
Freemartinism (B, C)
Intersex conditions (C)
Postpartum period
Heavy lactation
Primiparity
Periparturient disease

Less Common Causes

Mucometra
Hydrometra
Macerated fetus
Mummified fetus
Trichomoniasis pyometra
Anaplasmosis
Johne's disease
Caprine arthritis-encephalitis (C)
Pseudopregnancy (C)
Insufficient number of cycling herdmates

Uncommon Causes

Ovarian tumor
Segmental aplasia
Uterine foreign body
Ovarian hypoplasia
Zearalenone toxicity
Phytoestrogenism
Phosphorus deficiency
Copper deficiency
Cobalt deficiency
Manganese deficiency
Molybdenum toxicity
Progesterone implants
Schistosomiasis (exotic)
Lumpy skin disease (exotic)

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

Anestrus

Claudia Klein

Anestrus is the absence of estrous behavior and can be a physiologic state during pregnancy, lactation, or seasonal anestrus, or it may be a pathologic condition (Boxes 12-6 and 12-7). Anestrus can occur either in the face of ovarian activity or in the absence of the latter, in which case acyclicity is present. Causes underlying anestrus can be subdivided into physiologic and pathologic. The lack of estrous behavior due to ovarian inactivity is physiologic in seasonal species and is mediated via melatonin levels, which vary with day length. The mare is a long-day breeder, whereas the ewe and doe are short-day breeders, although breed variations occur in small ruminants.[35] Certain breeds of sheep are less affected by the season and can have longer breeding seasons or practically cycle year-round. Some sheep and goats near the equator have cycles throughout the year presumably because of the consistency of the photoperiod. Prepubertal animals naturally do not show signs of estrus, as do some dams during lactation. The most common physiologic cause for the lack of estrous behavior is pregnancy; mares, however, are an exception because some of them may display signs of heat despite being pregnant. In intensively managed cattle herds bred by artificial insemination, failure in heat detection is a major contributor to perceived cases of anestrus.[36] A plethora of pathologic conditions can lead to anestrus, and a thorough examination of the history and evaluation of the reproductive tract is required for a definite identification of the underlying cause. Congenital conditions such as ovarian aplasia, chromosomal abnormalities, or freemartinism in cattle, intersex conditions that occur in polled goats, and gonadal dysgenesis in the mare are accompanied by the lack of estrous behavior. These animals frequently have rudimentary or hypoplastic ovaries.[37] Uterus unicornis will lead to persistence of the ipsilateral CL and subsequently interfere with regular estrous behavior.[38] Nutritional anestrus due to a negative energy balance during times of high milk production can lead to anestrus in cattle.[39] In mares, anestrus due to nutritional deficiencies is less commonly observed than in cattle. In beef cattle nursing their offspring, a delayed resumption in ovarian activity is frequently observed.[40] This is related to both the physical act of the calf nursing and olfactory and auditory cues received by the dam from the calf. Anestrus related to lactation is not observed in mares. Mares foaling during the short day length period that have not been kept under lights for 2 months preceding parturition may show a first ovulation within the first 2 weeks postpartum (i.e., foal heat) but then revert to an anestrous state with cyclic activity not resuming until increasing day length. Persistent endometrial cups, a rare condition in mares, may also lead to the failure of presenting regular estrous activity in the period postfoaling.[41] Both conditions may easily be misinterpreted as cases of lactational anestrus. In mares, psychogenic factors have to be considered in the differential diagnosis for anestrus. A mare being overly protective of her foal or of nervous constitution may not show signs of heat. Teasing with a stallion may be necessary to elicit estrous behavior in these animals.

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A variety of conditions can lead to hypothalamic or pituitary suppression, preventing the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, in turn resulting in a lack of follicle-stimulating (FSH) and luteinizing hormone (LH) released by the pituitary. Consequent ovarian inactivity results in the absence of behavioral estrus. Most common underlying conditions are poor nutrition, heavy lactation, periparturient disease, weight loss, or idiopathic condition.

Any condition discussed in the "Irregular Cyclicity" section that results in prolonged luteal function will result in absence of overt estrous signs. Differential diagnoses further include the presence of cystic ovarian disease in cattle and anovulatory follicles in mares. Uterine abnormalities such as mucometra, hydrometra, and pyometra prevent the release of $PGF_{2\alpha}$ in ruminants.[42] Thus the CL persists and perceived anestrus results. Pyometra in the mare may result in anestrus if the endometrial damage is severe enough to prevent production of $PGF_{2\alpha}$. The presence of a mummified or macerated fetus in the ruminant uterus prevents release of $PGF_{2\alpha}$ and results in a persistent CL and perceived anestrus.[43] Ovarian atrophy leading to persistent anestrus can be seen in high-producing dairy cattle as a sequel to nutritional problems or can be occasionally encountered as an idiopathic condition in mares.[39] If no overt reason for ovarian atrophy can be identified, dysfunction at the hypothalamic-pituitary-ovarian axis has to be considered as a potential underlying cause. Iatrogenic causes of anestrus in mares, such as previous immunizations with GnRH or the application of a deslorelin implant, have to be considered, especially if the reproductive history of the mare is unknown.[44] Mares exposed to a deslorelin implant used to hasten ovulation can display pituitary downregulation induced by constant high GnRH input. Older mares undergo reproductive senescence, which is accompanied by atrophying ovaries and lack of cyclicity. Anecdotally, some mares coming off the race track show anestrous behavior and small ovaries on examination. No studies have been undertaken to determine the cause for this, but stress and possible medications during the racing career have been suspected.

Knowledge of the reproductive physiology of the species involved is essential to understanding the cause of anestrus. Determining the cause of anestrus relies on an in-depth general and reproductive history, a thorough physical examination, and evaluation of estrus detection programs involved. Pregnancy must be ruled out when dealing with any case of anestrus.

Repeat Breeder

Bruce W. Christensen

Managing repeat breeders is often frustrating and expensive. The repeat breeder is an animal that has been bred during three or more successive heat periods without being diagnosed pregnant.[45] An incidence of 10% to 15% repeat breeders is considered acceptable for dairies.[46] The incidence increases with the herd size and the level of milk production and with the use of artificial insemination.[46] This may be an even greater problem in the horse because pregnancy rates per cycle are normally between 60% and 70%, and 5% to 8% of mares lose their pregnancy in the first 4 months of gestation.[47] The use of ultrasonography and embryo collection indicates that the incidence of early embryonic death (EED) in the mare is likely even higher.[48] The syndrome of repeat breeders in mares is completely different from that in cows. In mares it is often associated with persistent endometritis. This is discussed in detail in Chapter 43.

The causes of repeat breeding are numerous and are related to male, female, and management factors (Boxes 12-8 and 12-9). The pathogenesis of repeat breeding involves either a failure of fertilization or EED.[46] Some etiologies, such as heat stress in the herd, may involve both mechanisms. Fertilization rates are normal in heat-stressed cows that are bred artificially, but heat stress increases the rate of EED. Heat stress can cause failure of fertilization by affecting spermatogenesis in males used in a natural breeding program.[49] When dealing with an individual repeat breeder, it is often wise to begin with the female. When several females are affected, the male should be eliminated as a source of the problem before proceeding. Management errors may be related to either male or female factors.

Fertilization failure is often the cause of repeat breeder syndrome. Studies have demonstrated delayed or inadequate release of LH, as well as consequent delayed ovulation, in repeat breeder cows compared with those cows showing normal fertility rates.[50] This observation has led to the investigation of GnRH (or its analogues) and prostaglandins as treatment options for repeat breeders, with some success.[51,52] In addition to LH abnormalities, repeat breeder cows showed prolonged duration of estrus, prolonged lifespan of the preovulatory follicle, and a late postovulatory rise in progesterone.[50] These changes negatively contribute to final oocyte maturation and competence in repeat breeder cows compared with unaffected cows.[53] Insulin has been shown to be an important mediator of follicular development, steroidogenesis, oocyte maturation, and subsequent embryo development,[54] and treatment with insulin has been shown to increase fertility in repeat breeder cows.[55] Workers in Japan have linked the repeat breeder syndrome with abnormal profiles of

BOX 12-8

Causes of Repeat Breeding in Mares

Common Causes

Transition season
Endometritis
Poor timing of artificial insemination
Pneumovagina
Metritis
Endometrial fibrosis
Poor heat detection
Ovulation failure
Twins
Uterine lymphatic lacunae
Endometrial cysts
Early foal heat breed
Poor uterine clearance
Ventral uterine sacculation

Less Common Causes

Diestrus breeding
Urovagina
Rectovaginal fistula
Malnutrition
Pyometra
Heat stress
Poor semen quality
Old age
Endophyte-infested fescue

Uncommon Causes

Salpingitis
Hydrosalpinx
Oviductal adhesions
Oophoritis
Uterine neoplasia
Cervical neoplasia
Ovarian neoplasia
Parovarian cysts
Contagious equine metritis
Iodine deficiency
True hypothyroidism
Phosphorus deficiency
Zearalenone toxicity
Intersexuality
Gonadal dysgenesis, sex reversal, trisomy
Other karyotype abnormalities
Teratogenic factors
Vitamin A deficiency
Cervical trauma
Luteal insufficiency

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BOX 12-9

Causes of Repeat Breeding in Ruminants

Common Causes

Heat detection
Poor timing of artificial insemination
Inadequate or delayed luteinizing hormone surge
Poor artificial insemination technique
Malnutrition
Follicular cysts
Endometritis
Heat stress
Trichomoniasis
Campylobacteriosis
Leptospirosis
Inadequate uterine involution

Less Common Causes

Poor semen quality
Inadequate male power (not enough males)
Infectious bovine rhinotracheitis (IBR) (B)
Bovine virus diarrhea (BVD) (B)
Bluetongue
Brucellosis
Anaplasmosis
Toxoplasmosis (C, O)
Border disease (C, O)
Selenium deficiency
Phosphorus deficiency
Ureaplasmosis
Urine pooling
Pneumovagina, pneumouterus
Oviductal bursal adhesions
Segmental aplasia
Rectovaginal fistula
Parovarian cysts
Zearalenone toxicity (B, O)
Fescue toxicity
Uterine tumors
Defective embryos
Dietary protein toxicity

Uncommon Causes

Johne's disease
Tuberculosis
Vitamin A deficiency
Zinc deficiency
Manganese deficiency
Cobalt deficiency
Copper deficiency
Molybdenum toxicity
Selenium toxicity
Iodine deficiency
Iodine toxicity (B, O)
Oophoritis
Fat necrosis (B)
Brasilia, toxicity
Ovarian tumors
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Polybrominated biphenyl toxicity (B)
Phytoestrogen toxicity (B, O)
Hydrosalpinx
Salpingitis
Cervical anomalies and cysts
Chromosomal abnormalities (1/29 or 14/20 centric fusions)
Fluoride toxicosis
Segmental aplasia
Uridine monophosphate synthase deficiency
Delayed ovulation
Schistosomiasis (exotic)
Tick-borne fever (exotic)
Epivag (exotic)
Leucaena leucocephala (exotic)
Besnoitiosis (exotic)
Maedi, visna (exotic)
Lumpy skin disease (exotic)
Onion grass toxicity (exotic)

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

endometrial epidermal growth factor (EGF). Assays of EGF have been suggested as diagnostic tools, and EGF treatment has been suggested to restore fertility.[56,57]

Early embryonic death also contributes as a cause of infertility in repeat breeders.[46,48] The interval between heats may help distinguish between EED and failure of fertilization. Failure of fertilization usually does not affect the interestrus interval. However, EED may prolong the interestrus interval if the fetal wastage occurs after the time of maternal recognition of pregnancy. Maternal recognition of pregnancy occurs at approximately days 15 to 17 after estrus in the cow, days 11 to 14 in the mare, and days 12 to 13 in the ewe.[58] Animals experiencing EED after pregnancy recognition often have interestrus intervals corresponding to multiples of a normal cycle length. Luteal insufficiency is suspected to cause EED in some repeat breeder cows, and trials of exogenous progesterone supplementation have shown promise for maintaining pregnancy in young late-lactation repeat breeders.[59]

Approach to Diagnosis

Clinical differentiation of EED from failure of fertilization is difficult. In addition to evaluation of heat detection and breeding techniques, it is important to obtain a detailed history. When dealing with a herd problem, the clinician begins by evaluating the male or males used or assessing the semen quality and techniques used for artificial insemination. When dealing with an individual repeat breeder, evaluation of the female is the first step.

Evaluation of the male should include evaluation of the animal's physical condition, including the genitalia. The quality of the semen should be checked. The male's libido and ability to mount should be determined by observation or through historic information. Examination of the male for venereally transmitted diseases, such as trichomoniasis and campylobacteriosis in the bull and contagious equine metritis in the stallion, may be warranted if other factors are ruled out. When dealing with an artificial insemination program, the semen quality should be evaluated and the thawing, transporting, timing, and deposition techniques should be evaluated.

Errors in heat detection and the timing of breeding are major management causes of repeat breeding. Discussing and observing the methods used to determine when an animal should be bred are important in dealing with both the individual animal and the herd. Milk or serum progesterone determinations at the time of breeding have proved helpful in determining the accuracy of heat detection and timing of insemination. In some dairies 40% to 50% of the cows are bred at the wrong time.

Examination of the female or females should begin with evaluation of the body condition. Poor nutrition has been associated with repeat breeding.[60] The reproductive examination should include evaluation of the vulva, vagina, cervix, uterus, oviducts, and ovaries. Poor vulvar conformation may lead to pneumovagina and endometritis, resulting in EED. The spermicidal effect of urine may cause failure of fertilization in the mare or cow that pools urine in the vagina. Cervical canal occlusion can prevent fertilization. An

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abnormal uterine environment may also lead to repeat breeding. Endometritis with minimal intraluminal pus may cause failure of fertilization but often results in EED. Unlike ruminants, the mare may continue to display estrus while experiencing pyometra. The volume of pus present in the uterus will cause failure of fertilization. Hydrosalpinx or salpingitis may lead to failure of fertilization by blocking sperm or ovum passage. Ovulation abnormalities such as delayed ovulation or ovarian cyst formation may result in failure of fertilization. Whenever possible, including a uterine culture, cytologic smear, and endometrial biopsy as part of the examination is likely to help determine the cause of the infertility.

Differentiation of EED from failure of fertilization in repeat breeders has been facilitated by the use of embryo flushing techniques and ultrasonography. Collection of unfertilized ova indicates failure of fertilization; collection of degenerating embryos indicates early embryonic death. In ruminants, failure to collect ova or embryos may indicate oviductal blockage resulting in failure of fertilization. This is not the case for mares because they usually retain unfertilized ova in the oviducts.

Ultrasonic determination of pregnancy in the mare and cow has made early detection of pregnancy possible. Loss of an embryo after detecting it with ultrasound at 10 days of gestation confirms EED. Pregnancy wastage can be confirmed later in gestation with sequential rectal palpations of the reproductive tract or ultrasonic evaluation. Hormone assays are also helpful for confirming embryo or fetal loss.

An assay for eCG, previously called *pregnant mare serum gonadotropin* (PMSG), can be used to determine if a mare was pregnant long enough to stimulate formation of the endometrial cups and eCG production. eCG can be detected at about 40 days of gestation with these kits. The endometrial cups continue to produce eCG until 120 to 150 days of gestation even if the fetus dies. Therefore eCG can be used to confirm EED but not failure of fertilization. Progesterone determination cannot be used to confirm pregnancy in the mare or ruminants. However, it can be used to confirm nonpregnancy if the progesterone level is low early in the expected gestation. A bovine early conception factor test can be used to confirm fertilization, but it does not rule out EED later.

The fetally derived hormone-metabolite estrone sulfate has been used to determine the presence of a live fetus. It is detectable in the serum or urine of the dam if the fetus is alive after 45 days of gestation in the doe, 70 days of gestation in the ewe, 100 days of gestation in the mare, and 120 days of gestation in the cow.[61,62] Thus a decline in estrone sulfate indicates death of the fetus. Estrone sulfate is probably most helpful in confirming fetal loss in the doe and ewe because other techniques are available in the larger species.

Boxes 12-8 and 12-9 list the causes of repeat breeding in mares and ruminants. The causes have been divided into expected frequencies of occurrence.

Pregnancy Loss

Mats H.T. Troedsson

Pregnancy loss refers to the failure of a conceptus to be maintained successfully to term. Pregnancy loss may be classified as early embryonic death (EED), abortion, or stillbirth, depending on the gestational stage when the pregnancy loss occurred. EED is the death of a conceptus before organogenesis is complete (≈55 days in horses, 45 days in cattle, and 34 days in sheep).[63] *Abortion* refers to pregnancy loss after the completion of organogenesis. *Stillbirth* refers to the delivery of a nonviable fetus at or near term.

Early Embryonic Death

The exact incidence of EED in any species is difficult to determine because most losses occur before pregnancy can be routinely diagnosed. Embryonic death early in pregnancy usually results in reabsorption of the embryonic tissues and fluids. Consequently, EED cannot be distinguished from failure of fertilization in most instances. However, despite the lack of clinical evidence, EED probably accounts for the largest percentage of reproductive wastage in large animals. The incidence of EED has been estimated at 5% to 24% in mares,[64] 30% to 35% in cows,[65] and 20% to 30% in ewes.[66] The rate of EED is much higher in subfertile or repeat breeder females and in older females.

Loss of the embryo before maternal endocrine recognition of the pregnancy (i.e., days 11 to 14 in the mare, days 15 to 17 in the cow, and day 12 in the ewe and doe) results in return to estrus at the normal time. Embryonic loss after this critical period may result in persistence of the CL in horses, pseudopregnancy in goats, or irregular returns to estrus in cattle.

Chromosomal and genetic defects of the oocyte, sperm, or embryo; a poor oviductal or uterine environment; endocrine dysfunction; and maternal stress are all considered important factors in the pathogenesis of EED.[64,67] Infectious agents such as *T. foetus* and *C. fetus* subsp. *venerealis* in cattle[67] and *Streptococcus zooepidemicus* and other bacteria in horses[68] can cause EED. Endogenous release of $PGF_{2\alpha}$ during the CL-dependent stage of gestation may result in luteolysis and subsequent embryonic loss or abortion in any large animal species. Luteal insufficiency associated with low plasma progesterone concentrations has been suggested as a possible cause of EED in horses, cattle, and sheep, although scientific evidence is limited.[65,69,70]

Abortion

The rate of abortion after pregnancy diagnosis at 60 days of gestation has been estimated to be approximately 10% in horses[71] and 3% to 4% in cattle.[72] Fetal death may result in abortion (expulsion of the fetus from the uterus) or retention of the fetus in the uterine lumen, with subsequent fetal maceration or mummification. In animals with a CL-dependent pregnancy for all or most of gestation (cows, goats, llamas), death of the fetus usually results in the abortion of an autolyzed fetus because of a delay between the time of fetal death and lysis of the CL. In species that do not depend on a CL for maintenance of pregnancy for most of gestation (e.g., mares and ewes), fetal death causes an immediate decrease in placental progesterone production and rapid expulsion of a relatively nonautolyzed fetus. Mummification is characterized by fluid reabsorption from a fetus retained in a sterile uterine environment. Fetal mummification is most common in multiparous species with a CL-dependent pregnancy (e.g., sows) and is rare in uniparous species that are CL independent for most of gestation (e.g., mares). *Maceration* refers to the degenerative changes that occur in a fetus after retention in a nonsterile uterine environment. Fetal maceration may be associated with significant maternal endometrial damage.

HORSES. Equine abortions may be characterized as infectious or noninfectious in origin. Most equine abortions occur secondary to placental dysfunction. One of the most commonly diagnosed infectious causes of abortion in horses is equine herpesvirus type 1 (EHV-1).[71] Abortion caused by EHV-1 usually occurs after 7 months of gestation and accounts for 10% to 15% of all diagnosed equine abortions. Exposure of pregnant mares to EAV may lead to abortion within 1 to 3 weeks after initial viral exposure. Abortion may be caused by vasculitis, edema, and necrosis in the endometrium and allantochorion.[73] Exposure to EAV at breeding will not cause a mare to abort later in gestation. Abortion rates may range from 10% to 70% during an outbreak.

Consumption of eastern tent caterpillars (larva of *Malacosoma americanum*) by mares causes abortion after approximately 40 days of gestation. The syndrome has been named *mare reproductive loss syndrome* (MRLS). Pregnancy loss at 40 to 150 days of gestation is characterized by hyperechoic amniotic and allantoic fluids on ultrasonographic examination along with a dead or dying fetus.[74,75] Near-term abortions are characterized by histologic lesions in the placenta and umbilical cord. In many cases, endometrial cultures are positive for non–beta-hemolytic streptococci and *Actinobacillus* species. Diagnosis of MRLS is currently based on four variable factors:

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placental lesions, culture of characteristic bacteria from fetal tissues, conformation of increased caterpillar exposure, and diagnostic elimination of other known causes of abortion (John Roberts, personal communication). The microscopic lesions observed in natural late-term MRLS cases are primarily the result of host response to bacterial infection, with the primary isolates being non–beta-hemolytic streptococci and actinobacilli.

During an outbreak in central Kentucky in 2001 and 2002, a variety of nonspecific lesions were reported that included placental edema, fetal pneumonia, and hemorrhages in the heart and placenta. During this outbreak, inflammation of the umbilical cord (funisitis), specifically the amniotic segment, was observed in 78% of cases.[76] Funisitis was also observed in necropsied cases during a 2006 Florida outbreak. The lesion is initiated as a suppurative to pyogranulomatous response between the outer circumferential stroma and the outer tunica adventitia of major umbilical vessels and progresses outward to involve or ulcerate the amniotic surface of the umbilical cord. Other causes of equine abortion such as noninfectious umbilical cord lesions, leptospirosis, and EHV should be ruled out by appropriate diagnostic tests. In addition, if a horse farm encounters unilateral endophthalmitis or pericarditis in the general population, MRLS should be elevated as a differential diagnosis for unsolved abortions.[77,78]

Crosiella equi, Amycolatopsis spp., and *Streptomyces* spp. have been associated with chronic placentitis and subsequent late-term abortion, stillbirth, and premature birth.[79,80] The condition is often termed *nocardioform placentitis* due to similarities of the causative agents to the *Nocardia* species. *Leptospira* species have also been identified as a significant cause of equine abortion in Kentucky.[81] Bacterial and fungal abortions in mares are primarily caused by infections that ascend through the cervix, causing placentitis and subsequent fetal infection. The bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus* species, *Escherichia coli, Pseudomonas* species, *Klebsiella* species, and *Staphylococcus* species. The most frequently recovered fungi are *Aspergillus* species.

The most common noninfectious cause of equine abortion is twin pregnancy.[71] Inability of the uterus to support two fetuses to term because of insufficient placental support may result in abortion at any stage of gestation but is most common after 7 months. Early diagnosis of pregnancy using ultrasonography allows for highly successful manual reduction of one twin if done before day 16 of pregnancy. This technique has significantly reduced the incidence of abortion caused by twin pregnancies.

RUMINANTS. Infectious bovine rhinotracheitis–infectious pustular vulvovaginitis (IBR-IPV) virus and bovine virus diarrhea–mucosal disease (BVD-MD) virus are two of the most common viral causes of abortion in cattle.[82] Bacterial abortions caused by *Brucella abortus, Arcanobacterium (Actinomyces) pyogenes, Bacillus* species, *Listeria monocytogenes, E. coli, Leptospira* species, and *Pasteurella haemolytica* and fungal abortions caused by *Aspergillus* species and *Mucor* species usually result from hematogenous spread and localization in the placenta.[83] Protozoal abortion, caused by *Neospora* organisms, has been recognized as a significant cause of abortion in cattle worldwide.[84] Epizootic bovine abortion (EBA) is a common cause of third-trimester abortion in susceptible heifers and cows inhabiting the foothills of the Sierra Nevada mountain range of California, Nevada, and Oregon.[85] A delta proteobacteria was recently identified as the causative agent of EBA.[86]

Campylobacteriosis (vibriosis), caused by *C. fetus,* and *C. fetus* subsp. *jejuni,* and enzootic abortion of ewes caused by *Chlamydia psittaci* are the most common infectious causes of abortion in sheep.[87] They are characterized by abortion in the last 4 to 6 weeks of gestation, premature births, stillbirths, and birth of weak, infected lambs. *C. psittaci* is also the most common cause of infectious abortion in goats in the United States.[88]

Noninfectious causes of large animal abortion include genetic or chromosomal factors, maternal stress, inadequate nutrition, vitamin or mineral deficiencies, ingestion of poisonous plants or other toxins, hormonal factors, environmental factors, physical factors, and certain medications.

Approach to Diagnosis of Abortion

A definitive diagnosis is reached in 20% to 40% of bovine abortions,[63] 50% to 60% of equine abortions,[71] and 30% to 40% of sheep abortions.[89] The generally low diagnostic success is a result of the complexity of the condition (Boxes 12-10 and 12-11). Abortion involves

BOX 12-10

Causes of Pregnancy Loss in Mares

Common Causes

Impaired oviductal and uterine environment (EED)
Chronic endometritis (EED, Ab)
Embryonic defects (EED)
Endometrial fibrosis (EED, Ab)
Twinning (Ab)
Equine herpesvirus type 1 (EHV-1) (Ab)
Bacterial placentitis (*Streptococcus* species, *Escherichia coli, Pseudomonas* species, *Klebsiella* species, *Staphylococcus* species) (Ab)
Fungal placentitis (Ab)
Umbilical cord abnormalities (Ab)

Less Common Causes

Endotoxemia (EED, Ab)
Leptospirosis (Ab)
Mare reproductive loss syndrome (MRLS) (EED, Ab)
Fetal anomalies (Ab)
Maternal stress, other disease (EED, Ab)
Chromosomal abnormalities (Ab, EED)
Fescue toxicity (EED, Ab)
Advanced maternal age (EED)
Equine viral arteritis (Ab)
Equine infectious anemia (Ab)
Uterine torsion (Ab)
Endocrine factors (EED)
Malnutrition (EED, Ab)
Drug-induced causes (EED, Ab)
Premature separation of the placenta (Ab)
Fetal asphyxia (Ab)
Placental insufficiency (Ab)

Uncommon Causes

Ehrlichia risticii (Potomac horse fever) (Ab)
Uterine body pregnancy (Ab)
Endometrial adhesions (EED)
Taylorella equigenitalis (contagious equine metritis) (EED)
Uterine lymphatic lacunae, cysts (EED, Ab)
Hyperlipemia (Ab)
Lymphosarcoma (Ab)
Iatrogenic causes (EED, Ab)
Fetal diarrhea syndrome (Ab)
Ergot toxicity (EED, Ab)
Brucellosis (Ab)
Mycobacterium infection (Ab)
Corynebacterium pseudotuberculosis (Ab)
Rhodococcus equi (Ab)
Mycoplasma infection (Ab)
Coccidioidomycosis (Ab)
Histoplasmosis (Ab)
Babesiosis (Ab)
Vitamin A deficiency (Ab)
Iodine deficiency (EED, Ab)
Granulosa theca cell tumors (Ab)
Cryptococcosis (Ab)
Sorghum, Sudan grass (Ab)
Locoweed (*Astragalus*) species
Hoary alyssum poisoning (Ab)
Salmonella abortus equi (Ab)

Ab, Abortion; *EED,* early embryonic death.

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BOX 12-11

Causes of Pregnancy Loss in Ruminants

Common Causes

Campylobacter infection (B: EED; O, C: Ab)
Epizootic bovine abortion (B: Ab)
Arcanobacterium (Actinomyces) pyogenes (B: Ab)
Bacillus species (B: Ab)
Bovine protozoal abortion (*Neospora* species) (B, C: Ab)
Infectious bovine rhinotracheitis—infectious pustular vulvovaginitis (IBR-IPV) virus (B: EED, Ab)
Leptospirosis (B, O, C: Ab)
Trichomoniasis (B: EED, Ab)
Brucellosis (B, O, C: Ab)
Bovine virus diarrhea (BVD) (B: EED, Ab)
Toxoplasmosis (O, C: EED, Ab)
Border disease (O, C: EED, Ab)
Chlamydiosis (O, C: Ab)
Embryonic defects (B, O, C: EED)
Bacterial abortion (B, O, C: Ab)

Less Common Causes

Twinning (B: Ab)
Prenatal asphyxia (B, O, C: Ab)
Akabane virus (B, O, C: Ab)
Q fever *(Coxiella burnetii)* (O, C: Ab)
Mycotoxicosis (B, O, C: Ab)
Anaplasmosis (B, O, C: Ab)
Ureaplasma infection (B, O: EED, Ab)
Mycoplasma infection (B, C: Ab)
Chromosomal abnormalities (B, O, C: EED, Ab)
Malnutrition, protein-calorie starvation (B, O, C: EED, Ab)
Bluetongue (B, O: EED, Ab)
Histophilus (Haemophilus) somni (B: Ab)
Tuberculosis (B: Ab)
Uterine torsion (B: Ab)
Water deprivation–salt toxicity (B, O, C: Ab)
Selenium deficiency (B, O, C: Ab)
Mycotic, fungal abortion (B, O, C: Ab)
Salmonellosis (B, O, C: EED, Ab)
Nitrate-nitrite poisoning (B, O: Ab)
Drug-induced causes (B, O, C: EED, Ab)
Endotoxemia (B, O, C: EED, Ab)
Cache Valley virus (B, O: EED, Ab)
Maternal stress (O, C: Ab)
Pregnancy toxemia (O, C: Ab)
Umbilical cord, placental abnormalities (B, O, C: Ab)
Fetal anomalies (B, O, C: Ab)
Deficiency of uridine monophosphate synthase (DUMPS) (B: EED)
Listeria (B, O, C: Ab)

Uncommon Causes

Pine needle poisoning (B: Ab)
Chlorinated naphthalene toxicity (B: Ab)
Osteopetrosis (B: Ab)
Lathyrus, poisoning (B, O, C: Ab)
Cobalt deficiency (B: EED, Ab)
Yersinia pseudotuberculosis (B, O, C: Ab)
Death camas (*Zigadenus* species) (O: Ab)
Foxglove (B: Ab)
Phosphate fertilizer toxicity (O: Ab)
α-Mannosidosis (B, O, C: Ab)
Ergot toxicity (B, O: EED, Ab)
Iodine deficiency (O, C: EED, Ab)
Hydrops fetalis (B, O: Ab)
Iatrogenic causes (B, O, C: EED, Ab)
Lead toxicity (B, O: EED, Ab)
Liver fluke disease (B, O, C: Ab)
Locoweed (*Astragalus, Oxytropis* species) (B, O, C: EED, Ab)
Ryegrass poisoning (B, O: Ab)
Sarcocystis infection (B, O, C: Ab)
Veratrum poisoning (O, C: EED, Ab)
Vitamin A deficiency (B, O, C: Ab)
Polybrominated biphenyl toxicity (B: EED, Ab)
Broomweed (*Gutierrezia* species) (B, O, C: Ab)
Bacillary hemoglobinuria (B, O: Ab)
Tetraglymia glabrata (O: Ab)
Copper deficiency (O, C: Ab)
Caprine herpesvirus infection (C: Ab)
Habitual abortion in Angora goats (C: Ab)

Ab, Abortion; *B,* bovine; *C,* caprine; *EED,* early embryonic death; *O,* ovine.

disease in the maternal, placental, and fetal compartments individually or together, and all these compartments have to be examined thoroughly. In addition, a "triad" of determinants for animal disease has to be considered: (1) the presence of a pathogenic organism, (2) the environment in which a host lives, and (3) the susceptibility of the host to the disease.[90] To enhance diagnostic success, information and samples must be collected from the fetus, placenta, dam, and herd. A thorough history should be obtained, including the gestational age of the fetus; reproductive, medical, and vaccination history of the dam and other individuals in the herd; previous abortions and diagnoses; new arrivals to the herd and contacts of the animal with other herds; potential causes of maternal stress; possible access to toxins and poisonous plants; and sources of water and nutrition.

A physical examination that includes all body systems should be performed on the dam. Samples should be collected from the vagina, uterus, or both, for culture and cytologic studies. Examination of the reproductive system should include palpation or ultrasonography of the reproductive tract per rectum, speculum examination of the vagina, and digital examination of the cervix. Paired serum samples from the dam and other females in the herd (10 animals or 10% of the herd, whichever is greater) may also help demonstrate an immunologic response to an infectious agent. Maternal serologic testing is generally most useful if paired samples are submitted, combined with accurate information about the animal's vaccination history. However, postabortion titers from cows that aborted can be compared with titers from unaffected cows in the herd at a similar stage of lactation. Demonstration of a fourfold rise in titer between acute and convalescent serum samples suggests recent exposure to an agent, but the presence of antibodies does not necessarily indicate that the agent caused the abortion. An exception can be made for brucellosis and leptospirosis, for which a high titer from a single sample can be diagnostic.

For optimal diagnostic efficiency, the entire aborted fetus and placenta should be submitted to a diagnostic laboratory for necropsy. If this cannot be done, a prompt necropsy should be performed and collections of fetal, placental, and maternal samples should be submitted to a diagnostic laboratory (Table 12-1).

A systematic necropsy must be performed on the aborted fetus. Fetal age and development may be assessed by measuring crown-rump length, hair patterns, and color. Meconium staining of the skin suggests uterine fetal distress. The condition of the fetus, including the degree of autolysis, should be noted. A careful examination for fetal anomalies (e.g., cerebellar hypoplasia, hydrocephalus, cleft palate, cardiac anomalies) should be performed. Histopathologic samples should be immersed in a volume of 10% buffered formalin (or Bouin fixative) equivalent to 10 times the volume of tissue. Samples for culture, virus isolation, and fluorescent antibody tests should be submitted on ice in separate sterile containers. A sample of abomasum and stomach contents should be aseptically collected for culture. Fetal heart blood or thoracic fluid may be collected for serologic evaluation. A late-term fetus is immunologically competent, and high titers may indicate activity of a pathogenic agent.

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TABLE 12-1

Tissue Samples to Be Submitted for Diagnosis of the Cause of Abortion

	Preservation Method	
Source	**Chilled or Frozen**	**Fixed***
Aborted fetus	Lung, liver, kidney, spleen, thymus, skeletal muscle, heart, heart blood, abomasum, and stomach contents	Lung, liver, kidney, spleen, thymus, skeletal muscle (diaphragm), heart, adrenal gland, lymph node, brain
Placenta	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion, amniotic fluid, cord blood	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion
Dam or herd	Paired serum samples, vaginal or uterine swabs	

*10% Formalin or Bouin fixative should be used.

Serologic testing of fetal fluids can be useful both in detecting a nonspecific active fetal immune response (total immunoglobulin [IgG]) and for titers against a specific antigen.

The fetal membranes should be examined for size, weight, degree of autolysis, condition, and completeness. Samples of placental tissue, especially areas with lesions, should be collected for histologic examination, impression smears, bacterial culture, virus isolation, and fluorescent antibody tests. The equine placenta should be examined for integrity, lesions, and distribution of chorionic villi. The normal equine placenta is everted after expulsion, with the allantoic surface presented outward and chorioallantois ruptured at the site of the cervical star. Blood may be collected from the free end of the cord. The allantoic surface should be examined for abnormalities such as multiple allantoic pouches that may indicate compromised fetal circulation.[91] The chorionic surface of the placenta should be examined for lesions and distribution of chorionic villi. Areas of avillous chorion are normally observed in association with the cervical star, narrow folds over large vessels, and areas opposing endometrial cups. Absence of chorionic villi over a circumscribed area is characteristic of twins and represents the region where two placentas were in contact. The region of the placenta adjacent to the cervix should be examined for loss of chorionic villi and the presence of inflammatory exudate, a hallmark of ascending infection. In cases of nocardioform placentitis, a characteristic thick and sticky exudate often covers an avillous area of the chorion at the ventral part of the site of the uterine body and base of the horn.

The cotyledons and intercotyledonary spaces of the ruminant placenta should be carefully examined for lesions. Autolytic changes of the placenta may be difficult to interpret. Some normal features of the bovine placenta must be kept in mind.[72] Amniotic plaques are present on the inner surface of the amnion and on the umbilical cord. They are most prominent at 3 to 7 months of gestation. Necrotic areas of the chorioallantois in the tips of the uterine horns are also normal and caused by insufficient vascularization to that area. Mineralization of the placenta is normal during the first months of gestation but may reflect placental injury associated with infection at the end of gestation.

All aborted fetuses and placental tissues should be handled with care, and tissues not submitted to a diagnostic laboratory should be burned or buried. Dams that have aborted should be isolated from the remainder of the herd.

Fescue Toxicosis

Karen J. McDowell

Tall fescue (*Lolium arundinaceum* [Schreb.] Darbysh.) is one of the most widely grown perennial grasses in the world and covers approximately 17 million hectares in the United States alone. It can be infected with an endophytic fungus, *Neotyphodium coenophialum,* which, in a symbiotic relationship with the plant, produces a variety of potentially toxic alkaloids that may adversely affect grazing livestock.[92,93] The ergot alkaloids, a class of compounds that includes ergopeptines, lysergic acid amines, and clavines, are the principle toxins responsible for fescue toxicosis in livestock.[94-96] Perennial ryegrass (*Lolium perenne* L.) may be infected with a similar endophyte, *N. lolli,* and also produces ergot alkaloids; it may result in a toxicosis that is similar to fescue toxicosis.[97] Tall fescue toxicosis is the major grass-induced toxicosis in the United States,[98] and ergovaline is the most abundant alkaloid in tall fescue.[95]

Clinical Signs of Fescue Toxicosis

Clinical signs of fescue toxicosis in livestock have been well documented,[98-104] and only those signs associated with reproduction will be reviewed here. Ergot alkaloids have an ergoline ring structure with a molecular architecture similar to various biogenic amines including dopamine, serotonin, norepinephrine, and epinephrine, and this structural similarity allows them to bind to the respective biogenic amine receptors.[95] As a result, endocrine responses such as hormonal changes, most notably decreased circulating concentrations of prolactin, and vasoconstriction occur with fescue toxicosis.

Historically, the endocrine hallmark of fescue toxicosis in several species has been the decrease in circulating concentrations of prolactin.[104,105] Prolactin is secreted from the lactotrophs of the anterior pituitary gland, and control of its secretion is complex and not completely understood. However, inhibition by dopamine (from the hypothalamus) is a major regulator of its release.[106] Dopamine exerts inhibition of prolactin by interacting with the dopamine type-2 (D2) receptor of the lactotroph.[104] Ergovaline is a dopaminergic agonist, and it is through interaction with this D2 receptor that it inhibits release of prolactin. Dopamine receptors in ovarian tissues including the CL have been reported for a number of species, including horses[107] and cattle,[108] but the role of those receptors in fescue toxicosis, if any, has not been elucidated.

HORSES. In horses the most frequently reported problems associated with endophyte-infected (E+) fescue consumption are in late pregnancy and include altered hormone concentrations, extended gestation, thickened placenta, premature placental separation, placental retention, dystocia, birth of dysmature foals, increased foal and placental weights, and agalactia.[101,105,109] Pregnancy may be prolonged as much as 2 to 4 weeks.[101,109,110] Mares do not produce a placental lactogen, and agalactia associated with fescue toxicosis may be severe. That fescue toxicosis causes decreased prolactin concentrations in horses other than late pregnant mares has been more difficult to demonstrate, and it is important to remember that concentrations normally vary with season. However, prolactin does exert a variety of effects in the pregnant and nonpregnant animals, including regulation of lactogenesis,[111] steroidogenesis (estrogens, progesterone, and testosterone),[112,113] hair growth and shedding,[113] libido,[114] and synthesis of surfactant by the fetal lungs,[115] so perturbations in prolactin secretion may affect a variety of systems.

Normally progestins in the maternal circulation of pregnant mares increase and estrogens tend to decrease in the last 60 days of gestation. Approximately 24 to 48 hours before parturition progestins decrease dramatically, thus causing an increase in the

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estrogen-to-progestin ratio.[116] However, studies have shown that late-gestation mares consuming E+ fescue do not have the decreased estrogens or increased progestins at the expected time of parturition.[99,101] In addition, the placental hormone relaxin tends to be lower when pregnant mares graze E+ fescue.[117] Alterations in these hormone concentrations, along with the possibility that the ergot alkaloids from E+ fescue may interfere with the maturation of the fetal hypothalamic-pituitary-adrenal axis and the ability of the fetus to produce cortisol and thyroid hormone,[105,118,119] may contribute to the extended gestation exhibited by mares consuming E+ fescue. Importantly, prolactin may also exert an effect on the feto-placental unit by altering steroid synthesis and/or metabolism, as well as maturation of the fetal adrenal-pituitary axis necessary for parturition.[99]

In addition to the well-documented signs of fescue toxicosis in late pregnant mares, mares may also experience reduced fertility and/or increased early embryonic mortality, but those effects are less well documented. It has been suggested that mares grazing E+ fescue pastures had a decrease in per-cycle pregnancy, but no significant differences between groups were detected compared with control mares.[120] Progesterone concentrations did not differ between E+ versus E– mares on days 0 through 14 of the estrous cycle and were only elevated after day 14 in some mares that experienced a prolonged diestrus (see Brendemuehl[120] later). Progesterone concentrations did not differ between E+ versus E– mares that had viable pregnancies through day 21 after ovulation. In another study, for mares grazing E+ fescue pastures versus E– fescue pastures from day 21 to day 300 of gestation, there were no differences in eCG concentrations between days 45 and 120, but progesterone concentrations were lower between days 90 and 100,[121] and there were no incidences of pregnancy loss in either group of mares. Youngblood and colleagues[122] fed pregnant mares, between 65 and 100 days gestation, either E+ or E– fescue seed, added to their diet, for 10 days. Serum concentrations of prolactin were not different between the treatment groups. Mean concentrations of progesterone were greater in the mares fed E+ fescue seed, but there were no incidences of pregnancy loss. However, endogenous catecholamine activity (of 3,4-dihydroxyphenyl acetic acid) decreased in the E+-treated mares, suggesting an endocrine disruptive effect of hypothalamic origin.

In cycling mares, Brendemuehl[120] reported that the length of diestrus was greater in some mares grazing E+ pastures compared with those grazing E– pastures. In contrast Hestad and McDowell[123] fed nonpregnant mares E+ fescue seed (19 μg ergovaline + ergovalinine/kg body weight) or E– fescue seed for one estrous cycle (interovulatory interval) and reported no differences in progesterone or estradiol concentrations or in interovulatory intervals. In that same study (unpublished) mean blood flow in the CL was significantly reduced. That E+ fescue causes vasoconstriction in horses has been demonstrated both in vivo[123-125] and in vitro,[126,127] and this vasoconstriction likely contributed to the decreased blood flow in the CL in cycling mares. Decreased blood flow in the CL, while not affecting interovulatory interval in the Hestad study, might have contributed to increased lengths of diestrus in the 1994 Brendemuehl study by contributing to CL resistance to $PGF_{2\alpha}$.[128]

Responses of individual horses grazing the same pastures are variable, and there are currently no convenient and inexpensive laboratory assays to determine fescue alkaloid concentrations in the circulation of horses grazing E+ pastures. Even if there were, the minimal amounts of alkaloids necessary for an animal to develop premonitory signs of fescue toxicosis have not been established. It has frequently been reported that pastures with ergovaline concentrations below approximately 300 ppb do not cause detrimental effects in horses.[129] However, minimal "safe" levels of ergot alkaloids that do not result in fescue toxicosis in horses are not known. In addition, a sensitive measure of biological responses to fescue toxicosis would be a necessary tool in such studies. McDowell and colleagues[123-125] have proposed that monitoring vasoconstriction of the palmar artery and perhaps blood flow in the reproductive tract may provide a convenient and satisfactory biomarker to determine premonitory signs of fescue toxicosis.

RUMINANTS. The most consistent deleterious health effects associated with fescue toxicosis in ruminants are due to vasoconstrictive properties of the ergot alkaloids. The vasoconstrictive effects of ergot alkaloids are well documented in cattle[130-132] and sheep[133] but are more prevalent in cattle. Fescue toxicosis in ruminants is best characterized by the two maladies of "summer slump" in warm climates and "fescue foot" in cold climates.[102-104] Summer slump is associated with decreased weight gain, elevated body temperature and respiration rates, shade-seeking behavior, rough hair coat, excessive salivation, and reduced milk production. Fescue foot is characterized by tenderness and/or swelling around the fetlock, lameness, tissue necrosis, and potential sloughing of the hoof, tips of ears, or tail switch. Clearly the above conditions may directly and indirectly affect reproductive performance, particularly elevated body temperatures and decreased weight gain associated with summer slump.

Fescue toxicosis associated with decreased reproductive performance in ruminants has been reported.[103,134] Cattle grazing E+ fescue pastures, compared with nontoxic forages, typically have reduced dry matter intake, reduced body condition scores, and reduced calving rates.[134-137] However, reports of reduced reproductive performance have not been consistent. Pregnancy rates for cows consuming E+ fescue were reduced 7% to 39% compared with control cows,[138,139] but other reports showed no reduction in pregnancy rates.[140,141] Serum progesterone concentrations may be reduced in heifers[142] and ewes,[143] and age of the animal may influence the effect of E+ fescue consumption on reproductive performance in cattle.[141] Jones and colleagues[142] reported that heifers consuming E+ diets had shorter estrous cycle lengths and lower midcycle progesterone concentrations than heifers on endophyte-free pastures.

Similar to horses, consumption of E+ fescue causes decreased concentrations of prolactin in cattle and sheep. This decrease in prolactin causes a decrease in milk production[144] but rarely a complete agalactia, because ruminants have placental lactogens that are thought not to be affected by fescue toxicosis.

Approaches to ameliorating adverse effects of fescue toxicosis in mares and heifers have been reviewed (see later) and include renovation to remove or reduce the amount of E+ fescue in pastures or removal of animals from E+-infected pastures during times of growth or reproductive performance that may be affected by E+ fescue. For pregnant mares, it is generally recommended that animals be removed from E+ fescue pastures 30 to 90 days before expected parturition. Both horses and cattle respond well to treatment with a dopaminergic D2 receptor antagonist such as domperidone.[105,142,145] Further discussions and dosing recommendations have been given by Cross,[105,146] Evans,[99] and Jones.[147]

Male Reproductive Function

Information on reproductive effects of E+ fescue in bulls, rams, and stallions is sparse. Looper and colleagues[135] reported that bulls grazing toxic E+ fescue pastures had reduced sperm motility and morphology compared with bulls grazing novel (nontoxic) E+ pastures and that semen quality in bulls grazing E+ pastures was decreased as ambient temperature increased. In other studies, ergot alkoids inhibited sperm motility[148] and reduced IVF embryo cleavage rates.[149] Jones and colleagues[150] reported that bulls fed a diet containing E+ fescue seed had increased scrotal temperature, reduced scrotal circumference, and increased sperm concentration compared with bulls fed a control diet.

There is little information on the effects of E+ fescue on stallion fertility. One study showed no adverse effects of E+ fescue seed consumption on sperm motility, number, morphology, or testicular size but did result in reduced gel-free semen volume compared with control stallions.[151] Clearly, much more information on potential effects of fescue toxicosis on male fertility is necessary.

Ergotism in Human Populations—In Medicine and Disease

For interesting discussions on ergotism in human populations, see Strickland and colleagues,[104] van Dongen and Groot,[152] and Schiff.[153]

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Approach to Diagnosis of Fescue Toxicosis

James P. Brendemuehl

Definitive diagnosis of fescue toxicosis involves identification of the causative endophytic fungus in forage or seed samples by microscopic examination (Boxes 12-12 and 12-13). Ergopeptine concentrations may additionally be determined by high-pressure liquid chromatography analysis or specific enzyme-linked immunosorbent assay (ELISA). A presumptive diagnosis of fescue toxicosis can be made in cattle on the basis of expression of the characteristic clinical signs of hyperthermia; excessive salivation; long, rough hair coat; necrosis of the tail and ear tips; and fat necrosis in association with consuming fescue forage. Hypoprolactinemia is supportive of the diagnosis, but the assay is not commercially available.

A presumptive diagnosis of fescue toxicity in the pregnant mare is based on the observation of failure of normal mammary development for gestational stage. Prolongation of gestation is commonly reported as well. An accurate breeding history should include dates of breeding, dates of confirmed pregnancy diagnosis, and absence of parturition at the anticipated time. A history of recent exposure to fescue pasture or hay is supportive. In tall fescue–endemic areas, pastures that contain tall fescue grass should be considered infected with the endophyte unless specific testing has confirmed otherwise. Determination of total plasma progestogen concentrations is a sensitive indicator of endophyte exposure after 300 days of gestation.[154]

Management of a mare suspected of endophyte exposure should consist of removing the mare from the suspected pasture or hay source and maintaining the mare in a stall or dry lot under close observation. High-quality hay, preferably legume, should be provided. Because of the increased incidence of dystocia in mares grazing endophyte-infected tall fescue, close monitoring of the mare and attendance at parturition is critical to minimize risk to the mare and loss of the foal. Removal of mares from infected fescue by day 300 of gestation has been demonstrated to alleviate the toxic effects on the mare and foal. Removal after day 300 carries an increased risk of prolonged gestation, agalactia, dystocia, and neonatal death. Induction of parturition is not recommended because of the high incidence of fetal dysmaturity, fetal oversize, and failure of pelvic relaxation associated with endophyte exposure. Elective cesarean section deliveries of postdate gestation mares have resulted in significantly higher foal survival rates than spontaneous deliveries.

Where removal of pregnant mares from infected fescue is not practical or mares are inadvertently grazed on endophyte-infected fescue beyond the recommended stage of gestation for removal, pharmacologic intervention is warranted. Several DA_2 dopamine receptor antagonists—perphenazine,[155] fluphenazine,[156] and domperidone[157]—and the dopamine depleter reserpine[158] have been investigated prophylactically to prevent or therapeutically to treat clinical fescue toxicosis. Perphenazine[155] and fluphenazine[156] have demonstrated mixed success in preventing toxicosis in restricted clinical trials. Reserpine[158] was ineffective in preventing prepartum agalactia and prolonged gestation but was sufficient to resolve postpartum agalactia. Domperidone[159] has demonstrated efficacy in both the prevention and treatment of clinical fescue toxicosis in clinical trials involving large numbers of mares in numerous locations.

BOX 12-12

Manifestations of Fescue Toxicity in Mares

Agalactia, hypogalactia
Hypoprolactinemia
Decreased relaxin prepartum
Prolonged gestation
Early embryonic death
Cyclic irregularity
Dystocia
Premature allantochorion separation
Allantochorion edema
Increased placental weight
Retained placenta
Corpus luteum persistence
Decreased pregnancy rates
Decreased total progestagens prepartum
Poor neonatal viability
Reduced colostral immunoglobulin G (IgG) absorption
Neonatal hypoadrenalism
Neonatal hypopituitarism
Neonatal hypothyroidism
Fetal oversize
Hirsutism
Hyperhidrosis

BOX 12-13

Manifestations of Fescue Toxicity in Ruminants

Agalactia, hypogalactia
Reduced calf birth weight
Hypoprolactinemia
Reduced serum cholesterol
Reduced conception rates
Reduced pregnancy rates
Early embryonic death
Cyclic irregularity
Delayed return to cyclicity postpartum
Dystocia
Hyperthermia
Hyperpnea
Hirsutism
Reduced weight gain
Photosensitization
Necrosis of the digits
Necrosis of the ears and tail
Fat necrosis

Prolonged Gestation

Bruce W. Christensen

Many factors influence the duration of gestation in horses and ruminants. Normal variations in length of gestation have been attributed to genetic, nutritional, and environmental factors.[160,161] The species, breed, and sex of the fetus; ambient temperature; and length of photoperiod are among factors that, within normal variations, affect the duration of gestation.[18,160-162] The duration of pregnancy in Thoroughbred mares ranges from 310 to 374 days,[162] in dairy cows from 275 to 292 days, in beef cows from 271 to 310 days, in ewes from 143 to 155 days, and in does from 146 to 155 days.[163] Prolonged gestation periods are those that exceed the normal gestational variation attributable to genetic, nutritional, and environmental factors. In pathologic prolonged gestation there is an impediment to the mechanisms that terminate gestation and initiate parturition. Pathologically prolonged gestation has been attributed to genetic, infectious, and toxic factors,[164] as well as to manipulation of the embryo.[165,166]

Of the several forms of prolonged gestation with genetic causes in cattle, the best described forms have been observed in Guernsey and Holstein cattle.[18,161,164,167] In each the fetus fails to initiate parturition at term because of fetal adrenal hypoplasia. Prolonged gestation, from 3 weeks to 3 months beyond normal term, has been observed in a number of dairy cattle breeds.[168] Graves, Hansel, and Krook[167] described a Holstein fetus of 441 days' gestation in which the pituitary pars distalis was aplastic and the adrenal and thyroid glands were severely hypoplastic. Two different types of fetuses have been associated with prolonged gestation in cattle.[160] In the first type, fetuses had a large skeleton and excessive growth of epidermal organ structures such as hair and hooves but no obvious deformities. The second type of fetus was mature or immature and exhibited cranial and central nervous system anomalies; growth ceased at about

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BOX 12-14

Causes of Prolonged Gestation in Mares

Fescue toxicity
Fetal mummification
Delayed embryonic development

BOX 12-15

Causes of Prolonged Gestation in Ruminants

Fetal mummification
Fetal hypothalamic-hypophysial-adrenal axis disorder
Autosomal recessive genetic disorder affecting Holstein and Guernsey cattle (B)
Vitamin A deficiency (B)
Veratrum album toxicity (B)
Veratrum californicum toxicity (cyclopamine) (O)
High environmental temperature (B)
Fescue toxicity
Hydrops amnii (B, O)
Bluetongue (B, O)
Bovine virus diarrhea (B)
Border disease (O)
Salsola tuberculata toxicity (Grootlamsiekte [exotic]) (O)
Akabane virus (exotic) (B, O)
Somatic cell nuclear transfer (B)

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

7 months of gestation. Both types of calves had hypoplastic or absent adrenal glands. These anomalies have been observed to be inherited as an autosomal recessive trait.[161,164]

Several infectious agents have been incriminated in prolonged gestation in ruminants. Bluetongue virus, bovine diarrhea virus, and border disease virus may cause severe cerebral lesions in the fetus, resulting in the absence of a hypothalamus and pituitary stalk. Again, by virtue of the lack of adrenocorticotropic hormone, the sequence of events necessary for parturition does not occur.[164]

The use of assisted reproductive techniques in cattle in the form of in vitro procedures and somatic cell nuclear transfer ("cloning") offers advantages for reproducing important genetic lines, but they have many accompanying complications that have yet to be overcome. Besides increased pregnancy loss, increased birthweight of calves, and increased incidence of dystocia and perinatal losses, another of these complications is prolonged gestation in recipient cows compared with embryo transfer recipient and artificially inseminated cows.[165] This technology has great potential for manipulating and preserving superior genetic potential.[169] The cow has been the most successfully cloned animal to date, but such cloning still has a low success rate (0% to 10%).[170,171] This is an active area of research, and it is likely that with further understanding the current pitfalls surrounding in vitro procedures and nuclear transfer will be overcome and use of the techniques will become more commonplace.[171]

Veratrum californicum contains the teratogenic agent cyclopamine. When pregnant ewes ingest cyclopamine on the 14th day of gestation, their fetuses lack a pituitary gland or have a malformed hypothalamic stalk. These defects result in prolonged gestation by virtue of secondary adrenal hypoplasia.[164]

Prolonged gestation in mares has been cited as an indication for induction of parturition.[172,173] However, the clinical significance of prolonged gestation in mares is undetermined because there is no apparent correlation between duration of gestation and readiness for birth. Dysmature neonatal foals have resulted from gestations of normal and longer than normal durations; alternatively, 399 days' gestation resulted in births of normal twin foals.[174] Prolonged gestation in the mare has not generally been associated with excessively large foals and dystocia.[175] Therefore in the absence of clinical signs that warrant induction of parturition in a high-risk pregnancy and the fulfillment of criteria for induced parturition, there is no reason to perform elective parturition induction in mares in which gestation is prolonged.

Approach to Diagnosis of Prolonged Gestation

Approach to the diagnosis of prolonged gestation in mares and ruminants is essentially similar (Boxes 12-14 and 12-15). If the client is concerned about what is apparently prolonged gestation in an otherwise normal dam, an accurate breeding history should be obtained. Because no pathognomonic clinical or laboratory findings are associated with prolonged gestation, the diagnosis is predicated on the history and a general physical examination of the dam. The overall condition of the dam should be determined. In addition to the reproductive history, exposure to infectious agents and toxic plants should be determined. The most important anamnestic factors are breeding dates, dates of confirmed pregnancy examinations, and absence of parturition at the expected time. The reproductive tract should be examined for the gravid uterus and evidence, although tenuous, of the term or near-term fetus. Diagnostic ultrasonography can be incorporated into the workup to enhance the assessment of viability and fetal well-being by determination of fetal heart rates, fetal size and movement, uteroplacental thickness, and estimation of allantoic fluid volume.[176,177] Parturition should not be induced unless the objective is fetal survival in the face of a high-risk pregnancy.[178] Otherwise, the mare should be examined and, if appropriate, the owner assured that the gestation is probably normal and that patience will likely result in a normal foal with adequate colostrum and passive immunity.[179]

Dystocia

Mats H.T. Troedsson

Dystocia is defined as difficult parturition; it may be a sign of either maternal or fetal conditions that impede fetal passage through the birth canal.[18] Dystocia in mares and ruminants is more likely to be attributable to fetal causes such as malpresentation, malposition, and malposture than to maternal conditions[18,180] (Boxes 12-16 and 12-17). The overall incidence of dystocia and incidences of types of dystocia vary among the species and breeds within a species.[181] Cattle, especially first-calving heifers and larger breeds, are more commonly affected by dystocia; the overall incidence of bovine dystocia ranges from 3% to 25%.[18] The incidence of dystocia among Thoroughbred mares is 4%,[180] and in does, 3% to 5%.[182] The incidence of dystocia is generally greater in sheep than in goats.[87] Dystocia represents an emergency situation that commands prompt resolution to afford the optimum prognosis for dam and fetus. Reposition, traction, fetotomy, and cesarean section are the obstetric procedures available for the management of dystocia.[183] The economics of large animal practice often play a significant role in determining which course to pursue in resolving dystocia. The lives of the dam and the fetus may be at risk. Although the objective should be the survival of both, unless otherwise advised by the owner and if conditions are not prohibitive, the well-being of the dam and her reproductive potential should have priority over the fetus.

Although parturition has been divided into three distinct stages for descriptive purposes, the stages overlap clinically and normal parturition is observed as a continuous process.[180] The equine fetus is lying in a ventral or ventrolateral position with head and forelimbs flexed during late gestation.[184] During the first stage of parturition the fetus plays an active role, along with myometrial contractions, in assuming correct extremity posture as it positions itself for delivery through the birth canal. The second stage of parturition commences with rupture of the chorioallantois and culminates in delivery of the fetus. Myometrial contractions continue during third-stage parturition, which ends with the expulsion of the placenta. In the mare parturition is a forceful, explosive act. The time between rupture of the chorioallantoic membrane and delivery of the fetus is normally

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BOX 12-16

Causes of Dystocia in Mares

Common Causes

Malpresentation
Malposition
Malposture
Abortion
Arthrogryposis
Twinning

Less Common Causes

Fescue toxicity
Preterm parturition
Torticollis
Vaginal, vulvar obstructions (hematoma, callus, abscess, tumor)
Pelvic injury, fracture

Uncommon Causes

Fetopelvic disproportion
Congenital defects
Hydrocephalus
Uterine dorsoretroflexion
Uterine torsion
Hydrops of fetal membranes
Rupture of prepubic tendon
Fetal mummification, maceration
Vaginal prolapse
Abdominal, inguinal hernia
Uterine inertia
Induction of parturition
Premature separation of chorioallantois from endometrium
Uterine laceration

BOX 12-17

Causes of Dystocia in Ruminants

Common Causes

Fetopelvic disproportion (B, common; C, O, uncommon)
Malpresentation
Malposition
Malposture
Twins, triplets (B)
Uterine torsion
Periparturient hypocalcemia (B)
Failure of cervix to dilate (B, O; rare in C)
Lymphedema

Less Common Causes

Preterm parturition
Abortion
Congenital defects (fetal monsters)
Hydrops of fetal membranes (B, O)
Emphysematous fetus
Hydrocephalus (more common in B than O, C)
Extremity ankylosis (more common in B than O, C)
Breeding immature, young, small-for-age females
Obesity (B)
Pregnancy toxemia (O, C)
Uterine inertia
Fetal mummification, maceration
Uterine, cervical, vaginal obstruction
Retained fetus
Pelvic fracture
Vaginal prolapse

Uncommon Causes

Phytoestrogen toxicity (B, O)
Rectovaginal constriction of Jersey cattle (B)
Uterine rupture
Abdominal, inguinal hernias
Lipomatosis (B)
Lupine poisoning, arthrogryposis (B)
Polybrominated biphenyl toxicity
Bovine fetal tumors
Rupture of prepubic tendon (B)
Hereditary edema, lymphedema in Ayrshire calves
Prolonged gestation (B, O)
Chlorinated naphthalene toxicity

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

about 20 minutes.[18] Separation of the fetal membranes from the endometrium may occur within 1 to 2 hours after the second stage of parturition commences; therefore the retained fetus must be delivered quickly or it will asphyxiate. Fetal expulsion in the ruminant is not quite as explosive as in the mare; second-stage parturition in the bovine usually requires ½ hour to 4 hours.[18] Ewes and does require a range of ½ hour to 2 hours to complete the second stage, or slightly longer if twins or triplets are present.[18] Primiparous animals generally require a longer time to expel the fetus than do multiparous dams.

Dystocia in large animals is often accompanied by forceful straining. The dam may attempt to lie down and stand repeatedly. This is characteristic of dams with dystocia that is caused by fetopelvic disproportion, malposture, or fetal impaction. Alternatively, the dam may stand quietly with minimal or no straining, as in cases of uterine inertia, uterine rupture, or exhaustion associated with prolonged dystocia of any cause. Whatever the presentation of the dam, the attending veterinarian must be prepared for unexpected behavior when attempting to perform obstetric examinations and procedures. The dam, fetus, attendants, and veterinarians must be protected from injury. The dam should be placed in open-ended stocks with movable sides or a straw-bedded box stall. During obstetric examination and manipulation, mares and cows may attempt to get up and lie down, or they may suddenly collapse. Such sudden movements may injure the dam and veterinarian if rigid, closed-end stocks are used. Minimum physical restraint should be used; however, restraint should be sufficient to permit completion of the obstetric examination and procedures with efficiency and safety. General anesthesia followed by elevation of the hindquarter will facilitate safe manipulation and vaginal delivery of a foal in mares with dystocia. This technique, if applied correctly, will likely result in less damage to the mare's reproductive tract.

Little is known about the pharmacokinetics of drugs in pregnant domestic animals. Accordingly, it must be assumed that sedative and anesthetic drugs will depress neonatal and fetal functions at least as much as those of the mare. The effects on myometrial activity of drugs administered to dams experiencing dystocia must also be considered. Acepromazine has little effect on the fetus and is generally considered safe for use in the pregnant mare. However, acepromazine was shown to have a suppressive effect on myometrial activity in cycling mares.[185] Xylazine causes significant fetal cardiovascular compromise in horses and has been reported to stimulate myometrial activity in cows and mares.[185-187] The fetal and myometrial effects of detomidine are similar but of longer duration compared with those of xylazine.[185,186] The effects of detomidine on myoelectrical activity in the uteri of cows and mares treated during the last trimester of pregnancy were dose dependent.[188,189]

As equipment is being organized and the process of evaluating the dam begins, a pertinent reproductive history should be obtained, including the dam's age, her previous breeding history, and the outcomes of previous pregnancies (i.e., abortion, normal parturition, dystocia). Her present gestational status should be determined; has parturition commenced at term, or is it a preterm or postterm delivery? Her udder should be examined to determine the stage of development. Information about the progress of the current parturition should be obtained. The time since rupture of the chorioallantoic membrane, the duration and intensity of labor, whether fetal membranes or parts have appeared at the vulva, and previous attempts to assist in delivery should be noted. If the dam is recumbent, the veterinarian should determine if she has attempted to or been able to

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rise. Although a complete examination of the dam is optimum, it should be postponed until after the delivery of the fetus. However, in obtaining the dam's reproductive history, questions about her current physical condition should be included. Such predisposing factors as recent weight loss, systemic disease, and trauma should be considered. She should be assessed for signs of hemorrhage, dehydration, and shock.

After the tail has been wrapped, the perineal area should be thoroughly and gently washed and rinsed. Examination of the dam's reproductive tract may cause some discomfort or pain. Temperance regarding analgesia and sedation must be practiced. Caudal epidural anesthesia (1 to 1.25 mL/100 kg of 2% lidocaine or other anesthetic) is often an excellent means of facilitating examination and resolution of dystocia and at the same time minimizing trauma to the dam, fetus, and operator. Lidocaine epidural anesthesia may cause hindlimb weakness and ataxia. Safe and effective analgesia can also be induced by epidural administration of xylazine (0.17 mg/kg diluted in 10 mL physiologic saline). A combination of lidocaine (0.22 mg/kg) and xylazine (0.17 mg/kg) resulted in an onset of analgesia within a few minutes and a duration of over 5½ hours.[190] Although both vaginal sensitivity and the Ferguson reflex are reduced by epidural anesthesia, myometrial contractions and abdominal press are not totally eliminated. General anesthesia will effectively eliminate myometrial contractions and abdominal press. This approach has to be combined with an elevation of the hindquarter of the dam, in order to provide sufficient space for safe manipulation of the fetus. Great care must be taken during the examination of the genitalia and fetus. In addition to the viability of fetus and dam, the dam's future reproductive potential is at risk and must be preserved. The vulva, vestibule, vagina, and cervix should be carefully examined. The location of the fetus in the birth canal, as well as its viability, presentation, position, and posture, should be determined. Schuijt and Ball[191] described a procedure to manually dilate the bovine birth canal before forced extraction is attempted. In the management of dystocia in any species, forced extraction should proceed only after maximal dilation of the caudal reproductive tract in order to minimize the potential for injuries to the dam during parturition (i.e., cervical, vaginal, and vulvar lacerations; hematomas; postparturient vaginal necrosis; and obturator, perineal, and gluteal paralyses).[18,192] Mares are especially susceptible to cervical lacerations, which may have detrimental consequences on the dam's future reproductive performance. Slow traction with continuous palpation of cervical stretching by the attending obstetrician is therefore recommended in equine dystocias.

The integrity of the birth canal, fluids, and fetal membranes serves as an indicator of the length of time the dystocia has persisted and the well-being of the fetus. Generous lubrication is required in all cases of dystocia and should be applied continuously during the management of dystocia to prevent damage to the dam's birth canal. Lubricating preparations consisting of methyl cellulose are superior to those consisting of mineral oil or soaps. Several liters of lubricants should be infused into the bovine and equine uterus by the use of a nasogastric tube.

Traction or forced extraction can usually be successfully implemented after correction of malpresentation, malposition, or malposture. In equine dystocia, if the foal is still alive and dystocia cannot be relieved quickly (20 minutes) or if it is determined that extensive manipulation will be required, general anesthesia may be induced. Because of the length of the extremities of the foal, manipulation is more difficult in the mare than in the cow and requires extensive repulsion to provide adequate room for manipulation. Examination and manipulation can be greatly facilitated by elevating the mare's hindquarters, enabling the fetus and viscera to recede cranially into the mare's abdominal cavity, thereby allowing more room for the operator.[193] If a nonviable fetus cannot be delivered by traction or forced extraction or if the owner is unwilling to select cesarean section, fetotomy can be performed.[183,193] Beyond the delivery of the nonviable fetus, fetotomy is indicated to save the mare and her subsequent fertility.[183] The advantages of fetotomy include avoiding major abdominal surgery (cesarean section) and its complications and preserving the birth canal because excessively large parts are not forced through it.[18,192-194] At the same time, the primary disadvantage of fetotomy, particularly if not properly performed by an experienced obstetrician, is trauma to the birth canal by instruments, wire, or bone.[18] The indications, equipment, procedures, and complications of fetotomy have been reviewed in several publications.[18,183,192-194]

Cesarean section is indicated for a dam with dystocia when attempts to deliver the fetus by reposition, traction, and fetotomy are unsuccessful or contraindicated, and continued attempts may compromise the fetus, the dam, or her subsequent fertility.[18,87,174,178,181,195-200] Cesarean section may be the only rational procedure for delivery of some fetuses (e.g., emphysematous fetuses, deformed fetuses, bicornuate fetuses). In addition, high-risk pregnancies caused by maternal conditions can be effectively and efficiently managed by cesarean section.[178] The specific indications, procedures, and complications of cesarean section have been reviewed in a number of publications.[18,174,178,181,195-200]

Management of a case of dystocia is not complete until a systematic examination, focusing on the dam's reproductive tract, has been conducted. Complications during dystocia involving the reproductive tract and other body systems can affect the outcome of the case.[18,175,201,202] As much as possible, examination of the dam's reproductive tract should rule out the presence of another fetus in the uterus or abdominal cavity.[18] The most common reproductive injuries incurred by dams during parturition include cervical, vaginal, and vulvar lacerations; hematomas; postparturient vaginal necrosis; and uterine hemorrhage.[179,192,202] Gastrointestinal complications, such as constipation associated with unwillingness to defecate, postpartum perineal inflammation, and bruising or rupture of entrapped or compressed segments of the gastrointestinal tract, can follow parturition in the mare.[202] Musculoskeletal and neurologic complications have been reported after parturition in cows and mares.[18] Retained placenta, delayed uterine involution, metritis, and laminitis may result from normal parturition but are more likely sequelae of dystocia.[18,202,203]

The signs associated with normal progression of each of the stages of parturition must be explained carefully to clients and farm managers. It is only through understanding the clinical signs associated with events of normal parturition that clients become proficient at recognizing abnormal events and know when to seek professional assistance.

Retained Fetal Membranes

Mats H.T. Troedsson

Retained fetal membranes represent the failure of the entire or partial placenta to be expelled within physiologic time limits. Although variation exists among species regarding the duration of time that must pass before a placenta is considered retained, the condition is one of the most common complications occurring in animals after parturition.

Retained Fetal Membranes in Mares

The anatomic structure of the equine placenta is described as diffuse, epitheliochorial, and microcotyledonary. It is composed of the allantochorion, the allantoamnion, and the umbilical cord.[204] During most normal foalings, the separation of fetal membranes from the endometrium and their subsequent expulsion occur within ½ hour to 3 hours of the delivery.[183,205,206] The incidence of retained fetal membranes is 2% to 10% in the mare, with a higher incidence in draft horses than in lighter horse breeds.[207] The cause of retained fetal membranes remains unclear, but it is believed that allantochorionic microcotyledons near the tip of the nongravid uterine horn have failed to separate as a result of an endocrine unbalance, a disturbance in normal myometrial contractions, or any swelling at the site of microcotyledons[208] (Box 12-18). Diagnosis of retained fetal membranes in the mare is straightforward when it is based on the observation of membranes hanging from the vulva beyond 3 hours after

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BOX 12-18

Causes of Retained Fetal Membranes in Mares

Common Causes

Dystocia
Preterm parturition
Abortion
Endometritis, metritis
Twinning
Induced parturition
Stillbirth

Less Common Causes

Fetotomy
Cesarean section
Placental edema at uterine horn tip
Placentitis
Drugs
Prolonged gestation
Fescue toxicity
Poor condition, poor environment, fatigue, increasing age, and other debilitating conditions
Hypocalcemia
Dropsy of fetal membranes
Entrapped placenta

BOX 12-19

Causes of Retained Fetal Membranes in Ruminants

Common Causes

Multiple births
Induced parturition
Placentitis (bacterial, fungal infection)
Hypocalcemia
Abortion
Stillbirth
Dystocia
Abnormal gestation length

Less Common Causes

Injury, inflammation, or edema of placentome
Cesarean section
Uterine torsion
Necrotic placentome secondary to uterine and systemic disease
Excessive weight gain during dry period
Uterine atony
Dropsy of fetal membranes
Entrapment of separated placenta
Prostaglandin $F_{2\alpha}$ deficiency
Trace mineral deficiencies (selenium and iodine)
Vitamin deficiencies (carotene, vitamins A and E)
Mineral deficiencies, imbalances (calcium and phosphorus)
Heat stress
Increasing age
Nitrate toxicity
High milk production

foaling. However, if the fetal membranes fall cranially over the pelvis, they remain within the uterus without being visible and the diagnosis must be made using vaginoscopy or ultrasonography or by digital intrauterine examination. If an early diagnosis of complete or partial retention of fetal membranes has been missed, the diagnosis may be made 1 to 2 days after foaling. At this time, clinical signs indicative of metritis are often present (i.e., fever, depression, colic, and/or laminitis).

After their expulsion, the fetal membranes should be stored until they can be scrutinized to determine if they are complete. The clinician should rinse the fetal membranes with water and, on a flat surface, thoroughly examine them for completeness.[209] Evidence that a part of the placenta is retained in the uterus or that an area of microvilli has been sheared off and retained in the endometrial crypts is an indication for digital endometrial examination or ultrasonographic examination and institution of appropriate therapy (see Chapter 43).

Approach to Diagnosis of Retained Fetal Membranes in Mares

HISTORY. Many cases of retained fetal membranes follow episodes of dystocia, cesarean section, and fetotomy. An increased incidence of retained fetal membranes has been reported in mares that abort after the seventh month of gestation.[207] However, no increase in the incidence of retained fetal membranes associated with abortion, stillbirth, twinning, and delivery of a weak or diseased foal was observed if it occurred without dystocia.[210]

PHYSICAL EXAMINATION. Fetal membranes must be examined after their expulsion to determine their entirety and integrity. Tears, missing areas of tissue, and areas of chorionic surface devoid of microvilli should be considered evidence of partly retained fetal membranes, and immediate action should be taken to enhance expulsion of retained tissue and minimize complications.

Vital signs may be normal early in cases of retained fetal membranes. A rectal examination should be performed to determine the degree of uterine involution. Aseptic intrauterine palpation can be performed to determine the area and extent of retention and the integrity of involved tissues and fluid.[209] Systemic signs of dehydration, septicemia, toxemia, and laminitis may accompany fetal membranes retained for 24 to 36 hours.[202] Occasionally mares with retained fetal membranes show signs of colic. Therapeutic approaches for retained fetal membranes in mares are discussed in Chapter 43.

Retained Fetal Membranes in Ruminants

The anatomic structure of the ruminant placenta is described as cotyledonary and epitheliochorial.[206] It is composed of the allantochorion, the allantoamnion, and the umbilical cord. Fetal membranes are considered pathologically retained in the cow if they are not expelled by 8 to 12 hours after calving.[183,205,206] The incidence of retained fetal membranes in dairy cattle is 3% to 12% after normal parturition.[211] Dairy cows are more commonly affected than beef cows.[211] The incidence of retained fetal membranes may exceed 50% after abnormal parturition or abortion and in brucellosis-infected herds.[211] The retained placenta itself is relatively innocuous, but the condition is important because cows with retained fetal membranes experience an increased incidence of postpartum complications such as metritis, pyometra, ketosis, mastitis, delayed conception, and abortion.[187,212] The principal cause of retained placenta in cattle is a disturbance in the loosening process between the fetal cotyledons and the maternal caruncles[213] (Box 12-19). The processes that lead to successful loosening and separation of the placentome occur during the months preceding parturition. Many infectious and noninfectious factors are believed to disrupt the separation and expulsion processes. An endocrine causal relationship does not appear to exist.[214]

Clinical signs of retained fetal membranes in the doe and ewe are similar to those in the cow. The placenta of the ewe and doe is considered retained if it is not expelled within 24 hours after parturition.[87] The incidence of retained placentas in does is 6.4%.[215] Placental retention for longer than 24 hours may cause metritis in ewes and does. Inadequate dietary selenium and inadequate nutrition and exercise during gestation have been seen as factors predisposing does to retained placentas.[215] There have been several reports on factors that predispose to retained fetal membranes.[183,205,206,211,213,216,217] Many infectious and noninfectious factors apparently contribute to the disruption of the process of loosening and separation of the placentome. Accordingly, it has been suggested that a retained placenta should be considered to be a sign of an underlying disease.[218]

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Approach to Diagnosis of Retained Fetal Membranes in Ruminants

HISTORY. A review of accurate breeding records correlates retention of fetal membranes with the duration of pregnancy. Gestational periods of abnormal lengths result in a higher incidence of retained placenta than do normal-term parturitions. Induced parturition, twinning, and late-term abortions have been associated with retained fetal membranes in cows. Many periparturient diseases and conditions affect the incidence of retained fetal membranes.[183,205,206,211,213,216,217]

PHYSICAL EXAMINATION. In cows that have calved spontaneously and without problem after a normal gestation period, little illness tends to be associated with retained fetal membranes, and treatment may be unnecessary. Transient decreases in appetite and milk production may be observed.[211] However, metritis, toxemia, and septicemia may be observed when retention of fetal membranes is associated with gestation of abnormal length, dystocia, nutritional deficiencies, or certain infectious diseases. Metritis affects up to 90% of cows with retained fetal membranes.[216] For considerations for the treatment of retained fetal membranes in cows, see Chapter 43.

Alterations in Lactation

Bruce W. Christensen

The mammary glands are modified cutaneous glandular structures considered accessory reproductive organs that function to secrete milk for the nourishment of the young.[219] The mammary glands are located in the prepubic region in the mare, cow, ewe, and doe. The cow's udder is composed of four mammary glands, whereas in the doe, ewe, and mare the udder has two mammary glands. One teat serves each mammary gland, and in the cow, ewe, and doe each teat has one streak canal. The mare has two streak canals per teat.

The mammary glands are ectodermal in origin, and most of their fetal development occurs during the first half of gestation.[220] Except for growth that occurs in association with some of the anomalous conditions of the mammary gland or as a result of the deposition of fat, there is little growth of mammary tissue between birth and puberty. Further mammary gland development occurs with each estrous cycle after the onset of puberty. Development of the duct system is primarily attributable to estrogen. Progesterone is the principal stimulant to development of secretory tissue. However, neither estrogen nor progesterone alone or in combination can cause optimum mammary gland growth and development.[221] Insulin, cortisol, thyroxine, prolactin, and growth hormone are necessary for full mammary gland development. During pregnancy the mammary gland attains maximum development under the control of pituitary, ovarian, adrenal, and placental hormones.[222] During parturition a process of interrelated neuroendocrine processes initiates lactogenesis, the production of milk. The secretion of milk and its release from the mammary gland after parturition depend on the availability of appropriate amounts of the hormones named previously, especially prolactin and oxytocin.

In addition to mastitis, conditions that manifest themselves as alterations in the mammary gland and lactation are fairly common in ruminants and horses. Problems caused by conditions that affect the mammary gland are often multifactorial in that they compromise the well-being of the patient, the nutrition of the offspring, and ultimately the economics, especially in commercial dairies.

Enlarged Mammary Gland

Many conditions and diseases of the mammary gland cause swelling or enlarging of the gland[223] (Boxes 12-20 and 12-21). Enlargement may involve one or more of the glands of the udder. However, the enlarged mammary gland is not necessarily inflamed. Several anomalies of the mammary gland cause noninflammatory enlargement of the gland (e.g., gynecomastia, precocious udder development).[223-225]

BOX 12-20

Causes of Enlarged Mammary Glands in Mares

Common Causes

Mastitis
Abscessation
Periparturient udder edema (physiologic)
Gland distention associated with weaning

Less Common Causes

Trauma (contusion, hematoma, seroma, laceration)
Neoplasia (malignant melanoma, carcinoma)
Cutaneous histoplasmosis (*Histoplasma farciminosus*)

BOX 12-21

Causes of Enlarged Mammary Glands in Ruminants

Common Causes

Mastitis
Periparturient udder edema
Abscessation
Trauma (contusion, hematoma, seroma, laceration)
Pendulous udder (B, C)
Blind quarters (aplastic duct) (B)

Less Common Causes

Eczema
Urticaria (irritants, caustic chemicals; contact dermatitis; insect bites)
Sarcoptic and psoroptic mange
Primordial mammarian tissue swelling (accompanies witch's milk)
Photosensitization
Sunburn
Frostbite
Cowpox (B)
Pseudocowpox (B)
Goat pox
Contagious ecthyma (orf) (C, O)
Furunculosis, abscesses
Staphylococcal folliculitis
Papillomatosis, warts
Caprine arthritis-encephalitis (C, O)
Zearalenone toxicity
Neoplasia (lymphosarcoma, malignant melanoma [C], squamous cell carcinoma [C])
Milk allergy (B)
Tuberculosis (B)
Ovarian neoplasia
Caseous lymphadenitis (O, C)
Cutaneous lipomatosis
Enzootic mycobacterial nodular-ulcerative mammillitis (B)
Bovine herpesvirus mammillitis (BHV-2) (B)
Precocious udder development (B, C)
Udder cysts (C)
Gynecomastia (C)
Pseudopregnancy (C)
Foot-and-mouth disease (exotic)

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

It is important to determine whether the enlargement of the gland is attributable to an infectious or a noninfectious cause. Trauma is probably the most likely cause of noninfectious inflammation of the mammary gland. Mastitis, with which a large number of organisms have been associated, is the most common cause of mammary gland inflammation (see Chapter 36).

Evaluation of a patient with an enlarged mammary gland should include the medical and reproductive histories. The age and sex of

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the animal may limit the considerations. Gynecomastia is seen in young bucks, rarely in rams and bulls, and never in stallions.[223,225] Congenital anomalies such as stenotic or absent teat canals are not determined until parturition occurs and lactation commences.[223] The animal should be given a complete physical examination, with emphasis on the affected mammary gland. Examination of the gland should include observation, palpation, and expression of its contents. Cytologic and bacteriologic examination of the secretion from the mammary gland may be helpful in determining the cause and establishing the prognosis of enlarged mammary glands. In postpartum cows the most common causes of enlarged mammary glands are periparturient udder edema and mastitis. Mastitis occurs most often in mares after weaning. Trauma to the udder is more likely to be problematic in cows and goats than in ewes and mares because the udder is more pendulous in the former.[223] Undesirable udder traits of genetic origin occur in the goat (e.g., hanging or saclike udder, polythelia, blocked teat).[226] Lacerations, superficial contusions, and seromas are detected by close examination of the affected gland. Diagnoses of other injuries may rely on examination of the gland's secretion for evidence of increased cellularity and hemorrhage. Mammary gland neoplasia is rare in mares, cows, and small ruminants.[223,227-229]

Udder Edema

Udder edema, one of the most common causes of enlarged mammary glands, results from the excessive accumulation of intercellular fluid in the mammary gland (Box 12-22). The disorder is observed during the late gestation and early postpartum periods and is common in both horses and ruminants, but it is probably more frequently seen in dairy cattle. One study reported an udder edema incidence of 18% in dairy cattle, of which less than 1% required veterinary treatment.[230]

Two forms of udder edema are seen in cattle.[231] In the physiologic or acute form, there is edema of the mammary gland during the late gestation and early postpartum periods.[231] The entire udder is usually symmetrically involved, and the edema may involve adjacent abdominal and perineal areas.[231] The condition is usually not obviously painful but may cause the cow some difficulty in lying down and walking because of the mammarian swelling. Chronic bovine udder edema differs from the acute form in that affected cows develop udder edema within 6 weeks after calving, and the edema may persist for several months.[231] The swelling may be localized in the form of plaques on the ventral aspect of the rear of the udder, or it may involve the ventral abdominal wall.[231]

Udder edema is a relatively common condition of dairy goats.[232] Two-year-old does kidding for the first time are most commonly affected; however, all ages can be affected. Affected does usually have colostrum at parturition, but within a few hours the udder is warm, hard, and agalactic.

BOX 12-22

Causes of Udder Edema

Mares

Periparturient udder edema (physiologic)

Ruminants

Periparturient udder edema (physiologic)
Hereditary predisposition
Overfeeding of grain prepartum
Excess dietary protein
Obesity
Excess dietary sodium, potassium
Hypomagnesemia (chronic udder edema)
Disturbances in udder blood and lymph circulations
Excessively long dry period
Anemia

Broodmares affected with udder edema have generalized ventral edema during the last 1 to 2 weeks of gestation and for as long as 2 to 3 days after foaling. The extent of ventral edema varies, ranging from local swelling of the udder and immediately adjacent subcutaneous tissues to a generalized swelling that may extend from posterior to the mammary glands forward, along the ventral abdomen and thorax, to the axillary or pectoral area. In the mare such edematous accumulations are referred to as *plaques of edema.* Affected broodmares seem to be uncomfortable and reluctant to move. Younger broodmares, especially primiparous mares affected with udder edema, appear to be in more pain than older mares, and some of the mares so affected refuse to allow their foals to suckle.

Agalactia

Any disease or condition that adversely affects the dam has the potential to compromise lactation. Agalactia, the failure of lactation after parturition, may be attributable to a primary endocrinologic or mammary gland problem, or it may be secondary to any of a multitude of systemic conditions and diseases (Boxes 12-23 and 12-24). True agalactia may be attributable to mammary gland anomalies or inadequacies among the numerous endocrinologic factors of development and pregnancy. Agalactia may be a complication of many conditions. In some animals the conditions to which agalactia is secondary manifest as alterations in a specific system, whereas other animals with agalactia may demonstrate such signs as fever, weight loss, anorexia, and anemia. Inadequate nutrition is rarely the cause of clinically observed agalactia. Fescue grass toxicity, caused by ingestion of the ergot alkaloid–producing *Acremonium coenophialum,* is an important cause of agalactia and hypogalactia[134,233] (see Clinical Signs of Fescue Toxicosis earlier).

Agalactia should not be confused with failure of milk ejection (milk letdown). Administration of oxytocin may enhance milk letdown but does not affect milk production. Oxytocin stimulates a release phenomenon that acts on previously secreted and stored milk. Although somatotropin may increase milk production in a normally lactating cow, its effect on agalactia has not been adequately studied.

Inexperienced or nervous mares with adequate milk are often reluctant to allow their offspring to nurse, in part because of the mare's inexperience. Such nervous mares need not necessarily be primiparous mares. Although not allowing their offspring to nurse is usually a manageable behavior problem, the mare's udder should be

BOX 12-23

Causes of Agalactia and Hypogalactia in Mares

Common Causes

Mammary aplasia, hypoplasia
Abscessation
Mastitis
Abortion
Premature birth
Postpartum complication

Less Common Causes

Endocrine dysfunction
Nutritional deficiencies, malnutrition
Neoplasia
Squamous cell carcinoma
Malignant melanoma
Pituitary adenoma
Lymphosarcoma
Other tumors
Fescue toxicity
Trauma to mammary gland
Periparturient disease
Dystocia
Anemias
Severe toxicity

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BOX 12-24

Causes of Agalactia and Hypogalactia in Ruminants

Common Causes

Mammary aplasia, hypoplasia
Mastitis
Abscessation
Caseous lymphadenitis (udder involvement) (C, O)
Caprine arthritis-encephalitis (CAE; hard udder) (C, O)

Less Common Causes

Endocrine dysfunction
Malnutrition
Water deprivation
Self-sucking (B, C)
Trauma
Chapped teats; teat dip irritation (B, C)
Milk allergy
Neoplasia
Malignant melanoma (C)
Lymphosarcoma
Squamous cell carcinoma
Carcinomas
Fescue toxicity
Papillomatosis
Mycoplasmal agalactia (C, O)
Anemias
Severe toxicity

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

examined for evidence of periparturient edema, inflammation, and painful conditions.

APPROACH TO DIAGNOSIS OF AGALACTIA. An accurate reproductive history should be obtained. It should be determined whether the dam is primiparous or multiparous. If primiparous, is she manifesting anxiety in the presence of her offspring? If multiparous, has she been agalactic at previous parturitions? Has she sustained recent trauma, perhaps during parturition, or was there exposure during gestation to infectious diseases or toxic plants? After a history has been determined and the dam and neonate have been observed, attempts to facilitate the youngster's suckling might be indicated. Is the dam agalactic, or does she simply refuse to let the neonate suckle? Such measures as twitching or tranquilizing the nervous and inexperienced mare may resolve that problem. If assessing the dam's behavior toward her offspring does not resolve the problem, a thorough physical examination should be initiated. The objective now should be to rule out or incriminate infectious and inflammatory conditions contributing to the agalactic state. The dam herself may be systemically affected, or the problem may be localized in the udder or a mammary gland.

In listing causes of agalactia and hypogalactia in Boxes 12-23 and 12-24, the authors included only those that have a direct effect on the anatomic integrity of the mammary gland or its function. Abnormalities involving any system may compromise lactation.

Galactorrhea and Precocious Mammary Gland Development

Galactorrhea, the abnormal manifestation of lactation (not the secretion of true milk), occurs occasionally from the primordial mammary gland of young foals and ruminants, including neonates.[223] The secretion is popularly known as *witch's milk.*

BOX 12-25

Causes of Galactorrhea and Precocious Mammary Gland Development in Horses and Ruminants

Impending abortion
In utero death of one twin fetus
Spontaneous (inappropriate prolactin secretion)
Placental separation
Zearalenone toxicity
Pregnancy (especially multiple fetuses)
Suckling
Pseudopregnancy (caprine)
Ascending infection during pregnancy, placentitis
Ovarian tumors

Precocious mammary gland development and galactorrhea occur in pregnant and nonpregnant mares and in some of the ruminant species (Box 12-25). Such premature udder development and subsequent lactation have been observed in nonpregnant and nonsuckled doelings and heifers.[223,234] Udder development and subsequent lactation have been observed in young nonpregnant heifers and does being suckled by other young animals.[223] In addition to the continued stimulation of suckling, other causes of premature mammarian development and lactation may be trauma and diseases of the pituitary, ovarian, and adrenal glands.[223] Zearalenone toxicity has been implicated in precocious mammary gland development and lactation in heifers.[235] Milk production is nonphysiologic in that it is of insufficient quality and quantity and does not justify milking the affected animals. There is no evidence that such abnormal development compromises normal lactation after parturition.[223]

Inappropriate lactation has been observed at various stages of pregnancy in most domestic species.[223] The most common cause of galactorrhea is abortion. Lactation may commence before or even without expulsion of the dead fetus. Lactation during pregnancy has also been observed in association with multiple fetuses, placentitis, and ovarian tumors. Accordingly, premature mammary gland development during gestation should be considered a warning of impending abortion, and the dam should be examined. Occasionally, pregnant mares develop mammarian enlargement during middle to late gestation that spontaneously regresses.[233] Some of these mares begin to lactate before parturition. It must be kept in mind that premature lactation and subsequent loss of colostrum is one of the most important causes of failure of passive transfer of immunoglobulins.[236]

Gynecomastia, the abnormal development of the male's mammary glands, has been observed in bucks in which rudimentary mammary glands and associated teats underwent development.[223,234] The aberrant structures, located on both sides of the buck's scrotum, can secrete up to 1 L daily of a substance that resembles milk. The cause is presumed to be endocrine imbalance but has not been determined. Lofstedt and colleagues[237] reported adrenal neoplasia as a cause of lactation in a wether.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 13

Musculoskeletal Abnormalities

CARTER E. JUDY and SAREL VAN AMSTEL, *Consulting Editors*

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Lameness and Stiffness

Randall B. Eggleston • John Maas • Carter E. Judy

Lameness is the term used to describe a condition in which an animal is incapable of normal locomotion. Generally lameness is characterized by an inability to maintain a normal gait, manifested by asymmetry in movement, apparent incoordination or weakness, and inefficient or ineffective motion of the limbs. Lameness can usually be assessed only when the animal is moving under its own power, although lameness severe enough to cause an inability to bear weight can be assumed at a standstill. The onset of lameness can be acute (e.g., fracture), chronic (e.g., degenerative joint disease), or acute on chronic (e.g., catastrophic fracture secondary to stress fractures).

Mechanisms of Lameness and Stiffness

The ultimate effects of any cause of lameness are restricted movement of the limbs or body, reduced performance, and abnormal gait. Causes of lameness are generally associated with conditions of the musculoskeletal system or nervous system. Most causes of lameness have both a musculoskeletal component (e.g., atrophy of the supraspinatus and infraspinatus muscles) and a neurologic component (e.g., suprascapular neurapraxia). Some causes of lameness have only a musculoskeletal component (e.g., upward fixation of the patella) and are not principally associated with either afferent nerve signs (i.e., pain) or efferent nerve signs (i.e., motor dysfunction). Similarly, other causes of lameness are solely related to a motor nerve deficit (e.g., radial neurapraxia).

Unlike the usual definition of lameness, *stiffness* refers to a generalized restriction in freedom of movement in a limb, the neck, or back. Stiffness is manifested by a limited range of motion by a joint, reduced length of stride, or decreased flexibility during bending or turning. For example, cellulitis and soft tissue swelling in the area of the tarsocrural joint can cause restricted freedom of movement of the hindlimb and an apparent lameness, yet there may be no specific musculoskeletal or neurologic cause. Stiffness may have either congenital or acquired causes, and the clinical signs may be mild and transient or severe and persistent. Stiffness may or may not be associated with pain.

Approach to Diagnosis of Lameness and Stiffness in Horses

The lameness examination is the most commonly performed assessment of the musculoskeletal system in the horse. The examination should be well planned, consistent, and thorough. Knowledge of all diseases capable of causing lameness is not required, as long as the examiner maintains an open mind and objectivity during the examination (Box 13-1). The goals of the lameness examination are to determine which limbs are affected, differentiate between supporting limb and swinging limb lameness, and establish the musculoskeletal and/or neurologic components producing the lameness.

1. History. The lameness examination begins with the client interview. A summary of the important historical features of the lameness should include answers to basic questions about the following:
   - Onset (e.g., When was the last time the horse was seen sound? Was the lameness acute in onset, or did it have a slow, insidious onset?)
   - Characteristics of the lameness (e.g., Is the lameness seen more in hand, at the lunge, or under saddle?)
   - Associated or inciting factors (e.g., injury) that may have contributed to or caused the lameness.
   - Changes in the characteristics, intensity, and duration of the lameness.
   - Responsiveness to treatment (e.g., Has the horse received any type of treatment, and, if so, what was the response?)
   - Time since the last hoof trimming and shoeing, and whether or not the horse's shoeing was changed.

   In addition, the signalment and activity that the horse undertakes (e.g., jumping vs. racing) should be ascertained and may be a guide in determining potential causes of the lameness (e.g., stress fractures are more common in racing Thoroughbreds, and osteochondrosis is more commonly diagnosed in young animals).
2. Observe from a distance—stationary phase. Observing the horse from a distance while it is stationary permits an assessment of the horse's conformation, position, and posture. The horse should be viewed from the front, from behind, and from both sides. From the front, special note should be made of any abnormality in the following:
   - Conformation. A number of conformational abnormalities have been associated with lameness (e.g., upright pastern conformation predisposes to pastern disease and foot lameness; offset or bench knees predispose to carpal disease; and straight through the hocks or postlegged conformation predisposes to upward fixation of the patella, suspensory desmitis, and fetlock disease). Poor conformation can affect the young horse when it is put into training or can cause a slow insidious onset of lameness. Recognizing these conformational abnormalities at the time of examination can be helpful in diagnosing potential causes of lameness. When a horse is evaluated for purchase, recognition of poor conformation should be noted and discussed as a source of future lameness problems.

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BOX 13-1

Causes of Lameness and Stiffness in Horses

Common Causes

Infections of the foot
Bruised or punctured sole
Hoof wall defects
Fractures
Septic (infectious) arthritis
Laminitis
Secondary (degenerative) joint disease
Navicular disease
Osteomyelitis
Fibrotic or ossifying myopathy
Rhabdomyopathy (tying up)
Sprain
Strain
Tenosynovitis
Contracted tendons (flexural deformity)
Ankylosis or arthrogryposis
Osteochondrosis or bone cyst
Cruciate or meniscal rupture
Luxation or subluxation (dislocations)
Upward fixation of the patella (locking patella)
Sesamoiditis
Muscle injury, soreness, bruise, trauma, compartment syndrome
Subcutaneous abscess, cellulitis
Angular limb deformities
Disruption of the suspensory apparatus (broken down)
Postanesthetic equine myasthenia
Tendon rupture, damage, tendonitis (bowed tendon)
Osteomalacia, osteodystrophy (rickets)
Bucked shins
Epiphysitis (physeal injuries)
Purpura hemorrhagica

Less Common Causes

Shivers (shivering)
Borreliosis (Lyme disease)
Equine monocytic ehrlichiosis (Potomac fever)
Chronic selenium toxicity
Hemangioma, hemangiosarcoma, angiosarcoma
Skeletal neoplasia
Rabies
Spondylitis, diskospondylitis
Spinal or vertebral neoplasia
Vertical column malformation
White muscle disease (nutritional myodegeneration)
Gunshot injury
Corynebacterium pseudotuberculosis
Hypothyroidism (goiter)
Actinobacillosis
Hyperparathyroidism
Ulcerative lymphangitis
Myotonia congenita
Vesicular stomatitis
Fistulous withers (*Brucella abortus* or other organisms)
Sporadic equine lymphangitis
Acute necrotizing equine vasculitis (with or without thrombocytopenia)
Peripheral arteriovenous fistula
Hypertrophic osteopathy or osteodystrophy

Uncommon Causes

Nocardiosis
Cutaneous blastomycosis
Pemphigus foliaceus
Tuberculosis
Multisystemic postexhaustion syndrome
Generalized steatitis
Cutaneous vasculitis
Sterile nodular panniculitis
Multiple clotting defects in ill foals
Salmonellosis
Factor VIII deficiency (hemophilia A)
Idiopathic equine aplastic anemia
Idiopathic equine thrombocytopenia
Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)
Lupus erythematosus (rheumatoid arthritis)
Phycomycosis
Bone fragility disorder

Poisons, Toxins, Deficiencies, and Excesses

Moldy sweet clover poisoning
Strychnine toxicity
Tetrachlorodibenzodioxin (dioxin) toxicity
Warfarin (dicumarol) toxicity
Vitamin K–induced renal toxicity
Calcinosis resulting from plant poisoning
Zinc toxicity
Phosphorus toxicity
Phosphorus deficiency
Vitamin D toxicity
Locoweed-associated limb deformities or stringhalt-like gait
Chronic fluoride toxicity

- Position of the head (e.g., tilted, turned).
- Distribution and equality of muscle mass along the neck and trunk.
- Topographic symmetry of the front limbs, from the dorsal region of each scapula to the hoof. From the rear, the height and mass of the hip musculature and the symmetry between the hindlimbs should be assessed. From each side, abnormalities in stance (e.g., camped out in front) or load bearing (e.g., dropped elbow) and the position of the head and neck (e.g., hyperflexed poll) should be compared.

3. Physical examination and palpation. Palpation enables a closer inspection of the horse and identification of abnormalities that may or may not otherwise be noticed. A thorough examination of the musculoskeletal system not only allows for identification of palpable abnormalities but also offers the opportunity for the practitioner to refine the identification of normal structures; subtle abnormalities cannot be appreciated unless the examiner is skilled at recognizing normal anatomy. There are also many instances in which normal structures palpate abnormally but are not necessarily associated with lameness (e.g., flexor tendon sheath [windpuffs, windgalls] and palmar or plantar metacarpophalangeal joint [MCPJ] pouch effusion [wind puffs]). The examination should be conducted consistently and thoroughly starting with the cervical neck and concluding at the tail. Abnormal findings should be described to identify their location on the limb, their size, and their orientation relative to normal anatomic landmarks. Palpation of the upper limb is often limited to the overlying muscle mass, with identification of any atrophy, hypertrophy, pain, or fibrosis. Articular structures and surrounding ligamentous structures can be difficult to palpate because of the overlying muscle. Deep palpation of the thoracolumbar and gluteal musculature can provide clues to potential hindlimb lameness and tack or rider issues. The pelvis, iliac arteries, and sublumbar musculature can be evaluated by rectal palpation while the horse is standing quietly; movement or crepitation can be assessed while swaying the horse from side to side.

Particular attention should be directed toward palpation of the limbs. The majority of lameness will originate from the carpus distally in the front limb. Common sources of lameness in the hindlimb can be identified from the stifle distally. All palpable structures

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should be evaluated, including skeletal structures, synovial structures (joints, tendon sheaths, and bursa), and soft tissue structures (tendons and ligaments). This portion of the examination can be performed using different methods, either by palpating each tissue in one pass of the limb or by making multiple passes of the limb, palpating each tissue structure separately. Regardless of the preferred technique, a consistent and complete examination should be performed. Once the limbs have been palpated in the weight-bearing position, the examiner should palpate them in the non–weight-bearing position. This allows for separation of the soft tissue structures and facilitates deep palpation of the suspensory apparatus. Comparing limbs is often useful for distinguishing an abnormality from an unusual or unique conformation.

The relative size, shape, and condition of the feet (e.g., contracted heel, scuffed toe); length of heel; and pattern of shoe wear (e.g., thinner branch on the outside of the shoe than on the inside) give clinically significant but often overlooked clues to the site and cause of lameness. Evaluation of the feet with hoof testers is mandatory; most lameness arises from problems in the forefeet.

Certain signs indicating trauma (e.g., wounds, swelling, hair loss, pain) may lead to more important findings such as underlying evidence of a fracture (e.g., bony crepitus, warm or cold areas, bony protuberance). Observe from a distance—the mobile phase. Observations made from a distance while the horse is moving can be evaluated critically once clues provided by the history, as well as observations made of any postural deformities, direct the practitioner's attention to a specific area of the horse's body. This part of the examination is conducted while the horse is moving in at least two gaits, the walk and the trot. Sometimes it is also helpful diagnostically to observe the horse move at other gaits (e.g., canter) or while under saddle. It may also be beneficial to observe the horse on different surfaces (hard and soft) to amplify different lameness issues. If possible, the horse should be evaluated under conditions similar to those under which it performs. At a walk the horse should be observed moving toward and away from the examiner. The breakover point of the foot at the toe, the arc of the foot flight, the distance covered by the foot in the swing phase, and the placement of the foot should be evaluated for each limb and should be compared between pairs of limbs. Although many abnormalities can often be observed only during a trot, some conditions may cause a subtle alteration in gait that can be observed only at a walk (e.g., fibrotic myopathy, stringhalt).

If a fracture is suspected (e.g., nondisplaced long-bone fracture) or if there is the possibility of exacerbating preexisting trauma, this part of the examination should either be abbreviated or not performed at all to preclude further damage or trauma. In such cases, immediate radiographic or other definitive diagnostic tests should be performed (Box 13-2).

BOX 13-2

Causes of Spontaneous Fractures in Horses and Ruminants

Pathologic fractures
Subclinical stress fractures
Tumors
Infection
Inflammation
Osteoporosis
Copper deficiency
Molybdenum excess
Phosphorus deficiency
Protein deficiency
Osteomalacia
Osteodystrophy (rickets)
Rapid growth
Lactation
Advanced pregnancy
Bone fragility disorder

Recognizing the asymmetric movement of the head and neck for frontlimb lameness and the asymmetric movement of the pelvis for hindlimb lameness is a common method of lameness identification. Hindlimb lameness issues often present the greatest challenge.

Sound horses at a trot show a perfect sinusoidal pattern for all midline body locations, including the head, withers, and tuber sacrale. The height of these structures falls from the beginning of the diagonal stance phase, reaching the lowest position at midstance, and then rising to the highest level at or shortly after the end of the stance phase (suspension). Correlating head and neck movement with the correct frontlimb lameness is relatively easy. It is well recognized that the head is elevated during the stance phase of the lame limb, with an increase in downward motion during the stance phase of the sound limb—"down on sound." Lameness can also be recognized by changes in the distal limb, including changes in the motion of the MCPJ. During the stance phase, the hyperextension of the MCPJ is decreased with increasing lameness in the lame limb, whereas in the contralateral sound limb an increase is seen. With respect to stride length and foot flight, with forelimb lameness the caudal phase of both the lame and the sound limbs becomes shortened, whereas the cranial phase remains unchanged. In the hindlimbs the opposite is seen; the cranial phase is shortened and the caudal phase remains unchanged. This may be explained by the significantly decreased suspension phase following the lame diagonal. In the forelimbs the arc of the lame front foot is unchanged, but there is an increase in the arc of the sound front foot. In the hindlimbs, the arc of the foot flight in the lame hindlimb is lower than the sound limb in most cases. The change in maximal hoof height during the swing phase appears to be the result of changes in trunk height and is no indication for reduced flexion in the upper joints or an effort to reduce the pain when the hoof lands. Medial (winging) or lateral (paddling) deviation of the distal limb during the flight phase can result in interference and trauma to other limbs and potential lameness. Conformational abnormalities, most commonly toeing in or toeing out, give rise to an alteration in the point of breakover and a change in the flight of the distal limb. Poor foot balance caused either by poor conformation or by poor trimming can result in similar flight patterns.

Plaiting describes adduction of the lame limb directly in front of or lateral to the opposite limb. In the front limbs, plaiting is commonly the result of faulty conformation, but in the hindlimbs it is more commonly associated with lameness. This pattern of travel is often associated with upper limb lameness but can also be seen with distal hock or proximal metacarpal disease.

A dampening effect also appears to occur as an adaptation to lameness. This effect is more pronounced in the hindlimb than in the frontlimb. Flexion of the shoulder and hock joints actually increases during weight bearing in the lame limb. This is probably an increase in the function of the shock-absorbing mechanism. The increased flexion cannot be related to increased loadings but has to be attributed to a gentler braking of the flexion by the extensor muscles. In such a way, the loading of the lame limb with the body weight occurs more gradually, reducing the peak forces in the hoof.

The tuber coxae are typically the landmark of choice in evaluating hindlimb lamenesses. Because the tuber coxae are more laterally located, the pattern is different from that seen in the head. Also, because the hindlimbs lack closely located segments, such as the neck and head, an enhancement of the vertical movements must be found in a rotation of the back around a longitudinal axis. Such a rotation is indicated by different vertical displacements of one tuber coxae during both stance phases. The vertical movement of the tuber coxae exhibits a characteristic pattern of a double-waved, slightly asymmetric line during one stride. The lowest point of the hip is reached in the middle of the stance phase of the right contralateral limb. The highest point of the hip is reached shortly after the stance phase of the contralateral limb, just before the stance phase of the left hindlimb.

Kinematic studies have more clearly defined the notion of "hip hike" and "hip drop" and have recorded regular patterns of pelvic movement in lame horses. Consistent findings in the overall pelvic

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movement in the lame horse include less downward movement during the midstance phase and less upward movement at the end of and after the stance phase of the lame limb. This can give the appearance of an overall pelvic elevation during the stance phase of the lame limb as compared with pelvic height during stance of the sound limb; a similar exaggerated pattern is seen in the tuber coxae. The tuber coxae also exhibit less downward movement during the midstance phase and less upward movement at the end of the stance phase in the lame limb. More notably, there is more downward movement during midstance of the sound limb (midflight of the lame limb) and more upward movement at the end of stance of the sound limb (impact of the lame limb), giving rise to the notion of a "hip hike." These changes result in an increase in the overall vertical movement of the tuber coxae on the lame side as compared with the sound side. Clinically, many find it easier to identify the exaggerated excursion of the tuber coxae to identify the side of the lameness.

Lateral movement or drifting of the hindend can also be seen in horses with unilateral hindlimb lameness. Horses tend to drift or move away from the side of the lameness. Subtle lameness with an absence of asymmetric pelvic movement may present with a consistent drifting to one side or the other.

Thorough and useful systems for grading the severity of lameness are available. Most systems are designed to enable the practitioner to compare how lameness changes with time, assess the characteristic of lameness among horses, and accurately record information and communicate information to other veterinarians. Simple and consistent schemes that are easy to remember and modify can be developed (Table 13-1).

Once the initial standing and mobile examinations are completed and the affected limb is identified and the lameness graded, isolating the specific region of the limb is the next goal of the lameness examination. Manipulative tests or stressing of articulations and associated soft tissue structures can provide additional information as to the location of the source of lameness. Flexion and extension tests are designed to stress selective regions of the limb and observe the effects of the manipulation on the lameness. These tests are also commonly performed on the sound horse to reveal potential areas of concern, particularly during prepurchase examinations. Flexion and extension manipulations also enable an assessment of range of motion. Interpretation of these tests should be approached with caution. They are seldom specific for one particular joint. For example, the fetlock flexion test not only stresses the fetlock joint but also places stress on the proximal and distal interphalangeal joints; the hock flexion test also flexes and stresses the stifle joint because of the presence of the stay apparatus. If a flexion test results in a positive response, the horse should be walked out of the response and observed before additional manipulations. Occasionally exacerbation of the lameness will persist for an extended period of time, which changes the baseline lameness and clouds the interpretation of additional manipulations.

TABLE 13-1

Five-Grade Lameness Scheme

Grade	Description
1	An inconsistently observable lameness visible under special circumstances (e.g., in a circle, flexion tests, hard surface)
2	A consistently observable lameness visible only under special circumstances (e.g., in a circle, flexion test, hard surface)
3	A consistently observable lameness at a trot in a straight line
4	A consistently observable lameness at a walk
5	A non–weight-bearing lameness; horse is unable to use the leg

Modified from the American Association of Equine Practitioners Newsletter, March:12, 1983.

It is common for horses to be presented with multiple lameness issues. Secondary lameness or compensatory lameness is the result of increased stress or overloading of the other limbs in response to the primary lameness. This most commonly occurs in the contralateral limb but can also occur between frontlimbs and hindlimbs. The secondary lameness can also be the result of shifts in body mass that produce an apparent or phantom lameness. Phantom lameness is less severe than the primary lameness. The following guidelines can be used to aid in the differentiation between a real or compensatory and an apparent or phantom lameness.

- Address the most severe lameness first.
- Horses with primary hindlimb lameness and apparent or phantom contralateral frontlimb lameness. Each lameness should be considered as real.
- Horses with a primary forelimb lameness and apparent or phantom ipsilateral hindlimb lameness. Each lameness should be considered as real.
- Primary forelimb lameness may produce asymmetric pelvic movement causing the perception of a contralateral hindlimb lameness. Example: left foreleg lameness (head elevation) causing apparent or phantom right hindleg lameness (hip drop).
- Horses with a primary forelimb lameness and apparent contralateral hindlimb lameness. Isolate out the front limb lameness first.
- Primary hindlimb lameness (>3 to 5/5) can mimic ipsilateral forelimb lameness. Example: A horse shows a cranial load shift during the stance phase of the lame limb that causes the head and neck to shift forward and nod down, giving the perception of ipsilateral lameness—"down on sound."
- Horses with a primary hindlimb lameness and apparent ipsilateral forelimb lameness. Isolate the hindlimb lameness first.

Assumptions as to the cause of a horse's lameness based solely on the physical examination and visual inspection should be avoided unless obvious signs, for example severe swelling or crepitus, are present. After the physical and visual examination, evaluation of the horse with diagnostic analgesia is mandatory for the accurate isolation and diagnosis of equine lameness. A thorough knowledge of anatomy and the structures desensitized by blockade of the appropriate peripheral nerves or synovial structures is essential (Table 13-2). *When performing perineural analgesia it is important to remember to block from distal to proximal.* Perineural anesthesia of proximal structures first may inadvertently anesthetize more distal pathology, resulting in misinterpretation of the region of pain affected. An improvement in gait indicates a favorable response to a nerve or joint anesthesia; complete elimination of gait asymmetry is unusual and generally should not be expected after intraarticular or peripheral nerve analgesia. If necessary, improvement in gait can be confirmed by repeating the successful block the next day. By that time residual effects from multiple blocks performed previously should be absent.

Common local anesthetics used in horses include solutions of lidocaine, mepivacaine, and bupivacaine. These solutions all share a common mechanism of action, specifically the ability to block or inhibit nociceptive nerve conduction by preventing the increase in membrane permeability to sodium ions. Lidocaine and mepivacaine are considered to be fast acting and have a duration of action of ½ to 3 hours and 2 to 3 hours, respectively. Bupivacaine on the other hand is intermediate in onset and has a much longer duration of action of 3 to 6 hours. Mepivacaine is reportedly less irritating to tissues than lidocaine.

Intrasynovial analgesia can be used to more specifically isolate a lameness to a joint, tendon sheath, or bursa. It can be used in combination with perineural analgesia or alone depending on the suspected source of the lameness. Proper patient restraint and strict aseptic technique, including aseptic preparation of the skin, wearing sterile gloves, and use of a new bottle of anesthetic, are imperative to avoid iatrogenic synovial sepsis. Lameness may be erroneously associated with a joint if intraarticular analgesia of several joints is performed within a short period of time; ample time (30 to 60 minutes) must be allowed between joint blocks to allow for adequate articular

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TABLE 13-2

Structures Desensitized by Commonly Performed Nerve Blocks

Nerve Block	Nerve(s) Affected	Structures Desensitized*
Palmar (plantar) digital	Palmar (plantar) digital	Heel bulbs; frog; bars; navicular bone and bursa; palmar regions of the third phalanx, distal interphalangeal joint, sole, and soft tissues
Abaxial sesamoid	Palmar (plantar)	Coronary band, interphalangeal joints, lamellar and solar corium
Low palmar (volar)	Palmar, palmar metacarpal†	Skin of medial and lateral pastern, metacarpophalangeal joint, proximal sesamoids, flexor tendons, tendon sheath
High palmar (volar)	Palmar, palmar metacarpal†	Skin and deep structures of palmar cannon region (flexor tendons, suspensory ligament except origin, interosseous ligaments of splint bones)
High two-point	Lateral palmar, medial palmar	Origin of suspensory ligament

*Includes all structures listed up to and including the particular block; first structure listed in each block is also the area that can be tested with point pressure to evaluate the effectiveness of the block.

†For hindlimbs, additional anesthetic (i.e., ring block) is necessary at the level of the particular perineural block to achieve the desired effect.

desensitization. Some intraarticular and intrasynovial anesthetic techniques may mimic the results of perineural anesthesia. An example is that of the coffin joint where intraarticular anesthesia of the joint has the same regions of anesthesia as that of the palmar digital nerve block. It is important not to overinterpret the results in such cases.

When performing intrasynovial analgesia it is not necessary to follow the distal to proximal rule. If intraarticular analgesia of a proximal joint results in no improvement in the lameness, immediate follow-up with distal limb perineural blocks is still possible. Exceptions to this rule exist with intrasynovial analgesia to the foot. When performing intrasynovial analgesia of the distal interphalangeal joint (DIPJ) or navicular bursa, it is important to take into consideration the volume of anesthetic used and the timing at which the lameness is reevaluated. The recommended volume of anesthetic for the DIPJ is 4 to 5 mL, and for the navicular bursa 3 to 4 mL. Once injections into these structures have been performed, the horse should be evaluated at 5-minute intervals to help with the interpretation of the response to the block because they may result in inadvertent anesthesia similar to the palmar digital nerve block.

Significant improvement in experimentally induced lameness to the navicular bursa can be seen at 5 minutes after intraarticular anesthesia of the DIPJ with 5 mL of 2% mepivacaine hydrochloride. Amelioration of bursal lameness is most likely caused by diffusion of the anesthetic into the bursa via an indirect or functional communication, or by diffusion of anesthetic into the periarticular tissues. The proximal palmar pouch of the DIPJ lies in close proximity to the palmar digital (PD) neurovascular bundles as they course along the medial aspects of the collateral cartilages, making it possible for anesthetic diffusion to block nerve conduction at that level.

Experimentally induced solar toe pain can also be ameliorated by intraarticular blockade of the DIPJ with 10 mL of mepivacaine hydrochloride. The structures innervated by the deep branch of the PD nerves include the DIPJ, navicular bursa, distal navicular ligament, laminar corium, and corium of the sole. The DIPJ capsule contacts the PD neurovascular bundle, and a local anesthetic injected into the DIPJ likely desensitizes the PD nerves below the level of the coronary band, as well as the structures innervated by them.

Variable responses are also seen with blockade of the DIPJ when different volumes of anesthetic are used. Blocking the DIPJ with 6 mL of mepivacaine (Carbocaine) results in significant improvement in lameness originating from the dorsal margin of the sole; however, lameness originating from the palmar sole shows no improvement. Using 10 mL of Carbocaine reduces lameness originating from the dorsal margin of the sole, as well as the palmar heel regions of the sole, but only after 30 minutes. The difference in response to analgesia of the DIPJ in attenuating pain at the dorsal margin of the sole versus the angles of the sole may be because these regions are innervated by different branches of the PD nerve. This may help distinguish between pain arising from the DIPJ or the navicular apparatus and palmar solar pain.

In contrast to the responses seen with blocking the DIPJ in the presence of navicular bursa disease, blocking the navicular bursa with 3.5 mL of mepivacaine hydrochloride in the presence of experimentally induced DIPJ lameness results in a significant improvement in lameness but only after 30 minutes. Experimentally induced lameness from the dorsal sole is improved by blockade of the navicular bursa; lameness originating from the palmar sole does not show significant improvement.

Knowledge of the previously described responses to intrasynovial analgesia of the DIPJ and the navicular bursa is helpful in localizing and interpreting lameness commonly seen in the horse. The anatomy and close approximation of the associated nervous and synovial structures of the foot give rise to a diffusion gradient associated with perisynovial infiltration of local anesthetic to peripheral nerves and variable responses to intrasynovial analgesia. Similar responses can be encountered with intraarticular analgesia of the carpus and distal tarsal joints. Instillation of anesthetic into the middle carpal joint and the tarsometatarsal joints can result in desensitization of the proximal suspensory ligament, a common site for soft tissue injury and lameness in the horse.

Once the lameness has been described and localized, a radiographic or ultrasonographic examination can be performed as the next step to confirm a clinical diagnosis. Radiography should be performed using proper technique, an ideal film/screen combination, and multiple views to construct a thorough study (Table 13-3). Comparing radiographs of affected and unaffected limbs can help confirm or refute a suspected abnormality, evaluate the severity of the disease, and identify possible bilateral limb involvement.

Although standard radiographic techniques are well documented and described, ultrasound is becoming more and more popular and useful in musculoskeletal imaging. Indications for ultrasonographic evaluation of a lameness include diagnosis of soft tissue injuries, including muscular, vascular, tendon, tendon sheath, ligament, joint capsule, or bursal defects; evaluation of articular surfaces (articular cartilage thickness, osteochondritis dissecans lesions); assessment of fluid accumulation (synovial effusions, seromas, or sepsis); evaluation of bony surfaces; monitoring of the progression of healing; and monitoring of the effects of training on soft tissue injuries such as tendonitis or desmitis.

When radiographic or ultrasonographic techniques are nondiagnostic, other methods such as thermography, nuclear scintigraphy, treadmill evaluation, computerized videographic gait analysis, force plate evaluation, computed axial tomography (CAT), or magnetic resonance imaging (MRI) may be useful. University hospitals and major regional referral centers are often the only locations where these adjunctive procedures can be performed because the procedures are expensive and technically complex and they require specialized equipment and experienced personnel. However, even these techniques have limitations; for example, nuclear scintigraphy may not identify the origin of an insidious (e.g., osteochondrosis) or chronic lameness as successfully as an acute lameness.

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TABLE 13-3

Recommended Radiographic Views of Extremities

Radiographic Series	Minimum Radiographic Views
Distal extremity (navicular)	45 degrees DP, 65 degrees DP (2), LM, flexor tangential*
Pastern	45 degrees DP, LO, MO, LM
Fetlock	45 degrees DP, LO, MO, LM, flexed LM
Metacarpal or metatarsal	DP, LO, MO, LM
Carpus	DP, LO, MO, LM, flexed LM, flexed skylines (distal radius, proximal and distal rows of carpal bones)
Tarsus	0 degrees DP, 10 degrees DP, LO, MO, LM
Radius-ulna or tibia-fibula	Cr-Cd, LO, MO, LM
Elbow	Cd-Cr, LO, LM
Shoulder	ML
Stifle	Cd-Cr, LM, flexed LM, Cd 30° L-CMO, patellar skyline

*View to highlight the flexor cortical margin of the navicular bone (50 degrees proximal palmarodistal oblique).

Cd-Cr, Caudocranial; *Cd 30° L-CMO,* caudal 30-degree lateral-craniomedial oblique; *Cr-Cd,* craniocaudal; *DP,* dorsopalmar (dorsoplantar); *LM,* lateromedial; *LO,* lateral oblique; *ML,* mediolateral; *MO,* medial oblique.

BOX 13-3

Alterations in Gait in Ruminants in Which Stiffness Can Be a Major Component

Chronic hypophosphatemia
Chronic fluorosis
Tetanus
Lupine alkaloid intoxication
Copper deficiency or molybdenosis
Acute laminitis
Nutritional myodegeneration (white muscle disease)
Ephemeral fever (3-day stiff sickness), exotic
Locoweed toxicity
Sweet clover poisoning
Rickets, osteomalacia, osteodystrophy
Bovine virus diarrhea (coronitis and cerebellar atrophy) (B)
Sarcocystis
Vesicular stomatitis (B)
Overgrown claws
Blue tongue (coronitis) (O)
Degenerative joint disease
Muscle trauma
Ionophore toxicity
Hemlock poisoning
Generalized calcinosis
Ergot or hyperthermia
Frostbite
Contracted tendons
Selenium toxicosis
Clostridial myositis
Claviceps spp.
Mycoplasma bovis polyarthritis and tenosynovitis (B)
Mycoplasma mycoides subsp. *mycoides* polyarthritis (C)
Caprine arthritis encephalitis virus (CAE) (C)
Muscle abscess
Ruptured anterior cruciate ligament or torn collateral ligament of stifle
Luxations and subluxations
Upward fixation of the patella
Epiphysitis
Locoweed toxicity

Approach to the Diagnosis of Stiffness, Lameness, and Abnormal Gait and Posture in Ruminants

Sarel Van Amstel • Jan K. Shearer

Clinical signs can be caused by neurologic deficits, pain, and muscular or skeletal disorders. Diagnosis requires a complete history, including review of information on lameness in dairy records; careful observation during standing and walking, including locomotion scoring; and examination and palpation of the foot and upper limb.

HISTORY. Historical details should be obtained in terms of duration, severity, onset of clinical signs, and previous treatment. Past history may help to establish if the condition is acquired or congenital. This is particularly important in order to distinguish among conditions with similar signs such as spastic paresis, upward patella fixation, and spastic syndrome. History should also include information regarding management and housing such as free stall size and bedding; evidence of overcrowding; types of walking surfaces; number of times a day milking; and accumulation of mud, manure, gravel, and stones on tracks in cases of pastured cattle. Finally, historical information regarding nutrition, including the use of supplements, water source, and possibility of toxicities should be included.

OBSERVATION. Detection of lameness may present a challenge because cows are good at disguising discomfort. Therefore careful observation both during standing and walking is important. Changes in weight bearing, posture, and conformation may be indicative of both the presence and type of lameness. Nearly 90% of lameness involves the foot; thus particular attention should be paid to alterations in weight bearing between claws. Observation is best carried out on a flat hard surface because subtle lameness may not show when the animal is walking on a softer earthen surface. Stiffness and rigidity may be major components of altered gait and posture. Common causes in which stiffness may be an important component are shown in Box 13-3.

PALPATION. For upper leg conditions, hands-on examination includes palpation during standing and walking, as well as manipulation of the leg with the animal in lateral recumbency. For examination of the hip, the examiner attempts to detect crepitation in the joint by placing both hands over the greater trochanter while an assistant abducts, adducts, and rotates the affected limb. For the stifle, examination in the standing animal involves palpation of the joint for fluid effusion and stability. Stability of the joint can be assessed in the following ways: (1) Standing behind the animal, the examiner reaches around the leg with both hands locking the fingers over the tibial crest while leaning into the back of the thigh. The leg is stabilized against that of the examiner while the tibia is pulled caudally. (2) Alternatively, the examiner stands in front of the affected leg and attempts to demonstrate laxity by pushing on the tibial crest. It is important to stabilize the foot during this procedure. Distention of the joint capsule can cause swelling between the patellar ligaments despite the presence of the fat pad. One should also note that there are extensions of the joint capsule between the quadriceps femoris muscle and the femur and distally around the tendons of the peroneus tertius and the long digital extensor muscle.

When evaluating the tarsus or hock, one should always assess the degree of flexion possible in this joint. Overflexion of the hock indicates gastrocnemius rupture, whereas overextension may be indicative of rupture of the peroneus tertius.

Swelling of joints and legs should be palpated for heat, pain, and consistency. Peritarsal bursitis causes a soft, nonpainful swelling on the lateral side of the hock, whereas a hard painful swelling may be associated with septic arthritis or degenerative joint changes.

In some cases it may be difficult to distinguish upper from lower leg problems. This can be done by placing a tourniquet at or slightly above the level of the fetlock joint followed by an intravenous injection of 20 mL of 2% lidocaine into a vein below the tourniquet. Remove the tourniquet after a few minutes or so, and immediately

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TABLE 13-4

Common Conditions of the Foot and Claw Horn

Foot and Claw Condition	Claw Zone	Cause
Sole ulcer	4	Overgrowth; laminitis
Toe ulcer	5 apex	Laminitis
Thin sole toe ulcer	5 adjacent to zones 1 and 2	Excessive wear
Heel ulcer	6 heel/sole junction	Overgrowth; laminitis
White line disease	3	Overgrowth; laminitis
White line disease	1, 2	Laminitis
Thin sole/heel	4, 5, 6	Excessive wear
Subsolar/heel abscess	4, 5, 6	Secondary to sole ulcer; white line disease; foreign body penetration
Sole/heel hemorrhage	4, 5, 6	Trauma; laminitis
White line hemorrhage	1, 2, 3	Weight bearing; laminitis
Vertical wall crack	abaxial/axial wall	Laminitis; trace mineral deficiency
Horizontal wall crack single	abaxial/axial wall	Calving, weaning
Horizontal wall crack multiple	abaxial/axial wall	Laminitis
Heel erosion	6, 10	Interdigital/digital dermatitis
Interdigital dermatitis	0	Slurry, manure, moisture
Interdigital hyperplasia (corn)	0	Chronic interdigital dermatitis
Digital dermatitis	0, 10	Infectious agent
Interdigital phlegmon (foot rot)	0	*Fusobacterium*

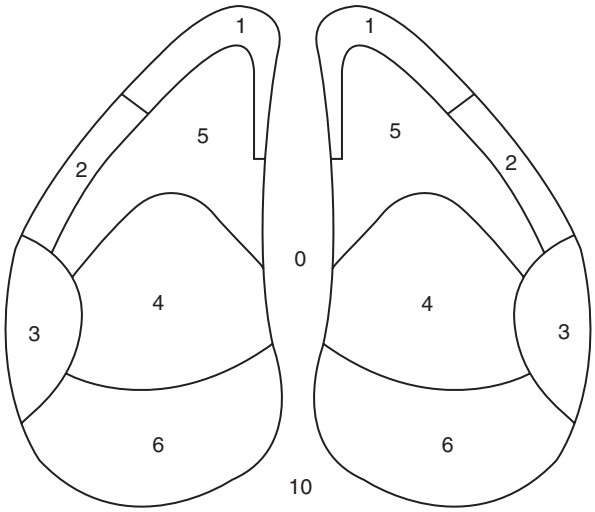


FIG. 13-1 Zones of ruminant claw.

allow the animal to walk. In cases of upper leg problems the lameness will persist. Pain and lameness associated with upper leg problems tend to become worse after a period of flexion.

Foot and claw conditions are diagnosed by visual appearance after appropriate restraint. The claw including the interdigital space is thoroughly cleaned. Claw horn and foot lesions should be identified, taking into consideration the location and the claw zone affected (Fig. 13-1). Common lesions are shown in Table 13-4. The presence of pain should be investigated if no lesions are visible. This can be done with a hoof tester. Important areas in which to apply pressure include the sole ulcer site in the axial region of zone 4 and the toe ulcer site in zone 5. Sole hemorrhages occurring in zone 4 should also be tested for pain.

Another area that should be examined includes the skin of the interdigital space and interdigital cleft (zones 0 and 10, respectively). Lesions found in these zones are shown in Table 13-4.

Postural Deformities

Carter E. Judy • John Maas

A postural deformity in horses or ruminants is an abnormal stance caused by neurologic deficit, pain, or a musculoskeletal problem.

TABLE 13-5

Examples of Postural Deformities and Possible Origins for Horses

Postural Defect	Likely Site of Origin
Contracted heels	Foot; flexor tendons
Bucked knees	Suspensory ligament
Dropped elbow	Motor nerves to forelimb; olecranon
Tiptoe stance	Foot; flexor tendons; interphalangeal joints
Non–weight bearing	Foot; any long bone; any limb articulation
Broken down (hyperextension) fetlock; dropped fetlock	Suspensory apparatus
Toe-out hindlimb and elevated hip	Coxofemoral joint; femoral neck
Basewide behind	Coxofemoral joint; femoral neck
Hyperextension of stifle and hock	Patella
Camped out in front	Bilateral forefeet
Carpal valgus	Distal metaphysis, physis, epiphysis, or carpal bones
Stiffly elevated head	Withers; cervical spine
Shifting weight between forefeet	
Recumbency	Any long bone; feet; spinal cord; myopathy

Postural deformities can range from subtle conformational faults such as broken forward foot axis to severe and unusual positions, such as when the animal is camped out in front. Inability to bear weight on a limb, asymmetric angles between joints, and lateral or medial deviations in the alignment of limbs are examples of postural deformities. Often the postural deformity itself is specific for certain diseases and conditions (Table 13-5).

Mechanisms of Postural Deformities

Postural deformities can be either congenital or acquired and result from maldevelopment, trauma, or disease. Congenital deformities may be caused by tendon contracture or laxity, osseous malformation, and hypoplasia or aplasia of osseous structures or soft tissues. Acquired deformities are most often caused by trauma or disease. Disuse atrophy secondary to an unrelated musculoskeletal abnormality can result in abnormal posture. Occasionally diseases affecting proprioception and consciousness may cause an abnormal stance

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that appears as a postural deformity (e.g., head pressing) but is unrelated to neurologic pain or a musculoskeletal problem.

Approach to Diagnosis of Postural Deformities in Horses

A history can help the examiner determine if a postural deformity is congenital, as with arthrogryposis, or acquired. Because most postural deformities in horses (Box 13-4) arise from traumatic injuries or overuse, a complete lameness examination is essential. Occasionally a postural deformity does not cause lameness; in these instances the veterinarian must consider nontraumatic causes associated with abnormal development, improper nutrition, and seemingly unrelated disease such as carpal valgus deformity.

Diagnosis of the cause of a postural deformity begins with a detailed description of the deformity and assessment of the position and asymmetry of the anatomic structures involved. If the nature and severity of the deformity cannot be determined by direct observation, palpation and manipulation of the affected structure are required. Radiography and ultrasonography can also assist in the diagnosis and provide information on which to base treatment recommendations and prognosis.

A postural deformity in ruminants is an abnormal stance caused by a neurologic deficit, pain, or a musculoskeletal problem such as abnormal conformation. Common postural deformities in ruminants and possible origins are shown in Table 13-6.

BOX 13-4

Causes of Postural Deformities in Horses

Common Causes

Infections of the foot
Hoof wall defects
Fractures
Septic (infectious) arthritis
Secondary (degenerative) joint disease
Laminitis
Angular limb deformities
Osteomyelitis
Sprain
Strain
Tenosynovitis
Contracted tendons (flexural deformity)
Laxity of flexor tendons in foals
Tendon rupture, damage, tendonitis (bowed tendon)
Upward fixation of the patella (locking patella)
Epiphysitis
Septic tenosynovitis
Muscle injury, soreness, bruise, trauma, compartment syndrome
Navicular disease
Congenital
Cuboidal bone hypoplasia

Less Common Causes

Disruption of the suspensory apparatus (broken down)
Lateral or medial patellar luxation
White muscle disease (nutritional myodegeneration)
Brucellosis
Sesamoiditis
Hypertrophic osteopathy or osteodystrophy
Ankylosis or arthrogryposis
Luxation or subluxation
Snakebite
Equine monocytic ehrlichiosis (Potomac fever)
Spondylitis, diskospondylitis
Spinal or vertebral neoplasia
Tick paralysis
Vertebral column malformation
Nigropallidal encephalomalacia (star thistle poisoning)
Postanesthetic equine myasthenia
Abscess caused by *Clostridium perfringens*
Hyperparathyroidism
Osteomalacia, osteodystrophy (rickets)

Uncommon Causes

Lupus erythematosus (rheumatoid arthritis)
Osteochondrosis
Cruciate or meniscal rupture
Patellar ligament injury
Malnutrition
Splenic rupture
Neonatal maladjustment
Subcutaneous abscess, cellulitis, foreign body
Vesicular stomatitis
Bucked shins (dorsal metacarpal disease)
Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)
Botulism (shaker foal)
Myotonia congenita
Skeletal neoplasia
Shivers (shivering)
Borreliosis (Lyme disease)

Approach to Postural Deformities in Ruminants

Sarel Van Amstel • Jan K. Shearer

The causes of postural deformities in cattle vary widely and may be congenital, nutritional, environmental, and infectious. History, visual inspection, manipulation, and palpation are important in the diagnosis of postural deformities in ruminants. Causes of postural deformities in ruminants are shown in Box 13-5.

APPROACH TO THE DIAGNOSIS OF POSTURAL DEFORMITIES IN RUMINANTS. In many instances the cause of the postural deformity can be identified through careful observation while standing and walking (Table 13-7).

TABLE 13-6

Common Postural Deformities in Ruminants and Possible Origins

Postural Deformity	Origin
Contracted fetlock and carpus	Contracture of flexor tendons, arthrogryposis
Flexed carpus and fetlock	Radial nerve damage/contracture of flexor tendons
Angular limb deformities	Nutrition, vitamin deficiencies
Dropped elbow	Proximal radial nerve/brachial plexus
Dropped fetlock	Flexor tendons; suspensory apparatus
Hyperextension of hock	Peroneal neuropathy; superficial flexor contracture; peroneus tertius rupture; spastic paresis
Crossed front legs	Lesions on the medial claws
Abduction of limb front or rear leg	Lesions on the outer claws
Basewide rear legs	Obturator nerve paralysis; hip subluxation
Outward rotation of back leg	Coxofemoral joint subluxation; stifle injuries
Hyperextension of stifle	Upward fixation of the patella
"Camped-out" posture under rear feet	Laminitis
Non–weight bearing	Fractures of the claw/foot, any joint or long bone
Tiptoe stance	Stifle injuries; foot lesions palmar or plantar region, sole and heel ulcer
Knuckling of fetlock	Peroneal and tibial neuropathies; spinal injuries; foot injuries/lesions palmar and plantar
Knuckling of proximal interphalangeal joint	Superficial flexor tendon contracture
"Camped-out" posture in front	Laminitis

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BOX 13-5

Causes of Postural Deformities in Ruminants

Common Causes

Congenital

Contracted tendons
Crooked calf syndrome (lupinosis)
Hemimelia (radial, tibial, ulnar hypoplasia)
Dactylomegaly in Shorthorns
Angular limb deformity
Syndactyly
Osteogenesis imperfecta
Dactylomegaly

Nutritional, Toxic

Rickets
Fluorosis
Crooked calf syndrome (lupinosis)
Osteomalacia
Locoweed-associated limb deformities
Epiphysitis
Chronic selenosis
Primary/secondary copper deficiency
Calcinosis caused by plant poisoning

Acquired

Secondary contracted tendons
Fractures
Degenerative joint disease
Ruptured gastrocnemius
Septic tenosynovitis
Peroneal neuropathy
Radial neuropathy
Suprascapular neuropathy
Obturator neuropathy
Severed or ruptured tendons
Luxations
Arthritis (septic)
Ruptured peroneus tertius
Muscle atrophy caused by denervation
Tibial neuropathy
Femoral neuropathy
Sciatic neuropathy
Myopathies

TABLE 13-7

Diagnosis of Postural Changes Associated with Lameness, Which Can Be Made Through Observation during Standing and Walking

Diagnosis	Characteristic Features
Ruptured Achilles tendon	Dropped hock when standing. Exacerbated during weight bearing.
Spastic syndrome	Intermittent spasticity of gastrocnemius. Characteristic high-stepping gait in rear legs with overflexion of the hocks.
Spastic paresis	Young animal, continuous spasticity of gastrocnemius. Overextension of hock. Stiff-legged gait.
Upward fixation of patella	Limb will "lock" while in full extension. This is followed by a stringhalt-type exaggerated motion during flexion.
Peritarsal bursitis/cellulitis	Soft, fluctuant, nonpainful swelling on lateral aspect of hock joint.
Straight (post) hocks	Straight hocks as viewed from side.
Peroneal neuropathy	Overextension of the hock and partial flexion of fetlock (knuckling).
Tibial neuropathy	Partial flexion of hock joint (dropped hock) and the fetlock joint (knuckling).
Sciatic neuropathy	Bilateral overflexion of the hocks (dropped hocks) and fetlocks (knuckling). Short stilted gait.
Ruptured flexors/suspensory ligaments	Overextension in fetlock. May be weight bearing on the plantar/palmar aspect of the foot.
Chronic digital dermatitis	"Boxy" claw. Periodic rhythmical lifting of foot.
Back foot	
Septic arthritis of the distal interphalangeal joint	Unilateral swollen foot including the coronary band abaxial to the insertion of the extensor. Sinus tract adjacent to extensor tendon.
Chronic laminitis	Dorsal wall (toe) curvature, poor-quality horn (flaky, dull), lateral deviation in growth (flare).
True (heritable) screw claw	Young animal, outer claws rear legs, abaxial to axial curve of wall, rotation of toe, absence of multiple horizontal grooves.
Acquired screw claw	Older animal, front and or rear feet, multiple grooves, abaxial to axial curved wall, rotation of toe.
Vertical wall crack	Vertical crack in the abaxial or axial wall.
Thimble	Full-thickness horizontal wall crack near toe forming loose cap.
Corn/Fibroma	Chronic interdigital hyperplasia of epidermis.
Proximal radial paralysis	Dropped elbow; overflexion of the fetlock and knee.
Contracted flexors/front	Overflexion of fetlock and/or carpus.

Changes in posture and weight bearing associated with lameness are shown in Table 13-8. The nature and interpretation of common postural changes are outlined below:

- Arched spine
- Nonspecific sign of lameness
- Leg symmetry

Overall symmetry of the limbs may be changed because of swellings originating from muscle, bones, or joints and muscle atrophy. Swellings could be caused by dislocations of joints such as the hip or fractures of any long bone caused by trauma or metabolic bone disease. Other swellings of joints include septic arthritis in which the joint is swollen and painful and there is a palpable effusion in the joint. In cases of degenerative joint disease the swelling is hard and often not painful. Swellings of the muscle could be hard (vitamin E/selenium deficiency); soft and fluctuant, such as with subcutaneous hematoma or abscesses; or crepitant, such as with subcutaneous emphysema or gangrenous myositis, such as caused by black leg.

Leg Angles. Straight hocks in excess of 175 degrees may predispose to degenerative joint disease. Bilateral excessive hock angle (sickle hock) is often associated with shallow toe angles and low heels. Cow hocks (inward hock rotation) on the other hand are often associated with overgrowth of the outer claws. Abduction of a single leg usually indicates pain in the inside claw, whereas a basewide stance in the front legs is indicative of pain in the outer claws. In the rear legs a basewide stance may also be due to obturator nerve paralysis, which affects the adductor muscles of the inner thigh of the rear legs.

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TABLE 13-8

Changes in Posture and Weight Bearing Associated with Lameness in Ruminants and Possible Causes

Change in Posture and Weight Bearing	Possible Cause
Arched back	May indicate presence of pain in foot or limb
"Camped-under" posture	Laminitis
Crossing of front legs	Laminitis; sole ulcers, white line disease affecting the medial claws
Shifting weight between feet/repetitive lifting of back foot	Pain; commonly seen with digital dermatitis
Basewide posture of front legs	Lesion in outer claws
Weight bearing on heel, particularly front leg	Lesion in toe; for example, toe ulcer
Inability to extend shoulder and abduct limb; atrophy of shoulder	Suprascapular nerve
Dropped elbow; inability to extend and advance elbow and lower limb	Proximal radial nerve
Inability to extend lower limb; elbow normal position; leg flexed position	Distal radial nerve
Walks on toes; knuckles forward; unable to straighten leg	Carpal and fetlock flexor deformity
Asymmetry in hips	Coxofemoral joint dislocation
Visible stifle laxity; audible sound during movement	Anterior cruciate, meniscal, collateral ligament tear
Limb locked in extension	Upward patella fixation
Overextended hock; cranial swelling on tibia	Peroneus tertius rupture
Overextended hock; knuckling of fetlock	Peroneal neuropathy
Straight hocks (post hocks); hock angle > 175 degrees	Heritable conformation defect
Sickle hocks; decreased hock angle	Shallow toe angle and low heels
Dropped hock; knuckling of fetlock	Tibial neuropathy
Bilateral dropped hocks; knuckling of both fetlocks	Partial sciatic neuropathy
Overflexion of the hock	Gastrocnemius rupture
Cow hocked; inward rotation of hocks	Overgrowth/pain of outer claws
Lateral swelling of hock/no lameness	Peritarsal bursitis in housed dairy cows
Hock swelling with lameness	Degenerative joint disease or septic tarsitis
Knuckling of rear fetlock joint	Spinal cord pathology; sciatic/peroneal neuropathy
Overextension of the fetlock joint	Flexor tendon/suspensory ligament rupture
Knuckling of the proximal interphalangeal joint	Superficial flexor tendon contracture
Inward rotation of the abaxial wall of the claw; rotation of the toe	Heritable or acquired screw claw
Multiple horizontal grooves on abaxial wall	Subclinical/chronic laminitis
Vertical crack on dorsal wall	Laminitis/trace mineral deficiency

Apart from a basewide stance, affected animals appear ataxic and are predisposed to splaying their back legs. With a camped underposture more weight is shifted to the rear legs and is often associated with pain in the front feet due to laminitis. Laminitis and pain may also cause the animal to cross the front legs in an effort to remove weight from the medial claws. Partial flexion of the front leg with inability or difficulty in advancing the leg may be associated with suprascapular or radial nerve injury or bicipital bursitis. The leg is held in semiflexion, and the elbow is dropped in case of damage to the radial nerve at the level of the brachial plexus.

Postural Changes Associated with the Stifle Joint. Instability within the stifle joint associated with cranial cruciate rupture is often seen when the animal is walking and may be accompanied by an audible sound. This is caused by sliding of the femoral condyles over the tibial plateau. The animal tends to stand with the fetlock slightly flexed and the heel raised. Weight bearing is on the tip of the toe. In cases of medial collateral ligament instability, the leg is held in an abducted position to relieve weight bearing on the medial side of the stifle and weight is placed on the medial claw when walking. With upward fixation of the patella the limb will "lock" while in full extension. This is followed by a stringhalt-type exaggerated motion during flexion. The animal may have a normal gait in between steps. Rarely the leg may become locked in extension.

Postural Changes Associated with the Hock Joint. Dropping (overflexion) of the hock during standing, but more so during walking, is often indicative of gastrocnemius rupture. Tibial nerve paralysis also results in a dropped hock and slight knuckling of the fetlock. The hock remains dropped while the animal is walking but does not sink during weight bearing compared with rupture of the gastrocnemius muscle. Overextension of the hock is associated with peroneal nerve damage, peroneus tertius rupture, upward fixation of the patella, flexor tendon contracture, and advanced degenerative joint disease. Intermittent spastic contracture of both legs with flexion of the hock is caused by spasmodic syndrome, whereas spastic contracture of one or both hind legs with overextension of the hock is due to spastic paresis. Cattle with damage to the peroneal nerve will stand with the foot knuckled over onto the dorsum of the pastern and fetlock joint. At the same time the hock joint will appear to be overextended. In mild cases the fetlock tends to knuckle over intermittently when the cow walks.

Postural Changes Associated with the Fetlock and Interphalangeal Joints. Knuckling of the fetlock joint is associated with neuropathy of the sciatic nerve and its branches, the peroneal and tibial. Other causes include lesions of the foot such as sole ulcer as well as conditions of the spine including trauma or spinal abscess or lymphosarcoma.

Postural Changes Associated with Nerves, Tendons, and Joints of the Front Legs. Postural changes and clinical signs of suprascapular nerve injury include stumbling, inability to support weight in severe cases, inability to support and extend the shoulder, a shortened stride, and abduction of the leg. Reflexes and sensation in the lower limb remain normal if the suprascapular is the only nerve affected, and atrophy of the supraspinatus and infraspinatus muscles can become visible in 5 to 7 days.

In calves, contracture of the flexors may cause flexion of both the carpus and fetlock. In such cases the leg usually cannot be straightened. Semiflexion of the knee can also be due to abnormal conformation or metabolic bone disease. Depending on the level of contracture of the flexors, only the fetlock may be in various degrees of flexion. In milder cases the animal may be able to walk on its toes and knuckle forward during weight bearing. In more severe cases the animal bears weight on the dorsum of the foot.

Postural Changes Associated with Conditions of the Foot (Defined as the Part of the Limb below the Fetlock). A symmetrical swelling of the foot sometimes extending to and above the fetlock is usually associated with foot rot, whereas a unilateral swelling of the digit is more often associated with a septic tenosynovitis, retroarticular space abscess formation, or sepsis of the distal interphalangeal joint. This can be confirmed through an aspirate of the distal interphalangeal joint and ultrasound of the flexor tendons

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TABLE 13-9

Common Causes and Diagnostic Approach for Front Upper Leg Lameness

Cause	Diagnostic Clinical Signs/Procedures
Suprascapular nerve	Atrophy of supraspinatus and infraspinatus muscles/inability to extend shoulder and abduct the limb/lower limb reflexes/sensation intact
Proximal radial nerve	Elbow: dropped/inability to extend elbow and lower leg and advance the leg/leg in flexed position/loss of skin sensation lateral and dorsal on lower limb
Distal radial nerve	Elbow: normal position/inability to extend lower leg/leg in flexed position/loss of skin sensation lateral and dorsal on lower limb
Bicipital bursitis	Decrease flexion of elbow/shortened stride/increased fluid in bursa on ultrasound
Carpal and fetlock flexor deformity (contracted tendons)	Walks on toes and knuckles forward/walks on dorsum of foot Unable to straighten the leg or bear weight Unable to rise Superficial and deep flexor contracture Tendons of flexor carpi radialis and ulnaris muscles tight on palpation
Septic arthritis	Joint swollen, hot, painful; joint effusion on palpation, ultrasound; joint fluid high white cell count and protein; predominant neutrophil population/degenerate/bacteria sometimes

TABLE 13-10

Common Causes and Diagnostic Approach for Back Upper Leg Lameness

Cause	Diagnostic Clinical Signs and Procedures
Hip joint dislocation craniodorsal	Animal up or down/asymmetry in hips/crepitation over hip area/leg shorter and hock higher than opposite leg/radiographs
Hip dislocation caudoventral	Animal down/femoral head in obturator foramen/radiographs
Anterior cruciate rupture	Increased laxity in stifle/audible noise during movement/joint effusion
Medial collateral ligament rupture	Increased joint space medially/instability of medial meniscus
Upward patella fixation	Limb locked in extension/exaggerated motion during flexion
Peroneus tertius rupture	Overextended hock/tibia and metatarsus can be extended to 180 degrees/swelling cranial on tibia
Peroneal neuropathy	Overextended hock/knuckling of fetlock/decreased skin sensation on dorsal surface of metatarsus and fetlock
Tibial neuropathy	Dropped hock/knuckling of fetlock/loss of skin sensation palmar aspect of lower limb
Partial sciatic neuropathy	Bilateral dropped hocks/knuckling of fetlocks

and structures in the heel. Toe ulcers, which may cause a heel-first foot placement or weight bearing toward the heel when standing can be seen in the apex of zone 5. The proximal interphalangeal joint may become subluxated with superficial flexor tendon contracture, resulting in knuckling of the joint.

Septic arthritis of the distal interphalangeal joint results in severe lameness with little to no weight bearing during both standing and walking. With white line disease in zone 3 of the rear outer claw the leg will be abducted to relieve weight bearing. Ulcers or hemorrhage in zones 4 and 6 could also be responsible for changes in gait and posture, which may include inward rotation of the hocks to reduce weight bearing on the outer claws of the rear legs, knuckling of the fetlock, crossing of the front legs, and abduction or adduction of the leg. White line disease in zones 1, 2, and 3 could also result in postural change.

The causes and diagnostic approach for upper leg lameness are shown in Tables 13-9 and 13-10.

Swellings and Enlargements (Soft and Hard Tissue)

Carter E. Judy • John Maas

Swellings and enlargements consist of soft tissue (e.g., tendon) or hard tissue (e.g., osseous) and can occur anywhere on an animal's body. Generally, clinically significant swellings and enlargements associated with the musculoskeletal system occur on the limbs.

Swellings and enlargements can be further divided into two principal groups, depending on whether or not they are associated with a specific anatomic structure. For example, a soft fluctuant swelling in the region of the left carpus may be caused by an abnormality of the antebrachialcarpal joint (e.g., septic synovial effusion) or may not involve the joint at all (e.g., subcutaneous abscess). Although lameness can be associated with such a swelling, clearly it is important to determine the cause of the abnormality because the one involving the joint may require the more immediate treatment.

Mechanisms of Swellings and Enlargements

The mechanism by which swelling or enlargement develops depends on the tissue involved (see Box 13-4). Soft tissue swelling is often produced by trauma, inflammation, infection, or neoplasia; it can consist of interstitial fluid (e.g., edema), fluid within an open space (e.g., synovial hernia), or a localized accumulation of cells or fibrous tissue. Localized edematous swelling is commonly caused by inflammation and/or obstruction of venous blood or lymph flow. Generalized edema is usually the result of increased hydrostatic pressure caused by circulatory failure or an altered capillary-tissue osmotic gradient stemming from hypoalbuminemia. Fluctuant swellings such as hematoma, synovial effusion, a purulent abscess, or a plasma-filled cyst contain free fluid. Granulation tissue, fibrous scar tissue, and tumor cells are the most common constituents of firm soft tissue swellings. Rupture of supporting or confining structures (e.g., prepubic tendon rupture) can result in unusual forms of soft tissue swelling caused by herniation of internal organs.

Many factors influence new bone formation. Trauma and infections initiate bony enlargement (e.g., callus) by disrupting the periosteum, producing inflammation and eventually ossification. The extent of periosteal new bone formation depends on the cause of the stimulus and the size of the affected area. Remodeled bone may also arise from nontraumatic events, usually associated with altered metabolism or neoplasia. Bony enlargements associated with the metaphysis and physis in young, growing animals are usually secondary to a combination of nutritional and traumatic factors. For example, dietary calcium, phosphorus, and vitamin D imbalance can lead to abnormal bone growth. A bony swelling develops gradually and may become noticeable only after it enlarges, interferes with normal function, or becomes a source of lameness.

Approach to Diagnosis of Swellings and Enlargements in Horses

For causes of swellings and enlargements in horses see Box 13-6.

1. History. A history should determine the number of horses involved, the duration of clinical signs, and the possibility that traumatic events or environmental factors are responsible for

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BOX 13-6

Causes of Swellings and Enlargements in Horses

Soft Tissue

Septic (infectious) arthritis
Secondary (degenerative) joint disease
Sprain
Strain
Hygroma
Tenosynovitis
Osteochondrosis
Suspensory desmitis or sesamoiditis
Infections of the foot
Insect bites or snakebites
Cellulitis
Abscess
Herniation
Neoplasia
Capped hock
Hematoma
Phycomycosis

Hard Tissue

Secondary (degenerative) joint disease
Fracture
Sequestrum
Osteomyelitis (periosteal new bone formation)
Epiphysitis
Luxation or subluxation
Osteochondroma
Osteomalacia (rickets)
Bucked shins (dorsal metacarpal disease)
Hypertrophic osteopathy
Ankylosis or arthrogryposis
Calcinosis caused by plant poisoning
Selenium toxicity

causing a swelling or enlargement. In addition, changes over time in the appearance and size of the swelling or enlargement can be informative.

2. Inspection and palpation. The location of the swelling and its proximity to anatomic structures often reveal the tissue involved and the probable cause of the condition. For example, swelling around a joint may indicate arthritis, periarthritis, or hygromas. Tendon swelling may indicate tendonitis or ruptured tendons. Swelling over ligaments may indicate rupture, subluxation, or inflammation around a ligament. Muscle swelling results from abscessation or fascial tears. Subcutaneous swelling may indicate hematomas, edema from inflammation around a ligament, or cellulitis. Bony enlargements can often be localized to the shaft of a bone (e.g., periosteal callus) or the ends of a bone (e.g., metaphyseal flaring). Periarticular new bone may be readily apparent (e.g., ringbone) or may not be found even on deep palpation. New bone formation can also be found associated with the axial skeleton and head. Palpation of a swelling can determine its consistency and association with anatomic structures. Osseous swelling indicates calcification, proliferation of bone, or fracture. Firm soft tissue swelling indicates inflammation, abnormal proliferation of soft tissue (e.g., granulation, tumor), or herniation. Warmth, redness, and pain associated with swelling indicate active inflammation. While new bone is forming, the swelling may be soft and sensitive to palpation. Cold and insensitivity to palpation suggest inadequate blood supply and possibly ischemia (e.g., gangrene). Lameness caused by an injury or condition that results in a hard swelling or enlargement may be accentuated by performing a stress test, such as trotting the horse in hand after direct pressure on the swelling. Intraarticular anesthesia may substantially reduce lameness caused by joint effusion associated with periarticular new bone.
3. Radiography, ultrasonography, and alternative imaging techniques. In addition to identifying definitively the nature of an osseous swelling or enlargement, radiography can gauge the severity and progression of the disease and help establish a therapeutic plan and prognosis. Ultrasound can often determine the position (e.g., depth, area) and volume of a soft tissue swelling and the optimum site for aspiration or biopsy. Thermography may help to identify subtle heat production secondary to inflammation and increased blood flow, before onset of a swelling, allowing for early treatment. Nuclear scintigraphy may help to localize the cause of swellings and identify whether they are bony or soft tissue in origin (e.g., tarsal effusion secondary to a sustentaculum tali osteomyelitis). CAT scanning is useful for evaluating bony swellings, especially of the head when swellings of the mandible and maxilla may be related to infected teeth and the determination of which teeth are involved is necessary before surgical intervention. MRI may prove useful for accurate imaging of soft tissue masses that cannot be accurately characterized with other diagnostic techniques.
4. Cytology, microbiology, and histology. A fine-needle aspiration, using aseptic techniques, should be performed to obtain samples for microbiologic culture (e.g., bacterial and fungal) of soft tissue swellings. If the material is very viscous, a large-gauge needle may be required. Fluid collected for cytology should be placed in tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent clotting before analysis. Tissue samples obtained by biopsy should be placed in 10% buffered formalin.

Swellings and Enlargements in Ruminants

Sarel Van Amstel • Jan K. Shearer

Swellings and enlargements can originate from soft tissue (muscle or tendons) or hard tissue (bone). Those associated with lameness usually occur on the limbs. Common causes and mechanisms of swellings and enlargements are shown in Table 13-11.

APPROACH TO SWELLINGS AND ENLARGEMENTS IN RUMINANTS

History. History will indicate whether it is congenital or acquired as well as the duration. Historical information should also include type of pasture, presence of lameness and the progression of the lameness signs, possibility of trauma, vaccination history, appetite and presence of systemic signs as well as the number of animals affected.

Examination Including Palpation. The anatomic location of the swelling may give an indication as to its origin (see Table 13-11). Palpation will provide information as to the nature and possible cause of the swelling. Soft fluctuant swellings on the upper leg are usually due to abscess formation following a small penetrating wound, or they may follow an intramuscular injection. Cattle on sweet clover may develop hematomas due to the presence of warfarin sodium, which inhibits vitamin K and thus the vitamin K–dependent factors (2, 7, 9, 10). Fluid effusion into a joint capsule, particularly into the extensions of the joint capsule of the stifle between the quadriceps femoris muscle and the femur, and also distally around the tendons of the peroneus tertius and the long digital extensor muscle will result in a soft fluctuant swelling. Those associated with septic joints are usually less fluctuant and warm and painful on palpation. Joint swelling associated with degenerative joint disease may be hard on palpation due to new bone formation and nonpainful. Fluid effusion into the joint space is usually present. Causes of degenerative joint disease may be hereditary (e.g., hip dysplasia, abnormal conformation such as straight hocks). Degenerative joint disease is common following traumatic rupture of the anterior cruciate ligament, meniscal tears, or joint instability caused by collateral ligament damage. Unilateral swelling of the foot is often associated with sepsis of the distal interphalangeal joint and the sheath of the flexor tendons. Bilateral swelling of the foot is typically associated with foot rot. Swelling immediately above the dew claws may be due to

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TABLE 13-11

Common Causes and Mechanisms of Swellings and Enlargements of the Limbs in Ruminants

Soft Tissue	Mechanism
Foot rot	Bacterial penetration into interdigital soft tissues
Septic tenosynovitis flexors	Primarily resulting from ascending infection through the sole
Interdigital epidermal hyperplasia	Chronic interdigital dermatitis/splayed claws
Subcutaneous abscess	Local or hematogenous infection
Peritarsal bursitis	Friction on lateral aspect of tarsal joint
Hygroma	*Brucella abortus*/pressure
Muscle rupture	Trauma; for example, peroneus tertius/gastrocnemius
Hematoma	Trauma/liver disease/warfarin-containing plants/vitamin K deficiency
Calcanean bursitis	Trauma/infection
Tendon rupture	Trauma
Skin neoplasia	Lymphosarcoma; squamous cell carcinoma
Papillomatous digital dermatitis	Chronic epidermitis caused by spirochete
Subcutaneous edema	Lymph/>hydrostatic, <oncotic pressures/>capillary permeability
Subcutaneous emphysema	Wound/ruptured lung/clostridial infection
Hard Tissue	**Mechanism**
Degenerative joint disease	New bone formation/periarticular fibrosis
Septic arthritis	Trauma/ascending infection/hematogenous
Osteomyelitis	Trauma/spread from neighboring soft tissue infection
Chronic fluorosis	High soil/water fluoride content
Osteosarcoma	
Osseous sequestration	Following osteomyelitis/ischemia/infection of bone fragment
Caprine arthritis encephalitis	Retroviral infection primarily through colostrum
Epiphysitis	Metabolic bone disease
Nutritional osteodystrophy	Copper, calcium, phosphorus deficiency
Fracture	Trauma/osteopenia/osteitis/osteomyelitis/neoplasia
Luxations/subluxations	Tendon contracture; trauma; tendon/ligament rupture
Lumpy jaw (actinomycosis)	Penetration of organism through oral mucosa

tenosynovitis, septic inflammation of the fetlock joint, rupture of the flexor tendons, or suspensory ligament. Generalized soft and nonpainful swelling of the leg that pits on pressure may be due to lymphatic obstruction, increased hydrostatic pressure, decreased oncotic pressure, or increased capillary permeability as is present with acute endotoxemia.

RADIOLOGY, ULTRASONOGRAPHY, AND CYTOLOGY

Carpal Joint. Ultrasound carried out in the longitudinal plane over the dorsal surface of the joint will facilitate arthrocentesis. Individual joint recesses that can be visualized include the radiocarpal, intercarpal, and carpometacarpal joints. In the absence of ultrasound, joint fluid can usually be obtained from the radiocarpal pouch with the carpus in slight flexion. A high white cell count in the presence of degenerate neutrophils confirms septic arthritis. Bacteria may not always be visible on the slide. In chronic cases the joint looks and feels thicker with a reduced range of motion. In such cases chronic degenerative changes will be visible radiographically. These changes can first be detected over the cranial surfaces of the proximal carpal row. The radiocarpal joint space is widened, and subchondral bone destruction may be present, which is eventually followed by new bone formation.

Coxofemoral Joint. Ultrasound-guided arthrocentesis can be carried out in cases where an increase in joint fluid can be visualized. Ultrasound is carried out in a longitudinal-oblique plane with the transducer placed parallel to the long axis of the femoral neck and moving it craniodorsally to where a line drawn between the two tuber coxae intersects the longitudinal axis of the vertebral column. Radiographs are useful in establishing the cause of lameness and may be accomplished by anesthetizing the animal and positioning it in dorsal recumbency for a ventro-dorsal radiograph. The size of the musculature will determine to a large extent the detail visible in the radiograph.

Stifle Joint. The following should be considered with arthrocentesis of the stifle. There is communication between the femoropatellar and medial femorotibial joint cavities. These compartments do not always communicate with the lateral femorotibial space. To enter this compartment, a needle is introduced behind the lateral patellar ligament and directed caudally. To enter the femoropatellar and the femorotibial compartments, the needle is inserted between the medial and middle patellar ligaments and directed slightly down and toward the medial lip of the trochlea. Use of ultrasound will confirm the presence of increased joint fluid and facilitate collection.

Paresis and Weakness

Richard A. LeCouteur

Paresis may be defined as a deficit of voluntary movement. It may be monoparesis (paresis of a single limb), paraparesis (paresis of both pelvic limbs), tetraparesis (paresis of all four limbs), or hemiparesis (paresis of a thoracic and pelvic limb on the same side). Paresis results from disruption of the voluntary motor pathways that extend from the cerebral cortex, through the brainstem and spinal cord, to the motor unit (peripheral nerve, neuromuscular junctions, and muscle fibers). Complete loss of voluntary movement is referred to as *paralysis (plegia)*. Voluntary movements must be differentiated from reflex movements on the basis of neurologic examination findings and general observations.

Weakness may be defined as impairment of strength and power. Most authors use the terms *paresis* and *weakness* synonymously; however, this may be confusing in some circumstances. For example, weakness may occur in the absence of paresis in some disorders of the nervous system, and weakness may result from many disease processes that do not primarily involve the nervous system (e.g., heart failure, respiratory insufficiency). The clinical signs of weakness may vary considerably and may include paresis, gait abnormalities, dysphagia, regurgitation, dyspnea, and dysphonia. Weakness may be present at rest or may occur after exercise. The distribution of involvement may be local, regional, or generalized. In addition, there may be gross deformities of muscle mass (e.g., atrophy, hypertrophy, skeletal deformities) associated with weakness.

This section focuses on paresis and weakness caused by conditions that affect the motor unit (Box 13-7). Diseases of other systems (e.g., respiratory and cardiovascular diseases or central nervous system disorders) that may result in paresis and weakness are discussed separately in other sections.

Mechanisms of Paresis and Weakness

Voluntary movement is initiated by the cerebral cortex. Muscular activity occurs subconsciously after activation of successively lower levels of the nervous system: basal nuclei, midbrain, pons and medulla, cerebellum, brainstem, spinal cord, and motor unit. The function of these lower levels is vital, and without their input voluntary movements become impossible.

Monoparesis (or monoplegia) is a common problem in horses and ruminants. It may be caused by dysfunction of the lower motor neuron or neuromuscular junction. Monoparesis is commonly

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BOX 13-7

Causes of Paresis and Generalized Weakness in Horses and Ruminants

Anemia
Cardiovascular disease
Chronic inflammatory disease
Drug-related conditions
Electrolyte disorders
Endocrine or metabolic disorders
Exhaustion
Fever or sepsis
Gastrointestinal disease
Motor unit disease
Neoplasia
Nervous system disease
Nutritional disorders
Respiratory system disease
Trauma
Toxicities

caused by trauma to a nerve or plexus, although neoplasia (e.g., lymphoma, neurofibroma) and inflammation or infection (e.g., early stages of rabies) of peripheral nerves have been reported to cause monoparesis.

Bilateral pelvic limb paresis, ataxia, or paralysis may occur as a result of a neurologic disorder localized to the spinal cord caudal to the T2 spinal cord segment. Various congenital vertebral and spinal cord malformations may result in pelvic limb paresis. Equine protozoal myeloencephalitis and equine degenerative myeloencephalopathy may result in lameness, weakness, and ataxia that may progress to tetraparesis. Musculoskeletal disorders resulting only in bilateral pelvic limb weakness and paresis are unusual. Possible causes include trauma (e.g., postcalving or postfoaling paralyses caused by lumbosacral nerve root compression or contusion), vascular disorders (e.g., thrombosis), and early stages of an infectious disorder that may progress to tetraparesis.

The causes of tetraparesis are numerous and include progression of many of the disorders mentioned previously. Outbreaks of intoxication with *Clostridium botulinum* occur sporadically in horses and ruminants; the condition results in a flaccid paralysis that starts with the pelvic limbs and progresses cranially. Depending on the amount of toxin involved, large numbers of animals may be affected. Polyneuropathies (congenital and acquired) and polymyopathies (congenital, metabolic, infectious, and immune-mediated) are causes of tetraparesis.

Muscle weakness may result either from a primary neuromuscular disease or disorders that affect muscle secondarily. In the latter category, problems of horses and ruminants that commonly result in weakness include poor diet, underfeeding, toxicity, and anorexia. Systemic diseases and disorders such as dehydration, low circulating blood volume, anemia, and metabolic abnormalities (e.g., acidosis or alkalosis) also may result in weakness. Disorders of bones (e.g., fractures) and joints (e.g., septic arthritis) affecting one limb also may affect the contralateral limb through overuse or misuse, and weakness of the contralateral limb may result.

Primary neuromuscular diseases are usually classified on the basis of the anatomic component of the motor unit that is involved. Such diseases are broadly subdivided into neuropathies (disorders of the neuron, its cell body, axon, and/or Schwann cells [myelin]); junctionopathies (disorders of the neuromuscular junction); myopathies (disorders of muscle fibers); and neuromyopathies (disorders of both the neurons and the muscle fibers).

Dysfunction of the motor unit results in lower motor neuron signs, seen clinically as muscle weakness. The expression of this weakness may vary considerably, and the distribution of involvement may be local, regional, or generalized. Atrophy, hypertrophy, and skeletal deformities may accompany the muscle weakness. Any patient with some form of clinical weakness should be viewed as potentially having a motor unit disorder. That the patient is "weak merely because it is sick" should not be readily assumed without meticulous evaluation of the motor unit.

Approach to Diagnosis of Paresis and Weakness in Horses

Establishing a diagnosis requires an informed and coordinated approach to defining a problem list through associations and direct observations (i.e., a diagnostic plan) (Box 13-8).

1. Signalment. Breed, age, sex, and use of the horse.
2. History. Feeding program, vaccination and deworming schedules, course of complaint, response to treatment, and possibility of exposure to toxins or trauma.
3. Physical examination. Presence and distribution of abnormal findings on physical and neurologic examinations should be recorded. Normal functions must be known before abnormal functions may be recognized. Abnormal functions must be recognized because neurologic diseases are manifested clinically almost entirely by dysfunction. It is uncommon for the clinical signs to include readily detectable anatomic changes. Therefore a clinician must rely on clinical signs of abnormal function to identify the location of the neurologic dysfunction. The first step in locating a neurologic lesion is to determine the level of the abnormality along the longitudinal plane of the neuraxis (i.e., brain, spinal cord, or motor unit). The second step is to further localize the lesion within an anatomic region (e.g., motor unit should be further localized to peripheral nerve, neuromuscular junction, or muscle). The third step is to determine the location of the lesion in the transverse plane at the appropriate longitudinal level (e.g., left or right side).
4. Minimum database. Complete blood count, serum biochemistry panel (including electrolyte determinations), fecal analysis, and urinalysis. Measurement of muscle-specific serum enzymes such as creatine kinase (CK), as well as aspartate aminotransferase (AST) and lactic dehydrogenase (LDH), may be helpful in identifying neuromuscular disorders in which myonecrosis is a principal pathologic feature. Elevated serum enzyme activities may help to differentiate myopathies from other neuromuscular disorders. Immunologic procedures for the detection of myoglobin that are becoming available may provide a sensitive means of detecting myolysis in the future.
5. Specific diagnostic tests: Electrodiagnostic testing. Electromyography (EMG) involves the detection and characterization of electrical activity (potentials) recorded from a patient's muscles. A systematic study of individual muscles permits an accurate determination of the distribution of muscles affected by a pathologic process.
6. Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies. In some instances, results of muscle biopsy analysis may provide a definitive diagnosis (e.g., polysaccharide storage myopathy of horses).

Approach to Diagnosis of Paresis and Weakness in Ruminants

Sarel Van Amstel • Jan K. Shearer

The approach to the diagnosis of disorders causing paresis and weakness in ruminants (Box 13-9) is essentially the same as that for horses. The following should be included:

SIGNALMENT. Age, sex, breed, use (pet; dairy; beef)

HISTORY. Feed composition and storage; calving difficulty; exposure to trauma or toxins; recently bought; vaccinations; housing

PHYSICAL EXAMINATION. Observe the animal from a distance to evaluate posture, signs of weakness or neurologic trouble such as

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BOX 13-8

Causes of Paresis and Weakness in Horses

Degenerative

Equine degenerative myeloencephalopathy

Anomalous or Congenital

Hydrocephalus
Vertebral and spinal cord malformations

Metabolic

Exertional rhabdomyolysis
Hyperkalemic periodic paralysis
Hypothyroidism
Hyperthermia
Hypocalcemia
Hypokalemia
Equine hepatic lipidosis
Vitamin A deficiency

Nutritional

Malnutrition, vitamin E (selenium) deficiency

Neoplastic

Brain or spinal cord tumor
Lymphosarcoma
Melanoma
Leukemia

Infectious or Inflammatory

Encephalitis, myelitis
Equine protozoal myeloencephalitis
Diskospondylitis
Botulism
Rabies
Ehrlichiosis
Tuberculosis
Rhinopneumonitis
Hepatoencephalopathy
Tick paralysis
Cerebrospinal nematodiasis
Equine protozoal myeloencephalitis

Toxic

Snakebite
Plant poisons (star thistle poisoning, oleander, moldy corn poisoning, white snake root, locoweed, larkspur, delphinium, onion, moldy sweet clover)
Vitamin D
Phosphorus
Heavy metals (lead, arsenic)

Traumatic

Vertebral fracture or luxation

Vascular

Postanesthetic hemorrhagic myelopathy

stumbling, and ataxia. Observe for knuckling, muscle fasciculation, and limb dragging. Look at mucous membrane color (conjunctiva or vulva). Look at the position of the eye (degree of retraction) and skin elasticity above the eye, the presence of dry mucous membranes, and capillary refill time to assess degree of dehydration. Palpate the rumen to assess rumen filling. In cases of acute rumen acidosis the rumen is usually fluid filled. Take a rumen sample to measure pH. Do a rectal examination and palpate the spine and pelvic bones to determine the presence of fractures or any bony prominences or lymph node enlargements.

OTHER DIAGNOSTIC TESTS. A hematocrit and total protein will give an indication of the degree of anemia or dehydration. A complete blood count including fibrinogen may indicate the presence of inflammatory disease. A blood smear should be examined for the presence of blood parasites and type of anemia present. Blood chemistry including electrolytes and the animal's blood gas status should be evaluated. A spinal tap should be considered, particularly in small ruminants including camelids where an eosinophilic pleocytosis is diagnostic for meningeal worm. A neurologic examination should be carried out. Reduced lower jaw and tongue tone, as well as dysphagia, may be indicative of botulism, rabies, polioencephalomalacia, or listeria. Other common cranial signs may include ptosis, anisocoria, delayed or absent pupil light response, dropped ears, facial asymmetry, delayed or absent sensory response to the face, head tremors, blindness, and star gazing. Intension tremors may indicate cerebellar disease, whereas head pressing may indicate problems with the cerebral cortex.

The degree of ataxia and weakness can be tested by walking the animal in a tight circle and observing the proprioceptive response or pulling the tail while walking next to it. Spinal reflexes can be done if the animal is recumbent. Box 13-9 lists causes of paresis and weakness in ruminants.

Muscle Spasms and Myoclonus

Richard A. LeCouteur

Muscle spasms are sudden, transient, and involuntary contractions of a single muscle or group of muscles, attended by pain and loss of function. Often all the muscles affected by a spasm are supplied by a single nerve. A painful, tonic, spasmodic muscular contraction is often referred to as a *cramp*.

Myoclonus may be defined as a disturbance of neuromuscular activity characterized by abrupt, brief, rapid, jerky, arrhythmic, asynergic, involuntary contractions involving portions of muscles, entire muscles, or groups of muscles, regardless of their functional association. The movements may be single or repetitive (10 to 50 per minute) and are similar to those that follow stimulation of a muscle. Myoclonus is seen primarily in muscles of the limbs, where involvement is often diffuse or widespread. Myoclonus may also be present in facial or masticatory muscles and muscles of the tongue, larynx, and pharynx. Myoclonus usually disappears during sleep.

This section describes muscle spasm and myoclonus as specific clinical signs associated with dysfunction of the musculoskeletal system.

Mechanisms of Muscle Spasms and Myoclonus

Spasms are usually of reflex origin and may result from irritation or stimulation at any level of the nervous system from the cerebral cortex to the muscle fibers. In most cases, however, spasms are caused by peripheral irritation affecting either muscles or nerves. Pain may cause either tonic or clonic spasms of muscles, especially if the painful stimulus is focal or discrete. Mechanical irritation may cause a localized spasm. There may be prolonged and characteristic muscle spasm associated with the hyperirritability of nerves and muscles in tetany or tetanus. Spasms may follow injury or irritation of peripheral nerves, particularly during the process of regeneration. Spasms may also result from irritation or diseases affecting cortical centers in the brain, motor nuclei in the brainstem, or descending motor pathways in the spinal cord.

There has been much discussion regarding the pathologic process underlying myoclonic movements. Although it was originally thought that the neural discharge that excites the muscular contraction of myoclonus was confined to the motor unit, it is now known that myoclonus may also result from dysfunction of the brain (e.g., cerebral cortex, brainstem, basal nuclei, thalamus), spinal cord, peripheral nerve, neuromuscular junction, or the muscle itself, alone or in combination. A variety of processes evidently lead to hyperexcitability of the cerebral cortex, subcortical structures, or even the

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BOX 13-9

Causes of Paresis and Weakness in Ruminants

Anomalous or Congenital

Progressive degenerative myeloencephalopathy of Brown Swiss cattle
Progressive ataxia of Charolais cattle
Inherited progressive spinal myelinopathy of Murray Grey cattle
Inherited myophosphorylase deficiency in Charolais cattle
Heart disease
Hydrocephalus

Metabolic

Hypoglycemia
Hypocalcemia
Hypokalemia
Hypomagnesemia
Rumen acidosis
Anemia
Hypothermia
Hepatic encephalopathy

Infectious or Inflammatory

Infectious diarrhea; for example, *Salmonella*
Tick paralysis
Botulism
Rabies
Parasitism
Pneumonia
Spinal abscess
Sepsis
Bovine spongiform encephalopathy
Severe mastitis
Endotoxemia
Encephalomyelitis

Nutritional

Starvation
Vitamin E/selenium
Polioencephalomalacia
Diarrhea
Water intoxication/salt poisoning
Copper deficiency

Neoplastic

Spinal lymphoma

Traumatic

Vertebral fracture or luxation
Calving paresis

Paracytic

Parelaphostrongylus tenuis

Toxic

Lead poisoning
Ionophore toxicity

BOX 13-10

Causes of Muscle Spasms and Myoclonus in Horses

Anomalous or Congenital

Myotonia congenita

Metabolic

Hyperkalemic periodic paralysis
Hypocalcemia
Hypoglycemia
Hypothermia
Exhaustion
Shivering

Neoplastic

Insulinoma

Infectious or Inflammatory

Tetanus
Rabies
Equine influenza
Tick-borne encephalitis
Meningitis

Idiopathic

Neonatal maladjustment syndrome

Toxic

Strychnine
Organochlorines
Chlorinated hydrocarbons

lower motor neurons alone. Myoclonic movements or muscle spasms may occur in a variety of conditions. They have been observed in association with encephalitis, meningitis, toxic and postanoxic states, metabolic disorders, degenerative diseases, and vascular and neoplastic conditions. Myoclonus has also been reported in association with lesions of peripheral nerves, nerve roots, and spinal cord.

Specifically, disturbances in plasma electrolyte concentrations, certain drugs, toxins, and poisons may elicit involuntary muscle activity. In general, the mechanism that is common to all causes of spasm or myoclonus involves an inappropriate stimulation of a nerve or muscle cell, causing the cell to fire a series of action potentials, resulting in muscle contraction. For example, toxins may act directly on the muscle cell membrane to stimulate the release of calcium into the cell from the sarcoplasmic reticulum, thereby causing involuntary muscle contraction. Alternatively, some toxins may cause efferent neurons to release neurotransmitter across the neuromuscular junctions, thereby stimulating receptors on the muscle cell membrane.

Approach to Diagnosis of Muscle Spasms and Myoclonus in Horses

A broad spectrum of diseases may be associated with muscle spasms or myoclonus in horses (Box 13-10). A thorough investigation is necessary to achieve an accurate diagnosis.

1. History. A comprehensive history should include evaluation of the environment and stablemates, description of any traumatic episodes, and any potential drug or toxin exposure.
2. Physical examination. Complete lameness and neurologic examinations should be done as extensions of a thorough physical examination.
3. Minimum database. Complete blood count, serum biochemistry panel (including muscle enzyme determinations), and cerebrospinal fluid analysis should be performed. In the case of muscle spasm and myoclonus, elevation in muscle enzymes may indicate secondary muscle damage rather than a primary muscle disease. A tetany panel, including serum calcium, phosphorus, and magnesium determinations, may be completed. Hypocalcemia may be a cause of muscle spasms in lactating horses, exhausted endurance horses, or horses transported long distances.
4. Specific diagnostic tests: Electrodiagnostic testing. A systematic study of individual muscles using EMG permits an accurate determination of the distribution of muscles affected by a pathologic process.
5. Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies. In some

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TABLE 13-12

Causes and Pathogenesis of Muscle Spasms in Ruminants

Sign	Pathogenesis
Posterior paralysis of Danish Red calves	Single Mendelian recessive factor from one bull
Inherited congenital myoclonus of polled Herefords and their crossbreeds	Decrease in inhibitory glycine receptors
Maple syrup urine disease in polled Herefords and their cross breeds	Deficiency of activity of mitochondrial enzyme branched-chain alpha-keto acid dehydrogenase
Lethal spasms in Jersey and Hereford calves	Autosomal recessive gene from one bull
Congenital brain edema in Herefords	Autosomal recessive gene
Hypomagnesemia (lactation tetany; grass tetany; grass staggers; wheat pasture poisoning)	Stress; transport; dietary deficiency (lush pasture; high potassium and nitrogen); inclement weather; lactation and pregnancy; individual susceptibility
Hypocalcemia	Onset of lactation; vitamin D deficiency; starvation; metabolic alkalosis; stress (sheep and goats); prepartum diets high in calcium; individual and breed susceptibility; IV oxytetracycline administration
Hypoglycemia	Failure to nurse; sepsis; bacterial meningitis; enterotoxigenic colibacillosis; cold exposure; twin or triplet lambs
Tetanus	Disinhibition of gamma motor neurons
Rabies	Encephalitis
Pseudorabies	Encephalitis
Meningitis	Bacterial infections; viral encephalitides
Coccidiosis	Possible labile neurotoxin
Chlorinated hydrocarbons	Cause repetitive discharge of motor and sensory neurons
Strychnine	Antagonist of glycine and acetylcholine and mainly affects the motor nerves in the spine
Organophosphates	Inactivation of cholinesterase
Cocklebur	Carboxyatractyloside (CAT)
Buckeye	Glycoside saponin (aesculin)

instances results of muscle biopsy analysis may provide a definitive diagnosis (e.g., myophosphorylase deficiency of Charolais cattle).

Approach to Diagnosis of Muscle Spasms and Myoclonus in Ruminants

The approach to diagnosis of muscle spasms and myoclonus in ruminants is essentially the same as that described for horses (Table 13-12). In ruminants a tetany panel (consisting of serum calcium, phosphorus, and magnesium determinations) should be completed in any animal exhibiting these signs. In lactating cattle on grass pasture and in sheep transported long distances, hypomagnesemia and hypocalcemia, respectively, are highly suspected initially. Several infectious (e.g., rabies, pseudorabies); toxic; and inherited causes of muscle spasms and myoclonus should be suspected in ruminants. In postparturient animals and animals with wounds or bites, or animals recently castrated or tail docked, tetanus should be considered as a possible cause of muscle spasms and myoclonus.

Suggested Readings

The Suggested Readings list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 14

Collapse and Sudden Death

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■ MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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The ruminant or horse that collapses and dies within 24 hours while being observed or is found dead with no premonitory signs of illness is often a diagnostic challenge. In these situations, clients are often distressed and frequently pressure the veterinarian to declare an immediate diagnosis. Sudden death in the absence of observed clinical illness is usually the most perplexing. Obligation to clients necessitates a systematic approach to derive a specific causative diagnosis, to determine the source and extent of the problem, and to recommend corrective measures. These goals are best accomplished by delineating the characteristics of normal animals within the herd and analyzing the distribution of the disease with respect to time, place, and a variety of exposure factors and environmental influences. These factors are then correlated with necropsy results and additional diagnostic testing.

Collapse versus Sudden Death

Collapse is easily identified as a state of extreme prostration and depression. However, sudden death has a somewhat tenuous meaning, lending itself to subjective impression. The timing parameter used to define sudden death ranges from 1 to 24 hours from the onset of the fatal episode. Some veterinarians restrict the definition to a narrower time span. The 12- to 24-hour interval is sometimes selected to coincide with the frequency of owner observation of the livestock. For our purposes sudden death means clinically unexplained, rapid death (12 to 24 hours) occurring during normal activity in apparently healthy animals. Generally a condition of this nature is associated with fatal dysfunction of the cardiovascular, nervous, respiratory, or gastrointestinal (GI) system. In addition, perturbations in general cellular metabolism (cyanide or hydrogen sulfide) may result in peracute death.

Approach to Diagnosis of Sudden Death

The causes of sudden death are investigated in much the same way as for any disease. The accompanying tables of differential diagnoses include infectious, metabolic, nutritional, physical, cardiovascular, toxic, and miscellaneous causes of sudden death. Diagnostic laboratories provide an array of tests and analytic procedures on the basis of veterinarians' needs in their service areas. Use of these facilities to support a definitive diagnosis is essential in sudden death cases. Diagnosis is rarely based on a single item of evidence and usually requires input from multiple testing procedures. Unless the cause of death is apparent, some important considerations required for effective use of a diagnostic laboratory include the following:

1. A detailed history, which consists of the herd incidence, management changes, past medical problems, vaccination records, new additions to the herd, a complete description of the environment (e.g., recent lightning?), and recognition of the frequency of animal observation. Owners and managers may not be candid for fear of being considered negligent. Inconsistencies among involved parties should be carefully evaluated. Recent changes in management practices should be scrutinized, including feeding habits and whether there have been any illnesses in commingled animals. Animals trailed or transported for long distances or introduced onto unfamiliar ranges are often poisoned by plant species normally avoided by indigenous livestock. The likelihood of foul play should be considered without creating undue alarm. Assigning blame should be left to the discretion of owners. Consideration of disgruntled former employees and equine insurance claims are particularly critical situations that may have legal implications. The precise cause of death is crucial for insured livestock (mostly horses) because of exclusion clauses in many insurance policies. Heavily insured horses should be subjected to a detailed, documented, and witnessed diagnostic evaluation. Toxicologic testing is especially critical in these cases. Evaluation of the environment before the animal is moved is necessary to eliminate questionable procedures in insurance claim cases. Evidence of struggling in the immediate area indicates a more protracted illness in contrast to collapse and death without a struggle. Suspicions should be aroused when evidence suggests the animal may have been dragged or carried to the current location.
2. The appropriate specimen is required by the diagnostic laboratory to perform the requested examination. Many cases of sudden death are attributed to central nervous system dysfunction; therefore it is necessary to remove the brain. Busy practitioners frequently do not take the time to remove this organ. There is a higher-than-normal probability of a poison being involved in sudden death cases, especially in equine insurance claims. For toxicologic examination, toxicants remaining in the GI tract must be considered, together with those in the major excretory organs, liver, and kidneys.
3. The correct amount and preservation of the sample depends on the specific test. Medicolegal cases demand that stringent photographic and written documentation, witnessing, and chain-of-custody protocol be followed during necropsy and sample collection. The amount of the sample is particularly important for chemical analysis. Sending insufficient quantities of sample may preclude multiple testing procedures. In general, 100 to 200 g of tissue or ingesta, 50 mL of urine, all fluid from both eyes, and 5 to 10 mL of blood or serum suffice for most analytic procedures. A midsagittal cut through the brain is performed to allow freezing of one half for chemical analysis and formalin preservation of the other. When poisoning is suspected, samples from possible sources such as feed, water, baits, poisonous plants, and suspect materials should be submitted. Usually 1 kg of each is adequate. Samples submitted for chemical analysis should be frozen in

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individual containers and labeled with date, location, and identity of the specimen. Specimens for bacteriology and virology are to be packaged separately and chilled. Dry ice should be avoided because gaseous carbon dioxide may kill some infectious agents. Tissues for histopathologic examination require fixing in 10% formalin with tissue slices 4 to 5 mm thick. Suspected poisonous plants are properly preserved by placing them in a plastic bag with wet paper towels or by drying them between sheets of paper.

Causes of Collapse and Sudden Death

Infectious Causes of Sudden Death in Horses (Box 14-1)

Foal actinobacillosis is an acute fulminant septicemia caused by *Actinobacillus equuli,* a gram-negative bacterium found in the upper respiratory tract, feces, and genital tract of normal adult horses. Other bacteria can also cause bacteremia/septicemia. Predisposing factors to foal septicemia with any agent include prematurity, failure of passive transfer, dam malnourishment during gestation, and environmental stress. A characteristic histologic finding is multiple bacterial emboli in renal glomerular capillaries without inflammatory infiltrate in neonatal foals. Acute anthrax may be rapidly fatal to horses after a period of excitement, depression, convulsions, and coma. Isolating the causative agent from blood confirms the diagnosis. Babesiosis is an erythrocytic parasite that may cause death within 24 hours. Identification of the organism in blood smears or complement fixation testing for parasite antibodies confirms the diagnosis.

Acute clostridial disease involving *Clostridium septicum, Clostridium chauvoei, Clostridium novyi,* and *Clostridium perfringens* has been associated with intramuscular injections of various parenterals such as ivermectin, vitamin B complex, vitamin E, prostaglandin, antihistamines, and flunixin meglumine when asepsis has been ignored. Clostridial myopathies are also associated with deep stab or puncture wounds. Botulism in foals (shaker foal syndrome) is caused by *Clostridium botulinum* (usually type B). Toxin may sometimes be demonstrated in feed and gut contents. The organism may be cultured from tissues or gut contents in toxico-infectious cases. *Clostridium sordellii* should be suspected in cases of foals having a history of colic, bloody diarrhea, and death within a few hours.[1] *C. perfringens* type C may induce a hemorrhagic enterotoxemia and death in foals as young as 4 days.[2] Severe intestinal lesions are caused by the beta-toxin produced by this species. Organisms may be demonstrated in smears of intestinal contents. *C. perfringens* type D also induces sudden death in the most aggressive foals in group-feeding situations. Similar enterotoxemia has also been associated with toxin-producing *Clostridium difficile*[3] and *Bacteroides fragilis.*[4]

Equine monocytic ehrlichiosis (Potomac fever), caused by *Ehrlichia risticii,* is a severe colitis with diarrhea and dehydration, followed by ileus, endotoxemia, and death in adult horses. Diagnosis is based on clinical findings combined with antibody and antigen detection using immunofluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) methods, respectively. Guttural pouch mycosis often results in nonfatal intermittent unilateral epistaxis. Occasionally a single episode of severe epistaxis from rupture of an aneurysm in the internal carotid artery may result in sudden death. Necropsy reveals blood in the nasal passages and guttural pouch with a diphtheritic plaque in the dorsocaudal aspect of the medial compartment. Salmonellosis is responsible for many cases of acute enterocolitis, especially when several animals are involved. The peracute syndrome may resemble colitis-X in mature horses with a course of 6 to 12 hours. Horses may die before diarrhea develops. Postmortem diagnosis is based on isolation of *Salmonella* spp. from bowel contents, bowel wall, and/or associated lymph nodes. Tyzzer disease is a rapidly developing fatal hepatitis of foals. The incidence is sporadic, and, because of the peracute development, clinical signs may not be observed before death. Diagnosis is based on histologic demonstration of the bacilli in bundles within hepatocytes surrounding necrotic areas.

Infectious and Parasitic Causes of Sudden Death in Ruminants

Infectious causes of sudden death range from acute septicemias and toxemias to rupture and release of abscess contents into the systemic circulation (Box 14-2). A liver abscess rupturing into the caudal vena cava; endocarditis, especially of the right atrioventricular valve, with subsequent pulmonary thromboembolism; and the rupture of a pituitary abscess are occasional causes of sudden death in individual animals. Acute anthrax and the clostridial infections, as well as ingestion of their preformed toxins, are more common causes of sudden death in ruminants. Anaplasmosis may cause sudden death in mature cattle under stress, without apparent icterus. In these cases anthrax may be mistaken for anaplasmosis because of the gross enlargement of the spleen. *Anaplasma* organisms may be demonstrated in blood smears, whereas newer diagnostic methods involve indirect fluorescent antibody and deoxyribonucleic acid probes. Of all domestic animals, cattle are the most susceptible to clostridial infections in which tissue invasion is present (blackleg). Because of this,

BOX 14-1

Infectious Causes of Collapse and Sudden Death in Horses

Acute colitis
Babesiosis
Botulism*
Clostridial myopathy
Clostridium difficile diarrhea
Clostridium perfringens enterotoxemia
Clostridium sordellii dysentery
Equine monocytic ehrlichiosis (Potomac fever)
Guttural pouch mycosis (hemorrhage form)
Hemorrhagic enterotoxemia in foals
Neonatal septicemia
Neonatal diarrhea
Salmonellosis*
Tyzzer disease

*Likely to involve several animals.

BOX 14-2

Infectious and Parasitic Causes of Collapse and Sudden Death in Ruminants

Abscess rupture at liver hilus or pituitary
Anaplasmosis* (B)
Anthrax*
Black disease, infectious necrotic hepatitis
Blackleg
Botulism*
Bovine lymphosarcoma
Clostridium hemolyticum, bacillary hemoglobinuria, redwater*
Clostridium perfringens, enterotoxemia
Coliform mastitis
Endocarditis
Leptospirosis
Listeriosis (C, O)
Liver flukes (O)
Malignant catarrhal fever (B)
Mycoplasmosis (C)
Neonatal septicemia
Neonatal diarrhea
Pasteurellosis, septicemic* (O)
Pseudorabies
Salmonellosis*
Septic metritis
Thromboembolic meningoencephalomyelitis* caused by *Histophilus somni* (B)

*Likely to involve several animals.
B, Bovine; *C,* caprine; *O,* ovine.

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vaccination status is important to ascertain. In addition, a fluorescent antibody test and isolation of the bacterium confirm the diagnosis. *C. perfringens* of various types is responsible for heavy losses caused by enterotoxemia in calves, lambs, kids, and feedlot cattle in apparent good health and on full feed. *C. perfringens* type D has been associated with focal symmetric encephalomalacia in lambs.[5] Coliform mastitis may result in peracute systemic disease and rapid death if not treated early. Diagnosis is based on culture of the organism from the affected gland. *Leptospira* may cause an acute septicemia with hemolytic anemia and rapid death in young ruminants. Demonstration of leptospires in fresh urine or by immunohistochemical staining of tissues may assist in making the diagnosis. The course of listeriosis in sheep and goats is rapid, and death may occur in 4 to 48 hours after the appearance of clinical signs.[6] Bacteriologic culture (isolation) or immunohistochemical staining of the organism in tissues is diagnostic. Acute fascioliasis *(Fasciola hepatica)* occurs seasonally in sheep and may cause sudden death within 6 weeks of initial infection. Anaerobic conditions induced by flukes in hepatic parenchyma predispose ruminants to the highly fatal clostridial hepatopathies such as *Clostridium hemolyticum* infection. Evidence of fluke infection is grossly visible. Individual animals with chronic or severe endoparasitism may present as acute collapse or sudden death if they are maintained in a herd/flock. This is especially true for South American camelids. Peracute malignant catarrhal fever (MCF) is a sporadic cause of sudden death in cattle that is usually associated with contacting ovine carriers, but most animals with MCF have diarrhea, keratitis, and other obvious clinical signs for days before death occurs. A septicemic form of mycoplasmosis has induced rapid death in kids.[7] Isolation of the causative organism is diagnostic. Sudden death is the usual manifestation of septicemic pasteurellosis in lambs. Pseudorabies is a consideration in sudden death cases of ruminants having contact with infected swineherds and feral hogs in the midwestern United States. Brain for microscopic examination and virus isolation should be submitted to confirm the diagnosis. Acute septicemic salmonellosis mainly affects young ruminants and may result in death within 24 hours. Acute septic metritis usually occurs secondary to complications of parturition. Endotoxic shock and rapid death may occur in severe cases. Thromboembolic meningoencephalomyelitis caused by *Histophilus somni* is a peracute septicemic disease of young calves. Many cattle die without showing clinical signs. It may be associated with prior respiratory problems in the herd or feedlot. Typical lesions or isolation of the causative organism is diagnostic. Adult lymphosarcoma associated with bovine leukemia virus can be a cause of sudden cardiac death when neoplastic cells infiltrate the cardiac conduction system.

Metabolic and Nutritional Causes of Sudden Death in Horses

Hypocalcemia in horses is most common in lactating mares, but it also occurs after transit. Animals may develop tetany, synchronous diaphragmatic flutter (thumps), muscle tremors, and sweating. Low serum calcium is diagnostic. White muscle disease (nutritional myodegeneration) is associated with selenium and vitamin E deficiency. Sudden death in adult horses after severe exercise is attributed to degenerative lesions in cardiac and skeletal musculature. Death in foals may occur within hours from pulmonary edema and heart failure. Diagnosis is based on measuring whole blood and/or liver selenium and vitamin E concentrations.

Metabolic and Nutritional Causes of Sudden Death in Ruminants

Metabolic and nutritional diseases are not often considered in cases of sudden death. The primary lesion in a disorder of cattle known as "falling disease" is progressive fibrosis of the myocardium. Sudden deaths characteristic of the disease are attributed to exercise-induced heart failure.[8] Rapid development of hypocalcemia is usually associated with the onset of lactation in cattle, with stressful circumstances in older lactating ewes, or with transport associated with fasting and weather stress. Hypomagnesemia may also develop under similar conditions, especially in ewes and cows in heavy lactation and on lush grass pastures. Polioencephalomalacia occurs most commonly in animals raised under intensive production techniques and can sometimes be traced to excessive sulfates in the diet and/or water. The clinical course tends to be most rapid in sheep. Severe cases of ruminal lactic acidosis, especially in animals unaccustomed to high levels of soluble carbohydrate in the diet, may induce death within 24 hours. Nutritional myodegeneration of the heart is a frequent cause of sudden death in young ruminants born to dams fed selenium-deficient diets during gestation. Diagnosis is based on histopathology and measurement of liver selenium concentration. Some cases of sudden death associated with myocardial necrosis are idiopathic.[9]

BOX 14-3

Cardiovascular Causes of Collapse and Sudden Death in Horses

Aortic ring (root) rupture
Central nervous system embolism
Coronary occlusion
Endocarditis
Massive abdominal or thoracic hemorrhage
Myocarditis
Pericardial rupture
Splenic rupture
Thrombi of verminous origin
Uterine arterial rupture

Cardiovascular Causes of Sudden Death in Horses

Diagnosis of sudden death caused by cardiovascular failure depends on a careful and methodic technique (Box 14-3). Usually a single animal is affected. Necropsy is necessary to identify the location and characteristics of the lesion, and further analysis may be necessary to establish the exact cause of death. Aortic ring (root) rupture in stallions is usually seen early in the breeding season, occurring immediately after servicing a mare. Rupture of the aorta may occur just distal to the aortic valve, resulting in cardiac tamponade and rapid death. Acute central nervous system embolism results from detached thrombi originating from endocarditic lesions or accidental intracarotid injection. Cerebral hematoma also can result from intracarotid injection. Endocarditis, especially of the aortic valve, may result in coronary thromboembolism and myocardial infarction. Coronary occlusion as a result of damage induced by *Strongylus vulgaris* larvae can be diagnosed by the presence of the larvae in the coronary thrombus. Massive abdominal or thoracic hemorrhage is found at necropsy, and the cause may be difficult to ascertain.[10] Racehorses mostly die from severe hemorrhage in the thorax. Myocarditis in horses up to 4 years of age resulting from recent respiratory infection may be diagnosed with histopathologic examination. Pericardial rupture and the associated heart damage is a result of violent trauma. Splenic rupture and fatal hemorrhage rarely occur because of the protection afforded by the thoracic wall. Massive thrombi of verminous origin have been observed in young horses that die suddenly while exercising. Uterine arterial rupture involving ovarian, uteroovarian, uterine, or external iliac arteries is observed in older mares, with death ensuing in 30 minutes to 20 hours postpartum.

Physical Causes of Sudden Death in Horses

Fatal air embolism can result from any open vein above the heart. Open needles or catheters and severe head wounds involving teeth and sinuses have resulted in sudden death from air emboli. Air is aspirated into the vein by the Venturi effect from blood surging past a portal and creating the necessary negative pressure to aspirate air into the vein. Between 700 and 6000 mL of air may produce a fatal air embolus in the right cardiac ventricle, where it obstructs the pulmonary artery. Cecal or colonic rupture in parturient mares results in sudden death within 8 hours.[11]

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Physical Causes of Sudden Death in Ruminants

Physical causes of sudden death often display gross evidence indicative of the diagnosis. Abomasal bloat occurs in calves and lambs drinking excessive quantities of warm milk replacer at infrequent intervals. Abomasal ulcers may occasionally perforate and cause rapid death in calves or adult cattle. Ruminal bloat is one of the more common physical causes of sudden death in intensively raised ruminants. When differentiating postmortem from antemortem bloat, note that bloat is the primary cause of death when there is congestion and hemorrhage in the anterior parts of the carcass and edema in the scrotal and ventral perineal areas. Bloat and hypersalivation are the most consistent clinical signs seen in cases of choke. Attempts to swallow firm fruits, tubers, or green ears of corn may occlude the esophagus and result in rapid ruminal tympany and death.

Sudden death is a major concern in feedlots because most such deaths occur in cattle near market weight. GI disturbances are seen with a high frequency in cattle in the late stages of the feeding program. Sudden death is the result of interactions among factors such as rumen acidosis, bloat, and endotoxemia.

Exposure to high-voltage currents in the form of lightning or electrical transmission wires may cause instantaneous death. The diagnosis of lightning strike is based on a history of an electrical storm, linear singe marks, food in the mouth, several animals dead in the same vicinity, and evidence of lightning damage in the immediate environment. Gunshot wounds may be deliberate or accidental, but in any case involving sudden death the head or heart is the usual target. Bullets may pass through or lodge in obscure locations, making retrieval difficult. Radiography can assist in locating a bullet. Heatstroke is a sporadic condition characterized by hyperthermia and collapse. High humidity, dehydration, obesity, and poor heat tolerance associated with young or old age are all factors that predispose animals to overheating. Fleeced animals such as sheep and South American camelids often succumb to heatstroke if the time of shearing is not appropriate. Summer slump induced by consumption of endophyte-infected fescue potentiates the heat intolerance. Internal bleeding may cause sudden death when a uterine artery is ruptured during parturition. This is readily apparent on necropsy. Tracheal edema, or "honker" syndrome, of feeder cattle is seen sporadically in feedlot cattle of the southern plains during hot weather. The pathoanatomic basis of this syndrome is extensive edema of the mucosa and submucosa of the lower trachea, with attendant dyspnea and obstructive asphyxiation. Increased respiratory movements stimulated by hot weather or exercise trigger the clinical illness, especially in heavy cattle during the latter part of the feeding period.[12] Traumatic reticuloperitonitis or reticulopericarditis is associated with lack of oral discrimination in cattle. Sudden death occurs because of acute hemorrhage or dysrhythmia when the heart is punctured.

Toxic Causes of Sudden Death in Horses

Toxic causes of sudden death are frequently related to management practices. An increase in specific disease syndromes or sudden death in a population of livestock with common potential exposures suggests involvement of a toxicant. Investigation of the premises and a familiarity with poisonous plants and pesticides used in the practice area should help narrow the list of possible causative agents (Box 14-4).

Horses ingesting a lethal dose of the avicide 4-aminopyridine have died within 2 hours of the onset of clinical signs. Diagnosis is based on chemical analysis of stomach contents. Fatal doses of arsenic-containing pesticides may induce cardiovascular collapse and death in horses within hours of ingestion. The presence of edema and fluid in the GI tract suggests the diagnosis, and chemical analysis of GI tract contents, liver, or kidney confirms it. Black flies swarm where swiftly flowing water provides the aeration necessary for the development of larvae. Massive attacks of these blood-sucking insects can rapidly kill livestock because a toxin present in the saliva of the flies increases capillary permeability.[13] Cantharidin poisoning can occur after ingestion of 4 to 5 g of blister beetles. Lesions suggestive of cantharidin toxicosis include blistering and ulceration of mucous membranes of the GI and urinary tracts and myocardial degeneration and necrosis. Sustained hypocalcemia and hypomagnesemia are features of the clinical pathology consistent with blister beetle poisoning. Identification of blister beetles in the hay and chemical analysis of urine and GI contents are suitable for diagnostic confirmation. In the past, ferrous fumarate, present in digestive inoculate and administered to foals immediately after birth, resulted in death in some cases in 12 to 96 hours. This illustrates the acute toxicity of iron to young animals in particular. Lesions induced were those of gross liver damage. *Fusarium moniliforme*–contaminated corn causes rapid death in horses after the sudden onset of bizarre neurologic deficits and behavioral effects. The lesion of this mycotoxin-induced leukoencephalomalacia is liquefactive necrosis in the subcortical white matter.

High intravenous doses of insulin[14] and potassium[15] induce sudden death without significant lesions. Chemical detection is often overlooked and difficult to perform and interpret in cases of deliberate poisoning. Immediate analysis of blood and circumstantial evidence of needle punctures in the jugular furrow are of diagnostic value. Monensin is quite toxic to horses, and fatal poisoning can occur within 12 hours of ingestion of poultry feed containing 100 g/ton or cattle premixes containing 300 g/ton. Lesions related to heart failure are seen on postmortem examination. Tissues collected for microscopic examination should include heart and diaphragm. Chemical analysis of feed samples and stomach contents will confirm exposure. Toxic gases such as nitrogen dioxide, hydrogen sulfide, and carbon monoxide may be responsible for sudden death in horses housed in poorly ventilated buildings with associated gas sources nearby. Organophosphate and carbamate insecticides may induce acute intoxication and death within hours. Diagnosis is based on a history of exposure, determination of acetylcholinesterase activity in the caudate nucleus of the brain, and chemical detection of specific compounds in gut contents.

Circumstances surrounding toxic plant ingestion and diagnosis of intoxication are described in the ruminant section of this chapter. Ingestion of wilted *Acer rubrum* (red maple) leaves and other *Acer* spp. may induce massive methemoglobinemia, causing marked tissue anoxia and death.[16] Red maple poisoning usually occurs during the late summer and early fall when trees are in full leaf. Ready access to wilted leaves follows windstorms. *Ricinus communis,* or castor bean, is also unique to this section. Seeds of this plant contain a phytotoxin

BOX 14-4

Toxic Causes of Collapse and Sudden Death in Horses*

4-Aminopyridine (Avitrol), an avicide
Arsenic
Black flies
Cantharidin*
Ferrous fumarate
Fusarium monoliforme–associated mycotoxicosis
Insulin and potassium
Monensin*
Nitrogen dioxide
Organophosphate and carbamate insecticides
Toxic plants
Acer rubrum (red maple)
Acer negundo (female box elder)
Blue-green algae*
Cicuta spp. (water hemlock)
Conium maculatum (poison hemlock)
Cyanogenic plants
Melilotus spp. (sweet clover)
Nerium spp. (oleander)
Nicotiana spp. (tobacco)
Ricinus communis (castor bean)
Taxus spp. (Japanese yew)

*Likely to involve several animals.

called *ricin,* which causes severe enteritis and rapid death in horses. About 150 beans (50 g) are sufficient to kill a 450-kg horse. Diagnosis can be verified by finding a toxic amount of ingested seeds in the gut contents.

Toxic Causes of Sudden Death in Ruminants

Intoxication of livestock is frequently suggested as a simple explanation for complex situations involving sudden death. Suspicions are warranted when a large number of animals die suddenly within a short time. Toxicants should be considered when the appearance of a disease or sudden death is temporally associated with a change in the environment (Box 14-5). An accurate diagnosis in many of these cases requires qualitative and quantitative analyses for suspect poisons. Selecting toxicants for which to analyze requires reasoned judgment supported by an extensive investigation of the environment and postmortem findings.

BOX 14-5

Toxic Causes of Collapse and Sudden Death in Ruminants*

4-Aminopyridine (Avitrol), an avicide
Anticoagulants
Arsenic
Botulism*
Carbamates
Carbon monoxide
Chlorinated hydrocarbons
Copper (B, O)
Crude oil
Gossypol*
Hydrogen sulfide gas*
Ionophores*
Lead*
Metaldehyde
4-Methyl-imidazole, bovine bonkers syndrome (B, O)
Nicotine sulfate
Nitrogen dioxide gas*
Organophosphates
Selenium, parenteral overdose
Strychnine
Urea, nonprotein nitrogen*
Water deprivation, sodium ion toxicity
Toxic plants
Aconium spp. (monkshood)
Asclepias spp. (milkweed)
Blue-green algae*
Calycanthus fertilis (bubby bush) (B)
Cicuta spp. (water hemlock)
Conium maculatum (poison hemlock)
Cyanogenic plants
Delphinium spp. (larkspur) (B)
Drymaria pachyphylla (inkweed)
Halogeton glomeratus (halogeton) (O, B)
Kalmia spp. (laurels)
Kochia scoparia (summer cypress)
Laburnum anagyroides (golden chain tree)
Lupinus spp. (lupine) (O)
Melilotus spp. (sweet clover)
Nerium spp. (oleander)
Nicotiana spp. (tobacco)
Nitrate-accumulating plants
Perilla frutescens (perilla mint)
Phalaris spp. (canary grass) (O)
Sarcobatus vermiculata (greasewood) (B, O)
Solanum spp. (nightshades)
Taxus spp. (yew)
Xanthium spp. (cocklebur) (B, O)
Zigadenus spp. (death camas) (O)

*Likely to involve several animals.
B, Bovine; *O,* ovine.

The avicide 4-aminopyridine is usually formulated with corn, making it a palatable poison for nontarget herbivorous livestock. Diagnosis is confirmed by chemical analysis of rumen contents or urine. Anticoagulant intoxication may induce sudden death when hemorrhage occurs in the cranial vault, abdominal cavity, pericardial sac, mediastinum, or thorax. The antemortem or postmortem sample for chemical analysis is whole blood or liver. Failure to detect an anticoagulant is not unusual because of the time lag between consumption and presence of the clotting defects, as well as the metabolism of the compound. Arsenic derivatives are a significant hazard to ruminants, especially in areas where such chemicals are widely used as cotton desiccants. Postmortem findings are consistent with microvascular injury to the GI tract. Diagnosis is confirmed by chemical analysis of rumen contents, liver, or kidney. In rare cases large doses of botulinum toxin may cause sudden death in ruminants. Sources of the toxin include the bones of dead animals eaten by osteophagic livestock, poultry carcasses in manure fed to cattle, stagnant pond water, animal tissues in silage or baled hay, and improperly ensiled silage or haylage.

Acetylcholinesterase-inhibiting agents such as the carbamate and organophosphate pesticides can kill livestock within hours. Agricultural practices result in the use of these pesticides in close proximity to livestock. This situation may lead to disaster. Acetylcholinesterase activity in the caudate nucleus of the brain is readily determined and interpreted, and specific compounds may be identified in rumen contents. Toxic gases such as carbon monoxide, hydrogen sulfide, and nitrogen dioxide become important differentials for sudden death in ruminants housed in poorly ventilated buildings, particularly over waste pits. Chlorinated hydrocarbon pesticides do not enjoy the widespread use they once did; however, old containers remain in obscure locations on many farms. When acute intoxication with these compounds is suspected, samples for analysis should include liver, brain, and rumen contents. In subacute cases, fat and milk are appropriate samples. Copper toxicosis is a frequent cause of sudden death in sheep and has been reported in cattle fed chicken litter.[17] Cattle feeds normally contain twice as much copper as sheep feeds and may cause copper toxicosis in sheep. Copper from treated fence posts also may poison sheep that either chew the posts or ingest contaminated forage in the vicinity. Samples required for chemical confirmation consist of whole blood or serum and liver. Close proximity of livestock to petroleum exploration and production activities in the major oil-producing states results in a variety of clinical problems, including sudden death.[18] Consumption of the more volatile petroleum constituents may induce rapid bloating and coating of the respiratory membrane when these substances are aspirated into the lungs. Gossypol toxicosis reportedly causes death without premonitory signs in calves (occasionally cows) and lambs fed cottonseed products containing this toxic pigment.[19,20] Poisoning appears abruptly after livestock have been fed the gossypol-containing ration for a period of weeks to months. Sudden death is attributed to heart failure. Postmortem examination reveals edema, centrilobular hepatic necrosis, and an enlarged heart. Ionophores may induce sudden death in species exposed to large overdoses, but delayed death is the usual course. Conditions conducive to lethal overdose include insufficient mixing or top dressing with monensin- or lasalocid-supplemented mineral. Degenerative-to-necrotic lesions in the heart are compatible with a diagnosis of ionophore poisoning.

Acute lead intoxication is another differential from the list of possibilities in sudden death cases. Lead poisoning is the most common toxicosis in cattle. Blood, liver, and kidneys are suitable specimens for lead analysis. Metaldehyde is an uncommon poison for ruminants; however, intoxication in cattle has occurred in low wetland areas where the chemical is used as a molluscicide. The palatability of metaldehyde baits promotes ingestion. Ammoniation of high-quality forage such as forage sorghum and Sudan grass, cereal grain, brome, and fescue hays is responsible for bovine bonkers syndrome, reportedly caused by the formation of 4-methyl-imidazole.[21] This sporadic intoxication causes central nervous system derangement and rapid death in cows and nursing calves. Ruminants may be

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poisoned by nicotine sulfate from ingestion of solution, treated foliage, and food or water from contaminated containers. The onset and progression of the syndrome are rapid, and death may occur within hours. Detection of nicotine in urine is easily performed by most toxicology laboratories. Iatrogenic selenium toxicosis and death in young ruminants can result from parenteral administration of excess doses. Rapid onset of violent tetanic seizures ending in death characterizes strychnine toxicosis. Samples suitable for chemical analysis include rumen contents, liver, and urine.

Urea toxicosis is a frequent cause of sudden death in feedlot livestock. In one particular case, 48 feedlot steers died within 2 days of delivery of a new lot of feed supplemented with urea.[22] Unusually high rumen pH, excess ammonia in serum, rumen contents, and eyeball fluid support the diagnosis. Water deprivation, with attendant sodium ion intoxication, is a known cause of sudden death in ruminants.[23] Some cases occur in hot weather, but frozen water supplies in cold weather can be equally as devastating.

Poisonous plant problems frequently present a unique set of circumstances associated with their ingestion. Overgrazing of pastures is probably the most significant factor affecting the ingestion of toxic plants. Other situations conducive to poisonous plant ingestion include lack of suitable forage in periods of drought and the incorporation of toxic forbs in hay or green chop. Plants normally avoided because of poor palatability may become acceptable when frosted or sprayed with herbicide. Toxic plants may also be the first green plant available early in the spring, when livestock are hungry for anything green and succulent. Livestock trailed or transported for long distances without food or water and then suddenly introduced to new pasture may fail to avoid toxic plants and often will eat anything within immediate reach. In general, diagnosis of plant poisoning is based on availability, grazing evidence or presence in the hay, and the existence of plant parts in the rumen contents. Diagnostic lesions are usually lacking, and analytic methods for toxic components are severely limited.

Aconitum spp. (monkshood) are rarely a cause of sudden death because of their limited availability. *Delphinium* spp. (larkspur), however, are closely related to monkshood and are responsible for more cattle losses in the western United States than any other poisonous plant. Larkspur grows in dense stands in the mountainous West and is readily consumed, especially during an early stage of growth. Mature stands are less palatable and not as toxic. Cattle poisoned by larkspur are often found close to a stand, collapsed, and bloated. Death from the cardiotoxic and neuromuscular blocking effects may occur within a few hours of ingestion. Sheep are less susceptible to larkspur and are seldom poisoned by it, partly because of their different grazing habits.[24] *Asclepias* spp. (milkweed) contain either cardioactive glycosides or neurotoxic compounds.[25] The most toxic species reside in the western and southwestern United States. These plants are not very palatable but are somewhat less objectionable when dried. Livestock will graze them in a drought, but the biggest problem is contamination of hay or green chop. Blue-green algae may cause sudden death in all classes of livestock within minutes of ingestion of toxins from certain neurotoxic species. Toxins from other hepatotoxic species may require 24 hours to induce death. Toxic blooms occur sporadically during certain environmental conditions of late summer and fall. Diagnosis is usually based on a history of exposure to a concentrated bloom, but some laboratories perform chemical and biological assays.

Calycanthus spp. (bubby bush) contain an alkaloid similar in structure and mechanism of action to strychnine. These species are of minor importance to the livestock industry in the Southeast and West but have induced death in cattle. Seeds and other plant parts may be identified in rumen contents. *Cicuta* spp. (water hemlock) may induce violent convulsions and death within an hour. Intoxication is most common in early spring, when plants growing along waterways are easily uprooted and the tuberous parts are eaten. A single root system from a large plant can kill a cow. This is one of the most toxic plants in North America, and it has been responsible for the deaths of numerous livestock and humans. *Conium maculatum* (poison hemlock) grows throughout the United States. Cattle are most sensitive, and sheep are relatively resistant. Poisoning is usually associated with heavily grazed pastures.

Cyanogenic glycosides are present at toxic concentrations in more than 250 plant genera, including *Sorghum, Prunus, Triglochin,* and *Linum.* Ruminants are especially susceptible to these glycosides because they possess the microorganism enzyme systems necessary for rapid liberation of hydrocyanic acid. Death may occur within 15 to 30 minutes of ingestion. Hyperoxygenated venous blood will be cherry red and slow to clot, and rumen contents may have the odor of almond extract. Samples of forage, blood, and rumen contents should be collected immediately, placed in airtight containers, and frozen for analysis. Negative results are often questionable because of the highly volatile nature of hydrogen cyanide. *Drymaria pachyphylla* (inkweed) has caused sudden death in cattle in the southwestern United States. The differential diagnosis in this part of the country includes anthrax. Diagnosis is based on examination of rumen contents for plant parts.

Halogeton glomeratus is a soluble oxalate-containing plant that grows best in disturbed soil along roadsides in the western intermountain states. *Sarcobatus vermiculata* (greasewood) grows in semiarid regions of the West. It also contains toxic levels of soluble oxalate. Unadapted sheep are most frequently intoxicated with these plants, and death may occur within 9 to 11 hours of onset of intoxication. Sudden death results from hypocalcemia and inhibition of cellular respiration. Postmortem findings include hemorrhagic rumenitis, hydrothorax, ascites, and the presence of oxalate crystals in the kidney and rumen wall. *Kalmia* spp. (laurel) are an occasional problem in winter or early spring, when they are the only conspicuously green plant available. Laurel grows in the wild in the eastern and western regions of the United States. Death may occur in 12 to 14 hours. Fragments of glossy, leathery leaves may be visible in rumen contents. *Kochia scoparia* (summer cypress or burning bush) sporadically causes a thiamine-responsive polioencephalomalacia in cattle. *Laburnum anagyroides* (golden chain tree) is a large ornamental shrub considered to be the second most poisonous plant in Great Britain. It also grows in much of the United States. The shrub contains quinolizidine alkaloids that may induce rapid death from respiratory failure. *Lupinus* is a genus with about 200 species in North America. There is considerable seasonal variation in toxicity, with the toxic species presenting a problem when plants are immature or when they have reached the seedpod stage. Acute intoxication and rapid death are likely only when large quantities of seeds are ingested within a short time. Toxic species cause more deaths in sheep than any other plant in Montana, Idaho, and Utah. Improperly cured hay and silage derived from *Melilotus* spp. (white and yellow sweet clover) may cause sudden death in cattle when hemorrhage occurs in the cranial vault, pericardial sac, mediastinum, or thorax. Induction of the disease requires consumption of the moldy forage for several weeks to allow sufficient depletion of vitamin K–dependent clotting factors. *Nerium* spp. (oleander) are widely cultivated in the South and West. Toxic in the green or dry state, these plants may border hay fields, and significant mortality of livestock may occur when dropped leaves or trimmings are incorporated into forage. Livestock are often poisoned when prunings are mixed with grass clippings and the bitter taste is disguised. Diagnosis is based on evidence of consumption and identification of plant parts in rumen contents.

The genus *Nicotiana* contains toxic species of wild and cultivated tobacco. Poor palatability usually hinders consumption; however, opportunities for intoxication and death sometimes occur in areas of the West where forage is scarce and in parts of the country where tobacco is cultivated. Nitrate-accumulating plants include certain annuals, weeds, and cool-season crops and grasses. Notable examples include pigweed, lamb's-quarters, Sudan grass, and oat hay. Under the right environmental conditions most plants can accumulate toxic concentrations of nitrate. Plant-associated nitrate poisoning is a serious problem only in ruminants because of the nitrate-reducing ability of rumen microbes. Onset of nitrate intoxication is rapid, and

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death may result within 6 to 24 hours of rapid ingestion of a toxic dose. Diagnosis is based on a brownish cast to the viscera and blood, together with chemical analysis of serum, aqueous humor, and forage for nitrate concentration.

Acute bovine pulmonary emphysema is associated with an abrupt change from dry range forage to lush green pasture high in L-tryptophan concentration. Less commonly, the pulmonary toxins of *Perilla frutescens* (perilla mint) can induce dyspnea and death in a few hours. Necropsy reveals incomplete collapse of lungs that are heavy and firm, with froth-filled airways. Histologic examination shows a proliferation of type II pneumocytes. *Phalaris* spp. (canary grass) have been reported to have caused sudden collapse and death of sheep in California.[26] Sheep that had been grazing a field containing canary grass were herded a short distance when six ewes collapsed and died. Bilaterally symmetric, greenish-gray discoloration was seen in the midbrain. The same gross discoloration was also seen in the renal cortex. Microscopic examination confirmed the presence of intracytoplasmic accumulation of this granular pigment. *Solanum* spp. (nightshades) grow throughout the United States, especially in waste areas and overgrazed pastures. Rapid ingestion of large quantities of highly toxic fruit can result in coma and rapid death. *Taxus* spp. (yew) poisoning in ruminants commonly results in sudden death. Poisoning is most likely to occur when ruminants are pastured adjacent to residential areas where yew is a common ornamental shrub. Diagnosis is based on evidence of exposure and identification of yew leaves in rumen contents. *Xanthium* spp. (cocklebur) are most toxic at the cotyledonary stage of growth. These species may induce death in calves within 12 hours of onset of clinical intoxication. Hypoglycemia and centrilobular hepatic necrosis are consistent findings. *Zigadenus* spp. (death camas) are of major importance to sheep grazing on western ranges. These plants begin growth in early spring, presenting a significant hazard at this time.[27]

Miscellaneous Causes of Sudden Death in Horses

Allergic reactions capable of causing sudden death include rupture of warble fly larvae. Warble fly larvae are seldom able to penetrate equine skin, and the fully matured larvae either die or are killed when the horse is saddled or harnessed. The ruptured larvae induce anaphylactic shock and pulmonary edema. Foam in the airways is found on necropsy. Penicillin or other antibiotics may cause an anaphylactic reaction with a similar outcome.

Perinatal sudden death may occur in foals as a result of meningeal hemorrhage caused by birth trauma. The sudden onset of profuse, watery diarrhea and rapid development of hypovolemic shock characterize colitis-X. A severe necrotic typhlitis is seen at necropsy, with destruction of colonic and cecal mucosa. Diaphragmatic rupture and hernia are associated with violent exercise or trauma, with or without bowel herniation. Electrocution occurs when a horse chews through or comes into contact with an uninsulated hot wire while well grounded. Death is instantaneous, usually with negative necropsy findings. Lightning strike may reveal burning or singeing of skin, hair, or underlying tissue. GI maladies that may cause sudden death include volvulus, intussusception, torsion, incarceration, gastric rupture from grain overload, tympanites, and small intestine rupture from ascarid impaction.

Gunshot wounds may be another cause of sudden death that is surprisingly difficult to verify, because bullet retrieval is necessary to establish the diagnosis. Tracking and finding a small metal object lodged in tissue is a time-consuming task at best. Heat or work stress is seen in horses in hot, poorly ventilated quarters or in poorly conditioned horses overworked in hot, humid weather. Collapse and coma are followed by death in a few hours. Necropsy reveals skeletal and cardiac muscle damage, GI ulceration, and renal necrosis. In pregnancy, unrecognized and untreated torsion of the gravid uterus may result in sudden death.

Exercise-induced respiratory tract injury may cause sudden death in well-conditioned horses.[28] Epistaxis and pulmonary hemorrhage occur at the peak of training, with most cases being of little concern. However, in fatal cases horses that die immediately after exercise often have subpleural hemorrhages in the caudal lung lobes, and rupture of these hematomas has resulted in extensive intrathoracic hemorrhage and sudden death. Rupture of lung tissue while exercising also may result in fatal hemorrhage.

Serum sickness (acute hepatitis) can be traced to administration of biologics of equine origin 50 to 90 days before the onset of clinical signs. Death may occur within 12 to 48 hours. The main lesion seen is liver necrosis with discoloration and accentuation of the lobular pattern on the cut surface. Fracture of the junction between the basisphenoid and basioccipital bone usually results from rearing over backward and striking the poll on the ground.

Miscellaneous Causes of Sudden Death in Ruminants

Fatal anaphylaxis occurs in sensitized animals after parenteral use of drugs or vaccines. This is most common with the penicillins and vaccines containing gram-negative bacteria or cell walls. Anaphylactic shock may also be an outcome of blood transfusion reactions. Immune-mediated hemolytic anemia (neonatal isoerythrolysis) from ingestion of colostrum-containing antibodies against a neonate's erythrocytes may induce sudden death if the specific antibody concentration is sufficiently high. A sudden death syndrome occurs in feeder cattle on high-concentrate diets. It usually occurs in warmer months and is limited to cattle fed high-concentrate rations for several weeks.[29] A malignant tumor that has been associated with sudden death is the thymoma, or thymic lymphosarcoma, seen most commonly in old goats. It appears as a large, pale, fleshy mass in the cranial mediastinum.[30]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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PART THREE

Disorders and Management of the Neonate

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• CHAPTER 15

The Peripartum Period

GUY D. LESTER, *Consulting Editor*

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Assessment of the Mare during Late Gestation

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An estimated 25% to 40% of mares that are bred do not produce a live foal.[1-3] Many factors contribute to this poor outcome, including infertility, early fetal loss, abortion, stillbirth, and perinatal death.[2] During late gestation, two of the most important causes of reproductive loss are fetoplacental infection and complications of delivery including dystocia and perinatal asphyxia.[2,4] As mares age, their pregnancy and foaling rates decline and their foals experience higher morbidity and mortality rates and decreased athletic ability.[1,3]

A 1997 National Animal Health Monitoring System (NAHMS) study of 7320 foals estimated a mortality rate of 1.7% within the first 48 hours of a live birth.[5] This includes an estimate of euthanasia and spontaneous deaths. Sepsis, asphyxia, and dysmaturity, including prematurity and postmaturity syndromes, are the leading causes of neonatal foal mortality during the first 2 weeks of life.[6] Despite dramatic advances in neonatal intensive care, many foals still die—not because their primary problem is untreatable, but because veterinary intervention was delayed, delivery was unattended, neonatal compromise was not recognized in a timely fashion, or critical care was unavailable or not economically feasible. Foals surviving severe peripartum illness often experience increased morbidity associated with chronic infections, suboptimal growth, or developmental orthopedic disease. The three periparturient events that have the most devastating effect on neonatal survival are hypoxia, infection, and derangement of in utero development. These events can result in behavioral abnormalities, multi-organ system failure, neonatal death, abnormal fetal development, or premature delivery.

Many of the periparturient events associated with increased fetal/neonatal morbidity and mortality have been identified in the mare (Box 15-1). Biochemical and biophysical techniques for monitoring fetoplacental well-being have been developed for use in the pregnant mare.[7-10] Mares with high-risk pregnancies should be identified early, treated appropriately, and monitored carefully through the birth process. Accurate assessment of fetal well-being is complicated and handicapped by the size of the dam and fetus.

Mares experiencing problem pregnancies can be assigned to one of three categories: (1) mares with histories of abnormal pregnancies, deliveries, or newborn foals; (2) mares at risk for a problem with the current pregnancy because of systemic illness or reproductive abnormality; and (3) mares with no apparent risk factor, which experience an abnormal periparturient event.[10] A list of important perinatal risk factors is presented in Box 15-2. Ideally, mares with high-risk pregnancies should receive some type of late-gestation fetal monitoring or at least be watched carefully during late gestation and attended at the delivery. Personnel attending the delivery of a high-risk foal should be trained in resuscitation techniques (see later).

A variety of biochemical and biophysical parameters can be measured in the late-term mare or fetus. Measurement of maternal progestagen concentrations in plasma may provide an indicator of fetal well-being. Maternal progestagen concentrations are relatively stable between days 150 and 315 of gestation, rising sharply over the remainder of the pregnancy, before falling greatly in the last 1 to 2 days prior to parturition. Progestagens are synthesized by the uteroplacental tissues from pregnenolone (P5) derived from the fetus.[11] Two abnormal progestagen patterns have been described.[12-15] In acute maternal illnesses, such as colic or torsion of the uterus, the progestagen concentration declines hours to days prior to abortion. In these mares the concentration may fall to less than 2 ng/mL.[15] In chronic disease states, such as laminitis or placentitis, there is a premature rise in the plasma progestagen concentration that can persist for weeks before abortion or premature delivery.[12] It has been suggested that a premature increase in maternal progestagens could reflect hastened or precocious fetal maturation. Removal of the stressful event can lead to normalization in progestagen concentrations and the subsequent delivery of a normal full-term foal. Progesterone RIAs and ELISA assays can be used to quantitate progestagens because of significant cross-reactivity. Measurement of progestagens may therefore be indicated to determine the need for progestin supplementation.[16]

Relaxin is a marker of fetoplacental well-being and periparturient complications in the mare.[17] The placenta is the sole source of circulating relaxin in mares.[18] In healthy pregnant mares, relaxin concentrations increase from about day 80 to a peak of 80 to 100 ng/mL at day 175, a value that persists until birth.[19,20] A recent study of mares with normal pregnancies reported slightly lower values over the final 7 weeks of gestation, with a mean weekly value of 63 ng/mL.[17] Plasma values drop at delivery and are cleared within 48 hours of passage of the fetal membranes. In mares with problematic pregnancies, low relaxin levels during late pregnancy have been indicative of placental insufficiency associated with a variety of causes including twinning, fescue toxicosis, oligohydramnios, placentitis, and pituitary neoplasia.[17] The variability in values make it difficult to rely on relaxin concentration as a marker of treatment efficacy in problem pregnancies.[17] Elevated concentrations of equine fetal protein were associated with twinning, placentitis, premature placental separation, uterine trauma, and fetal death, but further studies are required before this test can be applied accurately in a clinical setting.[10]

Several studies have demonstrated that ultrasound-guided transabdominal and allantocentesis can be performed relatively safely in the late gestation mare as long as the procedure is performed

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BOX 15-1

Common Causes of Abortion, Stillbirth, and Perinatal Death in Horses

Infectious Problems (In Order of Frequency)

Fetoplacental infection
- Bacterial
- Viral
- Fungal
- Unidentified

Noninfectious Problems (In Order of Frequency)

Neonatal asphyxia not associated with dystocia
Neonatal asphyxia associated with dystocia
Placental edema
Premature placental separation
Twin pregnancies
Contracted foal syndrome
Other congenital malformations
Umbilical cord abnormalities
Placental villous atrophy
Eastern tent *(Malacosoma americanum)* or processionary caterpillar *(Ochrogaster lunifer)* ingestion

Adapted from Giles RC, Donahue JM, Hong CB, et al. 1993. Causes of abortion, stillbirth, and perinatal death in horses: 3,527 cases (1986-1991). J Am Vet Med Assoc 203:1170.

BOX 15-2

Conditions Associated with the High-Risk Foal

Maternal Conditions

Past history of:
- Foals with neonatal isoerythrolysis, perinatal asphyxia syndrome, or congenital malformations
- Prematurely born, postterm foals that appear premature, or asphyxiated foals
- Dystocia or premature placental separation
- Foal rejection
- Recent exposure to infectious diseases associated with abortion and stillbirths, such as equine herpesvirus, viral arteritis, or *Leptospira* spp.

Systemic problems such as:
- Fever
- Anemia or hypoproteinemia
- Endotoxemia
- Gastrointestinal crisis, such as large bowel torsion
- Malnutrition
- Severe systemic infection
- Laminitis
- Prolonged recumbency from a variety of neurologic or musculoskeletal problems
- Excessive medication administration
- Persistent therapy with altrenogest or pergolide
- Prolonged transport before parturition

Reproductive, mammary gland, or localized problems, such as:
- Severe endometrial fibrosis
- Hydrops allantois or amnii
- Purulent vaginal discharge
- Prepubic tendon rupture
- Pelvic injuries
- Agalactia, such as from grazing on fescue pastures or treatment with pergolide
- Failure to produce good quality colostrum
- Premature lactation

Abnormalities of Labor or Delivery in Current Pregnancy

Premature parturition
Abnormally long gestation
Prolonged labor
Induction of labor
Dystocia
Early umbilical cord rupture; umbilical cord abnormality
Cesarean section
Premature placental separation

Neonatal Abnormalities

Meconium-stained fluid or neonate
Placental disease (e.g., placentitis, villous atrophy, edema)
Twins
Orphan
Delay in or lack of intake of colostrum
Dysmaturity or prematurity
Exposure to infectious diseases, such as influenza
Trauma (birth, predators, mother)
Adverse environmental conditions
Failure to be up and nursing by 2-3 hours of age
Congenital abnormalities
Weakness, poor appetite

aseptically and multiple attempts are not made.[10,21,22] However, the clinical usefulness of fetal fluid analysis in the horse remains to be determined. Studies attempting to relate the phospholipid profile in amniotic fluid with equine fetal lung maturation have been inconclusive to date.[10,23,24] Transabdominal-guided ultrasound amniocentesis has also been used to detect experimentally induced equine herpesvirus (EHV-1) fetal infection in utero.[25] The technique holds promise as a diagnostic aid to detect specific fetal diseases and as a potential therapeutic avenue to deliver medication *in utero*. Preliminary data demonstrated that mares that delivered healthy foals had a significantly higher amniotic fluid lactate concentration at the time of delivery than mares that delivered sick foals.[26] The significance of this finding is unknown.

Electrolyte concentrations in pre-partum mammary secretions may be monitored to predict impending parturition in the mare. As parturition approaches, the mammary concentration of sodium decreases and concentrations of potassium and calcium increase. An elevation in calcium concentration to over 40 mg/dL (400 µg/mL; 10 mmol/L) is a reliable indicator of readiness for birth and can be used to help determine whether elective induction or cesarean section should be performed. The increase in calcium occurs over the last 72 hours of gestation.[27,28] Test strips are commercially available to measure calcium and magnesium concentrations in a field setting (Predict-a-Foal test, Animal Health Care Products, Vernon, CA; Foalwatch Kit, CHEMetrics, Calverton, CA). The milk calcium test better predicts mares that are not likely to foal rather than accurately determining the timing of foaling.

There are increases in the mammary concentration of potassium and a decrease in the mammary sodium concentration over the final 7 days of the gestational period. The mammary concentration of potassium typically exceeds that of sodium between 1 and 5 days prior to foaling. This has been used by some practitioners as a predictor of birth, although one study concluded that the use of mammary electrolyte concentrations was not reliable because of individual variability both in raw concentrations and in percent changes.[29] The reversal of the milk sodium to potassium ratio was more accurate at predicting the day of birth than the milk calcium concentration in Martina Franc jennies, a breed that has longer mean gestational length.[30] The ratio reliably reversed 24 to 48 hours before parturition.

An arbitrary scoring system using calcium, sodium, and potassium concentration in the mammary secretions to assess fetal maturity has been described.[28] False-positive results (i.e., a value that inaccurately predicts imminent foaling) have been associated with vaginal discharge, placentitis, and premature lactation. False negatives occur commonly in mares with systemic illness or in animals that have undergone general anesthesia. In many mares the changes in the electrolytes occur only within hours of delivery; thus, if monitoring is not performed frequently, the changes will be missed.[29,31] Recently, a comparison was made among milk calcium carbonate concentration, refractometry index, and pH with respect

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to prediction of foaling in healthy Thoroughbred mares.[32] Milk pH declines from a mean of approximately 7.4 to 6.4 over the final week of parturition. The positive predictive value (PPV) of foaling within 72 hours and the negative predictive value (NPV) of foaling within 24 hours for calcium carbonate concentration (using a water hardness test kit) were 93.8% and 98.3%, respectively. The PPV within 72 hours and NPV within 24 hours for mammary secretion pH (using pH paper 6.2-7.6) were 97.9% and 99.4%, respectively. Both techniques were superior to handheld refractometry. The authors used cutoff values of 400 µg/g for calcium and 6.4 for pH. The decision on whether or not to induce parturition in a mare should not be based solely on the results of this type of testing.

Fetal heart rate (FHR) monitoring is routinely used in the human fetus to detect fetal distress, particularly hypoxia, during late gestation and labor and delivery. Doppler ultrasound is the most common technique used for FHR monitoring; this technology has been adapted for use in the mare.[7] First, the fetal heart is located using an ultrasound transducer; then the Doppler transducer is placed on the mare's abdominal wall directly over the fetal heart. Fetal movement is detected by a pressure transducer or by a hand placed on the mare's abdomen. Continuous FHR monitoring for at least 10 minutes is preferred to better detect abnormalities in heart rate and rhythm. Fetal electrocardiogram (ECG), a procedure that is relatively easy to perform, may also be used to assess fetal heart rate and rhythm after day 150 of gestation.[33-36] The left arm electrode is placed on the dorsal midline of the mare at the lumbar region, and the left leg electrode is placed 15 to 20 cm cranial to the mare's udder on the ventral midline. The hair should be clipped and ample gel or alcohol should be placed to ensure good contact of the electrodes. Poor fetal signals may result from poor electrode contact or placement, fetal movement, or electrical interference. An alternative method involves placement of the left leg lead on the left neck, the left arm lead in the left flank at the height of the hip, the neutral lead on the mare's croup, and the right arm lead over the linea alba cranial to the udder, and connecting the lead to a Televet 100 recording system (Kruuse, Marvel, Denmark). This configuration allows for simultaneous determination of the maternal and fetal ECG. Use of M-mode echocardiography makes it easier to obtain an FHR measurement because of the rapid motion of the normal equine fetus. Heart rate is normally regular and decreases from greater than 120 beats/min before day 160 of gestation to between 60 and 90 beats/min in late gestation.[9,33-35] In normal mares the FHR and heart rate variability are relatively constant over the final 10 days of gestation, and are therefore not useful indicators of foaling.[35] Cardiac accelerations in response to fetal movement are an indicator of fetal well-being. An early study reported an average of 10 heart rate accelerations (25 to 40 beats/min) in a 10-minute period; 95% of these were associated with fetal movement.[37] A more recent study reported that the number and duration of cardiac accelerations and decelerations remained relatively constant over the last 2 months of pregnancy. There were approximately 22 accelerations per hour lasting around 29 to 42 heartbeats, and around 24 decelerations per hour lasting 24 to 60 heartbeats.[35]

Persistent bradycardia is associated with fetal distress and is mediated by a vagal response to hypoxemia. Severe tachycardia and arrhythmias have been associated with impending fetal demise. Although persistent fetal tachycardia or bradycardia suggest fetal compromise, normal heart rate alone does not guarantee that the fetus is healthy. Prolonged periods of fetal inactivity, in the absence of maternal sedation, also suggest fetal compromise.

Transabdominal ultrasonography allows noninvasive evaluation of the intrauterine environment and fetal well-being. In the mare transabdominal ultrasonography can be used to evaluate the equine fetus after day 90 when the gravid uterus contacts the ventral abdominal wall. This technique is used more commonly during the second and third trimesters. Transducers with lower frequencies (2 to 4 MHz) are required because of the deep tissue penetration needed. The mare's ventral midline must be cleaned and clipped from the level of the umbilicus caudally to the mammary gland and a viscous coupling gel applied. Minimal maternal restraint is usually required. Chemical sedation should be avoided since drugs such as xylazine and detomidine induce fetal bradycardia and retard fetal movement. In the pregnant mare, transabdominal ultrasonography has been used to detect twins, document fetal position, estimate fetal size using fetal aortic diameter, evaluate fetal activity, evaluate placental integrity, determine fetal fluid clarity and volume, and monitor FHR and fetal breathing. After 9 months of gestation, most fetuses are in an anterior presentation and are unlikely to change that presentation prior to delivery.[38]

A biophysical profile has been developed that uses several parameters to establish an idea of the size and overall health of the equine fetus.[7,8,37] The parameters include fetal weight, as estimated by the fetal aortic diameter (mean, 2.1 cm at 300-d gestation to 2.7 cm at full term), FHR (decreases with advancing gestational age), movement (increases with advancing age), uteroplacental thickness, qualitative allantoic fluid appearance, and allantoic volume estimation. During late gestation the equine fetus should demonstrate good tone and moderate activity with only brief episodes of inactivity (<20 min). Fetal breathing is characterized by excursion of the diaphragm between the thorax and the abdomen with accompanying rib cage expansion. Regular breathing movements are observed intermittently in most late-term fetuses. It is difficult to differentiate fetal from maternal breathing movements. The average uteroplacental thickness viewed transabdominally ranges from 8 to 15 mm.[8] Thicker uteroplacental units may indicate placental edema, placental separation, or placentitis. Areas of separation between the uterus and chorion appear as black anechoic areas. The maximum ventral fetal fluid pocket depths average 8 cm for amniotic fluid and 13 cm for allantoic fluid.[8] Excessive fetal fluid accumulation is observed in cases of hydrops. Markedly decreased amounts of fetal fluids have been associated with placental dysfunction and the birth of a dysmature, hypoxic foal. As gestation advances, fetal fluids increase in turbidity. Sudden increases in turbidity can be associated with meconium passage, hemorrhage, or inflammatory debris.

Effects of Placental Insufficiency

The effects of uteroplacental vascular insufficiency on the newborn depend on the severity of placental compromise and the severity and duration of prenatal and perinatal asphyxia. Conditions associated with chronic asphyxia in the large animal fetus include chronic placentitis, villous atrophy, twin and postterm pregnancies, and ingestion of endophyte-infected fescue grass by the pregnant mare.

If decreased uteroplacental blood flow is long-standing, growth is concomitantly inhibited in the fetus. The pattern of growth retardation associated with chronic placental insufficiency is usually asymmetrical. This type of growth retardation is characterized by visceral wasting with relative preservation of fetal length and head circumference. Affected human infants are expected to be long and thin, with loss of subcutaneous fat and a large head relative to the body size. The same is probably true in the equine neonate. It has long been recognized that twin equine neonates and other abnormally small foals tend to have heads that are disproportionately large for their small bodies.[39]

In placental vascular insufficiency, the fetus has the ability to avoid overgrowing its nutrient supply and to maximize organ growth. Under metabolic stress, there is a fetal anti-insulin response with loss of fat and glycogen stores and muscle mass. Associated with the decrease in uteroplacental blood flow is an increase in uterine and fetal vascular resistance, and redistribution of cardiac output, with a greater percentage of blood flow going to organs such as the brain and heart. Unless uteroplacental insufficiency is very severe, brain growth continues at a relatively normal rate. In the human fetus, the redistribution of cardiac output also results in decreased blood flow to the lung and kidney and decreased production of fetal urine and lung liquid—two major components of amniotic fluid. A decrease in amniotic fluid volume is therefore associated with chronic fetal

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asphyxia. The regulation of these adaptations is not completely understood, but corticosteroids, catecholamines, and vasopressin, among others, play a role.[40,41]

Repeated episodes of hypoxemia during gestation slowly deplete cardiac glycogen stores and impair the ability of the heart to effectively pump blood during subsequent hypoxemic episodes, such as during labor. The newborn with depleted glycogen stores may also be at increased risk of developing hypoglycemia and hypothermia. Meconium aspiration and persistent arterial hypertension in the newborn period are a result of chronic fetal hypoxia. Immature skeletal ossification, particularly of the carpal and tarsal bones, has also been associated with growth retardation in the foal.[39]

There are certain advantages associated with fetal adaptation to chronic placental insufficiency. Growth-retarded premature human infants have a lower incidence of hyaline membrane disease than babies of the same gestational age that are appropriately sized.[42] Presumably, fetal hormones, such as the corticosteroids and catecholamines that are released in response to nutrient deprivation, stimulate the early maturation of the lung and surfactant system. Accelerated neurologic maturity has also been documented along with accelerated pulmonary maturity.[43] Therefore, the fetus that has been chronically exposed to an adverse in utero environment may be in some ways more tolerant of premature delivery and independent life outside the uterus than the "normal" fetus that is abruptly displaced through induction of labor or cesarean section. The low-birth-weight fetus therefore represents a successful adaptation to a nutrient-deprived environment. Its smaller size, decreased metabolic needs, and early organ maturation actually place it at lower risk of hypoxic injury at birth and aid its transition to independent life after delivery.[41] Further discussion of the characteristics, treatment, and prognosis of growth-retarded premature foals may be found in Chapter 17.

Premature lactation, purulent vaginal discharge, previous history of growth-retarded foals, advanced maternal age, and prolonged gestation are problems that should raise the suspicion of chronic uteroplacental insufficiency. The labor and delivery should be attended to minimize the chances of acute asphyxia. The newborn animal should be examined for evidence of growth retardation, infection (particularly in utero–acquired pneumonia resulting from placentitis), and metabolic and acid–base derangements. Ample colostrum should be administered, and body temperature and blood glucose should be monitored closely.

One author has suggested that intrauterine growth retardation is unlikely to pose any substantial additional threat to the neurodevelopment of premature human infants unless it is accompanied by chromosome abnormalities or accompanied by severe perinatal asphyxia or hypoglycemia, or unless growth retardation is very severe.[44] Human infants that display characteristics of asymmetric growth retardation commonly "catch up" by late infancy or early childhood; similar observations have been made in the foal. Many mildly to moderately growth-retarded newborn foals have also done well following discharge from the hospital and have grown to a normal size. Problems resulting from an immature musculoskeletal system, such as angular limb deformities, have been the most common complications noted in these individuals, but careful orthopedic management can result in a successful outcome.

Placentitis

Placentitis is a common cause of reproductive losses in horses. A study of 3527 mares revealed that more than 30% of pregnancy losses attributable to premature delivery or abortion were due to placentitis.[2] The most common cause of placentitis is ascending infection from the lower urogenital tract via a relaxing cervix. A far less common route of infection is the hematogenous avenue resulting in a diffuse or multifocal placentitis. Most cases of placentitis are the result of bacterial infection caused by typical equine pathogens including *Streptococcus equi* subsp. *zooepidemicus, Enterobacter agglomerans, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. In some regions a slightly different form of placentitis has been recognized and is characterized by focally extensive placentitis located predominantly at the base of the placental horns at the junction of the horns and the body of the placenta.[45] The affected area is covered with thick, tenacious brown mucoid exudate, and the underlying chorionic villi are necrotic and absent or reduced in size. This form is associated with infection by a group of gram-positive, branching, filamentous nocardioform actinomycetes, including *Crossiella equi, Amycolatopsis* spp., and less commonly *Cellulosimicrobium cellulans* and *Streptomyces* spp.[46] A link exists between some of these bacteria, which are part of the normal intestinal flora, and ingestion of eastern tent caterpillars *(Malacosoma americanum)* or processionary caterpillars *(Ochrogaster lunifer)*.[47,48] The eastern tent caterpillar is linked to mare reproductive loss syndrome (MRLS) in the United States and the processionary caterpillar is the causal agent of equine amnionitis and fetal loss (EAFL) syndrome in Australia.[49] The barbed setae likely penetrate the intestinal mucosa, thereby facilitating bacterial translocation.

Clinical signs of placentitis include vaginal discharge, premature udder development, and precocious lactation. The discharge may be evident on the vulva, tail, or inner thighs. Premature udder development is the result of placental compromise, fetal stress, a precocious increase in maternal progestagen concentration, and enhanced fetal adrenocortical activity. Despite even voluminous vaginal discharge, most mares with placentitis do not become febrile and do maintain a normal appetite. The dam's hematology and fibrinogen concentration usually remain within normal limits. Untreated mares with experimental placentitis caused by *Streptococcus equi* subsp. *zooepidemicus* had significant increases in serum amyloid A (SAA) within 96 hours of inoculation that persisted through to birth or abortion.[50] The increase in SAA was prevented in most treated mares.

Transrectal ultrasound can be used to identify placental separation and uteroplacental thickening of the caudal uterine body. This region is most commonly involved in mares with ascending placental infection. Measurement of the combined thickness of the uterus and placenta (CTUP) is established. The rectal transducer is placed at the cervical-placental junction where a branch of the uterine artery is seen between the uterus and the bladder. This measurement increases from around 6 mm at 7 months of gestation to 10 to 12 mm at term.[51,52] Mare parity has an impact on CTUP during mid-pregnancy (100 to 250 days), with primiparous mares having a greater thickness than multiparous mares.[53] The difference is lost in late pregnancy. A measurement greater than 12 mm at 11 months or greater than 15 mm at 12 months is consistent with placental pathology.[52] Measurement of CTUP alone can be misleading, so monitoring of the CTUP by ultrasound along with determination of the maternal progestagen concentrations has been recommended.[12]

Transabdominal ultrasonography can be used to evaluate other areas of the placenta to detect loss of placental integrity or increased uteroplacental thickening. Using transabdominal ultrasound, the uteroplacental unit should be less than 16 mm during late gestation. Other signs suggestive of placentitis include increased fetal fluid echogenicity, which might result from hemorrhage or purulent exudate. If placentitis is severe enough to alter placental function, reduced fetal movement, loss of heart rate variability, and absolute fetal bradycardia collectively indicate fetal compromise.

Practitioners should take cultures of samples of vaginal discharge and perform Gram stains. The goal of maternal therapy is to treat the placental infection and maintain the pregnancy, provided there is no evidence of severe fetal distress or demise. In many cases, because the infection is of long duration, the fetus has been chronically stressed and therefore is relatively mature for its gestational age and better prepared to tolerate preterm birth. If placentitis is suspected, following delivery, the foal should be considered a high-risk individual. Commonly encountered problems in the newborn foal that was exposed to placentitis are pneumonia, uveitis, growth retardation, incompletely ossified bones, and sometimes, systemic sepsis.

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Management of the High-Risk Late-Gestation Mare

Each mare should receive a complete physical examination, and foaling histories should be obtained. She should be evaluated regularly for clinical signs of impending parturition (sacroiliac ligament and perineal relaxation, mammary development, and mammary secretion pH and electrolyte concentration). The reproductive tract may be evaluated by rectal palpation, and transabdominal ultrasonography may be performed at regular intervals to detect changes in the fetus, fetal fluids, or placenta. Prolonged periods of starvation are best avoided to prevent maternal hypoglycemia.[10] Estimation of progestin concentrations in the maternal circulation, using a commercial progesterone assay, is recommended.[12]

When treating a pregnant mare for any medical or surgical condition, practitioners must also give consideration to the fetus. Any illness or disease that affects the mare's cardiovascular system has the potential to affect placental perfusion and the integrity of the fetoplacental unit. Hypotension, endotoxemia, and hypoxemia are examples of conditions that can alter uteroplacental bloodflow and jeopardize the pregnancy. Diseases that stimulate prostaglandin production have the potential to initiate labor and delivery. Illnesses that produce prolonged periods of anorexia in the late-term mare can also lead to premature delivery. The effect of various drugs on the placenta and fetus should be considered when treating the pregnant mare. Because of the epitheliochorial nature of the equine placenta, some drugs will not cross the placental barrier at all. However, many drugs will pass through the placental and fetal circulation and be cleared by the maternal liver and kidneys if delivery is not expected. If drugs are administered to the mare and the fetus is delivered shortly thereafter, the neonate must rely on its renal and hepatic function to process, degrade, and excrete those drugs. In most instances, as long as fetal well-being and placental integrity are closely monitored, the goal of most therapies is to treat the maternal condition and maintain the pregnancy as long as possible to achieve an acceptable degree of fetal maturation.

Studies using microdialysis probes inserted into the allantoic fluid of normal mares reported therapeutic concentrations of penicillin and gentamicin in the allantoic fluid after 22,000 IU/kg of potassium penicillin G (IV q6h) and 6.6 mg/kg gentamicin (IV q24h).[54] Studies in two mares with experimentally induced bacterial placentitis again confirmed passage of both drugs across the placenta. The combination of trimethoprim and sulfadiazine (30 mg/kg PO bid) and the phosphodiesterase inhibitor pentoxifylline (8.5 to 10 mg/kg PO bid) also readily crosses the fetal membranes in both healthy mares and in animals with experimental placentitis.[16] In many cases, medical treatment of the placental infection and prolongation of pregnancy is associated with a good outcome. Maternal treatment includes systemic antibiotics, flunixin meglumine, pentoxifylline, and altrenogest.[10,55] In an experimental model of placentitis, induced through inoculation of *Streptococcus equi* subsp. *zooepidemicus,* the combination of trimethoprim sulfamethoxazole, pentoxifylline, and altrenogest was highly effective at prolonging gestation and improving foal viability when contrasted with mares that received no treatment.[55] Because of the usual presence of mixed gram-positive and gram-negative placental and fetal infections, a broad spectrum antibiotic that reaches therapeutic levels in the fetus and fetal fluids should be selected. Therapeutic options include penicillin and gentamicin, trimethoprim-sulfonamide, or ceftiofur. Trimethoprim-sulfonamide combinations or doxycycline have in vitro activity against several nocardioform actinomycetes.[46] Low doses of flunixin can be administered to decrease inflammation and prevent prostaglandin-mediated induction of delivery. Altrenogest (0.044 to 0.088 mg/kg, 10 to 20 mL of 0.22% solution for 500 kg mare, PO q24h) is commonly used in late pregnancy to prevent preterm delivery, possibly through interference with prostaglandin regulation and oxytocin receptors.[16] The rationale for altrenogest use in late pregnancy has been questioned, because plasma progestagen concentrations are typically raised in mares with placental disease.[56] Altrenogest readily crosses the placenta and reaches relatively high concentrations in the fetal fluids and the newborn foal.[57] Concentrations in the healthy foal decline rapidly over the first 6 hours postpartum. The effects of altrenogest on the foal are largely unknown, but a reduced neutrophil to lymphocyte ratio in foal blood has been reported.[58] It has been recommended to withdraw altrenogest after 320 days' gestation if possible. A similar or longer withdrawal period (2 to 4 weeks) is also recommended for pregnant mares with PPID that are being managed with pergolide. The drug is anecdotally associated with prolonged gestation and decreased milk production.

If there are large areas of placental thickening, IV DMSO (0.5 to 1 g/kg as a 10% solution) can be administered to decrease placental edema. Pentoxifylline has also been administered in attempts to improve placental perfusion.

If premature delivery appears unavoidable, one to three doses of maternal corticosteroids can be used with the hope of stimulating and accelerating fetal lung maturation through enhanced surfactant production. This is done with the knowledge that corticosteroids are anecdotally associated with a heightened risk of laminitis, particularly in mares with underlying disease. Normal Thoroughbred mares given 100 mg IM of dexamethasone on gestation days 315, 316, and 317 delivered foals around 2 weeks earlier than saline-treated control mares.[59] The interval between the last dose and parturition was only 1 to 8 days. Resultant foals were smaller, but appeared mature and had normal neutrophil to lymphocyte ratios. Evidence existed of lingering adrenal suppression in some foals.

In the high-risk mare, it is very important that the delivery be attended by knowledgeable personnel, and that all supplies, drugs, and equipment required for diagnosing and correcting a dystocia as well as stabilizing the mare and foal be organized and close at hand. A spontaneous, vaginal delivery is generally preferred in the high-risk mare, both because of the profound problems associated with the untimely delivery of a premature foal, as well as the complications sometimes associated with induced labor or cesarean section[56,57] (see Chapter 17). There are instances, however, when an induced birth or cesarean section is indicated or preferred.

Induction of parturition should be considered with the following:

- Severe fetal distress noted on prenatal assessment
- Evidence of premature placental separation or a history of premature placental separation associated with dead or asphyxiated foals
- Hydrops allantois and/or amnion
- Unproductive stage I labor
- Uterine inertia
- Impending prepubic tendon rupture
- Life-threatening maternal illness

Indications for cesarean section may include the following:

- Pelvic injury or abnormality resulting in obstruction of the birth canal
- Gastrointestinal crisis requiring surgery
- Severe dystocia
- Insufficient, thickened placenta associated with fescue toxicity in the mare
- Catastrophic and terminal illness or injury in the mare, such as gut rupture or fractured limbs

If induction of parturition or cesarean section is elected, every effort should be made to ensure that the fetus is mature and is ready to be born; the usual result of induction at an inappropriate time is a nonviable newborn. Three essential criteria are (1) a gestation of longer than 330 days, (2) good quality colostrum in the udder, and (3) softening of the cervix.[60] The scheduling needs of the veterinarian or owner should never be the only criterion used for determining the timing of delivery. A slow continuous oxytocin infusion administered at a rate of 1 IU/min usually results in delivery within 20 to 40 minutes.[10] Alternatively, multiple intravenous or intramuscular injections of 10 to 20 IU of oxytocin every 10 minutes have been recommended.[60,61] Other investigators have shown that smaller intravenous doses of oxytocin (2.5 IU administered every 15 to 20 minutes until rupture of the chorioallantois or a total of 20 IU of oxytocin has been

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administered) are an effective, and perhaps more physiologic, method of induction.[62]

Induction of parturition in the mare has been associated with more violent, painful contractions than spontaneous labor and a higher incidence of premature placental separation and neonatal asphyxiation. Cesarean section also predisposes to neonatal peripartum asphyxia. Maternal hypotension resulting from general anesthesia and the weight of the maternal abdominal contents on the aorta and vena cava both compromise uteroplacental circulation. For further details concerning anesthesia of the late-term mare, the reader is referred to other texts.[63] Abdominal support with nonsteroidal antiinflammatory drugs and altrenogest has been used to maintain the pregnancy in a mare with hydrous amnion until day 321 when spontaneous delivery occurred.[64] The delivery was complicated by uterine inertia, maternal postpartum hypovolemic shock, and cardiac arrhythmia, but both mare and foal survived.

Foal Resuscitation

Guy D. Lester

The veterinarian attending or assisting in the birth should be prepared in the event that cardiopulmonary cerebral resuscitation (CPCR) of the foal is required. Detailed descriptions of CPCR are published elsewhere.[65-67] Foals born by cesarean section or assisted vaginal delivery are at increased risk of cardiac or pulmonary arrest. Mares suffering from systemic illness, hydrops, prepubic tendon rupture, placentitis, placental insufficiency, or premature placental separation are also at heightened risk for delivering foals with serious complications.

After delivery the at-risk foal should be positioned on a firm, flat surface with the withers against a wall to prevent movement if thoracic compressions are needed.[67] Quickly palpate the thorax for evidence of rib shaft fractures or costochondral dislocations. If fractures are detected, the affected side should be in contact with the ground. Initially place a nasal insufflation tube into one nasal passage to the level of the medial canthus of the eye, and deliver oxygen at 10 L/min. Assess the foal's breathing and circulation over the following 30 seconds, noting rates and effectiveness. The nasal passages should be examined for meconium staining, and any fetal membranes should be removed. Remaining fluid can be cleared using gentle postural drainage and a bulb syringe and soft catheter. Hanging foals from their pelvic limbs must be avoided.

Spontaneous breathing is stimulated by vigorous rubbing of the body and head with a dry towel. Gentle thoracic compression is also helpful. Other techniques used to improve breathing include tactile stimulation of the nasal mucosa or the ear canal. In other species, pouring of cold water into the ear canal or application of acupuncture needles to the nasal philtrum (absent in the foal) has been suggested.[68] If the foal fails to breathe or is making irregular gasping movements, positive pressure is urgently required.

The attendant can provide positive pressure using mouth-to-nostril resuscitation. The opposite nostril is occluded along with gentle pressure over the proximal esophagus, and breaths are delivered with the foal's head in extension. During each forced breath, the rise in the thoracic wall should be observed to ensure an appropriate tidal volume is delivered. Exhaled air is only 16% to 18% oxygen, but this is considered adequate in the face of failing perfusion.[67] Alternatively, a pump and face mask resuscitator can be used (McCulloch Medical Products, Glenfield, New Zealand). This device can be connected to a nasotracheal tube or a face mask and delivers a set volume of 780 mL, thereby avoiding volutrauma. The resuscitator device can also be easily adapted to suction the airway.

Cuffed nasotracheal tubes (7-, 9-, and 12-mm diameter; 55 cm long) should be available as part of the resuscitation kit, along with a self-inflating resuscitation bag (the bag component of a commercial air mask bag unit (AMBU [Ambu Inc., Glen Burnie, Maryland]). A 9-mm tube will suit most foals, although a large tube may be needed in foals greater than 55 kg. Passage of the nasotracheal tube is facilitated by keeping the head in extension. The tube is passed through the ventral meatus into the nasopharynx to the larynx. Rotation of the tube can aid in passage through the arytenoid cartilages and into the trachea. The tube is inserted fully to reduce dead space, so that the tube end is positioned in the mid-tracheal region and the cuff is inflated. An adult resuscitation bag (typically 1600 mL capacity with a 2600-mL oxygen reservoir bag) is connected to the tube and manually compressed to provide positive-pressure ventilation at an initial rate of 10 to 12 breaths/min. The bag has an adjustable escape valve that prevents barotrauma. The valve is typically set at 35 to 45 cm H_2O.[66] The thoracic wall should rise appropriately without air leaks around the cuff. Ideally the bag is connected to an oxygen cylinder using a flow rate of 8 L/min, but ventilation with room air is acceptable. The oxygen flow rate can be adjusted based on the minute volume that is delivered.[67] Assisted ventilation should be ceased every 3 minutes to monitor for spontaneous ventilation. The use of chemical respiratory stimulants, such as doxapram hydrochloride, is no longer indicated in the treatment of secondary apnea.

If asystole occurs or the heart rate is persistently less than 40 beats/min, cardiac compressions are indicated without delay. It has been recommended that compressions occur at a rate between 80 and 120 beats/min, with complete thoracic wall recoil between each compression.[65] The compressions should be forceful and contribute around 25% to 30% of normal cardiac output.

Drugs are indicated if the heart rate fails to increase with supported ventilation and thoracic compressions. The drugs can be administered intravenously via the jugular vein or intraosseously, using a 12-gauge intraosseous infusion needle.[65] The most popular medications for cardiovascular resuscitation include epinephrine and vasopressin. Epinephrine can be administered initially with a bolus dose of 0.01 to 0.02 mg/kg (1 mg/mL, 0.5 to 1 mL/50 kg foal), repeated every 3 to 5 minutes because of a short half-life. A higher dose is recommended if the foal fails to respond to other therapies (0.1 mg/kg; 1 mg/mL, 5 mL/50 kg foal). Vasopressin is a peripheral vasoconstricting agent that can be administered at a bolus dose of 0.6 U/kg IV.[67] The effects last approximately 10 to 20 minutes. The use of sodium bicarbonate in CPCR continues to be controversial, but evidence indicates a potentially deleterious effect of myocardial function; in the absence of any positive survival data, it is no longer recommended in human CPCR.[69]

Defibrillation is indicated in ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia without palpable pulse pressure.[66] The technique should not be used in the management of bradyarrhythmias or asystole. Recommendations include an initial defibrillation of 2 J/kg, followed by a discharge of 4 J/kg 30 to 60 seconds after treatment with epinephrine or lidocaine (1.5 mg/kg, repeated in 5 minutes), and continued cardiac compressions.[65] Amiodarone has been used in adult horses with refractory ventricular tachycardia; the recommended dose is 5 mg/kg/h as a CRI for 1 hour, followed by 0.83 mg/kg/h for 23 hours, although boluses of 5 mg/kg over 2 minutes have been used safely in normal adult horses.[70,71]

Resuscitation should be discontinued in the absence of spontaneous cardiac output within 10 minutes of initiating CPCR. Successful resuscitation is associated with spontaneous ventilation at a normal rate, depth, and effort, and a regular cardiac rhythm with a rate greater than 60 beats/min. The foal should be monitored closely over the following 60 minutes, and then at a lower level for a further 48 hours, since there is a heightened risk of postasphyxia complications.

Perinatal Asphyxia Syndrome

Perinatal asphyxia syndrome (PAS), also termed *hypoxic ischemic syndrome,* describes the clinical consequences of reduced oxygen delivery to tissues. The clinical effects of asphyxia can be widespread and can involve many systems including the nervous system, the kidneys, the gastrointestinal tract, and the cardiopulmonary system. The nervous system is the most commonly affected. The clinical features of nervous system disease in foals, along with a discussion of the pathophysiology of asphyxia, can be found in Chapter 17 under neonatal encephalopathy. The renal system is the second most

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common system affected by asphyxia. In most affected foals the impact is relatively small, with reduced glomerular filtration and mild tubular disease, resulting in few abnormal clinical or laboratory findings. The most common laboratory derangement is persistent elevation in creatinine concentration, or an increased level that is slow to normalize. In a small number of animals there is significant acute tubular necrosis resulting in anuria or oliguria, widespread edema, persistent elevation in serum creatinine concentration, and abnormal fractional excretion of electrolytes. Tissue edema can develop quickly, particularly if high rates of sodium-rich fluids are used. It is recommended to err on the side of fluid restriction rather than fluid excess when managing foals at risk for complications from PAS.[72] See Chapter 17 for fluid therapy guidelines in neonatal foals. Nephrotoxic drugs such as gentamicin or amikacin should be avoided if possible, unless therapeutic drug monitoring is available.

The management of oliguria or anuria can be difficult. Strategies to promote diuresis include a constant rate infusion (CRI) of dopamine at a rate of 2 to 5 µg/kg/min, or furosemide as a CRI (0.12 to 2 mg/kg/h) or boluses (1 mg/kg). The two treatments can be used concurrently.[73] The use of mannitol remains controversial but can be considered as another option if oliguria persists (see Chapter 34). Once urine flow is established, the use of diuretics and vasoactive drugs should be revised and serum electrolyte concentrations and blood pH monitored. Overuse of diuretics can promote excessive fluid and electrolyte losses.

The gastrointestinal tract is another common target for asphyxial injury. The clinical signs are often related to gastroparesis and intestinal ileus. These include colic, recurrent gastric reflux, abdominal distention caused by accumulation of intestinal gas and fluid, intestinal impaction, or diarrhea. In severe cases there is marked edema of the bowel wall, epithelial necrosis, and hemorrhage into the lumen. Damage to mucosal integrity can lead to translocation of bacteria with generalized peritonitis and systemic sepsis. The syndrome of necrotizing enterocolitis (NEC) is a significant cause of morbidity and mortality in preterm human infants.[74] The disease involves intestinal coagulative necrosis, bacterial overgrowth, pneumatosis intestinalis, and a marked inflammatory response. Although controversial, intestinal hypoxia or ischemia and infection with certain bacteria, such as *Clostridium perfringens,* may be important contributing factors.[74] A similar syndrome has been reported in foals associated with birth hypoxia and *Clostridium* spp.[75,76]

Preventive strategies include avoidance of overfeeding, monitoring of gastric and intestinal volume and wall movement with ultrasound, monitoring for increases in abdominal circumference using a soft tape measure, and avoidance of antacid medications. Decreased gastric acidity may be a partial explanation as to why preterm human infants are at heightened risk of NEC.[74] A small volume of milk is often fed to at-risk foals to promote intestinal health (or "trophic feeding"), but this falls short of what is required in terms of minimal caloric requirements.[77] The benefits of trophic feeding (12 to 24 mL/kg/day) in human neonates has been questioned, although it appears that the technique does not cause harm.[78] Calorie supplementation of foals with parenteral nutrition is strongly recommended, particularly when gastric reflux or hemorrhagic diarrhea is present and no enteral feeding is used.

Foals that have experienced an episode of hypoxia or ischemia are at increased risk for secondary infection and should be on broad-spectrum antibiotics. The use of aminoglycosides should be reconsidered if therapeutic monitoring is not available because of likely altered renal function. Immunoglobulin prophylaxis is recommended when serum IgG concentration is less than 800 g/dL (8 g/L), although there are no data that document decreased infection or improved survival with plasma therapy in at-risk foals. Plasma does have benefits in addition to immunotherapy, including improvement of osmotic pressure as well as provision of coagulation factors and buffer base.[72] Glucose homeostasis is commonly disturbed in post-asphyxiated foals, and concentrations should be monitored frequently. Hypoglycemia is frequently noted at the time of admission, but hyperglycemia is also common in response to modest replacement therapy. In some foals, glucose intolerance can be managed by insulin therapy (see Chapter 17).

Respiratory failure is uncommon in PAS foals, but periods of hypoxemia and/or hypercapnia are not uncommon. Intranasal delivery of humidified oxygen is often helpful in the early stages of treatment. Rates of 2 to 5 L/min are commonly used with the goal of raising the arterial oxygen concentration (PaO_2) above 80 mm Hg. This should be achieved along with maintenance of tissue perfusion, using judicious fluid therapy and vasopressive agents as necessary. Hypercapnia should be treated only if there is a poorly compensated respiratory acidosis. This can be managed using positive pressure ventilation or respiratory stimulants, such as doxapram or caffeine.

The short-term prognosis for foals with PAS is dependent on several factors, including the degree and duration of oxygen deprivation, as well as the organ systems involved, and the preparedness and training of attending personnel. The prognosis for most foals is good to excellent with survival rates commonly reported around 75%.[79,80]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 16

Assessment of the Newborn Foal

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Neonatal Behavior

A normal foal should have righting reflexes and sufficient muscle tone to be able to right itself to sternal recumbency within 2 to 3 minutes of birth. By 5 minutes the foal should be bright, alert, and responsive to visual, auditory, and tactile stimuli. Over the next 20 to 25 minutes the normal foal will be restless, alternating periods of sternal recumbency with lateral recumbency before beginning lurching attempts to stand. During this period the foal will often vocalize in response to maternal sounds or contact. Once standing, the initial posture is an unsteady basewide rocking stance, but this slowly improves such that by 60 minutes the foal should be standing securely without assistance. The suckle reflex is present within minutes of birth in most foals and should be present in all foals by 30 minutes. Once standing, the foal will seek the udder, a process that is initially very clumsy but improves once the foal has successfully sucked. There will be repeated nudges of the udder in order to facilitate milk letdown. The normal foal should be nursing from the mare within 2 hours (mean time of 111 minutes; range, 35 to 420 minutes), and most have nursed twice by 2.5 hours.[1] Sucking periods vary in duration between 1 and 5 minutes and are interspersed with periods of sleep that last around 7 minutes. It is important to watch the foal during sucking to confirm appropriate teat contact and swallowing movements. A foal that spends long periods at the udder may do so because of inability to nurse or inadequate milk from the mare. The daily milk consumption of most newborn foals is between 21% and 25% of their body weight.[2] This equates to around 12 to 12.5 L/day for a 50-kg foal. Based on the caloric density of milk, this reflects a daily intake of 120 to 150 kcal/kg body weight; half of this is used for basal metabolism and thermoregulation and half for growth.

Sleep periods first occur between 90 minutes and 4 hours after birth and last for about 7 minutes.[3] The foal spends one third of its time lying down during the first 2 months of life—compared with 5% to 10% for adults, most of which occurs overnight. Foals do not learn to follow their dams to the exclusion of any other moving object for the first 1 to 2 weeks of life. Foals identify their dams by sight and smell, and during the first week of life, they spend 85% of the time within 1 m of the dam, 94% to 99% within 5 m, and only very rarely are more than 10 m away from the dam.[4] Loss of affinity for the mare in a foal that seems otherwise healthy may be an early sign of the neurologic form of hypoxic-ischemic syndrome.

Recommendations to clients as to when veterinary intervention should be sought vary from practice to practice. The "1-2-3" rule states that foals should be standing unassisted by 1 hour, sucking from the mare by 2 hours, and the mare should have passed her fetal membranes by 3 hours. Clients may adopt a similar "2-4-6" rule to seek veterinary attendance, in which intervention should be sought if the foal has not stood by 2 hours, not sucked by 4 hours, or the fetal membranes are still in place by 6 hours. These recommendations are only used as a rough guide and will obviously be influenced by peripartum conditions and client experience.

A modified **Apgar Score** (Table 16-1) has been used in foals to semi-quantitate the severity of signs that occur in response to peripartum asphyxia.[5] The acronym used in equine practice differs from that used in human medicine and refers to *a*ppearance, *p*ulse, *g*rimace, *a*ctivity, and *r*espiration. *Appearance* refers to oral mucous membrane color; *pulse* uses 60 beats/min as a cut off; *grimace* is assessed in response to stimulation of the nasal mucosa, inside of the pinnae, and over the thoracolumbar area adjacent to the spine; *activity* reflects the degree of muscle tone; and *respiration* refers to ventilation rate and rhythm with 30 breaths/min as the cut off. Each category is scored from 0 to 2 points with a score of 10 being optimal. A score of 0 to 3 indicates marked depression; 4 to 6, moderate depression; and 7 to 8, mild asphyxial injury. Normal foals have a score of 9 or 10. Ideally the modified Apgar calculation should be made within the first minute after birth, but certainly within 15 minutes of delivery. Repeating the score 4 minutes later is recommended. Foals with low scores typically require aggressive resuscitation, whereas mildly affected foals may respond to vigorous rubbing, stimulation of the nasal mucosa, and limb movement.

Maternal Behavior

The behavior of the mare is critical and must be closely monitored. A good dam will pay close attention to its foal avoiding stepping or lying on it, protecting it from real or perceived threats, and facilitating the nursing process. The mare and foal will be in close contact over the first few days of life, within 5 m of each other for more than 95% of the time. Signs of concern are mares that avoid their foal, do not allow the foal to nurse, or are outwardly aggressive toward the foal.[6] It has been reported that maiden mares, older mares, mares

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TABLE 16-1

Apgar Score: Assessment of Neonatal Asphyxia[19]

Parameter	0 Points	1 Point	2 Points
Appearance	Gray or blue mucous membranes	Pale pink mucous membranes	Pink mucous membranes
Pulse (Beats per Minute)	Absent	<60, irregular	>60, regular
Grimace			
Nasal stimulation	No response	Grimace	Strong grimace, sneeze
Ear tickle	No response	Head and neck motion	Ear tickle, head shake
Thoracolumbar stimulus	No response	Head and neck motion	Attempt to stand with head, neck, limb motion
Activity (Muscle Tone)	Limp, lateral recumbency	Semisternal, some limb flexion	Sternal
Respiration (Breaths per Minute)	Absent	<30, irregular	>30, regular, can whinny

with a history of rejecting foals, and Arabian mares of Egyptian lineage are at greatest risk of **rejecting their foals.**[7] The health of either the foal or the mare can contribute to a failure to bond. For example, foals that are unable to stand or unable to suck are less likely to form a normal bond, and mares with painful mammary glands, or that are experiencing strong postpartum uterine contractions, are less tolerant of foals trying to suck.

Physical Assessment

There are numerous factors that influence a foal's body weight at birth, including breed, gender, gestational age, and intra-uterine environment. Estimates of body weight for newborn Thoroughbred foals for the purpose of drug calculation range between 40 and 55 kg, although many healthy foals may well exceed this range. The average daily weight gain for healthy foals is breed dependent but is typically between 1.3 and 1.7 kg/day for Thoroughbred-type foals.[8] Daily weight gain in hospitalized foals is determined by disease, calorie intake, and a lack of exercise, and is almost always less than that of healthy, active foals.

The degree of physical development should be considered in relation to the estimated gestational age. This assessment should be made in light of the variable gestational length in horses. Typically gestational length is calculated from the time of insemination through to birth—a figure that overestimates the true gestational period by as much as 7 days. The mean gestational period in Thoroughbreds is around 340 to 342 days, with 95% of mares foaling between 327 and 357 days.[9] A number of factors influence this period, including breed, gender, and time of year. Colts on average have a gestational length that is approximately 1.5 to 2.5 days longer than that of fillies; they are slightly heavier, slower to stand, and have a heavier placenta.[10] Mares that conceive early in the breeding season have pregnancies that may be up to 10 days longer than those that become pregnant late in the season.[9,11] The role of dam, sire, and the dam's sire in determining gestational period has been suggested in some, but not all, breeds.[12]

Physical characteristics of immaturity include low birth weight, small body size, short and shiny haircoat, doming of the head, periarticular laxity, and droopy ears. Foals with a shortened gestational period and signs of physical immaturity are termed *premature,* whereas foals that are physically immature in the face of an appropriate gestational length are termed *dysmature*. Foals born after 356 days should be regarded as *post-term*. This is distinguished from foals that are *post-mature,* a condition of increased morbidity as a consequence of failing placental function.[12] Post-mature foals tend to have a lean and lanky physical appearance.

Rectal Temperature

Rectal temperature in normal foals ranges between 37.2° and 38.9° C (99° F and 102° F) during the first 4 days after birth.[1] The upper end of the normal range, which is around 0.6° C (1° F) above the upper end of the adult range, is strongly influenced by environment and exercise. Temperature can be variable in foals with systemic sepsis; in the early stages of sepsis, the rectal temperature is commonly within the normal range or mildly elevated. Foals in septic shock will usually have a low rectal temperature, and those with localized infection will often be afebrile.

Ears

The ears of a normal foal are typically erect at the time of birth. Drooping of the ear pinnae is most commonly associated with prematurity or dysmaturity, and as such, is often accompanied by other physical signs of immaturity, such as small body size, short silky haircoat, and a domed head. Practitioners should examine inside the ear pinnae for evidence of dermal hemorrhages, because these can be a manifestation of systemic sepsis (see Chapter 17) or thrombocytopenia caused by disseminated intravascular coagulation (DIC) or alloimmune thrombocytopenia.

Eyes

The neonatal foal may not be able to close its eyelids completely (lagophthalmos), has reduced production of tears, and lacks a menace response. The menace response is a learned one and is usually acquired in the first 14 days of life. The pupil is oval, and pupillary light reflexes are present from birth, but are slower. Other normal ocular findings include persistence of the hyaline artery remnants, the blood supply to the developing lens, and a pale pink to red optic disc with smooth margins. Newborn foals also have very prominent lens Y sutures. Lens suture lines are apparent in most foals and can persist into adulthood. In an ophthalmic survey of older foals (mean age of 9.4 weeks), suture lines were observed in 95% of animals.[13] The anterior suture was predominantly Y-shaped, but the authors reported that posterior sutures were more variable, from "Y-shaped to sawhorse, to stellate." Posterior lens sutures are reportedly more difficult to recognize in Thoroughbred foals. The suture patterns are not consistently symmetric between eyes. Prominent lens sutures can be confused with congenital cataracts. Congenital cataracts are amenable to surgery in the absence of uveal tract inflammation, a normal retina, and an appropriate demeanor. Other abnormalities that can occur include atresia of the nasolacrimal system, dermoids, retinal dysplasia, and optic nerve hypoplasia.

The neonatal foal may have significant **corneal ulceration** without tearing, blepharospasm, or photophobia as a result of reduced corneal sensitivity when compared with older foals and adult horses.[14] Consequently, special attention is required to monitor for ocular disease. A daily fluorescein stain of the cornea in sick recumbent neonatal foals is recommended. The combination of lagophthalmos, recumbency, and seizure predisposes foals with encephalopathy to a high incidence of corneal ulceration.

Entropion (inward rolling of the eyelid margin) is the most common ocular problem of newborn foals. This usually occurs as a complication of dehydration and malnutrition and may lead to corneal abrasion and ulceration. Treatment is placement of vertical mattress sutures or staples to evert the offending lid while the primary

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condition is corrected. An alternative strategy is to inject procaine penicillin G subcutaneously into the lower lid to cause temporary eversion.

Examine the conjunctiva and sclera for signs of hemorrhage. This is commonly associated with birth trauma, and affected foals should be monitored closely for development of more classical post-asphyxia complications. **Episcleral injection** (engorgement and proliferation of scleral vessels) is a prominent feature of systemic sepsis. **Iridocyclitis** is usually associated with systemic sepsis and can include hyphema, hypopyon, and fibrin. These changes are not uncommon in foals with in utero–acquired infection and may be present at birth. Iridocyclitis is also seen in older foals with *Salmonella* or *Rhodococcus equi* infection.

Oral Cavity

Oral mucous membranes in healthy newborn foals should be pink, moist, and have a capillary refill time (CRT) of 1 to 2 seconds. Bright pink to red mucous membranes, accompanied with injected scleral vessels and hyperemia of the coronary bands, are consistent with the early stages of sepsis. During this early hyperdynamic phase the CRT may be shorter than normal. Darkening of mucous membranes with a delay in the CRT may indicate sustained sepsis. In severe cases, this is accompanied by petechial or ecchymotic hemorrhages.

Icteric mucous membranes are most commonly associated with systemic sepsis, but are also a feature of neonatal isoerythrolysis (NI), liver disease, internal hemorrhage, meconium retention, or infection with equine herpesvirus type 1. Pale membranes suggest anemia and can occur with external umbilical cord hemorrhage, internal hemorrhage from torn umbilical vessels, fractured ribs, or hemorrhage within gastrointestinal or urinary tracts. Pallor with icterus would normally indicate NI or internal hemorrhage. Petechial or ecchymotic mucosal hemorrhages suggest advanced sepsis when associated with darkened membranes and a prolonged capillary refill time, or alloimmune thrombocytopenia when the membranes are pink (Fig. 16-1). Blue to gray discoloration of the membranes is consistent with hypoxemic circulatory shock. Overt cyanosis is uncommon and should prompt close examination of the cardiovascular and respiratory systems.

In term foals, the central incisors usually erupt during the first 5 to 7 days of postnatal life. The middle incisors rise between 4 and 6 weeks of age, but the corner incisors do not erupt until around 6 to 9 months. In miniature horses and ponies, the eruption of the middle and corner incisors is delayed at 4 months and 12 to 18 months, respectively. The 12 temporary molars are present at birth or erupt within the first week of life. These teeth are replaced by permanent premolars at 2.5, 3, and 4 years of age. The three molar teeth do not erupt until 1, 2, and 3.5 years of age for molars 1, 2, and 3, respectively.



FIG. 16-1 Spontaneous mucosal hemorrhages and ulceration in a foal with alloimmune neonatal thrombocytopenia.

Dental problems are uncommon in foals with the exception of those associated with facial deformities such as maxillary prognathism, mandibular prognathism, and campylorrhinus. Maxillary prognathism (parrot mouth; bird face; overbite; brachygnathism; brachygnathia) describes the condition in which the mandible is shorter than the maxilla, producing an overjet or overbite. The condition may affect the incisors, check teeth, or both, and is the most common congenital oral malformation of foals. The majority of foals with maxillary prognathism suffer little impact to their quality of life, and the defect simply represents a cosmetic problem. In moderate to severely affected foals, the lack of incisor contact results in excessive growth of the lower teeth and secondary soft-tissue trauma to the palate caudal to the upper incisors. The premaxilla and incisive bones tend to bend forward and downward as growth continues because of the lack of an opposing force, normally provided by the mandible. This can lead to difficulty in grazing. Mandibular prognathism (sow mouth; monkey mouth; brachygnathia superior; underbite) describes the condition in which the maxilla is shorter than the mandible, producing an underbite. The condition occurs much less commonly than the maxillary equivalent and is most frequently seen in pony and small horse breeds. The defect in its most severe form can be associated with deformity of the nasal passages and nares, and there may be difficulty in breathing and an inspiratory stridor. Campylorrhinus lateralis (wry nose; wry face) describes the condition in which the premaxilla and nasal septum are deviated laterally. It may occur singularly or in combination with other deformities, such as wry neck, cleft palate, and maxillary or mandibular prognathism. If the deviation is severe, the foal may have great difficulty in sucking from the mare. There may also be problems with breathing. In most foals the deviation is mild and represents a simple but obvious cosmetic defect. Close attention must be paid to dental wear as maxillomandibular malocclusion occurs commonly.

Cleft palate is an uncommon congenital defect of foals that results from incomplete fusion of the lip and/or secondary palate during the early gestational period. Previous reports estimate the incidence at 0.1% to 0.2% of all horse births.[15] Almost all clefts occur in the secondary palate, the horizontal partition dividing oral and nasal cavities. The secondary palate includes all of the soft palate and most of the hard palate, with the majority of the defects restricted to the soft palate. The basis of this congenital defect is not known but could include a heritable component and/or exposure of the developing fetus to infection, toxins, or nutritional disturbances. The diagnosis is usually straightforward and centers on an appropriate history and signalment. Confirmation is through palpation using the third finger of an upturned hand, or by direct inspection of the oral cavity. It is important that the hand is clean before direct palpation. Endoscopic examination of the nasal passages or through the oral cavity under anesthesia may be required to detect small defects. Oral palpation is recommended for all sick neonatal foals prior to commencing potentially costly treatment. A cleft in the secondary palate permits the oral contents to pass directly into the nasopharynx and nasal passages. Consequently, the most common complaint is nasal regurgitation of milk immediately after sucking. As the foal matures, feed particles will also appear at the nares. Foals with small palate defects may have intermittent milk drainage from the nostril and consequently escape diagnosis during the neonatal period. Rarely, cases are initially diagnosed in adult horses. Most will develop an aspiration pneumonia that can be difficult to identify in its early stages because of immaturity of cough receptors. Surviving foals will typically be poorly grown and ill-thrifty. The presence of milk at the nares after feeding does not definitively indicate that a cleft is present and is more commonly associated with pharyngeal/laryngeal weakness or incoordination.

The tongue should be examined for evidence of candidiasis, appearing as small white plaques through to diffuse, thick, tan discoloration of the tongue. The condition can be local or systemic and is common in debilitated foals and those that have been on chronic

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antibiotic therapy. In severe cases the condition will cause reduced nursing and salivation.

Thyroid Gland

Hypertrophy of the thyroid gland (goiter) can occur in response to deficient or excess dietary iodine. One of the more common reasons for thyroid gland enlargement in neonatal foals is excess iodine supplementation during pregnancy.[16] Reports exist regarding neonatal goiter when seaweed was incorporated into the diet of broodmares or when pellets were fed to mares that had been formulated with excessive iodine.[17,18] Dysmature foals with thyroid hyperplasia and concurrent musculoskeletal problems have been identified in western Canada and the northwestern United States.[19,20] The syndrome results in hypothyroidism and may be related to the feeding of diets that are high in nitrate or low in iodine to mares during pregnancy. Thyroid hormone is an important cofactor in maturation of the respiratory system, and hypothyroidism has been linked to respiratory failure in a newborn foal.[21] In older foals, enlargement of the thyroid has been associated with dietary iodine deficiency and low circulating levels of T4.[16] Newborn foals have baseline T3 and T4 levels that are considerably greater than that of adult horses.[22] These levels decline over the first 12 days after birth.

Neck and Back

A number of **congenital anomalies** affect the alignment of the vertebral column. These include atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies, such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Arabian foals are most commonly affected, and a familial predisposition has been suggested.[23] There may be palpable abnormalities of the atlas and axis and altered head carriage. The diagnosis is confirmed using radiography where a range of abnormalities are seen, including atlantooccipital fusion, hypoplasia of the dens, and axis malformation. Prognosis is very poor because many have signs of ataxia and paresis involving all four limbs at birth. Some animals may have normal neurologic function. Foals with severe kyphosis or kyphoscoliosis often have underlying malformation of the thoracic vertebrae.[24]

Gastrointestinal System

Most foals display abdominal straining within a few hours of birth and pass most of the meconium within the first 1 to 4 hours after delivery, but passage may be delayed without concern for up to 12 hours. Differentiating straining to defecate from **meconium impaction** with straining to pass urine can be difficult in some foals. Typically foals straining to pass feces will have an arched appearance to their hindquarters (Fig. 16-2). A change in the color and consistency of the feces from a dark brown to black pasty material to a lighter brown, less tenacious material indicates that the meconium has been passed. The routine administration of an enema is performed commonly in healthy newborn foals in an attempt to reduce the straining associated with the passage of meconium. A variety of methods are used, with commercial glycerine phosphate–based products being the most common. These are relatively easy to administer, although care should be taken to avoid direct trauma to the rectal mucosa with the applicator tip. Many veterinary practices probably use gravity enemas, with 400 to 800 mL of warm soapy water delivered through a soft tube, such as a canine stomach tube or male urinary catheter. Acetylcysteine retention enemas are not administered routinely, but rather in foals with resistant meconium impactions.

Auscultation of the abdomen can provide an indirect assessment of intestinal contractility. The technique should be interpreted with caution as the presence of borborygmi does not equate to propulsive motility or ingesta transit. The changes in gastrointestinal sounds over time may be more useful in determining a diagnosis. For example, a silent abdomen that progresses to a hyperactive one could be indicative of inflammatory intestinal disease, whereas an abdomen with normal sounds that change to silent could be consistent with a surgical lesion. Percussion and ballottement are used to differentiate abdominal distention caused by gas or fluid accumulation. A tympanic sound on percussion is consistent with intraluminal or free peritoneal gas, and ballottement can detect waves of free abdominal fluid. Progressive abdominal distention, irrespective of the underlying cause, can be monitored using a soft measuring tape repeatedly positioned over small clipper marks. Gastric distention can cause a "sprung rib," a swelling that projects beyond the 18th rib.

Firm structures can be detected using transcutaneous abdominal palpation, assuming the foal is suitably relaxed. It is possible to palpate bowel impacted with meconium, fecoliths, intussusceptions, the urinary bladder, or enlargement of the internal umbilical remnants caused by infection or hemorrhage. The **external umbilicus** should also be palpated for enlargement or herniation; in colts, the inguinal rings and scrotum should be assessed for bowel herniation. These are typically soft and fluctuant swellings that are easily reduced when the foal is placed on its back and are managed by manual reduction and strapping. Incarceration is rare but bowel integrity can be assessed using ultrasound; devitalized bowel lacks motility and has a thickened and edematous wall. In some colts the intestine can protrude through a rent in the parietal vaginal tunic and migrate subcutaneously in what is described as a direct **inguinal hernia**[25] (Fig. 16-3). This is often associated with prepucial swelling and requires surgical intervention.

Digital rectal examination is indicated in a colicky foal or in any foal in which meconium passage has not been observed. Distal **meconium impaction** is typically apparent on rectal examination but high impactions are not. Intestinal atresia should be suspected if there



FIG. 16-2 A foal demonstrating a classical hunched appearance while straining to pass feces.

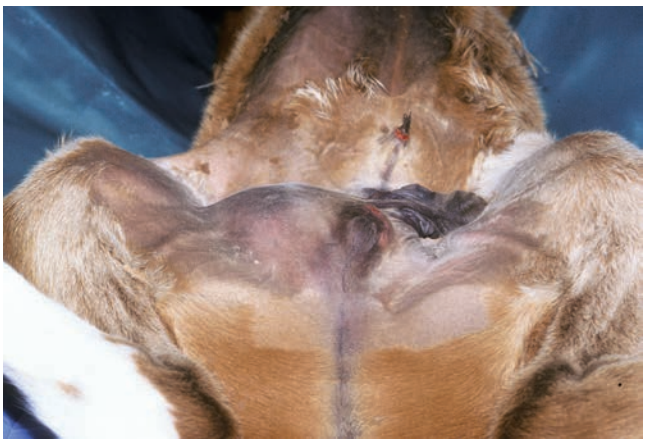


FIG. 16-3 A dissecting scrotal hernia prior to surgical repair.

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FIG. 16-4 Coprophagy is an important behavior in establishing hindgut flora.

is no history of fecal passage and clear or white mucus appears on the glove.

Passage of a nasogastric tube is an often overlooked diagnostic procedure in colicky neonatal foals. Removal of gastric fluid can reduce or eliminate colic signs as well as aid in the localization of disease. Gastric distention may also be present in sick neonates showing no signs of colic. The condition occurs with primary gastric outflow problems or mechanical or functional small intestinal obstruction. Functional obstruction caused by small intestinal ileus occurs more commonly in neonates as a result of a range of diseases, including hypoxic ischemic syndrome, sepsis, prematurity, enteritis, electrolyte derangements, and overfeeding.

Coprophagy is observed in normal foals from birth through 5 to 6 months of age.[26-28] Most foals demonstrate coprophagy by 7 days of age (Fig. 16-4). The consumption of feces is not driven by hunger, and foals have a selective preference to consume feces of their dams. The most likely basis for coprophagy is as a mechanism to populate the intestinal tract with bacteria, fungi, and protozoa essential for digestion of an herbivorous diet. Coprophagy precedes the passage of protozoa in foal feces and the development of the syndrome known as "foal heat diarrhea." This is a benign diarrheal disease of newborn foals and should not require treatment.

ABDOMINAL ULTRASOUND. Ultrasound is a key component in the examination of a foal abdomen. Numerous conditions are recognized on ultrasound, including uroperitoneum, bacterial peritonitis, hemoperitoneum, strangulating intestinal obstructions, meconium impaction, gastric enlargement, enteritis, necrotizing enterocolitis, and hernias. The foal can be scanned in lateral recumbency or standing; the latter is preferred because thickened or heavy structures will move to the dependent region of the abdomen, gas-filled structures will migrate dorsally, and visualization of peritoneal fluid is improved. Clipping is not essential if the hair is dampened with alcohol. The stomach is identified in the mid to ventral abdomen on the left side between the 6th and 12th intercostal spaces (ICS) and lies medial to the spleen. In contrast to adults, the stomach is commonly in contact with the ventral body wall during the first week of life and the contents are readily imaged.[29] Gastric wall thickness is typically around 2.0 mm during the first week of life. The duodenum is readily located in normal foals on the right side of the abdomen between the ventral and caudal aspect of the liver and the dorsal margin of the right dorsal colon, as well as ventral to the caudal pole of the right kidney. The remainder of the small intestine is also easily identified throughout the abdomen and should have a wall thickness less than 2.5 mm. The large intestine is differentiated from the small intestine by increased luminal diameter, bowel sacculations, and greater likelihood of gas. The colon wall should be less than 2.8 mm during the first week of life. The neonate with acute colic should be assessed with ultrasound for small intestinal intussusception. These are readily identified, are typically jejunojejunal, and are often located in the ventral abdomen when the foal is standing. They have a characteristic appearance with the intussusceptum surrounded by fluid and the intussuscipiens creating a "target" sign. Some will resolve spontaneously but most require surgical reduction. Meconium impactions have an echogenic ball or log appearance when in the small colon, or a more varied appearance when present in the large colon, a hypoechoic to hyperechoic mass that may be surrounded by fluid.[30] Thickening of the wall with intramural gas echoes is consistent with a strangulated obstruction or necrotizing enterocolitis. Abdominal hemorrhage results in a classical "smoke swirl" appearance to the peritoneal fluid.

ABDOMINAL RADIOGRAPHY. Radiography has been displaced as the principal imaging modality of the foal abdomen but still can provide essential information.[31] Contrast radiography remains an important technique to assess gastric outflow problems, intestinal transit, intestinal atresia, and high meconium impaction. The abdomen of most neonatal foals can be captured on a 35- × 43-cm cassette. A grid should be used to minimize film fogging. For a standing foal weighing around 50 kg, using a 400-speed film-screen system, a grid with a 10:1 grid ratio, and a focal spot-film distance of 100 cm, the appropriate technique should be in the range of 80 to 90 kV (peak) and 15 to 20 mA. This technique can be reduced slightly with lateral projections in the recumbent foal. The beam should be centered on the last rib. For upper GI contrast studies, 5 mL/kg of 30% wt/vol barium suspension is administered through a nasogastric tube; ideally foals are fasted for 4 hours before the procedure and should not be sedated. Barium typically empties rapidly from the stomach, allowing examination of the stomach and duodenum on initial films. The contrast should clear the small intestine by 3 hours and be completely cleared by 36 hours. The cecum should visible by 1 to 2 hours after administration. A barium enema can be used to evaluate the lower intestinal tract, specifically intraluminal obstruction and atresia. Sedation can be used because the procedure is not defining a dynamic problem. A 30-French Foley catheter with a 30-cm^3 balloon is inserted 6 to 10 cm into the rectum, the cuff inflated, and 300 to 500 mL of 30% wt/vol barium sulfate suspension infused. Volumes up to 20 mL/kg have been described; colonic or rectal rupture is a rare, but fatal, complication of the procedure. Computed tomography (CT) is an underutilized tool in the assessment of the foal abdomen, with most applications involving examination of limbs, head, or neck.[32]

ABDOMINOCENTESIS. Peritoneal fluid can also be evaluated by abdominocentesis. The technique has a greater complication rate in neonates, and ultrasound should be used to identify pockets of fluid for sampling. Most complications arise as a result of a combination of hypodermic needles, a moving patient, and a relatively thin bowel wall. If no fluid is identified, the procedure should not be performed. For small volumes it is recommended to use a blunt, small bovine teat cannula; for larger volumes a hypodermic needle can be used. Peritoneal fluid–nucleated cell counts are lower in foals than in adult horses.[33] Nucleated cell counts above 1.5×10^9/L may be considered abnormal in foals up to 4 months of age,[34] although another study suggested a value of 3.0×10^9/L as a cutoff for foals less than 75 days of age.[35] Cytologic evaluation is similar to adults with a predominance of large mononuclear cells (macrophages and mesothelial cells) with smaller numbers of lymphocytes and neutrophils. The relative percentage of neutrophils (15%) may be less than that seen in normal adult peritoneal fluid. The protein concentration of foal peritoneal fluid is similar to that of adults, below 20 g/L, and therefore values above this are considered abnormal. An increased total nucleated cell count, increase in the percentage of neutrophils with cell degeneration, and intra- and extra-cellular bacteria would be expected in foals with septic peritonitis. This would be accompanied by a low pH (<7.2), increased lactate concentration, and a

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discrepancy between serum and peritoneal glucose concentrations (>2.7 mmol/L).[33]

Cardiovascular System

Physical assessment of the cardiovascular system includes examination of visible mucous membranes, palpation of peripheral arterial pulses, assessment of extremities for warmth, detection of limb or ventral edema, and cardiac auscultation. The heart rate in newborn foals in the minutes after birth is influenced by vagal tone and varies between 36 and 80 beats/min. As the foal becomes active and struggles to stand, the heart rate will increase to 120 to 150 beats/min before stabilizing in a range of 80 to 100 beats/min over the first week of life.[36] Tachycardia is an important mechanism in neonates to improve cardiac output and blood pressure, and it is expected during periods of asphyxia and in response to hypovolemia, sepsis, anemia, or hypoxemia. A sustained increase in heart rate may also accompany pain or stress, or reflect a primary cardiac problem. Bradycardia can be due to hypothermia, electrolyte abnormalities, or hypoglycemia.

Cardiac arrhythmias are rarely recognized but occur in most foals during the immediate postpartum period with supraventricular premature contractions and sinus arrhythmia predominating.[37,38] Other arrhythmias include atrial fibrillation, ventricular premature contractions, ventricular and supra ventricular tachycardia, and idioventricular rhythm. These rhythm disturbances typically only last for 5 minutes and in most foals have disappeared by 15 minutes of age. Rarely they may persist up to 2 hours of age. The more severe arrhythmias are associated with a lower arterial oxygen concentration, suggesting a role for hypoxemia in the pathophysiology of these events. Arrhythmias that persist beyond this time frame should be investigated by electrocardiogram (ECG). Causes include electrolyte abnormalities, persistent hypoxemia, and sepsis.

Cardiac murmurs are expected in the early neonatal period. A patent ductus arteriosus (PDA) can result in a continuous machinery murmur with a point of maximal intensity high over the left heart base in the 3rd intercostal space.[39] These are typically audible up until 3 to 4 days of age.[40] As the DA begins to close, the systolic component of the murmur often remains audible. Low-intensity left-sided systolic murmurs are commonly heard through the first months of postnatal life. It has been suggested that these are most likely due to turbulence created during left ventricular ejection, although others have suggested that flow through the DA may persist for weeks to months.[41] Loud murmurs that persist beyond 7 days of age, or any murmur that is accompanied by signs of cardiac disease, such as poor growth, cyanosis, lethargy, or exercise intolerance, should be referred for echocardiography. Auscultation of both sides of the thorax is important because right-sided cardiac murmurs are a feature of several congenital cardiac anomalies. Occasionally serious cardiac defects may not be associated with audible murmurs. Although most congenital cardiac diseases are detected in foals or young horses, some defects do not become apparent until the horse is required to perform or may occur simply as incidental findings in older horses.

Distal extremities should be free of edema and warm to the touch. Limb edema can occur for several reasons, but most commonly as a result of asphyxia or in response to inappropriate fluid therapy in oliguric or anuric foals. Limbs that are cool or cold are poorly perfused and will typically have weak arterial pulses. However, the relationship between peripheral pulse pressure and hypotension is not consistent; hypotension is not always associated with weak pulses and, conversely, weak pulses do not always indicate hypotension.[42] Arterial thrombosis should be suspected if a single limb is cold, although an aortic thrombosis could result in decreased perfusion to both hindlimbs.[43] Pulse quality can be assessed in the distal limbs using the great or dorsal metatarsal arteries on the lateral aspect of the hind cannon bone. In the forelimbs the brachial artery can be palpated at the level of the medial collateral ligament of the elbow joint. Several methods are available to assess arterial blood pressure. Direct blood pressure monitoring is ideal because it is accurate and continuous, but it is invasive and difficult to maintain, and it can be complicated by vessel thrombosis or sepsis. More commonly blood pressure is monitored indirectly using oscillometry or Doppler-based devices over the coccygeal, brachial, or great metatarsal arteries. An infant-sized inflatable cuff (bladder, 52 mm) placed snugly around the base of the tail yields data that are comparable to mean arterial measurements taken directly from a catheterized great metatarsal artery in a day-old foal weighing between 44 and 69 kg.[44] The technique tended to underestimate systolic and overestimate diastolic values, although the differences were not large. The mean arterial pressure of a healthy Thoroughbred foal using an oscillometric device was reported to be 95, 100, and 101 mm Hg at days 1, 2, and 3, respectively.[45] Other noninvasive methods to measure cardiac output, such as volumetric echocardiography, have shown good correlation with more robust but invasive techniques in anesthetized foals. The question remains if this correlation will be sustained in conscious, critically ill foals.

Respiratory Tract

In newborn foals the nasal passages are examined for meconium staining and, if present, the passages should be suctioned using a dose syringe and soft catheter or other portable or fixed suction device. The early stages of pulmonary disease are difficult to recognize because cough and nasal discharge are typically absent. Immature cough receptors also contribute to a lack of awareness of ongoing milk aspiration into the major airways. Auscultation of the lung fields can also be very misleading in young foals. Fluid sounds are normally present immediately after birth, as are end-inspiratory crackles resulting from simple atelectasis of the dependent lung during or after lateral recumbency. These crackles should resolve when the foal has been standing for several minutes. Conversely, foals with bronchopneumonia may have minimal abnormal lung sounds until the pathology becomes severe. In the absence of advanced diagnostics, the clinician must rely on clinical signs, such as restlessness and agitation, increased respiratory rate and depth, or overt respiratory distress, to diagnose lower airway disease.

The normal response after delivery is an increase in minute ventilation, with elevations in both rate and tidal volume. The respiratory rate is usually rapid for the first hour of life, around 60 to 80 breaths/min, but should decline to a steady rate of 30 breaths/min thereafter in normal foals. Persistent elevations in the respiratory rate can be caused by a range of pulmonary and extra-pulmonary causes. Pulmonary causes include meconium aspiration, bacterial or viral pneumonia, atelectasis resulting from recumbency, congenital pulmonary disease, rib fracture or dislocation, or pleural effusion. Extrapulmonary causes include fever, pain, excitement, exercise, brain disease, a compensatory response to metabolic acidosis, or idiopathic or transient tachypnea syndrome. An increase in the effort of breathing may be the first sign of respiratory disease. As the disease progresses, the foal can develop paradoxical thoracic wall motion as a result of muscular fatigue where the thoracic wall paradoxically moves inward during inspiration and outward during expiration. This is more commonly seen in premature foals with lung disease and is a sign of impending respiratory failure. Another sign of failure is an expiratory "grunt"; foals will keep their glottis closed until the end of the breathing cycle in order to maintain sufficient pressure in the respiratory tract to prevent airway collapse.

Respiratory rhythm should be regular in awake foals, but may be irregular in normal foals during rapid eye movement (REM) sleep. This can also include body and limb movements and vocalization. Irregular or erratic breathing patterns in conscious foals, or in foals that are in coma or semi-coma, are consistent with central nervous system (CNS) disease, or less commonly metabolic or electrolyte disorders, hypothermia, or prematurity or dysmaturity. Patterns include periodic breathing, ataxic breathing, tachypnea, hypopnea or intermittent apnea, and apneustic breathing. Hypopnea or apnea in foals with CNS disease may result in severe respiratory acidosis, prompting the use of respiratory stimulants or mechanical ventilation. Doxapram administered as a CRI was more effective than oral caffeine at reducing the arterial carbon dioxide concentration ($PaCO_2$) in affected foals.[46]

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TABLE 16-2

Normal Blood Gas Values for Foals*

Age Group	Arterial O_2 (mm Hg)	Arterial CO_2 (mm Hg)	Arterial pH	Arterial Base Excess	Arterial HC^-_3 (mEq/L)	Venous O_2 (mm Hg)	Venous CO_2 (mm Hg)	Venous pH	Venous HC^-_3 (mEq/L)
Immediate post-foaling†	40-50	52-60	7.2-7.3	+2	24-26	—	—	—	—
2 hours†	68 ± 10	49 ± 2	7.37 ± 0.01	+4	26 ± 2	42 ± 2	56 ± 2	7.33 ± 0.01	28 ± 2
4-12 hours‡	75 ± 5	47 ± 2	7.39 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 2
24 hours‡	81 ± 6	48 ± 2	7.4 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 3
1-3 days‡	90 ± 6	148 ± 2	7.4 ± 0.01	+6	28 ± 2	43 ± 2	52 ± 2	7.38 ± 0.01	29 ± 2
4-14 days‡	86 ± 5	45 ± 2	7.41 ± 0.01	+6	28 ± 1	38 ± 2	53 ± 2	7.38 ± 0.01	31 ± 2
Premature† birth (320-330 days' gestation)—1 hour	39 ± 5	55 ± 4	7.27	−3	24 ± 1	—	—	—	—
	52 ± 4	48 ± 3	7.33	−1.3	25 ± 1	—	—	—	—

*Lateral recumbency.

†Data from Rose RJ, Rossdale PD, Leadon DP. 1982. Blood gas and acid-base status in spontaneously delivered, term-induced and induced premature foals. J Reprod Fertility 32:521.

‡Data from Stewart JH, Rose RJ, Barko AM. 1984. Response to oxygen administration in foals: effect of age, duration and method of administration on arterial blood gas values. Equine Vet J 16:329.

Respiratory distress or stertorous breathing can be caused by several uncommon conditions in the newborn foal. A range of congenital cardiac or respiratory tract malformations should be considered if abnormalities are present at or shortly after birth. Those involving the respiratory system include stenotic nares, choanal atresia, subepiglottic cysts, collapsing trachea, and lung lobe agenesis. Tearing of the diaphragm during birth with herniation of abdominal contents can also result in immediate respiratory distress. Similar distress can be seen with a dorsally displaced soft palate caused by neurologic or anatomic dysfunction. Soft fluctuant swelling in the parotid region could be consistent with guttural pouch tympany. The condition is more commonly seen in older foals but has been reported in the early neonatal period often associated with pharyngeal/laryngeal weakness and altered ostia function. This may also result in milk entering the pouch. A predisposition in fillies and certain breeds, including Arabians and Paints, has been reported.[47]

Localized or widespread crepitus of the subcutaneous tissues could be consistent with air leakage from respiratory tissues, most commonly from ruptured pulmonary bullae.[48] The thoracic wall should be palpated for evidence of rib shaft fractures or costochondral dislocation. Thoracic trauma and rib fracture occur most commonly as a complication of the birthing process. They are identified by observation of thoracic wall symmetry and synchrony, palpable crepitus, and localized edema. In addition, there may be an audible "click" on auscultation of the thorax. Affected foals may grunt on expiration and prefer to lie on the unaffected side. Diagnosis is confirmed by ultrasound or radiographic examination. On ultrasound examination there is disruption of the cortical surface and associated soft tissue edema. Management includes recognition and treatment of potential complications and avoidance of further thoracic trauma. Potential clinical complications of rib fracture include hemothorax, lung laceration and pneumothorax, and pericardial/myocardial puncture.

ARTERIAL BLOOD GAS COLLECTION AND ANALYSIS. Because of the limitations of physical examination in accurately assessing the respiratory system, arterial blood gas (ABG) analysis is commonly performed at referral practices during the initial assessment. It is a sensitive indicator of respiratory function.[49] The sample is usually collected from the dorsal metatarsal artery. Alternative sites include the brachial artery, located at the level of the medial collateral ligament of the elbow joint, or the carotid artery, but hematoma formation is a common sequel to aspiration from this site. The sample will remain useful for up to 90 minutes in a capped plastic syringe at room temperature. Contamination of the sample with room air will artificially increase the arterial oxygen concentration (PaO_2) and decrease the $PaCO_2$. Interpretation of blood gas values of venous blood can be very deceptive and should be restricted to evaluation of metabolic conditions and not pulmonary gas exchange.

Normal ABG values for neonates of different postnatal and gestational ages are presented in Table 16-2. Interpretation of the ABG sample involves consideration of the amount of struggling and position of the foal during sample collection. Foals that require considerable restraint to obtain a sample probably do not require sampling. Lateral recumbency can reduce the PaO_2 by as much as 30 mm Hg. Supplemental oxygen affects ABG values; a flow rate of 10 L/min (lpm) delivered by nasal insufflation increased the PaO_2 from 84 ± 6 mm Hg to 298 ± 69 mm Hg in healthy, full-term newborn foals.[50] This flow rate approximates to a fraction of inspired oxygen (FiO_2) of 1.0.[51] If the respiratory rate is rapid and the depth shallow, supplemental oxygen will be diluted by room air because of the large quantity of room air entering the upper respiratory tract, and the concentration of alveolar oxygen will be less than expected. A general guide for supplemental oxygen use is to use an initial flow rate of 5 lpm. Oxygen should be humidified if delivered at high flow rates or for long periods.

Hypoxemia (PaO_2 < 70 mm Hg) can occur with hypoventilation, ventilation/perfusion mismatching, or right-to-left shunting of blood.[49] The two most common respiratory-derived derangements are hypoxemia with normocapnia or hypocapnia, and hypoxemia with hypercapnia. The treatment of the former involves supplemental oxygen. The latter is usually indicative of severe respiratory disease but could reflect primary hypoventilation as may occur in cases of botulism. Acute hypercapnia is associated with a more substantial drop in blood pH and may lead to circulatory collapse and coma, particularly if accompanied by hypoxemia. Chronic exposure to elevated CO_2 permits adaptation and more subtle clinical effects. The change in pH is less dramatic because of enhanced bicarbonate reabsorption in the proximal tubules of the kidney, a process that begins within 6 to 12 hours and is maximal by 4 days. Hypercapnia can be exacerbated by fever or the administration of carbohydrates or bicarbonate. The latter is often clinically relevant and highlights the danger of giving large amounts of sodium bicarbonate to foals with pulmonary disease, potentially taking a primary metabolic acidosis and creating a more severe respiratory or mixed acidosis. Hypercapnia is also an expected response to metabolic alkalosis.[52]

Airway sampling either by transtracheal aspiration (TTA) or bronchoalveolar lavage is rarely performed in sick neonates because the added stress of the procedures on an already compromised neonate can have fatal consequences. The TTA procedure is more likely to cause additional complications in foals with high ventilation rates, including pneumomediastinum and subcutaneous emphysema.

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Pulmonary Imaging

Radiography can provide additional information that can assist in establishing a diagnosis, assessing the type and distribution of disease, and monitoring the response to treatment.[31] Radiographs are particularly useful in the diagnosis of rib shaft fractures, pneumothorax, pleural effusion, and diaphragmatic hernia. Radiographic changes associated with pulmonary disease tend to lag behind clinical changes, and it is difficult to differentiate atelectasis from pneumonia. Infiltrate tends to settle or move ventrally as the foal becomes ambulatory. Unfortunately, capturing diagnostic thoracic images in the field is difficult because of the amperage of portable machines and the limitation in plate size. The relatively low amperage results in long exposure times, which, in a poorly compliant patient with high respiratory rate, leads to motion artifact and a false interpretation of disease. Images tend to be limited to standing or recumbent lateral projections as positioning for ventrodorsal views can further compromise the cardiopulmonary system. Pleural and parenchymal diseases have a similar ultrasonographic appearance in newborn foals to that seen in adults. Anechoic pleural fluid can be seen with some infectious processes, in foals with uroperitoneum, or with some congenital anomalies. Echogenic or cellular fluid is seen with other infectious processes, and in hemothorax cases characteristic "smoke whirls" will be present.

Urogenital System

As the foal begins to move after birth, it causes stretch and breakage of the umbilical cord, typically around 3 cm beneath the abdomen. This can also occur when the mare rises after foaling.[53] Early separation of the cord has no detrimental effect, provided the cord is severed by stretch rather than sharp dissection. The volume of placental blood available for transfer to the foal under normal circumstances is relatively small, typically well below 200 mL.[54] Greater volumes may be lost if the cord is cut, preventing contraction of vascular smooth muscle. Hemorrhage should therefore be controlled with a commercial clamp or umbilical tape. Prolonged attachment of the cord is unlikely to be a significant problem, although blood flow between the placental membranes and the foal is partly gravity dependent, such that blood could flow preferentially from foal to membranes if the foal is above the level of the placenta. Manual breakage of the umbilical cord is recommended if it remains attached for more than 8 minutes. The preferred method for manual cord breakage is to grasp the placental side of the cord while holding the foal side of the cord with the other hand to prevent excessive traction on the abdominal wall. Gently twist and pull from the placental side such that the breakage will occur at the natural site of detachment. Intraabdominal umbilical arteries may continue to pulse for several days after delivery; this may result in a palpable pulse in the umbilical stump, but this is not associated with blood flow.[54] The umbilical stump should be treated once or twice daily until it becomes dried and sealed. A 0.5% chlorhexidine solution is preferred; however, it may cause delayed drying of the stump. Iodine solutions can also be used, but the concentration should be limited to 2% to prevent tissue necrosis.

Urine is one of the most important indicators of health in foals. As a consequence of a milk diet, normal neonatal foals produce a large volume of urine relative to their body weight, estimated at 148 mL/kg/day, or 7.4 L/day for a 50-kg foal. This value is approximately 5- to 10-fold greater than that of a healthy adult horse on a per-kilogram body weight basis.[55] The first passage of urine after birth occurs around 12 hours of age in normal foals, with colts passing urine earlier than fillies. The first urination in normal foals is concentrated with a specific gravity greater than 1.030, which will gradually decrease with subsequent urinations. The urine will become light in color and have a very low specific gravity, typically 1.001 to 1.008. Any foal observed to pass thick, concentrated urine should be assessed closely. Disruption to the urinary tract occurs relatively commonly and can be difficult to diagnose early in the clinical course. **Rupture of the urinary bladder** during delivery occurs more commonly in colts than fillies, although postpartum disruption to the tract in sick or hospitalized foals has no gender bias.[56,57] Signs often include prolonged straining, passage of small volumes of urine, progressive abdominal distention, lethargy, and weakness. Patency of the urachus is a common complication in sick newborn foals. Surgery is rarely required because most will close spontaneously by 2 weeks of age. Techniques to hasten closure generally involve chemical cautery, such as application of silver nitrate around the external opening. However, some believe that the resultant inflammation could predispose to infection of damage to internal structures and therefore limit their therapy to local disinfectants and systemic antibiotic therapy. Surgery would generally be recommended if the urachal leakage continued beyond 3 weeks of age.

In colt foals, the inguinal and scrotal region should be palpated for swelling and testicular descent. Inguinal and scrotal hernias occur relatively commonly but rarely result in clinical signs. Preputial edema may be present. Most congenital hernias are indirect, unilateral, easily reducible, and spontaneously resolve by 3 to 4 months of age. Positioning the foal on its back facilitates manual reduction. A figure-8 support wrap can assist in keeping the hernia reduced. Surgical correction is recommended if spontaneous resolution is delayed, if the hernia increases in size, or if signs of colic develop. Certain breeds appear to be at increased risk for herniation, including Tennessee Walking horses and Standardbreds. A rent in the parietal vaginal tunic can lead to subcutaneous dissection of intestinal loops; this requires surgical reduction, herniorrhaphy, and unilateral castration.[58] Although extremely uncommon in foals, signs of colic can occur if herniated loops of intestine strangulate.

At the time of birth most testes lie within the inguinal canal. The extraabdominal gubernaculum, which can be easily mistaken for a testicle, typically limits movement into the scrotum. Monorchidism has been reported in foals, and affected colts are usually mistaken as cryptorchids.[59] Congenital abnormalities of the penis are rare. Failure to drop the penis during urination can occur as a consequence of preputial edema, a common complication in colts that are straining to defecate or urinate. The free part of the penis is normally fused to the internal lamina of the prepuce for up to 1 month of age. This can make exteriorization of the penis difficult. "Kinking" of the penis has been described, which results in stranguria or pollakiuria.[60] Correction is achieved through manual straightening of the penis.

Umbilical Hernias

Umbilical hernias occur commonly in foals. The condition is generally considered to be a congenital defect with a likely hereditary basis, although umbilical infection may be an important postnatal predisposing factor. In a study of Dutch warmblood foals, 19 of 44 had a palpable abdominal wall defect between 2 and 6 cm at the time of birth.[61] In all but one of these foals, the defect had closed by 4 days of age; however, 28% of the foals developed a defect between 5 and 8 weeks of age. These were considered to be true umbilical hernias in that a hernial sac with contents was palpable in addition to the abdominal wall defect. The group included foals both with and without a palpable abnormality at birth. A study of hospitalized foals concluded that the defect was more likely to occur in fillies than males, and that the condition was more common in Thoroughbreds than Standardbreds.[62] Most clinicians recommend delay in treatment, since some defects will close spontaneously. Several techniques have been described for repair and vary from external clamps to surgical herniorrhaphy. There are rare complications associated with umbilical hernias or their repair. These include colic, enterocutaneous fistulae, umbilical abscessation, and intestinal incarceration.[63]

ULTRASOUND EXAMINATION OF THE UMBILICAL AND RELATED STRUCTURES. The examination can be performed with the foal either standing or in lateral recumbency using a mid- to high-frequency linear transducer (Fig. 16-5). Clipping is helpful but not necessary, and most examinations are adequately performed using alcohol with or without coupling gel. Images are obtained in a short-axis (transverse) plane with the probe orientated perpendicular to the vertebral column and in a long-axis (sagittal) plane with the

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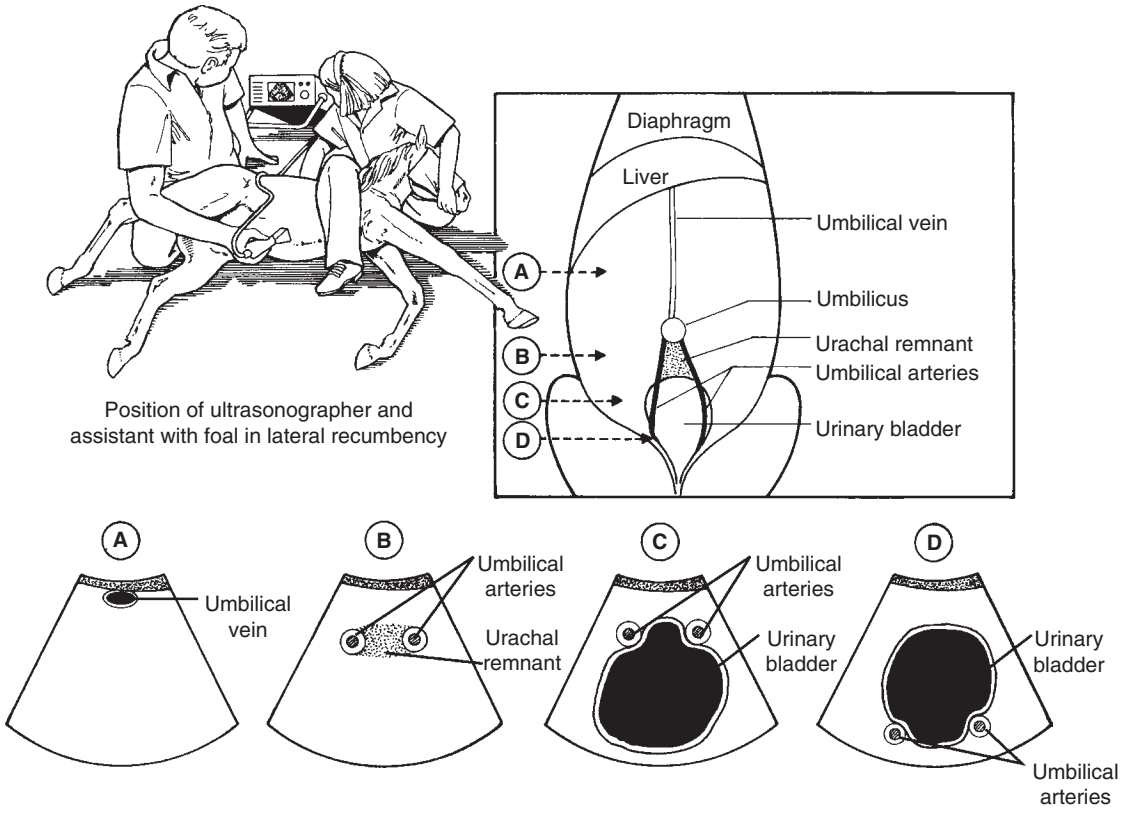


FIG. 16-5 Ultrasound evaluation of equine umbilical structures. Diagram depicts the positioning of the ultrasonographer and the assistant and the selected anatomic locations for ultrasound examination.

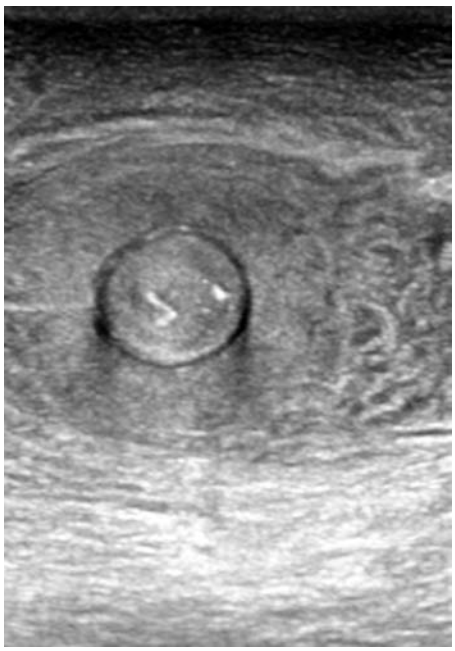


FIG. 16-6 An ultrasound image of an enlarged umbilical stump external to the body wall. The entire stump was 34 × 43 mm. Note the central core surrounded by thickened tissue.

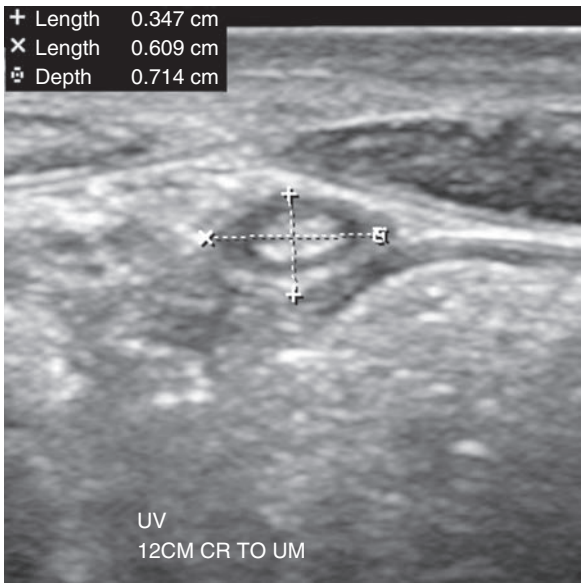


FIG. 16-7 A normal umbilical vein imaged transversely 12 cm cranial to the umbilicus.

probe parallel to the spine. The external umbilical stump can be assessed for size and echodensity; there are no published normal dimensions for size of the stump (Fig. 16-6). The umbilical vein runs cranially from the umbilical stump to the liver. It is located 1 to 2 cm deep to the skin and is a thin-walled ovoid structure that is 5 to 10 mm in maximal diameter (Fig. 16-7).[64] The paired umbilical arteries originate from the internal iliac arteries and run adjacent to the urinary bladder and urachus before emerging at the umbilical stump. The arteries atrophy postpartum and become the round ligaments of the bladder. They appear as thick-walled hyperechoic structures that should measure less than 13 mm in diameter (Fig. 16-8).[64] Asymmetry in size is common and there may be an echogenic core due to arterial clot (Fig. 16-9). Pulsation may also be noted in very young foals. The urachus connects the apex of the bladder to the umbilical stump. It can be difficult to image unless it is filled with fluid, as would occur during patency. At the level of the bladder apex,

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FIG. 16-8 A transverse image taken 2 cm caudal to the umbilicus showing the normal paired umbilical arteries and the apex of the bladder. The arteries measured 4.2 and 4.7 mm in diameter.



FIG. 16-9 A transverse image demonstrating asymmetry in size and echodensity between the two umbilical arteries. Both were considered normal and the combined measurement was within normal limits.

the combined diameter of the urachus and arteries in transverse view should be less than 25 mm. The bladder wall should be examined for defects; a full appearance to the bladder does not preclude a leak (Fig. 16-10).

Neurologic System

Differentiation of primary neurologic disease from systemic illness can be difficult because many critically ill foals are somnolent, recumbent, and unable to suck. Neurologic examination of the neonatal foal has several features that are unique to animals of that age.[65] Although a domed skull could be consistent with hydrocephalus, it is also a physical feature of immaturity. Furthermore, hydrocephalus and other congenital brain abnormalities may occur with a normal skull shape and size. Examination of the head should be done with the foal standing or in sternal recumbency. The eyes have a normal, slight ventromedial rotation in young foals. As described previously, pupillary light responses are present but sluggish and the menace response is typically absent in the first week of life, although the foal should withdraw its head in response to a threatening gesture.

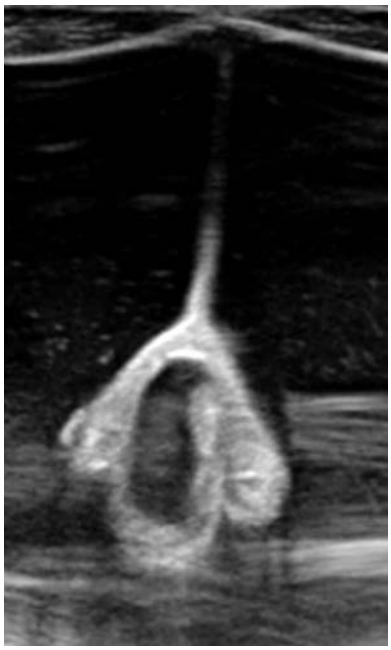


FIG. 16-10 A collapsed bladder attached to the body wall with a large volume effusion consistent with uroperitoneum. The arteries give the collapsed bladder a classic shape.

Further assessment of vision can be made through observations of behavior and navigation through obstacles.

The ability to suck and swallow milk should be evaluated. The suckle reflex should be evaluated using a clean, and preferably gloved, finger. Dysphagia can be recognized by nasal regurgitation of milk or milk coming out of the mouth. Although a cleft in the palate should be important to rule out, it occurs less commonly than pharyngeal/laryngeal weakness and incoordination caused by hypoxic-ischemic syndrome or systemic weakness. Uncommon causes include persistent dorsal displacement of the soft palate, subepiglottic cyst, esophageal disease, or nutritional myodegeneration. Esophageal diseases are rare in the newborn foal. Reported conditions include congenital dilatation or ectasia, tubular or cystic esophageal duplication, megaesophagus, motor dysfunction, and stricture. Most descriptions are in foals outside of the neonatal period. Aspiration of milk into the airway may be difficult to identify because of immaturity of cough receptors; auscultation over the trachea after nursing may identify fluid sounds.

Limb reflexes can be evaluated with the foal loosely restrained in lateral recumbency. Spinal reflexes, such as the patellar, sciatic, and cranial tibial reflexes, are hyperactive in the newborn foal and therefore easily elicited. The neonatal foal can have strong thoracic and pelvic limb–crossed extensor reflexes, where a stimulus to the distal limb causes flexion (withdrawal) of the affected limb and extension in the contralateral limb. This reflex is typically seen only in adults with severe or chronic upper motor neuron lesions.[66] The painful stimulus should also be recognized centrally.

The **gait** should be evaluated for evidence of paresis or ataxia. The normal gait is hypermetric and bouncy, but it should be precise and symmetric and be free of circumduction and toe-dragging.[65] Generalized hypotonia is seen with hypoxic-ischemic syndrome, sepsis, prematurity, botulism, white muscle disease, or heritable muscle disorders. A "bunny hopping" gait could be suggestive of a myelodysplasia, and examination of anus, tail, and perineum is indicated. Peripheral nerve damage can occur with birthing trauma, particularly brachial plexus or radial nerve injury from forelimb traction. Affected limbs are weak and hyporeflexic and may have regions of anesthesia.

Seizures can vary from localized or partial to generalized. As described previously, normal foals in REM sleep can be active, including galloping actions, neck extension, and vocalization. These

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FIG. 16-11 Collection of cerebrospinal fluid at the atlanto-occipital site using a hypodermic needle.



FIG. 16-12 Bilateral carpal and fetlock contracture in a newborn foal.

can last for several minutes and be confused with seizures. Narcolepsy/cataplexy should be suspected in foals that collapse, remain laterally recumbent for several minutes in a sleep state, and then recover uneventfully. The condition has been reported in American Miniature Horses, Morgans, Shetlands, and Suffolks.[65] It is possible to induce collapse and flaccidity by applying pressure to the thorax in normal newborn foals. The response is referred to as "squeeze-induced somnolence."[67] There is a decrease in respiratory and heart rate and activation of the hypothalamic-pituitary-adrenal axis. The response was originally thought to be a form of narcolepsy or cataplexy, but EEG data in a small number of foals were not consistent with REM sleep—a feature of true narcolepsy.[67] An exaggerated head nod, a basewide stance with truncal sway, and dysmetric gait without weakness may indicate cerebellar dysfunction. The most common cause would be cerebellar abiotrophy, an inherited condition of Arabian horses and Gotland ponies.

CEREBROSPINAL FLUID COLLECTION. Samples of cerebrospinal fluid (CSF) can be obtained from the atlanto-occipital (AO) or lumbosacral (LS) sites. The procedure is helpful in differentiating neonatal encephalopathy from bacterial meningitis. An AO CSF tap is a relatively straightforward procedure (Fig. 16-11). In comatose or profoundly somnolent foals, an AO tap can be performed using diazepam (0.05 to 0.2 mg/kg IV), local anesthesia, and adequate restraint. In more active foals, general anesthesia should be used. In most neonatal foals the tap can be performed using a 3.8-cm, 18- to 20-gauge hypodermic needle; in larger foals (>55 kg) a styleted spinal needle will be required. The needle is inserted at the intersection of a line drawn from the anterior wings of the atlas and the midline. The poll is flexed tightly and the needle is directed to the mandible. Alternatively, CSF can be collected from the LS site in the standing foal or in foals that are laterally recumbent without the need for general anesthesia. The landmarks for LS are the cranial borders of the tuber sacrale. A 3.5-inch styleted needle is inserted on midline approximately 5 mm cranial to a line intersecting the borders of the tuber sacrale after local anesthesia and a stab incision with a no. 15 blade. The sample should be analyzed within 30 minutes because of rapid cell degeneration. Normal CSF has 1 to 5 cells/μL with cells restricted to monocytes and lymphocytes. There should not be any neutrophils in normal foal CSF. Yellow discoloration (xanthochromia) and slight turbidity of the sample can be normal. Similarly CSF protein concentration can be elevated in foals during the first 2 days of life.[68]

Musculoskeletal System

The hoof wall of the newborn foal is covered by soft horn (or perionychium), a protective layer that is rapidly worn away when the foal begins to ambulate.[69] The coronary bands should be examined for hyperemia, an early indicator of systemic sepsis. Changes in hoof capsule temperature could also indicate regional or generalized perfusion problems. The limbs should be assessed for **flexural laxity** or **contracture** (Fig. 16-12). Mild to moderate limb contraction can make it difficult for the foal to stand and ambulate. In response to pain, foals with contracted tendons may have elevated heart and respiratory rates, as well as diffuse muscular tremor. In severe cases the foal may not be capable of standing. Treatment involves a combination of analgesia, splinting, and intravenous oxytetracycline. Repeated dosing of oxytetracycline is discouraged due to the risk of renal complications.[70] Extensor tendon rupture is a complication of flexural contraction and is recognized by discrete soft fluctuant swelling on the lateral aspect of the carpus. The condition usually responds well to conservative management. Fetlock laxity is common and can often be managed using heel extensions taped to the foot.



FIG. 16-13 Rupture of the gastrocnemius muscle has a guarded to poor prognosis in foals.

As part of the physical examination all peripheral joints and physes should be palpated for swelling, heat, pain, and edema. Although trauma is often implicated as the source of any lameness, infection should always be considered as the most likely cause until proven otherwise. Other problems that may be identified in the neonate include rupture of the gastrocnemius muscle (Fig. 16-13) or associated muscle and patellar luxation.

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FIG. 16-14 Swelling around the umbilicus caused by tearing of the urachus within the tissues of the body wall.

Premature or dysmature foals have **joint laxity** and **delayed ossification.** Joint laxity can predispose affected foals to angular limb deformities. These are managed through a combination of hoof trimming, exercise restriction, and splinting. Delayed ossification is assessed using radiography, centering on the cuboidal bones of the tarsus and carpus. The management of delayed ossification is difficult, and collapse or crush of cuboidal bones can sometimes be unavoidable. Preventive strategies include restricted exercise and splinting.

Supplementation of foals with selenium is recommended for those born in known selenium-deficient regions where mares have not been supplemented during pregnancy. Severe rhabdomyolysis has been reported in newborn foals, usually associated with selenium deficiency.[71] Glycogen-branching enzyme deficiency is an inherited cause of mortality in Quarter Horse foals.[72] Clinical signs are variable and include seizure, persistent recumbency, respiratory failure, and cardiovascular collapse. The generalized nature of the clinical signs would likely lead to a false diagnosis of other more common neonatal diseases.

Dermis

A short, silky hair coat is consistent with immaturity. **Lethal white foal syndrome** should be suspected in a neonate with a white hair coat and colic within the first 24 hours after birth. Affected foals can have 5% pigmentation and are most frequently seen in foals born to overo Paint sire and dam. Skin abrasions occur in foals with prolonged recumbency or as a consequence of seizures, colic, or frequent unsuccessful attempts to rise. Lesions are commonly seen on the elbows, around the eyes, or on other skeletal prominences. They usually begin as focal regions of moisture. A syndrome of ulcerative dermatitis with widespread crusting and erythema has been seen in foals with alloimmune thrombocytopenia.[73] Edema can form on the ventrum, axilla, perineum, and the periorbital region with fluid overload and renal dysfunction. Swelling under the axilla can also result from cellulitis, trauma, or fractured ribs. Ventral swelling over or around the umbilicus can occur with tearing of the urachus and urine leakage into tissues (Fig. 16-14).

Immunoglobulin G and Colostrum

An association exists between low serum immunoglobulin G (IgG) and morbidity and mortality, most commonly caused by sepsis. Measurement of serum IgG should be made between 12 and 18 hours of age. A normal foal that has consumed adequate amounts of colostrum will have a serum IgG measurement substantially greater than 8 g/L (800 mg/dL). Failure of passive transfer is generally defined as a serum IgG less than 4 g/L (400 mg/dL); partial failure of passive transfer is used when the serum IgG is between 4 and 8 g/L. Foals that have been exposed to chronic in utero infection can be born with IgG concentrations greater than 8 g/L. Furthermore, septic foals may catabolize immunoglobulins, resulting in lower concentrations than originally assessed. Tetanus prophylaxis, in the form of antitoxin (1500 IU), should be administered to foals with untreated **failure of passive transfer.**

Good-quality colostrum is typically yellow and highly viscous, but physical properties alone do not result in significant differences in foal IgG levels at 24 hours of age.[74] There is a strong linear correlation between colostral specific gravity and IgG concentration.[75,76] A modified hydrometer (Equine Colostrometer, Jorgensen Laboratories, Loveland, Colo.) is used to estimate the specific gravity of equine colostrum. It is important to accurately add the recommended volume of colostrum to the chamber. The temperature of the distilled water will also influence the final reading, and corrective tables are available. Handheld refractometers that measure sugar or alcohol content are also suitable for assessing colostral quality. The test can be performed rapidly by placing a single drop of mixed colostrum onto the glass prism of the refractometer. Values greater than or equal to 16 on the alcohol scale, or 23% on the BRIX sugar scale, correspond to a colostral IgG content of 60 g/L or greater.[74,77] The following guidelines have been recommended for evaluating BRIX readings: (1) 0% to 15% BRIX, 0 to 28 g/L IgG, poor quality; (2) 15% to 20% BRIX, 28 to 50 g/L IgG, borderline quality; (3) 20% to 30% BRIX, 50 to 80 g/L IgG, adequate quality; and (4) greater than 30% BRIX, greater than 80 g/L IgG, very good quality.[77]

A minimum dose of 60 to 90 g of IgG has been recommended in the first 6 hours after birth.[78] This represents 1 to 1.5 L of good-quality colostrum, as defined by an IgG content of greater than 60 g/L. Foals that received a minimum of 1 to 1.25 g IgG/kg body weight within this time period should achieve a serum IgG above 8 g/L.[79] The total IgG content in mammary secretions is highly variable, but was reported to be 183 ± 58 g (range, 112 to 336 g), equating to a mean volume of colostrum of 2.3 ± 0.5 L.[79] The specific gravity declines to below 1.040 by an average of 7 hours after parturition, reflecting a reduction in IgG concentration from a mean of 113 g/L to 35 g/L. Several factors influence colostral quality. Mares that are stressed or ill are less likely to produce good-quality colostrum, as are animals with adrenal hyperplasia resulting from pituitary dysfunction or those receiving exogenous glucocorticoids. Aged mares, particularly those older than 15 years of age, tend to produce colostrum with a lower IgG concentration.[78]

Laboratory Data

Hematology and biochemistry can provide a critical insight in identifying foals at risk of developing clinical disease, in assessing the magnitude of clinical problems, and in monitoring response to treatment. Normal hematology, biochemical, and electrolyte data are reported in Tables 16-3 and 16-4. Foals that have been exposed to an abnormal in utero environment will frequently have abnormalities on routine blood work that can predict future clinical problems. Several important variations to adult values must be considered when interpreting laboratory data.

WHITE BLOOD CELL COUNT AND DIFFERENTIAL. The total white blood cell (WBC) count at birth is similar to that in adult horses, but the proportion of neutrophils and lymphocytes is more variable. An elevated count at birth reflects a fetal response to placental infection with or without infection of the foal. Premature or dysmature foals with incomplete adrenal maturation will have low total WBC and neutrophil counts, and a neutrophil:lymphocyte ratio that is characteristically less than 1:1.[80] It is important to determine if sepsis is present because neutropenia is also a common feature of this condition. Evidence of shifting toward immature cell types and neutrophil toxicity should indicate primary sepsis or prematurity/dysmaturity complicated by sepsis. Premature foals that fail to improve their total WBC and neutrophil counts over the initial 24 to 48 hours of treatment have an even poorer prognosis for survival. Persistent decreases in lymphocyte counts (<1000/μL) in Arabian foals could be consistent with severe combined

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TABLE 16-3

Normal Hematology Reference Values for Neonatal Foals

Parameter	Gestational Age (Premature Foals) 300-309 Days Mean	310-319 Days Mean	320-334 Days Mean	Postnatal Age (Term Foals) 1 Day Mean ± SD	2-7 Days Mean ± SD
RBC ($\times 10^6/\mu L$)	9.6	10.1	11.3	10.5 ± 1	9.26 ± 0.8
Hb (g/dL)	13.1	14.1	13.2	14.4 ± 1.1	13.2 ± 1.2
PCV (%)	41	42	43	42.0 ± 3.6	36.5 ± 3.1
MCV (fl)	42.7	42.2	38.6	40.2 ± 3.6	39.4 ± 2.3
MCH (pg)	14	14.4	11.8	13.6 ± 1.1	14.5 ± 1.1
MCHC (%)	32.4	33.8	30.5	33.8 ± 2	36.2 ± 1.1
Icterus index (u)				40.0 ± 15	30.3 ± 15
Total plasma protein (g/dL)				6.1 ± 0.8	6.4 ± 0.6
Fibrinogen (mg/dL)				243 ± 74	310 ± 90
Total WBC/μL	5000	6800	4900	8632 ± 2570	9075 ± 2200
Neutrophils/μL	1230	1540	1940	6381 ± 2225	6528 ± 2000
Bands/μL			2960	<50	>50
Lymphocytes/μL	3720	5090		2021 ± 2225	2203 ± 575
Monocytes/μL				222 ± 160	305 ± 145
Eosinophils/μL				0	22
Basophils/μL				8	17
Neutrophil:lymph ratio	0.33	0.3	0.66	3.16	2.96

Hb, Hemoglobin; *MCH,* mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *PCV,* packed cell volume; *RBC,* red blood cell; *SD,* standard deviation; *WBC,* white blood cell.

TABLE 16-4

Normal Serum Biochemical Reference Values for Normal-Term Postnursing Foals

Parameter	Age 1 Day Mean ± SD	4-7 Days Mean ± SD
Sodium (mEq/L)	139.7 ± 6	139.5 ± 4.2
Potassium (mEq/L)	4.4 ± 0.9	4.5 ± 0.4
Chloride (mEq/L)	103.5 ± 3	101.3 ± 4
Bicarbonate (mEq/L)	22.9 ± 3.4	34.3 ± 2.1
Calcium (mg/dL)	11.7 ± 1.1	11.4 ± 0.8
Inorganic phosphorus (mg/dL)	5 ± 0.85	6.4 ± 0.8
Magnesium (mg/dL)	2.2 ± 0.35	2.7 ± 0.15
Glucose (mg/dL)	136 ± 40	150 ± 30
BUN (mg/dL)	18.9 ± 4.3	13.6 ± 536
Creatinine (mg/dL)	2.3 ± 0.6	1.3 ± 0.3
Total bilirubin (mg/dL)	4.3 ± 2.2	4.4 ± 1.1
Direct bilirubin (mg/dL)	0.5 ± 0.2	0.8 ± 0.4
Indirect bilirubin (mf/dL)	3.8 ± 1.5	3.5 ± 1.1
Alkaline phosphatase (IU/L)	2282 ± 1100	1949 ± 1100
GGT (IU/L)	29.6 ± 15	18.3 ± 7.3
SDH (IU/L)	2 ± 0.9	2 ± 0.9
AST (SGOT) (IU/L)	154 ± 55	225 ± 60
LDH (IU/L)	487 ± 100	490 ±100

AST, Aspartate aminotransferase (SGOT); *BUN,* blood urea nitrogen; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *SD,* standard deviation; *SDH,* sorbitol dehydrogenase.

immunodeficiency. Alloimmune neonatal neutropenia has been reported in foals and can persist for 2 to 4 weeks after ingestion of colostrum.[81] Affected foals are often outwardly normal but are considered to be at risk for sepsis and are therefore managed with prophylactic antibiotics.

RED BLOOD CELLS AND PLATELETS. The packed cell volume (PCV) at birth is 40% to 52%, but decreases to 32% to 46% after colostrum and milk intake by 24 hours of age.[82] Increases in PCV can reflect dehydration whereas decreases can be caused by blood loss (either internal or external), hemolysis, DIC, or prematurity. Platelet numbers are unaffected by age, but decreases are seen with alloimmune thrombocytopenia, DIC, and viral infection (e.g., EHV-1, equine viral arteritis).

PLASMA PROTEIN AND ACUTE PHASE PROTEINS. Plasma or serum protein concentrations are low at birth but increase with globulin ingestion from colostrum. The albumin concentration should remain constant.[33] Plasma protein levels are 40 to 60 g/L at birth and increase to 50 to 80 g/L at 24 hours of age.[82] Levels increase with dehydration and chronic infectious processes and are decreased with whole blood loss, gastrointestinal disease, renal disease, or failure of passive transfer.

Fibrinogen concentrations are relatively low in newborn foals (2.16 ± 0.72 g/L <12 hours of age; 3.10 ± 0.74 g/L at 3 days of age), before increasing to a maximum at around 5 months of age (4.97 ± 0.91 g/L), and then reducing to adult levels.[83] Hyperfibrinogenemia at birth is indicative of in utero sepsis and inflammation. Serum amyloid A (SAA) as determined by latex agglutination immunoturbidimetric assay in normal foals yielded median values of 0.9, 4.0, and 2.5 mg/L for days 1, 2, and 3, respectively.[84] These were contrasted against median values of 279.9, 195, 5.1, and 3.1 mg/L, for systemic sepsis, localized sepsis, failure of passive transfer, and NI cases, respectively. The authors concluded that values greater than 100 mg/L were suggestive of local or systemic sepsis in young foals.

GLUCOSE. Blood glucose concentrations are relatively low in newborn foals but increase after nursing. Baseline values are typically 50% of maternal values at birth and reach a low approximately 2 hours after birth.[33] Many diseases of foals can directly or indirectly affect blood glucose concentrations, but the change in glucose can be difficult to predict. Hypoglycemia commonly occurs in foals with decreased milk intake. Conditions that may be associated with increased metabolic demands, such as SIRS and sepsis or reduced gluconeogenesis, can contribute to hypoglycemic states. Gluconeogenesis is also impacted by SIRS and sepsis, as well as prematurity or in utero stress. Hyperglycemia is a consequence of overzealous glucose supplementation or can occur in conditions with slow or reduced insulin responses, insulin resistance, or inappropriate sustained gluconeogenesis. This can occur in foals with HIS, SIRS, sepsis, and prematurity.

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BLOOD L-LACTATE CONCENTRATION. Lactate levels reflect peripheral perfusion and tissue oxygenation. Increased concentrations are expected after hemorrhage, in foals with systemic sepsis, NI, or HIS. Increases can also occur in hypermetabolic states in which oxygen demand is increased; examples include seizures, increased muscle activity, and shivering. Lactate is cleared by the liver and kidney, and therefore decreased perfusion to those organs can contribute to increased systemic values. Reference ranges will vary slightly with different analyzers, but normal values should be less than 2.5 mmol/L in foals 24 to 48 hours of age or older.[42,85,86] Values during the first 24 hours after birth in normal foals are higher. The venous lactate concentration 20 to 140 min after birth (2.38 ± 1.03 mmol/L) was greater than at 24 hours (1.24 ± 0.27 mmol/L) in a small group of normal foals.[87] A second study reported mean values at birth, 12, 24, 36, and 48 hours of 3.8, 2.8, 2.1, 2.0, and 1.7 mmol/L, respectively.[85] There is a suggestion that lactate values in "healthy" premature or dysmature foals may be higher than in term foals.[88] Lactate concentrations at admission are correlated with outcome; foals with a value of 5 mmol/L or more were 5.63 times more likely to die than foals with a value less than 5 mmol/L.[85] When the cutoff value was set at 7.94 mmol/L, the odds of non-survival increased to 15.98. Other studies have identified lactate concentration cutoff points of 4.4, 5.5, and 6.9 mmol/L to predict survival.[88-90] As important as the initial concentration is the change in lactate concentration in response to treatment.[85,88] In non-surviving foals, elevated lactate levels typically persist beyond 24 hours of hospitalization. Samples should be analyzed within 10 minutes of collection, since erythrocytes can continue to produce lactate in lithium heparin tubes stored at room temperature.[91] If sampling is delayed, samples should be collected into sodium fluoride–potassium oxalate and stored at 0° to 4° C. In some point-of-care analyzers, a high hematocrit can interfere with lactate measurement.[91] Anion gap can be used to approximate lactate, although direct measurement is preferred.

CREATININE AND BLOOD UREA NITROGEN (BUN). Concentrations of both creatinine and BUN can be elevated due to prerenal, renal, and postrenal causes. Marked elevation in creatinine concentration in newborn foals typically reflects problems with the fetoplacental unit; these foals are at risk of postnatal complications because of in utero compromise. Assuming normal renal function, these elevated values should decrease by half within 24 hours and approach normal levels within 72 hours. Failure to drop or a delay in decrease should suggest concurrent renal disease or other causes of azotemia. Blood urea nitrogen is not typically elevated in cases of placental dysfunction. It can increase in conditions of increased catabolism.

BILIRUBIN, HEPATOBILIARY ENZYMES, AND BILE ACIDS. Relative to adult horses, newborn foals have increased total bilirubin concentrations that are attributable to the unconjugated component. The basis of the discrepancy is not known but could relate to accelerated breakdown of fetal and neonatal red blood cells or decreased uptake and conjugation of bilirubin. Concentrations peak shortly after birth before declining to adult levels by 2 weeks of age.[92] Increases in bilirubin above normal are seen with hemolytic conditions, such as NI, primary liver disease (including equine herpesvirus-1 infection, Tyzzer's disease, and cholangiohepatitis), sepsis, meconium impaction, and after internal hemorrhage or blood transfusion. Large increases in bilirubin can lead to the neurologic complication of kernicterus.

Gamma glutamyl transferase is normal at birth but increases between 5 and 14 days of age before decreasing to adult levels by 4 weeks of age. The increase is thought to be due to hepatic enzyme induction associated with normal maturation. The hepatocellular enzyme, sorbitol dehydrogenase, is not affected by age. Glutamate dehydrogenase concentration has not been well described in healthy newborn foals. These enzymes are increased in a range of conditions, particularly sepsis.[93]

The concentration of aspartate aminotransferase (AST) increases slightly after 7 days of age; an increase attributed to enhanced muscle activity rather than hepatobiliary changes. Serum alkaline phosphatase (ALP) concentrations are substantially increased over adult levels in the first few days of life, remaining elevated through the first week. The initial increases are attributed to intestinal activity, including the pinocytosis of maternal immunoglobulin, and to the osteoblastic activity in growing and adapting bones. Premature or dysmature foals with incomplete ossification will have ALP concentrations that are higher and persist for longer than levels in term foals.[33]

Serum bile acid (SBA) concentrations are also greater in foals during the first 6 weeks and are six to seven times greater than those in adults during the first 2 days of life.[94] Increased concentrations of bilirubin or triglycerides or hemolysis may interfere with SBA measurement under certain methodologies. Triglycerides increase from birth to the first day of life, peaking during the first week, and then gradually declining to adult levels by 3 months of age.[92] Serum cholesterol is also elevated during the first 2 weeks of life.

ELECTROLYTES. As with adult horses, serum electrolyte concentrations in foals are maintained within a relatively narrow range. Disruption of the urinary tract or primary renal disease classically produces a hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and hyperkalemia. Many of these changes reflect the electrolyte intake associated with a milk diet and are less likely to occur when foals have received intravenous fluid therapy. Rhabdomyolysis resulting from selenium deficiency can cause a similar electrolyte profile to that of uroperitoneum in milk-fed foals.[71] Although both conditions may be associated with increases in creatinine and BUN, concurrent and substantial increases in creatine kinase and AST are expected with rhabdomyolysis.

Hyponatremia, hypochloremia, and hypokalemia are commonly seen with diarrheal disease in foals. Severe hyponatremia is more commonly seen in older foals with diarrhea that are allowed to replenish fluid losses by consumption of plain water. Hyponatremia is also a feature of renal disease, but hypernatremia can occur when affected foals are treated with relatively high volumes of sodium-rich intravenous fluids in the face of inadequate urine output.

Elevated total and ionized calcium concentration can be present in foals born to mares with marked placentitis.[33] Clinical hypocalcemia results in signs of tachycardia, sweating, tremor, muscular rigidity, and a stiff gait or recumbency. The syndrome is rare but euthanasia is common due to failure to respond to calcium supplementation.[95] Parathyroid hormone concentrations may be elevated, decreased, or normal, suggesting differing syndromes.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 17

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Manifestations and Management of Disease in Foals

GUY D. LESTER, *Consulting Editor*

MANIFESTATIONS OF DISEASE

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General Principles of Treatment and Care of the Abnormal Foal

Guy D. Lester • Jane E. Axon • Wendy E. Vaala

Frequent monitoring of the ill newborn foal is essential because early recognition of subtle clinical changes can have a significant impact on outcome. This includes observations of behavior and repeated structured physical examinations. (Assessment of the foal is described in Chapter 16.) It is important that the clinician develop a routine method of examination that is consistently followed, irrespective of the perceived level of illness. This ensures that the assessment is complete and no abnormalities are missed. Delivering detailed and potentially expensive therapy to a foal with a significant congenital defect is potentially avoided by adopting this approach.

By the time that many sick newborn foals are examined by veterinarians, they are critically ill and require emergency therapy to restore circulation, tissue perfusion, and oxygenation. This approach is conserved across many diseases. After fluid resuscitation, there can be an investigation into underlying diseases and directed therapy instituted.

Catheter Selection and Placement

If high-volume fluid resuscitation is anticipated, a large-bore (14- or 16-gauge) catheter should be placed into the jugular vein. Identification of the vein can be facilitated by elevation of the hindquarters in lateral recumbency and by placing a rolled towel under the neck. Teflon catheters (Abbocath, Abbott Hospitals, North Chicago, Ill.) are more thrombogenic than silastic or polyurethane catheters, but they are usually easier and quicker to place. Short catheters placed in peripheral veins can be difficult to maintain and are not suitable for large-volume, rapid fluid replacement. Most referral hospitals use polyurethane catheters as they reduce the incidence of thrombophlebitis and eliminate the need for frequent catheter replacement. Using strict aseptic technique, the catheter is typically inserted using the "over-the-wire" (Seldinger) technique. Once positioned, the catheters can often be left in place for up to 3 weeks. A combination of superglue and sutures is very effective in keeping the catheters in place. Catheter sites are covered but monitored frequently for signs of infection. Insertion site swelling is not uncommon for 24 hours after placement of some catheters. Blood samples for culture, hematology, and biochemistry can be collected at the time of catheter placement if the condition of the foal is not highly critical.

Fluid Resuscitation

After placement of an intravenous catheter, warmed fluid can be delivered at a rate of 20 mL/kg over 15 to 20 minutes.[1,2] Typically the initial fluid of choice is a multi-electrolyte replacement solution, such as lactated Ringer solution (LRS) or Hartmann's solution. After the initial or subsequent fluid boluses the patient is reassessed, specifically noting changes in mucous membrane color, capillary refill time, pulse quality and rate, mentation, warmth of peripheral tissues, intestinal sounds, and urine production.[3] If there is minimal or no improvement, the bolus can be repeated a further three times, to a maximum of 80 mL/kg, or 4 L for a 50-kg foal. During this time essential laboratory data can be collected, including the packed cell volume (PCV), total plasma protein (TPP), and blood glucose concentration. Ideally, an arterial or venous sample is obtained for blood gas, electrolyte, and lactate determination. Factors that influence the rate or total volume of fluid used during resuscitation include a low TPP concentration (<35 g/L); preexisting limb, body, or head edema; or spontaneous hemorrhage.

Colloids are indicated in low protein states. Plasma is the most commonly used colloid in foal practice, but it is expensive and requires thawing and the use of an in-line filter. However, the benefits of fresh or fresh-frozen plasma are numerous, including

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improvement of osmotic pressure, provision of coagulation factors, to provide buffer base, and immunotherapy.[2] The administration of plasma has been associated with anaphylactic or anaphylactoid reactions, which can be fatal. For this reason, plasma is not routinely used for acute fluid resuscitation. Plasma should be administered at an average rate of 10 mL/kg/h. Give the first 100 mL slowly and monitor the foal's pulse, respiratory rate, and temperature. Synthetic colloids are less expensive, and they do not require special storage conditions nor use of a special filter, but they do not have the range of benefits of plasma. The use of synthetic colloids in foals has been questioned.[1-3] Hydroxyethyl starch (e.g., Hetastarch), however, has been used successfully for rapid fluid resuscitation in foals with few adverse reactions (3 mL/kg at a rate of 10 mL/kg/h).[4]

Correction of Dehydration

Once critical hypovolemia has been rectified, assessment can be made of residual dehydration.[3] Foals have a relatively greater proportion of extracellular fluid when compared with adults,[5] and in contrast to adults can appear thin or emaciated when dehydrated. Traditional clinical parameters used to assess hydration in adult horses, such as moisture of oral mucus and skin tenting, are less reliable when used in foals. The volume of fluid is, however, calculated in a manner similar to that used in adults. A foal with moderately to severely sunken eyes is estimated to be 8% to 10% (of body weight) dehydrated. The estimated fluid deficit in a 40-kg animal that is 10% dehydrated would be approximately 4 L. The calculated deficit should be replaced over the following 12 hours, along with consideration of maintenance fluid requirements and any ongoing losses.

If an animal is mildly dehydrated and the gastrointestinal tract is not seriously compromised, fluid requirements can be provided by the enteral route, using milk or commercially available dextrose and electrolyte mixtures.

Maintenance Fluid Therapy

When intravenous fluid therapy is used for maintenance of hydration, the Holliday-Segar formula has been advocated for calculation of fluid delivery rates in foals with impaired renal function, or in foals less than 3 days of age where renal function is not known.[2,3] The formula uses a principle that slight fluid deprivation is less critical than overhydration, particularly when sodium-rich fluids are used. For the first 10 kg of body weight, the foal receives 100 mL/kg/day; for 11 to 20 kg of body weight, the foal receives 50 mL/kg/day; and for each kilogram over 20 kg the foal is assigned 25 mL/kg/day.[2] For a 50-kg foal this is calculated as 1000 mL/day for the first 10 kg, 500 mL/day for the second 10 kg, and 750 mL/day for the remaining 30 kg of body weight, for a total daily volume of 2250 mL or an hourly flow rate of 94 mL.[2] For older foals, or foals with normal renal function, higher flow rates can be used, typically in the range of 2 to 5 mL/kg/h.[3,6]

Use of Inopressor Drugs

If hypotension persists in the face of fluid resuscitation, inopressor therapy may be indicated. It has been recommended that the aim of therapy is to raise the mean arterial pressure (MAP) above 60 mm Hg, although this does not imply that tissue perfusion is adequate.[7] Agents that are commonly used include dobutamine, dopamine, norepinephrine, and vasopressin.[7] Dobutamine is a positive inotrope that improves cardiac output primarily by improving stroke volume. The drug is administered as a continuous rate infusion (CRI) with a wide dose range of 2 to 20 μg/kg/min, but it is recommended to commence therapy at the low end of the range.[3] It is not uncommon to administer a vasopressor with dobutamine to improve tissue perfusion. Norepinephrine acts at α_1- and α_2-receptors to mediate vasoconstriction, as well as acting at β_1-adrenergic receptors, causing positive inotropic and cardiotropic effects.[7] The drug has a very short half-life and is given by CRI at a highly variable dose range, from 0.05 to 5 μg/kg/min. Again, starting at the low end of the range is recommended.

Dopamine also has some combined α- and β-adrenergic effects, in addition to moderate to strong affinity for dopamine receptors (DA-1 and DA-2 receptors).[7] Activity at dopaminergic receptors primarily mediates vasodilation, particularly in renal, cerebral, and splanchnic vascular beds. Lower infusion rates are used to improve renal and splanchnic perfusion (1 to 5 μg/kg/min), whereas higher infusion rates (10 to 25 μg/kg/min) will be required for patients in severe septic shock.

Vasopressin (0.25 to 1 mU/kg/min) acts at V1a receptors in the peripheral circulation, causing vasoconstriction, and at V2 receptors in the kidney to facilitate water reposition.[7] Low-dose vasopressin is commonly used in conjunction with norepinephrine infusion and is reported to be effective in the management of the hypotensive neonatal foal. Beneficial effects include an increase in MAP, a reduction in heart rate, and increased urine output.[8]

Glucose Supplementation

The fluid rate is in part dictated by the need to provide glucose supplementation. A rate of 5 mg/kg/min has been suggested as an initial CRI flow rate, based on the estimated placental supply in late gestation (6.8 mg/kg/min).[3,9] This equates to an hourly flow rate of 3 mL/kg (150 mL/h for a 50-kg foal) of a 10% glucose solution. Blood glucose concentrations should be monitored closely and the rate adjusted as required. Boluses of glucose solutions should be avoided because the resultant glucosuria will lead to urinary losses of fluid, electrolytes, and glucose. It can produce a marked rebound hypoglycemia.

Electrolyte Management

In most foals, electrolyte concentrations will normalize over time assuming adequate renal function and milk intake. There are, however, several conditions in which specific electrolyte supplementation or avoidance is important. Foals with uroperitoneum can develop life-threatening hyperkalemia. Specific management is discussed later in this chapter in the section on distended/painful abdomen. Fluid therapy is typically based on 0.9% saline, supplemented with glucose. Potassium supplementation may be required for critically sick neonates, anorexic foals, foals with diarrhea, or those receiving diuretic therapy. If serum concentrations fall below 2.5 mEq/L, intravenous supplementation is recommended. Potassium requirements are difficult to estimate from serum concentrations, but the following equation has been recommended:

$$\text{Replacement K (mEq)} = 0.4 \times \text{Body weight (kg)} \times \text{K deficit (mEq)}$$

Potassium can be added safely to fluids at a rate of 10 to 40 mEq /L, although when delivering fluids at a maintenance rate using the Holliday-Segar formula, concentrations up to 60 mEq/L may be used.[2] At higher concentrations it is very important not to exceed recommended rates of administration. Potassium supplementation should not exceed 0.5 mEq/kg/h, or 25 mEq/h for a 50-kg foal.

Sodium overload is a problem associated with prolonged use of salt-rich replacement solutions.[2] The problem is avoided by using specially formulated low-sodium, high-potassium replacement solutions that are supplemented with glucose, or using 5% dextrose in water as the base solution for fluid therapy. The principles of hyponatremia or hypernatremia treatment are discussed in Chapter 22.

Sodium bicarbonate is commonly given to foals that are acidemic, assuming that it is metabolic in origin. The initial approach to management should be rehydration and improvement in tissue perfusion. This is achieved using crystalloids, colloids, and inopressor agents. When bicarbonate is administered to foals where the acidosis has originated from poor tissue perfusion, the results are often disappointing. Bicarbonate supplementation is indicated in conditions in which there has been loss of buffer, such as diarrhea or renal tubular acidosis. If bicarbonate deficits are greater than 10 mEq/L (serum $[HCO_3^-]$ <15 mEq/L) after rehydration, then supplementation can be given using the following equation:

$$\text{Bicarbonate deficit (mEq)} = 0.6 \times \text{Body weight (kg)} \times \text{Base deficit (mEq)}$$

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Isotonic bicarbonate can be made by adding 150 mL of 8.4% bicarbonate solution to 850 mL of sterile water, or 200 mL of 5% bicarbonate solution to 800 mL of sterile water. Bicarbonate solutions should be given slowly. Bicarbonate should not be combined with any calcium-containing solution or else precipitation will occur. The effect of the bicarbonate replacement therapy should be monitored closely and the dose adjusted accordingly. Neonates with severe diarrhea because of ongoing losses of bicarbonate through the feces may need considerably more than the calculated deficit to maintain an adequate blood pH until the diarrhea subsides.

Plasma Transfusion for Failure of Passive Transfer of Immunoglobulin

Plasma is administered through an aseptically placed catheter using a blood administration set with an in-line filter. The rule of thumb for plasma administration for FPT is 20 mL/kg, or approximately 1 L for a 45-kg foal. In healthy foals, 1 L of plasma with immunoglobulin G (IgG) of 1200 mg/dL (12 g/L) raises the serum IgG 200 to 250 mg/dL (2 to 2.5 g/L). For foals with total failure of passive transfer, it may be necessary to provide 2 or 3 L of commercial plasma if the goal is to reach a serum IgG concentration of 800 mg/dL (8 g/L). The same amount of plasma has less effect in septic foals. Ill foals require relatively more plasma because the serum half-life of IgG is less, IgG may be sequestered in intravascular spaces or at sites of inflammation, and IgG may catabolize more readily.

Maintenance of Body Temperature

The thermoneutral zone describes an ambient temperature range in which heat production and heat loss are at a minimum.[10] The lower level of the range (Tlc) defines a temperature cutoff, below which the metabolic rate rises and the rate of evaporative heat loss increases. For 2-day-old pony foals, the Tlc was estimated to be 25° C,[10] a value much higher than the typical ambient temperature that many foals experience. However, healthy foals are able to maintain their core body temperature down to an ambient temperature of 5° C, but premature or sick newborn foals are often unable to maintain their body temperature and frequently require external heat sources during treatment. Foals on phenobarbital therapy are also susceptible to a reduction in body temperature.

It is critical to dry the foal and remove it from drafts to reduce convective heat loss. If the rectal temperature is less than 37.7° C (100° F), efforts should be made to warm the foal by raising the environmental temperature. Rewarming the periphery only with high external heat without simultaneously warming the body core can produce peripheral vasodilation and accentuate cardiovascular collapse. Warming can be achieved using forced air warmers (Bair Hugger, 3M, St. Paul, Minn.), radiant heat lamps, blankets, or careful use of heating pads. A heat pack can be made by placing a wet towel inside two rectal sleeves and microwaved to the desired temperature. It is important to address hypotension using warmed fluid therapy.

Bedding and General Environment

It is important that the environment for housing the sick foal is clean. A temporary barrier between the mare and recumbent foal facilitates treatment of the foal, yet keeps the dam within sight, sound, touch, and smell of her foal, which facilitates bonding. Many of these foals are recumbent, making them further vulnerable to contagious or opportunistic pathogens. Recumbency increases the risk of pneumonia, predisposes to ileus and constipation, increases the risk of milk aspiration, and exacerbates musculoskeletal weakness. Recumbent foals are also at risk for the development of decubital ulcers and should be bedded on a soft and absorbent surface. They should be carefully turned and assisted to stand every 2 hours. Placement into custom-made V-pads (Dandy Products, Goshen, Ohio) can help the foal rest in sternal recumbency, improving oxygenation and reducing the risk of lung atelectasis and secondary pneumonia (Fig. 17-1).

Special Considerations of Drug Therapy

Differences between neonatal and adult animals in drug effects generally can be attributed to differences in drug distribution, metabolism, or excretion. Some general characteristics of the neonatal period include better absorption of drugs from the gastrointestinal tract, less drug binding to plasma proteins, increased apparent volume of distribution of drugs that are distributed in the extracellular fluid volume, increased permeability of the blood-brain barrier, and slower elimination (i.e., longer half-life) of many drugs.[11]



FIG. 17-1 Sternal recumbency is facilitated by use of a V-pad.

Some of these responses are attributed to differences in body water between neonates and adult horses. Total body water (TBW) in day-old foals was 744 ± 24 mL/kg, compared with 670 ± 60 mL/kg in adult horses.[5,12] During growth, the intracellular fluid compartment remains relatively consistent relative to size, whereas the extracellular fluid (ECF) compartment decreases as a percentage of body weight, with an increasing body fat percentage. The ECF volume was estimated at 381 ± 18 and 394 ± 29 mL/kg, in 1- and 2-day-old foals, respectively.[5,13] This compares with reported values in adult horses of 214 to 253 mL/kg. Plasma volume is around 96 mL/kg in neonates, which again is much greater on a per-kilogram body weight basis than reported values in adults of 53 to 63 mL/kg.[5] Although the neonate has a higher percentage of TBW than the adult, it is more vulnerable to water loss because of increased basal metabolic rate, relatively greater surface area, predisposition to increased heat and water losses, and reduced urine concentrating ability.

Nutritional Support

Provision of adequate nutritional support to the compromised neonate is an essential component of critical care. Common reasons for not providing adequate nutrition include failure to estimate the nutritional requirements of the sick neonate, the need to use alternative methods and routes of delivery, and a gastrointestinal tract that is often compromised and intolerant of nutrient intake. The nutritional requirements for optimum growth of the normal-term foal are poorly defined, let alone for the premature, growth-retarded, or debilitated animal whose caloric, protein, mineral, and vitamin requirements might be very different.

Measurements of milk production of mares combined with data concerning the free-choice milk intake of normal orphan foals and premature and sick foals recovering from various illness suggest that a figure of 125 to 150 kcal/kg/day, or even higher, is close to the normal caloric intake.[14] Healthy full-term foals nurse an average of 2 minutes, seven times an hour, and consume between 20% and 30% of their body weight in milk daily, resulting in weight gain of 1.3 to 1.7 kg/day.[15-17] On this diet, a 50-kg foal would therefore consume 10 to 12.5 L of milk a day to provide 120 to 150 kcal/kg/day, 50% of which is used for growth and 50% for basal metabolism and

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thermoregulation. Factors that influence weight gain include caloric intake, the level of exercise, and the resting energy expenditure (RER). Weight gain is reduced in hospitalized newborn foals. RER is, however, less in ill foals, at approximately 44 to 49.5 kcal/kg/day, compared with 65 kcal/kg/day in healthy foals.[18] The general recommendation is to provide a minimum of 50 kcal/kg/day and aim for a weight gain of 0.6 to 1.0 kg/day.

If there is no medical contraindication for oral feeding, and the gastrointestinal tract is functional, then enteral nutrition is the preferred and most effective route of nutritional supplementation. Enteral feeding stimulates normal gut maturation, growth of intestinal villi, production of crypt cells, hepatic and biliary secretions, and brush border disaccharidase enzyme activity. Therefore, even in foals that must be fed parenterally, small volumes of enteral feeds are given to prevent gut atrophy.

Foals that are not nursing from the mare can be fed by bottle, bucket, or nasogastric tube. If an effective swallow reflex is present, bottle feeding can be used. Bucket feeding allows the foal to drink with its head and neck in a flexed position and is helpful for foals with a weak swallow reflex or foals destined to be hand raised. Milk should be introduced in a shallow handheld bowl and the foal encouraged to suckle the finger or nipple as its head is lowered into the milk. Foals less than 7 days of age should ideally be fed every 1 to 2 hours. Nasogastric intubation is required if ineffectual swallowing and sucking are present. A styleted small-bore flexible silicone tube (5- to 7-mm internal diameter) with a weighted tungsten end is preferred. Individual choice dictates whether the tube is passed for each feeding or left indwelling. Indwelling tubes can be sutured to the nares using a Chinese finger-trap suture technique,[19] or taped to half a tongue depressor, which is then taped to the foal's muzzle and/or fleece halter. Tubes should be sealed between feedings to avoid aerophagia. Recumbent foals should be maintained in sternal recumbency using a V-pad immediately after tube feeding to reduce the risk of gastroesophageal reflux and aspiration. If the dam is available and milk production is adequate, free-choice nursing is optimal. A nurse mare is the next best substitute. Popular enteral formulas include mare's milk, goat's milk, and artificial milk replacers. Goat's milk is acceptable and is higher in fat, total solids, and gross energy than mare's milk. Foals raised on goat's milk occasionally become constipated and can develop a mild metabolic alkalosis. Cow's milk is not as digestible and can cause diarrhea, but it can be used if additional sugar is added and some of the fat is removed. This can be accomplished by using 2% fat milk and adding 20 g of dextrose per liter of milk. A variety of artificial milk replacers are available. The ideal replacer should have approximately 22% crude protein, 15% fat, and less than 0.5% fiber on a dry matter basis. Calf milk replacer can be used if it is mixed with mare's milk. Complications associated with enteral feeding include colic, abdominal distention, diarrhea, constipation, flatulence, misplacement of the nasogastric tube, aerophagia, nasal and pharyngeal irritation from the tube, and aspiration pneumonia.

Parenteral nutrition (PN) is used to supply at least a portion of the daily nutritional requirements to critically ill foals. PN is indicated whenever feeding via the gut is inadequate or contraindicated. Candidates for partial or total PN include those individuals with diarrhea, postsurgical patients, foals with botulism, premature and septic animals, and other individuals with gastrointestinal tracts poorly tolerant of enteral feedings. PN involves administration of hypertonic solutions containing dextrose, amino acids, lipids, vitamins, electrolytes, and trace minerals. These PN solutions must be administered continuously through a jugular catheter. Complications include metabolic disturbances such as hyperglycemia/hypoglycemia, glucosuria/osmotic diuresis, insulin resistance, hypertriglyceridemia, azotemia, and imbalances of trace minerals, vitamins, and electrolytes.[20,21] Catheter-related problems include thrombosis, phlebitis, and sepsis. Commonly used stock solutions for PN include 50% dextrose, 8.5% or 10% amino acids, and 10% or 20% lipid emulsion. A variety of PN worksheets are available, some of which are complicated.[22] See Chapter 50 for more details and a worksheet.

A simplified formula for 50 kg that is well tolerated in most foals is 2.5 L of 8.5% amino acids, 1 L of 20% lipid, and 1.5 L of 50% dextrose added to an empty 5-L bag. This mixture contains 750 g of dextrose, 212.5 g of amino acids, and 200 g of lipid, and it provides 2550 kcal from dextrose (3.4 kcal/g), 850 kcal from amino acids (4.0 kcal/g), and 2000 kcal from lipids/glycerol (10.0 kcal/g). The PN solution has 47% of total calories from glucose, 16% from protein, and 37% from fat. It is recommended that foals should not receive more than 50% of non-protein calories from lipid. The solution can be run at 104 mL/h over 48 hours, providing approximately 54 kcal/kg/day. It is common to supplement the solution with multivitamin concentrate, trace minerals, and KCl (to a final concentration of 20 to 40 mEq/L). The PN solution is hypertonic (1233 mOsm/L), so it is common to run concurrently with low tonicity solutions or free water.

Foals receiving PN should have their blood and urine glucose monitored. Serum glucose concentration should remain greater than 80 mg/dL (4.4 mmol/L) and less than 180 mg/dL (10 mmol/L). Serum should be checked for gross lipemia. Heparin can be administered at 10 U/kg as an IV bolus to treat lipemia. Foals must be weaned onto and off of PN slowly. All IV lines must be checked routinely for signs of infection. Most commonly, parenteral and enteral nutrition has been used in combination; parenteral nutrient delivery is used to supplement, not totally replace, oral intake. Enteral nutrition helps to maintain the intestinal mucosa. Details concerning the use of PN compounds can be found in Chapter 50.

Weakness and/or Somnolence

Wendy E. Vaala • Guy D. Lester

Numerous conditions of the newborn foal can produce a primary complaint of weakness and/or somnolence. The gestational and postnatal age of the neonate should be established. If weakness has been present since birth, in utero–acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be placed higher on the list of differential diagnoses. Lethargy and loss of suckle are often the first signs of neonatal illness. A full udder on the dam accompanies poor nursing behavior in the neonate. If the neonate is somnolent and has injected mucous membranes and hyperemic coronary bands, sepsis is the primary differential and the most life threatening. If the neonate is relatively bright but is becoming progressively weaker, consider peripartum hypoxia and early signs of neonatal encephalopathy (NE). If the newborn shows signs of physical immaturity such as tendon laxity and silky hair coat, weakness may be due to fatigue, hypothermia, hypoxia, and/or hypoglycemia. Unfortunately, many weak foals begin to fade as a result of multiple problems. Glycogen branching enzyme deficiency in certain Quarter Horse and Paint lineages is an example of a genetic mutation associated with a range of abnormal signs that could include persistent recumbency.[23]

If weakness is present without accompanying somnolence, several other differentials should be considered, including trauma. If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with vigorous extraction from the birth canal should be ruled out. Affected limbs are weak and hyporeflexic, and there may be regions of cutaneous anesthesia.[24] The diagnosis is based on history and neurologic assessment and confirmed using electrodiagnostics after 10 to 14 days.[25] The prognosis for recovery is dependent on the severity of the neural lesion. Where axon continuity is preserved, the outlook is generally good with resolution within days to weeks; where there has been disruption to axons or whole nerves, the outlook is guarded. Regrowth and reinnervation of muscle is possible; axonal regrowth is estimated at 1 inch per month.[25] Foals with rupture of the gastrocnemius muscle will be unable to rise or stand unsupported.[26] The treatment includes limb stabilization and exercise restriction, with a guarded prognosis for an athletic career.

Neuromuscular diseases causing weakness without somnolence include botulism, nutritional myodegeneration (NMD; white muscle

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disease), and congenital myopathies. Botulism is an infection acquired via the gastrointestinal tract or through wounds or the umbilicus. Consequently, signs appear in neonates that are typically 10 days or older. Most cases of NMD associated with selenium and/or vitamin E deficiency occur during the first year of life among rapidly growing large animal neonates, but an in utero form of NMD may occur, resulting in clinical signs in affected foals soon after birth. Clinical signs associated with NMD may include localized (dysphagia) or generalized paresis. Rhabdomyolysis in foals may be precipitated by stress such as sepsis or excessive periparturient hypoxia. Affected foals are reluctant to move, paretic, and occasionally dysphagic.[27] Pelvic limb muscles are often palpably firm. Elevated serum creatine kinase and electrolyte disturbances of hyponatremia and hyperkalemia may be observed.

It should be determined whether drugs or anesthetics were administered to the dam before or at the time of delivery, as many agents cross the placenta and exert depressive and other adverse effects on the fetus. Phenylbutazone administered to normal pregnant mares crosses the placenta and results in substantial concentrations of phenylbutazone, and its active metabolite oxyphenbutazone, in the foal. Although clinical signs of phenylbutazone toxicity were not noted in the foals postnatally,[28] adverse effects are possible, particularly if other problems are present. Neonatal depression induced by drugs is particularly important following cesarean section deliveries. Maternally administered anesthetics and analgesics can suppress respiration and heart rate in the newborn. In horses, both xylazine and detomidine cause maternal and fetal bradycardia and reduced cardiac output.[29,30] These effects will cause a reduction in placental perfusion and fetal oxygenation. If the newborn shows depression associated with maternal administration of these drugs, an α_2-adrenergic antagonist, such as yohimbine, can be given. Adverse reactions to adrenergic antagonists in adult horses have been reported, some of which were fatal.[31]

Weakly basic drugs, when given to the mare, tend to concentrate in the fetus. Diazepam is an example of such a drug that crosses the placenta rapidly and accumulates in the fetal circulation, resulting in lethargy, hypotonia, and hypothermia in the neonate following delivery. Flumazenil has been used to reverse the sedative effects of benzodiazepines. Maternal systemic illness of various types may also result in a weak newborn.

Many neonatal disorders are associated with severe electrolyte and metabolic derangements that may clinically manifest as weakness, including hypoglycemia, acidosis, hyponatremia, hypernatremia, or hyperkalemia. Such abnormalities may occur before or at the time of birth, and laboratory assessment of the weak newborn is essential for accurate diagnosis. Young foals with hypocalcemia can present with stiff gait, muscular tremor, tachycardia, sweating, muscular tremor, and recumbency.[32] Profound weakness associated with metabolic acidosis is commonly observed in foals with diarrhea. Correction of the acidosis by rehydration or intravenous administration of bicarbonate usually produces rapid improvement.

A number of congenital bacterial, fungal, and viral infections that cause abortions and stillbirths may also result in the birth of a live, weak neonate. Clinical manifestations of fetal infections depend on the age of the fetus and virulence and trophism of the infecting agent.

Generally, weakness resulting from uroperitoneum, renal, and liver failure; postnatally acquired infections; and neonatal isoerythrolysis (NI) is not expected to appear during the first 24 hours of age. Rather, foals with NI are usually presented between 24 and 72 hours of age, foals with uroperitoneum at 2 to 5 days or older, and neonates with postnatally acquired infections most commonly at 2 to 5 days of age or older.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Occipitoatlantoaxial malformations (OAAMs) involve the occipital condyles of the skull and the first two cervical vertebrae.[33] Generally vertebral body malformations occur sporadically, with genetic, nutritional, and/or environmental factors being implicated.[34] Osteomyelitis and vertebral body abscess may be a sequel to bacteremia following neonatal sepsis or pneumonia. *Rhodococcus equi* vertebral body osteomyelitis, with or without associated pulmonary infection, has been reported in foals. Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances vertebral abscesses do not infiltrate the pachymeninges, so the cerebrospinal fluid (CSF) either is normal or has a mild elevation of protein and or a mild pleocytosis.

A complete neurologic examination is an important component of the work-up of the weak neonate. In particular, it should be noted if the weakness is accompanied by signs of somnolence and diffuse cerebral disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). For example, foals with severe spinal cord hemorrhage may have relatively normal mentation, but spinal reflexes may be greatly diminished, and profound weakness may be present. Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations) may also show weakness and ataxia yet have normal cerebral function.

Virtually any severe systemic disease such as generalized infection can cause both profound somnolence and weakness in a neonate without the presence of actual brain pathology. Primary neurologic disease in neonates is rare; commonly, neurologic dysfunction is associated with multisystemic disease. A thorough comprehensive physical examination and work-up is required to define a problem list and formulate an appropriate management plan. A complete blood count, blood cultures, and assessment of immunoglobulin status provide an indication of the likelihood of sepsis. Hypoxia and metabolic acidosis are ruled out by assessing arterial blood gas (ABG) status, and electrolyte disturbances and hypoglycemia are evaluated by measuring serum electrolytes and blood glucose concentration. Collection of CSF to assess the central nervous system is usually performed when disease in other organ systems that may account for the altered mental state has been ruled out and no improvement in the patient's condition is observed following correction of electrolyte, blood gas, and metabolic derangements.

Sepsis

L. Chris Sanchez

Sepsis is the major cause of morbidity and mortality in the equine neonate.[35,36] The response to microbial invasion of the bloodstream involves the systemic inflammatory response syndrome (SIRS), and it is this nonspecific inflammatory response, rather than the infectious organism, that is responsible for the classical signs of sepsis. Deterioration can occur rapidly, even in the face of aggressive treatment.

A variety of terms have been used to describe the host response to infection and associated processes and syndromes. A set of definitions were published by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992.[37] Briefly, *SIRS* refers to a systemic response, regardless of the inciting cause, which results in at least two of the following four clinical features: fever; tachycardia; tachypnea or hyperventilation; or leukocytosis, leukopenia, or a relative increase of circulating immature neutrophils. When SIRS occurs in response to a confirmed infectious process, the process is termed *sepsis*. *Infection* refers to the invasion of normally sterile tissue by microorganisms or the inflammatory response generated in response to those invading organisms. *Bacteremia* is the presence of viable bacteria in the bloodstream, *viremia* describes the presence of viable virus particles in blood, *fungemia* is the presence of viable fungal elements, and so on. When sepsis is associated with organ dysfunction, hypoperfusion, or hypotension, the event is termed *severe sepsis*. *Septic shock* is defined by sepsis-induced hypotension that persists despite adequate fluid therapy and is accompanied by hypoperfusion abnormalities or organ dysfunction.

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Manifestations of organ dysfunction can include coagulopathy, in addition to classical sites of renal, gastrointestinal, hepatic, cardiovascular, or pulmonary dysfunction.[38] The *multiple organ dysfunction syndrome (MODS)* describes alteration of organ function in an acutely ill patient such that homeostasis cannot be maintained. MODS can occur either as a primary event (e.g., as a direct result of trauma) or as a result of a host response. A syndrome of immunosuppression caused by an exaggerated systemic anti-inflammatory response with increased circulating levels of anti-inflammatory mediators, leukocyte anergy, or increased susceptibility to infection has been termed the *compensatory anti-inflammatory response syndrome (CARS)*. The *mixed anti-inflammatory response syndrome (MARS)* applies to fluctuations between episodes of SIRS and CARS.[39]

Infection with gram-negative bacteria occurs commonly in neonatal foals.[36,40-42] The pathophysiology of septic shock in gram-negative sepsis involves bacterial endotoxin and the subsequent release of pro- and anti-inflammatory cytokines.[43,44] Septic foals can have decreased gene expression of TNF-α and TNF-β, and increased expression of IL-8 relative to healthy foals,[45] or increased gene expression of IL-4 and TLR4[46] among other abnormalities.

Predisposing Factors

Factors that may predispose to infection are numerous and include maternal illness, increases or decreases in gestational length, partial or complete failure of passive transfer, poor environmental conditions, and inadequate or improper umbilical care. Maternal factors have been reported to play a central role in 24% of bacteremic foals.[47] These include dystocia,[48] premature placental separation, placentitis, and various other forms of maternal illness such as colic and respiratory disease. Many of these factors co-exist but some occur primarily, such as placentitis, whereas others are secondary, such as premature placental separation. In utero infection of the fetus typically occurs due to an ascending infection of the fetal membranes and often results in premature delivery.[49] Because chronic placentitis often results in accelerated or precocious fetal maturation, a resultant premature foal born to such a mare likely has a greater chance of being septic but has a higher probability of survival than a foal born at a similar gestational age to a mare without placentitis or other chronic stimulation.

Failure of transfer of passive immunity (FTPI) predisposes to an increased risk of postnatal infection. A number of studies have documented a close relationship between the foal serum IgG concentration and incidence of disease.[50-53] Colostrum administration via nasogastric tube was associated with disease in one report,[48] which supports the notion that route and timing of transfer are likely relevant, along with the potential for bacterial challenge. Farm management is important, including general hygiene, stocking density, exposure to disease, nutrition, and prepartum vaccination and deworming programs. Foals with partial failure of passive transfer were not at any greater risk of disease than those with adequate transfer on a well-managed Standardbred farm.[54]

Common postnatal routes of infection include umbilical remnants, gastrointestinal tract, and the respiratory tract. The umbilicus was traditionally regarded as the most important site for pathogen entry, but recently there has been recognition of the role of the gastrointestinal tract as an important portal for bacteria.[55] The absorption of macromolecules in the proximal small intestine occurs through specialized cells via pinocytosis, with little discrimination between maternal immunoglobulin and other macromolecules. Absorption peaks shortly after birth and declines to less than 1% by 20 hours.[56] Unlike other species, the absorption of immunoglobulins does not appear to be Fc-receptor mediated in the foal. The foal will selectively absorb IgG and IgM over IgA.[57] In neonatal pigs and lambs, deprivation of milk or colostrum can extend intestinal permeability to immunoglobulins by up to 5 days.[58] In contrast, intestinal permeability to immunoglobulins cannot be delayed through withholding of macromolecules to newborn foals.[59] It is not known if closure can be hastened by the feeding of macromolecules immediately after birth in foals. The other main postnatal factors beyond FTPI include gestational age and environmental conditions. Foals with exceptionally short or long gestational lengths may be at a heightened risk for development of sepsis.[60] Poor environmental conditions can result in an increased bacterial load to the gastrointestinal tract, especially during the initial periods of udder seeking.[55]

Causative Organisms

A summary of reported bacterial isolates is presented in Table 17-1. *Escherichia coli* is the predominant organism isolated from septic foals in recent studies, irrespective of location or methodology.[41,47,61-65] The next most common isolate varies with era and geographic location. In the late 1990s a group from the University of Pennsylvania reported an important role of gram-positive bacteria (*Enterococcus, Streptococcus, Staphylococcus* spp.), whereas the nonenteric gram-negative organism, *Actinobacillus* spp., accounted for approximately 30% of all isolates at Ohio State University in the late 1990s.[41,47] When trends were evaluated over time (1982-1989, 1990-1999, 2000-2007) *E. coli* remained the predominant isolate in a Florida population of sick foals; *Actinobacillus* spp. were more common in the 1980s relative to the 1990s and 2000s, *Salmonella* spp. were isolated less frequently in the 2000s relative to other decades, and enteric gram-negative organisms were less frequently isolated in the 2000s relative to the 1980s.[42]

Systemic fungal infections are uncommon in neonatal foals, with *Candida albicans,* a dimorphic fungus, the most frequently reported.[66,67] *Candida* infections have been associated with lengthy hospitalization and invasive monitoring techniques or immunodeficiency. Prolonged antimicrobial therapy and the administration of PN have been suggested as risk factors for the development of candidiasis. Infection should be suspected when there is a fever that is unresponsive to antimicrobial therapy. Most foals with systemic infection will also develop thrush (white plaques on the lingual surface) either concurrently or prior to showing clinical signs of systemic infection.

Physical Examination Findings

Physical examination of the mare and placenta are an important adjunct to the foal's physical examination. Any indication of placental or maternal abnormality should raise suspicion for neonatal illness. Initial clinical signs of sepsis in foals can be vague and highly variable. Frequently reported signs include decreased or absent milk intake, diarrhea, and lethargy, which may progress to recumbency. Examination should always include assessment of the mare's udder for fill; depressed foals will often stand with their head underneath the mare but fail to suck, leading to dried milk on their foreheads (Fig. 17-2). Clinical signs of dehydration occur as time progresses due to lack of intake. Tachycardia and tachypnea are common, but not always present. Oral, conjunctival, and vulvar mucous membranes can become hyperemic, injected, and/or petechiated. Petechiae may be noted along the internal pinnae of the ears, and hyperemia can be noted along the coronary bands. Capillary refill time may be rapid in hyperemic foals or substantially delayed in those that have become hypovolemic. Other signs of hypovolemia include decreased borborygmi, poor peripheral pulses, cool extremities, and decreased or absent urine output. Rectal temperature may be normal or mildly increased, or low if there has been progression to shock. Sepsis should not be ruled out on the basis of a normal or low rectal temperature. If untreated, these early signs can progress to septic shock, and often death.

Septic foals can also have localizing signs associated with specific foci of infection. Diarrhea is common and can be the first clinical sign noted. Other localizing signs include uveitis, seizures, joint effusion, lameness, physeal swelling, respiratory disease or distress, subcutaneous abscesses, patent urachus, and omphalitis.

Clinicopathologic Findings

Consideration of clinical signs and historical information are often sufficient for a provisional diagnosis of sepsis, but laboratory data will increase the index of suspicion. The most common hematologic

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TABLE 17-1

Summary of Selected Reported Frequency of Bacteria Isolated from Neonatal Foals*

	Wilson and Madigan[65]	Koterba et al[62]	Raisis et al[63]	Gayle et al[105]	Marsh and Palmer[41]	Stewart et al[47]	Henson and Barton[61]			Corley et al[40]	Russell et al[64]	Sanchez et al[42]		
Location	CA, USA	FL, USA	NSW, Australia	TX, USA	PA, USA	OH, USA	GA, USA			CA, USA	NSW, Australia	FL, USA		
Number of foals	47	27	24	29	155	101	250			85	110	423		
Blood cultures only?	No	Yes	No	Yes	Yes	Yes	No			Yes	Yes	Yes		
Admission only?	No	No	No	NS	No	Yes	No			No	Yes	No		
Years of study	1978-87	1982-83	1989-92	1988-95	1991-98	1993-2000	1986-90	1991-95	1996-2000	1995-2004	1999-2004	1982-89	1990-99	2000-07
Number of isolates	85	29	24	38	203	130	214	112	126	109	124	113	192	249
E. coli	30.6	58.6	50	36.8	18.7	30	59	29	26	40.3	31.4	39.8	29.7	28.1
Enterobacter spp.	3.5	3.4	12.5	18.4	12.3		18	8	9	1.8	8.1	5.3	6.2	5.2
Klebsiella spp.	12.9	6.9		10.5	3.9		16	15	7	4.6	0.8	7.1	8.3	5.6
Salmonella spp.		3.4	12.5	18.4	2.9		17	1	3			6.1	5.7	1.2
Actinobacillus spp.	18.8	6.9	12.5	2.6	8.9	23.1	11	8	7	19.3	6.5	8.8	1.6	2.4
Pasteurella spp.		3.4			1.5							1.8	6.8	7.2
Pseudomonas spp.	4.7	3.4		5.3	4.9							0.9	2.6	1.2
Enterococcus spp./ Group D *Streptococcus*					9.4		0	2	19	6.4	12	2.6	5.7	8.4
Streptococcus spp.	8.3		8	7.9	9.4		33	15	8	9.2	13	8	8.8	11.2
Staphylococcus spp.	3.5	3.4		5.3	9.8		7	8	15		9.7	3.5	3.6	2.4
Clostridium spp.	2.4	3.4									1.6	3.5	2.5	2.8
All gram-negative	75.3	93.1	91.7	78.9	62.6	72.3	77	69	58	74.3	57.3	77	67.2	63.9
All gram-positive	17.6	3.4	8.3	21.1	32.5	23.1	23	31	42	21.1	40.3	19.5	24.5	30.5
All anaerobe	2.4	3.4			3.4	4.6				4.6	2.4	3.5	6.8	2.8
All fungal/yeast					1.7							0	1.6	2.8
Overall survival (%)	31.9	25.9	70.8	48.3	NS	55	44			67	74.5	48	55.9	71.4

*Data are expressed as a percentage of the total isolates from each study.

Number of foals: Number of foals from which bacteria were cultured. Blood cultures only: Yes = Samples restricted to culture of blood only; No = samples included blood or infected tissue collected at necropsy. Admission only: Yes = Samples restricted to those obtained within 24 hours of a foal's admission to the hospital. *NS,* Not stated.



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FIG. 17-2 A septic somnolent foal standing under a mare that is spontaneously lactating.

finding in acute sepsis is leukopenia, characterized by neutropenia with shifting toward immature forms and toxicity (Dohle bodies, toxic granulation, and vacuolization). Septic foals younger than 1 week old have lower total white blood cell (WBC) counts, neutrophils, and lymphocytes, as well as a higher number of band neutrophils and monocytes than healthy age-matched controls.[68] Premature or dysmature foals will commonly have a decreased neutrophil count in the absence of sepsis, but without a degenerative left shift or evidence of toxicity, unless prematurity is complicated by sepsis. Age is an important factor in considering hematologic findings. In older foals (8 to 14 days) with confirmed sepsis, the total WBC count, neutrophil count, and number of band neutrophils were higher than in age-matched controls.[68] A high fibrinogen or serum amyloid A (SAA) concentration at or shortly after birth should raise the suspicion of in utero infection.[62]

Blood glucose concentrations are commonly abnormal in septic foals. Hypoglycemia (<100 mg/dL; <5.6 mmol/L) is common initially, especially in foals less than 24 hours of age.[62] Hypoglycemia is primarily related to decreased intake, but endotoxemia can also contribute to hypoglycemia. Hyperglycemia commonly occurs in response to dextrose infusion in septic foals. Other biochemical abnormalities common in septic foals include azotemia and hyperbilirubinemia,[36] as well as acidemia and hyperlactatemia.[69] Arterial hypoxemia and hypercapnia can occur in sepsis independent of pulmonary disease, but they are not consistent findings and are influenced by recumbency.

The coagulation and fibrinolytic systems of the septic newborn are often abnormal, with clinically relevant decreases in antithrombin III and elevations in prothrombin time (PT), activated partial thromboplastin time (APTT), fibrin degradation products, and D-dimer concentrations.[68,70] Some patients may develop active hemorrhage and/or thrombosis. This can include thrombosis of the aorta, iliac, femoral, or brachial arteries.

There are endocrine adaptations to illness, including sepsis, in neonatal foals. Increased concentrations of adrenocorticotropic hormone (ACTH) and cortisol have been documented in both septic and nonseptic hospitalized neonates.[71-76] Some septic foals are capable of a stress response, whereas relative adrenal insufficiency occurs in others. Consequently, non-survival has been associated with both higher and lower cortisol concentrations and a high ACTH : cortisol ratio.[71,72,74,75] Evaluation of basal total cortisol, ACTH, and the cortisol response to ACTH stimulation can provide information regarding hypothalamus-pituitary-adrenal (HPA) axis status in septic foals.[73]

Establishing a Definitive Diagnosis

Blood culture is the gold standard for diagnosis of systemic bacterial infection. Identification of a causative organism allows for directed antimicrobial therapy as well as monitoring for patterns of antimicrobial resistance. Samples for culture should be collected into a sterile syringe without anticoagulant from a large vein (usually jugular cephalic, or saphenous) after surgical preparation. The sample should be placed into appropriate blood culture media using volumes consistent with manufacturer recommendations. For those foals receiving antimicrobial therapy prior to sample collection, an appropriate medium with resins may improve microbial recovery.[77] Collection from a venous catheter is acceptable, provided it is done directly from the catheter at the time of placement without compromise of aseptic technique.

There are limitations to blood culture, including delayed results and reduced sensitivity. Many foals with histologic evidence of sepsis at necropsy have negative antemortem blood culture results. This can occur because of prior antimicrobial therapy or low circulating bacterial numbers. In one study, only 40% of *E. coli* infections were successfully identified by antemortem blood culture relative to recovery at necropsy.[65] These factors led to the development of scoring systems to predict sepsis.[78,79] The modified **sepsis score** is calculated using historical findings, physical findings, and laboratory data. The initial sensitivity and specificity of the score was reported at 92.8% and 85.9%, respectively,[78] but subsequent data indicated regional variability with lower sensitivity and/or specificity.[47,61,80] Because of the heavy weighting of historical information and related problems, moderate to severely premature foals often have a positive sepsis score without positive blood culture. Many of the maternal problems resulting in prematurity can also lead to systemic sepsis; consequently, this crossover is predictable. The problem with clinical application of these scoring systems is their relatively low specificity and negative predictive value. Although a "positive" score is supportive of sepsis, a "negative" score should not be used as a basis of withholding antibiotic therapy from an at-risk animal.

Therapy

ANTIMICROBIAL THERAPY. Antibiotics are the mainstay of therapy for septic foals. Initially a broad-spectrum bactericidal approach is recommended with selection influenced by costs, availability, and local knowledge of common isolates. Recommended dosages for commonly used antimicrobials are listed in Table 17-2. Reported antimicrobial susceptibility patterns of microorganisms isolated from equine neonates are presented in Table 17-3. Antimicrobial therapy should begin immediately when sepsis is suspected and should not be delayed pending blood culture results, since culture and sensitivity data typically require 3 to 4 days. Therapy can be altered if required when these data become available. A minimum therapeutic course of 2 weeks is recommended for bacteremic foals without localizing clinical signs. If localizing signs such as pneumonia or septic arthritis are present, a minimum course of 4 weeks is recommended.[60]

A commonly recommended initial therapeutic approach involves combining an aminoglycoside, typically amikacin or gentamicin, with penicillin or ampicillin. Alternatively, ceftiofur can be used alone, or in combination with an aminoglycoside. The use of amikacin or gentamicin should be tempered in light of the foal's cardiovascular and renal status. If a foal is severely hypovolemic and azotemic, a safer initial choice would likely involve a third-generation cephalosporin. If amikacin or gentamicin are used, therapeutic drug monitoring is recommended to ensure appropriate individual dosing. If not available, an alternative recommendation includes serial creatinine monitoring every 2 to 3 days and/or serial urinalyses, including sediment examination. Cefotaxime is a good choice for foals with gram-negative meningitis[81] or those with poorly responsive pneumonia. Oxytetracycline has been recommended in foals with suspected or confirmed septic osteomyelitis.[82]

Because of emerging resistance, trimethoprim/sulfa combinations should not be used in septic foals without documented

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TABLE 17-2

Recommended Antimicrobial Dosages

Agent	Preparation	Route	Frequency (h)	Dosage (/kg)	References
Amikacin	Sulfate	IV, IM	24	21-25 mg	116, 117
Gentamicin	Sulfate	IV, IM	36	12-15 mg	118
Ampicillin	Sodium	IV, IM	6	25 mg	
Ampicillin	Trihydrate	IM	12	25 mg	
Penicillin G	Potassium	IV	6	22,000-40,000 IU	
Penicillin G	Procaine	IM	12-24	22,000 IU	
Cefotaxime	Sodium	IV	6	40 mg	81, 119
Ceftiofur	Sodium	IV, IM	12	5 mg	120
Ceftiofur	Crystalline free acid	SC	72	6.6 mg	121
Cefpodoxime	Proxetil	PO	6-12	10 mg	87
Trimethoprim/sulfamethoxazole		PO	12	30 mg	
Oxytetracycline	Hydrochloride	IV	12-24	5-10 mg	

These represent recommendations only. Label indications and national or international rules regarding off-label usage of antimicrobials remain the responsibility of the provider.

TABLE 17-3

Reported Antimicrobial Susceptibility Patterns of Microorganisms Isolated from Equine Neonates

	Marsh and Palmer[41]	Henson and Barton[61]		Russell et al[64]			Sanchez et al[42]			
Isolates	*E. coli*	GP	GN	GP	GN	ALL	GP	NEGN	EGN	ALL
Amikacin	90	55	90	0	100	42	45.8	77.8	97.9	84.3
Gentamicin	80	50	75	34	74	56	62.0	79.2	92.1	83.6
Ampicillin	57	74	63	54	63	59	72.7	69.5	49.4	57.8
Penicillin		72	21	47	38	45	67.1	18.2	3.1	29.5
Ceftiofur	80	73	73	37	75	60	50	76.0	85.5	76.6
Ceftazidime							52.9	85.7	98.9	90.5
Chloramphenicol		90	75	73	83	78	92.2	94.4	84.6	87.5
Tetracycline		77	73	61	74	69	70.9	90.1	76.4	77.7
Trimethoprim-sulfamethoxazole	57	37	79	62	71	67	79.7	90.0	80.4	81.9
Enrofloxacin		100	100	37	93	70	74.6	94.5	97.6	91.8
Imipenem							86.7	82.1	100	94.9
Penicillin + gentamicin						72	84.1	78.9	92.1	88.0
Penicillin + amikacin							79.5	77.8	96.3	89.3
Ceftiofur + gentamicin						68				
Ampicillin + gentamicin							89.8	82.7	91.4	89.4
Ampicillin + amikacin							87.5	81.3	97.1	92.1

EGN, Enteric gram-negative isolates; *GN,* gram-negative isolates; *GP,* gram-positive isolates; *NEGN,* nonenteric gram-negative isolates.

Antimicrobial susceptibility is expressed as a percentage of all isolates for which susceptibility to a given antimicrobial were reported. See Table 17-1 for key to study details.

sensitivity—and then only as a long-term option following initial parenteral therapy. In contrast to older foals and adult horses, several aminobenzyl penicillins (amoxicillin and ampicillin) and first-generation cephalosporins (cefadroxyl and cephradine) have good bioavailability in young foals but have a limited spectrum of activity.[83-86] Cefpodoxime proxetil, a third-generation cephalosporin available for oral administration, was effective against 90% of *Klebsiella* spp., *Pasteurella* spp., and β-hemolytic streptococci, and an increase in the frequency of administration would likely increase the effectiveness against *E. coli*.[87] Fluoroquinolones, such as enrofloxacin, have an excellent spectrum of activity against gram-negative and some gram-positive bacteria, but have been associated with arthropathy in foals.[88,89] Therefore, use of this agent should be reserved for those cases where there is suspected resistance to other antimicrobial agents and informed owner consent.

ANTIFUNGAL THERAPY. Medical treatment options for systemic candidiasis include fluconazole, itraconazole, miconazole, and amphotericin B.[67,90] Fungal sensitivity profiles may help direct therapy if available. Pharmacokinetics of these drugs have not been established in foals. Amphotericin B has been administered at a range of 0.1 to 0.5 mg/kg IV q24h, starting therapy at the lower dose and increasing by 0.1 mg/kg increments per day.[67] Since this drug can cause potentially life-threatening nephrotoxicity, serum creatinine, urine production, and urinalysis should be monitored closely. Fluconazole has been administered previously at 4 to 10 mg/kg PO q24h. This agent is cheaper, easier to administer, and has far fewer side effects. Miconazole has also been used at a dose of 1 mg/kg IV q8h.[67] Voriconazole has also been used to treat pulmonary aspergillosis.[91]

ANTI-ENDOTOXIN THERAPY. Many septic foals have detectable plasma endotoxin concentrations.[68] Concerns exist regarding the potential for antibiotics to exacerbate the release of endotoxin through death of circulating gram-negative bacteria. In vitro work has shown that β-lactam antimicrobials appear more likely than aminoglycosides (alone or in combination with ampicillin) to induce endotoxemia and TNF-α activity during treatment of *E. coli* sepsis. Agents commonly used for the treatment of endotoxemia include flunixin meglumine, pentoxifylline, and polymyxin B sulfate.[92,93] Recommendations are extrapolated with caution from work in vitro and in adult horses. Flunixin and polymyxin B are potentially nephrotoxic, and flunixin has the potential for gastric ulceration. Pentoxifylline has also been shown to reduce mortality without adverse effects in septic neonates[94] but not adults.[95]

CARDIOVASCULAR SUPPORT. Cardiovascular support is critical in foals with hypovolemia, septic shock, or hypotension. When a foal presents in septic shock, initial fluid resuscitation choices commonly include a combination of crystalloid and colloid (such as

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hydroxyethyl starch) preparations. Arterial or venous lactate concentration, systemic blood pressure, cardiac output, and central venous pressure can provide additional information regarding volume status and estimation of tissue perfusion.[96] Once normovolemia is restored, neonates typically require approximately 80 to 100 mL/kg/day (5 L/day for a 50-kg foal) in order to maintain adequate hydration. Clinicopathologic variables to monitor in septic foals include arterial or venous blood gases, electrolytes (especially sodium and potassium), and glucose. Physical parameters of importance include careful examination for the development of edema (conjunctiva, prepuce, ventrum, distal limbs, etc.), urine output, vital signs, and temperature of the distal limbs. Derangements in any of the monitored parameters should be addressed as they arise. One should be particularly mindful of sodium load in the neonate, since requirements and sodium tolerance can differ widely between foals, and specific care should always be taken to avoid fluid overload.[2]

ANTI-ACID THERAPY. Although uncommon, sick foals can develop gastric ulcers in the glandular region of the stomach. The ulcers can preferentially occur in the cardiac gland region and may reflect reduced blood flow to the organ during hypovolemia. The use of prophylactic anti-acid therapy is controversial and highly dependent upon clinician preference. Gastric pH in critically ill foals can differ greatly from that seen in healthy foals.[97,98] Severely ill, predominantly recumbent patients frequently have alkaline pH profiles, and sick foals capable of acid production respond more variably to IV ranitidine administration than their normal cohorts.[98] Thus, glandular ulcer disease in sick neonates is likely not strictly an acid-related problem, and factors such as alterations in mucosal blood flow may contribute. In addition, gastric alkalinization can contribute to bacterial translocation.[99] The use of anti-ulcer medications (ranitidine, omeprazole) was associated with an increased risk of diarrhea in a large multi-center retrospective study.[100] In that report, anti-ulcer medications did not appear to protect against ulcer development in a small number of foals in which ulcers were detected. Should one choose to use them, options for acid suppression include ranitidine, omeprazole, and pantoprazole.[97,98,101-103] Sucralfate remains a possible alternative for ulcer prophylaxis, especially in foals receiving nonsteroidal antiinflammatory drugs, without altering intragastric pH.

ADDITIONAL THERAPY. In light of the relative adrenal insufficiency identified in some septic foals, low-dose corticosteroid therapy has been suggested for a subset of the septic foal population. However, given the wide variability seen in the septic foal population, more data are needed before such therapy is recommended.

Focal Infection and Potential Sequelae

The lungs are a very common location of focal infection in the septic foal, with a reported incidence of pneumonia ranging from 28% to 50%.[47,104] Many bacterial pneumonias are acquired in utero through aspiration of contaminated amniotic fluid. Respiratory rate and effort, thoracic auscultation, and rectal temperature can often alert the clinician to the possibility of pneumonia in a given animal. Respiratory function is best assessed in septic foals via ABG analysis.[96] Thoracic radiographs can provide an estimation of disease severity and distribution. In addition to hematogenously acquired pneumonia, septic foals can be at risk for aspiration of either meconium or milk, depending on their presentation. Directed antimicrobial therapy and maintenance of an acceptable arterial oxygen tension with intranasal oxygen insufflation are the most commonly administered forms of therapy. In those foals with severe hypercapnia in addition to hypoxemia, mechanical ventilation may be necessary.

Diarrhea and/or enteritis are very common in septic foals, with reported incidence between 16% and 38%.[47,60,104,105] Conversely, approximately 50% of neonates with a primary complaint of diarrhea are bacteremic.[106,107] Therefore, sepsis should be suspected in any diarrheic neonatal foal. Foals with *Actinobacillus* spp. bacteremia were six times more likely to have diarrhea than those with other isolates[47]; in another, gram-negative enteric bacteremia was positively associated with diarrhea.[42] With or without enteritis, septic foals can also display signs of ileus and/or colic. Most of these problems resolve with symptomatic treatment and systemic improvement. Analgesic therapy in colicky foals is somewhat limited, and flunixin meglumine should be used cautiously because of the potential for gastric ulceration. Butorphanol can be used intramuscularly to control gut pain in foals with colitis without increasing the risk of ulceration. Interestingly, diarrhea has been positively correlated with survival to discharge in one report of bacteremic foals.[42]

Omphalitis refers to infection of umbilical structures. Umbilical remnant infections are considered to be a common source of continued bacterial shedding. Ultrasonographic evaluation of these structures is critical, since external signs (pain, heat, and swelling) are frequently absent. Treatment options include long-term antibiotic therapy or surgical resection. The reported incidence in septic foals has ranged from 9% to 21%.[42,105] Many septic foals will develop a patent urachus without involvement of other structures. This problem will often resolve with continued antibiotic therapy, with or without topical therapy. Uroperitoneum in septic foals could result from ischemia and subsequent necrosis of the bladder and/or urachus. Most of these foals will not have classical serum electrolyte findings because of intravenous fluid therapy and limited milk intake. Routine ultrasonographic assessment of the umbilical structures is recommended in all hospitalized neonates in whom sepsis is either confirmed or suspected.

Meningitis is a rare but extremely serious complication. Major clinical signs include seizures and severe somnolence, although this is somewhat difficult to assess in a severely compromised foal. Other signs can include head tilt, strabismus, nystagmus, and extensor rigidity, depending upon the areas of involvement. CSF normally provides a definitive diagnosis, with a pleocytosis (normally neutrophilic) being the typical abnormality. Prognosis is poor to grave, but if therapy is attempted, third-generation cephalosporins (such as cefotaxime) have been recommended.[81] The major differential diagnosis for neurologic signs in a septic neonate is NE. Typically foals with NE present within 24 to 48 hours following birth, whereas the age of foals with meningitis is more variable. One report noted that none of 11 bacteremic foals with meningitis survived to discharge from the hospital.[42]

The most common ocular complication in the septic foal is corneal ulceration, noted in up to 12% of bacteremic foals.[42] Ulceration can occur due to entropion in a dehydrated foal or, more commonly, trauma. Because foals do not always show clinical signs of corneal ulceration, a daily ophthalmic examination, including fluorescein staining, should be performed in all hospitalized foals. Uveitis can also occur as an ocular extension of systemic disease.

Disorders of coagulation can occur in septic foals, manifested clinically by either hemorrhage or thrombosis. Probably the most common abnormality is jugular venous thrombosis at the site of an indwelling venous catheter. Other areas of thrombosis include the brachial artery, digital artery, metatarsal and metacarpal arteries, diffuse vascular thromboses throughout the distal limb, the aortic termination, the lungs, and the colon.[68,108-111]

Prognosis/Outcomes

Survival rates have increased from the 25% reported in the early 1980s.[62] More recent retrospective studies have reported short-term survival rates ranging from 45% to 55%.[47,61,105,112] Others have reported survival rates as low as 32% and as high as 70% to 72%.[63,68,104,113] Given the overall advances in neonatal care, it is not surprising that year of admission was positively correlated with survival in a University of Florida report (with an overall survival of 60%) from 1982 to 2007.[42]

Several factors have been associated with survival in retrospective studies. Barton and colleagues[68] found that foals infected with gram-negative organisms were more likely to die than those with gram-positive infections. In another study, the duration of illness prior to admission was inversely related to survival, whereas the ability to stand on admission was positively correlated with survival.[105] Foals were more likely to survive if they had a sepsis score

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less than 11, a negative blood culture at admission, blood glucose of 60 mg/dL (3.3 mmol/L) or more, body temperature 37.8° C (100° F) or greater, TCO_2 greater than 15 mmol/L, or a low or normal fibrinogen in a study from the University of Georgia.[61] In a Florida study, age at admission, septic arthritis, band neutrophil count, and serum creatinine concentration were negatively associated with survival, whereas year of admission, diarrhea, rectal temperature, neutrophil count, and arterial blood pH were positively associated with survival to discharge in bacteremic foals.[42] In an Ohio State study, foals with multiple blood isolates had longer periods of hospitalization, but not decreased survival.[47] Arterial lactate concentration, either at admission or 18 to 36 hours after admission, was a good predictor of survival in a further study.[69]

Few studies have addressed the long-term survival and performance of septic foals. In one report of bacteremic Thoroughbred foals, there was no significant difference in percentage of starters, percentage of winners, or number of race starts, relative to a control group of maternal siblings. However, bacteremic foals had a lower number of wins, total earnings, and Standard Starts Index, relative to control maternal siblings.[42] This is similar to that reported for overall neonatal intensive care unit (NICU) survivors, where the percentage of starters was lower than the control population, but performance over a 2-year period was not different in those animals able to make at least two starts.[113] Also, NICU treatment was found not to significantly affect sales performance.[114]

Preventive Strategies

Clearly, given the wide range of potentially devastating problems associated with sepsis, prevention will always outweigh treatment, but no one program will ever totally eliminate the risk of sepsis. Not surprisingly, methods of prevention coincide with the documented risk factors and routes of infection previously discussed. The following suggestions comprise a basic guide one can offer to clients. Although many of the presented options make sense, none has been proven to reduce the incidence of sepsis. Thus, the decision to implement some or all of these practices will depend upon the individual farm scenario.

MAINTAIN A CLEAN ENVIRONMENT. Although this is one of the most basic concepts in all of medicine, its importance cannot be overemphasized. With specific reference to the foaling situation, foaling stalls should be thoroughly cleaned and disinfected between mares. For each inhabitant, the stall should be cleaned at least daily, if not twice daily, and plentiful clean, dry, fresh bedding provided for the mare and foal.

REDUCE THE POTENTIAL BACTERIAL LOAD INTRODUCED DURING UDDER SEEKING. Ideally, Madigan[55] suggests that the mare's hind quarters, perineum, and udder should be thoroughly cleaned with soap and water prior to the foal's introduction. The key feature to this step, which is often overlooked, is that the mare must also be dried. This should be done just outside the stall, rather than in the stall, to prevent contamination of the foal's new environment. This step requires a great deal of commitment on the part of the farm, since it is fairly labor intensive.

ENSURE GASTROINTESTINAL INTAKE OF COLOSTRUM. The volume, quality, and timing of colostrum administration are all likely important, rather than just the quality. The ideal scenario involves feeding 6 to 8 ounces (180 to 240 mL) of good quality colostrum as soon as the foal develops a good, strong suckle reflex. One of the main concerns with this recommendation is the risk of milk aspiration when untrained individuals are trying to bottle feed newborn, potentially weak foals.

CONFIRM ADEQUATE TRANSFER OF PASSIVE IMMUNITY. Traditionally, transfer of passive immunity to the foal has been considered to be the most important factor in disease prevention. Although other factors clearly play a role, adequate immunoglobulin transfer should still be assessed and treated, if necessary. A complete discussion on treatment of FTPI is included elsewhere in this text.

ENSURE APPROPRIATE UMBILICAL CARE. This recommendation is followed by most horse owners, from the backyard client to the large breeding operation. No published studies in foals have critically evaluated the different preparations used for routine umbilical care. In human neonates, surprisingly few randomized, double-blinded clinical trials have broached this issue. In a recent review of published studies, 4% chlorhexidine was a popular choice and consistently reduced the risk of umbilical and periumbilical infections.[115] This concentration of chlorhexidine is also commonly used for foals, and thus appears to be a better alternative to previously used povidone-iodine solutions.

MONITOR FOALS CLOSELY AND TREAT SUSPECT FOALS QUICKLY. When identified early, sepsis can often be treated effectively on the farm with few complications. Thus, when prevention fails, early intervention is critical. Any foal with a fever, diarrhea, lethargy, or inappetence should be thoroughly evaluated and treated appropriately.

Septic Arthritis and Osteomyelitis

Rachael L. Smith

Neonatal foals are particularly susceptible to septic arthritis, osteitis, and osteomyelitis.[122] The incidence of this form of sepsis was estimated at 1% of all foals in the 1970s[123] but has likely reduced in recent decades as a result of improved management practices. This manifestation of sepsis represents significant loss to the industry, with reported survival rates to discharge from veterinary facilities between 42% and 81%[124-127]—but with only 30% of those with septic arthritis and 48% of those with septic osteomyelitis achieving long-term athletic soundness.[125,127] Prognosis is influenced by the number of joints affected, the number of bones involved, the age of the foal, and the presence of other medical problems.[125,128]

A classification scheme for septic arthritis and osteomyelitis has been developed based on radiologic and pathologic findings.[129] The "S-type" describes bacterial infection of the synovial membrane of one or more joints with no radiographic changes, but there is joint effusion and possible periarticular soft tissue swelling. This form is typically seen in the first 2 weeks of life and the most commonly affected joints include the carpus, stifle, and hock. The "E-type," or epiphyseal, classification describes infection of the joint and osteomyelitis of adjacent subchondral bone. It is usually seen at 3 to 4 weeks of age and common sites are femoral condyles, the distal radius, distal tibia, or patella. "P-type," or physeal-type, classification is used for cases of osteomyelitis of the physis on the metaphyseal side of the growth plate. This form occurs in foals 1 to 12 weeks of age and occurs most commonly in the distal radius or tibia as well as the distal metacarpi/tarsi. The "T-type," or tarsal, classification describes osteomyelitis of the cuboidal bones of the tarsus or carpus.

Etiology and Pathophysiology

Joint and bone infections most commonly result from persistent or transient hematogenous dissemination of bacteria.[129,130] Less commonly, infection can occur after direct trauma. Bacterial colonization of joints resulting from bacteremia is facilitated by the vascular pattern of neonates. Rapidly growing bones and joints require increased blood flow, derived from a main arteriole providing blood supply to the synovial membrane and epiphysis, and the nutrient artery supplying the metaphysis. In neonatal foals transphyseal vessels connect epiphyseal and metaphyseal blood supplies. Bacterial deposition in the synovium and subchondral bone occur as epiphyseal vessels branch toward the articular surface and form hairpin bends ending in wide venous sinusoids—regions of lower blood flow, oxygen tension, and pressure. The synovial membrane lacks a basement membrane; therefore, bacteria that are deposited in

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the subsynovial capillaries are able to readily migrate into the joint. Physeal infection is more likely to occur after closure of the transphyseal vessels, around 7 to 10 days of age, because of localization of the infection in metaphyseal vessel loops.[129,131] Colonization of bacteria in the articular, metaphyseal, and synovial vessels can lead to thrombosis and subsequent ischemic necrosis.[132] This can initiate a severe inflammatory response in associated tissues, producing classical clinical signs of joint effusion, heat, lameness, and pain on palpation of the periarticular tissues. Normal synovial fluid production and drainage is also impaired, leading to compromised articular cartilage metabolism. An influx of degradatory inflammatory mediators, white blood cells, serum proteins, and proteolytic enzymes leads to further disruption of chondrocyte metabolism and degradation of the cartilage.

The magnitude of the inflammatory response is determined by the virulence of the causative organisms, the size of the inoculum, and host resistance. The described sequelae resulting from infection highlight the importance of early diagnosis and treatment to achieve successful resolution before permanent degradative changes occur in the joint and periarticular tissue.

Diagnosis

Any lameness, joint effusion, or periarticular swelling in a neonatal foal should be considered significant and investigated regardless of history. Often reporting is delayed as owners commonly suspect mare-induced trauma to the foal, or they may describe the foal as moving "stiffly" or "slowly" rather than being overtly lame. Large joints such as the stifle, hock, carpus, and fetlocks are more commonly affected.[124,127,132,133] Pain in the foot or swelling of the coronary band could also be due to septic arthritis or osteitis/osteomyelitis.[82,134] Other causes of lameness and swelling associated with joints include cellulitis, hemarthrosis, fracture, trauma, and subsolar/solar bruising of the foot (Box 17-1).

The most consistent and early clinical sign of joint sepsis is effusion. Periarticular swelling, heat, pain on palpation of the bone or joint, and restricted passive movement of the joint is commonly reported. Less consistent clinical signs include lameness, an elevated rectal temperature, and hematologic changes consistent with infection. Lameness may escape identification if foals are systemically ill, weak, or recumbent. Lameness can take 8 to 24 hours to develop after bacteria have colonized the joints.[135] If there is swelling detected in one joint, thorough palpation of all other joints is recommended. Regardless of history and complete diagnostic findings, it is prudent to treat any joint swelling or lameness in a neonatal foal as septic until proven otherwise.

Hematologic changes can be inconsistent early in the disease course, but typically by 72 hours post inoculation there is leukocytosis and hyperfibrinogenemia. These findings lack both sensitivity and specificity. Fibrinogen levels greater than 900 mg/dL (>9 g/L) can be a useful indicator for epiphyseal or physeal osteomyelitis, but again this is neither sensitive nor specific.[136] Ultrasonography can be useful in detecting bone irregularities, defining and classifying joint effusion, as well as detecting associated problems such as pneumonia, omphalitis, or omphalophlebitis.

BOX 17-1

Lameness in Foals

Septic arthritis/osteitis/osteomyelitis
Fracture
Common sites: PIII, physis of PI, proximal sesamoid bones, olecranon
Hemarthrosis
Cellulitis
Flexural deformity
Rupture of the common digital extensor tendons
Rupture of the gastrocnemius muscle
Subsolar/solar bruising of the foot
Laminitis
Peripheral nerve injury

In order to reach a definitive diagnosis of septic orthopedic disease, additional diagnostic tests are required. These include diagnostic imaging and synovial fluid analysis following arthrocentesis, including cytology, Gram stain, and bacterial culture. To facilitate these procedures, adequate restraint of the foal is required. For neonatal foals, diazepam (0.1 mg/kg body weight IV) provides around 10 to 15 minutes of sedation to perform minimally invasive procedures. Prior to synoviocentesis, the skin should be clipped and aseptically prepared at the site of needle placement. Chlorhexidine or povidone-iodine scrubs are commonly used with isopropyl alcohol. Practitioners should not be overly vigorous in preparation of the skin and should avoid use of abrasive swabs as the skin of foals is particularly susceptible to trauma. It is likely that repeated scrubbing will be needed during the course of treatment, so preservation of the epithelial integrity is important. Lavage of the prepared area following the procedure with saline, drying the skin, and application of a topical antibiotic or antiseptic emollient cream is recommended prior to covering the site. Intraarticular administration of antibiotic into the joint following synoviocentesis is recommended, even if sepsis is not yet confirmed on cytology.

Any region of fluid distention of the joint, identified by bulging or balloting of the joint capsule, is appropriate for sampling, provided there is awareness of local anatomy. Ultrasonography is recommended to identify pockets of synovial fluid. In joints such as the stifle, carpus, and hock where multiple joint compartments are in close proximity, the potential for communication should always be considered. For this reason, arthrocentesis from each compartment should be performed, and the synovial fluid from each analyzed to determine the exact joint involvement. A 20- to 21-gauge needle can be used to aseptically collect synovial fluid. Fluid should be collected for cytologic examination into an EDTA tube and into a sterile serum tube for culture. Alternatively, synovial fluid can be injected into a blood culture medium to increase the chance of a positive culture. Confirmation of synovial sepsis from synovial fluid evaluation and testing is not always straightforward.[137]

Normal synovial fluid is of a light yellow to straw color, is transparent (should be able to see newspaper print through the tube and fluid), and has good viscosity. Signs consistent with sepsis include increased turbidity, darkening in color (dark yellow to orange), and reduced viscosity. In severe cases flocculent debris may be identified. The total protein (TP) of normal joint fluid is typically less than 20 g/L. Septic fluid usually has a TP greater than 40 g/L, but values greater than 20 g/L should be regarded as suspicious if other findings are supportive of synovial sepsis. The total nucleated cell count (TNCC) and differential nucleated cell count are considered the most useful evaluation of synovial fluid when diagnosing sepsis. Typically cell counts that are considered diagnostic of septic arthritis are greater than 30×10^9 cells/L, but infection should be suspected with values between 10×10^9 cells/L and 30×10^9 cells/L, particularly if the percentage of neutrophils is high.[131,137] Sequestration of WBCs into fibrin clots within the joint can result in lower-than-expected cell counts. Normal synovial fluid has less than 10% neutrophils. A cytological differential greater than 80% neutrophils is highly suggestive of sepsis.[138]

Sympathetic synovitis results from increased blood flow to a region, most commonly due to adjacent septic bone. The TNCC and TP of synovial fluid in sympathetic effusions are often elevated, but the percentage of neutrophils remains less than 80%.[129]

A Gram stain of synovial fluid should be performed, despite a low sensitivity for identification of bacteria. If bacteria are present, the results can guide antimicrobial selection while culture results are pending. Given the difficulty in culturing bacteria from joint fluid, a Gram stain result can sometimes be the only available option.[132] Synovial fluid should be submitted for aerobic and anaerobic culture. Positive cultures are only obtained in 55% to 78% of synovial fluid samples submitted.[126,139,140] A positive culture more accurately guides antimicrobial selection, but it is associated with a poorer prognosis.[140] If septic physitis or osteomyelitis is present, culture of débrided and necrotic bone is indicated at the time of surgery.

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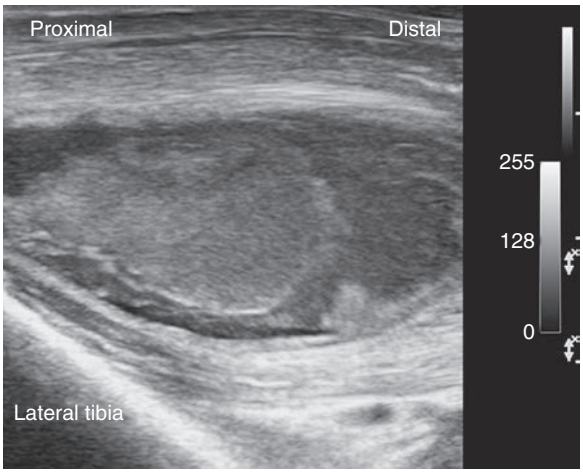


FIG. 17-3 A large mass of echogenic material consistent with fibrin within the distal aspect of the diverticulum of the lateral femorotibial joint surrounded in hyperechoic synovial fluid.

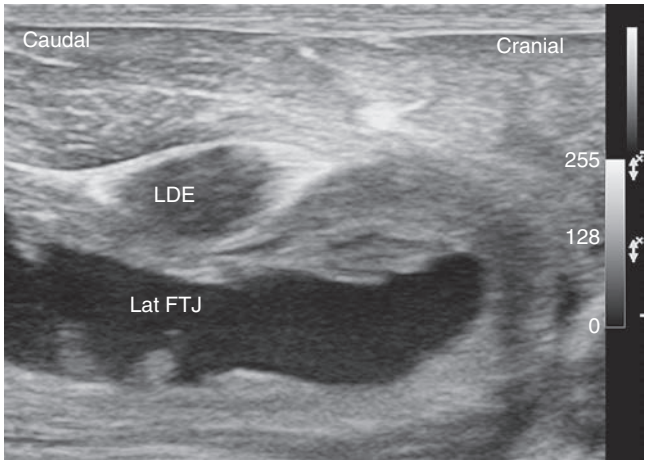


FIG. 17-4 The lateral femorotibial joint *(Lat FTJ)* compartment in cross-section positioned between the lateral tibia and the tendon the long digital extensor *(LDE)* tendon. The synovial fluid has increased echogenicity; the synovial lining and joint capsule is thickened with proliferative intrasynovial masses.

Ultrasonography can aid in quantifying synovial distention, identifying the presence of intrasynovial masses, thickening of the joint capsule and synovial membrane, and identifying irregularities of the subchondral bone and abnormalities of the physis. The contralateral limb is used for comparison when there are findings of questionable significance. Figs. 17-3 and 17-4 show both longitudinal and cross-sectional ultrasonographic images of the diverticulum of the lateral femorotibial joint, respectively, in a foal with septic arthritis. Radiographs of the affected and contralateral limb should be taken because concurrent infection of the physis and subchondral bone is common due to the vascular network of neonatal foal joints and extension of infection.[122,132] Bone infection has been reported in 38% to 80% of foals with septic arthritis.[63,82,124,127,129,132] In the initial stages of septic arthritis, radiographic changes may be absent or demonstrate mild soft tissue displacement as a result of joint distention. As progression occurs, joint space narrowing may occur, associated with articular cartilage destruction, periosteal reaction, and subchondral bone osteolysis. Radiographic changes of bone sepsis are not evident until 7 to 10 days after the onset of infection.[130] Baseline and serial radiographs over time can help to determine the progress of the disease and response to treatment.[132]

Computed tomography (CT) provides increased sensitivity and detail with improved detection and characterization of periarticular lesions and osteomyelitis, but it is subject to availability and often requires general anesthesia. Magnetic resonance imaging (MRI) offers superior imaging of periarticular soft tissue and cartilage, but the expense of the modality, the limited availability, the need for general anesthesia, and the time for image acquisition limit the use of the modality for the diagnosis of septic orthopedic disease.[130]

Treatment

The early diagnosis of disease and initiation of aggressive therapy are paramount to successful outcomes. The cornerstones of therapy include resolution of distant underlying sources of infection if present, systemic and local antimicrobial therapy, and drainage and lavage of the infected joint or joints. The choice of treatment regime will depend on facilities, economics, value of the foal, number and location of joints involved, any underlying disease process, presence of concurrent osteomyelitis, and identification of a causative organism.

Systemic Antibiotic Therapy

The selection of systemic antibiotics was discussed previously. Given the similarity between bacteria localized to joints of bone and those isolated from blood, the same initial protocols are warranted, pending culture data. Doxycycline (10 mg/kg PO bid) or oxytetracycline (5 to 10 mg/kg IV q12h) have recently been used successfully to treat septic arthritis and osteomyelitis.[82,141] Oxytetracycline has a relatively good spectrum of activity and penetration into bone and synovial fluid. If osteomyelitis is present, continued treatment with systemic antimicrobials for up to 2 months is recommended. Serial monitoring of synovial fluid analysis is useful to determine the trend in response to therapy, but normalization should not determine when antimicrobials are discontinued due to the risk of recrudescence of infection if treatment is ceased too early.

Local Antibiotic Therapy

The local administration of antimicrobials allows delivery of higher concentrations to the tissues of interest. Intraarticular administration of antibiotics results in significantly higher synovial fluid levels than systemic routes and coincides with synoviocentesis or immediately following joint lavage. The technique is preferred when tourniquet application and regional perfusion are difficult, such as the proximal limb or axial skeleton. Aminoglycosides, such as gentamicin (500 mg) and amikacin (125 to 250 mg), are commonly used (sid for 3 to 5 days) because of their effectiveness against many gram-negative pathogens. Ceftiofur sodium (125 to 500 mg) is also commonly used as an intra-articular therapy.

Regional limb perfusion techniques include intravenous (IVRP) and intraosseous (IORP) routes of antibiotic delivery, coupled with a tourniquet applied proximal to the affected joint or bone. IVRP or IORP can be performed concurrently with a joint lavage. A combination of sedation and local anesthesia or a short intravenous general anesthetic is usually required for these procedures, but these can be performed stall-side and should only take 30 to 40 minutes. The application of the tourniquet and the injection of the infusate can be painful; therefore, sedation and analgesia are required. Sedation can be achieved safely using diazepam (0.1 to 0.2 mg/kg IV) in combination with butorphanol (0.1 mg/kg IV). If general anesthesia is required, the regime just described serves as a good premedication, after which ketamine (2 to 2.2 mg/kg IV) can be used for induction. If additional time is required, the ketamine can be repeated. If the foal has minimal cardiovascular compromise, α_2 agonists, such as xylazine (0.5 to 1 mg/kg IV) or romifidine, in combination with butorphanol, also provide good sedation and analgesia; again, induction of anesthesia can be achieved through a bolus of ketamine.

The antibiotic is administered into a pressurized vascular environment, which aids in diffusion of the antibiotic from the vascular system into the interstitial tissues distal to the tourniquet. This allows high concentrations of antibiotics to be achieved in the poorly perfused and infected or ischemic tissues and exudate. Regional perfusion techniques typically achieve 5 to 50 times the MIC required to inhibit common pathogens in synovial fluid.[132,142,143] The techniques are preferred over simple intrasynovial administration if osteomyelitis is present.

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Administration of local anesthetic via the intravenous catheter or intramedullary screw prior to infusion of the antibiotic-saline combination is helpful in improving tolerance of the procedure, if general anesthesia is not used. The total dose of lidocaine used in the regional perfusion technique should be in the range of 1.3 to 5 mg/kg. Therefore, for a 50-kg foal, the amount used should be between 3.25 and 12.5 mL of 2% lidocaine, with the lower end of the range used in very young foals because of a lack of pharmacokinetic data.

Following sedation or induction of general anesthesia, an Esmarch bandage (or equivalent 5- to 12-cm-wide elastic or rubber bandage) or a pressurized tourniquet cuff can be applied proximal to the affected region, and it should only be left on for 30 minutes following infusion of the antibiotic, and a maximum of 60 minutes total tourniquet application time. For IVRP a 22-gauge butterfly needle, Teflon catheter, or polyurethane over-the-needle catheter is advanced into a superficial vein below the tourniquet. A small amount of cyanoacrylate glue can be used to fix the catheter to the skin to prevent removal, kinking, or movement. Commonly used veins include the saphenous or cephalic, or the palmar/plantar vessels. The perfusate (local anesthetic followed by antibiotic and saline) can be injected over 1 to 5 minutes.[144] Following injection the catheter is removed and gauze swabs placed over the site with several wraps of tape to provide pressure. This can be removed following the removal of the tourniquet after the appropriate time. The procedure is typically repeated at 24- to 48-hour intervals for three to five treatments, depending on the response to therapy.

The intraosseous route requires a custom-made cannulated cortical screw with a welded luer-lock adapter or an intraosseous infusion needle (Cook Critical Care, Bloomington, Ind.). A hole is drilled through the cortex of the metacarpus or metatarsus for placement of the screw, after which time perfusate can be injected. Because of the small size of foals and the specific equipment required, intraosseous perfusion is used in limited situations or equine hospitals. In addition, increased complications are recognized with the intraosseous technique.[144]

The aminoglycosides amikacin and gentamicin are commonly used since most joint infections are caused by gram-negative bacteria. Penicillin, cefazolin, and ceftiofur have also been used safely in local therapy, but only in response to culture and sensitivity testing. The size of foal and the area to be infused below the tourniquet should be considered when deciding on total volume, but volumes are typically between 30 and 60 mL, with 0.9% saline used to dilute the antibiotic. If local anesthetic is used, that volume is considered as part of the total perfusate. The daily systemic dose of aminoglycoside should be reduced by the amount used in the perfusion, and the total dose used in the perfusion should not exceed the total systemic dose. The procedure should be performed at the same time of day that the systemic dose is administered. Commonly recommended doses for foals are 250 to 500 mg of amikacin, 400 to 600 mg of gentamicin, and 500 mg of ceftiofur.[82,130]

Complications of IVRP or IORP include soft tissue swelling at the infusion site, thrombophlebitis, difficulty in injecting during IORP, and tissue sloughing. Most of these can be avoided with careful aseptic technique, by avoiding catheter repositioning, and by minimizing the number of procedures.[144]

Drainage and Lavage of the Septic Joint

Joint drainage, lavage, and débridement are important components in the management of synovial sepsis. The aim of lavage is to reduce the number of organisms in the synovial fluid, remove debris and inflammatory products, and reduce the level of pain associated with inflammation and joint distention. Techniques include needle lavage (ingress-egress, through and through), arthroscopic lavage and débridement, or arthrotomy. Needle lavage has the most beneficial effect if performed within 24 to 48 hours after the onset of infection, or more important, before accumulation of fibrin. Ultrasound can aid in determining the location for needle placement and determine the amount of intrasynovial fibrin. A large amount of fibrin or intrasynovial masses will compromise lavage as a result of needle plugging. It is also unlikely that fibrin will be removed by needle lavage. Aggregates of microorganisms can be sequestered in fibrin and escape the effects of antibiotics, resulting in persistence of clinical signs or recrudescence of infection once therapy has been discontinued.

For needle lavage, the skin should be clipped and aseptically prepared, and the foal sedated or anesthetized as described previously. Synovial fluid should be collected for confirmation of sepsis or for serial cytologic monitoring to assess response to treatment. If general anesthesia is not used, the joint can be distended with local anesthetic after a single needle placement. The ingress-egress lavage technique involves repeated distention of the joint with sterile saline, followed by aspiration using a single portal. The technique is indicated in joints that have difficult access or where additional needles have become plugged or displaced from the joint. Through-and-through lavage is more commonly used. After distention of the joint with sterile saline or local anesthetic, additional superficial pouches of the joint become visible, aiding in placement of further needles. Needle size is based on clinician preference, but usually 18- to 14-gauge needles are used. Practitioners placing additional needles must try to keep the joint distended to avoid iatrogenic damage to the cartilage. Precise landmarks for needle placement are not necessary, but a sound knowledge of the local anatomy and visualization of the three-dimensional structure of the joint will help to maintain correct placement of the needles during the lavage. Between 1 and 2 L of physiologic saline or lactated Ringer solution are typically used to complete the lavage. The bags can be pressurized and attached to the ingress needle, allowing the clinician to place additional needles and subtly adjust needle position to facilitate flow. The risk of using a pressure bag system is rapid delivery of saline outside the joint if the ingress needle position changes slightly. Joint lavage becomes futile once subcutaneous saline restricts the distention potential of the joint pouches. In joints with moderate periarticular soft tissue structures or swelling, the author prefers to use 20- to 30-mL syringes to lavage the joint. Any increase in resistance to injection is easily appreciated, and correction of needle placement can occur before fluid is delivered outside the joint (Fig. 17-5). The use of different ingress needles is recommended to increase turbulence and facilitate removal of joint debris, irrespective of whether syringes or pressurized bags are used. This also prevents the egress needles from plugging with fibrin. On completion of the lavage, as much fluid as possible should be expressed before removing all needles except one, which can then be used to administer intra-articular antibiotic.

The number and frequency of needle lavages is determined by the response to treatment. If the clinical signs progress in the face of 3 to 5 days of systemic and local antibiotic therapy and needle lavage, then reevaluation of the foal including ultrasound and radiography is indicated. Signs of treatment failure include persistent lameness or pyrexia, periarticular swelling, persistence or worsening of joint effusion, additional joint involvement, or failure to decrease synovial cell



FIG. 17-5 Lavage of a septic joint using a syringe and separate egress needle.

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counts or differential. It is important to identify if there has been subchondral bone lysis. Treatment failure may prompt an antibiotic change and/or more aggressive joint lavage via arthroscopy or arthrotomy, if arthroscopy is not available. Arthroscopy offers many advantages over needle lavage and arthrotomy and is the preferred choice for chronic or refractory cases of synovial infection. The technique permits superior visualization of most aspects of the joint, including the articular cartilage, bone, joint capsule, and synovial membrane. Targeted lavage and débridement can be achieved for removal of fibrin and debris, synovial resection, and débridement of necrotic cartilage or subchondral bone. Arthroscopic and arthrotomy approaches and intraarticular anatomy of commonly affected joints are reviewed comprehensively elsewhere.

Septic Osteomyelitis

Septic osteomyelitis occurs as a primary disease entity or concurrently with septic synovitis, with infections commonly occurring at the epiphysis of long bones, the metaphyseal side of growth plates, costochondral junctions, and the articular facets of vertebral bodies. Radiographic evidence of osteomyelitis includes regions of focal loss of bone density, osteolysis, or sequestrum formation. Necrotic bone can act as a nidus for continued bacterial growth. The treatment of osteomyelitis includes systemic and local antibiotics and possible débridement.[82,145] Necrotic subchondral bone can be débrided using arthroscopy, and infected physeal bone can be débrided under radiographic or fluoroscopic guidance. Débridement of necrotic bone is not indicated in extensive lesions where mechanical joint stability may be jeopardized, or where the surgical access and débridement would create significant surgical complications.[82,145] Evidence suggests that surgical curettage may not offer significant advantages over prolonged systemic and local antibiotic therapy alone.[82,141,146] In addition to the regional perfusion techniques described previously, there is occasional indication for implantation following débridement of antibiotic impregnated polymethylmethacrylate, calcium sulfate, or collagen sponges. These substances elute antibiotic at the site of bone infection.[131]

Intravenous tetracycline (5 to 10 mg/kg IV q12h) or oral doxycycline (10 mg/kg bid PO), along with local treatment with amikacin (IVRP or IA 250 to 500 mg), is indicated if culture and sensitivity results suggest susceptibility, or if culture results are unavailable. Surgical débridement is indicated if there is radiographic evidence of sequestrum formation, chronicity of the disease in the face of medical therapy, or progression of the osseous infection.

In cases of osteomyelitis, serial monitoring of fibrinogen or SAA may aid in determining the response to therapy. A positive response results in decreasing SAA levels over 48 to 72 hours, and this commonly precedes improvement in lameness.

Management and Adjunctive Therapy

Nonsteroidal antiinflammatory drugs (NSAIDs) are indicated in the management of septic orthopedic disease resulting from antiinflammatory, analgesic, and antipyretic effects. Commonly used NSAIDs include flunixin meglumine, ketoprofen, phenylbutazone, and less commonly, ibuprofen. Dosages cannot be directly extrapolated from adults since healthy foals have a greater volume of drug distribution and prolonged clearance.[147] For flunixin and ketoprofen, this results in a dose rate that is 1.5 times that of the adult dose and extension of the dosing interval to every 24 hours. The drugs should be used judiciously in compromised or critically ill foals because of the potential adverse effects such as gastrointestinal (GI) ulceration, nephrotoxicity, and platelet dysfunction. Oral meloxicam at a dose rate of 0.6 mg/kg every 12 hours achieves plasma concentrations that are likely therapeutic without evidence of drug accumulation in plasma. Foals appear to be more resistant to the adverse effects of meloxicam than adult horses, and drug clearance was more rapid in foals.[147] If additional analgesia is required, butorphanol (0.05 to 0.1 mg/kg IV or IM) or transdermal fentanyl patches (100 µg/h patch) can be used safely in foals. The clearance and systemic uptake of butorphanol is faster in foals, suggesting that higher doses may be required. A recent study showed a dose rate of 0.1 mg/kg of butorphanol-provided analgesia for 150 minutes in 4- and 8-week-old pony foals.[148]

The affected limb should be bandaged during treatment to cover needle/arthroscopy portals, to provide compression and support to the limb, to limit swelling and reduce pain, and to absorb exudate if an arthrotomy has been performed. Application of bandages with adequate padding in the secondary layer is recommended in the distal limb because of the combination of thin skin, bony protuberances, and minimal subcutaneous soft tissues. Adhesive dressings can be used over joints where a bandage cannot be maintained.

Restoration of joint health and range of movement is important following infection. Gentle forced flexion and extension of the joint while non–weight bearing will help maintain joint function and movement. The foal should be stall confined and weight-bearing exercise avoided for 3 to 4 weeks following the resolution of infection and clinical signs. The stall should have a deep bedding of clean straw to reduce the risk of pressure necrosis during recumbency. The stall should be cleaned two to three times a day to reduce the risk of the foal lying in feces or urine-soaked bedding. Handlers and clinicians should use strict personal hygiene when treating foals. Controlled hand walking of the mare on a daily basis for 1 to 2 weeks should be initiated prior to free turnout.

The decision to discontinue antibiotic therapy is based on clinical judgment and resolution of clinical, hematologic, radiographic, and cytologic abnormalities. Generally local antibiotic therapy and lavage are continued until normalization of the synovial fluid and cytology, and systemic antibiotic therapy is continued for 2 to 3 weeks beyond the resolution of clinical signs.

Prognosis

The prognosis of foals with septic arthritis/osteomyelitis is dependent on a number of factors, but short-term survival is considered good to excellent with studies reporting 71% to 81% survival to discharge.[82,124,127] The prognosis for future athletic performance is less favorable, with 30% to 48% of foals affected with septic arthritis/osteomyelitis going on to race.[82,127,133] Factors affecting prognosis include prolonged duration (>24 hours) of signs before the initiation of treatment, concurrent systemic disease, the number of joints infected, the location of infected joints, the presence of concurrent osteomyelitis, and the type and diversity of bacteria involved. The financial constraints for treatment, facilities, and technical skill available for treatment and the expected long-term use of the foal can also affect outcomes.[82,127,131-133] These factors and the high cost and long duration of treatment required for treatment should be considered when counseling owners.

Noninfectious Causes of Lameness

Rachael L. Smith

Fractures occur relatively commonly in young foals and are an important differential diagnosis for foals that are lame (see Box 17-1) and are most often due to traumatic insult or an isolated event. Fractures are differentiated from septic arthritis or osteomyelitis through history and physical findings; relevant laboratory data, including hematology and synovial fluid analysis; and most important, diagnostic imaging. Several factors may predispose foals to fracture, including prolonged stall confinement leading to osteoporosis and weakened soft tissue support structures, trauma from the dam or other horses, or management systems that allow overexercise.[149] Common sites of fracture in the distal limb include the distal phalanx, physeal fractures of the first phalanx, and the proximal sesamoid bones. Physeal fractures of other bones are also common due to the relative weakness of this structure and are described by the Salter-Harris classification system. Olecranon fractures are the most common fracture of the upper limb. Premature or dysmature foals are prone to crushing injuries of the cuboidal bones of the carpus or tarsus.

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FIG. 17-6 Rupture of the gastrocnemius muscle.

In foals, rupture of the common digital extensor tendon may be present at birth or develop within a few days of life. Rupture occurs within the carpal synovial sheath and produces swelling over the dorsolateral surface of the carpus at the level of the middle carpal and carpometacarpal joints. Palpation of the fibers reveals tearing of the tendon and can be confirmed with ultrasonography. Splinting of the limb is required in foals that continually buckle forward at the fetlock. Box confinement for the first 3 to 4 weeks usually results in healing. Surgery is not required and the tendon ends usually reappose over 6 months with minimal swelling and a good long-term prognosis.

Rupture of the gastrocnemius muscle at the level of its fossa in the femur can also occur during parturition, especially if assisted, or if the stifle is forced into extension during delivery while the hock is flexed. Hyperflexion of the hock occurs, and diagnosis of this is confirmed with concurrent flexion of the hock and extension of the stifle (Fig. 17-6). Ultrasound evaluation usually shows hemorrhage within the muscle belly and edema at the fossa of the femur. Treatment is complete stall rest if the foal can bear weight, but if the hock is severely flexed, a full limb case should be applied. The prognosis for long-term soundness is guarded.[26]

Congenital contractural deformities of joints can be bilateral or unilateral and present at birth. They are usually the result of external environmental factors during gestation, bone or joint malformation, or other physiologic causes such as intrauterine malpositioning. They are described with reference to the affected joint and can occur in the carpus, fetlock, pastern, coffin joint, or tarsus. Diagnosis of contractural deformities is relatively straightforward based on the inability to straighten affected joints and difficulty in standing and movement at birth as a result.[132] This predisposes to failure of passive transfer of immunoglobulin by impeding the ability to adequately nurse. The degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis.[150] Conservative therapy consisting of bandaging or splinting the limbs to induce tendon laxity may be helpful. Care must be taken to provide adequate padding under the splint and to reset the splint every day. Oxytetracycline (2 g slow IV) in combination with splinting induces relaxation of the musculotendinous unit, and although results can be remarkable, they are not always reliable[132]; repeat treatments are often required.

Twins, premature foals, foals that are small for gestational age, and foals with in utero–acquired infection are likely to have incomplete ossification of cuboidal bones at birth. Foals with substantially reduced ossification may damage bone with limb loading. Limited exercise may be prudent until ossification begins to increase radiographically, which can be within 7 days. Hypothyroidism has been identified in foals with angular limb deformities, contracted tendons, and tarsal bone collapse.

Young foals can suffer physitis when there is excess load caused by overexercise or weight on the newly forming bone, or as a result of normal loading on abnormal conformation. The physis of the distal metacarpus/tarsus or proximal phalanx is most commonly affected. Clinical signs can vary and be subtle, such as a stiff gait, shortened cranial phase of stride, trembling when standing, or buckling forward at the carpus or fetlock. Pain in the physis can lead to contracture of fetlock tendons. Treatment is aimed at reducing pain with antiinflammatory therapy and reducing exercise level or correcting underlying angular limb deformities.[132]

Other causes of lameness and swelling associated with joints include cellulitis, hemarthrosis, subsolar/solar bruising of the foot, and hoof wall cracks causing laminae pain.

Seizures

Guy D. Lester

Recognition

Foals have a lower seizure threshold than adult horses.[151] Seizures are generated by abnormal electrical activity within the cerebral cortex. Depending on the location and extent of the abnormal activity, the seizures may be partial or generalized. Generalized seizure activity is characterized by recumbency, widespread involuntary muscle activity, paddling of the limbs, and extensor rigidity. Partial seizure activity may be more difficult to identify and could be limited to mild movements of the face and jaw, or stretching of the limbs.[25]

Rapid eye movement (REM) sleep can be easily confused with seizure activity. The normal activity is particularly prominent in premature or dysmature foals. Signs can include motor activity, including rhythmic paddling of the limbs, neck extension, chomping of the lips, rapid eye movements, and vocalization.[152] Episodes can last for several minutes and can be distinguished from seizure activity by attempting to arouse the animal. A foal in REM sleep should be easily aroused to full consciousness.

A foal that is simply resisting restraint in lateral recumbency may also appear to be seizuring, and violent paddling of the limbs and occasionally opisthotonos are noted. If confusion exists as to the cause of the activity, the animal should be encouraged to stand, and its behavior reevaluated.

Once seizure activity is identified, a complete history should be obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations are performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and IgG status, combined with historic and physical examination parameters, results in an assessment of the likelihood of sepsis. Blood glucose and serum electrolyte concentrations should be determined promptly. A biochemistry panel, blood gas analysis, and bacterial cultures of blood and other body fluids, and possibly CSF analysis, complete the database in most cases.

CT or MRI scans are advanced diagnostic procedures for evaluating the anatomic causes of seizures. Premortem diagnosis of agenesis of the corpus callosum and associated malformations was made using CT scanning in a foal that had an abnormally shaped head and seizures refractory to anticonvulsant therapy.[153] Identification of the specific abnormalities early in the clinical course allowed the owners to make more of an informed decision regarding the treatment of the foal, and the clinicians to acquire valuable information regarding the prognosis of a specific malformation in the horse.

Causes (Box 17-2)

The most common cause of seizure activity in foals is described by the syndrome of **neonatal encephalopathy (NE).** The terminology can be confusing, with accepted synonyms that include hypoxic-ischemic encephalopathy (HIE), neonatal maladjustment syndrome

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BOX 17-2

Seizure Disorders in the Neonatal Foal

Neonatal encephalopathy
Bacterial meningitis
Viral encephalitis
Benign juvenile epilepsy
Lavender foal syndrome
Kernicterus
Hepatic failure
Congenital brain disease
    Hydrocephalus, hydranencephaly
Head trauma
Hypoglycemia
Electrolyte disorders
    Hypocalcemia, hyponatremia, hypernatremia
Tetanus
Toxicities
    Ivermectin, moxidectin
Glycogen storage disease IV
Hyperammonemia of Morgan foals

(NMS), barker foals, dummy foals, and wanderer foals. NE is preferred by some over HIE, since an overt history of hypoxia or ischemia is not a consistent finding.[6,154] NE is the neurologic manifestation of hypoxic-ischemic syndrome (HIS) or perinatal asphyxia syndrome (PAS). NE is reported to occur in 1% to 2% of all births.[155]

The common pathway is assumed to be reduced oxygen delivery to neuronal cells within the central nervous system (CNS). This could result from hypoxemia, anemia, or reduced blood flow. In many cases the signs are delayed and the injury is reversible, although in severe cases the signs are present at birth and are non-reversible. Neuronal cell death occurs in two phases: an initial phase that centers on energy failure resulting from oxygen and glucose depletion and a secondary delayed phase characterized by hyperemia and cytotoxic edema, accumulation of excitotoxins, and mitochondrial failure.[156] During the acute phase there is depletion of ATP and failure of cell-membrane ion pumps, resulting in membrane depolarization and accumulation of sodium and then water within the neuronal cell, leading to swelling and lysis. In addition, there is accumulation of the excitatory neurotransmitter, glutamate, in the extracellular environment as a result of increased release from neurons and failure of cellular neurotransmitter uptake, an energy-dependent process.[6] Glutamate can interact with AMPA receptors to amplify sodium movement into the cell, with passive movement of water. The secondary phase is complex; the excitatory neurotransmitters can facilitate calcium entry into cells through activation of specific glutamate receptors (*N*-methyl-D-aspartate; NMDA receptors).[156] Intracellular levels of calcium cannot be controlled because of pump failure, and produces a cascade of events including activation of enzymes (including phospholipases, proteases, and nitric oxide synthase), enhanced glutamate release, uncoupling of oxidative phosphorylation, and generation of oxygen-free radicals.[6] Macrophages within the CNS, the microglial cells, are stimulated to produce proinflammatory cytokines that further contribute to hyperemia and the development of edema. This culminates in cell death from necrosis or apoptosis. As discussed earlier, in many animals the level of insult is such that the pathology is reversible. Paradoxically, the inflammatory cells also contribute to the clearance of cellular debris as part of this process.

Clinical insults that could predispose to decreased oxygen delivery to the foal brain include maternal illness, placental disease, premature separation of the placenta, prolonged stage II of parturition, cesarean section, and postdelivery factors, including airway obstruction, pulmonary hypertension, or blood loss. In many foals the signs associated with the acute insult are minor or missed, with clinical signs classically delayed until 12 to 24 hours of age. Theoretically, the onset of signs could be delayed until 72 hours, but this is unusual. The resultant signs are diverse and are mainly related to cortical involvement, although in some more severely affected foals there are features consistent with involvement of the brain stem or spinal cord.[25] Signs include generalized weakness and somnolence, a lack of interest in the dam, loss of suck reflex, a weak tongue that may protrude from the mouth, compulsive licking, dysphagia, bizarre vocalization, abnormal posture, abnormal face and jaw movements, head pressing, cortical blindness, erratic breathing patterns, ataxia, recumbency, and seizure activity (Fig. 17-7). Given that NE is a manifestation of HIS, there may be signs of disease in other organ systems, most commonly the gastrointestinal and renal systems, that will complicate the clinical picture, treatment, and prognosis.



FIG. 17-7 Compulsive licking in a foal with neonatal encephalopathy.

The diagnosis of NE is based on history, physical findings, and exclusion of other differential diagnoses. If uncomplicated by involvement of other body systems or other diseases, such as sepsis or prematurity, then routine hematology, biochemistry, and electrolytes will typically be within normal limits. An elevated serum creatinine concentration could reflect placental dysfunction and, in one study, was present in 32% of affected foals, with the concentration of creatine kinase elevated in 61% of cases.[155] CSF is important in ruling out bacterial meningitis; in NE the sample is normal or xanthochromic, with increases in red blood cells and protein. An experimental biomarker of brain injury, ubiquitin C-terminal hydrolase 1, was significantly increased in foals with NE (6.75 ng/mL; range 2.35 to 11.90 ng/mL) when compared with healthy age-matched controls (2.53 ng/mL; range 1.40 to 4.01 ng/mL).[157] Increased concentrations reflect blood-brain barrier permeability and neuronal destruction; further studies are required in foals to document biomarker levels with other foal diseases.

Given that most foals with delayed onset of clinical signs will survive, the treatment of NE is primarily supportive. Maintenance of hydration and blood glucose concentrations is important. The rate of fluid administration is dictated in part by renal function, which can be impaired in foals that have undergone an asphyxial insult. Although the provision of small volumes of milk is important in maintaining enterocyte function, it is easy to overfeed because milk intolerance is common in asphyxiated foals. Intravenous fluid therapy for maintenance of hydration should be used (see the beginning of this chapter). The fluid rate is in part dictated by the need to provide glucose supplementation. A rate of 5 mg/kg/min has been suggested as an initial CRI flow rate, based on the estimated placental supply in late gestation (6.8 mg/kg/min).[3,9] This equates to an hourly flow rate of 3 mL/kg (150 mL/h for a 50-kg foal) of a 10% glucose solution. Blood glucose concentrations should be monitored closely and the rate adjusted as required. Boluses of glucose solutions should be avoided because the resultant glucosuria will result in urinary losses of fluid, electrolytes, and glucose. It can produce a marked rebound hypoglycemia.

It is critical that seizures are identified and treated, since ongoing seizure activity will increase cerebral oxygen consumption and further contribute to neuronal cell damage. Seizures are usually well controlled with **diazepam** (0.1 to 0.2 mg/kg IV). It is not uncommon to control two or three seizure episodes with diazepam before adding **phenobarbital** (10 mg/kg IV over 15 min, then 5 mg/kg PO q12h).[25]

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Phenobarbital acts by raising the seizure threshold, and its peak effect is seen at approximately 30 minutes. The major side effect of phenobarbital in foals has been mild sedation, ataxia, and hypothermia. Interactions between phenobarbital and other drugs usually involve induction of the hepatic microsomal enzyme system. Weaning from anticonvulsant therapy should be gradual to avoid recurrence of seizure activity. **Midazolam** (0.04 to 0.1 mg/kg IV) is an alternative to diazepam and can also be used as a CRI for control of intractable seizures (0.02 to 0.06 mg/kg/h IV).[158] Alternatively, intravenous general anesthesia with propofol or similar medications may be required for several hours to manage cases of intractable status epilepticus.[25]

Additional therapies are commonly used in foals with NE. The use of many of these drugs is based on theoretical or experimental data in other species, rather than results of clinical trials. **Magnesium** supplementation (0.05 g/kg/h, for the initial hour, followed by 0.025 g/kg/h IV CRI) is used to block the release of glutamate and antagonize the influx of calcium at the NMDA-activated channels.[159] **Mannitol** (0.25 to 1 g/kg IV as 20% solution over 20 minutes, repeated q12-24h) or **dimethyl sulfoxide** (0.5 to 1 g/kg IV as a 10% solution q12-24h) is used to treat cerebral edema and as free radical scavengers. Similarly **furosemide** (1 mg/kg IV q12-24h) has been used as an alternative therapy for cerebral edema. The effectiveness of these drugs to manage intracellular edema has been debated. Other putative free radical scavengers or antioxidants that have been used or recommended include **thiamine** (5 to 10 mg/kg IV or SC q24h), **vitamin E** (20 IU/kg SC or PO q24h), **vitamin C** (10 to 100 mg/kg/d IV), and **allopurinol** (44 mg/kg PO within 4 hours of insult).[6,25] NSAIDs such as **flunixin meglumine** (1.1 to 1.5 mg/kg IV q12-24h) are recommended, but corticosteroids are not indicated.

Whole body or selective head cooling to 33° to 34° C (91° to 93° F) is used as a treatment of hypoxic-ischemic encephalopathy in human neonates; if commenced within 6 hours after birth and applied for 48 to 72 hours, the treatment can significantly improve short-term survival and neurologic outcome of survivors.[160] Other therapies to decrease the cerebral metabolic rate in human neonates include permissive hypercapnia and high doses of barbiturates.[161] Hyperbaric oxygen therapy has also shown some experimental benefits and has been used in foals with NE.[162]

Nursing care remains one of the most important aspects of NE management. This includes care of the skin and respiratory tract by providing soft bedding and facilitating gas exchange through maintenance of sternal recumbency where possible. Regular vigorous stimulation and support to stand are also important. The prognosis for foals with uncomplicated NE is good, provided there has been a period of relative normality before the onset of neurologic signs. Most foals will respond within 3 to 5 days if managed appropriately, with reported survival rates to discharge typically around 75%. It is suspected that the long-term recovery is complete. The prognosis is poorer in foals that show signs at the time of birth, have evidence of brain stem or spinal cord involvement, or have significant involvement of other organs as part of HIS.

Bacterial meningitis should be suspected in a foal with neurologic disease and recent or current signs of generalized or localized sepsis. Agents causing meningitis are the same that cause systemic sepsis—most commonly, bacteria such as *Escherichia coli, Enterobacter* spp., *Salmonella* spp., and *Streptococcal* spp.[62,81,151,163] Signs can include hyperesthesia, neck rigidity, varying degrees of obtundation, seizure activity, opisthotonos, limb ataxia and paresis, or specific cranial nerve abnormalities.[25] The definitive diagnosis is dependent on CSF analysis, which reveals a pronounced neutrophilic pleocytosis. Hematology and serum biochemistry reflect sepsis, and the serum IgG concentration often reflects failure of passive transfer.

Antibiotic treatment should be guided by culture and sensitivity data. Successful treatment has been reported using courses of broad-spectrum, third-generation cephalosporins.[81] These include cefotaxime or ceftriaxone because of their excellent penetration into the central nervous system. Alternatives include ceftiofur, trimethoprim-sulfa combinations, chloramphenicol, or a combination of aminoglycoside with a β-lactam antibiotic. Based on data from human infants, one author has recommended the use of dexamethasone sodium phosphate (0.4 mg/kg IV q12h for 2 days).[25] In many cases, once the diagnosis is made, the infectious process is well advanced both in the brain and other tissues, resulting in a poor outcome. The prognosis is fair in foals where signs are limited to hyperesthesia and neck stiffness.[25]

Neonatal morbidity and mortality can be attributed to equine herpesvirus 1 (EHV-1), EHV-4, equine viral arteritis (EVA), and equine influenza (EI) viruses. The respiratory system is most commonly involved. **Viral encephalitis** is often quoted as an important differential for seizures in neonatal foals, but this appears to be a rare clinical entity in this age group.

Head trauma occurs commonly in neonates. Foals can receive direct blows to the head after kicks from the dam or other horses, as well as from head-on collisions with stationary objects. There is often external evidence of the trauma, such as hair loss, soft tissue swelling, asymmetry of the facial contour, fracture crepitus, or blood from the nares or ear canal. A range of neurologic signs may ensue that include varying degrees of obtundation; disorientation; head pressing and compulsive walking, often in circles; and seizure. Trauma to the poll can result in vestibular and facial nerve dysfunction, ataxia, and paresis, as well as changes in mentation. The diagnosis is based on history, physical, and neurologic findings, but is supported by imaging. The management of CNS trauma is discussed elsewhere in this text (Chapter 35).

Benign juvenile epilepsy is a well-described neurologic entity of Arabian foals of Egyptian origin.[164] The age of onset of generalized seizures varies between 2 days and 6 months of age, and the reported duration of seizures is between several seconds and 5 minutes, with most lasting less than 60 seconds. Common postictal findings include obtundation and transient blindness. Physical and neurologic examination during the interictal period is normal, but there may be electroencephalographic changes.[164] As the name suggests, the condition does not persist into adulthood, with cessation of seizures by 12 months of age in all foals. As described previously, active seizures can be treated with diazepam or midazolam and prevented using oral phenobarbital (5 to 10 mg/kg PO as loading dose, followed by 2 to 5 mg/kg PO bid) or potassium bromide (100 mg/kg PO as loading dose, followed by 25 mg/kg PO q24h).

The role of glucose and electrolytes in seizure disorders should not be discounted. **Hypoglycemia, hypocalcemia, hyponatremia,** or **hypernatremia** can all produce signs of spontaneous, involuntary muscle activity with varying degrees of consciousness. Specific electrolyte disturbances are discussed elsewhere in this text (Chapter 22).

Hydrocephalus is the most common congenital brain disease in foals. Distention of the cerebral ventricular system produces a loss of normal cerebral structure. It can also occur as a result of inflammatory changes associated with meningitis.[25] Although pronounced doming of the skull is expected, it is relatively uncommon. Furthermore, a domed head is a physical feature of immaturity seen in premature or dysmature foals. Although signs are variable, most foals are slow and somnolent and can have additional cerebral signs of head-pressing, aimless and compulsive walking, blindness, and seizure activity. The diagnosis is usually based on persistence of neurologic signs and ruling out of other causes of cerebral disease. The diagnosis is confirmed using CT or MRI. Dandy Walker–like syndrome has been reported as a cause of recurrent violent seizures in a newborn foal.[153] The condition involves agenesis of the corpus callosum with cerebellar vermian hypoplasia.

Tetanus is caused by the exotoxins produced by the anaerobe *Clostridium tetani*. Given the incubation period, clinical cases of tetanus are not likely before 7 days of age. Early signs include difficulty in locating and latching onto the teat and dysphagia. Signs then progress to include gait stiffness, elevation of the tail head, an anxious facial expression, prolapse of the third eyelid, tachycardia, and sweating. The foal will eventually become recumbent with recurrent bouts of tonic muscle contractions that are severe enough to mimic seizure activity. Foals are at risk of disease if the mare has not been adequately

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protected through vaccination or the foal has untreated failure of passive transfer of immunity. It is recommended that mares receive a booster of tetanus toxoid 28 days before the estimated parturition date. Tetanus is discussed in great detail in Chapter 35.

Ivermectin and **moxidectin toxicity** have been described in neonatal and older foals after overdosage.[165-167] Reported signs of ivermectin toxicity can include obtundation, blindness, ataxia, head pressing, and seizure, and they are caused by the opening of gamma-aminobutyric acid (GABA)-gated chloride channels with resultant membrane hyperpolarization and blockade of neuronal impulses. The related antiparasite drug, moxidectin, can also cause profound obtundation and coma when overdosed in juvenile animals.[168,169] Successful management of ivermectin toxicosis has included the use of intravenous lipid emulsions (20% soybean oil in water, 1.5 mL/kg IV bolus followed by 0.25 mL/kg/min for 30 min).[165] The benzodiazepine receptor agonist, sarmazenil (0.04 mg/kg IV q2h), has been effective in managing moxidectin toxicosis.[169]

Kernicterus is a rare but serious neurologic complication of NI.[170,171] The condition is also known as bilirubin encephalopathy or nuclear jaundice, and it results from deposition of unconjugated bilirubin in the brain, particularly the basal nuclei. The mucous membranes of affected foals are deeply icteric, and neurologic signs include altered mentation and seizures. The seizures are difficult to control, often necessitating euthanasia. In a retrospective study of 72 foals with NI, the heart rate at admission and the maximum serum bilirubin concentration were significant factors in the development of kernicterus.[171] The authors determined that foals with serum bilirubin concentration of 27.0 mg/dL or greater (≥466.1 µmol/L) were 17 times more likely to develop signs of kernicterus than foals with a peak bilirubin concentration less than 27.0 mg/dL. Tin-mesoporphyrin is an inhibitor of heme oxygenase and is a recommended therapy for severe hyperbilirubinemia in human infants.[172] The intramuscular therapy has been used in foals with NI at risk for kernicterus.[173]

Lavender foal syndrome (LFS), also referred to as coat color dilution lethal (CCDL), is an autosomal recessive gene disorder of Arabian foals of Egyptian bloodlines.[174] Affected foals have a dilute coat color and are unable to achieve sternal recumbency.[175] There are severe neurologic signs, including frequent episodes of opisthotonos, limb paddling, and rapid eye movements. Spontaneous death or euthanasia typically occurs before 72 hours of age.

Glycogen storage disease IV is an autosomal recessive disease of Quarter Horses and Paint Horse breeds.[176] The defect has been identified as a mutation in the glycogen branching enzyme, encoded by the GBE1 gene.[177] Clinical signs of foals not stillborn or aborted include profound muscular weakness and hypothermia. Foals may succumb to hypoglycemic seizures or cardiopulmonary failure. All affected foals have reportedly died or been euthanized by 18 weeks of age.[176]

Anemia

Guy D. Lester

Anemia is a common finding in neonatal foals. The normal ranges of hematologic parameters must be considered when determining the significance of any anemia. The PCV at birth is 40% to 52% but decreases to 32% to 46% after colostrum and milk intake by 24 hours of age. PCV, red blood cell (RBC) count, and the hemoglobin (Hb) concentration are similar to adult values at 24 hours of age, before decreasing over the first 2 weeks of postnatal life to values that are in the lower level of the normal adult ranges. These relatively low levels are sustained for several months.[178] The mean corpuscular volume (MCV) decreases over the first 4 months of life, leading to microcytosis and anisocytosis. The MCV increases after weaning.[178,179] Foals typically have reduced serum ferritin concentrations and increased total iron binding capacity when compared with adults. Serum ferritin increases significantly on day 1 and is attributed to ingestion of colostral iron, before reducing.[180] Data support relative iron deficiency as a cause of common foal anemia, but supplementation with iron does not improve RBC indices.[181] Supplementation of normal foals with a specific iron preparation, ferrous fumarate, resulted in acute hepatic failure and death.[182] There are reports of absolute iron deficiency anemia in foals,[183] including stabled Dutch Warmblood foals fed cut grass.[184] Findings include a low PCV, low serum iron and ferritin concentration, and normal to increased total iron binding capacity. Improvement is seen in those foals with oral iron supplementation.

Clinical Signs

Clinical signs of anemia are related to the magnitude and timing of the underlying disease process. Rapidly developing hemolytic anemias, such as NI, produce signs of weakness, lethargy and somnolence, mucous membrane pallor and icterus, tachycardia, and possible mild fever. Intravascular hemolysis will typically cause brown-red discoloration of urine. Cardiac murmur is accentuated. Foals with hemoabdomen or internal umbilical remnant hemorrhage are often colicky. Hemorrhage at the apex of the bladder can produce stranguria. Bleeding into the respiratory cavity can produce clinical signs of respiratory distress, and blood loss into the GI tract will cause melena. Lameness will be seen in foals with spontaneous hemarthrosis.

Causes

Hemolysis is most commonly seen after consumption of colostral antibodies that are directed against foal erythrocytes. The syndrome is known as NI and is discussed in detail in Chapter 53. Less common causes of hemolysis include non-NI immune-mediated hemolysis, intracellular RBC parasites, rapid administration of hypotonic or hypertonic solutions such as dimethyl sulfoxide, or equine infectious anemia. RBC hemolysis can be caused by bacterial toxins, most commonly associated with clostridial infections.

Blood loss occurs commonly with separation of the umbilical cord. Hemorrhage most commonly occurs externally but can occur internally into the umbilical remnants, the urinary bladder, or the peritoneal cavity. Most external cord hemorrhage is a small volume and rarely impacts hematologic parameters.[185] Trauma can cause both internal and external blood loss. Rupture of the spleen often leads to uncontrolled internal blood loss, potentially requiring splenectomy.[186] Hemoperitoneum can also occur as a result of rupture of juvenile granulosa cell tumors in foals.[187,188] Rib shaft fractures can cause hemorrhage into the pleural cavity; on rare occasions fatal hemorrhage can occur if a major vessel or myocardium is lacerated.

Blood loss can occur as a result of problems in homeostasis. Affected foals may have spontaneous hemorrhage into joints, muscle or subcutaneous tissues, or the GI tract. Disseminated intravascular coagulation (DIC) is an acquired homeostatic problem resulting from severe sepsis. Adult horses with DIC tend to present with signs associated with failure of fibrinolysis, such as widespread thrombosis. In contrast, septic foals often present with spontaneous or trauma-induced hemorrhage. Inherited disorders are discussed elsewhere in this text but include intrinsic platelet disorders, such as Glanzmann thrombasthenia, in which the glycoprotein complex IIb-IIIa is reduced or absent on the surface of platelets, and extrinsic disorders, including type 2 von Willebrand disease.[189]

Decreased erythrocyte production is associated with absolute or relative iron deficiency and chronic inflammatory diseases. Anemia of chronic disease (ACD) is a complex disorder that involves altered iron metabolism, bone marrow depression, and reduced production or action of erythropoietin. Increased levels of hepcidin, released in response to inflammation, may be pivotal in the development of anemia by decreasing iron absorption and iron recycling.[190] Classically ACD is reflected by low serum iron, normal or decreased total iron-binding capacity, and increased serum ferritin concentration.

A syndrome of bone marrow aplasia or hypoplasia was reported in three foals born to mares that were under therapy for equine protozoal myeloencephalitis. Therapy included sulfonamides, pyrimethamine, folic acid, and vitamin E.[191]

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Determination of the nature of the anemia may allow specific treatment. The treatment of NI is discussed in Chapter 53. Drug-induced or autoimmune anemias may be treated with corticosteroids (0.05 to 0.1 mg/kg dexamethasone bid IM or IV). Blood transfusion following crossmatch may be indicated when anemia develops rapidly or PCV drops below 12%. Associated conditions such as metabolic acidosis and hypoglycemia should be corrected. ACD requires correction of the primary disease condition.

Maturity/Dysmaturity

Guy D. Lester

The terminology associated with birth maturity is difficult in horses due to the variability in normal gestational length. Retrospective studies report wide variability in gestational age but frequently do not report physical characteristics or foal survival. Gestational age ranges of 305 to 365 days, 315 to 387 days, and 286 to 370 days have been described in Thoroughbreds.[192-194] The term *premature* simply refers to the birth of an infant or animal after a gestational period shorter than normal. A premature human infant is defined as one that is delivered at least 21 days before the mean pregnancy duration of 266 days. The use of a gestational age to classify equine prematurity has been described, with the most commonly reported definition being a foal born before 320 days of gestation.[195] This is loosely based on significantly lower birth weights and poor outcomes of foals born prior to 320 days.[196] It could be argued that foals born outside the lower 95% confidence interval of the normal gestational period would best fit the classification of premature; this would be less than 325 days in Thoroughbreds, using data extrapolated from Hintz and co-workers.[192]

Dysmaturity is a term commonly used to describe foals that have experienced some degree of intrauterine growth retardation. These foals typically demonstrate some signs of physical immaturity, such as a low birth weight. Dysmature foals can have shortened, normal, or prolonged gestation lengths. Other terms used to classify foals with incomplete maturation include *viable* and *nonviable.*[196] In a review on terminology, Koterba[196] suggested the terms *viable* and *nonviable* were inappropriate because outcomes of premature foals are heavily influenced by access to facilities and the value of the animal. The concept of *readiness for birth* was used to categorize foal outcomes based primarily on the degree of maturation of the fetal HPA axis. Although this plays a critical role in determining postpartum survival, other factors including the degree of physical maturation and the consequences of an adverse intrauterine environment are also relevant in determining the ultimate outcome. Premature maturation of the HPA axis often will take place at an inappropriate developmental stage for some body systems, causing asynchrony of organ maturation and postnatal problems.[197] Following on from the concept of *readiness for birth* Rossdale[195] introduced the term *twilight foals* to describe those foals with accelerated, but incomplete, maturation of the HPA axis at the time of birth.[198]

The physical characteristics associated with prematurity include a low birth weight and small body size, a short and shiny hair coat, a prominent rounded head, periarticular laxity, and droopy ears (Fig. 17-8). Foals will typically have moderate flexor laxity with elevation of the toe, but some will have contracture of the lower limb. Muscle development is usually poor. Most will demonstrate generalized weakness and hypotonia and will have difficulty in standing. Severely premature foals may have lids naturally sutured closed and little hair covering of their body. Many will have difficulty in maintaining body temperature, blood pressure, and blood glucose.

Dysmature foals commonly experienced some degree of intrauterine growth retardation (IUGR). This is usually reflected by the birth of a foal that is small for its gestational age. The average relative weight of the term foal to its dam is around 10%. Postmature foals usually have an acceptable birth weight with a large frame but poor muscle development. This gives the foal a lanky appearance. In contrast to premature animals, fetlock contracture is common, although laxity can be present. Consistent with their prolonged gestation, postterm or postmature foals will often have erupted incisors and a long haircoat. In term foals, the central incisors typically erupt during the first 5 to 7 days of postnatal life.



FIG. 17-8 A premature foal demonstrating a low birth weight and small body size, a short and shiny hair coat, and a prominent rounded head.

Causes

The pregnant uterus is highly responsive to contractile agents such as oxytocin and prostaglandins throughout gestation. Consequently, one of the most important causes of premature birth and perinatal morbidity and mortality is the induction of labor with exogenous oxytocin or prostaglandins. The adverse consequences of premature induction of parturition was identified in a study where parturition was induced either prior to 300 days' gestation or between 300 and 320 days' gestation.[199] The overall survival rate was only 5%, with the youngest surviving animal delivered after 318 days' gestation. Other surviving foals were all delivered after 320 days' gestation. The decision to prematurely terminate a pregnancy may be done deliberately in the "normal" mare or may be forced due to significant maternal disease. The latter frequently involves delivery of a compromised and often premature foal by cesarean section. Chemical induction of parturition has occurred when late-pregnancy intestinal problems are misinterpreted as ineffective labor. Premature birth can occur as a sequel to placental problems, including placental infection, edema, and/or detachment (premature placental separation). Placental insufficiency caused by twinning is another cause of intrauterine growth retardation.

The consumption by pregnant mares of tall fescue pasture infected with *Neotyphodium coenophialum* leads to a range of abnormal signs, including prolongation of gestation, perinatal mortality, and agalactia.[200] The large skeletal frame of the postmature foal predisposes mares to dystocia. The delay in parturition may be due to toxin-induced interference with fetal corticotropin-releasing hormone (CRH) and delay in maturation of the HPA axis. Foals born to mares grazing in endophyte-infected fescue pastures have normal thyroxine and reverse T3 but reduced tri-iodothyronine levels compared with control foals.[201] This is also consistent with failure of cortisol-induced maturation of thyroid function. A syndrome of congenital hypothyroidism has been reported in foals in western Canada.[202] Signs include prolonged gestation, dysmaturity, and a range of musculoskeletal abnormalities, including flexural deformities, delayed ossification, and mandibular prognathism. The specific cause has not been determined, although consumption of diets that contain nitrate or deficient in iodine are suspected.[203]

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Maturation of the Fetal Hypothalamic-Pituitary-Adrenal (HPA) Axis

The maturation of several organ systems coincides with changes in the fetal HPA axis.[197] Fetal cortisol is critical for organ maturation, but if the fetus is exposed too early in gestation or exposed to too large a quantity, intrauterine growth restriction may occur. The fetus is protected from cortisol during much of gestation. The type 2 isoform of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) converts excess biologically active cortisol into the inactive cortisone in the placenta, thereby reducing the exposure of the fetus. The postnatal adrenal gland, under influence of ACTH from the pituitary, can readily synthesize cortisol from cholesterol and pregnenolone (P5). Several important enzymes are required for this conversion, including 3β-HSD, P450scc, and P450C17. These enzymes are either inhibited or deficient during most of pregnancy, again protecting the developing fetus from excessive cortisol. Consequently, during the majority of gestation, the major products of steroidogenesis are progesterone and the 5α-reduced progestagens and not cortisol.[204] Foals, like other species studied, undergo enhanced adrenal activity prior to birth. This is reflected by high plasma cortisol and ACTH concentrations in term newborn foal plasma in the first hours after birth.[205] There is also a substantial change in the amount and localization within the adrenal gland of 3β-HSD, P450scc, and P450C17 around the time of birth.[206]

The trigger(s) for the process that results in fetal cortisol production, organ maturation, and birth are not known. Data from sheep indicate that upregulation of CRH mRNA in the fetal hypothalamus and proopiomelanocortin in the fetal pituitary as a key initiating event.[197,207] At the same time there is upregulation of ACTH receptors and key steroidogenic enzymes in the fetal adrenal glands. The consequence is a progressive increase in circulating ACTH and cortisol in the fetus. The rise in fetal cortisol has a direct effect on the placenta to increase prostaglandin H synthase 2, leading to secretion of prostaglandins such as PGE_2.[197,207,208] Prostaglandins further stimulate the fetal HPA axis, stimulate placental 11β-HSD-1 (which favors the production of cortisol from cortisone), and facilitate the conversion of estrogen from pregnenolone. It is not known if these events occur in the pregnant mare but do appear to be consistent across most species studied. An important difference between equids and other species is the timing of these events before parturition. In pregnant ewes, maturation of the HPA axis occurs during the final 20 days of a 150-day gestation. In contrast, the production of significant fetal cortisol appears to occur during the final 48 to 72 hours of pregnancy in mares.[209] There are a number of important maturational events that appear to be tightly associated with the prepartum increase in ACTH and cortisol.[204] These include changes in RBC and WBC parameters, most notably a large increase in the neutrophil to lymphocyte ratio.[209,210] Hepatic and renal glucose-6-phosphatase, a key enzyme of gluconeogenesis, also increases sharply around the time of birth, coinciding with increases in hepatic and skeletal muscle glycogen stores.[211]

The prepartum rise in plasma cortisol likely induces deiodination of the outer ring of T4 to produce the biologically active triiodothyronine (T3).[212] Adequate levels of T3 are required for a number of biological functions, including postnatal thermogenesis. Normal term foals have very high levels of thyroid hormones, including T3 at the time of birth.[213] These levels decline over the initial weeks or months of postnatal life. A relationship between circulating T3 levels and cortisol was reported in premature, dysmature, and mature foals and the increase in T3 appears to be dependent on maturation of the HPA axis.[198,214] Both cortisol and T3 are critical for lung maturation, particularly the normal postpartum reabsorption of lung liquid.[214]

Accelerated Maturation of the Fetal HPA Axis

Several factors can induce premature maturation of the fetal HPA axis. Hypoxemia is a potent stimulator of the axis in sheep with rises in fetal ACTH and cortisol.[215] The HPA axis can also be manipulated using exogenous glucocorticoids; betamethasone is commonly administered to women in danger of preterm birth in order to hasten HPA maturation and therefore improve the chances of postnatal survival. Poor nutrition before and after conception in sheep produces a shortened gestational period and hastened maturation of the fetal HPA axis.[207] Placental and/or fetal infection also can accelerate maturation of the HPA axis. The cytokines induced by infection increase prostaglandin synthesis and decrease metabolism. Prostaglandins exert a range of actions in addition to promoting cortisol production. These include important actions on the cardiovascular, renal, and respiratory systems.[216] The healthy newborn foal has higher concentrations of 15-ketodihydro-$PGF_{2\alpha}$ (PGM) in the days after birth than values in adult animals.

The stimuli associated with precocious HPA axis maturation in foals are not well described. The exception is infection of fetal membranes, where foals are often delivered preterm with laboratory findings consistent with axis maturation. Spatial and nutritional deprivation resulting from a Thoroughbred foal placed in a pony uterus using embryo transfer also leads to premature maturation of the fetal adrenal.[204,217,218] Many late-term maternal diseases do not appear to have a significant effect on foal maturity. Hypoxemia associated with anesthesia and colic surgery in pregnant mares during the final 60 days of pregnancy results in a high rate of preterm delivery of compromised foals that did not survive.[219] It is likely that the insult in these cases was so severe that the interval between surgery and delivery was inadequate for maturation of the axis to occur. Another important consideration in determining outcomes would be the effect of hypoxia and/or ischemia on other fetal organ systems.

Treatment of the At-Risk Late Pregnant Mare

The administration of corticosteroids to the pregnant mare appears to have little effect on maturation of the fetal HPA axis, at least when doses considered safe are used. Direct injection of $ACTH_{1\text{-}24}$ to the fetus results in increased fetal cortisol, but the effect is dependent on gestational age with maximal responses occurring at around day 313 with no measurable benefit when administered prior to day 295.[209] Direct administration of CRH, ACTH, or betamethasone to the fetus using ultrasound-guided IM injection results in increased maternal progestagen levels consistent with maturation of the fetal adrenal gland.[220,221] The procedure itself can lead to abortion in a small number of mares. Exogenous $ACTH_{1\text{-}24}$ administered to late pregnant pony mares had an impact on both gestational length and fetal maturation.[222] Depot $ACTH_{1\text{-}24}$ given to mares at 300, 301, and 302 days of gestation produced a shortened gestational length and lower birth weight, but evidence of HPA axis maturation. A confounding effect in this study was the time of conception, with the most significant findings observed in mares bred later in the breeding season.

It is preferable to maintain the fetus in utero to ensure not only adequate HPA axis maturation, but also effective ossification and maturation of other body systems. Consequently, the primary focus of therapy for a mare with placental infection is to eliminate the pathogenic organisms, reduce inflammation, and maintain the pregnancy. The specific management of placentitis is not the focus of this chapter, but treatment may involve broad-spectrum antibiotics, NSAIDs, pentoxifylline, β2-adrenoreceptor agonists, and altrenogest. The efficacy of altrenogest use in mares with placentitis has been questioned.[223]

The termination of postterm pregnancies is a difficult decision for practitioners, particularly with the angst that is common in many owners. Given the wide variation in gestational range, it is almost always in the best interests of the foal to let the pregnancy continue. If facilities are available, rectal and transabdominal ultrasound assessment of the fetus and chorioallantois should be made, looking carefully for thickening or detachment of the fetal membranes. Ideally, any induction of parturition should be based on appropriate changes in physical characteristics of the mare and in milk electrolytes. Mares grazing in endophyte-infected tall fescue can be medicated with dopamine receptor antagonists, such as domperidone.[200]

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Laboratory Assessment

The laboratory data will indirectly reflect the degree of HPA axis maturation. Premature or dysmature foals that fail to survive often have minimal cortisol secretion in the face of adequate endogenous ACTH. Furthermore, the change in plasma cortisol in response to exogenous $ACTH_{1-24}$ (0.125 mg IM) is inconsistent and usually inadequate. The foal with incomplete adrenal maturation will have low total WBC and neutrophil counts and a neutrophil : lymphocyte ratio that is characteristically less than 1 : 1.[210] It is important to determine if sepsis is present because neutropenia is also a common feature of this condition. Evidence of shifting toward immature cell types and neutrophil toxicity should indicate primary sepsis or prematurity/dysmaturity complicated by sepsis. Premature foals that fail to improve their total WBC and neutrophil counts over the initial 24 to 48 hours of treatment have an even poorer prognosis for survival. Changes in RBC indices have also been reported in nonstressed preterm foals.[210] Most notably is an elevated MCV in preterm foals. An elevated plasma fibrinogen concentration is considered to be a good prognostic factor in premature foals because it often reflects prepartum exposure to bacterial infection. Induced or spontaneously delivered term foals have a significantly higher plasma glucose concentration than premature foals.[224] Plasma creatinine levels are often elevated in newly born preterm or dysmature foals because of placental dysfunction. This increase is independent of foal renal function. Measurement of low cortisol levels coupled with increased progestagens would provide further evidence that effective maturation of HPA axis has not occurred in the foal prior to birth.[225]

Establish a Prognosis

The prognosis for survival of a prematurely delivered foal is dependent on a range of factors, including the gestational age, the reasons for delivery, complications associated with delivery, available resources (facilities and expertise), and financial limitations of the owner. Survival of very premature foals (280 to 300 days) would typically require a history of chronic in utero stress with resultant precocious maturation of the HPA axis and critical organ systems. The majority of these foals would still require a lengthy and costly period of hospitalization and experience a range of complications, some of which may be life threatening. Foals delivered prematurely as a consequence of chemical induction of parturition without evidence of chronic in utero stress or through cesarean section typically have a high mortality rate even when delivered close to calculated due dates. Foals delivered under these circumstances prior to 300 days will almost certainly die irrespective of available resources.

A complete blood count and fibrinogen estimation are key factors in determining short-term prognosis. A normal or elevated neutrophil count, neutrophil : lymphocyte ratio (N : L), or total WBC count are positive indicators of survival since they typically reflect maturation of the HPA axis. In a survey of 135 neonates admitted to the University of Florida with a gestational age of 320 days or less, short-term survival was in part predicted by total WBC count, neutrophil count, lymphocyte count, and the N : L ratio at presentation.[226] The N : L ratio of surviving premature foals (12.5 : 1) was well above that reported for both normal term foals (2.5 : 1) and that of nonsurviving premature foals. Many of the surviving animals were exposed to confirmed or suspected placental infection. In utero stress, with hastened maturation of the HPA axis, is a good prognostic factor for survival in foals that are delivered preterm. In many foals the greater the neutrophil count, the better the outlook, at least in terms of short-term survival. A high plasma fibrinogen concentration is also considered to be a positive factor. Reevaluation of the WBC indices on day 2 for appropriate increases also support a favorable prognosis.

A history of placental infection appears to be a positive factor when predicting survival in preterm foals. One obvious downside is that many of these foals are born with aspiration pneumonia (as a result of in utero aspiration of contaminated amniotic fluid) and/or systemic sepsis. This, coupled with the fact that many foals have an impaired immune system, warrants the use of broad-spectrum antimicrobial therapy.

Consideration should also be given to the long-term outcomes of preterm foals. These animals are at risk of significant and permanent musculoskeletal problems as a result of bone and ligamentous immaturity. Foals that survive the neonatal period are smaller than their peers, and this difference will often remain noticeable as weanlings and as yearlings. The differences may be less obvious at 2 years and older. Other common complications, such as pneumonia, will further reduce the growth rate in the first 6 months of life. There is nothing to indicate that premature fillies will experience fertility problems as adults.

Clinical Progression

The clinical progression will usually reflect the degree of endocrinologic maturity, additional perinatal stresses, and the extent of physical maturity. Typically, foals born prematurely but chronically exposed to an appropriate chronic in utero stress such as placental infection will appear weak and depressed in the immediate postpartum period. Some will require resuscitation. After a longer-than-normal period of postural adaptation, they will usually manage to stand but will often require assistance. Suckle reflex and appetite may be reduced or absent and many will need to be fed initially via nasogastric tube. They will frequently have trouble maintaining their body temperature and blood glucose levels. After the initial 24-hour period, many of these foals demonstrate improvement both in physical strength and mentation. Their appetite for milk will often exceed that of a healthy term foal. Foals with inadequate maturation of the HPA axis will frequently require immediate resuscitation. They may mimic the clinical progression of in utero–stressed premature foals up until 12 to 18 hours of age. This initial period after delivery can be deceptive, with many foals showing degrees of improvement, which often promotes owner optimism. The rise of hormones accompanying delivery may lead to improvement in alertness and strength. However, after this period a range of progressive abnormalities develop. These include systemic weakness, depression, seizures, respiratory failure, and intolerance to feeding. Cardiovascular collapse may ensue, the first sign of which is a reduction in the intensity of peripheral pulses, followed by a reduction in urine flow, development of subcutaneous edema, and deteriorating neurologic function. Poor tissue perfusion leads to lactate accumulation and a mixed metabolic and respiratory acidosis. Death will certainly occur without aggressive support, and even with high-level intensive care, mortality rates are very high.

Treatment of the Premature or Dysmature Foal

It is also critical to perform a thorough physical examination as problems of altered maturity can involve many organ systems. Successful outcomes are dependent not only on careful management of identified problems, but also on predicting the problems that may arise in the hours, days, or weeks to come. Most premature and dysmature foals will experience some degree of pulmonary insufficiency. Factors that predispose these foals to respiratory problems include structural and functional immaturity, a naïve and potentially immature immune system, altered pulmonary vascular reactivity, a highly compliant rib cage, and a propensity for prolonged or persistent recumbency. Final maturation of the respiratory system appears to be highly dependent on a functional HPA system. ABG analysis is an important tool in the assessment of respiratory function, and the lower arterial oxygen concentration in term newborn foals is further decreased in dysmature or premature foals (Table 17-4). Extrapulmonary shunts account for more than 30% of the cardiac output, in contrast to less than 10% in normal full-term foals.[227] Ventilation/perfusion mismatching also occurs as a result of a poorly reactive pulmonary vasculature and dependent atelectasis. Deficiency of lung surfactant is not likely to play a primary role in the respiratory dysfunction in most premature or dysmature foals since it is usually fully developed in most foals by 300 days, but could be delayed until after 340 days in some foals.[228] The most severe form of respiratory failure is neonatal respiratory distress syndrome (RDS), a disease

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TABLE 17-4

Normal Blood Gas Values for Foals*

	Arterial					Venous			
Age Group	O_2 (mm Hg)	CO_2 (mm Hg)	pH	Base Excess	HCO_3^- (mEq/L)	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HCO_3^- (mEq/L)
Immediate post-foaling†	40-50	52-60	7.2-7.3	+2	24-26	—	—	—	—
2 hours†	68 ± 10	49 ± 2	7.37 ± 0.01	+4	26 ± 2	42 ± 2	56 ± 2	7.33 ± 0.01	28 ± 2
4-12 hours‡	75 ± 5	47 ± 2	7.39 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 2
24 hours‡	81 ± 6	48 ± 2	7.4 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 3
1-3 days‡	90 ± 6	148 ± 2	7.4 ± 0.01	+6	28 ± 2	43 ± 2	52 ± 2	7.38 ± 0.01	29 ± 2
4-14 days‡	86 ± 5	45 ± 2	7.41 ± 0.01	+6	28 ± 1	38 ± 2	53 ± 2	7.38 ± 0.01	31 ± 2
Premature† birth	39 ± 5	55 ± 4	7.27	−3	24 ± 1	—	—	—	—
(320-330 days' gestation)—1 hour	52 ± 4	48 ± 3	7.33	−1.3	25 ± 1	—	—	—	—

*Lateral recumbency.

†Data from Rose RJ, Rossdale PD, Leadon DP. 1982. Blood gas and acid-base status in spontaneously delivered, term-induced and induced premature foals. J Reprod Fertility 32:521.

‡Data from Stewart JH, Rose RJ, Barko AM. 1984. Response to oxygen administration in foals: effect of age, duration and method of administration on arterial blood gas values. Equine Vet J 16:329.

characterized by progressive respiratory failure, severe hypoxemia and hypercapnia, coma, and death. A diffuse severe alveolar pattern is a classic radiographic finding. Intervention would ideally involve mechanical ventilation, bovine or synthetic surfactant, and glucocorticoids; however, outcomes are extremely poor irrespective of the level of care. Fortunately, RDS is relatively uncommon; most premature foals will, however, demonstrate a less severe manifestation of lung dysfunction characterized by reduced ventilation capacity, tachypnea, hypoxemia, and varying levels of hypercapnia. These foals are very susceptible to dependent lung atelectasis from recumbency. Most foals will benefit from supplemental intranasal oxygen with initial flow rates of 5 L/min recommended. Adjustment in flow rate is dictated by positive changes in ABG analyses or improvement in ventilation rate and depth. It is important to avoid prolonged periods of lateral recumbency in order to minimize the impact of atelectasis. If the foal is unable to stand, then placement in sternal recumbency is recommended. This is made easier by use of a specially constructed V-pad.

Failure of the cardiovascular system is common in foals with partial or incomplete maturation of the HPA axis. Management is challenging in part due to inconsistent responses to standard inotrope and vasoreactive therapy. Successful treatment is reliant upon early detection of reduced perfusion. This is reflected clinically by cool extremities, the presence of limb and ventral edema, and darkening of the mucous membranes with prolongation of the capillary refill time. As failure ensues, peripheral pulses will become difficult to palpate, blood pH will fall, and increases in plasma lactate and anion gap will occur. Indirect (or direct) measurement of mean blood pressure along with determination of blood lactate will help guide therapy. An initial approach to the treatment of failing perfusion may involve intravenous plasma followed, if necessary, by dopamine (3 to 5 μg/kg/min) and/or dobutamine infusion (5 to 20 μg/kg/min). The volume and type of fluids given should be carefully monitored, since fluid overload and hypernatremia are common. Urine output should be appropriate for the volume of fluids administered and anuria or oliguria treated aggressively. This may include low-dose dopamine or fenoldopam infusion, furosemide boluses or infusion, or mannitol infusion. Establishment of urine flow is critical in terms of survival.

Signs of gastrointestinal tract dysfunction are rarely evident on initial assessment of premature or dysmature foals; however, most will not tolerate aggressive force-feeding. These foals commonly develop intestinal stasis with reduced fecal passage, gas accumulation, and gastric distention. The combination of prolonged asphyxia and prematurity is also a risk factor for the development of necrotizing enterocolitis (NEC). Feeding should be restricted to very small volumes (e.g., 10 to 20 mL hourly) until the foal appears to be systemically stable. Concurrent PN is indicated in order to prevent loss of body weight. Foals should be monitored closely for signs of GI dysfunction irrespective of feeding volume or frequency. This includes assessment of fecal passage, changes in abdomen size (assessed using a measuring tape), testing for gastric reflux if a nasogastric tube is in place, and frequent assessment with transabdominal ultrasound.

Premature and dysmature foals are susceptible to hypothermia. Thermogenic mechanisms develop late in gestation and are related to circulating T3 levels. As discussed previously, thyroid hormone generation is closely tied to maturation of the HPA axis. Consequently, problems with thermogenesis are exacerbated in preterm foals with incomplete adrenal function. Body temperature needs careful management since rapid warming may result in peripheral vasodilatation and possible cardiovascular collapse. Initially, the foal should be covered by blankets and removed from any drafts. IV and oral fluids should be warmed before use. Once the foal begins to demonstrate vigor, heat lamps and circulating warm-water blankets can be used. The premature and dysmature foal often has inadequate gluconeogenic enzyme activity and limited glycogen stores at the time of birth. Consequently most will have difficulty maintaining a normal blood glucose concentration. This is managed acutely by infusion of 10 mL/kg of a 10% dextrose solution over several minutes, followed by a constant infusion at about 6 mg/kg/min (approximately 200 mL/h of a 5% dextrose solution to a 30-kg foal). Blood glucose should be monitored regularly to avoid hyperglycemia. Some foals with persistent hyperglycemia will benefit from insulin supplementation.

Skeletal maturity is assessed by radiographing a carpus and tarsus for evidence of incomplete ossification. Accelerated ossification does not appear to be a feature of foals born prematurely after exposure to chronic in utero stress. Incomplete ossification coupled with periarticular laxity predisposes the premature or dysmature foal to long-term skeletal problems. Foals with incomplete ossification and more than 30% reduction of the central and/or third tarsal bones with pinching or fragmentation of the dorsal aspects of affected bones commonly develop degenerative joint disease and have a guarded prognosis for future athletic performance. Restriction of exercise is recommended in order to minimize collapse of developing carpal or tarsal bones, but forced recumbency may predispose the foal to or exacerbate pulmonary disease. Furthermore, normal load bearing encourages ossification. Periarticular laxity predisposes the premature foal to angular limb deformities that facilitate abnormal load bearing and increase the risk of cuboidal bone crush injury of the carpus or hock. Splinting and attention to hoof care is recommended if angular limb deviation develops. In most cases flexural deformities

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and laxities will improve over time. Dorsal splints are recommended for flexural deformities involving the fetlock, and heel extensions are helpful to foals with flexural laxity.

There are several reasons why colostral transfer of maternal immunoglobulin may not occur in premature foals. Mares may have lactated prematurely or not at all and the foal may not be able to suck. It is crucial to ensure that the premature neonate receive ample amounts of high-quality colostrum (>20 mL/kg) in the first 6 hours after birth, although the intestinal tract may not be capable of efficient colostral uptake or may not tolerate large volumes of liquid. Consequently, plasma transfusion is often used even in foals less than 18 to 24 hours of age. A serum IgG level should be measured to confirm successful transfer of immunity (>800 mg/dL; >8 g/L).

The use of glucocorticoid therapy in the management of prematurity is controversial. Dexamethasone has been used in human medicine because of its potency, but it is associated with adverse side effects including hypertension, hyperglycemia, and catabolism.[229] Hydrocortisone has a shorter half-life and lower biological activity and is as effective for improving lung function in preterm human infants without the side effects of dexamethasone.

Disorders of Respiration

Wendy E. Vaala • Guy D. Lester

The transition from the fluid-filled lung of the fetus to an organ that is responsible for efficient gas exchange is both rapid and complicated. The process can be complicated by a number of factors, including prematurity or dysmaturity; aspiration of meconium or milk; and bacterial, viral, or fungal infection. A highly compliant chest wall, an inefficient immune system, and failure to derive adequate antibody from colostrum (partial or total failure of passive transfer) are additive factors that predispose the neonate to respiratory problems.

The detection of respiratory disease in the newborn foal can be difficult. Thoracic auscultation can be highly misleading. Minute ventilation (frequency × tidal volume) is increased in the healthy neonate, resulting in easily heard bronchovesicular sounds. There is no need to accentuate breath sounds with rebreathing techniques. During the first few hours after birth, fluid can normally be auscultated throughout both lung fields and within the trachea. End-inspiratory crackles are commonly heard over the dependent lung during and shortly after rising from lateral recumbency. This is presumably due to simple atelectasis. Foals with respiratory disease will frequently have abnormal lung sounds, such as crackles and wheezes, but neonates with even severe pulmonary disease will occasionally have little detectable abnormality during auscultation. Clinical signs that are often associated with pulmonary tract disease in older foals and adult horses are frequently lacking in the sick neonatal foal. Fetal foals develop and mature in a relatively hypoxic environment within the uterus and therefore are more likely to tolerate postnatal hypoxemia than older foals or adults. Cough is also uncommon, likely due to a postnatal delay in maturation of irritant receptors within airway and delayed onset of the larnyngopharyngeal cough reflex. This is clinically relevant in that aspiration of milk into the lower airway associated with force feeding can go undetected for several days. Of additional importance is that the respiratory rate and rhythm frequently do not accurately reflect arterial concentrations of oxygen or carbon dioxide. This is particularly relevant in foals that are showing signs suggestive of asphyxial injury, where rising arterial CO_2 concentrations occur in response to hypoventilation and fail to cause an increase in minute ventilation. In these foals the primary drive for ventilation is arterial O_2 rather than CO_2.

In the absence of ABG data or radiographic information, the clinician must rely on vague signs, such as restlessness and agitation, increased respiratory rate, or respiratory distress. Historical information may also aid in diagnosis. This should include an estimation of gestational age, recognition of any maternal problems (e.g., fever, dystocia, placentitis, or prepartum vaginal discharge), the presence or absence of meconium staining of amniotic fluid, and an assessment of colostral quality and quantity. Failure to make an early identification of pulmonary disease often results in unfavorable outcome, with chronic pneumonia resulting. Malformations, inflammation, or other abnormalities of the upper respiratory tract can cause clinical signs of respiratory distress, stridor, and dysphagia, and result in lower respiratory tract problems as well. A number of nonrespiratory conditions also cause clinical signs that mimic respiratory disease.

The ideal diagnostic tools for investigation of neonatal respiratory disease include ABG analysis and thoracic radiography. ABG analysis is the most sensitive clinical tool used to assess lung function. The sample is usually collected from the dorsal metatarsal artery, easily palpated in most foals on the lateral aspect of the third metatarsal bone. Alternative sites include the brachial artery, located at the level of the medial collateral ligament of the elbow joint, or the carotid artery, but hematoma formation is a common sequel to aspiration from this latter site. The sample will remain useful for up to 90 minutes in a capped plastic syringe at room temperature.

Interpretation of the ABG sample involves consideration of the amount of struggling and position of the foal during sample collection. Normal ABG values for neonates of different postnatal and gestational ages are presented in Table 17-4. Lateral recumbency can reduce the PaO_2 by as much as 30 mm Hg. The sample needs to be handled appropriately, paying strict attention to avoidance of air contamination, which will artificially increase the PaO_2 and decrease $PaCO_2$. The inspired oxygen concentration must also be considered when analyzing ABG values. With supplemental oxygen, PaO_2 is increased variably, depending on the inspired oxygen concentration (FIO_2), the amount of pathology present (particularly the extent of right-to-left shunting), the respiratory rate and tidal volume of the foal, and if the oxygen is delivered by nasal insufflation. A flow rate of 10 L/min, delivered by nasal insufflation, increased the PaO_2 to 298 ± 69 mm Hg in the normal, term newborn foal[227]—roughly equivalent to an FIO_2 of 1.0.[230] In the induced premature foal, the PaO_2 increased only to 111 ± 35 mm Hg.[227] If the respiratory rate of a foal is rapid and shallow, the supplemental oxygen will be diluted by room air because of the large quantity of room air entering the upper respiratory tract; the concentration of alveolar oxygen will probably be much less than 100%. The two most common respiratory-derived ABG derangements include hypoxemia with normocapnia or hypocapnia, or hypoxemia with hypercapnia. It is important to distinguish acute from chronic hypercapnia. Acute hypercapnia is associated with a more substantial drop in blood pH and may lead to circulatory collapse and coma, particularly if accompanied by acute hypoxemia. Chronic exposure to elevated CO_2 permits adaptation and more subtle clinical effects. The change in pH is less dramatic primarily because of enhanced bicarbonate reabsorption in the proximal tubules of the kidney. This effect begins within 6 to 12 hours of exposure to increased concentrations of CO_2 and is maximal by 3 to 4 days. Hypercapnia can be exacerbated by fever or the administration of carbohydrates or bicarbonate. The latter is often clinically relevant and highlights the danger of giving large amounts of sodium bicarbonate to foals with pulmonary disease.

Interpretation of blood gas values of venous blood (see Table 17-4) can be very deceptive and should be restricted to evaluation of metabolic conditions (e.g., metabolic acidosis) and not pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein, since the metabolic status of the head is usually stable. To obtain a sample representative of the whole body, mixed venous blood is drawn from the right atrium. Determination of mixed venous blood oxygen saturation is a good test for assessing the overall adequacy of oxygen delivery to tissues because it reflects the balance between oxygen delivery and oxygen use.

Several factors need to be considered when evaluating foal thoracic films. Thoracic radiographs are routinely taken only in the standing or recumbent lateral position in foals, with dorsoventral positioning reserved for the anesthetized or very depressed foal. In

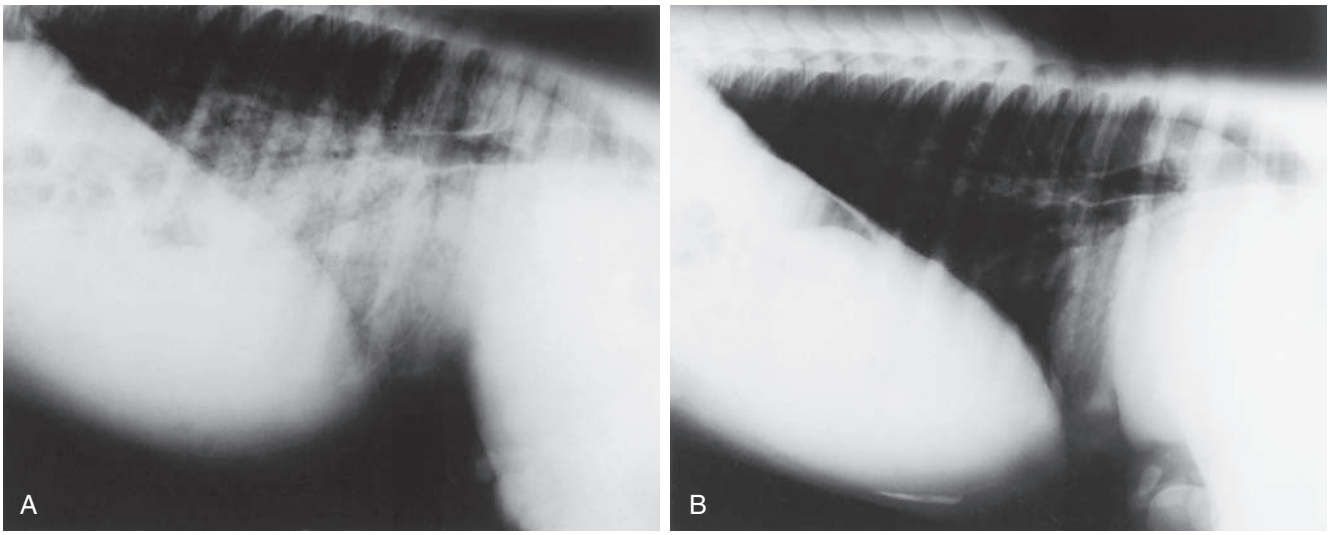


FIG. 17-9 Chest radiographs. **A,** Standing lateral chest radiograph of a 7-day-old TB foal with severe angular limb deformities that experienced an acute onset of severe respiratory distress and cyanosis after a walk outside the stall. Intubation and 100% oxygen administration raised the PAO_2 to only 48 mm Hg. Severe pulmonary interstitial disease is present in the caudoventral lung fields, and the tentative diagnosis was bacterial pneumonia. With no change in antimicrobials, she improved. **B,** Radiographs taken 3 days after the initial ones revealed marked resolution of the infiltrates. Pulmonary edema was suspected as the original problem.

healthy foals radiographs taken before 4 hours of age will reveal increased opacity associated with retention of fetal fluids.[231] Thus, interpretation can be limited because of positioning limitations. If the neonate has been in lateral recumbency for extended periods, atelectasis may result in diffuse or localized interstitial infiltrates that usually resolve once lung reexpansion occurs. It can be very difficult to accurately distinguish bacterial pneumonia from atelectasis and pulmonary edema on the basis of radiographic appearance alone. In these cases additional diagnostic aids (cultures, hematology, necropsy) should be used in conjunction with radiology to reach an accurate diagnosis. A false overinterpretation of disease is common due to motion artifact, caused by a combination of long exposure times, poor patient compliance, and high spontaneous ventilation rates. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial, nodular, alveolar, mixed), severity, and location (diffuse, perihilar, cranioventral, craniodorsal, caudodorsal, caudoventral) should be noted. Other soft tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones) should also be evaluated.

Serial thoracic radiographs are useful in monitoring the progress of a respiratory condition. Radiographic changes may either follow or precede changes in clinical condition, and major changes can occur surprisingly rapidly (Fig. 17-9). Clinical signs of pneumonia frequently resolve much earlier than chest radiographs and hemograms return to normal. Unfortunately, both ABG analysis and radiography are difficult to perform in field situations.

Ultrasonographic evaluation of the foal's thorax can yield useful information in a variety of disease processes, including pleural effusion, such as hemothorax or pleuritis, bronchopneumonia, or abscessation. It is also the preferred method for diagnosing rib fracture or dislocation, congenital heart disease, and thus is often a useful technique to differentiate cardiac and pulmonary causes of hypoxemia.

Specific Respiratory Conditions

UPPER RESPIRATORY TRACT DISORDERS. Upper respiratory tract disorders are relatively uncommon in neonates. Conditions affecting pharyngeal and laryngeal function are important because they predispose to aspiration pneumonia. Dyspneic neonates also have difficulty nursing and are subsequently likely to become malnourished. Congenital defects of the upper respiratory tract include collapsed trachea, stenotic nares, choanal atresia, epiglottal cyst, and guttural pouch tympany. There have also been reports of pharyngeal dysfunction as a cause of acute dyspnea, stridor, and dysphagia in neonatal foals.[232-234] Endoscopic examination of the upper airways of these foals reveals a variety of abnormalities that include a flaccid, collapsed and inflamed nasopharynx, intermittent or persistent dorsal displacement of the soft palate, or arytenoid paralysis (Fig. 17-10). Medical management with antiinflammatory drugs, enteral feeding via nasogastric tube, and broad-spectrum antibiotics (for any coexisting aspiration pneumonia) can result in permanent resolution of the problems within 1 to 14 days (mean of 5.5 days).[234] The underlying basis of the condition is not known but may be related to birth asphyxia.

Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and oral medication equipment. Compression of the larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea; aspiration pneumonia is a common sequela. Partial occlusion of the upper airway induces turbulent airflow and subsequently mucosal edema. Placement of a tracheostomy tube provides an alternative, sometimes life-saving, airway and rests the inflamed mucosa.

Nutritional myodegeneration, hyperkalemic periodic paralysis, and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia is a common sequela of pharyngeal and laryngeal dysfunction associated with nutritional myodegeneration and botulism. Exercise- and excitement-induced respiratory stridor has been described in foals with hyperkalemic periodic paralysis.[235]

Collapsed trachea is a rare congenital or acquired condition. It is most commonly reported in American Miniature horses, although those affected typically develop signs as adults.[236] Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. There is no stenosis of the trachea, but rather a dynamic dorsoventral collapse during inspiration. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the subsequent bony callus.

Diagnosis of most upper airway disorders can usually be made with a combination of radiography and endoscopy. A 7-mm O.D. endoscope is usually small enough to pass through the ventral meatus of horse and pony foals weighing over 14 kg. An integral part of the diagnostic approach to the neonate with suspected upper airway obstruction is assessment of the lungs for aspiration pneumonia. If the primary upper respiratory problem is not corrected and normal nursing is allowed, the pneumonic process will likely persist and become chronic.

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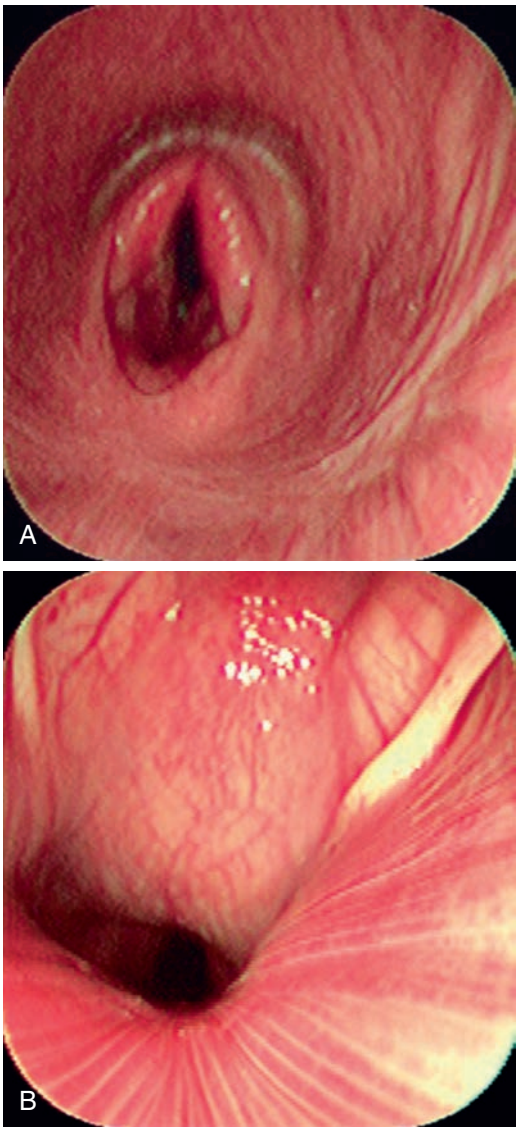


FIG. 17-10 Endoscopic images of a foal with dysphagia and stridor. **A,** Dorsal displacement of the soft palate. **B,** Collapse of the nasopharynx associated with pharyngeal weakness.

RESPIRATORY INFECTION. Bacterial infection of the lower respiratory tract most commonly occurs during or shortly after birth, but can also take place prior to parturition, through aspiration of contaminated amniotic fluid. This may take place in mares with bacterial placentitis. In the newborn foal, pneumonia can result from direct aspiration or inhalation of bacteria or from the hematogenous spread of organisms in foals that are bacteremic. The most common bacterial organisms that have been associated with pulmonary disease in foals are identical to those that cause systemic sepsis. The most common isolates include *Escherichia coli, Klebsiella pneumoniae, Pasturella* spp., *Actinobacillus* spp., and *Streptococci* spp. Less common isolates include, but are not limited to, *Salmonella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Serratia marcescens, Staphylococcus* spp., and *Yersinia pseudotuberculosis.*

The diagnosis of pneumonia involves identification of the causative organism. Isolation of bacteria can be attempted from blood culture, or culture of amniotic fluid or placental tissue if in utero infection is suspected. Lower airway culture can be difficult, since a tracheal aspiration can be dangerous in a compromised neonate. An alternative method involves passage of a guarded swab through a nasotracheal tube into the lower airway. A complete blood count and measurement of an acute phase protein, such as fibrinogen or SAA, may support a diagnosis of infection, but will not be helpful in localization of infection to the respiratory tract. The treatment of bacterial lung disease involves a combination of respiratory support techniques and antibiotic therapy. The neonatal foal readily develops dependent atelectasis in lateral recumbency. Consequently, positioning in sternal rather than lateral recumbency results in improved ventilatory capacity and higher arterial oxygen tension. Broad-spectrum antibiotic therapy should be commenced as soon as lung disease is suspected. The third-generation cephalosporins, such as ceftiofur, ceftazidime, ceftriaxone, or cefotaxime, have distinct advantages over aminoglycosides in the treatment of bacterial pneumonia. They have superior penetration into the lung, and effective tissue concentrations are easily achieved by intravenous or intramuscular routes. Because premature discontinuation of antibiotic therapy has resulted in relapse in a number of cases, repeat radiographs and hematology (complete blood cell count and plasma fibrinogen) are highly recommended before discontinuation of antibiotic therapy. A minimum course of therapy of 3 to 4 weeks' duration is not unusual in cases of severe pneumonia.

Several viruses can cause pneumonia in neonatal or young foals. These include equine herpesvirus type 1 (EHV-1) and type 4 (EHV-4), equine influenza, equine viral arteritis virus, and adenovirus.[237-240] Neonatal pneumonia caused by EHV-1 infection is frequently fatal, even in the face of aggressive supportive therapies such as antiviral medication and mechanical ventilation. Several factors appear common to EHV-1–infected foals, but none should be considered pathognomonic. These include leukopenia with neutropenia and lymphopenia, depletion of the myeloid cell lines on cytologic examination of bone marrow aspirates, and the presence of dilated retinal vessels and a red discoloration to the optic disc on fundic examination. Fatal broncho-interstitial pneumonia in neonatal foals (aged 2 to 12 days) infected with equine influenza virus occurred during the 2007 influenza outbreak in Australia.[238,240] Infection with adenovirus can be a problem in any immunocompromised foal, especially Arabian foals with severe combined immunodeficiency (SCID) syndrome.

In utero infection with *Histoplasma capsulatum* can result in placentitis, abortion, or birth of an infected foal with multiple organ disease, including granulomatous pneumonia.[241] An antemortem diagnosis can be difficult to establish, but is aided by airway cytology where characteristic yeastlike organisms (3 to 5 μm in diameter) are seen within macrophages. Infection with *Candida* spp. (especially *Candida albicans*) is an infrequent complication in foals with chronic bacterial infection. Lengthy antimicrobial use is an apparent risk factor for infection and many cases begin with oral candidiasis. The diagnosis is based on a history that often includes persistent low-grade fever, worsening respiratory disease or the development of synovitis, and isolation of the organism through blood culture. Successful treatment of neonatal candidiasis has been achieved with ketoconazole, amphotericin B, or fluconazole.

MECONIUM ASPIRATION SYNDROME. In utero asphyxia or umbilical cord occlusion can result in fetal passage of meconium into amniotic fluid. Hypoxia induces a redistribution of blood flow away from the GI tract, resulting in mesenteric vasoconstriction and secondary intestinal ischemia. Transient hyperperistalsis and anal sphincter relaxation occur, thereby allowing passage of meconium. Meconium aspiration may occur before, during, or immediately after delivery as a result of fetal breathing or gasping. Meconium can produce a variety of clinical signs, including mechanical airway obstruction and regional air trapping, chemical pneumonitis and alveolitis, alveolar edema, and displacement of surfactant.[242] This reduces lung compliance and causes small airway obstruction and focal atelectasis. These events lead to increased pulmonary vascular and airway resistance and ventilation/perfusion mismatching. Meconium may also enhance the growth of bacterial species within the respiratory tract, resulting in secondary bacterial pneumonia. It can be difficult to differentiate meconium aspiration from bacterial pneumonia, especially if the birth was unattended.

If meconium has been aspirated into the pharynx, then gentle suctioning of the nasal and oral cavities is recommended. The

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ideal time to suction the airways is while the animal is still in the birth canal, before it has taken its first breath. If the foal shows signs of meconium aspiration below the vocal cords, nasotracheal intubation and careful, aseptic suctioning are recommended. Intranasal oxygen should be administered during suctioning. ABG analysis dictates what long-term respiratory and metabolic support is necessary. Mild to moderate hypoxemia can be treated with humidified intranasal oxygen (2 to 10 L/min). Severe hypoxemia with accompanying hypercapnea requires positive pressure ventilation and is associated within increased mortality. If surfactant displacement and secondary atelectasis is contributing to hypoxemia, continuous positive airway pressure (CPAP) alone may improve oxygenation while avoiding any unnecessary increase in peak airway pressure. Exogenous surfactant administration has been advocated to treat the surfactant dysfunction, although efficacy data are lacking. Systemic antibiotic therapy is recommended to prevent secondary bacterial pneumonia. Good airway hygiene and coupage are crucial.

A diagnosis of meconium aspiration is based on a history of meconium-contaminated amniotic fluid and a meconium-stained newborn. Radiographs typically show a ventrocranial distribution of pulmonary infiltrate characteristic of aspiration. Clear, yellow to brown fluid may drip from the nose.

MILK ASPIRATION. Aspiration of milk into the lower airway may occur as a complication of a wide range of conditions. Most foals that aspirate milk will also demonstrate nasal regurgitation of milk. Unfortunately, the decreased sensitivity of the upper and lower airway to foreign material may make diagnosis of milk aspiration difficult. Aspiration can occur in foals with cleft palate, persistent dorsal displacement of the soft palate (DDSP), botulism, NE, or generalized weakness as a result of sepsis or prematurity. Iatrogenic contamination of the airway can occur when bottle-feeding is forced or if the foal is too weak or sleepy to receive feeding. Substantial and sometimes fatal pneumonia can result from inappropriate placement of a nasogastric tube.

The diagnosis of milk aspiration is supported by historical data (nasal regurgitation of milk), physical examination findings (abnormal lung and tracheal sounds), and laboratory data (inflammatory leukogram, elevated fibrinogen and/or SAA, arterial hypoxemia). Radiographic examination commonly reveals a heavy, perihilar, and/or ventrally located interstitial density, with or without air bronchograms.

The treatment of milk aspiration involves long-term, broad-spectrum antimicrobial therapy and prevention of further contamination of the airway. The underlying cause must be pursued diagnostically and treated. This may necessitate the use of further diagnostic tests, including endoscopy and plain and contrast radiography. Enteral feeding through a nasogastric or esophagostomy tube is indicated until the underlying problem has been resolved. Nasopharyngeal weakness will frequently resolve over time, but it may take weeks.

PNEUMOTHORAX, HEMOTHORAX, OR UROPERITONEUM. Pneumothorax is usually an iatrogenic sequela of positive pressure ventilation of diseased lungs, but it may occur spontaneously as a result of birth trauma and rib fracture, or from ruptured bullae within the lung parenchyma.[243,244] During mechanical ventilation, uneven alveolar ventilation leads to alveolar rupture and dissection of air into the interstitium. The air moves along bronchioles and other lung structures to pleural surfaces, forming blebs that can rupture into the pleural space. The condition should be strongly suspected if the respiratory condition suddenly worsens while an animal is being ventilated. Clinical signs may include respiratory distress, cyanosis, hypotension, or subcutaneous emphysema. Although auscultation may reveal decreased breath sounds, it may be misleading because of the wide referral of breath sounds in foals. Radiographs are indicated to confirm the diagnosis, but if radiology is unavailable or the animal is very distressed, a direct needle aspirate is both diagnostic and therapeutic.

Pneumothorax may be treated conservatively if no distress is associated with the air leak and the condition appears stable. Thoracic tube insertion is indicated with continuing air leak, if underlying pulmonary disease is causing respiratory distress, and in those patients receiving mechanical ventilation. A trocar catheter is introduced sterilely into the chest cavity, and the catheter is secured using a Chinese finger trap suture technique. Suction is applied at −15 cm H_2O until tube has drained no air for 12 hours. The tube may then be placed under water seal for an additional 24 hours, and, if no air accumulates, the tube may be removed.

Hemothorax is occasionally noted in the large animal neonate. It has occurred as a result of unstable fractured ribs, with puncture of the lung parenchyma resulting in hemorrhage into the pleural space. Occasionally hemothorax may remain undiagnosed until clinical signs of anemia, hypovolemia, or shock appear in the young animal.

Accumulation of pleural fluid is a relatively common feature of moderate to severe uroperitoneum.[245] In most foals the thoracic fluid is not recognized, but some foals develop tachypnea, tachycardia, hypercapnia, and hypoxemia. These signs can be exacerbated after removal of the abdominal fluid, potentially causing a "reexpansion pulmonary edema."[246]

TRANSIENT TACHYPNEA IN THE NEONATE. A syndrome observed in Clydesdale, Thoroughbred, and Arabian neonatal foals has been the combination of fever and tachypnea. The condition appears to be more frequent during hot, humid weather conditions. The pathogenesis of the condition is unknown, but it is speculated that it results from a transient problem in central or peripheral control of thermoregulation and/or respiratory rate and pattern.

Affected foals are usually of normal gestation and experience a normal birth. Most display normal activity for a variable period after birth, with a sudden onset of clinical signs. There are usually no signs of pulmonary abnormalities as assessed by thoracic radiographs or ABG analysis. Body temperature is variable between foals, ranging from 39° to 42.2° C (102° to 108° F). A poor response to antipyretics has been noted. The respiratory rate and breathing pattern often resemble panting (respiratory rate >80 beats/min). The condition usually resolves spontaneously within a few days to weeks.

Before idiopathic tachypnea is diagnosed, it is extremely important to rule out a pneumonic process or other pulmonary abnormality, other forms of infection, metabolic acidosis, and other causes of an increased respiratory rate. Hematology, chest radiographs, and ABGs should be within normal limits, and bacterial cultures should be negative.

Treatment is directed at controlling the body temperature; body clipping, alcohol baths, and maintenance in a cool environment are the most effective methods. If infection cannot be entirely ruled out, antibiotic therapy should be used.

Treatment of Respiratory Distress

Oxygen therapy is an important component in the management of respiratory distress. The decision to institute oxygen therapy is based both on clinical signs and on blood gas analysis. Increased respiratory rate, labored respiration, increased intercostal and abdominal muscle activity, and restlessness are considered indications for a trial of oxygen therapy. A Pa_{O_2} less than 55 to 60 mm Hg in lateral recumbency is considered an objective indication for oxygen therapy. If blood gas analysis is not available, clinical signs indicating a favorable response to oxygen therapy include a decrease in effort of breathing, decrease in respiratory rate, and a more comfortable-appearing animal. An absence of response may indicate a nonrespiratory origin of the clinical signs, severe lung pathology, a cardiac malformation, or inadequate inspired oxygen concentration.

The inspired oxygen concentration is most easily increased by nasal insufflation using a bias flow of humidified oxygen. Depending on the severity of disease and size of the individual, oxygen is initially delivered at a flow rate of about 5 L/min, and the response is noted. The oxygen catheter tip should be advanced into the nasopharynx, and the opposite end should be secured to the nostril using tape or

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sutures in active foals. The actual oxygen concentration delivered to the alveoli depends on several factors, including the position of the tube and the depth and rate of breathing. Oxygen therapy should be directed at maintaining a PaO_2 of 80 to 100 mm Hg, and the flow rate should be adjusted according to blood gas results. Oxygen therapy should be on a continuous basis, and weaning from support should be done gradually. Transtracheal oxygen delivery may be beneficial in larger foals; hypoxemic neonatal foals that have a very rapid, shallow breathing pattern; or foals with severe pulmonary disease that are unresponsive to nasal insufflation.[247] A percutaneous catheter system is placed using local anesthetic and secured to the skin. The distal location of the catheter bypasses a substantial volume of dead space and results in a higher alveolar oxygen concentration.

Oxygen therapy is not effective in correcting hypoventilation, and, if hypercapnia is progressive and accompanied by signs of increasing respiratory distress, some type of mechanical ventilatory support is usually indicated. This decision to provide mechanical ventilation must take into account several considerations, including the worth of the individual, the commitment of the owners, the facility and manpower availability, and the type of disease process present. For additional information on mechanical ventilation, the reader is directed to other reviews.[248]

Regardless of the level of respiratory support provided, the importance of meticulous respiratory supportive technique cannot be overemphasized. Maintenance in sternal position, frequent turning from side to side, regular coupage, and use of proper suction technique are all very important components of respiratory support.

Diarrhea in Neonatal Foals

Guy D. Lester • John E. Madigan

Diarrhea occurs commonly in foals of all ages and represents one of the most common medical conditions requiring veterinary intervention. The approach to diagnosis can be difficult, and establishment of a definitive diagnosis in a field setting is uncommon. The veterinarian must therefore consider a number of factors in order to construct a list of most likely causes. These factors include the age of the affected animal, the numbers of foals affected, the volume and character of the feces, and the duration of signs. Some limited diagnostic tests can be used to rule in or out many of the common causes of foal diarrhea.

In some foals diarrheal diseases are associated with signs of colic. The abdominal pain can be severe and can mimic that seen in foals with strangulating intestinal lesions, making case management difficult. Colicky signs frequently precede the onset of diarrhea. Passage of a nasogastric tube is equally important in colicky foals as it is in adults. Foals with intestinal ileus or inflammatory diseases of the small intestine will commonly produce large volumes of gastric fluid on reflux. The control of pain is required in order to reduce the chances of injury and to facilitate evaluation. Intramuscular butorphanol can be very helpful in providing pain relief in foals with colitis. $Alpha_2$-adrenergic agonists should be used with caution in neonates because of their depressive effect on the cardiopulmonary system. If they are to be used, then clinicians should start with lower doses or consider combining with butorphanol. NSAIDs should be avoided until a diagnosis is established. Neonatal foals generally tolerate flunixin well, but they require a slightly larger dose rate but reduced frequency compared with older animals.

There are many causes of diarrhea in young foals, including bacteria and bacterial toxins, viruses, nutrition, parasites, and antibiotic usage.[106] Normal physiologic adaptive processes can also produce diarrhea in most foals.

Bacteria

Escherichia coli is the most important mediator of systemic sepsis in newborn foals, but it is not a common primary cause of diarrhea in this age group. The organism is common in normal horse feces and is frequently isolated from animals with diarrhea,[249] but in the absence of typing, the role of *E. coli* is highly questionable. There are rare reports implicating an association between *E. coli* and diarrhea in foals. Enterotoxigenic *E. coli* was isolated from a 3-day-old diarrheic foal.[250] The isolate was of the 0101 serotype and was heat-labile (LT)-like toxin positive but negative for heat-stable (STa) toxin. Earlier inoculation studies indicated that F4 (formerly K88)–positive *E. coli* was not likely to cause diarrhea in foals, although it may have a synergistic role in foals infected with other potential pathogens, such as rotavirus.[251]

Intestinal disease mediated by clostridial toxins occurs in foals worldwide. The toxins are most commonly derived from biotypes A and C of *Clostridium perfringens* or from *Clostridium difficile*. Classic intestinal clostridiosis of foals is caused by *C. perfringens* biotype C and is characterized by colic, rapid dehydration, cardiovascular collapse, and hemorrhagic diarrhea. The disease occurs most commonly in foals less than 10 days of age, and often less than 36 hours of age. It is associated with a high mortality and outcomes are rarely influenced by treatment.[252] Death may occur rapidly and occasionally before any diarrhea has been passed. Biotype C produces both α and β toxins along with variable amounts of enterotoxin. Cases can occur sporadically or as outbreaks and, on some farms, occur annually presumably in association with carriage in specific mares. Biotype A of *C. perfringens* has become well recognized as a specific cause of foal diarrhea over the past decade. Biotype A produces α toxin and enterotoxin and is associated with a slightly lower mortality rate than biotype C. Affected foals are more likely to respond to directed or supportive care. The development of clinical signs is rapid and diarrhea may or may not contain blood; in the author's experience, passage of bloody diarrhea is common but usually very transient. Reported risk factors for *C. perfringens* diarrhea in neonatal foals in Colorado include breed (stock horse type); birth on dirt, sand, or gravel; housing in stalls or on dry lots during the first 3 days of life; and maternal feeding practices. Feeding a low-grain diet prepartum was associated with a decreased risk of neonatal disease. Hematologic findings are consistent with toxemia. This includes hemoconcentration; an initial leukopenia, characterized by a neutropenia with a left shift to immature forms and toxicity; and a lymphopenia. Chronic cases may develop a rebound leukocytosis and hyperfibrinogenemia. Altered coagulation may be evident clinically through prolonged bleeding or spontaneous hemorrhage, or through a propensity to develop thrombosis.

A definitive diagnosis of *C. perfringens* diarrhea is rarely established in practice. The diagnosis is usually based on signalment, clinical features, and outcome, rather than detection of specific clostridial toxins. Positive fecal culture is strongly supportive, noting that healthy foals may shed low numbers of *C. perfringens*. Identification of toxin is ideal but is limited due to availability of appropriate commercial assays. Fecal enterotoxin detection assays are available but lack sensitivity, particularly with biotype C isolates. Biotyping of *C. perfringens* isolates after culture can be achieved using PCR analysis for toxin gene sequences. This may be helpful in increasing the accuracy of the diagnosis but again falls short in establishing a definitive cause. Fecal Gram stain is easy to perform and may support an early clinical suspicion of disease if there are abundant numbers of large gram-positive organisms or spores present.

C. difficile can produce an identical clinical syndrome to *C. perfringens,* although it appears to be more variable with respect to fecal blood. The two pathogens were isolated together in several foals with fatal hemorrhagic diarrhea.[253] *C. difficile* also occurs as sporadic cases or as clusters or outbreaks. Identical strains can be recovered in mare-foal pairs, indicating cross-infection.[254] It is important to recognize that clostridial infection can produce a severe inflammatory syndrome that is restricted to the small intestine and may not cause diarrhea. Affected foals can present with signs that mimic strangulating small bowel disease, including severe abdominal pain, gastric reflux, and sanguineous peritoneal fluid. Two principal toxins can be liberated from *C. difficile:* an enterotoxin (toxin A) and a cytotoxin (toxin B). Both non-toxigenic and toxigenic strains exist and can only be differentiated after culture using molecular techniques.

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Consequently, commercial toxin tests (available for both toxin A and B) are recommended in addition to fecal culture to establish a diagnosis. As with *C. perfringens* cases, a fecal Gram stain can also increase suspicion. Hematologic changes associated with *C. difficile* infection can mimic those associated with *C. perfringens* disease.

Most cases of clostridial enterocolitis require aggressive medical intervention, irrespective of clostridial type. Antimicrobial therapy should be both specific and broad spectrum. Targeted antimicrobial treatment typically includes both metronidazole and penicillin. The majority of affected foals will require, at minimum, intravenous crystalloid solutions; some will also benefit from plasma or synthetic colloids, and inotrope and vasopressor therapy. Additional therapies include *C. perfringens* biotype C and D antitoxin, di-tri-octahedral smectite clay, and lactase enzyme replacement.[255,256] The use of *C. perfringens* antitoxin and toxoid is off-label and not without some risk. Pretreatment with antihistamines has been suggested before antitoxin.[255] Prevention of clostridial enterocolitis centers on hygienic housing practices and avoidance of overfeeding of late pregnant mares. Affected foals and their mares should be isolated and strict protocols instituted to limit cross-contamination. Administration of *C. perfringens* type C and D toxoid to pregnant mares has been used with anecdotal success on farms having recurrent problems with *C. perfringens* biotype C. The use of prophylactic metronidazole is highly controversial but understandable on properties with a high disease prevalence. Some isolates of *C. difficile* are reportedly resistant to metronidazole,[255] and although this appears to be dependent on geographic location, the widespread prophylactic use could promote resistance. Prophylactic use of probiotic preparations are commonly recommended, but there are conflicting efficacy data.[257,258]

Bacteroides fragilis is a gram-negative anaerobic rod and occurs in both enterotoxigenic and non-enterotoxigenic forms. Enterotoxigenic strains of *B. fragilis* have been incriminated with diarrhea in several species including lambs, calves, pigs, humans, and foals.[259] Enterotoxigenic *B. fragilis* was isolated from young foals (aged 2 to 60 days) with diarrhea.[260] Half of these foals had other potential pathogens detected, including *Salmonella* or rotavirus. In a study reviewing 20 isolates of *B. fragilis* from hospitalized foals with diarrhea, only 4 had the enterotoxin gene.[259] The most common isolate from foal feces was a non-enterotoxigenic strain, casting doubt as to clinical relevance.

Enterococcus (Group D *Streptococcus*) *durans* has also been implicated as a cause of diarrhea in foals.[261] Similarly, *Aeromonas hydrophila* was isolated more commonly from foals with diarrhea than control animals, suggesting a potential role in foal diarrhea.[262] *Rhodococcus equi* is an important cause of pulmonary disease in foals. Although abdominal involvement appears common, the relevance of *R. equi* as a significant primary enteric pathogen, in terms of number of animals affected, is likely small. An intestinal syndrome has been directly attributed to *R. equi* that involves necrosis of the small intestinal Peyer patches and multifocal thickening and necrosis of the cecum and large intestine.[263] The changes include multiple areas of intestinal ulceration with an associated mesenteric lymphadenopathy. The diagnosis of *R. equi* ulcerative colitis is difficult for a variety of reasons. In contrast to *Salmonella* infection, where recovery of the organism from the feces has significance, the recovery of *R. equi* is common in asymptomatic animals. Up to 100% of foals older than 2 weeks of age may shed large numbers of the bacteria.[264]

Salmonella infection of neonatal foals is also associated with high mortality. As with clostridial infection, cases can occur sporadically or as part of an outbreak. Mares provide the most important source of *Salmonella* to newborn foals, but it is rare that both mare and foal will develop clinical disease. Clinical signs can become apparent by 24 hours of age but are more common in older foals. The severity of signs is related to virulence of the serotype involved, inoculation dose, and level of host immunity. In contrast to adult infections, detectable bacteremia occurs commonly in affected foals. Consequently, foals that may survive the initial intestinal or systemic disease remain at risk for secondary complications that include osteomyelitis, synovitis, meningitis, uveitis, hepatitis, or pyelonephritis. In some foals these complications may not become clinically apparent until days or weeks after resolution of enteric disease. Therefore, appropriate and sustained broad-spectrum antibiotic therapy is important in known affected foals. The selection of antibiotic should be based on known sensitivity patterns, understanding that in vitro sensitivity may not accurately translate into clinical efficacy because of the intracellular location of *Salmonella*. For example, the limited distribution of aminoglycosides can lead to therapeutic failure despite often promising in vitro sensitivity.

Viruses

Rotavirus is the most common cause of infectious diarrhea in foals. There are seven known groups of rotavirus (A through G), and many different serotypes within each group. Group A is the primary cause of rotaviral diarrhea in foals, with G3 the most common serotype.[265] Rotaviruses have the ability to change their surface proteins over time, and this rearrangement of gene segments takes place during co-infections with other strains. This leaves the possibility for many variations of the virus.

Transmission may be direct from animal to animal or indirect through fomites. Disease occurs after a short incubation period. Experimentally, this period may be as brief as 48 hours.[266] Rotavirus replicates within the intestine and invades the lining of the proximal small intestine, causing villous cell death and a resultant loss of absorptive area. Diarrhea may result from several mechanisms: (a) a loss of absorptive capacity coupled with a decrease in lactase production can lead to an osmotic load of undigested lactose delivered to an immature hindgut, (b) a compensatory crypt cell proliferation may cause an increase in intestinal secretion, and (c) the virus produces an enterotoxin that causes or contributes to the development of diarrhea. The putative viral enterotoxin and cytotoxin, NSP4, is a nonstructural glycoprotein of rotavirus that is released from virus-infected enterocytes.[267] NSP4 is a noncompetitive inhibitor of the Na-glucose symporter and enhances intestinal chloride secretion.

Disease can be seen between 2 and 160 days of age but is most common in foals less than 60 days. Indeed, most clinical infections probably occur between 5 and 35 days of age. The presence and severity of diarrhea is highly dependent on the degree of hindgut maturation. Consequently, infection in foals less than 2 weeks of age may result in life-threatening watery diarrhea, whereas infected older foals may have minimal or no diarrhea because of effective colonic compensation of osmotic and fluid loads. Diarrhea when present is often watery, but nonfetid in odor.

Serologic evidence exists that broodmares may have an important role in propagation of the virus within a herd. Infections can occur as isolated cases or as outbreaks following periods of overcrowding and stress. Shedding after infection is usually complete by 10 days after the cessation of clinical signs but may occur intermittently for up to 9 months.[268] The virus can persist in the environment for up to 9 months, and disinfection usually necessitates the use of substituted phenolic compounds.

The diagnosis of rotaviral diarrhea is based on an appropriate signalment, clinical signs, and detection of the virus in feces. Tests include electron microscopy and commercial immunoassays (ELISA or latex agglutination). Virus is shed in large concentration early on during infection. Central to the management of affected foals is maintenance of hydration through enteral and/or IV fluid therapy.

Prevention involves good hygiene and reduction in crowding. Vaccination of mares during pregnancy has yielded variable results in terms of efficacy.[269,270] Some evidence suggests that vaccination may at a minimum delay the onset of disease, thereby reducing both the severity and duration of diarrhea.

Coronavirus can cause diarrhea in foals during the neonatal period; it was originally thought to be an uncommon, though severe, cause of diarrhea.[271,272] Recent survey data using real-time PCR analysis indicated a high rate of carriage in both healthy and

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diarrheic foals.[273] Antemortem diagnosis can also be made using electron microscopy, serology, or commercial fecal-capture ELISA. As with rotaviral infection, shedding is greatest in the early stages of disease.

Parasites

Strongyloides westeri is a common parasite of foals, with early infection of the foal occurring through mare's milk. Experimental studies have indicated that higher numbers of infective larvae than are found in milk are needed to produce diarrhea.[274] Furthermore, foals with high egg counts are often asymptomatic.

Cryptosporidium parvum is not considered to be an important pathogen of foals in terms of numbers of animals diseased, although it can be a problem in specific locations.[275] Based on epidemiologic studies, the parasite appears to be concentrated in some breeding operations.[276] Foals diseased with *Cryptosporidium* shed enormous numbers of infective oocysts into the environment. The parasite is considered to be coccidian-like, but it differs from coccidia in terms of size (4- to 6-µm diameter compared with 23 to 34 µm for other coccidia), host specificity (not host specific), pathogenesis (only invades epithelium), and drug sensitivity (resistant to many drugs). Infection is by the fecal-oral route. The oocysts can survive in the soil or water for months. They do not require a period of sporulation outside of the host to become infective. In a study of asymptomatic foals, between 15% and 31% of foals were shedding *Cryptosporidium,* and that shedding began between 4 and 19 weeks of age and persisted no more than 14 weeks.[277] All shedding had ceased by weaning and was not identified in adult horses. The diagnosis is usually made through microscopic examination of the feces. Acid-fast or Ziehl-Neelsen stains are required to detect oocysts. Immunofluorescence assays and flow cytometry techniques have also been described. *Cryptosporidium parvum* infection may be seen with concurrent enteric or systemic infections. The disease is generally self-limiting in immunocompetent animals. Historically, the pharmacologic control of *Cryptosporidium* has been difficult, but paromomycin, nitazoxanide, or azithromycin may be efficacious.

Giardia may be found in normal foals with infection rates reported from 17% to 35%.[277] *Giardia* is present in all age groups, and it is believed foals acquire infection from nursing mares. Concurrent infection with *Cryptosporidium* and *Giardia* may be observed. Disease should be suspected if large numbers of parasites are seen on fecal analysis. Affected animals should respond within a few days to treatment with metronidazole; failure to respond should alert to other pathogens.

Nutritional Causes

Nutritional causes of diarrhea include overingestion of milk (as might occur when the mare and foal are separated and rejoined) or overfeeding orphaned or sick foals. Overwhelming the ability of the small intestine to digest and absorb results in presentation of milk to the colon, where it is fermented and produces osmotically active sugars and acids. In a controlled study made of foals less than 5 days of age, an elemental isotonic diet produced diarrhea in healthy foals when fed as the sole source of nutrition. Older foals fed a similar diet apparently did not develop diarrhea.[278] Orphan foals and foals fed commercial mare milk replacer may experience diarrhea associated with these diets. Foals that are fed raw cow's milk frequently experience diarrhea and failure to thrive. Cow milk replacer uncommonly causes diarrhea but remains a less than ideal replacement. In contrast, foals fed goat's milk grow well and rarely develop diarrhea, although they may develop a metabolic alkalosis of minimal to no clinical significance.

Transient lactase deficiency has been proposed in foals. An oral lactose tolerance test is conducted after a 4-hour fast. Foals are administered 1 g/kg of body weight of a 20% solution of lactose powder, observing an increase of plasma glucose of 35 mg/dL (1.9 mmol/L) by 90 minutes.[279] Agents such as rotavirus that damage epithelial cells may cause prolongation of the diarrhea because of temporary lactase deficiency.

Foal Heat Diarrhea

Diarrhea developing during days 5 to 14 of life has been termed "foal heat diarrhea" because of the time relationship to the occurrence of post-foaling estrous in the mare. Diarrhea has developed in foals in this age group that have been raised separated from the dam on a consistent diet and isolated from pathogens, so it does not appear to be causally related to estrous. The most likely cause of foal heat diarrhea is the establishment of normal flora in the hindgut. Foal heat diarrhea is typically preceded by coprophagy 2 to 3 days prior to the onset of diarrhea. Classical foal heat diarrheas are mild and require no specific therapy. Continued diarrhea, fever, or depression with signs of reduced sucking activity on the mare should raise concern of other etiologic agents with appropriate diagnostic testing and treatment.

Treatment and Prognosis

The three main components of therapy of diarrhea in the neonatal foal consists of (1) fluid therapy (either oral or intravenous), (2) intestinal protectants/adsorbents, and (3) antibiotics if indicated to treat suspected bacteremia or clostridiosis. Sodium-containing isotonic IV fluids are an important component of diarrhea therapy in the compromised neonate. Potassium is lost in severe diarrhea and, if hyperkalemia is not present, should be supplemented by adding 15 to 20 mEq/L of KCl to fluids. Foals that are not nursing normally may have hypoglycemia and may need glucose-containing fluids. Acid-base correction by volume expansion and replacement of bicarbonate can be lifesaving and should be monitored frequently when significant intestinal fluid losses occur.

Ideally milk should not be withheld from foals with diarrhea. The clear exceptions are foals with colic and those with bloody diarrhea. The foal can be muzzled for 8 to 12 hours while the mare is milked out, and the foal provided oral fluids through stomach tube or a bottle if a suck reflex is present. Although labels of electrolyte replacers do not always specify for use in foals, many preparations used in calves have been used in foals. Most of these preparations provide insufficient energy and should be used for short intervals of no more than 24 to 36 hours unless PN of some type is provided to maintain blood glucose levels.

Intestinal protectants may be all that are required in uncomplicated cases or may be used in conjunction with other therapies. Bismuth subsalicylate, kaolin or pectin, and activated charcoal have been used for this purpose. Suggested advantages of bismuth subsalicylate are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity. Di-tri-octahedral smectite clay is also commonly used in the management of diarrhea.

Systemic antibiotics should be used in the neonate with diarrhea that may be septicemic or have compromised immunity. Blood cultures should be obtained before initiation of antimicrobial therapy. Antibiotics with a spectrum against gram-negative and gram-positive organisms should be used. In general terms renal toxicity associated with aminoglycoside use is uncommon in clinical practice. The clear exception would be foals that are dehydrated, most commonly due to ongoing losses through diarrhea. Consequently, the monitoring of renal function is indicated when using potentially nephrotoxic drugs.

Plasma therapy for hypoproteinemia associated with failure of passive transfer or protein-losing enteropathy is useful to maintain plasma oncotic pressure and expected protein binding of medications. Diarrheic foals with albumin levels below 20 g/L or total plasma protein levels less than 42 g/L may benefit from plasma therapy.

Prevention and Control

Prevention is best accomplished by minimizing the density of populations of horses, separating of age groups, providing appropriate sanitation and hygiene, and obtaining adequate colostrum of good quality (see Chapter 53). The risk of neonates developing diarrhea in

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a hospital environment is increased with the use of histamine type 2 receptor antagonists or omeprazole.[100]

Distended and/or Painful Abdomen

Wendy E. Vaala

The large animal neonate with a painful or distended abdomen can present a diagnostic challenge to the clinician. Medical and surgical causes of colic and GI disease in the foal include ileus and bowel distention associated with peritonitis, hypoxic gut damage and metabolic disturbances, enteritis caused by dietary changes, viral infections and bacterial pathogens, gastroduodenal ulcer disease, intussusception, thromboembolic disease, small intestinal volvulus, colon torsion, uroperitoneum, strangulating abdominal hernias, and congenital GI lesions. The clinical challenge is to distinguish medical from surgical lesions to permit rapid and appropriate therapy. Abdominal surgery in young foals, particularly neonates, is associated with increased morbidity and mortality and a higher incidence of intraabdominal adhesion formation when compared with mature horses.[280] Medical causes of GI disease such as enteritis and peritonitis carry an increased risk of generalized sepsis and death if the patient's cardiovascular status and metabolic parameters are not monitored and stabilized in a timely manner.

Physical examination findings can be very similar between neonates requiring surgical intervention and those with only an infectious problem, such as enteritis or enterocolitis. If abdominal distention is present, every effort should be made to identify its cause. Because the neonatal foal is considerably smaller than the adult, some of the diagnostic techniques routinely used in the adult (rectal palpation, assessment of shape of abdomen) are of limited value in assessing the acute abdomen in the neonate. Bilateral, tympanitic distention of the paralumbar fossae is suggestive of generalized ileus or large bowel obstruction (e.g., meconium impaction). Other diagnostic aids including abdominal radiographs, transabdominal ultrasonography, abdominal ballottement, and transcutaneous abdominal palpation are not practical in the adult but may be very helpful in the foal.

The approach to the neonate with a painful or distended abdomen should include a complete history, including any abnormalities noted during the perinatal period, the type and dose of any analgesics previously administered, and whether there is history of diarrhea in other foals or horses on the farm. The age of the foal helps determine the risk of certain conditions. Young foals less than 2 weeks of age are more likely to experience colic caused by meconium retention, clostridial enteritis, peritonitis associated with generalized sepsis, hypoxic gut damage, uroperitoneum, and congenital deformities including lethal white syndrome (e.g., mesenteric aganglionosis) (Fig. 17-11), inguinal and scrotal hernias, and atresia of the anus or colon.[281] Older foals are more likely to suffer from intussusceptions, enteritis, gastroduodenal ulceration, and thromboembolic disease.[281]



FIG. 17-11 A lethal white foal demonstrating colic at 18 hours of age.

The neonate's age at the onset of abdominal distress may also provide diagnostic clues. For example, foals with meconium impaction, congenital GI malformations, such as atresia coli, tend to be presented for treatment during the first 12 to 36 hours of age, whereas foals with uncomplicated ruptured urinary tracts are usually presented at about 3 days, when the abdomen is visibly distended. The character, quantity, and frequency of defecation and urination should be determined. Surgical GI lesions such as intussusception and large colon displacement have occurred as a result of enteritis. On the other hand, in the early stages, enteritis alone can cause severe abdominal distention or severe pain, in the absence of diarrhea. NEC and clostridial enteritis can be particularly painful conditions. Most foals with ruptured urinary bladders display abnormalities in urination, but in some cases, normal micturition has been noted. Reduction in urine output from a neonate with a distended abdomen is not pathognomonic for uroperitoneum. Urine volume is typically reduced as a result of dehydration caused by a variety of abnormalities, including GI disease. The colic associated with uroperitoneum is not usually severe.

Assessment of the degree of pain being exhibited is an important part of the examination of the neonate with a distended abdomen. In a retrospective study of foals undergoing exploratory celiotomy, uncontrollable pain and severe abdominal distention were the primary reasons the animals were taken to surgery.[282] Unfortunately, severe abdominal pain is not pathognomonic for a surgical lesion, since several foals with severe enteritis alone were taken to surgery for this reason. The degree of compromise to the cardiovascular and pulmonary systems should be assessed. A neonate with an abdominal crisis is often in need of immediate stabilization because of shock resulting from endotoxemia or hypovolemia. Exploratory celiotomy in neonates that receive inadequate presurgical supportive therapy is associated with a number of complications, including poor tolerance to anesthesia. The degree of respiratory compromise as a result of the abdominal problem should also be considered, particularly if the animal is a surgical candidate. For example, foals with long-standing uroperitoneum may have pleural effusion and pulmonary abnormalities as well as serum electrolyte abnormalities, all of which may predispose to anesthetic problems (hypoxemia, hypercapnia, cardiac arrhythmias).

It is very important to establish the likelihood of generalized or localized infection such as enteritis. Generalized sepsis can interfere with the function of many organ systems, including the GI tract. The first signs of enteritis are often severe abdominal distention and colic, with diarrhea becoming apparent a few hours to days later; the severity of these signs may warrant surgical exploration of the abdomen. Leukopenia may be observed in foals with septicemia, enteritis, peritonitis, and surgical GI lesions. An unexplained metabolic acidosis may also indicate impending enteritis.

Additional information on the physical examination of the abdomen and GI tract can be found in Chapter 16. It is difficult to distinguish fluid accumulation in the large colon from accumulation in the peritoneal cavity using physical examination alone, and additional diagnostic procedures are usually required to distinguish the two (see later in this chapter). In general, nasogastric intubation in the neonatal foal does not seem to be as useful a diagnostic technique as it is in the adult horse. Gastric reflux can be difficult to obtain, even if the stomach appears markedly distended on radiographs, and a moderate amount may be obtained in cases of ileus. If large volumes of reflux are obtained, however, obstructive disease (e.g., of the pylorus and small intestine) is considered more likely.[282]

Neonates with enteritis, uroperitoneum, and other abdominal problems can have markedly deranged serum electrolyte concentrations (hyperkalemia, hyponatremia, and metabolic acidosis are typical). Failure to recognize the severity of these abnormalities or adequately treat them can result in the death of the patient.

Abdominal radiographs can be very helpful in identifying segments of the intestinal tract that are distended, fluid in the peritoneal cavity, and the composition of ingesta in the gastrointestinal tract (e.g., sand, meconium) (Figs. 17-12 and 17-13). A good knowledge

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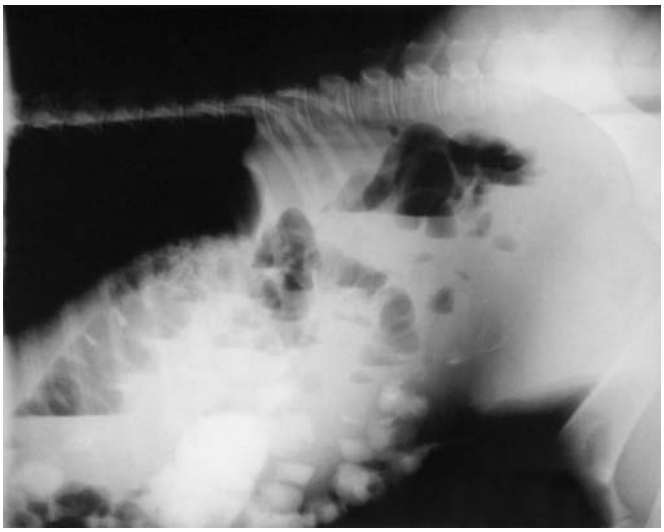


FIG. 17-12 Sand accumulation in the ventral colon of a 1-month-old foal with chronic diarrhea and intermittent colic.

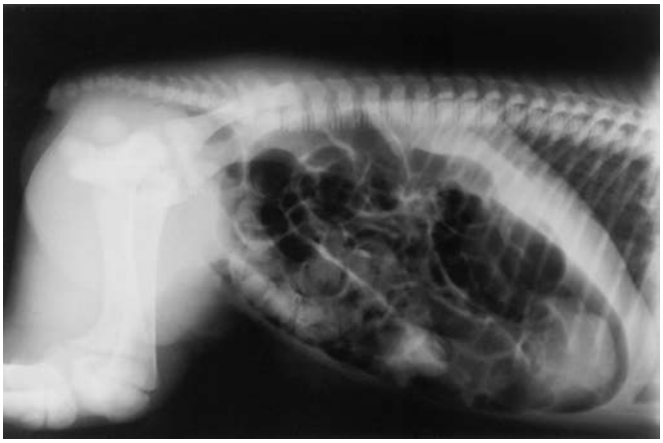


FIG. 17-13 Abdominal radiograph (lateral recumbency) of a 7-hour-old miniature horse foal with atresia ani, showing meconium packed into a gas-distended large colon. The extent of the atresia proximally from the anus is not visible.

of normal radiographic anatomy of the intestinal tract is important for accurate interpretation (Fig. 17-14). Adequate radiographs are obtained in foals up to 250 kg if available radiograph equipment includes a grid, rare earth screens, and sufficient mAs (5-28) and kVp (75-95). With experience in viewing normal and abnormal abdominal radiographs, the likelihood of an obstructive lesion versus simple ileus can be established in some, but not all, cases. The presence of erectile, distended loops of small intestine is most consistent with a diagnosis of obstructive disease. Intramural gas is suggestive of NEC. It can be very difficult to differentiate large colon torsion or displacement from simple gas and fluid distention resulting from ileus. Contrast radiography can help to define the location and nature of GI problems such as duodenal stricture and abnormalities of the small colon or rectum.

Abdominal ultrasonography can be of value in diagnosing certain conditions that may be contributing to a distended or painful abdomen, including fluid-distended small and large intestine, ascarid impaction, intussusception, colonic impaction, uroperitoneum, and abnormalities of the umbilical vessels and urachus. Ultrasonography also permits characterization of small intestinal motility, distention, and bowel wall thickness. Healthy foals have flaccid, fluid-filled loops of small intestine. The presence of rounded, distended loops of small intestine is suggestive of an ileus, enteritis, or possible small bowel obstructive disease. The location, amount, character, and

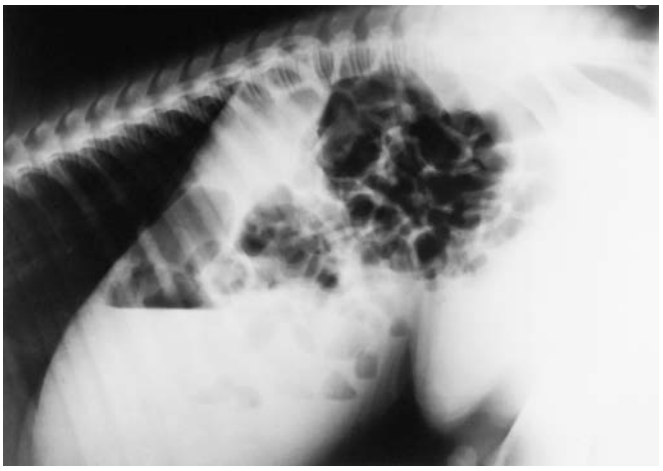


FIG. 17-14 Normal standing abdominal radiograph in a neonatal foal. Note the prominent fluid line in the stomach and the presence of gas in various portions of the tract.

echogenicity of free peritoneal fluid can also be determined. A large accumulation of peritoneal fluid with increased echogenicity (or fibrin) is suggestive of peritonitis, whereas an excessive volume of hypoechogenic peritoneal fluid is suggestive of uroperitoneum.

In the author's opinion, except in a couple of specific conditions, peritoneal taps are of limited value in diagnosis of the acute abdomen in the neonate. Extreme caution should be exercised to avoid perforating the bowel while attempting to acquire a sample of peritoneal fluid, particularly if intestinal distention is present. The intestine of the neonate is easily ripped by inadvertent perforation with a needle or teat cannula, even if the neonate is well restrained. It is probably safest to perform the procedure using ultrasonography to image the fluid pocket and the needle position. Foals with uroperitoneum are the ideal candidates for abdominocentesis. Clear yellow, urine-like peritoneal fluid is easily and safely obtained in these patients since the excessive volume of peritoneal fluid allows the abdominal viscera to float well above the ventral floor of the abdomen.

Normal peritoneal fluid is similar to that of the adult, except that the normal WBC count is lower (1500 cells/μL or less). Cytologic examination should also be performed to determine the cell types present and to detect the presence of bacteria and toxic neutrophils (suggesting peritonitis), and fecal material (suggesting either inadvertent gut tap or bowel rupture). The TP and WBC count may be elevated in a variety of conditions. These include severe enteritis, urachal, umbilical or severe bladder infection, and primary peritonitis, in addition to conditions in which there is ischemic bowel requiring surgical resection. On the other hand, as in the adult, normal peritoneal fluid has accompanied a number of surgical intestinal lesions, such as large colon displacement. Therefore, peritoneal fluid analysis is of limited value in distinguishing the surgical patient but can be useful in the diagnosis of peritonitis. In addition, peritoneal fluid analysis usually results in a straightforward diagnosis of uroperitoneum. In virtually all cases of uroperitoneum observed to date, peritoneal creatinine level was greater than the serum level (usually >2:1). Also, the acquisition of free-flowing blood from the abdominal tap usually allows a diagnosis of hemoperitoneum.

Endoscopy of the upper and lower GI tract of the foal can be performed if appropriately sized equipment is available (8- to 10-mm O.D., 180 to 250 cm long). The esophagus and stomach can be examined for erosion, ulceration, perforation, and other abnormalities. Suspected impactions or malformations of the rectum and small colon can also be examined.

In summary, accurate identification of foals with acute abdominal problems requiring surgery can be very difficult, even with the use of ancillary diagnostic procedures, and mistakes are commonly made because there are no clear-cut and consistent differences between medical and surgical cases. Findings suggestive of the need for

surgical exploration include severe and unrelenting pain and persistent tachycardia.

Specific Conditions

Meconium Impaction

Meconium impaction is the most common cause of colic in the newborn foal. This condition is more common in colts because of the narrow pelvic canal. Many foals show some degree of straining and discomfort while passing meconium, but in most instances it is passed uneventfully by 24 to 48 hours of age. The meconium most commonly becomes impacted in the rectum or small colon. The clinical signs associated with meconium impaction in the otherwise normal foal include repeated attempts to defecate, straining with the back arched, swishing of the tail, and restlessness. Nursing stimulates defecation through an oral-anal reflex, so signs of discomfort may appear shortly after each milk meal. If left untreated, meconium impactions lead to varying degrees of abdominal distention. The foal's abdomen becomes gas-distended with tympany detected over the paralumbar fossa. Digital examination often reveals a rectum packed with hard fecal balls. Occasionally, the impaction is located more proximally (large or small colon), and radiography or ultrasonography is required for diagnosis.

Low doses of analgesics such as flunixin meglumine (0.25 to 1 mg/kg IV) and butorphanol (0.01 to 0.1 mg/kg IV) may be required to prevent self-trauma during colicky episodes. Xylazine may exacerbate gut stasis and can cause respiratory depression and should be used with caution in newborn foals. A gravity enema with mild soap and warm water or a commercial enema usually results in prompt evacuation of the meconium. Refractory meconium impactions may respond to 4% acetylcysteine retention enemas. The supplies and procedure for a retention enema are as follows:

1. Mix together 150 mL water, 6 g of acetylcysteine powder, and 20 g of sodium bicarbonate (baking soda). Alternatively, commercial acetylcysteine solution (Mucomyst solution, 20% solution 40 mL added to 160 mL water) can be used.
2. Insert a well-lubricated 12- or 14-French, cuffed Foley urinary catheter into the rectum and inflate the cuff.
3. Slowly infuse 120 to 180 mL of the retention enema solution.
4. Plug the end of the catheter. Tape the catheter loosely to the foal's tail. Leave it in place for a minimum of 15 minutes, and then deflate the cuff and remove the catheter.

This procedure can be repeated several times. Care must be taken to avoid traumatizing the rectal mucosa by stiff tubing or multiple enemas with harsh detergents. Clinical signs associated with meconium impaction in the compromised foal may be absent. In asphyxiated or premature individuals that are receiving little or no enteral feeding, meconium may remain in the large colon for days, gradually forming into hard concretions that are diagnosed by palpation or radiographs or at postmortem examination. In these cases the routine administration of an enema is often ineffective in mobilizing the impaction because it is high in the large colon. Additional therapy includes IV fluids, oral fluids, and laxatives (60 to 120 mL of mineral oil with 0.5 to 1 oz of psyllium, 60 to 120 mL of Milk of Magnesia). If the gas distention becomes severe, transcutaneous bowel trocarization can be pursued. The author avoids the use of DSS as an oral cathartic since it can cause excessive irritation resulting in diarrhea and colic. Analgesics may also be helpful in controlling the neonate's discomfort and in reducing the risk of self-trauma. Although most meconium impactions can be successfully treated with aggressive medical therapy, those few foals that are refractory to treatment or display uncontrollable pain are candidates for surgical intervention.

Uroperitoneum

Uroperitoneum is a relatively common cause of abdominal distention and depression in the neonatal foal. The condition predominates in males but may occur in females as well. Uroperitoneum may be congenital or acquired. The congenital form occurs due to failure of the dorsal wall of the bladder to close during development. The most common cause of uroperitoneum is a ruptured urinary bladder, but other sites in the urinary tract may also leak, including the ureters, urachus, and urethra. Most cases of ruptured bladders are presumed to occur during parturition because of external pressure on a distended bladder. This form occurs most commonly in colts. Uroperitoneum can also occur as a result of ischemic necrosis or infection of the urinary bladder or urachus in the compromised foal. Critically ill, recumbent foals may rupture their bladders while being lifted and turned with a full bladder or from chronic overdistention associated with their generalized disease state. Foals with botulism may also rupture their bladder as a result of bladder atony and chronic overdistention. Older foals of either sex may experience bladder rupture resulting from focal infection of the umbilical arteries and/or urachus, or ischemic necrosis of the apex of the bladder.

Clinical signs of uroperitoneum are rarely noticed before 48 to 72 hours of age, particularly if the foal is not being watched closely. The first signs may be urinary incontinence or frequent attempts to urinate, with only small amounts voided. Sometimes, particularly in those animals that rupture sometime after birth, there is a history of a period of normal urination, which at some point stopped or became abnormal. Loss of suckle, mild colic, and increasing abdominal distention are usually accompanied by worsening depression and increasing heart and respiratory rate. If the condition is allowed to persist, foals become increasingly weak and dyspneic and may present in cardiovascular collapse. Fillies with ruptured ureters have been reported to have a characteristic protruding perineum, presumably as a result of retroperitoneal accumulation of fluid.[283]

Laboratory findings commonly associated with uroperitoneum are elevated serum creatinine and BUN, hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis. These changes are probably a result of the normal diet of the foal (milk being relatively high in potassium [25 mEq/L] and low in sodium [12 mEq/L]) and the third spacing of urine in the peritoneal cavity. With urine potassium concentration relatively higher than serum and urine sodium concentration lower than serum levels, the net effect of partial equilibration of serum with peritoneal fluid across a semipermeable membrane is hyponatremia and hyperkalemia, along with an inability to excrete the waste products of metabolism. Hyperkalemia may be severe enough to induce potentially fatal bradyarrhythmias. In hospitalized foals that developed uroperitoneum as a secondary complication, these typical electrolyte abnormalities are not consistently observed. Since most of those foals were receiving replacement IV fluids (high in sodium, low in potassium) and very little milk, it was theorized that intake has a great influence on the electrolyte abnormalities associated with uroperitoneum.[284] On the other hand, the electrolyte abnormalities typically associated with uroperitoneum are not pathognomonic for that disorder. Foals with renal failure, blocked urethra, white muscle disease, and enteritis have shown the same electrolyte changes.

A diagnosis of uroperitoneum often can be made quickly using transabdominal ultrasound and a 5- or 7.5-MHz transducer to visualize large volumes of free, nonechogenic fluid within the abdomen, and a small, irregularly shaped, collapsed bladder. Abdominocentesis usually produces a free flow of peritoneal fluid that contains a low cell count, low specific gravity, and at least twice the creatinine concentration of peripheral blood. If the creatinine is the same in both serum and peritoneal fluid, other explanations for the clinical signs should be investigated. The WBC count, TP, and cytology of the fluid should also be determined. Most uncomplicated cases of ruptured bladders have fairly normal values for peritoneal fluid. In some cases, however, an increased WBC count and TP as well as the presence of bacteria may suggest peritonitis. This may be a result of the urine in the abdomen, but more commonly there is a primary ongoing infectious problem (necrotic urachus or bladder; enteritis), and the prognosis becomes worse. If laboratory facilities are not available, new methylene blue can be injected into the bladder using a urinary catheter, and a few minutes later a sample of peritoneal fluid should

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have a blue discoloration if a ruptured bladder is present. However, this technique may not detect other causes of uroperitoneum such as a ruptured ureter or distal urachus. Positive contrast cystography using a 10% solution of water-soluble medium may be helpful in detecting the location of the urinary tract leakage. The ability to obtain urine on catheterization of the urinary bladder does not rule out uroperitoneum. Hematology and blood cultures should be performed to detect primary or secondary sepsis.

Treatment of uroperitoneum is surgical repair. However, the foal with uroperitoneum should not be rushed to surgery without first carefully stabilizing it. Serum electrolytes and blood gases should be run to determine the extent of hyperkalemia, hyponatremia, and acidosis present. Although the total amount of water in the body is usually grossly increased by the peritoneal accumulation of urine, effective circulating volume may be drastically reduced. If the eyeballs are sunken and pulse quality and capillary refill time are poor, aggressive fluid therapy is indicated to support the circulation. This is best performed by concurrently removing as much fluid as possible from the abdomen with a teat cannula, 14-gauge catheter, or peritoneal dialysis catheter to avoid worsening fluid overload and respiratory distress. The fluids of choice to treat the typical electrolyte alterations associated with uroperitoneum are saline, dextrose, and possibly sodium bicarbonate solutions, depending on the degree of acidosis present. In most instances continuous dextrose infusion is effective in decreasing the serum potassium level to an acceptable level, but values should be rechecked before anesthesia is induced. Insulin and dextrose may also be used to treat hyperkalemia, but the patient must be monitored for hypoglycemia. One suggested regimen is regular insulin at 0.1 to 0.2 U/kg SC or IV, accompanied by a continuous IV dextrose infusion (4 to 8 mg/kg/min). Some individuals also have pleural fluid accumulation and atelectasis as a result of the abdominal distention, so oxygenation and ventilation during and after surgery should be closely monitored. Broad-spectrum antibiotics should be started immediately after samples are taken for culture if infection is suspected.

The prognosis for uncomplicated ruptured urinary bladders is usually good (>80% survival), provided the animal is stabilized before anesthesia. The presence of concurrent septicemia carries with it a considerably poorer prognosis.[284] In one retrospective study among foals with uroperitoneum, 100% of those foals with a negative sepsis score lived and only 57% of foals with a positive septic score survived.[285]

Gas or Fluid Accumulation in the GI Tract: Ileus

Abdominal distention and colic resulting from excessive gas and/or fluid accumulation in all or a portion of the GI tract are common complications in the compromised neonate undergoing intensive care. The exact mechanisms responsible for the presumably altered GI motility are not well defined. Ileus is associated with the absence of intestinal sounds, abdominal distention, and intolerance of oral feeds characterized by gastric reflux. Auscultation of reduced GI borborygmi does not always correlate with the degree of intestinal compromise and decreased motility. Transabdominal ultrasonography helps identify absence of intestinal motility and the location and degree of intestinal distention. Ileus and the attending abdominal distention can cause severe colic and can induce respiratory distress in a weak or premature foal with preexisting pulmonary compromise.

Metabolic and infectious causes of ileus in the foal include hypokalemia, hypocalcemia, hypoxic-ischemic bowel injury, bowel obstruction, peritonitis, enterocolitis, and endotoxemia. Hypokalemia is associated with anorexia, diarrhea, and renal loss. Hypocalcemia is associated with prematurity, decreased dietary intake, excessive bicarbonate administration, diuretic therapy, and those conditions such as asphyxia, toxemia, and sepsis that stimulate release of cortisol and catecholamines. Peripartum hypoxia results in a preferential decrease in blood flow to the gut and kidneys. Poor perfusion of the intestines leads to varying degrees of mucosal damage and decreased motility. Severely damaged bowel requires a period of gut rest to allow healing to occur before restarting oral feeds. Premature resumption of enteral feeding is associated with colic, maldigestion, diarrhea (often bloody), and translocation of intraluminal bacteria across damaged bowel wall into the bloodstream. Some of the more common causes of bowel distention in the neonate include meconium retention, intussusception, ascarid impaction, and small intestinal volvulus. Peritonitis may be associated with intraabdominal abscessation, severe enteritis or gastroduodenal ulcer disease, and generalized septicemia. The most common causes of enteritis in foals include rotavirus, *Clostridia* spp., *Salmonella* spp., and dietary changes. Endotoxemia is usually part of generalized septicemia. Chronic bowel distention, regardless of the cause, further impedes return of normal gut motility. In the foal, aerophagia, particularly in the struggling or hypoxic neonate, often results in gas distention that is not easily removed through a nasogastric tube, since gas tends to move quickly through the GI tract. Abdominal distention is also commonly observed during mechanical ventilation in the foal and as a result of overfeeding in the calf. Foals with botulism are often intolerant of enteral feeding, probably because of altered gastrointestinal motility. Use of certain milk replacers can result in bloat, colic, and diarrhea, even in the apparently healthy orphan neonate. Discontinuation of or a decrease in the amount of enteral feeding and, if possible, increased activity of the patient usually results in resolution of the problem.

Abdominal radiographs reveal gas-distended loops of small or large intestine and may identify bowel obstruction. Sonographic examination permits evaluation of bowel wall thickness, peritoneal fluid volume and echogenicity, gut patency, intramural gas accumulation, location and degree of intestinal distention, and presence or absence of motility. An abdominal sonogram should be performed to rule out the presence of an intussusception or other obstructive lesion prior to initiating any prokinetic therapy.

Management of ileus includes nasogastric decompression, cessation or reduced volume, and frequency of enteral feeds if gastric reflux is present; parenteral alimentation if enteral feeding cannot be maintained at a rate of at least 10% of BW/day; enema administration to relieve distal meconium or fecal retention; correction of any underlying electrolyte abnormalities; exercise for ambulatory foals; and judicious use of prokinetic agents. The gut atrophies without enteral feeding. Prokinetic drugs should not be used when bowel obstruction or compromised bowel integrity is suspected. Prokinetic agents that have been used include metoclopramide, bethanechol, and erythromycin. There have been anecdotal reports of small intestinal intussusception after prokinetic use in neonatal foals.

Surgical Gastrointestinal Lesions

Most types of displacement, torsion, volvulus, and entrapments that occur in the adult horse may also occur in the neonatal foal, although probably at a lower frequency. Large colon displacement, intussusception, and small intestinal volvulus have also been observed as a result of enteritis and colitis.

Surgical correction of congenital gastrointestinal defects may be attempted. Atresia ani, atresia recti, and atresia coli have been well documented in the foal, and intestinal aganglionosis has been observed in association with recessive lethal white foals, which are usually the products of mating between two overo Paint horses.[176] Acute colic, progressive abdominal distention, and lack of meconium staining following repeated enemas have been the most common findings in newborn foals with atresia coli. Barium enemas may be of use in identifying foals with a short small colon, but may also be misleading. Surgical exploration of the abdomen offers definitive diagnosis of the severity of the malformation and the possibility of correction, but the owner should be informed before surgery of the high frequency of inoperable lesions and the high failure rate following reattachment. Before any surgery is contemplated, a thorough physical examination should be performed to identify any other congenital malformations. Surgical correction of atresia ani is often successful, particularly if the atresia is limited only to a persistent membrane blocking the anus and the anal sphincter is normal. The

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prognosis for atresia coli is guarded. Poor intestinal motility, technical difficulties of attaching bowel segments that differ so much in size, anastomosis breakdown, and peritonitis following surgery are common complications. An inguinal hernia is another congenital lesion occasionally requiring surgical intervention. These hernias occur in colts and may be caused by compression during parturition. Most congenital inguinal hernias are handled conservatively since the condition is often self-limiting by the time the foal is 3 to 6 months old. Treatment includes daily manual reduction of the hernia and frequent observation to detect possible bowel strangulation. Indications for surgical intervention in foals with congenital hernias include rupture of the common vaginal tunic, persistent colic, severe edema of the prepuce and scrotum, and trauma to the skin overlying the hernial sac. Surgical hernias are difficult to reduce manually and loops of intestines are often palpable in the subcutaneous tissues of the scrotum and medial thigh. Unilateral castration is usually performed on the affected side.

Other gastrointestinal lesions in foals that may require an exploratory laparotomy include intussusception, small or large intestinal volvulus, and mechanical obstruction (e.g., food or ascarid impaction, phytobezoar, fecalith). Intussusceptions are reported in young horses less than 3 years of age. An intussusception is formed when one segment of intestine and its mesentery invaginate into the lumen of the adjacent bowel immediately aboral to it. The invaginated segment is called the *intussusceptum* and the enveloping segment is called the *intussuscipiens*. Small intestinal intussusceptions can involve the jejunum, ileum, or ileocecal junction. Other sites of obstruction include cecocecal and cecocolic junctions. Intussusceptions are most common in foals less than 6 weeks old.[123] Causes of intussusception include segmental motility differences (e.g., a hypermotile section of bowel adjacent to an atonic segment of bowel) and local changes in the bowel wall (e.g., abscessation). Causes of altered peristalsis include enteritis, heavy ascarid infestation, mesenteric arteritis, and sudden dietary changes. Changes in the bowel wall have included granulomas, papillomas, and intramural leiomyoma. *Anoplocephala perfoliata* has been associated with ileocecal intussusceptions. Clinical signs include varying degrees of discomfort depending on the site of obstruction and its duration. Abdominal pain can be severe but is often low-grade and intermittent accompanied by decreased manure production. Ultrasonography is a useful diagnostic aid. Sonographically the cross-sectional view of the intussusception reveals a target-like pattern with a thick hypoechoic rim. The outer rim is created by severe edema of the entering and returning bowel walls of the intussusceptum.

Treatment involves a surgical exploratory. Early cases can be manually reduced followed by surgical resection. Because of the ileum's tenuous blood supply and the inaccessibility of the ileocecal junction, intussusceptions involving the ileum are usually treated with a side-to-side jejunostomy or ileocecostomy. Ileoileal intussusceptions have been reported to have a better prognosis than jejunal or ileocecal intussusception. Foals that have multiple sites of intussusception have a poor prognosis.

Volvulus may involve the small or large intestines. Small intestinal volvulus is the most common, especially among foals between 2 and 4 months of age. Signs include abdominal distention, gastric reflux, persistent tachycardia, severe pain, and sonographic evidence of uniform, severe bowel distention with bowel wall edema (>3 to 4 mm) and absence of motility. As expected, survival is poorer following correction of strangulating versus non-strangulating lesions. Strangulating lesions of the small intestines have a poor survival compared with large intestinal lesions and a higher incidence of fatal complications. Parasitic migration and abrupt dietary changes are among conditions thought to predispose to volvulus development.

Surgical colic in foals carries a poorer long-term prognosis than in adult horses. One study examined the survival rate among 67 foals less than 150 days of age undergoing colic surgery.[286] The most common lesions requiring a celiotomy were small colon impaction, large colon impaction, jejunal volvulus, and ascarid impaction. A poor prognosis was associated with strangulating lesions. Foals less than 14 days of age experienced more early postoperative complications and suffered poor long-term survival because of adhesion formation. Only 25% of foals less than 14 days of age survived in the short term compared with 71% out of a total of foals older than 15 days of age. Another study examined the outcome among 119 young horses less than 1 year of age that underwent exploratory celiotomy.[287] Among all foals the most common cause for surgery was small intestinal strangulation. Uroperitoneum and meconium impaction were the most common conditions in neonatal foals and intussusception and enteritis were more common among older foals. Significant elevations in PCV (37% to 54%), heart rate (80 to 134 bpm), nucleated cell counts and TP in peritoneal fluid (3.1 to $32.8 \times 10^3/\mu L$, 2.9 to 4.9 g/L), and rectal temperature (38.2° to 39.2° C) were observed in non-survivors compared with survivors. Non-survivors had significantly decreased serum bicarbonate, chloride, sodium, and venous pH values. Thirty-three percent of foals surviving surgery had evidence of intraabdominal adhesions.

Necrotizing Enterocolitis

NEC is a syndrome of acute intestinal necrosis that has been described in equine neonates.[288] The causes of NEC are not well defined, but predisposing factors include ischemic hypoxic gut injury, the presence of intraluminal bacteria, and enteral feeding. Following gastrointestinal ischemia, mucosal cell metabolism diminishes and the protective mucous layer is lost. This allows enzymes to break down the mucosal barrier, and intraluminal bacteria can then invade and multiply within the bowel wall. Enteral feeding provides substrate for the bacteria. Pneumatosis intestinalis develops, and the bowel frequently ruptures. Abdominal signs include abdominal distention, tenderness, ileus, and ascites. The condition may appear as a fulminant, rapidly progressive disease, or progress at a much slower pace.[154] One of the affected equine neonates was premature and was undergoing treatment for respiratory distress when the abdominal crisis occurred. The other was a term foal that had experienced a prolonged delivery and was presented at 24 hours of age for weakness and abdominal pain. Abdominal distention and abdominal pain, followed by ventral colon rupture, were noted in both foals.[288]

Clinical signs associated with varying degrees of hypoxic-ischemic gut injury include ileus, gastric reflux, colic, lethargy, abdominal distention, and diarrhea. Reflux and feces may be positive for blood. Generalized sepsis often accompanies NEC; NEC should be distinguished from intestinal ileus caused by other neonatal diseases, other surgical GI lesions, bacterial or viral enterocolitis, and intolerance to a milk diet. Although no single laboratory test is specific for NEC, the abdominal radiograph often reveals pneumatosis cystoides intestinalis, bowel wall edema, and an abnormal gas pattern consistent with ileus. Ultrasonography may reveal intramural gas accumulation (Fig. 17-15). If intestinal perforation has occurred, pneumoperitoneum and septic peritonitis may also be noted.[154,288] Intestinal perforation is associated with a poor prognosis.

Hemoperitoneum

Hemoperitoneum is a relatively uncommon cause of abdominal distention in the large animal neonate. The most common structures responsible for the hemorrhage are the umbilical vessels and rupture of the liver or spleen as a result of trauma. Occasionally other structures such as a ruptured granulosa cell tumor may bleed.[187] Depending on the cause and severity of the hemorrhage, clinical signs relating to hypovolemia and anemia may be mild or severe and appear shortly after birth or in the older foal. Diagnosis of hemoperitoneum is based on the retrieval of free-flowing blood on peritoneal tap and the detection of free fluid in the abdomen. Ultrasound examination may be of benefit in detecting the source of the bleeding. Of critical importance, regardless of the source of the hemorrhage, is prevention of hypovolemic shock, and intensive patient monitoring and intervention are often indicated. Whole blood replacement may be necessary. If an internally bleeding animal with an unstable cardiovascular system is

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FIG. 17-15 An ultrasound image demonstrating intramural gas in a foal with necrotizing enterocolitis.

rushed to surgery without prior stabilization, profound shock may occur, and a poor outcome usually results.

Umbilical Problems

John E. Madigan

Patent urachus is a persistence after birth of the tubular connection between the bladder and umbilicus. The urachus drains the bladder into the allantoic sac during gestation. Urine flow should gradually change, with some urine entering the amniotic sac through the urethra in later gestation. At birth, with umbilical cord rupture, the urachus should be closed, and urine should be voided through the urethra. Foals with a patent urachus may dribble urine from the urachus during or after urination or may simply present with a constantly wet umbilical stump.

A variety of causes have been suggested for failure of the urachus to close and completely involute. Early severance or ligation of the umbilical cord, inflammation, infection, and excessive physical handling of the neonate may contribute. Rather than being the original cause for hospital admission, patent urachus develops as a complication of hospitalization in a significant percentage of foals in neonatal intensive care. Weakness of abdominal musculature may contribute to the problem in sick foals.

Ultrasound may assist the diagnosis and determine the involvement of umbilical arteries or vein. Moist hairs around the umbilicus and visualization of fluid coming from the navel are diagnostic. Ultrasound examination of the internal structures of the umbilicus is strongly recommended.

Congenital patent urachus caused by excessive torsion on the umbilical cord in utero occurs in 6% of normal foals.[289] The obstruction of the urachus caused by the torsion causes retention of urine in the bladder and overdistends the proximal urachus, which interferes with normal involution.[289] Infection of umbilical structures or the urachus itself may result in inflammation and failure to completely involute. In a review of 16 cases of umbilical cord infections in foals, 13 had patent urachus.[290] The majority of these foals had acquired patent urachus after birth, with the youngest age of onset 3 days and the mean age of onset 12 days. Excessive manipulation and improper lifting of the foal's abdomen in the presence of high urethral sphincter tone may force urine within the bladder into the involuting urachus.

Therapy consists of either conservative management through monitoring or medical treatment for infection or cauterization of the urachus using silver nitrate sticks applied into the urachus. Persistence of urine dribbling despite cauterization, the detection of involvement of other umbilical structures through ultrasound, and a rent in the urachus that produces subcutaneous swelling are indications for surgery. Use of general anesthesia and removal of the entire urachus to the tip of the bladder are performed in foals with an infected or enlarged urachus. Associated arteries and veins should be ligated and removed if they are infected or necrotic. Merely ligating the exterior stump can trap organisms and cause infection. Complications are uncommon but may include bladder necrosis and uroperitoneum caused by extension of infection and inflammation of the urachus.

Omphalitis is inflammation of umbilical structures that may include the umbilical arteries, umbilical vein, urachus, or tissues immediately surrounding the umbilicus. The umbilicus consists of three types of structures and undergoes functional and anatomic changes at birth. Two umbilical arteries connect internal iliac arteries to the placenta. These later regress and become the round ligaments of the bladder. One umbilical vein connecting the placenta to the liver and porta cava regresses to become the round ligament of the liver within the falciform ligament. The urachus connects the fetal bladder to the allantoic cavity. Umbilical abscess or infection of any of the three components of the umbilicus may produce local infection or be a source of bacteremia. The source of infection is most commonly the external environment, coupled with failure of passive transfer. Omphalophlebitis may extend the length of the umbilical vein into the liver and result in liver abscessation.

When the umbilicus is enlarged and draining purulent material, infection is easily noted. In other cases the umbilicus may be dry and larger in diameter than expected. In addition, neonates may have a completely normal-appearing, dry external navel and be severely ill from infection of the urachus, umbilical arteries, or vein. In a septic neonate without external signs of infection, involvement of the umbilicus can be difficult to determine. The presence of pain on palpation of the umbilicus indicates inflammation. Ultrasound aids in the detection of involvement of urachus or arteries and vein. The umbilical area of neonates less than 20 days of age with fever of unknown origin should be scanned.

Overt signs of infection are heat, swelling, purulent discharge, or pain. Concurrent signs of systemic infection such as joint infection, pneumonia, diarrhea, meningitis, or uveitis may be noted. Infection in more than one umbilical vessel in the neonate is common, and urachal involvement is frequent. Umbilical abscessation that is walled off and does not involve deeper structures is a less severe problem and may be treated with drainage without surgical removal of the entire umbilicus. The depth of involvement may be determined by standing behind the neonate and pressing the hands together above the umbilicus to detect internal masses and painful areas.

Early treatment with antibiotics and supportive care as described for the septic foal may allow resolution before development of abscessation and distention of the urachus or the umbilical arteries and vein. Established infection, which may occur within 24 hours, may necessitate surgical removal of involved structures in addition to medical therapy.[290] When omphalophlebitis extends into the liver, the umbilical vein may be marsupialized to facilitate drainage and flushing. The prognosis is very good when adequate passive transfer of colostral immunoglobulins has occurred and when joints or other structures are not involved. Sequelae such as renal abscessation, joint or bone infection, peritonitis, and other complications described for septicemia may develop if therapy is started too late or discontinued prematurely.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 18

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The Peripartum Ruminant

JOHN K. HOUSE, *Consulting Editor*

Recent studies in Denmark, The Netherlands, North America, and Sweden indicate that the prevalence of bovine perinatal mortality is increasing, particularly in Holstein primiparae.[1] The peripartum period is a high-risk period for the fetus and dam. Approximately 5% to 10% of the annual calf crop and 15% to 20% of the annual lamb crop in the United States dies prior to weaning.[2-4] Between 50% and 70% of neonatal mortality occurs in the first 3 days of life with dystocia, starvation, and hypothermia responsible for 50% to 60% of these losses.[3,5] The incidence of dystocia is particularly high in Holsteins with reports of 50% of heifers and 30% of cows requiring calving assistance.[6] The risk of neonatal morbidity and mortality is largely influenced by sire selection (calving ease), maternal management, and subsequently maternal health during the peripartum period.

Late-Term Complications of Gestation

Uterine torsion, vaginal prolapse, hydrops allantois, hydrops amnii, and metabolic disorders are disorders of pregnancy and the peripartum period that negatively impact on the health of the dam and the fetus during late gestation. Over the past 10 years, there has also been increasing application of advanced reproductive technologies with the production of in vitro and cloned embryos. The initial application of these methods has been associated with a higher incidence of complications during pregnancy and neonatal mortality.

Uterine Torsion

Uterine torsion is more common in cattle than other domestic species. The exact etiology is unclear, with most occurring during late first-stage or early second-stage labor.[7] Proposed risk factors include poor maternal muscle tone, strong fetal movement, and reduced rumen fill. Retrospective studies have reported no significant seasonal affect but a higher incidence in Brown Swiss cows and a lower risk in Hereford, Angus, and Jersey cows compared with Holstein-Friesians.[8] Calf birth weight is typically above average and a greater proportion of fetuses are male (63%).[8] The incidence is also significantly higher in cows compared with heifers.[7]

Clinical signs associated with uterine torsions include fever, tachycardia, tachypnea, straining, anorexia, and vaginal discharge.[8] The diagnosis of uterine torsion is based on a history of advanced pregnancy and the presenting clinical signs. On transrectal palpation, the orientation of the broad ligaments is distinctly altered; depending on whether the torsion is to the left or the right, the respective broad ligament is pulled tightly across the uterus.[9] Approximately 60% of torsions involve the vagina, and spiral folds can be palpated per vagina.[9] Most torsions are to the left (counterclockwise); in general the uterus rolls toward and over the nongravid horn (approximately 60% of all pregnancies in the cow are in the right horn).[9] Torsions between 45 and 90 degrees are uncommon; 20% are 90 to 180 degrees, 57% are 180 to 270 degrees, and 22% are 270 to 360 degrees.[8] With severe torsion, circulation is compromised. Treatment involves correction of the torsion and delivery of the calf. In a retrospective study of 164 cases, vaginal delivery was possible after manual correction (20%) or rolling of the cow (18%). Cesarean section was performed immediately in 35% of the cases, after failed detorsion attempts in 7% and because of failure of the cervix to dilate following successful correction of the torsion in 20%. When manually manipulating the fetus per vagina, it sometimes helps to have a person assist by pushing on the calf externally. Fetal survival rate is generally low, with fetal death often occurring prior to presentation if there has been delayed recognition of parturition.

Vaginal Prolapse

The primary predisposition to cervicovaginal prolapse in cattle is elevated plasma estrogen concentrations during late gestation.[9] The higher prevalence in certain beef breeds implies a genetic predisposition, with Bos indicus, Herefords, Charolais, Limousin, and Shorthorns affected more frequently than other breeds.[10-12] Other factors that contribute to the risk of vaginal prolapse include increased intraabdominal pressure in late pregnancy, obesity, and poor vaginal conformation. The pathogenesis and development of vaginal prolapses is progressive; it starts with the exposure of some of the vaginal mucous membrane. The prolapsed mass moves in and out as the cow gets up and lies down. Exposed mucosa dries out and becomes irritated, leading to straining and further prolapse. The prolapsed tissues become edematous, leading to circulatory impairment and swelling. Ultimately the cervix and occasionally the bladder may become involved.[9] The objective of treatment in the case of pregnant animals is to replace and retain the vagina within the pelvic canal and to deliver a live calf. Numerous treatment options are described for vaginal and cervical eversions.[12] These methods include suturing the vulva (caslick, Bruhners), vaginopexy (Minchef procedure), or cervicopexy (Winkler procedure). Close observation of the cow for signs of impending parturition is required following suture of the vulva. Failure to release the sutures prior to parturition can lead to severe laceration of the vulva and potentially the death of the calf. If the patient is close to parturition, induction is recommended to expedite the process and prevent recurrence prior to parturition. Since vaginal prolapse is likely to recur during the next pregnancy, it is recommended that the cow be culled when the calf is weaned.

Ringwomb

Ringwomb, or incomplete dilation of the cervix, causes sporadic dystocia, mainly in multiparous ewes bearing multiple fetuses. It is most commonly observed in sheep and may be heritable in some instances.[13] Ringwomb has no predisposition associated with breed, age, or body condition score, but it is associated with a significantly higher lambing percentage.[13] Correction with gentle manual stretching can be attempted; the use of PGE 2, administered as an intracervical gel in the treatment of ringwomb in ewes, is not effective at causing dilation of the cervix.[14] Because of the significant risk of tearing, a cesarean delivery is often required.[15] Ewes with diseases that cause abortion as a result of infectious agents may exhibit signs similar to ringwomb, as can pregnancy toxemia, consumption of

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poisonous plants, consumption of estrogenic plants, and lasalocid toxicity.[15]

Early Dilation Syndrome

Early dilation syndrome is a condition of sheep that is similar to but considered separate from ringwomb. In early dilation syndrome, incomplete dilation of the cervix occurs approximately 7 to 14 days before term. The ewe has little or no udder development or a sudden overnight blooming of the udder and placental membranes protruding when presented. The cervix usually can be dilated by hand, but the lambs, although born alive, are not viable. The syndrome occurs most frequently in ewe lambs and first-lambing 2-year-olds, but occasionally in older ewes. Affected flocks can have over 30% morbidity. The syndrome occurs in all breeds and in all flock management situations. No common link has been found from nutritional, physiologic, toxicologic, or infectious disease investigations.[15]

Hydropic Conditions

Fetal loss associated with abnormal placentation occurs sporadically and is reflected by alterations in volume and composition of allantoic and amniotic fluid. In a study of 60 cases of bovine hydrops, 88% were hydrallantois, 5% hydramnios, and 7% a combination of both.[16] Hydrallantois is often associated with disease of the uterus and hydramnios with genetic or congenital defects of the fetus (e.g., Dexter cattle with bulldog calves, Angus calves with osteopetrosis, Guernsey calves with pituitary hypoplasia or pituitary aplasia).[17]

Hydrops Allantois (Hydrallantois)

Hydrops allantois is a sporadic condition of cattle in which progressive excessive accumulation of allantoic fluid occurs. Accumulation of allantoic fluid from mid gestation is associated with placental dysfunction.[9] Placental dysfunction is characterized by a reduced number of placentomes (normal 75 to 100) and the development of more primitive villous placentation.[18] An increased incidence of hydrops allantois has been reported with pregnancies derived from in vitro fertilization (IVF)–produced embryos. In a comparative study of IVF and artificial insemination (AI)–derived pregnancies, the percentage of cows with hydroallantois was 1.8% and 0.07%, respectively.[19] A herd outbreak of hydrops allantois has also been associated with severe nutritional deficiency.[9] Allantoic fluid volume may exceed 100 L (normal 8 to 15 L near term), leading to rapid abdominal enlargement; rectal examination reveals tight distention of the uterus. The fetus and placentomes are not palpable due to the tightness of the uterine wall. Affected cows become anorectic, leading to dehydration, constipation, and eventually recumbency.

The concentration of sodium and chloride in allantoic fluid of cattle during the last 12 weeks of gestation is normally low (Na = 52 ± 20 mEq/L and Cl = 17 ± 11 mEq/L) and the concentration of creatine high (1224 ± 458 µg/mL).[20] With hydrallantois, allantoic fluid sodium and chloride concentrations rise toward extracellular fluid concentrations (Na = 116 ± 13 mEq/L and Cl = 81 ± 12 mEq/L) and allantoic creatine concentration decreases (193 ± 73 mEq/L).[20] Normal amniotic fluid has electrolyte concentrations similar to those of plasma (Na = 132 ± 7 mEq/L and Cl = 115 ± 8 mEq/L) and a lower creatine concentration than allantoic fluid (70 ± 26 µg/mL).[20] Cows with hydrallantois are also often hyponatremic and hyperglycemic.[16,21]

Because of the poor prognosis, salvage slaughter is generally recommended. Parturition can be induced if the cow is reasonably close to term and is recommended for the salvage of the calf. Attempts at medical management of affected cows include slow decompression and supportive fluid therapy. The grossly distended uterus is slow to involute and prone to severe metritis. The prognosis for future fertility is guarded.

Hydrops Amnii (Hydramnios)

Hydramnios is rare, accounting for 5% to 10% of uterine dropsy cases.[22] It has been associated with a genetic (autosomal recessive) or congenitally defective fetus in which swallowing is impaired, and the amount of amniotic fluid gradually increases over several months.[22]

TABLE 18-1

Differential Diagnosis between Hydrallantois and Hydramnios in Cattle[9]

Characteristic	Hydrallantois	Hydramnios
Prevalence	85%-95%	5%-15%
Rate of development	Rapid (within 1 month)	Slow over several months
Shape of abdomen	Round and tense	Piriform, not tense
Transrectal detection of placentomes and fetus	Nonpalpable (tight uterus)	Palpable
Gross characteristics of fluid	Watery, clear, amber-colored transudate	Viscid, may contain meconium
Fetus	Small, normal	Malformed
Placenta	Adventitious	Normal
Refilling after trocarization	Rapid	Does not occur

From Drost M. 2007. Complications during gestation in the cow. Theriogenology 68:487.

It may affect only one of twin fetuses.[9] Normal amniotic fluid volume at parturition is about 4 to 8 L; cattle with hydrops amnii may accumulate 20 to 100 L of amniotic fluid.[23] The slowly progressive accumulation of fluid during the latter half of gestation means that the abdominal muscles become stretched and the cow develops the typical "pear-shaped" abdomen. In contrast to the situation with hydrallantois, placentomes and often the fetus are palpable per rectum. The prognosis for the life and future fertility of cattle that have hydramnios is good.[23] The fetus itself is invariably defective and will not be viable. If the owner elects to keep the cow, the genetic implications should be considered. Clinical features that distinguish hydrops amnii and hydrops allantois are presented in Table 18-1.

Abnormal Offspring Syndrome

The transfer of bovine embryos produced and manipulated in vitro results in abnormalities in some conceptuses, fetuses, placentas, and offspring.[24,25] The term *abnormal offspring syndrome* is used to describe the range of abnormalities observed.[26] The exact etiology of the syndrome is uncertain, although developmental abnormalities of the fetus, placenta, and offspring have been predominantly attributed to the presence of serum in the culture medium.[27] In utero manifestations include prolonged gestation, abnormal placental development (placentomegaly, hydroallantois, and edematous placentomes in reduced numbers), and suboptimal embryonic and fetal survival.[18,28] Increased birth weight and incidence of dystocia, congenital deformities, and perinatal mortality are neonatal manifestations of this syndrome. Respiratory disease is often a limiting factor in the survival of cloned calves during the neonatal period.[29] Possible causes of compromised respiratory function include hypoventilation, ventilation perfusion mismatch, right-to-left shunt resulting from persistent fetal circulation, and respiratory distress syndrome resulting from inadequate surfactant production. Nasal insufflation at birth is recommended to support the respiratory function of cloned calves.[29]

Maternal Nutrition

Reduced fetal viability often reflects mismanagement of maternal nutrition during the last trimester of pregnancy and/or during the prepartum and peripartum period. Maintenance of adequate nutrition throughout pregnancy is essential to provide for the growing fetus and to maintain a healthy dam capable of delivering and nursing the fetus. Pregnancy toxemia, hypocalcaemia, protein energy malnutrition, micronutrient deficiencies, and obesity may all impair the health of the fetus directly, or else indirectly by affecting the health or capacity of the dam to deliver the fetus.

Underfeeding of energy (40% to 70% of requirements)[30] or protein (65% of requirements)[31] during late gestation in beef cattle produces calves that are less able to generate heat to maintain body temperature

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BOX 18-1

Common Causes of Stillbirth and Perinatal Death in Ruminants[2,3,145,146]

Dystocia

Cold stress

Pneumonia (lambs)

Nutrition

Energy deficiency
Protein deficiency
Pregnancy toxemia
Mineral
- Copper excess/deficiency
- Iron excess
- Iodine excess/deficiency
- Selenium deficiency

Vitamin A deficiency

Infections

Viruses
- Infectious bovine rhinotracheitis virus
- Bovine virus diarrhea
- Border disease
- Bluetongue
- Akabane virus
- Cache Valley virus

Bacteria
- *Histophilus somni* (formerly *Haemophilus somnus*)
- *Brucella abortus*
- *Leptospirosis* spp.
- *Clostridium perfringens* type C and D
- *Streptococcus* spp.
- *Campylobacter* spp.
- *Listeria monocytogenes*
- *Yersinia pseudotuberculosis*
- *Histophilus ovis*
- *Brucella ovis*
- *Campylobacter fetus* var. *fetus*

Protozoa
- Neospora
- *Toxoplasma gondii*
- *Tritrichomonas foetus*

Fungus
- *Aspergillus* spp.

Rickettsia
- *Chlamydia* spp.
- *Coxiella burnetii*

Trauma

Obstetric
Castration, tail docking

Toxins

Plant toxins
- Monterey pine *(Pinus radiata)*
- Perennial broomweed *(Gutierrezia microcephala)*
- Locoweed *(Astragalus lentiginosus)*
- Lupines *(Lupinus sericeus* and *L. caudatus)*
- Poison hemlock *(Conium maculatum)*

Chemical toxins
Nitrate

Genetic

Epitheliogenesis imperfecta
Cardiac abnormalities (ventricular septal defects, tetralogy of Fallot)
Internal hydrocephalus
Cerebellar hypoplasia
Arthrogryposis/cleft palate
α, β Mannosidosis
Spider lamb syndrome
Bovine citrullinemia
Bovine maple syrup urine disease

after birth. This effect was observed despite no significant difference in birth weight.[30,31] The fetal response to growth-restrictive environmental conditions is to partition nutrients toward the development of organs essential to life, such as the brain, at the expense of less vital organs and tissues.[32,33] In humans, the repartitioning of nutrients to support fetal development has been demonstrated to have long-term effects on postnatal growth and metabolism, apparent as an increased propensity to develop insulin resistance, high blood pressure, more rapid weight gain, and increased adiposity.[34] Similarly, nutrient restriction during gestation has been demonstrated to alter postnatal glucose metabolism in calves.[35] The consequences of overnutrition during gestation on the developing fetus are less clear. A number of overfeeding trials have resulted in increased birth weight, whereas other studies have not.[36,37] Maternal consequences include deposition of fat in the pelvis that increases the risk of dystocia and subsequently fetal compromise.[38]

For high-producing dairy cows, good nutritional and cow management during the transition period is pivotal for maintaining cow health. Hypocalcemia and negative energy balance contribute to the risk of dystocia and subsequently the risk of neonatal morbidity and mortality.[39] Recently, there has been a paradigm shift in the thinking regarding the nutrition of nonlactating cows prior to calving. Previously, the focus had been on increasing the amount of energy in the ration fed to cows during the last 3 to 4 weeks prior to calving to meet the increasing energy needs associated with pregnancy in the face of the cows' declining dry matter intake.[40] Paradoxically, overfeeding energy during the dry period has been found to contribute to negative energy balance postpartum and an increased incidence of disease in the peripartum period.[41] This phenomenon appears to be associated with increased insulin resistance, similar to type 2 diabetes. The current recommendation is to feed cows throughout the nonlactating period a ration that meets but does not exceed caloric needs. Straw is added to the ration to promote rumen health and to prevent overeating.[39]

In regard to trace minerals, selenium and copper deficiency may contribute to neonatal morbidity and mortality. Copper deficiency has been associated with impaired fertility, weak calves, and high calf mortality.[42] In a larger Canadian study, myopathy and cardiomyopathy were common findings in stillborn and neonatal mortality, suggesting the possible contribution of nutritional myopathy.[43]

Investigation of perinatal morbidity and mortality should begin with assessment of maternal management. Some of the more common causes of stillbirth and perinatal mortality are listed in Box 18-1.

Environmental Management

Environmental stress prior to or around the time of parturition may also compromise the fetus or neonate. Heat stress affects fetal viability by impeding calf growth in the last trimester of pregnancy[44] and by depressing colostral quality[45] and immunoglobulin transfer.[46] Uterine blood flow and placental mass are reduced and endocrine profiles altered when cattle are heat stressed during the last trimester of pregnancy. Heat stress during the last 3 weeks of pregnancy lowers dry matter intake, contributing to a negative energy balance at this time and promoting mobilization of body fat and ketogenesis. Transfer of immunoglobulins to colostrum is impaired and the concentration of protein, casein, lactalbumin, fat, and lactose in colostrum reduced.[45] Cold, windy, and wet conditions also adversely affect calf survival. The magnitude of the effect of climate on neonatal survival

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depends on the age of the dam, the sex and size of the calf, and the incidence of dystocia in the herd.[47] Cold stress sufficient to cause hypothermia in calves leads to subcutaneous hemorrhages and delayed absorption of colostral immunoglobulins.[48]

ASSESSMENT OF FETAL VIABILITY. Fetal viability is rarely evaluated during the prepartum period in production animals but is a serious consideration when the prepartum dam is diseased or debilitated. Assessment of fetal viability is diagnostically challenging, but a number of methods are available to evaluate the fetus and fetal environment. During the physical examination of cattle, uterine blood flow, uterine tone, and presence of a vaginal discharge may be evaluated via rectal palpation and a vaginal speculum examination. Reduced fremitus in the uterine arteries and increased uterine tone may be appreciated by rectal palpation following fetal death. Abdominal ultrasound is useful for examining the uterus, placenta, and fetuses of small ruminants.[49] When the gestational age of the fetus is known, fetal growth retardation can be detected by using ultrasound by measuring abdominal circumference as well as femur and tibial length.[50] Examination of the fetus may detect gross congenital abnormalities, and ultrasound of the fetal chest allows visualization of a beating heart and determination of fetal heart rate. The normal heart rate of full-term lambs is 108 to 126 beats/min.[51] After fetal death, the following may be observed: absence of fetal heartbeat, thickening of the uterine wall, increased echogenicity of chorioallantoic and amniotic fluid, altered fetal posture and definition, altered contour of the amnion, and reduced definition and ultimately reduced size of the caruncles.

The uterus and placenta of cattle can be examined by transrectal ultrasound, but examination of the fetal calf via transrectal or transabdominal ultrasound is often compromised by limited access. Fortnightly ultrasound of the uterus and placenta of recipient cows carrying cloned calves is conducted to detect evidence of hydroallantois and placental edema in these high-risk pregnancies.[52] The absence of fetal heartbeat is a specific sign of fetal death. The presence of large quantities of echoic particles in uterine fluids is also a sign of fetal distress or death. Fetal hyperactivity or inactivity over a 30-minute period of examination suggests fetal compromise.[53] Repeated examinations are required since hyperactivity or sleeping periods have been infrequently observed in other species and the criteria for this classification are based on limited observations in cattle.[54] Measuring the heart rate of fetal calves is more difficult than of small ruminants but can be achieved via transabdominal Doppler using a 1.5-MHz probe. The normal heart rate of full-term calves is 90 to 125 beats/min.[55] In human medicine, fetal heart rate is used as a measure of fetal viability; fetal heart rate accelerations associated with fetal movement are considered a sign of fetal well-being, and persistent bradycardia or tachycardia are considered a sign of fetal stress.[56] Normal fetal heart rate patterns of ruminants need to be characterized in more detail before fetal heart rate measurements are used for prenatal clinical assessment of ruminant fetal well-being.[54,57]

Estrone sulfate is a marker of a viable fetoplacental unit and has been used to assess fetal viability in cattle.[58] Estrogen synthesized by embryonic tissue is converted to estrone sulfate by the endometrium, which contains the enzyme sulfotransferase. Estrone sulfate assays can be used to diagnose pregnancy in small ruminants after 50 days[59] and in cattle after 100 days.[60] Estrone sulfate may be measured in plasma or milk[44,60]; baseline values are low after fetal loss, regardless of the stage of pregnancy. Compromise of the fetoplacental unit reduces estrone sulfate production. In a study of the effects of heat stress on pregnant cattle, plasma estrone sulfate concentrations were significantly lower throughout pregnancy in cows that gave birth to low-birth-weight calves.[44] Plasma concentrations of estrone sulfate rise slowly during the second trimester of pregnancy from 0.74 ng/mL to 3.66 ng/mL between day 90 and day 210 of pregnancy. The last trimester of pregnancy is associated with a rapid rise in the concentration of estrone sulfate to 13.36 ng/mL around 10 days prior to parturition.[61]

In human medicine, diagnosis of surfactant deficiency is based on the ratio of two phospholipids in amniotic fluid: lecithin (L) and sphingomyelin (S). If the L/S ratio is greater than 2.0, the surfactant system is mature and respiratory distress syndrome is rare.[62] The L/S ratio in amniotic fluid collected from cattle may also be used to assess surfactant system maturity,[63] thus providing a measure of readiness for birth, but is rarely used in clinical veterinary medicine. Crude surfactant harvested from bovine lungs at a slaughterhouse has been used intratracheally with calves that appeared to be in respiratory distress shortly after birth.[64]

Induction of Parturition

Manipulation of parturition may be considered for maternal, fetal, or management reasons. Fetal viability following induced parturition is variable among species. The viability of calves induced within 14 days of anticipated calving date is good[65]; viability of lambs and kids induced greater than 5 days prior to anticipated parturition date is poor.[17] Absorption of colostral immunoglobulins by premature calves is reduced, so colostral transfer should be monitored closely in induced neonates.[66] Induction of parturition or cesarean section is often necessary to prevent mortality of small ruminants with pregnancy toxemia.[67] Fetal viability is often improved by induction of parturition with dexamethasone; however, delivery of the fetuses via cesarean section is often necessary due to the debilitated state of the dam. Secretion of glucocorticoid hormones from the adrenal cortex increases markedly during the final days of gestation. The prenatal increase in fetal glucocorticoid secretion plays an important role in the cascade of endocrine events leading to parturition, and it stimulates maturational events in the lungs, liver, kidney, and gastrointestinal tract in preparation for postnatal life.[68]

Steroids stimulate production of surfactant phospholipids by alveolar type II cells, enhance the expression of surfactant-associated proteins, reduce microvascular permeability, and accelerate overall structural maturation of the lungs.[69] Administration of flumethasone (10 mg) or dinoprost (25 mg) to pregnant cows 30 hours prior to elective cesarean section increases the lecithin-to-sphingomyelin ratio, thus improving lung function and reducing complications associated with respiratory acidosis in the calf.[70] Induction of parturition has been used to reduce the incidence of dystocia in herds or breeds experiencing a high incidence of dystocia associated with fetomaternal disproportion.[71] Large birth weights are strongly correlated with fetomaternal disproportion.[72,73] Induction of parturition within 14 days of anticipated calving date is associated with good calf viability and a 3.2-kg reduction in birth weight of beef calves.[65]

Exogenous glucocorticoids, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), or a combination may be used to induce parturition in cattle (dexamethasone 20 to 30 mg alone or in combination with 25 mg of $PGF_{2\alpha}$) or in sheep and goats (10 to 20 mg dexamethasone and/or 15 mg $PGF_{2\alpha}$).[17] Glucocorticoids are more effective than prostaglandin for inducing parturition in sheep.[74] A lower incidence of dystocia and higher viability of calves has been reported in cattle induced with glucocorticoids compared with cows induced with prostaglandin.[75] Cows treated with dexamethasone or prostaglandin within 14 days of the anticipated calving date usually calve within 72 hours of treatment.[65] Combination of dexamethasone with prostaglandin increases the efficacy and reduces the interval to parturition (36 hours).[76,77] Retention of fetal membranes is a common complication of induced parturition in cattle.[78] Induction of parturition with dexamethasone causes a failure of immune-assisted detachment of the fetal membranes and the accompanying release of chemotactic factors.[79] Retention of fetal membranes may be associated with reduced first-service conception and subsequent pregnancy rates.[80] Treatment of cows with prostaglandin at calving was reported to reduce the incidence of retained fetal membranes,[81] but subsequent studies failed to support this.[76,82] Induction of cattle by administration of 25 mg of triamcinolone (Opticortinol) at day 270 followed by treatment with dexamethasone and prostaglandin 6 days later appears to reduce the incidence of retained fetal membranes associated with induction.[78,83]

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TABLE 18-2

Arterial and Venous Blood Gas Values for Newborn Calves

	Parameters					
	Calf Age	pH	Po_2	Pco_2	HCO_3^-	Base Excess
Venous*	1 hour	7.219 (0.05)	NA	41.0 (5.9)	24.2 (2.7)	-2.9 (3.2)
Arterial†	1 hour	7.3 (0.05)	58.43 (11.61)	50.40 (5.27)	23.52 (2.78)	NA

*Blood taken from the jugular vein immediately postpartum.[97]

†Blood was taken from the brachial artery while the calf was in lateral recumbency (N = 30).[147]

NA, Not available.

Values represent mean with standard deviation in parentheses.

Where calving induction is used to align calving patterns to pasture availability, cows are induced to calve at around 7 months' gestation. Induced cows have increased rates of mastitis, metabolic disease, and retained placenta[84,85] and have reduced milk production in the lactation of treatment.[86,87] Calves born to cows induced at 7 months' gestation are often stillborn, die, or are subject to euthanasia shortly after birth because they are too weak or suffer from other neonatal diseases.[88,89]

Perinatal Adaptation

At birth, the fetus must successfully make a series of structural and physiologic changes to survive. Perinatal mortality is often attributable to cardiovascular, pulmonary, thermoregulatory, or metabolic/physiologic abnormalities. Dystocia and severe birth asphyxia compromise physiologic transitions, increasing the risk of neonatal mortality. Compromised neonates that survive the birth process are less likely to consume adequate colostrum and are subsequently more likely to die of hypothermia and infectious diseases.

The placenta functions as the respiratory organ of the developing fetus; efficiency of oxygen transfer to the fetus is increased by the high oxygen affinity of fetal versus adult hemoglobin.[90] In utero, the potential spaces of alveoli and the tracheobronchial tree are distended with fluid secreted by pulmonary tissue.[91] Oxygenated blood is delivered to the fetus via the umbilical vein, which anastomoses with the portal vein near the liver, and approximately two thirds of the blood flow is shunted via the ductus venosus directly into the caudal vena cava.[92] The caudal vena cava drains into the right atrium, where over 50% of the volume shunts directly into the left atrium via the foramen ovale.[92] The relatively hypoxic in utero environment causes constriction of pulmonary vessels and dilation of the ductus arteriosus.[92] Because pulmonary arterial resistance is higher than systemic arterial resistance, nearly 70% of pulmonary artery flow is shunted via the ductus arteriosus into the aorta, with the remainder perfusing the lung.[93] Left ventricular output is distributed to the systemic circulation via the aorta. The two umbilical arteries arise from the aorta in the region of the last lumbar vertebra to carry predominantly venous blood back to the placenta via the umbilicus.

At birth, some of the lung fluid is evacuated through the trachea during spontaneous delivery.[94] When the umbilicus ruptures, asphyxia triggers reflex gasping, respiratory movements, and increased peripheral vascular resistance.[93] The majority of lung fluid is absorbed through alveolar walls in the initial stages of ventilation.[94] This mechanism is prompted by activation of adrenaline-mediated α-adrenergic receptors in the pulmonary epithelium.[95] The rapidity of lung fluid absorption by the body is optimized at thoracic pressures between 35 and 40 cm H_2O.[94] Pulmonary ventilation reduces pulmonary vascular resistance, promoting perfusion of the ventilated alveolar tissue.[92] The increased oxygen saturation of blood stimulates closure of the ductus arteriosus within 4 to 5 minutes of birth.[93] The foramen ovale functionally closes within 5 to 20 minutes of birth when increased pulmonary venous return raises blood pressure in the left atrium, reversing the right-to-left shunt.[93] The septum secundum, a thin fold of tissue that lies in close apposition to the foramen, acts as a valve to close the opening. Healthy calves have mean pulmonary arterial pressures ranging from 40 to 82 mm Hg immediately after birth, declining to 22 to 25 mm Hg by 2 weeks of age.[96] Systemic arterial pressure is approximately 100 mm Hg and arterial saturation greater than 90%.[92] Transient mild metabolic and respiratory acidosis are observed following rupture of the umbilical cord as a result of anaerobic glycolysis in poorly perfused tissues during the transition between placental oxygen delivery and establishment of respiratory function. The mild acidosis is normally corrected within 1 to 4 hours of birth.[97] Anatomic closure of the foramen ovale and ductus arteriosus may take several weeks.[93] Normal blood gas values for the calf during the immediate postpartum period are presented in Table 18-2.

Dystocia is commonly associated with prolonged hypoxia and acidosis. Hypoxia and acidosis maintain constriction of pulmonary arterioles, and the subsequent maintenance of high pulmonary vascular resistance favors continuation of in utero right-to-left vascular shunts, which contributes to systemic hypoxia. Following dystocia, neonates are less active, slow to stand, slow to nurse, and prone to hypothermia and hypogammaglobulinemia. The normal duration of stage 2 labor (from appearance of fetal membranes at the vulva to delivery of the fetus) in ruminants is generally shorter in multiparous animals (~30 min) than primiparous animals (~60 min).[98] Fetal viability is improved with early intervention; multiparous animals should be assisted after 30 to 60 minutes of stage 2 labor and primiparous animals after 60 to 90 minutes.[73]

The range in ambient temperatures over which newborn animals are able to maintain homeothermy is much narrower than for growing or adult animals. Neonates are more susceptible to fluctuations in environmental temperature because of their large surface area to mass, evaporation of amniotic fluid, and limited caloric reserves. Starvation and hypothermia is the second leading cause of death of neonatal lambs.[3] Neonatal mortality increases with decreasing ambient temperature and with increasing precipitation on the day of birth.[47] Thermoneutrality is maintained by shivering and metabolism of brown adipose tissue. Normally at birth, blood glucose concentration in calves ranges between 50 and 60 mg/dL, rising to 100 mg/dL within the first 24 hours of life.[92] Lambs born in warm weather can survive for up to 4 days without supplemental nutrition. Severe weather stress may increase energy requirements by 500% and deplete the energy reserves of newborn lambs in 6 to 16 hours.[99] Starvation exacerbates the effects of environmental stress by reducing the available substrates for heat production, and energy depletion leads to hypoglycemia. Administration of glucose to hypothermic neonates prior to and during warming is important to avoid deaths from cerebral hypoglycemia induced by increased use of glucose by peripheral tissues.[100] Warming hypothermic lambs by immersion in 38° C (100.4° F) water is more efficient than infrared lamps or wrapping the lamb in a cotton cloth.[101]

No intrauterine transfer of immunoglobulin occurs in ruminants; hence, at birth, neonatal ruminants are agammaglobulinemic and immunologically naive. Infectious disease is the leading cause of morbidity and mortality in calves greater than 3 days of age.[102] Failure of passive transfer increases the risk of neonatal mortality.[103] Colostrum

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provides a concentrated source of energy and immunoglobulins. Immunoglobulins are concentrated in colostrum by an active, receptor-mediated transfer of IgG_1 from the blood of the dam across the mammary gland secretory epithelium beginning several weeks prior to parturition.[104] Colostral IgG_1 concentrations may be 5 to 10 times the maternal serum concentrations. IgM, IgA, and IgG_2 concentrations in colostrum are much lower.[105] The large numbers of leukocytes also contribute to providing passive immunity to the newborn.[106] Methods of assessing passive transfer and management of failure of passive transfer are discussed in detail in Chapter 19.

Dystocia

Between 40% and 60% of stillbirths are associated with dystocia. Calves that survive dystocia are more likely to have edema of the head and tongue, making suckling difficult. They are also weak and exhausted and likely to be recumbent for a longer period of time and expose themselves to more fecal pathogens.[107] Dystocia affects the uptake of immunoglobulins by the calf and calves that survive dystocia are more likely to become sick in the first 45 days of life.[108] Maternal variables correlated with dystocia and consequently calf mortality at birth include parity and conformation. Dystocia and stillbirths in heifers is most commonly caused by feto-pelvic incompatibility. Feto-pelvic incompatibility accounts for a lower proportion of dystocias in multiparous cows, but weak labor resulting from hypocalcemia, uterine torsion, and incomplete cervical dilation is more common in older cows.[38] The prevalence of stillbirths in dairy herds globally is reported to be increasing.[1] In the U.S. dairy industry, the incidence is 8% (11.3% in primiparae and 5.3% in pluriparae).[109] Dam pelvic diameter is an important determinant of dystocia for heifers.[110] Pelvic measurements can be used to identify abnormally small or abnormally shaped pelvises. Large frame size of the dam correlates with a reduced risk of dystocia; however, continued selection for large frame size tends to select for larger birth weight and dimensions of calves.[111] Age at first calving for heifers is not correlated with risk of dystocia as long as heifers are fed and managed to achieve appropriate growth and stature prior to calving.[112-114] The risk of dystocia in heifers is increased by poor nutrition in the last trimester.[115] Appropriate nutrition and management of replacement heifers to achieve appropriate size and stature at parturition reduces maternal and neonatal losses by reducing the incidence of dystocias. Maternal consequences associated with calving difficulty and delivery of a stillborn calf include decreased milk production and reduced reproductive efficiency. Reductions in milk production ranging from 100 to 400 kg have been reported to be associated with the birth of a stillborn calf. If the stillborn calf is delivered by cesarean section, the reduction in milk yield is on the order of 300 to 500 kg.[116] Delivery of a stillborn calf is also associated with depressed conception rates, increased services per conception, and delayed conception.

Use of calving ease bulls over primiparous cows helps to reduce the incidence of dystocia and subsequently mortality during parturition. The heritability of calving ease is relatively low; estimates of maternal calving ease range from 0.03 to 0.24[38,117,118] and paternal heritability around 0.147. Despite the relatively low heritability of calving ease, selection for calving ease should not adversely affect other production parameters in dairy cattle since the genetic correlation between calving ease and other dairy production traits are generally close to 0.[38] Calving ease evaluations are intended to increase the use of AI for heifers. To facilitate sire selection most breed associations provide guidelines regarding calving ease or expected progeny difference for calf birthweights. An example of such a scheme is the calving ease and reliability values assigned to AI Holstein bulls. In this system, the calving ease score is the expected percentage of difficult births predicted for calves delivered by primiparous cows.[119] The reliability score provides an indication as to the number of births that were considered in deriving the calving ease score. The higher the reliability score, the larger the number of observations the calving ease score is based on and the more likely it is that the calving ease prediction will accurately reflect the outcome.

Management variables that influence the risk of dystocia and perinatal mortality include stocking density of pre-parturient cows, timing of calving, and cow grouping. In a study of 123 beef herds, the dystocia rate was highest for cows housed in a barn and decreased progressively through barn/yard, barn/pasture, and pasture-only calving location categories.[120] The most common cause of dystocia in penned heifers was vulval constriction, whereas dystocias in paddocked heifers were most commonly associated with malpresentations.[121] Calving of beef heifers 6 weeks prior to cows has been recommended to allow the heifers longer to recover and conceive after calving than cows.[122] In a herd level comparative study, this practice was associated with a higher incidence of dystocia and stillborn calves.[120] Presumably because of better nutritional management, heifer dystocia rate is reduced the longer heifers are maintained as a separate group from cows prior to calving.[120]

Fetal variables that influence the risk of mortality include sex, size, and number. Calves born to primiparous cows, twins, and bull calves are more likely to die at birth than calves born from multiparous cows, single calves, and heifer calves.[47,123] Low- and high-birth-weight calves are at greater risk of mortality than average-birthweight calves.[47] Small calves experience greatest mortality at parities greater than one and large calves at first parity.[112] Fetal viability may be compromised in utero by a number of infectious agents. Common infectious agents associated with abortion and/or birth of weak calves are listed in Box 18-1. Manifestations of disease in the newborn are dependent on the time of exposure to the infectious agent.

Peripartum Assessment of Fetal Vitality

During parturition, fetal reflexes can be assessed to ascertain appreciable signs of life. The interdigital, bulbar, and swallowing reflexes can be assessed in calves presenting in an anterior presentation. The interdigital and anal reflex and pulse in the umbilical cord can be evaluated in calves presenting in a posterior presentation.[124] Depressed responsiveness is a feature of impaired acid-base status. An increasing proportion of calves fail to respond as the severity of the acidosis increases. Failure to elicit reflexes is not confirmatory of fetal death as an absence of reflexes has been observed in severely acidotic live calves.[125]

Criteria commonly used to assess the vitality of the newborn calf is presented in Table 18-3. Abnormal neonatal behavior in the immediate postnatal period is commonly a result of perinatal hypoxia and a combination of metabolic and respiratory acidosis. Calves and lambs normally have a head righting reflex almost immediately after birth. Sternal recumbency is usually attained within 2 to 4 minutes, followed rapidly by attempts to stand at 10 to 20 minutes for lambs and 15 to 30 minutes for calves.[126-128] Failure for calves to achieve sternal recumbency within 15 minutes of birth is highly predictive (84%) of compromised vitality and risk of mortality.[128] Hypoxic neonates may struggle and appear bright initially but have difficulty maintaining sternal recumbency, have depressed or absent suck reflex, appear slow to stand or remain recumbent, and develop a depressed mentation within hours.

The normal heart rate of calves is 100 to 150 beats/min immediately after birth. Heart rate normally stabilizes within minutes of calving, but in at-risk calves, peripartal tachycardia (>150 beats/min) is followed by a declining bradycardia.[124] Following experimentally induced hypoxia, nonviable hypoxic calves had similar heart rates (118 ± 36 beats/min) and body temperatures ($39.6° \pm 0.2°$ C) as viable calves but lower respiratory rates (14 to 18 versus normal 49 ± 12).[126] The rectal temperature of a normal newborn calf is higher than normal at calving 39° to 40° C (102° to 104° F) and gradually drops to normal within 3 to 5 hours. Calves that experience a protracted, difficult calving may experience hyperthermia (>39.5° C [>103° F]) at birth, which drops in the hours following birth and is slow to return to normal.[124]

The normal time taken to stand and nurse varies among species and breeds. The average time from birth to standing and nursing for beef calves is 35 and 81 minutes, respectively. Dairy calves are more variable and take approximately twice as long.[129] A high prevalence

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TABLE 18-3

Assessing the Newborn Calf[138]

Criterion	Good Vitality	Poor Vitality
Respiration	50-75 beats/min and thoracic breathing	Gasping, primary apnea, irregular, abdominal breathing, bellowing and secondary apnea
Hair coat appearance	Placental fluid-covered	Meconium-stained
Peripheral edema	None	Capital, lingual, or limb edema
Mucous membranes	Pink and normal capillary refill time	Cyanotic, pale, and slow capillary refill time
Response to reflex stimulation	Vigorous head shake, strong corneal, suck, or pedal reflex	Weak or no response
Muscle tone	Active with head-righting within minutes	Inactivity and flaccid musculature
Heart rate	100-150 beats/min and regular	>150 beats/min followed by bradycardia (<80 beats/min) and an irregular, decreasing rate
Rectal temperature	102°-103° F (39°-39.5° C) after calving, declining to 101°-102° F (38.5°-39° C) by 1 hour and stable	103°-104° F (39.5°-40° C) after calving, declining to 101° F (<38.5° C) by 1 hour and decreasing
Sternal recumbence	Achieved within 5 minutes	Prolonged lateral recumbence
Attempts to rise	Attempting to stand within 15 minutes Standing within 1 hour	Delayed or no attempts to rise
Suckling	Commences within 2 hours	Delayed or no attempts to suckle

of delayed first sucklings has been reported among dairy calves. Failure of the newborn to nurse may result from reduced neonatal vigor, poor mothering, poor maternal conformation, or adverse conditions such as slippery flooring.[130] Calves have difficulty locating teats on low-slung udders (<45 cm from the ground)[131] and difficulty nursing teats greater than 35 mm in diameter.[132] Small ruminants are generally quicker to stand and nurse than calves, with most lambs standing within 30 minutes[127] and nursing within 90 minutes of birth.

Observation of interaction between the newborn and dam in the immediate postnatal period allows early recognition of the compromised neonate and facilitates timely intervention if maternal conformation or behavior threatens to impede the neonate's efforts to nurse. Failure of maternal bonding is more common with primiparous dams and multiple offspring, and with following delivery via caesarean section. Maternal bonding in sheep is mediated by an olfactory mechanism.[133] Parturition alters the release of monoamines, amino acids, and oxytocin within the olfactory bulb, stimulating an attraction to amniotic fluid and acceptance of the lamb.[134] Artificial vaginocervical stimulation with a gloved hand induces similar alterations in the release of monoamines, amino acids, and oxytocin within the olfactory bulb and is useful for triggering formation of maternal bonds to foster lambs for at least 27 hours postpartum.[134]

In utero infections and congenital neurologic abnormalities should also be considered as possible causes of abnormal neonatal behavior. Collection of sera prior to feeding colostrum is useful for diagnosing in utero infections. Pre-colostral serum immunoglobulin concentrations in calves are very low (IgM 0.126 ± 0.015 mg/mL, IgG 0.044 ± 0.003 mg/mL).[135] Elevated serum concentrations of immunoglobulins prior to ingestion of colostrum may be observed with in utero infections.[135] Specific serologic tests are available for Cache Valley virus, Akabane virus, bovine virus diarrhea virus, *Neospora* spp., toxoplasma, and bluetongue virus.[136] Teratogens and inherited diseases that may cause the birth of weak neonates are listed in Box 18-1.

Resuscitation of the Neonate

Assisted deliveries are usually associated with moderate to severe fetal stress. Survival of the compromised fetus is facilitated by prompt initiation of supportive care. Suction is useful for clearing the pharynx and nasal passages and has been shown to improve pulmonary function in newborn calves.[137] Squeezing the trachea gently may also illicit a cough reflex, which assists airway clearance.[138] Suspending the newborn by the hind legs for less than 90 seconds after delivery is an alternative method for clearing the airways.[139] If the newborn breathes spontaneously, it is placed in sternal recumbency to facilitate efficient pulmonary gas exchange and correction of the mixed acidosis.[139] If the calf does not breathe or move spontaneously within a few seconds after birth, tactile stimulations (e.g., inserting a finger or a length of straw in the nasal cavity, pinching the nasal septum, rubbing the calf's body with straw or towel,[140] pouring cold water in the ear or over the head or body of the calf[137]) are necessary to initiate a gasping reflex. In dyspneic neonatal calves, the respiratory center can be stimulated with respiratory stimulants such as doxapram (2 mg/kg IV). Doxapram should be used judiciously since the stimulatory action of the drug is nonselective. Convulsions may be observed with repeated dosing, increasing the demand for oxygen in an already hypoxic neonate.[141]

Weak fetuses are often born with strongly beating hearts but have difficulty initiating adequate inspiratory efforts to expand their lungs. Positive pressure ventilation is required to overcome surface tension in alveoli and the elastic recoil of lung tissue. Fluid within alveolar spaces and the lumen of the tracheobronchial tree is absorbed into the pulmonary interstitium most efficiently at thoracic pressures between 35 and 40 cm H_2O.[94] Less pressure is usually needed for succeeding breaths. Observation of chest wall movement is a reliable sign of sufficient inflation pressure. Ventilation with a pulmonary resuscitation bag (ambu bag) with a pressure relief valve set at 42 cm H_2O avoids inadvertent overinflation.[142] Direct mouth-to-mouth resuscitation is generally ineffective for delivering air into the abomasum and poses a risk for contracting zoonotic diseases such as leptospirosis, brucellosis, or Q fever.

Thermoregulation is important since recovery from acidosis is delayed by hypothermia.[143] Cold stress leads to increased metabolic needs and produces hypoxia, hypercarbia, metabolic acidosis, and potentially hypoglycemia—metabolic sequelae that resuscitation is aimed at correcting.[144]

Resuscitation procedures for more critical neonatal calves and small ruminants is similar to the approach taken with foals, as discussed in Chapter 17.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 19



Initial Management and Clinical Investigation of Neonatal Disease

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Environmental Management

Maternal shedding of enteric pathogens increases around the time of parturition. In intensive dairy production systems, calf pathogen exposure and subsequently the risk of morbidity and mortality can be reduced by removing the calf from the dam after birth and placing the calf in a clean, dry, sheltered environment. Neonatal calves are cold tolerant when dry and sheltered from drafts. Wet drafty conditions lead to depletion of energy reserves and hypothermia. Hypothermia compromises colostral transfer and increases vulnerability of newborns to contagious and opportunistic pathogens. Under cold conditions calves generate heat by shivering and metabolism of brown adipose tissue. The calf is born with short-lived, stored energy in the form of muscular glycogen.[1] Colostrum is a critical source of concentrated energy to meet the metabolic demands of thermogenesis.

Colostrum Management

Ingestion and absorption of colostral immunoglobulins is essential for neonatal ruminants to thrive. Cows, sheep, and goats have an epitheliochorial type of placenta that does not allow passage of immunoglobulin; hence, neonates are born virtually agammaglobulinemic, rendering them susceptible to infection. Ingestion of colostrum provides maternal immunoglobulins that enterocytes selectively absorb by pinocytosis during the first 24 hours after birth. The ability of the enterocytes to absorb immunoglobulins decreases rapidly soon after birth, resulting in "closure" of the intestines by 24 to 36 hours postpartum. The immune system of the neonate starts to develop from birth, with endogenous immunoglobulin G (IgG) reaching functional levels at 3 to 6 weeks of age.[2] The uptake of maternal leucocytes by the calf also plays a significant role in the development of the neonatal immune system.

Inadequate colostrum consumption increases the risk of disease. Passive transfer achieving serum IgG concentrations 10 mg/mL or greater at 24 to 48 hours is associated with reduced risk for morbidity and mortality.[3-5] Provision of adequate good-quality colostrum also results in improved daily weight gain and feed conversion efficiency both preweaning and postweaning, although the effect of this on joining dates and age at first calving varies among studies.[5-7] Both serum IgG at 24 to 48 hours and the provision of adequate good-quality colostrum have been associated with increased milk production in the first and second lactations.[6,8]

The major factors influencing the effectiveness of passive transfer of immunoglobulins in calves are (1) the concentration of immunoglobulins in colostrum fed, (2) the volume of colostrum ingested, and (3) the age of the calf at first colostral feeding.

Colostrogenesis occurs several weeks before calving under the influence of prolactin and other lactogenic hormones. Colostrum is nutrient dense and has a higher level of energy and protein than is found in milk. Bovine colostrum contains approximately 45 mg/mL[9] of immunoglobulin and 10^6 leukocytes/mL.[10] IgG_1 is transported from blood in endosomes through the polarized mammary epithelial cell by a process known as transcytosis.[11] The IgG_1 is bound by the Fc-receptor of the neonate (FcRn) at the basal side and transferred to the apical side under the control of intracellular proteins termed *small GTPases*.[12] The FcRn receptor consists of two subunits: an integral membrane α-chain (Fc fragment of IgG, receptor, transporter, alpha [FcGRT]) and a β-light chain (β2 microglobulin [β2M]). In vitro, the expression of FcGRT and several of the small GTPases controlling the transfer of IgG are upregulated by estrogen and progesterone, and it is thought that this mechanism results in the marked increase in transport of IgG_1 observed in the 4 weeks prior to calving.[12,13] Immunoglobulins account for more than 95% of the whey protein at calving, and IgG_1 accounts for approximately 80% of this amount.[14] IgG_2, IgA, and IgM account for 10%, 7%, and 5%, respectively. The amount of IgA remains constant throughout all lactations, whereas the colostrum of cows in their first lactation contains less IgG_1, IgG_2, and IgM. Immunoglobulin levels in mature milk are much lower, comprising only 7% of the total whey protein, with an increase in the relative contribution of IgA. Older cows have a tendency to a higher ratio of IgG_1 to IgG_2.[15] This is consistent with a lower level of IgG_1 in the serum of heifers. The transport of IgG into bovine colostrum has been associated with a transient decrease in serum total protein, globulin, and IgG concentrations during the preparturient period, particularly in dairy cows. Up to 500 g of IgG_1 a week are removed from blood during the most active period of colostrum formation.[16] Passively derived immunoglobulins enhance neonatal immunity via functioning as neutralizers and opsonins. The association between failure of passive transfer (FPT) of immunoglobulins and neonatal infection has been well established in the calf.[17,18] Colostral leukocytes participate in regulation of the neonate's immune response. Comparison of the immune response of calves fed leukocyte-replete or leukocyte-depleted colostrum indicates that colostral leukocytes enhance humoral immunity and phagocyte function.[19-23] Following experimental *Escherichia coli* infection, calves fed leukocyte-replete colostrum recovered more quickly and shed fewer bacteria than calves fed leukocyte-depleted colostrum.[10] Transfer of cellular immunity via colostral leukocytes has also been demonstrated in sheep.[24] Colostral leukocytes are destroyed when

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TABLE 19-1

Composition of Colostrum of Holstein Cows[46*]

Item	Mean	SE
Fat (%)	6.70	4.16
Protein (%)	14.92	3.32
Lactose (%)	2.49	0.65
Total solids (%)	27.64	5.84
Ash (%)	0.05	0.01
IgG_1 (mg/mL)	34.96	12.23
IgG_2 (mg/mL)	6.00	2.82
IgA (mg/mL)	1.66	0.99
IgM (mg/mL)	4.32	2.84
Lactoferrin (mg/mL)	0.82	0.54
Retinol (µg/g)	4.90	1.82
Tocopherol (µg/g)	2.92	3.65
β-Carotene (µg/g)	0.68	0.63
Vitamin E (µg/g of fat)	77.17	33.51
Thiamin (µg/mL)	0.90	0.28
Riboflavin (µg/mL)	4.55	0.31
Niacin (µg/mL)	0.34	1.57
Vitamin B12 (µg/mL)	0.60	0.35
Pyridoxal (µg/mL)	0.15	0.07
Pyridoxamine (µg/mL)	0.21	0.07
Pyridoxine (µg/mL)	0.04	0.07
Ca (mg/kg)	4716.10	1898.00
P (mg/kg)	4452.10	1706.29
Mg (mg/kg)	733.24	286.07
Na (mg/kg)	1058.93	526.02
K (mg/kg)	2845.89	1159.89
Zn (mg/kg)	38.10	15.90
Fe (mg/kg)	5.33	3.09
Cu (mg/kg)	0.34	0.14
S (mg/kg)	2595.67	904.97
Mn (mg/kg)	0.10	0.11

*Data from 55 samples.

SE, Standard error.

colostrum is frozen, pasteurized, or fermented. Colostrum also contains hormones (growth hormone, relaxin, prolactin, insulin, and glucagon), essential fatty and amino acids, minerals, trace elements, and (pre-)vitamins (especially beta-carotene and vitamins A, B, D, and E) (Table 19-1), as well as cytokines, growth factors (members of the IgF system, including IgF binding proteins [IgFBP]), and nonspecific antimicrobial factors such as lactoferrin. Colostrum is a significant source of copper to the newborn calf but not of selenium or zinc.[25]

Colostrum has been shown to have many roles apart from establishment of the humoral neonatal immune system. Lactose intake is insufficient to maintain plasma glucose concentrations, and colostrum feeding increases plasma glucose, most likely due to stimulation of gluconeogenesis. Newborn calves are deficient in vitamin A and have a low lactoferrin status. Both are found in elevated quantities in colostrum compared with milk. Lactoferrin is an iron-binding glycoprotein, which is a potent antimicrobial factor in the milk cistern and in the alimentary tract of newborn animals. Digestive functions develop during fetal life and undergo the largest morphologic and functional changes during the first 48 hours of extrauterine life under the influence of insulin-like growth factor-1 (IgF_1), lactoferrin, and other bioactive substances, many of which are present in significantly higher concentration in colostrum than milk. These factors are key regulators in the development of the gastrointestinal tracts of bovine neonates, including stimulation of mucosal and submucosal growth, brush-border enzymes, intestinal DNA synthesis, increased duodenal villus size, apoptosis, protein synthesis and degradation, and digestion and absorption. They also exert systemic effects outside the GIT on metabolism and endocrine systems, vascular tone and hemostasis, activity and behavior, and systemic growth.[26-28]

Provision of Adequate Colostrum

Optimal transfer of immunoglobulin will occur when calves are administered 7.5% to 10% of body weight of first milking colostrum within 2 hours of birth followed by an additional feed of 5% of body weight at 12 hours (Table 19-2). The initial feed should provide the calf with a minimum of 100 g of IgG, and at least 150 g of IgG within 2 hours of birth are required to ensure 90% of calves have optimal passive transfer.[29] Dairy calves should be administered colostrum by nipple bottle or esophageal tube, since increased FPT occurs in dairy calves that are left on their dam.[9,30,31] This is due to the reduced volume of colostrum, and therefore mass of IgG, consumed by the calf if left to suckle naturally during the first 24 hours.[5] Conversely, separation of beef calves from the dam is not practical and may result in mismothering. Generally failure of passive transfer is less of a problem in beef cattle, since the lower volume of colostrum produced results in an elevated concentration of IgG, and supplementation is only recommended following dystocia.

Failure of Passive Transfer

FPT occurs when calves do not absorb sufficient immunoglobulins. Only small amounts of IgG and IgM to unknown antigens are made by the fetus, and they offer no protection against disease. It has been estimated that approximately 31% of preweaning mortality events occurring in the first 3 weeks of life can be attributed to failure of passive transfer.[32] The problem in mixed-source calf-rearing properties is significantly worse.[3] A high percentage (19.2% to 38%) of dairy calves are still found with significant FPT.[30,31,33] Some debate exists as to the serum IgG concentration that signifies FPT. Calves are generally defined as having FPT if the calf serum IgG concentration is less than 10 mg/mL when sampled between 24 and 48 hours of age.[34] It has been suggested that serum IgG concentration below 13.4 mg/mL constitutes FPT.[29,35] Ensuring that every calf has adequate passive transfer is challenging and rates of 10% are probably indicative of good management practices.[29]

Risk Factors for Inadequate Colostrum Uptake

There is a large variation in colostrum immunoglobulin concentrations between individual cows and a variety of influences: genetic, environmental, and physical on the uptake of colostral antibodies by the calf. Although calves born to beef cows with lower colostrum immunoglobulin concentration had an increased risk of mortality,[36] numerous other studies in beef and dairy calves have failed to demonstrate an association between the colostral immunoglobulin levels and the serum immunoglobulin of the calf at 48 hours of age.[37-41] Administration of a known volume and concentration of colostrum via oroesophageal feeder at a specific time after birth to dairy calves has been shown to have more linear correlation with calf serum IgG,[29,42] but administration of sufficient colostrum to provide 150 g of IgG within 4 hours of birth can still result in FPT.

Factors Affecting Colostrum Quality

At the herd level, colostrum quality is affected by breed, parity, and climate. For individual cows the biggest determinants are colostral volume and time from calving until milking.[43,44] Colostrum concentrations of Holstein-Friesian cows varied from 20 g/L of immunoglobulin to more than 110 g/L of IgG_1 in cows from a single herd.[43] First milking colostrum samples collected within 4 hours of milking from cows at 11 dairies in Pennsylvania varied from 9 to 166 g/L of IgG_1.[45] The mean concentration of IgG_1 in first milking colostrum in three large studies of dairy cows varied between 37.5 ± 30.2 and 48.2 ± 28.9 g/L.[43,45,46] Colostrum IgG concentration declines with time after calving even if the cow is not milked.[43,44,47,48] However, several studies have demonstrated that this decline is minimal until the cow has been calved 8 to 9 hours.[43,47] There is no increase in colostral volume if postpartum milking is delayed, so it appears that the declining IgG is not due to dilution.[44,48,49] During the colostrum phase, mammary cells have leaky tight junctions,[50,51] so it is likely that

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TABLE 19-2

Liters of Colostrum Required to Achieve Adequate Passive Transfer (Blood IgG Level ≥ 13.4 mg/mL) for Different Birth Weights, Absorption Rates and Colostrum Qualities

		Brix (%)				
		14-16	18-20	22-24	26-28	30-32
		Antibody Concentration (g/L)				
Calf Weight	Hours after Birth	20-30	40-50	60-70	80-90	100-110
30	0-3	5.6‡	2.8†	1.9*	1.5*	1.5*
	3-6	6.4‡	3.2†	2.1*	1.6*	1.5*
	6-9	7.1‡	3.6†	2.4*	1.8*	1.5*
	9-12	8.3‡	4.1†	2.8†	2.1*	1.7*
	12-18	9.4‡	4.7†	3.1†	2.3*	1.9*
	18-24	10.5‡	5.3‡	3.5‡	2.6‡	2.1*
40	0-3	7.5‡	3.8†	2.5*	2.0*	2.0*
	3-6	8.5‡	4.3†	2.8*	2.1*	2.0*
	6-9	9.5‡	4.8†	3.2†	2.4*	2.0*
	9-12	11.0‡	5.5†	3.7†	2.8*	2.2*
	12-18	12.5‡	6.3‡	4.2†	3.1†	2.5*
	18-24	14.0‡	7.0‡	4.7‡	3.5‡	2.8*
50	0-3	9.4‡	4.7†	3.1*	2.5*	2.5*
	3-6	10.6‡	5.3†	3.5*	2.7*	2.5*
	6-9	11.9‡	5.9†	4.0†	3.0*	2.5*
	9-12	13.8‡	6.9‡	4.6†	3.4*	2.8*
	12-18	15.6‡	7.8‡	5.2‡	3.9†	3.1*
	18-24	17.5‡	8.8‡	5.8‡	4.4‡	3.5*

*Calves should be fed 7.5% of body weight or, at a minimum, the volume shown. IgG levels would be enhanced by 5% of body weight 6 to 12 hours later.

†Calves should be fed 7.5% of body weight and an equivalent volume 6 to 12 hours later.

‡It is unlikely that adequate passive transfer will be achieved.

Calculations of total IgG required and apparent efficiency of absorption are based on Chigerwe et al (2008)[29,160] using blood volume calculations from Quigley et al (1998).[161] The correlation between the Brix refractometer reading and serum IgG levels was calculated using Quigley et al (2013).[49] This table was compiled with the assistance of Zoe Vogels from The Vet Group, Timboon, Victoria.

It is assumed that the minimum volume fed would be 5% of body weight even where good quality colostrum is available. It should be noted that below a Brix of 22%, it is not possible to achieve adequate passive transfer with a single feed of colostrum.

once parturition occurs, the active transcytosis of IgG_1 ceases and it is passively reabsorbed.

Studies of colostrum and calf immunoglobulin levels in specific beef breeds have failed to demonstrate consistent differences between specific breeds, and many studies have shown evidence of variations within breed lines. In dairy breeds, colostrum from Holstein cows was statistically lower in total IgG than colostrum from Jersey, Ayrshire, and Guernsey cows.[52,53] Prepartum dairy cows have a significantly greater decline in serum IgG compared with beef cows[13]; however, the colostrum of dairy cows has lower concentrations of IgG because of the much larger volume. Some studies have shown very low volumes of colostrum (<2 L) in beef cows.[54,55] The volume of colostrum produced and the concentration of immunoglobulin in the colostrum is markedly affected by differences in the onset of lactogenesis, and the resulting dilution of colostral immunoglobulins—hence it is likely that much of the variation observed among breeds, lines, and cows is an effect of colostrum volume. First and second calving beef and dairy cows often have a lower immunoglobulin concentration than cows of third or greater parity.[39,43,53,56,57] Similarly, calves born to beef heifers and second parity cows have a significantly lower mean concentration of serum IgG compared with that of calves born to mature cows.[56,58,59]

Genetic variance has been found in the genes encoding the FcRn receptor involved in transcytosis of IgG_1 into the mammary gland. In Holstein-Friesian cows, haplotype 5 of the FcGRT subunit has been shown to be significantly associated with a high colostrum IgG, and FcGRT haplotype 2 shows a similar trend.[60] FPT in beef calves from 16 breeds has been associated with FcGRT haplotype 3; conversely, calves with the FcGRT haplotype 2 were less likely to have high levels of serum IgG.[61] FPT in these calves is also associated with one of eight haplotypes of the β2M subunit of the FcRn receptor.[62] It is likely that variation in this receptor is impacting the concentration of IgG_1 in colostrum, rather than the uptake of IgG_1 by the calf; neonatal uptake does not involve the FcRn receptor. An estimated 10% of Holstein cows are capable of high mass transfer of IgG_1, resulting in an IgG mass more than 1 standard deviation above the mean.[45] Variation in the FcRn receptor is probably contributing to this variation, along with other genetic or hormonal regulation of transport. Opportunity may exist to enhance the concentrations of immunoglobulins in colostrum by genetic manipulation of IgG transport in the mammary gland. However, it should be remembered that serum IgG concentrations in the periparturient cow are already decreased as a result of IgG transport into colostrum[13]; further, decrease in immunoglobulins may exacerbate the immunosuppression that occurs during the peripartum period.

Numerous studies have failed to demonstrate an effect of often severe protein and/or energy restriction for up to 3 months before calving on colostrum immunoglobulin levels.[63-66] Protein restriction may result in an increase in IgG levels and a concurrent decrease in colostral volume, making the colostrum more viscous and difficult to suckle, especially in heifers, resulting in decreased IgG levels in the calves.[58,67] This is likely to be a direct volume response as shown by other studies of colostral IgG concentration.[13,43] There was no significant effect of dietary restriction on colostral IgM in any of the studies. Selenium supplementation has been shown to increase the IgG levels in the colostrum of selenium-deficient cows,[68] but not lambs. IgG uptake by the calf may also be affected by serum copper levels.[69]

Twins have not been demonstrated to affect colostrum IgG concentration in beef cows[36,56]; however, another study of sheep, goats, and dairy cows demonstrated an increase in total protein, whey protein, and IgG concentration.[70]

Short dry periods of 28 to 35 days do not affect colostrum IgG levels, but when the dry period was eliminated completely, there was a decrease.[71-73] Elimination of the dry period did not affect

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colostrogenesis in terms of cellular and fluid composition, and it is likely that the reduced quality is due to the lack of a period of secretion and accumulation. The mean colostral IgG of these cows remained close to 50 g/L so that 3 L of colostrum would provide the calf with adequate IgG. Treatment of cows with internal teat sealant at drying off has no effect on transfer of colostral antibodies following calving, but will help prevent leaking of colostrum prior to calving and the consequential reduction of the quality of the colostrum harvested.[74]

Few studies have looked at the effects of periparturient disease on IgG levels in colostrum. A decrease in colostral IgG has been observed in cows with periparturient infections and clinical mastitis,[36] and where colostral IgG was not measured, calves of cows with periparturient mastitis had a lower serum IgG.[56] The reported effect of subclinical mastitis is also inconsistent. At the quarter level a persistent infection at the time of calving, detected by serial cultures, results in a decrease in total volume of colostrum produced but no variation in IgG_1 concentration, compared with a matched quarter on the same cow.[75] At the cow level, an increased risk of colostrum with an IgG content of less than 30 g/L is found in cows with a somatic cell count greater than 50,000 cells/mL, measured at the herd recording after calving.[57] At the herd level, cows from farms with an average count less than 200,000 in the month prior to sampling produced colostrum with higher levels of IgG_2, tocopherol, vitamin A, potassium, and total solid levels; however, no significant variation was noted in IgG_1.[46]

Environmental temperatures have an effect on colostral IgG concentrations with several large studies in dairy cattle demonstrating an increase in colostral IgG concentration in the summer[57,76,77]; however, at the extreme, heifers exposed to heat stress had decreased colostral IgG concentration.[78] Photo period has no effect on colostral IgG concentration or volume.[44]

Factors Affecting Colostrum Uptake by the Calf

TIME AND METHOD OF FIRST FEEDING. The key influences on immunoglobulin absorption by the neonatal calf are the concentration of immunoglobulins in the colostrum, volume fed, and time between birth and colostrum feeding. When small volumes are fed, the method of feeding can also affect the final serum IgG level.

Early ingestion of colostrum is crucial because IgG is absorbed by the intestinal epithelial cells of the newborn ruminant, and the ability of enterocytes to transport immunoglobulin declines linearly from 2 to 20 hours and completely ceases (intestinal closure) between 24 and 36 hours.[79] Serum IgG concentrations peak around 32 hours and then decline until the production of antibodies by the neonate exceeds the decay of passively acquired antibodies. Any delay in first feeding of colostrum results in decreased absorption of immunoglobulin and a lower serum IgG.[29,80] Absorption of immunoglobulins occurs along the whole length of the small intestine in calves, with the amount transported increasing from the duodenum to the ileum,[81] whereas in lambs and kids there is virtually no absorption from the duodenum and the majority occurs in the jejunum.[82,83] IgG and other macromolecules are mainly absorbed by micropinocytosis, although some receptor-mediated endocytosis has been demonstrated; however, this does not involve the neonatal Fc receptor FcRn.[81,82,84] Preferential absorption of homologous IgG has been observed in pigs; however, recent studies in kids and lambs have shown that similar IgG transfer can be achieved by feeding bovine colostrum, although in lambs the apparent efficiency of absorption is lower.[85-87]

The age of the calf when it receives its first feed and the amount of immunoglobulins received will influence the time of closure of the intestinal permeability to colostral immunoglobulins and the final serum immunoglobulin levels of the calf.[88-92] Cessation of absorption occurs by 24 hours in calves that receive a full feed of colostrum within the first 4 hours after birth. When the colostrum volume is less than 2 L, the gut will remain permeable for a longer time and the rate of absorption will increase in response to a subsequent feed. If the calf is older than 12 hours when it receives its first feed, there is a significant increase in the possibility of the calf being agammaglobulinemic. It is likely that the time of closure is related to the immunoglobulin concentration of the colostrum as well as the volume fed. Delay in colostrum feeding will also result in lower plasma insulin and IgF_1 for up to 48 hours after first colostrum intake and reduce plasma concentrations of β-carotene, retinol, and α-tocopherol for nearly a month after birth.[93,94]

The IgG concentration of the colostrum has the greatest effect on the mass of IgG fed and will determine the effectiveness of transfer of passive immunity when dairy calves are fed a fixed amount of colostrum. Therefore, it is important to implement routine measurement of colostrum IgG content on dairy farms. Provision of a high concentration of IgG in the initial feeding results in a much higher calf serum IgG than feeding increased volumes of lower-quality IgG.[95] When different volumes and concentrations of colostrum have been fed to calves after birth, increased volumes of high-quality colostrum resulted in a 50% increase in the calf serum IgG concentration at 24 hours, whereas the magnitude of effect of increased volume was much lower when low immunoglobulin colostrum was fed.

Calves should be fed 150 g of IgG within 4 to 6 hours of birth and earlier whenever practical. The volume at each feed should be determined after measuring colostrum IgG levels and is more important to optimize where lower-quality colostrum is the only source. There is no difference in the IgG concentration at 48 hours when 40-kg calves are administered either 3 or 4 L of colostrum with equivalent immunoglobulin levels regardless of IgG concentration.[29,42] Similarly with lower-quality colostrum, higher serum IgG levels will be achieved when two feeds of 2 L are given at 2 and 6 hours postpartum than if 4 L are given in one feed.[95] The pathophysiology underlying these observations is not fully understood, but 22% of the variation in the effective absorption of colostrum is attributed to abomasal emptying rate, and it is likely that the excessive mechanical distention of the abomasum with 4 L of colostrum delays outflow.[42,95,96]

Therefore, feeding regimens should be based around feeding 7.5% of body weight liters within 4 hours of birth, or a minimum of 150 g if availability is restricted and quality is higher than 50 g/L. Calf serum IgG levels will be significantly boosted by a further feed of 5% of body weight of colostrum within 12 hours of birth,[95] and if less than 150 g of colostrum was fed at the initial feeding because of limitations of quality or volume, then a further 7.5% should be fed.[35] Emphasis should be placed on feeding colostrum with the highest concentration of colostrum at the initial feed when the effectiveness of absorption is higher. Many farmers are currently feeding 10% to 12% of body weight as a single initial feed. Although this will provide good levels of IgG where colostrum quality is adequate, it may result in moderate depression and discomfort in the calf.[97] Good-quality colostrum is a precious resource, and more efficient use is possible by knowing colostrum quality, limiting the initial feed to 7.5% of body weight, and placing emphasis on a second feed of good-quality colostrum before the calf reaches 12 hours of age.

Method of feeding also has a significant effect on colostrum intake. A high proportion of calves left to suckle their dams shows evidence of failure of passive transfer, compared with those artificially fed by teat or esophageal feeder.[9,98,99] This is due to the reduced volume of colostrum, and therefore mass of IgG, consumed by the calf if left to suckle naturally during the first 24 hours. Therefore, it should be strongly recommended that dairy calves be administered colostrum containing 150 g IgG within 2 hours of birth.[5] Teat-feeding stimulates a reflex closure of the esophageal groove allowing colostrum to pass directly to the abomasum, where it clots before moving to the small intestine for absorption. When an esophageal feeder is used, this reflex does not occur and the colostrum passes to the reticulorumen.[100,101] Promotion of the advantages of closure of the esophageal groove has resulted in the use of a nipple bottle as the more common method of administering colostrum. However, several studies have demonstrated that there is no difference in immunoglobulin concentrations at 48 hours between calves that sucked larger volumes of colostrum from a nipple bottle and those that were administered a similar quantity via an esophageal feeder, although there may be a delay of approximately 3 hours before the serum IgG

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increases in the tube-fed calves.[97,102-104] This delay is not due to the deposition of colostrum in the reticulorumen, since all except 400 mL will immediately pass into the abomasum because of the pressure gradient resulting from the placement of the reticulorumen dorsal to the abomasum in the neonatal calf.[105] Instead, the delay is likely to be due to delayed abomasal emptying as a result of distention and changes in physiologic and neuronal control mechanisms.[96,106]

Calves fed by a nipple bottle will commonly not ingest sufficient colostrum to minimize the risk of FPT and should be encouraged to ingest the maximum volume they will voluntarily ingest within 1 to 4 hours of age.[35] Calves should be fed as soon as they are standing; delaying up to 6 hours after birth or provision of a heat lamp will not increase the amount of colostrum suckled.[35,107] Calves that have a high degree of vigor during the first hour of life and during colostrum suckling will consume more colostrum from the bottle, as will larger calves.[107] Bottle-fed calves that do not ingest their full allocation of colostrum at either their first or second colostrum feed should be targeted for immediate esophageal feeding, and the total remaining should be fed.

In order to minimize trauma when an esophageal feeder is used, the calf should be standing with its rump against a solid wall or corner. The feeder used should have a total volume of at least 3 L so that intubation only has to occur once. The calf should be encouraged to swallow prior to insertion by sucking a finger to produce saliva or by feeding a few mouthfuls of colostrum. The tube should be introduced without physical exertion, and the head should be positioned slightly downward to allow swallowing as the tube is inserted into the esophagus. Before feeding, the knob at the end of the tube should be palpated on the left-hand side dorsal to the trachea to ensure that positioning is correct. At this point the calf head may be tilted slightly upward as the bottle is elevated to administer the colostrum.

On beef properties, routine administration of colostrum to the newborn calf is disruptive and delays the time until first sucking[108] but will decrease the incidence of FPT.[37,109] Feeding colostrum to high-risk calves is likely beneficial, most commonly after dystocia. Beef cows often produce smaller colostrum volumes, and where volumes less than 1.5 L are fed, use of a nipple bottle is recommended, since serum IgG at 24 hours is higher compared with calves administered colostrum with an esophageal feeder.[110] This most likely occurs because a greater percentage of the total colostrum is deposited into reticulorumen. Where dairy colostrum was fed, this was also shown to be a biosecurity risk.

OTHER FACTORS INFLUENCING COLOSTRUM UPTAKE. Calves that have experienced dystocia are more likely to have failure of passive transfer.[5,58,59,111] Decreased vitality of the neonate and, in many cases edema of the head and tongue, result in a slower time to stand and inadequate colostrum intake as a consequence. Calves born to primiparous cows are more endangered than those born to multiparous cows. Respiratory acidosis did not result in a decreased level of IgG at 37 to 48 hours in studies where blood gases were measured promptly using arterial blood, although delayed absorption was observed in one study.[112,113] The effects of twinning are equivocal, with two large studies, both in beef herds, demonstrating opposite effects of twinning on calf serum IgG. This is likely to be related to management, since the study that showed an increase in IgG with twinning moved all cows with twins to a barn for care and observation.[56,111]

It has been shown that the conformation of the dam's udder and ventral abdomen has a significant effect on the average teat seeking time prior to first suckling. There was nearly half an hour delay in the time to suckle.[114] The overall effect on calf IgG was not measured, but a separate study demonstrated a significantly lower serum IgG in cows with pendulous udders.[115]

Protein restriction in the last third of gestation may affect uptake of IgG by the calf,[116] although IgM concentration was unaffected. This finding was attributed to the selective absorption of IgM in newborn calves, which is highly efficient when colostrum intake is low. IgM is the primary immunoglobulin that provides protection to the neonatal calf during the first few days of life, and it has been suggested that the efficient absorption of IgM is a compensatory measure that provides immunity to calves even when they are hypogammaglobulinemic.[117,118]

There is a seasonal variation in the IgG levels of calves and efficiency of absorption after colostrum feeding, being lower in the winter in cold climates and lower in the summer in hot climates.[38,119-122] Colostrum immunoglobulin concentration is reduced in hot and cold weather,[76-78] and this is exacerbated by calves also being less willing to suckle in extremes of temperature. Heat stress results in smaller calves that may be less vigorous,[121,123] and one study has shown that calves subjected to a cold and wet environment had a slower rate of colostral absorption,[124] although the serum immunoglobulin at 24 hours was not significantly different from the control calves. In that study the calves exposed to cold temperatures were fed colostrum via an esophageal feeder. The effect would be exacerbated in cold-stressed calves, since they are less likely to suckle voluntarily.

There is some evidence that IgG levels in calves at 24 and 36 hours have low to moderate heritability. The breed of the sire and dam has some effect, but there is variation within lines of the same breed.[39,41,59,125] Haplotypes of both the FcGRT and β2M genes coding for the FcRn receptor are associated with FPT in neonatal beef calves, as discussed previously.[61,62] Since this receptor is not involved in the uptake of IgG by the calf, it is likely that the risk factor for FPT is the colostrum quality of the dam.

Management to Ensure Adequate Passive Transfer (Boxes 19-1 and 19-2)

ENSURING ADEQUATE QUALITY

Colostrum Harvesting, Handling, and Storage. Colostrum collection should occur as close to parturition as possible. Fresh

BOX 19-1

Best Practice Colostrum Management for Dairy Calves

- Milk cows as soon as possible after calving. IgG concentration declines by 3.7% for each hour after calving.
- Remove calves from the calving area at least twice daily.
- Measure quality of colostrum (Brix refractometer). This will determine the quantity of colostrum to be fed. For the first feed, administer colostrum containing 150 g IgG within 4 hours of calving. Feed a maximum of 7.5% of body weight. If calf does not suckle the full amount, top with esophageal feeder.
- Feed an additional 5% to 7.5% of body weight by 12 hours of age. If the calf did not receive 150 g of colostrum in the first feed, it would be preferable to supplement 7.5% of body weight at the second feed.
- On farms with a history of Johne's, salmonella, mycoplasma, or leukosis, pasteurize colostrum.
- Avoid pooling colostrum where possible. If pooling of colostrum is unavoidable, mix colostrums of similar quality.
- Implement a monitoring program for failure of passive transfer.

BOX 19-2

Best Practice Colostrum Management for Beef Calves

- Avoid severe restriction of dietary intake prior to calving; this will reduce volume and make colostrum more difficult to suckle.
- Minimize disruption of calving cows.
- Ensure that calves receive colostrum within 6 hours of calving (active suckling): intervene when there is dystocia or dumb calf.
- Intervention may be by restraining the dam and encouraging suckling, or by administration of colostrum by a nipple bottle. An esophageal feeder should only be used when volumes greater than 1.5 L are available, or if the calf will not suck.

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cows should be removed from the calving area and milked out at least twice daily to help ensure optimal colostrum quality. Colostrum collected from cows who have leaked milk prior to calving, have signs of ill health, or have evidence of mastitis should not be fed to neonatal calves. Not only will there be a compromise in colostrum quality, but there is also increased potential for the presence of infectious pathogens, such as mycobacterium paratuberculosis, *Salmonella* spp., *Mycoplasma bovis, Staphylococcus aureus,* bovine diarrhea virus, and bovine leukemia virus.[126-128] Neonatal enteric pathogens such as cryptosporidium may also be present.[129,130] Consequently, unpasteurized colostrum is a potential risk factor for calf diarrhea and neonatal septicemia.[131,132] Unpasteurized colostrum is also a biosecurity risk, and the use of colostrum from cows from a different property should not be recommended. Risk will be increased significantly if colostrum is pooled as organisms are disseminated, subsequently infecting a larger number of calves.[132-134] This is exacerbated further if storage is poor, resulting in pathogen proliferation.[131] Colostrum with high bacterial levels not only present a significant disease risk, but also affect absorption of IgG by direct blocking of uptake and transport of immunoglobulin molecules across intestinal epithelial cells or by binding free immunoglobulin in the gut lumen.[34,135] Pooling of colostrum will also result in reduced IgG concentrations because of the overrepresentation of high-volume, low-immunoglobulin colostrum and consequently is associated with an increased level of FPT.[30,136] When pooling is necessary for pasteurization, the colostrum IgG should be estimated using a Brix refractometer and low-quality colostrum excluded.

Microbial contamination of colostrum compromises colostral quality and subsequently calf health. Bacterial contamination may occur during harvest, storage, or administration.[126,131,137] Possible sources of contamination include cow skin, milking cup liners, hoses, milking buckets, storage, and feeding utensils. Contamination of colostrum with pathogens during harvest can be avoided by careful and hygienic teat preparation in fresh cows prior to applying cups.[126] This may involve washing and drying of teats and application of a premilking teat disinfectant.[138,139] Thorough and effective cleaning and disinfection of collection, storage, and feeding equipment is essential. It is important that separate, clearly marked esophageal feeders are used for feeding colostrum and are not used for sick calves, since this may also be a significant disease risk. Milk feeding equipment should not have cracks or scratches that allow for buildup of bacteria. Equipment should be rinsed in lukewarm water, and then actively scrubbed in water hotter than 50° C (122° F) containing detergent and bleach, or dry chlorinated detergent, to remove any residue. Bottle brushes should be used to clean esophageal feeders, nipples, and feeding bottles. Finally, they should be rinsed in water containing acid or an acid rinse and then allowed to completely dry before stacking or storage. When concern exists regarding hygiene practices, plating 10 µL of colostrum onto a blood plate and incubating at 37° C (98.6° F) overnight provides a simple crude assessment of microbial contamination of colostrum being fed to calves and allows identification of the origin of any process failure. Fresh colostrum fed to calves should have a total bacteria count less than 100,000 colony-forming units/mL and less than 10,000 coliforms/mL.[126,132]

Short-term storage of colostrum is necessary in order to deliver known good-quality colostrum to neonatal calves within hours of birth to reduce the risk of failure of passive transfer. When colostrum is stored at ambient temperatures, bacterial proliferation leads to fermentation, thus reducing total solids, protein, fat, and lactose content. Refrigeration of colostrum delays bacterial growth. Producers should aim to feed refrigerated colostrum within 2 days of collection. Storage of colostrum in the refrigerator for more than 24 hours will result in a decreased amount of IgG absorbed, and this may lead to FPT if stored for more than 48 hours.[140] The addition of 10 mL of 50% potassium sorbate solution per liter of colostrum at the time of collection to colostrum (0.5% wt/vol), in combination with refrigeration, inhibits bacterial growth for 4 days.[131]

Pasteurization of colostrum is an effective way to control colostrum bacterial load, reducing the risk of infectious disease transmission from cow to calf.[141] Degradation of immunoglobulins may be a problem with large-batch colostrum pasteurizers. Calves fed large-batch pasteurized colostrum have significantly lower serum IgG levels than those fed unpasteurized colostrum.[34] However, pasteurization of small batches of colostrum (57 L) at 67° C (152.6° F) or less caused a minimal decrease in the immunoglobulin concentration of colostrum compared with pasteurization of large batches (95 L), or batches at higher temperatures (76° C [168.8° F]) and has little effect on the subsequent serum immunoglobulin in calves at 24 hours of age.[142,143] At this temperature *Mycobacterium paratuberculosis* may still survive.[144,145] Heat treatment of colostrum (at 60° C [140° F] for 60 minutes) at a commercial level has been shown to effectively reduce colostrum microbial counts while maintaining IgG concentration.[146] Calves fed such colostrum were also found to have a reduced morbidity.[147] This critical temperature appears to significantly reduce the bacterial load while not denaturing the IgG or changing the viscosity of colostrum.[148]

Longer-term preservation of colostrum can be achieved by freezing or lyophilization without change in the immunoglobulin and nutritional content.[149-151] However, the cellular content of colostrum is destroyed by freezing, which may have longer-term effects on the development of the immune system.[152] In kids, the feeding of lyophilized colostrum resulted in higher IgG levels than feeding frozen colostrums.[153] Colostrum should not be thawed in a microwave, since the defrosting of a large volume in this way results in uneven heating and clots.[102] It should be stored in 1- to 2-L aliquots in flat plastic bags and allowed to thaw at room temperature in a fridge or in a rocking heated water bath with a water temperature no more than 40° C (104° F).

Monitoring Colostrum Immunoglobulin Quality. The quality of colostrum has traditionally been measured by visual inspection or by the use of a colostrometer (a hydrometer). The level of IgG in colostrum cannot be accurately predicted based on its appearance,[154] hence the need for more objective instruments. The colostrometer measures the specific gravity of a liquid, which in the case of colostrum is associated with the protein content. Globulins contribute greatly to this protein, so the colostrometer has been used to determine the immunoglobulin content of colostrums.[155] Although they are relatively quick to use on farm, colostrometers have limited sensitivity (0.32) and specificity (0.97) for detection of low-quality colostrums.[156] Consequently, two of every three low-quality colostrum samples were incorrectly classified as acceptable. Colostrometer readings are also significantly affected by temperature,[157] and for a known quality of colostrum, the colostrometer can differ by 0.8 g/L for every 1° C (1.8° F) change in temperature. The specific gravity of colostrum can also differ among breeds and can be influenced by lactation number, month of calving, year of calving, and protein yield in the previous lactation.[77] Field experience has shown that colostrometers are most accurate for diagnosing samples of moderate or inferior quality but may indicate erroneously high readings for samples in the superior range.[40] It should be noted that the markings on a colostrometer are calibrated for Holstein cows. However, as a comparative field test, it can still be a useful tool, where calves are force-fed colostrum. In a non-interventionist situation, the dam's colostral immunoglobulin is not a good predictor of the level of immunity that the calf will attain.[37,38] From a practical perspective, colostrometers are very fragile because they are made of glass, which can render them unsuitable in a farm environment.

Cow-side immunoassay kits for measuring colostral IgG are available and have been shown to have an acceptable sensitivity and specificity for this purpose.[158] However, their lack of availability on a global scale limits their use along with financial constraints.

Optical and digital Brix refractometers can be used to measure the quality of colostrum using fresh and frozen samples.[159] The optical Brix refractometer demonstrated a specificity of 85% and sensitivity of 90.5% using a cutoff of 22% Brix. A cutoff of 22% Brix was deemed to equate to 50 g/L of immunoglobulin using radial immunodiffusion (RID); thus samples greater than 22% Brix were considered to be of adequate quality.[159] In another study, the results

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showed a cutoff point of 21% was estimated in samples greater than 50 g/L, as measured by RID.[49]

The benefits of the Brix refractometer are that they are not affected by ambient temperature and they are robust, easy, and economical to use at an on-farm level.[160] It has been found that high-quality colostrum samples can yield a "fuzziness" through the viewfinder of a Brix refractometer. Generally this happens in samples greater than 22%. A smaller sample size on the prism can help with clarity in these high-quality samples. The poorer the quality of colostrum, the clearer the value is to read.

Brix refractometers are inexpensive, easily available, and robust, and as such should be standard dairy farm equipment. Farmers should be advised to purchase a refractometer that only measures degrees Brix with a scale from 0% to 32% so that they are easy to read. To get an accurate reading, it is necessary to press the cover plate firmly over the prism while looking through the viewfinder, since some thick samples will cause the cover plate to lift off the prism. It is also important that each sample is placed on a clean, dry prism.

Enhancing IgG Uptake. Numerous attempts have been made to artificially augment passive transfer by addition of substances to colostrum that aim to increase efficiency of absorption or provide an increased concentration of immunoglobulins. Addition of dried colostrum powder,[95,162] casein, or concentrated whey protein[163,164] had no benefit or a detrimental effect on colostrum absorption. Feeding of colostrum containing 1000 IU vitamin E to calves does not influence uptake of IgG by the calves, but did result in higher levels of vitamin E in the calf plasma.[165] Similarly, the addition of 30 g of sodium bicarbonate to colostrum had no effect on uptake.[166] However, some studies have demonstrated positive benefit. The addition of spray-dried bovine serum to lower-quality colostrum to provide the equivalent level of IgG as found in a high-quality colostrum resulted in a higher level of IgG at 12 and 24 hours.[167]

The addition of 5 g/L of the mineral adsorbent zeolite (clinoptilolite), up to a total of 0.5 g/kg body weight/day, has been shown to increase the rate of absorption of colostrum in the first 16 hours and in some cases increase serum IgG at 24 and 48 hours, especially where lower colostrum volumes were fed.[168-170] The exact reason for this has not been explained, but it is thought that clinoptilolite may bind some degradation products of colostral proteins in the gut, such as ammonia, thus preventing their negative effects on mucosal epithelial cells designated for immunoglobulin absorption. It may also slow the passage rate of digesta through the intestine, allowing increased time for absorption. The addition of 1 and 2 g/kg of body weight/day has a negative effect on IgG levels at 24 and 48 hours, but when colostrum from cows vaccinated against K-99 and F-41 antigens of *E. coli* was provided, calves fed 1 and 2 g/kg body weight/day had increased blood serum levels of specific antibodies against *E. coli* at 12, 24, and 48 hours.[171,172] In all of these studies, very high-quality colostrum was fed (80 to 100 g/L) and no more than 2 L was fed at any one feeding and often 0.75 L to a 35-kg calf. The benefits of clinoptilolite when larger volumes of lower quality colostrum are fed has not been evaluated. When clinoptilolite is added to milk replacer as well as colostrum, an added benefit of increased hemopoiesis is seen, presumably because this mineral is high in iron.[172,173]

Increased uptake of IgG also occurs when a gut-active carbohydrate (mannan-oligosaccharide) is added to colostrum at a rate of 5 g/L. A 4.5-L amount of colostrum was fed at 2, 12, and 24 hours after parturition and calves receiving the gut-active carbohydrate had a higher level of IgG from 6 hours after birth right through until 21 days postpartum.[174] Again, the mechanisms responsible for this effect have yet to be elucidated. Bacteria in colostrum may directly block uptake and transport of immunoglobulin molecules across intestinal epithelial cells or bind free immunoglobulin in the gut lumen.[34,135] Gut-active carbohydrates have been shown to adsorb pathogens expressing type 1 fimbriae, reducing their ability to colonize the gastrointestinal tract; in addition, carbohydrates play a role in uptake of IgG from the gastrointestinal tract, and gut-active carbohydrates could enhance IgG uptake in a direct manner.

These studies demonstrate that it is possible to influence uptake of IgG with specific additives, and further research is required to investigate their potential while accommodating the variation in colostrum IgG concentration and standard management practices within herds.

MONITORING FOR SUCCESSFUL PASSIVE TRANSFER. Monitoring programs for FPT are an integral step in neonatal calf disease outbreaks and proactive calf health programs. A range of tests have been used to assess passive transfer.[175-177] The RID is considered the gold standard and is a direct measure of serum IgG. However, its usefulness is compromised by the processing time and expense. There is some variation in the published research as to the level of serum IgG that indicates adequate passive transfer, but most researchers use 10 mg/mL (1000 mg/dL).[113,175,178,179]

The sodium sulfite and zinc sulfate turbidity tests use salts to precipitate serum proteins, in particular the larger-molecular-weight immunoglobulins. A measured amount of calf serum is added to a standard volume of solution and incubated at room temperature for up to 30 minutes. The test results are quantified according to the degree of cloudiness of the mixture caused by protein precipitation. The sodium sulfite turbidity test has traditionally been described as a three-step semi-quantitative test using 14%, 16%, and 18% solutions. The sensitivity, specificity, and degree of association with IgG are similar to measuring serum protein with a refractometer, but the test is more complicated to perform.[175] The sensitivity has been estimated between 85% and 100% and the specificity between 53% and 87% using an 18% solution (1+ endpoint).[175,179] The zinc sulfate turbidity test can be influenced by hemolysis, making it difficult for routine use.[136] The standard test is carried out by adding 0.1 mL of calf serum to 6 mL of 208 mg/L zinc sulfate and incubating the mixture for 1 hour at 23° C (73.4° F). The test has a sensitivity of 100% and a specificity of 55%, which is lower than serum protein or sodium sulfite turbidity.[175] The specificity of the test can be improved by increasing the strength of the solution to 300 or 350 mg/L.[180] These solutions resulted in an increase of the specificity to 65% and 76%, respectively, with little decrease in sensitivity.

Measurement of serum γ-glutamyltransferase (GGT) in calves aged 24 hours can indicate positive ingestion of colostrum but has poor correlation with actual serum IgG levels.[181] A limitation of this test is that serum GGT declines rapidly during the first week of life.[182] Thus, accurate records reflecting the age of the calf are vital for this test to be interpreted accurately. Both colostrum and milk contain GGT, but activities in milk are considerably lower than in colostrum.[183] GGT rises quickly after the ingestion of colostrum and then falls rapidly over the subsequent 24 hours followed by a slow decline for the next 2 months. Calves that do not ingest colostrum have serum GGT activities similar to adult cattle. GGT is a useful test when assessing the passive transfer status of clinically ill calves less than 21 days of age where disease confounds interpretation of serum proteins. A GGT cutoff of 50 IU/L classifies 93% of calves correctly (sensitivity 93%, specificity 92%).[184]

The on-farm lateral flow immunoassay is one method for identifying calves with less than 10 mg/mL serum IgG. It takes approximately 20 minutes to perform and is relatively inexpensive but is not commercially available worldwide. The test yields only a positive or negative result as opposed to the actual level of serum IgG. This is considered a limitation of the test.[34] Published results show the sensitivity ranges from 93% to 99% and specificity from 88% to 89%.[179,185]

An optical handheld clinical refractometer may be used to measure serum protein of calves aged between 24 hours and 7 days of age. Although it is not a direct measurement of IgG concentration, it is considered an accurate indicator of the immunoglobulin status of the animal (Table 19-3).[186] Studies have compared refractometry to turbidity testing and GGT activity and have shown that it is equivalent or superior to these assays in the proportion of calves classified correctly.[3,175,181,182] This method is easier to standardize among laboratories and operators than many other indirect methods and is cheaper, quicker, and easier than most direct tests for IgG.[3] A

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TABLE 19-3[175]

Relationship between Serum Protein and Serum IgG* ($R^2 = 0.76$)

Serum Protein (g/dL)	Serum IgG (mg/mL)
6.5	22.4
6	17.9
5.5	13.4
5.2	10.7
5	8.9
4.5	4.4
4	0

*It should be recognized that there is variation among refractometers.[189]

minimum of 12 calves need to be sampled and, when interpreted on a group level, provides a good correlation between serum protein and serum IgG, as measured by RID.[34] Sick (scouring) calves should not be included in the sample set because dehydration will falsely elevate the serum protein. It has been suggested that the accuracy of serum protein could be improved if a PCV was also measured as a proxy for hydration status.[184] The benefits of this method are that it is quick and inexpensive and samples do not need centrifugation.[187] This has an added advantage since it can be implemented at the farm level on large calf-rearing units to monitor for failure of passive transfer in groups of calves. A serum protein concentration less than 5.0 g/dL reflects failure of passive transfer and 5.0 to 5.5 g/dL marginal passive transfer. At a herd level the target should be for 80% of calves to have serum protein concentrations greater than 5.5 g/dL.[126] Assessment of serum protein using a refractometer is not a reliable estimate of IgG levels in calves that have received colostrum substitutes or replacers.[188]

TREATMENT OF FPT. Calves may be treated for FPT by the administration of bovine plasma at 20 to 40 mL/kg. The initial rate of administration should be 5 mL/kg with close observation for adverse effects, which most commonly include trembling, hives, edema, piloerection, stertorous breathing, and increases in heart rate and respiratory rate. If no adverse effects are noted in the first 30 minutes, the rate can be increased to 10 to 20 mL/kg/h with continued monitoring.[190] Whole blood can also be used, but the dosage should be increased to account for the presence of red blood cells.[136] Calves should be monitored as for plasma transfusions; adverse reactions are very uncommon on first-time transfusions since there are a large number of blood types in cattle. Plasma or whole blood may also be administered via the intraperitoneal route. An area in the center of the left paralumbar fossa is clipped and surgically prepared. A 14- to 16-gauge, 1.5-inch needle is used to penetrate the skin, abdominal musculature, and peritoneum, and the serum is administered through a giving set.[136] Precautions should also be taken to minimize risk factors for infection in these calves, including minimizing potential exposure to pathogens. Colostrum may be fed beyond the period of closure to provide protection at the level of the gut lumen. Where the environment is less than desirable, the prophylactic administration of broad-spectrum parenteral antimicrobials in calves with FPT should be considered.

Long-Term Benefits of Adequate Colostrum Uptake

In on-farm monitoring programs for effectiveness of passive transfer, IgG levels are often inferred by measuring serum total protein. A serum protein below 5 g/dL (approximately 9 mg/mL IgG) will result in a 2.4 to 6 times greater risk of mortality up to 6 months.[3,4,191,192] There is still an increase in relative risk of mortality when serum protein is between 5 and 5.5 g/dL compared with greater than 5.5 g/dL (IgG 13.4 mg/mL), but it is not as marked, and the cost benefit of ensuring all calves achieve a serum protein greater than 5.5 g/dL to prevent mortality is questionable.

On any farm, the baseline mortality will reflect management, nutrition, and the pathogens present. The risk of mortality associated with varying level of passive transfer is independent of baseline mortality rate. Hence, where the baseline mortality is high, adequate passive transfer will not prevent calves dying, but as serum immunoglobulin level decreases below 13.4 g/L, the risk of mortality will increase relative to that herd's specific baseline mortality. It is important to recognize that the majority of calves with total FPT will survive, especially where baseline mortality is low.[3,193] The role of the passive transfer of immunity in preventing morbidity per se is well documented, but the effect of immunoglobulin levels on prevalence of specific disease syndromes varies. Epidemiological studies reflect the variation in management, environment, and disease pathogens among properties, and a greater impact of other risk factors on disease incidence. Consequently, there are inconsistent results on the impact of adequate passive transfer on both of the main calfhood diseases: diarrhea and pneumonia, also reflecting study design and varying serum IgG levels used to define FPT.[4,5,18,194-197] Studies on the risk of pneumonia generally demonstrate FPT as a risk factor, but the impact of FPT as a risk of diarrhea is less consistent. Often where a significant effect of IgG levels on the incidence of a specific disease has not been demonstrated, increasing the sample size to look at the correlation with all calves treated with antibiotics or all morbid calves within the study has demonstrated a significant benefit of adequate passive transfer. The benefits of adequate passive transfer on disease incidence is likely to be long lasting, with evidence of ongoing prevention of postweaning disease, particularly feedlot pneumonia, although again not all studies demonstrate this effect.[4,7,198]

A better indication of the effect of passive transfer on disease appears to be consistent positive correlation demonstrated between adequate passive transfer and average daily weight gain, both preweaning and postweaning.[5-7,196,197,199] It is likely that much of the variation in weight gain is a result of changes in the incidence of disease.[4,198,199]

Navel Treatment

Omphalitis occurs in 1% to 14% of newborn calves.[200,201] It can lead to reduced growth, joint ill, and other adverse sequelae associated with bacteremia.[202] Prevention of navel ill is based on maintenance of maternity pen hygiene, reducing the residency time of calves in unhygienic maternity pens, ensuring adequate early intake of good quality colostrum, and navel antisepsis.[203] Literature on the efficacy of navel treatment at reducing calf mortality is divided. In a study of 104 dairy farms, a farm policy of navel treating newborn calves had no significant effect on calf mortality rates. A significant beneficial effect was observed when the navels of calves that had assisted deliveries were dipped with chlorhexidine; other navel treatments such as iodine tended to be associated with an increased odds of dying.[204] In a controlled clinical trial investigating the efficacy of navel dips, a reduction in the incidence of omphalophlebitis was observed in calves when navels were dipped with tincture of iodine (7% iodine), dilute iodine (0.5% or 0.2%), or a commercial product (Navel Guard [NG], Sirius Chemical Group, McDonough, GA) as compared with calves with nondipped navels.[200] Conversely, navel treatment with iodine was associated with significantly higher mortality in another study of 48 farms; however, the association of navel treatment with mortality on these farms may have reflected the response of producers to high neonatal mortality rather than indicating iodine navel treatment as a risk factor for high calf mortality.[205]

Nutrition

Although the neonatal calf stomach has four parts, the rumen is not functional at birth. At birth the abomasum is the only truly functional part and has a capacity twice that of the other compartments. Liquid is shunted past the reticulorumen into the abomasum via the esophageal groove. The groove is closed by a reflex that is stimulated by the intake of liquids; milk is the best, and electrolyte and glucose water is usually effective, but straight water becomes ineffective in

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closing the groove fairly early in life. The first enzyme to start the process of milk digestion is salivary lipase. When whole milk enters the abomasum, casein is denatured by the acidic (pH 2.0) conditions. Rennin cleaves a specific peptide bond in k-casein, which, in the presence of calcium ions, causes coagulation of the casein proteins. Fat is trapped within the coagulum, but the whey proteins, lactose, and soluble minerals and vitamins are excluded into the liquid portion (whey) as the coagulum contracts. The soluble components enter the small intestine within 2 to 3 hours after a meal, whereas the casein coagulum is digested more slowly.[206] Casein is partially digested by the abomasal protease pepsin. Polypeptides released from caseins enter the small intestine for further digestion. Milk fat trapped in the abomasum undergoes some digestion by the enzyme pregastric lipase, which is secreted in the mouth. The products of its action are diacylglycerols and free fatty acids, which enter the small intestine for further digestion and absorption. Lactose is hydrolyzed to its component sugars, glucose and galactose, by the intestinal brush-border enzyme lactase, and the monosaccharides are absorbed into the epithelial cells by specific active transport proteins.[206] The age at which ruminal digestion begins is dependent on the diet of the calf. Transition to ruminal digestion begins at 3 to 4 weeks of age; the earlier dry feed is provided, the earlier ruminal development starts.

The energy requirements of the calf may be divided into maintenance and growth requirements with the magnitude of maintenance requirements influenced by environmental conditions. The basal maintenance requirement for neonatal calves is between 44.7 and 52.4 kcal/kg of body weight/day.[207,208] Energy requirements for growth are between 268 and 307 kcal/100 g of body weight gain.[208,209] Since whole milk contains about 70 kcal/100 mL, a 40-kg neonatal calf needs about 3 L of whole milk for maintenance and an additional 4 to 5 L to gain 1 kg of body weight. Many calves are raised according to the "calf starter method," which became popular in the early twentieth century.[210] According to this method calves are fed limited amounts of milk (approximately 10% body weight). Milk intake is limited to encourage intake of calf starter, facilitating weaning at about 7 to 8 weeks of age. Forage feeding is discouraged during the milk feeding phase since it lowers starter intake. Rumen papillae growth is stimulated by volatile fatty acid production, in particular butyrate, which is highest in calves consuming larger volumes of starter.[211] During the past decade several studies have challenged the "calf starter method." Limit feeding calves has been shown to lead to poor weight gains,[212] higher risk of disease, and abnormal behaviors, indicating reduced calf welfare.[213] Providing greater quantities of milk or milk replacer improves growth and feed efficiency.[213] To achieve biologically appropriate growth, milk feeding rates are approximately twice those of the calf starter method. A rule of thumb is to provide 1.5% of body weight as milk solids during the first week of life, then 2% of body weight from the second week of life until the week before weaning, when one feeding is dropped.[214] Intake of starter lags behind calves fed on conventional systems, but increases at approximately the same rate once the amount of liquid is cut back.[214] To avoid or minimize growth slumps around weaning, calves should not be weaned until they are consistently eating 1 kg of starter daily.[206] Higher rates of growth observed early in life are associated with reduced breeding age[215] and higher milk yield when the calf matures.[216] Approximately 25% of the variation in first-lactation milk production is explained by preweaning average daily body weight gain.[216]

Cold stress significantly increases energy requirements. A 45-kg calf at −20° C requires about 725 g/d of milk replacer powder just to meet maintenance requirements and maintain body temperature, compared with about 382 g/d of powder under thermoneutral conditions.[206] Similarly, heat stress increases maintenance energy requirements by 20% to 30%.[206] Energy requirements of calves managed at different temperatures is presented in Table 19-4. The requirements for the sick, stressed calf are not well established.

Conventional milk replacers contain 20% to 22% crude protein (CP), but calves benefit most from the increased feeding when milk replacers contain higher protein and lower fat (up to 30% CP with 15% to 20% fat).[217] The digestible protein requirement for maintenance is 0.5 g/kg of body weight, and the amount required for growth is about 22 g/100 g gain in body weight. Digestibility of the protein is an important concern in the evaluation of milk replacers. Some milk replacers substitute legume proteins for milk-derived proteins. Legume-derived proteins contain antinutritional factors (ANFs) that include antigenic proteins, lectins, and trypsin inhibitors.[218] Trypsin provides a protective mechanism against clostridial disease by cleaving the clostridial beta toxin.[219] Soybean flour has been used to experimentally induce *Clostridium perfringens* type C enterotoxemia in lambs.[220]

TABLE 19-4

Maintenance Requirements for Metabolizable Energy as Affected by Body Weight (BW) and Environmental Temperature in Calves Less Than 21 Days Old

	Environmental Temperature (°C)				
	20	10	0	−10	−20
BW (kg)	(Maintenance ME, Mcal/d)				
30	1.28	1.63	1.97	2.38	2.67
40	1.59	2.02	2.45	2.96	3.31
50	1.88	2.39	2.90	3.50	3.91
60	2.16	2.74	3.32	4.01	4.48

Data from National Research Council. 2001. Nutrient requirements of dairy cattle, ed 7. National Academy Press, Washington, DC.

ME, Metabolizable energy.

Clinical Investigation of Neonatal Disease

The principles of clinical investigation of neonatal disease are similar to those of adults; however, the neonate signalment carries with it a higher risk for sepsis, congenital malformations, and a number of specific neonatal diseases resulting in a shift in the emphasis of history, physical examination, and diagnostic work-up. When a single individual is involved, observation from a distance, recording of vital signs, and a physical examination guide the clinician to the selection of appropriate diagnostic tests to establish a cause, make a diagnosis, and evaluate the prognosis. For conditions that affect a flock or herd of animals, the examination of affected individuals remains an essential component of the diagnostic work-up, but evaluation of records, the environment (housing and other animals), nutrition, colostrum, treatment, and vaccination protocols is also needed.

History

The investigation of neonatal disease problems is facilitated by the defined period of risk and temporal distribution of the more common disease syndromes. For health problems involving individuals or the flock/herd, it is best to start at birth and work forward. For the individual, a history of dystocia indicates the likelihood of neonatal compromise and the possibility of failure of passive transfer. The risk of specific diseases may be influenced by pathogen-specific immunity, which may be manipulated through either maternal or neonatal vaccination. Details of the farm's vaccination protocol should be collected. At a herd level, the likelihood of failure of passive transfer and the efficacy of maternal vaccination are determined by colostrum management. From a herd perspective, it is important to determine the farm's protocol for harvesting, storing, and administering colostrum since these protocols determine immunoglobulin and microbial quality and the likelihood of achieving adequate passive transfer.

Risk of neonatal infectious disease is determined by the balance between host immunity, environment, and pathogen dose and virulence. Management should strive to maximize host immunity through good colostral management, provision of adequate nutrition, and minimization of environmental stress. The risk of pathogen

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TABLE 19-5

Guide to Assessing the Degree of Dehydration and the Base Deficit of Calves with Neonatal Diarrhea[222]

Clinical Signs	Percentage of Dehydration (%)	Approximate Base Deficit (mmol/L)
History of diarrhea with minimal clinical signs	5	5
Eyes beginning to sink (2-4 mm), skin turgor decreased (skin tent duration of 1-2 seconds), suckling reflex present	About 7 (mild dehydration)	10
Eyes sunken (4-6 mm), skin turgor more decreased (skin tent duration of 2-5 seconds), mucous membranes tacky, suckling reflex decreased, cool extremities, calf depressed, able to stand but with difficulty	About 9 (moderate dehydration)	15
Eyes deeply sunken (6-8 mm), skin tents and does not return or very slowly (5-10 seconds), dry mucous membranes, suckling reflex very weak or absent, cold mouth, cold extremities, calf depressed, unable to stand and possibly comatose	About 11 (severe dehydration	20
Eyes very deeply sunken (8-12 mm), calf comatose or dead	<12 (fatal dehydration)	>20

exposure is influenced by environmental conditions at birth, amount of time spent with the dam, facility hygiene, colostrum and milk hygiene, personnel hygiene, and neonate age grouping. Defining the onset and progression of disease is useful because certain diseases are more likely to occur at different times. Response to treatment or lack thereof may provide clues regarding pathogen involvement, and details of treatment protocols may identity inappropriate ineffective treatment. Occasionally disease is iatrogenic, so it is important to collect details of all products administered, specifically how much, at what time, frequency, and by what route.

Examination from a Distance

The physical examination begins with examination from a distance with assessment of behavior, body condition, and stance. Drooping of the head and ears is an early sign of illness. Sick calves spend increasing amounts of time recumbent and are less inclined to drink. In beef calves, lambs, and kids, this may be reflected by udder distention in the dam. With dairy calves the calf feeder may report that the calf requires stimulation to stand and fails to drink. Abdominal contour should be noted with consideration of the neonate's reported appetite; an apparently normal abdominal contour may be abnormal if the calf has not eaten for a couple of days. Observing the neonate navigate its environment provides a simple assessment of vision. From a distance, mentation, posture, vision, abdominal contour, stance, lameness, respiratory rate, breathing effort, characters of nasal and ocular discharge, and spontaneous coughing can be evaluated. Abnormal postures exhibited by patients with respiratory conditions may be recumbency, open-mouth breathing, abnormal extension of the head and neck, head tilt, or reluctance to lie down. Abnormal breathing characteristics include prolongation of the inspiratory or expiratory phase of respiration, an expiratory abdominal press or snap, marked tachypnea, frequent spontaneous coughing, stridor, or inspiratory or expiratory noises. Abnormal mentation of neonatal ruminants may be the result of meningoencephalitis, hypoglycemia, hypoxic-ischemic encephalopathy, calving injury, or severe metabolic acidosis. Abnormal posture of the head and neck are exhibited by neonates with respiratory difficulty, but meningoencephalitis, otitis media, hypernatremia, polioencephalomalacia, congenital defects of the central nervous system, and lasalocid toxicity should be considered.

Examination from a distance on farm also provides an opportunity to assess the neonate's environment. Environmental and/or management-induced compromise in the form of inappropriate stocking density, mixed age groups, inadequate ventilation or shade, wet muddy conditions, inadequate protection from adverse weather, evidence of poor hygiene, inappropriate feed on offer, and excessive fly challenge may all contribute to the risk of disease.

Hands-on Examination

PHYSICAL APPEARANCE, BODY WEIGHT, AND BODY CONDITION. Congenital disorders may present with subtle changes in physical appearance and behavior. For example, Saler calves with β mannosidosis have moderately domed heads, mild superior brachygnathism, and a slight head tremor.[221] Similarly, in utero infections that lead to growth retardation may be reflected by low birth weight and poor body condition.

Head. Observation of facial expression provides an opportunity to assess cranial nerve function. Normal eyeball position and movement is consistent with normal function of cranial nerves (CNs) 3, 4, 6, and 8. Normal facial expression as well as ear and eyelid position suggest normal function of CN 7. Vision (CN 2) is assessed by watching the neonate navigate its environment. Because the menace response is learned and does not appear for several weeks after birth, it is not particularly useful in very young animals. Normal sucking behavior is consistent with normal function of CNs 5, 7, 9, and 12. Absence of atrophy of the neck is consistent with normal function of CN 11. Function of CNs 5, 6, and 7 is further assessed by the palpebral and corneal reflexes and CN 2 and 3 by the pupillary light response. Eyeball position and skin tent duration are used to assess dehydration and estimate base deficit in calves with diarrhea (Table 19-5).

Depressed mentation is a feature of a number of neonatal diseases. Sepsis and diarrhea are both commonly associated with depressed mentation as a result of toxemia and/or metabolic derangements. Bacterial meningitis is common in neonates following bacteremia; diarrhea, septic arthritis, omphalophlebitis, and uveitis are frequent concurrent clinical problems. The clinical signs of meningitis in neonates, lethargy, anorexia, and recumbency are nonspecific. Concurrent metabolic derangements may appear to provide an adequate explanation for the observed depressed mentation. In a retrospective study of 32 cases of bacterial meningitis in calves, concurrent metabolic derangements included hyperkalemia (15/25, 60%), respiratory acidosis (11/24, 46%), hypernatremia (3/20, 15%), and hypoglycemia (3/7, 43%).[223] The more classic clinical signs described for bacterial meningitis in older animals—fever, opisthotonos, extension of the head, convulsions, hyperesthesia, and signs of neck pain—may not be evident or not perceived in neonates. Seizures in calves are often subtle, manifested as facial twitches or jaw champing. Common causes of cerebral disease in lambs and kids include polioencephalomalacia and focal symmetrical encephalomalacia. Affected animals are typically depressed and blind but have normal pupillary light reflexes.

Mouth. Examination of the mouth includes assessment of the mucous membranes, moisture, color, and capillary refill time. Mucous membranes are moist and pale pink with a capillary refill time of less than 2 seconds. Gray or cyanotic mucous membranes are associated with severe hypoxia, circulatory collapse, hypovolemic shock, cardiovascular anomalies causing a right-to-left shunt, and/or severe pulmonary disease. Absence of cyanosis is not a reliable indicator of adequacy of oxygenation in the neonate, since the partial pressure of oxygen may reach very low levels (<35 to 40 mm Hg) before cyanosis is observed. Cardiac and pulmonary causes of cyanosis must be distinguished. Petechiae on the oral or nasal mucous membranes are consistent with sepsis-induced vasculitis or thrombocytopenia

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FIG. 19-1 Petechial hemorrhages on the underside of the tongue of a calf with thrombocytopenia.

induced by type II bovine virus diarrhea (BVD) (Fig. 19-1). Proliferative lesions may be observed with bovine popular stomatitis in calves or lambs. Oral erosions are often observed with BVD infections in calves. Common congenital defects include cleft palate and brachygnathism (inferior and superior). The hard and soft palate should be evaluated; animals with cleft palate may have milk run from the nose and are prone to developing aspiration pneumonia. Examination of the mouth should include assessment of breath odor. A malodorous breath may be present with necrotic pharyngeal injuries, necrotic laryngitis, cleft palate, or aspiration pneumonia. Application of slight pressure on the larynx exacerbates inspiratory stridor associated with necrotic laryngitis. Airflow from each nostril should also be assessed. Conditions causing occlusion of the upper airway, such as choanal atresia, necrotic laryngitis, pharyngeal swelling or edema, often induce pronounced inspiratory dyspnea, stridor, and/or open-mouth breathing.

Eyes. Eyes should be examined for the presence of entropion, ectropion, corneal abrasions or ulcers, uveitis and hyphema, congenital cataracts, microphthalmia, corneal dermoids, scleral injection, and scleral hemorrhage. Entropion is a relatively common cause of corneal edema and ulceration, conjunctivitis, and lacrimation in lambs. Entropion should be corrected promptly before serious corneal ulceration and keratitis develops. Mild cases may respond to subcutaneous injections of procaine penicillin G into the lower eyelid. Alternatively, entropion may be corrected by placement of vertical or horizontal mattress sutures in the affected eyelid to correct the problem. Treatment following correction of entropion includes topical administration of 1% atropine to dilate the pupil and relieve ciliary body spasm and topical antibiotics to prevent bacterial infection.

Examination of the sclera is useful to detect icterus, scleral injection, and scleral hemorrhage. Icterus may be observed as a result of liver or hemolytic diseases; both tend to be uncommon in newborn milk-fed neonatal ruminants. Conversely, scleral injection is a common finding and suggests sepsis. Observation of fibrin in the anterior chamber of the eye of a neonate is highly indicative of sepsis. Ecchymotic hemorrhages may be observed on the sclera with type II BVD infections, bovine neonatal pancytopenia, disseminated intravascular coagulopathies, or following birth trauma.

Ears. Bilateral drooped ear carriage is a common observation with sick calves and should prompt a closer examination. Unilateral ear droop may be observed with otitis and facial nerve paralysis. *Mycoplasma* spp., *Pasteurella* spp., and *Haemophilus* spp. are reported to cause otitis in calves. Clinical signs may include facial and vestibular nerve deficits and a purulent discharge from the ear. Calves infected with *Mycoplasma* spp. may also present with tenosynovitis and respiratory disease. Poor perfusion is reflected by cold extremities. A high incidence of pinna abscesses usually reflects contamination of equipment used to place ear tags. Ears should be warm and mobile.

Neck and Back. A number of congenital anomalies affect the alignment of the vertebral column, including atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies, such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Holstein calves affected by the hereditary condition complex vertebral malformation may present with a range of abnormalities that include retarded growth, malformation of the head (dysplasia or palatoschisis), bilateral symmetric flexion of the carpal and metacarpophalangeal joints, posterior arthrogryposis, and interventricular septal defects. Of these, growth retardation, vertebral malformation, and symmetric arthrogryposis are the most consistent findings.[224]

The neck and brisket should be examined to evaluate jugular fill and to detect brisket edema. Distention of the jugular veins and brisket edema are consistent with right-sided heart failure but may be absent with left-sided heart failure. Examination of the skin on the side of the neck is a good place to detect lice and fleas, and a skin fold test is performed to assess hydration. Parotid and prescapular lymph nodes should also be palpated to assess size and symmetry. Enlargement of all peripheral lymph nodes may be observed with juvenile lymphoma. Enlargement of specific nodes suggests a localized inflammatory response.

Thorax. Heart and respiratory rates vary with activity, excitement, and feeding. Tachypnea can be attributed to elevated temperature humidity index, fever, thermoregulation dysfunction, excitement, pain, stress, respiratory disease, hypoxia (cardiac disease, pulmonary disease, shock), dehydration, shock, toxemia, or metabolic acidosis. Periodic apnea and abnormally slow respirations are often the result of metabolic disturbances (hypoglycemia, hypocalcemia), hypothermia, prematurity, or hypoxia-induced suppression of the respiratory center. Tachycardia may be present with excitement, pain, injury, inflammation, toxemia, dehydration, shock, infectious disease, metabolic acidosis, hypokalemia, hypocalcemia, or heart disease. Bradycardia of neonatal ruminants may be associated with hyperkalemia, central nervous system dysfunction, hypothermia, or starvation.

Cardiovascular disease in neonates may be primary or secondary to other disease processes. Congenital cardiac anomalies may be asymptomatic. Dyspnea and coughing are often the predominant clinical signs of congestive heart failure in calves. Cardiac auscultation should be carried out systematically with the aim of evaluating cardiac rhythm and detecting normal heart sounds and cardiac murmurs. In most calves the first and second heart sounds are easily audible. The third heart sound is not normally heard in calves, and fourth heart sounds are heard infrequently.[225] Cardiac murmurs are not uncommon during the newborn period. Various congenital anomalies of the heart occur in cattle as the result of defective septa and formation of the cardiac chambers.[226] The prevalence of congenital heart disease in cattle has been reported to be approximately 0.7%,[227] with ventricular septal defects representing the most common type.[228] Other frequent defects include non-cyanotic anomalies (atrial septal defect, patent ductus arteriosus without pulmonary hypertension) and cyanotic anomalies (tetralogy or pentalogy of Fallot, Eisenmenger's complex associated with a reversion of a previously left-to-right shunt resulting from pulmonary hypertension).[226] The prevalence of the different congenital heart diseases in calves is shown in Table 19-6. Serious heart anomalies may not be accompanied by any murmur, whereas a closing ductus arteriosus may cause a murmur that is very loud. This normal ductal murmur is best ausculttaed on the left side of the chest at the third intercostal space at the level of the shoulder. In some instances, however, it is described as a continuous machinery-type murmur, but far more commonly a grade II-V/VI holosystolic murmur is auscultated. Cardiac auscultation will determine heart rate, rhythm, and the presence of murmurs. Abnormal radiation of heart sounds caudal to the fifth intercostal space or dorsal to the level of the scapulohumeral joint on either side of the thorax should be noted. Thoracic percussion may be used to

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TABLE 19-6

Prevalence of the Most Common Congenital Heart Diseases in Calves, According to Ohwada and Murakami (2000)*[226,229]

Congenital Heart Diseases	No. of Cases
Ventricular septal defects	198
Atrial septal defects	148
Double outlet right ventricle	66
Aortic stenosis	53
Double cranial vena cava	50
Patent ductus arteriosus	45
Anomaly of the caudal vena cava	42
Tetralogy of Fallot	32
Hypoplastic left ventricle	25
Transposition of the great arteries	24
Abnormal pulmonary vein connection	21
Total	704

*A total of 469 cases of congenital heart diseases were studied.

identify the presence of thoracic fluid, cranioventral consolidation, or atelectasis in neonatal ruminants.

Cardiac arrhythmias are observed sporadically in neonates, often associated with diarrhea. Metabolic acidosis resulting from losses of electrolytes and water causes a transcellular shift of potassium ions into the extracellular fluid in exchange for hydrogen ions.[230] Hyperkalemia decreases the membrane potential and slows down impulse conduction by inactivating Na channels.[231] As serum potassium increases (>5.5 mEq/L), aberrations in cardiac excitability occur and are manifested as progressive atrial standstill, progressing to ventricular fibrillation and asystole.[232] The response of the myocardial cells to catecholamines decreases with the reduction of blood pH.[231] Influxed H+ ions repress ventricular contraction by competing with $Ca2^{+}$ ions in binding to myocardial troponins.[231] Tachyarrhythmias may be observed in calves with cardiomyopathies, ionophore toxicosis,[233] or hypomagnesemia.

Cardiomyopathy resulting from selenium deficiency, gossypol, monensin, or lasalocid toxicity may present as a syndrome of sudden death during periods of excitement precipitated by feeding or moving calves out of hutches into group pens.[234]

Inspiratory stridor is often a feature of extra-thoracic airway obstruction, and increased abdominal effort on expiration is an indication of pulmonary disease causing reduced lung compliance. Lung disease in the newborn is usually diffuse and is the result of infection acquired in utero or postpartum and/or lung atelectasis associated with immaturity, recumbency, or surfactant dysfunction. Signs of lung disease include increased work of breathing characterized by nostril flare, rib retractions, and increased abdominal effort. A cough and nasal discharge, salient features of respiratory disease in older neonates, are infrequent findings in newborns with lung disease. Animals with few or no audible thoracic abnormalities may have severe respiratory disease.

Auscultation of the trachea, thorax, and occasionally the nasal passage is an essential element of the respiratory examination. Tracheal compression should not induce multiple coughs. Lung sounds of neonates are typically easier to hear than adults; however, lung sounds do not always correlate well with the severity of the respiratory condition that is present. Interpretation of the intensity of thoracic breath sounds can be validated by comparison to tracheal breath sounds. The intensity of tracheal breath sounds is gradually attenuated as the stethoscope is moved from trachea to the lung hilus and again to the anteroventral thorax and finally to the caudal thorax in normal animals. Loud tracheal breath sounds that are not attenuated over the thoracic area may be indicative of atelectasis, lung consolidation, or cardiac enlargement. Added breath sounds such as crackles or wheezes should be noted but may not be heard without augmenting the depth and frequency of the breathing effort with the use of a rebreathing bag.

Abdomen. Much can be learned about gastrointestinal function by observing abdominal contour, appetite, and fecal consistency and volume. A normal abdominal contour and vigorous appetite associated with the passage of an appropriate volume of pasty stool suggests normal gastrointestinal function. Examination of the neonatal ruminant should include assessment of abdominal size and contour.

Gradual abdominal distention may be observed with congenital atresia of the gastrointestinal tract. Atresia may be observed in the colon (coli), rectum (recti), or anus (ani); the spiral loop of the ascending colon (spiral colon) is the most commonly affected segment of intestine affected in calves.[235] Neonates presenting with atresia often have a distended abdomen and a history of a declining appetite. Astute owners may notice the lack of or reduced volume of feces.

External palpation of the abdomen can be rewarding, depending on the cooperation of the individual and the tenseness of the abdominal musculature. In calves it is usually possible to palpate enlargement of the umbilical vein and arteries. The inguinal rings and umbilical area should also be palpated for hernias. Abdominal auscultation, although important, is not used for forestomach and intestinal motility parameters typically evaluated in the adult ruminant, but the procedure, along with simultaneous auscultation and succession, ballottement, or percussion, may show evidence of gas, fluid, or disordered motility. Abnormal forestomach function in neonatal ruminants is often reflected by altered abdominal contour. Left and right abomasal displacement and abomasal torsion are observed sporadically in calves. Succussion (simultaneous auscultation and percussion) is useful for delimiting the boundaries of distended visci. Passage of a stomach tube helps distinguish rumen and abomasal distention and facilitates collection of a rumen fluid sample. A putrid odor to neonatal rumen fluid is common with putrefactive indigestion when milk is delivered to the rumen in greater quantities than normal by escaping the esophageal groove or via excessive backflow from the abomasum. Reflux of abomasal contents into the reticulum and rumen, independent of feeding, occurs in connection with abomasal inflammation and obstructions.[236] Evaluation of rumen fluid pH and renin activity are useful for distinguishing abomasal reflux from esophageal groove overflow. Rumen fluid pH is usually 7 or greater with rumen putrefaction, and low to normal with abomasal reflux.[236] Chymosin (renin) is normally present in abomasal juice, and renin activity in rumen fluid suggests abomasal reflux.[237] Renin activity is measured by adding 2 mL of rumen juice to 2 mL of whole milk on a California mastitis test (CMT) plate. Presence of renin in the ruminal fluid causes coagulation of the casein in the milk. Chloride ion concentration in rumen fluid from calves is higher than adults (55-102 mmol/L calves,[238] 25 mmol/L adults[236]), possibly reflecting the high chloride content of milk (45 mmol/L); as such, the chloride concentration of rumen fluid is not useful for identifying abomasal reflux in calves.

Abomasal ulceration may lead to localized or generalized peritonitis. Normal peritoneal fluid from calves has a higher nucleated cell count than that of adult cattle (3350 cells/μL vs. 1371 cells/μL). The total protein concentration in peritoneal fluid of calves is similar to that of adults (2.5 g/dL vs. 3.1 g/dL).[239]

Umbilicus. After rupture of the umbilical cord, the two umbilical arteries retract actively, and the urachus is pulled back passively by these vessels into the abdomen. Smooth-muscle contraction brings about luminal closure. The umbilical arteries ultimately become the lateral ligaments of the urinary bladder.

The umbilical vein does not retract, but collapses in association with some minor smooth muscle contraction. The umbilical sheath shrinks and dries within 3 days postpartum. The body wall closes completely around the umbilical structures within days to a few weeks.[240]

During the physical examination, the navel is assessed for diameter, discharge, and pain while the neonatal ruminant is standing and again while it is in lateral recumbency. Abdominal palpation, using both hands pressing together, is useful for evaluating the umbilicus

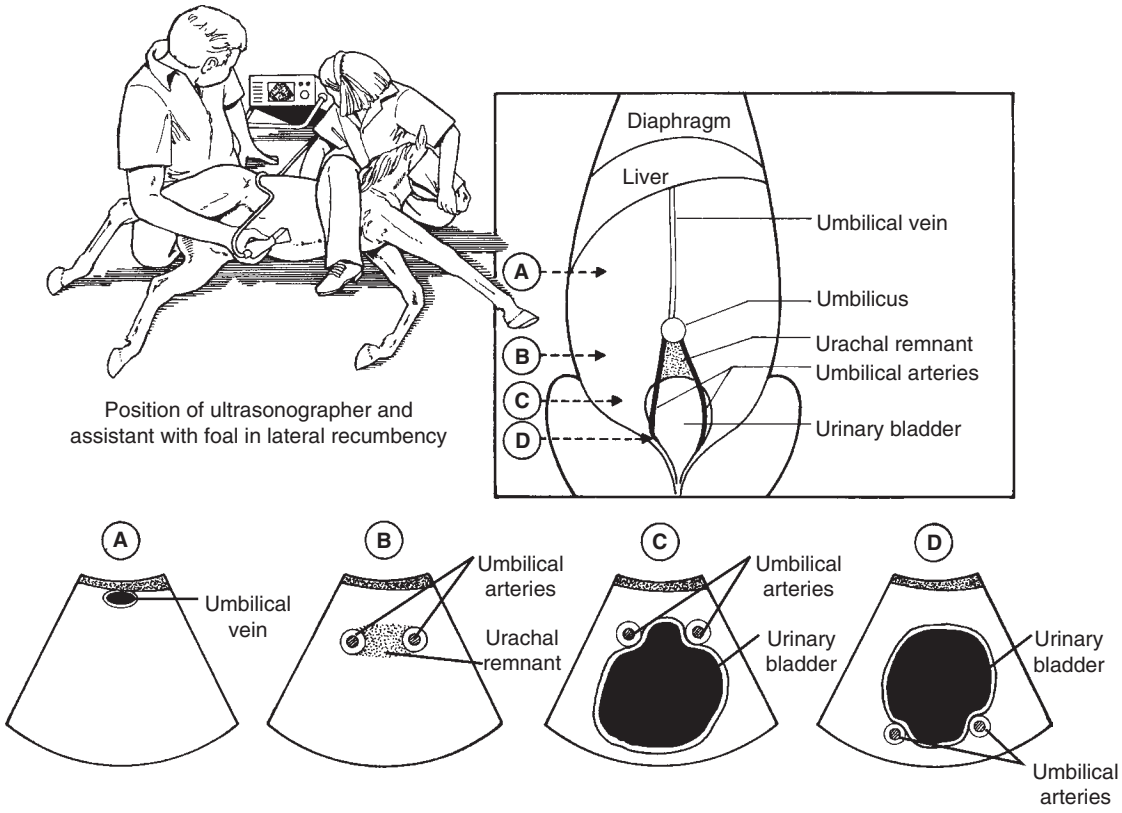


FIG. 19-2 Ultrasound evaluation of umbilical structures. Diagram depicts the positioning of the ultrasonographer and the assistant and the selected anatomic locations recommended for ultrasound examination.

of standing calves. Enlargement of the umbilical arteries can be palpated coursing caudally toward the bladder and enlargement of the umbilical vein coursing cranially to the liver. Application of pressure caudal to the xiphoid often elicits a soft grunt from calves with a septic umbilicus and associated peritonitis. Extensive adhesion of bowel to inflamed umbilical structures produces a large, easily palpable intraabdominal mass. The uterine vein and artery may also be traced within the abdomen with the calf in recumbency. Common abnormalities of the calf umbilicus include umbilical hernias, omphalophlebitis, external umbilical abscess, urachal abscess, and omphaloarteritis. Patent urachus is uncommon in calves. Disorders of the urachus or the umbilical arteries are often associated with pollakiuria and a prolonged stance of urination. Umbilical hernias in cattle do not tend to close spontaneously and are believed to be hereditary.[241]

Ultrasound examination of the calf is performed with the calf standing; occasionally the umbilical vein is easier to identify with the patient in left lateral recumbency (Fig. 19-2).[242] The umbilical vein courses from the umbilicus to the liver, which in the calf is located on the right side (see Fig. 19-2). The lumen is generally larger near the body wall with a diameter ranging from 10 to 25 mm. It appears as a round-to-oval anechoic to hypoechogenic structure (Fig. 19-3). Within 3 weeks after birth, ultrasonographic identification of the intraabdominal umbilical vein becomes impossible in up to 50% of the healthy calves. If still visible, the vein appears hypoechogenic to the surrounding tissue and indistinctly marginated.[240] In cattle, the umbilical arteries and urachus retract into the abdominal cavity when the cord ruptures and thus cannot be identified in the external umbilical stalk in normal calves.[242] The umbilical vein of calves is scanned from the umbilical stalk to the liver along the right abdominal wall. The umbilical vein enters the liver caudoventral to the gallbladder. The umbilical arteries are most easily located adjacent to the urinary bladder and cannot normally be identified much beyond the apex of the urinary bladder, unless enlarged and abnormal (Figs. 19-2 and 19-4). The identification of a urachal remnant in calves is abnormal.[242]

MUSCULOSKELETAL SYSTEM. The musculoskeletal system should be examined for evidence of birth trauma including fractured ribs, long bones, and mandibles; brachial plexus injuries; and soft tissue trauma including an edematous head and tongue from excessive traction or compression in the pelvic canal. The vertebral column, ribs, and limbs should be palpated carefully to elucidate swelling, heat, or painful areas. Strenuous manipulation during a dystocia can result in Salter Harris type 1 fractures characterized by disruption of the distal physis in one or more limbs. Femoral nerve paralysis occurs as a sporadic complication of dystocias associated with so-called hip lock in calves.[243]

Dwarfism is a relatively common inherited problem in most cattle breeds. Osteopetrosis has been reported in Angus, Hereford, and Simmental breeds of cattle. Syndactyly is considered an inherited disorder in Holstein-Friesian cattle, and affected animals are also predisposed to hyperthermia. Growth retardation, vertebral malformation, and bilateral symmetric arthrogryposis affecting the carpal and the metacarpophalangeal joints are features of complex vertebral malformation in Holsteins, a genetic condition associated with a mutation in the gene SLC35A3 coding a uridine-diphosphate-*N*-acetylglucosamine transporter.[224]

Peripheral pulses in the middle coccygeal, brachial, and auricular arteries should be strong and regular and the peripheral extremities warm. Assessment of pulse quality includes consideration of pulse strength and frequency. Concurrent cardiac auscultation is useful to verify heart rate and rhythm matches the pulse. With cardiovascular disease, the pulse may be weak and or uneven and may not correlate with the heart rate and rhythm.

The limbs should be examined for laxity, flexural, and angular limb deformities. Flexor tendon laxity occurs more commonly in calves born prematurely and in calves that are small for their gestational age. Unilateral or bilateral hyperextension of the tarsus can be encountered in newborn calves following forced extraction. A rupture of the peroneus tertius causes the hyperextension of the tarsus (Fig. 19-5). The gait is abnormal but it does not appear to be

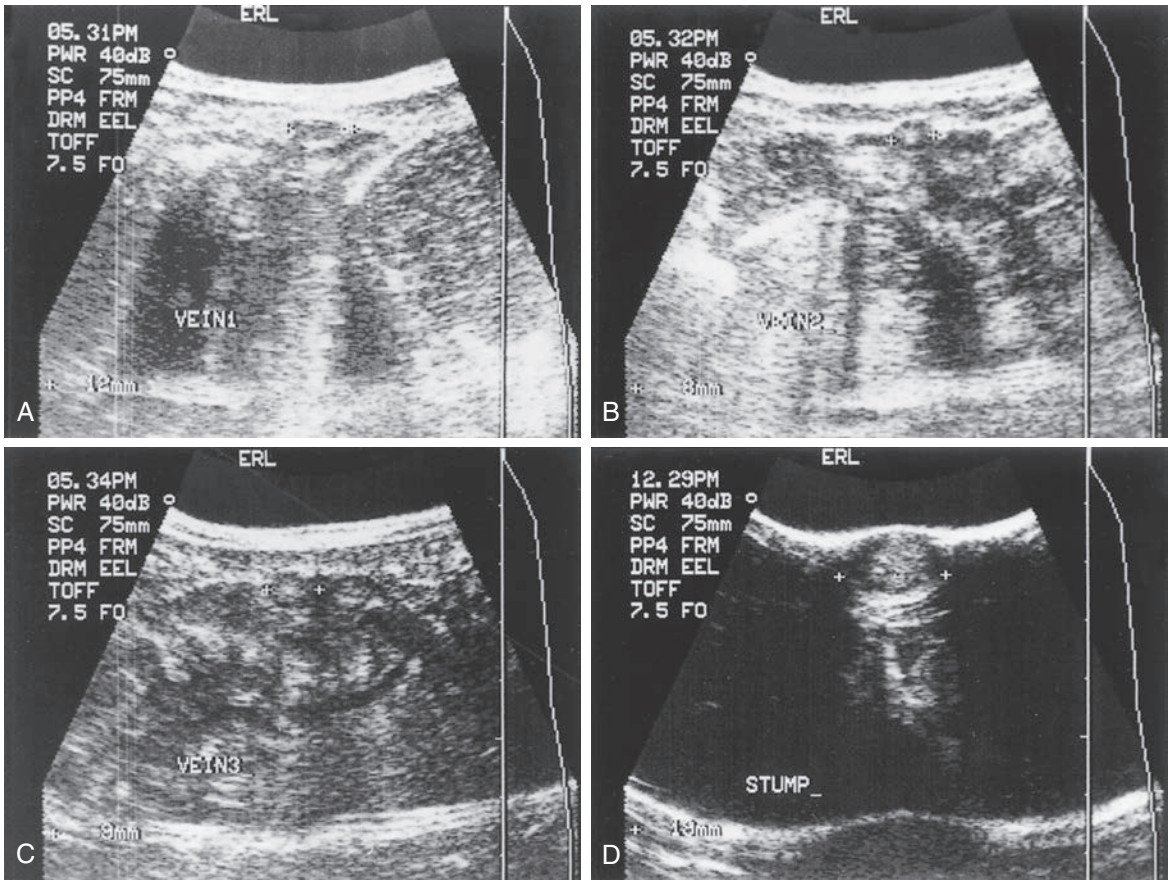


FIG. 19-3 Ultrasonogram images of four views of umbilical structures: umbilical vein views 1 **(A),** 2 **(B),** and 3 **(C),** and umbilical stump **(D).** Refer to the text for the definition of the views.

painful.[244] Congenital contracted flexor tendon is a common defect in cattle; etiologic origins include inherited factors, in utero malpositioning, and overcrowding caused by the size of the fetus relative to the dam. Contracted tendons may occur with other congenital abnormalities, such as cleft palate, dwarfism, and arthrogryposis.[244] Arthrogryposis, abnormal fixation of joints because of damage to or contracture of soft tissues, may be hereditary as a result of infection in fetal life with teratogenic viruses or result from ingestion of teratogenic plants. Following teratogenic viral infections, the clinical presentation is a result of mild–extensive loss of ventral horn motor neurons in the spinal cord gray matter and Wallerian degeneration of ventral spinal motor nerves.[245] Hereditary congenital deformity in Hereford cattle is characterized by arthrogryposis, kyphosis, torticollis, scoliosis, and cleft palate.[246] Ingestion of lupines by pregnant cows between 40 and 70 days' gestation has also caused various degrees of arthrogryposis with other associated congenital defects.[247]

Skeletal muscle myopathy is an important differential for lame neonatal ruminants. Affected neonates may present with a history of falling behind the mob when mustered and dropping into sternal recumbency. Close examination reveals firmness of the triceps and quadriceps. Deep palpation of affected muscles elicits a pain response. Lambs and kids with selenium and/or vitamin E deficiency are often mentally bright, reluctant to stand, and walk with a stiff gait and cry when forced to move. Evaluation of serum creatine phosphokinase, blood selenium, and plasma vitamin E concentrations is useful to confirm the diagnosis.

Any heat, swelling, edema, or pain around the joints or physes, or lameness, should be noted. Because of the propensity of neonates to succumb to sepsis, a swollen joint should be considered infected until proven otherwise. When sepsis is present, it is not uncommon to observe enlargement of the corresponding prescapular or prefemoral lymph node in the affected limb. When multiple animals on the same property are affected, it may reflect an infectious etiology such as salmonellosis or mycoplasma; alternatively, poor colostral management may contribute to a high incidence of opportunistic infections of immunologically compromised neonates leading to joint ill. An inflammatory leukogram provides supportive evidence of a septic process, and aseptic collection of joint fluid for cytology and culture provides confirmatory evidence. When interpreting neonatal hematology and biochemistry results, it is important to be aware of age-associated normal values (Table 19-7).

In older neonates, metabolic bone disease should be considered as a differential diagnosis for lameness associated with flaring of the physis. Diets high in energy and protein that have low calcium and high phosphorus promote rapid weight gain, thus increasing the physical load on metabolically compromised growing bones. Damage to the growing physis may result in the subsequent development of angular limb deformities. Calcium deficiency in calves leads to reduced mineralization of bone. The transverse processes of the lumbar vertebrae become soft and bend when palpated. Copper deficiency causes metabolic bone disease that is manifested by physitis and brittle bones reflected by a propensity to spontaneous fractures.

Posterior paresis is common in neonates; causes include border disease, enzootic ataxia, vertebral body abscesses, caprine arthritis encephalomyelitis virus, and vertebral body fractures associated with dietary copper deficiency or calcium phosphorous imbalance. These neurologic problems are discussed in Chapter 35.

Perineal Region

The examination from the rear includes assessment of body condition, measurement of rectal temperature, palpation of the coccygeal artery to assess pulse, examination of mucous membranes (female), and collection of urine and feces. Examination of the tail may also

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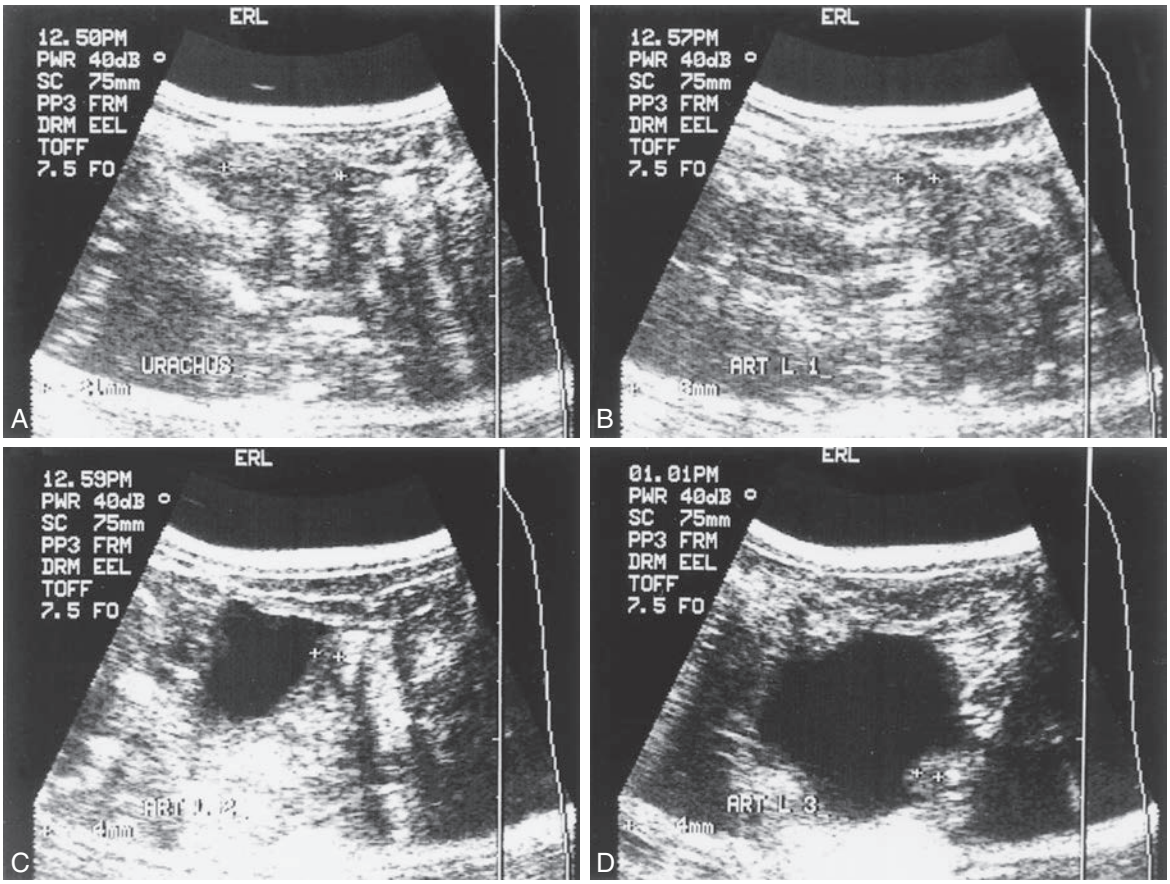


FIG. 19-4 Ultrasonogram images of four views of umbilical structures: urachus **(A),** and umbilical arteries views 1 **(B),** 2 **(C),** and 3 **(D).** Refer to the text for the definition of the views.



FIG. 19-5 Peroneus tertius rupture. **A,** Standing. **B,** Extended, showing hyperextension of the tarsus with concurrent flexion of the stifle.

reveal evidence of diarrhea. Chronic diarrhea may be reflected by poor body condition and hair loss from the caudal surface of the rear hind limbs.

BODY TEMPERATURE. Rectal temperature in calves ranges between 37.2° and 38.9° C (99° and 102° F) during the first 4 days after birth. Abnormalities of vital signs in neonatal ruminants may be difficult to interpret because a fever can be transient and patients with septicemia, infection, dehydration, or circulatory shock can be hypothermic or normothermic. Premature calves are prone to hypothermia.[248] Hyperthermia during the first week of life has been reported to be common in cloned calves.[249]

FECES. In contrast to the adult, rectal palpation of the abdominal structures of the large animal neonate is of limited value. Small amounts of blood may be observed in the feces of healthy calves. Passage of blood and fibrin is associated with inflammatory bowel disease induced by pathogens such as *Salmonella* and coronavirus that damage the gastrointestinal mucosa. Passage of melena may be associated with infectious enteritis (e.g., clostridiosis, salmonellosis)

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TABLE 19-7

Normal Hematology Reference Values for Neonatal Calves[118,119]

Parameter	Age			
	Birth	24 Hours	48 Hours	3 Weeks
RBC ($\times 10^6/\mu L$)	9.35 ± 1.02	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
Hb (g/dL)	12.86 ± 1.85	10.93 ± 2.05	10.49 ± 1.8	11.32 ± 1.02
PCV (%)	41 ± 6	34 ± 6	32 ± 6	35 ± 3
MCV (fl)	43.2 ± 2.4	41 ± 2.8	41.1 ± 2.3	39.1 ± 1.9
MCHC (g/dL)	31.3 ± 1.1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
Total WBC/μL	13.99 ± 5.73	9.81 ± 2.8	7.76 ± 1.95	8.65 ± 1.69
Neutrophils/μL	10,940 ± 5700	6480 ± 2660	4110 ± 2040	2920 ± 1140
Bands/μL	100 ± 150	310 ± 460	210 ± 450	10 ± 30
Lymphocytes/μL	2980 ± 2730	2730 ± 820	2850 ± 880	5050 ± 800
Monocytes/μL	590 ± 660	230 ± 210	350 ± 280	620 ± 330
Eosinophils/μL	0	20 ± 40	20 ± 30	20 ± 40
Basophils/μL	0	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.04
TP (g/dL)	4.8 ± 0.3	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
Fibrinogen (mg/dL)	258 ± 138	288 ± 105	335 ± 116	283 ± 147
Urea nitrogen (mg/dL)	6.36 ± 2.36	7.52 ± 2.13	7.52 ± 2.13	
Creatine (mg/dL)	4.14 ± 1.27	1.69 ± 0.35	1.27 ± 0.24	
Total bilirubin	0.34 ± 0.66	1.28 ± 0.5	0.89 ± 0.41	
Sodium (mEq/L)	141 ± 3.77	135 ± 2.86	135 ± 3.68	
Potassium (mEq/L)	6.1 ± 1.86	5.46 ± 0.56	5.63 ± 0.96	
Chloride (mEq/L)	97.39	95.76	95.28	
Calcium (mg/dL)	12.24 ± 1.64	10.22 ± 1.2	10.65 ± 0.56	
Phosphorus (mg/dL)	8.16 ± 1.39	7.22 ± 0.87	7.46 ± 0.87	
Creatine phosphokinase (U/L)	83 ± 42	531 ± 532	256 ± 364	
Aspartate aminotransferase (U/L)	18 ± 19	99 ± 18	72 ± 25	
γ-Glutamyl transferase (U/L)	8 ± 3	1761 ± 1058	846 ± 517	

and necrotizing enterocolitis resulting from hypoxic-ischemic bowel injury. Infectious diarrhea is the leading cause of mortality in calves between 3 and 21 days of age. Typically, more than one pathogen is involved and the physical examination provides no indication of the etiologic agent. Fecal pH may be used as an indicator to distinguish secretory diarrhea (enterotoxigenic *E. coli*) from diarrhea associated with malabsorption and maldigestion. Secretory diarrhea produces an alkaline pH, whereas malabsorption and maldigestion are associated with an acidic fecal pH.[250] Infectious agents causing diarrhea and ancillary tests available to establish an etiologic diagnosis are discussed in Chapter 20.

URINE. Normal urine osmolarity in the 2- to 3-day-old calf has been reported to be 286 to 391 mOsm/L, and urine volume voided per day of 34 mL/kg/day.[251] Congenital abnormalities of the urinary system include ruptured urinary bladder, ruptured ureter, ectopic ureter, blocked urethra, renal agenesis, fused kidney and polycystic kidneys. Rupture of the urinary bladder at parturition is uncommon in ruminants. Hemodynamically mediated renal disease is observed sporadically in calves following chronic enteritis.[252] Prolonged reduced renal perfusion resulting from hypovolemia may lead to ischemia and acute tubular necrosis. Failure to thrive following apparent recovery from diarrhea may reflect compromised renal function.

EXTERNAL GENITALIA. The external genitalia of both sexes should be examined for congenital malformations. In the calf, congenital defects described include ovarian aplasia, duplication of the cervix in Hereford cattle, persistence of the hymen (white heifer disease), and rectovaginal constriction in Jersey cattle. Congenital urolithiasis has been described in calves and lambs. Calcium oxalate is the most commonly reported congenital form of urolithiasis and may be associated with other congenital abnormalities.[253] A report of renal oxalosis in a number of beefmaster calves suggests a possible recessively inherited metabolic defect resulting in primary hyperoxaluria in this breed.[254] Freemartins (XX/XY chimeras) occur in over 90% of bovine[255] and 1% of ovine[256] female heterosexual twins. Typically, freemartins are sterile and have hypoplastic ovaries and internal tubal genitalia; the external genitalia normally are not affected. Males should be examined for cryptorchidism and male pseudohermaphroditism, and both sexes for evidence of hermaphroditism (gonads of both sexes). Mucous membrane color and capillary refill time may be assessed by examining the vulva mucosa in heifers.

Problem Solving

The process of diagnostic investigation for neonates is similar to that for adults. A problem list is developed at the conclusion of the physical examination. Differential diagnoses for each problem are considered and the likelihood of differentials ranked according to the history, signalment, and physical findings. This process progresses to a tentative diagnosis and development of diagnostic/treatment plans. Details regarding the presentation, diagnosis, and treatment of common neonatal diseases are presented in Chapter 20.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 20

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Manifestations and Management of Disease in Neonatal Ruminants

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Weakness and/or Depressed Mentation

Geof W. Smith

If weakness has been present since birth, in utero–acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be considered on the list of differential diagnoses. A number of congenital bacterial, fungal, and viral infections that cause abortions and stillbirths may result in the birth of a live but weak calf. In cattle, brucellosis, salmonellosis, leptospirosis, listeriosis, *Escherichia coli, Corynebacterium* spp., and *Aspergillus* spp. may cause placentitis and disease in the newborn. In sheep, in utero infection with chlamydia, *Campylobacter, Coxiella,* bluetongue virus, and border disease may cause disease in the newborn. Congenital viral infections of neonates are listed in Box 20-1. Clinical manifestations of fetal infections depend on the age of the fetus and the virulence and trophism of the infecting agent (see individual diseases).

Neonatal calves with storage diseases primarily affecting the nervous system may appear reasonably normal for a short period after birth and then show progressive signs of neurologic dysfunction, including tremors, spasms, depression, recumbency, and coma. Differential diagnoses for weakness and depressed mentation after a period of apparently normal strength and mentation include sepsis, electrolyte and acid-base disturbances, hypoglycemia, and hypothermia. A complete history is obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations are performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and immunoglobulin G (IgG) status, combined with historical and physical examination parameters, results in a high suspicion of sepsis. Blood glucose, blood gas, serum electrolyte concentrations, and passive transfer status should be determined promptly. Blood cultures and cerebrospinal fluid (CSF) analysis are useful for verifying central nervous system (CNS) involvement and targeting antimicrobial therapy.

Septicemia

Neonatal septicemia is the third most common cause of calf mortality in the United States (behind diarrhea and respiratory disease) and occurs most commonly in calves associated with failure of passive transfer (FPT). The phagocytic and bacterial killing function of neutrophils (PMN) is a crucial component of the primary immune response against invading pathogens. Despite a larger number of neutrophils in the circulation of normal calves at birth, neutrophils from neonatal calves are functionally less effective than adult cells. Reduced Fc-receptor expression in neonatal PMNs may contribute to impaired phagocytosis and antibody-dependent cellular cytotoxicity.[1-3] Depressed PMN bacterial killing[4] may be related to reduced superoxide anion[5] and myeloperoxidase-hydrogen peroxide-halide antibacterial activity.[3] Adult-level superoxide activity in fetal PMNs suggests some of the deficits in neonatal PMN function may be a manifestation of perinatal PMN suppression.[6] Calves have elevated cortisol levels for the first 10 days of life, which may contribute to depression of neutrophil function.[7] Dexamethasone depresses neutrophil phagocytosis, antibody-dependent cellular cytotoxicity, and bacterial killing.[8,9] Undefined serum factors also appear to be important for PMN function, as phagocytosis and bacterial killing by neonatal PMNs is similar to that of adult PMNs when bacteria are opsonized with adult serum but is reduced when bacteria are opsonized with neonatal serum.[4] T-helper cells ($CD4^+$) play a central role in humoral and cell-mediated immunologic memory. Lymphokines produced by $CD4^+$ cells, interleukin-2 (IL-2), IL-4, and interferon-γ (IFN-γ) are essential components of antigen-specific immunity. Virtually all IL-4 and most IFN-γ produced by polyclonally activated adult human $CD4^+$ cells is mediated by a subset of "functional memory cells."[10] Leukocyte production of IL-4 and IFN-γ is reduced in human neonates[10] and IFN-γ in bovine neonates (Dr. David Van Metre, UC Davis, unpublished data), possibly reflecting their antigenically naive status. Depressed lymphocyte proliferation and IL-2 activity in the perinatal period correlates with elevated cortisol levels.[7]

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BOX 20-1

Differential Diagnoses for the Weak or Depressed Ruminant Neonate

Bacterial Infection: In Utero or Postnatally Acquired
Septicemia
Joint and bone
Enteritis
Pneumonia
Meningitis
Peritonitis (primary or secondary)

Congenital Viral Infection
Bovine virus diarrhea virus (B)
Bluetongue virus (B, O)
Infectious bovine rhinotracheitis virus (B)
Akabane virus (B)
Parainfluenza (B)
Caprine herpes (C)
Border disease virus (O)

Prematurity/Postmaturity
Weak calf syndrome
Bacterial or fungal placentitis

Birth Asphyxia
Placentitis
Dystocia
Cesarean section
Premature placental separation
Induced parturition
Birth trauma
Brachial plexus injuries
Fractured rib, pneumothorax, hemothorax
Ruptured bladder

Congenital Malformations
Cardiac malformations
Central nervous system malformations (e.g., hydrocephalus, hydranencephaly)
Angular limb deformities
Arthrogryposis

Metabolic Derangements
Hypoglycemia
Hyponatremia
Hypokalemia or hyperkalemia
Hypocalcemia
Acidosis (respiratory or metabolic)
Uroperitoneum (with electrolyte abnormalities)
Renal failure

Severe Anemia
Blood loss
Neonatal isoerythrolysis

Brain Disease
Hemorrhage
Ischemia, edema, necrosis
Traumatic injury
Meningitis
Malformations

Spinal Cord Disease
Spinal cord hemorrhage
Vertebral malformation (e.g., atlantooccipital)
Vertebral abscessation or osteomyelitis
Vertebral fracture or other trauma to spinal cord

Peripheral Nerve and Muscle Disease
White muscle disease
Tetanus
Congenital myopathy, polymyositis
Neuropathy of spinal roots or peripheral nerves

Liver Disease
Hepatitis
Severe hypoxic insult

Storage Disorders
Maple syrup urine disease
Citrullinemia
Shaker calf syndrome (neurofilament accumulation)
GM1 gangliosidosis

Ingestion of Drugs or Toxins
Transplacental transfer of anesthetics and sedatives
Inadvertent oversedation of neonate

Gastrointestinal Disease
Gastrointestinal ulceration
Necrotizing enterocolitis

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

Acquisition of humoral immune competence is age and antigen dependent.[11] Neonates are capable of producing humoral immune responses to good immunogens (protein antigens) but may fail to respond to lesser immunogens (sugars and lipids). Calves less than 3 months of age vaccinated with modified live or killed salmonella vaccines produce an adult-type humoral immune response to salmonella protein antigens but do not respond to salmonella lipopolysaccharide.[12] Ingestion of colostrum suppresses the humoral response to some antigens but not others.[11]

Adverse management and environmental conditions further compromise neonatal immunity. Cold stress depresses neutrophil chemotaxis, and vasoconstriction reduces delivery of leukocytes to peripheral tissues.[13] Protein energy malnutrition in calves is associated with depressed lymphocyte IL-2 activity, lymphocyte proliferation, and humoral immune responses.[7] Micronutrient deficiencies also depress immunity. Selenium, zinc, copper, and vitamin E deficiencies depress lymphocyte and phagocyte function.[14,15]

Inherited defects in immune function are sporadically observed in neonates and should be considered when recurrent or atypical infections are observed, such as bovine leukocyte adhesion deficiency in Holsteins.

If invading bacteria are not quickly controlled by the immune system, they can establish focal infections in areas such as the joints, meninges, heart valves, or growth plates. Septicemia refers to a bacterial infection of the blood associated with adverse systemic signs. If not successfully treated, this can lead to multiple organ dysfunction, septic shock, and death. Meningitis is particularly difficult to treat successfully and therefore prevention of septicemia through good colostrum management is essential.

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TABLE 20-1

Bacterial Species Found to Be Associated with Neonatal Septicemia in Calves

	Fecteau et al[19]	Hariharan et al[17]	Lofstedt et al[20]
Escherichia coli	26 (50%)	17 (65%)	29 (55%)
Klebsiella spp.	7 (14%)	0	0
Salmonella spp.	4 (8%)	0	0
Campylobacter spp.	2 (4%)	2 (8%)	8 (16%)
Staphylococcus spp.	4 (8%)	0	5 (10%)
Streptococcus spp.	2 (4%)	3 (12%)	1 (2%)
Other gram positives*	3 (6%)	2 (8%)	1 (2%)
Other gram negatives†	0	1 (4%)	4 (8%)
Anaerobic bacteria‡	4 (8%)	0	1 (2%)
Total cases reported	51	26	50

**Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Bacillus* spp., *Listeria monocytogenes*.

†*Pseudomonas aeruginosa, Mannheimia haemolytica*.

‡*Clostridial* spp., *Bacteroides* spp., *Prevotella* spp.

Blood culture studies of debilitated calves indicate that gram-negative bacteria account for approximately 80% of bacterial isolates; *E. coli* is the most common bacteria isolated.[16-18] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to be bacteremic; *E. coli* accounted for 51% of the isolates; other gram-negatives, 25%; gram-negative anaerobes, 5.9%; gram-positive cocci, 11.8%; and gram-positive rods, 5.9%.[16] Other common bacterial isolates include *Salmonella, Campylobacter, Klebsiella,* and different *Staphylococcus* species. A summary of bacterial pathogens found to be responsible for septicemia are listed in Table 20-1. Polymicrobial infections are common in septicemic calves (28%).[18]

Calves lack a normal adult intestinal flora, and when born in a heavily contaminated environment, colonization of the GI tract with virulent bacteria may occur prior to the establishment of normal flora. Septicemia may also result from bacterial colonization of another site such as the umbilicus. Bacterial infection and the host inflammatory response should be differentiated. The immune response, in combination with the reticuloendothelial system, prevents the development of sepsis from an opportunistic or pathogenic invasion. However, this initiates an inflammatory cascade involving highly toxic mediators, which, if uncontrolled, will eventually lead to the systemic inflammatory response syndrome (SIRS) and subsequent multiple organ dysfunction syndrome (MODS). There is a balance between an appropriate, yet effective, immune response and an overzealous response to the bacteria or their toxins.[21]

The interaction between endotoxin (lipopolysaccharide) and the immune system triggers a complex inflammatory cascade involving cytokines and other inflammatory mediators. Initiation of the cascade results in the production of arachidonic acid metabolites, release of myocardial depressant factors, activation of the complement system, as well as the production and release of many other mediators of sepsis.[21] The results include dehydration, tachycardia, pyrexia, leukopenia, hypotension, a decrease in systemic oxygen delivery and cardiac output, and generalized weakness. There is a severe and complex pulmonary vasculature response to endotoxin, leading to hypoxemia. Cattle are very sensitive to endotoxin, and even small doses can produce severe lung injury. Severe endotoxemia is frequently associated with death from respiratory failure in both calves and adult cattle. Therefore, nonsteroidal antiinflammatory drugs (NSAIDs) are critical in blocking the formation of reactive metabolites (e.g., thromboxanes) and restoring lung function.

Neonatal septicemia should be seriously considered whenever there is multiple organ dysfunction, or when severe cardiac and/or respiratory signs are encountered. Classic septicemia is described as a condition affecting newborn calves between 2 and 8 days of age. The progression is rapid and most often fatal. Very early in the disease, the clinical signs are vague, nonspecific, and likely attributed to other disease. An alteration in mental status ranging from a mild depression to coma is commonly observed. Lack of suckling ability or enthusiasm toward nursing are early nonspecific clinical signs.[21] Abnormal rectal temperature (fever or hypothermia) is not consistent; however, sustained tachycardia and eventually tachypnea develop. Hyperemia of the mucous membranes and scleral injection is frequently observed. Capillary fragility may initiate petechiation of the mucous membranes. Eventually, hypotension and clinical signs that are associated with poor cardiac output (slow capillary refill, diminished peripheral pulse, cold extremities, and decreased urine output) become prominent. Dehydration usually develops. Diarrhea is not present in all cases but is common in the terminal stages of septicemia.

Early clinical signs of septicemia can be subtle and nonspecific. Sepsis scoring models have been developed for calves but lack good sensitivity and specificity.[19,20] The most useful parameters for predicting septicemia in calves as determined by these studies include toxic changes in neutrophils, FPT, presence of a focal infection, or elevated serum creatinine concentrations. Ultimately, the presence of clinical signs including lethargy, pyrexia, diarrhea, tachypnea, polyarthritis, uveitis, omphalitis, and meningitis, along with documented presence of FPT, should make the clinician highly suspicious of septicemia. If multiple clinical signs are present, the likelihood of disease is increased. However, the definitive diagnosis of septicemia can only be based on a blood culture. The jugular vein should be clipped and scrubbed prior to sampling. An amount of 10 mL of whole blood is drawn using a sterile syringe and needle, and the blood is placed into a blood culture bottle using a new sterile needle. Taking two samples (from blood collected 1 hour apart) is sometimes recommended to increase the chances of isolating the bacteria and to facilitate the interpretation of results if opportunistic or contaminating bacteria are found in one sample.[21] The bottle is then submitted to the laboratory for culture and susceptibility testing. If the bottle is not submitted immediately, it should be stored at room temperature or at 37° C. A negative blood culture must be interpreted with caution since many factors may interfere with bacterial isolation from a blood culture. Cultures of other body fluids such as joint, cerebrospinal, peritoneal, or pleural fluids may be helpful for bacteriologic diagnosis whenever the blood culture is negative.

Some laboratory findings may increase the suspicion of septicemia. Hematologic abnormalities of septicemia vary with the severity of the disease. Abnormal neutrophil count (neutrophilia and neutropenia) and increased immature forms (bands) are frequently seen. Fibrinogen concentration is often elevated. Thrombocytopenia may be present in severe cases. One study of suspected septic shock in calves found that 8 out of 12 calves had at least three abnormal coagulation parameters, most commonly activated partial thromboplastin time (APTT) and prothrombin time (PT).[22] Hypoglycemia, or less often hyperglycemia, may be observed. A metabolic acidosis is also frequently present in septic calves. Lactic acidosis occurs as the disease progresses. Some calves will develop respiratory disease (respiratory distress syndrome) or pneumonia and will suffer from hypoxemia and/or hypoventilation.

Neonatal septicemia is a severe disease with high mortality. The primary goals of treatment are to (1) control the infection, (2) modulate the inflammatory response, and (3) support the animal during the disease. Treatment is based on selecting an appropriate antimicrobial drug and dosage, antiinflammatory therapy, and supportive therapy (including fluids). Differences between neonatal and adult animals in drug effects generally can be attributed to differences in drug distribution, metabolism, or excretion. Some general characteristics of the neonatal period include better absorption of drugs from the gastrointestinal tract, less drug binding to plasma proteins,

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increased apparent volume of distribution of drugs that are distributed in the extracellular fluid volume, increased permeability of the blood-brain barrier, and slower elimination (i.e., longer half-life) of many drugs. In general terms, antimicrobials have longer elimination times in neonates (<2 weeks of age) than adults and as such larger doses are administered with a longer dosage interval to achieve similar peak and trough antimicrobial concentrations. Antimicrobial therapy should begin as soon as possible in order to minimize the bacteremia. The choice and the dosage of antibiotic depend on several factors, and personal preference, along with past experience, is often important. It is generally accepted that the intravenous route is preferable whenever possible and that broad-spectrum drugs are preferred. Appropriate antimicrobial choices include third- or fourth-generation cephalosporins (ceftiofur 5 to 10 mg/kg/day IM or IV), sodium ampicillin (10 to 20 mg/kg tid IV), and florfenicol, although even when given intravenously at the extralabel dosage of 20 mg/kg bid, it only exceeds the MIC_{90} value in plasma for 1 hour.[23] Combinations of drugs can be used to broaden the spectrum of activity (such as ampicillin-ceftiofur or ampicillin-trimethoprim-sulfonamide). Fluoroquinolones can also be effective in countries where their use is permitted. Once the pathogen has been identified and the susceptibility pattern determined (on the individual or on the farm), the most appropriate antibiotic can be chosen.

As just described, the inflammatory response if uncontrolled often causes severe clinical signs. Therefore, NSAID therapy should be considered for ancillary treatment. Possible side effects of aggressive NSAID treatment include abomasal ulcers and renal toxicity, particularly in dehydrated animals. The duration of NSAID treatment is often limited to 2 to 3 days because of their potential toxicity. NSAIDs should not be continued for any longer than they are considered essential for survival.

Supportive treatments for septicemic calves include correction of secondary problems, administration of fluids, plasma transfusion, oral or parenteral nutrition, and oxygen administration. Problems that must be addressed include hypovolemia, hypoglobulinemia, hypoglycemia, metabolic acidosis, electrolyte abnormalities, and hypoxia. IV fluids (or oral as a compromise on the farm) should be administered. Dextrose (5%) combined with normal saline (0.9%) should be administered at a rate of at least 50 mL/kg/day. Nutrition is important and septic calves either nurse reluctantly or are inappetant; as a result, they do not ingest an adequate amount of milk. If the animal refuses to nurse, tube feeding should be used to ensure that the calf ingests at least 10% to 15% of its body weight of milk per 24 hours. The feeding schedule may involve several (three to five) feedings per day and should be gradually increased in amount to prevent abdominal distention. If the gastrointestinal system does not tolerate the tube feeding regimen, parenteral nutrition should be considered. There is usually no need for total parenteral nutrition since most animals will continue to nurse or tolerate tube feeding up to 5% of their body weight.

Multiple cases of septicemia occurring on the same farm calls for careful inspection of the environment and management practices. Clusters of septicemia could be related to specific risk factors. As an example, feeding heavily contaminated colostrum could be the origin of the septicemia on some farms.[22,24] Prevention through excellent cleanliness and management practices is the most effective means of controlling and preventing neonatal sepsis.

Meningitis

Bacterial meningitis is an important complication associated with neonatal septicemia in calves. Exactly how bacteria get into the meninges is poorly understood. Specific mechanisms may include the development of a sustained and high-grade bacteremia in the highly perfused dural venous system and choroid plexuses, adherence of fimbriae from some strains of *E. coli,* or the phagocytosis of the pathogens by circulating monocytes and endocytosis through the microvascular endothelial cells.[21] Once they gain access to the CNS, bacteria survive and proliferate well in the poorly defended CSF. Complement is essentially nonexistent in CSF, which, when combined with low numbers of specific antibodies, leads to inadequate opsonization of meningeal pathogens. The sequelae of meningitis are associated with the release of cytokines and the direct effects of bacterial invasion. Bacteria may release endotoxin, leading to inflammatory infiltrates that cause thromboses of the arachnoidal or subependymal veins. Congestion or hemorrhagic infarction may follow with subsequent necrosis of nerve cells. Inflammatory changes in the subarachnoid space may affect the choroid plexus, decreasing the absorption of fluid and potentially creating hypertensive hydrocephalus.

Although bacterial meningitis may occur as a primary entity, it more commonly is a result of generalized septicemia in neonates with FPT. Agents that cause meningitis are the same agents that cause septicemia, most commonly the gram-negative enteric bacteria such as *E. coli, Enterobacter* spp., and *Salmonella* spp. In a review of 32 cases of meningitis in calves, the clinical signs of CNS disturbance observed were lethargy, recumbency, anorexia, loss of suckle reflex, coma, opisthotonos, convulsions, tremor, and hyperesthesia.[25] Leukocytosis and a left shift were evident in 11 of 15 calves (73%). Concurrent metabolic problems were common and included hyperkalemia, respiratory acidosis, hypernatremia, hyponatremia, hypomagnesemia, and hypoglycemia. Analysis of CSF revealed pleocytosis, xanthochromia, turbidity, and high total protein concentration. Cytologically, neutrophils predominated in the CSF in calves with acute disease. Mononuclear cells dominated in calves with chronic disease. Microscopically, bacteria were evident in 10 of 22 (45%) of the antemortem CSF samples, and bacteria were isolated from slightly more than half (11 of 19). All of the calves in this review died.[25]

Calves with meningitis are often presented because they have lost their suckle reflex and appear lethargic. Previous treatment for diarrhea is common. Fever is often present unless NSAIDs have been given or if the animal is in an extremely cold environment. The calves may have an extended head and neck, and attempts to flex or reposition the neck can result in a tonic extension and thrashing of the limbs. Calves with meningitis almost always have abnormal mentation. As the disease progresses, profound depression develops and eventually the animal becomes comatose and nonresponsive or may develop seizures. Presumptive diagnosis of bacterial meningitis is based on demonstration of FPT, presence of a septic focus such as omphalophlebitis or septic arthritis, and the presence of abnormal neurologic signs. However, the definitive diagnosis is based on an abnormal CSF analysis. Collection of CSF from the lumbosacral space is easy and safe in calves. For collection of fluid from the lumbosacral space, a 20-gauge, 1- to 2-inch needle with a clear hub may be used. A change in resistance is felt when the needle penetrates the dural membranes, and CSF appears in the plastic hub as soon as the subarachnoid space is entered. Approximately 5 to 10 mL of fluid may be removed safely.

Urinary reagent strips can be used to rapidly obtain general information about the fluid. If blood is detected, the sample should be spun down after the cytologic examination. Red blood cells contaminating the sample will settle, and the supernatant should be colorless. If hemorrhage occurred before the procedure, the sample remains xanthochromic (yellow). Glucose should be present in "trace" or "positive" (+) amounts in the normal sample. Negative values in the adult suggest severe meningitis, but in the neonate they may also be caused by profound hypoglycemia. CSF analysis is most useful in determining the presence of septic meningitis. A summary of CSF findings from calves with meningitis is presented in Table 20-2. Generally an elevation in total protein and white blood cell concentration are strongly suggestive of meningitis, combined with a high percentage of the cells being neutrophils. The ratio of CSF to plasma glucose concentration is less than 1 in animals with bacterial meningitis because of bacterial metabolism of glucose in the CSF. Xanthochromia (yellow color) is inconsistent. Free or intracellular bacteria may be observed in some cases. An elevated albumin quotient suggests increased blood-brain permeability and can be seen in both

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TABLE 20-2

Cerebrospinal Fluid (CSF) Findings in Calves with Meningitis

	Normal	Green et al[25]	Scott et al[25a]
Specific gravity	<1.007	NR	1.011
Total protein	<0.4 g/L	3.07 g/L	3.2 g/L
White blood cell concentration	<10 cells/μL	4004 cells/μL	2400 cells/μL
Percent lymphocytes	>80%-90%	NR	Range of 1%-17%
Percent neutrophils	<10%-15%	73%	Range of 78%-100%
Culture positive		6 of 9 cases	11 of 19 cases

TABLE 20-3

Cerebrospinal Fluid-to-Blood Concentration Ratios (Penetration) of Antibiotics Available for Treatment of Meningitis in Calves[23,26]

	Concentration CSF/Concentration Serum (%)	
Antimicrobial*	Human	Animals
Ampicillin	13-14	8-12
Florfenicol		46 (calves)
Gentamicin	0-30	21-25
Penicillin	5-10	5-6
Trimethoprim-sulfamethoxazole	<41	35-39

*The list is not conclusive, reflecting the paucity of available data.

CSF, Cerebrospinal fluid.

hypoxic-ischemic brain injury and meningitis, but an elevated IgG index indicates increased intrathecal IgG production and is more compatible with a diagnosis of meningitis.

When treating calves with meningitis in a hospital environment, the mortality rate is high; however, aggressive early treatment can be successful. The economics and welfare implications of treating commercial calves in a field setting are questionable. Empiric antimicrobial therapy for meningitis in neonatal calves should include a gram-negative and gram-positive spectrum. Antibiotics enter the CSF predominantly via passive diffusion down a concentration gradient. The major determinant of CSF penetration is lipid solubility. Lipophilic agents diffuse via transcellular pathways; peak concentrations in CSF occur relatively rapidly, and entry into CSF is affected minimally by the presence of inflammation. In contrast, hydrophilic agents enter the CSF through paracellular pathways; their transport depends on the opening of tight junctions, and peak concentrations are relatively delayed.[26]

Table 20-3 lists CSF-to-blood concentration ratios (penetration) derived from multiple species for a handful of antimicrobial drugs available for use in cattle.

In a CSF pharmacokinetic study of florfenicol in calves, the maximum concentration of florfenicol attained in CSF was 4.67 ± 1.51 μg/mL following a single intravenous dose of 20 mg/kg.[23] The levels remained above the minimum inhibitory concentration (MIC) for *Histophilus somni* (formerly *Hemphilus somnus*) over a 20-hour period. This concentration is below the MIC_{90} for *E. coli*. Bactericidal antibiotics are proposed to be more effective for treatment of meningitis in humans, and it is recommended that the concentration of antibiotic in the CSF should be maintained at 10 times the MIC of the target pathogen.[26] Unfortunately, owing to the lack of CSF pharmacokinetic data in cattle, antimicrobial treatment of meningitis is an inexact science. Antiinflammatory therapy and nursing care should be instituted as described previously for neonatal septicemia. Convulsions in calves can be treated with diazepam (0.1 to 0.2 mg/kg IV). This can be repeated every 30 minutes until convulsions are controlled.

Metabolic Acidosis

Profound weakness associated with metabolic acidosis or "strong ion" acidosis is commonly observed in calves with diarrhea and sporadically in kids ("floppy kid syndrome") and calves without other clinical signs of disease.[27,28] This acidosis is often associated with an increased concentration of D-lactate (the anion of D-lactic acid) resulting from bacterial fermentation of carbohydrates in the gastrointestinal tract of milk-fed calves. Clinical signs of impaired CNS function including ataxia and coma in sick calves have been attributed at least partially to the increased D-lactate concentrations.[29,30] Assessment of weak neonatal ruminants for the presence of metabolic acidosis is a critical part of the physical examination. Correction of the acidosis by intravenous administration of bicarbonate produces a rapid recovery. An improvement in mentation and strength should be observed within 12 hours; persistent depression is likely to reflect incomplete correction of acidosis, sepsis, hypoglycemia, hypernatremia, or hyponatremia.

Hypoglycemia

Hypoglycemia is a common sequela to withdrawal of milk for more than 48 hours, especially in cold weather. Affected calves are weak or recumbent but appear to be normally hydrated or minimally dehydrated.[31] They are often emaciated and can occasionally have neurologic signs including facial twitches, convulsions, opisthotonos, and coma. They will respond to a bolus of 50% dextrose or infusion of 5% glucose, but often this response is temporary, especially in calves with severe malabsorptive disease. It is important to rapidly restore adequate energy intake to ensure resolution of these cases. Starvation and hypothermia resulting from mismothering are common causes of weakness in neonatal lambs. Similarly, weakness, poor body condition, and increased susceptibility to infectious diseases are observed with protein-calorie malnutrition induced by feeding poor-quality or incorrectly mixed milk replacers.[32] Hypoglycemia is also frequently seen in calves with neonatal septicemia, as discussed previously.

Hyponatremia

Hyponatremia occurs when loss of isotonic fluid through the gastrointestinal tract is replaced by free water or hypotonic solutions. The latter often occurs when too much water is added when making up an oral electrolyte solution. Hyponatremia may also occur when isotonic oral electrolyte solutions are administered to calves with compromised sodium absorption capacity. This may be a result of severe pathologic changes or an inadequate level of agents that facilitate sodium cotransport within the oral electrolyte solution. Hyponatremia results in a fluid shift from the extracellular space to the intracellular compartment along the osmotic gradient, and the resultant swelling of the cells can result in neurologic disturbances, depression, disorientation, and even convulsions.[33] Hyponatremia should be considered in calves with serum sodium less than 132 mmol/L; calves with serum sodium less than 120 mmol/L have severe hyponatremia.

The goal of therapy is to restore serum sodium levels to greater than 125 mmol/L over the first 6 hours and then to restore to normal levels over 24 hours.[33] In hypovolemic calves the initial treatment should be achieved using normal saline, and in normovolemic calves hypertonic saline should be used for the initial treatment, since the administration of large fluid volumes will exacerbate cerebral edema. If the calves are also suspected to be acidotic, this should be corrected with sodium bicarbonate solutions of appropriate tonicity.

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The amount of sodium required in the first 6 hours to raise the sodium level to 125 mmol/L can be calculated as follows[33]:

$$\text{mEq Sodium} = (125 - \text{Measured mEq serum sodium}) \times (0.6 \times \text{Body weight in Kg})$$

Calves should then be maintained on a sodium-containing isotonic fluid, such as normal saline or lactated Ringer, and treated with oral electrolyte solution as appropriate. The sodium level should be monitored frequently in the first 24 hours because of unknown losses through the gastrointestinal tract as well as unknown kidney function in a severely dehydrated patient.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration greater than 152 mmol/L (although only levels greater than 170 mmol/L have been associated with nervous dysfunction).[34] Hypernatremia in food animals is generally caused by one of the following: (1) excessive loss of free water (e.g., water deprivation, heat stress), (2) iatrogenic administration of IV crystalloid solutions to animals that do not have access to water, and (3) excessive intake of sodium without an adequate volume of free water. This last cause is by far the most common syndrome in calves. Most cases result from mixing oral electrolyte solutions improperly, or in some circumstances, hypernatremia has been seen with very high osmolality milk replacers.

During hypernatremic states, water will follow concentration gradients and move into the relatively hyperosmolar CSF and plasma. This results in cellular dehydration and brain shrinkage (neurons shrink when the water moves out). Neuronal cells will increase their intracellular osmolality in an attempt to minimize the water efflux; however, this adaptation can only compensate for mild increases in sodium concentrations. Severe hypernatremia leads to neurologic disease in calves.

Early clinical signs of hypernatremia include lethargy and depression, which, without blood work, cannot be differentiated from many other possible diseases such as acidemia, dehydration, hypoglycemia, or hypothermia. More advanced clinical signs of hypernatremia include twitching of facial muscles, muscle rigidity, tremors, and myoclonus.[34,35] Calves will demonstrate seizure and/or coma activity near death. Prognosis in these calves is often guarded to poor even with aggressive treatment.

Treating hypernatremia is very difficult. If the sodium concentration is lowered too quickly, water follows a concentration gradient and moves into neurons, resulting in cerebral edema. When sodium concentrations are higher than 160 mEq/L, it is very easy to produce cerebral edema with any isotonic fluid, even those that contain sodium, because of the large difference between the calf's extracellular fluid sodium concentration and the sodium concentration in the fluids. Therefore, it becomes necessary to add supplemental sodium to standard fluid types. The fluids must be formulated so that the sodium concentration is equal to or slightly lower than the calf's sodium concentration.[34] The calf's sodium concentration should be reassessed at least one to two times per day and fluids reformulated. The goal would be to return the sodium concentration to normal over a period of several days, decreasing it by 3 to 4 mEq/L/day.[35] This approach is expensive (requiring frequent blood work) and difficult and is not always successful. Some calves will still develop cerebral edema even with careful fluid therapy.

For example, if a calf has a sodium concentration of 177 mEq/L, the goal would be to give fluids with a sodium concentration somewhere in this range (175 to 177 mEq/L). Since isotonic (0.9%) saline has a sodium concentration of 154 mEq/L, the clinician needs to add 22 to 23 mEq/L of additional sodium to the liter of fluids. Hypertonic saline (7.2%) contains sodium at a concentration of 1.2 mEq/mL. This would be equal to 19 mL of hypertonic saline per liter of isotonic saline ($1.2 \times 19 = 23$). After about 12 hours of fluid therapy, it is recommended to reassess the calf's sodium concentration and re-formulate fluids. Hypertonic saline could also be added to isotonic sodium bicarbonate (which has a sodium concentration of 156 mEq/L) if the calf had a metabolic acidosis in addition to hypernatremia. Although not always successful, a report of treating several hypernatremic calves with 5% dextrose either alone or in combination with sodium bicarbonate has been published.[36] In this study calves were given 2 to 4 L of 5% dextrose at a slow drip (about 500 mL/h) and had serum sodium concentrations decreased much faster than is usually recommended. However, the four calves in the case report were treated successfully. Although this approach may not always work and could easily result in cerebral edema, it may be practical for times when the clinician does not have the ability to formulate fluids or monitor serum sodium concentrations frequently.

If the calf's neurologic signs get significantly worse after fluid therapy has started, cerebral edema should be suspected. Treating cerebral edema is difficult but imperative to prevent further brain damage and/or death. Corticosteroids are the easiest choice normally; however, they are only marginally effective in treating moderate to severe cases of cerebral edema. Mannitol (25%) at 1 g/kg given IV over 30 minutes or an oral solution of glycerin diluted 1:1 with water has also been recommended for severe cases of cerebral edema but can be more difficult to obtain.[34]

Neuromuscular and Musculoskeletal Disease

Primary neuromuscular or musculoskeletal disease should be considered when weakness is not associated with depressed mentation. Weakness associated with micronutrient deficiencies results from myodegeneration (white muscle disease, selenium, and vitamin E) or demyelination (copper, enzootic ataxia). If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with birth trauma should be ruled out (see Box 20-1). Femoral nerve paralysis may be observed in calves following a "hip lock" dystocia.[37] A condition resembling congenital myasthenia gravis has also been described in Brahman calves.[38]

Nutritional myodegeneration associated with selenium and or vitamin E deficiencies may produce localized (dysphagia) or generalized paresis. Neonatal small ruminants appear to be particularly susceptible. Affected lambs may be unable to rise; others can stand but may be unable to nurse because they are unable to raise their heads. Diagnosis is based on clinical signs, increased serum creatine kinase concentration, and reduced whole blood glutathione peroxidase and/or selenium concentrations (see Chapter 42). Vitamin E deficiency is observed when pregnant ewes are fed stored forage low in vitamin E; the clinical signs in affected lambs are identical to selenium deficiency, but selenium status is adequate. Since vitamin E is labile, serum should be harvested quickly after blood collection, frozen, wrapped in aluminum foil, and sent express mail on ice.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Generally vertebral body malformations occur sporadically; genetic, nutritional, and environmental factors have been implicated.[39,40] In older calves, underlying metabolic bone disease (copper, vitamin D, or phosphorous deficiency) may increase the propensity for fractures to occur. Osteomyelitis and vertebral body abscess may be a sequel to bacteremia following neonatal septicemia or pneumonia.[41] The frequent isolation of *Trueperella pyogenes* from vertebral body abscesses in ruminants suggests that chronic respiratory infections is more frequently the source in these species.[42,43] Vertebral body abscesses in lambs are occasionally a sequel to infected docking wounds. Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances vertebral abscesses do not infiltrate the pachymeninges, so the CSF either is normal or has a mild elevation of protein and/or a mild pleocytosis.[41,42]

Differential diagnoses for paresis in goat kids include caprine arthritis encephalitis virus (CAEV) and enzootic ataxia. Enzootic ataxia is also common in lambs. Progressive ataxia and paresis or

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paralysis is a feature of both diseases. There are two forms of enzootic ataxia (swayback): the neonatal and the delayed types. In the neonatal condition animals are affected at birth in the delayed type; signs of incoordination appear at 14 to 30 days of age.[44] Most affected kids are afebrile, bright, and alert, and they will continue to eat if it is physically possible. Enzootic ataxia is associated with low liver copper content, and occasionally, low serum copper concentration.[45] It has been proposed that reduction in the activity of the copper-dependent enzyme cytochrome oxidase impairs phospholipid synthesis and subsequently myelin production. Microcytic anemia and increased fragility of bones may be observed in more chronic cases.[46] The copper, molybdenum, and sulfur content of the maternal diet should be evaluated and adjustments made for copper deficiency or molybdenum or sulfur excess (see Chapter 32).

Goat kids with the neurologic form of CAEV will have mild to moderate fevers and evidence of cerebral involvement. Cerebral signs commonly identified include depression, head tilt, torticollis, and circling.[47] Evidence for CAEV would include CSF pleocytosis and increased CSF protein and a positive CAEV (AGID) or enzyme-linked immunosorbent assay (ELISA) test. Both the neurologic form of CAEV and enzootic ataxia carry a poor prognosis.

A complete neurologic examination is an important component of the work-up of the weak neonate. In particular, it should be noted if the weakness is accompanied by signs of depression and diffuse cerebral disease. Strength is preserved if ataxia is caused by cerebellar disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations, enzootic ataxia) may also show weakness and ataxia yet appear clinically to have normal cerebral function. Virtually any severe systemic disease such as generalized infection can cause both profound depression and weakness in a neonate without the presence of actual brain pathology. Intermittent signs of severe weakness and depression may be caused by the narcolepsy-cataplexy syndrome.

Respiratory Distress

Sheila M. McGuirk

Respiratory conditions of the neonatal ruminant can be attributed to upper airway problems, pulmonary pathology, CNS dysfunction, cardiac disease, metabolic derangements, or other nonpulmonary disorders (Box 20-2).

Examination

A complete examination of the neonate is essential when clinical signs are indicative of a respiratory condition. When a single individual is involved, observation from a distance, recording of vital signs, and a physical examination guide the clinician to the selection of appropriate diagnostic tests to establish a cause, make a diagnosis, and evaluate the prognosis. For respiratory conditions that affect a flock or herd of animals, the examination of affected individuals remains an essential component of the diagnostic work-up, but evaluation of records, the environment (housing and other animals), nutrition, colostrum, treatment, and vaccination protocols is also needed.

From a distance, mentation, posture, respiratory rate, breathing effort, characters of nasal and ocular discharge, and spontaneous coughing can be evaluated. Abnormal postures exhibited by patients with respiratory conditions may be recumbency, open-mouth breathing, abnormal extension of the head and neck, head tilt, or reluctance to lie down. Abnormal breathing characteristics include prolongation of the inspiratory or expiratory phase of respiration, an expiratory abdominal press or snap, marked tachypnea, frequent spontaneous coughing, stridor, or inspiratory or expiratory noises.

BOX 20-2

Causes of Respiratory Distress

Upper Airway Conditions

Pharyngeal trauma
Necrotic laryngitis
Choanal atresia (nasopharyngeal atresia)
Laryngeal edema
Tracheal malformation: stenosis, collapse

Developmental Disorders

Pulmonary hypoplasia
Diaphragmatic hernia

Lung Parenchymal Diseases

Pneumonia (bacterial or viral)
Atelectasis
Hyaline membrane disease
Pulmonary edema, congestion
Aspiration syndromes
Air leaks (e.g., pneumothorax)
Pulmonary hemorrhage
Transient tachypnea syndromes

Nonpulmonary Causes

Congestive heart failure
Central nervous system lesions
Metabolic derangements (e.g., acidosis, hypoglycemia)
Severe anemia
Hypovolemia
Fractured ribs
Nutritional myodegeneration of thoracic muscles or diaphragm
Persistent pulmonary hypertension
Birth asphyxia
Pain, abdominal crisis
Fever, high environmental temperatures
Excitement
Pleural effusion (e.g., pleuritis)
Endotoxemia and gram-negative sepsis

Practitioners must assess airflow from each nostril and evaluate ocular, oral, pharyngeal, and vaginal mucous membrane characteristics, including temperature, color, moisture, and capillary refill time. The hard and soft palate should be evaluated. Animals with cleft palate may have milk run from the nose and are prone to developing aspiration pneumonia. Gray or cyanotic mucous membranes are associated with severe hypoxia (i.e., $Pa_O < 35$ to 40 mm Hg), and/or circulatory collapse as seen with hypotensive, endotoxic, or hypovolemic shock. Cardiac and pulmonary causes of cyanosis must be distinguished. Cyanosis from congenital cardiac disease of the neonatal ruminant frequently reflects right-to-left shunting of blood that may be from a tetralogy of Fallot, transposition of the aorta, great vessel anomalies, or Eisenmenger complex. Absence of cyanosis is not a reliable indicator of adequacy of oxygenation in the neonate, since the partial pressure of oxygen may reach very low levels (<35 to 40 mm Hg) before cyanosis is observed.

Auscultation of the trachea, thorax, and occasionally the nasal passage are essential elements of the respiratory examination. Tracheal compression should not induce multiple coughs. Lung sounds of neonates are typically easier to hear than those of adults; however, lung sounds do not always correlate well with the severity of respiratory condition that is present. Interpretation of the intensity of thoracic breath sounds can be validated by comparison to tracheal breath sounds. The intensity of tracheal breath sounds is gradually attenuated as the stethoscope is moved from the trachea to the lung hilus, again to the anteroventral thorax, and finally to the caudal thorax in normal animals. Loud tracheal breath sounds that are not attenuated over the thoracic area may be indicative of atelectasis, lung consolidation, or cardiac enlargement. Added breath sounds such as

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crackles or wheezes should be noted but may not be heard without augmenting the depth and frequency of the breathing effort with the use of a rebreathing bag. Cardiac auscultation will determine heart rate, rhythm, and the presence of murmurs. Abnormal radiation of heart sounds caudal to the fifth intercostal space or dorsal to the level of the scapulohumeral joint on either side of the thorax should be noted. Thoracic percussion may be used to identify the presence of thoracic fluid, cranioventral consolidation, or atelectasis in neonatal ruminants.

Heart and respiratory rates vary with activity, excitement, and feeding. Tachypnea can be attributed to elevated temperature humidity index, fever, thermoregulation dysfunction, excitement, pain, stress, respiratory disease, hypoxia (cardiac disease, pulmonary disease, shock), dehydration, shock, toxemia, or metabolic acidosis. Periodic apnea and abnormally slow respirations are often the result of metabolic disturbances (hypoglycemia, hypocalcemia), hypothermia, prematurity, or hypoxia-induced suppression of the respiratory center.

Abnormal posture of the head and neck are exhibited by neonates with respiratory difficulty, particularly upper airway obstruction, but meningoencephalitis, otitis media, hypernatremia, polioencephalomalacia, congenital defects of the CNS, and lasalocid toxicity should be considered.

Conditions causing occlusion of the upper airway, such as choanal atresia, necrotic laryngitis, pharyngeal swelling, or edema, often induce pronounced inspiratory dyspnea, stridor, and/or open-mouth breathing. Expiratory stridor and increased and prolonged expiratory effort are usually associated with lower airway disease. A malodorous breath may be present with necrotic pharyngeal injuries, necrotic laryngitis, cleft palate, or aspiration pneumonia. Inspiratory stridor is often a feature of extra-thoracic airway obstruction and increased abdominal effort on expiration an indication of pulmonary disease causing reduced lung compliance.

Lung disease in the newborn is usually diffuse and is the result of infection acquired in utero or postpartum and/or lung atelectasis associated with immaturity, recumbency, or surfactant dysfunction. Signs of lung disease include increased work of breathing characterized by nostril flare, rib retractions, and increased abdominal effort. A cough and nasal discharge—salient features of respiratory disease in older neonates—are infrequent findings in newborns with lung disease. Animals with few or no audible thoracic abnormalities may have severe respiratory disease.

Respiratory Condition Diagnostic Testing

A complete blood count, serum chemistry profile, electrolyte concentrations, arterial or venous blood gas concentrations, and a test of immune transfer status provide useful information to the clinician concerned about a respiratory condition in a neonatal ruminant. Normal values for neonatal calves are presented in Table 20-4.

Knowing whether there is anemia, evidence of infection, endotoxemia, organ dysfunction, metabolic abnormalities, hypercarbia, hypoxemia, or FPT of immunity may distinguish upper airway problems from lower airway disease or pulmonary disease from a nonpulmonary cause of respiratory difficulty.

Arterial blood gas concentrations provide a useful measure of respiratory function. Optimal sites for collection of arterial blood samples from neonatal calves are the brachial artery proximomedial to the elbow[50] or the caudal auricular artery.[51] Normal arterial blood gas values for neonates of different postnatal and gestational ages are presented in Table 20-5.

Several factors can interfere with accurate interpretation of blood gases in the neonate. First, significant inaccuracies can occur if the blood sample is collected, handled, or measured improperly. The most common artifact is the introduction of room air into the sample, with an artificially increased Pa_{O_2}, decreased Pa_{CO_2}, and more alkaline pH resulting. The position of the patient and amount of struggling during sample collection may also cause transient changes in all blood gas values. The inspired oxygen concentration should always be considered when analyzing arterial blood gas values. With supplemental oxygen, Pa_{O_2} is increased variably, depending on the inspired oxygen concentration (FI_{O_2}), the amount of pathology present (particularly the extent of right-to-left shunting), and the

TABLE 20-4

Normal Hematology and Serum Chemistry Reference Values (for Neonatal Calves)[48,49]

	Age			
Parameter	Birth	24 hrs	48 hrs	3 weeks
RBC ($\times 10^6/\mu L$)	9.35 ± 1.02	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
Hb (g/dL)	12.86 ± 1.85	10.93 ± 2.05	10.49 ± 1.8	11.32 ± 1.02
PCV (%)	41 ± 6	34 ± 6	32 ± 6	35 ± 3
MCV (fl)	43.2 ± 2.4	41 ± 2.8	41.1 ± 2.3	39.1 ± 1.9
MCHC (g/dL)	31.3 ± 1.1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
Total WBC/μL	13.99 ± 5.73	9.81 ± 2.8	7.76 ± 1.95	8.65 ± 1.69
Neutrophils/μL	10,940 ± 5700	6480 ± 2660	4110 ± 2040	2920 ± 1140
Bands/μL	100 ± 150	310 ± 460	210 ± 450	10 ± 30
Lymphocytes/μL	2980 ± 2730	2730 ± 820	2850 ± 880	5050 ± 800
Monocytes/μL	590 ± 660	230 ± 210	350 ± 280	620 ± 330
Eosinophils/μL	0	20 ± 40	20 ± 30	20 ± 40
Basophils/μL	0	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.04
TP (g/dL)	4.8 ± 0.3	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
Fibrinogen (mg/dL)	258 ± 138	288 ± 105	335 ± 116	283 ± 147
Urea nitrogen (mg/dL)	6.36 ± 2.36	7.52 ± 2.13	6.93 ± 3.13	
Creatine (mg/dL)	4.14 ± 1.27	1.69 ± 0.35	1.27 ± 0.24	
Total bilirubin	0.34 ± 0.66	1.28 ± 0.5	0.89 ± 0.41	
Sodium (mEq/L)	141 ± 3.77	135 ± 2.86	135 ± 3.68	
Potassium (mEq/L)	6.1 ± 1.86	5.46 ± 0.56	5.63 ± 0.96	
Chloride (mEq/L)	97.39	95.76	95.28	
Calcium (mg/dL)	12.24 ± 1.64	10.22 ± 1.2	10.65 ± 0.56	
Phosphorus (mg/dL)	8.16 ± 1.39	7.22 ± 0.87	7.46 ± 0.87	
Creatinine phosphokinase (U/L)	83 ± 42	531 ± 532	256 ± 364	
Aspartate aminotransferase (U/L)	18 ± 19	99 ± 18	72 ± 25	
γ-Glutamyl transferase (U/L)	8 ± 3	1761 ± 1058	846 ± 517	

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TABLE 20-5

Normal Arterial Blood Gas Values for Calves

Age Group	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HCO_3^- (mEq/L)
1 hour	58.43 ± 11.61	50.40 ± 5.27	7.30 ± 0.05	23.52 ± 2.78
4 hours	62.30 ± 9.27	47.92 ± 3.97	7.34 ± 0.03	24.49 ± 2.35
12 hours	67.23 ± 9.32	45.36 ± 3.97	7.38 ± 0.03	25.74 ± 2.37
24 hours	70.53 ± 11.47	44.04 ± 3.45	7.40 ± 0.03	26.44 ± 1.87
48 hours	63.85 ± 10.82	45.25 ± 3.69	7.42 ± 0.01	27.98 ± 1.91

respiratory rate and tidal volume. Hypoxemia resulting from hypoventilation is usually addressed by increasing inspired PO_2 via a face mask or intranasal oxygen.

Common patterns of arterial blood gas derangement in the neonatal ruminant include hypoxemia (PaO_2 < 70 mm Hg) with low or normal $PaCO_2$ and hypoxemia with hypercapnia ($PaCO_2$ > 50 mm Hg). If there is hypercapnia and resulting respiratory acidosis, ventilation is inadequate or there is ventilation-perfusion inequality. Hypoventilation in neonatal ruminants may reflect depression of the respiratory center, medullary trauma, ischemia, hemorrhage or encephalitis, lack of surfactant in the premature neonate, compromised muscle function (white muscle disease), or fractured ribs.

Interpretation of venous blood gas can be deceptive and should be limited to evaluation of metabolic conditions such as metabolic acidosis but not considered adequate for assessment of pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein, since the metabolic status of the head is usually stable.

Plasma lactate measurement may provide prognostic value for calves with acute bronchopneumonia.[52] Acute phase proteins such as haptoglobin, fibrinogen, serum amyloid A, and lipopolysaccharide-binding protein have also been evaluated for diagnostic and prognostic value in bovine respiratory disease (BRD) but they are not specific for BRD, vary with etiology and stage of infection, and do not offer a clear distinction between normal and abnormal animals.

Thoracic radiographs are helpful in diagnosing the presence, type, and extent of respiratory disease in neonatal ruminants. Shortly after birth the smaller vessels posterior to the heart and in the caudodorsal lung fields should be clear. The heart, posterior vena cava, and aorta should be clearly defined. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial, nodular, alveolar, mixed), severity, and location (diffuse, cranioventral, caudodorsal) should be noted. Other soft tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones of the forelimb) should also be evaluated. Thoracic radiographs are routinely taken in the standing or lateral recumbent position in calves. Cranioventral consolidation is a common radiographic finding of infectious bronchopneumonia in calves. Radiographic changes may either follow or precede changes in clinical condition, and sometimes major changes can occur surprisingly rapidly. Clinical signs of pneumonia frequently resolve before the thoracic radiographs return to normal.

Ultrasonographic evaluation of the neonatal ruminant thorax is useful for identification of aspiration of amniotic fluid, atelectasis, pleural effusion, nonventilated lung, pleuritis, and chest wall abscesses, and for the detection of congenital heart defects. It appears most suitable for detecting pathologic processes close to the pleura.[53]

Respiratory endoscopy can be used for evaluation of the nasal cavity and septum, oropharynx and nasopharynx, epiglottis, larynx, and trachea. It is particularly useful for diagnostic evaluation of neonatal ruminants with respiratory stridor, stertorous breathing, malodorous breath or nasal discharge, inspiratory dyspnea, or related clinical signs indicative of upper airway problems.

Airway sampling is useful to determine presence, type, and etiology of respiratory inflammation and infection of neonatal ruminants. Deep pharyngeal swabs with a guarded catheter, transtracheal fluid aspirate, tracheobronchial lavage fluid, or bronchoalveolar lavage fluid analyses and cultures have been described. Techniques, sample handling, and interpretation are described in Chapter 31. For a neonate in respiratory distress, airway sampling may not be indicated until the patient is stabilized. Selection of the appropriate airway sampling method will depend on the patient condition and demeanor, supplies and equipment, test cost, technical assistance, clinician preference, anticipated etiology, sample handling, processing, and interpretation expertise. Specific airway sample, culture, PCR, ELISA, and other available tests for respiratory bacterial, *Mycoplasma, Chlamydia,* and viral pathogens are discussed in Chapter 31. Test-positive and test-negative predictive values may be improved when used for herd level testing, rather than for individual animal test interpretation.

Postmortem examination is a useful diagnostic tool for evaluation of respiratory conditions of neonatal ruminants. In addition to the examination of the upper and lower respiratory tract, brain, heart, gastrointestinal tract, immunologic sites, navel, other mucosal surfaces, and cavity fluids can provide information pertinent to a diagnosis. Lung culture, pathology, and immunohistochemistry (IHC) results can be particularly useful.

Upper Respiratory Tract Disorders

Conditions of the upper airway of neonatal ruminants are not common, but choanal atresia, stenotic nares, congenital cysts, cleft palate, pharyngeal trauma, pharyngeal and laryngeal edema, pharyngeal dysfunction, necrotic laryngitis, and tracheal collapse have been described. With the exception of necrotic laryngitis, most upper respiratory conditions of neonatal ruminants are present within the first week of life but may become progressive with age. Upper airway conditions, particularly those affecting pharyngeal and laryngeal function, predispose to aspiration pneumonia.

Diagnosis of most upper airway disorders can usually be made with a careful physical examination in combination with arterial blood gas concentrations, radiography, and/or endoscopy. Clinical signs of upper airway conditions include inspiratory effort, dyspnea, upper respiratory noise, stridor, malodorous nasal discharge, or cough. Dysphagia, poor appetite, milk reflux from the nostril, and aspiration pneumonia may be noted. Dyspnea is likely to result in failure to thrive and malnourishment.

Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Sporadic outbreaks of pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and oral medication equipment. Compression of the larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea. Edema and necrosis of the larynx may be observed with infectious bovine rhinotracheitis virus infections in neonatal calves.[54,55] *Fusobacterium necrophorum* typically causes necrotic laryngitis in weaned calves but sporadically infects neonates following pharyngeal trauma.[56] Partial occlusion of the upper airway induces turbulent airflow and subsequently mucosal edema. Placement of a tracheostomy tube provides an alternative, sometimes life-saving, airway and rests the inflamed mucosa.

Nutritional myodegeneration and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia are

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common sequela. Collapsed trachea is a rare congenital or acquired condition. In this condition, there is a dynamic dorsoventral collapse of the trachea during inspiration, but no stenosis is present. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the bony callus that develops with healing. Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. Treatment of collapsed trachea in the calf by surgical reconstruction has been attempted, but the prognosis is poor.[57-60]

Respiratory Infection

A number of respiratory disease syndromes may be observed in neonatal calves. Pneumonia in calves less than 5 days of age is most likely hematogenous in origin, a consequence of neonatal septicemia or aspiration pneumonia from inhalation of fetal fluid, meconium, colostrum, or milk as a complication of recumbency, obtunded mentation, large-volume forced feeding, large holes in teat nipples, poor esophageal tubing technique, or pharyngeal dysfunction (white muscle disease). Fever, cough, and nasal discharge are not consistently present in the early stages of pneumonia in the neonate. With hematogenous pneumonia, evidence of infection in other organs is frequently present, including omphalophlebitis, meningitis, enteritis, and polyarthritis. Without early and aggressive treatment, sepsis can progress to shock, multiple organ dysfunction, and death relatively rapidly. *E. coli* or other gram-negative bacterial organisms are incriminated most commonly. With aspiration pneumonia, a mixture of gram-positive, gram-negative, and anaerobic bacteria can be cultured from the lungs, inciting a severe inflammatory response, toxemia, and occasionally sepsis. For hematogenous and aspiration pneumonia, broad-spectrum antimicrobial coverage must be instituted early and be accompanied by antiinflammatory drug therapy, fluid therapy, nutritional supplementation, and supportive care. Long-term treatment is frequently necessary, and prognosis for survival is guarded.

Bacterial pneumonia of dairy calves, frequently described as affecting calves 2 to 6 months of age, may occur as early as 2 weeks of age and frequently peaks in incidence at 5 to 6 weeks of age. In bacterial pneumonia of calves, inhaled pathogens first colonize the bronchoalveolar junction, overcome host defenses, incite inflammation at that site, and go on to spread through the contiguous airways or through adjacent lung tissue. Pneumonia occurs as an endemic problem on many farms but can also occur as an outbreak. Frequently the problem is multifactorial, including bacterial organisms, individual, and farm or environmental risk factors.

Clinical signs of bacterial pneumonia in young calves usually include a combination of the following: fever, nasal discharge, lacrimation or ocular discharge, cough (spontaneous or inducible by tracheal compression), depression, reduced appetite, rough hair coat, expiratory effort, or an abdominal breathing effort. Concurrent signs of otitis may be noted. Subjective parameters like attitude, appetite, appearance, activity level, or respiratory character that are used to detect pneumonia on farms can be insensitive and delay the pneumonia diagnosis and treatment. Remote recording devices that monitor objective parameters such as core body temperature, activity levels and behavior, and frequency and volume of milk consumption are becoming more common and will improve farm pneumonia detection.

Bacterial agents are frequently the primary pathogens in calf pneumonia. Alone or in combination, *Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis,* or *Mycoplasma dispar* are the most common bacterial isolates cultured from airway samples early in the infection. *Histophilus somnus* or *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) are found in more advanced pneumonia cases. Although any *Salmonella* species can cause pneumonia, *Salmonella* Dublin can be the cause of fulminating pneumonia in 1- to 8-month-old calves. Outbreaks of respiratory disease in this age group may be associated with mixed bacterial infections, including *M. bovis,* or with primary or concurrent viral infection with bovine respiratory syncytial virus (BRSV), bovine coronavirus (BCV), or bovine virus diarrhea virus (BVDV) infection. Viral infections increase the risk of opportunistic bacterial infections by their immunosuppressive effects and damage to the respiratory epithelium and pulmonary clearance mechanisms. Pleuritis is an uncommon feature of most neonatal respiratory infections but may be a manifestation of a generalized polyserositis with specific pathogens such as *Mycoplasma* infections of ruminant neonates[61] and occasionally *Pasteurella* infections in lambs.[62]

FPT of immunity is one of the most important risk factors for the development of calf pneumonia in individual animals and in herds. Poor nutrition is another risk factor for pneumonia in dairy calves that are limit-fed milk or milk replacer. A number of pathogens capable of causing respiratory disease are shed in milk. These include *Mycoplasma* spp.,[61,63,64] caprine arthritis encephalitis virus (CAEV),[65,66] and *S.* Dublin. The practice of feeding unpasteurized mastitic milk or nonsaleable milk to neonates increases the risk of disease transmission, including *S.* Dublin, an invasive host-adapted *Salmonella* serotype to cattle, and *Mycoplasma* spp. infections of goat kids and calves and CAEV to goat kids. CAEV produces a number of disease syndromes in goats, including mastitis, arthritis, encephalitis, and pneumonia. Encephalitis and subclinical respiratory disease typically occur in kids 2 to 4 months of age and occasionally in kids as young as 1 month of age.[65,67] Goat kids infected with *Mycoplasma mycoides* subsp. *mycoides* (large colony type) are often very painful, febrile, and reluctant to stand, and have multiple hot swollen joints from acute polyserositis. Approximately 50% of kids develop pneumonia or pleuropneumonia manifest by an increase in respiratory rate and auscultable lung sounds.[61] Outbreaks of mycoplasma pneumonia in calves are usually caused by feeding waste milk contaminated with *M. bovis*.[68,69] Clinical signs include an increased rate and effort of breathing associated with pneumonia, joint and tendon sheath distention reflecting arthritis, polyserositis, tenosynovitis, auricular discharge, and a head tilt reflecting otitis media/interna[63,69] and decubital abscesses.[70] Clinical signs associated with *Mycoplasma* otitis include cranial nerve (CN) 7 and 8 deficits, unilateral or bilateral ear droop, ptosis, epiphora, head tilt, and recumbency in severely affected calves. Pasteurization of milk fed to goat kids and calves is recommended.

Additional environmental risk factors for pneumonia include extremes of temperature, poor ventilation, dust, ammonia, and overcrowding. Overcrowding, especially with commingled age groups of calves, creates a high risk for pneumonia. Housing factors associated with reduced respiratory disease prevalence in naturally ventilated dairy calf barns are solid panels between calves that prevent contact, deep bedding, and low airborne bacterial counts.[71] A minimum space requirement of 28 to 30 ft^2 per calf is associated with low airborne bacterial counts and less respiratory disease for calves in individual and group pens. Increased time between successive occupants of individual or group calf pens reduces the environmental exposure to disease organisms. An all in–all out housing system on farms reduces the chance for endemic pneumonia problems. Other risk factors for pneumonia include poor-quality feed, limited availability of water, stress, inappropriate medications, over-vaccinating, parasitism, and concurrent infection.

Herd-based pneumonia problem solving is needed where respiratory disease in calves is endemic. Routine calf care, herd vaccinations, navel care, colostrum feeding, feed types, amounts, times, and additives are important. Practitioners must learn the pneumonia definition, screening method, and treatment protocols, as well as review records to find seasonal trends, relationship to passive transfer of immunity, age at first diagnosis, and related management factors. Survival curves and incidence calculations can be useful. Practitioners should observe people and procedures and examine animals, as well as determine how many current cases have been detected and treated. Successful management of endemic pneumonia problems requires early detection, effective treatment, and resolution of the most important risk factors.

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For treatment consideration, many antibiotics are labeled for BRD. Treatment plans for individual animals or farm protocols should be based on valid diagnostic information, recent examinations, and responsible use of antibiotics. Compliance with prescribed dose, route, and frequency of administration is factored into antibiotic selection. For one-dose respiratory treatment protocols, enrofloxacin, tulathromycin, ceftiofur, florfenicol, gamithromycin, or tildipirosin may be considered. For antibiotics like spectinomycin, enrofloxacin, ceftiofur, and florfenicol, multiple-dose treatment protocols are also effective for BRD.

Mycoplasmas are susceptible to antimicrobial agents that affect DNA, RNA, protein synthesis, or the integrity of the cell membrane. Mycoplasmas are not susceptible to agents that interfere with synthesis of folic acid or that act on the cell wall. Tylosin, tetracyclines, erythromycin, tilmicosin, tulathromycin, gamithromycin, florfenicol, aminoglycosides, and fluoroquinolones have been shown to have activity against one or more *Mycoplasma* species.[72] However, the efficacy of antimicrobial therapy to eliminate the organism is limited and, although animals may recover, chronic infections may persist.[73]

Prevention of neonatal ruminant respiratory conditions includes appropriate vaccination programs, frequent observation of adults and neonates, uncomplicated births, adequate colostrum, navel care, optimal nutrition, and housing that is clean, dry, and draft free.

Neonatal Apnea and Irregular Breathing Patterns

Periods of apnea in the neonate are commonly associated with nonrespiratory factors, including infection, CNS disorders, hypothermia, and metabolic causes such as hypoglycemia. Seizure activity may be expressed by changes in breathing rate and pattern, and neonatal asphyxia may induce respiratory depression, whether or not cerebral lesions are present.[74] Neonatal respiratory distress may also cause apnea resulting from respiratory center depression or diaphragmatic fatigue. There are two mechanisms of apnea: central apnea, resulting from cessation of diaphragmatic activity, and obstructive apnea, resulting from obstruction of the airway, usually at the pharyngeal level.

Abdominal Distention

Geof W. Smith

Ruminal Bloat

Ruminal bloat is uncommon in calves less than 5 weeks of age because of the relatively undeveloped state of the neonatal rumen. Causes of ruminal bloat in calves include ruminal putrefaction, obstruction of the cardia or esophagus, and vagal indigestion (Box 20-3).

If milk arrives in the rumen in greater quantities than normal by escaping the esophageal groove, it can be subjected to putrefactive decomposition by proteolytic bacteria. Normally the rumen of neonatal calves has a stable aerobic bacterial population. Anaerobic conditions are rapidly established when appreciable amounts of fermentable substances enter the rumen.[75] Clinical signs include diarrhea, poor development, rough haircoat, and recurrent bloat. Reducing the volume of milk fed per feeding, feeding from nipples rather than buckets, and introducing calf starter to promote ruminal development help prevent the condition. A course of oral antibiotics (500 mg oxytetracycline) once daily for 3 or 4 days may help affected calves by killing the putrefactive gut flora.

Bloat is occasionally observed as a complication of severe bronchopneumonia in calves as a consequence of swollen mediastinal lymph nodes compressing the esophagus or compression or inflammation of the vagus.[76] Relief of rumen distention is important for return of rumen function. Chronic ruminal bloat may be relieved by placement of a rumen fistula (Buff's screw trocar). Correct placement of the screw, as described by Dirksen and Garry,[77] reduces the risk of inducing peritonitis. The rumen must be bloated so that it lies firmly against the body wall as the trocar is screwed into place. The site for the trocar is shaved and scrubbed, a small skin incision is made, and the trocar is quickly and forcefully screwed into the belly wall and rumen. After removal of the stylet, the outer rim of the trocar is kept under constant outward tension so that the ruminal wall is held tightly against the parietal peritoneum by the last ridge of the screw. To fix the trocar in this position, gauze soaked in antibiotic should be wrapped around the stem of the trocar between the outer rim and the body wall.[77]

BOX 20-3

Causes of Abdominal Distention

Obstruction

Foreign body (hairballs in calf)
Malformation (atresia coli, recti, ani)
Intussusception
Volvulus, torsion or strangulation

Uroperitoneum

Ruptured bladder (uncommon)
Torn or necrotic urachus, ureter

Peritonitis

Generalized infection
Devitalized bowel
Perforated gastric or intestinal ulcer
Severe umbilical infection

Gas and Fluid Accumulation in Abomasum, Intestinal Tract

Abomasal bloat
Abomasal torsion
Intolerance to diet
Ileus
Gastric, abomasal, duodenal ulceration
Necrotizing enterocolitis
Ruminal bloat

Miscellaneous

Hemoperitoneum
Ruptured umbilical vessels
Ruptured spleen or liver
Congenital tumor

Ascites

Severe liver or renal failure
Severe hypoproteinemia

Abomasal Ulcers

Abomasal ulcers are usually asymptomatic in young calves, but if perforation occurs, peritonitis and shock rapidly develop. It is often difficult to determine the underlying cause of abomasal ulcers; however, several possibilities have been identified including trauma to the mucosa from the addition of coarse roughage feeds, pica resulting from enteritis, abomasal bezoars, environmental and physical stress, hyperacidity, vitamin E deficiency, lactic acidosis, mycotic infection, and low immune status associated with copper deficiency.[78] Several bacteria including *E. coli* and *Sarcina* and *Clostridium* species have also been isolated from various calves with ulcers; however, no infectious component has been identified in cattle, unlike in humans, where *Helicobacter pylori* and gastric ulcers routinely occur together.

Four categories of ulcers are described in calves:

Type 1: Nonperforating ulcer—The ulcer does not perforate the abomasal wall, and intraluminal hemorrhage is minimal.

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Type 2: Nonperforating ulcer with severe blood loss—The ulcer does not perforate the abomasal wall, but erodes a major vessel in the submucosa, resulting in severe intraluminal hemorrhage.

Type 3: Perforating ulcer with local peritonitis—The ulcer perforates the abomasal wall, and abomasal contents leak into the peritoneal cavity or omental bursa. Peritonitis is localized by fibrin deposition, and the abomasum becomes adhered to the peritoneum, omentum, or surrounding viscera.

Type 4: Perforating ulcers with diffuse peritonitis—The ulcer perforates the abomasal wall and abomasal contents quickly leak into and spread throughout the peritoneal cavity, resulting in diffuse peritonitis.[78]

Abomasal ulcers can be very difficult to diagnose antemortem in calves. Clinical signs are vague and include sudden death, abdominal distention, pain on abdominal palpation, expiratory grunt, drooling saliva, bruxism, and melena. Less commonly a syndrome of chronic abdominal pain is observed after abomasal perforation.[79] Absence of inflammatory changes suggests the gut is unlikely to be perforated or necrotic. Severe hypoproteinemia is common with diffuse peritonitis presumably because of the combination of poor colostral uptake and loss of protein into the abdominal exudate. Obtaining peritoneal fluid from normal calves is difficult; if peritonitis is suspected, collection of abdominal fluid is facilitated by locating pockets of peritoneal fluid via abdominal ultrasound.

In general, treatment is limited to calves with bleeding or deep, nonperforated ulcers. Therapy can include blood transfusions, antibiotic administration, changes to the diet, oral administration of antacids, and administration of histamine type 2 receptor antagonists. Aluminum hydroxide/magnesium hydroxide ($Al(OH)_3$/$Mg(OH)_2$) antacids neutralize acid in the abomasum and require three doses per day. Antacids are an inexpensive option for treatment of cattle with ulcers and have a potential therapeutic advantage. $Al(OH)_3$ directly absorbs pepsin, thus decreasing the proteolytic action of pepsin in the stomach.[80] Also, $Al(OH)_3$ and $Mg(OH)_2$ bind bile acids, thus protecting against ulceration caused by bile reflux.[80] Ahmed and colleagues[81] found that healthy calves given 25 to 50 mL of oral antacid had a transient increase in abomasal luminal pH. This effect appeared to be dose related and the extent of the acid neutralization was increased when not given with milk replacer.

Histamine type 2 receptor antagonists reduce acid secretion of parietal cells by selective and competitive antagonism of histamine at H2 receptors on the parietal cells. Cimetidine and ranitidine are synthetic H2 antagonists that inhibit basal as well as pentagastrin- and cholinergic-stimulated gastric acid secretion. Daily oral administration of cimetidine at 10 mg/kg for 30 days in veal calves was found to aid healing of abomasal ulcers.[82] Oral administration of cimetidine (50 to 100 mg/kg q8h) and ranitidine (10 to 50 mg/kg, q8h) caused a dose-dependent increase in abomasal luminal pH; and ranitidine had greater potency than cimetidine.[83] Omeprazole, a proton pump inhibitor, has also been studied in calves. Once daily oral administration of omeprazole (4 mg/kg) to calves increased the mean 24-hour luminal pH by 1.3-pH units; however, this increase in pH was less pronounced with subsequent daily treatments.[84]

Surgical repair of ulcers can be performed on selected cases. Calves need to be in an operable condition and have isolated ulcers. Surgery needs to be performed early in the disease process. Typically ulcers are diagnosed during a laparotomy and can be either resected or the serosa can be inverted with a mattress suture. One study reported a survival rate of 74% following surgical repair, with survival being defined as calves living at least 3 months past surgery date or those dying because of another disease.[85]

Abomasal Displacement

Abomasal displacement is rare in neonatal ruminants. Clinical signs include reduced appetite, poor weight gain, recurrent tympany (left side), and diarrhea. An association of left-sided abomasal displacement with pneumonia in calves suggests that altered vagal function may be involved in the pathogenesis of the condition.[86,87] Typically, left-sided abomasal displacement in calves occurs between 6 and 14 weeks of age, but younger calves may be affected. Displacement of the abomasum is diagnosed by auscultation and percussion; affected animals may have a hypochloremic metabolic alkalosis. Correction can be attempted by rolling the calf on its back or via surgery.

Abomasal Bloat

Acute abdominal distention, colic, depression, and sudden death have been reported in neonatal calves with abomasal ulcers, abomasitis, and abomasal bloat. Possible sequelae to abomasal dilation include abomasal torsion, perforation, and rupture. Abomasal bloat is a syndrome in young calves characterized by anorexia, abdominal distention (either left sided or bilateral), and often death in 6 to 48 hours. At necropsy most of these calves will exhibit abomasal tympany, forestomach and abomasal edema, hemorrhage, mucosal necrosis, and occasionally mural emphysema. This condition occurs most commonly in dairy calves and seems to have a sporadic occurrence with some farms having multiple outbreaks at times. Numerous causes have been postulated, including dietary changes, in particular the addition of coarse roughage feeds; abomasal bezoars; copper deficiency; and various microorganisms. Roeder and colleagues[88] isolated *C. perfringens* type A from a group of eight calves affected by this syndrome and subsequently experimentally reproduced the disease by intraruminal inoculation of the organism.[89] *Campylobacter* and *Sarcina* species have been incriminated in other studies. Histopathologic evaluation of abomasums from 38 affected calves at necropsy revealed that 31 contained abundant gram-positive bacteria associated with the damaged abomasal mucosa.[90] *Campylobacter*-like organisms were demonstrated in 9 and *C. perfringens* in 14 of the 38 cases.[90] Studies of range cattle in west-central Nebraska and Wyoming suggest subclinical trace mineral deficiencies of copper and/or selenium may be involved in the pathogenesis of the condition in this region.[91]

Recently the abomasal bloat syndrome was experimentally reproduced by drenching young Holstein calves with a carbohydrate mixture containing milk replacer, corn starch, and glucose mixed in water.[92] The authors of this study proposed that the pathophysiology of abomasal bloat is primarily related to excess fermentation of high-energy gastrointestinal contents. Although the exact pathogenesis of abomasal bloat is not completely understood, the disease is likely to be multifactorial in origin. Having large amounts of fermentable carbohydrate present in the abomasum (from milk, milk replacer, or high-energy oral electrolyte solutions) along with the presence of fermentative enzymes (produced by bacteria) would likely lead to gas production and bloat.[93] This process would be exacerbated by anything that slows abomasal emptying or causes gastrointestinal ileus. Risk factors for abomasal bloat that potentially delay abomasal emptying include high osmolality milk replacers, feeding a large volume of milk in a single daily feeding, poor mixing of milk replacers, offering cold milk (or milk replacer), not offering water to calves, and allowing erratic feeding schedules. Thus, control of abomasal bloat should be aimed at dietary management more so than therapeutic or prophylactic medications.

Clinical signs are often mild and may inconsistently include diarrhea, mild abdominal distention with fluid and gas, splashing on abdominal succession, and mild depression. Hyperglycemia (189 to 516 mg/dL) with an accompanying glucosuria (1000 to 2000 mg/dL) consistently develop. In severe cases the calves are usually dehydrated and colicky and have prominent abdominal distention and diarrhea and become recumbent. Gross lesions include hemorrhage, edema, and necrosis of abomasal and ruminal mucosae.

Treatment generally involves placing the calf in dorsal recumbency and inserting a needle or catheter into the abomasum to relieve the gas.[94] Attempting to deflate the bloat in a standing calf is often unrewarding since it generally fails to completely drain the abomasum and carries a high risk of inducing peritonitis.[95] Kumper[96] describes good results with paracentesis using a 14-gauge, 50-mm needle when the calf is turned upside down and the abomasum is deflated by inserting a needle in the highest point of the distended

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abdominal wall between the umbilicus and xiphoid. With this technique, 20 of 21 calves with abomasal tympany were successfully managed without complications. Repeated paracentesis carries a high risk of inducing peritonitis; if after paracentesis the calf's condition deteriorates or tympany recurs, a right flank laparotomy is performed to correct a possibly torsed abomasum.[96] Intravenous fluids are administered to correct dehydration, electrolyte, and metabolic derangements. Antibiotic therapy may also be indicated in these calves (most likely parenteral procaine penicillin or oral β-lactam antibiotics to target *Clostridium* bacteria).

Abomasal bloat is a significant problem in artificially raised lambs. Feeding systems that allow lambs to drink large quantities of milk replacer at infrequent intervals and housing lambs on litter are predisposing factors.[97,98] Proliferation of *Lactobacilli, E. coli,* and *C. perfringens* has been implicated in the disease process.[98,99] Fermentation of sugars contained in milk replacer produces carbon dioxide distending the abomasum.[100] Lambs may die within hours because of acute abdominal tympany compromising vascular return and respiration. Early treatment of bloated lambs with oral doses of antibiotics is sometimes an effective treatment. Addition of 0.1% formalin (37% formaldehyde) to milk replacer reduces the incidence of the condition.[99]

Intestinal Atresia

Intestinal atresia is the most common cause of abdominal distention of calves in the first week of life.[79] Typically calves are born normally but develop progressive abdominal distention shortly after birth. Signs of mild colic are occasionally observed. The spiral loop of the ascending colon is usually the site of atresia.[101] Other congenital abnormalities may be present (18% of cases).[101] Pregnancy diagnosis by palpating the amniotic sac before 40 days of gestation may cause colonic atresia in cattle[102]; however, an autosomal recessive inheritance in Holstein cattle has recently been proposed.[103] Surgical repair by resection of the distended proximal blind end and anastomosis of the proximal segment of intestine to the descending colon have been described, but breeding affected animals is not recommended.[101] Long-term survivors are likely to have loose feces and do not tend to grow well.[101]

Intussusception

Intussusception occurs most commonly in the jejunum, but the frequency of ileocecal and colon intussusceptions appears higher in calves than adults.[104] Commonly there is a history of diarrhea. Clinical signs may include intermittent colic, absence of feces, and melena; however, these are inconsistent. The inconsistency of clinical signs and inability to perform a rectal examination makes the diagnosis more difficult in calves than adults.[104] Abdominal ultrasound may be useful. The prognosis following surgical correction is strongly influenced by the duration of the condition prior to correction.

Twisting of the intestinal mass around the cranial root of the mesentery is a rare event but occurs more frequently in calves than adults.[104] Clinically the condition is characterized by a sudden onset of severe colic (kicking at the abdomen, dropping to the ground) that rapidly progresses (abdominal enlargement, tachycardia, tachypnea, reduced or absent fecal passage) to signs of shock and recumbency. Early diagnosis and rapid surgical correction, using either a right paralumbar or ventral midline, together with a supportive fluids approach allow for a good prognosis.

Neonatal Diarrhea

Matthew Izzo • Alison A. Gunn • John K. House

Herd management variables that impact the risk of neonatal death losses in housed calves include efficiency of passive transfer, calf nutrition and environmental management (pathogen exposure), calving area sanitation, and cow vaccination status and health. Successful calf rearing is based on good management. A goal of less than 5% death loss from diarrhea is achievable. With neonatal death losses in pasture or range animals, it is important to determine the incidence of dystocia, physical management and nutritional status of the calving and nursing herds, the cleanliness of the calving and nursing areas, the provision of shelter from wind, and any biosecurity risks.

Rotavirus, cryptosporidia, coronavirus, enterotoxigenic *E. coli,* and *Salmonella* are recognized as the major pathogens associated with diarrhea in calves (Table 20-6). Rotavirus, cryptosporidia, coronavirus, and enterotoxigenic *E. coli* are common pathogens in beef calves (Fig. 20-1).[105-108] *Salmonella* is more frequently implicated in intensive calf rearing systems.[107-109] Enteropathogenic strains of *E. coli* are occasionally implicated in calf diarrhea; the true prevalence of disease associated with these strains is unknown due to the lack of routine definitive diagnostic tests. Torovirus has recently been associated with neonatal calf diarrhea (NCD) in Canada, the United States, and Europe.[110-113] Bovine virus diarrhea is infrequently associated with diarrhea in young calves.[114,115] A variety of other agents have been implicated as causes of neonatal diarrhea, but their importance in the field situation is unknown (see Table 20-6). The incidence of the various etiologic agents varies with the age of the calf, and this is useful in establishing the likelihood that a particular agent is involved (Fig. 20-2). It is usually impossible to make a definitive etiologic diagnosis on clinical grounds. It is possible to detect signs of straining or passage of frank blood and mucus that suggest the presence of colitis, implicating possible salmonella, coronavirus, BVDV, enteropathogenic *E. coli,* or coccidial infections.

Pathogenesis

Diarrhea can be the result of either increased secretion or decreased absorption. Bacteria such as enterotoxigenic *E. coli* and, to some extent, *Salmonella* cause neonatal diarrhea by secreting enterotoxins that stimulate increased intestinal secretions.[116,117] These changes are thought to be mediated by cyclic AMP or cyclic GMP, calmodulin, and changes in protein kinase activity.[118,119] The cell's structure is not affected, but the activity of the membrane pumps is altered and there is increased secretion of chloride, sodium, bicarbonate, and potassium.[120,121] Heat-stable enterotoxin induces bicarbonate secretion through the tyrosin kinase pathway.[121] Sodium absorption linked to glucose and amino acid transport across the mucosal epithelium is not affected.[122,123]

Protozoa and enteric viruses cause neonatal diarrhea as a result of the destruction of the absorptive villous epithelial cells.[124-127] Diarrhea results because intestinal digestive secretions continue while absorption is impaired.[128,129] In rotavirus and coronavirus infections, this is further exacerbated by compensatory hyperplasia of the crypt cells. The crypt cells have secretory functions and their multiplication adds to the secretory load.[128] Rotavirus can also stimulate intestinal secretion both at a cellular level and by stimulation of the enteric nervous system. This is associated with a viral nonstructural protein NSP4.[130,131]

Continued feeding may result in more nutrients presented to the small intestine than the damaged villi can absorb[132,133]; excess nutrients being fermented in the large intestine promoting bacterial overgrowth[118,134]; and generation of organic acids and other deleterious compounds. The osmotic effect of the unabsorbed nutrients drags water into the gut and contributes to the diarrhea.[128] Marked inflammation is a feature of salmonellosis and clostridiosis. This contributes to diarrhea by increasing mucosal pore size and hydraulic pressures within the intestinal wall by destroying absorptive cells and increasing prostaglandin production, which in turn stimulates secretory mechanisms within the enterocytes.[118,128]

On an individual animal basis, diarrhea is significant because of fluid and electrolyte losses. As long as the neonate can compensate for these losses, it will remain fairly bright and continue to suck. If the losses exceed intake, systemic effects of dehydration (salt and water loss) or acidosis are seen. Fluid is lost preferentially from

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TABLE 20-6

Evaluation of the Pathogenicity of Various Infectious Agents*

Agent Name	Experimental Production of Diarrhea		Isolated with Higher Frequency from Diarrheic Calves	Organism Associated with Intestinal Pathology
	Gnotobiotic Calves	Conventional Calves		
Bacterial				
Enterotoxigenic *Escherichia coli*		+	++/–	+
Enterohemorrhagic *E. coli*	+	+/–		++++
Salmonella spp.	++	+	+	
Campylobacter fecalis		+		
Campylobacter coli		++	– –	
Campylobacter jejuni		++	+/–	
Clostridium perfringens				
Type A	+	–	+	+
Type C	+			++
Clostridium sordelli	+			
Viral				
Rotavirus	++	++	+++	+++
Coronavirus	+++	+	+	+++
Bovine virus diarrhea	+	+++		+
Bovine torovirus (Breda virus)	+++		+	+
Calicivirus	+	–	+	+
Parvovirus		+/–		+
Astrovirus		–		
Parasitic				
Cryptosporidium spp.		++++	++	+
Eimeria spp.		++		+

*As gauged by their ability to experimentally produce diarrhea in calves, field surveys of the incidence of infection in diarrheic and healthy calves, and similarity in the distribution of intestinal pathology and the infectious agent.

–, Negative finding; +, positive finding.

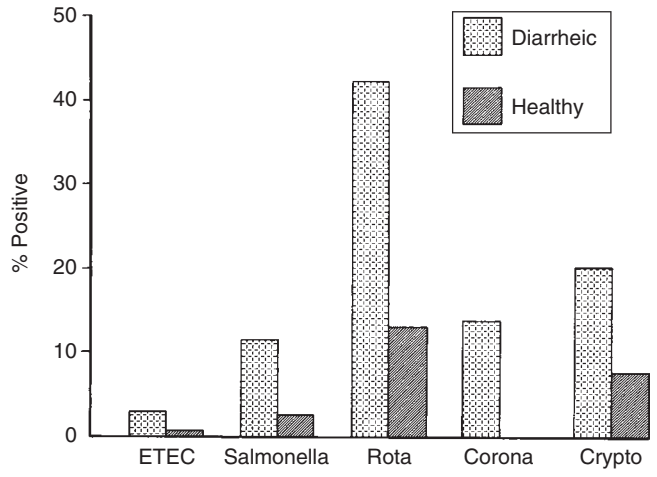


FIG. 20-1 Common enteropathogens in dairy calves. The comparative incidence of isolation from diarrheic and normal calves is shown. *(Data from Snodgrass DR, Terzolo HR, Sherwood D, et al. 1986. Aetiology of diarrhoea in young calves. Vet Rec 119:31.)*

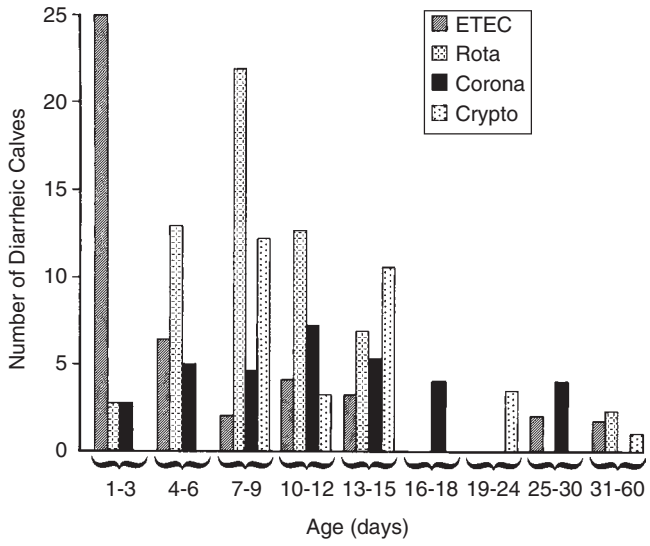


FIG. 20-2 Age incidence of isolation of different enteropathogens from diarrheic beef calves. The data are based on a retrospective records survey of 245 diarrheic calves admitted to the Western College of Veterinary Medicine over a 2-year period.

the vascular compartment[135,136] and cardiovascular collapse results. Acidosis has several causes including fecal loss of bicarbonate, endogenous synthesis of L-lactic acid in response to dehydration and poor tissue perfusion, and D-lactic acid production through bacterial fermentation of undigested or malabsorbed milk within the gastrointestinal tract.[137-142] Acidosis contributes to the calf's malaise by increasing vascular resistance and impairing cardiac function by direct effects and by inhibiting the action of catecholamines. Esophageal groove function may be compromised in acidotic calves, promoting ruminal drinking with the consequences of further production of D-lactic acid in the rumen and subsequent ruminal acidosis.[142,143]

The neonate becomes depressed, loses its suck reflex, and becomes weak; if the disease progresses, recumbency and coma may develop. One cause of death is believed to be heart failure as a result of

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myocardial potassium imbalance caused by the combined effects of potassium losses into the gastrointestinal tract and the redistribution of potassium from the cells to extracellular fluid as a result of acidosis.[144-146] Hypothermia will also contribute to cardiac failure. In cases of enterotoxigenic *E. coli,* cryptosporidia, rotavirus, and coronavirus infections, correcting the fluid, electrolyte, and acid-base imbalances restores the neonate's ability to walk and suck. A residual degree of malaise may persist, which can be attributed to inflammation within the gut wall and damage to the integrity of the mucosal barriers, allowing invasion of enteric microbes or their toxins. If malabsorption persists, cachexia can develop—particularly if milk continues to be withheld as part of therapy—and death from malnutrition or hypoglycemia may occur.

Salmonella are invasive and release endotoxins in the systemic circulation. Clostridia produce exotoxins. Both endotoxins and exotoxins have profound systemic effects that are often directly responsible for malaise, microcirculatory failure, and cardiovascular collapse. Correcting fluid and electrolyte disturbances in these infections will aid the neonate but will not overcome the effects of toxemia or bacteremia.

Etiology

Bacteria

ESCHERICHIA COLI. *E. coli* are part of the normal flora of the bovine gastrointestinal tract. Pathogenic strains of *E. coli* possess virulence attributes that are involved in the pathogenesis of disease. Virulence attributes include adhesins, enterotoxins, and cytotoxins. Pathogenic strains of *E. coli* may be shed by adult cattle with transmission to neonates by the fecal-oral route. Sick neonates amplify environmental contamination via prolific fecal shedding.

ENTEROTOXIGENIC *E. COLI*. Enterotoxigenic *E. coli* (ETEC) possess two virulence factors: fimbriae (pili) and enterotoxins. F5 (K99) and/or F41 fimbriae mediate adherence and thermolabile (LT) and thermostable (STa and STb) enterotoxins stimulate a secretory response by intestinal crypt cells. Although some bovine-origin ETEC produce LT, most strains that cause diarrhea in neonatal calves produce STa heat-stable enterotoxins.[147] The STa enterotoxin and F5 antigen are plasmid-mediated virulence factors. Susceptibility to ETEC is age dependent according to the binding specificity of pili antigens to immature enterocytes.[148] Disease is typically observed in calves less than 3 days of age; however, concurrent infection with rotavirus may extend this window to 7 to 14 days of age.[149,150] Intestinal cells of calves greater than 2 days of age acquire natural resistance to F5 adhesion.[148] Despite this, F5-positive *E. coli* have been isolated from healthy 4- to 12-week-old calves and F5-positive ETEC are shed in feces for several weeks following experimental infection of newborn calves.[151]

ATTACHING AND EFFACING *E. COLI* AND SHIGA TOXIN–PRODUCING *E. COLI*. Attaching and effacing *E. coli* (AEEC) and Shiga toxin–producing *E. coli* (STEC) have also been identified as causes of diarrhea and dysentery in calves.[152,153] Disease is mediated by cytotoxic damage to the intestinal mucosa. Lesions may be observed in the ileum, cecum, and descending colon.[154] AEEC (Vero or HeLa toxin producing) induce a mucohemorrhagic colitis, with petechial or ecchymotic hemorrhages in the wall of the colon and rectum.[155-157] *E. coli* that carry this toxin often belong to O serogroups 5, 26, 111, 118, and 145.[156,158] Naturally occurring outbreaks have been reported in 2-day-old to 4-week-old calves.[159] Diarrhea and enteritis have been associated with naturally occurring *E. coli* O157:H7 in 1- to 3-week-old calves in Argentina, the United Kingdom, and Korea.[160-162] The most common clinical sign is diarrhea, but dysentery, dullness, reluctance to move, weight loss, anorexia, abdominal pain manifested by bruxism, and dehydration are seen in some cases. The feces of affected calves can appear normal, but more commonly feces are watery yellow with blood.

STEC serotypes associated with dysentery in calves include O5:H-, O26:H11, O111:H-, and O113:H21[163]; these serotypes may produce Shiga toxins, those that are immunologically similar to the Shiga toxin produced by *Shigella dysenteriae* (Stx1), and those that are immunologically distinct from *S. dysenteriae* Shiga toxin (STx2).[164] Bovine STEC produce either STx1, STx2, or both.[165] AEEC, which causes disease and does not produce enterotoxins or Shiga toxin, is referred to as enteropathogenic *E. coli* (EPEC).

The prevalence of AEEC and STEC in calves and the incidence of disease caused by these strains are not clearly defined, since most diagnostic laboratories do not routinely screen for AEEC and STEC. In a study aimed at determining the clinical significance and prevalence of AEEC *E. coli* in Swiss cattle,[165a] fecal swabs of 93 cattle from two farms with calf diarrhea, and of 54 cattle from two similar farms without clinical problems, were screened for AEEC by PCR and colony-blot hybridization. On average, 21% of all cows were positive for AEEC by PCR, without differences between farms with and without diarrhea problems. By contrast, AEEC were detected by PCR in 60% of animals younger than 2 years from farms with diarrhea problems, whereas only 32% of comparable control animals from farms without clinical problems had AEEC.

The importance of AEEC and STEC has increased in recent years because of the zoonotic potential of the organisms. Cattle are a major reservoir of STEC and EHEC, including *E. coli* O157:H7, which is the EHEC serotype most often associated with hemorrhagic colitis and hemolytic uremic syndrome in humans.[162,166]

SALMONELLA. There are over 2200 reported serotypes of *Salmonella*, yet fewer than 2% of these account for approximately 80% of the disease reported in livestock[167] (see also Chapter 32). In cattle, over 95% of salmonella associated with disease is in serogroups B, C, D, and E. *Salmonella* induces a wide spectrum of disease in cattle of all ages, ranging from inapparent subclinical infections to acute fulminant bacteremia, endotoxemia, and death. The variable manifestations of disease reflect the tissue trophisms of different *Salmonella* serotypes and the influence of challenge dose and host immunity. Common clinical signs associated with "salmonellosis" include fever, diarrhea, anorexia, depressed mentation, and dehydration. Many of the clinical signs are associated with endotoxemia. Systemic signs of endotoxemia include fever, tachypnea, tachycardia, scleral injection, leukopenia/leukocytosis, and weakness. Some serotypes, particularly *Salmonella* Typhimurium, have a tendency to induce severe inflammation of the bowel mucosa resulting in dysentery, and passage of fibrin and mucosal casts. Fluid, electrolyte, and protein loss may progress rapidly and become life threatening if not corrected. With severe disease, animals rapidly become emaciated because of the catabolic state induced by release of TNF-α. Sequelae occasionally observed following invasive *Salmonella* infections in neonates include septic osteoarthritis and meningitis.

Immunity to *Salmonella* changes rapidly during the first 3 months of life. At 2 weeks of age the LD_{50} for some virulent strains is 10^5,[168] at 6 to 7 weeks 10^7, and at 12 to 14 weeks 10^{10}.[169] In contrast, administration of 10^{10} salmonella to 24- to 28-week-old calves failed to induce clinical signs of disease.[169] The numbers cited reflect the influence of age on immunity but should not be interpreted as absolute. Different age predilections, manifestations of disease, and virulence are observed between *Salmonella* serotypes and between different strains of the same serotype.[170,171] Although adults may serve as carriers and a source of infection of *S.* Dublin infection for neonates, disease in adults is less common in mature cattle compared with calves. In contrast, *S.* Typhimurium tends to manifest disease in an epidemic manner, causing illness in all age groups.

Calves on endemically infected farms are commonly exposed to *Salmonella* in the first few days of life.[172] *Salmonella* exposure may occur via contaminated colostrum or milk, or surface contamination of teats and udder, personnel, equipment, or the environment. Chronically infected carriers may shed 2.5×10^8 salmonella in milk per day (25 kg of milk containing 10^5 salmonella/mL).[173] Feeding utensils and personnel often play a significant role in transmitting

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Salmonella among calves.[174] *Salmonella* infects the salivary glands and is shed in saliva and nasal secretions.[175,176] Adequate cleaning and disinfection of feeding and medicating utensils is necessary to remove *Salmonella* contamination. *Salmonella* is sensitive to most disinfectants, but removal of contaminating organic debris is imperative since the activity of disinfectants is reduced by the presence of organic matter.[177]

CLOSTRIDIA. Although clostridia are not commonly considered a major pathogen causing NCD, there are a number of reports associating clostridial infections with enteritis and abomasitis.

Clostridium perfringens is the most important cause of clostridial enteric disease in calves. Some types of *C. perfringens* (mainly type A) are consistently recovered from the intestinal tracts of animals and from the environment, whereas others (types B, C, D, and E) are less common in the intestinal tracts of animals and can occasionally be found in the environment in areas where disease produced by these organisms is enzootic[178] (see also Chapter 32). Disease is usually precipitated by management factors that lead to the proliferation of the organism within the gastrointestinal tract or attenuated digestion of clostridial toxins within the lumen of the alimentary tract.

C. perfringens type A has been associated with acute hemorrhagic abomasitis in neonatal calves. Clinical signs include acute abdominal distention, colic, depression, and sudden death. Onset of clinical signs is rapid; affected animals become anorexic, depressed, or restless. Signs of abdominal discomfort are observed in approximately half of the cases and include treading on the spot and kicking at the abdomen. On physical examination splashing and metallic sounds are heard on succussion of the distended abdomen; passage of a stomach tube fails to relieve the distention. Fecal output is reduced and melena may be observed. Gross pathology may include abomasal ulcers, abomasitis, and abomasal tympany.[88,89] Trace mineral deficiencies of copper and/or selenium may also be involved in the pathogenesis of the condition.[91] A decreased prevalence of abomasal tympany and ulceration were reported in neonatal calves from herds having a history of these problems following implementation of a *C. perfringens* vaccination program.[91,179] Enterotoxemia caused by *C. perfringens* type A has been described in 2- to 4-month-old calves with the condition observed more often in beef calves than dairy calves.[180] The disease is characterized by a high-case fatality rate, sudden deaths, lesions of necrotic and hemorrhagic enteritis of the small intestine, and, most often, an absence of other clinical signs.[181]

C. perfringens type B is not commonly associated with neonatal diarrhea in calves. *C. perfringens* type C infections are most frequently observed in neonates less than 10 days of age.[182] Newborn animals are typically most susceptible, perhaps because of ready colonization of the gut by *C. perfringens* in the absence of well-established normal intestinal flora.[178] Alteration of the flora by sudden dietary changes may also be an inciting factor in type C infections. Vigorous, healthy calves develop hemorrhagic, necrotic enteritis and enterotoxemia, often accompanied by evidence of abdominal pain and neurologic signs that may include frenzied bellowing, aimless running, tetany, and opisthotonos. Death may be peracute, occasionally without other clinical signs, but may also follow a clinical course of several days.

Clostridium difficile has recently emerged as a pathogen in both human and veterinary medicine. Toxins released cause epithelial cell death and activation of the enteric nervous system, resulting in a malabsorptive and secretory diarrhea.[183] The role of *C. difficile* as a primary pathogen has not been established because it has been detected in both healthy and diarrheic calves[184] and experimental infection has not induced disease.[185]

***CAMPYLOBACTER* SPP.** The clinical significance of *Campylobacter* spp. in calf scours is inconclusive. *Campylobacter* spp. are part of the normal intestinal flora. Experimental challenge studies have demonstrated the capacity of *C. jejuni* to cause enteritis in calves.[144,186-188] However, there is a paucity of convincing reports that demonstrate a causal association in naturally occurring cases.

Viruses

Intestinal viruses multiply within enterocytes. As the epithelial cells are destroyed, villous atrophy develops. The various agents cannot be readily separated on clinical grounds. Diarrhea can vary in severity from soft to watery feces.

ROTAVIRUS. Rotaviruses are the most common cause of neonatal diarrhea in calves.[189,190] Affected calves are generally 5 days to 2 weeks of age, although disease can occur at 24 hours, particularly in colostrum-deprived calves (see Fig. 20-2).[191,192] This age predilection is thought to be because many cows secrete anti-rotavirus antibody in their colostrum, which confers local protection against rotavirus attack until antibody levels in milk decline 48 to 72 hours postpartum.[193,194] Resistance to infection is not age dependent, but age-dependent resistance to clinical disease has been demonstrated.[195] Age restriction may be related to acquired immunity, since neutralizing antibodies increase with age and virus exposure. In addition, the expression of intestinal mucins and the rate of epithelial cell replacement and fluid absorption are also age dependent and have been shown to affect rotavirus infection and disease expression.[196]

Mature villous enterocytes of the small intestine are the main target for rotavirus.[127] Infected enterocytes are rapidly shed and replaced with immature squamous and cuboidal cells from the crypts, resulting in villous blunting.[127,197] Intestinal secretions are increased due to the compensatory hyperplasia of crypt cells and enterotoxigenic activity of the viral nonstructural protein NSP4.[130,131] Both increased secretory load and impaired absorption caused by villus hypoplasia contribute to the diarrhea. It is thought that virulent strains replicate more quickly and infect a larger area of epithelium. Difference in rotavirus replication rates in the gut and age-dependent differences in the rate of enterocyte loss and natural replacement rate may explain the differences in clinical outcome. Concurrent infection with ETEC has also been shown to cause clinical signs at a later age than with a single infection of either agent alone.[198]

Rotavirus of calves, lambs, kids, pigs, foals, mice, and children are morphologically identical. They are classified by the antigenic properties and/or sequence of the genes encoding the viral capsid proteins. Viral protein (VP) 6 is used to separate them into seven antigenically distinct serogroups A-F. Rotaviruses from serogroups A, B, and C have been isolated from cattle, and serogroup A is the most common cause of diarrhea in calves. Group B rotaviruses have been isolated from calves and adult cattle; however, there is less information regarding their significance and prevalence in cattle.[199-203] Group B rotavirus are more common in lambs than calves.[204] Group C rotavirus have only been isolated from adult cattle.[202] Each serogroup may be classified further by G-types (glycoprotein) and P-types (protease-sensitive protein) that correlate to the serotype and/or genotype of capsid proteins VP7 and VP4, respectively.[205] A range of both serotypic and genotypic diversity and virulence has been reported within serogroup A.[195,206-208] Rotavirus is shed in the feces of infected animals, and transmission is primarily fecal-oral. Clinical signs occur 1 to 3 days after infection and last for 5 to 9 days. Virus excretion commences with the onset of clinical signs and continues for 3-7 days.[195,209] Adult cows can be subclinically infected and intermittently shed the virus during pregnancy and especially at parturition.[210-212] This is likely the most common source of infection, with carrier cows infecting their calves and then these calves infecting other calves.[213] Calves from carrier cows have a significantly higher risk of clinical disease, and the birth of calves from known carrier cows has been associated with the beginning of an outbreak. Recovered calves can become reinfected and shed virus.[214]

The environment may be an important source of infection. Rotaviruses can survive in fresh water for more than 2 weeks at 23°C and for months in water or soil less than 5°C.[215] They are also stable in feces and effluent for up to 9 months and therefore are likely to remain in calving areas from year to year.[216]

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CORONAVIRUS. BCV commonly causes diarrhea in calves 5 days to 1 month of age.[107,112,217,218] Disease can occur within 24 hours in colostrum-deprived calves and has also been recorded in calves up to 5 months of age.[219] Respiratory infections are common in older calves and may be important in the epizootiology of enteritis.[219]

Calves may be infected with coronavirus by the oral or respiratory route.[209] Fecal shedding commences 3 days after infection and persists for up to a week; nasal shedding can be detected 2 days after infection and persists for 2 weeks. Once infected, calves initially excrete high levels of virus and are potent sources of contamination. Infection persists for weeks in apparently recovered calves, and these excrete low levels of virus for weeks.[220] Subclinical infection is common. Disease is more common in the winter months, and coronavirus survives in the environment from year to year.

Calves may be infected by virus shed by persistently infected cows.[221] Coronavirus has been detected in the feces of more than 70% of clinically normal cows.[212] The rate of virus excretion increases at parturition and in the winter months.[210,222] Calves born to carrier animals are at a significantly increased risk of developing diarrhea.[210]

The pathology of coronavirus is often more severe than rotavirus, resulting in a muco-hemorrhagic enterocolitis. The virus infects both the small and large intestine. In the spiral colon there is widespread destruction of the cells of the colonic ridges.[124,126] Virus replication occurs in the surface epithelium, especially in the distal half of the villi, resulting in stunting and fusion of the villi. Immature cells replace epithelial cells, and in severe infection there can be areas of complete desquamation. Intestinal secretions continue and absorption is impaired by reduced surface area. Undigested lactose accumulates in the intestinal lumen, often resulting in a secondary bacterial overgrowth, fermentation, lactate production, and an osmotic imbalance that draws fluid into the intestinal lumen. Most infections are self-limiting because the virus rarely attacks crypt epithelial cells.[221] In response to infection the mitotic rate of crypt cells increases, producing immature cells that are more resistant to virus infection and that migrate up the villi to replace the damaged cells.

In experimental challenge studies, diarrhea develops 48 hours after infection. Calves are initially depressed and anorexic for the acute phase and may become dehydrated and pyrexic in a severe infection.[221] Severe infections can result in death as a result of dehydration, acidosis, shock, and cardiac failure. Respiratory signs are generally mild. Rhinitis, sneezing, and coughing may occur. Lesions may be found in the lungs, but clinical signs of pneumonia are rare, except when secondary infection occurs.

BOVINE VIRAL DIARRHEA VIRUS. BVDV occasionally causes diarrhea and thrombocytopenia in young calves outside the confines of the persistently infected disease model.[114,115] Colostral antibodies generally protect young calves from BVDV infection, but disease may occur as a result of FPT or the introduction of novel BVDV strains with new cattle or viral mutation in persistently infected homegrown cattle. BVDV is also thought to exacerbate infections because of other pathogens.[223] It has also been implicated in necrotic enteritis, an acute enteritis of 7- to 12-week-old beef calves reported in the United Kingdom.[224] Affected calves usually show oral ulcerations, particularly on the hard and soft palate. The buccal papillae are often blunted and the tips may be ulcerated.[225] Some variants of the virus produce intestinal bleeding, petechiation, ecchymosis, or prolonged bleeding from venipuncture sites as a result of thrombocytopenia.[114,226-228] Hematologic findings often include leukopenia and thrombocytopenia. The disease must be differentiated from other causes of enteritis that are complicated by bovine papular stomatitis infection. Bovine papular stomatitis (see Chapter 32) is common in neonatal calves. It produces oral lesions that are hyperemic and red, with a central white area of necrosis and often a raised rim of proliferating epithelial cells. These lesions often involve the mucosa around the molars. They are usually of little consequence, and their importance lies in the fact that they may be confused with BVDV. One feature that helps identify BVDV ulcers is that they lack the zones of epithelial proliferation seen in bovine papular stomatitis.

BOVINE TOROVIRUS (BREDA VIRUS). Bovine torovirus has been detected worldwide[229-232] and has recently been implicated as an important cause of calf diarrhea.[110,111] Initially known as Breda virus, it is part of the Coronaviridae family. It has been relatively infrequently reported because it is difficult to recognize by EM and it cannot as yet be grown in cell culture, which has precluded the development of routine immunospecific diagnostic tests.[110] Laboratory studies using PCR have implicated it as the sole pathogen isolated in between 25% to 30% of fecal samples from calves with diarrhea under 6 weeks of age.[110,111] It is also found in the feces and nasal secretions of asymptomatic animals,[110,112] implying that the epizootiology is likely to be similar to that of rotavirus and coronavirus, with asymptomatic carriers acting as a reservoir of infection within a herd.[210] It is mainly a disease of calves less than 3 weeks of age with diarrhea commencing as early as 1 to 3 days after birth,[231,232] but clinical signs have been observed up to 10 months of age.[111,233] Clinically it produces mild to moderate diarrhea in calves under both experimental and field conditions.[181,232,234] The virus infects the distal half of the ileum, jejunum, and colon, resulting in necrosis of the crypts and villous enterocytes.[235,236] Clinical signs develop 24 to 72 hours after experimental infection.[232] It has also been isolated from the respiratory tract of cattle and associated with respiratory signs in calves at 1 month and 4 to 6 months of age.[237]

OTHER VIRUSES. Calicivirus, astrovirus, adenovirus, parvovirus, and picobirnavirus have all been associated with neonatal calf diarrhea.[238-242] The pathogenicity and contribution of these viruses to field outbreaks are uncertain.

Protozoa

CRYPTOSPORIDIUM. Four species of *Cryptosporidium* have been identified in cattle: *Cryptosporidium parvum, C. andersoni, C. bovis,* and *C. ryanae.*[243] *C. parvum* has been implicated as the main cause of diarrhea in dairy calves worldwide.[244,245] *C. andersoni* has been found in the abomasum of adults and young calves, but its significance is still dubious.[246] *C. parvum* and *C. andersoni* have morphologically distinct oocysts and differ genetically.[247] *C. bovis* and *C. ryanae,* which are morphologically identical to *C. parvum,* were detected using PCR and are mainly responsible for diarrhea in postweaned calves,[248-251] but they have also been found in all age groups of cattle.[252]

C. parvum was initially thought to be a single species that affected both humans and a broad range of animals. Later, it was recognized that two distinct genotypes were present: type 1, which was found in human sources, and type 2, which was considered to be zoonotic and could be isolated from bovines and other farm animals such as sheep and goats.[253,254] The most recent molecular work recognizes that *C. parvum* genotype 1 isolates are *Cryptosporidium hominis*, a human-specific pathogen that is responsible for the majority of cases of cryptosporidiosis in humans in the United States.[255] Calves generally become infected between 1 and 4 weeks of age and display clinical signs for 4 to 14 days. Animals of all ages can be infected, but diarrhea is mainly associated with calves preweaning.[256] Cryptosporidial infections are asymptomatic in cattle older than 4 months of age. *C. parvum* mainly infects the distal small intestine, but lesions are also found in the cecum and colon and occasionally the duodenum.[257] The parasite invades the superficial cells of the mucosa in the intestine but is surrounded by an invagination of the host cell membrane and remains extracytoplasmic. Parasitic invasion of the mucosa leads to epithelial destruction and mild to moderate villous atrophy, with microvillous shortening and destruction. This leads to impaired nutrient digestion and transport and a resulting malabsorption diarrhea. Recent studies have also documented increased mucosal prostaglandin secretion, resulting in crypt secretion of chloride and bicarbonate combined with inhibition of villous sodium chloride absorption.[258]

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Affected calves often show no sign other than diarrhea but can show depression, dehydration, and anorexia.[259] Pyrexia and tenesmus have been noted.[260,261] Variable levels of morbidity have been reported and mortality is generally low.[259,260,262] Other pathogens can be involved and are likely to contribute to the severity of the disease. Affected calves can take 4 to 6 weeks to recover. Cryptosporidiosis occurs less frequently in suckler calves at pasture, but when these calves are affected, outbreaks were reported to be more severe than those in dairy calves, with mortality rates up to 30%.[246] High mortality rates have been attributed to lack of herd immunity in seasonal calving herds where the transmission cycle is broken. Neutralizing antibodies in colostrum and milk reduce infectivity by immobilizing the parasite, blocking invasion, and inhibiting adhesion to host cells or direct cytotoxicity to *Cryptosporidium* sporozoites.[263] High mortality rates have also been associated with concurrent low levels of selenium, inadequate nutrition, presence of concurrent enteric infections, and specific management practices.[246]

Transmission is fecal-oral by ingestion of an encysted, sporulated oocyst. Transmission can be direct from host to host, by ingestion of contaminated food or water, and probably mechanically via flies.[264] A study of oocyst shedding in experimentally infected neonatal calves demonstrated a prepatent and a patent period ranging from 3 ± 6 and 4 ± 13 days, respectively.[265] The parasite is capable of autoinfection, sporulating within the intestine and immediately infecting adjacent cells, which can result in protracted clinical illness and relapses. The ability to autoinfect results in huge parasite burdens following very small infective doses. Calves aged 1 week to 4 months of age are most likely to be actively shedding significant numbers of oocysts with peak shedding occurring between 1 and 3 weeks of age.[256,265-267] Infected calves can shed in excess of 10^6 oocysts/g of feces.[265,268] *C. parvum* oocysts have also been isolated from adult cows with herd prevalence ranging from 7% to 100%.[256,269-271] Mean shedding intensity reported for adult cows has ranged from 3 to 900 oocysts/g of feces.[271-273] It is likely that carrier cows are a source of infection for young calves.

The most critical factor affecting environmental oocyst survival is the temperature. Drying of oocysts has been shown to dramatically reduce their viability and infectivity in mice.[274,275] Oocysts can enter watercourses and ground water by direct contact with cows or from run-off of rain or irrigation water from pastures and manure storage areas.[246,276] *Cryptosporidium* oocysts have been shown to survive in water for at least 12 weeks at 4° C.[277] Oocysts are resistant to chlorination of water and most disinfectants[246] and have also been shown to survive in silage.[278] Wildlife may be a significant reservoir for *C. parvum* and act as a method of amplification and infection in the environment.[269,279,280]

Cryptosporidia cause diarrhea and sometimes death in 3- to 30-day-old lambs. Protracted infections and mortality are most common in lambs infected in the first few days of life, since age resistance is seen after about 3 weeks of age.[137,281-283] Cryptosporidiosis has also been described in goats where it affected 5- to 20-day-old kids, signs lasted from 3 to 7 days, relapses were not uncommon, and there was a moderate mortality rate.[284]

People working with diarrheic neonates should be warned of the risk of zoonotic disease. An outbreak of cryptosporidiosis has been described in caregivers in a veterinary hospital treating diarrheic calves. Affected people suffered from watery diarrhea, cramping, flatulence, and headache.[285] One person became infected as a result of handling soiled clothing.

GIARDIA. Giardia is often found in diarrheic calves in association with other pathogens, but its relevance as a pathogen in its own right is unclear. Several authors have documented cases of diarrhea where giardia infection has been implicated as the causative agent either by itself or in conjunction with *C. parvum* and rotavirus.[286-288] Affected calves are at least 2 weeks old, and often older than 1 month of age, with infection often becoming chronic and lasting for several months.[266,286,289-291] Giardia has a prepatent period of 7 to 8 days, and the delayed interval between birth and infection is likely to relate to high levels of colostral protection against *Giardia* but low protective levels in milk.[292] Many calves were shown to have a poor specific immune response to the infection, accounting for the chronicity of the infection.

The significance of *Giardia* as a primary pathogen has been questioned by the observation of similar or lower rates of infection in calves with diarrhea compared with asymptomatic calves.[266,293] Treatment of affected calves with fenbendazole reduces the duration but not the number of diarrhea episodes.[288]

COCCIDIOSIS. Thirteen species of *Eimeria* have been reported in cattle.[294] *Eimeria bovis* and *E. zuernii* have historically been the most common pathogenic species; however, there are increasing reports of *E. alabamensis* causing disease.[295-297] Transmission is fecal-oral. Infected animals pass unsporulated oocysts in their feces that then sporulate and become infective. The sporulated oocysts are protected from the environment by a double cyst wall.[298] Moist, temperate, cool conditions favor sporulation, and oocysts can survive for several years. Sporulated oocysts can resist freezing to −8° C for several months but are destroyed by high temperatures and dry conditions within a few weeks.[299] Under optimal conditions sporulation can occur within a few days. The prepatent period of the two main pathogenic species is 15 to 20 days, and the patent period around 11 days. *Eimeria alabamensis* has a prepatent period of only 8 days and a patent period of 5 days.

Calves start shedding at about 1 month of age and shed for 3 to 4 months. *E. bovis* and *E. zuernii* schizonts first reproduce in the lower small intestine and then produce second-generation schizonts and gamonts in the cecum and colon, where they attack crypt cells.[294] These latter stages induce both local and more extensive lesions.

Outbreaks of disease in calves and lambs are often related to overcrowded and confined conditions. Up to 95% of infections are subclinical, causing decreased growth rates that are often unnoticed.[300] Clinical disease can be chronic or acute and is generally found in calves aged 3 weeks to 6 months, although animals of 2 years of age or older may be affected. In beef cattle the most common reports of clinical disease are associated with weaning stress.[301] Clinical signs may include diarrhea, ill thrift, increased susceptibility to pneumonia, tenesmus, increased mucus in feces, and hematochezia. Pyrexia, dehydration, and anemia may also be observed. The disease is usually self-limiting without reinfection. Chronic disease is often underdiagnosed.[300] Calves appear weak and listless with pasty feces, drooping eyes, and a staring coat. Fecal oocyst count is low or negligible. Disease results from continual reinfection resulting from a heavily contaminated environment.

Nutritional Diarrhea

Producers often express the opinion that scours is caused by calves consuming too much milk. However, there is no documented research in healthy calves to support this. Calves fed 16% to 20% of body weight per day or allowed ad libitum access to milk have not developed problems with diarrhea.[302,303] However, in studies in which calves are also infected with enteric pathogens, the diarrhea and depression were exacerbated by feeding normal amounts of whole cows' milk in the early stages. Villous atrophy as a result of attack by an enteropathogen reduces the ability of the calf to digest nutrients,[129,133] and this predisposes to gastrointestinal overload with fermentation of milk in the large intestine. Deliberate underfeeding of healthy calves also predisposes to diarrhea.

Studies in Scotland have shown that poor clotting ability of milk is associated with diarrhea and abdominal distention in calves aged 1 to 3 weeks of age in beef suckler herds.[304-306] Milk should clot within 7 minutes when incubated with rennet; the milk from the affected cows took at least 1 hour to clot and in some cases more than 24 hours. Diarrhea may be due to the rapid passage of undigested milk through the bowel, or a result of infection by enteric pathogens facilitated by the conditions created in the bowel. Milks with poor clotting ability were shown to have low ultrafilterable calcium levels and low total magnesium levels.[306] Calves responded to treatment with 30 mL

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of 1 molar solution of CaCl administered three times daily PO and relapsed when this treatment was stopped. The majority of the milk samples clotted when 100 µL of 1 mol/L calcium chloride solution was added prior to the addition of rennet. The exact cause of the impaired clotting ability was not determined. The diet of one group of affected cows was shown to be low in calcium.[304,305] After a mineral mixture containing additional calcium was added to the diet of these cows, the clotting time was reduced to less than 12 minutes; treatment of the calves was stopped and there was no recurrence of clinical symptoms.[304]

Calves seem to experience more problems with diarrhea on certain milk replacers. One study showed that calves performed well on milk replacers containing soy protein when healthy, but that during an outbreak of salmonellosis, there was better weight gain and less mortality in calves fed whole milk.[307]

Establishing an Etiologic Diagnosis

An etiologic diagnosis is useful in selecting specific diagnostic and preventive regimens for bacterial infections. Establishing an etiologic diagnosis for viral infections will allow establishment of specific control methods and development of an appropriate vaccination strategy. Diagnosis of salmonellosis, cryptosporidiosis, and giardiasis can have public health implications. Once an agent has been identified, one of the major problems is in interpretation of whether or not that agent is responsible for diarrhea in the individual or herd, since most agents can also be found in a percentage of normal calves (see Fig. 20-1).

Sample Collection

Appropriate selection of diagnostic specimens is required to achieve a meaningful diagnosis. Best results are obtained when fresh samples and specimens are collected from calves early in the course of disease. In order to establish causality, a fresh necropsy is informative because it provides an opportunity to relate the presence of pathogens to a disease process. The quality of the information gathered is to a large extent determined by the quality of the samples submitted to the diagnostic laboratory. Autolysis and bacterial invasion of gut mucosa begin within 5 minutes of death. Autolysis is a common cause of poor tissue sections for histopathology; this may reflect prolonged postmortem interval or poor tissue preparation, handling, or transport. To avoid autolysis, formalin needs to distribute into the lumen of intestinal sections; hence, intestinal specimens should be no longer than an inch long and the tissue to formalin ratio should be no greater than 1:10.

Diagnostic Tests

Bacterial Pathogens

ESCHERICHIA COLI. *E. coli* is a normal inhabitant of the gastrointestinal tract. Isolation of *E. coli* from fecal samples or gut contents is therefore of no significance unless the isolates are demonstrated to possess virulent attributes that are consistent with the clinical and or pathologic presentation. Virulence attributes include adhesins, enterotoxins, and cytotoxins. Enterotoxigenic *E. coli* adhere to enterocytes in the jejunum and ileum.[308] On gross pathology, enterotoxigenic *E. coli* is associated with fluid-distended loops of bowel without enteritis.[309] Calves infected with enterotoxigenic *E. coli* have a mild inflammatory reaction in the small intestinal wall and some villous atrophy. In fresh specimens, sheets of gram-negative bacilli can be seen adhering to the small intestinal wall.[308] Definitive diagnosis of enterotoxigenicity rests on demonstration of the ability of the *E. coli* to dilate intestinal loops.[310] Enterotoxigenic *E. coli* can also be identified by the presence of the F5 (K99) using antigen-specific immunoassays, including latex agglutination,[311] ELISA,[312] fluorescent antibody,[313] slide agglutination,[313] multiplex PCR,[165] real-time RT-PCR,[314] and rapid dipstick tests. A potential limitation of immunoassays is the specificity of the antibodies used; strains of enterotoxigenic *E. coli* using non-F5 fimbriae will not be detected by these tests.[153,315]

Attaching and effacing *E. coli* (AEEC) and Shiga toxin–producing *E. coli* (STEC) mediate disease by cytotoxic damage to the intestinal mucosa. The confirmatory diagnosis of AEEC is made by microscopic examination of the small intestine and colon. A distinct histologic appearance occurs at the attachment sites where clusters of gram-negative rods attach and form a scalloped appearance to the epithelial cells.[159,316] Diagnosis of *E. coli* infection may be achieved using phenotypic differentiation of pathogenic strains from nonpathogenic normal flora *E. coli* via bioassays or immunoassays for toxins and fimbriae. Immunoassays have been developed to identify the presence of Stx1 and Stx2 in feces as a presumptive test for the detection of STEC in cattle feces.[317-319] An alternative approach to identify and differentiate ETEC, AEEC, and STEC is to use PCR to identify virulence-associated genes commonly found in these *E. coli* strains (F5, F41, enterotoxin, intimin, Stx1, and Stx2).[165] The significance of STEC, EPEC, and AEEC in bovine enteritis is unknown due to a lack of appropriate assays for routine detection and because of the widespread presence of verotoxin-producing *E. coli* strains in healthy cattle that complicate the interpretation of detecting fecal shedding in sick animals.[320-322] Demonstration of verotoxin in cultures from bovine enteritis is not sufficient to imply a causative association.

***CLOSTRIDIUM* SPP.** *C. perfringens* has been associated with enterotoxemia and hemorrhagic abomasitis in calves.[178,181] *C. perfringens* are normal flora of the gastrointestinal tract; hence, isolation of *C. perfringens* from feces is not in itself diagnostic. Pathogenic strains of *C. perfringens* produce exotoxins, and five of these (α, β, ε, ι, and enterotoxin) are involved in the pathogenesis of disease.[178] The complete pathogenesis of enterotoxemia and abomasitis has yet to be completely elucidated. Production of specific toxins can only be demonstrated in a proportion of cases.[323] Isolation of toxin-positive *C. perfringens* from intestinal contents does not confirm a clinical diagnosis of bovine enterotoxemia as almost as many *C. perfringens* isolates from normal calves produce toxin and toxin production cannot be demonstrated in as many as 40% of affected calves.[324]

A fresh necropsy is required to definitively diagnose clostridial enteritis. Observing many gram-positive bacilli in the mucosa associated with hemorrhagic enteritis is suggestive of clostridial enterotoxemia. Quantitative bacterial counts of intestinal contents at the site of the lesion have proved to be one of the most reliable methods for diagnosing enterotoxemia.[181] A *C. perfringens* count greater than 10^6/mL of intestinal contents is consistent with a diagnosis of enterotoxemia.[181] Demonstrating the presence of *C. perfringens* toxins or the capacity to produce toxins provides support for the diagnosis. Tests for detecting toxins or the bacteria's capacity to produce toxins include bioassays, immunoassays, Western blot, and PCR.[325] The basis of the bioassay is to demonstrate protection of mice using antitoxin. *C. perfringens* enterotoxin is produced during sporulation. In vitro detection of enterotoxin production capacity by a *C. perfringens* isolate using Western blot or immunoassays requires sporulation to occur. In vitro techniques to induce sporulation are not 100% efficient, so detection of enterotoxin using these methods is less sensitive than PCR at detecting the genes required to produce enterotoxin.[326]

***SALMONELLA* SPP.** Salmonellae are capable of causing disease in cattle of all ages. Neonatal infections are common. The classic pathologic lesion is fibrinous or fibrinonecrotic to ulcerative enteritis.[327] The severity of lesions is usually greatest in the distal small intestine and proximal large bowel. Hypertrophy of the mesenteric lymph nodes is a common finding.[328] Serosal hemorrhages may be observed in the small and large intestine. Septic infarcts in the kidneys and inflammation of the gallbladder are less common findings. Pneumonia is a common finding with *S.* Dublin infections, and gangrenous necrosis of distal extremities may also be observed.[329] Bacteremia is a feature of neonatal salmonellosis and may manifest as osteomyelitis and/or meningitis.

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Isolation of salmonella from the feces of calves with diarrhea is consistent with a diagnosis of salmonellosis but in itself does not necessarily establish causality because salmonella may be isolated from the feces of apparently healthy calves.[330] Isolation of salmonella from tissues at necropsy is indicative of invasive salmonellosis. A definitive diagnosis of salmonellosis is based on the clinical presentation, pathologic lesions, and isolation of salmonella from tissues at necropsy.

Numerous methods exist for isolating and detecting the presence of salmonella. These include direct culture, enrichment cultures, PCR (both conventional and real time), immunoseparation, and immunoassays.

The process of directly inoculating tissues or other samples onto plating media, except in the case of acute infections, is usually nonproductive. Typically, with subclinical infection the number of salmonellae shed in feces is low relative to the high number of other bacteria. Fecal samples should be inoculated into selective enrichment media for optimal recovery of Salmonella. Selective-enrichment broths are formulated to selectively inhibit other bacteria while allowing Salmonella to multiply to levels that may be detected after plating. Internal organs that are normally sterile do not need to be inoculated on selective media; rather, they should be inoculated onto nonselective (blood agar) or weakly selective (MacConkey agar) media.

A number of rapid detection methods have been developed to expedite the detection of salmonella. These methods include electrical conductance and impedance, immunologic techniques, nucleic acid–based assays, and PCR. These methods generally take 24 to 52 hours to screen for or detect and identify salmonella. The majority of these tests, particularly the enzyme-linked immunologic techniques, require 10^5 cells/mL for reliable results. Accordingly all these tests involve a pre-enrichment stage, and some also involve a selective enrichment culture.[331] When salmonella is causing disease, clinically affected calves may shed 10^9 salmonella per gram of feces.[332] Detection of salmonella in clinical samples when it is the inciting cause of the disease process is not normally difficult when multiple samples are collected from a representative sample of the affected population.

Viral Enteropathogens

Viruses are usually identified by direct examination of the feces, immunoassays, or fluorescent antibody examination of intestinal mucosa. Molecular techniques involving conventional PCR and real-time RT-PCR have been described for most pathogens but are not routinely available in all diagnostic laboratories. Electron microscopic examination of feces is not a sensitive means of detecting virus particles, but it has the advantage in that many different types of viruses can be detected, including those such as parvovirus that are not recognized as common causes of diarrhea. The recent development of relatively inexpensive immunoassay diagnostic test kits makes these an attractive option; limited test-specific data regarding test sensitivity and specificity limit the application of some of these tests.

CORONAVIRUS. Coronavirus replication occurs in the epithelial cells of the distal half of the villi of the lower small intestine and colon. Infected cells die, slough, and are replaced by immature cells. In the small intestine these changes result in stunting and fusion of adjacent villi, and in the large intestine they lead to atrophy of the colonic ridges. On histopathology the tall columnar epithelial cells are replaced by cuboidal and squamous epithelial cells; in severe infections there may be areas of complete desquamation.[333] Virus is shed in respiratory secretions and feces. There are several methods for detecting BCV in feces. These include isolation of the virus in cell culture,[334] electron microscopy,[335] immunoelectron microscopy,[219] immunoassays,[212,312,336-339] and molecular techniques including dot-blot hybridization assays[340] and conventional and real-time RT-PCR.[341-344] Isolation of BCV using cell culture techniques is not often performed in diagnostic laboratories because the technique is difficult and requires viable virus (fresh samples or shipped on dry ice).[345] Electron microscopy has been used as a standard diagnostic method for BCV. Although the intact virion of BCV is fairly characteristic in appearance, it is not uncommon for the identifying surface projections of the virus to be lost during sample preparation or storage, making it difficult to properly identify virus particles by EM.

Numerous ELISA assays have been described for the detection of BCV antigen in feces. A number of companies have developed commercial kits using this technology. The use of monoclonal antibodies rather than polyclonal antibodies is reported to increase the sensitivity and specificity of BCV ELISAs.[339] The limit of detection for ELISA assays ranges from 10^4 to 10^5 virions per milliliter of feces.

A one-step RT-PCR assay, targeting a 730-bp fragment of the nucleocapsid gene of BCV, as well as a nested PCR assay, targeting a 407-bp fragment of the nucleocapsid gene, has been developed to detect BCV. Compared with an antigen-capture ELISA, the limit of detection for the RT-PCR and nested PCR was 10^3 and 10 virions/mL, respectively, compared with 10^5 virions/mL for the ELISA.[346,347]

Two qRT-PCR methods have been used for detection of coronavirus in feces: the TaqMan and the SYBR Green assays.[343,344] Detection levels achieved using the TaqMan assay for coronavirus have been on the order of 10^1 to 10^9 RNA copies and were shown to be 1 log more sensitive than gel-based RT-PCR. The SYBR Green chemistry assay had similar detection levels but was unable to differentiate among different coronaviruses like the TaqMan assay.

ROTAVIRUS. Bovine rotavirus infects enterocytes, which are predominantly in the distal one third to one half of the villi. The age at the time of infection influences the distribution of the virus in the gastrointestinal tract and the number of virions shed in feces. In experimental challenge studies, infection of day-old calves resulted in a uniform distribution of virus throughout the small intestine.[348] Challenge of 10-day-old calves led to a patchy distribution of the virus with maximal viral load observed in the mid small intestine.[348] Villous stunting is more pronounced in young calves.

Methods for detection of rotavirus include cell culture, fluorescent antibody staining, electron microscopy, immunoelectron microscopy, immunoassays, electrophoretic procedures, and conventional and real-time RT-PCR.[199-203,311,312,337,349-352] Bovine rotavirus is difficult to isolate in cell cultures because of the cytotoxic nature of feces and fecal filtrates and because the virus is inconsistent in production of cytopathic effects.[350] The fluorescent antibody technique is simple, rapid, and specific; however, rotaviral antigen is usually difficult to detect within 24 to 72 hours after the onset of diarrhea because rotavirus-infected epithelial cells are rapidly shed from the tips of the villi.[353] Comparative studies evaluating methods of detecting rotavirus in feces give good agreement between antigen capture assays (ELISA, latex agglutination) and electron microscopy.[311,337,350,354] Direct immunofluorescence testing of fecal samples gives good agreement (90%) with electron microscopic examination for rotaviruses when samples are collected during the 24 hours following the onset of diarrhea,[355] but poor agreement (33%) for field specimens submitted to a diagnostic laboratory.[350]

Real time RT-PCR detection for rotavirus has been shown to be both highly sensitive and specific when the correct primers and probes are identified.[352] Real-time RT-PCR assays have the ability to increase the sensitivity of detection by up to 100-fold compared with one-step RT-PCR.[356]

BOVINE VIRUS DIARRHEA. BVDV rarely causes diarrhea in neonatal calves.[115] Sporadic disease may be observed in persistently infected calves. Pathologic lesions include ulceration of the oral cavity, particularly on the hard and soft palate, and blunting of the buccal papillae.[225] Erosions may be observed in the esophagus, and necrosis of Peyer patches may be observed in the ileum. Thrombocytopenia has been observed with BVD type II infections. Outbreaks of neonatal disease have been observed with this strain. Petechial and ecchymotic hemorrhages are a feature of this

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condition.[114,227,228] Hematologic findings often include leukopenia and thrombocytopenia.

Several options are available for the detection of BVD; these include virus isolation,[357,358] RT-PCR,[359] immunohistochemistry,[360] and antigen-capture ELISA.[361] Immunohistochemistry and antigen-capture ELISA assays are used in most commercial laboratories. Maternal antibodies reduce the sensitivity of the ELISA assay in young calves.[359]

BOVINE TOROVIRUS (BREDA VIRUS). Bovine torovirus produces cytolytic infections of villi and crypt enterocytes in the small and large intestine.[362] Bovine torovirus does not grow in tissue culture, cell culture, or embryonated eggs.[363] Therefore, the large-scale preparation of reference antisera and antigens for the development of diagnostic tests has been precluded. Torovirus is capable of causing diarrhea in cattle with disease observed most frequently in calves less than 3 weeks of age.[112,232,234,236,364,365] Like other enteric viruses, bovine torovirus has been detected in feces of normal calves; therefore, detection of the virus in feces from diarrheic cattle cannot be interpreted as causal. The lack of diagnostic reagents has limited the study of bovine torovirus, leaving questions about its epidemiology and relative importance in calf diarrhea.[111] Diagnostic methods that have been used to detect bovine torovirus include electron microscopy, immunofluorescence, antigen-capture ELISA, and RT-PCR.[111,232]

Protozoa

***EIMERIA* SPP.** *Eimeria* spp. are host specific. *E. bovis* affects primarily the mucosa of the cecum and the proximal part of the large intestine, whereas *E. zuernii* affects the mucosa of the cecum as well as the entire large intestine, including sometimes the rectum.[366] The clinical signs of bovine coccidiosis are associated with the final stages of the eimerian life cycle and commence shortly prior to oocyst shedding. Gross lesions in the cecum and large intestine range from semi-liquid contents with little or no blood and few areas of epithelial sloughing to extensive hemorrhage and large areas of epithelial sloughing and necrosis of the mucosa.[366] The serosal surface is often reddened opposite the affected mucosal area and the submucosa and external muscular layers thickened by edema.

Oocysts usually can be recovered 2 to 4 days after the onset of diarrhea.[367] Oocysts can be identified microscopically by direct smear, flotation, or centrifugation methods. Oocyst counts of 5000 or greater per gram of feces are considered significant in cattle.[298] Identification of oocysts in feces is not diagnostic for clinical coccidiosis because the parasite is frequently detected in small numbers in the feces of healthy cattle.[368] When investigating scour problems, multiple samples should be collected for oocyst counts to provide an indication as to the level of infection within the group. The potential for discord between clinical signs and fecal shedding limits the diagnostic utility of a single sample from an individual animal.

GIARDIA. Giardia infection is not associated with changes in intestinal villous height or crypt depth. However, transmission electron microscopy has been used to demonstrate a reduction in microvillous surface area.[369] Diagnostic methods for detection of *Giardia* include direct microscopy, immunomagnetic separation, fluorescent antibody staining,[287,370] ELISA,[371] and PCR.[372] When using direct microscopy, fecal samples should be examined within 24 hours of collection. Concentration of trophozoites and cysts via density gradient centrifugation or filtration followed by fluorescent antibody staining is the diagnostic method used in most veterinary epidemiologic studies of Giardia in calves.[266,373,374] The use of other immunoassays and PCR techniques are emerging in human diagnostic laboratories.[371,372]

CRYPTOSPORIDIA. *C. parvum* infections are mainly concentrated in the distal small intestine, but lesions may also be found in the cecum and colon, and occasionally in the duodenum.[375] The pathologic findings associated with *Cryptosporidium* are a mild to moderate villous atrophy, villous fusion, and changes in the surface epithelium with infiltration of mononuclear cells and neutrophils in the lamina propria.[375]

Calves infected with *C. parvum* usually develop diarrhea in 72 to 96 hours; diarrhea is observed for 4 to 23 days,[376] during which time oocysts are excreted in feces. Oocysts are stable in feces for many days at room temperature.[377] Laboratory methods for the diagnosis of cryptosporidial infections include microscopic examination of fecal smears or fecal preparations, immunoassays, and PCR. Cryptosporidia oocysts are small (4 to 6 µm in diameter) and are easily missed on a fecal smear. Because fecal smears do not concentrate the oocysts, this technique is less sensitive than fecal flotation. Concentration of the protozoa is achieved by salt[378] or sugar flotation. Special stains may be used to facilitate detection of cryptosporidia during microscopic examination. Differential staining techniques are useful to distinguish *Cryptosporidium* oocysts from other fecal components (especially some yeasts) of similar size and shape.[379-382]

A number of immunoassays have been developed for the detection of cryptosporidia. The detection threshold of the different methods have been reported to be 3×10^5 oocysts/g for a monoclonal antibody-based antigen-capture ELISA, compared with 1×10^6 oocysts/g^{-1} detected by examination of acid-fast stained fecal smears and 1×10^3 oocysts/g^{-1} detected by indirect immunofluorescence.[383] The detection threshold may be further enhanced by using a combination of immunomagnetic separation coupled with immunofluorescent microscopy. With this combination it is possible to detect as few as 10 oocysts/g^{-1}.[384] A number of dipstick immunoassays have also been developed; the detection threshold for this technology is reported to be 1×10^3 oocysts/g^{-1}.[385] This technology offers the potential for rapid, cost-effective detection of cryptosporidia in fecal specimens.

Molecular techniques have been described for detection and typing of cryptosporidia.[249,253] The capacity to differentiate the different genotypes makes this approach useful for epidemiologic studies of cryptosporidia.[249]

Multiplex Real-Time PCR

Several multiplex real-time RT-PCR assays have been developed for the simultaneous detection of the major enteric pathogens.[386] The multiplex qRT-PCR offers significant advantages over individual pathogen testing in that 96 fecal samples can be tested at the same time within 4 hours. This offers increased efficiency through decreased cost, labor, and turnaround time. Another major advantage of RT-PCR is the ability to detect and measure the accumulation of amplicon during the reaction, thus allowing precise quantification, which can be important in determining causation. The major disadvantage of RT-PCR is that the equipment required is expensive and significant expertise is needed in order to run the assays.

Risk Factors for Neonatal Calf Diarrhea

It is important to identify risk factors, both to set up effective preventive programs and to initiate control in the face of a disease outbreak. The etiology of calf diarrhea is multifactorial; consequently, it is common for several factors to contribute to the outbreak and perpetuation of disease in a herd.

Dystocia

Dystocia is associated with neonatal calf diarrhea in more intensive beef and dairy systems,[106,387] and it is a risk for preweaning mortality with over 40% of preweaning deaths occurring in calves born to cows suffering dystocia.[388-390] Dystocia affects the ability of the calf to suckle colostrum, resulting in decreased serum IgG levels; consequently, calves that survive dystocia are two to four times more likely to become sick in the first 45 days of life.[391-393] Calves that experience dystocia are likely to have edema of the head and tongue, making suckling difficult. They are weak, exhausted, and likely to be recumbent for longer, increasing exposure to fecal pathogens.[217]

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Stocking density and cow grouping of preparturient cows, timing of calving, breed, cow pelvic area, multiple calvings, calf sex, gestation length, and dam nutrition all influence the risk of dystocia.[394,395] Low- and high-birth-weight calves are at greater risk of mortality.[389] Small calves experience greatest mortality at parities greater than one and large calves at first parity.[396] Increased feed intake before calving will increase calf birth weight but does not increase the risk of dystocia unless cattle become obese.[397-399] Weight loss is associated with prolonged labor, increased dystocia, and increased perinatal mortality.[399,400]

Dam Parity

Calves born to first and second parity cows have an increased mortality compared with those born to older cows, and the risk of diarrhea in calves born to heifers is 3.9 times greater than that in those born to cows.[389,401,402] Heifers have an increased risk of dystocia, lower colostrum quality, and inferior mothering ability.[391,392,402-404] The difference in the rate of dystocia between the first and second parity is usually much greater than between second and subsequent parities.[405] The stocking density of heifers is often increased prior to calving to facilitate observation, with the consequence of exposing their calves to a greater environmental pathogen load. These factors are all likely to contribute to increased morbidity, and consequently the percentage of heifers in the herd will affect the risk of diarrhea. Calves from carrier heifers shedding rotavirus and BCV are more likely to develop clinical disease than calves born to carrier cows.[210] Studies in dairy herds have shown that there is a positive correlation between the number of young stock in the herd, the overall herd size, and herd production with the risk of neonatal calf diarrhea.[406-408]

Colostrum Management

Many studies have shown that FPT results in increased risk of neonatal calf diarrhea in beef and dairy herds.[409-415] Calves are only able to absorb immunoglobulins for a limited time after birth, and the subsequent serum immunoglobulin concentration is determined by the perinatal state of the calf, timing of colostrum ingestion, and the mass of immunoglobulin consumed.[416] Colostrum also provides local (enteric) immunity with the major benefits lasting for about 3 to 4 days after birth.[417-419] After this period, milk contains little immunoglobulin and most colostral antibody has been cleared from the intestine. Colostral antibodies protect against rotaviral infections in the first 4 days of life[193,194]; in contrast, anti-F5 (K99) *E. coli* antibody is present in low amounts in unvaccinated cows,[420] and enteric *E. coli* infections are usually seen in very young calves. After 4 days, the protective effects of colostrum are primarily due to systemic antibodies, and there is evidence that these can leak back into the gut and probably give limited long-term protection against diarrhea.[421] Colostral quality is affected by colostral volume, genetics, nutrition, parity, timing of collection, climate, and periparturient vaccination.

Beef Cow Herd Management

In beef herds, high stocking rates in the calving area and the use of one calving area are major risks for neonatal calf diarrhea.[422,423] The practice of leaving nursing dams and calves with calving cows further increases stocking rates and promotes disease transmission.[411] The weather at calving affects both pathogen survival and calf comfort; shelter in the nursing area is associated with decreased mortality resulting from neonatal calf diarrhea.[401] Major calf scour pathogens can survive in the environment for months or years in cool wet conditions, and consequently both the incidence and mortality from diarrhea increase with prolonged use of the same paddock or a longer calving season, and the incidence of diarrhea increases as the calving season progresses.[390,401,402] Adverse weather conditions cause cows to move to shelter and shade, concentrating cows and calves in small contaminated areas. Calves born into a contaminated environment potentially become infected during or shortly after birth and shed enteropathogens even when they remain clinically normal. This further increases the environmental load of infectious agents, infecting adult cattle as well as calves. The outcome of host pathogen interactions is largely influenced by the pathogen challenge dose and the age of the animal, with clinical disease becoming more frequent both in younger animals and as pathogen exposure increases (Fig. 20-3).



FIG. 20-3 Cow on a farm with a high incidence of neonatal diarrhea. Note that the mud is so deep around the feeders that it covers the cow's hocks. As a result the teats will be contaminated by manure and enteric pathogens.

Farms that purchase replacement calves aged less than 4 weeks have an increased mortality resulting from neonatal calf diarrhea.[401] Purchased calves may introduce new pathogens that challenge a susceptible population. Stress from transport and arrival at a new location may increase shedding and predispose to clinical disease, increasing the environmental pathogen load. The risk of pathogen introduction increases when introduced calves are commingled from multiple properties prior to introduction.

Intensive Calf-Rearing Systems

Intensively reared calves have an increased risk of diarrhea associated with housing, nutrition, and weaning. Variables that have been observed to increase the risk of scours include feeding milk once versus twice a day within 14 days of birth,[424] placing preweaned heifers in groups of seven or more, damp versus dry bedding,[424] a male having primary responsibility for the care and feeding of preweaned heifers, calves not receiving hay or other roughages until greater than 20 days old, and feeding mastitic or antibiotic milk versus whole milk.[425] Use of individual calf hutches has been reported to increase the risk of scours but to reduce mortality.[424]

In regard to the risk of cryptosporidia, infection factors significantly associated with a decreased risk of infection included ventilation in calf-rearing areas, daily addition of bedding, feeding of milk replacer, daily disposal and cleaning of bedding, and use of antibiotics. Postweaning practices that reduced risk of infection included moving animals after weaning, cleaning of soiled bedding, and use of antibiotics and ionophores as preventive measures. Maternity management factors that reduced risk of infection included use of fresh colostrum to feed calves and having a concrete floor in the calving area. General management factors that influenced risk included the total number of dairy cattle, total number of other species of agricultural animals on the farm, and the distance of the barn water source from the septic system.[426]

Herd Strategies to Prevent Neonatal Diarrhea

Management practices that reduce the risk of calf scours also promote good health, improve growth rates, and reduce the risk of transmitting other enteric pathogens such as *Mycobacterium paratuberculosis*. The principles of prevention are to minimize pathogen exposure, ensure adequate colostral intake, boost specific and nonspecific immunity, and promote farm biosecurity.

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Minimizing Pathogen Exposure

Enteric pathogens may be shed in large numbers by calving cows, scouring calves, and asymptomatic cohorts, especially those aged up to 4 months of age. All enteric pathogens can survive in the environment for months or years in moist, damp conditions. Other sources of infection include people who have treated or handled infected calves, contaminated water, contaminated colostrum, milk, or solid feed and equipment that has been used to feed or medicate infected calves.[175,210,212,246,272,427-429]

MINIMIZING PATHOGEN EXPOSURE IN DAIRY HERDS. Strategies to prevent disease in dairy calves focus on calving cows in a clean environment, removing calves from cows at birth, feeding adequate good-quality colostrum, placing calves in a clean dry environment separate from other stock, feeding good-quality milk or milk replacer, providing adequate shelter, and providing access to water and high-quality calf pellets. Microbial contamination is an important determinant in the quality of colostrum and milk. Good sanitary practices are required for the harvest, storage, and feeding of both products. Microbial contamination of colostrum compromises passive transfer and, in the case of pathogens like salmonella, may lead to a direct pathogen challenge. Similarly, feeding milk with a high bacteria count increases the risk of diarrhea. On-farm heat treatment of colostrum (60° C for 1 hour) significantly decreases bacterial numbers without affecting IgG levels.[430] Calves that are fed heat-treated colostrum have significantly higher IgG levels and lower incidence of neonatal calf diarrhea when compared with calves fed untreated colostrum.[431]

In dairy systems, where calves are reared by hand, the number of young stock on the farm and the incidence of respiratory disease are positive predictors for calf diarrhea.[406] Cleanliness of the calving area is important, bedding should be changed between each calving, and large numbers of cows should not be cycled through a few stalls.[406] Prior to calving, the udder and the perineum of the cow should be cleaned. The calf should receive adequate colostrum.[423] In recent years the use of calf hutches has gained widespread acceptance for managing calves after they have been separated from their dam. This system provides individual isolated housing for each calf. Cleaning is facilitated because the hutches can be moved to new sites between calves. Keeping preweaned calves in groups larger than six puts them at increased risk of diarrhea.[408]

Cleaning and disinfection after each calf batch plays an important role in reducing contamination in housed calves. The key to decontamination is the physical cleaning. Physical removal of organic contamination through scrubbing is preferred to application of high-pressure sprays, which can aerosolize organisms, allowing dissemination. On smooth, ideal surfaces, physical removal of visible contamination by thorough washing with soap and water removes 99% of the microbial load (2 logs). However, on typical housing surfaces, washing only removes 90% (1 log). Application of disinfectant following washing is important to eliminate remaining pathogens and to prevent bacterial pathogens from proliferating. Physical cleaning cannot be replaced by applying disinfectants in larger quantities because organic material neutralizes most disinfectants. In regard to disinfectants, pathogen elimination is time dependent.[432] Other important variables that influence the effectiveness of disinfectants and rate of pathogen reduction include concentration, temperature, pH, and water hardness.

In addition to cleaning between batches, it is important to clean nipple buckets and other feeding utensils between each feed. Separate equipment should be used to administer oral electrolytes and colostrum. Salmonella and coronavirus are shed in saliva and can contaminate equipment used for oral medication. Washing with warm soapy water is required to remove the fat residue left by milk and colostrum-handling equipment.

Several microbial characteristics should be considered when disinfecting equipment that contacts calves. Rotavirus is susceptible to sodium hypochlorite but is relatively resistant to many common disinfectants, such as chlorhexidine. As a nonenveloped virus, rotavirus is not affected by soaps; washing with soap alone may actually spread the virus around on the washed surface.[433] Coronavirus is an enveloped single-stranded RNA virus and is not as stable in the environment as rotavirus. Because of their envelope, these viruses retain infectiousness better at lower rather than higher relative humidity[434] and are considerably more sensitive to soaps and common disinfectants than are nonenveloped viruses. Because *Cryptosporidium* can autoinfect the original host, the infectious dose can be small. In the environment, cryptosporidia are extremely resistant to most veterinary disinfectants except 5% ammonia, 6% hydrogen peroxide, 10% formalin, or 2% cresolic disinfectants.[274,435-437] They survive very well in water, requiring 4 to 11 weeks to decline by 1 log.[438] On the other hand, cryptosporidia are susceptible to drying with oocyst infectivity, declining in 1 to 4 days.[275]

The most readily cleaned surfaces are made of smooth impervious materials such as plastic and varnished wood (Table 20-7). Usually buildings are cleaned and then either disinfected or fumigated.[439] Many disinfectants are inactivated by organic matter; viruses, coccidia, and particularly cryptosporidia may be resistant to their action (Table 20-8). Disinfectants may also be toxic and are best applied by personnel wearing rubber gloves and respirators (if indoors). In general, potent phenolics such as cresol (cresylic acid) are very useful for disinfecting dirty surfaces because they are not inactivated by organic matter and are effective against gram-negative bacteria and viruses. The phenolics are highly toxic and leave lingering odors. Hypochlorite solutions (5 g available chlorine/L) have a broad spectrum of action but are rapidly inactivated by organic matter. They would be useful as a final disinfectant on previously cleaned surfaces. Because hypochlorite is unstable, it is unlikely to leave toxic residues. Iodophors are not very effective against rotavirus, particularly if organic matter is present. Virkon, a newer disinfectant/cleaner containing potassium monopersulfate as the active ingredient, is effective for all pathogens except cryptosporidia. Normally, a 1% solution is used and is prepared by mixing 10 g of powder to 1 L of water. Contact time should be a minimum of 10 minutes. Virkon has the advantage of having a detergent action that facilitates cleaning.

Formaldehyde is one of the few agents that are effective against cryptosporidia. It requires a long contact time and is highly toxic. It is usually used for terminal fumigation in buildings that can be tightly sealed. Formaldehyde gas is best generated by heating paraformaldehyde (5 g/m^3 of building) in an electrically heated pan at 204° C. Some manufacturers of paraformaldehyde provide pans especially designed for this purpose. The pans should be placed no more than 30 m apart and arranged so that electricity to the pan can be

TABLE 20-7

Ability of Bacteria to Persist on Various Types of Surfaces Found in Farm Buildings

	Total Bacterial Count/100 cm^2	
Material	Uncleaned	Cleaned
Brick	76,000	
Painted wood	34,000	
Block board	116,000	
Ply board	77,000	23,000
Fiber board	57,000	
Chip board	35,000	
Formica	29,000	
Polystyrene	29,000	
Metal		14,000
Concrete		13,000
Plastic	16,000	100
Varnished wood	5,000	

Modified from Morgan-Jones SC. 1981. p 199. In Collins CH, Disinfectants: their use and evaluation of effectiveness. Academic Press, London.

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TABLE 20-8

Efficacy of Disinfectants against Enteropathogens[408,446-451]

Group	Compound	Efficacy		
		Gram-Negative Bacteria	Rotavirus	Cryptosporidia
Phenolics	Hexachlorophene	+	++	
	Triclosan	+	++	
	Cresol (coal tar derivation)	++	++	–
	Phenol	±	–	–
Halogens	Povidone-iodine	+	–	–
	Hypochlorite	+	+	
Biguanides	Chlorhexidine	++	–	
Aldehydes	Formaldehyde*	+	+	+
	Glutaraldehyde	+		
Quaternary ammonium	Benzalkonium chloride	+	+	–
	Cetrimide	+		
Ammonia	Ammonia			+
Oxidizing agent	Potassium monopersulfate	+	+	–

*Requires long contact time: 18 hours to kill cryptosporidia.

++, Highly effective, not inactivated by organic matter; +, moderately effective, inactivated by organic matter; ±, some effect; –, little effect.

controlled from outside the building. There must be a safety mechanism to ensure that the pan does not overheat and cause a fire. The building must be sealed for at least 24 hours and cannot be entered until it has been thoroughly ventilated. Formaldehyde gas can also be generated by boiling formalin or by adding potassium permanganate to formalin. The latter method generates a violent chemical reaction and carries risks of explosion. Formalin aerosol generators are ineffective.[440] Following cleaning and disinfection, one should allow a rest period for the building to ventilate before reintroducing calves. It is very important that cleaning and disinfection be thorough. Attention should also be given to rodent control since these can be a reservoir for *Salmonella*.[441]

MINIMIZING PATHOGEN EXPOSURE IN BEEF HERDS. In beef herds, calving areas should be located to take advantage of natural shelter and drainage and rotated from year to year to avoid pathogen buildup.[402,422,442,443] Pregnant cattle are moved into a clean paddock no more than 2 weeks prior to the start of calving. It is best that cows and heifers are managed separately until after calving. This gives the opportunity to provide better feed to the heifers and to minimize infection between the groups. Confined, wet, or muddy areas should be avoided for calving cows; where they need to be used, the stocking rate should be decreased. Feed-out areas should be rotated to encourage cow disposal and separated from watering points. When pasture for calved cows is limited, supplementary feed should be fed to dry cows to ensure enough fresh pasture for calving and nursing cows. Clean water should be available in a trough that is accessible to cows and calves. Chronically sick animals, weak calves, and cows with no milk should be removed from the calving paddock and kept isolated from the herd.

Grazing and reproductive management have a significant impact on pathogen load. Where appropriate to grazing management, calving paddocks should be left vacant during the summer. For producers that manage periparturient cows in smaller calving paddocks to facilitate supervision, the emphasis should be on minimizing the stocking density in the calving paddock by removing cows and calves shortly after parturition.[422,442] Alternatively, cows can be moved away from cows with calves every 1 to 2 weeks or more frequently in large herds. Young calves in the calving paddock will markedly increase the rate of pathogen buildup and the subsequent challenge to newborn calves. Moreover, the increased stocking rate will amplify stress, affecting both transfer of passive immunity and the ability of young calves to rest. Often calving areas are small due to the perceived need to assist cows for dystocia.[443] Well-grown and appropriately fed heifers mated to suitable sires can minimize this need. Beef cows with calves at foot moved from the calving paddock should be moved into nursing groups that have a maximum age range of 4 weeks and a low stocking rate. Groups should not be mixed until all calves are at least 4 weeks old.[422,442,443] Reproductive management influences pathogen load by determining the age spread of the calves. Sick calves amplify environmental contamination. A prolonged calving period leads to a buildup of contamination so that calves born later in the calving period experience an increased pathogen challenge. It is desirable to maintain a calving period that is less than 60 days.

Boosting Specific and Nonspecific Immunity

Ensuring adequate passive transfer is necessary to achieve enhanced pathogen-specific immunity through maternal vaccination. Colostrum management is discussed in detail in Chapter 19.

ENTEROTOXIGENIC *E. COLI*. The protective efficacy of enterotoxigenic *E. coli* bacterins is well documented.[444-447] Because ETEC scours occurs during the first 3 days of life, the neonate does not have time to mount a protective immune response to vaccination. Protection is afforded by vaccinating cows in late gestation in order to ensure high concentrations of anti-F5 (K99) colostral antibodies. Good maternal management is required to ensure that the calf receives the maternal antibodies. Anti-pilus antibodies block the adhesion of the pathogen to enterocytes and subsequently prevent disease.[447a] In general, it is recommended that the vacci nes are given 6 and 3 weeks prior to calving. Studies with some vaccines have shown that the vaccine is still effective if the priming dose is given 18 months before calving and boosting is carried out in the second half of gestation.[448] Clinical experience in beef farms suffering severe outbreaks of *E. coli* F5 (K99) diarrhea indicates that vaccinating cows that are more than 10 days from parturition can give considerable protection against death from enterotoxigenic *E. coli* infection.

Products containing monoclonal antibodies against F5 (K99) antigen have been shown to reduce the severity of diarrhea when calves are experimentally challenged a few hours after receiving the product.[449] In field situations, however, monoclonal products can have a low efficacy, presumably because a single dose only provides a short period of enteric protection. Antibody supplements are expensive and vaccination of the dam to boost colostral immunity will usually be more cost effective. On farms experiencing an outbreak of neonatal diarrhea caused by F5 (K99) *E. coli,* there may be a place for the use of these products until vaccinated cows begin to calve. However, short-term administration (once a day for the first 3 days of life) of an antibiotic to which the *E. coli* is susceptible is also highly effective in preventing diarrhea in herds experiencing outbreaks of enterotoxigenic *E. coli*.

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SALMONELLA. The successful reduction of *Salmonella* prevalence in livestock on a national level via implementation of a *Salmonella* control program emphasizing immunoprophylaxis with modified live and killed *Salmonella* vaccines indicates the potential benefits that can be derived from the application of effective *Salmonella* vaccines.[450] *Salmonella* vaccine studies in cattle have focused on killed whole cell (bacterins), bacterial fractions (subunit), and attenuated modified live *Salmonella*.

There are conflicting reports regarding the efficacy of *Salmonell* a bacterins. The reported efficacy of *Salmonella* bacterins ranges from good to ineffective.[451-459] The overall consensus of these reports is that vaccination of cattle with *Salmonella* bacterins provides partial protection against *Salmonella* challenge. In the only reported controlled field trial, an autogenous *Salmonella* bacterin was not found to have any effect.[459] Adverse reactions in the form of anaphylactic reactions are occasionally reported in cattle vaccinated with *Salmonella* bacterins. The cause of these reactions is unknown but has been suggested to be associated with the LPS content of these products. Similar allergic-type reactions in humans caused by *Salmonella* bacterin vaccination during typhoid outbreaks are well documented.[460]

A commercial subunit vaccine has become available in the United States that is based on purified extracts of siderophore receptors and porins (SRP) of *Salmonella* Newport.[461] The SRP proteins are critical for iron acquisition and are highly conserved between most gram-negative organisms.[462] There have been no peer-reviewed studies examining the efficacy of the vaccine for the prevention of diarrhea.

Several naturally occurring and genetically manipulated attenuated *Salmonella* strains have been used to immunize cattle against salmonellosis. The most widely tested genetically altered *Salmonella* mutant vaccines in cattle are the auxotrophic strains. Aromatic amino acid (aro) and purine (pur) auxotrophs of *Salmonella* are attenuated and have decreased virulence.[463-469] Comparative vaccine trials indicate that modified live attenuated *Salmonella* vaccines provide greater protection against virulent *Salmonella* challenge than *Salmonella* bacterins.[457,469,470] Vaccination with modified live *Salmonella* vaccines attenuates the severity of clinical signs and pathologic lesions and reduces *Salmonella* shedding and mortality.[450,465,471]

Calves immunized with modified live *Salmonella* vaccines are protected from homologous and heterologous *Salmonella* serotypes when challenged within 3 weeks of vaccination.[472-474] Live *Salmonella* vaccines induce transitory T-cell–independent nonspecific protection, which disappears about 1 month after immunization following clearance of the organisms from the reticuloendothelial system. Thereafter, protection to oral challenge is species and serotype specific with recall of immunity presumably involving specific antigen recognition.[475,476]

The level of passive protection of calves achieved via feeding colostrum from vaccinated cows is questionable. A number of reports suggest immune colostrum provides passive protection and others report no protective effect. In trials in which protection was achieved, calves were challenged at 1 week of age; trials in which no protection was observed involved challenging calves at 3 weeks of age, suggesting that the duration of passive immunity associated with colostral transfer is relatively short. Considering that many calves are exposed to *Salmonella* in the first week of life, colostral protection may be useful.

ROTAVIRUS AND CORONAVIRUS. BCV is associated with a number of diseases in cattle; all BCV isolates are believed to belong to a single serotype.[477] Differences in hemagglutination-inhibition characteristics have been used to classify strains as type 1 through 3.[478] Seven serogroups of rotavirus with group A exist, accounting for the majority of pathogenic isolates. Members of the group A rotaviruses are further classified according to antigenic and genetic differences in their outer capsid proteins, G and P. Both of these proteins are involved in neutralization of infectivity in vitro and in vivo.[479] In the United States, 8 G serotypes/genotypes and four P serotypes/genotypes have been identified in cattle isolates.[206] The genome of rotavirus is composed of 11 gene segments that can be exchanged among isolates when animals are infected by more than one virus at the same time.[480] Genetic reassortment can generate new progeny viruses that can evade what was once a protective immune response, thus allowing persistence of rotavirus in susceptible populations.[479]

Two approaches have been taken with immunoprophylaxis against rotavirus and coronavirus infections in calves. The first approach involves oral vaccination of neonatal calves with a modified live vaccine. Calves begin producing detectable levels of local secretory IgM within 4 to 6 days of vaccination.[481] Calves are resistant to challenge from the initial appearance of local IgM antibodies.[481] In order to consistently elicit an effective immune response, the vaccine must be administered orally, immediately after birth, and before the calf has nursed because the colostrum of most cows contains virus-neutralizing antibodies that interfere with the vaccine.[482] There are conflicting reports of efficacy with these types of vaccines. In double-blind field studies that include vaccinated and nonvaccinated calves, the vaccine was not shown to be effective.[483] Conversely, when all calves were either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality were significantly reduced.[483]

The second approach involves intramuscular vaccination of pregnant cows with either modified live vaccine or inactivated viral vaccines to stimulate high levels of specific viral-neutralizing antibodies in colostrum and milk during the first several days of the calf's life. Infectious viral particles are neutralized within the gut lumen, preventing infection of intestinal villous enterocytes. One advantage of passive immunization is the fact that cross-protection between serotypes is less of a problem. This is due to the fact that vaccination of a mature cow that has had natural rotavirus exposure leads to cross-serotype stimulation of heterotypic antibodies.[484] Single serotype vaccination therefore stimulates antibody production to a wide range of rotavirus serotypes, negating the need for multivalent rotavirus vaccines. Passively absorbed anti-bovine rotavirus IgG1 antibodies are transferred to the small intestinal lumen, where they protect against experimental challenge.[485] Antigen-sensitized maternal lymphocytes also confer partial protection against challenge with virulent bovine rotavirus.[486] Colostrum and milk with a high virus-neutralizing antibody titer are highly protective while it is being consumed by the calf. For example, administering 400 mL of immune colostrum daily to calves from day 2 to 12 reduced the incidence of diarrhea from 41% to 3% in one study.[487] The concentration of rotavirus- and coronavirus-neutralizing antibodies in milk of vaccinated cows falls below protective levels by 3 to 7 days following parturition.[488-490] In lieu of complete protection, the manifestations of passive immunity to bovine rotavirus that are often noted are (1) a delay of a few days in the onset of clinical signs, and/or (2) a reduced severity of clinical signs, and/or (3) a reduction in the length of the period of viral shedding associated with infection.[491] Although there are reports of successful field trials involving bovine rotavirus/bovine rotavirus-coronavirus–vaccinated cows,[446,492,493] negative results have also been reported.[494] A common problem with commercial vaccines on the market in the United States and Europe is a lack of vaccine-specific data supporting efficacy claims. Protection correlates with serum titers; independent studies have sometimes failed to demonstrate effective seroconversion with some products.[495]

Nonspecific Immunity

DIET. The microbial quality of the diet is an important factor in preventing diarrhea. Calves that are fed milk from mastitic quarters or antibiotic-containing milk are at increased risk of diarrhea.[408] Following fresh colostrum feeding, young calves have less diarrhea if placed on whole cows' milk rather than other diets. Pasteurizing surplus colostrum and waste milk reduces the incidence of diarrhea on these diets.[496] It is also important to offer good-quality calf starter from about 2 to 3 days of age; at first, little will be ingested, so producers should offer small amounts and keep it fresh.

Some producers routinely administer vitamin A to neonatal calves. Many, but not all, studies in human children indicate that supplementation can reduce the incidence of diarrhea in areas where

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clinical and subclinical vitamin A deficiency is endemic.[497] In cattle, vitamin A deficiency is most likely when a diet of unsupplemented straw and grain is fed. Calves born to cows fed good-quality green forage or to cattle receiving a vitamin A supplement should not require supplementation, particularly if they received adequate colostrum. Enteric absorption of vitamin A is diminished in calves with cryptosporidiosis so the systemic route should be used in calves with this type of infection.[498]

BIOSECURITY. Infectious diseases are often purchased with brought-in stock. Operations that buy in calves for rearing purposes should be encouraged to buy from as few sources as possible. Direct purchase from one farm is best; assembling collections of calves through auction markets should be avoided if possible.

Treatment of Individual Calves

Examination

Physical examination of the diarrheic calf is the first step in establishing therapeutic needs. It is important to determine the presence of any intercurrent disease. Treatment of uncomplicated cases of diarrhea depends on the estimation of dehydration, severity of acidosis, likelihood of intercurrent infection, presence or absence of hypothermia, and hypoglycemia. The severity of dehydration is gauged from the eyeball position and skin tent (Table 20-9). In acute diarrhea the degree of enopthalmos is the most reliable indicator of dehydration, but because the position of the eye within the orbit is also dependent on body fat stores, the skin tent in the cervical region may be the most reliable in calves with chronic diarrhea or cachexia.[499] Skin tent can be measured over the eyelids and neck. Best results are obtained when the neck is held straight and the skin of the mid-neck is tented in the direction of the long axis of the neck to avoid the natural skin folds that run across the neck. Some have claimed that a relationship exists between severity of dehydration and acidosis. However, this has not been borne out in studies of diarrheic calves.[500] Instead, acidosis can be gauged from the calf's suckling/drinking drive and the degree of weakness and the age of the calf (Fig. 20-4).[500,501] Estimation of severity of acidosis from either laboratory or physical findings is very important to the successful therapy of severely depressed calves. A recent study has questioned the relationship between metabolic acidosis and clinical signs since administration of hypochloric acid failed to induce abnormal clinical signs in calves.[502] The clinical signs associated with metabolic acidosis are mainly attributable to elevations in D-lactate.[140,143] Rectal temperature measurement will determine whether or not the calf is hypothermic.

Heart rate is variable in diarrheic calves. Bradycardia (<90 beats/min) is clinically important and may indicate the presence of hypothermia, hypoglycemia, or hyperkalemia. Cardiac arrhythmias occur[501] and are usually due to severe hyperkalemia (K^+ above 8 meq/L) (Fig. 20-5). Hyperkalemic arrhythmia can usually be differentiated from arrhythmia resulting from cardiomyopathy (selenium deficiency) because the heart rate is not elevated. The presence of bradycardia or arrhythmia indicates the need for immediate fluid therapy with bicarbonate-containing solutions to prevent death.

Body condition is usually good at the start of an attack of diarrhea. Poor condition often indicates chronic infection, mismothering, or poor feeding programs, which may be exacerbated by milk withdrawal for therapeutic purposes.

It is important to check for intercurrent infections; these are easily missed even with careful examination. The lungs should be examined for signs of pneumonia; the navel palpated for pain, swelling, and wetness; and the joints checked for signs of distention and lameness. The boundary between calves in which the primary insult is septicemia with a secondary diarrhea and those in which primary diarrhea is complicated by septicemia is blurred. Calves that are recumbent, are under 1 week of age, have lost their suck reflex, or have evidence of intercurrent infection are more likely to be septicemic and require concurrent antibiotic therapy.[503] Calves in which septicemia has progressed to produce signs of meningitis (e.g., extended neck with reluctance to flex neck), joint involvement, or ophthalmic signs (congested scleral vessels with hypopyon or iridospasm) carry a poor to very poor prognosis. It is best to identify these cases prior to instigating therapy so that the owner can decide whether treatment is economically feasible.

The laboratory is useful in quantifying metabolic disturbances in diarrheic calves. Blood gas analysis will accurately determine the degree of metabolic acidosis. The development of point of care devices (such as i-STAT, Abbott Laboratories, Abbott Park, Ill.), which are relatively affordable, has enabled practitioners to evaluate acid-base abnormalities in the field. The portable analyzers are capable of quantifying concentrations of Na^+, K^+, iCa^{2+}, and tCO_2 as well as determining pH, PCO_2, PO_2, base excess, and hematocrit. Correlations between the i-STAT and a reference analyzer in cattle and sheep were good or excellent for most variables.[504] Alternatively, blood can be collected into a heparinized syringe, capped, placed in a styrofoam cup surrounded by ice, and transported 4 hours or more to a laboratory. The practice laboratory may also have a total CO_2 (Harleco) analyzer or access to serum bicarbonate estimation as part of a serum chemistry profile. Total CO_2 or bicarbonate is a useful index of the severity of metabolic acidosis. Blood glucose can be readily determined using a handheld glucometer.

Fluid Therapy

The most common causes of death in diarrheic calves are dehydration and acidosis.[505] The immediate objective in treating depressed diarrheic calves is to restore them to a normal systemic state. In some calves it may also be necessary to correct hypoglycemia or hypothermia, to restrict milk intake, or to give antibiotics.

The estimated severity of dehydration can be combined with estimates of losses through diarrhea and for the maintenance of essential functions to give the total daily fluid requirement (see Table 20-9). The hydration status of the calf can be estimated from the degree of enopthalmos, the degree of skin tent on the neck, and evaluation of the mucous membranes (see Table 20-9). The volume (L) required to replace the deficit is % dehydration × calf body weight (kg). The ongoing losses through diarrhea should be estimated from the nature and volume of the diarrhea. Fecal losses can range from 1 to 6 L in diarrheic calves.[506] Maintenance requirements have been estimated at 50 to 100 mL/kg/day.[31,506] The degree of hydration and the volume of feces passed should be reassessed daily and the treatment adjusted accordingly. Only 60% to 80% of oral fluids are absorbed, and this needs to be accounted for in the calculation.[507]

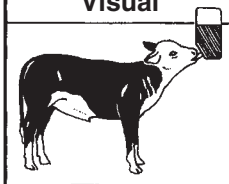
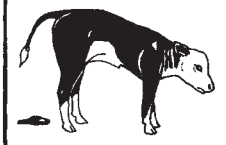
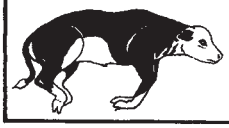
TABLE 20-9

Guidelines for Assessing Dehydration in Neonatal Calves

Dehydration (%)	Eyeball Sunkenness	Neck Skin Tent (Seconds)	Mucous Membranes
0	None	<1	Moist
1-5	None to slight	1-4	Moist
6-8	Slight separation of eyeball and globe	5-10	Tacky
9-10	Gap, <0.5 cm, between eyeball and orbit	11-15	Tacky to dry
11-12	Gap, 0.5-1 cm, between eyeball and orbit	16-45	Dry

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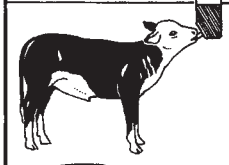
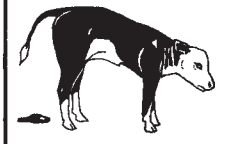
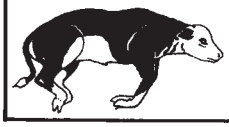
Bicarbonate requirements for diarrheic calves ≤8 days of age

Clinical assessment		Base deficit (mmol/L)	Therapy						
Visual	Descriptive		30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg
	Standing, strong suck reflex	0	Oral*						
	Standing, weak suck reflex	5	Intravenous†						
	Sternal recumbency	10	150	175	200	225	250	275	300
	Lateral recumbency	10	150	175	200	225	250	275	300

*Should contain at least 60 mmol/L of acetate or bicarbonate.
†Total bicarbonate requirement for intravenous fluid therapy, mmol.

A

Bicarbonate requirements for diarrheic calves >8 days of age

Clinical assessment		Base deficit (mmol/L)	Therapy						
Visual	Descriptive		30 kg	35 kg	40 kg	45 kg	50 kg	55 kg	60 kg
	Standing, strong suck reflex	5	Oral*						
	Standing, weak suck reflex	10	Intravenous†						
	Sternal recumbency	15	225	262.5	300	337.5	375	412.5	450
	Lateral recumbency	20	300	350	400	450	500	550	600

*Should contain at least 60 mmol/L of acetate or bicarbonate.
†Total bicarbonate requirement for intravenous fluid therapy, mmol.

B

FIG. 20-4 Prediction of severity of metabolic acidosis from body position, strength of suck reflex, and age. **A,** Calves 8 days of age or greater. **B,** Calves less than 8 days of age.

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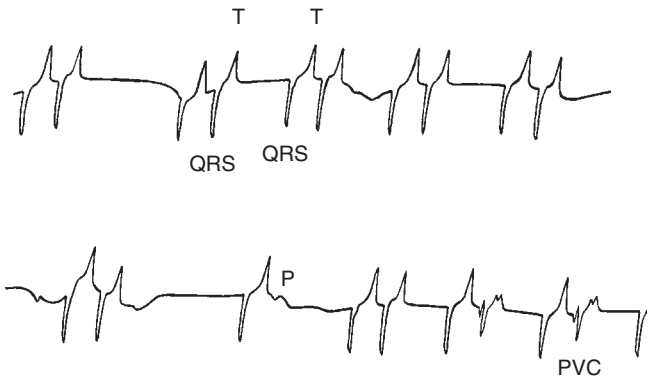


FIG. 20-5 Bradycardia and atrial standstill in a severely hyperkalemic diarrheic calf. Heart rate is 84 beats/min. There is bigeminy, and the T waves are abnormally large. There is only one P wave, and it is not conducted. Serum potassium was 8.9 mmol/L, and sodium 116 mmol/L.

Bicarbonate requirements can be calculated from base deficit values (based on blood gas measurements or estimated from physical findings) as follows:

$$\text{mmol bicarbonate} = \text{Body weight (kg)} \times \text{Base deficit (mmol/L)} \times \text{Volume of distribution (0.6 in calves)}$$

A chart of bicarbonate requirements for various body weights and base deficit values is available in Table 20-10.

Measurements of serum total carbon dioxide content or bicarbonate are also reliable estimates of bicarbonate requirements.[508] Bicarbonate requirements are as follows:

$$\text{mmol bicarbonate} = \text{Body weight (kg)} \times (30 - TCO_2) \times 0.6$$

For example, a 40-kg calf has a serum bicarbonate or TCO_2 of 10 mmol/L. The calf has a bicarbonate deficit of 30 mmol/L − 10 mmol/L = 20 mmol/L, so 40 kg × 20 mmol/L × 0.6 = 480 mmol bicarbonate is required to replace existing deficits. Ongoing diarrhea may require additional bicarbonate.

Calves that are unwilling to suck and are severely depressed are best treated with IV fluids. Calves that are only moderately depressed may also be treated with intravenous fluids if the condition is worsening rapidly. Catheterization is easier if a no. 15 scalpel blade is used to nick the skin. If it proves very difficult to catheterize the calf it can be suspended upside down so that blood will pool and distend the jugular veins. The calf's neck should be clipped and prepared prior to inversion and the calf lay flat as soon as the catheter is placed. It should be possible to place a catheter in less than a minute even in severely dehydrated calves using this technique. Alternatively, the auricular vein can be easily catheterized using a 20-gauge catheter, or fluids may be administered by intraosseous infusion in the critically ill neonate when IV access is not possible. In calves, intraosseous fluids may be administered via placement of a 16- or 14-gauge needle in the head of the femur or humerus. A 16- or 14-gauge needle is inserted in a longitudinal plane. Neonatal bones are soft, so the needle can be drilled into the bone using finger pressure. Commonly a core of bone will plug the needle, requiring the drilling needle to be discarded and replaced with a new needle placed in the same hole. After placement of the needle, attach a 60-mL syringe and inject sterile saline under slight pressure to start the flow. As the fluid is administered, check for subcutaneous leakage to ensure the needle is correctly placed within the bone marrow. Between 1 and 2 L of saline or isotonic bicarbonate administered to the severely dehydrated calf is often sufficient to restore blood pressure for placement of an IV catheter.

Once the catheter is placed, fluids can be administered. If the calf is hypothermic, these should be warmed prior to administration because cold fluids can decrease cardiac output and may kill a critically ill calf. Fluids can be warmed by a number of methods; one convenient technique is to run the fluids through a coil of tubing immersed in a bucket of hot water (check the temperature regularly) on the way to the calf.

Saline-based fluids are suitable for rehydration (Table 20-11); most severely depressed calves are acidotic and more consistent recovery is obtained if an alkalizing agent is also used. A wide variety of alkalizing agents are available (lactate, acetate, gluconate), but clinical trials show that only bicarbonate is consistently effective in severely acidotic calves (Fig. 20-6).[138,509] Many diarrheic calves require large amounts of bicarbonate to correct their acidosis.[136] An isotonic solution (156 mmol/L) of bicarbonate can be readily made by dissolving 13 g of sodium bicarbonate (baking soda) in 1 L of water.[510] Sodium bicarbonate solutions can be mixed with saline; there is a possibility that precipitates may form if bicarbonate is mixed with calcium-containing solutions such as Ringer solution.

Some clinicians may prefer to rehydrate the neonate first and then reconsider the need for bicarbonate if it is not up and sucking within 12 hours of therapy. However, this is time consuming. It is not always necessary to completely correct acidosis; blood pH from 7.25 to 7.45 has little adverse effect (normal calves have a venous blood pH of 7.34, bicarbonate of 30 mmol/L, and a base excess of 5 mmol/L).

Ideally, dehydration and acidosis should be corrected over a 24-hour period. However, it is unusual to see problems when the fluid and acid-base deficits are corrected over 4 hours, although the calf may continue to improve after this period. Rapid resuscitation techniques include the administration of either hypertonic saline (with or without dextran) or hypertonic sodium bicarbonate. Hypertonic saline (7.2% NaCl) or hypertonic saline dextran (7.2% NaCl containing 6% dextran 70) administered at 4 mL/kg body weight during a 4-minute period concurrently with an isotonic alkalizing oral electrolyte solution is effective in resuscitating dehydrated calves with

TABLE 20-10

Calculation of Bicarbonate Requirement from Calf Body Weight and Severity of Acidosis

Calf Weight (kg [lb])	Base Deficit (mmol/L)	Bicarbonate Requirements (mmol)	Volume in Liters 1.3% $NaHCO_3$ (L)*
30 (66)	5	75	0.5
	10	150	1.0
	15	225	1.5
	20	300	1.9
35 (77)	5	88	0.5
	10	175	1.1
	15	263	1.6
	20	350	2.3
40 (88)	5	100	0.6
	10	200	1.3
	15	300	1.9
	20	400	2.6
45 (99)	5	113	0.7
	10	225	1.4
	15	338	2.1
	20	450	2.9
50 (110)	5	125	0.8
	10	250	1.6
	15	375	2.4
	20	500	3.2
55 (121)	5	138	0.9
	10	275	1.8
	15	413	2.7
	20	550	3.6
60 (132)	5	150	1.0
	10	300	1.9
	15	450	2.9
	20	600	3.8

*Isotonic 1.3% sodium bicarbonate solution is prepared by adding 13 g of sodium bicarbonate to 1 L distilled water (155 mmol of bicarbonate/L).

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TABLE 20-11

Fluids Commonly Used in Intravenous Therapy

Item	Concentration (mmol/L)									
	Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^-	$Lactate^-$	$Acetate^-$	$Gluconate^-$	Glucose
0.9% saline	155				155					
1.3% sodium bicarbonate*	156					156				
Ringer solution	147	4	5		156					
Lactated Ringer solution†	130	4	3		107		30			
Ionalyte (diluted)†	139	10		3	101			55		167
Normosol R†	140	5		3	98			25	25	
Plasmalyte 148†	140	5		3	98			27	23	
5% dextrose (D_5W)‡										278

*Do not mix sodium bicarbonate with calcium-containing solutions; precipitates may form. Mixtures of 1.3% sodium bicarbonate and saline are usually used for treating recumbent diarrheic calves.

†Multiple electrolyte solutions are equivalent, with the exception that one should be careful of using Ionalyte in severely hyperkalemic neonates. All are suitable for rehydrating neonates that can stand.

‡Intravenous fluids are often spiked with 50% dextrose to give a final concentration of 5% dextrose in the drip when hypoglycemia is suspected.

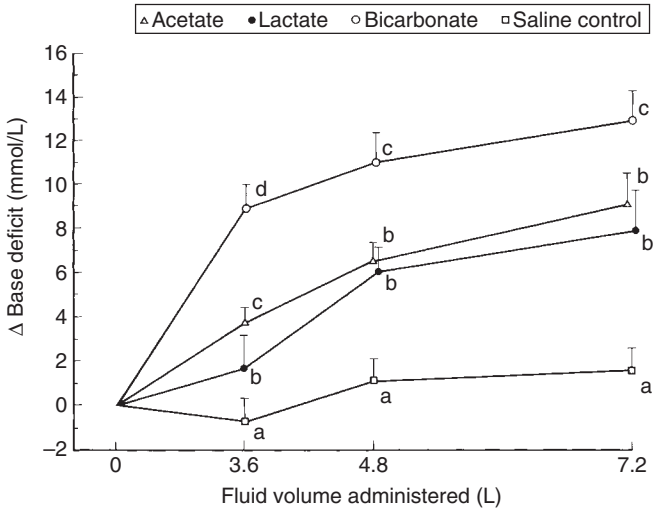


FIG. 20-6 Comparison of the alkalizing effect of various bases in diarrheic calves with severe dehydration and acidosis. At the start of the trial, all calves were at least 8% dehydrated and had a mean blood pH of 7.032 and a base deficit of 18 mmol/L. All calves received a total of 7.2 L of fluid containing 102 mmol/L of saline plus 50 mmol/L of the sodium salt of the respective alkalizing agent. Letters *(a, b, c, d)* are statistically different ($p < 0.5$) from one another at that point. *(From Kasari TR, Naylor JM. 1985. Clinical evaluation of sodium bicarbonate, sodium L-lactate, and sodium acetate for the treatment of acidosis in diarrheic calves. J Am Vet Med Assoc 187:392.)*

diarrhea.[511,512] Hyperosmotic sodium bicarbonate solutions may also be used to rapidly resuscitate acidotic dehydrated calves.[513-515] The base deficit can be corrected by administering 8.4% sodium bicarbonate 10 mL/kg body weight over 8 minutes.[515a] Hypertonic fluids should always be given concurrently with an isotonic oral electrolyte solution. After 24 hours of appropriate therapy, one would expect the calf to be standing and show a good suck reflex. Persistent depression is usually a sign of uncorrected acidosis or toxemia.

Most diarrheic calves are not markedly hypoglycemic, but glucose supplementation is needed to treat severe hypoglycemia (glucose concentrations <2 mmol/L or <36 mg/dL). Severe hypoglycemia is treated by adding glucose to the IV fluids to a final concentration of 2.5% to 5%. Severe hyperkalemia is seen in some dehydrated diarrheic calves, but this responds to rehydration (restores renal perfusion and dilutes out potassium) and correction of acidosis (redistributes potassium into the cells). Nutritional support is not needed if the calf is in good body condition but should be given if the calf is emaciated or if the calf has been deprived of milk for more than 3 days.

There are increased losses of potassium in diarrhea; potassium depletion can result in weakness. When necessary, potassium supplementation can be estimated using the following equation:

$$\text{Replacement K (mEq)} = 0.4 \times \text{Body weight (kg)} \times \text{K deficit (mEq)}$$

Potassium can safely be added to fluids at a rate of 20 to 30 mEq/L. The rate of potassium administration should not exceed 1 mEq/kg/h. If acidosis is present, hydrogen ions are exchanged for intracellular potassium ions, resulting in a relative increase in serum [K]. As the acidosis is corrected, there will be an influx of K ions back into cells, resulting in potential hypokalemia, which must be anticipated during fluid therapy.

Once the calf is able to nurse or drink, therapy is usually switched to oral electrolytes. This is also the route of choice for treatment of mildly affected calves on the farm. Calves with weak suck reflexes and calves that are unused to hand feeding can be tubed. Oral electrolyte solutions need to supply sufficient sodium to facilitate normalization of extracellular fluid deficits, nutrients to facilitate absorption of sodium from the intestine, alkalizing agent to treat metabolic acidosis, and supplemental energy.[516] The first two requirements depend on the coupled active transport of glucose and sodium ions across the brush border membranes of enterocytes, which results in passive absorption of water and other electrolytes.[517] This function remains largely intact in calves with enterotoxigenic *E. coli* diarrhea, but where there is endothelial damage, it may be impaired. Certain amino acids (glycine, L-alanine, L-glutamine) enhance the absorption of sodium and water,[517] as do acetate and propionate.[518] In order to effectively combat acidosis, oral electrolyte solutions need to contain 50 to 80 mmol/L of alkalizing agent. Acetate, lactate, citrate, gluconate, or bicarbonate are all used as alkalizing agents. Bicarbonate combines with hydrogen ions directly whereas the other agents remove hydrogen ions during their metabolism within cells.[506] Electrolyte solutions that contain more than 40 mmol/L of bicarbonate or citrate have marked adverse effects on milk clotting.[519] Bicarbonate raises abomasal pH, whereas citrate binds calcium, so the presence of either interferes with the normal clotting of milk in the abomasum. Breakdown of abomasal milk clots results in the gradual release of some nutrients into the small intestine. Bicarbonate also reduces milk digestibility. A reduced growth rate was recorded when electrolyte solutions with bicarbonate were given to milk-fed calves.[520] Solutions containing bicarbonate may also alkalize the gastrointestinal tract of milk-fed calves and promote bacterial overgrowth in the small

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intestine as well as ETEC attachment and toxin production.[521] Acetate is the best alkalizing agent to include in electrolytes that are to be fed to calves that are still receiving milk; it has excellent alkalizing ability and does not interfere with milk clotting in the abomasum. Any of the commonly used alkalizing agents are likely acceptable for calves held off milk.[519]

There are a wide variety of oral electrolyte preparations on the market, and different products are suited to different situations. Almost all of the products contain water and electrolytes and are suitable for rehydration (Table 20-12). Beware of products that are designed for medicating hundreds of liters of water—the final solution is often very dilute (<10 g electrolytes/L) and will not rehydrate sick calves. These products are often marketed as "boosters" and "stress relievers." Glucose and glycine are usually added to oral electrolyte solutions to facilitate sodium absorption. Research in people has shown that adding glycine to solutions containing 110 mmol/L of glucose aids rehydration. It is probable, however, that there is little additional benefit to supplementing solutions that contain more than 200 mmol/L of glucose with glycine. Solutions that contain large amounts of glucose are hyperosmolar and are absorbed more slowly than isotonic solutions, but the differences are too small to be clinically important.[522] The ionic composition also affects absorption; mixtures of sodium chloride and citrate, bicarbonate, or acetate have improved absorption over chloride salts alone. Oral electrolyte solutions are almost completely absorbed in healthy calves, but absorption can be as low as 60% in severe *E. coli* diarrhea.[523]

The ability to counteract acidosis varies greatly between oral electrolytes. Some have a net acidifying effect whereas others alkalize blood (Fig. 20-7). These differences are therapeutically important and are responsible for differences in survival rates among products. Highly alkalizing solutions give the best results; one study showed that it was more important that an electrolyte solution contain bicarbonate than chloride.[524] This is particularly important in older calves. Recently there has been interest in adding glutamine to oral electrolyte solutions because it is an important fuel for the gastrointestinal tract and can promote mucosal repair.[525-527] However, studies show that oral electrolytes containing glutamine as the sole amino acid are no more effective in diarrheic calves than other well-designed solutions that use glycine as the amino acid.[528] Psyllium has been added to some oral electrolyte solutions for a number of perceived benefits, but controlled studies show no clinical advantages, although there may be some moderation of bacterial fermentation within the gastrointestinal tract.[529,530]

The other problem to be considered in the chronically scouring calf is the need for nutritional support. Maintenance metabolizable energy requirements for a 50-kg calf are about 2000 kcal, and 3500 kcal are required to support a weight gain of 0.5 kg/day. These requirements can be met by 3.3 and 5.7 L of whole cows' milk, respectively. Comparative studies indicate that weight loss in calves fed oral electrolytes are inversely proportional to the energy content of the solutions.[531] Assuming a 4-L daily intake and 100% digestibility of oral electrolyte nutrients, regular electrolyte solutions supply between approximately 15% and 25% of energy needs. As a result diarrheic calves that are held off milk for prolonged periods lose weight[532] and can become emaciated. When maintaining body condition is a concern, and little milk or solid food is being ingested, then a high-energy oral electrolyte should be fed. Products such as Biolyte, Lifeguard/Enterolyte HE, and RESTART HE provide about 50% of energy requirements if fed twice a day (total intake 4 L) and about 75% if fed three times a day (total intake approximately 6 L). The energy contents of various oral electrolyte solutions are presented in Fig. 20-8.

MILK WITHDRAWAL. Milk withdrawal can reduce the severity of diarrhea and depression in severe scours. This is because malabsorption exacerbates diarrhea through the osmotic effect of unabsorbed milk nutrients and promotes bacterial overgrowth and possibly malfermentation with production of organic acids. Milk also has a trophic effect on epithelial cells and maintains higher gastrointestinal tract enzyme activities as well as providing protein for repair of damaged intestinal epithelium.[518] In experimental trials, continued feeding of milk maintained weight gain; however, when calves were fed enough milk to fully meet their requirements and the undrunk milk was tube fed, calves initially had greater inappetence.[520,533] Withdrawal of milk without a high-energy alternative can rapidly result in cachexia and malnourishment.[520] In many calves, particularly the less severely affected, there is often a considerable degree of residual absorptive capacity—enough to support body weight gain if limited amounts of milk are fed. Milk withdrawal is recommended if the calf is depressed and not interested in sucking. In most cases electrolyte therapy will restore a calf's vigor and sucking drive within 1 to 2 days. Milk can then be reintroduced in small amounts (e.g., 1 L given bid or qid). However, forced feeding (by tubing or drenching), causing dysfunction of the reticular groove reflex, or reflux of abomasal contents, may result in ongoing acidosis as a result of production of D-lactate from fermentation of carbohydrates entering the reticulorumen.[143] If the calf is not interested in drinking or gets depressed when reintroduced to milk, a high-energy oral electrolyte preparation can be tried instead. Studies indicate that diarrheic calves have a generalized malabsorption rather than specific lactose intolerance.[133] Thus, it may be more important to manage calves with milk intolerance by giving smaller amounts of milk in each feed rather than by changing carbohydrate source. There is little point in withdrawing milk from calves that remain alert and interested in nursing, because it is unlikely to result in clinical improvement. This is particularly likely to be the case when the calf receives whole cow's milk in frequent small quantities (i.e., by natural sucking of the dam).

Role of Antimicrobials

Some controversy exists regarding the use of antimicrobials for the treatment of calf scours. Reports questioning the use of antimicrobial therapy are derived from lack of efficacy, the potential for adverse effects, the potential for violative residues, and selection for antimicrobial resistance. Conversely, there are reports describing attenuation of clinical disease, reduced pathogen shedding, and lower mortality following the use of antimicrobials to treat scouring calves.

THERAPEUTIC TARGETING. Bacterial pathogens associated with neonatal calf diarrhea include *Salmonella* and *E. coli*. During disease outbreaks caused by these pathogens, antimicrobial use may be targeted at the specific pathogen. Beneficial responses to antimicrobial therapy have also been reported in field trials involving undifferentiated pathogens.[534,535] Calves with diarrhea often have increased coliform bacterial numbers in the small intestine, regardless of etiology,[536-538] and this colonization is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia.[538] Calves with diarrhea are more likely to have failure or partial failure of passive transfer, and this group of calves, in turn, is more likely to be bacteremic.[21,539] Blood cultures indicate that gram-negative bacteria account for approximately 80% of bacterial isolates; *E. coli* is the most common bacteria isolated.[17,18,539] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to be bacteremic. *E. coli* accounted for 51% of the isolates; other gram-negatives, 25%; gram-negative anaerobes, 5.9%; gram-positive cocci, 11.8%; and gram-positive rods, 5.9%.[539]

Antimicrobial therapy may therefore be targeted at a specific bacterial enteric pathogen isolated from sick calves or in severely ill calves (as manifested by reduced suckle reflex, greater than 6% dehydration, weakness, inability to stand, or clinical depression) and used prophylactically to manage the risk of bacteremia. This application emphasis should be directed toward gram-negative organisms, particularly *E. coli*.

ANTIMICROBIAL SUSCEPTIBILITY. Antimicrobial susceptibility testing of fecal isolates is not a good predictor of clinical outcome. Three studies have reported no correlation between in vitro antimicrobial susceptibility of fecal *E. coli* and *Salmonella* spp. isolates and clinical response to antimicrobial treatment.[540-542] Antimicrobial

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TABLE 20-12

As-Fed Composition of Some Available Oral Electrolyte Solutions for Calves

Product	Company	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	HCO_3^- (mmol/L)	Acetate (mmol/L)	Citrate (mmol/L)	Propionate (mmol/L)	Glucose (mmol/L)	Glycine (mmol/L)	Alkalizing Ability (mEq/L)	Additional Contents
Advance Arrest	MS Specialty Nutrition	46	7	?	?	?	?	?	97	0	?	Protein and minerals
Advance Pro-Lyte Plus	MS Specialty Nutrition	117	23	?	?	0	?	0	200	?	?	Probiotics and protein
ASGOLD	Volac	84	10	74	19	0	0	0	103	0	19	Fecal bulking agents and vitamins
Blue Ribbon	Merrick's Inc.	156	20	?	?	?	?	?	200	?	?	Probiotics
BlueLite C	TechMix, Inc.	48	34	57	0	0	?	0	?	0	?	
Bounce Back	Manna Pro	150	9	122	37	0	0	0	166	0	37	
Calf GoldLyte	Bio-Vet	154	27	92	?	0	?	?	?	?	?	Vitamins, minerals and probiotics
Calf Quencher	Vedco	142	24	80	86	0	0	0	399	0	0	
Calf Restart One-4	TechMix, Inc.	261	153	?	0	0	?	0	?	0	?	Immunological and dietary protein, additional water-soluble carbohydrates (energy), probiotics, vitamins and minerals
Calf-Gel 95	Van Beek Scientific LLC	42	9	?	?	0	?	?	?	0	?	Mucopolysaccharides and vitamins
C.H.E.E.R.S.	Nouriche Nutrition Ltd.	90	30	50	0	?	?	?	40*	40	?	
Comeback	AgriPharm	112	24	?	0	0	?	0	?	?	?	
Deliver with Dialine	AgriLabs	77	14	16	37	0	4	0	82	0	49	Fecal bulking agents
Deliver Extra with Dialine	AgriLabs	95	19	?	?	0	?	?	?	0	?	Glutamine, probiotics, psyllium, and natural vitamin E
Diaque	Boehringer Ingelheim	87	12	54	?	?	?	0	155	7	?	Probiotics and fecal bulking agents
Electrate	Bimeda	165	10	103	0	82	0	0	142	0	82	
Electrolyte with Thickener	DVM Formula (Vets Plus)	110	20	50	80	0	0	0	132	25	80	Fecal bulking agents
Electrolytes Plus Supplement	Sav-A-Caf (Milk Products)	137	7	?	18	0	0	0	249	30	18	Kaolin, probiotics, and additional energy as starch
Ener-Lyte	Aspen	132	19	?	?	0	0	0	?	0	?	Probiotics, vitamins, minerals, and bulking agents
Entrolyte	Pfizer Animal Health	106	23	46	80	0	0	0	166	22	80	Additional amino acids
Entrolyte HE	Pfizer Animal Health	100	23	45	78	0	0	0	449	38	78	
EPIC Calf Electrolyte	Bioniche Animal Health	99	20	86	0	57	0	0	?	0	57	Immunoglobulins and immune cofactors
Formula 911	Advantech	132	19	?	?	0	0	0	?	?	?	Probiotics, vitamins, and minerals
Hydrafeed	Vet Pharm	115	11	62	86	0	14	0	96	32	128	Protein, fiber, and lactose (glucose and galactose)
Hydra-Lyte	Vet-A-Mix	85	30	45	0	60	10	0	368	16	90	
Hy-sorb	Bimeda	113	9	64	38	0	9	0	53	38	66	
Land O'Lakes Electrolyte System Base	Land O'Lakes	99	21	?	0	0	?	0	?	0	?	Vitamins
Land O'Lakes Electrolyte System Base + Add Pack	Land O'Lakes	140	21	?	40	0	?	0	?	?	?	Vitamins
Lifeaid Extra	Norbrook	90	25	60	0	20	7	10	175	0	50	
Nutri-Sorb	AgriPharm	70	16	63	23	0	0	0	125*	0	23	Glutamine and psyllium
One Day Response	Farnam	81	10	?	?	0	?	0	?	0	?	Psyllium and additional energy as fat
Re-sorb	Pfizer Animal Health	80	26	80	0	0	2	0	129	45	5	
Revitilyte	Bomac Vets Plus, Inc.	110	20	50	80	0	0	0	174	25	80	Starch
Revitilyte-Gelling	Bomac Vets Plus, Inc.	110	20	50	80	0	0	0	132	25	80	Starch as a gelling agent

Updated table based on Naylor JM. 1999. Oral electrolyte therapy. Vet Clin North Am Food Anim Pract 15:487. Calculated from information listed in the Compendium of Veterinary Products, 2007, and product labels. Additional information obtained from Jones C, Kehoe S, Heinrichs J. Comparison of some available oral rehydration products. Pennsylvania State University, 2006, Department of Dairy and Animal Science. Available at http://www.das.psu.edu/pdf/electrolytetable.pdf.

Note: Concentrations of calcium, magnesium, phosphate, and sulfate not included. Molarities assume that all compounds dissociate completely in solution. Where a maximum and minimum value for a compound was provided, the mean value has been used.

*Contain maltodextrins (glucose polymers). It has been assumed that these will be completely digested to provide glucose.

?, Published information insufficient to provide reasonable estimate.

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efficacy is best evaluated by the clinical response of a number of calves to treatment, with calves randomly assigned to treatment groups, rather than the results of in vitro antimicrobial susceptibility testing performed on fecal *E. coli* isolates.[543]

Antimicrobial susceptibility testing has more clinical relevance for predicting the clinical response to antimicrobial treatment when applied to bacteria isolated from blood or tissues of bacteremic calves because the minimal inhibitory concentration break points are based on achievable antimicrobial concentrations in human plasma and MIC_{90} values for human *E. coli* isolates, which provide a reasonable approximation to achievable MIC values in calf plasma and MIC_{90} values for bovine *E. coli* isolates.[543] Even within a given herd, there will be a diversity of bacteria isolated from bacteremic calves, so the collection of blood cultures and assessment of antimicrobial susceptibility does not necessarily provide information applicable to the next case.

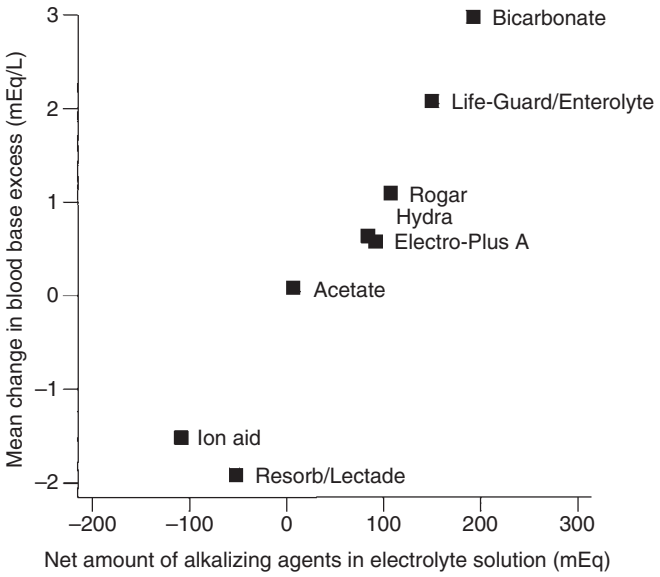


FIG. 20-7 Comparison of the alkalizing abilities of various oral electrolyte solutions. The Y axis shows the mean alkalizing effect after administration of one treatment (1.9 to 2.25 L) of the fluid to healthy calves, and the X axis shows the net amount of alkalizing agents in the solution. Bicarbonate and acetate are experimental solutions. (Life-Guard/Enterolyte manufactured by SmithKline Beecham Labs, Hydra manufactured by Vetrepharm, Electro-Plus A manufactured by Pitman-Moore, Ion Aid manufactured by Syntex, and Re-Sorb manufactured by Beecham. Rogar is Rogar STB's electrolyte powder.) *(Modified from the Proceedings of the 14th World Congress for Diseased Cattle, 1986, 1:362.)*

ANTIMICROBIAL SAFETY. A number of antimicrobials have been demonstrated to produce deleterious effects when administered orally to healthy milk-fed dairy calves. The addition to milk replacer powder of procaine penicillin (2 to 60 mg/kg of milk replacer) increased the incidence and duration of diarrhea and decreased growth rate compared with untreated controls in a total of 36 milk-fed calves.[544] Penicillin is not labeled for treatment of calf scours and has an inappropriate antimicrobial spectrum to prevent or treat calf scours. Administration of neomycin sulfate (300 mg PO q24h for the first 4 days of life) tended ($P = .060$) to increase the proportion of calves developing diarrhea (99/233 = 43%) compared with the proportion in an untreated control group (58/174 = 33%).[545] Administration of neomycin sulfate (25 mg/kg PO q6h, n = 10), ampicillin trihydrate (12 mg/kg PO q8h, n = 6), or tetracycline hydrochloride (11 mg/kg PO q12h, n = 6) for 5 days increased the occurrence of diarrhea and decreased glucose absorption through unknown mechanisms compared with untreated controls (n = 6).[546] Two other studies did not observe adverse side effects in calves administered tetracycline hydrochloride (40 mg PO q12h; 11 mg/kg PO q12h).[547,548]

EFFICACY OF ORAL ANTIMICROBIAL THERAPY. The response to oral antimicrobial therapy is variable with many formulations failing to demonstrate a beneficial effect.[543] Apramycin administered orally at either 20 or 40 mg/kg significantly decreased mortality.[535] Trials with orally administered neomycin reduced the duration of diarrhea but did not reduce mortality.[549,550] Similarly, trials with orally administered ampicillin failed to demonstrate a significant reduction in mortality.[551] The results of trials with orally administered trimethoprim have been variable with no significant improvement in outcome observed in a large field trial[552] and a significant reduction in mortality observed in an experimental *Salmonella* challenge study where calves were administered trimethoprim 5 mg/kg and sulfadiazine 25 mg/kg PO daily for 5 days.[553] Orally administered amoxicillin trihydrate has been demonstrated to reduce mortality and the duration of diarrhea when administered at a dose of 10 mg/kg PO q12h.[122,554]

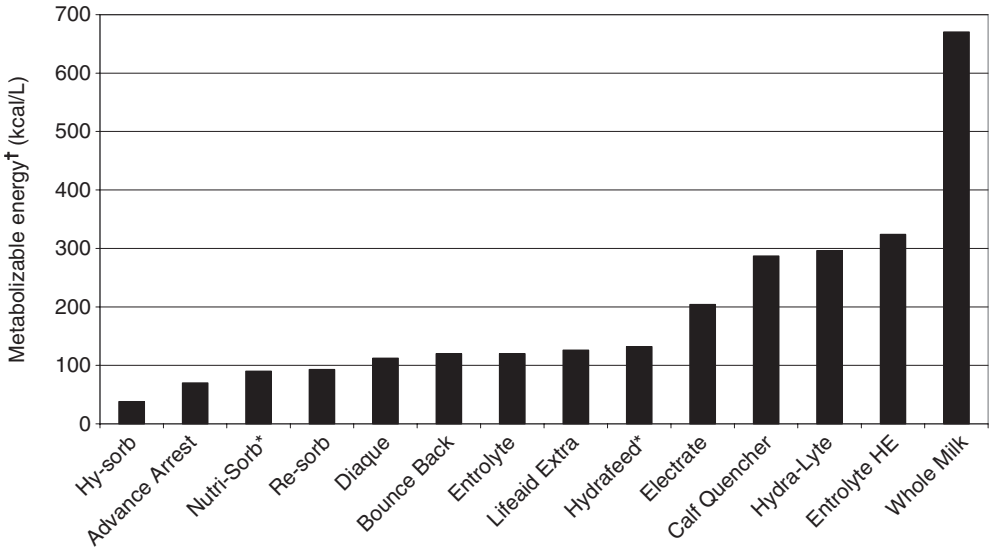


FIG. 20-8 Comparison of the energy contents of various oral electrolyte solutions. Milk is also shown for comparative purposes. This figure assumes electrolyte solutions are fed to neonatal calves prior to rumen development. (See text for manufacturers.) *ME estimated from water-soluble carbohydrate composition. †ME estimated from glucose and other water-soluble carbohydrate composition of as-fed electrolyte solution assuming 1 g (cry matter) of carbohydrate = 4 kcal.

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In an epidemiologic study of *Salmonella* in dairy calves conducted in the United States, feeding medicated milk replacer and hay to calves from 24 hours of age to weaning was associated with a reduced risk of *Salmonella* shedding.[555] This observation contradicts an experimental study in which feeding chlortetracycline in milk replacer increased the severity of disease and the rate and duration of *Salmonella* shedding.[556] Similarly, in another experimental trial, daily drenching of calves with 50 or 100 mg of chlortetracycline failed to alter the excretion pattern or the number of organisms excreted by calves infected orally with 10^6 *S.* Typhimurium.[557]

EFFICACY OF PARENTERAL ANTIMICROBIAL THERAPY. Antimicrobial drugs with an appropriate gram-negative spectrum of activity include third-generation cephalosporins (ceftiofur), potentiated penicillins (amoxicillin), trimethoprim sulfonamide combinations (TMS), aminoglycosides, sulfonamides, florfenicol, and tetracyclines. There is a paucity of efficacy data to support the use of aminoglycosides, tetracycline, nonpotentiated sulfonamides, and florfenicol.

Ceftiofur has an appropriate antimicrobial spectrum, and therapeutic drug concentrations can be maintained with once daily dosing. In an *S.* Typhimurium challenge experiment, intramuscular administration of ceftiofur hydrochloride (5 mg/kg q24h for 5 days) reduced the severity of clinical signs and reduced fecal shedding of *Salmonella*. The MIC of the challenge strain in this experiment was 1 μg/mL, and the therapeutic protocol maintained plasma concentrations above this concentration for the duration of therapy.[332]

Potentiated sulfonamides have been evaluated in enterotoxigenic *E. coli* and *Salmonella* challenge experiments. Mortality in 2- to 3-week-old calves medicated with trimethoprim sulfadiazine (in a 1:5 ratio) for 5 days 24 hours following *S.* Dublin oral challenge was reduced.[553] Administration of either sulfadiazine or trimethoprim alone did not reduce mortality.[553] TMS may be used to treat sepsis in neonatal calves, but its half-life rapidly declines as rumen function develops. In ruminating (6- to 8-week-old) calves, subcutaneous or oral administration of trimethoprim sulfa leads to high serum levels of sulfadiazine but little or no serum trimethoprim.[558]

Intramuscular administration of amoxicillin reduced mortality in *S.* Dublin–challenged calves.[559] In a comparative trial of amoxicillin and trimethoprim sulfadiazine, both drugs were found to have equal efficacy in reducing adverse clinical signs of disease when dosage regimens were based on the MIC of the pathogen.[560]

The frequency of bacteremia is sufficiently high such that treatment of calves with diarrhea that are severely ill (as manifested by reduced suckle reflex, greater than 6% dehydration, weakness, inability to stand, or clinical depression) should include routine treatment against bacteremia, with emphasis on treating potential *E. coli* bacteremia.[543] Parenteral administration of a broad-spectrum β-lactam antimicrobial—ceftiofur (5 mg/kg IM q24h), amoxicillin (10 mg/kg IM q12h), or trimethoprim sulfadiazine (20 mg/kg sulfadiazine with 5 mg/kg trimethoprim IV or IM, q24h for 5 days)—is recommended for treating calves with diarrhea and systemic illness. (Note that these are off-label doses and require an extended meat-withholding period.) Antimicrobial therapy is not recommended for calves with diarrhea and no systemic illness (normal appetite for milk or milk replacer, no fever).[543]

Antiprotozoal Drugs

Drugs reported to have some efficacy against cryptosporidia in calves include halofuginone,[561-567] paromomycin,[568,569] azithromycin,[570] decoquinate,[571,572] and β-cyclodextrin.[573] Halofuginone appears to be the most efficacious. A meta-analysis of 15 cohort and clinical studies showed that prophylactic use of halofuginone delayed the shedding of *Cryptosporidium* with a lower prevalence of shedding at days 4 and 7 but a higher prevalence at day 21 when treated calves were compared with controls.[574] Prevalence of diarrhea was also lower on days 4 and 7 in treated calves. The efficacy of decoquinate is questionable with the only controlled clinical study failing to demonstrate a beneficial therapeutic effect with daily treatment at 2 mg/kg/day.[572] Lasalocid has been trialed for treatment of cryptosporidia. With a toxic dose of 8 mg/kg, it was found to reduce the shedding of cryptosporidia; however, the calves suffered adverse side effects. At a dose of 0.8 mg/kg, lasalocid was not effective.[575] The registered dose for preventing coccidiosis in calves is 1 mg/kg/head/day.

Coccidiosis is uncommon in calves less than 6 weeks of age. In hand-reared calves, coccidiostats (lasalocid, amprolium, or decoquinate) may be added to milk replacer. Prophylactic options for beef calves are restricted to coccidiostat-medicated pellets (monensin, lasalocid, amprolium, or decoquinate) or water (amprolium or sulfonamides). Therapeutic options include amprolium or sulfonamides such as sulfadimidine.

Both fenbendazole (5 mg/kg once daily for 3 days PO) or albendazole (20 mg/kg once daily for 3 days PO) have been shown as effective treatments for *Giardia*.[288,369,576] Because of the high level of subclinically affected animals, all cows and their dams need to be treated and reinfection is likely to occur unless calves are removed from environmental sources of infection.

Antiinflammatory Drugs

The benefit of routine administration of an NSAID could be due to their analgesic, antiinflammatory, or antipyretic properties. Meloxicam has been shown to increase feed intake, hydration score, and fecal consistency and to decrease signs of visceral pain when given at the onset of diarrhea.[577,578] A nonstatistical trend toward decreased morbidity has been reported in a study evaluating the benefits of a single or double injection of flunixin meglumine in scouring calves.[579] The routine administration of a corticosteroid to calves with diarrhea is not recommended because corticosteroids suppress the immune system and diarrheic calves have been shown to have high levels of plasma cortisol compared with healthy calves.[580]

Probiotics

Probiotics are a food or drug containing live microbes that are expected to confer beneficial physiologic effects to the host animal through microbial actions. Bacterial and fungal species included in these products include *Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium bifidum, Enterococcus faecium, Streptococcus salivarius* subsp. *thermophilus, Aspergillus oryzae,* and *Candida pintolopesii*. General mechanisms of action that have been prescribed to probiotics include competition for receptor sites on the intestinal surface, immune system stimulation, excretion of antimicrobial substances, and competition with pathogens for intraluminal nutrients.[581]

The number of controlled clinical trials evaluating probiotic formulations in calves is limited. In one report feeding antimicrobial-resistant *Streptococcus faecalis* to calves reared on an antibiotic-containing diet reduced *Salmonella* intestinal colonization of calves.[582] An improvement in weight gain and a reduction in diarrhea have been reported when calves were fed either 3×10^9 *Bifidobacterium pseudolongum* or *Lactobacillus acidophilus* daily from 1 to 56 days of age or a cell mixture containing 10^{10} colony-forming units (cfu) of *Bacillus thermophilum,* 10^{10} cfu of *E. faecium,* and 10^9 cfu of *L. acidophilus* for 28 days.[583]

OLIGOSACCHARIDES. Oligosaccharides are sugar polymers that are present in cows' milk and competitively bind to K99 fimbriae from enterotoxigenic *E. coli*.[584] The prophylactic addition of exogenous oligosaccharides to milk replacer resulted in similar fecal scores seen in calves fed milk replacer–containing antibiotics.[585] Overall, there are insufficient data to recommend the routine administration of oligosaccharides to calves with diarrhea.

Intestinal Protectants

A number of products that include intestinal protectants are marketed for treatment of calves with scours. Intestinal protectants

include bismuth subsalicylate, kaolin or pectin, and activated charcoal. No efficacy data are available regarding the use of kaolin in scouring calves. Suggested advantages of bismuth subsalicylate are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity.[586,587] The results of one prospective study indicated that the aforementioned nonantibiotic treatments for calf diarrhea resulted in a longer duration of treatment and increased morbidity and mortality when compared with medicated milk replacer and parenteral antibiotic treatment.[588]

GASTROINTESTINAL MOTILITY MODIFIERS. Drugs that inhibit gastrointestinal motility (such as hyoscine *N*-butyl-bromide) are contraindicated because reduction in intestinal motility potentially leads to the buildup of pathogenic bacteria and toxins.

Prognosis

The prognosis for recovery decreases with the severity of depression. Severe hypothermia and the presence of intercurrent disease are grounds for a guarded prognosis.[589-591] An initial examination should be performed. Calves with a primary problem of septicemia carry a guarded prognosis.

Summary

Calf scours is caused by a variety of infectious agents. At the present time, the need to make a definitive diagnosis of enterotoxigenic *E. coli* and salmonella infections has been established; these diseases can be controlled by antibiotics and prevented by vaccination.[592] There are public health implications to the diagnosis of cryptosporidiosis and salmonellosis. Vaccination may help control rotavirus and coronavirus infections. Treatment of neonate diarrhea is primarily based on correcting dehydration and acidosis through the use of oral and intravenous electrolytes. Only in the case of bacterial infections can direct action be taken against the invading organism, but antibiotics may still be useful in preventing secondary bacteremias. Good colostrum management helps reduce the risk of neonatal diarrhea. Management is very important in the control of diarrhea, and since infectious agents are almost always present at some exposure level, the underlying theme is to minimize the level of pathogen exposure and stress on the calf. In approaching a problem of neonatal death losses, the areas to be examined should include calf immunoglobulin status, calf feeding, calf housing, cleanliness of environment, calving area, cow vaccinations, diagnosis of specific infectious agents, and treatment protocols.

Lameness and Reluctance to Walk

John K. House

Septic Arthritis

Septic arthritis may result from direct trauma or contamination of the joint, by extension from periarticular infection, or via hematogenous spread from another site. Systemic sites of infection include enteritis, pneumonia, and inflamed umbilical structures. FPT increases the risk of sepsis. Destruction of the epiphysis and extension of infection into the joint may be primary in some cases, rather than starting as a primary synovial membrane infection that spreads to the epiphysis/physis. The most common pathogens isolated from septic joints of neonatal calves are enteric organisms including *E. coli* and *Salmonella* spp. *Streptococcus* spp., *Staphylococcus* spp., and *Trueperella pyogenes* are less common isolates. *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is the most frequently isolated organism from the joints of older calves.[593-595] Vertebral body osteomyelitis is another manifestation of hematogenous bacterial spread with localization of bacteria in the vertebral veins. The presumed origin of the bacteremia most frequently is from pulmonary or umbilical infections in calves and tail docking wounds in lambs.[596] The etiologic agent usually is *T. pyogenes* or *Fusobacterium necrophorum,* alone or as part of a mixed infection.[597] The clinical signs vary depending on location of the compressive abscess. Affected animals often have clinical signs pertaining to other body systems (e.g., coughing, diarrhea, decreased weight gain compared with herdmates) before the onset of neurologic signs. The diagnosis of vertebral osteomyelitis is made by history, clinical signs, laboratory findings suggestive of chronic infection (elevated fibrinogen, globulin, and neutrophil count), and radiographs that demonstrate the affected vertebrae. Spinal fluid analysis is variable, but in most cases, it is normal or has a pleocytosis (macrophages and some neutrophils) caused by chronic inflammation of the dura mater.[596]

Bacteria commonly isolated from septic joints in lambs include *Streptococcus* spp., coliforms, *Trueperella pyogenes, Erysipelothrix rhusiopathiae,* and *Fusobacterium necrophorum*.[455] Predisposing factors include poor docking hygiene and contaminated sheep dip. Sporadic outbreaks of polyarthritis in lambs, kids,[61,598,599] and calves[600] are associated with *Chlamydia* and *Mycoplasma* spp. infections. Chlamydia infections may occur in utero or postnatally; mycoplasma infections often result from ingestion of mycoplasma-contaminated milk.

Diagnosis of septic arthritis is based on the combination of clinical signs, radiographic examination, bacterial culture, and cytologic analysis of synovial fluid. A bacterium is isolated in only 60% of cases of septic arthritis in bovine medicine.[601] Synovial fluid cytologic analysis is useful for the differentiation between infectious and noninfectious arthritis. Trauma is the chief differential. Lambs and kids with septic arthritis often fail to nurse and may present with significant weight loss. Typically polyarthritis caused by *Mycoplasma* spp. and *Chlamydia* is associated with high fevers and respiratory and occasionally neurologic disease. High morbidity and mortality are common. Conjunctivitis is commonly observed with chlamydial infections.[598] Cytologic findings consistent with septic arthritis include a synovial fluid total protein concentration greater than 4.5 g/dL, a nucleated cell count greater than 25,000 cells/mL, a polymorphonuclear cell count greater than 20,000 cells/mL, and percentage of polymorphonuclear cells of greater than 80%.[602] Chlamydial inclusions may be found in Giemsa-stained smears of synovial cells and the organism isolated from joint fluid or plasma in early cases.[598] Isolation of *Mycoplasma* spp. requires specific media (Hayflick media) and microaerophilic conditions. Normal synovial fluid does not rule out septic physitis or osteomyelitis, because the infection may be in the physis or small tarsal bones.

Careful examination of high-quality radiographs is important for the detection of bone lysis indicating infection. Initial radiographs may be normal because the degree of damage is often not detectable for 10 to 14 days after initial infection occurs. Radiographic features of septic arthritis include soft tissue swelling, widening or collapse of the joint space, osteoporosis, and osteosclerosis. Ultrasound may be used to confirm involvement of the joint and rule out periarticular or tenosynovial infection to avoid iatrogenic contamination of the joint during arthrocentesis. Joint distention and hyperechogenic fragments in the synovial fluid are suggestive of septic arthritis. Normal synovial fluid is anechoic.

Acute septic arthritis in neonatal ruminants may be treated effectively via joint lavage combined with systemic and local antimicrobial treatment. Typically, however, neonatal ruminants are presented with a chronic disease process. Treatment options include joint lavage or arthrotomy to remove destructive inflammatory products and long-term antimicrobial therapy. Joint lavage is rarely efficacious in the treatment of chronic septic arthritis in calves because accumulation of fibrin and pocketing of purulent material often make adequate joint drainage impossible.[603] Joint lavage may be facilitated via use of a rigid arthroscope or, in the case of simple joints (elbow and stifle), arthrotomy.[604] Empirical antimicrobial therapy should include a

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gram-negative and gram-positive spectrum. Culture of synovial fluid facilitates antimicrobial selection.

Therapeutic synovial concentrations of penicillin, oxytetracycline, ampicillin, and cefapirin can be attained in inflamed and normal joints of calves following systemic administration.[605-608] The distribution of trimethoprim sulfadiazine, penicillin, oxytetracycline, and cefapirin in joints is not enhanced or reduced by inflammation.[605-607] Penicillin, trimethoprim, and sulfadiazine equilibrate in 0.5 to 1 hour, and oxytetracycline in 4.5 to 6 hours.[606] The subsequent decline in antibacterial drug concentration in synovial fluid parallels that in serum.[605] Synovial inflammation accelerates distribution of antimicrobial drugs into joints[606] but has little effect on the peak drug concentration achieved in synovial fluid.[605,606] The peak concentration of ampicillin in synovial fluid following a single intramuscular injection of ampicillin trihydrate at a dosage of 10 mg/kg is higher in normal and inflamed synovial fluid than in sera.[608] There is a paucity of bovine derived data regarding the distribution of the newer generation antimicrobials into synovial fluid following systemic administration. Studies in other species suggest that most classes of antibacterial drugs are capable of crossing the synovial membrane. Synovial tissue is very vascular and does not have a basement membrane. In humans, synovial fluid concentrations of most antibacterials generally average at least 60% to 70% of serum drug concentrations at the time of peak serum concentrations and frequently exceed those in serum immediately before the subsequent systemic dose in patients with septic arthritis.[609] Antimicrobial dosing is targeted to achieve a peak antibacterial concentration that exceeds the MIC of the infecting organism by fivefold to tenfold.[609] The duration of therapy is dependent on the antimicrobial sensitivity of the pathogen and the immune status of the patient; prolonged (4 to 8 weeks) antimicrobial therapy is commonly required.

In a review of 81 cases of septic arthritis in cattle, a 72% recovery was achieved with a combination of surgical treatment (opening of the joint capsule; débridement; and excision of the synovium, infected cartilage, and bone), joint immobilization, and systemic antibiotic therapy. Of cattle treated conservatively with systemic and intraarticular antimicrobials, 43% recovered.[610]

Noninfectious Lameness

Neonatal ruminants with nutritional myodegeneration often have a stiff, stilted gait. Lambs and kids may have difficulty nursing if they are unable to lift their head and may cry with pain when assisted to stand (see Chapter 42).

Contracture of joints or tendons of the limbs produces difficulty in movement and predisposes to FPT by impeding the ability to adequately nurse. Degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis. Conservative therapy consisting of splinting the front limbs to induce tendon laxity may be helpful. Calves with severe digital flexor tendon contractures often require surgical resection of one or both digital flexor tendons, followed by bandaging or casting and stall rest for 3 to 4 weeks.

Peripheral nerve injuries may occur as a result of dystocia, trauma, or injection site reactions causing damage to peripheral nerves in the proximity of the injection site. The femoral nerve and brachial plexus are more commonly affected in calves. Femoral nerve damage is usually a result of stretching the nerve during a "hip lock" dystocia. Clinical signs of femoral nerve paralysis include the inability to extend the stifle and advance the limb and analgesia of the medial aspect of the limb down to the tarsus. Atrophy ("dished-out appearance") of the quadriceps is noticeable in 7 to 10 days if there is complete tearing of the femoral nerve.[596] Atrophy of the quadriceps predisposes to patella luxation. Complete or partial avulsion of the brachial plexus has also been observed in calves following dystocia.[611] The clinical presentation will depend on the severity of the injury. Clinical signs include abnormal positioning of the limb, abnormal locomotion, paresis, muscle atrophy, hyporeflexia, and sensory loss.[596]

Umbilical Enlargement

The umbilicus consists of three types of structures and undergoes functional and anatomic changes at birth. Two umbilical arteries connect internal iliac arteries to the placenta. These later regress and become the round ligaments of the bladder. One umbilical vein connecting the placenta to the liver and porta cava regresses to become the round ligament of the liver within the falciform ligament. The urachus connects the fetal bladder to the allantoic cavity.

Patent Urachus

Patent urachus is a persistence after birth of the tubular connection between the bladder and umbilicus. The urachus drains the bladder into the allantoic sac during gestation. Urine flow should gradually change, with some urine entering the amniotic sac through the urethra in later gestation. At birth, with umbilical cord rupture the urachus should be closed, and urine should be voided through the urethra. Neonates with a patent urachus may dribble urine from the urachus during or after urination or may simply present with a constantly wet umbilical stump.

Differentials include concurrent infection of the navel (omphalophlebitis). Ultrasound may assist the diagnosis and determine the involvement of umbilical arteries or vein. Moist hairs around the umbilicus and visualization of fluid coming from the navel are diagnostic. A complete physical examination should be performed. If abnormalities are noted, serum IgG, complete blood cell count, and urinalysis are helpful for detecting susceptibility to infection and presence of systemic or urinary tract infection. Surgical resection of the urachus to the tip of the bladder is the treatment of choice. Associated arteries and veins should be ligated and removed if they are infected or necrotic. Merely ligating the exterior stump can trap organisms and cause infection.

Omphalitis

Omphalitis is inflammation of umbilical structures that may include the umbilical arteries (omphaloarteritis), umbilical vein (omphalophlebitis), urachus, or tissues immediately surrounding the umbilicus. Umbilical abscess or infection of any of the three components of the umbilicus may produce local infection or be a source of septicemia. The source of infection is most commonly the external environment, coupled with failure of passive transfer. Bacteria isolated from calf umbilical cord remnant infection include *T. pyogenes, E. coli,* and *Proteus* and *Enterococcus* spp. The urachus is the most commonly affected structure in calves and the umbilical arteries the least.[612] Omphalophlebitis may extend the length of the umbilical vein into the liver and result in liver abscessation.

When the umbilicus is enlarged and draining purulent material, infection is easily noted. When the urachus is fixed to the abdominal wall, calves are prone to cystitis and may show signs of pollakiuria and dysuria. In other cases the umbilicus may be dry and larger in diameter than expected. In addition, neonates may have a completely normal-appearing, dry external navel and be severely ill from infection of the urachus, umbilical arteries, or vein. In a septic neonate without external signs of infection, involvement of the umbilicus can be difficult to determine. Abdominal palpation of the umbilical vein and arteries is a useful simple effective means of assessing their size and for detecting pain associated with these structures. Inflamed structures may be identified by standing behind the neonate and pressing the hands together above the umbilicus. Ultrasound is also a useful ancillary diagnostic aid.[613] Persistent dilation of the umbilical vein or arteries with a hypoechoic-to-echogenic fluid, intraluminal gas, and wall thickening are findings consistent with infection. In calves the urachus normally retracts up into the abdomen at birth, and ultrasonographic identification of a urachal remnant is abnormal.[614]

Overt signs of infection are heat, swelling, purulent discharge, or pain. Concurrent signs of systemic infection such as joint infection,

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pneumonia, diarrhea, meningitis, or uveitis may be noted. Calves with urachal abscesses may show signs of dysuria or pollakiuria.[615,616] Infection in more than one umbilical vessel in the neonate is common, and urachal involvement is frequent. Umbilical abscessation that is walled off and does not involve deeper structures is a less severe problem and may be treated with drainage without surgical removal of the entire umbilicus.

Early treatment with antibiotics and supportive care may allow resolution before development of abscessation and distention of the urachus or the umbilical arteries and vein. Established infection usually requires surgical removal of involved structures in addition to medical therapy.[612] When omphalophlebitis extends into the liver, the umbilical vein may be marsupialized to facilitate drainage and flushing.[617] Prognosis is improved when adequate passive transfer of colostral immunoglobulins has occurred and when joints or other structures are not involved. Sequelae such as renal abscessation, joint or bone infection, peritonitis, and other complications described for septicemia may develop if therapy is started too late or discontinued prematurely.

Anemia

Anemia in the neonate should be interpreted in the context of the realization that normal hematologic values of the neonate may vary from those of the adult. In calves the incidence of anemia (hemoglobin <10 g/dL) is quite high, ranging from 15% to 30% in many herds, and is normocytic, normochromic, and poikilocytic.[618,619] Anemia is reported to be a result of iron deficiency.[618,619] Potential causes are reduced amounts of iron in milk, poor placental transfer of iron, or decreased intestinal absorption. Anemic calves with poikilocytosis have similar levels of serum iron, total iron binding capacity, and marrow iron and plasma copper levels compared with normal calves.[620] Anemic calves do not appear to have an increased incidence of disease or decreased growth rates.[621] An overall higher plane of nutrition versus iron supplementation alone produces higher PCVs and hemoglobin levels.[620] Calves less than 6 weeks of age have three types of hemoglobin in various amounts: adult, 28%; fetal, 40%; and neonatal, 25%. The poikilocytosis may be a function of erythrocyte membrane defects or maturation transitions.[620]

In addition to frank blood loss from an injury, diseases causing anemia in the neonate include neonatal isoerythrolysis (NI), non-NI immune-mediated hemolytic anemia,[622] blood loss caused by gastric ulcer, anemia resulting from bone marrow necrosis, and anemia of chronic disease associated with localized infections. Hemolytic disease of newborn calves is uncommon but has occurred after vaccination of pregnant cows against anaplasmosis or babesiosis. The presence of red cell antigens in the vaccine causes the production of antierythrocyte antibody, primarily against the A and F systems.[623] Cows mated to bulls carrying these red cell antigens may have hemolytic disease develop in their A- and F-positive calves after ingestion of colostrum-containing alloantibodies.

Hemolytic disease processes produce signs of weakness, pale or jaundiced mucous membranes, fever, and depression. Blood loss produces weakness and pale mucous membranes. Intestinal parasitism does not normally lead to anemia during the neonatal period. Intravascular hemolysis may produce hemoglobinuria and hemoglobinemia. Icterus develops when the ability of the liver to conjugate bilirubin is exceeded. Mainly, indirect bilirubin is elevated. Anisocytosis is observed in responsive anemias. Nonspecific stimulation of bone marrow may produce a leukocytosis. Anemia has also been reported in calves infected with BVDV as a result of bone marrow necrosis.[624]

Determination of the nature of the anemia may allow specific treatment. Blood transfusion may be indicated when anemia develops rapidly or PCV drops below 14%. Associated conditions such as metabolic acidosis and hypoglycemia should be corrected. Anemia of chronic disease requires correction of the primary disease condition.

Fever

Differentials for fever in neonates include bacterial or viral infections, excitement, seizures with subsequent generation of heat by muscular overactivity, and environmentally induced hyperthermia. Fever is an unreliable indicator of sepsis in neonatal calves.[19] Septic neonates often have a normal or subnormal temperature. Older ruminants with localized infection such as in joints or bone are more likely to have fever. Fever may be beneficial. The need to administer antipyretics to the febrile neonate is controversial. Body temperatures lower than 40.8° C (105.4° F) are not considered detrimental unless they are associated with heat stroke or seizures,[625] in which case cooling and antipyretics are indicated. Because many antipyretics are antiprostaglandins that can cause deleterious gastrointestinal and renal effects, these agents should be used judiciously. Correction of the initiating cause and maintenance of fluid balance are also important.

Cyanosis

Cyanosis is the purple-blue coloration observed on mucous membranes or skin caused by reduced or poorly oxygenated hemoglobin in blood.[626] Cyanosis may be caused by congenital heart disease, respiratory impairment, or any circulatory condition producing a right-to-left shunt (Box 20-4). The degree of cyanosis depends on the arterial oxygen saturation, hemoglobin concentration, pH, peripheral circulation, and temperature of the neonate.[626] Shock and hypothermia are important causes of peripheral cyanosis. The affinity of hemoglobin for oxygen is reflected in the standard oxyhemoglobin dissociation curve. This curve is similar for neonates but is affected by the amount of 2,3-diphosphoglycerate (DPG) in the erythrocyte. Calves' erythrocytes have higher levels of 2,3-DPG, but the higher levels do not affect the affinity of hemoglobin for oxygen. A separate fetal hemoglobin exists in calves to increase affinity for oxygen.[627] Severe hypothermia and acidosis cause the oxygen dissociation curve to shift to the right and therefore contribute to tissue hypoxia.

BOX 20-4

Causes of Cyanosis

Cardiovascular Origins

Tetralogy of Fallot
Tricuspid atresia
Truncus arteriosus
Pentalogy of Fallot
Double outlet right ventricle
Single ventricle
Eisenmenger complex
Ventricular septal defect
Patent ductus arteriosus

Respiratory Causes

Alveolar hypoventilation
Drug-induced central nervous system (CNS) depression
CNS trauma or hemorrhage
Hypoglycemia or hypocalcemia
Altered neurologic function of spinal nerves (of respiratory muscles)
Thoracic cage abnormalities: pneumothorax, fractured ribs
Diaphragmatic hernia
Upper airway obstruction
Restrictive pleural space disorders: hemothorax, pleuritis
Hypoplastic lung

Impaired Diffusion

Pulmonary: pneumonia, edema, atelectasis
Shunting
Anatomic (congenital heart defects)
Pathologic: pulmonary hypertension
Ventilation-perfusion mismatch

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Cyanosis can be either central or peripheral.[626] Peripheral cyanosis results from increased peripheral extraction of oxygen from normally saturated blood or a significant decrease in the perfusion to an extremity.[626] In the neonate, causes include septic shock and severe hypothermia. Central cyanosis is more common in neonates and is related to congenital heart disease that causes right-to-left shunting or severe respiratory conditions that result in hypoxia. Examination and clinical pathologic evaluation for metabolic causes of cyanosis, hypothermia, and cardiac abnormalities should be conducted. History, medication use, auscultation, thoracic radiographs, and arterial blood gases are useful in determining the degree of the respiratory component to cyanosis. Echocardiography may be required for identification of cardiac anomalies.

Heart Murmur

Heart murmurs in the neonate may be heard normally before physiologic closing of the ductus arteriosus during the first 1 to 5 days of life. Other causes for murmurs include congenital anomalies, severe anemia, or infectious valvular disease. Physical examination for other signs of heart disease helps determine the severity of the murmur. Jugular pulse, weak or irregular arterial pulse, and palpable thrill indicate a serious condition. Dyspnea, cyanosis, tachypnea, and failure to gain weight are common signs of congenital heart disease in calves. Timing and location of the heart murmur should be determined. Thoracic radiography may aid in determining heart size and in detecting pulmonary edema or distended pulmonary vessels. Echocardiography may reveal atrial or ventricular enlargement, thickened ventricular walls, anomalous orientations of outflow tracts, or ventricular septal defects (VSDs).

Patent ductus arteriosus produces a continuous murmur localized over the left heart base. The diastolic component may not be heard with auscultation over other parts of the heart. As pulmonary hypertension develops, the murmur is shortened to a holosystolic type with normal arterial pulse. Large shunting of blood produces a bounding arterial pulse caused by wide fluctuations of systolic and diastolic pressures. Radiographs may reveal an enlarged heart with increased vascularity caused by left-to-right shunting of blood. Echocardiography may reveal an increased left atrial and left ventricular diastolic dimension/volume and hyperdynamic septal and left ventricular wall systolic motion (depending on the degree of right-to-left shunt).

VSD produces a large, harsh, holosystolic murmur that is heard loudest on the right cranial region of the thorax and is softer over the left heart base. Radiography may reveal heart size increase, left atrial enlargement, and dilated pulmonary vasculature. Two-dimensional echocardiography may show aortic and septal discontinuity. Injection of saline bubbles into the left ventricle and observation of bubbles in the right atrium or ventricle document a left-to-right shunting of blood. Tetralogy of Fallot or other types of complex malformations often produce loud murmurs and are associated with cyanosis, weakness, fatigue, and stunted growth. Tetralogy of Fallot produces a systolic ejection murmur heard at the left heart base. Echocardiography may reveal a thickened right ventricular wall, septal echo dropout in the area of the VSD, rightward displacement of the aortic root, and an abnormal pulmonary outflow region. Saline injection into the jugular vein demonstrates right-to-left flow from the right ventricle to the left ventricle or the aorta.

Icterus

Icterus is a relatively uncommon finding in neonates; it may be observed with sepsis, anorexia, liver disease, and hemolytic anemia. Liver disease in the neonate may be caused by exposure to hepatotoxins, by sepsis-producing bacterial hepatitis, or as a result of hypoxia. *C. perfringens* type A has been implicated in an enterotoxemic condition in nursing lambs, kids, and calves characterized by icterus, hemoglobinuria, anemia, and intravascular hemolysis.[88]

Failure to Thrive: Cachexia and Weak Calf Syndrome in Beef Calves

John Maas

In calves the weak calf syndrome has been reproduced by feeding low-protein diets to prepartum cows that subsequently calved in environments in which the temperature was well below the thermoneutral zone for calves.[628] The dietary recommendation for crude protein (CP) intake for third-trimester pregnant cows and heifers is 0.9 kg (2 lb) of total CP/day. This is particularly important for heifers and cows calving early in the spring calving season when temperatures well below freezing can occur. Cold rains, however, can also produce the hypothermic conditions that aid in precipitating this syndrome.

Cows weighing 450 kg (1000 lb) therefore need to consume 9.9 kg (20 lb) dry matter of good- to excellent-quality hay that is 10% CP or more. A quadratic equation has been developed to predict CP intake of the dams if their serum total proteins, urea nitrogen, and creatinine are known.[629] This equation predicts the daily CP intake on a continuing basis.

$$\text{Daily CP consumption (kg)} = 0.1806 + 0.04327\,(\text{BUN}) - 0.33497\,(\text{creat}) + 0.06963\,(\text{TP}) - 0.00025\,(\text{BUN})^2 + 0.06049\,(\text{creat})^2 - 0.00666\,(\text{BUN} \times \text{creat})$$

where *BUN* is serum urea nitrogen (mg/dL), *creat* is serum creatinine (mg/dL), and *TP* is serum total protein (g/dL).

Also, the use of this formula could predict CP intake for pregnant heifers and pregnant cows. This relationship may prove to have important clinical applications when weak calf syndrome or protein-calorie malnutrition is suspected and the gestation diet of the dams is not available for analysis (as under some range conditions). Supplements such as molasses licks that contain urea may tend to overestimate CP intake.[630]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Colostrum and Milk Replacers

SANDRA GODDEN and ROBERT E. JAMES, *Consulting Editors*

The goals of colostrum and milk feeding programs for preweaned calves and small ruminants are to achieve optimal rates of gain, support and develop a strong immune system, maximize health, and stimulate ruminal development—all in a cost-effective manner. Although feeding high-quality, clean maternal colostrum and whole milk may be considered by many to be gold standards, the use of high-quality colostrum replacement products and milk replacers may be attractive to producers for a variety of reasons, including for consistency, for convenience, as a means of breaking the transmission cycle of some infectious diseases, or simply to capture economic efficiencies. This chapter reviews important considerations in the manufacture, selection, and use of high-quality colostrum replacement and milk replacer products.

Colostrum Supplements and Replacements

The principles of colostrum management are reviewed in Chapter 19. Although feeding 3 to 4 L of clean, high-quality maternal colostrum shortly after birth remains the gold standard, farms can experience periods when an adequate supply of high-quality fresh or stored maternal colostrum is not available. Also, it may not always be practical or convenient to harvest first milking colostrum from fresh cows within a timely manner after calving (<1 to 2 hours). Contributing to this shortage, some producers may discard colostrum from cows testing positive to such pathogens as *Mycobacterium avium* subsp. *paratuberculosis* or *Mycoplasma bovis*.[1-3] Under such circumstances, feeding commercially available colostrum supplement (CS) or colostrum replacement (CR) products may offer a simple, consistent and convenient means of delivering the necessary immunoglobulins (Ig) to newborn calves while reducing the risk of pathogen exposure. The following section discusses types of CS and CR products, manufacture and licensing, evaluation of product efficacy (e.g., IgG dose, efficiency of IgG absorption, passive transfer levels, calf health and performance), impact of Ig source on antibody profiles, monitoring of passive transfer, and use of CR or CS products in minor species. Although some studies have demonstrated that supplementation of the milk diet with Ig from either maternal colostrum or CS may reduce the severity of rotavirus or coronavirus scours occurring during the first 14 days, the current discussion is limited to use of CS and CR products in the first 24 hours after birth.[4-6]

Colostrum Supplements versus Colostrum Replacements

Colostrum supplements, which typically cost between $9 and $18 USD per dose, are designed to provide exogenous IgG to calves to supplement poor-quality maternal colostrum (colostral IgG < 50 g/L).[7] Most CSs provide between 25 and 60 g of IgG per dose, which is reconstituted in 1 to 2 L of water. Feeding one dose of a CS will not provide a sufficient mass of IgG to prevent failure of passive transfer (FPT) in young calves, nor will it provide sufficient levels of nutrients necessary for calf survival or optimum growth.[7,8] By comparison, CR products, which typically cost between $25 and $40 USD per dose, are designed to be fed instead of maternal colostrum. They should provide a minimum of 100 g of IgG per dose and should provide sufficient levels of nutrients to the calf. It is recommended that CS or CR products be mixed in water, according to the manufacturer's label directions, and fed as a separate meal after any natural colostrum has been fed.[9]

Manufacturing

Immunoglobulins in commercial CR and CS products are most often derived from spray-dried bovine colostrum or spray-dried bovine serum. For colostrum-derived CR products, fresh-frozen bovine colostrum is collected from grade A dairies and assembled at a manufacturing plant where it undergoes testing for IgG concentration, pooling, heat treatment, spray drying, and then packaging. The concentrations of most non-Ig colostral components (e.g., nutrients, hormones, growth factors), with the exception of cellular fractions (i.e., leukocytes, bacteria), will be similar in colostrum-derived CR products compared with maternal colostrum. For serum-derived CR or CS products, blood is collected from abattoirs under USDA inspection, centrifuged to separate plasma and/or serum from red blood cells, ultrafiltered, spray dried to produce a concentrated powder containing approximately 20% Ig, and then mixed with other ingredients (e.g., lactose, dry fat blend, dextrose, vitamin/mineral premix). The final product may be irradiated. Exact manufacturing methods will vary among manufacturers and products.

Is the Colostrum Replacer or Colostrum Supplement Licensed?

In Canada, it is required that all CR products are licensed through the Canadian Food Inspection Agency (CFIA) Center for Veterinary Biologics (CVB, Ottawa, Ontario, Canada).[10]

Serum- or plasma-derived CR or CS products are not permitted in Canada. In the United States, only some manufacturers have acquired a license through the U.S. Department of Agriculture (USDA) Center for Veterinary Biological Products (CVB, Ames, IA). To attain a CVB license and label for prevention or treatment of FPT of Ig, the IgG in U.S. CR products must come from bovine colostrum collected from grade A dairies, must be processed by heat treatment or ionizing radiation using accepted protocols, and must undergo regular purity, potency, and efficacy testing.[11,12] Purity requirements allow a specified total bacteria count. However, coliforms, *Salmonella* spp., and fungi may not be present. Potency tests require a minimum IgG content for FPT products as determined by a validated radial immunodiffusion (RID) kit or assay. Efficacy testing for FPT products requires that, in 90% of animals, the increase in IgG concentration (pretreatment vs. 24-hour posttreatment) must be at least equal to concentration of the IgG Species Standard approved by the USDA's Animal and Plant Health Inspection Service (APHIS) (e.g., ≥10 mg/mL serum IgG for neonatal calves) (USDA: 9CFR 113.450; 9CFR 113.499).[11] Samples of product from every serial release (batch) are

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submitted to a central CFIA or USDA laboratory for testing. Also, the overseeing regulatory body completes annual site inspections to review processes and records. As such, licensed products can guarantee safety, potency, efficacy, and traceability. Table 21-1 (Section A) lists CVB-licensed products currently available in Canada and the United States.

Although products that do not have a USDA Veterinary Biologics license are not legally able to claim to supply IgG or to purport to be used as either CS or CR for prevention of FPT, their use for this purpose is widespread in the United States. The Ig in nonlicensed products is technically not considered a feed but is being used in feeds. As such, these products fall under Association of American Feed Control Officials (AAFCO) guidelines (www.aafco.org). Under AAFCO guidelines, every state (i.e., local State Department of Agriculture) adopts and regulates its own animal feed per its applicable laws and regulations. Feed testing programs are in place and regulated in Canada. In the United States, there is a system to identify feed products, but there currently is no system to regulate them through the USDA, FDA, or the State Departments of Agriculture. Although all U.S. manufacturers of non-CVB licensed CR and CS products will conduct some kind of internal quality control testing, these programs are at the manufacturer's discretion. External product testing or plant inspections by regulatory authorities (e.g., State Department of Agriculture) are not typically completed for non-CVB licensed products unless a problem or complaint is brought to their attention. Table 21-1 (Sections B and C) lists some of the many non-CVB licensed CR and CS products available in the United States.

Evaluating the Efficacy of Colostrum Replacement Products

Producers are strongly encouraged to select CR or CS products that have undergone independent evaluation of efficacy in controlled field studies. Evaluating efficacy should ideally consider passive transfer of adequate IgG, nutritional support, and calf health and performance. Passive transfer of IgG will be primarily determined by the dose of IgG (in grams) administered as well as the efficiency of absorption of IgG. Each product must be independently evaluated, since differences in manufacturing processes can have a significant impact on both apparent efficiency of absorption percentage (AEA %) and final dose of IgG in a package.[13,14] Head-to-head studies are necessary to make valid comparisons among products. Table 21-2 presents the results of field efficacy studies for commercially available CR and CS products that were mixed and fed according to label directions.

DOSE OF IgG PROVIDED. Although experts originally estimated that producers should feed a minimum mass of 100 g of IgG in the first colostrum feeding, more recent studies have shown that at least 150 to 200 g of colostral IgG must be fed to consistently achieve acceptable passive transfer (APT) rates (serum IgG ≥ 10 mg/mL) in the majority (≥90%) of calves.[15-18] This dose effect was demonstrated in one study wherein three groups of calves fed either 100 or 200 g of IgG in a colostrum-derived CR product or 3.8 L of fresh maternal colostrum achieved a mean serum IgG concentration at 24 hours of 9.6 mg/mL (46% with FPT), 19.0 mg/mL (0% with FPT), or 20.7 mg/mL (9% with FPT), respectively (see Table 21-2).[18] Although many CR products are packaged to provide 100 to 130 g IgG per dose, some CR products now provide a larger mass of IgG per dose and/or provide label directions that suggest feeding increased masses of IgG.

APPARENT EFFICIENCY OF ABSORPTION (AEA %) OF IGG. Grams are more important than percentages; under most circumstances, the total dose (g) of IgG fed will be the most important predictor of APT in calves fed CR products. That said, simply examining the mass of IgG provided by the CR is not an adequate predictor of product efficacy.[19] There can be significant differences in AEA % among products resulting from, but not limited to, such factors as manufacturing methods and quantity, the type of other nutrients or additives, and the age (in hours) at which the calves were fed. The apparent efficiency of absorption (AEA %) is the percentage of IgG administered that is absorbed systemically.[13] To calculate AEA %, one needs to know the serum IgG (mg/mL is equal to g/L), the grams of IgG originally fed (estimated from testing the maternal colostrum or indicated on the label of the CR or CS fed), and the weight of the calf (in kilograms) from which the plasma volume is estimated (e.g., plasma volume in liters = 9.1% of body weight in kg). The serum IgG (g/L) is multiplied by the plasma volume (L) to calculate the total grams of IgG in the blood. This is then divided by the total grams of IgG fed, and then multiplied by 100 to express efficiency as a percentage. For example, a 43-kg calf has an estimated 3.9 L of plasma (43 kg × 0.091). If the serum IgG concentration of the calf is 10 g/L (10 mg/mL), then the calf has 39 g of IgG in the blood (10 g/L × 3.9 L). If that calf was originally fed 100 g of IgG from maternal colostrum or a CR product, then the AEA would be 39% (39 g/100 g × 100%). Controlled field studies using commercially available CR or CS products, mixed and fed according to label directions, have reported widely varying AEA % values (see Table 21-2). The AEA % reported for CS products has ranged from 16% to 28%.[20,21] The AEA % reported for CR products has ranged from 14% to 51%.[18,22-29] By way of comparison, the AEA % of IgG reported for calves fed 3 to 4 L of fresh maternal colostrum within 6 hours of birth has ranged from 21% to 36%.[18,20,21,27,29]

The debate continues over whether the IgG in colostrum- or serum-based CR or CS products is more efficiently absorbed. However, relatively few head-to-head field trials exist to investigate this question. In one early CS study in which calves were fed two doses of a colostrum-derived CS (50 g IgG), two doses of either 60 g or 90 g IgG of serum-derived CS, or 3.8 L of maternal colostrum, the AEA % reported for the colostrum-derived CS (16%) was inferior to that of the two serum-derived CS products (24% or 28%) and to maternal colostrum (22%) (see Table 21-2).[20] However, because all three CS products delivered an insufficient dose of IgG as compared with maternal colostrum, all three CS products failed to provide APT to calves. Thus far, only two head-to-head controlled field studies have compared the AEA % of commercially available serum- versus colostrum-derived CR products. In one study calves fed 150 g of a lacteal-derived CR had significantly improved AEA % and serum IgG concentrations (AEA = 38.2%; IgG = 14.7 mg/mL) as compared with calves fed 130 g of a serum-derived CR (AEA = 28.4%; IgG = 9.6 mg/mL) (see Table 21-2).[26] In this study the improved final serum IgG values for the colostrum-derived CR group were attributed both to increased dose fed (in grams) and improved AEA %. In another recent study, calves fed 150 g of a serum-derived CR had inferior AEA % (21.6%) compared with calves fed 100 g of a colostrum-derived CR (38.8%).[30]

PASSIVE TRANSFER LEVELS, AND HEALTH AND PERFORMANCE OF CALVES FED COMMERCIAL CS OR CR PRODUCTS. If given alone, CSs will result in significantly lower serum IgG concentrations and a high risk of FPT in calves as compared with feeding 3 to 4 L of maternal colostrum (see Table 21-2).[19-21,31,32] There is no added benefit to feeding a CS if feeding 3 to 4 L of high-quality maternal colostrum.[33,34] Although an opportunity may exist for producers doing on-farm testing of colostrum, using such instruments as the Brix refractometer, to supplement poor-quality colostrum with a CS, the effectiveness of this strategy requires further study.[35,36]

Studies have demonstrated that several commercially available CR products, when administered at a high enough dose (150 to 200 g IgG) within a few hours after birth, can provide acceptable–to–very good serum IgG concentrations and APT rates in calves (goal of ≥ 90% of calves with serum IgG ≥ 10 mg/mL) (see Table 21-2).[18,23-26,28,29,32] Relatively few studies have been designed with sufficient sample sizes to evaluate the effects of feeding CR on health and performance outcomes in calves. In one early study of 457 calves on 12 upper Midwest dairy farms, there was no significant difference

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TABLE 21-1

CVB-Licensed and Selected Non-Licensed Colostrum Replacements and Supplements*

Product Name	Manufacturer	Country	Ig Provided (g)	CS or CR	Ig Source
Section A. CVB-Licensed CR and CS Products†					
CALF'S CHOICE TOTAL-HiCal	Saskatoon Colostrum Co. SK, Canada	Canada, U.S.	100 g IgG in 700 g pack	CR	Colostrum
CALF'S CHOICE TOTAL	Saskatoon Colostrum Co. SK, Canada	Canada	100 g IgG in 470 g pack	CR	Colostrum
CALF'S CHOICE TOTAL—Gold (or HEADSTART)	Saskatoon Colostrum Co. SK, Canada	Canada, U.S.	60 g IgG in 225 g pack	CS: 1 pack CR: 2 or 3 packs	Colostrum
COLOSTRUM PLUS 100 Bovine IgG with *Escherichia coli* Antibody	La Belle Associates, Inc. WA, U.S.	Canada, U.S.	100 g IgG in 500 g pack	CR	Colostrum
FIRST START 50 Bovine IgG Colostrum Supplement	La Belle Associates, Inc. WA, U.S.	Canada, U.S.	50 g IgG in 350 g pack	CS	Colostrum
Immu-Start 50 Bovine IgG *Escherichia coli* Antibody	Immu-Tek Animal Health, Inc., CO, U.S.	Canada, U.S.	50 g IgG in 400 g pack	CS	Colostrum
Land O' Lakes COLOSTRUM REPLACEMENT Bovine IgG	Saskatoon Colostrum Co. SK, Canada (Permittee: LO'L. MN)	U.S.	100 g IgG in 470 g pack	CR	Colostrum
Land O' Lakes COLOSTRUM REPLACEMENT for Kid Goats & Lambs Bovine IgG	Saskatoon Colostrum Co. SK, Canada (Permittee: LO'L. MN)	U.S.	150 g IgG in 700 g pack	CR	Colostrum
Kid's Choice Total or Lamb's Choice Total Colostrum Replacer	Saskatoon Colostrum Co. SK, Canada	Canada, U.S.	100 g IgG in 700 g tub	CR or CS	Colostrum
Section B. Selected Examples of Non-CVB Licensed CR Products					
100 ADVANTAGE; 150 BENEFIT	La Belle Associates, Inc. WA, U.S.	U.S.	100 or 150 g Ig/pack	CR	Colostrum
COLOSTRX Colostrum Replacer 130	APC, Inc. IA, U.S.	U.S.	130 g globulin protein in 500 g pack	CR	Serum
First Day Formula Colostrum Replacer	Milk Products, LLC. WI, U.S.	U.S.	150 g globulin protein in 500 g pack	CR	Colostrum
Genesis 100 or Genesis 150 Colostrum Replacer	APC, Inc. IA, U.S.	U.S.	100 or 150 g globulin protein in pack	CR	Serum
LIFELINE RESCUE (formerly ACQUIRE)	APC, Inc. IA, U.S.	U.S.	150 g globulin protein in 550 g carton	CR	Serum
OptiPrime Calf Colostrum Replacer	Milk Products, LLC. WI, U.S.	U.S.	150 g globulin protein in 500 g pack	CR	Colostrum
Rite Start Complete Colostrum Replacer	Milk Specialties Global Animal Nutrition IL, U.S.	U.S.	100 g globulin protein in 454 g pack	CR	Colostrum
Sav-A-Calf Ultra-Start 150	Milk Products, LLC. WI, U.S.	U.S.	150 g globulin protein in 350 g pack	CR	Colostrum
Secure Original or Secure 175 Calf Colostrum Replacer	APC, Inc. IA, U.S.	U.S.	125 or 175 g globulin protein per pack	CR	Serum
Section C. Selected Examples of Non-CVB Licensed CS Products					
COLOSTRX Colostrum Supplement	APC, Inc. IA, U.S.	U.S.	55 g globulin protein in 454 g packet	CS	Serum
COLOSTRX Multi Species Colostrum Supplement	APC, Inc. IA, U.S.	U.S.	20 g globulin protein in 454 g packet	CS	Serum
First Day Formula Colostrum Supplement	Milk Products, LLC. WI, U.S.	U.S.	60 g globulin protein in 200 g packet	CS	Colostrum
Genesis 50 Colostrum Supplement	Provimi North America. OH, U.S.	U.S.	50 g globulin protein in 454 g packet	CS	Serum
LIFELINE PROTECT (formerly LIFELINE)	APC, Inc. IA, U.S.	U.S.	50 g globulin protein in 454 g carton	CS	Serum
RANCH 40; SHIELD 50; SALUTE 60	La Belle Associates, Inc. WA, U.S.	U.S.	40, 50, or 60 g/dose	CS	Colostrum
Sav-A-Calf Ultra-Start Multi Colostrum Supplement	Milk Products, LLC. WI, U.S.	U.S.	30 g globulin protein in 454 g packet	CS	Colostrum

*Product list may change in the future; specifications may change in the future, so read the label.

†Centers for Veterinary Biologics (CFIA or USDA).[10,59]

CR, Colostrum replacement; *CS,* colostrum supplement; *CVB,* Centers for Veterinary Biologics (CFIA or USDA).

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TABLE 21-2

Selected Efficacy Studies of CS and CR Products*

Citation	Colostrum Supplement or Replacer Product Fed	N	Total IgG Fed (g)	Age Fed (hr)	AEA IgG (%)	Serum IgG (mg/mL)	APT (%)
Colostrum Supplement Studies							
Arthington et al, 2000[20]	First Milk Formula CS (CD)	10	50 g (2 doses)	<2 h & 12 h	≈16%†	2.2†	NR
	Colostrx CS (SD)	10	60 g (2 doses)	<2 h & 12 h	≈24%‡,§	3.5‡	
	Lifeline CS (SD)	10	90 g (2 doses)	<2 h & 12 h	≈28%‡	6.8§	
	Maternal Colostrum	10	200 g (3.8 L)	<2 h & 12 h	≈22%†,§	12.1‖	
Santoro et al, 2004[21]	Lifeline CS (SD)	12	100 g (2 doses)	<2 h & 12 h	22.7†	4.5†	0%†
	Maternal Colostrum	12	200 g (4 L)	<2 h & 12 h	21.0†	15.7‡	100%‡
Smith and Foster, 2007[19]	First Day Formula CS (CD)	21	100 g (2 doses)	<3 h	NR	7.5†	5%†
	First Day Formula CS (CD)	21	150 g (3 doses)	<3 h		9.1†	24%†
	Maternal Colostrum	21	NR g (3.8 L)	<3 h		17.6‡	95%‡
Colostrum Replacement Studies							
Foster et al, 2006[32]	Immu Start 50 CS (CD)¶	21	100 g (2 doses)	<3 h	NR	7.0†	10%†
	Land O' Lakes CR (CD)¶	21	100 g (1 dose)	<3 h		11.6‡	81%‡
	Land O' Lakes CR (CD)¶	21	200 g (2 doses)	<3 h		16.9§	95%‡
	Maternal Colostrum	21	448 g (3.8 L)	<3 h		27.2‖	90%‡
Swan et al, 2007[37]	Acquire CR ± Lifeline CS (SD)	218	125 g (CR) ± 45 g (CS)	<4 h ± 12 h	NR	5.8†	7%†
	Maternal Colostrum	239	291 g (3.8 L)	<4 h ± 12 h		14.8‡	72%‡
Godden et al, 2009[18]	Land O' Lakes CR (CD)¶	24	100 g (1 dose)	<1 h	36%†	9.6†	54%†
	Land O' Lakes CR (CD)¶	23	200 g (2 doses)	<1 h	37%†	19.0‡	100%‡
	Maternal Colostrum	22	271 g (3.8 L)	<1 h	32%†	20.7‡	91%‡
Godden et al, 2009[22]	Land O' Lakes CR (CD)¶	24	100 g (1 dose)—Bottle	<1 h	51%†	12.5†	100%†
	Land O' Lakes CR (CD)¶	24	100 g (1 dose)—Tube	<1 h	41%‡	9.9‡	42%‡
	Land O' Lakes CR (CD)¶	24	200 g (2 doses)—Bottle	<1 h	41%‡	19.7§	100%†
	Land O' Lakes CR (CD)¶	25	200 g (2 doses)—Tube	<1 h	39%‡	18.7§	100%†
Shea et al, 2009[23]	Land O' Lakes CR (CD)¶	8	105 g (1 dose)	<2 h	41%†	10.7†	80%†
	Land O' Lakes CR (CD)¶	8	210 g (2 doses)	<2 h & 12 h	31%‡	14.5‡	90%‡
Brakefield et al, 2010[24]	Calf's Choice Total Bronze CR (CD)¶	27	200 g (2 doses)	<2 h	30%†	20.0†	100%†
	Calf's Choice Total Bronze CR (CD)¶	28	200 g (2 doses) + Probiotic	<2 h	29%†	20.1†	100%†
Morrill et al, 2010[25]	Calf's Choice Total Gold CR (CD)¶ + dam not fed anionic salts prepartum	10	198 g (3 doses)	<1 h & 6 h	27%†	13†	80%†
	Calf's Choice Total Gold CR (CD)¶ + dam fed anionic salts prepartum	10	198 g (3 doses)	<1 h & 6 h	26%†	13†	90%†
Poulson et al, 2010[60]	Secure CR + Lifeline CS (SD)	146	170 g (1 CR + 1 CS)	<2 h & 12 h	NR	13.5†	71%†
	Maternal Colostrum	141	NR g (3-4 L)	<2 h ± 12 h	NR	18.7‡	82%†
Place et al, 2010[26]	Land O' Lakes CR (CD)¶	36	150 g (1.5 doses)	<2 h	38%†	14.7†	94%†
	Colostrx 130 CR (SD)	38	130 g (1 dose)	<2 h	28%‡	9.6‡	37%‡
Fidler et al, 2011[27]	Colostrx 130 CR (SD)	22	130 g (1 dose)	<2 h	≈20%†	7.4†	14%†
	Colostrx 130 CR (SD)	22	260 g (2 doses)	<2 h	≈14%‡	10.6‡	86%‡
	Maternal Colostrum	22	211 g (3 L)	<2 h	≈36%§	21.4§	95%‡
Cabral et al, 2012[28]	Calf's Choice Total Gold CR (CD)¶	13	191 g (3 doses/1 feeding)	<1 h	32%†	15.8†	92%
	Calf's Choice Total Gold CR (CD)¶	13	191 g (3 doses/2 feedings)	<1 h & 6 h	33%†	16.8†	100%
Pithua et al, 2013[29]	Land O' Lakes CR (CD)¶	295	200 g (2 doses)	<6 h	27%†	15.2†	89%†
	Maternal Colostrum	273	80 g (3.8 L)	<6 h	29%†	7.5‡	30%‡

*Limited to studies of commercially available products mixed and fed according to label directions.

†,‡,§,‖Means within column within study with different superscripts differ ($P < 0.05$).

¶Product licensed through Center for Veterinary Biologics (CFIA and/or USDA).

AEA, Apparent efficiency of absorption of IgG (%); *APT,* proportion (%) of calves with acceptable passive transfer (serum IgG ≥ 10 mg/mL); *CD,* colostrum-derived IgG source; *CR,* colostrum replacement; *CS,* colostrum supplement; *N,* number of calves per treatment group; *NR,* not reported; *SD,* serum-derived Ig source.

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in morbidity or mortality in 218 calves assigned one dose of a serum-derived CR product providing 125 g Ig, as compared with 239 calves fed 3.8 L of fresh maternal colostrum, despite the fact that the CR group had lower serum IgG concentrations and higher FPT rates than calves fed maternal colostrum (see Table 21-2).[37] A companion study reported that calves fed the CR program at birth were at significantly reduced risk to test positive for infection with *Mycobacterium avium* subsp. *paratuberculosis* as adults (7.6% test positive; odds ratio 0.52 [0.27 to 1.003]), as compared with control calves fed maternal colostrum (11.9% test positive), thus demonstrating that CR products may be a useful management tool for dairy herds attempting to reduce the prevalence of Johne's disease.[38] This study also reported that the colostrum treatment group had no overall effect on longevity, milk production, or reproductive performance during the first three lactations.[39] Preliminary results from a more recent study of 568 calves on one California dairy reported higher serum IgG concentrations, very good APT rates, and improved health in calves fed 200 g of IgG in a colostrum-derived CR product, as compared with calves fed 3.8 L of very-poor-quality maternal colostrum (only 80 g IgG fed from maternal colostrum) (see Table 21-2).[29]

Does Immunoglobulin Source Affect the Antibody Profile in CR or CS Products?

Veterinarians frequently ask if the antigen-specific antibody profile in CR products will complement the antigen profile on their clients' dairy farms. Because the colostrum used to manufacture CVB-licensed colostrum-derived CR or CS products is collected from cows living on commercial North American grade A dairy farms, this author considers it a safe assumption that these cows will have been exposed to, and therefore produce colostral antibodies against, most of the common pathogens endemic on most commercial dairies (e.g. *Escherichia coli, Salmonella* spp., rotavirus, coronavirus, *Cryptosporidium*), either through natural exposure and/or through vaccination programs. However, published studies to verify this hypothesis are extremely limited as relates to colostrum-derived CR products, and lacking entirely for serum-derived CR products. One recent Alabama field study reported that calves fed 200 g IgG in a colostrum-derived CR had greater levels of BVDV-neutralizing antibodies in serum, and similar levels of antibodies to BHV-1, BRSV, and PI3V in serum, as compared with calves fed 3.8 L of maternal colostrum.[40] Additional studies are needed to describe antigen-specific antibody concentrations, particularly to enteric pathogens, found in CR or CS products.

Another frequent question asks whether the antibody profile in colostrum-derived CR products is superior to that of serum-derived products. Although the concentrations of the subclasses IgG_1 and IgG_2 are approximately equal in serum (50:50 ratio, or 50% IgG_1), IgG_1 occurs in much higher concentrations than IgG_2 in colostrum (7:1 ratio, or approximately 90% IgG_1) as a result of the selective transfer of IgG_1 into the mammary secretion of cows.[41-43] IgG is the main class of Ig secreted into the bovine intestinal tract.[44-46] Furthermore, IgG_1 is the predominant Ig subclass secreted into the bovine intestinal tract, lung, nasal secretions, vaginal secretions, and saliva.[47-49] Studies have demonstrated that secretion of serum IgG_1 rotavirus immunoglobulin into the intestinal lumen, if in sufficient quantity, provides protection against rotavirus infection.[44,46,47,50-52] In a review of this topic, Thornsberry and Wood[13] stressed the importance that newborn calves consume a sufficient mass of IgG_1 prior to closure of intestinal absorption of Ig molecules. All else being equal, one could theorize that the increased proportion of IgG_1 found in colostrum-derived CR products (90% IgG_1) should result in improved calf health, as compared with serum-derived CR products (50% IgG_1). However, studies are as yet lacking to investigate this hypothesis. It has been argued that the relative content of IgG_1 in a CR may be immaterial for consideration (provided that a sufficient total mass of IgG is provided), because studies have demonstrated that both colostrum- and serum-derived CR can achieve desired goals of calf production.[13]

Monitoring Passive Transfer Rates When Feeding CR or CS Products

Measurement of serum total protein (STP) by handheld refractometer offers a convenient, simple, rapid, and inexpensive method by which producers can monitor the colostrum program. For calves fed maternal colostrum, STP test endpoints of 5.0 or 5.2 g/dL yield the most accurate results in estimating the adequacy of passive transfer (serum IgG ≥ 10.0 mg/mL; sensitivity > 0.80; specificity > 0.80; proportion classified correctly > 0.85).[53,54] However, are the same STP cutpoints accurate when feeding a CR or CS? Three studies of colostrum-derived CR products have reported that an STP cutpoint of 5.0 or 5.2 g/dL most accurately predicts APT.[26,30,32] However, a significant association was not found between STP and serum IgG in one study wherein calves were fed a colostrum-derived CS product.[32] For serum-derived CS or CR products, the relationship between STP and serum IgG in calves may be very different depending on the source, level of inclusion, and/or degree of absorption of non-Ig proteins. Studies of different serum-derived CS or CR formulations have reported widely varying STP cutpoints ranging between 4.2 and 5.4 g/dL.[14,26,30,37,55] Given the large variation in predicted STP cutpoints, particularly for the serum-derived products, veterinarians are encouraged to use refractometry to monitor the effectiveness of a CR feeding program only if studies are available describing the relationship between STP and serum IgG for the specific commercial CR product in use on the farm. If such studies are not available, veterinarians are advised to periodically submit frozen serum samples for serum IgG analysis using direct methods such as the zinc sulfate turbidity test, radial immunodiffusion, turbidimetric immunoassay, or enzyme-linked immunosorbent assay.[53,56,57]

Use of Colostrum Supplements or Replacements in Minor Species

Although most CS and CR products target calves, products exist for minor species including goat kids, lambs, foals, llama or alpaca cria, pigs, fawns, and elk calves (see Table 21-1). Although most products available for minor species are not licensed, CVB-licensed products do exist for goat kids and lambs, meeting CFIA and USDA standards, thus guaranteeing purity, potency, efficacy, and traceability (see Table 21-1, Section A).[58] Because the dose of IgG required for multispecies CR or CS products will vary by species, producers should follow individual product label directions for feeding.

Summary

High-quality CR products can offer a consistent and convenient source of Ig for newborn calves for when high-quality, clean maternal colostrum is not available; they may also be a useful management tool to help break the transmission cycle of some infectious diseases (e.g., Johne's disease). Additional controlled field studies are needed to further describe and compare efficacy among various CR products, and particularly to describe the effects of feeding CR on short- and long-term health and performance outcomes. However, studies conducted to date demonstrate that, fed a large enough dose (150 to 200 g IgG) of a high-quality CR product within a short period of time after birth, calves can achieve at least equal passive transfer levels and health outcomes as compared with fresh maternal colostrum. Given the significant differences in quality and efficacy among various commercially available products, producers may want to consider whether a product is CVB-licensed, and they are strongly encouraged to select CR or CS products that have demonstrated efficacy in independently conducted controlled field studies.

Milk Replacers

The digestive anatomy of the newborn calf consists of a four-compartment stomach like that of the adult, but the abomasum predominates with 60% of the total stomach capacity. During the first weeks of life, the calf is essentially monogastric because milk is shunted directly to the abomasum by closure of the esophageal

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groove. Closure is stimulated as a behavioral response associated with milk feeding by bottle or bucket. During this time the calf depends upon the consumption of highly digestible nutrients provided by food grade feedstuffs because it depends upon enzymatic digestion of proteins, fat, and simple sugars in the form of lactose. The consumption of limited quantities of dry feed along with free-choice water stimulates rapid colonization of the stomach with ruminal microorganisms and rapid differential growth of the stomach tissue, which enables it to digest more complex carbohydrates and vegetable proteins. The impact of diet on rumen development is depicted by Heinrichs.[61]

There are multiple goals in feeding the preweaned calf, which require a degree of compromise. Ultimately, the goal should be to provide the conditions that enable the calf to achieve its genetic growth potential with minimal health problems at a reasonable cost. There are different philosophies in what constitutes a successful calf rearing program. A goal favored in more traditional programs has been limit feeding of the liquid diet to encourage dry feed intake as well as early weaning. This practice reduces feed costs during the preweaning period, and there has been the perception that digestive disturbances could be substantially reduced by transitioning the calf to a dry diet as soon as possible. This feeding program provides only enough energy from the liquid diet to meet maintenance requirements with little remaining to support growth. More recent research supports calf feeding programs that provide nutrients to encourage more biologically normal growth rates of 700 to 1000 g/day during the preweaning period. These programs cost more per day, but frequently result in lower costs per unit of gain. Studies have also demonstrated that higher protein and energy intake result in lower morbidity and mortality, particularly during the winter months.[62] Ultimately, the goal for the milk-feeding program should be to foster the growth of the animal, which results in the most economical lifetime performance, rather than the lowest daily rearing cost during the preweaning period.

Liquid Diets for the Dairy Calf

Calves can grow well on whole milk, waste milk, or milk replacers. Although the most recent NAHMS[62a] survey indicates that over 60% of calves are fed milk replacer, there is increased interest in the use of waste milk for calves, particularly on larger farms that pasteurize it prior to feeding to reduce risk of disease and improve acceptability. Pasteurized waste milk has been viewed as a means of increasing nutrient intake and reducing feed cost. However, the manager must be aware of the challenges involved in these feeding systems.[63,64]

Milk replacers were first developed in the early 1950s with the goal of reducing costs and increasing the convenience of feeding dairy calves. These milk replacers resembled gruels and frequently resulted in poor calf performance. The challenge in using milk replacers is to provide sufficient nutrients to encourage acceptable growth at less cost than feeding whole milk. Table 21-3 compares the nutrient content of one gallon of either average quality whole milk with a typical 20% protein:20% fat milk replacer diluted to approximately 12.5% solids. These milk replacers fed in the limited amounts shown here allow lower daily feed costs, encourage early starter intake but at reduced rates of gain and possibly impaired health. More recent research has been directed toward achieving gains more similar to whole milk feeding programs. The quality of milk replacers and expected performance are influenced by ingredients used and manufacturing practices and quality control.

Ingredients Used in Milk Replacers

Ingredients used in milk replacers providing the protein, fat, carbohydrate, and minerals should be of high digestibility for the young calf. Traditionally, these ingredients originate as products from the processing of milk as shown in Fig. 21-1. The skim milk and cream

TABLE 21-3

Comparison of 4 L of Whole Milk to 4 L of a 20:20 Replacer Diluted to 12.5% Solids

Parameter	Whole Milk	20:20 Milk Replacer
Total solids (%)	12.5	12.5
Fat % (liquid/DM)	3.6/28.8	2.5/20
Protein % (liquid/DM)	3.0/24	2.5/20
Fat g/4 L	144	100
Protein g/4 L	120	100

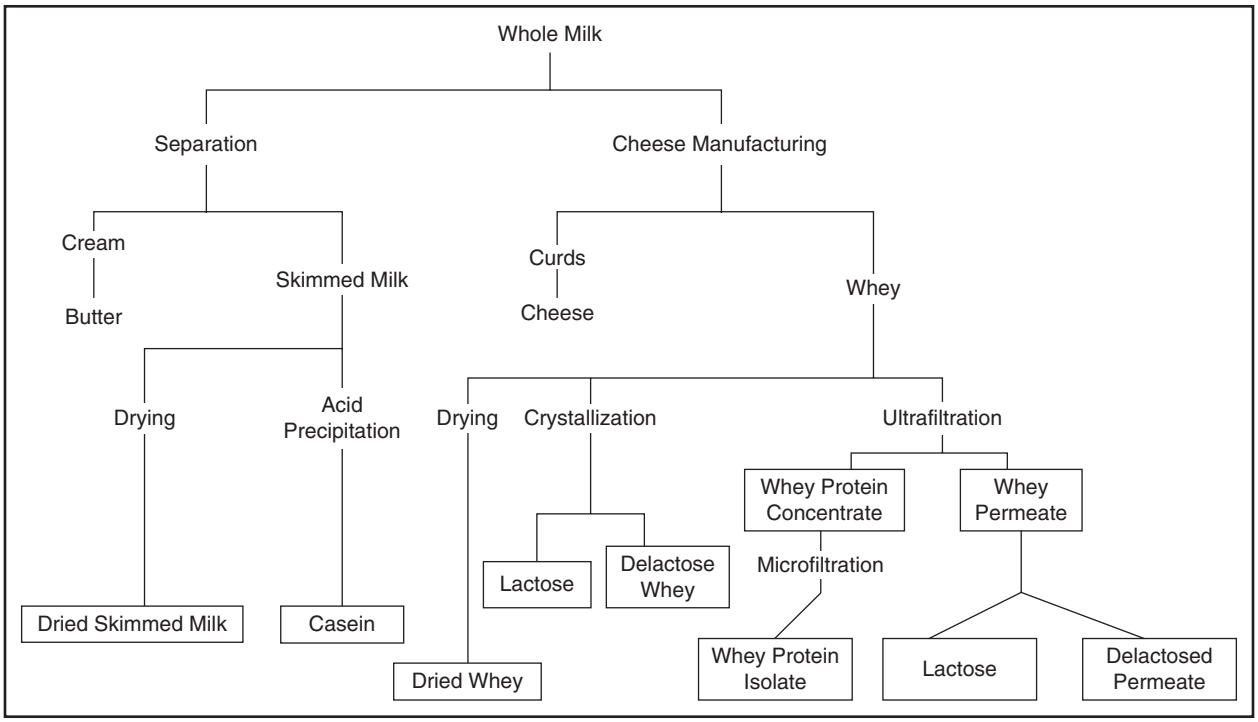


FIG. 21-1 Steps in milk processing and by-products potentially used in manufacture of milk replacers. *(Courtesy of T. J. Earleywine.)*

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TABLE 21-4

Chemical Composition of Ingredients Commonly Used in Milk Replacers[65-67]

Ingredient	Dry Matter (%)	Crude Protein (%)	Crude Fat (%)	Crude Fiber (%)	Lactose (%)	Ash (%)	Salt (%)
Whole milk solids	100	25.6	29.6		29.2	5.6	
Dried skim milk	98	34	0.1		52-54	8.5	3.5
Whey protein concentrate	98	33.5	2.5-3.5		50-52	7.0	2.5
Delactosed whey	98	21	1.0-1.5		55	16-18	
Dried whey	98	11.5	1.0-2.0		70-72	6-7	1.8-2.3
Soy protein isolate	94	85-89	<1.0	0.2	<1.0	4.0-6.0	
Soy protein concentrate	95	66-70	1.0-2.0	3.6-4.5		4.0-7.0	
Soy flour	95	50-53	1.0-1.5	2.5-3.3		6.3	
Modified wheat protein	94	79-81	5.0-7.0	<0.5		1.0-3.0	
Animal plasma	97	68-82	0.5-2.0	<0.5		8.0-10.0	
Spray dried whole egg	95	41-47	39-41.5			3.5-3.65	

portions, although highly desirable, are generally too expensive to be considered in milk replacer manufacture.

PROTEIN SOURCES. Common proteins used in the manufacture of milk replacers can be classified as either milk or alternative proteins. Most milk-derived proteins used in milk replacers have originated from the whey fraction. Whey can be processed through evaporation or filtration to separate the lactose and minerals from whey proteins to yield ingredients commonly used in milk replacers. The nutrient value of these different fractions is shown in Table 21-4.

Many feeding trials have evaluated the nutritional value of different protein sources on calf growth, health, and feed efficiency. Variation in nutrient content and digestibility of whey proteins is due to the type of cheese that is being manufactured and efficacy of the different processes used. Special care must be taken during the drying process to prevent denaturation of the protein. Digestibility of whey-based ingredients generally exceeds 85% and more commonly exceeds 90%. One concern with the use of whey-based proteins is that unlike casein in skim milk protein, these proteins do not form a clot in the abomasum shortly after being consumed. It would seem that the failure to clot would impair protein digestion and utilization by the calf. However, Terosky and colleagues[68] formulated milk replacer diets containing 0%, 33%, 67%, and 100% replacement of skim milk protein with whey protein concentrate. During the 8-week experiment, daily gains were similar, although calves in which 100% of the protein was from whey protein concentrate experienced a slightly lower incidence of scouring.

The value of whey protein concentrate has increased from approximately $0.34/lb in 1985 to as much as $1.50/lb in 2012. This occurred due to the increased use of whey proteins as nutritional supplements and high-protein snack bars for human consumption. As a result, the study of the use of alternative proteins in milk replacers has been an active field of research. The nutritional content of milk-derived and alternative ingredients found in milk replacers is shown in Table 21-4. There are two major concerns with the use of alternative proteins. One is the digestibility by the calf, particularly for the calf less than 2 weeks of age. Research on the alternative proteins has shown a wide range in digestibility of these proteins from as low as 54% to more than 90%. Variation is due to the processing and the age of the calf receiving the liquid diet. Soy proteins probably offer the greatest promise. Untreated soybean protein is strongly antigenic, causing infiltration of the lamina propria of the small intestine with T and B lymphocytes, hypersensitivity reactions, villous atrophy, and decreased intestinal absorptive ability.[69] Soybeans are treated to remove the fat and all or part of the carbohydrate and reduce these antigenic properties. Soy flour represents the least processing whereas isolated soy protein is the result of extensive processing with an alkali wash, acid precipitation, alkali resolubilization, and drying. A trial reported by Tomkins and colleagues[67] noted that feed conversion by calves 1 to 14 days of age that were fed soy protein concentrate containing milk replacers was reduced by as much as 30%. However, more recent research has shown improved responses. Unfortunately, because of extensive processing, the cost of isolated soy protein is not always economically feasible.

Wheat gluten is protein derived from wet milling of wheat after separation of the starch. The protein is rather insoluble and has antigenic properties that cause reactions by intestinal tissue. However, acid treatment to partially hydrolyze the wheat protein increases its solubility and reduces antigenicity. Although the digestibility of wheat gluten is comparable to whey proteins, it is deficient in lysine. Wheat gluten proteins have found wide use in veal-type diets, but research has shown that growth in replacement heifers less than 14 days of age is seriously depressed. At higher rates of feeding the depression in average daily gain becomes ever more evident.[69]

Animal plasma proteins from porcine or bovine blood have been used in milk replacers. The protein has an excellent amino acid profile that compares well with skim milk protein. Several studies[70,71] have shown that calves fed milk replacers in which 25% of the whey proteins had been replaced with plasma proteins grew at a slightly lower rate during the first 28 days. However, growth rates were similar over a 56-day feeding period.

Spray dried whole egg is an undesirable alternative protein in milk replacers because incorporation at levels above 5% of the total dry matter results in depressions in calf growth.[72]

Other proteins, including, pea, lupine, potato, fish, red blood cells, meat solubles, yeast, and bacterial proteins, have shown to be unacceptable sources of proteins for milk replacers because of poor solubility, low digestibility, or inadequate amino acid content.[73]

Research appears to support the supplementation of vegetable protein–based milk replacers with lysine and methionine.[74] At the present time there does not appear to be merit in supplementing milk protein–based milk replacers with amino acids.

CARBOHYDRATES. The intestine of the young calf has limited carbohydrase activity except for lactase during the first weeks of life. The only carbohydrates usable in large amounts are lactose, glucose, or galactose. Lactose from whey is the main carbohydrate source in milk replacers. Whole milk contains approximately 29% lactose, 29% fat, 20% casein, 5% whey protein, and about 5% ash on a dry matter basis. The most popular milk replacers containing 20% protein and 20% fat would have substantial space for the addition of more lactose than is present in whole milk given that high levels of ash are undesirable. Consumption of higher amounts of lactose from milk replacer than might be present in whole milk does not appear to be a concern.[66] The inclusion of starch and other carbohydrates in milk replacers is not advised for calves less than 2 to 3 weeks of age because of limited amylase and maltase activity. Toullec and colleagues[75] suggest limits of 2% to 3% starch in dry matter intake for younger calves.

LIPIDS. Milk fat is highly digestible; however, it is too expensive to be included in milk replacers. Tallow, lard, choice white grease, and coconut and palm oil are the primary sources for fat used in

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TABLE 21-5

Fatty Acid Composition of Milk Replacers Based on Different Sources Compared with Whole Milk[76]

Fatty Acid (% total fat)	Animal Fat Source	Coconut Oil	Palm Oil*	Whole Milk
C4:0 butyric	0.40	0.41		3.30
C6:0 caproic	0.20	0.92		3.00
C8:0 caprylic	0.36	9.18		2.00
C10:0 capric	0.40	5.06		3.00
C12:0 lauric	0.99	23.63	0.20	3.50
C14:0 myristic	2.12	9.91	1.10	10.20
C16:0 palmitic	23.31	14.51	44.00	26.30
C16:1 palmitoleic	2.29	0.90		2.30
C18:0 stearic	12.75	6.73	4.50	12.00
C18:1 oleic	38.35	19.15	39.20	25.10
C18:2 linoleic	14.07	7.30	10.20	2.40
C18:3 linoleic	0.63	0.36	0.40	0.80
Other	4.05	1.94	0.40	6.10

*See www.chempro.in/fattyacid.htm.

TABLE 21-6

Classification of Protein Sources Used in Milk Replacers Suitable for Young Calves[73]

Acceptable	Acceptable	Marginal	Not Acceptable
Dried whey protein concentrate	Soy protein isolate	Soy flour	Meat solubles
Dried skim milk	Protein modified soy flour		Fish protein concentrate
Casein	Soy protein concentrate		Wheat flour
Dried whey	Animal plasma		
Dried whey product	Wheat gluten or isolate		

Other alternative protein sources continue to be researched and yield mixed results (egg protein).

milk replacers. A comparison of the fatty acid composition of a tallow-based milk replacer with one based on coconut oil to whole milk is shown in Table 21-5. Although the digestibility of tallow and lard is somewhat lower than that of milk fat, performance is adequate. In general, highly unsaturated vegetable oils are poorly tolerated by the young calf.

Two fat sources that have been used, particularly in Europe, are palm and coconut oil. These fats are higher in medium chain fatty acids found in milk fat. Mills and colleagues[76] studied the effect of adding medium chain fatty acids at rate of 32% of the fat as coconut oil or oil high in caprylate. No differences were found in body composition intake or fecal score between the animal fat–based milk replacer or coconut oil treatments. Empty body fat was about 5% higher and livers contained 15% more fat for heifers fed coconut oil than those containing animal fat. Calves fed milk replacers in which part of the animal fat was replaced by low levels of coconut oil or blends of coconut and canola oil had higher average daily gains and less scouring than calves fed diets with only animal fat.[77,78] The formulation of milk replacers with special attention to fatty acid composition is an active field of research.

VITAMINS AND MINERALS. Vitamins and minerals are generally added to milk replacers to provide levels similar to those found in whole milk. The most recent (seventh) edition of the National Research Council (NRC)[79] recommended a substantial increase in vitamin A from 4000 to 9000 IU/kg of DM. Vitamin E recommendation was increased from 40 to 50 IU/kg of milk replacer DM. These levels are sufficient to prevent deficiencies under stressful conditions of digestive or respiratory disease and to avoid a toxic response with higher levels of milk replacer observed with more intensive feeding programs. Recommended vitamin D is 600 IU/kg of DM. Water-soluble vitamin and trace mineral recommendations are also described in the latest edition of Nutrient Requirements of Dairy Cattle.[79] Osorio and colleagues[80] evaluated the impact of supplementing organic trace minerals to calves fed diets formulated for a low or high plane of nutrition (568 g vs. >1000 g milk replacer solids/day). Calves fed at a high plane but not a low plane of nutrition responded with increased growth. This suggests that growth of calves on a lower feeding rate was limited by factors other than trace mineral nutrition.

Recommended Protein and Fat Levels in Milk Replacers

The most important factors influencing the price of a milk replacer are the protein and fat content and the source of each. Replacers labeled as all milk will usually contain blends of dried whey, delactosed whey, and whey protein concentrate. Those milk replacers with alternative proteins will have some of the whey proteins (up to 50%) replaced by soy, wheat, or animal plasma proteins. Table 21-6 represents industry classifications of the suitability of protein sources for milk replacers.

It should be noted that dried skim milk and casein are rarely present in milk replacers in significant amounts to impact nutrient content or quality as a result of their high cost. For the calves less than 3 weeks of age, digestibility and amino acid content of milk-derived proteins tend to be more suitable.

Commercially available milk replacers contain between 18% and 28% protein. The level of protein and fat depends upon the desired performance and conditions of the calf's environment. The seventh edition of the NRC[79] continues to recommend limited feeding of milk and milk replacer solids to calves (454 g/day) to encourage the early intake of calf starter and early weaning. At this level of intake, 18% to 20% protein is adequate with minimal rates of daily gain. However, more recent work that has focused on the nutritional requirements of calves growing to their genetic potential has resulted in the manufacture of milk replacers with higher protein content fed in amounts as high as 1.1 kg of milk or milk replacer solids/day.[81-83] Work by Blome and colleagues[81] suggests that lean tissue growth is optimal between 26% and 28% CP at higher feeding rates.

Calf milk replacers usually contain between 10% and 25% fat. This is lower than the level found in cow's milk, which would be in excess of 28% with milk containing 3.6% fat on a liquid basis. The impact

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of the fat content of the milk replacer upon body composition and calf growth depends upon the feeding rate and environmental conditions. At lower feeding rates (454 g solids/day), body fat deposition increases as the level of fat increases in the milk replacer. The optimal level of body fat for the preweaned calf has not been determined. Body fat at birth is heavily dependent upon the body condition of the dam. During the end of the first week of life it is not uncommon for calves to have less than 2% body fat.[84] This is probably an inadequate reserve should the calf become ill, decrease dietary energy intake, and have increased energy requirements as a result of environmental temperature or the response to disease. Therefore, there is probably some benefit to the calf experiencing accretion of body fat, especially during the first weeks of life. As fat percentage and daily fat intake from milk replacer increases, calf starter grain intake is delayed or occurs at a lower rate. Most milk replacers contain approximately 10% to 20% fat, which is adequate over a wide range of intake levels and protein percentages. Research by Bascom and colleagues[84] suggested that smaller calves would benefit from higher levels of fat in the diet during periods when the environment is below the thermoneutral zone. However, during warmer months, there appears to be little benefit to milk replacers with more than 15% fat. Milk replacers specially formulated to contain desired fatty acid composition with 10% fat provide sufficient energy for desired growth during summer months.

Manufacturing Milk Replacers

Production of milk replacers begins with procurement of quality ingredients and having a strict quality assurance program in effect at the plant.[69,85] Whey products are monitored for protein, fat, ash, pH, sodium, moisture, color, solubility, dispersibility, bacterial growth, lactic acid production, and evidence of overheating. With fats and oils, color, melting point, odor, peroxide, free fatty acid content, and fatty acid profile are considered. Most manufacturers rely on supplier histories as each incoming load of ingredient is tested. The main variables influencing the nutritional value of whey proteins are the type of cheese produced, heating history, length of storage, and sanitation. Sanitation factors are critical since they influence microbial load and peroxide addition to the final product. Standard plate count must be less than 30,000 cfu/g, less than 10 cfu coliforms/g, less than 10 mold or yeast colonies/g, and no detectable *Salmonella*. Excessive heating can lead to denaturation of the protein, whereas underheating contributes to excessive microbial growth. Reputable manufacturers only use ingredients that are edible by humans rather than feed grade.

The next process in producing a milk replacer is to combine the ingredients into a product that has good wettability and mixability characteristics and does not separate. *Wettability* is a measure of how fast the powder breaks water tension and drops below the surface of the water. A test used is the amount of the powder that drops below the surface of the liquid within 60 seconds. This is related to ingredients used and the amount of surfactant that is added. *Mixability* is how completely the powder goes into solution and stays in suspension. Although wettability appears to make the product more convenient, mixability is more important in regard to the calf. *Separation* is how much the ingredients separate from the rest of the solution, including those that float to the surface and those that sink to the bottom. Ingredients low in fiber (e.g., milk proteins, plasma, wheat gluten, and soy isolate) have better mixing characteristics than soy protein concentrate or flour. A powder that has all of the nutritional characteristics of a desirable milk replacer must also have physical characteristics that enable the calf to consume a uniform, digestible, and palatable product.

Several methods are used in manufacturing milk replacer powders: dry blending, chilling towers, and agglomeration. Each method can provide a finished product of desirable nutrient content. However, differences in the three characteristics mentioned previously may impact the nutrients consumed by the calf. Dry blending is the simplest because the dry protein and fat sources are mixed together with additional liquid fat sprayed on later. The issue with dry blended products is getting fat into suspension since it is very hydrophobic. The nature of the fat product greatly determines how this is accomplished. Some fats used in milk replacers have protein sprayed on their surface, which improves mixing, whereas others use higher amounts of emulsifiers. Milk replacers may also be agglomerated to enhance wettability and mixability. These processes result in encapsulation of difficult ingredients such as fat with more hygroscopic ingredients and increase particle size, resulting in a powder that goes into solution quicker and stays in suspension. The process of agglomeration generally provides a finished product that is easiest to mix on the farm. Ideal mixing temperature for a milk replacer is heavily dependent upon the ingredients and processing method used. Excessive temperature can result in disruption of the agglomerated product and separation of the fat and protein. Low temperatures will result in inadequate mixing. One must closely follow the recommendations for mixing temperature provided by the manufacturer. Typically dry blended milk replacers require higher mixing temperatures.

Another small but important detail is how milk replacer powder is mixed. Ideally, about 50% to 70% of the total water needed for a batch is added, followed by the powder, and then they are mixed. Remaining water is added to obtain the final desired volume. During cold weather, temperature should be warmer because the liquid will cool prior to feeding, especially in slower feeding systems. A thermometer should always be used to check mixing temperatures (see manufacturer recommendations) and feeding temperature (37.8° to 40.6° C [100° to 105° F]).

Ideally, both the water and powder should be weighed for each batch of milk replacer liquid. Most milk replacer powders are approximately 96% to 97% dry matter. When powder is diluted, the final solution should be fed at a solids concentration of 10% to 15%. The influence of solids level on calf performance is relatively small within this range. However, formulation of liquid diets with higher DM percentage permits delivery of more nutrient solids within a given volume. Delivery of more nutrients can be challenging with feeding systems using two quart/liter bottles and twice daily feeding. Under such systems, it is difficult to deliver more than 454 g/day to calves. Feeding milk replacer at solids levels as high as 20% has been associated with increased scouring in calves, especially if free choice water is not available. For this reason, many calf operations have switched to the use of three quart/liter bottles.

A degree of confusion exists in many operations on how to calculate the level of milk solids in a liquid feeding system. Adding 150 g of powder to 1 L of water does not result in a 15% solids solution because 150 g of powder + 1000 g of water = 1150 g of final weight, or 150/1150 = 13.04% solids.

Acidification of Milk Replacers

Workers in Canada[86] have described a system of free-choice feeding either cold milk or milk replacer treated with formic acid, which lowers the pH of the liquid to approximately 4.5. This system results in higher levels of intake of liquid diet and lower initial calf starter intake, but noticeable improvements in gains and labor efficiency. However, at the present time, formic acid is not permitted as a feed ingredient in the U.S. dairy industry. Nocek and Braund[87] observed more gain in calves fed ad libitum to 35 days compared with limit-fed calves offered a non-acidified milk replacer. However, there were not significant differences in scouring, and calves of both treatments reached 136 kg of body weight in the same number of days, likely because of weaning challenges and postweaning diets that were not adjusted for body weight differences. Jaster and colleagues[88] compared calves fed twice daily at 10% of body weight either "sweet" or acidified milk replacers containing 12.5% solids. Citric acid was used to decrease the pH to 5.3. No differences were found in gains with a slight reduction of scours in calves fed the acidified replacer. Acidified milk replacers using combinations of organic acids other than formic acid are commercially available. Cold liquid feeding systems will reduce feed efficiency because of the impact of liquid temperature on the energetic requirements of the calf.

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TABLE 21-7

Commonly Used Milk Replacer Medications

Medication	Use Level	Statement	Withdrawal
Oxytetracycline/Neomycin 1:1 ratio[72a]	To provide 0.05 to 0.1 mg/lb of body weight daily (10/20g/ton of milk replacer powder)	For increased rate of weight gain and improved feed efficiency	None
	To provide 10 mg/lb of body weight daily (500-2500 g/ton of milk replacer powder). Can be fed as a treatment for 7 to 14 days in calves up to 250 lb body weight	For treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *P. multocida* susceptible to OTC; treatment and control of colibacillosis caused by *E. coli* susceptible to Neomycin	5 days before slaughter
Decoquinate[73]	12.9 to 90 g/ton to provide 22.7 mg decoquinate/100 lb body weight	For prevention of coccidiosis in calves and cattle caused by *Eimeria bovis* and *Eimeria zuernii*	None
Lasalocid[73]	1 mg lasalocid per 2.2 lb body weight	For control of coccidiosis caused by *Eimeria bovis* and *Eimeria zuernii*	None

Additives to Milk Replacers

Prior to 2010, neomycin (400 g/ton) and oxytetracycline (200 g/ton) were added to milk replacers to aid in the control of bacterial enteritis. Beginning in late 2010, this policy was changed to limit the continuous feeding of these antibiotics to inclusion rates of 10 to 20 g/ton neomycin and 10 to 20 g/ton oxytetracycline with a label to increase weight gain and improve feed efficiency. Therapeutic inclusion rates of 1600 g/ton neomycin and 1600 g/ton oxytetracycline are limited to 14 days of continuous feeding. Commonly used milk replacer medications are shown in Table 21-7.

Additional additives used in milk replacers include yeast products, probiotics, and fermentable fibers. Heinrichs and colleagues[89] found similar performance of calves fed a milk replacer diet with no additives or supplementation with the pre-2010 level of oxytetracycline/neomycin or 4 g/day of mannan oligosaccharide (MOS). Addition of either the antibiotic or MOS reduced scours. Calf starter intake increased at a faster rate for those calves fed MOS. Inclusion of fermentable fibers from psyllium to a milk replacer powder at 1.1% of the dry matter intake increased populations of bifidobacteria and lactobacilli in the rumen and reticulum of preweaned dairy calves. It also increased the mass of the gastrointestinal tract.[90] Daily addition of probiotics in the form of *Lactobacillus acidophilus* had no effect on body weight over a 6-week trial, but calf health and growth were improved during the first 2 weeks of life.[91] The study of the efficacy of additives continues as the milk replacer industry seeks to find replacements for antibiotics in milk replacers.

Feeding Recommendations for Dairy Calves

Traditional calf feeding programs consisted of daily consumption of 454 g of milk or milk replacer solids in 4 L of liquid divided into two daily feedings. These recommendations existed solely to encourage calves to begin consumption of dry feed and promote early weaning. There is little evidence to support this from a biological perspective because such limited intake during the first 2 to 3 weeks of age barely provided sufficient energy and protein to meet maintenance requirements in calves under thermoneutral conditions between 10° C and 25° C. During periods of cold stress, intake of milk or milk replacer should increase by 30% to 50%. More recently, research has shown the benefits of "accelerated" or "intensive" calf-feeding programs in which liquid diet intake of milk or milk replacers with up to 28% protein are fed at rates up to 1 to 1.2 kg of solids per day. These terms are probably misnomers, since the intake of milk or milk replacer is more similar to liquid feeding programs for sheep, pigs, and beef cattle. Ollivett and colleagues[92] showed that calves challenged with *Cryptosporidium parvum* recovered faster and gained weight shortly after challenge if fed this more appropriate plane of nutrition while controls fed the traditional diet continued to lose weight. The seventh edition of the Nutrient Requirements[79] for dairy cattle uses the factorial approach to estimate requirements for growth and maintenance with consideration for environmental temperature. More progressive calf feeding programs encourage enhanced growth, higher feed efficiency, and more economical gains, especially during the first 3 weeks of life when calf starter intake is minimal. One concern expressed is that calf starter intake is delayed. However, calves quickly adjust, and weaning by 6 weeks of age is achievable.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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PART FOUR

Collection of Samples and Interpretation of Laboratory Tests

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• CHAPTER 22

Clinical Chemistry Tests

HENRY STÄMPFLI, *Consulting Editor*
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MAJOR BIOCHEMICAL ABNORMALITIES OR PROBLEMS ENCOUNTERED

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Laboratory data are discussed here in relation to case management. The focus is on interpretation of an abnormal finding in the typical clinical situation. An in-depth pathophysiologic explanation of these alterations is beyond the scope of this section. Should additional information be required, a textbook on veterinary clinical pathology should be consulted.[1,2]

All samples should be submitted with specific objectives in mind. In general, these objectives fall into one of the following categories:

- Evaluating organ system involvement or functional impairment
- Confirming a diagnosis or ruling out a disease condition
- Directing therapy formulation
- Assessing response to therapy
- Formulating a more accurate prognosis

Submission of Laboratory Samples

Veterinary Diagnostic Services

The clinician must be aware of inherent limitations of laboratory evaluation in certain clinical settings. In general, veterinary diagnostic laboratories are preferred to general medical laboratories because human medical laboratories may be less familiar with animal diseases and the responses of animals to disease. There may also be differences in test methodology and interpretation. These species differences can cause confusion when results are evaluated on the basis of human criteria that may not apply to animals.

Various desktop or portable handheld point-of-care devices are available to veterinarians for determination of serum chemistry, electrolytes, and acid-base balance. Many of these devices use self-contained strips, cartridges, or rotors and thus reduce errors associated with the maintaining, measuring, and mixing of reagents. In addition, some of these devices can use whole blood rather than serum or plasma. Some devices require refrigerated storage of reagent cartridges, which must then be warmed to room temperature for use. There are relatively few independently published data comparing the results obtained with these point-of-care devices and those obtained with standard laboratory procedures. A widely used handheld device (iSTAT) has been shown to yield comparable results for blood electrolyte concentrations and acid-base balance in dogs and horses.[3] However, it was noted that the correlation between results from this device and from standard laboratory techniques was poor for sodium in the dog and for hematocrit in the horse. A study using the same handheld device in cattle, horse, and sheep showed that except for sodium concentration and hematocrit in horses and sheep, correlation was good or excellent for most variables reported.[4] Portable point-of-care devices can provide rapid, accurate, and relatively inexpensive results. As technology continues to improve, wider and more general application of these devices in many large animal practice settings can be anticipated. Important requirements are the establishment of normal values with these devices for our large animal species of important age or production groupings as well as clear definition of the limitations and possible idiosyncratic reactions in certain species or clinical settings.

Selection of Procedures

Selection of specific laboratory tests fosters logically integrated thinking and concentrates on evaluation of the primary medical problems. However, the sophisticated autoanalyzers used by large commercial laboratories can perform a wide battery of tests quickly and efficiently with little additional cost. These panels may be broadly defined (e.g., a general large animal health panel) or may offer a more focused evaluation of a specific organ system (e.g., liver, kidney, or muscle). The clinician must ensure that the panel selected contains all the appropriate tests for a thorough evaluation of the individual patient's medical problems.

The following recommendations for diagnostic panels are intended to provide a clear indication of organ damage and/or dysfunction. The most directly applicable diagnostic procedures are listed under "Recommended," and additional procedures that may be of benefit in certain circumstances are listed under "Optional."

GENERAL PANEL. The broadly based general chemistry panel should provide a balanced evaluation of the most likely medical problems.

*Contributions to previous editions by Gary P. Carlson are acknowledged.

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Recommended
Glucose
Blood urea nitrogen (BUN)
Creatinine
Creatine kinase (CK)
Aspartate aminotransferase (AST)
Sorbitol dehydrogenase (SDH)
γ-Glutamyltransferase (GGT)
Alkaline phosphatase (ALP)
Bilirubin (direct, indirect, and total)
Total protein
Albumin
Globulin
Albumin/globulin ratio (A/G ratio)
Haptoglobulin
Serum amyloid A (equine now in some laboratories routinely reported)
Bicarbonate or total carbon dioxide (total CO_2)
Sodium
Potassium
Chloride
Calcium
Phosphate

Optional
Fibrinogen
Venous or arterial blood gases
Ionized calcium
Ionized magnesium

MUSCLE PANEL. The muscle panel should detect active skeletal and cardiac muscle injury (rhabdomyolysis) and the degree of secondary renal damage. The possible causative factors are evaluated as optional procedures, depending on the history, clinical findings, or special circumstances. Muscle biopsy with special staining may be critical to the diagnosis of specific muscle diseases such as polysaccharide storage myopathy, immune mediated myopathy, and mitochondria myopathy. Special tests for muscle function and the genetic basis for some myopathies are discussed in the chapters on muscles and genetic tests (see Chapters 42 and 52).

Recommended
CK
AST
Muscle biopsy
Urinalysis
BUN or creatinine

Optional
Myoglobin
Blood selenium
Venous blood gases
DNA analysis (HYPP, PSSM)
Calcium (ionized and total)
Magnesium (ionized and total)
Fractional excretion of:
- Sodium
- Potassium
- Chloride
- Myoglobin

LIVER DISEASE PANEL. The liver panel should detect active damage to the hepatic parenchyma, involvement of the biliary system, and alteration in hepatic function.

Recommended
SDH
AST
GGT
ALP
BUN
Bile acids
Blood glucose
Fibrinogen
Total protein
Albumin
Globulin
Bilirubin (direct, indirect, and total)
Complete urinalysis

Optional
Liver ultrasound
Liver biopsy/culture
Blood ammonia
Clotting panel
BSP clearance test (BSP $t_{1/2}$)

RENAL DISEASE PANEL. The kidney panel should provide a rough quantitative estimation of compromised renal function and should indicate the location and nature of the damage to the urinary tract.

Recommended
BUN
Creatinine
Na
K
Cl
Calcium
Phosphate
Protein
Albumin
Complete urinalysis

Optional
Renal ultrasound
Renal biopsy
Urine culture
Urine/plasma osmolality ratio
Urinary CK/creatinine ratio
Fractional excretion of:
- Sodium
- Potassium
- Chloride
- Endogenous creatinine clearance
- Sodium sulfanilate clearance

GASTROINTESTINAL DISEASE PANEL. The gastrointestinal disease panel should include evaluation of acid-base status, fluid and electrolyte balance, and renal function, which are common complicating features of gastrointestinal diseases. Additional optional or special diagnostic procedures may be necessary in calves or foals with neonatal diarrhea, in horses with colic, and in ruminants with gastrointestinal stasis or displacement.

Recommended
Packed cell volume (PCV)
Total plasma protein (TPP)
Sodium
Potassium
Chloride
Calcium (ionized and total)
Venous blood gases, pH, bicarbonate
Anion gap
BUN
Creatinine
Glucose
Peritoneal fluid cytology
Peritoneal fluid protein
Fecal occult blood
Fecal parasites
Ruminal fluid pH and analysis
Rumen fluid chloride

Optional
Peritoneal fluid (glucose and pH)
Serum immunoglobulin

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Plasma lactate (D and L forms)
Fecal protozoa
Fecal culture
Fecal *Clostridium difficile* toxin testing
Fecal cytology
Rectal biopsy (histology, culture)
Absorption test:
- Glucose
- D-Xylose
- Oral lactose tolerance test

Metabolic Profiling

The health status and productivity of dairy cattle, swine, and other food animals maintained in large confined groups involve a fragile balance between metabolic events, nutrition, agents of disease, management, and environmental factors. In these production units, the health status of the herd as a whole is of paramount importance. Subclinical disease or nutritional imbalance may contribute to suboptimal productivity. Most productivity problems in these settings are multifactorial. Defining and finding solutions to these problems can be a difficult and complicated task. Sequential assessment of weight gains, body condition scores, milk quality (fat and protein concentrations), and milk production are useful measures of the presence of subclinical production disorders but do not identify the cause. Metabolic profiling is a tool that has been used in some situations. Blood samples are drawn from a number of randomized individuals as representative of the group as a whole. Some have recommended the submission of pooled serum samples from representative individuals, much like the use of bulk tank tests as a reflection of the general level of mastitis in a herd. Sampling may be done routinely and sequentially (longitudinally). In dairy cattle this may be done during gestation or lactation but frequently focuses on the periparturient period when a combination of nutritional and metabolic events often contributes to costly production disorders.

Metabolic profiles might include most of the parameters listed under the recommended general panel with the addition of magnesium, total cholesterol, nonesterified fatty acids (NEFA), and β-hydroxybutyrate (BOHB). BOHB, NEFA, and cholesterol may provide an indication of energy balance, whereas BUN, creatinine, total protein, albumin, and CK may be helpful in assessing protein status along with urea levels in milk. In certain settings, trace minerals or fat-soluble vitamin concentrations may be important indicators of underlying nutritional problems. Metabolic profiling is not a substitute for careful clinical examination, analysis of husbandry practices, and ration analysis, but it may play a useful role in some modern large-scale operations in which a variety of subclinical problems can quickly translate into financial disaster.

Sources of Variation in Normal Values

Laboratory

One of the most commonly overlooked sources of variation in clinicopathologic data is the difference in results obtained by different laboratories. This can result in fivefold to tenfold differences in the normal range of certain enzyme activities among laboratories using similar but not identical methodologies. In the past there was marked variation in the units of measure used to express the activities of different serum enzymes. The standard method of representing serum enzyme activity is in international units per liter (IU/L), which is used in this text. Correction factors for converting the commonly used but older units of measure to international units are given in Table 22-1. The normal values given in Tables 22-2 and 22-3 are those currently used at the Ontario Veterinary College or are from the literature.[2] It is always best and crucial to use normal values and reference intervals established for the species, age, and production type by the diagnostic laboratory to which samples are submitted.

Species

There is relatively modest variation among species for most clinicopathologic parameters. Notable exceptions are plasma electrolyte concentration, erythrocyte potassium concentration in some breeds of sheep, and serum bilirubin concentration, which is higher in horses than in other species. Urea nitrogen (UN) is a less reliable indicator of renal function in ruminants and horses than creatinine because UN can be metabolized by the intestinal microflora. Donkeys and burros have a much higher GGT level than horses and cattle. Calves will have very high GGT levels compared with other species because of increased concentrations of this enzyme in bovine colostrum.

Breed

Significant differences in hematologic parameters exist between hot- and cold-blooded horses. Hot-blooded horses include most of the athletic breeds of horses (Thoroughbred, Quarter Horse, Standardbred, and Arabian breeds). Cold-blooded horses include the pony and draft breeds. Cold-blooded horses have lower red blood cell (RBC) values both at rest and after exercise and maintain a slightly lower leukocyte count; they also have lower resting and fasting indirect bilirubin concentrations.

Age

Several important differences in hematologic and clinical chemistry exist between neonatal and adult animals within species. The effects of age have been studied most carefully in horses and cattle. In comparison to adult animals, suckling neonatal animals tend to have lower BUN, slightly lower total protein and globulin, moderately higher GGT and phosphate, and markedly greater alkaline phosphatase. Creatinine in foals can be a bit higher in well-muscled foals (up to 2.5 mg/dL) and occasionally very high (up to 8 mg/dL) shortly after birth and returning to normal values within 24 hours, and it is thought to be due to defective placental transfer.[3]

Sex

With the obvious exception of sex hormone concentrations, there are few recognized differences in clinical chemistry values between sexes. In most domestic animals the intact male tends to have a slightly higher erythrocyte count, hemoglobin concentration, and PCV than the female or neutered male. This sex-related difference has been demonstrated most clearly in the horse.

Factors Influencing Results or Their Interpretation

Many factors influence the reliability and interpretation of results obtained by laboratory analysis. Sample collection and handling are very important factors. The sample collection site (e.g., jugular vein, mammary vein, tail vein, cephalic vein, lateral thoracic vein, ear vein or carotid artery, transverse fascial artery, metatarsal artery) can have an important effect on the results of tests such as blood gas evaluation, glucose, or ketones. The choice of anticoagulants depends on whether the samples are to be submitted for serum, plasma, or whole blood analyses. The specific sample requirements for the most commonly ordered clinical chemistry determinations are listed in Table 22-4. Serum is required for most chemistry parameters, and serum separator tubes work very well in most settings. There have been some indications that results of some serum hormone assays may be influenced by collection of blood in serum separator tubes. Sodium or lithium heparin is the anticoagulant of choice for most chemical determinations requiring plasma. Historically fluoride-oxalate was the anticoagulant of choice for blood glucose determination because it did halt glycolysis by the RBCs. However, fluoride may interfere with certain chemical procedures (specifically the glucose oxidase method for blood glucose determination) and should be used only for blood lactate determination or in selected circumstances in which glucose determinations are required and samples must be held for some period of time without refrigeration. Citrate is the anticoagulant of choice for clotting tests and blood typing.

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TABLE 22-1

Conversion of Conventional Units to International Units[2]

Component	Conventional Unit	Multiply By	International Unit (IU)
Chemistry			
Ammonia	µg/dL	0.5872	µmol/L
Bilirubin	mg/dL	17.1	µmol/L
Cholesterol	mg/dL	0.02586	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L
Lactate	mg/dL	0.111	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Electrolyte			
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Calcium	mg/dL	0.2495	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
Phosphorus	mg/dL	0.3229	mmol/L
Blood Gas			
P_{O_2}	mm Hg	0.1333	kPa
P_{CO_2}	mm Hg	0.1333	kPa
Bicarbonate	mEq/L	1	mmol/L
T_{CO_2}	mEq/L	1	mmol/L
Protein and Hematology			
Protein	g/dL	10	g/L
Albumin	g/dL	10	g/L
Fibrinogen	mg/dL	0.01	g/L
Hemoglobin	g/dL	10	g/L
Iron	µg/dL	0.1791	µmol/L
Transferrin	mg/dL	0.01	g/L
Haptoglobin	mg/dL	0.01	g/L
Hormone			
Cortisol	µ/dL	27.59	nmol/L
Triiodothyronine (T_3)	ng/dL	0.01536	nmol/L
Thyroxine (T_4)	µg/dL	12.87	nmol/L

kPa, Kilopascal; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide; T_{CO_2}, total carbon dioxide.

Ethylenediaminetetraacetic acid (EDTA) is the anticoagulant most often used for hematologic evaluation. Both citrate and EDTA are chelating agents, which may interfere with a wide variety of chemical analyses.

Samples should be submitted as soon after collection as possible, but circumstances may require storage of some samples for 12 to 24 hours. For collection of serum, whole blood should be allowed to clot before refrigeration. Serum should be separated from the RBCs immediately after clot formation and then kept refrigerated. Samples should be stored in clean containers free from exposure to sunlight, medications, or chemicals. If whole blood is left at room temperature for longer than 60 minutes, blood glucose will be falsely low as a result of RBC glycolysis. Storage of whole blood may result in in vitro hemolysis, with the potential for misleading increases in the serum or plasma enzymes AST and lactate dehydrogenase (LDH) and potassium and phosphorus concentrations as a result of hemolysis. In addition, failure to separate serum or plasma from the RBCs within an hour of collection may lead to leakage of erythrocyte potassium and a falsely elevated serum or plasma potassium concentrations.

Stress, transportation, excitement, and handling produce physiologic responses in animals that affect a variety of hematologic and biochemical parameters. This is most evident in the horse, which shows marked increases in RBC mass and to a lesser extent plasma protein concentration in response to excitement, exercise, or catecholamine administration. The RBC count, hematocrit, and hemoglobin concentration can increase by as much as 50%, whereas plasma protein concentration may increase by 1 to 2 g/dL. Leukocytosis mainly seen as neutrophilia is induced as the marginating leukocyte pool is mobilized into the general circulation. Prolonged stress results in the release of endogenous corticosteroids, which produce the typical "stress response" in the leukogram. A similar leukogram is found in racehorses some 4 to 6 hours after racing. The combination of catecholamine and glucocorticoid release associated with stress, transport, and excitement, as well as with many gastrointestinal catastrophes, may result in markedly elevated blood glucose concentrations (up to 400 mg/dL). Modest elevations (twofold to fourfold increase) in muscle-derived enzymes occur in association with prolonged transport or endurance exercise.

Large losses or compartmentalization of sodium-containing fluid accompanies many systemic disorders, particularly digestive problems such as diarrhea, colic, displacement of viscera, excessive sweat losses, and some urinary tract diseases. These forms of dehydration lead to decreases in plasma volume, which are indicated by moderate-to-marked increases in the PCV and TPP concentration. The concentration of other compounds dissolved in the plasma may also increase as a result of decreases in the plasma volume. The concentrations of compounds that are largely protein bound, such as calcium, are generally closely related to albumin concentration. More than 50% of serum calcium is bound to albumin. Increases or decreases in plasma protein concentration normally result in proportional changes in total serum calcium concentration, whereas the physiologically active ionized calcium may remain unchanged.

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TABLE 22-2

Clinical Chemistry: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Chemistry					
Total bilirubin	mg/dL	1.0-2.0	0.01-0.5	0.1-0.5	0-0.1
Direct	mg/dL	0-0.4	0.04-0.44	0-0.27	0-0.1
Indirect	mg/dL	0.2-2.0	0-0.3	0-0.12	0-0.1
Cholesterol	mg/dL	75-150	80-120	52-76	80-130
Creatinine	mg/dL	1.2-1.9	1.0-2.0	1.2-1.9	1.0-1.8
Glucose	mg/dL	75-115	45-75	50-80	50-75
Fibrinogen	mg/dL	100-400	300-700	100-500	100-400
Haptoglobin	mg/dL	0.01-0.17	0.0-0.05	NA	NA
Serum amyloid A	mg/dL	0-2.0	NA	NA	NA
Protein (total serum)	g/dL	5.2-7.9	6.7-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Urea nitrogen	mg/dL	10-24	20-30	8-20	10-20
Enzyme					
ALP	IU/L	143-395	0-488	68-387	93-387
AST	IU/L	226-366	78-132	60-280	167-513
CK	IU/L	108-430	44-211	64-158	104-219
GGT	IU/L	7-54	15-39	40-79	20-56
LDH	IU/L	162-412	697-1445	238-440	123-392
LDH-1	%	6.3-18.5	39.8-63.5	45.7-63.6	29.3-51.8
LDH-2	%	8.4-20.5	19.7-34.8	0-3.0	0-5.4
LDH-3	%	41-65.9	11.7-18.1	16.4-29.9	24.2-39.9
LDH-4	%	9.5-20.9	0-8.8	4.3-7.3	0-5.5
LDH-5	%	1.7-16.5	0-12.4	10.5-29.1	14.1-36.8
SDH	IU/L	1.9-5.8	4.3-15.3	5.8-27.9	14-23.6
Electrolyte					
Sodium	mEq/L	132-146	132-152	139-152	142-155
Potassium	mEq/L	2.4-4.7	3.9-5.8	3.9-5.4	3.5-6.7
Chloride	mEq/L	99-109	97-111	95-103	99-110
Calcium	mEq/L	11.2-13.6	9.7-12.4	11.5-12.8	8.9-11.7
Phosphorus	mEq/L	3.1-5.6	5.6-6.5	5.0-7.3	6.5
Magnesium	mEq/L	2.2-2.8	1.8-2.3	2.2-2.8	2.8-3.6
Osmolality	mOsm/kg	270-300	270-300	NA	NA
Anion gap	mEq/L	6-15	14-20	NA	NA
Acid-Base (Venous Blood)					
pH		7.32-7.44	7.31-7.53	7.32-7.54	NA
P_{CO_2}	mm Hg	38-46	35-44	37-46	NA
Bicarbonate	mEq/L	20-28	17-29	20-25	NA
T_{CO_2}	mEq/L	24-32	21-32	21-28	26-30
Special					
Red blood cell acetylcholinesterase	IU/L	450-790	1270-2430	640	270
Ammonia	µg/dL	13-108	NA	NA	NA
BSP ($t_{1/2}$)	min	2.0-3.7	2.5-4.0	1.6-2.7	2.1
Serum iron	µg/dL	73-140	57-162	166-222	NA
TIBC	µg/dL	200-262	63-186	NA	NA
Lactic acid	mmol/L	1.11-1.78	0.56-2.22	1.00-1.33	NA
Ketones					
Acetone	mg/dL	NA	0-10	0-10	NA
Acetoacetate	mg/dL	NA	0-1.1	NA	NA
BHB	mg/dL	NA	0-10	NA	NA

Data from Kaneko JJ, Harvey JW, Bruss ML, eds. 2008. Clinical biochemistry of domestic animals, ed 6. Academic Press, Burlington, MA; and the Normal Values Clinical Pathology Ontario Veterinary College and Animal Health Lab-Guelph, 2012.

ALP, Alkaline phosphatase; *AST,* aspartate aminotransferase; *BHB,* β-hydroxybutyrate; *BSP ($t_{1/2}$),* bromsulphalein clearance halftime; *CK,* creatine kinase; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *NA,* not applicable; *P_{CO_2},* partial pressure of carbon dioxide; *SDH,* sorbitol dehydrogenase; *T_{CO_2},* total carbon dioxide; *TIBC,* total iron-binding capacity.

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TABLE 22-3

Serum Protein Electrophoresis: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Total protein	g/dL	5.2-7.9	6.74-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
α1	g/dL	0.06-0.7	NA	NA	NA
α2	g/dL	0.31-1.31	NA	NA	NA
α	g/dL	NA	0.75-0.88	0.3-0.6	0.5-0.7
β1	g/dL	0.4-1.58	NA	0.7-1.2	0.7-1.2
β2	g/dL	0.29-0.89	NA	0.4-1.4	0.3-0.6
β	g/dL	NA	0.8-1.12	NA	NA
γ_1	g/dL	NA	NA	0.7-2.2	NA
γ_2	g/dL	NA	NA	0.2-1.1	NA
γ	g/dL	0.55-1.9	1.69-2.25	NA	0.9-3
Albumin/globulin (A/G) ratio		0.62-1.46	0.84-0.94	0.42-0.76	0.63-1.26

Data from Kaneko JJ, Harvey JW, Bruss ML, eds. 1997. Clinical biochemistry of domestic animals, ed 6. Academic Press, Burlington, MA.
NA, Not applicable.

TABLE 22-4

Recommended Anticoagulants for Hematologic or Clinical Chemistry Evaluation

Anticoagulant	Specimen	Test or Procedure
Ethylenediaminetetraacetic acid (EDTA)	Whole blood	Complete blood count, cross-match, platelet count
	Whole blood	Blood selenium
	Plasma	Refractometric protein and fibrinogen
	Peritoneal fluid	Fluid analysis
	Bone marrow	Hematologic evaluation
	Synovial fluid	Fluid analysis
Heparin	Whole blood	Blood pH, blood gases
	Plasma	Electrolytes, osmolality
	Synovial fluid	Mucin clot test
Fluoride and oxalate	Plasma	Lactate
Citrate	Whole blood	Blood typing
	Plasma	Coagulation tests (PT, PTT, factor analysis)
None, serum separator tubes	Serum	Most chemistries, electrolytes, osmolality
		Protein electrophoresis
		Hormones (cortisol, T_3, T_4)
		Immunoglobulins (IgG, IgM, IgA)

Modified from Brobst DF, Parry BW. 1987. Normal clinical pathology data. In Robinson NE (ed), Current therapy in equine medicine, ed 2. Saunders, Philadelphia, PA.
PT, Prothrombin time; *PTT,* partial thromboplastin time; *T_3,* triiodothyronine; *T_4,* thyroxine.

Diseases that cause a reduction in effective circulating fluid volume often also cause alterations in renal function. This so-called prerenal azotemia results in moderate to marked elevation in BUN and creatinine. Although this is generally considered primarily a prerenal azotemia, real pathologic changes in the kidneys often are associated with the systemic processes initiated by these disorders. Longitudinal reevaluation of renal function (urinalysis, serum BUN, and creatinine) in these patients during the course of disease is important because it affects prognosis, response to fluid administration, and the potential for nephrotoxicity and systemic toxicity of a variety of chemotherapeutic agents used in such patients.

Fasting laboratory data are important for evaluation of many disease conditions in human and small animal patients. Truly fasting conditions are rather difficult, given the large and complex gastrointestinal tract of most herbivores and are thus seldom used. The feeding of animals in relation to sample collection, however, can have an impact on the data obtained. Hay-feeding in horses is reported to affect sodium, potassium, and protein concentrations within the first few hours after feeding. Animals feeding on lush green pasture or large amounts of silage may have slightly different parameters from those fed high-concentrate rations. The anion-cation balance of the ration has an impact on relative serum electrolyte concentration, acid-base balance, and urine pH and urinary electrolyte excretion. Lactescent (cloudy) plasma may be observed in samples from nursing foals or calves. The fluid intake of the normal nursing neonate may range from 100 mL/kg/day to more than 250 mL/kg/day. This high fluid intake is reflected by a commensurately high output of urine with a low specific gravity and low osmolarity.

The administration of certain medications may have an impact on some laboratory parameters. Tranquilization may be necessary for restraint and safe sample collection. The practitioner should be aware that tranquilizers often decrease RBC mass and plasma protein concentration. This is particularly true of the phenothiazine-derivative tranquilizers when used in the horse. Xylazine administered to large animals produces a modest catecholamine release, which may be evidenced by the slight sweating response seen in many horses sedated with this drug. Glucose concentration will increase modestly in response to the xylazine-induced catecholamine release. Repeated intramuscular injections with certain antibiotics (especially erythromycin and tetracycline) or other preparations that are locally irritating may produce slight-to-moderate elevations in muscle-derived serum enzyme activities. Intravenous administration of certain drugs and compounds such as dimethyl sulfoxide (DMSO) can produce intravascular hemolysis and hematuria. The amount of hemolysis in these circumstances is relatively small and of little consequence, except that it can cause confusion as to why hemoglobinuria occurred.

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Fluid and Electrolyte Balance

Packed Cell Volume and Total Plasma Protein

PCV and TPP concentration are simple and convenient indicators of acute fluid alterations. Changes in the plasma volume generally are reflected by changes in the PCV and the TPP concentration. In dehydrated humans, changes in the PCV are believed to be the more reliable guide to changes in plasma volume because substantial protein fluxes into and out of the circulation have been shown to occur. However, in most animal species the range of normal for the PCV is much wider than for the TPP concentration. This is particularly true of horses, in which excitement, pain, or catecholamine release can produce variable mobilization of splenic erythrocytes, making it difficult to obtain a truly resting PCV. For these reasons, precise quantitative estimation of a change in plasma volume using these parameters is more complex and less reliable in large animal species. As plasma volume increases or decreases, the change in the PCV is always less than the change in the TPP concentration. However, a large disparity in the changes in the PCV and the TPP concentration in a patient with a history of loss of sodium-containing fluid and clinical evidence of reduced effective circulating fluid volume suggests blood or protein loss. Marked increases in the PCV with a normal-to-low TPP concentration frequently are encountered in animals with acute protein-losing enteropathies such as salmonellosis or equine toxic enteritis, or enterocolitis. In horses undergoing treatment for diarrhea, the excessive administration and retention of sodium-containing fluids is a key factor in the development of edema and hypoproteinemia. Blood loss generally results in a decrease in both PCV and TPP concentration with a lag time of up to 24 to 48 hours.

Serum Sodium

The serum sodium concentration is a function of the exchangeable cation content (i.e., the exchangeable sodium [Na] in the extracellular fluid [ECF] volume plus the exchangeable potassium [K] in the intracellular fluid [ICF] volume relative to total body water). The ECF *sodium* content determines the ECF volume, whereas the ICF volume is a function of ICF *potassium* content.

Changes in the sodium concentration reflect the net changes in this relationship and often do not represent accurately the changes in sodium balance. Changes in water balance are thus primarily responsible for changes in the serum sodium concentration and one should always consider the hydration status of the patient for sodium concentration interpretation. Hyponatremia is an indication of a relative water *excess,* whereas hypernatremia is an indication of a relative water *deficit*.

Dehydration is defined as a loss of body water (fluid volume contraction). It occurs in a variety of clinical circumstances. The serum sodium concentration provides a means of categorizing dehydration in a physiologically meaningful way. Hypertonic dehydration, which occurs when water losses exceed the losses of sodium and potassium, is indicated by hypernatremia (free water loss or hypotonic fluid losses). The response of horses to feed and water deprivation is an example of this form of dehydration. Isotonic dehydration occurs with a balanced loss of water and electrolytes—that is, approximately 140 to 150 mEq of sodium plus potassium (Na + K) for each liter of water lost. Because the relative water balance has not changed, the serum sodium concentration remains unchanged despite the accumulation of what may have been a substantial body sodium deficit. The early stages of acute diarrhea and the dehydration of heavily sweating endurance horses are examples of isotonic dehydration. Hypotonic dehydration occurs when the losses of exchangeable cations (Na + K) exceed the net change in water balance; this condition is indicated by hyponatremia. Hypotonic dehydration often is seen in animals with subacute or chronic diarrhea that develop substantial water and electrolyte deficits but then replace part of the water deficit through water consumption. Fig. 22-1 shows the compartmental distribution of fluid between the ECF volume and the ICF volume in four situations.

HYPONATREMIA. Hyponatremia results from retention of free water or excess loss of sodium. It is often but not invariably associated with conditions that cause sodium depletion such as vomiting, diarrhea, excessive sweat losses, and adrenal insufficiency. The fluid losses in these conditions are most often hypotonic or isotonic, and initial fluid and electrolyte deficits do not result in hyponatremia until water intake, renal water retention, or both disturb the balance between the remaining exchangeable cations and the total body water.

The accumulation of sodium-containing fluid in body cavities or the gut lumen caused by ascites, peritonitis, or rupture of the bladder or by displacement, torsion, or volvulus of the gut is referred to as a *third-space problem.* When such accumulations develop rapidly, the plasma volume is reduced, and the serum sodium concentration subsequently may decrease as compensating renal responses cause

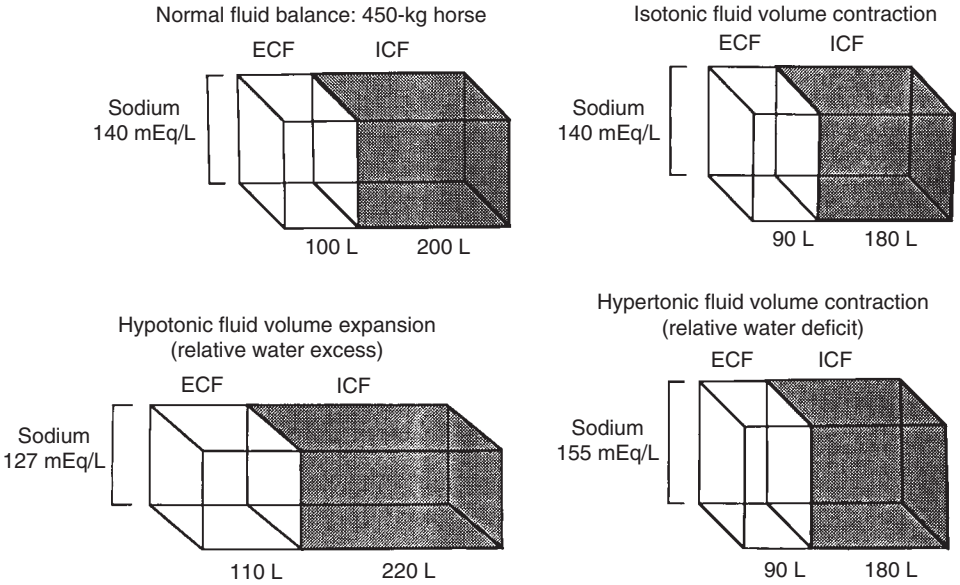


FIG. 22-1 Compartmental distribution of fluid between the extracellular fluid (ECF) volume and the intracellular fluid (ICF) volume in a 450-kg horse with normal fluid balance, with isotonic fluid volume contraction, with hypotonic fluid volume expansion, and with hypertonic fluid volume contraction. *(Modified from Kaneko JJ, Harvey JW, Bruss ML, eds. 2008. Clinical biochemistry of domestic animals, ed 6. Elsevier Academic Press, New York.)*

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BOX 22-1

Causes of Hyponatremia

Common Causes

- Relative water excess
  - Loss of sodium-containing fluid (decreased effective circulating volume)
    - Diarrhea
  - Excessive sweating
  - Blood loss
  - Fluid drainage
    - High-volume gastric reflux
    - High-volume pleural drainage
- Adrenal insufficiency
- Sequestration of fluid (third-space problems)
  - Peritonitis
  - Ascites
  - Pleuritis
  - Ruptured bladder
  - Torsion or volvulus of the gut
  - Excessive administration of 5% dextrose to patient with renal disease
- False hyponatremia
  - Hyperlipidemia
  - Hyperproteinemia
  - Hyperglycemia

Uncommon Causes

- Water retention with normal effective circulating volume
  - Psychogenic polydipsia
  - Renal disease
  - Inappropriate antidiuretic hormone secretion
  - Use of diuretics

BOX 22-2

Causes of Hypernatremia

Common Causes

- Pure water losses
  - Panting
  - Water deprivation
- Sodium excess (water restriction)
  - Salt poisoning
  - Feeding only electrolytes, no free water

Uncommon Causes

- Water loss exceeds electrolyte loss
  - Vomiting
  - Diarrhea
  - Burns
  - Intrinsic renal disease
  - Diuretics
  - Diabetes insipidus
    - Central
    - Nephrogenic
  - Hypertonic saline or sodium bicarbonate administration
  - Mineralocorticoid excess

water retention. Rupture of the bladder in neonatal foals is associated with marked hyponatremia and hypochloremia. As fluid intake continues and dilute urine accumulates in the abdomen, sodium, chloride, and other ions are drawn from the rest of the ECF into this accumulating fluid. No sodium or chloride has been lost from the body, and the observed decreases in the electrolyte concentration are caused by changes in the relative water balance ("water follows solute"). The neurologic signs seen in these foals are largely caused by the effects on the central nervous system of the rapidly developing and marked hypotonic hyponatremia. Progressively severe neurologic disturbances may be seen as the serum sodium concentration falls below 115 mEq/L and then below 100 mEq/L. The severity of the neurologic abnormalities is a function of both the rate at which hyponatremia develops and the absolute degree of hyponatremia. Neurologic disturbances can occur iatrogenically if excessive amounts of free water (usually given as 5% dextrose) are administered to patients with altered renal function.

Mastitis results in an increased loss of sodium in the milk, and a low-grade mastitis problem in a dairy herd on a marginal dietary salt intake may result in sodium depletion and medullary washout. Decreased milk production, polyuria, hyposthenuria, and a low urine sodium level may be noted, although the serum sodium concentration may remain within the lower range of normal.

The most common causes of hyponatremia are listed in Box 22-1. Marked hyperlipidemia or hyperproteinemia produces a falsely low sodium concentration value because lipid or protein occupies a significant volume in the serum or plasma sample and because sodium is present only in the aqueous phase. This potential cause of hyponatremia is indicated by an increase in the osmolar gap between measured and calculated osmolality. The use of direct ion-selective electrodes (direct potentiometry; all modern blood gas machines) for electrolyte determinations avoids this potential cause of a falsely low sodium concentration value.

Marked hyperglycemia causes a reduction in the measured serum sodium concentration of approximately 1.6 mEq/L for every 100 mg/dL increase in the glucose concentration. Increases in the plasma glucose concentration generate osmotic forces that result in the movement of cellular water into the ECF, diluting the plasma sodium concentration.

HYPERNATREMIA. Hypernatremia can develop if water is lost in excess of sodium or if sodium is ingested in excess of water. Hypernatremia can occur in the initial stages of diarrhea, vomiting, or renal disease if water loss exceeds electrolyte loss (Box 22-2). When water losses are replaced by increased water consumption, enhanced renal water retention, or both, the serum sodium concentration decreases. Food and water deprivation in normal horses and cattle is associated with substantial reduction of renal and fecal output, but continued cutaneous and respiratory insensible water loss may result in hypernatremia (primary water loss). Hypernatremia may occur transiently as a result of sodium excess after administration of hypertonic saline or hyperosmolar sodium bicarbonate if water intake is restricted or impaired. Hypernatremia has been reported in calves fed an inappropriately mixed oral electrolyte replacement solution as their only fluid intake.[5] The hypernatremia observed with salt poisoning in cattle and swine is the result of water restriction in animals that have been maintained on a high-salt intake.

Serum Potassium

Potassium is the major intracellular cation. Between 60% and 75% of total body potassium is found within muscle cells and in bones. Only 5% is in the ECF and not always a reflection of total body potassium. The serum potassium concentration is influenced by factors that alter internal balance (the distribution of potassium between the ECF and the ICF) and those that change external balance (potassium intake and output). Potassium is higher in foals compared with adult horses. Generally, herbivores have a net positive intake in potassium, which is usually carefully regulated by the renal system. Serum potassium concentrations correlate relatively well with total body potassium content in cattle but not in horses. Changes in the serum potassium concentration occur in a wide variety of clinical circumstances and have profound neuromuscular effects that are largely the result of changes in cell membrane potential. The responses to dehydration and acid-base imbalance often complicate the evaluation of the potassium concentration. For example, calves with acute diarrhea often develop body potassium depletion because of excessive losses and inadequate intake, but the serum potassium concentration of these animals is usually normal to increased as the result of renal shutdown and the metabolic acidosis induced by dehydration,

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BOX 22-3

Causes of Hypokalemia

Common Causes

Altered External Balance*

Vomiting
Vagal indigestion with internal vomiting
Diarrhea
Third-space problems (gut or abomasal torsion or volvulus; peritonitis)
Excessive sweat losses
Dietary deficiency
Prolonged anorexia

Altered Internal Balance

Metabolic alkalosis

Uncommon Causes

Altered External Balance

Mineralocorticoid excess
Use of corticosteroids with mineralocorticoid activity
Diuretics
Renal tubular acidosis
Postobstruction diuresis

Altered Internal Balance

Excessively rapid sodium bicarbonate administration
Insulin and/or glucose administration
Catecholamine administration or endogenous release

*External balance refers to the relative changes in potassium intake and output; internal balance refers to the distribution of potassium between the extracellular and the intracellular fluid compartments.

BOX 22-4

Causes of Hyperkalemia

Common Causes

False hyperkalemia
- In vitro hemolysis
- Prolonged storage of blood (over 6 hours) without separation of serum or plasma

Altered external balance
- Hypovolemia with renal shutdown

Altered internal balance
- Metabolic acidosis
- Vigorous exercise

Uroperitoneum

Uncommon Causes

False hyperkalemia
- Markedly elevated leukocyte or platelet count

Altered internal balance
- Hyperkalemic periodic paralysis in Quarter Horses
- Diabetes mellitus
- Tissue necrosis
- Renal disease
- Addison disease

sodium depletion, and hypovolemia. Hypokalemia may become evident only as other fluid and electrolyte losses are replaced.

Measuring the erythrocyte potassium concentration is relatively easy and has been suggested as an aid in assessing the need for potassium supplementation in racehorses with recurrent muscle disease or in alert downer cows early postpartum. However, experimental studies in horses indicate that the erythrocyte potassium concentration does not always accurately reflect potassium deficits.

HYPOKALEMIA. Hypokalemia increases resting membrane potential, resulting in muscle weakness, impaired urine concentration ability, and arrhythmias. Hypokalemia may result from depletion of the body's potassium stores or from a redistribution of potassium from the ECF into the ICF space (Box 22-3). Hypokalemia is most commonly seen with altered intake and absorption and with excessive potassium losses from the gastrointestinal tract caused by vagal indigestion, torsion of the abomasum, ileus, or diarrhea. Excessive renal loss may result from mineralocorticoid excess, certain diuretics, or altered renal function, as reported in horses with renal tubular acidosis. Marked hypokalemia develops when reduced dietary intake caused by anorexia is associated with excessive potassium losses (e.g., causing muscle paresis in dairy cows early postpartum).

Hypokalemia without potassium depletion results from the movement of extracellular potassium to the intracellular space. This form of hypokalemia occurs in response to an acute alkalosis and to the administration of insulin or glucose. Overzealous and rapid administration of sodium bicarbonate can produce an alkalosis with a profound and rapidly developing hypokalemia. Animals with moderate potassium deficits that are vigorously treated with sodium bicarbonate to correct a coexisting mild metabolic acidosis may be particularly prone to this problem. The initial response to catecholamine administration is a modest, transient increase in potassium caused by α-adrenergic stimulation, which is often followed by hypokalemia caused by β-adrenergic receptor responses.

Pseudohypokalemia is seen in severe lipemia with potassium measured with indirect potentiometry (e.g., automated profile chemistry analyzers).

HYPERKALEMIA. Hyperkalemia may develop in vitro as a result of hemolysis or leakage of erythrocyte potassium after storage of whole blood (Box 22-4). The release of potassium from leukocytes or platelets into the serum after clot formation is a potential cause of hyperkalemia if marked leukocytosis or thrombocytosis is present. Hyperkalemia also results from renal potassium retention in Addison disease, acute renal failure (ARF), and renal shutdown. A number of factors contribute to the movement of intracellular potassium into the ECF, resulting in hyperkalemia. Hyperkalemia is often associated with metabolic acidosis, particularly when the acidosis results from volume depletion and is complicated by renal shutdown. Hyperkalemia has been reported in animals with massive muscle necrosis, but neither hyperkalemia nor metabolic acidosis is a common feature in horses with exertional rhabdomyolysis. Vigorous short-term exercise of horses at high intensity results in a marked but transient hyperkalemia (9 to 10 mEq/L) that may be associated with the profound lactic acidosis seen with anaerobic workloads.[6] Potassium returns to normal within minutes, and often a modest hypokalemia occurs later in the recovery period. Episodic hyperkalemia and muscular weakness are associated with the condition of hyperkalemic periodic paralysis (HYPP).[7] HYPP is inherited as an autosomal-dominant trait in horses, with a specific Quarter Horse lineage having a sodium channel defect[8] (see Chapter 42 for a more complete discussion of this disorder). The disease is the result of a single DNA base pair substitution that leads to the production of an abnormal voltage-regulated sodium channel at the cell membrane.[9] Sudden marked increases in the serum potassium concentration, up to 8 to 9 mEq/L, are the result of transcellular movement of potassium and are associated with profound electrocardiographic abnormalities and fluid shifts.

In drug-induced hyperkalemia, trimethoprim has been associated with hyperkalemia by inhibiting normal sodium reabsorption in the cortical renal collecting duct.

Serum Chloride

Chloride is a major ECF anion and very important with sodium for osmolality and acid-base balance. Together with sodium it is the main component of the strong ion difference (SID). Alterations in the chloride concentration are usually associated with nearly

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BOX 22-5

Causes of Hyperchloremia

With Proportional Increase in Sodium

Common Causes

- Relative water deficit
  - Panting
  - Water deprivation
  - Salt poisoning

Uncommon Causes

- Vomiting
- Diarrhea
- Burns
- Intrinsic renal disease
- Diuretics
- Diabetes insipidus
  - Central
  - Nephrogenic
- Hypertonic saline administration
- Mineralocorticoid excess

Without Proportional Increase in Sodium

Common Causes

- Hyperchloremic metabolic acidosis
- Renal tubular acidosis

Uncommon Cause

- Compensation for respiratory alkalosis

BOX 22-6

Causes of Hypochloremia

With Proportional Decrease in Sodium

Common Causes

- Relative water excess
  - Diarrhea
  - Excessive sweating
  - Blood loss
  - Fluid drainage
  - High-volume gastric reflux
  - High-volume pleural drainage
  - Sequestration of fluid (third-space problems)
    - Peritonitis
    - Ascites
    - Ruptured bladder
  - Renal disease
- False hypochloremia
  - Hyperlipidemia
  - Hyperproteinemia
  - Hyperglycemia

Uncommon Causes

- Psychogenic polydipsia
- Inappropriate antidiuretic hormone secretion
- Adrenal insufficiency

Without Proportional Decrease in Sodium

Common Causes

- Metabolic alkalosis
  - Exhaustive disease syndrome
  - Abomasal torsion
  - Vagal indigestion with internal vomiting
  - Response to furosemide in horses

Uncommon Cause

- Compensation for respiratory acidosis

proportional changes in the sodium concentration as the result of changes in relative water balance. In addition, the chloride concentration tends to vary inversely with the bicarbonate concentration; therefore, when disproportionate changes in the chloride concentration relative to sodium occur, significant acid-base imbalances should be anticipated. Disproportionate increases in chloride are associated with a normal-to-low anion gap hyperchloremic metabolic acidosis, but they also are seen as a result of the compensating responses for a primary respiratory alkalosis (Box 22-5). A striking hyperchloremic metabolic acidosis has been reported in horses with renal tubular acidosis.[10,11] Iatrogenic hyperchloremic acidosis can be induced by overzealous NaCl fluid treatment.[12]

Disproportionate decreases in chloride relative to sodium are characteristically seen in metabolic alkalosis, but also may be seen as part of the compensating response for chronic primary respiratory acidosis (Box 22-6). Hypochloremic metabolic alkalosis is a common feature in many digestive disorders of ruminants and is caused by loss of chloride-rich fluids or sequestration of such fluids in the abomasum and forestomachs. It is also seen in horses with diarrhea as chloride is absorbed in the ileum and colon. Horses treated with diuretics (e.g., furosemide-induced metabolic alkalosis) may show hypochloremia.[13] Heavy sweating in horses is associated with hypochloremic metabolic alkalosis.

Osmolality

ECF osmolality is maintained around 300 mOsm (isotone). Measurement of the serum osmolality provides an indication of relative water balance in much the same way the serum sodium concentration does. In most circumstances these parameters are closely correlated. Comparing the measured osmolality with the calculated osmolality, as determined from the measured concentrations of the major solutes in serum (sodium, chloride, glucose, and urea), provides a means of determining if the serum water content deviates widely from normal or if foreign, low-molecular-weight substances are present in the blood. The difference between the measured osmolality and the calculated osmolality is called the *osmolar gap.* Decreases or increases in the osmolar gap could indicate laboratory error, but increases of more than 10 mOsm/kg generally are the result either of a decrease in the serum water content (caused by hyperlipidemia or hyperproteinemia) or of the presence of abnormally high concentrations of low-molecular-weight substances in the serum. These substances can include a variety of exogenous and potentially toxic compounds such as mannitol, ethanol, methanol, propylene glycol, ethylene glycol, isopropanol, ethyl ether, acetone, trichloroethane, and paraldehyde. All hypernatremic animals are hyperosmolal. Hypo-osmolality is always associated with hyponatremia, but not all cases with hyponatremia are hypo-osmolal (e.g., concurrent hyperglycemia).

Serum Calcium

Calcium plays a vital role in many of life's processes, including maintenance of neuromuscular excitability, permeability of cell membranes, conduction of nerve impulses, muscle contraction, and blood clotting. For these reasons the serum calcium concentration or, more correctly, the ionized calcium concentration is normally maintained within a relatively narrow range, despite wide variation in intake and output. Calcium metabolism is regulated by dietary factors, vitamin D and its active metabolites, and the hormones parathormone and calcitonin. Compared with ruminants in horses, a relatively larger percentage of calcium is excreted in the urine. The serum calcium concentration is maintained by adjusting intestinal absorption, renal excretion, and mobilization of available calcium from the large stores in bone. Calcium exists in the serum in three forms: ionized calcium, complexed calcium, and protein-bound calcium. Ionized calcium, which normally constitutes 40% to 60% of the total calcium, is the physiologically active form of calcium. Protein binding can cause confusion (protein-bound calcium normally constitutes 40% to 50% of the total calcium and most of it is bound to albumin). Hyperalbuminemia may result in a modest hypercalcemia, whereas hypoproteinemia, especially hypoalbuminemia, regularly results in a moderate

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BOX 22-7

Causes of Hypocalcemia

Common Causes

Parturient paresis (milk fever)
Grass tetany
Hypoalbuminemia (decreased total calcium; ionized calcium may remain unchanged)
Fat necrosis
Lactation tetany
Transport tetany
Synchronous diaphragmatic flutter
Blister beetle toxicosis (cantharidin)
Acute renal failure
Anorexia in lactating cows
Colic in horses

Uncommon Causes

Acute toxemia and associated anorexia in lactating dairy cows
Hypoparathyroidism
Exertional rhabdomyolysis
Malignant hyperthermia
Pancreatic disease
Oxalate toxicity
Tetracycline administration
Furosemide administration
Alkalosis induced by excessive bicarbonate administration

BOX 22-8

Causes of Hypercalcemia

Common Causes

Chronic renal failure in horses
Hypervitaminosis D
- Excessive dietary supplements
- Plant intoxication
  - *Cestrum diurnum* (day blooming jasmine)
  - *Solanum malacoxylon*

Excessive or too rapid intravenous administration of calcium

Uncommon Causes

Neoplasia (pseudohyperparathyroidism)
- Lymphosarcoma
- Gastric squamous cell carcinoma

Hyperparathyroidism

hypocalcemia. The ionized calcium concentration, usually measured with ion selective electrodes, generally remains within normal limits, despite increases or decreases in total calcium associated with the change in protein concentration. The acid-base balance has additional influence on the amount of ionized and protein-bound calcium. Alkalosis reduces ionized calcium and increases protein binding, whereas acidosis produces the opposite effect. Ion-specific electrodes are available for determining the ionized calcium level, which can be very useful if blood samples are handled appropriately. Most diagnostic laboratories provide the total serum calcium value, which is composed of ionized, complexed, and protein-bound calcium.

HYPOCALCEMIA. Large increases or decreases in the serum calcium concentration generally are the result of a failure in the normal mechanisms of calcium homeostasis rather than a reflection of absolute calcium deficits or calcium-phosphorus imbalances. Hypocalcemia occurs with some frequency in domestic animals, particularly in high-producing dairy cattle at the onset of lactation. In cattle the serum calcium concentration normally decreases to less than 8 mg/dL with the stress of parturition and the onset of lactation (Box 22-7). Failure to mobilize sufficient calcium to maintain serum calcium results in the clinical syndrome of parturient paresis (see Chapter 41 for a more detailed discussion of this syndrome). Most animals are recumbent with a calcium level of 6 mg/dL or less, and fatalities may occur if the level drops below 4 mg/dL. Parturient paresis is associated with a normal to increased serum magnesium level, hypophosphatemia, and hypocalcemia. Change in the cation-anion balance in the diet (increased proportion of strong anions) of dairy cattle during the periparturient period has modest effects on the acid-base balance and enhances calcium mobilization from storage sites, thus reducing the incidence of milk fever in cows at high risk. Grass tetany is associated with marked hypomagnesemia and modest hypocalcemia, whereas the inorganic phosphorus level remains within the normal range.

Systemic diseases resulting in anorexia (e.g., traumatic reticuloperitonitis, ketosis, and displaced abomasum) or acute toxemic conditions (e.g., coliform mastitis, septicemia, or aspiration pneumonia) that produce anorexia in lactating cattle frequently result in hypocalcemia. Hypocalcemia is also seen in sheep on marginal rations if stressed by inclement weather or when being moved. Hypocalcemia is seen in cattle with fat necrosis, presumably as the result of incorporation of calcium with the fat as a form of soap. Horses sweating or with exhaustive disease syndrome or transit tetany often develop decreases in ionized calcium with resultant muscle cramps and synchronous diaphragmatic flutter, which generally respond to intravenous calcium and electrolyte administration. Horses, cattle, and sheep usually respond initially to acute renal tubular damage with mild hypocalcemia and hyperphosphatemia. Idiopathic hypocalcemia, which may exist in foals 4 to 5 days old, has poor prognosis and a cause is not established.[14] Transport tetany and lactation tetany of horses are associated with hypocalcemia. In lactation tetany of mares, this is correlated with high milk production.

HYPERCALCEMIA. Marked hypercalcemia, with a serum calcium level ranging from 14 to 20 mg/dL, and modest hypophosphatemia are frequently observed in horses with chronic renal failure (CRF) that are fed a high-calcium diet such as alfalfa hay (Box 22-8). In these horses, blood samples collected in standard EDTA tubes may actually clot. This occurs because the serum calcium concentration is so high that there is insufficient EDTA to bind all the calcium, and some free calcium is available to complete the clotting process. Vitamin D intoxication can develop as a result of excessive dietary supplementation or the ingestion of certain plants such as *Cestrum diurnum* (day blooming jasmine) and *Solanum malacoxylon,* which contain toxic quantities of vitamin D analogs. Primary hyperparathyroidism is exceedingly rare in large animals, but pseudohyperparathyroidism with hypercalcemia occasionally can develop in animals with tumors that produce protein substances with parathormone-like biologic activity. This has been reported in a few animals with lymphosarcoma or gastric squamous cell carcinoma.

Serum Phosphorus

Phosphorus is found primarily in the skeleton and teeth in close association with calcium in the intricate and dynamic crystalline structure of bone. Intracellularly, phosphate plays an essential role in the degradation and synthesis of many compounds. Also, in the forms of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP), it is the primary form of energy storage and transfer required for almost all of life's processes. Phosphorus in the ECF exists primarily in the organic and inorganic form specifically as the "buffer" pair H_2PO^{-3} and HPO^{-4} and plays a role in acid-base balance. Like calcium, phosphorus is regulated by dietary factors, the active metabolites of vitamin D, and the hormones parathormone and calcitonin. Imbalances of calcium and phosphorus or the presence of compounds that bind these substances in the gut can produce serious imbalances that are not always evident on analysis of serum samples. Measurement of urinary output or creatinine clearance ratios for calcium and phosphate are simple and helpful procedures. They provide an indication of an imbalance while more definitive procedures such as ration analysis are contemplated.

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BOX 22-9

Causes of Hypophosphatemia

Common Causes

Chronic renal failure in horses
Parturient paresis in cattle
Postparturient hemoglobinuria

Uncommon Causes

Brassica toxicity
Inadequate dietary intake
Starvation or chronic wasting diseases
Hyperparathyroidism, pseudohyperparathyroidism

BOX 22-10

Causes of Hyperphosphatemia

Common Causes

Acute renal failure
Nutritional secondary hyperparathyroidism (excess phosphate intake)
Endurance exercise in horses
Higher normal range in neonates

Uncommon Causes

Acute rhabdomyolysis
Vitamin D toxicity

HYPOPHOSPHATEMIA. Serum phosphorus concentrations are not always an accurate guide to phosphate balance, but dietary deficiencies of phosphorus are frequently manifested by hypophosphatemia. Hypophosphatemia is a common feature in cattle with parturient paresis (see also Chapter 41) and horses with CRF (Box 22-9). It has been reported in animals with experimental oxalate toxicity, in chronic wasting states, or with starvation. Postparturient hemoglobinuria is a disorder of cattle, primarily lactating dairy cattle, that often is associated with diets low in phosphorus. Although marked hypophosphatemia is often reported, it is not an invariable feature of this disorder.

HYPERPHOSPHATEMIA. Age-related differences exist in the normal range of serum phosphorus concentration. Young animals have much higher values than adults, with values for neonates commonly up to 7 to 9 mg/dL. The serum phosphate concentration declines progressively with age. Hyperphosphatemia is seen in animals with vitamin D toxicity, transiently in horses after long-distance endurance rides, and initially in horses with ARF (Box 22-10).

Serum Magnesium

Between 20% and 30% of magnesium is bound to mostly albumin and 60% is free (ionized) or bound to phosphorus or other components. Free magnesium can be measured with ion-selective electrodes. Disturbances of magnesium metabolism occur principally in cattle and sheep. Complex nutritional and environmental interactions contribute to a variety of clinical syndromes attributed to magnesium deficiency and the onset of tetany in grazing animals.

HYPOMAGNESEMIA. Hypomagnesemia is reported in cattle with grass tetany, transport tetany, winter tetany, and in sheep with grass staggers (Box 22-11) (see also Chapter 41). A serum magnesium level below 1.8 mg/dL is considered low; values below 1 mg/dL are considered severe and are likely to be associated with clinical signs. Hypomagnesemia caused by dietary magnesium deficiency has been reported in calves reared in confinement and fed a milk diet exclusively (milk tetany). In chemistry panels of normal horses, hypomagnesemia (total serum magnesium) is often reported to be close to or below 1 mg/dL without clinical signs and is mostly considered irrelevant by the clinician.

BOX 22-11

Causes of Hypomagnesemia

Common Causes

Grass tetany
Winter tetany
Grass staggers
Calves on a milk-only, magnesium-deficient diet
Endurance exercise
Fatty liver syndrome

Uncommon Cause

Undernutrition

BOX 22-12

Causes of Hypermagnesemia*

Epsom salt ($MgSO_4$) overdose given orally or as an enema
Intravenous administration of magnesium in excessive amounts
Use of $MgSO_4$ IV

*Hypermagnesemia is an uncommon condition in large animals.

TABLE 22-5

Acid-Base Imbalances and Compensatory Responses

Disorder	pH	$[H^+]$	Primary Imbalance	Compensatory Response
Metabolic acidosis	↓	↑	↓ $[HCO_3^-]$	↓ P_{CO_2}
Metabolic alkalosis	↑	↓	↑ $[HCO_3^-]$	↑ P_{CO_2}
Respiratory acidosis	↓	↑	↑ P_{CO_2}	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓ P_{CO_2}	↓ $[HCO_3^-]$

$[HCO_3^-]$, Bicarbonate concentration; P_{CO_2}, partial pressure of carbon dioxide.

HYPERMAGNESEMIA. Hypermagnesemia occurs infrequently but may be seen with overzealous administration of Epsom salts ($MgSO_4$), either orally as a drench by means of nasogastric intubation or as an enema for the treatment of digestive disorders (Box 22-12). Intravenous administration of magnesium produces muscle relaxation but does not alter consciousness, and hypertonic $MgSO_4$ solutions are not considered a humane means of euthanasia.

Acid-Base Imbalance (Traditional Approach)

Using the traditional approach to acid-base balance, the four primary acid-base imbalances and their compensating responses are presented in Table 22-5. Acidosis is associated with an increase in the hydrogen ion concentration (decreasing pH), whereas alkalosis is caused by a decrease in the hydrogen ion concentration (increasing pH). When the primary imbalance is associated with a change in the bicarbonate concentration, the acid-base imbalance is called a *metabolic disorder.* The compensating response for a metabolic acid-base imbalance is mediated by the respiratory tract, which alters the partial pressure of carbon dioxide (P_{CO_2}) to counterbalance the primary imbalance and to partly restore the pH toward normal, but this mechanism has a very limited capacity quantitatively to correct bicarbonate concentrations back to normal values (maximum only about 2 mEq/L) (Fig. 22-2). Primary respiratory imbalances are related to changes in alveolar ventilation, which result in an increased

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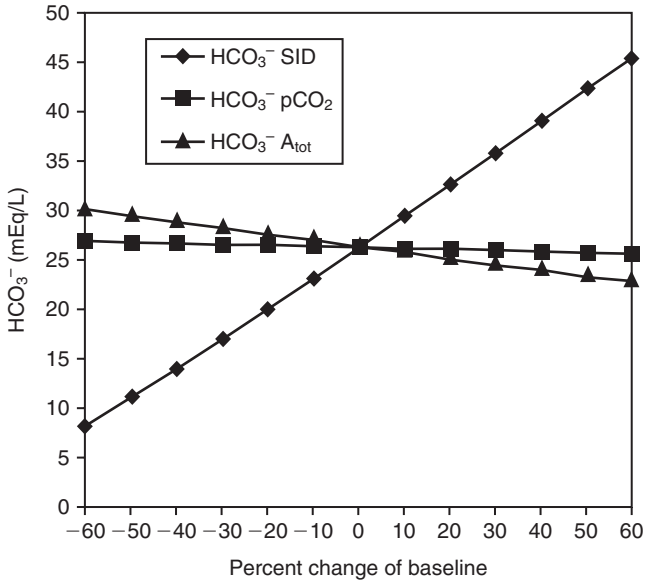


FIG. 22-2 Spider plot graphically showing the dependence of plasma bicarbonate (HCO_3^-) concentration on changes in the three independent variables (SID, P_{CO_2}, and A_{tot}). The spider plot was obtained by systematically varying one independent variable while holding the other two independent variables at their reference values (y axis values at 0 on the x axis) for plasma. Please note how little changes in P_{CO_2} affect concentrations of HCO_3^-.

P_{CO_2} in respiratory acidosis and a decreased P_{CO_2} in respiratory alkalosis. The compensating response for these primary respiratory acid-base imbalances is mediated by the kidneys through presumed alterations in the excretion or retention of hydrogen ions and bicarbonate. Heparinized blood samples for acid-base evaluation must be drawn anaerobically and sealed immediately. Arterial blood samples should be submitted for evaluation of primary respiratory disorders and for evaluation of ventilation in patients under general anesthesia. Venous blood samples are easier to obtain and provide reliable data for most primary metabolic acid-base abnormalities.

Blood gas analysis should be performed as soon after collection as possible. However, appropriately collected blood samples yield reliable results for as long as 4 hours if held in ice water. The patient's rectal temperature should be provided to the laboratory so that corrections can be made for variation in body temperature. Changes in body temperature have a major impact on the partial pressure of oxygen (P_{O_2}) as well as the P_{CO_2}, but relatively little effect on estimations of bicarbonate or base balance. During brief exercise at maximal intensity, the temperature of the central venous blood may exceed the rectal temperature by as much as 3° C. In these circumstances, the central blood temperature is more appropriate than the rectal temperature for correcting blood gas determinations. The blood sampling site (arterial, venous, or capillary blood) has a significant impact on the blood gas values obtained.[15] Arterial blood samples yield higher values for pH and lower values for P_{CO_2} than venous blood, but the bicarbonate is higher in venous blood. The use of blood gas data for evaluation of acid-base imbalances in animals has been reviewed.[16,17] In addition, a review of the traditional and nontraditional approaches to evaluation of acid-base balance as related to fluid therapy in small animals has application to many large animal situations and is well worth reading.[18]

Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH and bicarbonate concentration. Metabolic acidosis is traditionally thought to be produced by the addition of hydrogen ions or the loss of bicarbonate ions. The most common causes include the lactic acidosis of ruminal overload, hypovolemia associated with loss or compartmentalization of sodium-containing fluid, ketoacidosis in ketosis and pregnancy toxemia, loss of sodium bicarbonate–rich saliva with oral diseases or esophagostomy in cattle, gastrointestinal loss of sodium bicarbonate as a result of diarrhea, and renal failure, which may result in decreased ability to excrete hydrogen and thus to retain bicarbonate (Box 22-13). Other causes include ingestion of certain drugs or toxic compounds such as salicylate, methanol, ethylene glycol, or paraldehyde (very rare in large animals). Increased ventilation provides a respiratory response for metabolic acidosis, and a decline in the P_{CO_2} generally begins within minutes. This temporarily minimizes the fall in blood pH, but long-term correction of metabolic acidosis requires classically explained renal bicarbonate retention and enhanced acid excretion. Complete correction of metabolic acidosis may be difficult in patients with intrinsic renal disease or those with diseases such as renal tubular acidosis that impair the ability of the kidneys to excrete acid or retain bicarbonate, or both.

BOX 22-13

Causes of Metabolic Acidosis

Common Causes

Rumen overload (lactic acidosis)
Ketosis
Pregnancy toxemia
Hypovolemic shock
Acute diarrhea
Colic with strangulated bowel
Strangulating abomasal torsion
Peritonitis
Uroperitoneum (ruptured bladder)
Exercise above anaerobic threshold (normal response in horses)

Uncommon Causes

Renal failure
Renal tubular acidosis
Urea toxicity
Salicylate toxicity
Methanol toxicity
Paraldehyde toxicity
Ethylene glycol toxicity

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increase in pH and bicarbonate. It occurs fairly commonly in domestic animals, particularly in association with digestive disturbances in ruminants. An initiating process capable of generating alkalosis is necessary and must be coupled with additional factors to maintain metabolic alkalosis. Generation of metabolic alkalosis is traditionally thought to be caused by excessive hydrogen loss, bicarbonate retention, or contraction alkalosis (Box 22-14). Contraction alkalosis occurs when the ECF volume is reduced because of loss or sequestration of fluids high in sodium and chloride but without proportionate loss of bicarbonate, which really contradicts electroneutrality of watery solutions. This is thought to be traditionally a contributing mechanism for the generation of the metabolic alkalosis reported in heavily sweating endurance horses and in response to the diuretic furosemide in the horse. The most common causes of increased hydrogen ion loss are the gastrointestinal losses caused by salivary secretions in ponies after surgical esophagostomy[19]; massive gastric reflux associated with anterior enteritis, ileus, or small bowel obstruction in horses; and sequestration of fluid in the abomasum and forestomach associated with a variety of gastrointestinal displacements or functional disturbances (vagal indigestion) of ruminants. Continuous salivary losses in horses after surgical esophagostomy result in transient metabolic acidosis followed by progressive metabolic alkalosis. Most of these disorders cause significant dehydration and sodium, chloride, and potassium deficits.

The factors responsible for maintaining metabolic alkalosis involve classically explained impaired renal bicarbonate excretion. These factors are associated with the renal response to decreases in

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BOX 22-14

Causes of Metabolic Alkalosis

Common Causes

Sequestration of fluid in the abomasum and forestomach in ruminants (internal vomiting for abomasal reflux)
Gastric reflux in horses with ileus
Massive sweat loss in horses (endurance horses)
Chloride depletion
Potassium depletion
Contraction alkalosis (extracellular fluid volume contraction without bicarbonate loss)
Salivary loss of chloride in horses with esophagostomy
Use of diuretics (especially furosemide)
Functional pyloric stenosis

Uncommon Causes

Excessive bicarbonate supplementation or therapy
Mineralocorticoid excess

BOX 22-15

Causes of Respiratory Acidosis

Common Causes

Primary pulmonary disease
- Obstruction of the upper airway
- Laryngeal edema
- Aspiration pneumonia
- Pneumonia
- Pneumonia and pleuritis complex
- Pneumothorax
- Chronic obstructive pulmonary disease

Depression of the respiratory center of the central nervous system
- General anesthesia with inappropriately assisted ventilation
- Drugs
  - Opiates
  - Anesthetics
  - Tranquilizers

Central nervous system diseases

Uncommon Causes

Cardiac arrest
Muscle weakness or dysfunction
Tetanus
Botulism
Myasthenia
Severe hypokalemia
Neonatal respiratory distress syndrome

the effective circulating fluid volume, chloride depletion, or potassium depletion. Renal tubular sodium resorption is enhanced in response to hypovolemia. Maintenance of electroneutrality requires that sodium resorption in the proximal tubule be accompanied by a resorbable anion, whereas in the distal tubule, sodium resorption is associated with the secretion of another cation, usually hydrogen or, to a lesser extent, potassium. Chloride is the only resorbable anion normally present in appreciable quantities in the proximal tubular fluid. In metabolic alkalosis, plasma bicarbonate is increased and the chloride concentration is generally decreased as a result of disproportionate chloride losses. The relative lack of the resorbable anion chloride in the proximal tubule thus allows a larger amount of sodium to reach the distal tubule, where aldosterone and other factors enhance hydrogen or potassium loss into the tubular lumen in exchange for sodium. Potassium depletion reduces or eliminates potassium exchange as a means of sodium retention, thus classically explained placing greater emphasis on hydrogen ion exchange, which stoichiometrically and quantitatively is very difficult to explain. Because renal hydrogen excretion is linked with bicarbonate resorption, the excess bicarbonate cannot be eliminated, and metabolic alkalosis is maintained. Thus the traditional explanation is the reason for the paradoxic aciduria seen in some patients with metabolic alkalosis, and it is the reason these patients respond when given intravenous fluids containing sodium, chloride, and potassium. The compensating respiratory response to metabolic alkalosis is hypoventilation, resulting in an increase in the P_{CO_2}. Excessive sodium bicarbonate administration is an additional potential cause of metabolic alkalosis. Most normal animals can tolerate large doses of sodium bicarbonate, and excesses are rapidly eliminated by renal excretion.[20] However, patients with decreases in effective circulating fluid volume, particularly when coupled with potassium or chloride deficits, may not tolerate a bicarbonate load because renal clearance of excess bicarbonate is likely to be impaired. Attempts to alter the acid-base balance, and thereby affect the athletic performance of racing horses, by prerace administration of high doses of sodium bicarbonate–containing "milkshakes" have become a major concern around the world. This has stimulated substantial research on the acid-base balance of horses before and after racing. In many racing jurisdictions stringent prerace or postrace standards for blood pH or bicarbonate or T_{CO_2} levels (or both) have been enacted to control this practice. The prerace administration of the diuretic furosemide is allowed in several racing jurisdictions of North America. This drug results in a mild metabolic alkalosis with increased bicarbonate, and allowances for this may be included in some regulations. Racing supplements (which may contain sodium bicarbonate), bicarbonate precursors, and diets that supply a high positive cation-anion balance also have the potential to produce a significant metabolic alkalosis.

Respiratory Acidosis

Respiratory acidosis is characterized by a decrease in pH and an increase in P_{CO_2}, which develop because of decreased effective alveolar ventilation. CO_2 diffuses through the lungs much more readily than oxygen; thus, diseases that compromise ventilation normally result in decreases in P_{O_2} before significant increases in P_{CO_2} develop. The most common causes are acute upper respiratory obstruction and primary pulmonary diseases, including pneumonia, pneumothorax, pulmonary edema, and chronic obstructive pulmonary disease (Box 22-15). Diseases or drugs that affect the respiratory center of the central nervous system may also produce respiratory acidosis, as can general anesthesia. The compensating response for respiratory acidosis is classically thought to be renal retention of bicarbonate. This response requires days to develop and is seen only in chronic respiratory acidosis. Exogenous bicarbonate does not correct respiratory acidosis and should not be administered to affected patients.

Respiratory Alkalosis

Respiratory alkalosis is caused by hyperventilation, which may be stimulated by hypoxemia associated with pulmonary disease, congestive heart failure, severe anemia, or neurologic disorders (Box 22-16) or residence or extended stay at high altitudes. The initial compensating response to acute respiratory alkalosis is a modest decline in the ECF bicarbonate concentration—the result of cellular buffering. Subsequent renal responses result in a decrease in the ECF bicarbonate concentration through reduced renal bicarbonate resorption. The decline in bicarbonate may be offset by chloride retention; thus, hyperchloremia and decreased P_{CO_2} may be associated with compensated respiratory alkalosis, as well as with compensated metabolic acidosis. Compensating renal responses for chronic respiratory alkalosis that lasts several weeks actually may be sufficient to return pH to normal.[21]

Mixed Acid-Base Imbalances

Mixed acid-base disorders occur when several primary acid-base imbalances coexist. Metabolic acidosis and alkalosis can coexist, and either or sometimes both may occur with either respiratory acidosis or respiratory alkalosis. The following factors should be considered when evaluating possible mixed acid-base disorders:

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BOX 22-16

Causes of Respiratory Alkalosis

Common Causes

Hypoxemia
- Pulmonary diseases
- Congestive heart failure
- Severe anemia

Stimulation of the respiratory center of the central nervous system
- Psychogenic hyperventilation
- Excitement, fear, transport, pain
- Gram-negative septicemia
- Neurologic disorders

Uncommon Causes

After correction of metabolic acidosis
Inappropriate mechanical ventilation
Salicylate toxicity

- Compensating responses to primary acid-base disturbances do not result in overcompensation.
- Compensating responses, except for long-term renal compensation, rarely correct pH to normal. A normal pH in a patient with an acid-base imbalance is an indicator of a mixed acid-base disturbance.
- A change in pH in the opposite direction to that predicted for a known primary disorder indicates a mixed disturbance.
- Bicarbonate and P_{CO_2} always deviate in the same direction with primary acid-base disturbances. If these parameters deviate in opposite directions, a mixed abnormality exists.
- If the change in the anion gap does not approximate the change in bicarbonate, a mixed acid-base imbalance should be suspected.

Mixed acid-base abnormalities occur with some frequency in domestic animals and often are overlooked. The practitioner must be aware of the potential for mixed acid-base imbalances to correctly interpret blood gas data in complex clinical situations.

Anion Gap

The anion gap can be an extremely helpful tool for categorizing causal factors in acid-base imbalances and may prove a useful prognostic guide in animals with serious digestive disorders. The anion gap can be calculated as the difference between the major cations (sodium plus potassium) and the measured anions (chloride plus bicarbonate). The anion gap normally is 12 to 16 mmol/L and provides an approximation of the so-called unmeasured anions. These are anions that are not measured routinely in the clinical laboratory; they include "physically" the anionic equivalents of plasma proteins (debatably albumin in particular; ≈95% of total anion gap in normal adult animals), sulfate, phosphate, lactate, ketones, and a variety of inorganic anions. Significant differences exist in the normal range of the anion gap among species, and there may also be age-related differences. Foals are reported to have a larger anion gap than do adult horses.

Hypoproteinemia and hyperchloremic metabolic acidosis are the most common causes of a decrease in the anion gap. The cause of normal to low anion gap hyperchloremic metabolic acidosis often can be differentiated on the basis of the serum potassium concentration. Animals with hyperchloremic metabolic acidosis associated with gastrointestinal fluid losses or renal tubular acidosis most often manifest hypokalemia, whereas hyperkalemia generally is seen in patients with decreased mineralocorticoid secretion (Addison disease) or renal failure with renal shutdown. Decreases in the anion gap also result from overhydration caused by decreases in the protein concentration and changes in the relative concentration of plasma sodium and chloride.

Most commonly, high anion gap acidosis is associated with accumulation of a metabolizable acid, most commonly lactic acid associated with anaerobic exercise, grain overload, acute gastrointestinal accidents, or hypovolemic shock (e.g., diarrhea in young calves). The commonly used laboratory procedures (mostly automated blood gas machines) for the determination of lactate only measure the L form of lactate. Microbial fermentation in the gastrointestinal tract may result in the production of both the D and L forms of lactate. Recent studies have shown in milk-fed calves and kids that accumulation of D-lactate is a major factor in the profound acidosis associated with certain digestive disorders.[22,23] Unfortunately, at present, determination of D-lactate requires special procedures, which are now available only in special diagnostic commercial kits. Ketoacidosis, uremic acidosis, and poisoning with a variety of anionic poisons result in increases in nonmetabolizable acids that are also causes of an increased anion gap (rare in large animals). When a high anion gap metabolic acidosis is found, a thorough search for the potential causes of the accumulated unmeasured anions is indicated. The anion gap is also useful for identifying mixed acid-base imbalances. A mixed metabolic acid-base imbalance should be suspected when the change in the anion gap does not approximate the change in bicarbonate. Increases in the anion gap can be associated with dehydration and contraction alkalosis caused by changes in the protein concentration and the relative concentration of plasma sodium and chloride.

Bicarbonate and Total Carbon Dioxide

Bicarbonate accounts for approximately 95% of the measured CO_2; thus, the total CO_2 (T_{CO_2}) or "CO_2 content" of serum or plasma provides a measure of metabolic changes in the acid-base balance. Most automated chemistry profiles now provide the bicarbonate level directly, whereas some may still provide the T_{CO_2}. Bicarbonate or T_{CO_2} is decreased in metabolic acidosis and increased in metabolic alkalosis. However, the bicarbonate or T_{CO_2} values provide only a crude indication of acid-base status. When acid-base abnormalities are suspected, appropriate samples should be submitted for blood gas and electrolyte determination run on the same analyzer. It should be pointed out that bicarbonate levels are always calculated on automated measuring systems.

Buffer Base, Standard Bicarbonate, and Base Excess or Base Deficit

The terms *buffer base, standard bicarbonate,* and *base excess* (or *base deficit*) represent derived calculated estimates of the metabolic component of acid-base balance and do not really physically exist. The buffer base indicates the sum of all the buffer anions in blood under standardized conditions. The standard bicarbonate is the plasma bicarbonate concentration that would be found under specific conditions that eliminate respiratory influences on the values obtained. The base excess or base deficit is often supplied in routine assessment of acid-base balance; it indicates the deviation of bicarbonate from normal. The calculated base deficit provides a means of estimating the amount of bicarbonate required to correct metabolic acidosis. The conundrum is that bicarbonate cannot be given without a cation (mostly Na). The bicarbonate estimate is calculated by multiplying the base deficit by the probable sodium bicarbonate space (about 30% to 50% of body weight), as in the following equation:

$$\text{mEq } NaHCO_3^- \text{ needed} = \text{mEq base deficit} \times \text{kg body weight} \times 0.3 \text{ or } 0.5$$

It should be pointed out that normal ranges of plasma bicarbonate concentrations are different in humans and large animals, with normal large animals being an average of 4 to 5 mEq/L higher compared with normal humans. Modern blood gas machines providing base excess calculations most commonly will use human equations with normal bicarbonate concentrations of 24 mEq/L. When given clinical interpretations of values of base excess, this should be taken into consideration when applying the above equation to calculate $NaHCO_3^-$ deficits. The factor of 0.3 to 0.5 actually represents the sodium space in adult and young animals encompassing the ECF compartment.

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STRONG ION-CENTERED APPROACH TO ACID-BASE BALANCE. In the strong ion-centered approach (also known as the Stewart approach or physicochemical approach), acid-base balance is determined by three independent variables: strong ion difference (SID), the partial pressure of CO_2, and the total concentration of nonvolatile weak acids (A_{tot}), the principal components of which are plasma proteins and, to a lesser extent, inorganic phosphate.[18,24] Bicarbonate and pH are dependent variables determined by these three independent variables. Briefly, this approach is a quantitative approach applying physical laws of chemistry of watery solutions to calculate parameters involved in determining acid-base equilibria and disequilibria. These laws include electroneutrality (Σ cations = Σ of anions), dissociation equilibria, and mass conservation. If one of the independent variables (strong electrolytes, proteins, or PCO_2) changes the other dependent variables, pH, bicarbonate, and weak electrolytes adjust. Several studies have adapted the physicochemical approach for practical application in human and veterinary medicine.[17,24-29] Experimentally determined species-specific A_{tot} and Ka data are now available for horses, cattle, dogs, and humans.[30-33]

Strong Ion Difference

Strong electrolytes are completely dissociated in aqueous solution and chemically nonreactive. The SID is simply the difference between the total concentration of strong cations (sodium, potassium, calcium, and magnesium) and the total concentration of strong anions (chloride, sulfate, lactate, acetoacetate, and β-hydroxybutyrate) with sodium, potassium, and chloride normally being quantitatively the principal determinants of SID. In fluids with little or no protein, such as cerebrospinal fluid (CSF), bicarbonate concentration is the same as the SID, but it should be noted that the chloride concentration is higher (≈10 to 11 mEq/L) and SID is lower compared with blood; thus, normal acid-base equilibria in such fluids are different from acid-base equilibria of blood. Abnormalities in PCO_2 are viewed in essentially the same manner in both the traditional and nontraditional approaches to acid-base balance. Plasma albumin debatably makes up the majority of A_{tot}. The A_{tot} exists in both dissociated A^- and undissociated forms. A decrease in A_{tot} (A^-) resulting from hypoalbuminemia causes an alkalosis with an increase in bicarbonate, whereas hyperalbuminemia has the opposite effect. Increases in A^- can cause an increase in anion gap, whereas decreases in A^- result in a decrease in anion gap. A change in protein concentration has effects on acid-base balance. The literature describes hyperproteinemic acidosis or hypoproteinemic alkalosis.[25] Details are outlined in Figs. 22-2 and 22-3.

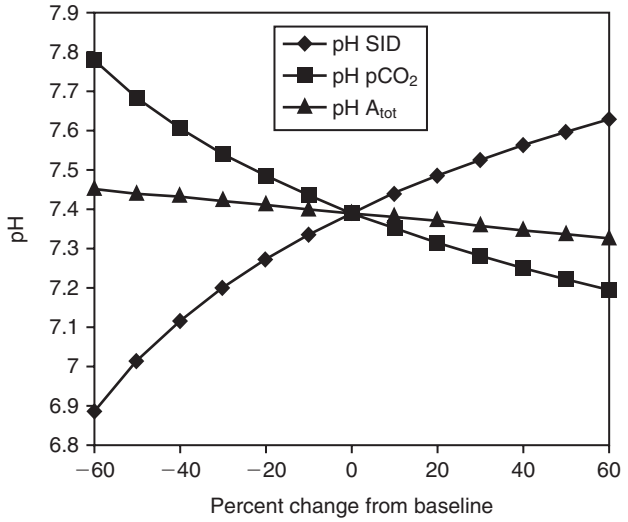


FIG. 22-3 Spider plot graphically showing quantitatively the dependence of plasma pH concentration on changes in the three independent variables (SID, PCO_2, and A_{tot}). The spider plot was generated by systematically varying one independent variable while holding the other two independent variables at their reference values (y axis values at 0 on x axis) for plasma.

When protein and inorganic phosphate remain within the normal range, acid-base balance is controlled by changes in PCO_2 mediated by the respiratory system, and changes in SID, which are largely under the control of the kidneys. Heavy sweat loss in an endurance horse, displaced abomasum in a cow (trapping of chloride in abomasum), or the prerace administration of the diuretic furosemide (chloruresis) in a racehorse produces metabolic alkalosis (mainly observed abnormalities are decreases in serum chloride concentrations). In each case the alkalosis is the result of a disproportionate loss of chloride relative to sodium, yielding hypochloremia and an increase in SID. The dissociation of serum bicarbonate concentrations will adjust to fulfill electroneutrality requirements of watery biologic solutions. Correction of the alkalosis is brought about by the provision of relatively more chloride relative to sodium, generally as sodium chloride or potassium chloride. This results in changing SID to more normal concentrations and thus a return of bicarbonate and pH toward normal. Metabolic acidosis with a large base deficit is generally treated with sodium bicarbonate with sodium being the strong cation added to the ECF and bicarbonate adjusting according to its dissociation equilibrium and sodium added without a strong anion. Other metabolizable anions (short-chain fatty acids such as lactate, acetate, gluconate, and propionate, added with Na as the cation) could be substituted for bicarbonate and achieve similar effects. Short-chain fatty acids are quickly metabolized to glucose and ATP as sources of energy for the body; in physicochemistry, this will result in a relative increase of the SID.

Calculation of SID is simple and provides useful insight in patients with metabolic acid-base disturbances. Factors that influence SID range from changes in free water, to sodium-chloride imbalances that result from excessive losses or disproportionate retention of sodium or chloride, to the accumulation of strong organic anions (most commonly lactate). Organic acidosis can be produced by the accumulation of exogenous as well as endogenous anions. The anion gap does not always accurately predict the presence of unmeasured strong anions. Mathematic methods have been developed as a means for the detection of unmeasured anions[23,34] and for the calculation of the simplified strong ion gap.[35]

Both the traditional and the nontraditional or strong ion approaches to acid-base balance have proven useful to address practical problems in both research and medical settings. The traditional approach to acid-base balance is more widely accepted and user-friendly. The strong ion approach may provide a better understanding as to why the bicarbonate concentration is changing as it integrates acid-base and electrolyte disorders. The strong ion approach has recently gained wider acceptance from members of the human critical care community, who have found it useful for the analysis of the complex fluid, electrolyte, and acid-base problems of patients in intensive care units. Several easy-to-use computer or calculator programs have been developed for the mathematically challenged that facilitate implementation of the strong ion approach to acid-base balance.

Serum Enzymes

Serum enzyme levels are proportional to their cell or tissue concentrations and activity. A number of variables affect the appearance in serum or plasma. The amount of any single enzyme in serum depends on concentration in the cell, total tissue mass, magnitude of cell/organ damage, normal death of the cell, apoptosis, degradation rate of the enzyme in serum or its half-life, and whether the injury is single or continuous.[2] Some of the common and less common causes of elevated serum enzyme activity are listed in Box 22-17.

Sorbitol Dehydrogenase

Sorbitol dehydrogenase (SDH) reversibly oxidizes D-sorbitol to D-fructose with the cofactor NAD. It is a liver-specific enzyme in all large animal species. Increases in this enzyme indicate hepatocellular damage and leakage of enzymes. Increases in SDH are also seen with

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BOX 22-17

Causes of Elevated Serum Enzymes

Elevation of Sorbitol Dehydrogenase (SDH)

Common Causes

Severe anoxia
Acute liver failure
Liver abscess
Secondary to damaged bowel
- Strangulating intestinal lesion
- Acute toxic enteritis

Chronic liver failure

Less Common Causes

Acute and severe anemia
General anesthesia
Anoxia

Elevation of γ-Glutamyltransferase (GGT)

Common Causes

Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Alkaline Phosphatase (ALP)

Common Causes

Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Creatine Kinase (CK)

Common Causes

Exertional rhabdomyolysis (azoturia, myositis, tying-up)
Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
Nutritional myodegeneration (selenium, vitamin E deficiency)
Post-endurance ride multisystemic disorder
Alert downer cow syndrome (muscle crush syndrome)
Malignant hyperthermia
Malignant edema
Prolonged recumbency with inability to rise

Uncommon Causes

Normal postexercise modest increase
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections

Elevation of Lactate Dehydrogenase (LDH)

Common Causes

Muscle disease
- Exertional rhabdomyolysis (azoturia, myositis, tying-up)
- Polysaccharide storage myopathy

Streptococcus equi–associated myopathy
- Nutritional myodegeneration (selenium, vitamin E deficiency)
- Post-endurance ride multisystemic disorder
- Alert downer cow syndrome (muscle crush syndrome)
- Malignant hyperthermia
- Malignant edema

Liver disease
- Acute liver failure
- Chronic liver failure
- Cholangiohepatitis
- Cholelithiasis

In vitro hemolysis

Uncommon Causes

Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections
Fatty liver

Elevation of Aspartate Aminotransferase (AST)

Common Causes

Muscle disease
- Exertional rhabdomyolysis (azoturia, myositis, tying-up)
- Polysaccharide storage myopathy

Streptococcus equi–associated myopathy
- Nutritional myodegeneration (selenium, vitamin E deficiency)
- Post-endurance ride multisystemic disorder
- Alert downer cow syndrome (muscle crush syndrome)
- Malignant hyperthermia
- Malignant edema

Liver disease
- Acute liver failure
- Chronic liver failure
- Cholangiohepatitis
- Cholelithiasis
- Liver flukes
- In vitro hemolysis

Uncommon Causes

Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections
Fatty liver

obstructive or strangulating gastrointestinal lesions and with acute toxic enteritis as a result of liver damage associated with absorption of bacteria or their toxins (or both) from the damaged bowel into the portal circulation. This enzyme is a sensitive indicator of liver damage, and modest increases may be seen with anoxia, acute anemia, or general anesthesia. The half-life of SDH in the circulation is short (a matter of hours), and elevations indicate active and ongoing liver damage. This enzyme is not stable when stored at room temperature (only for 5 hours), but refrigerated samples may yield useful results up to 24 to 72 hours if frozen.

Creatine Kinase

Creatine kinase (CK) is present in high concentrations in the cytoplasm of myocytes; it catalyzes the reversible phosphorylation of creatinine to form creatinine phosphate, which is a major storage of high-energy phosphate in the muscle. It is a "leakage" enzyme and a

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highly sensitive and specific indicator of muscle damage in domestic animals. Normal values of CK activity vary according to physical activity, restraint, age, and sex. Although CK is found in both cardiac and skeletal muscle, elevations of this enzyme most commonly are associated with exertional myopathies (rhabdomyolysis) and are seen as musculoskeletal manifestations of systemic disease. Intramuscular injections, vigorous exercise, or prolonged shipping may result in modest releases (up to a fourfold increase over resting values) of CK into the circulation without producing histologic evidence of muscle damage. Endurance exercise may lead to moderate elevation of CK (2000 to 15,000 IU/L) in some horses that show no recognizable sign of exertional myopathy. The half-life of this enzyme in the circulation is very short (2 hours in horses and 4 hours in cattle); its activity peaks at 6 to 12 hours and even marked elevations in CK may return to normal within 24 hours after a single muscle insult. Although marked elevation of CK can be a guide to the extent of muscle damage, the short half-life and the potential for continuing myonecrosis have a marked influence on the enzyme activity observed at any point in time. A persistent elevation of CK suggests a process resulting in active and continuing muscle damage and provides grounds for resting athletic horses; it can also be used as a prognosticator in downer cows (>3500 IU/L carries a guarded prognosis). Elevated CK provides no information on the factors responsible for the rhabdomyolysis; more precise information regarding the etiology can be obtained by muscle biopsy and its histologic and histochemical examination. Hemolysis or delayed separation of serum from clot may produce falsely high values for CK as a result of inadvertent muscle penetration during venipuncture.

Aspartate Aminotransferase

Aspartate aminotransferase (AST) is found in high concentrations in a variety of tissues, including skeletal and cardiac muscles, the erythrocytes and kidneys, and the liver. AST enzyme catalyzes the transfer of the α-amino group of aspartic acid to α-ketoglutaric acid resulting in formation of oxaloacetic acid and glutamic acid. This enzyme is a nonspecific indicator of tissue damage and tends to be less sensitive to mild insults than the tissue-specific enzymes SDH and CK. The half-life of AST in the circulation is relatively long (more than 2 days in large animals), and elevations may persist for as long as 10 days after an episode of myonecrosis or liver damage. As a general rule, extensive muscle necrosis tends to produce much higher elevations of AST than severe liver necrosis. This enzyme is most useful when compared with the tissue-specific enzymes as determined sequentially over the time course of a disease process. Elevations of CK and AST indicate muscle damage, whereas elevations of SDH and AST indicate liver damage. Marked but transient elevations of CK and SDH are associated with a single insult to the muscles and liver, respectively, whereas AST increases gradually and remains elevated for a much longer time. Thus, a moderate to marked increase in AST in an animal with progressively declining SDH or CK indicates that some tissue damage occurred within the past 7 to 10 days, but also that the process may no longer be active. This often is a favorable prognostic indicator. Persistent elevation of or a progressive increase in CK or SDH and AST over time indicates an active, continuing process of tissue damage, and the prognosis is more guarded. AST is relatively stable at room temperature, but hemolysis or lipemia may interfere with the assay.

γ-Glutamyltransferase

γ-Glutamyltransferase (GGT) is a membrane-bound enzyme that functions in the γ-glutamyl cycle where it catalyzes the transfer of γ-glutamyl groups from γ-glutamyl peptides. It is important in glutathione metabolism, amino acid absorption, and protection against oxidant injury. This enzyme is found in the biliary tract from where it derives the serum activity in health and disease, therefore making it an important marker of hepatobiliary disorders and cholestasis in large animals. GGT is also found in the pancreas, gastrointestinal tract, urinary tract, mammary gland, and reproductive tract; it does not increase in serum in disorders involving these organs. GGT is quite stable, and reliable results can be obtained from samples submitted several days after blood samples have been drawn, provided the serum is refrigerated. The half-life of GGT activity in blood is not known, but it has been suggested to be a half-life of 3 days in horses. The activity of this enzyme is highest in the cells of the periportal region of the liver, in the pancreas, and in the renal tubular cells. Pancreatic diseases resulting in inflammation and necrosis are relatively rare in large animal species. Damage to the renal tubular cells leads to a release of GGT into the tubular lumen and the urine. Because this enzyme is a relatively large molecule, it is not resorbed into the systemic circulation, and renal tubular damage does not result in elevated serum GGT activity. Increases in GGT relative to creatinine in the urine have been used as an index of acute renal tubular damage. However, the validity of the normal range for this ratio in horses has been questioned.

In large animal species, an elevation in serum GGT is one of the more reliable indicators of damage to the liver and biliary obstruction. Disease processes such as pyrrolizidine alkaloid intoxication (in subclinical liver diseases showed a 75% sensitivity and 90% specificity); chronic active hepatitis, cholangiohepatitis, and cholelithiasis produce liver damage, primarily in the periportal region, leading to marked and persistent elevation of GGT activity in the serum.[36] In these instances, elevations in serum ALP activity are generally associated with the increase in GGT. Two syndromes—fatty liver syndrome in dairy cows and hyperlipemia syndrome of periparturient mares of pony and miniature horse breeds—are associated with liver damage, which is often reflected by elevation of GGT.

Most suckling neonatal large animals, except horses, have high levels of GGT activity in their serum. This is the result of absorption of maternal GGT, which is present in relatively high levels in the colostrum, making its serum levels a sensitive indicator of passive transfer. Elevation of GGT in neonates should be regarded as a normal finding unless it is associated with other evidence of liver disease. The normal range of serum GGT activity for burros, donkeys, and asses may be substantially higher (two to three times) than the normal range of serum GGT activity for horses. Caution should therefore be used when evaluating this enzyme in these species. Elevation in serum GGT activity has been reported in Thoroughbred racehorses that are performing below expectations. The reasons for the increase in GGT are not known, but horses often respond to a period of rest or reduction in workload. These horses show little histologic evidence of liver damage, and other indices of liver damage and dysfunction usually are within normal limits. The stress of training may be associated with an elevated GGT. Certain trainers, often highly successful trainers, appear to have a disproportionately large number of horses with elevations of this enzyme. The normal range for GGT of Thoroughbreds in race training may be slightly higher than that of normal sedentary horses.

Alkaline Phosphatase

Alkaline phosphatase (ALP) is used in most species as a marker for intrahepatic or extrahepatic obstruction of the biliary system. The enzyme is also released by osteoblasts from metabolically active bone. This may be the reason that young, rapidly growing animals normally have high levels of serum ALP. Elevations in ALP are also reported in cases of rickets and healing fractures. The intestinal isoenzyme of ALP is very similar to the ALP isoenzyme found in neutrophils. Elevations in the ALP activity of abdominal fluid in horses with intraabdominal disease may reflect the release of this enzyme from the neutrophils rather than being a specific marker of damage to the bowel.

ALP has been useful for evaluating liver disease in large animals, particularly in horses with pyrrolizidine alkaloid intoxication, chronic active hepatitis, and cholangiohepatitis, and in some patients with cholelithiasis. A profound elevation in ALP activity is thought to reflect periportal liver damage and biliary obstruction in these patients. A moderate to marked elevation in ALP may be observed in a wide range of disorders resulting in hepatic necrosis and intrahepatic cholestasis. Because this enzyme is not organ specific in large

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animals, elevations in ALP activity must be interpreted in relation to more organ-specific enzymes such as SDH and GGT.

Other Enzymes

LDH is a metalloenzyme that hydrolyzes many types of phosphate esters at an alkaline pH in the presence of zinc and magnesium ions. It is found in relatively high concentrations in a variety of organs and tissues of the body from the heart, liver, muscle, and kidney to the erythrocytes and leukocytes. An elevation in serum LDH enzyme activity must be evaluated in relation to other, more organ-specific enzymes. LDH isoenzyme analysis can be helpful in differentiating organ system damage, but the analysis is time consuming and not always available. An elevation in LDH activity is expected in hepatic necrosis and serves as an indicator of an active disease process. Extensive muscle damage and rhabdomyolysis tend to result in a more massive release of enzyme and much higher serum enzyme activity. A modest elevation in LDH may be seen in some hemolytic disorders and some cases of leukemia. Blood samples must be handled with care, because hemolysis results in falsely elevated serum LDH activity.

Glutamic dehydrogenase (GLDH) and ornithine carbamoyltransferase (OTC) are two enzymes that are reported to be sensitive indicators of hepatic necrosis in ruminants. GLDH is a mitochondrial enzyme that catalyzes the conversion of glutamate to 2-oxoglutarate. Injury to the hepatocyte has to be severe enough to damage the mitochondria. It is suggestive of either hepatocyte death or sub-lethal hepatocyte injury. In large animals, it is more liver specific than AST and has better storage stability than SDH. OTC is a hepatic-sensitive enzyme that catalyzes the reaction between ornithine and carbamoylphosphate-forming citrulline and inorganic phosphate. OTC has been used mostly to evaluate fatty liver in cattle and as a prognostic indicator in abomasal displacement and fatty liver.[37] Alanine aminotransferase (ALT) is an important liver-specific enzyme that has wide application in small animals and is often included in automated chemistry profiles. This enzyme has not been useful for evaluation of liver disease in large animal species, and occasionally horses with marked rhabdomyolysis and no other evidence of liver disease show an elevation in serum ALT activity.

Bilirubin

Bilirubin is a breakdown product of the heme component of the hemoglobin molecule and to a lesser extent to the breakdown of other porphyrin-containing compounds (e.g., myoglobulin, cytochrome P_{450}, peroxidase, catalase). Bilirubin exists in the serum in two forms and is responsible for the yellow color known as *icterus,* or *jaundice,* of the mucous membranes. Unconjugated, prehepatic, albumin-bound bilirubin is also known as *indirect-reacting bilirubin,* which used to be determined by the van den Bergh reaction; currently total bilirubin is measured by the 2,5-dichlorophenyldiazonium (DPD) method, and direct bilirubin is determined by the method of Jendrassik and Grof.[38] Indirect-reacting bilirubin must be taken up by the liver cells, where it is conjugated and then excreted in the bile. Conjugated bilirubin is known as *direct-reacting bilirubin,* as determined by the van den Bergh reaction. Horses normally have a much higher serum bilirubin level than ruminants, and hot-blooded horses have a higher bilirubin level than cold-blooded horses of the pony and draft breeds. The horse also differs from ruminants in that horses often develop moderate icterus in response to fasting or anorexia associated with many systemic diseases. The increase in the bilirubin concentration in these horses is caused almost entirely by an increase in unconjugated (indirect-reacting) bilirubin, and within a few days the bilirubin can increase from the normal range up to 6 to 8 mg/dL. Therefore, the total serum bilirubin concentration is of little diagnostic value in the ill horse unless both the direct- and indirect-reacting bilirubin values are determined. However, in general terms unconjugated hyperbilirubinemia occurs when there is increased production of bilirubin or when either hepatic uptake or conjugation of bilirubin is diminished.

BOX 22-18

Causes of Elevated Serum Bilirubin

Elevation of Total Serum Bilirubin

Common Causes

Hemolytic anemia
Liver failure
Secondary to systemic disease or anorexia in horses

Uncommon Cause

Chronic liver failure in cattle

Elevation of Indirect-Reacting Bilirubin

Common Causes

Secondary to systemic disease or anorexia in horses
Liver failure
Hemolytic anemia

Uncommon Cause

Chronic liver failure in cattle

Elevation of Direct-Reacting Bilirubin

Common Causes

Liver failure
Cholelithiasis
Cholangiohepatitis
Neonatal isoerythrolysis

Uncommon Cause

Hemolytic anemia

Conjugated hyperbilirubinemia is caused either by intrahepatic cholestasis or extrahepatic bile duct obstruction.

Total serum bilirubin is elevated in animals with hemolytic anemia, and this increase is caused largely by an increase in indirect-reacting bilirubin (Box 22-18). The degree to which bilirubin is elevated in hemolytic anemia is a function of the rate of RBC destruction and the capacity of the liver to excrete the newly formed bilirubin. The total bilirubin rarely exceeds 10 mg/dL in hemolytic anemia. An exception is the hemolytic anemia of neonatal isoerythrolysis in newborn foals, which is often associated with marked clinical icterus. In these foals the serum bilirubin may exceed 25 mg/dL, a variable but substantial proportion of which (40% to 60%) is likely to be direct-reacting bilirubin causing kernicterus in some cases.

The second major cause of clinical icterus and increased serum bilirubin is liver failure. Liver failure results in impaired uptake and excretion of bilirubin. Acute liver failure caused by hepatic necrosis results in marked to moderate increases in both direct- and indirect-reacting bilirubin. In horses with acute liver failure, bilirubin often exceeds 10 mg/dL, and this increase is caused primarily by increases in indirect-reacting bilirubin. Direct-reacting bilirubin rarely exceeds 25% of the total bilirubin in the horse, and increases of this magnitude suggest an intrahepatic or extrahepatic biliary obstruction. With chronic liver failure, icterus is more variable, and total bilirubin rarely exceeds 10 mg/dL. Liver failure in ruminants, particularly chronic liver failure, is associated with a much less striking elevation in serum bilirubin than occurs in horses. In the absence of hemolytic anemia, a bilirubin value above 2 mg/dL indicates impaired hepatic function in ruminants. Hyperbilirubinemia without clinical icterus may be observed in cattle and in sheep with fatty liver associated with ketosis/acetonemia; in such cases, the predominant pigment is unconjugated bilirubin. In horses, unconjugated hyperbilirubinemia can occur a few days after prolonged halothane anesthesia.[39]

Glucose

Blood glucose concentration represents an equilibrium among dietary intake, hormonal interactions (insulin, glucagon, gluco-

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BOX 22-19

Causes of Hypoglycemia

Common Causes

Inappetence in newborns
Sepsis
Pregnancy toxemia
Endotoxic shock (late stages)
Hepatic failure

Uncommon Causes

In vitro glycolysis by red blood cells
In vitro glycolysis by eperythrozoonosis

BOX 22-20

Causes of Hyperglycemia

Common Causes

Acute severe colic in horses
Stress and excitement
Cushing syndrome
Glucocorticoid administration
Xylazine administration

Uncommon Causes

Overly rapid administration of dextrose
Diabetes mellitus

corticoids, catecholamines, and growth hormone), and biochemical pathways (glycogenolysis, gluconeogenesis, and glycolysis). Glucose is an essential substrate for brain cells and for erythrocytes. Major storage sites for glucose in the body are skeletal muscles and liver in the form of glycogen.

Hypoglycemia

Hypoglycemia is either the result of poor sample handling, pathologic states, or fasting. Delayed separation of serum from the blood cells may allow time for these cells to consume glucose, thus causing false low glucose levels. Fasting usually does not result in hypoglycemia except in neonatal animals (Box 22-19). Newborns have limited energy reserves, and any disease (mainly septicemia and diarrhea), injury, congenital defect, maternal rejection, agalactia, or management error that limits energy intake can result in marked hypoglycemia associated with profound depression, even coma. In calves with acute severe diarrhea, blood glucose may fall below 40 mg/dL (2.2 mmol/L) in 30% to 50% of cases.[40] One study has shown that 34% of critically ill foals are hypoglycemic.[41] Hypoglycemia may also be seen in animals with acute toxic enteritis, coliform mastitis, septicemia, and colic associated with strangulated bowel, as well as in the later stages of endotoxemia and in some horses with exhaustion after prolonged exercise, hepatic insufficiency, islet B cell neoplasia, hepatocellular carcinoma, and surreptitious injections of insulin. Hypoglycemia is a reasonably consistent feature with primary ketosis and fat cow syndrome in cattle, with pregnancy toxemia in sheep and goats, and in hyperlipemia syndrome, which is seen primarily in pregnant or lactating ponies. Rapid, semiquantitative field tests for blood glucose (Dextrostix, Boehringer Mannheim Diagnostics, Inc., Indianapolis, Ind.) or handheld human glucometers provide a practical means of early recognition of this problem. It should be pointed out that this method reads glucose concentrations slightly low compared with standard laboratory procedures by 10% to 15%.[42]

Hyperglycemia

Hyperglycemia may be seen with excitement, transportation, or stress and probably is mediated by increases in catecholamine and glucocorticoid hormones (Box 22-20). The stress and pain of acute severe colic in horses frequently results in hyperglycemia occurring in approximately 50% of the colic cases, and elevations of blood glucose above 250 mg/dL are associated with a poor prognosis in such cases. In a recent study all the animals with colic that did not survive had a mean glucose level of 234 mg/dL.[43] Endotoxemia initially results in a transient hyperglycemia that may be followed by marked hypoglycemia in the terminal stages of the toxemia. The later stages of Cushing syndrome in horses are generally associated with a non–insulin-responsive hyperglycemia and glycosuria. Similar changes can be induced transiently when exogenous glucocorticoid hormones are administered at a high dose rate. Insulin-responsive diabetes mellitus rarely occurs in large animals but has been reported in association with destructive pancreatic lesions. Hyperglycemia in large animals has also been associated with iatrogenic hyperadrenocorticism, pheochromocytomas, after strenuous exercise, after prolonged halothane anesthesia, administration of xylazine or detomidine, during administration of glucose, endotoxemia, proximal duodenal obstruction in cattle, and pituitary pars intermedia dysfunction in horses.

Creatinine

Creatinine is generated by muscle metabolism and is derived from the cyclic use of phosphocreatine—the muscle energy store—resulting in the production of inorganic phosphate and creatine that degrades into creatinine. In the resting animal, this process occurs at a relatively constant rate. The absolute muscle mass and level of physical activity may influence the rate of creatinine production and thus the serum concentration. Starvation, with loss of muscle mass, may result in a slightly reduced serum creatinine level, whereas serum creatinine may be slightly higher in muscular, athletic individuals compared with sedentary animals. Creatinine is distributed throughout the body water and is not reused. Creatinine is normally excreted by the kidneys, primarily by glomerular filtration, and is not normally reabsorbed in the tubules. In azotemic patients a substantial part of creatinine is metabolized and excreted by nonrenal routes. Serum or urine creatinine concentrations determined by the standard alkaline picrate reaction may be falsely elevated by the presence of noncreatinine chromogenic compounds in the serum. These chromogens include glucose, fructose, ascorbic acid, hippuric acid, urea, ketones, cephalosporins, amino acids, and several other compounds. The contribution of these compounds can be reduced or eliminated, and most automated chemical laboratories use such methodology. However, if inappropriately high creatinine is reported in patients without other evidence of renal failure, the method of creatinine measurement should be ascertained.

The serum creatinine concentration provides a crude measure of the glomerular filtration rate. However, serum creatinine, like BUN, is not a very sensitive or early indicator of changes in renal function. Alterations in renal blood flow caused by decreases in effective circulating fluid volume (hypovolemia) produce an elevation in serum creatinine and BUN; this can be considered a prerenal azotemia (Box 22-21). It occurs with some frequency in animals with acute enteritis, peritonitis, acute heart failure, massive blood loss, and some forms of colic and in horses with exhaustive disease syndrome. An important point is that many of these disorders initiate the release of inflammatory mediators, which may cause renal damage and impaired renal function above and beyond that associated with impaired renal blood flow and hypovolemia. Prerenal azotemia is usually seen in animals that are dehydrated and volume depleted and that have a history of loss or compartmentalization of sodium-containing fluid. Prerenal azotemia often can be marked (creatinine level above 6 mg/dL), but if uncomplicated, it generally responds rapidly to fluid replacement therapy. Urine production, the urine sodium concentration, and the fractional excretion of sodium are usually low, and the urine specific gravity is usually elevated. The ratio of urine to plasma urea or creatinine, as well as the urine-to-plasma ratio of osmolality, is reported to be higher in horses with

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BOX 22-21

Causes of Elevated Creatinine

Common Causes

Prerenal azotemia
- Reduced renal perfusion
- Hypovolemia
- Congestive heart failure
- Dehydration after endurance exercise

Renal azotemia
- Acute renal failure
- Chronic renal failure

Postrenal azotemia
- Urolithiasis
- Renal calculi
- Ureteral calculi
- Urethral calculi

Ruptured bladder

Uncommon Causes

False azotemia
- Noncreatinine chromogens in serum or plasma

Perirenal abscess
Renal carcinoma
Renal dysgenesis
Carcinoma of the bladder
Post-exhaustion multisystemic syndrome in horses
Severe exertional rhabdomyolysis with myoglobinuria
Severe intravascular hemolysis with hemoglobinuria
Intoxication or poisoning
- Heavy metal poisoning
- Nonsteroidal antiinflammatory drug intoxication
- Aminoglycoside intoxication

prerenal azotemia compared with renal azotemia.[16] In ruminants, creatinine is a more reliable indicator of renal failure than is BUN. Urea nitrogen can be secreted in saliva and metabolized by the ruminal microflora; this frequently results in a disparity between BUN and creatinine levels in ruminants with renal failure.

Although small increases in creatinine may be seen with progressively compromised renal function, nearly two thirds to three fourths of the nephrons must be nonfunctional before the serum creatinine level clearly exceeds the normal range. Both ARF and CRF are usually associated with elevated creatinine. ARF, especially in animals with anuria or oliguria, is usually associated with progressive daily changes in blood parameters. In contrast, blood parameters of animals with CRF tend to remain relatively constant. A transient but markedly elevated serum creatinine has been observed in some newborn foals that have no other evidence of compromised renal function. Many of these foals are born to mares that had medical problems before parturition. Alterations in placental function may allow the accumulation of creatinine in the foal's circulation. In most of these otherwise normal foals, this marked elevation in serum creatinine resolves within the first few days of life. There is no clinical significance to decreased serum creatinine levels.

Blood Urea Nitrogen

The term *blood urea nitrogen* (BUN) is ingrained in the veterinary literature, despite the fact that urea nitrogen determinations usually are performed on serum (SUN) or plasma samples. This is of little consequence, because the actual difference in urea concentrations of whole blood and serum or plasma is relatively small. Urea provides a nontoxic means of excreting ammonia generated by amino acid catabolism and the intestinal microflora. It is distributed throughout the body water. In the intestine, urea is broken down by urease, which is produced by the intestinal microflora, and the nitrogen, as ammonium ion, is recycled to the liver. Urea is excreted by the kidneys, primarily by glomerular filtration, intestine (in high concentration in horses), saliva, and sweat. Ruminants excrete urea into the gastrointestinal tract where it is converted to ammonia and amino acids that result in protein production.

BOX 22-22

Causes of Decreased Blood Urea Nitrogen

Common Causes

Liver failure
Neonatal animals (blood urea nitrogen is normally lower than in adults)

Uncommon Causes

Low-protein diet
Anabolic steroid administration

BOX 22-23

Causes of Increased Blood Urea Nitrogen

Common Causes

Prerenal azotemia
Reduced renal perfusion
- Hypovolemia
- Congestive heart failure
- Dehydration after endurance exercise

Renal azotemia
- Acute renal failure
- Chronic renal failure

Postrenal azotemia
- Urolithiasis
- Renal calculi
- Ureteral calculi
- Urethral calculi

Ruptured bladder

Uncommon Causes

Gastrointestinal bleeding
Perirenal abscess
Renal carcinoma
Renal dysgenesis
Carcinoma of the bladder
Postexhaustion multisystemic syndrome in horses
Severe exertional rhabdomyolysis with myoglobinuria
Severe intravascular hemolysis with hemoglobinuria
Intoxication or poisoning
- Heavy metal poisoning
- Nonsteroidal antiinflammatory drug intoxication

Aminoglycoside intoxication

Urea production occurs almost exclusively in the liver and is synthesized by hepatocytes from ammonia derived from amino acid catabolism. Blood or serum urea is dependent on hepatic urea production and renal tubular flow rate. Urea excretion is not solely determined by GFR, because once in the tubules, at rapid flow rates, 40% of the urea is reabsorbed. However, at slow flow rates as occurs in hypovolemia, 60% is reabsorbed, thus increasing urea levels in serum or blood. Liver failure is frequently associated with a decrease in BUN (Box 22-22). Urea nitrogen tends to be low in nursing animals because of their high fluid intake and urine output and their anabolic state of rapid growth. Urea nitrogen may be reduced slightly in animals given anabolic steroids or fed diets low in protein but of adequate calorie content.

Starvation or other processes that result in rapid tissue catabolism such as fever, burns, exercise, and increased protein digestion (e.g., hemorrhage in the gastrointestinal tract) decreases GFR, or corticosteroid administration may result in modest increases in BUN (Box 22-23). BUN, along with creatinine, provides a crude index of altered

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renal function in most animal species. BUN is influenced more directly by dietary factors than is creatinine, and creatinine is generally a better guide to renal failure. This is particularly true in ruminants, in which BUN may remain within normal limits in animals with marked impairment of renal function.

The BUN/creatinine ratio has been used to try to aid in differentiating prerenal azotemia and intrinsic renal azotemia based on the proportion of increases of each substance in the ratio. However, given the wide variation in BUN and creatinine concentration along with the differences of species, it is not a reliable indicator. In the horse a BUN/creatinine ratio of less than 10:1 is expected with ARF; when it exceeds 15:1, CRF is more likely. With these considerations in mind, the discussion of prerenal, renal, and obstructive causes of azotemia in the creatinine section apply to BUN.

Serum Protein

The serum or plasma proteins consist of albumin and globulin fractions. These are discussed in detail in Chapter 26.

Urinalysis

Urinalysis can be an extremely useful diagnostic tool, providing information on many systemic disorders. Ideally urine is collected at the same time as blood for clinical chemistry and before any treatment is administered. The interpretation of certain abnormalities in urine (e.g., glucosuria, ketonuria) is facilitated by concurrent knowledge of chemistry results. Urinalysis is essential in the evaluation of primary renal disease. Urine normally is collected as a voided sample or after catheterization. Voided urine samples are safe and easy to collect but are easily contaminated. Catheterization is preferred for bacteriologic evaluation, but the resultant mild trauma may result in a slight increase in urine RBCs and protein. Because of the urethral diverticulum at the level of the pelvis, it is difficult to successfully catheterize male ruminants. Urethral obstruction is common in male small ruminants, and percutaneous aspiration may be the only way to obtain a urine sample in affected animals. Urinalysis should be performed as soon after collection as possible (within 30 minutes) to avoid degeneration of cellular elements, changes in pH, or bacterial overgrowth (cytolysis, crystallization). If this is not possible, samples should be refrigerated but brought back to room temperature before tests. Urine volume and composition are influenced by feed and water intake, salt supplementation, environmental factors, exercise, stress, systemic disease, and drug administration. Urine samples collected after administration of a diuretic are dilute and unsuitable for routine urinalysis. The tranquilizer xylazine, which is often used to assist in the catheterization of male horses, may alter the results of the urinalysis because it produces diuresis as a result of glycosuria and specifically also kaliuresis.

When urinalysis is performed, the color should be noted along with the organoleptic characteristics of the urine such as the fact that an adult horse's urine has a lot of mucus and becomes cloudier at the end of urination.

Specific Gravity

Specific gravity is defined as the weight of urine relative to the weight of distilled water (=1 at 4°C [60°F]). The normal specific gravity of serum is approximately 1.008 to 1.012. The urine specific gravity is an indicator of renal function, because it reflects the action of the renal tubules and collecting ducts on the glomerular filtrate by providing an estimation of the number of particles dissolved in the urine (e.g., whether the urine is concentrated or diluted via serum). It is usually measured by refractometry on urine supernatant. Urine dipsticks with reagent pads for estimating the urine-specific gravity in humans should not be used for this purpose in domestic animals, because a poor correlation has been reported compared with refractometry in large animals.[44] Normal animals have the capacity to dilute their urine specific gravity to less than 1.010 and to concentrate to greater than 1.050. The normal range reported for most adult large animals is 1.020 to 1.050. Suckling neonatal animals normally produce a very dilute urine with a specific gravity below 1.010. Although this could represent immature renal function, it more likely reflects their high-volume fluid intake, because normal neonates can concentrate their urine if fluids are withheld.

Failure to produce a concentrated urine, as reflected by a specific gravity below 1.020, in the face of dehydration is an indication of altered renal function, which may be caused by primary renal disease, diabetes insipidus, medullary washout, or nephrogenic diabetes insipidus. With severe and chronic sodium depletion, tubular sodium may be insufficient to sustain normal countercurrent mechanisms for water resorption. This process is called *medullary washout* and has been reported as a cause of polyuria in lactating dairy cattle on a salt-deficient diet. At least 50% of renal function must remain for highly concentrated urine to be produced. Isosthenuria, a urine-specific gravity that remains around 1.010 despite variation in hydration, occurs when renal disease progresses to the point at which renal function is reduced to less than a third of normal. Altered renal function in these animals is usually reflected by a moderate to marked elevation in BUN and creatinine levels and by other changes in the urinalysis. Hyposthenuria occurs when the specific gravity remains below 1.010; this indicates altered release of or response to antidiuretic hormone, which occurs with diabetes insipidus, medullary washout with chronic sodium depletion, nephrogenic diabetes insipidus, psychogenic polydipsia, and chronic liver failure in some horses. Hypersthenuric urine occurs when SG is greater than 1.030-1.035, and it occurs commonly in states of dehydration. It is also common in horses fed a high percentage diet of hay and in those living in hot environments.

pH

The normal range of urine pH for adult herbivores is alkaline, with values ranging from 7 to 9. Neonatal foals tend to have a slightly acid urine with a pH below 7. Aciduria in adults may be seen in postrace samples collected from racehorses, after prolonged fasting, with ketosis in ruminants, or in response to metabolic acidosis. A paradoxic aciduria is seen in ruminants with hypochloremic, hypokalemic metabolic alkalosis and has been recently attributed to K concentration changes in the urine.[45] Urine pH is also influenced by the cation-anion balance of the diet. The SID of urine, specifically the potassium concentration, has the strongest influence on urinary pH in dairy cattle and most likely in horses as well.[45]

Protein

Protein normally is not detected in urine, although a false-positive protein reaction may be noted on urine dipsticks if the sample is strongly alkaline. Urine with a positive reaction for protein on dipsticks should be checked for protein by a chemical method. Proteinuria should be evaluated in relation to the other findings in the urinalysis. Persistent and strongly positive reactions for protein in the absence of leukocytes, RBCs, bacteria, or casts suggest glomerular protein loss, as in glomerulonephritis or amyloidosis. The presence of bacteria and leukocytes with proteinuria suggests sepsis in the urinary tract, whereas hemorrhage or inflammation in the urogenital tract is often associated with proteinuria. A transient postexercise proteinuria is observed in performance horses at submaximal or maximal levels of exertion.

Glucose

Glucose is not found in the urine of normal large domestic animals unless the blood glucose level increases above the renal threshold, which is thought to be approximately 100 to 140 mg/dL in ruminants and approximately 160 to 180 mg/dL in horses. The causes of hyperglycemia and glycosuria were described in a previous section; they include Cushing syndrome, stress, and catecholamine or glucocorticoid hormone release. Hyperglycemia and glycosuria can be created iatrogenically when glucose-containing fluids are administered at

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an excessive rate. Glycosuria is a fairly consistent finding in sheep with enterotoxemia type D (pulpy kidney). The presence of glycosuria without hyperglycemia strongly suggests renal tubular damage resulting from a toxic or ischemic insult.

Occult Blood

Both myoglobin and hemoglobin give a positive reaction on urine occult blood dipsticks. In most instances proteinuria shows a positive result as well. A tentative clinical impression sometimes can be formed to differentiate myoglobin from hemoglobin in dark urine if the sample is shaken vigorously in a closed, transparent container. Myoglobin tends to produce a brown foam, whereas hemoglobin produces a reddish foam. Hemoglobinuria caused by intravascular hemolysis is generally associated with clinical and hematologic evidence of a hemolytic anemia. Hematuria may result in a positive occult blood reaction if lysis of some of the intact RBCs has occurred. This is likely to happen if the urine is very dilute or if it is held at room temperature for an extended period before analysis. False-positive reactions can occur if microbial peroxidase or oxidizing contaminants are present. Hematuria should be confirmed by cytologic examination of the urine sediment.

Myoglobin

Myoglobinuria should be associated with clear clinical and clinicopathologic evidence of extensive muscle damage. The ammonium sulfate precipitation method of differentiating hemoglobin from myoglobin is imprecise and frequently fails to detect myoglobin in the dark, coffee-colored urine of horses with severe rhabdomyolysis. Accurate differentiation of these compounds in urine requires more sophisticated procedures.

Cells

Cytologic evaluation of urine is deemed essential in cases of unexplained fever, hyperfibrinogenemia, weight loss, and complicated neurologic disease. The normal range for cells is generally considered to be up to five RBCs or leukocytes per high-power field. An increased number of erythrocytes indicates hematuria, which may be caused by neoplasia, trauma, inflammation, or coagulopathy. Pyuria, an increase in urine leukocytes, indicates an inflammatory process; when associated with bacteriuria, it indicates a septic process in the urinary tract. The presence of sheets or rafts of transitional cells suggests neoplasia. Foal's urine has relatively more epithelial cells compared with urine of adult animals.

Casts

Casts are accumulations of protein and cellular material that form in the renal tubules, and when present in the urine, they indicate renal damage or tubular disease. Casts can consist of erythrocytes, leukocytes, or renal tubular cells. As cellular degeneration proceeds, the cell type is more difficult to determine, and the casts become granular and then waxy. Hyaline casts are noncellular and are formed from mucoprotein. They may be seen with glomerulonephritis, fever with passive congestion, or severe dehydration with altered renal blood flow. However, casts are soluble in alkaline pH, which is the usual urine pH of large animals, thus making their documentation in urine sediment difficult. If present, they indicate tubular involvement.

Crystals

The crystalline structures in the urine of large animals are those usually associated with an alkaline urine. Calcium carbonate crystals normally are found in abundance in horse urine, particularly if the horse has been fed alfalfa hay. Triple phosphate and calcium oxalate crystals are frequently observed in relatively small numbers. In foals calcium oxalate crystals are more prevalent. The major crystals involved in urolithiasis of feedlot cattle is struvite ($MgNH_4PO_4 \cdot 6H_2O$). In the western United States, silicate stones are most common in livestock under range conditions. Carbonate and oxalate stones are common causes of urolithiasis in small flocks of backyard sheep and goats fed alfalfa hay.

Bacteria

Bacteria sometimes are seen in small numbers in voided urine samples and may represent surface contaminants. Bacterial infections of the urinary tract are usually associated with significant pyuria. When this is noted, a catheterized sample (horse) or clean midstream catch (ruminant) should be obtained for Gram stain, culture, and sensitivity testing. Results from ruminant samples must be carefully interpreted, because male ruminants routinely urinate within the prepuce, thus heavily contaminating samples. Fortunately, urinary tract infections in male ruminants and horses are rare.

Urine Creatinine Clearance Ratio[46]

Urinary electrolyte excretion is affected by a variety of factors, including dietary intake, alterations in renal function, and specific hormones that regulate renal electrolyte excretion. Determination of electrolyte concentrations from randomly collected urine samples is easily done and can be clinically useful when these concentrations are compared with serum concentrations. The presence of substantial amounts of sodium in the urine of an animal with hyponatremia suggests excessive renal sodium loss caused by altered renal function or hormonal control. However, marked variation in the rate of urine production can lead to serious problems in the interpretation of urine electrolyte concentrations. The standard physiologic methods of determining renal electrolyte clearance are complicated by the need for quantitative urine collection and are not well suited to most practical clinical situations. One means of overcoming these difficulties is expression of the renal electrolyte clearance relative to the endogenous creatinine clearance. Expression of the renal clearance as a ratio eliminates the need for quantitative urine collection. This derived value is known as the *creatinine clearance ratio* or the *fractional excretion* (FE), and it is calculated by the following formula:

$$\mathrm{FE} = \mathrm{Urine}/(\mathrm{X})\mathrm{Serum}/(\mathrm{X}) \times \mathrm{Serum}/(\mathbf{C})\mathrm{Urine}/(\mathrm{C}) \times 100$$

where *X* represents the electrolyte concentration and *C* represents the creatinine concentration.

The FE fluctuates somewhat during the day in relation to physical activity and feed and water intake. However, under standardized conditions, there is close agreement between the FE determined from single random samples of blood and urine and that based on samples quantitatively collected during a 12- to 24-hour period.[16] The FE of electrolytes has a very wide range of normal values. The principal sources of this variation are differences in dietary intake and environmental or experimental conditions. The FE of electrolytes has been useful for detecting specific dietary deficiencies or imbalances. Dietary salt deficiency is associated with an extremely low FE of sodium and chloride, whereas the plasma concentration of these ions generally remains within normal limits. In a similar fashion, dietary calcium and phosphorus imbalances seldom are reflected by the serum concentrations of these ions. Calcium deficiency and phosphorus excess are relatively common dietary problems in large animals and result in a low FE for calcium and a high FE for phosphorus. There are technical problems with the determination of the urine calcium concentration in horses because of their normally alkaline urine and the resultant precipitation of calcium carbonate in the urine. Mixed urine samples from horses must be acidified (hydrochloric acid can be used) to solubilize the calcium. It has favored the use of fractional excretion of phosphorus to diagnose nutritional secondary hyperparathyroidism in horses.

Increases in the FE of sodium are noted with renal tubular damage and impaired sodium resorption. The sodium FE increase has been a useful indicator for the differential diagnosis of prerenal azotemia, which almost invariably results in a low sodium FE, from the azotemia caused by primary renal disease, in which the FE for sodium often is markedly increased. Specific criteria of interpretation in horses have been suggested. In the case of the FE_{Na+}, the reference range varies between 0.01% and 1.0%. A level lower than 0.02% indicates Na^+ conservation by the kidney; an increase may

result from excess of dietary intake, Addison disease, and more commonly tubular insufficiency. FE_{K+} normal values are considered between 15% and 80%; values below 15% have been associated with potentially recurrent myositis and chronic laminitis. FE_{Cl-} has not been reported with a diagnostic value. FE_{Ca++} normal values are between 0% and 33% when used in association with FE_P. The reference values for FE_P have been reported up to 0.5% and as a sensitive diagnostic indicator of calcium and phosphorus balance in horses. An increase above 0.5% is mainly considered an indicator of possible nutritional secondary hyperparathyroidism, renal tubular disease, or pseudohyperparathyroidism.

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Collection and Submission of Samples for Hematologic and Cytologic Evaluation

CATHERINE J. BENSON and JED A. OVERMANN, *Consulting Editors**

Proper test choice and sample acquisition, preparation, and submission of specimens to a reference laboratory are crucial to making diagnostic decisions to aid in patient care and treatment. Numerous preanalytical factors such as incorrect labeling of samples, presence of interfering substances, use of incorrect collection tubes for a certain test, sampling the wrong tissue for cytologic evaluation, and samples with low cellularity can all impact data results and interpretation. Hematologic and cytologic sample quality can also be affected by the ambient storage temperature and the time interval between collection and evaluation. Care should be taken to eliminate or minimize sources of preanalytical errors to ensure high-quality laboratory results. Hematologic data and cytologic results should always be interpreted in light of the clinical history, physical examination findings, and other diagnostic testing such as imaging or histopathology results. If there are questions regarding sample collection, submission, or handling, contact the reference laboratory.

Venipuncture Site and Technique

Venipuncture site should be based on where it is safe to access a vein that will not collapse when blood is withdrawn.[1] In horses and goats, the jugular vein is most commonly used for blood collection. Alternative but often less recommended sites for venipuncture in horses resulting from safety concerns include the facial sinus, cephalic vein dorsal to carpus, and the saphenous veins. In cattle, the jugular and coccygeal (tail) vein can be accessed. Less often, the mammary vein is used due to the risk of personal injury and of hematoma formation at the blood draw site. Depending on the venipuncture site, species, and size of the animal, an 18- to 22-gauge needle and syringe or a double-ended needle and sheath or Vacutainer system (Becton Dickinson and Co., Franklin Lakes, NJ) with collection tube can be used to collect blood after the site of venipuncture is cleaned with an absorbent and 70% isopropyl alcohol and the vein is digitally occluded. After venipuncture, digital pressure should be applied over the site where the needle is removed to prevent hematoma formation.[2] Good technique is important because traumatic venipuncture can result in platelet activation and clumping of platelets. This can falsely decrease the measured platelet count generated by hematology analyzers.

*Contributions to previous editions by Debra Deem Morris are acknowledged.

Handling and Transportation of Samples

Samples for complete blood cell counts (CBCs) should be submitted in ethylenediaminetetraacetic acid (EDTA) tubes, filled to the proper amount indicated on the container, and inverted several times to ensure proper mixing of the blood with the anticoagulant. Too little blood may result in a falsely decreased pack cell volume (PCV) caused by shrinkage of red blood cells (RBCs). When collecting for both a CBC and serum biochemical profile, blood should first be put in an EDTA tube and then in a serum tube that does not contain anticoagulant. Care must be taken to avoid contaminating the blood remaining in the syringe with retrograde flow of EDTA blood, since this can alter calcium and potassium values on the serum biochemistry.[1] Samples for coagulation testing (prothrombin time and activated partial thromboplastin time) should be placed in a sodium citrate tube at a proportion of 1:9 with blood. Concurrently sending blood from a clinically healthy animal can serve as a control to help assess artifacts if there is a delay in sample transit. Samples for plasma fibrinogen concentration can be submitted either as whole blood in EDTA tubes or in sodium citrate tubes.[3] Consultation with the reference laboratory is advised because the technique used by a specific laboratory will dictate how the sample should be submitted.

Blood smears for microscopic evaluation should be made immediately to minimize artifacts from deterioration of cells. Blood smears should also routinely be made for manual differential counting and to evaluate for hemoparasites and atypical cells that would otherwise not be detected. Hematologic results are affected by the ambient storage temperature and the time interval between collection and evaluation. If samples cannot be run immediately on a hematology analyzer, they should be refrigerated. In cattle and goats, if blood samples are handled appropriately, hemoglobin concentration, RBC count, and total white blood cell (WBC) count are stable for the first 24 hours after collection. PCV is stable for up to 12 hours with mild increases at 24 hours.[4] Blood should not be frozen because this will rupture the cells.[1] Shipping and packaging of samples for hematologic and cytologic evaluation should follow guidelines from the reference laboratory.

General Principles for Submitting Cytology Samples

Proper labeling of slides will help ensure accurate record keeping and help minimize error. Slides that have one edge that is frosted should be labeled with a pencil with the patient identification and sample

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site before the sample is put on the slides. This is preferred to "permanent" ink marking pens because the preparation stains and fixatives used in the staining process will often wash off the ink.[5] When submitting samples to a diagnostic laboratory, it is important to fill out a complete history including the patient signalment, tissue sampled, location, duration of the mass or illness, a description of the mass or lesion (color, three-dimensional size for masses, shape, texture, consistency, etc.), other important clinical findings (bloodwork, surgical, imaging results), and differential diagnoses. Minimizing the amount of blood present on slides is also important, especially in cases in which inflammation is suspected. In these cases, cytologic findings may need to be interpreted in conjunction with CBC data to aid in determining if inflammation is present or if leukocytes are blood associated. Samples can be obtained by fine needle aspirate, impression smears, scrapings, and swabs of lesions. Depending on the sample, blood smear, squash, or roll preparations can be made to spread cells on the slide. Once air-dried samples are made, they can be stained with Romanowsky type stains (Wright-Giemsa, Diff-Quik, etc.). Although stained slides may be submitted, it is also important to include some unstained slides when submitting samples to a diagnostic laboratory. Keep unstained cytology samples away from formalin when histopathology samples are also being prepared and submitted because the formalin fumes can render cytology samples nondiagnostic.[5]

Bone Marrow Aspirates and Core Biopsy Samples

Please refer to Chapter 28.

Lymph Node Aspirates

Lymph nodes should be manually stabilized and aspiration or non-aspiration techniques as have been previously described can be used to collect cells.[6] In both techniques, the needle should be maintained within the lymph node, and it can be redirected to obtain cells from multiple areas. Peripheral lymph node samples tend to be highly cellular because the lymphocytes tend to exfoliate well and blood contamination is often mild. As a result, it is very important to spread the cells out well, which can be done by the squash preparation or blood smear technique. Evaluation of poorly stained thick areas should be avoided. Lymphocytes are often very fragile and are prone to lysis; it is therefore important to be gentle when making the preparations. Evaluate only intact lymphocytes because ruptured lymphocytes can appear larger than normal, leading to the misdiagnosis of lymphoma.

The main differential diagnoses for lymph node aspirates include normal lymph node, reactive lymph node, various inflammation (lymphadenitis), lymphoma, and metastatic neoplasia.[6] Normal lymph nodes are composed of mostly small lymphocytes with fewer medium and large lymphocytes. Low numbers of plasma cells, macrophages, eosinophils, non-degenerate neutrophils, and rare mast cells can also be seen. In reactive lymph nodes, small lymphocytes still predominate, but there are increased numbers of medium and large lymphocytes and plasma cells. Reactive lymph nodes are a relatively nonspecific finding in animals with antigenic stimulation, inflammation, or neoplasia. Increased numbers of degenerate or non-degenerate neutrophils, macrophages, or a combination of these two cell populations should prompt evaluation for an underlying infectious organism (bacteria or fungus) and for metastatic neoplasia. Eosinophilic inflammation can be seen with parasitic disease, with some fungal diseases, and with allergic conditions.[6]

General Principles for Various Body Fluids

Fluid should be collected in both EDTA tubes and in tubes without anticoagulant. EDTA tubes are best for cell counts, cytologic examination, and total protein measurement, whereas tubes lacking anticoagulant are used for biochemical and microbiological analysis. At least 1 mL of fluid should be collected in each tube if possible.[7] It is recommended to consult with a reference laboratory for the most current guidelines regarding sample collection, storage, and transport for culturing abdominal, pericardial, thoracic, cerebrospinal, and synovial fluids. Direct preparations of highly cellular turbid fluid or concentrated preparations of low cellularity clear fluid should be made as soon as possible, especially when a delay in transportation cannot be avoided. Cytologic findings that may be seen with delayed processing of fluid samples include erythrophagocytosis, vacuolization of large mononuclear cells, and pyknosis. Bacterial overgrowth can also impair interpretation.[8]

Body Fluid Analysis

Abdominocentesis, thoracocentesis, and pericardiocentesis techniques have been previously described in horses[2,7,9,10] and cattle.[2,11] Gross impressions such as the amount of fluid, color, and consistency should be evaluated. Normal fluid should be light straw-colored and clear.[11] Samples from thoracic, abdominal, and pericardial fluid should be evaluated based on total nucleated cell counts (TNCC) and total protein concentration (TP). The TNCC and TP together aid the clinician in classification of the fluids into the broad categories of transudate, modified transudate, and exudate. However, microscopic analysis should always be performed to evaluate the cellular differential and to assess for neoplastic cells, organisms, or evidence of chronic hemorrhage. In adult horses, samples from the thoracic cavity are generally transudates if they have fewer than 5000 cells/μL and a total protein of less than 2.5 g/dL, are modified transudates with 5000 to 15,000 cells/μL and a total protein of 2.0 to 5.0 g/dL, and are exudates if the TNCC is greater than 10,000 to 15,000 cells/μL and have a TP of greater than 3.0 to 3.5 g/dL.[12] Samples from the peritoneal cavity are similar except that modified transudates can have a TNCC of 1500 to 10,000 cells/μL and a TP of 2.5 to 3.5 g/dL.[8] TNCC and TP interpretations vary widely in cattle, and appropriate references should be consulted.[11] Further information can be obtained in Chapters 30, 31, and 32.

Synovial Fluid Analysis

Collection of synovial fluid should be aseptic, and a full description of techniques is found in other sources.[13,14] Synovial fluid should be placed in an EDTA tube for cytologic analysis as well as in a serum tube or heparinized tube if a mucin clot test is desired.[13] The gross and microscopic appearance of the synovial fluid, the total nucleated cell count, protein concentration, viscosity, and mucin quality (assessed via the mucin clot test) are all important features to analyze when making interpretations of joint fluid.[14] Normal joint fluid is clear to pale yellow, does not clot, and is highly viscous. Although there is some variability in the TNCC obtained from normal joints from various locations, generally, synovial fluid samples are of low cellularity (often < 1000 cells/μL). Hemarthrosis should be distinguished from blood contamination and the overall differential cell count should be interpreted in light of the degree of blood contamination. Overall, the percentage of neutrophils in normal joint fluid should not be greater than 10% in the absence of significant blood contamination. Large mononuclear cells and small lymphocytes predominate in normal joint fluid. Neutrophilic inflammation can be due to septic inflammation, immune-mediated disease, or acute trauma. Bacterial cultures and sensitivities are recommended to rule out infectious organisms. Immune-mediated diseases affecting joints are relatively uncommon in the horse.[13]

Bronchoalveolar Lavage/Tracheal Washes

Please refer to Chapter 31.

Cerebrospinal Fluid Analysis

Please refer to Chapter 35.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 24

Alterations in the Erythron

LESLIE C. SHARKEY and JED A. OVERMANN, *Consulting Editors**

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MAJOR ALTERATIONS

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The erythron is defined as the total mass of circulating erythrocytes and their precursors within the bone marrow. Alterations in the erythron are common in clinical practice and developing an approach to interpreting these abnormalities is important. Initial assessment of the erythron is generally accomplished through evaluation of a complete blood cell count (CBC). Major alterations include anemia and erythrocytosis. Based on the results of the CBC, clinical history, and physical examination, additional diagnostic tests can then be selected to further characterize these abnormalities in an attempt to identify a specific underlying pathophysiologic process.

Erythropoiesis

Erythrocytes are produced in the bone marrow, largely under the influence of erythropoietin (EPO), with increased erythropoiesis occurring in response to blood loss or hemolysis. Horses are unique in that equine erythrocytes generally remain in the bone marrow until fully mature before they are released into circulation. As a result, peripheral indicators of regeneration used in other species such as polychromasia and reticulocytosis are typically absent or unreliable in the horse. Detection of relatively low numbers of reticulocytes in the peripheral blood of anemic horses, however, has been described using an automated hematology analyzer, which may be a more sensitive means of detecting these cells than the manual methods used previously.[1,2]

Laboratory Evaluation of Erythrocytes

General reference intervals are presented for common erythrocyte parameters in large animals (Table 24-1); however, laboratory- or instrument-specific reference intervals should be used whenever possible. A complete discussion of age- and breed-related influences on erythrocyte parameters is found elsewhere.[3-5] What follows is a brief review of common laboratory evaluators of the erythron.

Hematocrit, Packed Cell Volume, Hemoglobin Concentration, and RBC Count

Hematocrit (HCT), packed cell volume (PCV), hemoglobin (Hgb) concentration, and red blood cell (RBC) count are all ways of quantifying the erythrocytes in peripheral blood, and these measures tend to increase (erythrocytosis) or decrease (anemia) together. HCT and PCV are similar in that they are describing the percentage volume of whole blood occupied by erythrocytes. The HCT is a calculated value and is a function of the mean cell volume and RBC count, whereas the PCV is determined by centrifugation of whole blood in a microhematocrit tube. The Hgb concentration and RBC count are measured values generated by hematology analyzers.

Mean Cell Volume

The mean cell volume (MCV) is directly measured by most hematology analyzers and represents the average erythrocyte volume. An increased MCV can be the result of a regenerative anemia in the ruminant and occasionally in the horse. Decreased MCV is seen with iron-deficiency anemia (also copper) and can also be seen in healthy calves and foals.[3,4]

Mean Cell Hemoglobin Concentration and Mean Cell Hemoglobin

The mean cell hemoglobin concentration (MCHC) is the cellular Hgb concentration per average erythrocyte and is calculated from the Hgb concentration and HCT. A decreased MCHC can be seen in ruminants with regenerative anemias, but this would not be expected in the horse. Both horses and ruminants can have decreased MCHC as the result of iron-deficiency anemia. A low MCHC has also been reported in calves (<5 weeks) as an age-related change.[6] Increased MCHC values are almost always false increases and can be seen with hemolyzed, severely icteric, or lipemic samples, or those with large numbers of Heinz bodies present.

Mean cell hemoglobin (MCH) is the amount of hemoglobin per average erythrocyte (in picograms). This is a calculated value based on the Hgb concentration and the RBC count. In general, MCH is affected in a similar manner to MCHC. MCHC, however, is considered more useful since it takes into account cell volume and is thus preferred over MCH when evaluating the erythron.

Erythrocyte Morphology

ANISOCYTOSIS. Anisocytosis is variation in erythrocyte size. A mild to moderate degree of anisocytosis can be seen in healthy ruminants, whereas mild anisocytosis can be seen in healthy horses. Increased anisocytosis can be the result of a regenerative anemia in ruminants and occasionally in horses. The RBC distribution width (RDW) provides an index of the variation in erythrocyte size.

POLYCHROMASIA. Polychromatophilic erythrocytes are slightly immature, macrocytic cells that appear blue-gray on a Wright-stained blood smear because of their retained cytoplasmic RNA. An increase in these cells in the peripheral blood is indicative of a regenerative response in ruminants. Increased polychromasia is not expected

*Contributions to previous editions by Debra Deem Morris are acknowledged.

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TABLE 24-1

Reference Intervals for Ruminants and Horses

	Cattle*	Sheep*	Goats*	Horses (Hot-Blooded Breeds)†	Horses (Cold-Blooded Breeds)†
PCV/HCT (%)	22-33	27-45	22-38	32-53	24-44
Erythrocytes ($\times 10^6/\mu L$)	5.1-7.6	9-15	8-18	6.8-12.9	5.5-9.5
Hemoglobin (g/dL)	8.5-12.2	9-15	8-12	11-19	8-14
MCV (fL)	38-50	28-40	16-25	37-58.5	—
MCHC (g/dL)	36-39	31-34	30-36	31-38.6	—
Reticulocytes	—	0	0	—	—

*From George JW, Snipes J, Lane M. 2010. Comparison of bovine hematology reference intervals from 1957-2006. Vet Clin Pathol 39:138.

†From Jain NC. 1986. Schalm's veterinary hematology, ed 4. Lea & Febiger, Philadelphia, PA.

in horses because in this species erythrocytes complete maturation in the bone marrow prior to release into circulation. Polychromatophilic erythrocytes are relatively analogous to reticulocytes; however, not all reticulocytes will be viewed as polychromatophilic erythrocytes on a peripheral blood smear. Thus, a reticulocyte count is considered a more objective and sensitive means of detecting a regenerative response, particularly if performed by an automated hematology analyzer. If a reticulocyte count is not available, a moderate to large degree of polychromasia observed on a peripheral blood smear is a good indicator of a regenerative response in ruminants.

HOWELL-JOLLY BODIES. Howell-Jolly bodies are small, dark, circular structures consisting of nuclear material within erythrocytes. These can be present in small numbers in healthy horses. Increased numbers can be associated with regenerative anemias and splenic dysfunction. Note that in cattle Howell-Jolly bodies can appear similar to *Anaplasma marginale* and can be difficult to differentiate from these organisms in some cases.

NUCLEATED ERYTHROCYTES. Nucleated erythrocytes (nRBCs) are not normally seen in the peripheral blood of healthy horses or ruminants. In ruminants, small numbers associated with regenerative anemias can sometimes be present, but should be accompanied by a significant degree of polychromasia. Bone marrow damage (e.g., toxic damage, hypoxia, neoplasia) can also result in circulating nRBCs. The presence of nRBCs and basophilic stippling in the absence of significant anemia should prompt consideration of lead toxicity (more common in ruminants).

BASOPHILIC STIPPLING. Basophilic stippling is seen as multiple small basophilic inclusions within erythrocytes and is the result of staining of ribosomal aggregates. Basophilic stippling is often seen in association with regenerative anemias in ruminants. As described previously, it can also be seen in cases of lead toxicity.

HEINZ BODIES. Heinz bodies form in erythrocytes as a result of oxidative damage that leads to precipitation of Hgb. They are recognized on Wright-stained blood smears as rounded, pale pink staining structures that protrude from the edge of erythrocytes. Heinz bodies can be confirmed by visualizing them with use of a new methylene blue stain that stains Heinz bodies as dark, rounded structures associated with the erythrocyte membrane. Ingestion of oxidants such as wilted red maple leaves, onions, and garlic; phenothiazine; *Brassica* spp.; and copper toxicity can result in Heinz body formation in large animals. Heinz body formation causes affected erythrocytes to be more susceptible to both intravascular and extravascular hemolysis.

ECCENTROCYTES. Eccentrocytes also form as a result of oxidative damage. In the case of eccentrocytes, oxidative damage results in partial fusion of the erythrocyte membrane causing displacement of Hgb contents to one side of the erythrocyte. Oxidants listed as causes of Heinz bodies can also result in eccentrocyte formation. Eccentrocytes have also been reported in horses with glucose-6-phosphate dehydrogenase deficiency and flavin adenine dinucleotide deficiency. Both are rare erythrocyte enzyme deficiencies that result in the affected animal's erythrocytes being more susceptible to oxidative damage by endogenous or exogenous sources.[7]

ROULEAUX. Rouleaux formation is seen as linear stacking of erythrocytes on a peripheral blood smear. Rouleaux formation is common in healthy horses. A consequence of rouleaux formation is that equine blood samples tend to have a relatively high erythrocyte sedimentation rate, and as a result, whole blood samples should be thoroughly mixed before evaluation. Rouleaux formation is uncommon in healthy ruminants but can be seen with increased plasma proteins such as fibrinogen and immunoglobulins. Increases in these plasma proteins can also enhance rouleaux formation in horses. In any species, care should be taken to differentiate rouleaux from erythrocyte agglutination.

AGGLUTINATION. Agglutination is the result of surface-associated antibody on erythrocytes causing clumping. When viewed microscopically on a peripheral blood smear, aggregation produces clumps of erythrocytes that are described as having the appearance of "clusters of grapes." Agglutination is significant in that it is indicative of immune-mediated hemolytic anemia (IMHA). In some cases it may be difficult to differentiate prominent rouleaux from agglutination. A saline dilution test can be done to confirm true agglutination. This test is accomplished by diluting whole blood with saline and evaluating a wet preparation. Rouleaux will disperse with dilution, whereas true agglutination will persist. Generally a 1:2 to 1:4 dilution will disperse rouleaux; however, occasionally higher dilutions are needed. Agglutination confirmed by a saline dilution test is generally considered to preclude the need for Coombs testing. Agglutination in the horse has also been described as a result of treatment with unfractionated heparin.[8]

Erythrocyte Parasites

A variety of erythrocyte parasites can be detected by review of peripheral blood smears. Examples include *Mycoplasma* spp., *Anaplasma* spp., *Theileria* spp., and *Babesia* spp.[9]

The Coombs Test

The Coombs test or direct antiglobulin test is used to detect erythrocyte surface-associated antibody. Positive Coombs test results support a diagnosis of IMHA (including neonatal isoerythrolysis). A negative Coombs test result, however, does not rule out IMHA because this test is known to have a relatively low sensitivity (i.e., many false negatives).

Evaluation of the Anemic Patient

Anemia develops from one or more of three main pathophysiologic mechanisms: blood loss, hemolysis, and decreased production of erythrocytes. More specific causes are often categorized in terms of these three main mechanisms (Boxes 24-1 and 24-2). Specific causes of anemia are also sometimes grouped in terms of whether they cause a regenerative or non-regenerative anemia. Anemias that are the

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BOX 24-1

Causes of Anemia in the Horse

Common Causes

Blood Loss

Trauma
Surgery
Ectoparasites (lice, ticks)
Intestinal parasites (strongyles)
Gastrointestinal bleeding (ulcers, neoplasia)
Immune-mediated thrombocytopenia
Equine purpura hemorrhagica

Hemolysis

Neonatal isoerythrolysis
Red maple leaf toxicosis
Equine infectious anemia

Decreased Erythrocyte Production

Anemia of inflammatory disease (chronic inflammation, neoplasia)
- Chronic abscessation
- Chronic pneumonia or pleuritis
- Lymphoma

Less Common Causes

Blood Loss

Bleeding diathesis associated with disseminated intravascular coagulation (DIC)
Guttural pouch mycosis
Hematuria
Hemoabdomen
Moldy sweet clover toxicosis
Rodenticide toxicity (brodifacoum)
Congenital coagulation factor deficiencies (hemophilia A)
Platelet function disorders (von Willebrand disease, Glanzmann thrombasthenia)

Hemolysis

Fragmentation (DIC, vasculitis)
Immune-mediated hemolytic anemia (idiopathic)
Immune-mediated hemolytic anemia (secondary)
- Clostridial infections
- Penicillin therapy
- Lymphoma

Theileriosis/Babesiosis
Onion toxicosis
Phenothiazine toxicosis
Glucose-6-phosphate dehydrogenase deficiency

Decreased Erythrocyte Production

Anemia of chronic renal failure
Bone marrow neoplasia (leukemia, metastatic neoplasia)
Myelofibrosis
Aplastic anemia (idiopathic, drugs including phenylbutazone)

BOX 24-2

Causes of Anemia in Ruminants

Common Causes

Blood Loss

Trauma
Intestinal parasites *(Haemonchus)*
Ectoparasites (lice, ticks)
Abomasal ulcers

Hemolysis

Anaplasmosis
Brassica spp. toxicosis
Leptospirosis
Onion toxicosis
Clostridial infections
Chronic copper toxicosis

Decreased Erythrocyte Production

Anemia of inflammatory disease (chronic inflammation, neoplasia)
- Chronic pneumonia
- Chronic abscessation
- Johne's disease
- Chronic bovine virus diarrhea infection
- Lymphoma

Less Common Causes

Blood Loss

Hemorrhagic enteritis
Hemoabdomen
Bleeding diathesis associated with disseminated intravascular coagulation (DIC)
Moldy sweet clover toxicosis
Caudal vena cava syndrome
Severe acute pyelonephritis

Hemolysis

Babesiosis
Theileriosis
Mycoplasma spp. infection
Postparturient hemoglobinuria
Immune-mediated hemolytic anemia

Decreased Erythrocyte Production

Anemia of chronic renal failure
Bracken fern toxicosis (also hemorrhage in enzootic hematuria)
Radiation toxicosis
Myelofibrosis (pygmy goats)
Myelophthisis

result of blood loss or hemolysis are typically regenerative, whereas those that are the result of decreased erythrocyte production will be non-regenerative.

A regenerative response in the ruminant is best identified by a moderate to marked degree of polychromasia or a reticulocytosis. Note that following an acute episode of hemorrhage or hemolysis in ruminants, it takes 2 to 4 days for the bone marrow to respond by beginning to release increased numbers of polychromatophilic cells/reticulocytes into circulation. Peak bone marrow response generally occurs within 7 days. This time frame must be kept in mind when assessing peripheral blood for indicators of regeneration. Other findings that can support the regenerative nature of an anemia would be an increased MCV, a decreased MCHC, basophilic stippling, nRBCs, increased numbers of Howell-Jolly bodies, and increased anisocytosis. It may take 2 to 4 weeks or more in ruminants for the HCT to return to normal after an episode of hemorrhage or hemolysis.

As noted previously, classifying an anemia as regenerative or non-regenerative is more difficult in the horse because of the relative absence of peripheral indicators of regeneration (e.g., polychromasia, reticulocytosis). In these patients, serial CBCs can be performed to detect increasing HCT over time. Similar to ruminants, it takes about 4 days for the bone marrow to begin to respond to an episode of hemorrhage or hemolysis. Mild increases in the MCV can be seen in some horses with regenerative anemias. The bone marrow response to anemia in horses is relatively sluggish compared with other species, and it may take up to 1 to 2 months following severe hemolysis or 2 to 3 months following severe hemorrhage for HCT values to return to normal.[10] In both horses and ruminants, the regenerative response to hemolysis is generally considered to be somewhat more vigorous than the response to hemorrhage. It is suggested that this may be in part due to the fact that in hemolysis, iron (from Hgb) is not lost from that body and is then made available for production of new erythrocytes. Evaluation of bone marrow can also be performed in horses to evaluate for a regenerative response. Enumeration of polychromatophilic cells and reticulocytes in the bone marrow, assessment of overall cellularity, and calculation of the myeloid to erythroid ratio (M:E) are used to determine if a regenerative response is

present. Excessive hemodilution of the bone marrow sample and the variable M:E ratios present in normal animals, however, can complicate interpretation in some cases.

Blood Loss

Immediately following an episode of acute blood loss, the HCT and plasma protein concentration are generally within the reference interval. The HCT in horses can actually increase mildly above baseline in some cases as a result of splenic contraction. It is only after fluid shifts have occurred from the interstitial space into the vasculature that the HCT and plasma protein concentration begin to decrease. Increased thirst and renal conservation of free water contribute to the fluid shifts that will continue to occur over a 24- to 48-hour period as vascular volume is restored. Hypoproteinemia concurrent with anemia is supportive of hemorrhage as the cause, assuming there are no other significant sources of protein loss (e.g., gastrointestinal [GI] or renal). Evidence of regeneration should also be present if sufficient time has passed since the episode of blood loss. In some cases, the source of blood loss is obvious (e.g., trauma, surgery, severe epistaxis), whereas in other cases more cryptic sources of blood loss must be investigated. Evaluation of the patient for endoparasites, ectoparasites, hematuria, GI blood loss (e.g., ulcers, neoplasia), and hemoabdomen is warranted in these instances. Chronic blood loss, commonly from parasitic causes, GI ulcers, or GI neoplasia, can result in an iron deficiency anemia. Supportive findings for iron deficiency anemia are decreased MCV, decreased MCHC, hypochromic erythrocytes, and a mild degree of erythrocyte fragmentation (i.e., schistocytes and keratocytes). Iron-deficiency anemia is initially regenerative but, if ongoing, can become poorly regenerative to non-regenerative. Hypoproteinemia may be present; however, protein concentration is within the reference interval in some animals because protein loss is compensated by increased production by the liver. Iron deficiency anemia can also occur in young foals and calves as a result of low dietary intake.[11] An iron panel can be performed to confirm iron deficiency.

Hemolysis

Hemolysis results in a regenerative anemia often with a normal to increased plasma protein concentration. Erythrocyte morphology should be assessed for evidence of Heinz bodies, eccentrocytes, schistocytes, erythrocyte parasites, and agglutination. Hemolyzed plasma and hemoglobinuria are supportive of an intravascular hemolytic process, whereas icterus and hyperbilirubinemia support extravascular hemolysis. Hemoglobinuria, however, should be differentiated from hematuria and myoglobinuria, and liver disease and anorexia (in the horse) should be ruled out as causes of the icterus and hyperbilirubinemia. Feed and/or pasture should be evaluated if ingestion of an oxidant is suspected. Additional diagnostics to consider in cases of hemolytic anemia are Coombs testing (IMHA) and Coggin testing (equine infectious anemia).

Decreased Erythrocyte Production

Anemia of inflammatory disease, often the result of infection, inflammation, or neoplasia, is the most common cause of a mild to moderate non-regenerative anemia. An inflammatory leukogram and hyperfibrinogenemia would be supportive of the presence of a systemic inflammatory response. Chronic renal failure can also result in a non-regenerative anemia of variable severity (moderate to severe) and can initially be assessed by a serum biochemical profile and urinalysis. Feed and/or pasture conditions and drug history should be determined to prioritize other causes of anemia resulting from decreased erythrocyte production. Bone marrow evaluation is indicated to investigate unexplained non-regenerative anemias, especially when other cytopenias are present.

Erythrocytosis

Erythrocytosis (polycythemia) refers to an increased RBC count, Hgb concentration, and HCT. Erythrocytosis can be either relative or absolute in nature (Box 24-3). In general, relative erythrocytosis is far more common than absolute, and these causes should be considered or ruled out first. With relative erythrocytosis, there is no actual increase in total body erythrocyte mass; however, hemoconcentration or splenic contraction causes apparent increases in these measures in the peripheral blood. Hemoconcentration is most often due to dehydration and loss of plasma volume (e.g., diarrhea, excessive sweating, water deprivation, diuresis). Endotoxic shock can also result in hemoconcentration because of increased vascular permeability and subsequent fluid shifts from the intravascular to extravascular space. In both cases, plasma volume is decreased, effectively concentrating the erythrocytes in circulation. With dehydration, increased plasma protein concentration and clinical evidence of dehydration (e.g., skin tent, tachy mucous membranes, sunken eyes) would be supportive. Epinephrine-mediated splenic contraction as the result of excitement, pain, fright, or vigorous exercise can also cause a relative erythrocytosis as a result of redistribution of relatively high HCT splenic blood into the peripheral circulation. This is most often seen in the horse. Plasma protein concentration is not expected to increase with splenic contraction as compared with dehydration. Erythrocytosis caused by splenic contraction is a transient change and typically normalizes within a few hours if the inciting stimulus has been removed.

BOX 24-3

Causes of Erythrocytosis in Large Animals

Relative Erythrocytosis

Dehydration
Endotoxic shock
Splenic contraction

Absolute Erythrocytosis

Primary

Primary erythrocytosis

Secondary Appropriate

Chronic pulmonary disease
Right-to-left cardiovascular shunting
Residence at high altitude

Secondary Inappropriate

EPO-secreting neoplasms
Renal pathology causing local hypoxia

Absolute erythrocytosis occurs when there is a true increase in total erythrocyte mass as a result of increased erythropoiesis and can be primary or secondary in nature. Absolute erythrocytosis is considered secondary when it is in response to increased erythropoietin (EPO) levels or activity. This can be an appropriate physiologic response to chronic hypoxemia (e.g., chronic pulmonary disease, right-to-left cardiovascular shunting, or animals living at high altitude); however, tumor production of EPO or EPO-like substances or renal pathology causing local tissue hypoxia can result in a secondary erythrocytosis in the absence of systemic hypoxemia. Primary absolute erythrocytosis is considered a chronic myeloproliferative disease (primary erythrocytosis or polycythemia vera) where erythropoiesis occurs independent of EPO. There are rare reports of primary erythrocytosis in the horse.[12] Absolute erythrocytosis of unknown cause has also been described in a herd of Jersey calves and in a Japanese black heifer.[13]

Clinical evaluation of animals with an erythrocytosis should first begin by considering causes of relative erythrocytosis, since these are much more common. If dehydration, shock, and splenic contraction are ruled out and if the increased HCT persists over time without response to fluid therapy, then the erythrocytosis may be considered absolute. Arterial blood gas, thoracic radiographs, and echocardiography can help to identify decreased cardiorespiratory function and systemic hypoxia as the cause. Neoplasia (e.g., lymphoma,

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hepatoblastoma, hepatocellular carcinoma) and renal disease should also be ruled out before considering the erythrocytosis primary in nature.[14-18] Bone marrow aspiration and biopsy are generally not helpful in differentiating causes of absolute erythrocytosis (i.e., primary vs. secondary) because erythroid hyperplasia would be expected in both cases. Serum EPO concentrations would be expected to be normal to low in primary absolute erythrocytosis and increased in secondary absolute erythrocytosis. This assay, however, is not widely available, and there is likely some overlap in EPO levels among patients with primary and secondary absolute erythrocytosis, making interpretation difficult in some cases.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Alterations in the Leukogram

LESLIE C. SHARKEY and JED A. OVERMANN, *Consulting Editors**

■ MAJOR ALTERATIONS

Neutrophilia, 382
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Interpretation of the leukogram in the context of the clinical history, physical examination, and the rest of the minimum laboratory database (complete blood cell count, serum biochemical data, and urinalysis) can provide valuable insights into the diagnostic process in large animal species. Often, leukogram data are used to evaluate patients for the presence of inflammation or hematopoietic neoplasia. Careful attention to sample collection and handling (see Chapter 23) will help ensure high-quality results. Key components of the leukogram include the total white blood cell count (WBC), differential cell counts including the absolute numbers of each leukocyte type, and a microscopic evaluation of the blood film. Blood film evaluation is necessary to visually verify the WBC, to generate the differential, and to evaluate the leukocytes for important morphologic abnormalities that contribute to the diagnostic interpretation of the quantitative data. Although the newer automated hematology analyzers will generate leukocyte differentials for numerous species, the Clinical Laboratory Standards Institute still considers the manual differential cell count to be the reference standard.[1] Microscopic examination of the blood film for the presence of toxic change, band neutrophils, reactive changes in lymphocytes, neoplastic cells, and organisms is required for a full characterization of the leukogram. The concurrent measurement of acute phase proteins can augment the diagnostic interpretation of leukogram data.

When evaluating the leukogram, clinicians should remember that each data set is a snapshot in time of a dynamic system in which the numbers of cells in the circulation reflect a balance between the release of cells from the bone marrow and egress of cells into the tissues. Serial monitoring of patients often provides more information than a single time point. It is also important to keep in mind that the numbers of cells trafficking in the circulation may not be reflective of the tissue content of cells; therefore, cytology or biopsy of tissues may be necessary to confirm the presence of inflammation or hematopoietic neoplasia.

Leukocytes

Leukocytes are partitioned into granulocytes (neutrophils, eosinophils, basophils) and mononuclear cells (lymphocytes, monocytes). In postnatal life, the main source of hematopoiesis is the bone marrow, except for lymphocytes, which migrate from the bone marrow to tissues such as the lymph nodes, spleen, and mucosal-associated lymphoid tissue after birth. The following sections will briefly describe the biology of each type of leukocyte, as well as the interpretation of high and low values and common morphologic abnormalities. Note that the reference intervals for some leukocyte subtypes encompass zero, making the detection of low values difficult and therefore the interpretation of questionable clinical significance (Table 25-1). Although reference intervals are provided here for guidance, clinicians should use laboratory-specific reference intervals because of the potential effect of instrumentation and geographic variation on leukocyte parameters. Other factors that influence reference intervals in large animal species include age, reproductive and lactation status, and other husbandry issues that are explored in further detail elsewhere.[2-4]

Neutrophils

Neutrophils develop from hematopoietic stem cells in a process that usually takes about 6 days under the influence of an array of cytokines. Some species can accelerate the process in situations of increased demand, but that capacity appears to be limited in cattle.[5] There is a storage pool of neutrophils in the marrow; however, once that is depleted, earlier precursors, including band neutrophils and sometimes metamyelocytes or even myelocytes, may be observed in the peripheral circulation in a phenomenon known as a "left shift." Neutrophils circulate for only a few hours after release, existing in either the circulating pool where they can be measured, or in the marginal pool along the endothelial surface where they are not recovered during blood sample collection. Shifts between the circulating and marginal pools in response to hormonal mediators can result in rapid changes in neutrophil numbers measured in the leukogram.

Neutrophils migrate into tissues, especially the gastrointestinal and respiratory tracts and the skin, through selectin-mediated rolling followed by integrin-mediated adhesion of neutrophils to the endothelium. Transmigration between or through endothelial cells allows neutrophils to enter the tissues, where they will bind to chemokines that direct them toward targets in the tissue. Receptor-mediated phagocytosis of bacteria and other particulate matter is followed by proteolytic digestion and/or the respiratory burst using granule contents. Neutrophils also amplify local inflammation and interact with cells of the adaptive immune response.[6] These mechanisms can result in damage to normal tissues in addition to the killing of infectious agents, contributing to acute respiratory distress syndrome and multiple organ failure. Senescent neutrophils undergo apoptosis in tissues and are cleared by tissue macrophages.

Some of the morphologic abnormalities that can be relevant to the interpretation of the leukogram in large animals include toxic change, Pelger-Huët and pseudo–Pelger-Huët anomalies, and the

*Contributions to previous editions by Debra Deem Morris are acknowledged.

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TABLE 25-1

Normal Values for Leukogram Data (Adult Animals)

	Cattle	Sheep	Goats	Horses
White blood cells ($\times 10^3/\mu L$)	4.9-12	4-12	4-13	5.4-14.3
Neutrophils ($\times 10^3/\mu L$)	1.8-6.3	0.7-6	1.2-7.2	2.3-8.6
Bands ($\times 10^3/\mu L$)	Rare	Rare	Rare	0-1
Lymphocytes ($\times 10^3/\mu L$)	1.6-5.6	2-9	2-9	1.5-7.7
Monocytes ($\times 10^3/\mu L$)	0-0.8	0-0.75	0-0.55	0-1
Eosinophils ($\times 10^3/\mu L$)	0-0.9	0-1	0.05-0.65	0-1
Basophils ($\times 10^3/\mu L$)	0-0.3	0-0.3	0-0.12	0-0.29
Neutrophil/lymphocyte (N/L) ratio	0.4-2.34	0.3-0.7	0.6-3.6	0.8-2.8

presence of intracellular organisms including *Anaplasma phagocytophilum*. The common components of toxic change include cytoplasmic basophilia and vacuolization and the presence of Dohle bodies in the cytoplasm of neutrophils; rarer manifestations include nuclear abnormalities, toxic granulation, and increased cell size. Toxic change is subjectively evaluated during the blood film evaluation and graded as 1+ to 4+. These changes occur in the neutrophil cytoplasm during the development in the marrow and signal the likelihood of inflammation; toxic change may be accompanied by a left shift. Pelger-Huët anomaly is an incidental asymptomatic congenital condition in which a defect occurs in the segmentation of leukocyte nuclei, giving the impression of a severe left shift in the absence of toxic change or other signs of inflammation.[7] In contrast, pseudo–Pelger-Huët is pathologic hyposegmentation that occurs as a result of severe inflammation and is accompanied by toxic change and inflammatory disease. *Anaplasma phagocytophilum* is a tick-borne bacteria common to humans as well as small and large animal species that survives in neutrophils by avoiding the bactericidal mechanisms.[8] Organisms are most likely to be identified microscopically in acute infection, when serologic methods for detection may still be negative.

Eosinophils

Eosinophil development in the marrow is very similar to that of neutrophils, although it occurs under the influence of distinctive cytokines. Normally, eosinophils spend a short time in the circulation before entering the tissues using similar mechanisms to neutrophils, although the numbers in the peripheral blood are usually quite small. The tissue survival time of eosinophils is usually short; however, they may persist in tissues for longer periods if appropriate survival factors are present. Recirculation is even possible under some conditions. Although eosinophils have the capacity for phagocytosis, more prominent functions include defense against parasites by externalization of granule contents and modulation of inflammation, particularly allergic and hypersensitivity disorders. Eosinophils are primarily tissue dwelling cells, so numbers in the circulation may not accurately reflect tissue eosinophilia.

Basophils

Basophil development largely parallels that of eosinophils, although it is associated with a specific growth factor repertoire. Basophils are the least numerous leukocyte in the peripheral blood under most conditions, where, like other granulocytes, they circulate briefly before entering tissues through similar mechanisms. With even less phagocytic and bactericidal potential than eosinophils, basophils are important in hypersensitivity responses and allergic conditions, which they mediate through release of their granule contents into the local environment. The accuracy of basophil counts by automated analyzers has been questioned.

Lymphocytes

Lymphocytes encompass a heterogeneous group of mononuclear leukocytes fundamental to the adaptive immune response, although some, like natural killer cells, are aligned with innate immunity. Circulating lymphoid cells are generally divided into natural killer cells, B-cells, and T-cells, with an expanding number of T-cell varieties being characterized, each with a specific function. Advanced diagnostic techniques such as flow cytometry are required to identify cells from different lymphocyte subsets, which are not routinely distinguished during blood film evaluation. All originally derive from bone marrow stem cells; however, T-cells complete maturation in the thymus and participate in cell-mediated immunity, whereas B-cells develop in the marrow and other peripheral tissues to eventually disperse throughout the body to effect humoral immunity. Unlike most leukocytes in the peripheral blood, lymphocytes have significant potential for proliferation. Lymphocytes continually recirculate among tissues in a process called "trafficking," which is most relevant for T-cells because B-cells release antibodies that are carried by the circulation to relevant sites. At any given time, only a tiny fraction of an animal's lymphocytes are present in the circulation, so the peripheral blood lymphocyte count is not reflective of total body lymphoid activity. Likewise, advanced diagnostic techniques are required to characterize the lymphocyte subsets in circulation, which may change with different pathologic processes.

Monocytes

Monocytes develop in the bone marrow and enter the circulation, where they persist longer than other leukocytes. Like other leukocytes, monocytes migrate into tissues; however, they have the potential to differentiate into a variety of macrophage subtypes (e.g., Kupffer cells, alveolar macrophages, microglial cells) depending on the local microenvironment. Monocytes can re-enter the circulation from the tissues. Unlike mature granulocytes that are post-mitotic, monocytes have a limited capacity for replication in tissues. The major functions of macrophages once in the tissues include inhibiting the growth of intracellular pathogens, antigen processing, removal of dead cells and debris, control of iron metabolism, and complex regulation of the inflammatory response. Depending on the stimuli, macrophages can develop into proinflammatory M1 macrophages or antiinflammatory M2 cells.[9]

Principles of Leukogram Interpretation

As noted previously, the absolute numbers of leukocyte subtypes are interpreted in the context of appropriate reference intervals. If there are questions about the validity of available reference intervals, clinicians should consider the option of submission of samples for comparison from one or more age- and sex-matched unaffected individual(s) sharing the husbandry conditions and genetics of the patient of interest. Although individual abnormalities are discussed in the following sections, integration of all of the leukogram data to identify diagnostic patterns is often the best approach.

Neutrophilia

Although bacterial infection is the most common cause of neutrophilia in large animal species, noninfectious inflammatory processes such as traumatic tissue damage, surgery, and immune-mediated hemolytic anemia can also cause increased neutrophil concentrations (Boxes 25-1 and 25-2).[10] A left shift and toxic change provide

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BOX 25-1

Causes of Neutrophilia in Horses

Common Causes

Excitement, exercise
Stress, exogenous corticosteroid administration
Chronic pneumonia, pleuritis
Strangles (*Streptococcus equi* infection)
Chronic peritonitis, abdominal abscess
Other internal abscessation
Chronic salmonellosis or colitis
Thrombophlebitis
Purpura hemorrhagica (vasculitis)

Less Common Causes

Bacterial endocarditis
Cellulitis
Pyelonephritis
Chronic hepatitis, cholangiohepatitis
Cholelithiasis
Lymphosarcoma
Meningitis/meningoencephalitis
Other internal neoplasia
Pituitary adenoma (equine Cushing syndrome)
Autoimmune hemolytic anemia
Granulocytic leukemia
Systemic fungal infections

BOX 25-2

Causes of Neutrophilia in Ruminants

Common Causes

Stress, exogenous corticosteroid administration
Chronic pneumonia
Chronic traumatic reticuloperitonitis
Peritonitis
Internal abscessation
Caseous lymphadenitis (O, C)
Mycoplasmal or chlamydial polyarthritis (O, C)
Chronic pyelonephritis
Chronic metritis
Liver abscesses
Enteritis
Umbilical abscessation
Chronic salmonellosis
Septic arthritis

Uncommon Causes

Autoimmune hemolytic anemia
Toxins
Pregnancy toxemia (O, C)
Bovine granulocytopathy syndrome

C, Caprine; *O,* ovine.

BOX 25-3

Causes of Neutropenia in Horses

Common Causes

Acute salmonellosis
Acute toxic colitis
Acute peritonitis (ruptured viscus)
Gram-negative septicemia, endotoxemia
Neonatal septicemia
Acute pleuritis
Acute metritis
Proximal enteritis (duodenitis, proximal jejunitis)
Equine influenza
Equine herpesvirus type 1 infection

Less Common Causes

Equine ehrlichial colitis (Potomac fever, *Ehrlichia risticii* infection)
Equine ehrlichiosis (*Anaplasma phagocytophilum* infection)
Idiopathic aplastic anemia
Equine viral arteritis
Radiation toxicosis
Myelophthisic disease (e.g., leukemia)
Alloimmune neonatal neutropenia

BOX 25-4

Causes of Neutropenia in Ruminants

Common Causes

Gram-negative septicemia, endotoxemia
Septic metritis
Septic (coliform) mastitis
Diffuse peritonitis
Ruptured uterus with peritonitis
Ruptured abomasal ulcer
Acute salmonellosis
Acute pneumonia
Toxemia- or toxin-induced bone marrow suppression
Fat cow syndrome (fatty liver)
Clostridial infection

Uncommon Causes

Bovine virus diarrhea
Bracken fern toxicosis
Trichloroethylene toxicosis
Radiation toxicosis
Idiopathic aplastic anemia

additional evidence of an inflammatory cause for neutrophilia, but they may not always be present, especially with mild or chronic compensated inflammation. In fact, normal neutrophil numbers do not exclude infectious or inflammatory diseases because the numbers of circulating cells do not reflect tissue activity in all conditions. Neutrophilia can signal the presence of otherwise difficult-to-detect processes such as extrapulmonary *Rhodococcus equi* infection in foals,[11] musculoskeletal *Corynebacterium pseudotuberculosis* infection,[12] meningitis/meningoencephalomyelitis in horses,[13] and liver abscesses in dairy cattle.[14] Stress resulting from causes such as transport and changes in housing can be another important cause of neutrophilia in cattle.[15] Marked neutrophilia occasionally follows a period of neutropenia induced by inflammation (overshoot effect), and very rare genetic causes such as bovine leukocyte adhesion deficiency have been documented. Some authors advocate the use of a neutrophil:lymphocyte ratio to augment the interpretation of absolute neutrophil and lymphocyte numbers on the basis that ruminants have been described to have greater numbers of lymphocytes than neutrophils in the circulation under normal circumstances. Recent information on bovine leukocyte reference intervals suggests that clinicians should exercise caution with that approach and consider laboratory- and herd-specific information when interpreting the ratio.[16]

Neutropenia

Endotoxemia results in rapid redistribution of neutrophils from the circulating pool to marginal pool and tissues. Neutropenia resulting from bone marrow depletion is often observed in large animal species during the first 24 to 48 hours of an acute inflammatory episode, especially in cattle (Boxes 25-3 and 25-4).[17] Persistent neutropenia is a poor prognostic sign or may indicate bone marrow pathology if other peripheral cytopenias are present. Transient viral infections in cattle such as bovine viral diarrhea virus and bluetongue virus can cause neutropenia, as can some tick-borne diseases. As for any species, toxic damage to the marrow or bone marrow necrosis,

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BOX 25-5

Causes of Eosinophilia in Horses

Uncommon Causes

Internal parasitism
Cutaneous habronemiasis
Systemic hypersensitivity reaction
Lymphosarcoma
Eosinophilic leukemia

BOX 25-6

Causes of Eosinophilia in Ruminants

Uncommon Causes

Milk allergy
Atypical interstitial pneumonia
Acute bovine pulmonary emphysema
Sarcocystosis
Toxoplasmosis
Migrating parasite larvae, such as:
- Lungworms
- Ascarids
- Flukes
- *Trichostrongylus* spp.
- *Hypoderma* spp.
- *Parelaphostrongylus* spp.

BOX 25-7

Causes of Lymphocytosis in Horses

Common Cause

Excitement, exercise

Uncommon Causes

Lymphocytic leukemia
Equine infectious anemia

BOX 25-8

Causes of Lymphocytosis in Ruminants

Persistent lymphocytosis (bovine leukemia virus infection)
Lymphocytic leukemia
Chronic infections (pneumonia, peritonitis, pericarditis, liver abscess)

BOX 25-9

Causes of Lymphopenia in Horses

Common Causes

Stress, exogenous corticosteroid administration
Equine influenza
Equine herpesvirus type 1 infection
Endotoxemia, septicemia
Acute peritonitis (gastrointestinal rupture)

Less Common Causes

Malnutrition, starvation
Equine viral arteritis
Combined immunodeficiency disease

BOX 25-10

Causes of Lymphopenia in Ruminants

Common Causes

Stress, exogenous corticosteroid administration
Gram-negative septicemia, endotoxemia
Septic mastitis
Diffuse peritonitis
Ruptured abomasal ulcer
Acute pneumonia
Infectious bovine rhinotracheitis

Uncommon Causes

Bovine virus diarrhea
Immunodeficiency

BOX 25-11

Causes of Monocytosis in Large Animals

Uncommon Causes

Granulomatous disease
Chronic bacterial infections

fibrosis, or neoplasia can result in generalized peripheral cytopenias, including neutropenia. Alloimmune neonatal neutropenia has been reported in horses.[18]

Eosinophilia

Eosinophilia is not common in large animal species, even when parasitism can be demonstrated (Boxes 25-5 and 25-6). This may be related to the tissue predilection of eosinophils and the relatively short transit time from marrow to target tissue. Rare hypereosinophilic syndromes have been described that are accompanied by peripheral eosinophilia, such as idiopathic chronic eosinophilic pneumonia in horses.[19] Paraneoplastic eosinophilia resulting from lymphoma has been reported in multiple species. Although eosinopenia may characterize the corticosteroid response in most species, it is difficult to recognize because the lower limit of the reference interval is often zero.

Basophilia

Basophilia is rare in large animal species and is often attributed to hypersensitivity responses; basopenia is not recognized as clinically significant.

Lymphocytosis

Lymphocytosis characterizes an epinephrine response (especially in young horses), as well as antigenic exposure (Boxes 25-7 and 25-8). The lymphocytosis caused by antigenic stimulation may be accompanied by morphologic changes in lymphocytes, including reactive lymphocytes that have increased amounts of cytoplasm, cytoplasmic basophilia, increased azurophilic granules, or larger cell size. Spontaneous lymphoid leukemias are described sporadically in horses, whereas bovine leukemia virus causes persistent lymphocytosis in a third of infected cattle and leukemia in approximately 4%.[17]

Lymphopenia

The most common cause of lymphopenia in large animal species is corticosteroid effects, although the acute phase of systemic infectious diseases may also be associated with a transient period of lymphopenia (Boxes 25-9 and 25-10). Rarely, congenital combined immunodeficiency syndromes, especially in Arabian and Arabian-cross foals, cause severe lymphopenia and global depletion of lymphoid tissues.

Monocytosis

Monocytosis can be seen with inflammation, tissue necrosis, or occasionally as part of a stress leukogram. Because the reference intervals for monocytes approach or include zero, monocytopenia is not a diagnostically useful observation (Box 25-11).

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Approach to Interpretation of the Leukogram in Horses

Reference intervals for equine patients are often wide due to the inclusion of a range of ages and breeds; the benefits of using more specific reference intervals must be balanced against the preference for reference intervals generated by the laboratory performing the testing.[20] As an approximation, 20,000 leukocytes/μL indicates a moderate leukocytosis, 30,000/μL is marked, and greater than 30,000/μL is considered extreme. Marked rebound neutrophilia can be observed after an episode of neutropenia resulting from neutrophil depletion caused by acute inflammation/endotoxemia. Foals often have greater absolute numbers of neutrophils and lower numbers of lymphocytes than adult horses for the first several months of life. Variable effects of training on leukocyte counts have been reported.

Epinephrine-mediated (physiologic) leukocytosis is observed more frequently in horses than in many other species, particularly in young warm and hot bloods and horses that are not habituated to transport or handling. This type of leukocytosis is typically characterized by a mild mature neutrophilia and a moderate lymphocytosis that persists for about 20 to 30 minutes. In contrast, the corticosteroid leukogram is less age or breed specific and includes a moderate mature neutrophilia with no left shift or toxic change, lymphopenia, eosinopenia, and inconsistent monocytosis. Corticosteroid leukograms are more persistent than physiologic leukocytosis and can frequently be superimposed on inflammatory leukograms because of the stress of illness.

Leukemias are rare but have been reported in horses. Lymphocytic leukemia is the most common, frequently associated with high lymphocyte counts and/or immature lymphocytes. Other forms of myeloid leukemia may present with large numbers of atypical cells originating from any myeloid lineage. Disruption of the hematopoietic microenvironment by proliferating neoplastic cells often suppresses the production of other cell lines.

Approach to Interpretation of the Leukogram in Ruminants

Most sources report that neutrophils predominate in neonatal calves and lambs, with a reversal of this ratio about a week after birth.[17] One study examining reference interval data in Holstein cows longitudinally from 1957 through 2010 suggests that over time, mean neutrophil counts have increased while other leukocyte counts have dropped.[16] A survey of other laboratories suggested that this observation had been made elsewhere but was not universal. Potential causes hypothesized include genetic selection, changes in management practices, and decreased prevalence of viral pathogens such as bovine viral diarrhea and bovine leukosis virus. Because a predominance of neutrophils compared with lymphocytes regardless of whether absolute cell counts deviate from the reference intervals has been used as an indicator of inflammatory disease in cattle, these findings may be significant to ruminant leukogram interpretation. In light of these findings, clinicians should be especially attentive to the source of reference intervals provided by laboratories.

Corticosteroid leukograms are relatively common in ruminants, as opposed to the changes associated with excitement, which are rare. Stress leukograms are commonly observed in cattle, sheep, and goats in the periparturient period. Stress leukogram changes are often superimposed on inflammation. As described previously, cattle have a sluggish marrow response to increased demand for neutrophils, resulting in the frequent observation of neutropenia in the first 24 to 48 hours after an acute inflammatory stimulus. Persistent neutropenia of more than 3 to 4 days indicates marrow suppression or inability of the marrow to respond to excessive tissue demands. As in the horse, rebound neutrophilia may ensue, often accompanied by a significant left shift that may include myelocytes and metamyelocytes in addition to band neutrophils. The left shift will resolve as neutrophil numbers increase with marrow compensation for increased demand. In chronic or low-grade inflammation, there may be no abnormalities in the leukogram, in which case evaluation of acute phase proteins may be helpful. The leukogram responses of sheep to inflammation generally mirror the bovine, whereas goats tend to respond more like small animal species with less frequent periods of leukopenia in response to inflammation.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 26

Alterations in Blood Proteins

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MAJOR ALTERATIONS

Hyperproteinemia, 387
Panhyperproteinemia, 387
Hyperglobulinemia, 388
Acute phase response, 388
Hypoproteinemia, 390
Hypoalbuminemia, 390
Panhypoproteinemia, 391

Serum or plasma protein measurements constitute a vital component of laboratory diagnostic evaluations. Globulin and total protein measurements will be higher in plasma than serum because of the presence of coagulation proteins, particularly fibrinogen. It is vital to use appropriate reference intervals for the sample type. The following measurement techniques are widely used (units for the following serum or protein measurements are g/dL or the SI unit g/L):

Refractometry: The total protein concentration of serum, plasma, or body fluids can be determined via refractometry. The principle of measurement is that the degree of light refraction by a solution is proportionate to the concentration of solids. Refractometers are calibrated under the assumption that the solids are entirely proteins. However, other substances can increase the refractive index of a solution and falsely increase the total protein reading (e.g., marked hyperglycemia with glucose concentration of 700 mg/dL or azotemia with blood urea nitrogen concentration of 300 mg/dL can falsely increase the protein reading by 0.6 g/dL).[1] Hemolysis does not alter refractometer protein readings. The effect of marked icterus is unclear.[2]

Biuret reaction: Serum protein is commonly measured via modified biuret testing on automated analyzers. The principle involves basic spectrophotometry measuring color change following copper binding to peptide bonds. Depending on the specific assay, hemolysis can cause a positive interference (e.g., hemoglobin of 400 mg/dL can cause a 12% positive bias).[3] This method is not sensitive to very low protein concentrations (e.g., in cerebrospinal fluid).

BCG albumin binding: Albumin concentration in serum or plasma is usually measured via the bromocresol green (BCG) reaction. The principle involves basic spectrophotometry measuring color change when BCG binds to albumin. Nonspecific BCG binding to globulins can artifactually inflate the albumin value, particularly with a very low albumin concentration.[4] Plasma albumin values can be increased over serum values because of nonspecific plasma globulin binding. Also, heparin interference can increase or decrease an albumin reading depending on the assay.[5] Globulins are typically calculated by subtracting the albumin value from the total protein value.

Protein electrophoresis (PE): Serum or plasma proteins can be separated into albumin and globulin fractions electrophoretically. The principle of measurement is that an electrical charge is applied to a cellulose acetate or agarose gel matrix, allowing serum/plasma proteins to migrate through the matrix and separate into bands based on their charge and size. The acetate or gel is stained to detect the protein bands and read via densitometry to generate a tracing. Albumin has a low molecular weight (roughly 66 kD), is highly anionic, and migrates the farthest to form a band near the anode. The identical nature of all albumin molecules and therefore their migration to a single band generates a single sharp, narrow-based peak on the tracing. Globulins are divided into α-, β-, and γ-globulin regions in ruminants. In horses, globulins are further divided into α_1-, α_2-, β_1-, β_2-, and γ-globulin regions (Fig. 26-1). The heterogeneity of globulin fractions results in broad-based peaks for each, as the diverse proteins in each region migrate slightly differently. Rarely, a narrow-based peak will be seen in the γ-globulin region (see Hyperglobulinemia section). The presence of coagulation proteins will cause higher globulin peaks on protein electrophoresis of plasma (PPE) versus serum (SPE). In particular, fibrinogen will migrate into either the "late-beta" peak or the β-γ junction, and in rare cases might obscure the presence of a monoclonal peak.[6,7] Both α- and β-globulins include many acute phase proteins (see later), whereas immunoglobulins (antibodies), primarily IgG, comprise the γ-globulins. IgA and IgM are immunoglobulins that migrate in the β_2 or β-γ junction regions, but they are not detected in health via PE testing.

Immunoelectrophoresis: Immunoelectrophoresis is a specialized technique for quantification of each immunoglobulin subtype (e.g., IgG, IgM) via electrophoresis followed by immunoprecipitation using subtype-specific antibodies. Units are usually given in mg/dL. Other immunoglobulin measurements are designed specifically for detection of IgG in neonatal samples and are discussed under failure of passive transfer (see Chapters 19 and 53).

Reference values for proteins vary by species (Table 26-1). When evaluating protein concentrations in a patient, some clinicians use the ratio of albumin to globulins (A:G ratio). However, it is often simpler to evaluate albumin and globulins separately because the A:G ratio can change with alterations in one or both parameters.

Biologic variation with life stage: Transfer of immunoglobulins from the dam to the neonate via colostral ingestion is a key process that determines the neonate's subsequent immunocompetence and is often reflected in serum globulin levels in the first few weeks of life. In addition, neonates generally have lower serum albumin levels; for example, calves had decreased albumin values in the first 8 days of life.[8] Total protein levels in calves are decreased at birth, rise immediately following colostrum intake, then fall below the reference interval again at about 2 weeks of age and remain subnormal for some time.[8] IgG measurement also reflects

*Contributions to previous editions by Debra Deem Morris and Janet K. Johnson are acknowledged.

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the combined presence of maternal and neonatal proteins (Fig. 26-2). Studies in cows found gradually increasing plasma globulin levels during pregnancy until 4 weeks pre-parturition, then a steady drop until parturition.[9] IgG_1 production is greatly increased at parturition and the half-life is decreased, corresponding with transfer to colostrum.[10] Serum total protein steadily increased during lactation in Danish landrace goats.[11] In pregnant and lactating mares, significant differences in albumin, globulins, and total protein were not found at any stage.[12] Aging can be associated with alterations in some laboratory parameters. However, no significant differences in biochemical parameters or specific concentrations of IgG, IgA, or IgM were found in aged horses, despite alterations in lymphocyte populations.[13,14]

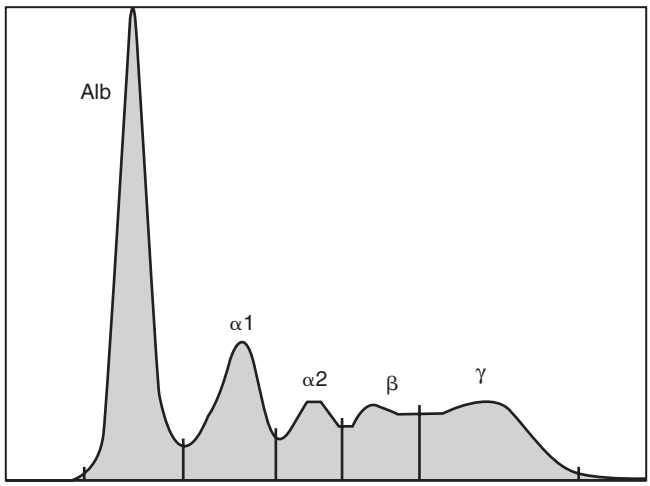


FIG. 26-1 Normal equine serum protein electrophoresis. *alb,* Albumin.

Hyperproteinemia

Hyperproteinemia can result from an increase in both albumin and globulins (panhyperproteinemia) or only globulins (hyperglobulinemia) (Boxes 26-1 and 26-2).

Panhyperproteinemia

An increase in the concentration of all blood proteins results from hemoconcentration. Dehydration (resulting from decreased fluid intake, excessive fluid loss, or both) causes panhyperproteinemia with an associated increase in packed cell volume (PCV). This is due to a relative increase in protein and RBC concentrations as they become more concentrated in blood. True hyperalbuminemia (i.e., increased albumin synthesis) does not occur. Hyperalbuminemia is an insensitive indicator of dehydration. If the true albumin level is decreased, a dehydrated patient may have a normal albumin result, masking effects of hemoconcentration. Similarly, a dehydrated, anemic animal may have hyperproteinemia with a normal or decreased PCV. In an animal with a plasma protein concentration of 7.0 g/dL in health, a 10% decrease in plasma volume (severe dehydration) will result in a plasma protein concentration of 7.8 g/dL.[2] As with albumin measurement, the total plasma protein measurement will underestimate the degree of dehydration if the patient is losing protein along with fluid. This is relatively common in renal disease, in protein-losing enteropathy with diarrhea, and in third-space loss when fluid and protein accumulate in the thoracic and/or abdominal cavity. Dehydration alone can result from GI fluid sequestration, including intestinal obstruction, vagal indigestion with internal vomiting, and grain engorgement. Less common causes of dehydration include polyuria with renal failure, exudation from extensive skin wounds, and excessive sweating. Physiologic responses to dehydration include increased urine concentration and decreased urine output, increased fluid absorption from the gastrointestinal (GI) tract, and increased thirst.

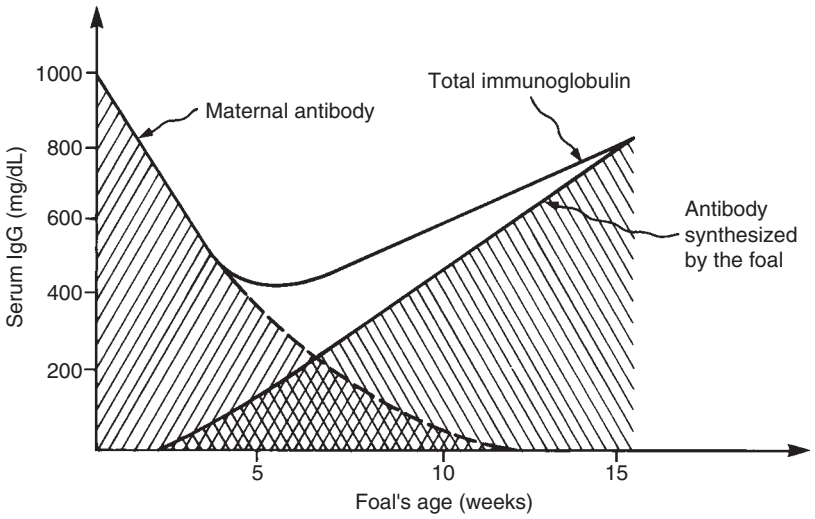


FIG. 26-2 Immunoglobulin in foal serum during the first 15 weeks of life. *(From Tizard I. 1987. Veterinary immunology, ed 3. WB Saunders, Philadelphia, PA.)*

TABLE 26-1

Normal Serum Protein Values for Horses, Cows, Sheep, and Goats

	Value	Horse	Cow	Sheep	Goat
Total	g/dL	5.2-7.9	6.74-7.46	6-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Fibrinogen	g/dL	200-400	200-700	200-500	200-300

From Appendix VIII: Blood analyte reference values in large animals. 1997. In Kaneko JJ, Harvey JW, Bruss ML (eds), Clinical biochemistry of domestic animals, ed 5. Academic Press, San Diego, CA.

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BOX 26-1

Causes of Hyperproteinemia in Horses

Panhyperproteinemia-Dehydration

Common Causes

Acute toxic colitis of unknown cause
Acute salmonellosis
Potomac horse fever
Intestinal clostridiosis
Intestinal strangulating obstruction
Proximal enteritis
Gram-negative sepsis, endotoxemia
Botulism
Choking (esophageal obstruction)

Less Common Causes

Chronic renal failure
Chronic hepatic disease
Guttural pouch mycosis with dysphagia
Equine protozoal myelitis
Salt toxicity
Toxins, poisonous plants
Lead toxicity
Yellow star thistle poisoning (dysphagia)
Dysphagia of unknown cause

Hyperglobulinemia

Common Causes

Abdominal (mesenteric) abscess (including "bastard" strangles)
Pulmonary abscess
Chronic pleuritis
Purpura hemorrhagica
Equine infectious anemia

Less Common Causes

Chronic hepatic disease
Strongylosis
Lymphoma
Immune-mediated cytopenia

BOX 26-2

Causes of Hyperproteinemia in Ruminants

Panhyperproteinemia-Dehydration

Common Causes

Ruminal acidosis (grain overload)
Abomasal torsion
Acute salmonellosis
Peritonitis
Sepsis, toxemia (mastitis, metritis)
Intussusception
Vagal indigestion
Oral or pharyngeal foreign body with dysphagia
Coccidiosis
Diarrhea, undifferentiated
Salt toxicity
Toxins, poisonous plants

Less Common Causes

Renal amyloidosis
Lymphoma
Pregnancy toxemia
Rabies

Hyperglobulinemia

Common Causes

Abdominal abscess (traumatic reticuloperitonitis, uterine tear, other)
Chronic pneumonia
Umbilical abscess
Lymphoma
Caseous lymphadenitis (sheep and goats)
Other abscess

Less Common Causes

Parasitism
Pregnancy

Hyperglobulinemia

The most common cause of hyperglobulinemia with normal hydration status (i.e., without hemoconcentration) is inflammation resulting in increased production of numerous globulins, including many acute phase proteins (see Acute Phase Response section). Chronic inflammation frequently results in a nonspecific increase in γ-globulins *(polyclonal gammopathy)* resulting from production of different immunoglobulins by plasma cells in response to chronic antigenic stimulation. A broad-based peak will be seen on SPE in the γ region, and can extend into the β region as a result of production of IgM and/or acute phase β-globulins. An increase in both β- and γ-globulin fractions (β-bridging) can occur with intense antigenic stimulation, chronic active hepatitis, or lymphoma. Increased IgG in the γ-globulin fraction is termed *hypergammaglobulinemia* and can be seen in a range of chronic inflammatory diseases, including internal abscessation, chronic hepatitis, immune-mediated diseases (e.g., immune-mediated hemolytic anemia or thrombocytopenia), and lymphoma. Infection with the agent of epizootic bovine abortion triggered significant increases in IgG in clinically affected heifers.[15]

Increased production of a single immunoglobulin by a clonal population of B lymphocytes/plasma cells is known as a *monoclonal gammopathy.* On SPE, the monoclonal peak is as narrow-based and sharp as the albumin peak as a result of the identical migration of the monoclonal immunoglobulins (also known as paraproteins). Monoclonal gammopathies are usually the result of neoplasia of B lymphocytes or plasma cells, including B-cell lymphoma, multiple myeloma, and B-cell lymphocytic leukemia. Increased susceptibility to hemorrhage can occur with monoclonal gammopathy as a result of impaired platelet function caused by immunoglobulin coating, and it can be exacerbated by hyperviscosity syndrome.

Acute Phase Response

Acute inflammatory processes can trigger an acute phase response. Infectious causes are common but many noninfectious causes (e.g., trauma, strenuous exercise) are also documented. The body's response to the inflammatory insult is altered liver production of many proteins, termed *acute phase proteins* (APPs). A few proteins are negative APPs and their production decreases with acute inflammation. Albumin is the most prominent negative APP, and levels will decrease in circulation proportionate to its half-life in each species. For example, the albumin half-life is 19.4 days in horses and 16.5 days in cattle, so hypoalbuminemia caused by inflammation will take several weeks to develop in these species.[4,16] Transferrin and transthyretin (prealbumin) are other negative APPs, as is apolipoprotein A-1 (see following sections on specific APPs). The presumed role of decreased production of certain proteins is to shift available amino acids to the synthesis of proteins that are useful in host defense.[17]

Most reactants are positive APPs, meaning production increases with inflammation. They migrate in the α- and β-regions on SPE or PPE. The positive APPs are a diverse group including proteins involved in coagulation, opsonization, iron regulation, and limiting of tissue injury. Protein electrophoresis can reveal increased globulin fractions that are comprised largely of APPs. Some diseases cause fairly specific alterations (e.g., internal parasitism in diarrheic horses caused increased β-1 globulin levels that were significantly higher than those in diarrheic horses with other disorders).[18] Nonprotein assays are also used to diagnose an acute phase response (e.g., serum iron outperformed plasma fibrinogen as an indicator of acute inflammation in horses).[19]

Measurement of individual APPs can be useful diagnostically and is not limited to blood; assays for APPs in milk and saliva have also proven useful.[20-22] The following is a list of major APPs in large animals.

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BOX 26-3

Causes of Hyperfibrinogenemia in Horses

Abscess (abdominal or other)
Chronic peritonitis
Pleuritis
Pneumonia
Osteomyelitis
Septic arthritis
Cholelithiasis
Neoplasia with inflammatory response
Vasculitis (equine purpura hemorrhagica)
Cellulitis
Gastrointestinal inflammation
Salmonellosis

BOX 26-4

Causes of Hyperfibrinogenemia in Ruminants

Acute mastitis, especially coliform
Abscess
Traumatic reticuloperitonitis, pericarditis
Salmonellosis
Gastrointestinal inflammation
Pyelonephritis
Endocarditis
Pleuritis
Pneumonia
Chronic peritonitis
Necrotic rumenitis
Lymphoma
Septic arthritis
Cellulitis
Omphalophlebitis
Osteomyelitis

TABLE 26-2

Useful Acute Phase Proteins (APPs) in Large Animal Species

APP	References for Use in Each Species
Haptoglobin	Cattle*; goats[76-78]; pigs[56,79]; sheep[44,45,80-83]
CRP	Cattle[48]; horses[49]; pigs[56,79]
SAA	Cattle†; goats[76]; horses[65]; pigs‡; sheep[83]
Apo-A1	Pigs[55,56]
CP	Horses[53]; sheep[80]
α2-AP	Horses[28]
PigMAP/ITIH4	Cattle[57]; pigs[55,56,85]
Ferritin	Horses[86]
α1-AG	Cattle[61]; goats[76]; sheep[83]

*References 20, 21, 43, 73-75.
†References 20, 21, 42, 43, 73, 74.
‡References 55, 56, 79, 84.

Fibrinogen

Fibrinogen is a useful marker of inflammatory disease in large animals. Increased plasma fibrinogen, termed *hyperfibrinogenemia,* can occur in a myriad of conditions. Fibrinogen is semiquantitatively measured via the heat precipitation method, along with total plasma protein, as part of the routine CBC. Serum samples cannot be used to measure fibrinogen. The heat precipitation method cannot be used to detect hypofibrinogenemia (see Chapter 27).

As for other proteins, fibrinogen can be increased as a result of dehydration. Calculating the plasma protein : fibrinogen (PP : F) ratio is useful when fibrinogen is increased. If the PP : F is greater than 15, hyperfibrinogenemia is due to dehydration. If the PP : F is less than 10, the patient has true hyperfibrinogenemia (caused by inflammation).[23] Severe inflammatory disease in horses and ruminants consistently causes hyperfibrinogenemia, although the increase in fibrinogen may not be proportionate to the degree of inflammation. Increased fibrinogen often precedes development of an inflammatory leukogram in ruminants, particularly in cattle.[23] Hyperfibrinogenemia can persist for a period of time postoperatively. In one study, more than half of horses undergoing subchondral bone cyst removal still had hyperfibrinogenemia 15 days postoperation[24]; in another, fibrinogen remained increased through day 11 following laparotomy and other procedures.[25]

In adult horses, a number of conditions including colic, sterile inflammation, surgical intervention, and chronic internal abscessation are all associated with hyperfibrinogenemia (Box 26-3).[24,26-28] Vaccination of horses induces an acute phase response including increases in both fibrinogen and serum amyloid A.[29] Fibrinogen response in foals is more variable. In healthy neonatal foals, fibrinogen levels are initially lower than adult values and then equilibrate within a few weeks of age.[30,31] Hyperfibrinogenemia lags behind leukocytosis as an indicator of inflammation.[30,32] Fibrinogen was an unreliable marker of foal sepsis in one study,[33] although marked hyperfibrinogenemia of 900 to 1500 mg/dL had utility as a diagnostic marker of foal osteomyelitis.[34] Fibrinogen may be useful as an indicator of foal pneumonia resulting from *Rhodococcus equi;* one study found that hyperfibrinogenemia had greater specificity than leukocytosis, but another reported better diagnostic performance (encompassing both sensitivity and specificity) for leukocytosis over hyperfibrinogenemia.[35,36]

Fibrinogen is a particularly useful indicator of inflammation in cattle and other ruminants as they develop substantial hyperfibrinogenemia in response to inflammation (Box 26-4).[37] A number of inflammatory diseases in cattle are associated with hyperfibrinogenemia including peritonitis, mastitis, and pneumonia. Lymphoma and uncomplicated displaced abomasum (without peritonitis) did not present with hyperfibrinogenemia.[37] Fibrinogen is reportedly low to undetectable in neonatal calves.[38] One study of healthy calves reported a peak in fibrinogen at postnatal day 6 (mean value 400 mg/dL), then a gradual decline until reaching a mean nadir of 250 mg/dL at day 50 followed by a slight rise; values always remained within the reference interval for adult cattle.[8] Fibrinogen was significantly increased in calves with suspected septic shock.[39]

Other Acute Phase Proteins

The usefulness of individual APP measurement in diagnosis of inflammatory disease varies by species (Table 26-2). The following APPs have proven utility in one or more large animal species.

Haptoglobin

When haptoglobin enters the circulation, it immediately binds hemoglobin to form a complex that is then internalized by hepatic Kupffer cells.[40] Increased haptoglobin during the acute phase response occurs as a result of transcriptional activation. Haptoglobin may regulate and modulate the immune response during inflammation.[41] Haptoglobin is increased in the first week postpartum in dairy cows.[42] Measurement of haptoglobin in milk is superior to measurement in serum for diagnosis of mastitis, although serum measurement is also useful.[20,43] Haptoglobin performs well as an acute phase marker in sheep, with increases found during inflammatory diseases including bacterial metritis and pneumonia.[44,45]

C-Reactive Protein

In health, C-reactive protein (CRP) is present in trace amounts in circulation. Inflammation and tissue necrosis can markedly upregulate CRP levels.[46] The role of CRP in the acute phase response may be clearance of endogenous or exogenous substances (e.g., microorganisms, cellular debris), but it may also worsen inflammatory tissue damage via complement activation.[47] Dairy cattle have increased CRP levels during lactation that are highest at peak lactation and

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decline thereafter; mastitis and other inflammatory diseases caused further increases (e.g., a threefold increase in CRP levels in mastitic cows compared with healthy lactating cows).[48] Increased CRP has been associated with pneumonitis, enteritis, and arthritis in horses.[49]

Serum Amyloid A

The serum amyloid A (SAA) protein family of apolipoproteins includes both constitutively expressed proteins and acute phase reactants that are markedly upregulated during inflammation.[50] The induced proteins chemotactically recruit leukocytes and are implicated in the pathogenesis of chronic inflammation, since they are precursors of the amyloid A protein in amyloidosis. As with haptoglobin, SAA is increased in the first postpartum week in dairy cows, and measurements of milk SAA levels are superior to serum levels to diagnose mastitis, although both are useful.[20,42,43]

Apolipoprotein A-1

Apolipoprotein A-1 (Apo A-1) is a negative acute phase reactant in humans and domestic animals. Apo A-1 is associated with high-density lipoproteins. A role as a constitutive antiinflammatory factor has been posited for Apo A-1.[51]

Ceruloplasmin

Ceruloplasmin (CP) plays a key role in iron metabolism, and CP-bound copper accounts for 95% of plasma copper concentration. CP interacts with several proteins including ferritin, neutrophil myeloperoxidase, and lactoferrin.[52] Equine CP increases with sterile inflammation and surgical manipulation. Transient changes in CP occur in mares immediately before and after foaling.[53]

α2-Antiplasmin

α2-Antiplasmin (α2-AP) is a fibrinolytic inhibitor via its specific inactivation of plasmin. Measurement of increased plasmin α2-AP complexes is one indicator of fibrinolysis. α2-AP is increased in horses with colic, as is plasminogen, and may reflect a role as an acute phase biomarker.[28,54]

Pig Major Acute Phase Protein

Pig major acute phase protein (pigMAP; ITIH4) is the porcine homolog of a human kallikrein-sensitive protein and is a useful indicator of inflammatory diseases.[55,56] The related proteins in humans, pigs, and rats have been designated collectively as ITIH4, a new member of the inter-α-trypsin inhibitor (ITI) protein family with unknown biological function. Recently the utility of ITIH4 as an acute phase reactant in cattle was also described.[57]

Ferritin

Ferritin is an iron storage and transport protein. Ferritin levels can markedly increase during infectious and other inflammatory disorders, presumably to sequester iron and limit availability to microbes.[58] Species-specific assays are generally needed to measure ferritin. An equine-specific assay is available and has some cross-reactivity with other species.[59] Ferritin has shown usefulness as a biomarker in horses. Strenuous exercise also causes an increase in ferritin that persists for up to 2 days.[60]

α1-Acid Glycoprotein

Also known as orosomucoid, α1-acid glycoprotein (α1-AG) is a carrier of basic substances including therapeutic drugs and steroids. Increased α1-AG values have been found in cattle with various inflammatory disorders, including mastitis and traumatic pericarditis.[61]

Hypoproteinemia

Hypoalbuminemia

Albumin is the most abundant of the plasma proteins. It accounts for approximately 75% of plasma colloidal oncotic pressure (COP), and in turn its synthesis is primarily regulated by COP. Albumin is a nonspecific transport protein for a number of substances including calcium, lipids, and hormones and serves as an amino acid source for body tissues. Hypoalbuminemia is caused by a decrease in albumin production and/or an increase in albumin loss, most commonly renal or GI loss (Boxes 26-5 and 26-6). As described previously, decreased albumin synthesis is a common component of the acute phase inflammatory response. Overall hypoproteinemia does not occur, partly because the decrease in albumin is usually mild and partly because of the corresponding increase in globulins.

Albumin production can decrease with chronic insufficient intake of amino acids. In particular, protein-energy malnutrition can lead to hypoalbuminemia more quickly than total starvation.[62] Hypoalbuminemia is an indicator of chronic malnutrition given albumin's relatively long half-life, and clinical signs relating to hypoalbuminemia develop over a prolonged period. GI disorders that disrupt normal protein digestion and absorption can lead to decreased protein synthesis and are discussed as follows under protein-losing enteropathies.

BOX 26-5

Causes of Hypoproteinemia in Horses

Hypoalbuminemia

Common Causes

Parasitism
Glomerulonephritis
Pyelonephritis
Idiopathic granulomatous enteritis
Intestinal lymphosarcoma
Parasitism
Salmonellosis
Equine ehrlichial enterocolitis (Potomac horse fever)
Colitis
Clostridiosis
Nonsteroidal antiinflammatory drug toxicosis

Less Common Causes

Chronic hepatic fibrosis (pyrrolizidine alkaloid toxicity and other causes)
Hepatic neoplasia
Chronic hepatitis
Amyloidosis
Tuberculosis
Histoplasmosis
Chronic eosinophilic gastroenteritis
Starvation/malnutrition

Panhypoproteinemia

Common Causes

Excessive fluid therapy or water intake
Acute blood loss
Gastrointestinal ulceration
Strangulating gastrointestinal obstruction, infarction
Protein-losing enteropathy (chronic granulomatous bowel disease)
Acute severe peritonitis
Nonsteroidal antiinflammatory drug toxicity
Glomerulonephritis

Less Common Causes

Blood-sucking gastrointestinal or external parasites
Intestinal lymphosarcoma
Urinary blood loss
Congenital vascular disorders: renal trauma
Renal calculi
Pyelonephritis
Neoplasia
Cystic calculi
Disseminated intravascular coagulation
Immune-mediated thrombocytopenia
Congestive heart failure

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BOX 26-6

Causes of Hypoproteinemia in Ruminants

Hypoalbuminemia

Common Causes

Protein malnutrition, starvation
Amyloidosis
Pyelonephritis
Glomerulonephritis
Salmonellosis
Johne's disease
Trichostrongylus infection

Less Common Causes

Chronic liver failure
Intestinal lymphangiectasia
Intestinal lymphoma

Panhypoproteinemia

Common Causes

Excessive intravenous fluid therapy or water intake
Acute blood loss
Abomasal ulceration
Blood-sucking gastrointestinal or external parasites
Gastrointestinal ulceration

Less Common Causes

Ingestion of caustic chemicals
Strangulation, infarction of intestine
Congestive heart failure
Pyelonephritis
Urinary tract blood loss

Although albumin is produced by the liver, synthesis generally does not decrease in acute liver disease. Chronic, diffuse liver diseases such as chronic hepatitis, fibrosis, and hepatic neoplasia may cause hypoalbuminemia. Because the half-life of albumin is longer in horses and cattle than in dogs and humans, hypoalbuminemia is uncommon in large animal hepatic disease but can occur in conditions such as chronic hepatic lipidosis or chronic pyrrolizidine alkaloid toxicosis. In one study, 6% of horses with acute liver disease and 18% of those with chronic liver disease were hypoalbuminemic; increased globulins were found in 64% of all horses with liver disease.[63] Decreased albumin and increased globulins can indicate a poorer prognosis in horses with liver disease.[64] A potentially more useful indicator of liver disease in horses than hypoalbuminemia is a post-albumin shoulder (a small hump on the right [cathodal] side of the albumin peak) on SPE; this shoulder can also appear with acute inflammatory disease or severe hypoalbuminemia.[23,65]

Excessive albumin loss usually occurs through the urinary and GI tracts. Less common causes include chronic blood loss (acute blood loss is associated with panhypoproteinemia) and burns or other exudative skin disease. Normal urine contains little or no protein as a result of resorption of filtered small proteins in the proximal tubule. Transient physiologic proteinuria, sometimes referred to as "functional proteinuria," can occur with exercise, stress, seizures, and excessive protein intake, as well as following colostrum ingestion in neonates. These are (mostly) prerenal sources of proteinuria and do not cause hypoproteinemia.[66]

Renal proteinuria arises as a result of diseases of the glomeruli and/or proximal tubules; hemorrhage or inflammation within the kidney is another cause but is often categorized under postrenal proteinuria. Albumin is readily filtered through defects in the glomerular basement membrane because of its lower molecular weight. Proteinuria caused by glomerular lesions consists largely of albumin and can result in hypoalbuminemia and overall hypoproteinemia, whereas tubular proteinurias do not produce hypoalbuminemia.[66] Glomerulonephritis, amyloidosis, and less commonly pyelonephritis are top differentials for glomerular disease leading to proteinuria and hypoalbuminemia.[67]

Protein-losing enteropathy (PLE) is a GI condition resulting in net loss of protein from the body, as a result of abnormal loss of protein from the GI tract and/or inability of the GI tract to absorb proteins. PLE is not a disease itself; it is a manifestation of numerous GI disorders. The diagnosis of PLE includes ruling out urinary protein loss, body cavity effusion, increased protein catabolism, and decreased synthesis resulting from liver disease. The clinically important mechanisms of PLE are defective lymphatic transport, increased mucosal permeability, GI parasitism, exudative inflammation, and/or ulcerative blood loss. Hypoalbuminemia can be useful both diagnostically and prognostically in PLE. In a study of horses with diarrhea, albumin was lower in horses that died than in those that survived, likely reflecting albumin leakage across inflamed intestinal mucosa.[18]

In horses, the most common cause of PLE is idiopathic granulomatous enteritis, one of the chronic inflammatory bowel diseases of the horse.[12] Other causes of equine PLE include acute enterocolitis including bacteria-associated disease; GI lymphoma and other GI neoplasia; nonsteroidal antiinflammatory drug (NSAID) toxicity, including phenylbutazone; GI parasitism; and other conditions in the chronic inflammatory bowel disease group, including intestinal tuberculosis, histoplasmosis, and eosinophilic gastroenteritis. Proliferative enteritis of foals or yearlings caused by *Lawsonia intracellularis* infection often presents with hypoalbuminemia or panhypoproteinemia.[68,69]

The most common cause of chronic PLE in ruminants is infection with *Mycobacterium avium* subsp. *paratuberculosis,* or Johne's disease. Intestinal protein loss in Johne's disease arises both from mucosal lesions and secondary intestinal lymphangiectasia.[70] Other differentials include parasitism such as *Trichostrongylus* infection, intestinal lymphangiectasia, and GI lymphoma.

In addition to the previously mentioned causes of decreased albumin production and increased albumin loss from the body, hypoalbuminemia can also arise from dilution within the body. Redistribution of albumin into subcutaneous tissues and higher-protein body cavity effusions can result in hypoalbuminemia. Edema and peritoneal effusions may be contributory to the severe acute hypoalbuminemia described in fescue toxicity in horses.[71] Some edematous and effusive disorders such as congestive heart failure (see next section) can cause either hypoalbuminemia or panhypoproteinemia.

The clinical sequelae of hypoalbuminemia relate to the decrease in COP and subsequent fluid shift. Severe hypoalbuminemia (e.g., from protein-losing nephropathy or chronic liver disease) can cause a very low-protein effusion called a *transudate*. Other clinical signs of hypoalbuminemia include edema of the limbs, head, and ventrum. The albumin level generally must be below 1.5 g/dL in horses and below 1 g/dL in ruminants before clinical signs occur. A correlate of the longer albumin half-life in large animals is that albumin replacement is also slower, resulting in more clinically significant edema resulting from hypoalbuminemia.[65]

Panhypoproteinemia

Vigorous fluid therapy or excess water intake can cause dilution of plasma proteins and subsequent relative panhypoproteinemia. Panhypoproteinemia resulting from both dilution and increased GI protein loss occurs frequently in patients with acute GI disease receiving intravenous fluid therapy.

Acute blood loss with subsequent interstitial fluid shift into the vasculature, as well as volume expansion during pregnancy, can also cause relative panhypoproteinemia. Acute blood loss results in loss of all plasma proteins; interstitial fluid then rapidly shifts into the intravascular space to help maintain volume. This dilution effect is intensified by increased water intake that commonly occurs after acute blood loss. Acute hemorrhage resulting from trauma, severe epistaxis, or internal vascular rupture should be ruled out in a hypoproteinemic, anemic animal.

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GI disorders can lead to panhypoproteinemia via loss of either blood or protein alone. Differentials for GI blood loss include abomasal or gastric ulcers, blood-sucking parasites (e.g., *Haemonchus contortus* in ruminants), viral or bacterial infection, azotemia, neoplastic invasion, or exposure to caustic chemicals. NSAID toxicosis and strangulating GI obstructions or infarctions can result in mucosal necrosis and leakage of plasma proteins into the gut lumen. Although protein-losing enteropathy usually initially causes hypoalbuminemia, panhypoproteinemia often develops over time. Proliferative enteropathy of young horses (described previously) often results in panhypoproteinemia.[68] Acute severe peritonitis with massive protein exudation caused by GI rupture can also quickly lead to hypoproteinemia.

Other conditions resulting in clinically significant blood loss include urinary tract disorders caused by congenital vascular disorders, renal trauma, renal or cystic calculi, pyelonephritis, and renal neoplasia. Coagulopathies, including disseminated intravascular coagulation (DIC) or immune-mediated thrombocytopenia, may cause either external blood loss via the GI or urinary tract or internal bleeding into body cavities.

Congestive heart failure may cause either hypoalbuminemia or panhypoproteinemia via several mechanisms including dilutional effects from plasma volume expansion, protein loss into ascitic fluid and the interstitium, and decreased albumin synthesis caused by hepatic congestion and/or concurrent inflammation.[72]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 27

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Alterations in Hemostasis

JENNIFER L. JOHNS, *Consulting Editor**

MAJOR ALTERATIONS

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The standard diagnostic test panel to evaluate coagulation in large animals includes platelet count, plasma fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), and serum fibrin and fibrinogen degradation products (FDPs). Proper collection and preparation of blood samples are paramount in obtaining accurate results (see Chapter 23). Platelet counts are routinely performed as part of the complete blood cell count (CBC). Citrated blood is required for coagulation testing and can also be used for platelet analysis. It is critical to have a 1:9 ratio of citrate to whole blood. The patient's hematocrit can affect coagulation results when whole blood is used. When the hematocrit is over 55%, correction to a lower citrate volume is recommended to prevent overcitration and prolonged coagulation times.[1] If the laboratory does not have reference intervals for a particular species, plasma from two or more healthy animals should be collected and assayed in a similar manner for comparison. Table 27-1 shows reference values for platelets and fibrinogen, but laboratory-specific values are preferable for these analytes and are necessary for other coagulation parameters.

Platelet Parameters

The platelet count is technically the platelet concentration in whole blood. Units = [platelets] × 10^3/μL; SI units = [platelets] × 10^9/L. Automated analyzers are routinely used to generate a platelet count. A rough estimate can be made via manual smear review: at 100× oil objective, the total number of platelets in 10 fields is counted. This count is then divided by 10 to yield an average number. This average is multiplied by a 15,000 to 20,000 conversion factor to yield [platelets]/μL.[2] Both this estimate and the automated platelet count will be artifactually decreased if platelet clumps are present. Cattle normally average around 8 to 10 platelets per 100× oil objective field, and horses normally have 5 platelets or more per field.[2]

Mean Platelet Volume

The mean platelet value (MPV) is the mean or average platelet volume and is measured in femtoliters (fL). This value is an average and does not represent the range of platelet volumes. Increased MPV is consistent with increased release of large/giant platelets and usually indicates a platelet regenerative response. The measurement of reticulated platelets (analogous to reticulocytes) may become widely accepted as another index of platelet regeneration.

*Contributions to previous editions by Debra Deem Morris are acknowledged.

Platelet Distribution Width

The platelet distribution width (PDW) is a calculated range of platelet volumes (representing anisocytosis), analogous to the red blood cell (RBC) distribution width. It is expressed as a percentage, and a higher percentage indicates a greater variation in platelet volume. The PDW in combination with the MPV value can indicate whether there are increased numbers of smaller and/or larger platelets.

Thrombocrit

Also called the platelet-crit, the thrombocrit value is a function of the platelet count and the mean platelet volume. It is a better indicator of the total platelet functional potential than the platelet count, as a result of the greater functional capacity of larger platelets.[3]

Thrombocytopenia

A decrease in the circulating platelet count is termed *thrombocytopenia*. Thrombocytopenia is caused by one of three basic mechanisms: platelet sequestration, decreased platelet production, and decreased platelet lifespan caused by consumption or destruction (Boxes 27-1 and 27-2). Spurious thrombocytopenia occurs occasionally in horses when blood is collected into EDTA anticoagulant, causing in vitro platelet clumping.[4] Platelet clumps are visible in the stained blood smear and may be indicated by error messages on an analyzer. Collection of a second sample into sodium citrate can yield an accurate platelet count and confirm a suspicion of spurious thrombocytopenia. Heparinized samples are not recommended for platelet counts because heparin-induced clumping can occur in any species. If citrated samples are used for platelet counts, the count must be corrected for citrate dilution (i.e., multiplied by 1.1).

Splenic platelet sequestration can occur as a result of splenomegaly. Splenomegaly occurs due to various disorders including infiltrative diseases such as lymphoma, leukemia and multiple myeloma, and infectious and other inflammatory diseases such as immune-mediated hemolytic anemia that result in splenitis, lymphoid hyperplasia, and/or splenic extramedullary hematopoiesis. In addition, congestive splenomegaly occurs when the venous outflow is occluded by torsion, intestinal displacements, or congestive heart failure. Platelet sequestration is a relative thrombocytopenia resulting from redistribution (vs. an absolute thrombocytopenia), is reversible, and does not result in increased bleeding tendency.

Decreased platelet production can occur with various bone marrow disorders, including myelophthisis (replacement of normal marrow). Myelophthisis is often due to marrow infiltration with neoplastic cells (e.g., plasma cells in multiple myeloma) and can result in

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TABLE 27-1

Normal Values for Hemostatic Data in Ruminants and Horses

	Horses	Cattle	Sheep	Goats	Llamas	Pigs
Platelet count ($\times 10^{-3}$/L)	100-600	100-800	250-750	300-600	*	200-500
Fibrinogen (mg/dL)	200-400	200-700	200-500	200-300	100-400	200-400

Modified from Duncan JR, Prasse KW, Mahaffey EA (eds). 1994. Veterinary laboratory medicine, ed 3. Iowa State University Press, Ames, IA; and Kaneko JJ, Harvey JW, Bruss ML (eds). 1997. Clinical biochemistry of domestic animals, ed 5. Academic Press, San Diego, CA.

*Insufficient data available.

BOX 27-1

Causes of Thrombocytopenia in Horses

Common Causes

Disseminated intravascular coagulation
Immune-mediated thrombocytopenia (drugs: penicillin, trimethoprim-sulfadoxine)
Endotoxemia, septicemia (e.g., acute toxic colitis, intestinal strangulating obstruction, neonatal septicemia)
Equine infectious anemia
Equine anaplasmosis *(Anaplasma phagocytophilum)*
Lymphoma

Less Common Causes

Salmonellosis
Equine viral arteritis
Equine influenza
Myeloproliferative disease (myelogenous leukemia)
Plasma cell myeloma
Aplastic anemia
Stachybotryotoxicosis
Neonatal alloimmune thrombocytopenia

BOX 27-2

Causes of Thrombocytopenia in Ruminants

Common Causes

Disseminated intravascular coagulation
Bracken fern *(Pteridium aquilinum)* toxicosis
Septic mastitis or metritis (endotoxemia)

Less Common Causes

Salmonellosis
Gram-negative sepsis
Trichloroethylene-extracted soybean meal
Lymphoma
Plasma cell myeloma
Immune-mediated thrombocytopenia
Stachybotryotoxicosis
Myelofibrosis (pygmy goats)

pancytopenia. Familial myelofibrosis was reported in pygmy goats and resulted in marked pancytopenia, including thrombocytopenia with myelophthisis.[5] Toxic damage to the marrow (e.g., from bracken fern toxicosis or nonsteroidal antiinflammatory drug administration) can result in myelosuppression and potentially aplastic anemia. Immune-mediated destruction of megakaryocytes, a variant of immune-mediated thrombocytopenia, causes decreased platelet production and release. Infectious agents can cause decreased platelet production via either indirect effects on megakaryocytes (e.g., equine infectious anemia virus) or by direct infection of megakaryocytes (e.g., acute bovine viral diarrhea infection).[6,7] Evaluation of a bone marrow aspirate and core biopsy is indicated to evaluate megakaryocyte numbers and assess for dysplasia in a patient that is either persistently thrombocytopenic without evidence of peripheral consumption or destruction, or pancytopenic.

Blood loss is a rare cause of thrombocytopenia; it is more likely that any concurrent bleeding is the result rather than the cause of severe thrombocytopenia. Studies in dogs found that acute severe blood loss induces a mild to moderate thrombocytopenia, with up to 50% reduction in platelet count.[2] Rapid dilution of the blood volume with aggressive fluid therapy can decrease the platelet count as well as other hemostatic elements. The decrease is generally mild to moderate.

Platelet lifespan can be reduced by destruction of platelets or by platelet consumption in widespread coagulation. Immune-mediated platelet destruction is a common cause of thrombocytopenia in horses. Immune-mediated thrombocytopenia (IMT) can be either idiopathic or a result of various etiologies including viral and bacterial infections, drug administration, and hemic neoplasia.[7-10] Thrombocytopenia caused by idiopathic IMT is often marked, in contrast to thrombocytopenia from other causes. The thrombocytopenia of equine anaplasmosis resulting from infection with *Anaplasma phagocytophilum* is apparently multifactorial; an element of IMT is possible but not supported by experimental studies.[11,12] Neonatal alloimmune thrombocytopenia has been reported in horses, mule foals, and pigs and is caused by colostral antibodies against foreign (paternal) epitopes on the neonate's platelets.[2]

Excessive consumption of platelets occurs with disseminated intravascular coagulation (DIC). DIC is a clinical condition of disordered hemostasis that arises as a result of severe trauma; infectious or other inflammatory diseases, including septicemia; and disseminated neoplasia.[13] Examples include DIC in horses with colic, calves with septic shock, and pigs with spontaneous heatstroke.[14-17] The diagnosis of DIC in most species relies on finding evidence of both platelet and coagulation factor consumption (thrombocytopenia with one or more coagulation test abnormalities, described later) along with evidence of increased fibrinolysis (see the Increased Fibrin and Fibrinogen Degradation Products section). Snake envenomation directly causes platelet destruction in the absence of typical DIC as some snake venoms contain platelet-activating factors. Endothelial damage or necrosis (e.g., resulting from equine viral arteritis infection) can also result in platelet destruction with or without concurrent DIC.[18]

Clinical Signs of Thrombocytopenia

Thrombocytopenia is characterized by petechial or ecchymotic hemorrhages on the oral, nasal, and/or vaginal mucous membranes and the nictitans, sclerae, pinnae, and ventral abdomen. Epistaxis, melena, hyphema, and/or hematuria may occur, although spontaneous hemorrhage is rare unless the platelet count drops below 10,000 to 20,000/μL. Concurrent inflammation can increase a thrombocytopenic patient's propensity for spontaneous hemorrhage.[19] Prolonged bleeding from injections or wounds and a propensity to form hematomas with minor trauma are relatively common with a platelet count below 40,000/μL.

Thrombocytosis

Thrombocytosis is an increase in platelet count over the reference interval. A physiologic increase in platelet count can occur at high altitude.[2] Relative thrombocytosis resulting from redistribution from splenic and other tissue stores can occur with exercise or epinephrine

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release. Splenectomy can result in thrombocytosis for several weeks because of both increased production as well as decreased platelet sequestration and destruction in the absence of the spleen.[2]

Absolute thrombocytosis can occur in a number of conditions as a secondary reactive change. Thrombocytosis resulting from any cause does not result in increased risk of thrombosis or any other clinical abnormalities; it is a reflection of the underlying disease(s). Many infectious and other inflammatory disorders including immune-mediated diseases can cause reactive thrombocytosis, as can surgery, neoplasia, and other inflammatory disorders. One infrequent cause of thrombocytosis in some species is iron deficiency, but this is not well documented in large animal species; chronic blood loss can be associated with thrombocytosis, and iron deficiency may be one factor. Administration of vincristine or vinblastine can result in thrombocytosis. Thrombocytosis can also occur as a rebound effect following prior thrombocytopenia. A rare cause of persistent severe thrombocytosis is primary thrombocythemia or other chronic myeloproliferative disease; bone marrow evaluation is indicated in this situation.

Platelet Function Defects and Von Willebrand Disease

Defects in platelet function have been described in large animals, but diagnosis can be challenging. The template bleeding test is routinely performed in small animals to assess primary hemostasis (e.g., platelet number/function and von Willebrand factor [vWF] function), but it is criticized for poor reproducibility in both humans and animals, including horses.[20] Template bleeding tests have been useful for monitoring effects on aspirin therapy on hemostasis in horses, and may be suitable for serial monitoring of a patient if other factors such as platelet count remain constant. Aggregometry is considered a gold standard assay for platelet function but can be cumbersome; automated platelet function analysis with the PFA-100 device has become a standard platelet function assay in human medicine and is emerging as a valuable assay in veterinary medicine. More specific assessment of platelet function can require specialized assays.

Glanzmann's thrombasthenia is a disorder resulting in poor platelet aggregation and clot retraction in humans and animals, and it is caused by one or more defects in quantity or quality of platelet surface glycoprotein IIb/IIIa. A Peruvian Paso mare was diagnosed with hereditary Glanzmann's thrombasthenia; the mare was 17 years old at the time of diagnosis.[21] Other hereditary thrombopathias are infrequently described in animals. Chediak-Higashi syndrome is reported in Hereford, Japanese Black, and Brangus cattle. The bleeding diathesis associated with this syndrome is defined by substantial impairment of platelet aggregation in response to collagen.[22] A hereditary thrombopathy in Simmental cattle is characterized by impaired platelet aggregation, with clinical signs including periodic epistaxis and severe hemorrhage following surgical procedures.[23] Inheritance of this thrombopathy appears to be multigenetic, and aggregometry was not useful at differentiating carrier versus clear animals. A variant form of von Willebrand disease has also been described in a Simmental calf.[24] Von Willebrand disease has been reported in Quarter Horses and consisted of a deficiency in high-molecular-weight multimers of vWF, consistent with type 2 von Willebrand disease in other species.[25]

Acquired defects in platelet function are common as a result of drug administration. Drugs that impair platelet function include aspirin, phenylbutazone, sulfonamides, estrogens, and phenothiazines.[14] Several underlying medical conditions can also negatively affect platelet function, including uremia and liver disease. Production of high levels of immunoglobulins, particularly IgM, in monoclonal gammopathies hinders platelet function via protein coating of platelet surfaces.

Prolonged Prothrombin Time

The PT, or one-stage prothrombin time, is a measure of the extrinsic (tissue factor) and common pathways of coagulation (Fig. 27-1). The assay tests the time after the calcium-thromboplastin reagent is added to the plasma sample until formation of a fibrin clot. The PT is prolonged when the fibrinogen level drops below 100 mg/dL or with a marked deficiency of one or more coagulation factors in the common pathway (factors II [prothrombin], V, and/or X) or the tissue factor pathway (VII).

Acquired defects in coagulation factors are much more common than inherited defects and generally involve deficiencies in multiple rather than single coagulation factors. Causes of acquired defects include hepatic disease, vitamin K antagonism (e.g., moldy sweet

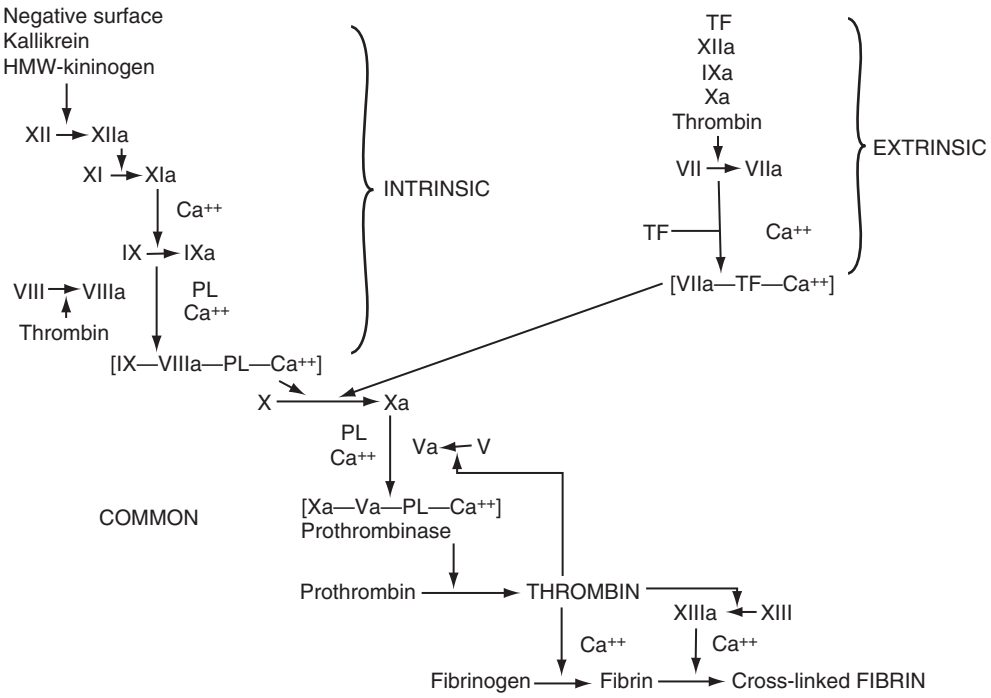


FIG. 27-1 Coagulation pathways.

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BOX 27-3

Causes of Prolonged Prothrombin Time in Horses

Common Causes

Disseminated intravascular coagulation
Anticoagulant/rodenticide toxicosis
Acute hepatic necrosis
Pyrrolizidine alkaloid toxicosis
Aflatoxicosis
Chronic hepatic fibrosis

Less Common Cause

Moldy sweet clover (*Melilotus* species) toxicosis

BOX 27-4

Causes of Prolonged Prothrombin Time in Ruminants

Common Causes

Moldy sweet clover (*Melilotus* species) toxicosis
Disseminated intravascular coagulation

Less Common Causes

Anticoagulant/rodenticide toxicosis
Pyrrolizidine alkaloid toxicosis
Rubratoxicosis
Aflatoxicosis
Bitterweed (*Hymenoxys odorata*) toxicosis
Chronic hepatic fibrosis
Hereditary fibrinogen deficiency

BOX 27-5

Causes of Prolonged Activated Partial Thromboplastin Time in Horses

Common Causes

Disseminated intravascular coagulation
Anticoagulant/rodenticide toxicosis
Acute hepatic necrosis

Less Common Causes

Moldy sweet clover toxicosis
Hemophilia A (deficient factor VIII:C)
Congenital deficiencies of factor IX, factor XI, prekallikrein, or high-molecular-weight kininogen
Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)

BOX 27-6

Causes of Prolonged Activated Partial Thromboplastin Time in Ruminants

Common Causes

Moldy sweet clover toxicosis
Disseminated intravascular coagulation

Less Common Causes

Congenital deficiency of factor XI
Anticoagulant/rodenticide toxicosis
Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)
Hereditary fibrinogen deficiency

clover poisoning), and increased consumption via DIC (Boxes 27-3 and 27-4). The PT is usually the first abnormal coagulation test with decreased coagulation factor production in chronic liver disease.[14] Widespread coagulation and consumption in DIC also causes a prolonged PTT and thrombocytopenia, along with increased fibrinolysis. In addition to quantitative deficiencies, coagulation factors may be functionally impaired by increased FDPs or circulating anti-factor antibodies.

Vitamin K is necessary for hepatic production of functional coagulation factors II, VII, IX, and X as well as anticoagulant proteins C and S. The action of vitamin K is inhibited by coumarin compounds acquired via moldy sweet clover hay or anticoagulant rodenticide ingestion, or by therapeutic administration (e.g., warfarin in horses). Vitamin K inhibition results in deficient carboxylation of coagulation factors and a resulting inability to bind endothelium stably. These incompletely carboxylated factors are termed PIVKAs (or proteins induced by vitamin K antagonism/absence). A modified PT assay called the thrombotest PT is specific for defects in factors II, VII, and/or X and can be used in cases of suspected coumarin toxicosis; specific tests for PIVKAs are not available for domestic animals.

Clinical signs of coagulation factor deficiencies include spontaneous hemorrhage (e.g., epistaxis, melena, and hematuria) or prolonged bleeding after trauma, diagnostic procedures, or surgery. Hematomas or hemarthroses are common after minor trauma or normal exercise, and bleeding into body cavities can occur. Coagulation times are designed primarily for screening purposes and are very insensitive to minor defects of one or more factors (e.g., the PT was prolonged with factor VII levels ranging from 16% to 39% in one study).[1] Less severe coagulation defects may require specific factor assays for diagnosis.

Prolonged Activated Partial Thromboplastin Time

The partial thromboplastin time (PTT) is a measure of the intrinsic (contact activation) and common coagulation pathways (see Fig. 27-1). The activated PTT is now the only test used and measures time from the addition of calcium to plasma with partial thromboplastin reagent and a surface activator until clot formation. The PTT is prolonged with deficiencies or defects in factors XII, XI, IX, and VIII:coagulant (VIII:C) as well as prekallikrein (PK). Most PTT assays detect PK deficiency, and the assay can be corrected to prove that a PK abnormality is the cause of prolonged PTT. The activated coagulation time (ACT) is a simplified variation of the PTT that can be tested by mixing whole blood with activator and calcium. It is less sensitive to factor defects, since prolonged ACT may not occur until a single factor is at 5% to 10% of normal function, and it can be prolonged also with severe thrombocytopenia.[1] As with all tests, reference values vary by species; for example, alpacas have substantially shorter PTTs normally than horses or cattle.[26] Age may also play a role, since healthy newborn foals have PTTs and PTs that are longer than adult reference values.

The most common cause of a prolonged PTT is increased consumption of clotting factors induced by DIC (Boxes 27-5 and 27-6). Liver failure and vitamin K antagonism prolong both the PTT and PT. Single factor defects will prolong the PTT and not affect the PT. Inherited deficiencies of factors VIIIa (the precursor form of VIII:C), IX, and XI, as well as PK, have been described in horses.[27-31] Congenital factor VIIIa deficiency (hemophilia A) is sex linked and males are clinically affected; carriers cannot be detected via PTT as factor levels are insufficiently decreased. The level of factor VIIIa must drop below 5% of normal before spontaneous bleeding occurs. Clinical signs of coagulation factor deficiencies are those of hemorrhagic diathesis as described in the previous section. Inherited factor XI deficiency is transmitted in Holstein cattle by an autosomal recessive trait.[32] Cattle deficient in factor XI rarely demonstrate bleeding tendencies.

Although both the PT and PTT can be prolonged during DIC, it is not uncommon for only one test to be abnormal initially. Serial analyses should reveal a trend toward prolongation of both tests along with decreasing platelet count. When a persistently prolonged

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BOX 27-7

Causes of Elevated Fibrin and Fibrinogen Degradation Products in Large Animals

Common Causes

Disseminated intravascular coagulation
Thrombophlebitis
Postoperative state
Severe inflammation
Immune-mediated thrombocytopenia

Uncommon Causes

Massive internal hemorrhage
Primary hyperfibrinolysis

BOX 27-8

Causes of Reduced Antithrombin III in Horses

Common Causes

Disseminated intravascular coagulation
Protein-losing enteropathy (e.g., granulomatous enteritis, intestinal lymphoma, nonsteroidal antiinflammatory drug toxicosis)
Chronic glomerulonephritis

Less Common Causes

Acute toxic enteritis
Acute hepatic necrosis
Venous thrombosis

BOX 27-9

Causes of Reduced Antithrombin III in Ruminants

Common Causes

Disseminated intravascular coagulation
Renal amyloidosis
Johne's disease

Less Common Causes

Venous thrombosis
Hepatic failure

PTT is the only laboratory abnormality, hereditary factor deficiency should be suspected. As with PT, the PTT is a relatively insensitive screening test. The assays generally have prolonged times when at least one factor is decreased to 30% or less of normal function. Both the PT and PTT can be shortened (times will be below reference interval) with increased fibrinogen, factor V, and/or factor VIII (PTT only). These shortened times are not reliable indicators of clinical hypercoagulability.

Increased Fibrin and Fibrinogen Degradation Products

FDPs can be comprised of fragments of fibrin and/or fibrinogen. Assays are either serum or plasma specific, since fibrinogen present in plasma can react to the polyclonal antibody of the serum assays, and are relatively species specific. A study in horses found that two FDP assays, one serum based and one plasma based, had low sensitivity for FDPs in horses with colic.[33] At the same time, a plasma D-dimer assay was a useful adjunct test. D-dimer (one form of FDP) is a cross-linked fibrin fragment and is therefore specific for fibrinolysis, whereas FDPs as a group are less specific. When measurable, increased levels of FDPs and/or D-dimer generally indicate increased fibrinolysis in response to excessive coagulation (Box 27-7). In addition to DIC, localized intravascular fibrin deposition following surgery, internal hemorrhage, sepsis, and other severe inflammatory processes may cause increased FDP levels. Plasmin perturbations may occur with snake envenomation, heat stroke, surgery, or administration of plasminogen activators and can lead to fibrinogenolysis and increased FDPs.[1] Decreased FDP clearance caused by hepatic or renal disease can also lead to increased FDP levels.

Increased serum FDPs can contribute in turn to hemorrhagic clinical manifestations of DIC by interfering with thrombin activity, fibrin polymerization, and platelet aggregation. Interpretation of FDP or D-dimer tests depends on evaluation of the other components of the hemostasis profile (platelet count, PT, PTT) in concert with the patient's history and clinical signs. Serum FDP levels over 40 µg/mL or plasma levels over 20 µg/mL most often occur with DIC; lower values do not exclude DIC. Horses have measurable D-dimer concentrations in health, so an upper cutoff value must be used to report abnormal values.[33] In one study, horses with clinical evidence of DIC resulting from colic had decreased D-dimer levels consistent with hypofibrinolysis during hypercoagulation.[17]

Decreased Plasma Antithrombin III

The physiologically most important inhibitor of coagulation is antithrombin or antithrombin III (ATIII). This low-molecular-weight glycoprotein primarily neutralizes activated factors IX, X, and II (thrombin) along with other coagulation proteins. Heparin is a necessary cofactor to potentiate ATIII and enable its rapid inhibitor activity. ATIII is measured via chromogenic assays to evaluate functional activity; activity is expressed as the percent relative to a species-specific plasma pool from healthy animals. Plasma ATIII levels may be reduced by decreased liver production, excessive use, loss from the intravascular compartment, or increased catabolism. Inherited ATIII deficiency is not reported in animals. Newborn foals normally have lower ATIII levels than adult horses.[34]

Chronic liver disease may result in failure to produce ATIII and a number of other important plasma proteins. However, horses with chronic liver disease were shown to have increased plasma ATIII levels.[35] These findings suggest that ATIII may behave as an acute-phase protein in horses, since some horses also had increased fibrinogen levels. A second group of horses in the study with acute diarrhea/colitis had decreased ATIII levels. ATIII is variably reported as a positive or negative acute phase protein in animals.[1,35] Estrogens may contribute to ATIII deficiency because of negative effects on synthesis.[1]

In conditions such as DIC, ATIII is consumed and can be decreased as a result of binding to activated coagulation factors and subsequent hepatic clearance of the ATIII-factor complexes. Any pathologic activator of coagulation including trauma, neoplasia, or sepsis may cause reduction of plasma ATIII (Boxes 27-8 and 27-9). ATIII can be reduced as a component of coagulopathy as a result of endotoxemia in foals.[36] Administration of unfractionated or low-molecular-weight heparin leads to decreased ATIII levels via increased activity and subsequent clearance of ATIII.[37]

Diseases that cause massive proteinuria or protein-losing enteropathy result in loss of ATIII in addition to other plasma proteins. Because of the small size of ATIII, it is lost in approximately the same proportion as albumin. Nephrotic syndrome in humans and animals may lead to secondary hypercoagulability and thrombotic disease caused by urinary ATIII loss and other complicating factors; hypoalbuminemia can be a useful predictor of thrombotic risk given concurrent loss of ATIII and albumin and may also play a contributory role.[38,39]

The major clinical sequela of ATIII deficiency is a tendency to develop venous thrombosis. Thrombosis in nephrotic syndrome was discussed earlier. Venous thrombosis is commonly recognized in horses with severe toxic colitis or endotoxemia, but the potential role of ATIII deficiency is unknown. Decreased ATIII has been documented in nonsurviving horses with colic and horses with strangulating obstructions.[40] The contribution of ATIII consumption in DIC to

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the clinical manifestations is complex and difficult to evaluate; however, use of ATIII concentrates in human patients with acute DIC has improved survival in some instances.[35] As with all components of the hemostatic system, plasma ATIII must be evaluated in combination with other hemostasis values.

Hypofibrinogenemia

Decreased fibrinogen concentration, termed *hypofibrinogenemia,* can be detected via a modified thrombin time (TT) test, the Clauss TT, or via immunoassay using anti-fibrinogen antibodies. Heat precipitation is useful to detect increased fibrinogen but is too insensitive to detect hypofibrinogenemia. Plasma fibrinogen levels represent the balance between fibrinogen production and degradation, an important concept in large animals because fibrinogen production is often increased as a result of inflammation and increased consumption may be masked. Pregnancy can also cause increased fibrinogen.[41]

Hypofibrinogenemia may result from impaired hepatic synthesis, increased consumption with DIC, or uncompensated loss during massive hemorrhage (Boxes 27-10 and 27-11). Decreased plasma fibrinogen is uncommon in liver disease of large animals; increased production caused by concurrent inflammation appears to be more common. With DIC and fibrinolysis, decreased fibrinogen concentration caused by consumption is expected in most species. However, hypofibrinogenemia is not common in horses with DIC. Horses with colic in one study had evidence of increased coagulation postoperatively, including decreased ATIII and increased D-dimer, with concurrent hyperfibrinogenemia.[42] Hypofibrinolysis has also been shown in horses with DIC.[17]

Hereditary afibrinogenemia has been described in a family of Saanen dairy goats with a hemorrhagic diathesis in newborn kids that included umbilical bleeding and recurrent hemarthroses.[14] Fibrinogen was undetectable in the affected animals, while heterozygotes had hypofibrinogenemia.

Other Tests of Hemostatic Function

Other tests of hemostasis may be indicated in specific disease situations and include the following tests.

Thrombin Time

The standard thrombin time test measures the rate of fibrinogen to fibrin conversion and can be a useful assay for the effects of FDPs, heparin, and paraproteins (e.g., a prolonged thrombin time can indicate the presence of FDPs that interfere with fibrin polymerization). This test also evaluates for the presence of hypofibrinogenemia, but the Clauss thrombin test (described earlier) is a better assay for that purpose because any interference effect from FDPs, heparin, and other factors is largely eliminated.

BOX 27-10

Causes of Hypofibrinogenemia in Horses

Uncommon Causes

Acute hepatic necrosis
Acute severe disseminated intravascular coagulation
Severe hepatic fibrosis

BOX 27-11

Causes of Hypofibrinogenemia in Ruminants

Uncommon Causes

Hereditary afibrinogenemia (goats)
Acute severe disseminated intravascular coagulation

Specific Factor Assays

Specific factor assays are generally indicated for the diagnosis of hereditary factor deficiencies. Prolonged PTT values along with the signalment, history, and clinical picture may indicate that specific factor assays are needed. In DIC, specific factor analysis is unlikely to be useful.

α_2-Antiplasmin

α_2-Antiplasmin (α_2-AP) binds plasmin to cleave and inactivate it, and then the complexes are cleared from circulation. In humans, α_2-AP is decreased by severe liver disease (reduced production) and with DIC (consumption). Experimental studies in ponies suggest that α_2-AP may be reduced with chronic DIC.[43] Conversely, increased α_2-AP is reported in horses with colic as part of the acute phase response (see Chapter 26).

Protein C

The protein C pathway provides the second major anticoagulant mechanism that regulates hemostasis. Protein C is activated by thrombin complexed to thrombomodulin and subsequently inactivates factors Va and VIIIa via proteolysis and using the cofactor protein S. In humans, decreased protein C can occur in liver failure or DIC, increasing risk of thrombotic disease, and decreased protein C is reported in horses with severe colic.[40]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Collection and Analysis of Bone Marrow

ANDREA A. BOHN, *Consulting Editor*

The hematopoietic system is composed of erythrocytes, leukocytes, and platelets, their precursor cells, and the tissues that support the continuous cycles of cell differentiation required for maintenance of oxygen delivery, protection from infectious agents, and hemostasis. A single multipotent stem cell is the precursor for all hematopoietic cells. From this cell arise progenitor cells directed toward various cell lineages. Postnatally, hematopoiesis to replenish circulating erythrocytes, granulocytes, monocytes, and platelets predominantly occurs in the bone marrow. Although lymphocytic precursor cells continue to travel from the bone marrow to the thymic cortex and enteric mucosa for differentiation postnatally, most circulating lymphocytes are associated with the extramedullary lymphoid organs.

Constantly replenishing blood cells, the bone marrow is one of the most active tissues in the body. Blood cell turnover is rapid; for example, neutrophils have a circulatory half-life of approximately 10 hours. The lifespan of platelets, on average, is approximately 7 to 10 days, and the lifespan of large animal erythrocytes is approximately 5 months, with slightly shorter half-lives reported in some breeds.[1-3] Readers are referred to a veterinary hematology textbook for more in-depth information on the hematopoietic system.[4]

Indications for Bone Marrow Aspiration or Biopsy

Bone marrow evaluation provides important diagnostic information on the hematopoietic status of an animal; it is typically performed to evaluate hematopoiesis and to detect evidence of neoplastic or infectious disease (Box 28-1). The complete blood cell count (CBC) is the most common method used to evaluate the hematopoietic system, but a more comprehensive evaluation includes bone marrow aspiration and/or biopsy. Bone marrow aspiration is commonly used to evaluate the cause of cytopenia. Unexplained nonregenerative anemia, neutropenia, thrombocytopenia, and pancytopenia are indications for bone marrow aspiration. In these cases, bone marrow evaluation is used to determine if the cytopenia is more likely a result of lack of production or of consumption or destruction of the cell in question. If an animal's clinical presentation and other laboratory data provide a reasonable explanation for cytopenia, a decision to perform the procedure may not be justified. For example, if another disease process is present that could explain nonregenerative anemia, such as a chronic inflammatory disease or chronic renal failure, bone marrow aspiration is not indicated in most cases.

Another common reason for bone marrow aspiration is the observation of atypical cells, unexplained immature cells, or abnormal blood cell morphology on a peripheral blood film. In these cases bone marrow is evaluated for the diagnosis of leukemia, myelodysplastic syndromes, and infiltrative disease. Potential infiltrative disease is sometimes detected radiographically, and the presence of lytic or proliferative bone lesions can also be an indication for bone marrow aspiration. Because abnormalities within the bone marrow are not always reflected in the peripheral blood, it may be prudent to perform bone marrow aspiration if a neoplastic or infectious process is clinically suspected but cannot be found elsewhere. This suspicion may arise from finding cytopenias or detecting an unexplained hypercalcemia or monoclonal gammopathy, conditions that are often associated with neoplasia; identifying a fever of unknown origin; or recognizing the probability of an infectious agent that may have bone marrow involvement.

Even though complication rates are low, bone marrow aspiration should not be performed indiscriminately; as for all testing, the clinician should consider what question is being asked and if bone marrow evaluation is the appropriate diagnostic test for answering that question. Examination of a peripheral blood film often provides clues as to the necessity of bone marrow evaluation. In general, cytopenia should be persistent and confirmed before bone marrow evaluation is performed. Rechecking a low cell count by drawing a new blood sample, especially if initial results do not fit with the clinical presentation of the animal, is recommended. An ethylenediamine tetraacetic acid (EDTA)-associated pseudothrombocytopenia has been reported in horses,[5] which can be ruled out by drawing blood into a heparin or sodium citrate tube for platelet counts. A low platelet count can also be artifactual if platelet aggregation occurs during blood collection. The presence of clumped platelets on a peripheral blood film is an indication that platelet aggregation has occurred and that a low platelet count should be viewed with skepticism. Repeated CBCs can also be used to assess persistence of an abnormality. It can take up to 5 days for the bone marrow to respond to acute anemia and for regeneration to be evident in the peripheral blood. Bone marrow aspiration is typically not indicated when there is evidence of regeneration in the peripheral blood. Evidence of erythroid regeneration in the peripheral blood includes an increase in the number of reticulocytes or polychromatophilic cells, basophilic stippling, and macrocytosis. Because the changes typically associated with regenerative anemia are rarely seen in horses, bone marrow aspiration is often the only way to assess erythropoiesis in this species.

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BOX 28-1

Indications for Bone Marrow Evaluation

To assess regeneration in anemic horses
To investigate cause of cytopenia
- Unexplained nonregenerative anemia
- Unexplained neutropenia
- Unexplained thrombocytopenia
- Pancytopenia

To investigate for neoplasia
- Atypical cells in peripheral blood
- Lytic or proliferative bone lesions
- Hypercalcemia
- Monoclonal gammopathy

To investigate for infectious disease
- Fever of unknown origin

Lytic or proliferative bone lesions

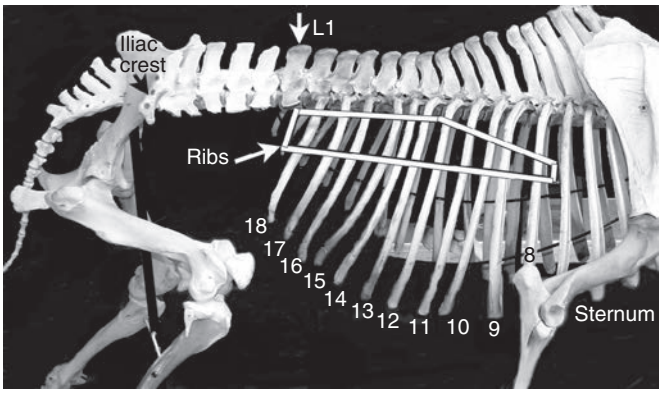


FIG. 28-1 Equine skeleton depicting sites for bone marrow aspiration: the sternum, iliac crest, vertebral ends of ribs 8 to 18, and first lumbar vertebra.

(See Color Plate 28-1, *A-D,* for an example of erythroid hyperplasia in a horse.) Evidence of regeneration in granulocytes includes the presence of a left shift and toxic changes.

Cytologic evaluation of a bone marrow aspirate is more commonly performed than core biopsy because results can be attained more quickly and the morphology of the cells is superior, allowing a more accurate assessment of cell types. The disadvantage of an aspirate versus biopsy is that architecture cannot be assessed with an aspirate and it can be impossible to confirm whether a poorly cellular sample is a result of a pathologic process or an unsatisfactory sampling. The core biopsy provides a better assessment of bone marrow cellularity and is necessary for the confirmation of myelofibrosis, generalized bone marrow suppression, or necrosis. (See Color Plate 28-2, *A-D,* for core biopsy samples of generalized bone marrow hypoplasia from a bovine.) The core biopsy also provides a more accurate assessment of metastatic neoplasia because architecture can be assessed. When collecting a bone marrow sample for cytologic evaluation, some clinicians will also collect a core biopsy to store in formalin in the event that histologic evaluation is later recommended.

If a bone marrow sample is being submitted for evaluation, it is recommended to always submit a concurrent peripheral blood sample for a CBC because interpretation of the bone marrow is dependent on CBC results and changes can occur quickly in the blood.

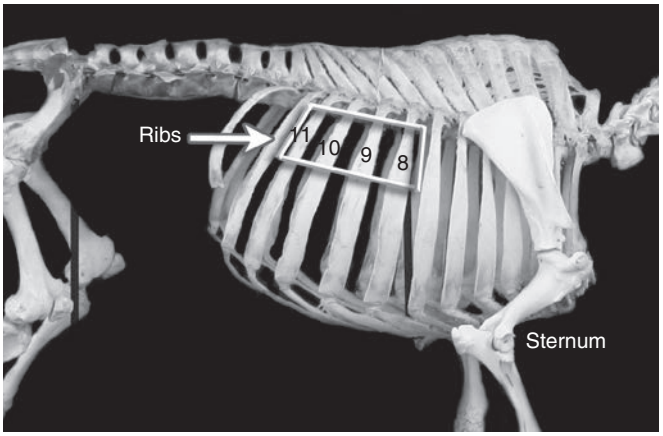


FIG. 28-2 Bovine skeleton depicting sites for bone marrow aspiration: the sternum and vertebral ends of ribs 8 to 11.

Bone Marrow Collection

Sites

Hematopoietically active bone marrow is most consistently found in the flat bones (sternum, ribs, pelvis, vertebrae) and proximal ends of long bones (humerus, femur). The most commonly described sites for bone marrow aspiration in large animals are the sternum, ribs, and iliac crest (Figs. 28-1 and 28-2). Which location is chosen may depend on species, age, and temperament of the animal as well as available facilities.

The ventral sternum is the preferred site in adult horses, small ruminants, and camelids (Figs. 28-3 to 28-6). It is one of the preferred sites in cattle (Fig. 28-7). The advantages of the sternum are that it is covered by only a thin layer of bone, it has areas not covered by thick muscles, and samples can be reliably obtained from the site. The disadvantages of the sternum are that it is near vital organs and that the operator is in an awkward position when working on a standing animal. A procedure for sampling the cranial aspect of the sternum has also been described in horses[6] (see Fig. 28-3). This approach involves going through more muscle.

The ribs are one of the preferred sites for bone marrow aspirates in cattle. The dorsal ends of ribs 8 to 11 can be accessed for sequential aspirations (see Fig. 28-2).[7] Ribs can also be used in the horse, but the needle slips off the bone more easily. In calves, sheep, and goats,

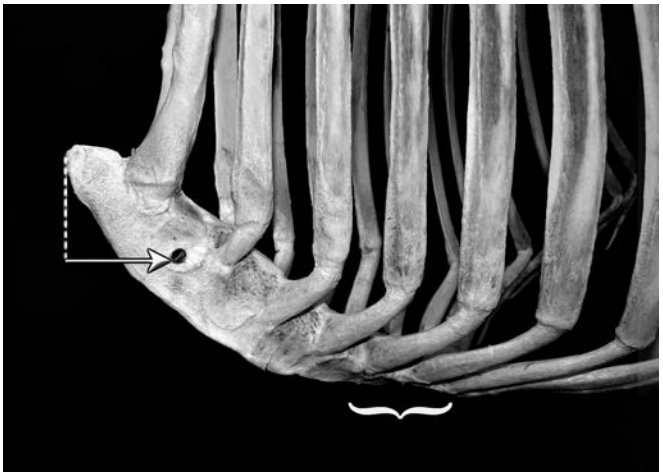


FIG. 28-3 Lateral view of equine sternum. The ventral sternum is the most popular site for sampling bone marrow in the adult horse *(bracket),* but the cranial sternum can also be used. The aspirate site of the cranial sternum is reached by going one hand width below *(dotted line)* and one hand width lateral to its cranial tip. From there, the needle is advanced in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse *(arrow).*

the marrow cavity of the rib is small and more difficult to hit,[8] and in camelids the rib marrow is less consistent in location than the sternum.[9] Successful collection from ribs has been described in camels, with the fifth to eighth ribs as the best sites.[10]

The iliac crest is the site often used in foals for bone marrow sampling and can also be used in young adult horses up to a couple

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FIG. 28-4 Ventral view of equine rib cage and sternum. *Arrows* depict optimal sites for sternal bone marrow aspiration or biopsy, on midline between the elbows of the horse.



FIG. 28-5 Cross-section of sheep sternum. The needle is entering the second sternebra. The second through fourth sternebrae are recommended as optimal sites for bone marrow collection.

of years in age[11] (Fig. 28-8). Samples can also be obtained from older horses at this site, but the needle must be inserted more deeply, needle placement is more critical, and it becomes difficult to obtain a successful sample in horses more than 9 years old.[12] The wing of the ilium is generally considered too thin for bone marrow aspiration

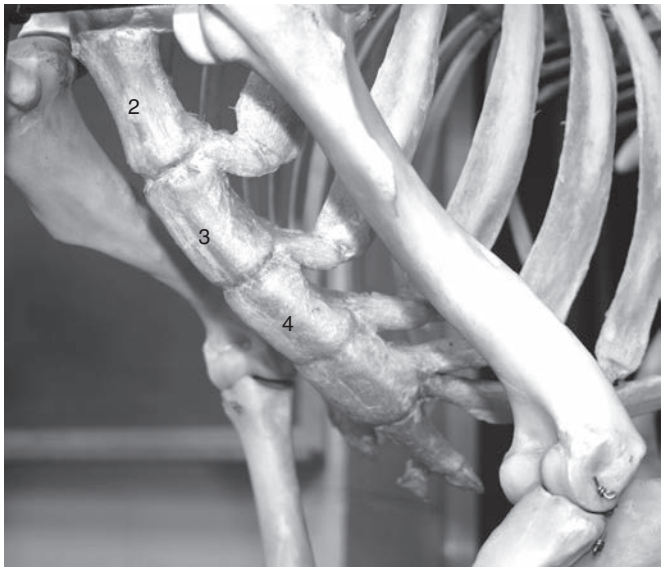


FIG. 28-6 Llama sternum. The llama sternum can be sampled at ventral midline, inserting the needle vertically through the callosity, or from a lateral approach, inserting the needle dorsal to the callosity.

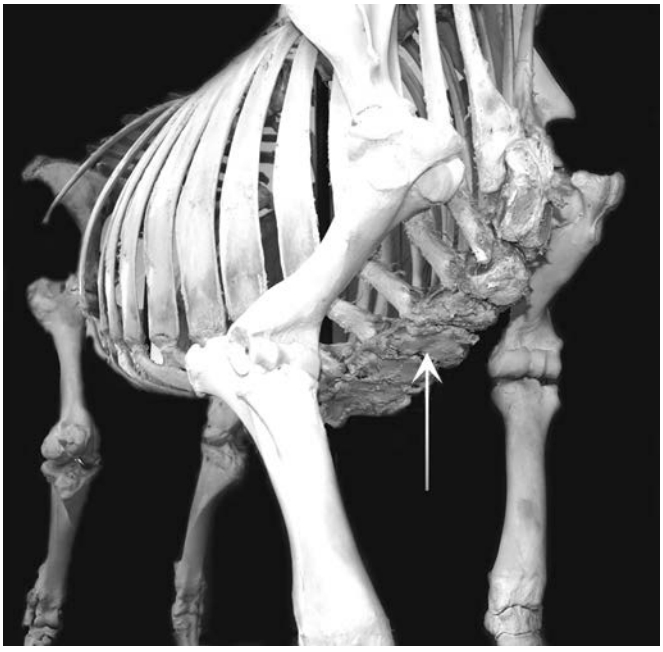


FIG. 28-7 Bovine sternum. The third and fourth sternebrae are recommended for bone marrow collection. The *arrow* is pointing to the fourth sternebra.

in camelids,[9] although successful bone marrow aspiration from the iliac crest of a 2-year-old alpaca has been reported[13] (Fig. 28-9). The iliac crest can also be used in sheep (Fig. 28-10).

Another site informally described for horses is the spinal process of the first lumbar vertebra (Fig. 28-11). It is usually vertical, whereas the adjacent processes tend to be more angled. The tip of the process is wider than the shaft and has a thin layer of bone. The needle is advanced straight down into the marrow cavity, which is narrow, but if the needle is close to correct placement, the walls of the process help guide the needle into the marrow cavity. The advantage of this site is that the operator is not working under the horse. The spinal process is reported to be a poor site to sample in the cow.[14]

APPROACH TO THE STERNUM. In the horse, bone marrow aspiration is typically performed in the standing animal. Sedation or a twitch may be used if necessary. The preferred site is on the ventral

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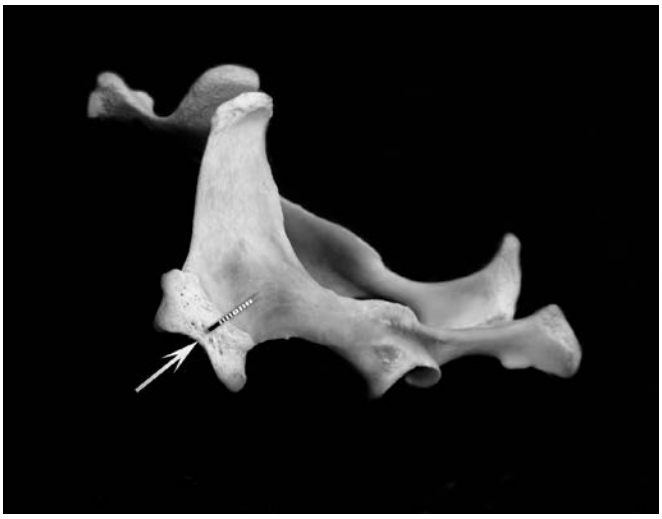


FIG. 28-8 Equine pelvis. To obtain bone marrow, the needle should be placed near the center of the tuber coxae *(arrow)* and advanced toward the opposite coxofemoral joint *(dotted line)*.



FIG. 28-9 Llama pelvis. The wing of the ilium *(arrows)* is generally considered too thin for easy bone marrow collection in camelids.



FIG. 28-10 Bone marrow aspirate from the ileum of a sheep. This sheep was undergoing necropsy, and the wing of the ileum has been dissected out.

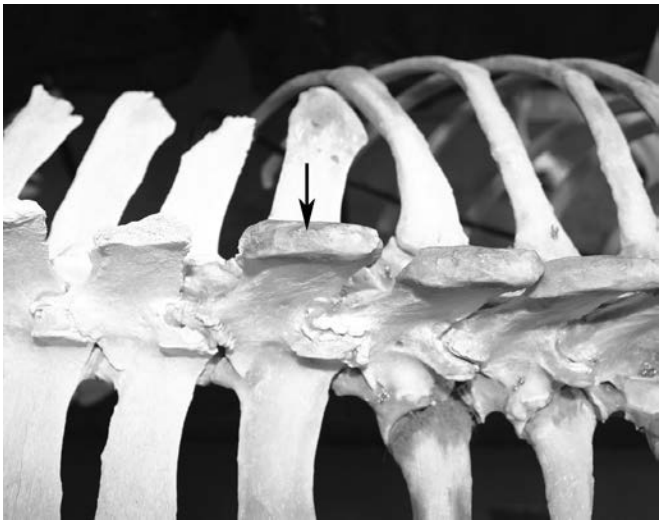


FIG. 28-11 First lumbar vertebra of a horse. Although not widely used, the spinal process of L1 *(arrow)* is another site from which bone marrow can be obtained in the horse.

midline in the cleavage between the deep pectoral muscles where a line connecting the points of the elbows would cross[15] (Figs. 28-4 and 28-12). The manubrium of the sternum can also be sampled in horses by finding the cranial end of the sternum and going one hand width below and one hand width laterally from the end (see Fig. 28-3). From this spot the needle is advanced through the muscle in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse.[6]

Sternal bone marrow can be sampled from adult cattle standing in stocks or a squeeze chute. It may be necessary to use techniques to prevent kicking, such as jacking the tail, or sedation. Unruly adult cattle and large calves can be cast and held in lateral recumbency. The upper front leg of the cast animal is held extended along the neck, exposing the sternum, after the other legs are secured with a rope.[16] Calves that weigh less than 300 lb can be placed in dorsal recumbency and secured by assistants or with ropes.[8] The needle should be placed on the midline and inserted perpendicular to the third or fourth sternebra. The appropriate sternebra is located by palpating the third or fourth rib and following it to the sternum.

For the sternum of a small ruminant to be sampled, the animal is placed in dorsal recumbency with legs secured, or it can be restrained in a sitting position with an assistant standing behind, supporting the animal and holding a foreleg in each hand.[8] The location of the appropriate site is midline, between the front legs. The second through fourth sternebrae can be used in sheep (see Fig. 28-5). A prominence may be felt between the first and second sternebrae. The appropriate sternebrae can also be located by palpating ribs and following them to their articulations.[17] In sheep, the needle will advance approximately 0.5 cm into the bone (2.5 to 3.8 cm from the skin) before entering the marrow cavity.[17]

The sternum of llamas can be sampled with the animal either standing in a chute or lying in left lateral recumbency, usually while sedated[18] (see Fig. 28-6). The sample can be taken by inserting the needle perpendicularly through the callosity on the ventrum of the

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FIG. 28-12 Bone marrow aspiration in a horse. The animal was placed in a stock and sedated. **A,** The ventral sternum between the horse's elbows is clipped and surgically scrubbed. **B,** After local anesthetic, a stab incision is made on midline. **C,** A spinal needle is inserted to collect marrow.

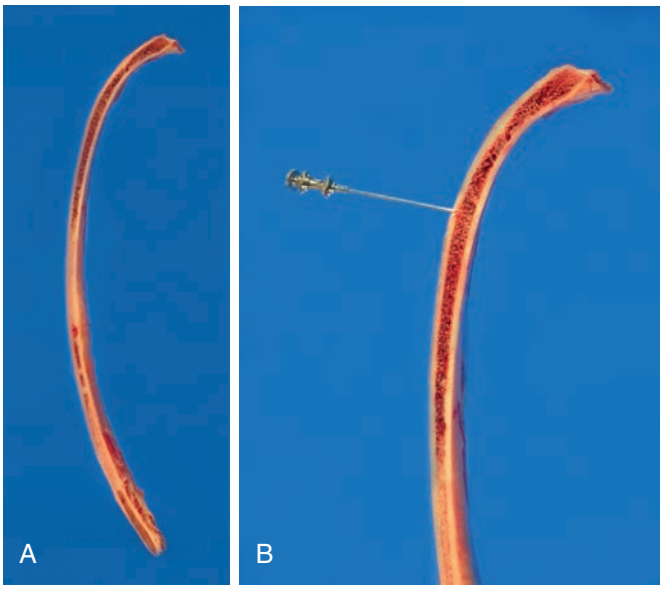


FIG. 28-13 Cross-section of bovine rib 10. **A,** Bone marrow is more consistently present in the vertebral end. **B,** A Rosenthal bone marrow needle is inserted into the rib approximately 3 inches below the costovertebral junction.

sternum or with a lateral approach, approximately 3 to 4 cm dorsal to the callosity with the needle directed medially and slightly dorsally to engage bone.[9] Marrow will be approximately 2.5 cm deep in an adult. The sample is normally more dilute with blood than in other species.[9]

When the ventral sternum is sampled, unless a lateral approach is used, the needle should be placed on the midline, as near to the center of the bone as possible, and advanced perpendicular to the bone. A sudden reduction of resistance may be felt when the marrow cavity is entered, but because the sternal cortex is so thin, especially in horses, there may be no obvious change. Care needs to be taken to not enter the thoracic cavity. Because a change in resistance may not be felt, once the tip of the needle is firmly seated in the bone, an aspiration attempt should be made.

APPROACH TO THE RIB. The vertebral end of the rib more consistently contains marrow than the sternal end of the bone[19,20] (Fig. 28-13). Palpation can be used to find the rib that has the least amount of fascia covering it. In the horse, the eighth to eighteenth ribs can be used, going as high as possible but below the latissimus dorsi and serratus posticus muscles[19] (see Fig. 28-1). In cattle, place the needle approximately 3 inches ventral to the ninth or tenth costovertebral junction[14] (Figs. 28-2 and 28-14). The needle should be inserted perpendicularly at the middle of the rib, midway between the anterior and posterior borders (see Fig. 28-14, *A*). To help keep the needle from sliding off the bone, a scalpel can be inserted first until it touches the bone to be used as a guide.[11]

APPROACH TO THE ILIAC CREST. The iliac crest is often used in foals (see Fig. 28-8). The needle should be placed midway between the two tuberosities of the tuber coxae and somewhat toward its posterior border. With regard to angle, the needle should be pointing at the coxofemoral joint of the opposite side. Bone marrow will be hit when the needle is inserted approximately ⅛ inch for foals, whereas in adult horses bone marrow may be more than 2 inches deep. The main benefit of using this method is that there is no risk of inadvertently entering the thoracic cavity.[12]

Preparation for Bone Marrow Aspiration or Biopsy

Bone marrow aspiration should be performed as a sterile procedure. After the animal has been restrained and the site of approach identified, hair should be clipped and the area surgically scrubbed (see

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FIG. 28-14 Bone marrow aspirate of a cow. The animal was placed in a head-gate and sedated, and a tail jack was applied. **A,** The area over the vertebral end of rib 11 has been clipped and surgically scrubbed. The cranial and caudal edges of the rib are palpated approximately 3 inches down from the costovertebral junction, and the midpoint of the rib is identified for aspiration location. **B,** At the chosen aspiration site, lidocaine is injected from skin to periosteum. **C,** After a stab incision has been made and the Jamshidi-type bone marrow needle inserted through the skin, the needle is forcibly pushed forward through cortical bone as it is rotated alternately in a clockwise–counterclockwise motion. **D,** After a decrease in resistance is felt, the stylet is removed. **E,** A syringe is attached to the needle, and a few sharp pulls on the plunger are needed before the sample is noted in the hub of the syringe.

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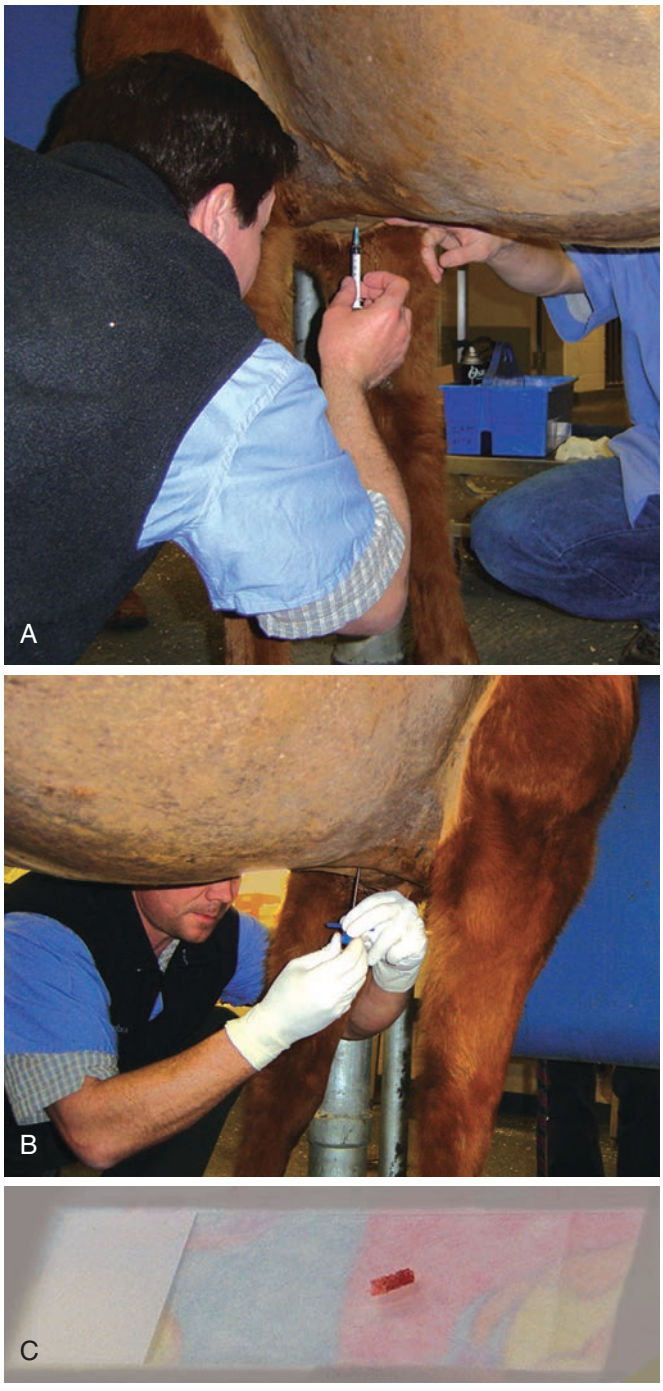


FIG. 28-15 Core bone marrow biopsy of a horse. The animal was placed in a stock and sedated; the ventral sternum between the elbows was clipped and surgically scrubbed. **A,** Lidocaine is injected from the skin to the periosteum. **B,** After a stab incision, the Jamshidi bone marrow biopsy needle is advanced into cortical bone. Here the stylet is about to be removed before the needle is advanced further. **C,** Core biopsy sample.

Fig. 28-12, *A*). Local anesthetic is injected at the site where the needle will be inserted, from the skin to the periosteum (see Figs. 28-14, *B*, and 28-15, *A*). A small stab incision is typically made with a scalpel to aid the needle's approach to the bone (see Fig. 28-12, *B*). If the rib is to be sampled, the scalpel blade can be held in place to act as a guide for the needle. It is important to be organized and have all supplies ready so that the procedure will flow smoothly and the sample will not clot before it can be processed (Box 28-2; Fig. 28-16).

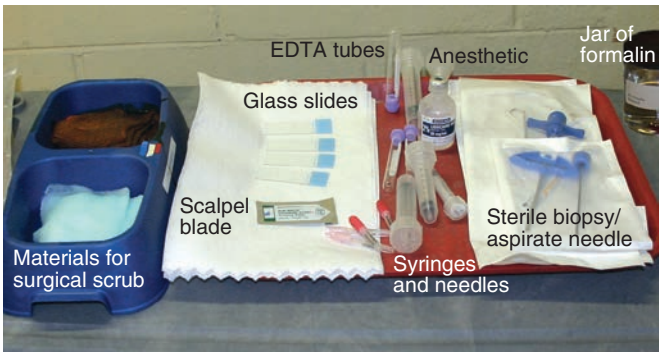


FIG. 28-16 Supply table is set up and ready for bone marrow aspiration. Sterile gloves were opened on an adjacent table. *EDTA,* Ethylenediamine tetraacetic acid.

BOX 28-2

Supply Checklist for Bone Marrow Collection

Clippers
Surgical scrub
Lidocaine
    Syringe and needle
Sterile gloves
Scalpel blade (no. 15 adequate)
Bone marrow needle
    ≥16 gauge, 1½ inches
10- to 20-mL sterile syringe
Glass slides
Jar of formalin for core biopsy
Optional:
    Anticoagulant
    EDTA blood tubes
    Petri dish or watch glass

EDTA, Ethylenediaminetetraacetic acid.

How the sample will be ultimately handled will dictate some of the available supplies needed: glass slides, Petri dish, EDTA blood tubes, and/or anticoagulant. One option is to prime the syringe that will be used for aspirating the sample with anticoagulant. To prevent clotting, 1 to 2 mg of EDTA is recommended per milliliter of blood. One to two drops of a 3% to 15% EDTA solution should be adequate. The EDTA solution can be aspirated from a purple-topped blood tube. Priming the syringe with anticoagulant, although it adds a preparatory step, decreases the worry that the sample will coagulate and allows more time for processing the sample. If the syringe is not primed, as soon as the sample is seen in the syringe hub, the syringe needs to be disconnected immediately from the needle and the sample quickly processed before it has a chance to clot. If a reticulocyte count is to be performed to assess erythroid regeneration, supravital stains, such as new methylene blue and brilliant cresyl blue, require mixing with a portion of anticoagulated, liquid sample before slides are made; therefore, placing at least some of the bone marrow sample in an EDTA tube is recommended.

The sample in the syringe may be processed by expressing it directly onto several clean glass slides, into an EDTA blood tube, or into a Petri dish or watch glass. The Petri dish or watch glass must contain anticoagulant if no anticoagulant was used in the syringe. The anticoagulant commonly used is EDTA, which can be used in solution or as a salt, but other anticoagulants such as sodium citrate are also effective. Samples placed in an anticoagulant should be gently mixed immediately.

Collecting the Sample

The goal of bone marrow aspiration is to obtain a good sample of hematopoietic cells with minimal blood contamination.

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FIG. 28-17 Bone marrow needles with stylets separated. On the *left* is a 14-gauge, 2¾-inch Rosenthal needle. On the *right* is an 11-gauge, 4-inch Jamshidi needle.

Anatomically, within the bone marrow, hematopoietic cells are extravascular and found in spaces dissected by venous sinuses and a central vein.[21] To collect the sample, a bone marrow or spinal needle with stylet should be used. Commonly used needles include Rosenthal, Illinois sternal-iliac, and Jamshidi bone marrow needles (Fig. 28-17). Some needles come with a guard that can be adjusted to prevent deeper penetration than desired. The needle used should be 16 gauge or larger and at least 1½ inches long. Larger needles may be needed, depending on the site of aspiration and the age and size of the animal.

After an animal has been properly prepared, the bone marrow needle is inserted through the skin, perpendicular to the bone (see Fig. 28-12, *C*). Once the needle contacts bone, it can be advanced using manual pressure and a clockwise-counterclockwise twisting motion (see Fig. 28-14, *C*). One hand can be used to stabilize the needle angle and placement while the other hand is on the needle hub pushing and turning the needle.[15] If the needle is going through dense bone, a wood mallet can also be used to advance it.

Once it is suspected that the needle has entered the marrow cavity, either because of detection of a sudden reduction in resistance or because of needle depth, the stylet should be removed and an aspiration attempted (see Fig. 28-14, *D*). In dense bone, pliers may be helpful in removing the stylet.[8] After the stylet is removed, a 10- to 20-mL sterile syringe is securely attached to the needle, and the plunger of the syringe is pulled back quickly and sharply, creating negative pressure in order to dislodge bone marrow particles (see Fig. 28-14, *E*). Suction can be repeated two or three times. As soon as blood is seen in the hub of the syringe, suction should be discontinued, the needle and syringe removed from the animal, and the sample processed promptly. Additional suction will likely only result in hemodilution of the sample. The first drop of blood is the most cellular, and further aspiration results in lower cellularity of the sample.[22]

If the initial aspiration does not obtain any material, remove the syringe, replace the stylet, and carefully advance the needle a little further. If a sample still cannot be obtained after additional advancement of the needle and repeated suction, slowly withdraw the needle while applying suction to the syringe. Ultimately, repositioning the needle to a different site, such as moving a couple of centimeters cranially or caudally, may result in a successful aspiration.[9]

Processing the Sample

Whether the bone marrow sample is directly applied to glass slides or expressed into a Petri dish or watch glass, processing needs to proceed rapidly to prevent clotting or drying out of the sample. When on the slide, if the sample contains a lot of excess blood, the slide can be briefly tilted so that the fluid portion can run off into an absorbent surface, leaving behind adherent particles for spreading (Fig. 28-18, *C*; Fig. 28-19, *A*). If the sample is placed into an EDTA tube or Petri dish with anticoagulant, spicules (small grayish particles) can be transferred out of the bloody sample using a pipette and placed on a glass slide[23] (see Fig. 28-18).

To spread the sample on a slide, place a second glass slide flat on top of the sample, allowing the sample to form a thin layer between the slides (see Fig. 28-19, *B*). Without additional pressure other than the weight of the slide, gently pull the slides apart from each other horizontally and without vertical separation, which can create suction and rupture cells (see Fig. 28-19, *C*). This typically results in a nicely spread sample with intact particles and nice monocellular layers for evaluation. Several slides should be made. After slides are made, they should be allowed to air dry, kept away from formalin fumes, and stored at room temperature until staining.

Some bone marrow slides are stained with a Romanovsky-type stain (Wright, Giemsa, Diff-Quick) for cytologic examination, and some should be left unstained in the event that special staining procedures are wanted. It is highly recommended to stain at least one slide right away for microscopic examination in order to determine sample quality and to make sure bone marrow elements are present while the animal is still available and prepped, in the event that the first aspiration is nondiagnostic and additional attempts will be needed (Fig. 28-20). If a hemodilute sample without spicules is obtained, it may be possible to acquire diagnostic information by centrifuging the sample in Wintrobe hematocrit tubes and making smears from the buffy coat. Staining for reticulocytes requires that an anticoagulated, liquid bone marrow sample be mixed and incubated with a supravital stain before slides are made.

If a core biopsy sample is obtained, the tissue can be gently rolled on a slide to make an impression smear for cytologic evaluation. The biopsy tissue should then be placed in 10% neutral buffered formalin for preservation. A larger gauge needle (10 to 13 gauge) is generally recommended for core biopsy. The Jamshidi needle, designed so that the distal tip tapers to help retain the sample, is the most popular needle for biopsy. The needle and stylet are initially inserted as for aspiration (see Fig. 28-15, *B*). Once the needle enters the bone marrow, the stylet is removed and the needle advanced farther with the same twisting motion. Ideally, the needle is inserted at least an additional 1 to 2 cm, but this may be limited by location. After the needle is advanced to obtain the core, it is rotated and rocked forcibly to help break the core at its base for successful removal. Once the needle is removed from the animal, a probe is inserted into its lumen at the distal tip, pushing the sample out the hub end (see Fig. 28-15, *C*).

Often, bone marrow aspirates are placed into an EDTA blood tube for submission to an outside laboratory. In this case it is still recommended to make slides of the sample to submit along with the fluid sample. If the sample is left in the fluid phase, cells can deteriorate during transit, and it is always helpful for the cytologist to have a freshly prepared sample to examine (of both bone marrow and peripheral blood). In addition, a slide can be stained and evaluated for diagnostic quality before the sample is shipped.

If repeated aspirates all result in samples of low cellularity, a core biopsy may be indicated. Cytologically, it is usually impossible to differentiate low cellularity caused by a pathologic process from that resulting from poor sampling; therefore, a biopsy may be needed for the evaluation of cellularity.

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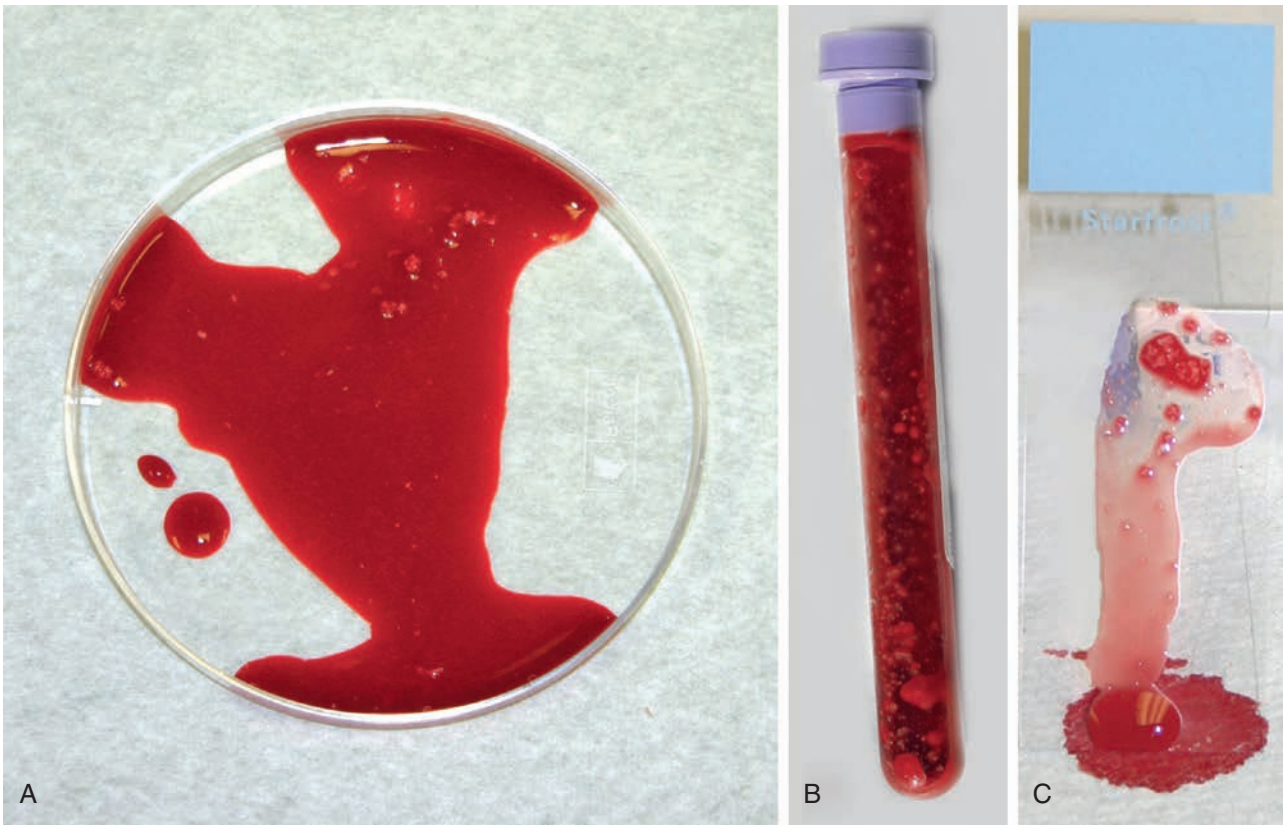


FIG. 28-18 Bone marrow spicules (small grayish particles) should be seen in the aspirated sample. **A,** Particles can be picked out of background blood from a Petri dish. **B,** Particles can be seen adhering to the sides of an EDTA blood tube. **C,** Particles will adhere to a glass slide while excess blood runs off.

Bone Marrow Evaluation

Bone marrow evaluation requires expertise (advanced training and experience), and in most cases it is anticipated that samples will be sent to a trained cytologist for evaluation. To obtain the most information from a bone marrow aspirate, it is important to have a good-quality sample. Even if not reading the sample oneself, it is recommended to stain a slide to confirm that a diagnostic sample was obtained (stain the worst slide; if it is acceptable, one can expect the others to also be acceptable). Recent CBC results and freshly made blood films are also essential for full interpretation of a bone marrow sample. Relative changes among different cell lines are assessed in the evaluation of hematopoiesis because absolute cell counts are unreliable in bone marrow aspirates.[22] Knowledge of the peripheral blood picture is necessary to assess whether changes (or lack of changes) in the bone marrow are consistent with normal hematopoiesis. Freshly made blood films are important to have when comparing the morphology of cells in the bone marrow with the morphology of those in the peripheral blood. Results from cytologic evaluation of bone marrow should ultimately be correlated with history, clinical presentation, and other laboratory data.

Cytologic Examination

In general, the evaluation of bone marrow includes assessment of the following parameters. On low magnification the cellularity and quality of the sample as a whole are assessed, as well as the cellular density of bone marrow particles. Iron stores are evaluated within the particles. Megakaryocyte numbers are also best assessed at low magnification. On high magnification the sample is evaluated for the presence of myeloid and erythroid cell lines. The cell lines are evaluated for orderly maturation, and cell morphology is assessed for evidence of dysplastic changes. The relative proportion of myeloid to erythroid cells is determined by subjective assessment or by counting cells to derive a myeloid-to-erythroid (M:E) ratio. The sample is also evaluated for the presence of other cell types or infectious organisms. Results from the bone marrow evaluation are then interpreted in accordance with peripheral blood abnormalities.

Cellularity of bone marrow spicules is subjectively determined by assessing how much area of a particle is composed of cells versus fat. Cellularity of normal marrow can vary according to the age of an animal, with higher cellularity in younger animals and lower cellularity in older animals. Examples of differing cellularities are depicted in Fig. 28-21. Iron stores are assessed within spicules and typically described as *present, decreased,* or *increased* (Fig. 28-22).

Maturation of bone marrow cell lines follows somewhat of a pyramidal pattern, with cells dividing as they mature, resulting in higher numbers of cells in the more mature cell stages (Figs. 28-23 and 28-24). In bone marrow of healthy animals, rubriblasts and myeloblasts will typically comprise at most a small percentage of the total cell population. Twice as many prorubricytes and promyelocytes may be seen. Numbers of cells in each stage increase up to polychromatophilic rubricytes and metamyelocytes, after which there are relatively stable numbers between the subsequent maturational phases. In general, for each blast there are 16 mature granulocytes or erythrocytes. Mitotic figures are normally present in low numbers.

The M:E ratio is most accurately determined by counting a minimum of 500 cells. Nucleated cells of all maturational stages are included in the count and categorized as myeloid or erythroid. The ratio is calculated by simply dividing the total number of myeloid cells by the total number of erythroid cells. It is important to include several different areas of the sample to make it as representative of the whole sample as possible. Blood contamination can also affect the M:E ratio, especially if leukocytosis is present. Reported M:E ratio ranges for healthy animals of different species have been variable. In some sources the M:E ratio in cattle is listed as less than 1, although ranges from 0.27 to 2.59 have been reported.[7,20,24-26] The range of M:E

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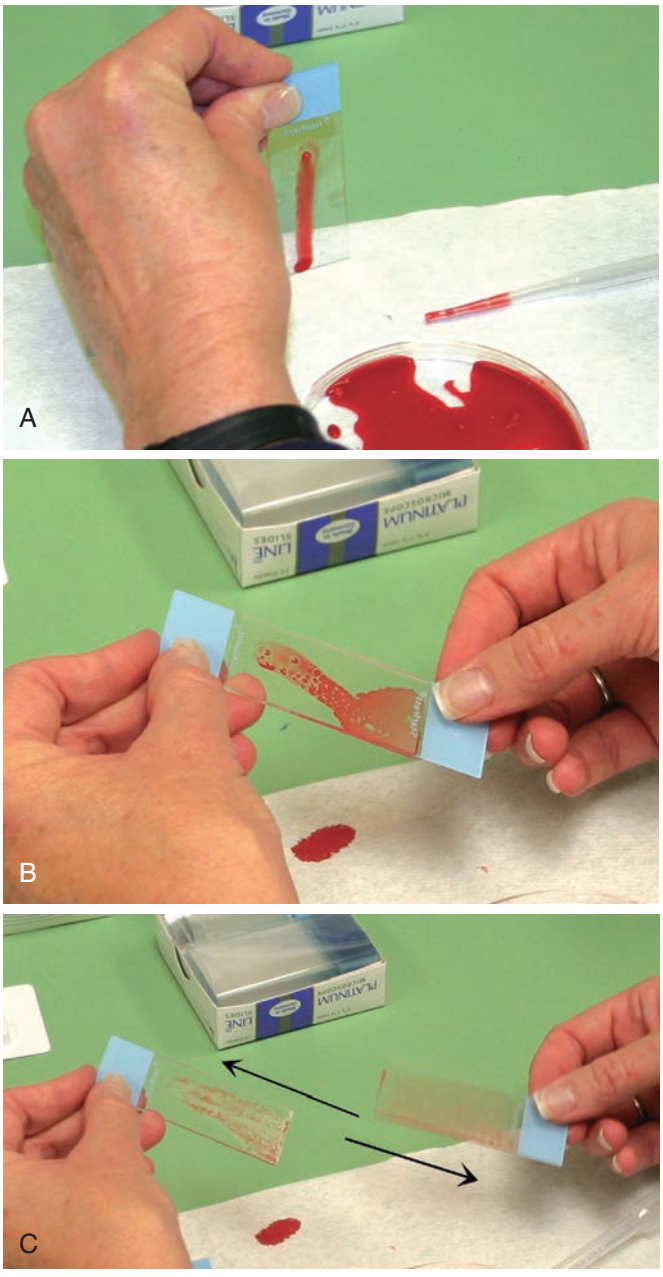


FIG. 28-19 Making slides of a bone marrow sample. **A,** Excess blood is allowed to run off the slide onto an absorbent surface while the spicule stays adhered to the slide. **B,** A second slide is laid on top of the sample, causing the sample to spread out between the slides. **C,** The slides are horizontally pulled apart, then allowed to air-dry.

ratios in ten 3- to 6-year-old pregnant sheep was reported as 0.77 to 1.68.[17] The reported range for the M:E ratio in a low number of llamas is 0.9 to 2.9.[18] Llama, alpaca, and vicuña have a lower M:E ratio at high elevation (4200 m) versus low elevation.[2] M:E ratios in horses generally range from 0.5 to slightly greater than 1, with 1.5 sometimes reported as the upper value.[6,27-29]

Evidence of dysplastic changes in hematopoietic cells includes asynchronous maturation between the cytoplasm and nucleus, large cell forms, and abnormal nuclei, such as ring-shaped nuclei. Cell types other than hematopoietic cells should be evaluated as to their presence and proportion of the total cell population. Low numbers of macrophages (<1%), plasma cells (<2%), and small lymphocytes (<10%) are commonly seen in bone marrow samples.

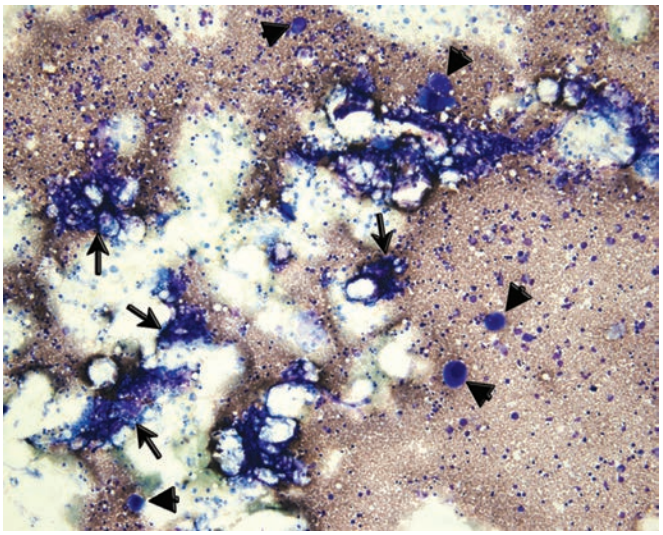


FIG. 28-20 Stained slide of adequate bone marrow aspirate sample. Megakaryocytes *(arrowheads)* and particles *(arrows)* are present. There is also increased cellularity compared with peripheral blood. (Wright-Giemsa stain, 10× objective.)

Interpretation

It is easy to make a conclusion about bone marrow cellularity if the sample is highly cellular, but a poorly cellular sample is more difficult to interpret if adequate particles are not present. A core biopsy may be needed to differentiate between a poorly cellular marrow and a nonrepresentative sample. In general the bone marrow will become more cellular in a hyperplastic or regenerative response.

In many cases it is adequate to describe iron stores as being present without quantification. When assessing the cause of anemia, an abnormality in iron stores may provide useful diagnostic information. Lack of iron stores would suggest iron deficiency, whereas abundant iron stores are associated with anemia of chronic inflammation. Perl's iron stain (Prussian blue reaction) can be used on bone marrow slides to confirm low iron stores. Llama bone marrows normally contain abundant iron.[18]

No definitive criteria for megakaryocyte numbers have been determined. If thrombocytopenia is not present, any number of megakaryocytes is acceptable. Many megakaryocytes are expected to be seen within individual particles when there is regeneration associated with thrombocytopenia. Higher numbers of immature megakaryocytes may also be seen; these will be smaller cells (still larger than other bone marrow cells) with a higher nuclear-to-cytoplasmic ratio, deeper basophilic cytoplasm, and fewer lobes to the nucleus. If megakaryocytes are not frequently seen in the bone marrow from an animal with thrombocytopenia, this suggests hypoplasia or destruction of megakaryocytes.

When assessing bone marrow for normal, progressive maturation of cell lines, it is expected that all developmental stages will be present, with greater numbers of the more mature cells. Variation from normal can be seen for a variety of reasons, often reflected by a shift to the left or what appears to be a maturation arrest. A shift to the left is the situation in which all maturation stages are represented but there is a higher proportion of the less mature cells (the proliferating pool) than normal. *Apparent maturation arrest* is a term used when maturation appears to terminate at a particular stage; the earlier maturation stages are present, but later stages are poorly represented. Suppression of hematopoiesis can result in abnormalities in maturation progression but often is reflected by a decrease in all stages of maturation. If the number of cells within a cell line is too low, progression of maturation can be difficult to evaluate. Destruction of cells, such as with immune-mediated disease, at a particular maturation stage will result in decreased numbers of cells of the affected type as well as cells at all later stages, which can appear

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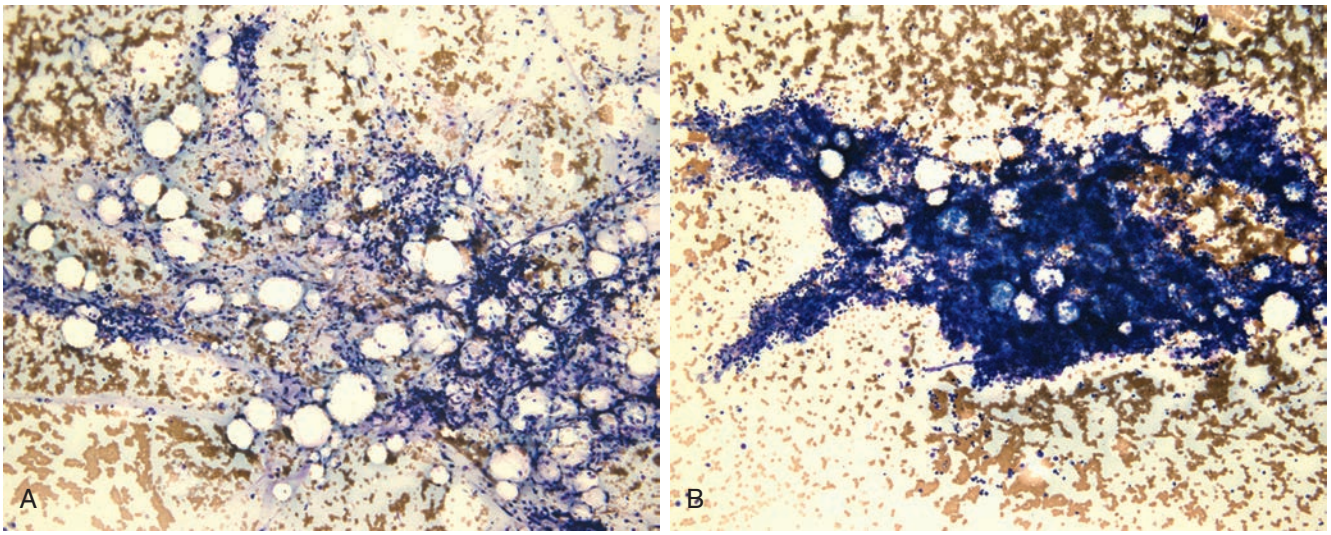


FIG. 28-21 Bone marrow particles. The particle in **A** is of low cellularity. Only a small proportion of the particle is composed of nucleated cells. The particle in **B** is of high cellularity. At least 75% of the particle is composed of nucleated cells. (Wright-Giemsa stain, 10× objective.)

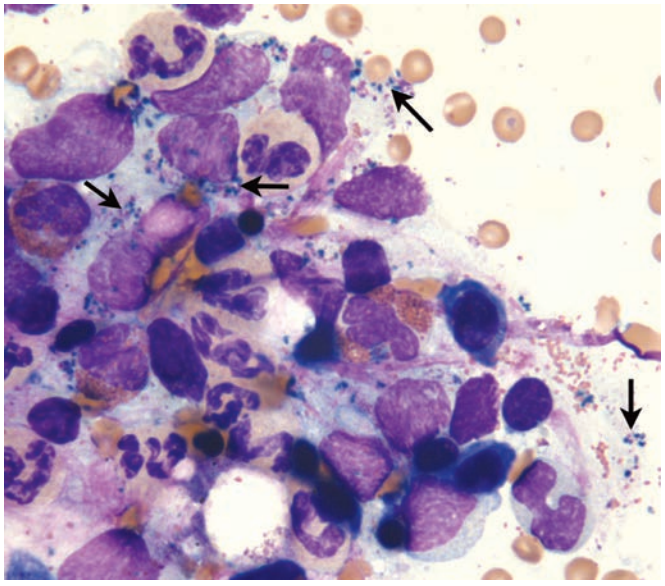


FIG. 28-22 Bone marrow aspirate. The blue-black granules visible extracellularly and within macrophages represent iron stores *(arrows)*. Iron stores can also be seen as brown crystalline material within particles. (Wright-Giemsa stain, 100× objective.)

as a maturational arrest. If a disease process results in large demand or rapid mobilization of cells out of the bone marrow, depletion of the more mature cell stages can appear as a maturational arrest. In such cases a left shift also is often associated with the increased demand. Acute leukemia is typically reflected as an apparent maturational arrest or left shift. Therefore, it can be difficult to differentiate between hyperplastic marrow in which there has been rapid mobilization of mature cells out of the marrow and a myeloproliferative disorder on cytologic examination alone. In some instances sequential bone marrow aspirations can be useful in helping to determine disease pathogenesis. Abnormalities in maturational progression may also be reflected by the presence of dysplastic changes.

The M:E ratio is used to help determine if the erythrocyte or myeloid cell lines are hypoplastic or hyperplastic. An equal number of nucleated erythroid and myeloid cells will result in an M:E ratio of 1. An M:E ratio greater than 1 (or greater than the reference interval) often indicates that granulocytic production exceeds erythroid production, but it could also indicate a decrease in erythropoiesis. Likewise, an M:E ratio less than 1 (or less than the reference interval) often indicates that erythropoiesis exceeds granulopoiesis, but it could also indicate suppression of the latter. Determining which interpretation is appropriate requires knowledge of concurrent CBC results. An increase in the M:E ratio would be appropriate in an animal with neutrophilia, but if the neutrophil count is normal and anemia is present, it would indicate erythroid hypoplasia. In the face of anemia, a decrease in the M:E ratio would indicate erythroid hyperplasia and regeneration, but a decrease in a neutropenic animal that is not anemic would indicate myeloid hypoplasia. In some disease states both the myeloid and erythroid series may be affected, which could potentially exacerbate or mask alterations.

Whereas most species readily reflect an erythroid regenerative response in the peripheral blood, horses do not. Reticulocytes are rarely seen in equine peripheral blood, and in one investigation it took several days of severe anemia (PCV of 13% to 14%) in horses before a reticulocytosis of 1% to 2% was seen.[30] An increase in mean corpuscular volume (MCV) may be detected in the peripheral blood of horses with chronic anemia or acute, massive hemolytic or hemorrhagic anemias,[29-32] but the best way to assess erythropoiesis in horses is to examine the bone marrow. The number of reticulocytes significantly increases in the bone marrow of horses with regenerative anemia. In the study of acute blood loss in which only 1% to 2% of reticulocytes were seen in peripheral blood, bone marrow reticulocytes went from 4.1% (before blood loss) to as high as 66.5%.[30] Reticulocytes typically comprise less than 2% of erythrocytes in normal bone marrow, and a regenerative response is considered present if reticulocytes comprise greater than 5%.[11] Determining the number of reticulocytes per 1000 erythrocytes after staining with a supravital stain such as new methylene blue is the most reliable method, but an estimate can be made by counting the number of polychromatophils per 100× oil objective field in a Wright-stained smear (assuming the field of view includes approximately 100 cells; this can vary with the microscope). In the face of anemia, greater than 5 polychromatophils/oil field is considered a good regenerative response, and less than 2 is indicative of erythropoietic suppression.[33] Care should be taken not to dilute the sample with peripheral blood, since this will dilute the number of reticulocytes from the bone marrow.

Other bone marrow parameters that indicate erythrocyte regeneration in horses include a decreased M:E ratio (<0.5) and a left shift of erythroid precursors.[29,33] Depending on the type of blood loss, it could take several weeks to reduce the M:E ratio below the reference interval.[34] With regeneration, a doubling of the proliferating pool of

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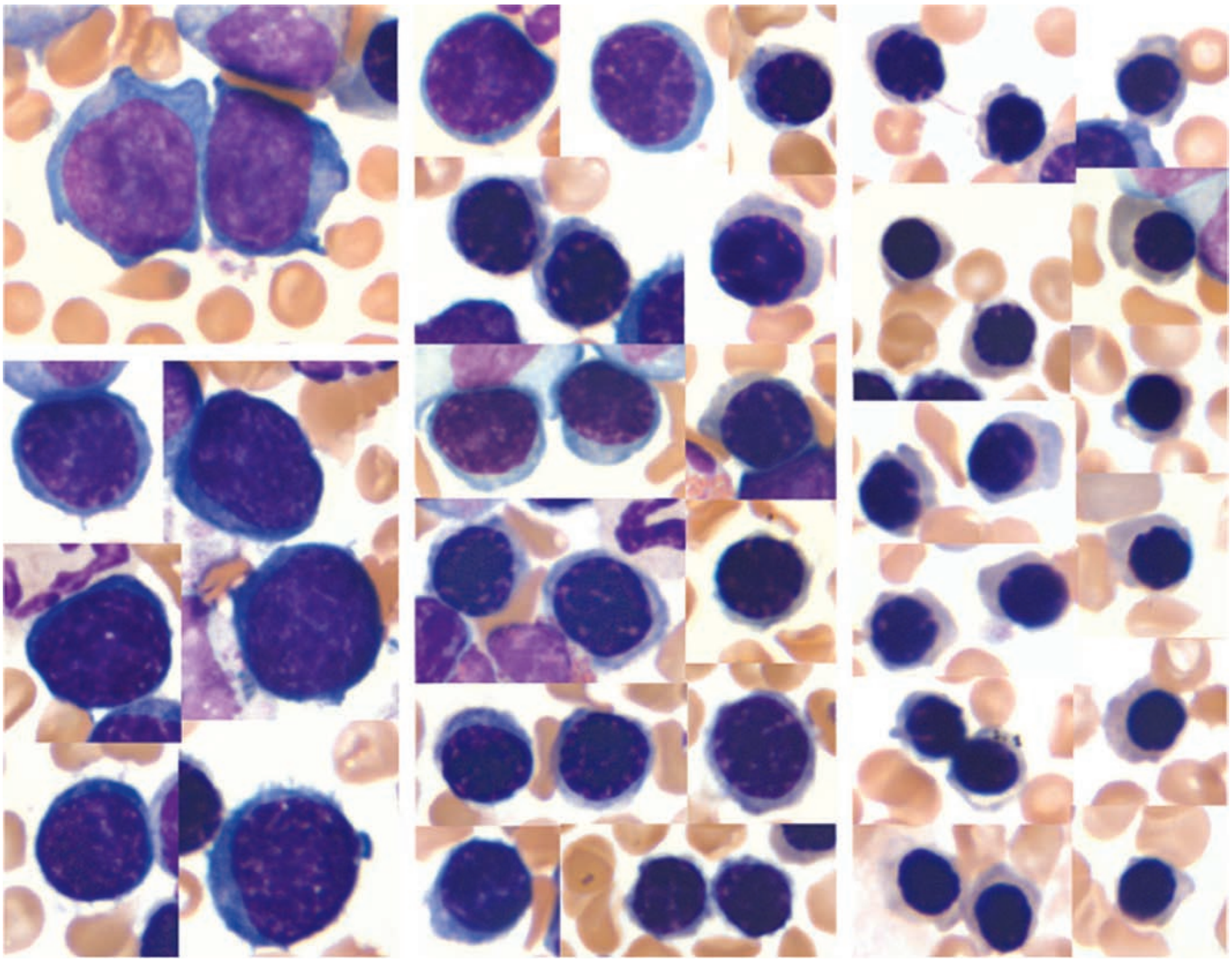


FIG. 28-23 Maturational stages of erythrocytes within the bone marrow. The *left panel* contains rubriblasts in the upper square with prorubricytes below. Rubriblasts are large cells with large nuclei containing coarse-grained chromatin and nucleoli; a perinuclear halo is present within scant deeply basophilic cytoplasm. Prorubricytes have a more mature nucleus; chromatin condensation begins, and no nucleoli are present. The *middle panel* contains basophilic and polychromatophilic rubricytes; chromatin condensation is distinct and the cytoplasm is paler, grayer, or polychromatic. The *right panel* contains metarubricytes with dark, intense chromatin condensation and pink cytoplasm. (Wright-Giemsa stain, 100× objective.)

erythrocyte precursors can occur within 3 days of an acute severe hemorrhage, with maximal response at 9 days.[35] The proportion of basophilic and polychromic rubricytes can reach 39% to 55% of all cells in the regenerative equine bone marrow.[29]

Atypical cell populations in the bone marrow can represent a myeloproliferative disorder, an infiltrative neoplastic process, inflammation, or antigenic stimulation. Atypical cell populations can be a result of significant increases in cell numbers of types normally seen in the marrow. Blast cells normally constitute only a small percentage of total cells in the bone marrow. A diagnosis of acute leukemia is typically associated with blast cells that constitute greater than 20% to 30% of cells within the bone marrow. Cytologic results need to be correlated with other clinical data because granulopoiesis characterized by a marked left shift in bone marrow precursor cells with rapid mobilization of more mature cells from the bone marrow can resemble a myeloproliferative disorder.

Another cause of increased numbers of cells normally residing in the bone marrow is inflammation. Suppurative inflammation can be seen, typically associated with septicemia. Histiocytic or granulomatous inflammation is characterized by increased numbers of macrophages. Both suppurative and histiocytic inflammation can be associated with infectious or noninfectious disease processes. If inflammation is present, the sample should be thoroughly inspected for organisms, and culture may be indicated.

Increased numbers of lymphocytes and plasma cells can be seen with antigenic stimulation or with neoplasia. In general, it is rare to see the proportion of lymphocytes or plasma cells exceed 20% with antigenic stimulation. The morphology of lymphocytes and plasma cells should be well differentiated if they are associated with nonneoplastic processes. Cells associated with neoplasia can also appear well differentiated; therefore, cell morphology alone may not be useful in establishing a diagnosis. Clinical presentation and ancillary testing (e.g., serum protein electrophoresis, flow cytometry) can be helpful in interpreting lymphocytoses and plasmacytoses.

The presence of cells not typically seen in the bone marrow or cells exhibiting a high degree of pleomorphism or other criteria of malignancy should raise suspicion of a neoplastic process. Neoplasia can arise from within the bone marrow or can metastasize to the bone marrow from other sites.

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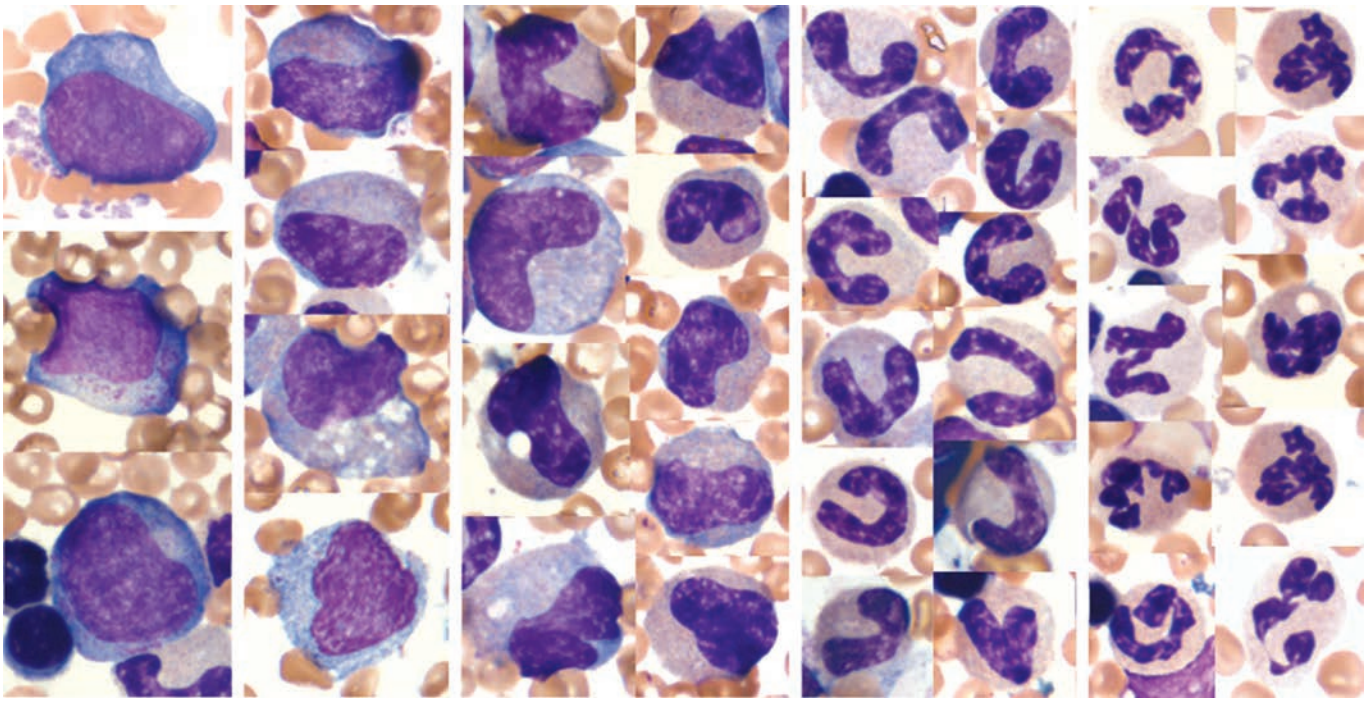


FIG. 28-24 Maturational stages of granulocytes within the bone marrow. The *left panel* contains a myeloblast in the upper square with promyelocytes below. Myeloblasts are large cells with large nuclei containing fine reticular chromatin and nucleoli; the cytoplasm is basophilic and agranular. Promyelocytes contain coarse cytoplasmic granulation; nuclear chromatin is beginning to condense, and nucleoli are present. *Subsequent panels,* moving to the right, contain myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Myelocytes have a lower nuclear : cytoplasmic ratio and contain fewer and finer cytoplasmic granules; the nucleus is round to kidney shaped and contains no nucleoli. As maturation progresses, the cells become smaller, the cytoplasm becomes more eosinophilic, the chromatin becomes more condensed, and the nucleus indents and segments.

Degenerative cells or amorphous proteinaceous debris suggests bone marrow necrosis. This can occur as a result of infarction, neoplasia, or inflammation. Degenerative cells are often unidentifiable.

After cytologic evaluation of bone marrow and correlation with CBC results, a determination can be made as to whether any of the cell lines are hypoplastic or hyperplastic and whether there is evidence of maturational arrest, dysplasia, neoplasia, or inflammation. This information can then be correlated with the clinical information to determine appropriate differential diagnoses and likely disease pathogenesis.

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• CHAPTER 29

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Molecular Diagnostics in Large Animals

NICOLA PUSTERLA and CHRISTIAN M. LEUTENEGGER, *Consulting Editors*

Molecular Diagnostics in Large Animals

Christian M. Leutenegger • Nicola Pusterla

Of the four classes of organic molecules that compose the basic physical structure of all living beings, nucleic acids are the only molecules that carry replicable instructive information. Nucleic acids differentiate themselves from lipids, carbohydrates, and even proteins in their ability to organize the basic unit of life, the cell. Even minor alterations in DNA and RNA molecules can disrupt the fine balance between health and disease. The field of molecular diagnostics seeks to elucidate the variations and mutations in genetic material that can cause disorder in the otherwise intricately organized body.

The amplified era of molecular diagnostics for infectious diseases began in 1983 when Dr. Kary Mullis of Cetus Corporation first conceptualized the polymerase chain reaction (PCR). He went on to win the Nobel Prize in Chemistry for this revolutionizing technology 10 years later.[1,2] Since the inception of PCR technology, infectious disease diagnostics has been at the forefront of molecular medicine, with the promise of detecting contagious pathogens in a safer and more sensitive way to aid in controlling their spread. Infectious disease testing is expected to continue to dominate the molecular diagnostic market for large animals in the foreseeable future. The use of amplified and nonamplified tests to assay the molecular makeup of the host rather than the pathogen is growing. Whereas cancer diagnostics is in its infancy for large animal testing, parentage and forensic testing together with single-nucleotide polymorphism (SNP) detection using in situ hybridization (ISH), fluorescent in situ hybridization (FISH), and sequencing technologies is gaining importance in assessing the presence and prognosis of genetic diseases.

The ability of molecular diagnostic assays to sensitively and specifically detect the primary cause of a disease, with short turnaround time, is giving significant advantages to disease diagnostics. Molecular tests are able to detect a specific unknown. Such tests are binary by nature; they provide a yes-or-no answer. However, certain tests when used quantitatively provide more insight into the medical manifestation induced by *Clostridium perfringens* toxins, for example. The clinically valuable information rests in determining the presence or absence of a specific pathogen in a biological sample derived from an animal. Because detection of viral, bacterial, rickettsial, fungal, or parasitic nuclear material in a biological sample gives clinically important information, molecular tests have direct clinical utility. However, the clinical context is always important to consider when making an interpretation on a molecular test. Determining the presence of a gene sequence per se without the clinical context does not necessarily correlate with a given clinical action, since diseases are generally multifactorial. In contrast, establishing the presence of the neuropathogenic form of equine herpesvirus (EHV)-1 in an equine patient's blood sample has direct association with EHV-1 infection, whether this translates into a symptomatic stage or not. The binary nature of molecular tests, which establishes the presence or absence of genetic material in a sample with a high degree of accuracy, has an accepted clinical value for infectious disease diagnostics because of its correlation with clinical signs.

Rapid results have tremendous clinical value in curtailing infection. Molecular methods can provide results in hours compared with days for culture-based or alternative technologies. The high sensitivity and specificity of molecular testing is particularly valuable in early determination of infection and makes it advantageous compared with antibody and antigen testing without amplification techniques. In most cases pathogens enter the host and replicate exponentially; early detection provided by the higher sensitivity allows for earlier clinical intervention and a better prognostic outlook. Molecular tests have been shown to produce fewer false-positive and false-negative results compared with other test platforms. Therefore, molecular tests are becoming the gold standard in the laboratory in terms of sensitivity and specificity. Key features for the adoption of molecular diagnostics for infectious agents are as follows:

- Superior sensitivity and specificity compared with most immunoassays
- Automated platforms that significantly increase throughput
- Quantitative assessment of viral load, which is clinically useful
- Fast turnaround time that speeds detection and reduces overall costs
- Simultaneous analysis of multiple analytes
- Standardized environment with the potential for full comparability across lab systems
- Ability to tightly quality control and monitor all aspects of the test workflow, including sample quality, DNA and RNA quantity, contamination situation during extraction and in the lab in general, presence of inhibition, and performance of the PCR test and reagents.

Technological Superiority of Molecular Tests

The relative technological superiority of molecular methods makes them likely to partially replace other types of more conventional methods such as culture-based tests or certain direct antigen and antibody tests to determine the presence of an infectious pathogen in a sick animal. Whereas antibody testing is more of a broad

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screening tool, molecular diagnostics allow accurate detection of the genome of a pathogen in a clinically sick animal. Culture-based tests have a turnaround time of days and are labor intensive. In addition, certain infectious agents are difficult to culture or biohazardous for laboratory personnel (e.g., *Mycobacteria* species, fungi, *Mycoplasma* species, *Lawsonia intracellularis*). In such instances, molecular detection of selected pathogens has already supplanted conventional culture.

Rapid and High-Throughput Applications Promote Molecular Tests

Rapid and specific detection of infectious disease agents is crucial for the prevention or containment of outbreaks. In the case of avian flu, the rapid detection of H5N1 strains of that virus is critical for containment. The avian flu pandemic concerns necessitate rapid and high-throughput molecular tests to maintain the well-being of animal and human community health. Similarly, West Nile virus (WNV) screening of mosquito pools and birds as well as screening for exotic Newcastle disease are additional examples of high-throughput applications with predominance for molecular tests.

Increasing Adoption of Molecular Tests by University and Commercial Laboratories

Since the advent of molecular platforms in the diagnostic laboratory, most molecular tests in veterinary medicine are performed by several commercial and public laboratories (Table 29-1). Unlike the market in human molecular diagnostics, which is dominated by four large players (Roche, Bayer, Gen-Probe, and Abbott), veterinary molecular diagnostics shows significant fragmentation in particular with many university diagnostic laboratories. However, the transition to the more advanced real-time PCR platform within the past 5 to 7 years and the abandonment of conventional PCR tests by many laboratories has led somewhat to a concentration process in the veterinary diagnostic landscape for a good reason: real-time PCR is the more advanced method and is considered a fully matured technological platform with great incentives for automation, operational efficiency, and affordability.

Simultaneous Testing of Multiple Pathogens

Parallel testing of multiple infectious agents in highly standardized platforms is a central advantage of molecular assays; it essentially allows several tests for both DNA and RNA pathogen targets to be performed simultaneously on a single sample, therefore condensing the medical message obtained on a given diagnostic sample. This development is a noteworthy driver for molecular diagnostics because it allows acquisition of more meaningful data from a single sample. This so-called panel strategy allows an efficient workup of complex clinical syndromes with general symptomatology that do not allow etiologic diagnosis based on clinical signs. These clinical cases are complex for the decision-making process for the veterinarian dealing with patients unable to communicate the pain matrix. In complex organ-related problems with general or unspecific symptomatology, multiple infectious agents can be responsible for a clinical picture or aggravate other primary events in the differential workup. Even though veterinarians tend to make a single-pathogen diagnosis, it has become more evident in recent years that many syndromes are caused by multiple infections present at a given time. Panel testing on a large scale will uncover unknown co-infections in animals, which can diffuse the clinical picture. It has long been speculated, for example, that seemingly clinically irrelevant EHV-2 infections in horses may be a predisposing factor for *Rhodococcus equi* pneumonia in foals. More characteristic examples include respiratory infections in companion animals, often initiated by subclinical viral or bacterial infections that lead the way to secondary infections. In addition, many vectorborne pathogens have a high tendency to persist in infected animals and therefore may facilitate viral infections or aggravate preexisting conditions such as feline immunodeficiency virus or feline leukemia virus infection. Sepsis caused by infectious agents is expected to become an important segment for equine molecular diagnostics, especially in neonatal medicine. Molecular diagnostics enable fast turnaround time with rapid initiation of treatment. In the future, panel testing for the most important sepsis-inducing agents could be complemented by the addition of assays targeting antimicrobial resistance genes. This would allow the modification of treatment regimens in case antimicrobial resistance is detected.

Indications for Use of Polymerase Chain Reaction Assays for Infectious Diseases

Diagnostic tests such as PCR assays offer the potential for fast and accurate determination of the presence of an infectious agent, which can lead to an improved clinical outcome because of the faster initiation of more etiologic-based treatment and the possibility for quantitative treatment monitoring. Even if molecular-based tests are more expensive than more traditional diagnostic assays, their overall impact will lead to reduction in treatment costs.

Key indications for use of a molecular test are the speed and accuracy of molecular assays. In comparison with traditional culture for bacteria, rickettsial organisms, fungi, and viruses, molecular testing offers direct detection of the target pathogen within a fraction of the time. Owing to its speed, PCR assays have the potential to replace traditional culture methods for infectious agents that are difficult to culture or not cultivable at all.

Compared with serology testing, molecular tests offer the advantage of detecting an infectious agent before an immune response occurs and a detectable antibody titer is developed. Immunoglobulin M (IgM) analysis in certain applications (such as WNV) can alleviate this problem; however, molecular testing methods are more reliable in picking up early virus replication and allow a faster epidemiologic assessment and earlier patient treatment.

In certain instances, for the discrimination of a clinically relevant EHV-4 infection from a latent infection, the detection of viral DNA is not informative. In such cases the quantitative assessment of viral loads is necessary.[3] Similarly, the choice of RNA or DNA affects the ability to distinguish disease (active virus replication and production of viral transcribed RNA) from nondisease (viral DNA of latently infected cells) status.

Molecular Biology Technologies

The main methodologies used for molecular diagnostics include the following:

- Nucleic acid capture, probe hybridization
- ISH, FISH
- Isothermal amplification of nucleic acids[4]
- Transcription-based amplification methods
- Signal amplification by branched-chain DNA
- Qualitative pathogen identification using nucleic acid amplification
- Quantitative assays
- Genotyping assays
- Genotype sequencing assays
- Multianalyte testing panels

Genotyping assays are usually used to test for known mutations associated with inherited genetic conditions such as hyperkalemic periodic paralysis (HYPP) in horses, an autosomal dominant condition that causes potassium-induced attacks of skeletal muscle paralysis. Many of these assays depend on sequence-specific probes designed to hybridize with known genetic variations. For infectious agents, genotyping or speciation is achieved by using highly specific PCR- or hybridization-based assays or by restriction enzyme fragment length polymorphism (RFLP) assays. In these assays, amplified material is digested with a certain restriction enzyme that characterizes the difference between two target sequences.

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TABLE 29-1

Examples of Molecular Diagnostic Laboratories in the United States*

Laboratory	Website URL	PCR Platform		Panels
		Conventional	Real-Time	
Arizona Veterinary Diagnostic Laboratory	http://microvet.arizona.edu	X	X	
Arkansas Livestock and Poultry Commission Laboratory	http://alpc.arkansas.gov/lab	X		
Auburn University VMTH	http://www.vetmed.auburn.edu		X	
Biogenetics	http://www.biogeneticservices.com/	X	X	
California Animal Health and Food Safety Laboratory	http://cahfs.ucdavis.edu	X	X	
Clemson University, Veterinary Diagnostic Lab	www.comptroller.clemson.edu	X		
Clongen	www.clongen.com	X		
Colorado State University	http://csu-cvmbs.colostate.edu/vdl/molecular-diagnostics	X		
Colorado State University Veterinary Diagnostic Laboratory	www.dlab.colostate.edu/security2	X	X	Yes
Connecticut Veterinary Medical Diagnostic Laboratory	http://cvmdl.uconn.edu/	X		
Cornell, Animal Health Diagnostic Lab	http://diaglab.vet.cornell.edu	X		
Diagnostic Vet Labs	http://dvl.datacorner.com	X		
Florida Department of Agriculture and Consumer Services	http://www.freshfromflorida.com/Divisions-Offices/Animal-Industry/Consumer-Services/Consumer-Protection/Diagnostic-Laboratory-Testing-Services	X	X	
Georgia University, Veterinary Diagnostic Laboratories	www.vet.uga.edu/dlab	X		Yes
Health Gene, Toronto, Canada	www.healthgene.com/vet	X		
Illinois Department of Agriculture, Veterinary Diagnostic Lab	www.agr.state.il.us/AnimalHW/labs	X		
Illinois VMTH Diagnostic Lab	www.cvm.uiuc.edu/vdl	X	X	
Indiana Animal Disease Diagnostic Laboratory	www.addl.purdue.edu	X		
Iowa State University	http://vetmed.iastate.edu/diagnostic-lab	X	X	
Kansas DMP Diagnostic Lab	www.vet.ksu.edu	X		
Kentucky Livestock Disease Diagnostic Center	http://ces.ca.uky.edu/lddc	X		
Louisiana State University Vet Medical Diagnostic Lab	http://laddl.lsu.edu	X		
Real-time PCR Research and Diagnostics Core Facility/UC Davis	www.vetmed.ucdavis.edu/vme/taqmanservice		X	Yes
Diagnostic Center for Population and Animal Health/Michigan State University)	http://www.animalhealth.msu.edu/	X		
Minnesota University, Veterinary Diagnostic Lab	www.vdl.umn.edu/vdl/ourservices/guidelinefiles/moleculardiagnostics/home.html	X		
Missouri (Veterinary Medical Diagnostic Laboratory)	www.cvm.missouri.edu/vmdl	X		
Montana Veterinary Diagnostic Laboratory	http://liv.mt.gov/lab	X		
Nebraska University, Vet Diagnostic	http://nvdls.unl.edu	X		
North Carolina Department of Agriculture and Consumer Services	http://www.ncagr.gov/vet/ncvdl/	X	X	Yes
Ohio State, Animal Disease Diagnostic Laboratory	www.ohioagriculture.gov	X		
Oklahoma Animal Disease Diagnostic Laboratory	www.cvm.okstate.edu/OADDL	X		
Oregon State University, Veterinary Diagnostic Lab	http://oregonstate.edu/vetmed	X	X	
South Dakota Animal Disease Research and Diagnostic Laboratory	http://www.sdstate.edu/vs/adrdl	X		
Texas A&M Veterinary Medical Diagnostic Laboratory	http://tvmdl.tamu.edu	X		
Texas A&M Gastrointestinal Laboratory	http://vetmed.tamu.edu/gilab	X		
Vita-Tech	www.vita-tech.com/dnabasedtests.cfm	X		
Veterinary Molecular Diagnostics, Inc.	www.vmdlabs.com	X		
Washington Animal Disease Diagnostic Laboratory	www.vetmed.wsu.edu	X	X	
Wisconsin Vet Diagnostic Laboratory (emphasis in Avian)	www.wvdl.wisc.edu	X		
Wyoming State Vet Lab	http://wyovet.uwyo.edu	X		
Zoologix	www.zoologix.com/dogcat/Menu.htm	X	X	

Statistics

Percentage of labs that use conventional and real-time PCR	31%
Percentage of labs that use conventional PCR only	64%
Percentage of labs that use real-time PCR only	5%

*American Association of Veterinary Laboratory Diagnosticians (AAVLD)-accredited laboratories are listed if they offer commercial molecular diagnostic services available to veterinarians.

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The Polymerase Chain Reaction in Veterinary Molecular Diagnostics

Because of its predominance in research and diagnostic applications, PCR assays will be discussed in more detail in later chapters. To give practitioners guidance about what to look for when PCR-based molecular diagnostic assays are offered, we will discuss some aspects such as design guidelines, differences between traditional and real-time PCR assays, sampling, controls, and interpretation of results in greater depth.

PCR testing in its pure form is a three-cycle event: denaturation of double-stranded target (or in later cycles PCR products), annealing of target and primers, and extension of the DNA strand from the primer.

Comparing Real-Time Polymerase Chain Reaction with Traditional Polymerase Chain Reaction Testing for Diagnostic Applications

Real-time PCR testing was introduced into the marketplace in 1996 and replaced the tedious gel electrophoresis step to detect PCR products after amplification. In one survey, 98% of equine veterinarians knew about PCR testing and 79% of equine veterinarians at universities knew the difference between conventional and real-time PCR testing.[5] During gel electrophoresis, the PCR products are separated by size and visualized using a dye (ethidium bromide) that intercalates with the double-stranded DNA. Real-time PCR detects the PCR products by using an internal probe that is labeled with two fluorescent dyes: a reporter dye and a quencher dye. The fluorescent activity of the reporter dye is absorbed (quenched) by the quencher dye. The probe binds to the PCR products between the two PCR primers. If the primers are extended by the DNA polymerase, the 5′ nuclease activity of the DNA polymerase digests the internal probe (hence hydrolysis probe) and releases the quenched fluorescence. Alternatively, hybridization probes can be used that are not digested during amplification and that allow melting curve analysis. This single change in the protocol regarding how to detect the PCR products revolutionized the use of PCR testing for both research and diagnostic applications. Most of the advantages resulting from this principle originate from the fact that the PCR tube does not have to be opened after a PCR assay for analysis. This principle is called *closed-tube detection.* The advantages are as follows:

1. Because of the closed-tube detection format, PCR products cannot escape from the PCR reaction containers. If escape occurs, it leads to the contamination of the PCR laboratory and subsequently the next PCR reactions. The consequence is false-positive PCR results. Real-time PCR efficiently eliminates this risk of PCR product carryover. There is also a second safety system called AmpErase UNG (Invitrogen, Grand Island, NY),[6] which eliminates contaminating PCR products.
2. Real-time PCR is a kinetic PCR principle, underlining the fact that PCR product accumulation is measured during every single PCR cycle in real time. Because of this fact, real-time PCR is a quantitative method.
3. The real-time PCR platform introduced in 1996 consisted of a laser-based thermocycler, software to design real-time PCR assays, reagents, disposables, and protocols. Because of its integrated design, PCR assays generated with the new system were highly standardized.
4. Data analysis is run on an attached computer that collects fluorescent data points. This principle eliminates all laboratory steps after the real-time PCR cycling is finished. Because of the computer-formatted end analysis, results can be fed directly into the information and management systems of diagnostic laboratories. Real-time PCR has also enabled rapid cycling to finish the PCR process in less than 1 hour. Real-time PCR results therefore can be turned around significantly faster than with traditional PCR testing (normally within a 24-hour period).
5. Because of the probe used to detect the PCR products, real-time PCR is also a more specific assay than single-round traditional PCR. Only specific PCR products are detected by the probe. Real-time PCR testing, essentially a liquid-based hybridization method, is considered as specific as Southern blotting, which is a solid-based hybridization method.
6. Because real-time PCR incorporates hot-start enzymes, the specificity is even greater than with regular non–hot-start DNA polymerases. Hot-start enzymes are inactive at ambient temperatures and have to be heated to 95° C for 20 seconds to 10 minutes in order for the DNA polymerase activity to begin. Because of the hot-start nature, nonspecific binding of primers does not lead to unspecific PCR products and results in an overall increased specificity of the assay.
7. In combination, real-time PCR is described to be as sensitive as or more sensitive than double-round (nested) traditional PCR. Analytic sensitivity and limit of detection using real-time PCR testing is normally in the single molecule range, whereas the limit of quantitation with traditional PCR testing is in the range of 10 to 20 molecules.

Preanalytic Variables

In general, molecular diagnostic laboratories provide strict recommendations for sample collection, including shipping instructions. These instructions include specimen type, volume, anticoagulant, and specimen transport, storage, and handling. The sample type is largely influenced by the pathogenesis of the disease and plays a key role in the performance and interpretation of the test results. Veterinarians are advised to adhere to these recommendations, because the quality of the result is directly correlated to the quality of the sample and preservation of the nucleic acid content. Molecular assays often offer the convenience of using a small specimen acquired with a minimally invasive procedure. The diagnosis of herpesviruses is a classic example in which culture and neutralization assays have been largely replaced by PCR testing on a small volume of aspirate or swabs from mucosal surfaces. Molecular tests can detect the presence of small numbers of organisms, and the probability of detection increases when a larger volume of specimen is added to the amplification reaction. Because molecular assays do not need viable organisms for testing, more flexibility in specimen transport is possible than with culture methods.

Appropriate specimen collection and transport conditions are important to ensure successful extraction of intact nucleic acid and to prevent cross-contamination. Specimen transport and storage conditions are likely to vary among specimen types and between RNA and DNA tests. RNA is more susceptible to degradation but in general, molecular diagnostic samples should be cooled in order to slow the nucleic acid degradation within the sample. Because of the difficulty of maintaining a freeze chain, molecular diagnostic samples should only be cooled throughout the collection, storage, and transportation process in order to minimize sample deterioration. Detailed storage and shipping instructions are crucial for a successful molecular diagnostic workup. Practitioners should be aware of these recommendations and consider using appropriate cooling containers when samples are collected in the field. Such samples maintain stability if stored appropriately in a cooled environment. Freezing and in particular the thawing process often adversely affects the quality and should be avoided if not otherwise instructed by the laboratory.

Sampling errors are among the many preanalytic variables that can affect the outcome of the results. It is therefore recommended to have the appropriate labeling material available for blood containers or other sample types. Blood or body liquid contamination on the outside of the containers is an obvious cause of sample cross-contamination before the samples are manipulated in the laboratory. Proper collection procedures are essential to prevent these kinds of artifacts.

Nucleic Acid Extraction

Many commercially available manual and automated methods have been successfully applied to infectious disease testing using a variety

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of clinical materials. Especially in veterinary molecular diagnostics, the variety of sample types can be challenging for processing through a single platform but can be achieved by validating sample type specific pretreatment procedures in order to create a lysate of similar viscosity and nucleic acid concentration, which maximizes the extraction efficiency. Automated or semiautomated platforms are rapid and usually require only a small volume of specimen. In general, these systems are total nucleic acid extraction systems and support the parallel analysis of DNA and RNA pathogens from the same sample in a panel configuration. In addition, commercially available automated systems can reduce hands-on labor requirements and speed up the process significantly, leading to even shorter turnaround times. Most systems can accommodate sample volumes ranging from 100 to 500 µL and even 1 mL of specimen lysate. Nucleic acid binding capacity varies and can be as high as 200 µg per individual extraction position, which allows the maintenance of a good limit of detection even when many infectious agent targets are analyzed in parallel for a given panel.

Interpretation of Results

Interpretation of results obtained with molecular assays for infectious diseases requires understanding of the pathogenesis and biology of the target organisms. Some challenges are unique to molecular tests and are different from considerations in interpreting other microbiologic tests. Such differences are related to the distinction of viable from nonviable organisms and the correlation of nucleic acid detection with presence of disease or disease association.

Interpretation of a negative result includes information about the sensitivity and nucleic acid extraction efficiency. A false-negative result may be caused by a degraded or unstable sample. Insufficient volume or inappropriate sample type, inadequate sampling procedures, and transport problems are additional sources for potentially false-negative results. Sample-specific internal positive controls targeting endogenous genes such as the universal 18S rRNA (ssrRNA) or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene help to identify these problems. These so-called internal positive controls allow the quantification of the sample specific nucleic acid (both DNA and RNA) and allow validation of a diagnostic sample for its use in PCR; samples below a certain quantity of DNA are at risk of being called false negative; therefore, repeat collection can be recommended. In addition, inhibition phenomena originating from difficult sample matrixes such as feces, urine, or environmental samples contaminated with trace amounts of soil (humic acid) have to be controlled with internal positive controls to assess the inhibitory effects.

The factors requiring consideration for the interpretation of positive results include assay specificity and contamination issues. PCR testing or any other target amplification method is subject to these considerations. Real-time PCR testing using closed-tube detection procedures reduces the risk of PCR product carryover as a source of false-positive results and the availability of systems, which mark the PCR products when produced with certain types of nucleotides (uracil instead of thymidine), allows the specific degradation of contaminating PCR products before the next PCR amplification is taking place (AmpErase UNG system). Combined with air movement control in the molecular diagnostics lab (overpressurized clean lab and negative-pressurized sample preparation lab) and limited access to trained laboratory technicians, great safety can be achieved, leading to valid results.

In general, molecular assays do not provide information about the viability of an infectious agent. Exceptions to this are DNA viruses, bacteria, and parasites analyzed for transcribed genes instead of their genomic DNA. This approach allows the assessment of the replication competence of a target and therefore is highly correlated with viability. Examples are toxin quantification, differentiation of vaccination versus infection, and herpesvirus quantification in order to differentiate between lytic (acute) and chronic (latent) infection, which has immediate implications to the ability of the virus to cause or contribute to clinical signs. In addition, spliced RNA occurs only if viral genes are actively transcribed and provides a means for obtaining information about the replication activity of a virus and the stage of infection. In other cases, targeting the ribosomal RNA of parasites such as *Toxoplasma* and *Cryptosporidium* is a means for obtaining viability information and also may increase the analytic sensitivity.[7]

Detection of the nucleic acid of a pathogen does not necessarily ensure that the organism is the cause of the disease. A primary example is herpesvirus infections (EHV-1 and EHV-4), in which the detection of DNA may indicate the presence of lytic, non-replicating, or latent virus. Studies indicated that high viral loads of EHV-4 DNA allow the formulation of a cutoff value to differentiate between lytic and latent infection.[8] In this particular case, high viral loads were associated with the presence of clinical signs and the presence of viral RNA transcripts. Therefore, quantitative real-time PCR testing can provide a means to obtain much improved disease association and invalidates the notion that PCR "just detects dead DNA."

Reporting of Molecular Results

Reporting results for qualitative assays in infectious disease monitoring is simple: a sample either does or does not contain the nucleic acid of a target organism. Further relevant information includes the nucleic acid extraction efficiency, nucleic acid stability, and sample integrity determined with the various quality controls.

Reporting results for quantitative molecular infections is more complex. For veterinary medicine, some quantitative applications have been established and are progressively phased into diagnostic routine analysis. Such quantitative PCR tests combined with fully standardized protocols will continue to expand within the veterinary diagnostic market as our understanding of the biology and pathology of infectious agents grows.

Regulatory Considerations of Molecular Laboratories

Veterinary molecular diagnostics is an emerging market with a growing level of regulation. Standards such as those defined by the American Association of Veterinary Laboratory Diagnosticians (AAVLD; http://www.aavld.org), Molecular Diagnostic Methods for Infectious Diseases (NCCLS; www.nccls.org), or MIQE (minimum standard guidelines for fluorescence-based quantitative real-time PCR experiments) are adopted by commercial laboratories aiming to provide a comprehensive diagnostic service. Other sources for guidelines are U.S. Food and Drug Administration (FDA) guidelines (www.fda.gov) for the detection of nucleic acids; ASTM guidelines (*Standard Guide for Detection of Nucleic Acid Sequences by the Polymerase Chain Reaction Technique;* www.astm.org); and the Association for Molecular Pathology (AMP) (*Recommendations for In-House Development and Operation of Molecular Diagnostic Tests;* www.ampweb.org).

Guidelines for Clinicians to Select Molecular Diagnostic Laboratories

Veterinarians can use a variety of guidelines to select laboratories for molecular diagnostics. However, there are some major factors worth considering before samples are submitted. First, it is worthwhile to obtain information about the nature of the PCR test (traditional vs. real-time). Second, questions addressing the quality control and quality assurance system within a particular laboratory should be asked. Third, turnaround time, pricing, and the level of guidance with result interpretation and availability of consulting resources are additional factors worth investigating before samples are submitted.

Summary

As with any methodologies, quantitative PCR is a work in continuous progress and development and improvement. Although all of the methods described in this review use the Nobel Prize–awarded PCR process, the advantages and disadvantages of subtle differences in

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assay format, accuracy, and reliability of quantitation have to be rigorously compared. The next generation of quantitative real-time PCR processes will be increasingly automated, standardized, and miniaturized. The time for nucleic acid preparation and PCR amplification will be further reduced by using small microtiter-formatted microfluidic cards or silicon-based chip technology.[9-11] Amplification time has been brought down to several minutes by using an advanced nucleic acid analyzer (ANAA) consisting of a battery-powered array of silicon-based PCR microchips with thin-filmed resistive heaters, thus enabling ultrafast amplification, further pushing the technological possibilities in order to improve the diagnostic results output.[10]

How will these new systems be incorporated in routine veterinary diagnostics? Veterinary medicine will experience a broad adoption of many quantitative assays for infectious agents and genetic abnormalities in the near future. The ability to standardize assays will allow high-throughput applications that have not been possible with traditional molecular methods. For this reason, applications for veterinary medicine may experience not only quantitative but also qualitative growth. These assays will help improve patient management and client satisfaction.

Molecular Testing for Infectious Diseases in Horses

Nicola Pusterla • Christian M. Leutenegger

The ready availability of a correct etiologic diagnosis, particularly in contagious infections, enables the veterinarian to make early decisions regarding the patient's care and management, address appropriate treatment, and allow timely notification and discussion of management issues pertaining to the prevention of disease spread. The past two decades have seen a revolution in the understanding, management, diagnosis, control, and prevention of infectious diseases.[1,2] This period has encompassed the discovery of emerging equine agents, antimicrobials and vaccines, as well as a wealth of improved diagnostic tests for equine practitioners. Despite these advances, infectious diseases remain a leading cause of equine morbidity and mortality, with resurgence of certain infections (e.g., West Nile virus), an increasing population of elderly, more susceptible horses, and an increasing international equine commerce, expanding the geographic distribution of pathogens.[3,4] The focus of rapid diagnosis of infectious diseases has also shifted during this time. The most obvious change has been the appearance and increasing importance of nucleic acid (NA) amplification-based techniques, primarily the polymerase chain reaction (PCR), at the expense of traditional methods of clinical microbiology.[5] The PCR has become an increasingly important tool in microbial diagnosis in recent years, mainly because of its rapidity, high sensitivity, and high specificity. These superior characteristics have propelled the field of PCR-based molecular diagnostics into the arena of applied diagnostics for infectious agents. Because the number of published and offered PCR assays is steadily rising, there is a need for critical evaluation, comparison of performance, and eventually standardization of methods to enable equine practitioners to select the optimal methodology.

Sample Submission

Nucleic acid (NA) techniques to detect the presence of infectious agents in biological specimens require stringent quality guidelines. These guidelines aim to ensure the stability of NAs (both genomic DNA and total RNA), which are the target for molecular-based diagnostic methods. Whole blood samples are collected aseptically into evacuated blood tubes containing EDTA; body fluids (e.g., thoracic, abdominal, joint, cerebrospinal, tracheal wash, bronchoalveolar, and guttural pouch lavage fluid) and tissues should be collected into serum tubes without additives; nasal or nasopharyngeal secretions should be collected with rayon- or Dacron-tipped swabs and are best kept in a sterile serum or conical tube (virus transport medium is recommended for the detection of viruses); fecal material should be collected into small fecal cups or serum tubes (Table 29-2; Fig. 29-1). All samples must be sent cooled on blue ice by express mail overnight to the laboratory. Freezing of samples should be avoided. Short-term storage for a period of 2 to 3 days before shipment (over a weekend) should be done in a refrigerated compartment. Each sample should be properly labeled and accompanied by a submission form containing information pertaining to the patient, owner, veterinarian, sample, and pathogen (s) to be tested (most submission forms can be downloaded from the respective laboratory website). The laboratory should be notified in advance and inquiry should be made about the availability of the offered tests as well as turnaround time and associated costs. Incoming samples normally are processed the same day and PCR results usually are available within 24 to 48 hours if the NA passes quality control.

TABLE 29-2

Tissue Samples Commonly Used for the Molecular Detection of Common Equine Pathogens

Pathogen	Tissue Submission
Anaplasma phagocytophilum	Whole blood
Babesia caballi	Whole blood
Clostridium difficile (antigen and toxin A and B)	Feces
Corynebacterium pseudotuberculosis	Aspirate from abscess, body fluid
Cryptosporidium spp.	Feces
Equine arteritis virus	NPS, uterine swab, placenta, aborted fetus
Equine coronavirus	Feces
Equine herpesvirus 1	NPS, whole blood, TW, BAL, CSF, CNS, uterine swab, placenta, aborted fetus
Equine herpesvirus 2	NPS, whole blood, TW, BAL
Equine herpesvirus 4	NPS, TW, BAL
Equine herpesvirus 5	NPS, whole blood, TW, BAL
Equine influenza virus	NPS, TW, BAL
Equine rhinitis A virus	NPS, urine
Equine rhinitis B virus	NPS
Equine rotavirus	Feces
Lawsonia intracellularis	Feces, intestinal biopsy
Leptospira spp.	Urine, blood, uterine swab, placenta, aborted fetus
Neorickettsia risticii	Whole blood, feces
Neospora hughesi	CSF, CNS
Rhodococcus equi	TW, BAL, feces
Sarcocystis neurona	CSF, CNS
Streptococcus equi subsp. *equi*	NPS, NPL, GPL, lymph node aspirate
Salmonella spp.	Feces
Theileria equi	Whole blood
West Nile virus	Whole blood, CSF, CNS

BAL, Bronchoalveolar lavage fluid; *CNS,* cerebrospinal tissue; *CSF,* cerebrospinal fluid; *GPL,* guttural pouch lavage; *NPL,* nasopharyngeal lavage; *NPS,* nasal/nasopharyngeal swab; *TW,* tracheal wash fluid.

Clinical Applications

An array of NA amplification techniques may be offered by laboratories in order to establish an etiologic diagnosis of equine infectious diseases. Several published studies have shown the benefit of NA amplification techniques in comparison to conventional microbiological techniques. Current efforts are aimed at improvement of the diagnostic efficiency of molecular techniques, both for common and less common infections. To facilitate a decision on which pathogens should be evaluated for a specific case, some laboratories offer panels covering specific organ systems (e.g., respiratory, gastrointestinal, neurology, bloodborne). Such panels test several common pathogens for each organ system. Some of the diagnostic PCR applications most

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relevant for equine practice are presented as follows, along with their advantages and potential pitfalls.

Respiratory Pathogens

Respiratory pathogens are often contagious, and infections must be diagnosed rapidly in order to prevent a disease outbreak and institute the appropriate management plan. The short turnaround time and reliability of PCR makes this molecular technology an ideal tool for the diagnosis of respiratory pathogens.

Equine influenza is commonly diagnosed by virus isolation or detection from nasopharyngeal swabs collected from horses during the early febrile stage of the disease. Virus can be grown from nasopharyngeal swabs by inoculation and incubation of embryonated chicken eggs or passage through Madin-Darby canine kidney cells. Although isolation of the virus is essential to allow antigenic and genetic characterization of the strain, this technology is time consuming and successful isolation is, at best, to be expected in 50% of the cases. Further, since mutations have been reported to occur during the process of viral culture, recovered isolates must be viewed critically. In recent years new methods for virus detection, such as antigen-detection enzyme-linked immunosorbent assays (ELISAs) and PCR, have been described. Collectively these detection methods have shown higher sensitivity than virus isolation and antigen-capture ELISAs (Table 29-3).[6-9] Amplification of the single-stranded RNA of equine influenza viruses is performed by reverse transcription-PCR (RT-PCR) technology, using either a one-step, nested, or real-time approach. The hemagglutinin, nucleoprotein, and matrix gene are the commonly targeted genes for these molecular assays. Unfortunately, comparison of the different PCR assays is precluded by the use of different technologies, the lack of standardization among the assays, and variation in targeted genes. Nucleotide and deduced amino acid sequences of portions of the hemagglutinin gene are now routinely used for phylogenetic characterization of outbreak strains. Further, novel real-time assays can be used as a viable replacement for the more traditional methods of quantifying equine influenza virus in vaccine efficacy studies. Another advantage of assays such as antigen-detection ELISAs and PCR is their ability to detect nonviable virus, a situation that may occur when nasopharyngeal samples are frozen or not adequately stored and/or shipped to a diagnostic laboratory, allowing a rapid diagnosis in the acute phase of infection. The commercially available Directigen Flu A (Becton, Dickinson and Company, Franklin Lakes, NJ) detects nucleoprotein, one of the type-specific antigens of type A influenza viruses, and was designed for use in cases of human influenza infection. Although this assay has the shortest turnaround time of all antigen tests (i.e., 15 minutes), its sensitivity decreases when low titers of virus are present, for example, in a partially immune horse with subclinical signs or in a clinical case past the acute onset of disease. In recent years, PCR-based assays have been described for the identification of equine influenza.

Equine herpesvirus (EHV)-1 and EHV-4 are important, ubiquitous equine viral pathogens that cause important economic losses in the equine industry. Both are double-stranded DNA alphaherpesviruses that affect the equine respiratory tract and can establish lifelong latent infection after primary exposure. Traditionally, virus isolation has been the gold standard for diagnosing EHV-1 and EHV-4 infections. The sample of choice is a nasal or nasopharyngeal swab, which should be taken early in the febrile phase of the disease. The swabs should be kept in viral transport medium and shipped on ice to a veterinary diagnostic laboratory. Because of the lymphotropism of EHV-1, virus isolation can also be attempted from citrated or heparinized whole blood. Virus isolation requires the maintenance of specific cell culture lines, making this process relatively expensive and time consuming. EHV-1 can be propagated in a broad range of cell lines; however, EHV-4 only grows in cell lines of equine origin. Virus isolation is often hampered by the fragility of the virus, intermittent viral shedding, and the interference with local antibodies. PCR offers an alternative to virus isolation and has proven to be a sensitive method of detecting EHV-1 and EHV-4 in respiratory secretions, peripheral blood lymphocytes, and other tissues.[10-12] Many conventional PCR assays have been established to study the pathophysiology and improve the diagnosis of these viruses. Conventional one-step or nested PCR assays do have inherent risks of carry-over contamination as a result of post-amplification steps required to detect the PCR products. Novel molecular platforms such as the real-time PCR have strongly reduced the risk of contamination. PCR assays used in routine diagnostics are based on the detection of viral genomic DNA and are therefore unable to distinguish between lytic, dead, or latent virus. Alternative molecular approaches have recently been established using the real-time PCR to allow discrimination among the different viral states in horses naturally infected with EHV.[13,14] Discrimination among the different viral states is now possible by (1) targeting several genes (e.g., glycoprotein, latency-associated transcripts), (2) detecting viral genomic DNA and transcriptional activity of the target genes at the messenger RNA (mRNA) level, and (3) using absolute quantification (Table 29-4). Viral threshold loads are used in selected human infectious diseases (i.e., HIV, HCV) to determine disease stage and response to antiviral therapy. A similar

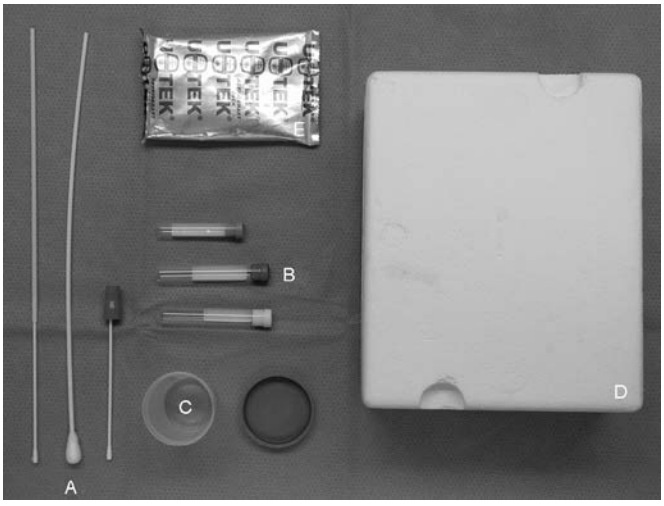


FIG. 29-1 Collection and shipping material routinely used to submit equine tissue samples for molecular detection. **A,** Three sterile swabs of different lengths. **B,** Three sterile, evacuated tubes with and without additives. **C,** A sterile cup with lid. **D,** A Styrofoam shipping container. **E,** A cooling element to keep the samples cooled.

TABLE 29-3

Comparison of Different Viral Detection Methods Using Nasopharyngeal Secretions from Naturally and Experimentally Infected Horses with Equine Influenza Virus

Infection Type	Number of Horses	Collection Type	Detection Method (Mean Detection Days)			Reference
			VI	DFA	RT-PCR	
Experimental	4	Sequential postexposure	4/4 (5.5)	2/4 (3.5)	4/4 (6.0)	6
Natural	11	Single at peak of disease	5/11	7/11	9/11	7
Natural	171	Single at peak of disease	8/171	14/171	35/171	8

DFA, Directigen Flu A; *RT-PCR,* reverse-transcription polymerase chain reaction; *VI,* virus isolation.

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TABLE 29-4

Differentiation Between the Different Viral States of EHV-1 and EHV-4 by Targeting Several Genes and Detecting Either Viral Genomic DNA or Transcriptional Activity of the Target Genes at the Messenger RNA Level

Target Gene and Nucleic Acid Type	Viral State		
	Non-Replicating Virus	Lytic or Replicating Virus	Latent Virus
Glycoprotein B gene using gDNA	Yes	Yes	Yes
Glycoprotein B gene using mRNA	No	Yes	No
Latency-associated transcripts using mRNA	No	No	Yes

gDNA, Genomic DNA; *mRNA,* messenger RNA.

TABLE 29-5

Comparison of Culture and PCR for the Detection of *Streptococcus equi* in Equine Nasopharyngeal Secretions (Swab and Wash), Guttural Pouch Lavage Fluid, and Abscesses Following Natural Outbreaks

Number of Specimens	Sample Type	Detection Method		Reference
		Culture	PCR	
117	Nasal swabs and washes	15/117	37/117	Timoney and Artiushin[15]
61	Nasopharyngeal swabs	18/61	34/61	Newton et al[16]
70	Guttural pouch washes	41/70	53/70	
28	Nasal swabs	4/28	13/28	Gronbaek et al[17]
15	Abscesses	5/15	12/15	

PCR, Polymerase chain reaction.

concept is used diagnostically for EHV-1– or EHV-4–infected horses in order to discriminate between lytic and non-replicating virus, to determine their infectious risk based on viral load in nasal secretions, and to monitor their response to treatment.[13,14]

Streptococcus equi subsp. *equi (S. equi)* infection is rarely associated with detection difficulties when using conventional cultures in clinically affected horses. Culture of nasal swabs, nasal or guttural pouch washes, or exudates aspirated from an abscess remains the gold standard for the detection of *S. equi*. Culture, however, may be unsuccessful during the incubation, and early clinical phases of infection and the presence of other β-hemolytic streptococci, especially *S. equi* subsp. *zooepidemicus,* may complicate interpretation of cultures. Available PCR assays are designed to detect the DNA sequence of the *S. equi* M protein (SeM) gene, the gene for the antiphagocytic M protein of *S. equi*. This gene offers enough nucleotide variations between the two *S. equi* subspecies to allow full discrimination in clinical specimens. The test can be completed in a few hours and results may be available on the same day that samples are taken. One of the pitfalls of PCR has been its inability to distinguish between non-viable or live organisms; therefore, positive results have in the past been considered presumptive until confirmed by culture. Nowadays, the viability issue can be addressed by quantitation of the SeM gene or detection of transcriptional activity of the SeM gene at the RNA level. In several studies, PCR proved to be up to three times more sensitive than culture (Table 29-5).[15-17] PCR accompanying culture on a nasal swab or guttural pouch lavage may be used in a control program to select possible carrier animals, because PCR is capable of detecting *S. equi* DNA in guttural pouch lavages for weeks after disappearance of live organisms. Such is not the case for the nasopharynx, in which the efficient mucociliary apparatus removes organisms and DNA at the same time. PCR should be considered to detect asymptomatic carriers, establish the *S. equi* infection status of asymptomatic horses, and determine the success of elimination of *S. equi* from the guttural pouch. A particular problem in the management of strangles outbreaks is the lack of a suitable assay to differentiate between wild-type and vaccine *S. equi* strains. Recent studies have shown gene variations in the N-terminal region of the SeM gene of various field isolates, allowing epidemiologic analysis of disease transmission.[18] Further, a deletion in the *aroA* gene of a live attenuated strangles vaccine marketed in Europe (Equilis StrepE, Merck Animal Health, Walton Manor, Walton, Milton Keynes, UK) has allowed the development of a PCR assay able to differentiate between wild-type and vaccine strains.[18] Such assay has, however, not yet been developed to differentiate between the intranasally applied attenuated live vaccine marketed in North America (Pinnacle I.N., Zoetis, Overland Park, KS) and field isolates. However, when needed for forensic reasons, differentiation can be done via the morphology of colonies, biochemical analysis, genotyping, and restriction digest.[19] Together, these assays allow differentiating between wild-type and vaccine/ancestor strains.

Rhodococcus equi is an important cause of chronic suppurative bronchopneumonia with extensive abscessation in foals 3 weeks to 6 months of age. Culture of the organism from tracheal wash (TW) fluid currently is considered the gold standard for diagnosis.[20] However, it can be difficult to reliably grow *R. equi* from a single TW sample, possibly because of prior antimicrobial administration or overgrowth by multiple pathogenic bacterial species.[21,22] Hillidge[23] reported that only 62% of foals with positive *R. equi* cultures at necropsy and 64% of those with radiographic evidence of lung abscessation yielded *R. equi* on culture of TW fluid. PCR has been evaluated in order to increase the diagnostic sensitivity of TW fluid samples. Strains of *R. equi* isolated from sick foals uniformly contain an 85- to 90-kb plasmid that carries the gene responsible for expression of a 15- to 17-kDa antigen (vapA) of undetermined function.[24,25] Environmental strains of *R. equi* not associated with disease do not contain this plasmid. Therefore, detection of the vapA gene of *R. equi* in a TW fluid sample from a foal with pneumonia can be considered diagnostic. Both culture and PCR, however, may detect environmental contaminants of *R. equi* in TW fluid, but PCR has the ability to distinguish between virulent and avirulent strains. Foals, however, may have virulent or avirulent strains of *R. equi* present as contaminants in their airways that are not responsible for clinical signs of pneumonia. This situation may be more likely on farms in which *R. equi* problems are endemic. In a study evaluating the sensitivity of conventional culture, PCR and serology from 53 foals with pneumonia, PCR of TW fluid was found more sensitive and specific for the diagnosis of *R. equi* pneumonia than the other two available diagnostic tests.[26] PCR should be used in conjunction with standard culture because of the probability of the presence of multiple bacterial pathogens and the inability of PCR to determine antimicrobial sensitivity

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of *R. equi*. PCR with its higher sensitivity and specificity may be useful to rule out *R. equi* pneumonia in culture-negative foals that have failed to improve with standard antimicrobial therapy and have clinical signs consistent with *R. equi* pneumonia. It may also be useful in monitoring response to therapy and deciding when to discontinue therapy in foals that are confirmed to have *R. equi* pneumonia. In clinical situations in which the severity of the respiratory signs of the patient prevents the collection of TW fluid, feces have been shown to be a sensitive surrogate specimen for the molecular detection of *R. equi*.[27] The study determined that fecal PCR had a similar diagnostic accuracy as that of culture of TW fluid samples, and that false-negative fecal PCR results for *R. equi* were associated with prior use of antimicrobials.

Equine rhinitis A and B virus and equine arteritis virus, although less commonly associated with infectious upper respiratory disease (IURD), should also be considered as target pathogens during respiratory outbreaks.[28-30] The role of EHV-2 and EHV-5 in nasal secretions of horses with IURD is still unclear.[31] Because of their high prevalence in horse populations and in order to avoid dilemmas with the interpretation of PCR results, the testing of gamma herpesviruses is at this time not recommended. Infection with EHV-5 has been associated with equine multinodular pulmonary fibrosis, a novel pathogenic entity with characteristic gross and histopathologic pulmonary lesions.[32] In such cases, antemortem diagnosis can be supported by the PCR detection of EHV-5 in bronchoalveolar lavage or pulmonary biopsy tissue samples.[33]

Neurologic Pathogens

Although highly sensitive and specific PCR assays have been developed for detection of viral and protozoal genomes in the cerebrospinal fluid (CSF) of neurologic patients, these methods are often of limited value in the routine diagnosis of these diseases because viremia is often very short-lived or the pathogen has no affinity to the cells of the CSF. Consequently, pathogens are usually no longer detectable at the onset of systemic or central nervous system (CNS) signs.

Equine protozoal myeloencephalitis (EPM), caused by the protozoal apicomplexa parasites *Sarcocystis neurona* and *Neospora hughesi,* represents one of the greatest diagnostic challenges for equine practitioners. Detection of the parasite at necropsy is considered the gold standard. Therefore, clinical diagnosis is based on clinical findings, exclusion of other neurologic diseases, and the use of serologic assays (e.g., Western immunoblot, indirect immunofluorescent assay) on serum and CSF.[34-36] Molecular diagnostics have also been investigated but their sensitivity was found to be low.[37]

Apparently, intact merozoites rarely enter CSF and free parasite DNA is destroyed rapidly by enzymatic action.[38] Based on its low sensitivity, PCR testing of CSF should not be recommended for routine diagnosis of EPM. In contrast, PCR testing of neural tissue has been shown to be useful as a postmortem test.[39] Sequence analysis is routinely used to identify *S. neurona* and *N. hughesi* isolates and to determine the heterogeneity and evolutionary relatedness within these and related species.[40,41] Detection and isolation of *S. neurona* from peripheral blood has only been reported in experimental studies.[42,43] Therefore, molecular detection of *S. neurona* in blood is very insensitive and should not be used in order to document or rule out EPM in a neurologic horse.

Diagnosis of West Nile virus (WNV) encephalitis in horses currently is based on observation of compatible clinical signs (e.g., ataxia, paresis, paralysis, hyperesthesia, muscle fasciculation, seizures, fever) and one or more of the following: isolation of WNV from blood, CSF, or tissue; a fourfold increase in plaque reduction neutralization test antibody titers on paired serum samples taken 2 weeks apart; or the detection of IgM antibody to WNV by IgM-capture ELISA.[44,45] Given the nonspecificity of the IgM ELISA (i.e., does not differentiate between disease and exposure) and the time required to serologically confirm WNV infection, alternative tests able to rapidly detect WNV in clinical specimens are important. RT-PCR using either a one-step, nested, or real-time approach has been evaluated to investigate antemortem cases of suspected WNV encephalitis in horses and humans using blood. The diagnostic sensitivity of WNV RT-PCR using either serum or whole blood was very low.[46-48] However, 57% to 70% of CSF samples from human beings with serologically confirmed WNV infection tested positive by real-time RT-PCR.[46,47] The reduced ability to detect WNV in CSF or serum from patients with serologically confirmed WNV infection is likely due to the short-lived viremia in dead-end hosts, and it emphasizes the fact that in order to detect WNV in blood or CSF, the sample should be collected early during the disease process. Investigation of the sensitivity of RT-PCR on CSF from horses with WNV encephalitis has not yet been reported. RT-PCR has also been shown to accurately identify WNV in field-collected mosquito pools, avian tissues, and human and equine brain tissue samples with a degree of sensitivity approaching that of virus isolation in Vero cells.[47-49]

Myeloencephalopathy is an uncommon presentation of EHV-1 infection and should always be considered as a differential diagnosis when a horse develops sudden neurologic signs (e.g., ataxia, paresis, urinary incontinence), especially if multiple horses on the premises are involved or when a recent history of fever, abortion, or viral respiratory disease in the affected horse or herdmates is reported.[50] Diagnosis is often based on history, clinical signs, and xanthochromia and elevated total protein concentration in CSF resulting from vasculopathy. Attempts to isolate virus from the blood or CSF of patients are often unsuccessful because the peak of viral shedding has usually passed by the time neurologic signs appear.[51] However, affected horses can shed the virus in nasal secretions and thus represent a risk of infection for unaffected in-contact horses. This outcome has been reported in a hospital setting in which horses developed neurologic disease after having been exposed to horses with EHV-1 myeloencephalopathy.[52] Therefore, it is imperative to determine the risk of shedding in a suspected horse in order to initiate an appropriate infectious disease control protocol. PCR, as previously shown for viral respiratory diseases, is a fast and sensitive molecular diagnostic tool and should be performed on blood and nasal or nasopharyngeal swabs to document viremia and nasal shedding, respectively.[39,53,54] The dilemma as to whether the virus is in a lytic, non-replicating, or latent state can be addressed by using absolute quantitation or transcriptional activity of the target gene similar to the approach used for EHV-4.[13] Research groups have recently identified a region of variation in the genome of different EHV-1 strains that correlates directly with their ability to cause neurologic disease.[55]

A single nucleotide polymorphism at position 2254 of the DNA polymerase gene (ORF 30) has been associated with a higher risk of EHM development. Rapid PCR assays have been established to allow differentiation between neuropathogenic and non-neuropathogenic strains.[56-58] However, such assays have moderate specificity, since 76% of EHV-1 strains associated with EHM have been shown to be of the neuropathogenic genotype.[59] Therefore, these assays should be used judiciously and the results should always be interpreted in the context of clinical presentation. Further, these assays should be coupled with additional assays targeting conserved regions of the EHV-1 genome.

Gastrointestinal Pathogens

The detection of equine gastrointestinal pathogens using conventional or molecular tests is often very challenging because these pathogens either are difficult to grow in cell culture systems or can be present in pathogenic or non-pathogenic forms, making interpretation of positive results difficult. Furthermore, the use of fecal material for molecular diagnostics has been associated with false-negative results because of the presence of inhibitory substances in the feces that can interfere with NA extraction or amplification.[60] However, development and use of specific extraction kits (DNA Stool Mini Kit, QIAGEN, Valencia, CA) have improved the yield of NA from feces.[61]

Neorickettsia risticii is the rickettsial agent responsible for Potomac horse fever (PHF), a serious enterocolitis of horses. Because of the nonspecific nature of the clinical signs, a provisional diagnosis of PHF is often based on the presence of typical clinical signs and the seasonal and geographic occurrence of the disease. A definitive

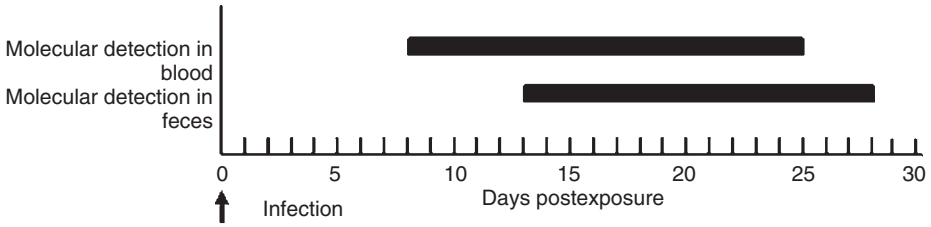


FIG. 29-2 Molecular detection period of *Neorickettsia risticii* in blood and feces of experimentally infected horses. *(From Pusterla N, Madigan JE, Leutenegger CM. 2006. Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases. J Vet Intern Med 20:3. Reprinted with permission of the American College of Veterinary Internal Medicine.)*

diagnosis of PHF, however, should be based on isolation or detection of *N. risticii* from blood or feces of infected horses.[62] Isolation of the agent in cell culture, although possible, is time consuming and not routinely available in many diagnostic laboratories. The recent development of *N. risticii*–specific PCR assays has greatly facilitated the diagnosis of PHF.[63-64] These molecular assays have contributed to the investigation of the epidemiology of PHF, allowing the discovery of helminthic vectors and intermediate and definitive helminthic hosts as well as determining the natural route of infection.[65-67] Nucleic acid of *N. risticii* can be detected in the blood and feces of naturally or experimentally infected horses, but the detection period does not necessarily coincide between the two sample types (Fig. 29-2). Based on these results, we recommend analyzing both blood and feces from suspected horses in order to enhance the chance of molecular detection of *N. risticii*. Another application of PCR has been the recent description of the first equine cases of PHF from Nova Scotia using formalin-fixed and paraffin-embedded colon tissue.[68]

An emerging equine gastrointestinal pathogen, *Lawsonia intracellularis,* has been described in young horses.[69] This obligate intracellular bacterium is the causative agent of proliferative enteropathy (PE), a transmissible enteropathy known to affect a wide range of domestic and wild animal species.[70] This disease has a worldwide distribution and likely is underrecognized in horses. Antemortem diagnosis can be challenging and is based on interpreting clinical signs (e.g., lethargy, anorexia, fever, weight loss, subcutaneous edema, diarrhea, colic), clinicopathologic results (e.g., hypoproteinemia resulting from hypoalbuminemia), ultrasonographic findings (e.g., thickened small intestinal walls) and excluding other causes of similar gastrointestinal findings.[71] Currently, culture of the organism is difficult and is not routinely offered by laboratories. Antemortem diagnosis relies on serology and PCR.[72,73] The combination of both tests as well as repeated fecal sampling for PCR from target animals will increase the chance of diagnosing the disease. Novel PCR assays, such as the real-time PCR, have increased the sensitivity of molecular detection, compared with initial conventional assays.[74,75] PCR has the advantage of being fast and can yield positive results in the early stage of disease, when antibodies are not yet measurable. Prior use of antimicrobials can negatively affect the molecular detection of *L. intracellularis* in feces. Therefore, in a suspected case, fecal collection for PCR testing should be performed prior to the institution of any antimicrobial treatment.

In recent years, PCR assays for the detection of *Salmonella* spp. in fecal samples from horses admitted to veterinary hospitals have been evaluated.[76-80] Collectively, these studies have shown an unquestioned higher analytic sensitivity for the detection of *Salmonella* spp. PCR assays when compared with conventional microbiological culture. The higher detection rate of *Salmonella* by PCR has been attributed to the detection of nonviable organisms and of previously undescribed *Salmonella*-like bacterial organisms. The use of novel virulence target genes for the molecular detection of *Salmonella* spp. has considerably improved the performance and accuracy of such assays. More and more veterinary hospitals across North America are switching from conventional microbiological culture to PCR for the testing of *Salmonella* as part of their infectious disease control program. In such instances, PCR is performed on fecal and environmental samples following a 24-hour selective enrichment step. The use of PCR is very cost effective and has the potential to reduce contamination risks and turnaround time, with results being available within 22 to 28 hours from sample collection (18 to 24 hours enrichment time, 4 hours for DNA purification and amplification). Further, the use of absolute quantitation allows assessment of the infectious nature of hospitalized animals and may be an excellent alternative to conventional culture methods for surveillance and research studies.[80] Although PCR for *Salmonella* spp. is an accurate and fast screening test, one must still consider microbiological culture to confirm positive molecular results and to determine the serovar and antibiogram of the isolated *Salmonella* spp.

The detection of equine coronavirus (ECoV) by PCR in the feces of foals with fever and diarrhea is difficult to interpret because ECoV has also been detected in the feces of healthy foals. Healthy foals have been found to be infected mostly by ECoV in a single infection without any other co-infecting agents, whereas ECoV was found exclusively in association with other co-infecting agents in sick foals.[81] This is in agreement with coronaviruses in other species, where the virus may not have enough pathogenic potential to cause disease but causes local immune suppression, allowing secondary infections to take place more efficiently. In adult horses ECoV causes a self-limiting disease characterized by depression, anorexia, fever, and less frequently changes in fecal character and colic.[82,83] More epidemiologic studies are needed to better understand the impact of this emerging disease.

Equine rotavirus poses a challenge each foaling season to farm managers and veterinarians in intensive horse-breeding areas throughout the world. A quick and reliable diagnosis is essential in order to separate affected foal with diarrhea and reduce the spread of this virus. The diagnosis of rotavirus infection has in the past relied on direct virus detection using a rapid antigen-capture ELISA. Recently developed PCR assays have shown high analytic sensitivity, specificity, and accuracy in the diagnosis of equine rotavirus infection[81] and will likely replace the less sensitive ELISA test in the near future.

Miscellaneous Pathogens

Equine granulocytic anaplasmosis (EGA) is caused by *Anaplasma phagocytophilum,* a rickettsial pathogen transmitted by *Ixodes* spp. ticks. Diagnosis is often based on awareness of the geographic area for infection, typical clinical signs, abnormal laboratory findings, and identification of characteristic pathogen inclusions in the cytoplasm of neutrophils and eosinophils in a peripheral blood smear. PCR has been used for many years to study several aspects of the epidemiology and pathophysiology of EGA.[84,85] For clinical purposes, the material of choice is whole blood. PCR has been shown to be a very sensitive and specific tool, supporting the diagnosis especially during the early and late stage of the disease, at times when the number of organisms is too small to be detected via microscopy (Fig. 29-3).[86]

Corynebacterium pseudotuberculosis is a common cause of external and internal abscesses in horses from arid regions of North America.[87] The epidemiology has been investigated with the help of PCR, and flies have been identified as potential vectors.[88,89] *Corynebacterium pseudotuberculosis* is easy to grow on culture and use of PCR on clinical samples is restricted to specific situations (e.g., culture-negative aspirates or body fluids).

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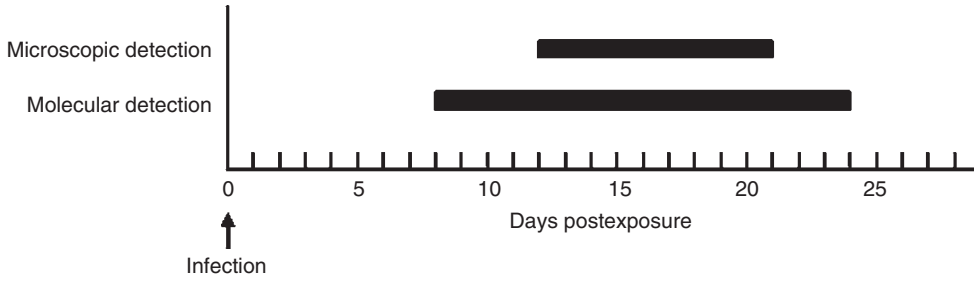


FIG. 29-3 Microscopic and molecular detection period of *Anaplasma phagocytophilum* in the blood of horses experimentally infected with *Ixodes scapularis. (From Pusterla N, Madigan JE, Leutenegger CM. 2006. Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases. J Vet Intern Med 20:3. Reprinted with permission of the American College of Veterinary Internal Medicine.)*

Additional PCR assays for *Borrelia burgdorferi* sensu lato, *Leptospira* spp., *Mycobacterium* spp., *Mycoplasma* spp., *Babesia caballi, Theileria equi, Clostridium difficile* (antigen and toxin A and B), toxigenic *Clostridium perfringens, Cryptosporidium* spp., and methicillin-resistant *Staphylococcus aureus* have been developed and are being used in the research setting.[81,90-100] These assays will likely be offered in the near future for diagnostic purposes when additional epidemiologic information has been evaluated and accuracy of the tests has been validated using clinical samples from infected horses.

Molecular Testing for Infectious Diseases in Cattle, Sheep, and Goats

Beate M. Crossley • Sharon K. Hietala

The availability of molecular-based diagnostic technologies designed to identify infection or genetic conditions by detecting specific genome targets in the host or agent DNA or RNA have expanded logarithmically in the past decade. Diseases and genetic conditions affecting cattle, sheep, and goats are now commonly studied and diagnosed using a variety of molecular techniques and, in particular, polymerase chain reaction (PCR) assays and genome sequence analysis. Molecular-based approaches, which by nature can be extremely sensitive for the detection of infectious agents, were once considered useful only in research laboratories based on concerns ranging from the risk of laboratory contamination and false-positive findings to high per-assay costs. With the commercial availability of specialized instrumentation, reagents, and technical training, the criticisms have largely been overcome. Molecular technologies are now generally available for routine diagnostic services provided by state and federal diagnostic laboratories, university laboratories, and commercial laboratories. The technical complexity of molecular-based diagnostics, paired with the wide range of assays available to diagnose genetic and infectious diseases of food animals, means that no single laboratory can feasibly provide comprehensive testing for all species and all diseases. Instead, laboratories tend to focus on the diseases or genetic conditions of primary significance to their allied industries, and use the technologies that provide the most rapid, reproducible, and economic results for their particular group of clients. Largely based on this specialization within laboratories, molecular-based assays may be developed and put into use without significant effort toward assay standardization and validation. The list of PCR-based assays available for detection of infectious agents, in particular, has grown significantly in the past decade, although with no guarantee that the assays have been suitably designed, tested in the field, or clearly advertised as to their "fitness for purpose." For PCR-based assays, the selection of the genetic sequence (DNA or RNA) used as the target of the diagnostic assay is heavily dependent on the proposed use of the test and on the availability of known genomic sequence(s) for development of the assay. All genomes accumulate mutations over time, with some genes being highly mutable to allow evolutionary advantage, such as those genes that encode antimicrobic resistance or protein conformations for evading the host immune system. Other genes such as those encoding specific functions (e.g., replication) tend to remain highly conserved and stabile to protect the survival of the organism. Assays used to detect a specific agent, such as bovine viral diarrhea (BVD) virus, can be designed to target a conserved region of the genome that is shared by all members of the species. Alternatively, assays used to characterize or subtype particular strains or isolates, such as BVD virus type 1b, can be designed to target regions with significantly more mutability or sequence variation. Assays designed as "fit" for surveillance testing must often sacrifice the ability to discriminate closely related pathogens, such as BVD virus from the genetically related Border disease virus, in order to have the needed surveillance sensitivity to detect the broad range of potential BVD virus isolates. Similarly, assays designed for test and cull, or related disease control programs, must have a high diagnostic specificity for detecting only the agent or trait of interest. These assays tend to sacrifice diagnostic sensitivity or detection level in order to minimize the risk of false-positive results. Although molecular diagnostics provide a powerful and rapidly advancing tool, the clinician is advised to use molecular-based assays with appropriate awareness of their individual strengths and weaknesses, including the designated use or "fitness for purpose." Unquestionably, molecular technologies will continue to be developed and implemented in veterinary medicine. Although it can be expected that some technologies will replace existing procedures, it should be expected that other molecular tools will be no more than a supplement to traditional diagnostic approaches.

Sample Submission

As with any diagnostic technology, the specimen used must be appropriate for the disease or genetic condition and take into consideration the timing and pathogenesis of the disease process and availability of the intact genetic material being targeted by the diagnostic assay. Among the important criteria in the selection and use of molecular-based assays are onset and duration of agent replication in the host, specific tissue(s) affected, and the relative abundance of target DNA or RNA over the course of the infection. In addition to tissues obtained from postmortem investigation or surgical sampling, antemortem diagnostic testing can target genetic material recovered from swabs of mucous membranes; blood, urine, milk, or skin scrapings; or fecal material as appropriate to the disease process.

Since all molecular-based diagnostics detect genomic material in one form or another, the isolation and purification of nucleic acids (DNA or RNA) from the diagnostic specimen is critical to the success of the assays. Dependent on the tissue or specimen used for diagnostic testing, recovery of sufficient quantities and quality of nucleic acid can be problematic. Common sources of assay failure include substances in the sample that can interfere with the chemistries used in detection or PCR-based amplification steps. Examples include, but are not limited to, heparin, iron, peroxidases, hemoglobin, and myoglobin, as well as the relative abundance of total DNA or RNA associated with the different specimen types. This type of assay error is controlled in some PCR assays by the inclusion of internal controls

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prior to initiating the assay in order to monitor for specimen-based interference or related-assay failure. Another common source of assay failure is destruction of target nucleic acids in the specimen prior to testing, commonly as a result of enzymes associated with postmortem autolysis. Because of the complexities of nucleic acid recovery and target nucleic acid detection, assays developed for use with one matrix, such as whole blood, may not be suitable for use with other matrices, such as milk or feces. Appropriate sample collection buffers, storage temperatures, and shipping requirements are available from the laboratories performing the specific testing.

Molecular-Based Diagnostic Technologies

Nucleic acid fragments, either DNA or RNA, can be detected by binding to a complementary fragment of nucleic acid that has been marked with a reporter dye or enzyme. The short strands of DNA or RNA, generally chemically synthesized and referred to as oligonucleotides, are identified as *hybridization probes* when marked with a reporter dye or enzyme. Radioactively labeled probes, although once the standard, have largely been replaced by enzymatic tags, such as avidin-biotin, peroxidase, or chemiluminescent tags. Target nucleic acids can be detected directly in the diagnostic specimen when sufficiently abundant, or they may be detected following PCR-based amplification of the nucleic acid target.

Southern Blots, Northern Blots, and Dot-Blots

There are a variety of techniques used to immobilize genetic material prior to detection steps, with or without prior PCR amplification. As a group, the techniques are referred to as "blots." Dot-blots and Southern blots refer to DNA bound to nitrocellulose membranes, whereas Northern blotting is the terminology used when RNA is immobilized onto membranes. In Southern and Northern blots, nucleic acid fragments are first separated by size using an electric current running through a semi-solid gel, a technique referred to as gel electrophoresis. The nucleic acid detection step for DNA and RNA blots may include a specific hybridization probe or may simply use the molecular weight of the DNA or RNA fragment. Related terminology includes Western blot, which describes protein immobilized on a membrane, and immunoblot, referring to detection of the immobilized protein using specific antibody as an immunologic marker. Variations of this approach, using proteins or capture antibodies immobilized on specialized paper strips, form the basis for lateral flow ("dip-stick") pen-side tests, including those developed for the rapid field detection of foot-and-mouth disease virus.

The laboratory technique referred to as in situ hybridization allows for localization and observation of a DNA or RNA target within a histologic tissue section.[1-4] The hybridization probes are typically end-labeled with a radioactive or enzymatic reporter molecule. Fluorescent in situ hybridization (FISH) is a relatively new staining approach showing promise for future rapid diagnostic applications. In situ hybridization using RNA probes (riboprobes) is another rapidly advancing technology, with improved detection sensitivity compared with DNA probes, although to date it has been used primarily for studying viral infection and gene expression rather than for diagnostic applications. In situ hybridization technology can be applied to frozen or formalin-fixed tissues, with best results provided when the tissue is fixed as soon as possible postmortem to avoid loss of target nucleic acids during tissue autolysis. Nucleic acids from veterinary pathogens have been shown to be stable in formalin-fixed, paraffin-embedded tissues for up to 15 years.[1,5] Because of technical complexity, in situ hybridization is not yet widely applied to routine diagnostics, but appears to be rapidly advancing in that direction.

Polymerase Chain Reaction

PCR is the most commonly applied of the molecular technologies and can be grouped roughly into standard PCR and the more rapid real-time or quantitative PCR. Both techniques amplify minute quantities of target DNA to levels that are detectable using laboratory instrumentation or special staining procedures. The principal difference in the two approaches is that standard PCR is divided into two major processes in the laboratory: (1) the amplification of the DNA target, followed by (2) the detection of the amplified target DNA. Real-time PCR combines the two steps, so that target detection occurs during the DNA amplification process. The advantages of PCR over standard isolation and identification techniques is the significantly reduced time required to obtain a result, with PCR results generally provided in hours instead of days. Real-time PCR results can be reported as dichotomous results (positive, negative) or on a continuous numeric scale, generally as a cycle threshold (Ct) with the lower numeric values correlating with higher concentrations of the target pathogen or genetic marker. Diagnostic caution is generally needed in interpreting "weak positive" real-time PCR results caused by technical limitations and the nature of how real-time PCR results are captured in the laboratory. PCR-based technologies are a particularly powerful tool when designed to detect the presence of organisms that are extremely slow growing or difficult to culture, such as the *Mycobacterium avium* subsp. *paratuberculosis* (Johne's disease) bacterium, *Leptospira* spp., and bluetongue virus, among others. Since PCR-based assays detect nucleic acids, they do not require that the organism is viable in the sample. This is considered an advantage for those agents that may be easily destroyed during sample transport to the laboratory but a disadvantage where fragments of a pathogen's genome may persist for weeks or months after the animal has become noninfectious. An excellent example of this is the bluetongue virus, in which PCR can detect non-replicating viral genome adherent to red blood cells for several weeks after live virus can be recovered from the blood. With the proliferation of PCR assays being developed in research laboratories, state diagnostic laboratories, and commercial laboratories, it is often difficult for the practitioner to know which genetic marker or gene fragment was used in the design of a particular assay. This is of particular diagnostic importance because different gene segments in an individual pathogen's genome may favor screening assays (high detection sensitivity, greater risk of cross-reactivity with lower diagnostic specificity) versus confirmatory assays (high specificity for the target, but lower detection sensitivity). The number of different assays, often identified by just the name of the agent, creates confusion and frustration for those faced with selecting the appropriate assay to use. It is important when selecting and interpreting results of PCR assays to remember that not all assays targeting a specific pathogen will have the same genomic target, or are even designed to have equivalent sensitivity in detecting an infection, making direct comparison of results between laboratories difficult. Quality diagnostic laboratories will be able and willing to discuss the assays performed in their laboratory, including the designated diagnostic purpose of the specific assay, as well as the benefits and pitfalls identified during the assay validation process.[6,7]

STANDARD PCR. Standard PCR is used for detection of DNA or RNA and can be applied to mammalian, microbial, or viral genomes. The PCR technique is based on the natural cross-linking of complimentary (matching) nucleic acids to form double-stranded DNA. When DNA is sufficiently heated, double-stranded DNA separates into single strands, each of which can then be used as a template for chemically (or biologically) generating an exact copy. Specific heat-stabile polymerase enzymes are used in the laboratory for the process of DNA replication. The PCR reaction amplifies DNA using multiple cycles of heating double-stranded DNA to generate a single-strand template and cooling sufficiently to allow the polymerase enzyme to generate a new double-stranded DNA made up of the original strand and its test-tube synthesized copy. For diagnostic assay purposes, it is necessary to copy only a small but diagnostically characteristic fragment of any particular genome. This fragment is generally referred to as the PCR target or target sequence. PCR primers are short chemically synthesized fragments typically 10 to 30 nucleic acids in length that are used to mark the beginning and end of the selected target sequence, and, as their name implies, are used to prime or start the initial PCR amplification process. The choice of

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target sequence as well as appropriate primer design is critical to the accuracy and efficiency of PCR-based diagnostic assays. For detecting target RNA, as is needed for the PCR diagnosis of an RNA virus, the technique of reverse transcriptase PCR (RT-PCR) is used. The reverse transcriptase enzyme converts target RNA into DNA, identified as cDNA or copy DNA for use in the PCR steps. The PCR amplification process typically takes 2 to 6 hours to complete and is followed by detection steps that require additional hours to days to complete. Detection of the amplified DNA fragment, often referred to as an amplicon, uses techniques that identify the DNA fragment by molecular weight, by marking a specific target sequence in the amplified DNA with hybridization probes, or by a combination of both (PCR/probe). PCR amplification followed by hybridization probe detection offers increased specificity, thus less chance of a false-positive finding, and often provides a tenfold or greater increase in detection sensitivity. Dependent on the stringency designed into the assay by balancing such measures as temperature, length of replication cycles, and enzyme concentrations, false-negative results will occur when the sequence of the primers or probe does not precisely match the sequence of the target. In some cases, PCR assays are very precise and designed to recognize a single nucleic acid polymorphism (SNP analysis) in the target sequence, and in other cases are intentionally designed with lower stringency to allow some degree of variability among isolates or strains being detected by the assay. Because RNA viruses in general lack the proofreading enzymes found in DNA viruses, bacteria, and protozoa, they are at greater risk for appearance of random mutations at primer or probe sites. PCR false-negative results associated with primer or probe mismatches resulting from random genomic mutations at the primer or probe binding sites are of particular concern for RNA viruses, and they provide ample justification for a laboratory to investigate with alternative or additional technologies when negative PCR-assay results clearly do not match a clinical or epidemiologic pattern of disease.

NESTED PCR. Nested PCR is a PCR technique modification generally used to increase the detection sensitivity of an assay.[8] During nested PCR, an initial PCR reaction amplifies a selected fragment of DNA, which is then used as a template in a second round of PCR. The second or nested PCR reaction targets one or more unique fragments of DNA within the initially amplified region. The two-step process has the advantages of increasing detection sensitivity and detection specificity and of diluting the impact of interference from potential PCR inhibitors found in some tissues and clinical materials. Nested PCR assays have been described for West Nile virus, malignant catarrhal fever virus, and *Chlamydia* spp., among others. The significant disadvantage of the two-step process comes from handling the first round of amplified DNA in the laboratory. With the high concentrations of target DNA available following PCR amplification, laboratories must take rigorous precautions to mediate the risk of contaminating laboratory workspaces, equipment, and reagents with the amplified DNA. The significant risk and associated costs of laboratory contamination and resulting false-positive results is used in many diagnostic laboratories as justification for charging additional fees or for not offering nested PCR techniques.

Diagnostic assays originally developed using standard PCR approaches are increasingly being converted to real-time PCR and real-time quantitative PCR (qPCR) technology, to take advantage of the speed, technical efficiency, and cost reduction often associated with this approach.[9] Because real-time PCR technology completes both amplification and detection in the same reaction tube or well, there is no need for the laboratory to handle amplified DNA and risk workspace contamination. This noteworthy modification to PCR technology has been responsible for a significant expansion in use and general availability of PCR-based diagnostic assays. More importantly, the combination of amplification and detection in a single reaction vessel has allowed expansion of PCR-based assays into high-throughput, portable, and on-site formats as described for foot-and-mouth disease virus, anthrax detection, and others. Real-time PCR offers an additional advantage of supporting quantitative approaches to amplification and detection of the original target in the sample tested. Quantitative PCR answers a frequent criticism of standard PCR, specifically that detection limits, potentially as low as a single cell or viral particle, may produce a positive finding that is biologically irrelevant to clinical disease. Quantitative PCR allows the relative amount of target nucleic acid to be correlated with the associated clinical presentation.

MULTIPLEX PCR. Multiplex PCR expands the use of PCR or real-time PCR-based detection from a single target to multiple targets simultaneously from a single specimen.[10-12] The ability to include multiple genome targets for a single virus or bacteria in a PCR assay minimizes the risk of a PCR false negative as a result of genetic diversity within the agent of interest. Inclusion of targets for multiple closely related viruses has been used to differentially detect related pathogens, such as the closely related sheep and wildebeest-associated forms of malignant catarrhal fever, to subtype BVD viruses, and to differentially detect virulent *E. coli*. Multiplex PCR also has broad application in syndrome-based testing where several pathogens may produce very similar to identical clinical pictures. A single diagnostic specimen could theoretically be used in a multiplex format to detect one or more agents associated with a particular clinical presentation, such as the multiple viral and bacterial agents in shipping fever complex. Prototypes of this approach have been developed, but are not yet widely deployed, and there are technological limits to the number of PCR assays that can be combined without significant loss of assay performance. In real-time PCR formats, three to five unique assays have been the practical limit, based on the technical limitations of commonly available equipment and detection dyes.

Isothermal Amplification

These techniques use alternate chemistries to PCR and are carried out at a single temperature. Among the isothermal amplification technologies that have been used for the detection of veterinary pathogens are nucleic acid–based amplification (NASBA), loop-mediated isothermal amplification (LAMP), rolling circle amplification, and direct signal amplification systems.[13,14] None of these technologies has seen widespread diagnostic application, possibly as a result of the complexity in initial assay design, but they may offer future PCR alternatives that can be more automated, portable, or developed as fully integrated self-contained testing units.

Arrays of DNA or RNA fragments, variously referred to as genechips and microarrays, consist of thousands of oligonucleotides attached in a specific pattern to a solid surface, typically a glass slide or silica chip.[15-21] The sample nucleic acids compete with fluorescently labeled competitor oligonucleotides for binding to the chip. A fluorescent detector and computer software are then used to analyze the patterns of fluorescence, indicating where nucleic acids have (or have not) been bound to the chip. Microarrays have been used primarily as research tools focused on detecting and understanding gene expression. The practical application to veterinary medicine includes studies such as the evaluation of genetic resistance to naturally occurring nematode infections, including *Hemonchus, Trichostrongylus,* and *Ostertagia* in sheep. Microarray technology has not seen wide use in veterinary diagnostic laboratories, largely because of the large initial investment required for equipment. However, examples of diagnostic microarrays have shown promise, and it is expected that once established, the technology will be cost effective on an individual animal basis. In human diagnostic medicine, microarrays designed with genetically conserved sequences for all major groups of microorganisms have been used to identify or "mine" for unknown pathogens. This approach was used to detect and identify the SARS virus, before it was initially recovered and characterized by virus isolation techniques. Alternately, genotyping arrays have been designed to target specific virulence-associated genes, allowing differentiation of disease-associated subtypes of organisms from other members of the same or closely related species, such as enterotoxigenic *E. coli* and multi-drug–resistant *Salmonella* strains.

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An alternative to genechip technology is liquid array technology, in which the nucleic acids are captured by oligonucleotide probes bound to a microbead, rather than to a flat surface. Bead sets are internally labeled with different colored dyes used to distinguish the specific agents being measured. Liquid array systems use flow cytometry, laser technology, and signal processing to recognize the internal color of the beads and measure associated surface-binding of a target-specific fluorescent hybridization probe. The bead-based modification to microarray technology allows a laboratory to create a flexible diagnostic-test panel in a single assay by adding or removing target beads based on the unique clinical presentation, diseases suspected, or species specificity of interest. In theory, 100 different targets are detectable in a single assay.

Molecular techniques provide a valuable tool for genotypic characterization or subtyping of viral, bacterial, and parasitic agents. Subtype characterization[22-25] is essential for, among other things, taxonomic classification, differential detection of virulent strains, identification of genetic sources of antimicrobic resistance or virulence factors, recognition of vaccine escape mutants, epidemiologic investigation of disease outbreaks, and identification of inter species transmission of specific pathogens. Restriction fragment length polymorphism (RFLP) is a technique useful for subtyping of pathogens based on genetic sequence variation within specific genes.[26] Target DNA, which may or may not previously have been PCR amplified, is digested using one or more well-characterized restriction enzymes. Characteristic profiles or patterns produced by the different-sized DNA fragments remaining after enzyme digestion are detected by gel electrophoresis. RFLP has been used to investigate interspecies transmission of enterotoxigenic *Staphylococcus aureus* associated with intramammary infections in cattle, sheep, and goats.[27] Random amplified polymorphic DNA (RAPD) analysis is a technique that has proved useful in detecting genetic variation and for strain typing.[28] Rather than amplifying a specific region of a genome, RAPD relies on random amplification of genomic DNA using short arbitrary sequences as PCR primers. RAPD does not require prior knowledge of an organism's DNA sequence for specific primer design and can be applied to very small amounts of template DNA. The RAPD technique has been applied, for example, to rapid differentiation of pathogenic from non-pathogenic coccidia of sheep, including *Toxoplasma gondii and Sarcocystis* spp. Identification of non-culturable, slow-growing, and atypical bacterial species using sequence analysis of the 16s ribosomal RNA (rRNA) gene has become recognized as a valuable diagnostic tool in recent years. The basis of the 16s RNA typing technique is the highly conserved nature of the 16s rRNA gene within bacterial species, as well as among species of the same genus.[12,29,30] Automation developed to support 16s rRNA amplification, sequencing, and data analysis is available to and currently in place in selected veterinary diagnostic laboratories. Although the technique is not currently cost effective for routine identification of all microbial isolates in a clinical setting, the technology is used for identification of atypical, slow-growing, and rarely encountered species.[31] Because 16s rRNA databases continue to be updated to include pathogens of veterinary and zoonotic interest, it is likely that the technology will see broader application.

Nucleic acid sequence analysis is used to identify and compare the exact nucleic acid sequence of a gene fragment, gene, or possibly entire genome for forensic purposes, to investigate disease outbreaks, to track evolutionary changes in rapidly mutable microorganisms, or for precise phenotype or genotype analysis of animals or organisms. The technology used for sequence analysis is progressing exponentially since initially introduced in the 1970s. Equipment and computational strength used for sequence analysis were once limited to specialized research laboratories and reference centers, but they are increasingly available in well-equipped diagnostic laboratories. Next-generation, also called second-generation, sequence analysis approaches use bench-top commercialized equipment based on DNA synthesis, ligation, or ion semiconductor technology for the rapid and highly accurate genome sequencing of pathogens. The complete genomic sequence of individual pathogens can be completed within a matter of hours to days using Next Generation Sequencing technologies. For diagnostic purposes sequencing may be paired with PCR amplification of specific genetic markers or regions of known pathogens, or may be used in *de novo* applications which determine the genetic sequence and identity of an unknown or previously uncharacterized pathogen.[19,20] Sequence analysis is most commonly used to confirm the identity of a pathogen testing positive in a PCR assay, to detect genetic variants or diagnostically important mutations in a pathogen's genetic makeup, and for forensic investigation into the source of an agent or disease outbreak based on specific genetic markers in the recovered pathogens. Nucleic acid sequencing of the sheep prion protein (PrP) gene allele has been used as a flock management tool associated with scrapie control.[32]

Genetic Diseases

Diseases that are linked to genetic mutations in specific breeds, such as bovine leukocyte deficiency (BLAD) and complex vertebral malformation (CVM) in Holstein cattle, β-mannosidosis in cattle or goats, and spider-lamb syndrome in sheep, can be controlled by selective breeding using PCR-based testing to identify carriers of the defective gene. Similarly, susceptibility to certain diseases has been linked to specific genetic haplotypes that can be detected by molecular analysis.[33] Although at times controversial, rapid PCR-based genotyping of sheep has been used for selective breeding programs targeting the genetic alleles associated with "scrapie resistance." DNA testing for genetic selection, parentage confirmation, coat color, and related management purposes is also available for cattle, sheep, and goats. For genetic testing, the appropriate sample is typically whole blood, from which genomic DNA is extracted, the gene of interest is amplified by PCR, and then mutations are detected by sequence analysis, microsatellite target testing, and restriction enzyme analysis to identify the mutations in the gene of interest.[34,35]

Summary

For molecular diagnostics, as with any new technological advance, there was initial hesitation or mistrust of the techniques, followed by a rush to take advantage of new diagnostic tools. With routine implementation of PCR, sequence analysis, and associated molecular diagnostic techniques have come significant advantages in diagnostic sensitivity and specificity, in the speed that a laboratory diagnosis can be reached, and in the potential for in-depth genome-level investigation of disease occurrences. At the same time, molecular techniques have introduced a new level of complexity to diagnostic medicine. The use and interpretation of molecular-based diagnostic results require sufficient understanding of the techniques used in order to judge the reliability and the relevance of the findings. Molecular techniques have become, and will continue to grow as, an extremely valuable diagnostic tool, but like any tool in diagnostic medicine, they must be used with caution and with a clear understanding of their strengths, limitations, and appropriate applications to specific clinical investigations.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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PART FIVE

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Disorders of the Organ Systems

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Diseases of the Cardiovascular System

VIRGINIA B. REEF, *Consulting Editor*
SHEILA M. MCGUIRK

Performing the Electrocardiogram

No single electrocardiographic lead system has been universally accepted for use in large animals. Bipolar leads (I, II, III, base-apex, X, Y, and Z of the orthogonal lead system) and unipolar leads (aV_F, aV_R, aV_L, thoracic) have been described, but the amplitude, duration, and configuration of the different waveforms vary widely depending on an animal's breed, size, body type, and sex. In addition, there is lability of certain waveforms within each animal depending on the level of exercise, excitement, or organic heart disease. Large animals have a deeply penetrating Purkinje system, and depolarization from the ventricular endocardium to the epicardium occurs explosively and in many directions at once. This period of ventricular activation is responsible for the electrocardiographic criteria that indicate ventricular enlargement in small animals but contributes little to generating the QRS complex of large animals. Establishing specific diagnostic criteria for chamber enlargement in large animal species has been difficult because changes in the QRS complex are not sensitive or specific for ventricular enlargement.

The electrocardiogram (ECG) is used primarily to detect cardiac arrhythmias. For this purpose a single-channel machine can be used, and the lead system chosen can be any that generates distinctive P, QRS, and T complexes. If an arrhythmia is detected, another lead should then be obtained to further characterize the QRS and T complexes and confirm their origin. The lead system should be easy to apply, and the tracing free of artifacts created by muscle tremors, skin movement, shifting of weight, and changes in limb position. Two such leads commonly used to obtain a rhythm strip for the diagnosis of cardiac arrhythmias are the base-apex lead[1] and the Y lead of the orthogonal lead system.[2] The base-apex lead is attached by placing the positive electrode from one of three standard bipolar leads (lead I, II, or III) on the left thorax in the fifth intercostal space at the level of the elbow or at the location where the apex beat is most readily palpable. The negative electrode is attached to the skin of the right jugular furrow two thirds of the way from the ramus of the mandible to the thoracic inlet or at the top of the right scapular spine. The ground electrode can be attached to any site remote from the heart. Electrical contact is improved by clipping hair or wetting the skin with alcohol. The base-apex lead ECG is recorded by switching the machine to the bipolar lead that has been attached to the horse and recording the ECG (Table 30-1). Lead Y is attached by placing the positive electrode over the xiphoid and the negative electrode cranially to the front of the chest.

Continuous electrocardiographic recording over a 24-hour or longer period (Holter monitoring) or with radiotelemetry is also useful for evaluating horses with arrhythmias. Continuous ECG recording can be performed with contact electrodes covered with moist sponges to maintain contact, electrode patches that are held against the skin with a surcingle, or electrode patches attached to shaved skin with a cyanoacrylate adhesive and protected underneath a surcingle.[3,4] With bipolar contact electrodes using a single lead system, the positive electrode is placed over the left cardiac silhouette or over the sternum and the negative electrode is placed over the dorsum to the left of the withers where the electrode will lie flat and remain in contact with the skin.[3] The electrodes are kept moist with alcohol and are then held in position with a tight surcingle. With electrode patches the electrodes are taped to a small square of cardboard to provide them with some rigidity. The best recording with a three-lead system is usually obtained with the left arm electrode placed on the sternum, the right leg electrode on the right side in the fifth intercostal space at the level of the point of the shoulder, and the right arm electrode placed on the left side in the fifth intercostal space at the level of the point of the shoulder. These electrodes are then held in position with a tight surcingle after removal of the plastic that covers the conducting material overlying the electrode. The electrodes are connected to a digital recorder that records the animal's heart rhythm for the entire monitoring period (Holter monitor) or a telemetry device that sends the ECG signal back to the receiver to be displayed on a monitor. The entire recording or monitoring period can be stored on a smart card for subsequent analysis. The continuous 24-hour Holter ECG is useful for diagnosing arrhythmias that occur intermittently or for monitoring cardiac rhythm during exercise for later analysis. Radiotelemetry electrocardiography is useful for real-time cardiac rhythm monitoring during treatment or exercise.

In the base-apex lead the P wave is positive in most horses and ruminants. The P wave is most frequently bifid in horses. In many horses a T_a wave, indicative of atrial repolarization, occurs as a negative deflection after the P wave (Fig. 30-1). The QRS complex begins with a small positive deflection (rS) and is followed by a large negative deflection that terminates in the ST segment. The T wave is variable and can be positive, negative, or biphasic in horses and ruminants. Frequently the appearance of the T wave is variable within one recording. Fig. 30-2 illustrates a typical base-apex ECG recorded from both a cow and a horse at a 25-mm/s paper speed with the gain set at 10 mm/mV.

When a systematic approach is used to analyze the ECG, diagnosing arrhythmias is not difficult. The following step-by-step approach can be used:

1. Identify all the QRS complexes. Each QRS complex should be followed by a T wave, and the QT interval should be similar for

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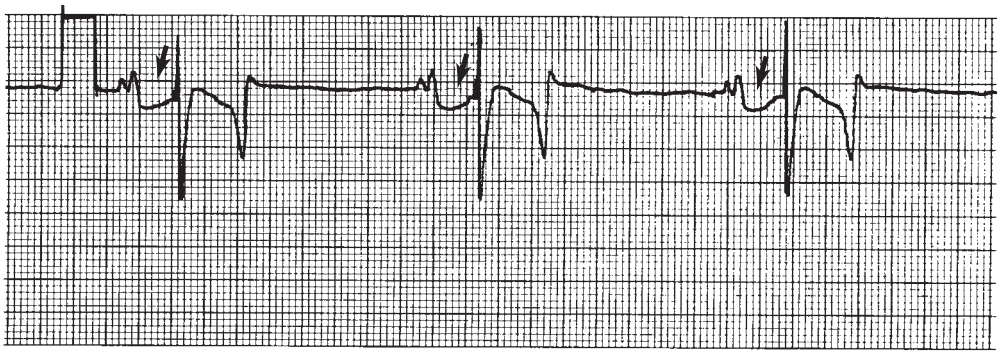


FIG. 30-1 Base-apex lead ECG recorded from a horse. *Arrows* point to the atrial repolarization wave (Ta) frequently seen in normal horses. It follows the notched P wave and precedes the QRS complex. Paper speed 25 mm/s, calibration 1 cm/mV.

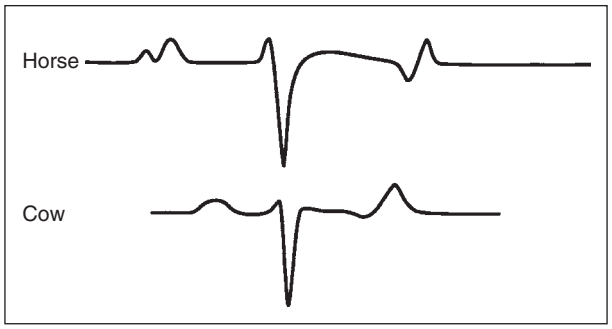


FIG. 30-2 Schematic representation of a typical base-apex lead ECG recorded from a cow and horse. In horses the P and T waves may be variable in appearance.

TABLE 30-1

Standard Bipolar Electrocardiographic Leads

Lead	Positive Electrode	Negative Electrode
I	Left arm	Right arm
II	Left leg	Right arm
III	Left leg	Left arm

all QRS configurations unless there is a marked change in heart rate. Identify the remaining complexes. Are P waves, "F" (flutter) waves, or "f" (fibrillation) waves present? Are there any artifacts?

2. Determine the atrial and ventricular rates. Are they identical? Is one too fast or too slow? This determines whether there is a tachycardia or bradycardia.
3. Are the P-P and R-R intervals regular? Determine whether an irregular rhythm has underlying regularity that is interrupted by irregular intervals or whether the rhythm is consistently irregular. Second-degree atrioventricular (AV) block and atrial and ventricular premature beats are arrhythmias with underlying regularity, whereas atrial fibrillation, sinus arrhythmia, and sinus arrest are truly irregular rhythms.
4. Are P waves present? If so, is there a P wave preceding every QRS complex? If not, there are premature depolarizations, escape beats, or atrial fibrillation. Are all P waves followed by QRS complexes? If not, second-degree AV block may be present. Is the resultant P-R interval constant? If not, there may be a wandering pacemaker or first-degree AV block.
5. Are all P waves and QRS complexes identical or normal in contour? If not, this signifies more than one pacemaker, premature depolarizations, or escape beats.

Use of Echocardiography in Large Animals

Echocardiography is a noninvasive diagnostic tool that uses sound waves in the range of 1.5 to 10.0 MHz to visualize the heart in motion, using either a single icepick (M-mode) or a two-dimensional (2D; B-mode) image. Noninvasive evaluation of blood flow in the heart and great vessels is performed with pulsed wave, color flow, and continuous wave Doppler echocardiography. Precise localization of abnormal flow within the heart and great vessels is performed with pulsed wave and color flow Doppler echocardiography, whereas continuous wave Doppler echocardiography is used to determine the peak velocity of blood flow and to noninvasively estimate pressure gradients. In contrast to M-mode and 2D echocardiography, in which the best image is obtained with the ultrasound beam perpendicular to the structures being imaged, optimal Doppler signals are obtained with the ultrasound beam parallel to the blood flow being evaluated. For accurate peak blood flow velocities to be recorded with continuous wave Doppler echocardiography, the ultrasound beam should be as close to parallel as possible (<20-degree angle) to the direction of blood flow being measured. This alignment is difficult or impossible to achieve in most large animals with valvular heart disease, so accurate peak blood flow velocities often cannot be obtained from large animals with valvular heart disease. Noninvasive estimations of pressure gradients are inaccurate in these instances. Alignment of the ultrasound beam parallel to shunt flow is possible with most ventricular septal defects (VSDs) because of the typical location of the VSD in the membranous or perimembranous portion of the interventricular septum. A more extensive review of the theory and application of echocardiography in horses and cattle has been published.[5-11] More recently, tissue Doppler imaging (TDI) has been used in horses to evaluate atrial and ventricular myocardial wall motion.[12-17]

Echocardiography is particularly useful in evaluating large animals with cardiovascular disease, because the examination is noninvasive and can be performed in a timely fashion in most standing unsedated animals. Diagnostic criteria for valvular, myocardial, pericardial, and congenital lesions of the heart are well established, and the information obtained assists the practitioner in confirming a diagnosis, assessing the extent of the disease, determining the severity of cardiac dysfunction, monitoring the response to treatment, and providing an accurate prognosis. Large animal echocardiographic equipment should provide satisfactory resolution of images at depths of 26 cm or greater. Portable ultrasound machines are available that can display depths of up to 40 cm for equine and bovine cardiology. These machines are available with pulsed, continuous wave, and color flow Doppler. However, Doppler echocardiography is used mainly in specialty practices and referral institutions because performing and interpreting the echocardiogram, including Doppler, requires a significant amount of training and expertise. In addition, state-of-the-art color flow and tissue Doppler equipment remains fairly expensive, although it has decreased in price.

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Echocardiographic examination is performed in a systematic way, using standardized images to obtain information about chamber size, wall thickness, myocardial function, valve appearance, valve function, great vessels, blood flow, and presence of abnormal structures or echodensities. The standard equine or bovine echocardiogram is performed from the right parasternal window (right fourth intercostal space in horses and third intercostal space in ruminants) with a 2.5-MHz or lower frequency transducer. Higher-frequency transducers should be used to examine younger or smaller animals, South American camelids, and small ruminants. Both long- and short-axis views of all cardiac structures should be evaluated. The cardiac valves should be carefully examined for any abnormalities of structure or function (dysplasia, thickening, prolapse, ruptured chordae tendineae, fenestrations, flail valve leaflet, vegetative lesion, or high-frequency vibrations). The relative size, shape, and relationship of the cardiac chambers and great vessels should be assessed, and an evaluation of myocardial function and blood flow performed. Standard measurements of left ventricular internal diameter, left ventricular free wall thickness, interventricular septal thickness, and right ventricular internal diameter should all be obtained at end diastole and peak systole from the M-mode echocardiogram. The diameter of the aortic root and left atrial appendage, the distance between the interventricular septum and the peak opening of the septal leaflet of the mitral valve (septal to E point separation), and the left ventricular ejection time (ET) should also be determined. End-diastolic measurements are obtained at the Q wave of the ECG, whereas peak systolic measurements are made from the peak downward deflection of the interventricular septum. Calculations of fractional shortening (FS) and ejection fraction (EF) can then be performed to assess left ventricular function using the following formulas:

$$FS = \frac{LVID_d - LVID_s}{LVID_d} \times 100$$

$$EF = \frac{LVID_d - LVID_s}{LVID_d} \times ET \times 100$$

in which $LVID_d$ is the left ventricular internal diameter at end diastole (cm), $LVID_s$ is the left ventricular internal diameter in systole (cm), and *ET* is the left ventricular ejection time (seconds).

Echocardiograms should also be performed from the left cardiac window when the entire heart cannot be successfully imaged from the right side; atrial fibrillation is present; abnormalities of the mitral valve, aortic valve, pulmonic valve, aorta, pulmonary artery, left atrium, left ventricle, or outflow portion of the interventricular septum are suspected or detected; or murmurs originating from the mitral, aortic, or pulmonic valves are detected or a pericardiocentesis is planned. The maximal diameter of the left atrium should be obtained at peak systole from the left cardiac window at the level of the left coronary artery, parallel to the mitral valve (Fig. 30-3). The diameters of the aorta and pulmonary artery should be measured from similar locations in the vessel on the 2D echocardiogram and compared. Echocardiography should be considered a useful diagnostic test to evaluate patients with the following complaints, physical examination findings, or tentative diagnoses:

1. Cardiac murmur, to determine the etiology of the murmur
   a. Any grade 3/6 or louder holosystolic or pansystolic murmur on the left side of the thorax
   b. Any grade 4/6 or louder holosystolic or pansystolic murmur on the right side of the thorax
   c. Any holodiastolic decrescendo murmur
   d. Any continuous machinery murmur
2. Congenital heart defects, especially atrial septal defects (ASDs) and VSDs
3. Acquired valvular heart disease
4. Cardiac enlargement
5. Cardiac arrhythmias not associated with high resting vagal tone
6. Unexplained exercise intolerance or collapse or exercise intolerance attributed to cardiac causes

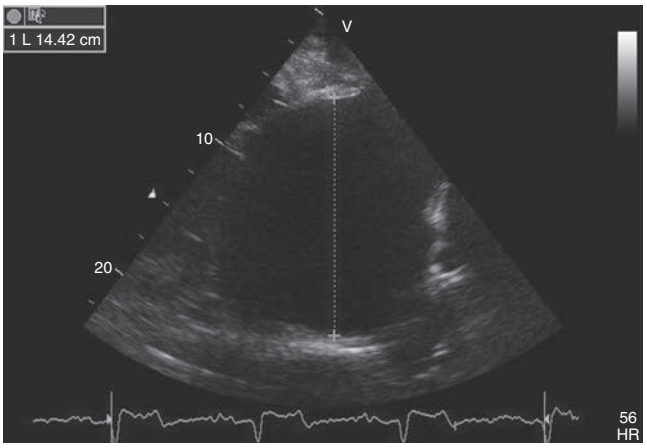


FIG. 30-3 Two-dimensional echocardiographic image of the left atrial diameter obtained from the left parasternal long-axis window in a horse with mild left atrial enlargement secondary to cardiomyopathy and mitral regurgitation.

7. Muffled heart sounds, pericardial friction rubs, or pericardial effusion
8. Myocarditis or myocardial dysfunction
9. Congestive heart failure (CHF)
10. Pulmonary hypertension
11. Cardiovascular neoplasia
12. Aortic rupture or other abnormalities of the great vessels
13. Ionophore toxicity or exposure to other myocardial toxins

Color flow or pulsed wave Doppler echocardiography should be used to map the size and location of a turbulent jet associated with an intracardiac or extracardiac shunt, valvular regurgitation, or stenosis (rare) and to semiquantitate its severity.[18,19] Continuous wave Doppler echocardiography can then be used to measure the peak velocity of blood flow in the jet, estimating (noninvasively) the pressure difference between cardiac chambers using the Bernoulli equation and assessing the hemodynamic significance of the lesion. This can be accurately performed in most patients with a VSD but is difficult to impossible to accurately perform in many patients with valvular insufficiencies because of the limited windows available for interrogating blood flow in large animals and the inability to align the ultrasound beam to within 20 degrees of the abnormal blood flow. This poor alignment of the ultrasound beam with the regurgitant jet results in an underestimation of the peak regurgitant jet velocity. Contrast echocardiography, a technique involving microbubble-laden injections of saline, carbon dioxide, or indocyanine green, can also be used to demonstrate valve dysfunction and the direction of intracardiac shunts (VSDs, ASDs) and extracardiac shunts (patent ductus arteriosus [PDA], truncus arteriosus). TVI should be performed to look for left atrial dysfunction (left atrial stunning) post conversion of atrial fibrillation.[16] TVI is also useful in identifying ventricular myocardial dysfunction.[13]

Cardiac Catheterization in Large Animals

Cardiac and great vessel catheterization can be performed in standing unsedated large animals to determine the following data:

- Pressure and waveforms (shape of the pressure curve)
- Oxygen tension, oxygen saturation, oxygen content
- Cardiac output and other indicators of ventricular size and function

Cardiac catheterization is also used for special diagnostic studies such as angiocardiography, nuclear angiocardiography, and indicator dilution studies. These data are used to determine the direction and size of intracardiac and extracardiac shunts, chamber size and contractility, and valvular and myocardial function. Much of this information is now obtained noninvasively with echocardiography, minimizing the need for more invasive techniques.

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Cardiac catheterization is usually reserved for specialty practices and referral institutions, owing to the equipment needed and skills required for acquiring and interpreting accurate data. Results are not always specific, but catheterization can add quantitative measurements that increase diagnostic and prognostic accuracy for certain cardiac conditions and may provide a direction for therapy.

Blood Pressure Measurements

Normal blood pressures for cattle and horses are listed in Table 30-2.[20-23] The values for horses represent a summary of data from numerous authors as cited in the references given. Accuracy of pressure recordings is greatly influenced by the choice of catheter and the recording equipment used. Pulmonary artery wedge pressure (PAWP) is an indicator of left atrial mean pressure so long as balloon inflation of the catheter occludes flow in the segment of the pulmonary artery that is catheterized. PAWP is superior to central venous pressure (CVP) as a monitor of left ventricular function and fluid therapy.

The shape of the pressure curve in the ventricles, aorta, or pulmonary artery may have diagnostic significance in conditions like constrictive pericardial disease (Fig. 30-4); pulmonic stenosis (giant A wave), rare as an isolated defect in large animals; or tricuspid or mitral valve regurgitation (large V wave). These conditions are more commonly assessed by echocardiography. An abnormal rise in pressure going from one chamber to the next indicates a stenotic lesion (uncommon in large animals) at the level of the pressure gradient. The size of the pressure gradient can be used to determine the severity of the lesion.

TABLE 30-2

Cardiac Pressure Measurements in Normal Horses and Cattle*

	Horses[20]	Cattle[21]
RA	12 to 28/22 to 5 (4 to 10)	(5)
RV	30 to 59/24 to 14 (9 to 25)	42 to 56/0 to 1 (19 to 28)
PA	34 to 48/14 to 22 (16 to 30)	33 to 46/19 to 21 (24 to 31)
PAW	13/3 (8)	(5 to 21)[22]
LV	140 to 148/15 to 17	(120 to 144)[23]
AO	131 to 144/86 to 100 (110 to 115)	
CA	142 to 157/98 to 119 (113 to 124)	160 to 208/110 to 147 (135 to 175)

*Pressure ranges are reported as systolic/diastolic (mean) in mm Hg unless otherwise designated. *AO,* Aorta; *CA,* carotid artery; *LV,* left ventricle; *PA,* pulmonary artery; *PAW,* pulmonary arterial wedge; *RA,* right atrium; *RV,* right ventricle.

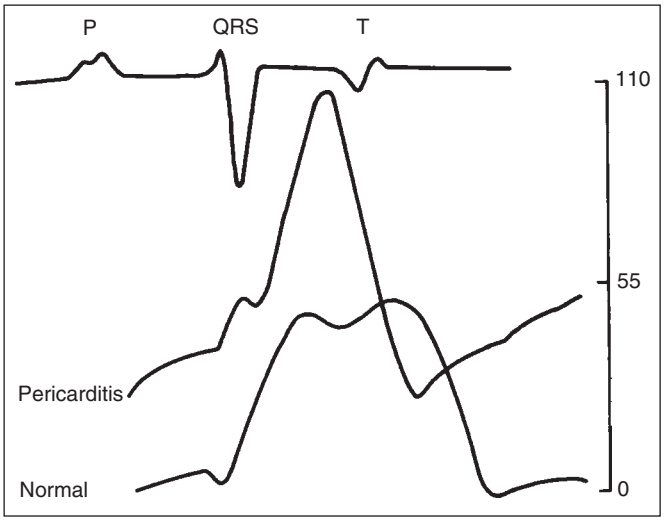


FIG. 30-4 Schematic representation of ventricular pressure curves recorded from a normal horse and a horse with pericarditis, showing the relationship between pressure changes and the ECG. With pericarditis, the ventricular end-diastolic and systolic pressures are elevated and pressure declines sharply in early diastole.

Blood Oxygen Measurements

Blood oxygen measurements are taken from the chambers on the right side of the heart to detect abnormal elevations indicative of a left-to-right shunt (ASD, VSD, PDA). Criteria for oxygen step-ups have not been established for large animals, but human guidelines have been accepted for qualitative assessment of shunts.[24,25] In humans, oxygen content step-ups of the following magnitude are considered abnormal and indicative of a left-to-right shunt[26]:

- ≥1.9 volume percent from the superior vena cava to the right atrium
- ≥0.9 volume percent from the right atrium to the right ventricle
- ≥0.5 volume percent from the right ventricle to the pulmonary artery

Because oxygen content depends on hemoglobin concentration, oxygen saturation, which is independent of hemoglobin concentration, may be a more accurate indicator of shunts in anemic or polycythemic patients. Changes in the animal's physiologic status during sampling (cardiac output, ventilation, oxygen consumption), incomplete mixing of shunted blood, and variable time intervals between sampling can be potential sources of error. Several samples within a single chamber improve reliability of results. Small shunts and shunts in animals with low systemic arterial oxygen tension may not be detected by this technique.

Shunt calculations can be made once oxygen saturation or content has been measured in each of the right heart chambers, the pulmonary artery, and a systemic artery. For a left-to-right shunt, the pulmonary flow/systemic flow ratio (QP/QS) is determined as follows:

$$QP/QS = \frac{SAO_2 - MVO_2}{SAO_2 - PAO_2}$$

in which SAO_2 is the arterial blood oxygen content, MVO_2 is the mixed venous blood oxygen content, and PAO_2 is the pulmonary artery oxygen content. A 2:1 QP/QS represents a 50% left-to-right shunt, indicating that 50% of the pulmonary flow is from the left side of the heart. For a right-to-left shunt, the QP/QS is determined as follows:

$$QP/QS = \frac{SAO_2 - MVO_2}{PVO_2 - MVO_2}$$

in which PVO_2 is the pulmonary venous oxygen content (assumed to be 98% of oxygen capacity plus 0.3 mL of dissolved oxygen).[27]

Cardiac Output and Ventricular Function Assessment

Cardiac output is determined by indicator dilution methods (usually by dye dilution or thermodilution or, more recently, by lithium dilution), by the Fick method, or by using 2D or Doppler echocardiography. The Fick method requires use of a face mask and simultaneous determination of mixed venous and arterial blood samples. Dye dilution and thermodilution results are comparable when 30 to 40 mL of 5% dextrose are injected rapidly at 32°F (0°C).[25] Lithium dilution compares favorably with thermodilution in anesthetized horses and foals.[28,29] Volumetric echocardiography using the Bullet method achieves results similar to those obtained with the lithium dilution method in anesthetized foals.[30] Transthoracic Doppler echocardiography was closely correlated with thermodilution in standing horses.[31]

Cardiac output values in the resting horse range from 32 to 40 L/min.[32] Cardiac index is the cardiac output divided by a measure of body size (body weight in kilograms) and is expressed in mL/kg/min.[32] The normal cardiac index for the adult horse ranges from 72 to 88 mL/kg/min.[32,33] Cardiac output values of 20.9 to 23.6 L/min have been reported in normal anesthetized horses.[28] In cattle a

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cardiac index of approximately 110 mL/kg/min has been reported.[23] Cardiac output measurements in clinical patients vary with heart rate, excitement, hydration, and many other factors and are best determined in the pulmonary artery. Electronic integration and computation of area under the curve by means of battery-powered units that can display results instantly provide the most reliable results.[34]

Cardiac output results or indicator dilution curves can provide quantitative and qualitative assessment of cardiac shunts. Characteristic changes in the temperature-time curve (thermodilution methods) or dye concentration-time curve indicate the presence of a left-to-right, right-to-left, or bidirectional shunt. Calculation of the cardiac output in the chamber just proximal to the shunt and distal to it can give a quantitative estimate of the size of the shunt.[25]

Angiocardiography

Angiocardiography is used in neonates or animals small enough to have the entire cardiac silhouette visualized on a single radiograph cassette. The contrast medium must be injected rapidly, and in most cases this is done with a pressure injector. Specialized radiographic requirements include rapid film change capabilities, rapid image sequence acquisition, or cineradiography. Angiocardiography is used to confirm the presence of an intracardiac shunt (ASD, VSD) or extracardiac shunt (PDA, truncus arteriosus) or valve dysfunction, to visualize chamber size, or to estimate contractility. Angiocardiography is performed in anesthetized animals.

Nuclear Angiocardiography

In nuclear angiocardiography, specialized equipment captures sequential digitized images of the right side of the heart, lung, and left side of the heart after rapid injection of radiographic tracer into peripheral circulation. A more extensive review of this subject has been published.[35] Nuclear angiocardiography can be used to confirm valvular dysfunction, which is manifested by chamber enlargement or prolonged washout of affected vessels or cardiac chambers and is quantitated by the regurgitant fraction. It also can reveal enlargement of chambers and prolonged washout resulting from cardiac failure. The presence of intracardiac or extracardiac shunts can be demonstrated by the simultaneous visualization of left- and right-side cardiac chambers or slow washout downstream of the shunt. In addition, nuclear angiocardiography can be used to calculate cardiac output and ejection fraction (EF) and other indices of cardiac function.

Congenital Cardiovascular Disease

The cause of congenital cardiac defects has not been established, although hereditary factors may be responsible for some defects. In humans, additional factors such as maternal infection, age, and nutritional status have been identified; fetal anoxia from placental insufficiency, fetal infection or metabolic dysfunction, or other causes may contribute to the development of congenital cardiac defects. The same factors may apply in animals. Congenital cardiac defects in large animals can occur alone or in combination. The most commonly reported is VSD.[18,24,36-39] Multiple cardiac anomalies including PDA,[40,41] tetralogy of Fallot,[42,43] truncus arteriosus,[44,45] total anomalous pulmonary venous connection,[46] and Eisenmenger complex in calves[47] have been reported. Congenital anomalies of the tricuspid,[44,48-50] mitral,[51] and pulmonic valves[44,52,53] are uncommon. Congenital abnormalities of the aorta are reported in calves and foals but are also uncommon.[39,54,55] ASD occurs more commonly in calves than in foals and is frequently accompanied by other defects.[39,45,56,57] Hypoplasia of the left and right ventricles has been infrequently reported in calves and foals.[39,58,59]

Congenital cardiovascular disease should be suspected in a young patient if examination reveals a holosystolic (pansystolic), holodiastolic, or continuous murmur or a murmur with a palpable thrill or wide radiation over the thorax. Cyanosis at rest or with exercise in a patient with a cardiac murmur warrants consideration of a right-to-left cardiac shunt, obstructive pulmonary disease, or severe stenosis of the structures of the right side of the heart. The presence of any of these findings in a young animal with a history of lethargy, weakness, or failure to thrive constitutes grounds to suspect congenital cardiovascular disease.

Ventricular Septal Defect

Definition and Etiology A VSD is an opening in the interventricular septum that creates a communication between the left and right ventricles. In large animals most defects occur in the perimembranous septum and are imaged ventral to the right and/or noncoronary leaflet of the aortic valve and cranioventral to the septal leaflet of the tricuspid valve, including or adjacent to the fibrous part of the interventricular septum.[18,24,37,39] VSD can occur as a single defect or as part of a complex anomaly. Many cardiac malformations such as tetralogy and pentalogy of Fallot, truncus or pseudotruncus arteriosus, common atrioventricular canal defect, tricuspid atresia, and double outlet right ventricle include a VSD. The cause of VSD is unknown, although it has been documented to be a heritable defect in Limousine[39] and possibly Hereford[60] cattle. VDSs are more common in Welsh Mountain ponies (Section A) and in the Arabian, Standardbred, and Quarter Horse breeds, suggesting a possible hereditary predisposition.[61,62] The defect is thought to result either from failure of fusion of a part of the endocardial cushion and the muscular ventricular septum or failure of fusion of the truncal and conal septa.[63]

Clinical Signs and Differential Diagnosis The clinical signs of an isolated VSD vary and depend on the size of the defect, direction of the shunted blood, and presence of concurrent valvular or myocardial disease. In isolated VSD the blood flow is shunted from the left ventricle to the right ventricle through the defect in the interventricular septum. The size of the shunt depends on the size of the defect and the pressures in the left ventricle, right ventricle, and pulmonary artery.

VSD is suspected when there is a loud, harsh, plateau-shaped pansystolic murmur with its point of maximal intensity (PMI) in the tricuspid valve area, and a slightly softer, more crescendo-decrescendo holosystolic murmur that is loudest in the pulmonic valve area. The murmur on the left side has its PMI in the pulmonic valve area, associated with a relative pulmonic stenosis (increased blood flow across a normal pulmonic valve). A palpable cardiac thrill usually is present over the tricuspid valve region, and occasionally there is splitting of the second heart sound. The murmur may be the only clinical sign identified if the defect is small. On the other hand, poor growth, lethargy, dyspnea, exercise intolerance, and signs of CHF can be exhibited by animals with a moderate to large VSD. This usually develops by the time the animal is 5 years old. Occasionally there is a diastolic murmur of aortic insufficiency associated with a large VSD, the location of which compromises the support of one of the aortic valve cusps.[9,18,38] Cardiac arrhythmias, particularly atrial fibrillation, may be associated with VSD when there is cardiac enlargement or failure.

If the systolic murmur is loudest on the left side of the thorax, a subpulmonic VSD or a complex anomaly with pulmonic stenosis (or some form of right ventricular outflow tract [RVOT] obstruction) should be suspected.[9,18,38,64] The pulmonic murmur is usually louder than the tricuspid murmur in large animals with tetralogy of Fallot. Large animals with tetralogy of Fallot may have cyanosis at rest (uncommon in horses) or with exercise or exertion. Cyanosis is also a distinguishing feature of Eisenmenger complex, a defect in which right-sided heart resistance to blood flow causes the shunt associated with VSD to become right to left. Congenital abnormalities of the mitral and tricuspid valves cause a loud systolic murmur audible on both sides of the thorax. The PMI of the left-sided systolic murmur is more caudally located (in the mitral to aortic valve area) than the relative pulmonic stenosis murmur. Usually the murmur of mitral regurgitation is the louder of the two murmurs. In addition, congenital mitral or tricuspid valve dysplasia is rare in large animals. An innocent flow murmur of neonates can usually be distinguished from

VSD by its crescendo-decrescendo shape, PMI at the left heart base, lack of radiation, and low to moderate intensity.

Clinical Pathology Echocardiography is the diagnostic technique of choice for identifying a VSD. With 2D echocardiography the VSD can be imaged directly (Fig. 30-5) and the shunt size, location, and direction demonstrated with pulsed wave Doppler, continuous wave Doppler, color flow echocardiography, or injection of microbubbles. Careful scanning of the interventricular septum should be performed with 2D echocardiography to directly image the VSD and measure its maximal diameter in two mutually perpendicular planes.[9,18,38] The typical perimembranous VSD (≤2.5 cm in both planes) is missed if the long-axis view of the left ventricular outflow tract (LVOT) is not examined. The membranous VSD is located underneath the right and/or noncoronary leaflet of the aortic valve and ventral to the septal leaflet of the tricuspid valve. If a perimembranous defect is not found, the entire septum should be carefully scanned in all imaging planes to detect the VSD. The subpulmonic location, more common in calves, is easy to miss. This defect is usually best imaged in the short-axis view, scanning the interventricular septum between the LVOT and RVOT. With a left-to-right shunt a high-velocity turbulent jet is depicted from the right parasternal window, originating in the left ventricle, traversing through the defect in the interventricular septum into the right ventricle with color flow Doppler echocardiography (blood flow toward the transducer), whereas a negative contrast jet is imaged in the right ventricle with a right-sided injection of microbubbles.[9,18,38] M-mode echocardiography should reveal septal discontinuity when traversing the interventricular septum from the apex of the heart to the aortic root (septal dropout). Moderate to large VSDs show left atrial and left ventricular enlargement, right ventricular enlargement, and pulmonary artery dilation. The left atrial–to–aortic root ratio is increased. Aortic valve prolapse and aortic regurgitation may also be detected because of loss of support of the aortic root from the VSD, more likely with larger VSDs and VSDs with malalignment of the ascending aorta with the upper portion of the interventricular septum. Myocardial dysfunction and subsequent CHF may occur with a large VSD. Most horses with VSDs that are compatible with a normal life expectancy ultimately develop mitral regurgitation secondary to the chronic left atrial and ventricular volume overload. Continuous wave Doppler echocardiography can be used to noninvasively assess the hemodynamic significance of the shunt (see Fig. 30-5, *B*). A peak shunt flow velocity of 4.5 m/s or greater indicates a restrictive VSD with normal or near-normal right ventricular pressures.[62] Nuclear angiocardiography can also be used to demonstrate simultaneous opacification of the left and right ventricles. The radiographic presence of cardiomegaly and increased vascularization of the lungs provide only nonspecific evidence of VSD. If polycythemia is found, a complicated VSD should be suspected.

Cardiac catheterization can be used for qualitative and quantitative assessment of the VSD but has largely been supplanted by echocardiographic diagnosis. Elevated cardiac pressures provide qualitative evidence of a VSD. Right ventricular systolic pressure elevation is most common and may equal left ventricular pressure with a large VSD. Pulmonary artery pressure can be increased as a result of increased blood flow from the left-to-right shunt or increased pulmonary vascular resistance and decreased flow (restrictive pulmonary hypertension). Elevation of left or right ventricular diastolic pressure provides evidence of cardiac failure in the patient with VSD. Oximetric data (oxygen content or oxygen saturation) can be used to locate the shunt and provide some evidence of the size of the defect. A step-up in oxygen content or saturation between the right atrium and the pulmonary artery suggests a moderate or large VSD. Because most VSDs are located high in the RVOT, there may be inadequate mixing of shunted blood in the right ventricle to detect the shunt in this chamber unless the catheter is directed to the outflow tract for sampling. When the oxygen step-up is detected first in the pulmonary artery, a PDA cannot be ruled out. A small shunt may be missed by oximetry as described earlier under oxygen sampling.

By using the indicator dilution methods described previously, the shape of the concentration-time or temperature-time curve can be used to demonstrate the left-to-right shunt of a VSD. A comparison of the cardiac output measured in the right ventricle with the cardiac output measured in the pulmonary artery can give an estimation of the percent of pulmonary blood flow coming from shunted blood and therefore an estimation of the size of the defect.[25]

Angiocardiography can be performed in the anesthetized neonate and can definitively demonstrate VSD if there is simultaneous opacification of the left and right ventricles when dye is injected into the left ventricle.

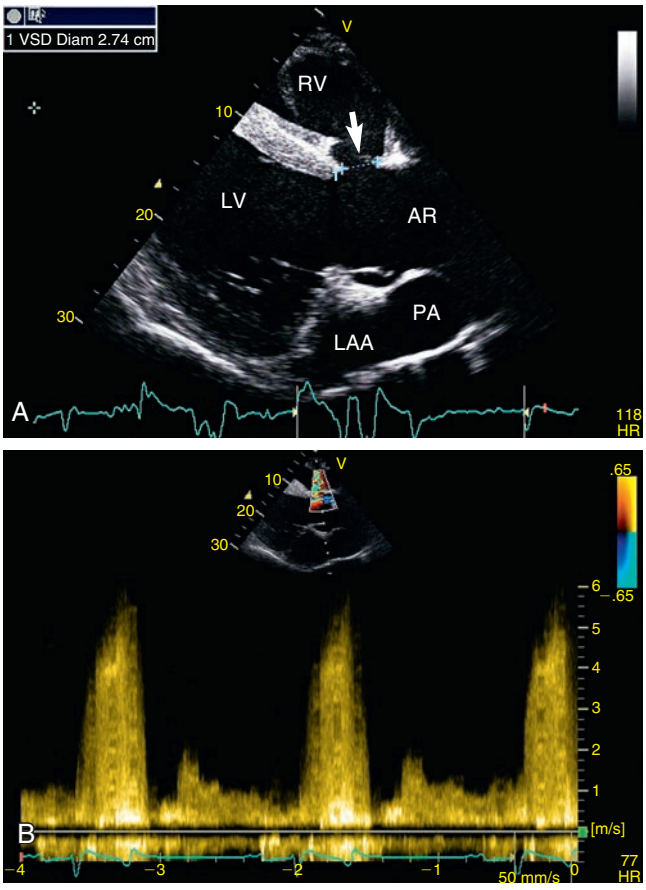


FIG. 30-5 Two-dimensional echocardiographic image **(A)** and continuous wave Doppler spectral tracing **(B)** of a ventricular septal defect (VSD) *(arrow)* in a Thoroughbred gelding who presented for poor racing performance. The VSD is located just underneath and cranial to the septal leaflet of the tricuspid valve and just ventral to the noncoronary and right coronary cusp of the aortic valve and measured 2.74 cm in this view. There is significant left ventricular enlargement in this gelding. The right ventricle *(RV),* left ventricle *(LV),* left atrial appendage *(LAA),* aortic root *(AR),* and pulmonary artery *(PA)* are all visible in this view. The spectral tracing shows a peak shunt velocity of over 5 m/s in systole. Some turbulent flow (spectral broadening) is also detected in diastole, with a peak flow velocity of approximately 1.75 m/s.

Pathophysiology A small VSD may provide enough resistance to flow that the left-to-right shunt is minimal and the patient remains asymptomatic. Horses can race successfully with small VSDs (≤2.5 cm in diameter with peak shunt velocities ≥ 4.5 m/s), although they are not usually successful as elite racehorses.[9,18,62] In smaller horses and ponies or very large horses, a VSD-to–aortic root ratio that exceeds 0.3 is likely to be hemodynamically significant.[61,62] VSDs produce a left-to-right shunt because the pressure in the left ventricle exceeds the pressure in the right ventricle. A peak shunt velocity of 3.5 to 4.5 m/s indicates an increased right ventricular pressure and a less restrictive VSD, but the defect is usually compatible with a normal life expectancy. A peak shunt velocity of less than 3.5 m/s is

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indicative of a large shunt that is hemodynamically significant. These animals usually develop CHF by 5 years of age. Occasionally the VSD is so large that the pressure between the two chambers is equalized. The right ventricle, pulmonary circulation, left atrium, and left ventricle must compensate for this volume overload, which generally results in dilation of cardiac chambers and development of pulmonary hypertension.

Simultaneous pulmonary disease or left-sided heart failure due to chronic volume overload can increase pulmonary vascular resistance. In addition to volume overload, the right ventricle is subjected to a chronic pressure overload that may be sufficient to reverse the direction of the shunt (Eisenmenger complex, more common in cattle than horses). Because of the pressure and volume overload with moderate to large VSDs, patients with this condition run a greater risk of developing CHF.

Considerable turbulence associated with left-to-right shunts and endocardial damage increase the risk of endocarditis in patients with VSD.[65] Because the VSD is usually located high in the LVOT, structural support of the aortic valve cusps may be lost, especially with large VSDs and/or malalignment VSDs, and aortic insufficiency may develop.[9,18,62] Significant aortic regurgitation adds to the left ventricular volume overload caused by the VSD.

Epidemiology The true incidence of VSD in large animals is unknown, although it is recognized as the most common congenital cardiac defect. In one study, 36 calves had 78 congenital cardiac defects, of which 11 were VSDs.[39]

Necropsy Findings VSD is usually located high in the interventricular septum just ventral to the right or noncoronary cusp of the aortic valve in the left ventricle and underneath the septal leaflet of the tricuspid valve or caudal or ventral to the crista terminalis in the right ventricle.[62] It can be an isolated defect or accompanied by other cardiac or organ anomalies. If the defect is moderate or large, there is right ventricular, left atrial, and left ventricular enlargement and pulmonary artery dilation. Increased pulmonary blood flow can lead to lung congestion, and secondary pneumonia is not uncommon. If pulmonary vascular resistance is increased, right ventricular hypertrophy may be present. There may be secondary endocarditis (infrequent in large animals)[65] or endocardial lesions as a result of turbulent blood flow across the defect.

Treatment and Prognosis There is no practical treatment for VSD in large animals. A complete echocardiographic examination is indicated to identify the presence and significance of a VSD. The size of the VSD, peak shunt velocity through the VSD, degree of left atrial and left ventricular volume overload, presence of aortic valve prolapse, detection of aortic or mitral regurgitation and myocardial function all have to be assessed to determine the VSD's significance. It is important to identify those animals with moderate to large defects, because the prognosis for normal production or function is poor. Horses with large defects (>3.5 cm or VSD/aortic root ratio >0.3) and peak shunt velocities through the defect of less than 3.5 m/s are likely to develop CHF early in life and have a shortened life expectancy. Animals with small defects may remain asymptomatic throughout life. Very rarely, spontaneous closure of the VSD may occur.[66] It is important to recognize that small defects, which provide a large resistance to flow, can produce loud murmurs, so murmur intensity is not a good predictor of defect size.

VSDs may be heritable in some breeds, and because of the increased risk of heart failure and other cardiac complications, breeding animals with this defect is not advised. As a general rule, bull studs do not accept animals with this defect into a breeding program.

Patent Ductus Arteriosus

Definition and Etiology A PDA is persistent patency of the vessel (normally present in the fetus) that connects the pulmonary arterial system to the aorta. The ductus arteriosus fails to close at birth when breathing begins and placental circulation is removed. Closure of the ductus arteriosus occurs in response to decreasing pulmonary vascular resistance and increased systemic vascular resistance.

A PDA can occur as a single defect (rare in large animals) or with other cardiac anomalies. In large animals the most common other defects reported with PDA are tetralogy of Fallot and pseudotruncus arteriosus.

Clinical Signs and Differential Diagnosis The clinical signs of PDA depend on the length and diameter of the ductus arteriosus, direction of the shunted blood, and presence of other cardiac defects. A PDA should be suspected when a continuous high-pitched murmur, frequently referred to as a "machinery murmur" because of its alternating intensity, is auscultated. The murmur may be heard on the left and right sides of the thorax but is usually loudest in the left third or fourth intercostal space at the level of the point of the shoulder. The intensity of the murmur increases with increased heart rate, exercise, or excitement. The arterial pulses are usually bounding because of the runoff of blood from the systemic to the pulmonary circulation. Occasionally the PDA is manifested by a holosystolic murmur,[67] because the diastolic component is barely audible except at the left heart base. Large PDAs can exist without producing a murmur. In the animal with increased pulmonary vascular resistance and reversal of the shunt, there may be cyanosis of the caudal parts of the body if the PDA enters the aorta caudal to the brachiocephalic trunk. Stunting of growth may also occur.

Other causes of a continuous murmur in large animals are extremely rare, but detecting a continuous machinery murmur should lead the veterinary clinician to suspect a complex congenital cardiac defect that includes a PDA, rather than an isolated defect. In older horses an aorticocardiac fistula should be suspected, particularly if the machinery murmur is of recent onset and is loudest on the right side of the chest. A systolic and diastolic murmur can be present in young animals with a large VSD causing aortic insufficiency. A similar murmur is possible with vegetative endocarditis of one of the atrioventricular or semilunar valves, producing insufficiency and stenosis of the affected valve. These latter conditions should not have the machinery murmur characteristic of the PDA. A loud systolic ejection murmur, which is confused with a PDA, frequently can be heard at the left heart base of foals shortly after closure of the PDA. This murmur may persist for 2 to 3 months.[40]

Clinical Pathology No characteristic clinicopathologic changes are associated with a PDA. Radiography may show enlargement of the cardiac silhouette and pulmonary overcirculation in an uncomplicated PDA. Pulmonary venous congestion, interstitial pulmonary edema, and alveolar edema are evidence of a large PDA with left-sided heart failure. These signs are not specific for PDA and can be present with any congenital heart defect that results in a left-to-right shunt. No consistent electrocardiographic pattern has been identified with PDA. Echocardiographic detection of an enlarged left atrium and left ventricle, with a pattern of left ventricular volume overload and increased values for the ratio of the left atrial to aortic root dimension, are diagnostic.[9,38,67,68] Direct visualization of the ductus arteriosus is difficult with echocardiography but is most successful when performed from the left cardiac window. A PDA arising from the pulmonary artery has been imaged echocardiographically in an 11-month-old Friesian-Holstein heifer.[41] High-velocity turbulent flow in the pulmonary artery and ductus arteriosus is detected throughout the cardiac cycle with pulsed wave, continuous wave, or color flow Doppler echocardiography.[9]

Cardiac angiocardiography and nuclear angiocardiography using a selective aortic angiogram provide definitive evidence of a PDA. Oximetric data show a step-up in oxygen content or saturation in the pulmonary artery proportional to shunt size. Indicator dilution methods also provide evidence of a left-to-right shunt occurring in the pulmonary artery in cases of an uncomplicated PDA. Pulmonary arterial and right ventricular pressures may be increased with a large PDA.

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Pathophysiology Normally the ductus arteriosus narrows near term and constricts rapidly after birth in response to lowered pulmonary vascular resistance, increased systemic vascular resistance, increased blood volume, and increased left ventricular pressure when breathing begins and the placental circulation is removed. If the ductus arteriosus is large or the resistance to flow across the ductus is minimal, there is a significant left-to-right shunt that produces a large left ventricular volume overload. The left ventricular response may be failure or, with time, dilation (primarily) and hypertrophy. Pulmonary hypertension and congestion result. The right ventricle can be affected by the pulmonary pressure load, and right ventricular hypertrophy can also develop. If the pulmonary resistance equals or exceeds the systemic vascular resistance, a right-to-left shunt occurs.

Epidemiology Normal foals may have a PDA for a few days after birth, but functional closure of the ductus arteriosus is expected by 96 hours of age.[67] Normal ruminants rarely have a PDA after birth, and if one is present it is considered abnormal. Functional closure may precede anatomic closure of the PDA. This defect is uncommon in older animals. No evidence suggests that this is an inherited defect in horses or cattle.

Necropsy Findings The ductus arteriosus can be of variable length and diameter but is patent between the aorta and pulmonary artery. The PDA often enters the aorta caudal to the origin of the brachiocephalic trunk. Changes in the left and right ventricles and lung and pulmonary vasculature are variable and depend on the size of the shunt. When the PDA is large, there may be cardiomegaly with left atrial and left ventricular dilation, right ventricular hypertrophy, pulmonary congestion, and edema.

Treatment and Prognosis There is insufficient evidence on which to base a prognosis for animals with PDA. The condition can be corrected surgically in neonates, but future performance has not been documented. Animals with small defects may remain asymptomatic throughout life. The prognosis is poor if the defect is large, because the risk for left (primarily) and right ventricular failure is increased. Pharmacologic closure of the PDA using inhibitors of prostaglandin synthesis has been successful in humans but is not without risk of complications and recurrence. The efficacy of prostaglandin inhibitors has not been evaluated in large animals.

Tetralogy and Pentalogy of Fallot

Definition and Etiology Tetralogy and pentalogy of Fallot are characterized by biventricular origin (overriding) of the aorta, VSD, obstruction of pulmonary arterial flow, and secondary right ventricular hypertrophy. When there is an associated ASD, the anomaly is referred to as *pentalogy of Fallot*. The defect is caused by abnormal development of the conal septum in the embryonic heart, which leads to narrowing of the right ventricular infundibulum (pulmonic stenosis), an inability of the conal septum to participate in closure of the interventricular foramen (VSD), and overriding of the aorta. Right ventricular hypertrophy due to pulmonary outflow obstruction develops.

Clinical Signs and Differential Diagnosis Tetralogy of Fallot is one of the more common congenital cardiac defects that cause cyanosis in large animals. Resting cyanosis is rare in horses, although it may be detectable after exercise. Cyanosis of the oral and nasal mucosa, tongue, vaginal mucous membranes, and occasionally the nose and skin of light-colored animals is noticed when more than 5 g/dL of hemoglobin are reduced (unoxygenated). Exercise intolerance is often marked and is characterized in most cases by dyspnea or collapse. Frequently the owner complains of slow growth or small size. A loud pansystolic murmur associated with a palpable thrill is loudest in the left third to fourth intercostal space. The murmur may be a crescendo-decrescendo murmur of pulmonic stenosis or the harsh, plateau-shaped murmur of a VSD; one of these usually predominates. A harsh band-shaped pansystolic murmur is also auscultated in the tricuspid valve area but is usually one or two grades softer than the pulmonic stenosis murmur. Excitement of the animal may result in auscultation of a gallop rhythm or an early systolic ejection click. A continuous machinery murmur associated with continuous shunting through the PDA can be auscultated in some patients.

Tetralogy and pentalogy of Fallot must be distinguished from other causes of cyanosis in young animals. Respiratory distress syndrome of neonates can be distinguished by the presence of tachypnea, dyspnea, and abnormal lung sounds in the absence of a cardiac murmur. Cyanosis caused by central nervous system disease has other neurologic manifestations. Cyanosis from congenital cardiac disease may be caused by a right-to-left shunt or by heart failure with pulmonary edema. Cyanosis resulting from heart failure or respiratory disease improves with oxygen administration, whereas the patient with a right-to-left cardiac shunt fails to improve. Right-to-left cardiac shunting does or can occur with tetralogy and pentalogy of Fallot, reverse PDA or VSD, tricuspid valve or right ventricular atresia, left ventricular hypoplasia, persistent truncus arteriosus, pseudotruncus arteriosus, and other complex congenital cardiac disease, all of which may occur with cyanosis and a cardiac murmur. A complete echocardiographic examination using a segmental approach to cardiac anatomy is necessary to accurately diagnose the correct congenital cardiac malformation, and has widely supplanted other methods of diagnosing complex congenital cardiac disease in large animals. Radiography and cardiac catheterization provide supplemental information that may be helpful in distinguishing among the causes of right-to-left cardiac shunting.

Clinical Pathology Increased packed cell volume (PCV), red blood cell count, and hemoglobin concentration (polycythemia) may be present in some animals with tetralogy and pentalogy of Fallot.[43] However, polycythemia is uncommon in foals with cyanotic congenital cardiac disease and is usually less than 45% in most calves. The degree of arterial hypoxemia is variable, depending upon the amount of right-to-left or bidirectional shunting. Electrocardiographic changes are usually nonspecific, but a right-axis deviation may be detected.[43] Radiographs of the lungs may show decreased vascularity. Echocardiography easily visualizes the four components of tetralogy of Fallot. The VSD and overriding aorta are usually clearly visible with 2D echocardiography. The malalignment VSD is usually large and located just below the right cusp of the aortic valve, separated from the pulmonic valve by the crista supraventricularis. The aortic root is usually large, dextroposed, and overrides the septal defect. Echocardiography shows increased thickness of the right ventricular wall, ventricular septal hypertrophy, paradoxical septal motion, and similar left and right ventricular internal dimensions. Narrowing of the RVOT, pulmonic stenosis, or a hypoplastic pulmonary artery (most common) may be imaged as the cause of the RVOT obstruction. Pulsed wave and color flow Doppler echocardiography can be used to further characterize the abnormalities of blood flow associated with tetralogy of Fallot, in particular the severity of the RVOT obstruction. Contrast echocardiography also nicely demonstrates the path of blood flow with a peripheral venous injection. Contrast echoes are imaged entering the right ventricle from the right atrium, and then simultaneous opacification of the pulmonary artery, left ventricle, and aorta occurs.

Cardiac catheterization can be used to demonstrate equalization of ventricular pressures and a pressure gradient between the right ventricle and pulmonary artery. Oximetry should demonstrate decreased oxygen content in the left ventricle compared with the pulmonary vein. Angiocardiography demonstrates simultaneous filling of the right ventricle, left ventricle, and overriding aorta, with decreased pulmonary artery filling and increased right ventricular trabeculation (hypertrophy).

Pathophysiology The VSD is usually large, resulting in equalization of pressures in the two ventricles and the aorta. The degree

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of shunting is controlled by the resistance across the stenotic RVOT compared with the resistance across the aortic valve. If the RVOT is severely obstructed, the clinical signs of cyanosis are more marked. Excitement, drugs, or increased myocardial contractility from any cause decreases right ventricular volume and worsens clinical signs. Right ventricular failure usually is not a consequence of the pressure overload because of equalization of the ventricular pressures.

Epidemiology The prevalence of tetralogy and pentalogy of Fallot in large animals has not been documented, but these defects seem to be more common in calves than in foals. There is no evidence that these disorders are inherited.

Necropsy Findings Examination of the heart reveals a rounded apex caused by right ventricular enlargement. A high, usually large VSD, a dextroposed overriding aorta that straddles the VSD and the left and right ventricle, right ventricular hypertrophy, and septal hypertrophy are present. There is usually right ventricular infundibular narrowing and a hypoplastic pulmonary artery, although there may be valvular pulmonic stenosis with a poststenotic dilation. The right and left atria may be enlarged.

Treatment and Prognosis There is no practical treatment for tetralogy and pentalogy of Fallot in large animals. When cyanosis or exercise intolerance is present or growth is stunted (the latter two are common findings in affected animals), the prognosis for long-term survival, production, or performance is poor. Affected foals should not be used for performance or broken to ride if they live long enough. As with many congenital cardiac diseases, the intensity of the murmur is not a good predictor of the severity of the condition, and further diagnostic tests are indicated.

Other Congenital Cardiac Defects

ATRIAL SEPTAL DEFECT. ASD is a connection between the left and right atria at the septal level. The most common type of defect is the ostium secundum defect, of which patent foramen ovale (PFO) is seen most frequently. PFO is relatively common in calves and is due to failure of the septum primum, the valve of the foramen ovale, to become adherent to the crista dividens after birth, when changes in left and right atrial pressures produce functional closure of the foramen ovale. PFO is frequently associated with PDA in calves.[39]

Animals with an ASD are frequently asymptomatic, but a holosystolic crescendo-decrescendo murmur may be heard at the left heart base. The shunt is usually left to right, and the murmur is the result of increased volume being ejected across the pulmonic valve. If the defect is large, right atrial, right ventricular, and left atrial dilation may be present. Differential diagnostic considerations are a functional murmur, pulmonic stenosis, VSD, or PDA. A definitive diagnosis can be made by 2D echocardiography, in which an enlarged right atrium, right ventricle, and left atrium are imaged. Pulsed wave Doppler, color flow, or contrast echocardiography can be used to demonstrate the shunt through the ASD.

PULMONIC VALVE STENOSIS. Pulmonic valve stenosis is uncommon as a single defect but has been reported in a foal with VSD and as one of multiple defects in calves and foals.[9,39,53] Clinical signs of cardiac murmur, cyanosis, and polycythemia are variable and depend largely on the other cardiac defects present. Characterization of the severity of the pulmonic stenosis and other associated cardiac defects can be performed with a complete echocardiographic examination.

TRICUSPID VALVE ATRESIA. Tricuspid valve atresia has been reported in foals[44,48-50] in conjunction with other cardiac defects. The abnormalities associated with tricuspid atresia include PFO, VSD, small right ventricle, large left ventricle, and large mitral valve orifice. The foals showed cyanosis and a crescendo-decrescendo or band-shaped holosystolic or pansystolic murmur audible over the left and right heart base. Tachycardia, tachypnea, and weak peripheral pulses also were present. Polycythemia was commonly reported. Echocardiographic diagnosis of tricuspid atresia in foals has been reported.[44,49] A thick echo in the region of the tricuspid valve that does not separate in diastole (absent tricuspid valve), an ASD (usually PFO), a VSD, a small right ventricle, a large left ventricle, and a large mitral valve orifice are the echocardiographic findings in tricuspid atresia. Blood flow (right to left) through the PFO into the left atrium and left ventricle, followed by simultaneous opacification of the aorta and right ventricle, is detected with contrast echocardiography. Affected foals rarely live past weanling age. Necropsy showed tricuspid atresia, along with ASD, VSD, small right ventricle, and large left ventricle. Pulmonic valve stenosis and dextropositioning of the aorta have also been reported.

MITRAL VALVE DYSPLASIA. Mitral valve dysplasia is a rarely reported early developmental anomaly in the horse.[9,51,69] The affected foals had a grade 3 to 5/6 holosystolic decrescendo or coarse-type murmur loudest in the mitral to aortic valve area. On echocardiography, the mitral valve leaflets appeared thickened, bright, and irregularly nodular in the foal with mitral valve dysplasia. A cleft was imaged in the midportion of the free wall leaflet, with small papillary muscles and shortened, unevenly thickened chordae tendineae.[51] The other foal was missing the right papillary muscle, and the parachute configuration of the mitral valve was readily imaged echocardiographically.[69] One foal died, and the foal with the parachute mitral valve was humanely euthanized because it was stunted and had a poor prognosis. Other congenital variation in the configuration of the mitral valve leaflets resulting in mild mitral regurgitation occurs more frequently in horses, usually compatible with a normal life expectancy.

VENTRICULAR HYPOPLASIA. Ventricular hypoplasia has been reported in foals and calves.[39,58] The defect may be present with other cardiac defects and is usually associated with early death. The defect was present in three closely related Holstein calves, suggesting possible genetic factors.[39]

TRUNCUS OR PSEUDOTRUNCUS ARTERIOSUS. *Persistent truncus arteriosus* refers to the condition in which one arterial vessel leaves the heart above a VSD. The coronary and pulmonary arteries and aorta arise from this vessel. Persistent truncus arteriosus has been diagnosed in foals and calves.[45] Subclassifications of this condition have been applied to humans, depending on the origin of the pulmonary trunk or arteries. Pseudotruncus arteriosus has also been described in foals and a calf and is characterized by the presence of a remnant of an atretic pulmonary trunk.[44,70] With pseudotruncus arteriosus, the pulmonary blood supply comes from bronchial arteries or a PDA. Clinical manifestations of these conditions include tachycardia, exercise intolerance, and a cardiac murmur. The murmur may be a continuous machinery murmur if a PDA is also present, holosystolic and crescendo-decrescendo and loudest at the left heart base, or the coarse murmur of the VSD may be auscultated, although the relative pulmonic stenosis component is absent. Cyanosis, dyspnea, or syncope may be seen with exercise or excitement. CHF and stunted growth may be noticed. Polycythemia was detected in a calf with a pseudotruncus arteriosus.[70] The presence of cyanosis with the cardiac murmur helps differentiate this condition from a simple VSD or PDA. Definitive diagnosis may be made by echocardiography, angiocardiography, or nuclear angiocardiography. These foals and calves have a guarded to grave prognosis. Their life expectancy depends upon the magnitude of their pulmonary blood flow.

AORTIC ANOMALIES. Dextropositioning or transposition of the aorta are the most common aortic anomalies of foals and calves and are seen most frequently with other defects. Other aortic anomalies of foals and calves are persistence of the right aortic arch and double aortic arch, which may cause esophageal compression. The clinical presentation is one of esophageal obstruction. Interruption of the aortic arch in two foals with VSD, ASD, and PDA has been reported.[55]

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The foals showed weakness, lethargy, cyanosis, and tachycardia. The murmur was pansystolic and plateau shaped, with the PMI on the right side of the thorax. Radiology showed cardiomegaly and increased vascularization of the lungs. Cardiac catheterization showed left ventricular failure.

Bicuspid and quadricuspid cusps of the aortic and pulmonic valves occur in large animals and usually result in both stenosis and valvular insufficiency. An aneurysm of the sinus of Valsalva was detected in a 3-year-old Thoroughbred gelding as an incidental finding.[71] Occasionally a diastolic murmur may be associated with aortic insufficiency in horses with sinus of Valsalva aneurysms.[72] These sinus of Valsalva aneurysms usually rupture later in life, and the horse develops acute distress, colic, and uniform ventricular tachycardia (VT). A continuous machinery murmur associated with the presence of an aorticocardiac fistula is usually present on the right side of the thorax.

EISENMENGER COMPLEX. Eisenmenger complex has been described in a stunted 24-month-old Holstein heifer that had a loud, crescendo-decrescendo, pansystolic murmur heard best over the pulmonic valve.[47] The heifer had a prominent gallop rhythm from a loud fourth heart sound, exercise intolerance without cyanosis, and polycythemia. Cardiac catheterization showed increased pressures in the right atria, right ventricle, and pulmonary artery, with normal left-sided pressures. The echocardiogram was characterized by a VSD, overriding aorta, and dilation of the pulmonary trunk, a feature that distinguished this from tetralogy of Fallot. Left ventricular function was decreased, and at necropsy the heart was enlarged and rounded with a dilated pulmonary trunk and small aorta. The right ventricle was dilated and hypertrophied, whereas the left atria and ventricle were only mildly dilated.

ECTOPIA CORDIS CERVICALIS. Ectopia cordis cervicalis is a relatively common defect of cattle.[39,54] Although this defect usually results in the heart being in the cervical region, a few animals may have the heart in the pectoral region (14%) or abdomen (3%).[54] Various defects are associated with ectopia cordis cervicalis, including defects of the heart, great vessels, neck (torticollis), ribs, and sternebrae. The heart is usually contained within the pericardium under the muscles of the skin in the ventral cervical area, with the double apex of the heart pointing craniodorsally. The ligaments of the pericardium are most frequently attached to the mandibles and the parotid fascia cranially, the cervical fascia laterally, and the first rib or manubrium caudally. The lung may lack the cardiac notch and often protrudes to the base of the heart. Although the prognosis for a productive life is poor, some calves lived until about 1 year of age.

MISCELLANEOUS CARDIAC DEFECTS. Other cardiac defects can occur, but either the significance of the lesion is questioned or the defect has been recorded infrequently. Complete atrioventricular canal defect has been reported in several foals.[56,57,73] Anomalous coronary artery development has been reported at postmortem examination in both calves and horses and has been thought to be the cause of death in most cases.[74,75,76] Congenital hematomas of the atrioventricular valves also have been noted, but the significance is unknown.[39] Endocardial fibroelastosis, an anomalous development of the endocardium associated with left ventricular hypertrophy, is usually a severe defect resulting in death of the animal. The frequency of this defect in large animals is not established.

Valvular Heart Disease

Definition and Etiology In adult animals, disorders of the tricuspid, pulmonic, mitral, or aortic valves are usually acquired and most commonly result in insufficiency of the affected valve. These disorders may be the result of degenerative changes, infection (bacterial or viral endocarditis or myocarditis), inflammation (valvulitis), trauma, myocardial disease (cardiomyopathy), or unknown causes. They are usually manifested by a cardiac murmur, most frequently of valvular regurgitation, with the PMI at the location of the affected valve or in the direction of the regurgitant blood flow. The mitral and aortic valves are the most common location of degenerative valve disease in horses.[77] Chronic active infection such as foot abscesses, rumenitis, reticular abscess, or other septic process may lead to sustained or recurrent bacteremia, predisposing the animal to the development of bacterial endocarditis, particularly in cattle, or a nonvegetative valvulitis, probably more common in horses. Experimentally, valvular vegetative endocarditis can be induced by intravenous (IV) administration of bacteria without preliminary damage to a valve.[78] Rupture of a valve leaflet or chordae tendineae can cause valvular heart disease, as can dilation of a cardiac chamber from any cause or rupture of the aortic root or of a sinus of Valsalva aneurysm.[72,79-81] In rare cases neoplasia, primarily lymphosarcoma of cattle, can cause valvular heart disease. Congenital valvular heart disease in adult animals is rare. The most common bacterial isolates from equine and bovine endocarditis cases are streptococci and *Pasturella* or *Actinobacillus* spp. and *Trueperella pyogenes* (formerly *Arcanobacterium [Actinomyces] pyogenes*) in horses and cattle, respectively, although a wide variety of organisms has been isolated from large animals with endocarditis.[82-89]

Clinical Signs and Differential Diagnosis Most animals with valvular heart disease have no clinical signs, but a cardiac murmur is detected during a routine examination. Clinical signs vary depending on lesion severity and its rate of development. Murmurs of valvular heart disease are frequently holosystolic (Fig. 30-6), pansystolic, or holodiastolic (Fig. 30-7). They radiate from the PMI in the direction of the abnormal blood flow; are coarse and band-shaped, crescendo or honking (if systolic), or decrescendo and blowing or musical (if diastolic); and are usually moderate to loud in intensity (≥grade 3/6) but may be softer if holodiastolic. All these characteristics help distinguish these murmurs from functional or innocent murmurs, which generally occur early or late in systole or diastole but can be holosystolic; are soft and blowing or crescendo-decrescendo in quality; are localized to a small area; do not radiate; and are soft to moderate in intensity (≤3/6). Murmur intensity is not a reliable indicator of lesion severity except in horses with tricuspid regurgitation, in which the longer, louder murmurs are associated with a larger jet of tricuspid regurgitation.[90] In cattle in particular, severely involved valves (usually in cattle with endocarditis) commonly have faint or no audible murmurs.

The location of the PMI of the murmur is helpful in distinguishing which valve is involved, although more than one valve can be

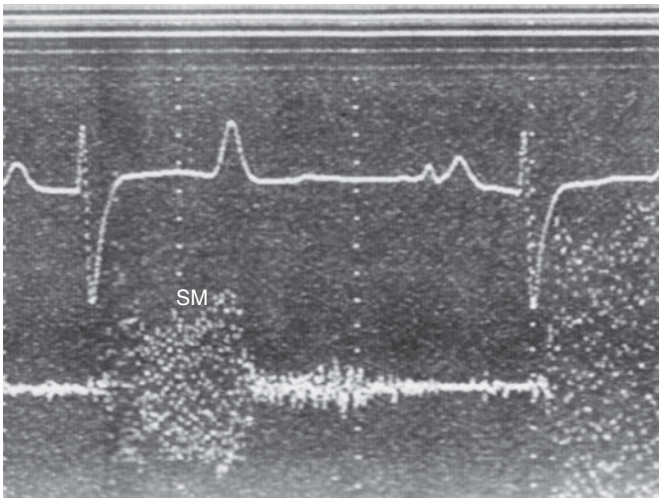


FIG. 30-6 Phonocardiogram obtained from a horse with a ruptured mitral valve chorda tendineae. A loud plateau-shaped holosystolic murmur *(SM),* which is variable in intensity, occurs when the free wall leaflet of the mitral valve is prolapsing into the left atrium.

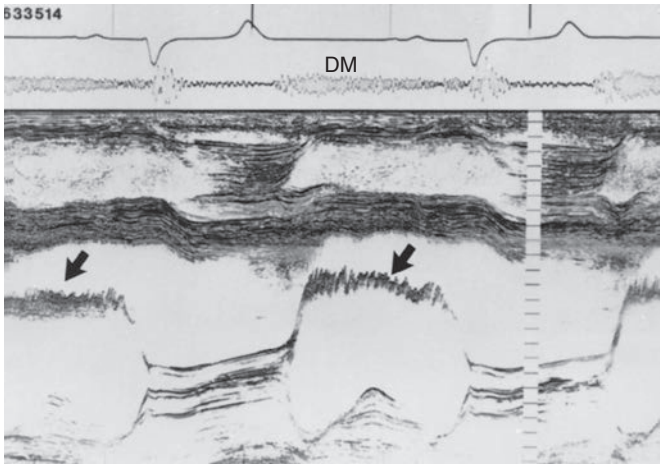


FIG. 30-7 Phonocardiogram and M-mode echocardiogram obtained from a horse with a holodiastolic murmur *(DM)* caused by aortic valve regurgitation. The M-mode echocardiogram shows diastolic flutter *(arrows)* of the septal mitral valve leaflet, characteristic of aortic valve insufficiency.

affected in the same animal. The PMI for lesions of the mitral valve is often in the mitral valve area, although murmurs of mitral regurgitation usually radiate dorsally toward the left heart base and aortic valve area. Therefore loud systolic murmurs with the PMI in the aortic or mitral valve area in horses are usually mitral regurgitation murmurs. Disorders of the tricuspid valve commonly have the PMI on the right side of the thorax (third to fourth intercostal spaces [horses] or second to third intercostal spaces [cattle]). Infrequently the murmur may also be heard on the left side of the thorax cranial to the pulmonic valve location in the second intercostal space. Aortic and pulmonic valve lesions produce murmurs with the PMI at the left heart base in the fourth or third intercostal space, respectively. Acquired valvular lesions of the mitral and tricuspid valves produce primarily systolic murmurs.[19,82,83,85,90-95] Diastolic tricuspid flow murmurs have been reported, however, and may be associated with right-sided mural or valvular masses in horses[65] or may be physiologic, associated with normal blood flow across the atrioventricular valves.[96,97] Lesions of the aortic and pulmonic valves may produce diastolic murmurs, systolic murmurs, or both,[82,98-100] but diastolic murmurs of regurgitation are most common in large animals. Aortic regurgitation associated with degenerative valve disease is most common in horses, whereas pulmonic regurgitation associated with bacterial endocarditis is more common in cattle. Aortic valve lesions in horses have primarily holodiastolic, decrescendo, musical murmurs (see Fig. 30-7) but can also be decrescendo, soft, and blowing. Aortic regurgitation murmurs are accompanied by a water-hammer or bounding arterial pulse if the aortic regurgitation is associated with a significant left ventricular volume overload.[19,82,101] The musical quality of the murmur (harmonic) indicates that some part of the aortic valve is vibrating during diastole. The arterial pulse quality becomes more bounding as the aortic regurgitation becomes more severe, and is a good clinical indicator of the degree of left ventricular volume overload. Ventricular premature beats and atrial fibrillation may also be detected in horses with significant aortic regurgitation.

Besides the cardiac murmur, animals with valvular heart disease may have exercise intolerance, arrhythmias, weight loss, or signs of CHF evidenced by tachycardia, coughing, respiratory distress, jugular venous distention, subcutaneous edema, and ascites (uncommon in large animals, especially horses). In adult cattle, mammary vein distention is another sign of CHF.[83] Cardiac enlargement may be noted as an increased area of auscultation and/or percussion or caudal dislocation of the apical impulse of the heart. Atrial fibrillation may be present. This development is usually an indicator of atrial enlargement in animals with valvular heart disease. If tricuspid valve regurgitation is present, there may be abnormal systolic jugular venous pulsations. If mitral regurgitation is present there may be tachycardia, tachypnea, poor recovery to resting respiratory rate after exercise, coughing, and frothy pulmonary edema (uncommon). Lung sounds may be harsh at rest and on deep inspiration may include crackles or moist bubbly sounds (both of the later auscultatory findings are rare). Most horses with pulmonary edema have only harsh breath sounds that are detected at rest and on deep inspiration.

One of the clinical signs of bacterial endocarditis is a cardiac murmur, the PMI and timing of which depend on the valve or valves affected. Other signs may include tachycardia, arrhythmias, auscultation of prominent heart sounds, tachypnea, coughing, recurring fever, anorexia, weight loss, or signs of CHF. Evidence of disseminated sepsis such as pneumonia, hematuria, or pyuria is usually present. Shifting leg lameness and swollen joints or tendon sheaths are common but usually have an immune-mediated cause, although a horse with bacterial endocarditis and septic tenosynovitis has been reported.[86] Mastitis and decreased milk production are common in cattle. The presence of weight loss, fever, and signs of recurring sepsis help distinguish bacterial endocarditis from other forms of acquired valvular disease.

The clinical signs of a major mitral valve chordal rupture (major chorda tendineae) or its characteristic murmur distinguish this disease from other mitral valve diseases. The murmur is usually a widely radiating murmur of mitral valve regurgitation (see Fig. 30-6) with a distinctive honking quality (the honking quality is consistent with vibration of the mitral valve chorda tendineae or leaflet with blood flow in systole). However, the honking quality may be absent and replaced by a band-shaped pansystolic murmur. There may be evidence of acute hemodynamic collapse. Acute onset of respiratory distress with coughing and expectorating foamy pulmonary edema fluid (this fluid is also detected at the external nares) is a relatively consistent feature with rupture of a major chorda tendineae. Signs of right-sided heart failure (jugular venous distention, subcutaneous edema, and ascites) may develop rapidly. Atrial arrhythmias, most frequently atrial fibrillation, often develop secondary to atrial enlargement. Supraventricular arrhythmias have also been reported in foals with a ruptured mitral chorda tendineae.[93] Acute onset of respiratory distress, along with a honking systolic murmur, distinguishes mitral valve chordal rupture from other causes of mitral regurgitation. The honking systolic murmur of a ruptured mitral valve chorda tendineae can also be heard in the absence of any clinical signs in horses with a minor chordal rupture. The murmur of mitral valve prolapse is also a distinctive murmur and should be suspected in horses whenever a mid- to late-crescendo systolic murmur is auscultated with the PMI over the mitral valve area.[19,102] A similar murmur is frequently auscultated in horses with tricuspid valve prolapse. Murmurs of mitral or tricuspid valve prolapse can be detected in horses with all degrees of valvular insufficiency. Most frequently, however, only small amounts of valvular regurgitation are associated with valvular prolapse. An increased prevalence of mitral and tricuspid regurgitation has been reported in young horses in training.[103-106]

Clinical Pathology Diagnosis of valvular disease is best performed with a complete echocardiographic examination including M-mode, 2D, and Doppler echocardiography. Two-dimensional echocardiography is superior to M-mode for detection of valvular abnormalities (Figs. 30-8 and 30-9), measurement of valvular masses (see Fig. 30-9, *B*), and global assessment of ventricular function, but chamber enlargement, high-frequency vibrations of the valve leaflets, and shortening fraction (an indication of ventricular systolic function) can be determined by both. Pulsed wave, continuous wave, and color flow Doppler echocardiography can be used to semiquantitate the severity of valvular regurgitation and should be performed from both sides of the thorax, interrogating the left atrium in multiple imaging planes.[9,102,107,108] The size of the regurgitant jet at its origin and the extent of the jet within the left atrium detected with pulsed wave and/or color flow echocardiography are two indicators of the severity of the valvular insufficiency.[19] Detection of proximal flow convergence indicates hemodynamically significant mitral regurgitation. The duration of the mitral regurgitation jet is also important in

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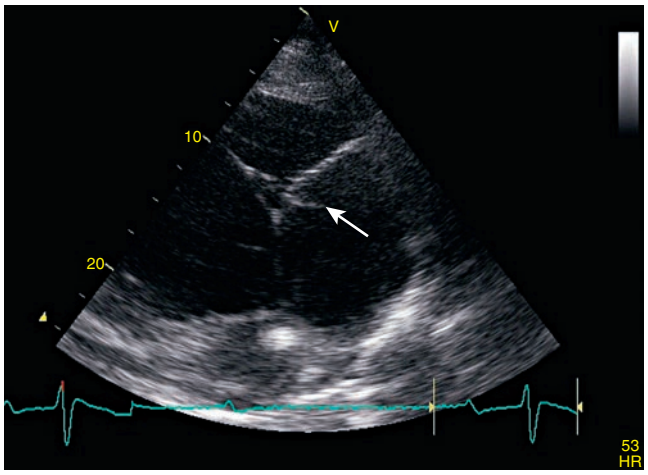


FIG. 30-8 Two-dimensional echocardiographic image obtained from the left parasternal window of a ruptured mitral chorda tendineae *(arrow)* in the left atrium of a gelding with mitral regurgitation and a honking pansystolic murmur.

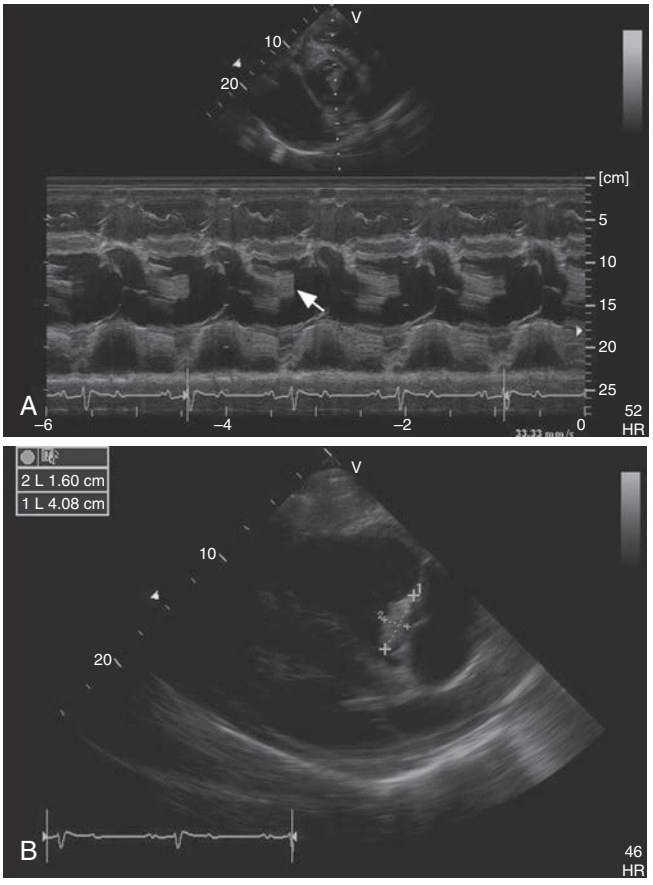


FIG. 30-9 Echocardiograms of a bacterial endocarditis lesion on the aortic valve of a horse. The lesion can be seen on the aortic valve M-mode **(A)** as a thick echoic band *(arrow)* and is measured in the two-dimensional echocardiographic image of the left parasternal long-axis view **(B).**

assessing severity. Clinically insignificant jets of regurgitation are detected only just behind the valve when it is closed. Valvular insufficiency is mild when the jet occupies one third or less of the receiving chamber, moderate when the jet occupies greater than one third but less than two thirds of the receiving chamber, and severe when the jet occupies greater than two thirds of the receiving chamber. The intensity and shape of the spectral Doppler tracing of the mitral regurgitation jet also provide information about its severity. Severe

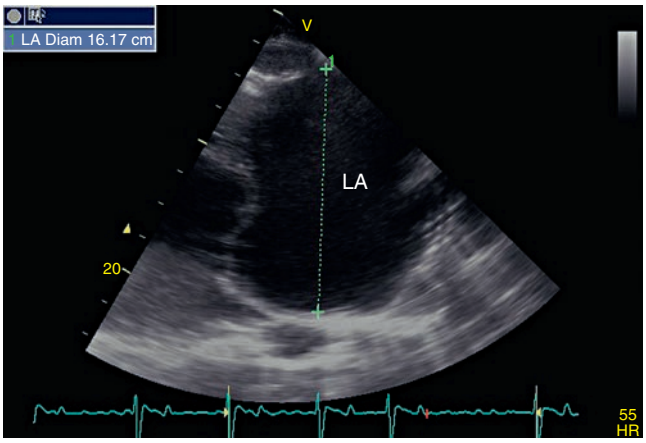


FIG. 30-10 Left parasternal echocardiographic image of the left atrium *(LA)* and mitral valve from a horse with left atrial enlargement (16.17 cm).

mitral regurgitation is associated with an intense triangular rather than parabolic signal that increases rapidly at the onset of systole.

Echocardiographic signs of mitral regurgitation are increased left atrial (Fig. 30-10; also see Fig. 30-3) and left ventricular dimensions, rounding of the left ventricular apex, and a pattern of left-sided volume overload. Left ventricular function may be normal (if mitral regurgitation is mild) or the FS may be increased (if there is a significant left ventricular volume overload associated with acute moderate to severe mitral regurgitation), unless there is concomitant myocardial disease. Normal or decreased contractility is present with chronic severe mitral regurgitation. A round, turgid left atrium with bulging of the interatrial septum toward the right is another indication of hemodynamically severe mitral regurgitation. A larger-than-normal pulmonary artery (larger than the aortic root) is compatible with severe pulmonary hypertension and left-sided heart failure. A smaller-than-normal aortic root is detected echocardiographically in horses in low-output left-sided heart failure.[9,19,93,94,102]

The cause of the valvular regurgitation can often be determined. Endocarditis (see Fig. 30-9), ruptured mitral valve chordae tendineae (see Fig. 30-8), a flail valve leaflet, valvular prolapse, or thickening of the valve leaflet are readily imaged echocardiographically.[94] The regurgitant jet detected with pulsed wave or color flow Doppler echocardiography usually originates from the site of the valvular abnormalities detected with 2D echocardiography. In some animals, the lesion responsible for the valvular insufficiency is not visualized with 2D echocardiography, but the regurgitant orifice is detected with pulsed wave or color flow Doppler echocardiography.[5,9,108] A ruptured mitral valve chorda tendineae is diagnosed by finding a mobile linear echo everting into the left atrium (see Fig. 30-8) or a flail leaflet that may prolapse into the left atrium during systole, systolic and chaotic diastolic mitral valve flutter, rapid mitral valve opening with increased excursion of the affected leaflet, and lack of coaptation of the mitral valve in systole. The asynchronous movement of any portion of the valve leaflet during any phase of the cardiac cycle indicates the presence of a flail valve leaflet.[9,19,91,94]

Tricuspid regurgitation may produce echocardiographic evidence of right atrial and right ventricular enlargement with paradoxical septal motion. Frequently the cause of tricuspid valve regurgitation in cattle is bacterial endocarditis, and the incompetent valve can be visualized. In cattle, neoplasia of the right atrium, tricuspid valve, or right ventricle can usually be visualized when present.[109] Tricuspid regurgitation is common in horses with no obvious valvular lesion.[97,104,110]

Aortic valve regurgitation is diagnosed echocardiographically by observing left ventricular dilation, increased aortic root diameter (Fig. 30-11), increased left ventricular FS (if the aortic regurgitation is moderate to severe and left ventricular function is normal), diastolic fluttering of the septal mitral valve leaflet (see Fig. 30-7), or less

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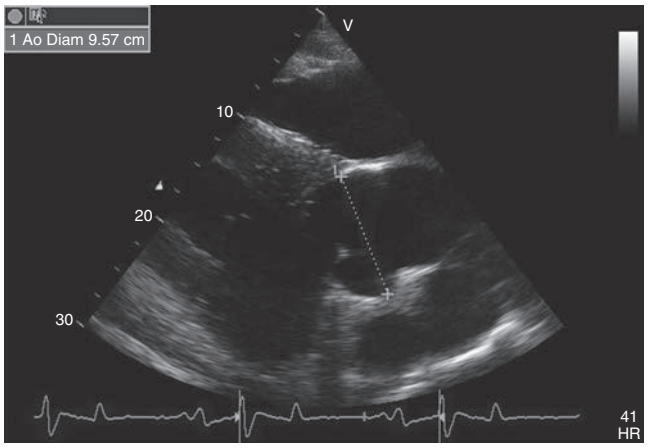


FIG. 30-11 Two-dimensional echocardiographic image of an enlarged aortic root (9.57 cm) obtained from an aged gelding with moderate aortic regurgitation that has been present for several years.

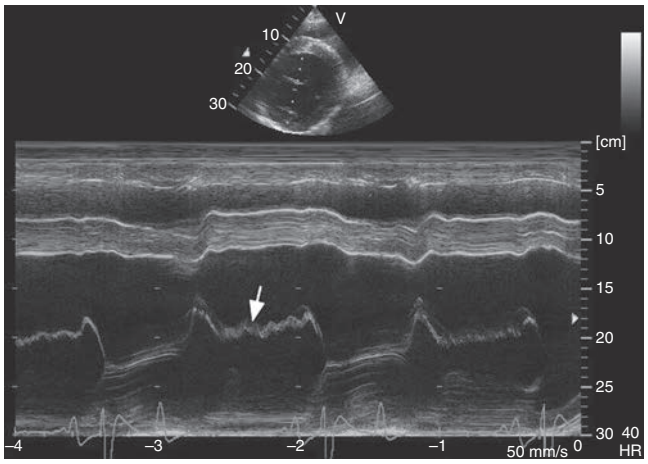


FIG. 30-12 M-mode echocardiogram obtained from a gelding with moderate chronic aortic regurgitation. Notice the high-frequency vibrations *(arrow)* on the interventricular septum.

frequently by observing high-frequency vibrations of the interventricular septum or aortic valve in diastole (Fig. 30-12).[9,19,99,101,111] Rarely, premature closure of the mitral valve is detected. Thickening of the left cusp of the aortic valve is frequently detected echocardiographically, but prolapse, fenestration, and tears of the aortic cusps also occur.

Acquired pulmonic valve lesions are uncommon in large animals and when present are usually associated with bacterial endocarditis.[100,112] Diagnosis is established by finding the mass associated with the pulmonic valve. Severe pulmonic regurgitation associated with pulmonic valve rupture has been reported in one horse.[113] Pulmonic regurgitation is most common in horses with pulmonary hypertension and CHF but is rarely detected clinically.

Lesions of bacterial endocarditis (see Fig. 30-9) may have a shaggy, ragged, or cystic appearance on 2D echocardiography.* Occasionally the only abnormality noticed is valve thickening, with ventricular hyperkinesis and enlargement of the chambers on the side of the affected valve. Acoustic reverberation and production of microbubbles have also been associated with valvular bacterial endocarditis.[93,96] Other laboratory evidence of bacterial endocarditis includes anemia, neutrophilia (a left shift may be present), an increased serum globulin concentration, and hyperfibrinogenemia. Liver enzymes are frequently mildly elevated, and a urinalysis sometimes shows hematuria or pyuria. Positive blood cultures taken during febrile episodes confirm the diagnosis when associated with these findings, but many times culture results are negative in large animals with bacterial endocarditis. Other laboratory evidence of disseminated sepsis includes neutrophilic response in peritoneal, tracheal wash, or joint fluid. Ventricular arrhythmias are frequently detected electrocardiographically in individuals with mitral or aortic valve endocarditis. Radiographic or sonographic evidence of disseminated pneumonia also may be found with bacterial endocarditis, usually in large animals with a right-sided lesion.

Other laboratory evidence of valvular heart disease is nonspecific. The ECG is not reliable for detecting chamber enlargement associated with valvular incompetence, but is valuable for documenting cardiac arrhythmias occurring secondary to chamber enlargement or the underlying myocardial disease. Radiographic findings of cardiac enlargement, increased pulmonary vascular pattern, or pulmonary edema are also nonspecific. Cardiac catheterization can be performed, and pressure measurements help determine the degree of cardiac dysfunction. Nuclear angiocardiography shows cardiac enlargement or prolonged washout of contrast material. Time-activity curves can be helpful in accurately documenting ventricular dysfunction and the valvular regurgitant fraction.[35]

Pathophysiology

Acquired valvular heart disease that is slow in onset or gradually progressive may be asymptomatic at first, but cardiac changes occur that eventually may lead to CHF. Valvular incompetence from endocarditis, degenerative changes, chordal rupture, or other causes results in volume overload of the recipient chamber. Initially the output of the chamber is increased to maintain forward output, but the increased end-diastolic volume of the recipient chamber leads to compensatory dilation and a mild elevation in end-diastolic pressure. Compensatory hypertrophy may also result. In the later stages of valvular regurgitation, contractile function of the volume-overloaded chamber may diminish, leading to further elevation of end-diastolic pressure and decreased compliance. In the case of severe aortic and mitral regurgitation, this causes elevation of left atrial pressure and eventually pulmonary venous hypertension. PAWP is higher at rest and during exercise in horses with moderate mitral regurgitation.[115] With severe tricuspid regurgitation, right atrial pressure or CVP increases. Increased myocardial oxygen consumption is a natural sequela, and biventricular failure can ensue.

If valvular heart disease is acute in onset, as with major chordal rupture of the mitral valve, the regurgitation and volume overload are imposed on the left atrium, which cannot dilate and adapt acutely to the increased diastolic filling. The sudden hemodynamic change leads to pulmonary venous hypertension and acute pulmonary edema. However, most horses with mitral regurgitation do not have acute fulminant pulmonary edema. Instead, chronic pulmonary hypertension leading to subtle respiratory signs associated with interstitial pulmonary edema and the subsequent development of right-sided CHF are common in horses with severe mitral regurgitation.[94] In one study, 12 of 14 horses with CHF had jugular distentions or pulsations, 10 had abnormal lung sounds (crackles), and 9 had a cough.[116]

Bacterial endocarditis of the mitral or tricuspid valve may lead to rupture of the chordae tendineae. Mitral chordal rupture has been reported in adult horses and foals with bacterial endocarditis, leading to acute left-sided CHF.[93] In addition to the hemodynamic load placed on the heart from an incompetent valve, bacterial endocarditis also results in disseminated sepsis. The vegetations are made up of layers of fibrin, blood cells, necrotic tissue, and bacteria and are relatively resistant to short-term antimicrobial therapy. Disseminated sepsis may be the cause of death or the reason for culling of the animal. Myocardial necrosis of a papillary muscle was associated with mitral chordal rupture in one foal.[93]

Epidemiology

Acquired valvular heart disease is common in large animals, involving 356 of 1557 horses (22.9%) in one abattoir survey.[77] Endocarditis, one form of valvular heart disease, was

*References 65, 85, 87, 88, 93, 99, 100, and 114.

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reported in 4% of cattle in another study.[117] Bacterial endocarditis most commonly affects the tricuspid valve in cattle but has been reported on the pulmonic, mitral, and aortic valves as well.[83,95,99,100] Most cases of tricuspid valve bacterial endocarditis have been reported in horses with septic jugular vein thrombophlebitis.[82,85,118] Tricuspid valve endocarditis has also been reported in a horse with a VSD.[65] Aortic and mitral valve endocarditis are most common in horses, occurring with nearly equal frequency.[84,85] In the largest survey of acquired valvular heart disease in horses, the aortic valve was affected most commonly with degenerative valve changes, followed by the mitral valve, tricuspid valve, and (uncommonly) pulmonic valve.[77] Not all valvular lesions are associated with incompetency of the valve. Degenerative valvular changes, particularly changes involving the aortic valve, are seen more commonly in older horses.

Necropsy Findings Acquired valvular disease is associated with finding nodular thickening, fibrous bands, valve fenestrations, rupture of mitral valve chordae tendineae, fibrinous masses typical of endocarditis, or combinations of these lesions on postmortem examination. There may be associated or secondary changes varying from enlargement of a chamber or vessel to degeneration, inflammation, and fibrosis. Enlargement (primarily dilation) of the chamber receiving the regurgitant flow, in addition to enlargement (primarily dilation) of the chamber or vessel from which the regurgitant flow arises, is commonly detected. Jet lesions, usually found in the receiving chamber, are associated with the high-velocity turbulent regurgitant blood flow.

Subcutaneous edema, congestion and mottling of the liver, and increased pericardial, pleural, or peritoneal fluid may be present and indicate CHF. Ascites associated with CHF is uncommon in large animals, particularly in horses. A primary source of chronic or active infection, along with evidence of bacterial embolization, may be seen in cattle with endocarditis but is rare in horses.

Treatment and Prognosis Treatment and prognosis of acquired valvular heart disease depend on the cause, onset, duration, and severity of the lesion. In general, the prognosis is guarded to poor when evidence of valvular incompetence includes tachycardia, exercise intolerance, signs of CHF, or echocardiographic evidence of severe chamber enlargement. Degenerative valve disease may be asymptomatic except for a cardiac murmur, or it may be mild, but it generally is slowly progressive and therefore historically has been given a guarded prognosis. A more accurate prognosis for horses with murmurs can now be obtained from a complete echocardiographic examination, including Doppler echocardiography.[9,19] The valve affected, the lesions detected on the valve leaflets, the degree of chamber enlargement and volume overload detected, the echocardiographic assessment of myocardial function, and the severity of the regurgitation determined with Doppler echocardiography, coupled with the animal's age and intended use, can be used to formulate a prognosis.[9,19] Valvular regurgitation associated with no detectable abnormalities, valvular prolapse, and mild valvular thickening usually has a fair to good prognosis if the amount of valvular regurgitation is small.[9,19,119,120] Individuals with ruptured chordae tendineae, flail valve leaflets, and marked valvular thickening usually have moderate to severe regurgitation, which is likely to progress more rapidly and usually warrants a guarded to poor prognosis.[9,19,94,121] Mitral regurgitation is the most likely valvular insufficiency to be associated with clinical signs of cardiovascular disease, whereas primary aortic regurgitation and tricuspid regurgitation infrequently result in the development of CHF or the death of the animal, except in horses with severe aortic regurgitation. Bacterial endocarditis has a guarded to grave prognosis, even with long-term antibiotic therapy, and frequently results in sudden death of the animal, although bacteriologic cures have been reported.

Despite the guarded long-term prognosis, palliative therapy can be applied for most forms of acquired valvular heart disease. Bacterial endocarditis is treated with long-term administration (ideally intravenously) of bactericidal antimicrobials, the choice of which is based on blood culture and sensitivity results. Continuous IV infusion of antimicrobials is the ideal initial treatment when feasible. In cattle, initial therapy is directed at the likelihood of a gram-positive infection. Combination antibiotic therapy consisting of penicillin and an aminoglycoside is recommended for broad-spectrum coverage in a horse until the results of culture and sensitivity testing are available. Using rifampin at an oral (PO) dose of 5 mg/kg twice daily in combination with another antibiotic with appropriate spectrum has improved the short-term outlook for large animals with bacterial endocarditis. Aspirin (100 mg/kg/day PO, ruminants; 10 mg/kg/day, horses) and subcutaneous (SC) low-dose sodium heparin (30-40 units/kg twice daily, ruminants and horses) may be used in patients with valvular endocarditis in an attempt to prevent platelet adhesion and increased size of the valvular mass. Early diagnosis and aggressive treatment with the appropriate antimicrobials for a prolonged period are important for successful treatment of bacterial endocarditis. The long-term outcome for successfully treated cases is still poor because the scarring that results as the endocarditis lesion heals may lead to severe valvular regurgitation and death of the animal, particularly with left-sided bacterial endocarditis lesions.[19,85-87,122] Compliance and economics are also major drawbacks in treating endocarditis.

The hemodynamic consequences of valvular heart disease (volume overload or CHF) may be improved by using diuretics. Furosemide has been used most commonly at a dose of 1 mg/kg as needed. With the low bioavailability of PO furosemide, IV administration is preferred to obtain the maximal diuretic effect.[123] Digoxin can be used to improve contractility when CHF has occurred. Conditions such as aortic valve or mitral valve regurgitation may show little or no long-term improvement, although many individuals improve for 2 to 6 months before the CHF becomes refractory to treatment. Administration of a maintenance dose of digoxin at 2.2 µg/kg IV twice daily or 11 µg/kg PO twice daily has resulted in therapeutic plasma digoxin concentrations and clinical improvement in horses with CHF, with no significant adverse effects (Box 30-1).[124] Loading doses are rarely used, because of problems with digoxin toxicity.[125] An IV loading dose of 12 to 14 µg/kg can be used in horses but must be divided into three administrations, followed by a maintenance dose of 6 to 7 µg/kg daily.[126] Digoxin is administered IV to cattle at a loading dose of 22 µg/kg followed by a maintenance dosage of 11 µg/kg three times daily or, preferably, at an infusion rate of 0.86 µg/kg/h.[127] Although the 11 µg/kg IV tid dosing may slightly increase the risk of digoxin toxicity, it is more practical than the q4h administration of 3.4 µg/kg IV. Horses appear to benefit from the use of vasodilators, as do other species. Clinical and echocardiographic improvement has been seen in numerous horses with moderate mitral or aortic regurgitation treated with angiotensin-converting enzyme (ACE) inhibitors. Quinapril at 120 mg/horse/day resulted in an increase in stroke volume and cardiac output that was statistically significant after 8 weeks of treatment in horses with mitral regurgitation.[128] Clinical and

BOX 30-1

Guidelines for Digoxin Therapy in Horses and Cattle

Horses

Priming dose IV: 4.4-7.5 µg/kg q12h for 2 doses (rarely used)
Maintenance dosage IV: 2.2 µg/kg q12h (most commonly used)
-3.75 µg/kg q12h
Maintenance dosage PO: 11 µg/kg q12h (most commonly used)
-17.5 µg/kg q12h

Cattle

Priming dose IV: 22 µg/kg
Maintenance dosage IV: infusion of 0.86 µg/kg/h, or give 11 µg/kg tid

IV, Intravenous; *PO,* by mouth; *tid,* three times daily.

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echocardiographic improvement has been seen in horses with CHF. Although the ACE inhibitor enalapril appeared to be effective in horses with moderate to severe mitral or aortic regurgitation and in horses with CHF, at a dose of 0.5 mg/kg PO twice daily, oral enalapril (single dose or once-daily administration) did not significantly reduce ACE activity in normal horses and ponies.[129,130] Ramipril at 50 µg/kg daily PO was beneficial in treating one horse with CHF.[131] Benazepril at 0.5 mg/kg PO once daily has recently been shown to be the most effective at inhibiting serum ACE activity in healthy horses.[132] Clinical improvement has been seen with hydralazine at 0.05 to 1.5 mg/kg PO twice daily. Although the short-term outlook may be improved with use of cardiovascular drugs, the prognosis is guarded for long-term survival or production.

Prevention and Control Many causes of acquired valvular heart disease cannot be controlled. Appropriate therapy for chronic active infections and careful attention to asepsis with IV medication and other invasive procedures may help prevent endocarditis and possibly nonvegetative valvulitis. Effective parasite control measures may eliminate some predisposing causes of valvular heart disease such as trauma to heart valves, microembolism, or infarction in horses.

Brisket Disease, Cor Pulmonale, and Pulmonary Hypertension

Definition and Etiology *Cor pulmonale* is a term used to refer to the effect of lung dysfunction on the heart and is therefore a secondary form of heart disease. Regardless of the cause, the underlying feature is pulmonary hypertension that leads to right ventricular hypertrophy, dilation, or failure. The primary cause of cor pulmonale in cattle is high-mountain disease (HMD, also called *high-altitude disease* or *brisket disease*), which leads to hypoxic vasoconstriction from high-altitude dwelling. Some cattle are resistant to developing cor pulmonale when grazed at high altitudes, but others are genetically much more susceptible.[133,134] Pneumonia, lungworm, and prolonged exposure to cold temperatures contribute to the development of HMD. The disease is worsened by ingestion of locoweed (*Oxytropis* and *Astragalus* spp.).[135,136] Chronic pulmonary disease such as bronchopneumonia or lungworm infection in cattle can also result in cor pulmonale.[137] In the horse, right-sided heart dysfunction (e.g., decreased cardiac output, increased right ventricular end-diastolic pressure, increased right atrial pressure or CVP, jugular venous distention, or subcutaneous edema) associated with chronic pulmonary disease is rare but may be more common than previously recognized. However, right-sided heart dysfunction associated with pulmonary hypertension and left-sided heart dysfunction is a common cause of CHF.

Clinical Signs and Differential Diagnosis Frequently the primary presenting clinical sign of brisket disease is subcutaneous edema of the brisket, ventral thorax, submandibular area, and occasionally the limbs. Lethargy, weakness, bulging eyes, diarrhea, collapse, and death occur.[133] Jugular venous distention or pulsations may be present. Dyspnea and tachypnea are frequently exhibited. Tachycardia is present, and a gallop rhythm may be auscultated. Splitting of the second heart sound (S_2) is a variable finding. Pulmonary hypertension may accentuate the separation of the aortic and pulmonic valve closures, producing audible splitting of S_2 that is most noticeable during inspiration. In some horses with moderate or severe recurrent airway obstruction (RAO) and increased vascular impedance, however, pulmonic valve closure occurs early and only a single S_2 is audible.[138]

A cardiac murmur may be auscultated, caused either by tricuspid insufficiency or a pulmonic valve ejection murmur. The murmur of tricuspid insufficiency, which is secondary to right ventricular dilation, is regurgitant or plateau shaped, with the PMI over the right thorax or, less frequently, the left second intercostal space. The pulmonic valve ejection murmur, found less commonly, is audible as a crescendo-decrescendo murmur at the left heart base.[5] Pleural or pericardial effusion is not common with cor pulmonale.[139] In horses with RAO leading to cor pulmonale, tachypnea, labored breathing, coughing, and exercise intolerance are common complaints. Wheezes are usually auscultated bilaterally in the thorax of affected horses.

These clinical signs are not specific for brisket disease (cor pulmonale) and largely reflect right-sided heart failure. Other considerations when signs of right-sided heart failure are present should be bacterial endocarditis or tricuspid insufficiency from any cause, cardiomyopathy, cardiac lymphosarcoma or other thoracic neoplasms, traumatic reticulopericarditis or other causes of pericarditis, left-sided heart failure, pleuritis or pleural effusion, and congenital pulmonic valve stenosis (rare). With pericarditis, heart sounds may be muffled, or the characteristic "washing machine murmur/rub" may be audible. Left-sided heart failure is frequently accompanied by pleural effusion, pulmonary edema, and weak peripheral pulses. In horses, however, expectoration of pulmonary edema fluid occurs only with sudden onset of severe left-sided heart failure. In horses with chronic left-sided heart failure, tachypnea, coughing, poor recovery after exercise, and harsh lung sounds may be all that is detected.

Clinical Pathology A complete blood cell count (CBC) may reveal a neutrophilia in cases of cor pulmonale caused by primary lung disease. Radiography of the thorax reveals primary pulmonary disease such as bronchopneumonia, bronchiectasis, or chronic bronchitis in cattle that have developed this disease at low altitudes. Radiographic findings in horses with RAO usually reveal an interstitial pattern. Arterial blood gases demonstrate the presence of hypoxia and may also show hypercapnia. Transtracheal wash fluid cytology and bacterial culture may provide evidence of the cause of the primary lung disease. Fecal sedimentation helps rule out parasitic bronchitis or pneumonia. Electrocardiographic findings are not specific. An echocardiogram may provide further evidence of pulmonary hypertension and right-sided heart dysfunction by showing right ventricular hypertrophy and dilation, increased septal thickness, and abnormal septal motion (Fig. 30-13).[140,141] Dilation of the pulmonary artery is also detected with 2D echocardiography and is a sensitive indicator of pulmonary hypertension or increased flow through the pulmonary artery. A dilated pulmonary artery has been reported in horses with cor pulmonale and in horses with acute pulmonary obstruction from RAO.[141,142] Cardiac catheterization reveals elevated pressure in the pulmonary artery, right ventricle, and right atrium. Elevation of right ventricular end-diastolic pressure is a sign of right ventricular failure.

Pathophysiology Pulmonary arteriolar constriction is the response to hypoxia from high-altitude dwelling or pulmonary disease. The response to hypoxia varies depending on the amount of smooth muscle in the pulmonary arteries. In cattle, increased pulmonary vascular resistance and pulmonary hypertension frequently develop. Chronic pulmonary artery hypertension causes a pressure overload on the right ventricle, which responds to the increased workload with hypertrophy, dilation, or failure, depending on the speed with which the condition develops. The disease is progressive, and at some stage the right ventricular myocardium is unable to compensate, dilates, and fails. With failure come the typical signs of jugular venous distention and development of subcutaneous edema. Chronic right-sided heart failure may result in diastolic dysfunction of the left ventricle.

Epidemiology The disease is more common in cattle than in other animal species, especially when cattle are kept at altitudes over 6000 feet, where the incidence has been estimated at 0.5% to 5% in cattle native to high altitude.[133,134] In cattle adapted to low altitude and moved to higher altitude for grazing, however, the incidence is much higher.[133,134,143] Mainly calves and yearlings are affected. A genetic predisposition to develop pulmonary arterial constriction when

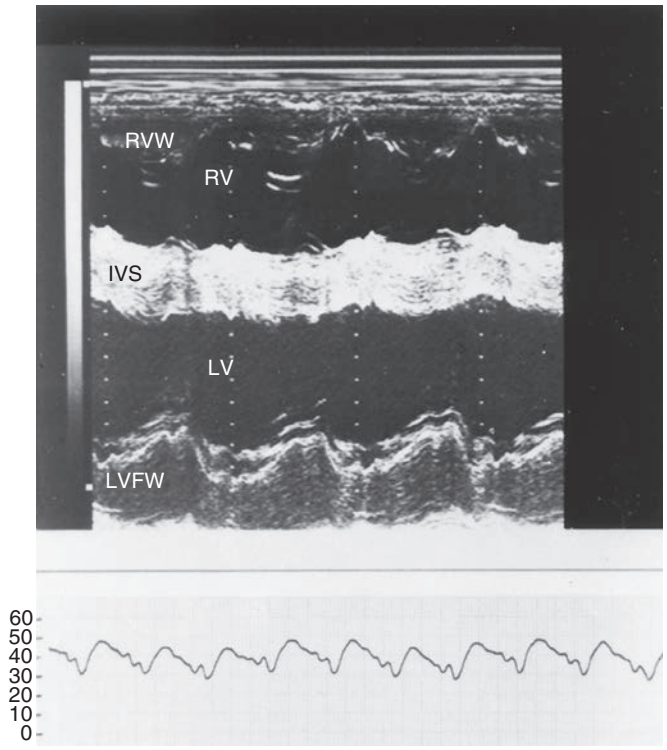


FIG. 30-13 M-mode echocardiogram and pulmonary artery pressure curve obtained from a cow with pulmonary hypertension and cor pulmonale. The echocardiogram shows mild thickening of the right ventricular wall *(RVW)* and interventricular septum *(IVS),* dilation of the right ventricle *(RV),* and abnormal septal motion. *LV,* Left ventricle; *LVFW,* left ventricular free wall. The pulmonary artery pressure curve demonstrates elevated systolic and diastolic pressures. (Pulmonary artery pressure curve in millimeters of mercury [mm Hg].)

subjected to hypoxia at high altitude is present in many breeds. Some breeds and pedigrees within breeds are more resistant than others to the effects of high altitude, and the inheritance appears to be complex.[133,134] More cases of HMD are detected in the fall and winter and are due to cold weather exacerbating pulmonary hypertension.[134] Ingestion of swainsonine contained in locoweed (*Oxytropis* and *Astragalus* spp.) also predisposes cattle to right-sided heart failure at high altitudes by causing toxic myocardial damage.[135] Pulmonary hypertension has also been detected in cattle fed ionophores at high altitude.[133]

Necropsy Findings There is evidence of right-sided heart failure (e.g., subcutaneous edema) in the submandibular area, brisket, and ventral abdomen. Findings include dilation and hypertrophy of the right ventricle, congestion of the liver, and ascites. Perirenal edema, mesenteric edema, and pleural effusion are often present. The lung may have evidence of concurrent pneumonia, bronchitis, bronchiectasis, or emphysema. Lesions of locoweed toxicity may be found in other organs in cattle.[135] Lesions of chronic interstitial pulmonary disease are found in horses with RAO.

Treatment and Prognosis Removing the animal from high altitude, treating the primary lung disease, and administering oxygen may help eliminate the hypoxia and thus the pulmonary hypertension. Cor pulmonale from high altitude is potentially reversible when the animal is returned to a lower altitude. However, cattle with other lung disease and a mean pulmonary artery pressure (PAP) of 50 to 55 mm Hg rarely have their mean PAP return to an acceptable level for high-altitude living.[133] The heart failure can be treated with digoxin and diuretics. Beneficial effects of vasodilator therapy have not been documented. Once heart failure signs have developed, the prognosis is guarded even with appropriate treatment. Removing the horse from the environment inducing RAO is critical to treating the cor pulmonale. A more detailed discussion of the treatment and management of horses with RAO can be found in Chapter 31.

Prevention and Control Selection of breeding stock with low or normal pulmonary arterial pressures at altitudes above 5000 feet (mean PAP < 35 mm Hg) helps eliminate the predisposing genetic susceptibility to the effects of hypoxia of high altitude.[133,134,143] Recently, more specific guidelines have been formulated for the selection of cattle to be kept at high altitudes.[133] Cattle older than 12 months of age with a mean PAP of less than 41 mm Hg at over 5000 feet elevation are good to select for breeding stock for high altitudes and should have a low risk of HMD. Cattle with a mean PAP of 49 or higher at any elevation are at high risk for developing HMD and should not be selected as high-altitude breeding stock.[133] Cattle with a mean PAP in between these two guidelines are at risk and should be used with caution at high altitudes.[133] The disease can also be controlled by removing susceptible animals from high altitude and preventing locoweed ingestion. Herd health practices such as avoiding crowding and poor ventilation and using appropriate vaccinations to reduce the incidence of pulmonary disease help reduce the incidence of other causes of cor pulmonale.

Myocardial Disease: Myocarditis and Cardiomyopathy

Definition and Etiology *Myocarditis* is inflammation of the myocardium caused by bacterial, viral, or parasitic organisms or thromboembolic disease caused by these organisms. In large animals, recognized bacterial causes include *Staphylococcus aureus, Streptococcus equi, Clostridium chauvoei,* and *Mycobacterium* spp. Myocarditis can also occur after bacteremia, septicemia, pericarditis, or endocarditis, regardless of the causative agent. Known viral causes of myocarditis include foot-and-mouth disease, equine infectious anemia, equine viral arteritis, equine influenza, and African horse sickness. Parasitic causes of myocarditis may include strongylosis[144] or onchocerciasis in horses, and toxoplasmosis, cysticercosis, or sarcocystic infection in ruminants.[145,146] Currently it is thought that infection with the spirochete *Borrelia burgdorferi* may be a cause of myocarditis in domestic animals, as it is in human beings.[147] Cardiomyopathy is a subacute or chronic disease of the ventricular myocardium that occurs without anatomic valvular disease, congenital malformations of the heart or vessels, or pulmonary disease. In large animals, dilated cardiomyopathy is the only cardiomyopathy of known significance. Dilated cardiomyopathy is associated with ventricular dilation, increased ventricular mass, and decreased systolic function. Although the cause is frequently undetermined,[109,148,149] several conditions have been related to or identified with cardiomyopathy. An inherited cardiomyopathy thought to be linked to the red Holstein gene has been found in Holstein-Friesian cattle in Canada, Japan, Australia, the Netherlands, and Switzerland.[150-153] There is also a cardiomyopathy associated with a curly hair coat in polled Herefords.[154] Cardiomyopathy has been associated with ingestion of monensin, lasalocid, salinomycin, gossypol, *Cassia occidentalis,* and *Phalaris* spp. Vitamin E and selenium deficiency, copper deficiency, excessive molybdenum, or high sulfates (secondary copper deficiency) may cause cardiomyopathy.[155-165] Myocardial infiltration by neoplasia such as lymphosarcoma or fibrosarcoma also may cause cardiomyopathy. A fibrofatty infiltration of the right ventricle and interventricular septum that appears to be similar to arrhythmogenic right ventricular dysplasia has been reported in horses.[166-168] The most common cause of cardiomyopathy in horses is probably myocarditis, although the inciting insult is usually difficult to identify.

Clinical Signs and Differential Diagnosis The manifestations of myocarditis are highly variable depending on the extent of the disease, location of the inflammation within the myocardium, and associated systemic illness. Myocarditis can easily be missed because of the lack of specific cardiac signs or the predominance of

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signs related to the organ system with primary involvement (e.g., strangles in horses or mastitis in cattle). Animals suspected of having myocarditis are often febrile or have a recent history of fever and may have tachycardia. The elevated heart rate may be caused by sinus tachycardia or other paroxysmal or sustained supraventricular or ventricular arrhythmias, because cardiac arrhythmias are common. Premature beats are also commonly detected in large animals with suspected myocarditis and may be present in animals with a normal or increased heart rate. Occasionally, acute myocarditis is associated with auscultation of a pronounced gallop rhythm or a cardiac murmur of either tricuspid or mitral valve insufficiency. Jugular venous distention, other signs of CHF such as peripheral edema, and signs of circulatory collapse may be present. Horses may show evidence of myalgia, reluctance to move, or exercise intolerance. With these signs it may be difficult to distinguish myocarditis from colic, respiratory disease, lameness, or septicemia. If signs are more clearly cardiac (e.g., murmur, arrhythmia, jugular venous pulsations), the practitioner should rule out endocarditis, cardiomyopathy, cardiac neoplasia, and CHF from another cause.

The clinical signs associated with dilated cardiomyopathy can also be variable but are usually more clearly associated with heart disease. Most animals have signs of cardiac failure such as peripheral edema and jugular venous distention or pulsations (Fig. 30-14). Auscultation frequently reveals tachycardia, gallop rhythm, muffled heart sounds, or a cardiac arrhythmia. Cardiac murmurs of tricuspid or mitral valve insufficiency are usually present secondary to the ventricular dilation. Breath sounds are increased, tachypnea is present, and percussion of the thorax frequently reveals signs of pleural or pericardial fluid. Occasionally, respiratory distress is evident with hyperpnea, dyspnea, coughing, and presence of a bloody froth at the nostril. Nonspecific signs of cardiomyopathy such as exercise intolerance, syncope, diarrhea, or anorexia may also be present. In cattle, decreased milk production and abomasal displacement have been associated with dilated cardiomyopathy.[150] Palpable liver enlargement has also been reported in cattle with cardiomyopathy.[151] Most affected cows develop clinical signs within 3 months of calving.[151]



FIG. 30-14 Holstein cow with cardiomyopathy showing signs of CHF (submandibular and brisket edema, jugular venous distention, and pulsations).

Sudden death can be a feature of myocarditis or dilated cardiomyopathy, and it frequently follows stress or exercise. Recumbency, collapse, and sudden death are common presenting signs in animals with ionophore toxicosis.[155-161,163,165] In many animals with inherited cardiomyopathy, death occurs within 6 months of age.[152,154] In Holstein-Friesian cattle with suspected inherited cardiomyopathy, heart failure and death may not occur until cattle are 2 to 4 years old.[150,151] Other acquired causes of cardiomyopathy can occur at any age.

When animals show clinical signs of dilated cardiomyopathy, many differential diagnoses should be considered. If the animal is young, other congenital heart defects, cor pulmonale, and nutritional myodegeneration should be considered. In adults, bacterial endocarditis, cardiac neoplasia, thoracic abscess, pericarditis, pleuritis, and diaphragmatic hernia may also have similar clinical manifestations. Although the cause of dilated cardiomyopathy may be difficult to determine, nutritional (vitamin E, selenium, or copper deficiency), toxic (monensin, gossypol, salinomycin, lasalocid, *Cassia* spp., or *Phalaris*), infectious (viral, bacterial, or parasitic), or drug-induced causes should be investigated.

Clinical Pathology Depending on the cause of the myocardial disease, the clinicopathologic findings may vary. Routine CBC may be normal, or a neutrophilic leukocytosis may be present. No consistent changes are expected in the serum chemistry profile, but serum albumin concentration may be slightly decreased, and serum urea nitrogen, creatinine, γ-glutamyltranspeptidase (GGT), sorbitol dehydrogenase (SDH), and bilirubin concentrations may be increased because of congestive liver disease when signs of CHF are present. Serum concentrations of creatine kinase (CK) and lactic dehydrogenase (LDH) may be elevated, but hepatic and skeletal muscle contribution to these elevations cannot be ruled out. Large elevations of the myocardial isoenzymes of CK (myocardial bound [MB]) and LDH (LDH_1) were detected in one outbreak of monensin toxicosis[158] and have been detected in other horses with myocardial necrosis of unknown etiology. A better indication of myocardial disease may be the elevation of cardiac troponin I (cTnI), which has been detected in horses with acute gastrointestinal (GI) disease as well as in many types of myocardial diseases.[169,170] Marked elevations of cTnI have been reported in a horse with multiform VT and myocardial necrosis of unknown cause,[171] and in a horse with VT and aortic septal rupture.[172] Elevations of cTnI were detected in horses following exposure to lethal and sublethal concentrations of monensin and lasalosid.[164,165,173] Analysis of pericardial or pleural fluid reveals a transudate with low protein concentration (<2.5 g/dL) and cellularity (white blood cell [WBC] count < 2500/μL), with the predominant cell type being mononuclear cells unless the myocarditis is an extension of pericarditis. Serum should be tested for serologic evidence of bovine leukosis (BLV) infection in adult cattle, α-tocopherol, glutathione peroxidase, and copper concentrations. Whole blood selenium levels should be determined. In infectious myocarditis or inherited cardiomyopathy, results of these tests will most likely be normal. A negative BLV test result essentially eliminates lymphosarcoma as a cause of the myocardial disease; a positive test result does not confirm a causal relationship. In horses, serum should be tested for serologic evidence of a variety of equine viruses, particularly influenza, equine viral arteritis, and herpesvirus. Hemoglobinuria, if present, suggests consideration of monensin, gossypol, or nutritional myodegeneration as the cause of myocardial disease. Arterial blood oxygen tension may be reduced below 80 mm Hg in animals with myocardial disease.

An ECG may demonstrate sinus tachycardia or other cardiac arrhythmias; the frequency and severity of these arrhythmias are best demonstrated with continuous ECG monitoring. There may be some evidence of conduction abnormalities in the base-apex lead, but these findings are not specific for myocardial disease. Echocardiography may be normal in animals with myocarditis, or the abnormalities detected may be caused by the arrhythmias present. A small left ventricular internal diameter, thickened left ventricular free wall and interventricular septum, small aortic root diameter, and decreased FS

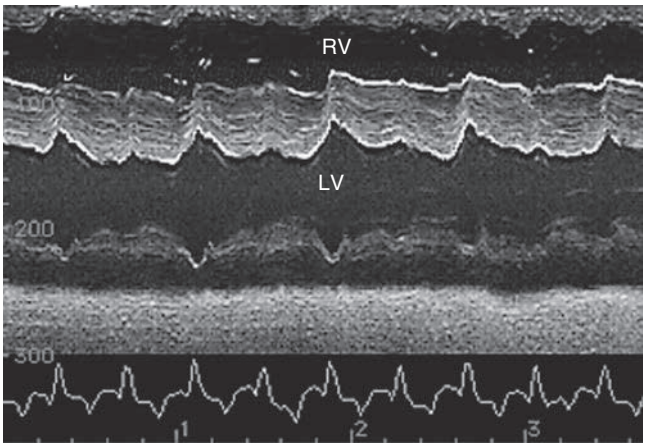


FIG. 30-15 M-mode echocardiogram of the left ventricle *(LV)* obtained from a mare with sustained uniform ventricular tachycardia. Note the small end-diastolic and end-systolic dimensions of the left ventricle and the little variation between systole and diastole in this dimension. *RV,* Right ventricle.

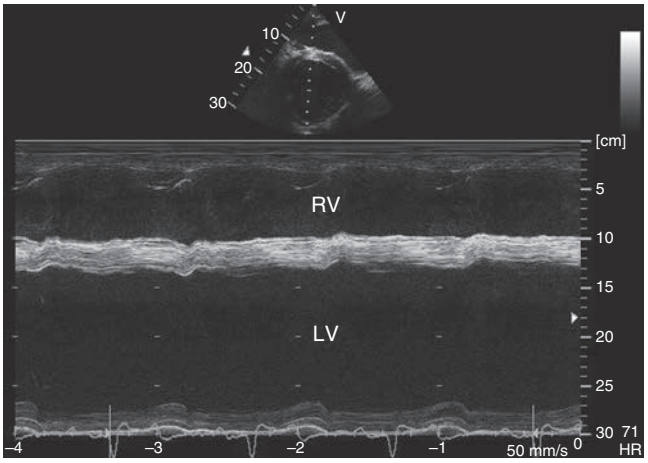


FIG. 30-16 M-mode echocardiogram of the left ventricle obtained from a mare with cardiomyopathy and severe left ventricular dysfunction. Note the large end-diastolic dimension of her left ventricle *(LV),* the thin interventricular septum and left ventricular free wall, and the poor left ventricular contractility. The fractional shortening in this mare varied from 2% to 8%. *RV,* Right ventricle.

may be detected in animals with sustained VT and decreased cardiac output (Fig. 30-15). More frequently, however, there is increased ventricular chamber size, decreased thickness of the interventricular septum and left ventricular free wall, and decreased myocardial function (decreased FS, decreased EF, and myocardial dyskinesis), especially in more severe cases of myocarditis and in animals with dilated cardiomyopathy (Fig. 30-16). In humans with myocarditis there may be evidence of abnormal left ventricular wall motion, paradoxical motion of the interventricular septum, or an echo-free pericardial space.[155] Additional echocardiographic features of dilated cardiomyopathy are increased end-systolic and end-diastolic dimensions of the left and right ventricles (see Fig. 30-16), increased left atrial size, and an increased left atrial–to–aortic root dimension ratio. There may be abnormal mitral valve closure (increased EF slope) and increased separation of the septal mitral valve leaflet and interventricular septum. A decreased aortic root diameter may be detected along with a shortened ET in animals with low-output left-sided heart failure. An enlarged pulmonary artery indicative of pulmonary hypertension (Fig. 30-17) may also be present.

Cardiac catheterization may reveal elevated intracardiac pressures (right atrial, right ventricular, pulmonary artery, pulmonary capillary wedge, and left ventricular end-diastolic) in animals with dilated cardiomyopathy. Horses with acute infectious myocarditis may show hypotension and a narrow pulse pressure. Nuclear angiocardiography

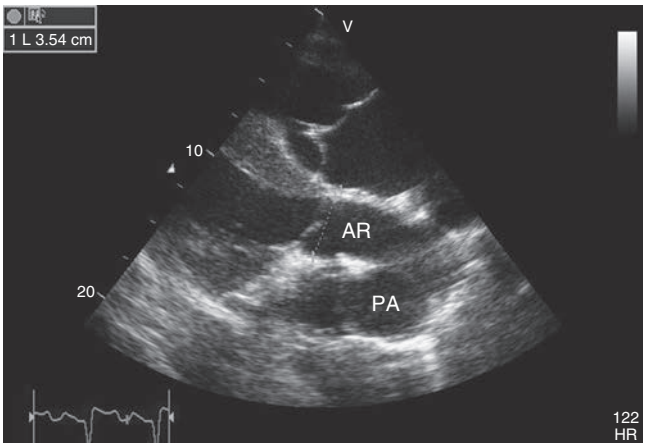


FIG. 30-17 Two-dimensional echocardiogram of the aorta *(AR)* and main pulmonary artery *(PA)* obtained from a foal with cardiomyopathy and severe mitral and tricuspid regurgitation. The pulmonary artery is larger than the aorta, indicative of pulmonary hypertension and impending left-sided CHF. The aorta measured 3.54 cm at its origin.

may be used to show decreased EF[35] in animals with myocardial disease.

Pathophysiology The pathophysiologic changes associated with myocardial disease depend on the specific nature and extent of the disease. Acute myocarditis or angiopathic myocardial lesions[144] may go on to develop into idiopathic dilated cardiomyopathy. It is speculated that changes in cellular metabolism occur with either acute myocarditis or dilated cardiomyopathy, resulting in ECG abnormalities and reduced myocardial performance (reduced cardiac output). In an attempt to compensate for reduced cardiac output, circulating fluid volume is increased by activation of the renin-angiotensin-aldosterone system, and arterial resistance is increased. These compensatory mechanisms frequently lead to only minor improvement in the cardiac output of the failing heart, and the increase in ventricular preload (venous return) and afterload (arterial resistance) may cause pulmonary edema and a further reduction in cardiac contractility. Ventricular dilation, further reduction in cardiac output, and signs of heart failure occur.

Epidemiology The prevalence of acute myocarditis is difficult to estimate because frequently the disease goes undiagnosed, is mild or masked by disease in another organ system, or the animal recovers spontaneously. Similarly, it is difficult to assess the clinical significance of postmortem findings of myocardial inflammation and fibrosis. The morbidity of myocarditis in large animals is probably underestimated because it is rarely the cause of mortality and is associated with viral, bacterial, and parasitic infections that manifest without specific signs of cardiovascular disease.

Inherited cardiomyopathy has been reported in cattle in Japan, Australia, the Netherlands, Canada, and Switzerland, with the incidence in inbred populations reaching 3% to 5%.[151] A familial form of dilated cardiomyopathy has also been reported in cattle in Sweden, Denmark, Australia, and the United Kingdom.[151] These cattle may be genetically linked by the presence of the red gene in Holstein-Friesian cattle.[150] Although in some cattle, inherited cardiomyopathy resulted in death by 6 months of age,[152,154] other cattle failed to show clinical signs until 2 to 6 years of age.[109,149,151,153] No sex predilection is recognized in inherited cardiomyopathy of cattle.

The morbidity and mortality from cardiomyopathy stemming from other causes in cattle and horses is not known. From the number of clinical reports, inherited cardiomyopathy seems to be more prevalent in cattle than in horses. Idiopathic dilated cardiomyopathy or cardiomyopathy secondary to viral or bacterial infections may be more common in horses and is a cause for the acute onset of CHF in horses of racing age.

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Necropsy Findings There may be no gross lesions associated with myocarditis. Depending on the relationship between death and the occurrence of myocarditis, microscopic examination of the myocardium may show increased fibrous tissue in the interstitium in the absence of inflammation, or there may be foci of inflammatory cells (typically mononuclear cells), variation in the cross-sectional area of the cardiac myocytes, degeneration of adjacent myocardial fibers, myocardial necrosis, and fibrosis. Replacement of the myocardium by fibroadipose tissue has been reported in horses that experienced unexpected sudden death and were thought to have arrhythmogenic right ventricular cardiomyopathy at postmortem examination.[166-168] Focal interstitial nephritis and fibrosis were reported in eight of nine Holstein-Friesian cattle with dilated cardiomyopathy in Scotland.[151] Often the inciting cause of myocardial necrosis in horses is unknown.[171] Samples of gastric or ruminal contents should be obtained and submitted for analysis of ionophores if ionophore toxicosis is suspected. Feed samples should also be obtained and submitted for ionophore analysis in these cases.

On gross examination, the lesions of cardiomyopathy are recognized more easily as enlargement of the heart, which may be rounded to globose. Biatrial, biventricular, and pulmonary artery dilation are usually present. Patchy or uniform streaks of myocardial pallor may be detected. In rare cases, one of the chambers or major vessels (usually pulmonary artery) may rupture. Generalized edema is frequently found as ascites (uncommon in horses), pericardial or pleural effusion, and edema of the mesentery and subcutaneous tissues. There may be evidence of vascular congestion of the liver, lungs, and spleen. The kidneys may be pale and swollen and have an irregular, granular, pitted surface.

Microscopically the lesions of cardiomyopathy are characterized as myocardial vacuolation and degeneration with necrosis and fibrosis. Calcification may be associated with these lesions. Occasionally there is increased vascularization with proliferative regeneration of myofibers. Loss of cardiac myocytes and replacement by fibrofatty tissue has been described in horses with arrhythmogenic right ventricular cardiomyopathy.[166-168] In some cases of cardiomyopathy, no histopathologic abnormalities are found.

Treatment and Prognosis Treatment of myocarditis includes treating the underlying causative agent if it is recognized and controlling complications such as arrhythmias, CHF, or shock. Thromboembolism is rarely a complication recognized in animals. Prompt administration of vitamin E may be beneficial to the survivors in cases of ionophore toxicosis. Performance animals should be rested. Corticosteroids may be beneficial in animals with severe toxemia, complicated arrhythmias, or intractable heart failure, but their use in early cases of myocarditis or in infections suspected of having a viral cause is controversial because viral recrudescence may occur. However, in many cases corticosteroids appear to have a beneficial effect. Prognosis is good if there are no signs of heart failure and if cardiac arrhythmias are managed successfully. Prognosis is guarded to poor if signs of CHF are present.

Therapeutic strategies currently used for treatment of dilated cardiomyopathy include positive inotropic agents (digoxin), diuretics, vasodilators, rest, and in some cases removal of pleural or abdominal fluid. The advantages of vasodilators (venodilators to relieve pulmonary edema and arterial dilators to reduce preload and afterload and improve contractility) in the treatment of cardiomyopathy are recognized in humans and small animals.[174]

Digoxin is the positive inotropic agent used almost exclusively in large animals but is contraindicated in animals with acute monensin toxicosis. A priming or loading dose can be used in horses with acute severe CHF, followed by a maintenance dose, or more frequently, the horse is started on a maintenance dose from the onset of therapy. In horses, the drug can be administered PO or parenterally. In cattle, low bioavailability limits its use to the IV route of administration.[158] Guidelines for the use of digoxin are given in Box 30-1.[124,175,176] In general, maintenance dosages are used because of the lowered risk of adverse reactions. A peak and trough serum digoxin concentration should be obtained 3 to 5 days after digoxin therapy is begun, and the dosage should then be adjusted accordingly. Ideally the peak and trough digoxin concentration should be 1 to 2 ng/mL.

Dehydration, acid-base imbalance, and electrolyte abnormalities should be corrected before digoxin therapy. The dose of digoxin should be decreased in animals with elevated creatinine or blood urea nitrogen (BUN) until these values return to normal. In horses, the IV loading dose of digoxin should be administered slowly or divided and given at a rate of one third of the loading dose hourly until completion.[175] Alternatively, therapy can be initiated with the maintenance dose. Close monitoring of body weight, appetite, electrolyte concentrations, creatinine or BUN concentration, and cardiac rhythm is essential during therapy. Therapeutic drug monitoring with digoxin plasma concentrations can be helpful during initial therapy, when the volume of distribution of the drug and the patient's body weight may be in a state of flux. Samples for determination of peak serum digoxin concentrations should be obtained 1 to 2 hours after digoxin administration and should not exceed 2.5 ng/mL.[124,177]

The diuretic used most commonly in large animals is furosemide. It is administered parenterally at the rate of 1 mg/kg twice daily or as needed to control edema. Oral absorption of furosemide is poor or variable in horses.[123] A continuous-rate infusion of furosemide is recommended in horses when rapid profound diuresis is needed.[178] The half-life and diuretic effect of bumetanide, a sulfonamide diuretic, are shorter than those of furosemide in horses.[179] Electrolyte concentrations and water consumption should be monitored closely in patients receiving diuretics.

The vasodilators used most frequently in horses include hydralazine and ACE inhibitors (enalapril, quinapril, ramipril, and most recently, benazepril). These vasodilators have resulted in clinical improvement in animals treated for CHF. Hydralazine is administered PO at a dose of 0.5 to 1.5 mg/kg twice daily. Enalapril has been used at a dose of 0.5 mg/kg PO twice daily in the management of horses with moderate to severe mitral or aortic regurgitation and in the treatment of horses with CHF. However, after a single 0.5-mg/kg oral dose of enalapril, neither enalapril or enalaprilat was detectable in the serum, and ACE activity was not significantly reduced.[129] Ramipril was reported to result in clinical and echocardiographic improvement of a horse with CHF at a dosage of 50 µg/kg daily PO.[131] The ACE inhibitor most commonly used in horses is quinapril at a dose of 0.25 mg/kg PO once daily. Quinapril has also been shown to increase stroke volume and cardiac output in horses with mitral regurgitation after 8 weeks of therapy.[128] However, benazepril at 0.5 mg/kg daily PO has recently been shown to be most effective at suppressing ACE activity in normal horses.[132]

Control of cardiac arrhythmias should be attempted in animals that are hemodynamically unstable or threatened with development of worsening arrhythmias. Quinidine is usually the drug of choice for control of atrial and ventricular arrhythmias in cattle and is one of the drugs of choice in horses. Procainamide, lidocaine, and propafenone have also been successful in treating ventricular arrhythmias in horses (Table 30-3). Although administration is limited to the IV route in cattle, oral or IV administration in horses results in adequate plasma concentrations to control arrhythmias. Quinidine is administered IV by infusion or by divided bolus injections as shown in Box 30-2.

When quinidine is used IV, concurrent IV administration of a balanced electrolyte solution at the rate of 3 to 4 mL/kg/h may be desirable to maintain blood pressure in animals with severely compromised cardiovascular status.

Prognosis for animals with dilated cardiomyopathy is poor. Echocardiography is useful in determining the severity of the myocardial dysfunction and in formulating a prognosis. The results of the initial echocardiographic examination were the best prognostic indicator of survival in a recent outbreak of monensin toxicosis.[158] Recovery of animals with cardiomyopathy is unusual, constant therapy is required for maintenance of animals with CHF, and sudden death can occur at any time. Some animals may have significant myocardial

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TABLE 30-3

Drug Therapy for Ventricular Tachycardia

Drug	Usual Dose
Bretylium tosylate	0.5-5 mg/kg IV for life-threatening ventricular tachycardia or ventricular fibrillation
Dexamethasone	0.05-0.22 mg/kg, IV or IM
Furosemide	1-2 mg/kg IV as needed for pulmonary edema
Lidocaine	*Equine:* 0.25-0.5 mg/kg slowly IV every 10-15 min; repeat up to a total of 1.5 mg/kg *Bovine:* 0.5 mg/kg, slowly IV; can repeat in 15 min
Magnesium SO_4	IV infusion at 1 g/min to effect, up to a maximum of 25 g
Procainamide	1 mg/kg/min IV to a maximum of 20 mg/kg
Propafenone	2 mg/kg PO tid 0.5-1 mg/kg in 5% dextrose slowly IV over 5-8 min for refractory sustained ventricular tachycardia (not available in United States)
Propranolol	0.03 mg/kg IV
Quinidine gluconate (IV)	1-10 mg/kg IV; total dose in 0.25- to 0.5-mg/kg boluses 5-10 min apart

IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *tid,* three times daily.

BOX 30-2

Quinidine Administration in Horses and Cattle

Horses

IV: 1.5 to 2 mg/kg every 10 to 20 min until conversion or desired effect, not to exceed a total dose of 12 mg/kg

PO: 22 mg/kg (1 g/100 lb of body weight) q2h until conversion or desired effect, not to exceed a total dose of 132 mg/kg q2h. If quinidine plasma concentrations cannot be obtained promptly, a total dose of 88 mg/kg q2h should not be exceeded.

Cattle

IV: 48 mg/kg infused IV over a 4-hr period

IV, Intravenous; *PO,* by mouth.

dysfunction without CHF and are "cardiac cripples," comfortable at pasture but not safe to use for performance. These animals may later develop CHF.

Prevention and Control Maintenance of a good vaccination program may limit the bacterial and viral causes of myocarditis. Parasite control may also reduce myocardial injury that predisposes to myocarditis or cardiomyopathy in horses. Toxic myocardial diseases are prevented by proper mixing of feeds containing monensin, salinomycin, or lasalocid in feed mills in which horse feed is not made, by not shipping bulk horse feed in trucks in which medicated ionophore-containing feed has been transported, and by preventing horses from ingesting these medicated feeds. Gossypol toxicity can be prevented by feeding no cottonseed meal or cottonseed meal with low gossypol content, especially when feeding preruminants.[180] Feeding of cottonseed meal can be limited by providing more forage or additional protein sources in the diet of ruminants so that ingestion of gossypol is limited to concentrations of 1 to 2 g/kg or less of feed for adult cattle and 0.5 to 1 g/kg or less of feed for immature cattle.[181] Nutritional myocardial disease can be prevented by adequate feeding of vitamin E, selenium, and copper with supplementation as required. Inherited cardiomyopathy is controlled by avoiding breeding of known or suspected carriers of the polled Hereford and Holstein-Friesian breeds.

Pericarditis

Definition and Etiology *Pericarditis* is inflammation of the pericardium that results in accumulation of fluid or exudate between the visceral and parietal pericardium. Pericarditis in large animals can be caused by trauma from penetration of ingested foreign objects or external wounds, hematogenous spread (septicemia) of infection, extension of infection from the lung or pleura, viral infections such as equine viral arteritis or equine influenza, and neoplasia. Pericarditis has also been associated with the mare reproductive loss syndrome (MRLS), with *Actinobacillus* species isolated in the majority of these horses.[182] Idiopathic pericarditis, characterized by an aseptic inflammatory exudate, is not uncommon in horses and has recently been reported in cattle.[183-190] Autoimmune, hereditary, and metabolic causes of pericarditis have not been documented in large animals.

Clinical Signs and Differential Diagnosis The clinical presentation of pericarditis can vary depending on the volume and rate of development of the pericardial effusion and the cause. Nonspecific clinical signs—fever, anorexia, depression, or weight loss—may be the chief complaints, but more frequently, peripheral edema, jugular venous distention and pulsations, tachypnea, or dyspnea is the presenting clinical sign. Cattle may exhibit pain by an abnormal stance characterized by abducted elbows, a spontaneous or induced expiratory grunt, reluctance to move, or preference to stand with the forequarters elevated. Horses may show signs of colic or syncopal episodes.

The most consistent findings on auscultation are tachycardia, muffling of heart sounds, and absence of lung sounds in the ventral thorax. Dorsally the lung sounds are louder than normal. These findings are in contrast to pleuritis, an important diagnostic rule-out for pericarditis, in which lung sounds are muffled ventrally but heart sounds are not, and radiation of the heart sounds occurs over a wider area than normal.[191] In cattle, splashing sounds are frequently audible in the cardiac auscultation area, a sound some refer to as a "washing machine murmur or rub." This is attributed to accumulation of gas and fluid in the pericardium and is indicative of the presence of gas-forming (anaerobic) organisms and a grave prognosis. In cattle this murmur distinguishes pericarditis from cardiac neoplasia or other causes of CHF. The splashing sounds are absent in horses and muffled heart sounds are the rule, but pericardial friction rubs may be auscultated, especially after pericardial fluid accumulation has been relieved.[186] A gallop rhythm may be auscultated in either horses or cattle.

Mucous membranes may be congested and have a prolonged capillary refill time. Jugular venous distention and pulsations usually are present. Arterial pulses are weak. The latter findings may help distinguish pericarditis from primary pleuritis. Percussion of the thorax reveals ventral dullness, and pleural effusion is frequently present in horses with pericarditis. A concurrent pleuropneumonia or septic pleuritis is present in some horses.[188,192-195] Ascites is infrequently detected in horses with pericarditis, but concurrent peritonitis has been reported.[196]

Clinical Pathology CBC changes are nonspecific and depend on the cause of the pericarditis. There may be hemoconcentration if the animal is dehydrated or toxemic, or there may be a mild anemia associated with chronic infectious pericarditis. WBC count may be normal or increased. There may be an absolute neutrophilia or a lymphopenia. Frequently the fibrinogen concentration is elevated. Serum chemistries are usually normal except for albumin concentration, which may be low[185,186] and accompanied by an elevation in globulin concentration. Liver enzyme, bilirubin, serum urea nitrogen, and creatinine concentrations are frequently mildly elevated, consistent with the development of CHF. Laboratory evidence of dehydration (increased PCV, total protein, serum urea nitrogen, and creatinine concentrations) may be exaggerated when diuretics have been administered previously. Although total serum LDH concentration may be elevated, more specific information may come from

finding an increase in the cTnI or the myocardial isoenzymes CK and LDH. An elevated cTnI was reported in one cow with hemorrhagic pericarditis.[189] Electrolyte concentrations are frequently normal, but serum calcium and potassium concentrations may be low because of anorexia. Decreased sodium and chloride concentrations have been reported in horses with pericarditis.[186] No consistent abnormalities in arterial or venous blood gas concentrations have been reported in large animals with pericarditis.

Radiography is not a sensitive diagnostic test for pericarditis in horses, although an enlarged rounded cardiac silhouette is detected with large pericardial effusions. In cattle, traumatic pericarditis frequently results in fluid and gas accumulation in the pericardium that is detectable radiographically and relatively specific for this disease. A metallic foreign body is usually detected radiographically in the cranial reticulum or caudal thorax in cattle with traumatic pericarditis (Fig. 30-18). Radiographic changes may not be detected in early or uncomplicated pericarditis. If fluid accumulation is large and there is concurrent pleural effusion, changes are indistinguishable from those associated with pleuritis. An enlarged, rounded cardiac silhouette is not specific for pericarditis and can be seen with other causes of generalized cardiomegaly. An obscured cardiac silhouette, vena cava, and diaphragm, with dorsal displacement of the trachea, may be seen with pericarditis or pleuritis. The lungs, which may be aerated only dorsally, frequently have interstitial infiltrates.



FIG. 30-18 Lateral radiograph of the caudal thorax and cranial reticulum showing a wire *(arrow)* in a cow with traumatic reticuloperitonitis.

The ECG changes most commonly associated with pericarditis in large animals are decreased amplitude of the QRS complexes (<1.5 mV in the base-apex lead)[186,187,196] (Fig. 30-19), electrical alternans (altered configuration of the P, QRS, or T complexes on a regular basis), and ST-segment elevation or slurring.[185,186,192,196,197] A right-axis deviation in the standard limb leads may be apparent.[185,197] Cardiac arrhythmias (usually atrial or ventricular premature beats) may be detected in affected animals, suggesting a concurrent myocarditis (Fig. 30-20). In some animals, no ECG changes are evident.[198]

Echocardiography reveals findings specific for pericarditis and is used to confirm the diagnosis noninvasively. An echo-free space between the visceral and parietal pericardium is evident (Fig. 30-21) and apparent even with a minimum amount of fluid accumulation.[191,192] Frequently, hypoechoic to echoic strands that correspond to fibrin are imaged in the pericardial space, with a hypoechoic to echoic layer covering the epicardial surface of the heart in large animals with pericarditis (Fig. 30-22). The pericardial effusion is often anechoic to hypoechoic, but more echoic pericardial fluid is occasionally seen, consistent with a more exudative fluid. Bright hyperechoic pinpoint echoes representing free gas are often imaged in cattle with pericarditis (Fig. 30-23). Gas in the pericardial sac of cattle with splashy heart sounds may limit the ability to obtain an echocardiographic evaluation of all cardiac structures. The visualization of intrapericardial gas is a sensitive indicator of anaerobic pericarditis. Pericardial effusion is differentiated from pleural effusion by finding the fluid- or fluid and gas–filled space surrounding the right ventricle and left ventricular free wall within the pericardial sac. Pericardial effusion is rarely imaged behind the left atrium, whereas pleural fluid is frequently imaged there. Right ventricular diastolic collapse (see Fig. 30-22) and right atrial collapse are common

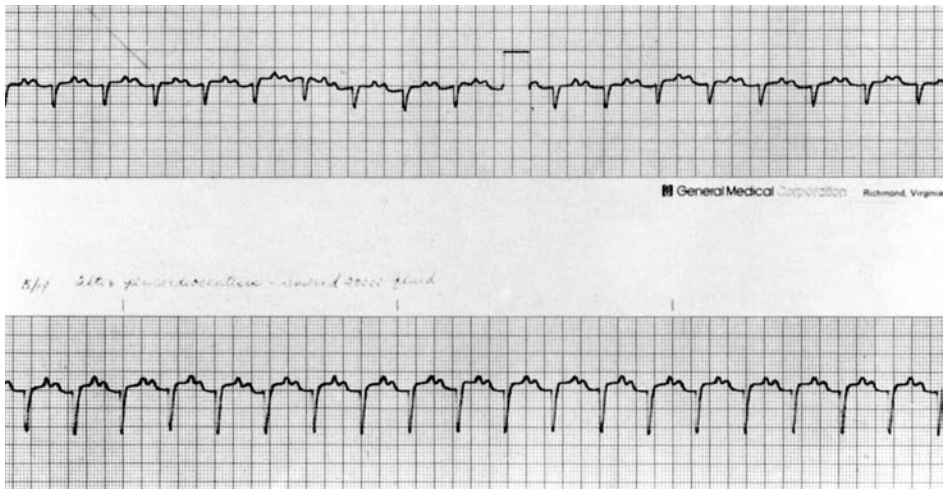


FIG. 30-19 Base-apex lead ECG taken from a cow before *(upper strip)* and after *(lower strip)* removal of 2 L of pericardial fluid. The markedly decreased amplitude (0.6 mV) of the QRS complexes is improved (1.2 mV) after pericardiocentesis.



FIG. 30-20 ECG (rhythm strip) obtained from a horse with pericarditis and junctional tachycardia. Note the P wave at the same place in the QT interval.

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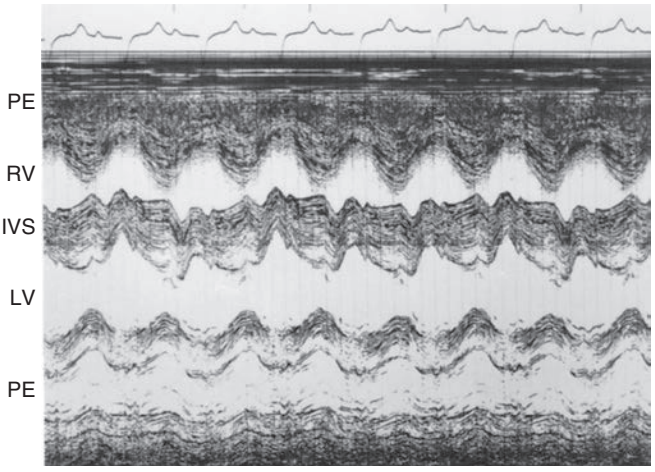


FIG. 30-21 M-mode echocardiogram obtained from a cow with traumatic pericarditis. There is a separation between the visceral and parietal pericardium cranial to the right ventricle *(RV)* and caudal to the left ventricle. The cranial pericardial effusion *(PE)* is echogenic, suggesting that fibrin or debris is present. The left ventricular *(LV)* dimension is reduced, and there is marked cranial motion of the interventricular septum *(IVS)* just before the QRS complex.

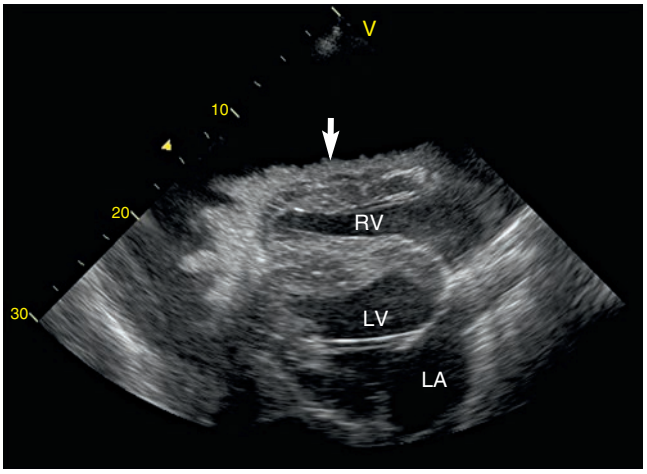


FIG. 30-22 Two-dimensional echocardiogram obtained from a horse with fibrinous pericarditis. Note the thick layer of echoic fibrin *(arrow)* covering the epicardial surface of the heart. There is a large anechoic pericardial effusion causing right ventricular *(RV)* collapse. The left atrial *(LA)* and left ventricular *(LV)* dimensions are reduced.

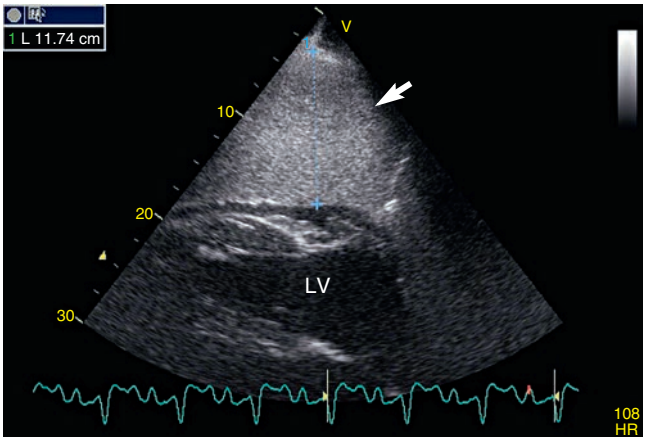


FIG. 30-23 Two-dimensional echocardiogram obtained from a cow with anaerobic pericarditis. Note the large amount (11.74 cm) of hyperechoic fluid *(arrow)* between the pericardium and left ventricle *(LV)* consistent with gaseous fluid.



FIG. 30-24 Insertion of a pericardial chest tube into the left fifth intercostal space for drainage and lavage of the pericardial space. Note that the left foreleg is being pulled forward, the clinician is inserting the large-bore Argyle chest tube into the left fifth intercostal space above the lateral thoracic vein, and the cow is wearing a radiotelemetry ECG system underneath the surcingle.

findings with large pericardial effusions and are an indication of the development of cardiac tamponade and hemodynamically significant pericardial effusion.[187] Other echocardiographic findings consistent with pericarditis are decreased left ventricular chamber dimension, decreased left ventricular free wall motion, and decreased parietal pericardial motion.[187,188,192,199] Increased (see Fig. 30-21) or paradoxical motion (cranial motion beginning before the QRS complex) of the interventricular septum may be apparent.[199]

The site for pericardiocentesis should be selected echocardiographically. Pericardial fluid is obtained most commonly from the left fifth intercostal space 2.5 to 10 cm dorsal to the olecranon, above the level of the lateral thoracic vein, the safest site for pericardiocentesis. When there is a large volume of pericardial effusion, pericardiocentesis can be productive from the right at about the same location. If at all possible, a pericardial catheter (large-bore Argyle tube) should be inserted into the pericardial space at the time the initial pericardiocentesis is performed to enable repeated drainage and lavage of the pericardial sac (Fig. 30-24). Fluid analysis and bacterial and viral culture results depend on the cause. In cattle with traumatic pericarditis, fluid analysis usually reveals elevated protein concentration (>3.5 g/dL) and an elevated WBC count (>2500/μL) composed primarily of neutrophils. The fluid is urine colored to slightly blood tinged and foamy, and it has a foul odor. A mixed population of gram-positive and gram-negative aerobic and anaerobic bacteria (GI flora) usually are present. Protozoa may be found in unusual circumstances. Hemorrhagic effusion has been reported in several cows with idiopathic pericarditis that responded favorably to pericardial drainage (usually with lavage) along with systemic antimicrobial therapy.[189] In horses, protein concentration of the pericardial fluid is elevated (≥2.5 g/dL) and the WBC count is normal or elevated with a population predominantly of neutrophils, although red blood cells, lymphocytes, eosinophils, mesothelial cells, and histiocytes have been observed.[185-187,192,196] Bacterial (aerobic and anaerobic) cultures and viral cultures may be negative. *Actinobacillus* organisms were frequently isolated from mares with pericarditis in association with the mare reproductive loss syndrome.[182] Paired serum may support a viral cause. Analysis of pleural and peritoneal fluid (when present) usually reveals fluid characterized as a modified transudate or that is mildly inflammatory.

Cardiac catheterization demonstrates an elevation in central venous or right atrial pressure, and the atrial and ventricular pressure curve may be abnormal in appearance. Right atrial, right ventricular, and pulmonary artery end-diastolic pressures may equilibrate.[197] In combination these findings are relatively specific for pericarditis.

■ ***Pathophysiology*** Accumulation of fluid in the pericardium occurs as a result of inflammation. The rate of fluid accumulation and

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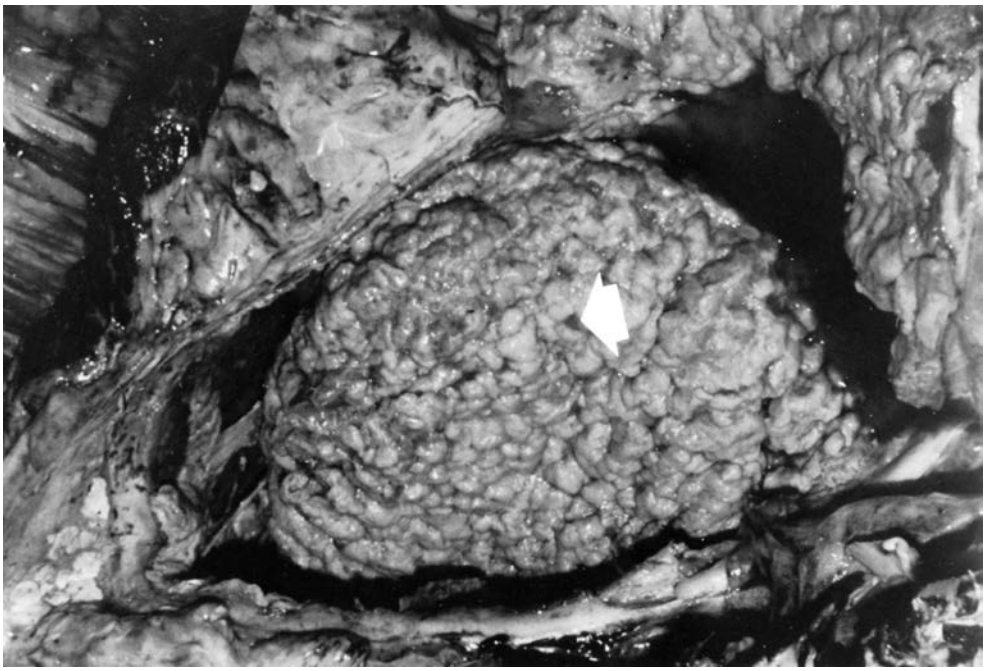


FIG. 30-25 Postmortem photograph of a cow with constrictive pericarditis. The pericardium is opened and reflected, revealing the epicardium *(arrow)* covered in fibrinopurulent exudate.

the degree to which the pericardial pressure increases determine the pathophysiologic consequences. Generally pericarditis results in decreased distensibility (increased ventricular end-diastolic pressure) of the heart, which impairs the ability of the heart to fill during diastole. The elevation in end-diastolic pressure and impairment of ventricular filling elevate atrial pressure and reduce venous flow or venous return to the heart and diastolic perfusion of the myocardium. The result is a depression of ventricular contractility, stroke volume, and consequently cardiac output. In addition, arterial pressure and renal blood flow are decreased. Initially, compensatory mechanisms consisting of vasoconstriction, increased heart rate, and sodium retention (increased vascular volume) may maintain cardiac output. Failure to maintain cardiac output results in circulatory collapse.

Pericarditis can be classified as primarily effusive, constrictive, or a combination of both.[197] The hemodynamic consequences of effusive pericarditis are primarily caused by the physical presence of pericardial fluid, whereas constrictive pericarditis is classified as such because the reduction in ventricular compliance is due to fibrinous or fibrotic involvement of the pericardium and epicardium. Removal of pericardial fluid results in improved cardiac performance in effusive pericarditis but is of limited usefulness in constrictive pericarditis.

Epidemiology

Pericarditis is uncommon in horses; when it does occur, it is most frequently idiopathic and can occur in a horse of any age. History of a recent respiratory tract infection is not uncommon. Exposure of horses to Eastern tent caterpillars was the greatest risk factor for the development of fibrinous pericarditis during the epidemic of mare reproductive loss syndrome.[200] Traumatic pericarditis has been reported in horses but is rare.[201] Traumatic pericarditis is not uncommon in cattle, but it occurs in less than 10% of cattle with traumatic reticuloperitonitis.[60] Most cattle are affected in late gestation or at parturition. Idiopathic pericarditis is rare in cattle. Several cows with idiopathic hemorrhagic pericarditis later developed cardiac lymphosarcoma.[183]

Necropsy Findings

Gross postmortem examination shows distention of the pericardial sac with serosanguineous or urine-colored fluid that is foamy and may be malodorous (cattle). There may be organization of fibrinous exudate and fibrosis that is also evident on the epicardium (Fig. 30-25) and may infiltrate the myocardium. Pleural effusion may be present. Other signs of CHF such as pulmonary congestion, pulmonary edema, and chronic passive congestion of the liver may be present. If the cause is traumatic, the offending object may be well contained in a fibrous tract located between the reticulum and the pericardium.

Histopathologic examination reveals pericardial, epicardial, and occasionally myocardial fibrosis and inflammation with neutrophilic, lymphocytic, eosinophilic, or plasma cell infiltrates. Bacteria may be visible. The liver may show diffuse centrilobular necrosis, fatty change, dilation and congestion of sinusoids, and perivenous fibrosis.

Treatment and Prognosis

Treatment of traumatic pericarditis in cattle is unrewarding and usually is addressed toward salvage or short-term survival to calving. Repeated pericardial drainage by means of pericardiocentesis or a fifth rib resection, lavage, or pericardiectomy may be useful for short-term survival, but the prognosis for return to normal function is poor because CHF results from involvement not only of the pericardium but also the epicardium and myocardium (see Fig. 30-25). Thoracotomy by a split-rib technique followed by pericardiectomy has been effective in treating some cattle with traumatic, restrictive pericarditis.[202]

Treatment of pericarditis not caused by trauma has been successful in horses, but the initial prognosis should be guarded. Aggressive treatment of horses with moderate to large pericardial effusions should include the placement of a large-bore indwelling chest tube into the pericardial sac under echocardiographic guidance and drainage and lavage of the pericardial sac, with local infusion of antibiotics in addition to the initial broad-spectrum antimicrobial therapy. Obtaining a sample for cytologic examination and culture and sensitivity testing via a pericardiocentesis should be postponed until an indwelling catheter can be safely inserted, because it is difficult to insert the catheter once the pericardiocentesis has been performed. The pericardial drainage and lavage, performed once or twice daily as needed, has been very effective in treating idiopathic or septic pericarditis in horses.[9,187,188,192,196] The indwelling tube should remain in situ until the fluid recovered at the time of drainage is consistently

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less than or equal to the volume instilled in the pericardial sac with antimicrobials 12 to 24 hours earlier. The ECG should be monitored because occasionally cardiac arrhythmias occur during the therapeutic procedure or during a routine pericardiocentesis. All horses with pericarditis should initially be treated for septic pericarditis with systemic broad-spectrum bactericidal antimicrobial drugs. The antimicrobial choice should be based on the most likely causative agents and modified as needed by the results of culture and sensitivity testing. Fibrinous pericarditis has been successfully treated in horses with broad-spectrum bactericidal antimicrobials when the amount of pericardial fluid detected echocardiographically was too small to safely obtain a sample for cytologic evaluation and culture and sensitivity testing. Treatment of idiopathic pericarditis with corticosteroids should be initiated only after the results of these studies demonstrate no evidence of sepsis. Pericardiotomy or (preferably) pericardiectomy are the treatments of choice if signs of constrictive pericarditis are present. However, the long-term prognosis for large animals following this surgery is guarded. A partial pericardiectomy was performed in one horse with constrictive pericarditis but was only transiently successful.[193]

In traumatic pericarditis the antibiotic selected must be capable of covering gram-positive and gram-negative aerobic and anaerobic bacteria. Nonsteroidal antiinflammatory drugs (NSAIDs) have been deemed useful as adjunctive therapy, as have corticosteroids if bacterial culture of the fluid is negative and no evidence of sepsis is detected cytologically.

Although diuretics are effective in eliminating the severity of peripheral edema, they further reduce venous return and preload in animals with pericarditis. The result is further compromise of cardiac output and worsening of heart failure.

Prevention and Control Traumatic pericarditis in cattle can be prevented by routine administration of magnets to heifers at the time of pregnancy diagnosis. At each subsequent pregnancy diagnosis, the cattle should be checked for the presence of the magnet in the reticulum. It is not beneficial to have more than one magnet present at one time.

Some types of infectious pericarditis in horses may be controlled by routine vaccination against the common respiratory pathogens.

Cardiac Tumors

Definition and Etiology The heart may be the primary site of neoplastic disease or be involved secondarily by tumors from adjacent structures such as the lungs, pleura, lymph nodes, or diaphragm. Cardiac neoplasia is uncommon in large animals. The most common primary cardiac tumor is lymphosarcoma. Mesotheliomas, fibrosarcoma, adenocarcinomas, lipomas, and other carcinomas, especially squamous cell carcinomas in horses, may involve structures adjacent to the heart and may extend to the heart or heart base, producing signs of heart disease.[203,204] An infiltrative cardiac lipoma has been reported in a horse, but no signs of cardiac disease were attributed to it.[205] A metastatic anaplastic pulmonary carcinoma caused signs of CHF in one horse,[204] and disseminated hemangiosarcoma with myocardial involvement was thought to be responsible for ventricular arrhythmias in another horse.[206] Primary pericardial hemangiosarcomas have also been reported in a horse.[207]

Clinical Signs and Differential Diagnosis The clinical signs of cardiac neoplasia are nonspecific and depend on the cardiac site involved and other sites of tumor manifestation. Nonspecific signs of neoplasia are common and include anorexia, depression, weight loss, and fever. These signs can be produced by any site of chronic disease, and in large animals pneumonia, peritonitis, enteritis, and liver and kidney disease are considered differential diagnoses, among others. If the tumor involves the pericardium, signs of pericarditis or pericardial effusion such as tachycardia, pain, jugular venous distention, peripheral edema, and weak arterial pulses may be seen. Myocardial involvement of the neoplasia, as is most common with lymphosarcoma, may result in cardiac signs that include tachycardia, cardiac arrhythmias, and cardiac murmur (atrioventricular valve insufficiency) or signs of CHF such as peripheral edema, ascites, and diarrhea. Clinical signs attributable to tumor involvement of the endocardium (e.g., obliteration of a cardiac chamber, valvular obstruction or damage, embolic showering) are rare in large animals.

Tumor involvement of other organ systems and tissues can be manifested by lymphadenopathy, peripheral edema, diarrhea, melena, dysphagia, tachypnea, pleural effusion, or rectal palpation of abdominal masses.

Clinical Pathology Cardiac tumors present no consistent clinicopathologic feature. The CBC from horses or cattle with lymphosarcoma may reveal neoplastic lymphocytes. The absence of leukemic changes does not rule out lymphosarcoma. Cattle with lymphosarcoma may test positive for fecal occult blood. A serum chemistry profile may reveal nonspecific changes such as hypoalbuminemia, hyperglobulinemia, or elevated liver enzyme concentrations, depending on the other organ systems affected by the tumor or the animal's debilitation. Diagnosis of the cardiac tumor is based on histopathology of tumor tissue. Tumor cells may be found in pericardial or pleural fluid or adjacent lymph nodes. Serologic evidence (agar gel immunodiffusion or radioimmunoassay) of BLV infection does not confirm a diagnosis of lymphosarcoma, but a negative test result virtually rules out the adult or enzootic form of lymphosarcoma in cattle. No evidence of BLV infection will be found in cattle with the thymic form of lymphosarcoma.

If electrocardiographic evidence of cardiac tumors is present, it is nonspecific. Cardiac tumors may produce cardiac arrhythmias, reduce amplitude of the QRS complexes, or alter the normal appearance of the P, QRS, and T complexes. Two-dimensional echocardiography or an ultrasound examination of the lungs or pleura may show evidence of the cardiac tumor by providing direct evidence of abnormal echogenic masses involving the heart or surrounding tissue, abnormal fluid accumulation, or myocardial functional changes. Ultrasound findings can determine whether any masses can be safely biopsied to confirm the diagnosis.

Radiographs may provide evidence of cardiac tumors by showing abnormal soft tissue densities in the thorax that obscure the cardiac silhouette or ventral lung borders.

Pathophysiology Lymphosarcoma, the most common cause of cardiac tumors in cattle, has a predilection for the right atrial myocardium. Right ventricular myocardial involvement is not uncommon; left atrial or left ventricular involvement is rarer. Involvement of the right side of the heart may result in little or no evidence of heart disease. More commonly the myocardial involvement results in dilation of the chamber involved. As a consequence, the tricuspid valve ring may be dilated, and tricuspid valve insufficiency occurs. Chamber enlargement or infiltration of the myocardial conduction system may cause cardiac arrhythmias. Myocardial function may be impaired, so that signs of right-sided heart failure become apparent, including tachycardia, peripheral edema, jugular venous distention or pulsations, pericardial or pleural effusion, hepatic congestion, and ascites.

Epidemiology Cardiac tumors are rare in large animals. The most common cause in cattle is lymphosarcoma. Although more than 50% of cattle in some parts of the United States are infected with BLV, only 1% to 5% develop lymphosarcoma.[208-210] In herds with more than 50% of cattle infected with BLV, the incidence of lymphosarcoma may be higher. Cardiac involvement is common in cattle with the adult or enzootic form of BLV, a disease that occurs most commonly in cattle over 4 years old.[211] Thymic lymphosarcoma, which is not associated with BLV infection, also involves the heart but is much less common, occurring in cattle under 30 months of age.

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FIG. 30-26 Postmortem photograph of a cow with lymphosarcoma demonstrating right atrial myocardial infiltration by a tumor and extension of the tumor into the atrial lumen.



FIG. 30-27 Postmortem photograph of a horse with pericardial mesothelioma. Note the huge heart base tumor mass, along with several smaller masses.

Lymphosarcoma, mesothelioma, and squamous cell carcinoma are probably the most common causes of neoplastic involvement of the equine heart, but the prevalence is not documented.

Necropsy Findings Necropsy findings depend on the type of cardiac tumor. Direct involvement of the myocardium with lymphosarcoma is associated with finding diffuse infiltration by a pale, tan, homogeneous tissue that frequently causes enlargement of the cardiac chamber. Involvement of the right atrium (Fig. 30-26) is the most common manifestation of adult enzootic BLV, but any area of the myocardium and pericardium may be involved. Intracavitary extension of the tumor may be evident (see Fig. 30-26). Histologic evaluation of the tumor shows diffuse infiltrates of lymphoblastic cells that obliterate the normal architecture of the myocardium.

Other tumors such as fibrosarcoma, squamous cell carcinoma, pulmonary carcinoma, thymic lymphosarcoma, and mesothelioma (Fig. 30-27) may involve the heart by extension or metastasis from other sites in the thorax.

Treatment and Prognosis No definitive treatment exists for neoplasias involving the heart, and the prognosis for survival is poor. Death can be expected within 6 months with most cardiac tumors. Lymphosarcoma of the heart in cattle has a grave prognosis and is usually associated with death within a few months. Short-term improvement has been achieved in cattle with lymphosarcoma treated with a combination of corticosteroids, L-asparaginase, and cytotoxin. Thoracoscopic pericardiotomy has been used as a palliative treatment in a cow with pericardial lymphoma.[212]

Prevention and Control Prevention and control of BLV can be accomplished by isolation of BLV-positive and BLV-negative animals; use of individual or sterilized supplies such as needles, rectal examination sleeves, tattooing, dehorning, and ear-tagging equipment on each animal; rigorous attention to a vector control program; and feeding colostrum from serologically negative cows only.[209,213] Frequent testing (at least every 6 months) and isolation of serologically positive animals over 6 months of age should be performed. Prevention and control of other cardiac tumors is not possible.

Vascular Disease: Aneurysms, Thrombosis, and Embolism

Definition and Etiology *Aneurysms,* which are vascular dilations, develop from weakening of the medial elastic coat of blood vessels. The medial weakness may be primary or caused by a progression of an intimal atherosclerotic lesion that has enlarged from hemorrhage, calcification, ulceration, and thrombus formation. The specific causes of aneurysms in large animals are unknown, but trauma (internal or external), sepsis, parasite migration, degenerative vascular disease, atherosclerosis, or aging changes (dilation, elongation, and loss of elasticity of blood vessels) may play a role.[214-216] Congenital aneurysms of the sinus of Valsalva have been reported in horses.[72,79-81] Hypertension can accelerate degeneration of the wall.

Thrombosis is the formation of a clot that obstructs blood flow in the circulatory system. The causes of thrombosis are numerous and include trauma, venous stasis, and catheterization for administering medication or fluids. Needle penetration, indwelling catheters,

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thrombogenic solutions, or bacterial contamination can cause thrombosis associated with catheterization. Secondary thrombosis can result from perivascular inflammation caused by cellulitis, lymphangitis, or other sources of bacterial invasion around the blood vessel. Mural thrombi, which occur in cardiac chambers associated with low-flow states and/or a coagulopathy, also may occur in large animals, although they have been rarely diagnosed antemortem.[217] Thrombosis usually occurs when intimal disease is present, but it may occur in arteries with no intimal disease when a hypercoagulable state exists, such as with dehydration, endotoxemia, anemia, hypotension, stress, or stasis.[218-220] This type of thrombosis is frequently a complication of acute infectious disease (particularly acute toxic enteritis or colitis), neoplasia, or any chronic debilitating disease.

An *embolism* is foreign material carried in the bloodstream. Emboli frequently arise from an arterial or venous thrombus, but unusual emboli include catheters and other foreign bodies inadvertently introduced into the circulatory system. In large animals, emboli occur most commonly in bacterial endocarditis, thrombophlebitis, omphalophlebitis, and parasitic arteritis. Aortoiliac thromboembolism has been reported as a complication of valvular endocarditis in a calf and mural endocarditis in a cow.[221,222]

Clinical Signs and Differential Diagnosis Sites of thrombosis associated with thrombophlebitis are likely to have pain, swelling, redness, and palpable thickening of the involved vein. These signs frequently occur within 12 to 24 hours after catheter removal when the thrombus is associated with catheterization. If there is bilateral jugular venous thrombosis, sudden, marked swelling of the head may occur. If the thrombosis involves the terminal aorta and iliac arteries in horses, the signs are frequently a vague hindlimb lameness, exercise intolerance, or poor performance. These nonspecific signs make it necessary to rule out lameness from other causes, cardiac disease, or respiratory problems. Failure to ejaculate has been reported in breeding stallions with aortoiliac thrombosis.[223] Aortoiliac thrombosis in horses also is characterized by heavy sweating after exercise, except over the hindlimbs, which are cool. With severe aortoiliac thrombosis the affected limb can be cool to the touch at rest or can be cold with no palpable femoral arterial pulse. Saphenous vein filling is slow or nonexistent in affected horses, and the metatarsal and other peripheral arterial pulses of the hindlimbs are weak. Rectal examination may be normal, or weak, absent, or asymmetric iliac pulses may be palpated. Fremitus of the iliac arteries or terminal part of the aorta may be palpated. The terminal part of the aorta may feel larger or firmer than normal, or an aneurysmal dilation may be detected. Similarly with verminous arteritis of the cranial mesenteric artery, a thickened, dilated cranial mesenteric artery or aorta may be palpated that may be firmer than normal and have a weak pulse, or fremitus may be palpated. In calves with aortic or aortoiliac thrombosis weakness, lameness, knuckling, paresis or paralysis of the hindlimbs, inability to rise, and cold hindlimbs lacking a femoral arterial pulse have been described.[221,224-226]

The signs attributable to embolism and thrombosis may be identical. Embolism usually is manifested by an acute episode of pain or fever, abnormal pulsation in a peripheral vessel, or a change in skin temperature. If there is peripheral vessel showering, superficial veins may be collapsed, and muscular weakness may be present. Embolic showering usually occurs in animals suspected of having or known to have thrombus formation.

Clinical signs associated with an aneurysm depend on its location and may vary from being asymptomatic to being a noticeable enlargement or mass associated with a blood vessel or causing colic, syncope, seizures, or sudden death on rupture. In a peripheral artery, a pulsatile expansile mass may be visualized or palpated. Other considerations for this finding are a false aneurysm and an arteriovenous fistula. A false aneurysm is clinically indistinguishable from a true aneurysm but can be distinguished ultrasonographically. A false aneurysm is caused by a break in the continuity of all three coats of the arterial wall rather than in the tunica media alone. This results in extravascular accumulation of blood in adjacent tissues. Signs attributable to low blood flow (e.g., lameness, colic, edema) may be present with arterial aneurysms. Aneurysms of the cranial mesenteric artery frequently manifest as chronic episodes of colic. With involvement of major cardiac vessels there may be pain, an auscultable heart murmur, rapid tachycardia, signs of CHF, acute onset of pulmonary edema, or sudden death when the aneurysm ruptures. The latter signs make aneurysms difficult to distinguish from the clinical signs of a horse with valvular heart disease or cardiomyopathy. One cause of an aorticocardiac fistula in horses is the result of rupture of an aneurysm of the sinus of Valsalva.[72,79-81]

Clinical Pathology Aneurysms or pseudoaneurysms may be visualized radiographically as soft tissue density masses continuous with a vessel wall (true aneurysm) or extending outward from a vessel wall (false aneurysm).[215,216] However, the majority of the aneurysms involving the aorta and aortic root are not visible radiographically. Echocardiography is useful in the diagnosis of aneurysms involving the aortic root (Fig. 30-28).[64,69-71] Angiography can be used in the diagnosis of peripheral vessel swelling or suspected thrombosis but is of little use in diagnosis of aneurysms of major vessels in adult animals. Ultrasonography may be used for the diagnosis of aneurysms or thrombosis of major arteries and peripheral vessels. In aortoiliac thrombosis of horses, ultrasound has been used to determine the origin of the thrombus and the extent of occlusion of the involved arteries (Fig. 30-29).[227] Abdominal ultrasonography of the

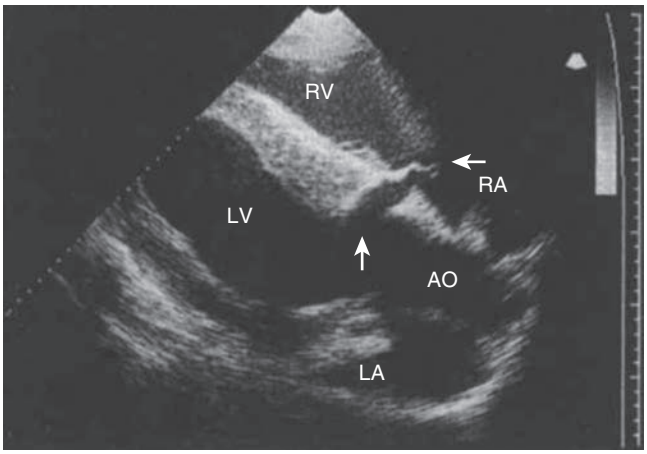


FIG. 30-28 Two-dimensional echocardiogram of a horse with a ruptured sinus of Valsalva aneurysm. Note the defect in the right side of the aorta at the sinus of Valsalva *(vertical arrow)* extending into the right atrium *(horizontal arrow)*. The right atrium *(RA)*, right ventricle *(RV)*, left ventricle *(LV)*, left atrium *(LA)*, and aorta *(AO)* can be seen in this left ventricular outflow tract view.

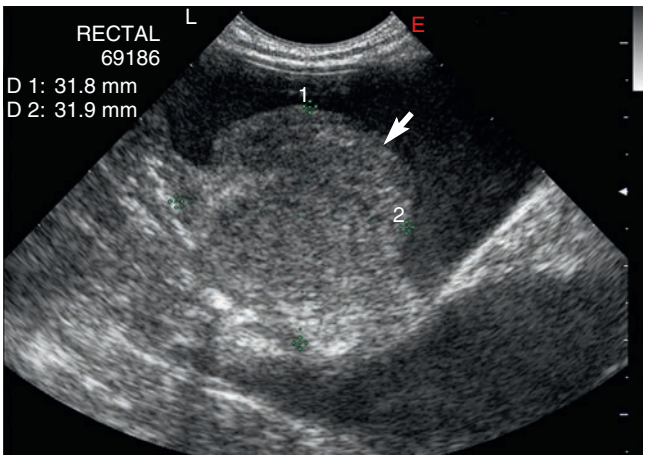


FIG. 30-29 Transverse transrectal sonogram of a large somewhat heterogeneous thrombus *(arrow)* in the terminal portion of the aorta measuring 31.8 mm by 31.9 mm in diameter.

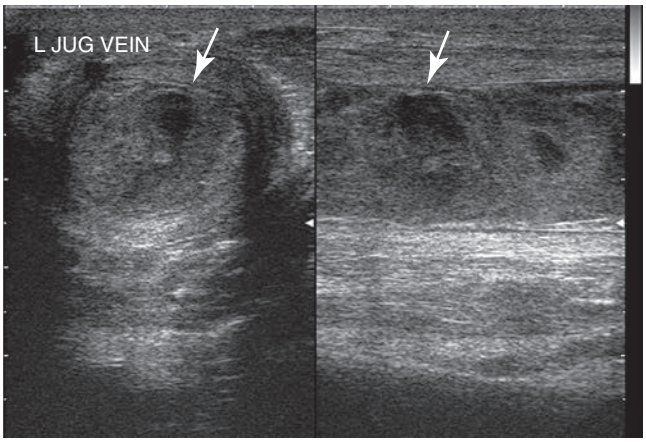


FIG. 30-30 Sonogram of the left jugular vein from a horse with septic thrombophlebitis. Note the cavitary appearance in the center of the thrombus *(arrows)* consistent with infection.

upper left flank dorsal to the left kidney has been used to diagnose aortoiliac thrombosis in calves.[224] Diagnostic ultrasound has been used to detect thrombi in the caudal vena cava in cattle.[228,229] Although the occluding thrombus is not imaged, detecting a distended oval or round caudal vena cava rather than the normal triangular vessel in the eleventh and twelfth intercostal spaces is consistent with this diagnosis in cattle. Thrombi have been detected ultrasonographically in the hindlimb in both horses and cattle.[230-234] Jugular vein thrombophlebitis has also been diagnosed ultrasonographically in both horses and cattle (Fig. 30-30).[235,236] Similarly, diagnostic ultrasound has been used to image the cranial mesenteric artery, its branches, and the aorta in horses with verminous arteritis.[237] Aneurysms appear as dilated vascular structures or vascular outpouchings continuous with the vessel wall,[71] whereas a thrombus is apparent as a hypoechoic to echogenic mass within a blood vessel.[236] Cavitation of an occlusive thrombus is suggestive of septic thrombophlebitis (see Fig. 30-30), whereas a nonseptic thrombus usually has a homogeneously hypoechoic to echoic appearance.[236] Complete occlusion of the vessel can be determined ultrasonographically, or flow within an aneurysm or alongside a thrombus determined. Doppler ultrasound provides a more sophisticated method for determining blood flow and vessel patency.

In the case of catheter-associated thrombosis, a positive catheter tip culture (>10^3 colony-forming units) along with a positive blood culture provides evidence of septic thrombophlebitis.[238] An aseptic ultrasound-guided aspiration of the cavitary lesion within a heterogeneous thrombus can be performed, and the aspirate submitted for culture and sensitivity testing.[236] Septic thrombophlebitis from any cause or embolic showering of septic thrombi may be accompanied by neutrophilic leukocytosis and elevation in fibrinogen concentration.

Pathophysiology

Irritation of the intimal lining of a blood vessel, stasis of blood flow, or existence of a hypercoagulable state triggers the clotting cascade and sets the stage for development of thrombosis. Further injury causes hemorrhage, more thrombosis, ulceration, and calcification. These in turn can compromise the media of the vessel, predisposing to aneurysm formation, and impinge on the lumen of the vessel, causing obstruction to blood flow. Either aneurysm or thrombosis can occlude blood flow to vital structures or organs, resulting in ischemia.

Thrombosis in any sizable vein causes venous hypertension, passive congestion, and subsequent edema and pain of the structure. As the thrombus matures, it adheres to the wall more, but with clot retraction and lysis, recanalization may occur. However, parts of the thrombus may protrude into the moving bloodstream and serve as the source of embolic showering, even during thrombus organization. The most common site for an embolus to lodge has not been established in large animals; the femoral and iliac arteries are common locations in humans. Emboli usually lodge at bifurcations, where the caliber of the artery is suddenly reduced.

The most common outcome of aneurysm of a major vessel is thought to be rupture. Rupture of sinus of Valsalva aneurysms into the right atrium, right ventricle, and interventricular septum has been reported in the horse.[79-81] VT often occurs with rupture of an aortic sinus of Valsalva aneurysm and dissection into the interventricular septum.[80,81] Unruptured aneurysms may have other complications such as thrombosis or embolization of the thrombus. The frequency of rupture or embolic showering from thrombosis is unknown in animals.

Epidemiology

The significance of thromboembolism in large animals is poorly defined. Spontaneous thromboembolism is commonly associated with parasitism in horses, and the aorta and cranial mesenteric arteries are the sites most frequently involved.[144] Aortoiliac thrombosis is also a recognized syndrome diagnosed most frequently in heavily exercised horses. Although historically parasitism has been associated with aortoiliac thrombosis in horses, other causes of this syndrome are probable but have not been elucidated. Thrombotic disease can occur in any animal having repeated IV injections or being catheterized for administration of medication or fluids, but it is particularly common in horses with acute toxic enteritis, colitis, or sepsis. Careful skin preparation and aseptic technique are important factors in minimizing the likelihood of the patient developing catheter-related thrombophlebitis. Low doses of heparin have been effective in limiting the development of catheter-related thrombophlebitis in cattle.[239] Large intestinal disease, hypoproteinemia, endotoxemia, salmonellosis, fever, diarrhea, and locally produced fluids have all been identified as risk factors for catheter-associated thrombophlebitis.[220,240,241]

Arteriosclerosis is recognized in horses and in cattle. In cattle the lesion is most frequently caused by excessive vitamin D_3 supplementation or ingestion of calcinogenic plants such as *Solanum malacoxylon, Cestrum diurnum,* or *Trisetum flavescens.*[242] In horses the arteriosclerotic lesions were caused by lesions induced by *Strongylus vulgaris.*[82]

Aneurysms are uncommon in large animals but have been documented as the cause of sudden death in breeding stallions and racing Thoroughbred and Standardbred horses.[81,82] Aneurysms of the sinus of Valsalva are one cause of aortic rupture in older horses and are probably congenital in horses, as they are in humans.[71,79-81] Aortic root rupture also occurs without the presence of a preexisting aneurysm and has been associated with medial necrosis of the aorta.

Necropsy Findings

Aneurysms are detected grossly as dilations of the involved blood vessel. Aneurysms of the sinus of Valsalva are characterized by an absent tunica media in the wall of the aorta, causing the aneurysmal dilation.[61,71] Rupture of a sinus of Valsalva aneurysm may occur into the right atrium, right ventricle (Fig. 30-31), or interventricular septum, resulting in an aortic cardiac fistula and volume overload.[61,71,72,80,81] Rupture through the tricuspid valve or chordae tendineae may also occur. Subendocardial dissection of blood down the interventricular septum may occur. Subsequent rupture into the left ventricle and of the mitral chordae tendineae have also been reported. Aneurysms of the major vessels leaving the heart may involve more than one vessel by dissection and hemorrhage. Aneurysms may contain thrombi or parasites, and there may be evidence of embolic showering of thrombi into peripheral vessels or other organ systems, especially the lungs. Histologically there may be necrosis and inflammation at the site of the aneurysm with foci of mineralization.

Thrombosis and arteriosclerotic lesions are recognized as rounded, well-demarcated fibrous plaques frequently located in the thoracic and cranial abdominal aorta (Fig. 30-32). The plaques may contain a central calcified core or parasitic larvae. Microscopically there is a thin layer of fibrin, platelets, and inflammatory cells in early lesions, whereas older lesions have a greater fibrous component. Thrombotic

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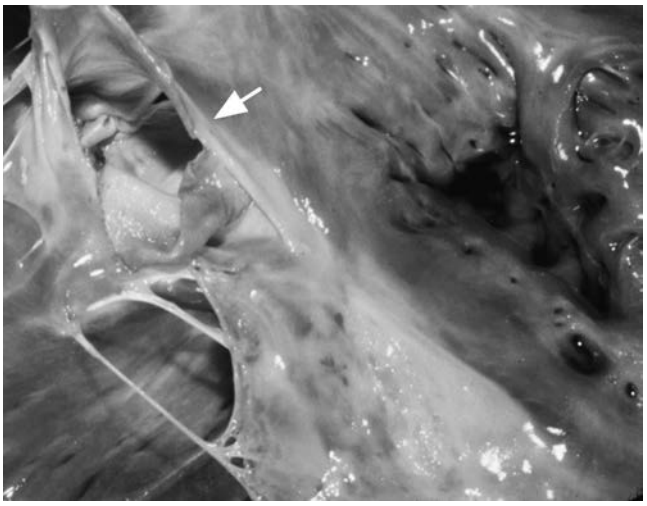


FIG. 30-31 Ruptured sinus of Valsalva aneurysm in a horse with acute onset of colic and right-sided congestive heart failure. The large aneurysm *(arrow)* ruptured through the tricuspid valve, creating an aortic-cardiac fistula.



FIG. 30-32 Ascending aorta from a horse that experienced an acute onset of uniform ventricular tachycardia after exercise and died within 3 hours of onset. Note the irregular calcified surface of the aorta, consistent with atherosclerosis.

lesions may be associated with proliferation of the underlying aortic intima. In horses, parasitic larvae may be found.

Treatment and Prognosis Aneurysms of major vessels carry a guarded to grave prognosis because surgical correction is rarely attempted and spontaneous rupture is thought to be relatively common. Intact aneurysms of the sinus of Valsalva can be detected echocardiographically, and once an aneurysm has been detected, the horse should be removed from all athletic competition because of the risk of rupture.[71]

Treatment of thrombosis consists of removal of the catheter, if present, and resting the affected vessel. Warm compresses or hydrotherapy may be helpful in some animals. Topical NSAIDs (diclofenac sodium) may also be useful. Support wraps may be useful to control swelling. The effectiveness of anticoagulant therapy (aspirin at 100 mg/kg once daily PO, ruminants; 10 mg/kg once daily, horses; or sodium heparin at 30-40 units/kg SC twice daily) or antiinflammatory drugs for dissolving a thrombus is questionable. Anticoagulant therapy may be useful in preventing additional thrombus formation or propagation of the existing thrombus. Ultrasonographic guidance can be used to obtain a sterile aspirate of the cavitated area of the thrombus for culture and sensitivity testing when septic thrombophlebitis is suspected.[236] Broad-spectrum bactericidal antimicrobial therapy should be instituted for suspected septic thrombophlebitis or when a cavitated thrombus is detected ultrasonographically and modified, if necessary, based on the results of culture and sensitivity testing.[236] Bacterial endocarditis, particularly involving the tricuspid valve, is a potential complication of septic jugular vein thrombophlebitis. With the exception of a jugular venous thrombus, surgical removal of an embolism or thrombus is rarely attempted in large animals. Surgical resection of a jugular vein with septic thrombophlebitis has been performed successfully when the surgeon could ligate the affected vein above and below the thrombus. Jugular vein thrombectomy with removal of the contents of the affected portion of the vein has been performed successfully in horses.[243] Although the prognosis for complete resolution of the thrombophlebitis is guarded, especially if the thrombus is infected, many veins do recannulate with complete resolution of the thrombus and without vascular stricture. However, the time course is slow, and persistent local induration and obstruction to blood flow may persist. The prognosis for non–racehorses to return to the same level of performance is good.[244] However, Standardbred racehorses in this same study had a decreased chance of returning to racing at the same level.[244]

The prognosis for horses and calves with aortoiliac thrombosis is guarded. Although most calves with aortoiliac thrombosis have died or were euthanized, two calves have survived. One calf received antithrombotic treatment with unfragmented heparin and aspirin, and the other was treated with ketoprofen, acepromazine, and local heat. A wide variety of medical treatments have been proposed for horses with aortoiliac thrombosis, including sodium gluconate, larvicidal deworming, phenylbutazone, and a controlled exercise program. Success has been variable. Surgical thrombectomy has also been successful in some horses.[245-247]

Prevention and Control Thrombosis and embolization from IV catheters can be prevented by aseptic insertion, stabilization of the catheter, use of topical antiseptics, application of a sterile dressing, daily inspection of the catheter and vein, and replacement of the catheter at another site (preferably in another vein) if phlebitis occurs. Dwell time is a significant factor in the development of thrombophlebitis, and catheters should be replaced by new ones at another site every 72 hours.[248] Attempts should be made to place long-term catheters in large peripheral or central veins where contact between the endothelium and catheter is minimized and medications administered are diluted by the large volume of blood flow. Catheters left in place for prolonged periods should be of silicone rubber or polyurethane.[238] Aspirin (100 mg/kg PO once daily, ruminants; 10 mg/kg/day, horses) and low-dose heparin (30-40 units/kg SC twice daily, ruminants and horses) therapy should be considered to prevent thrombus formation in septic or endotoxic patients. Horses are much more prone to jugular thrombosis than are ruminants.

Parasite control is important in the control of thromboembolic disease and aneurysm in horses. Aneurysms of the sinus of Valsalva may be detected by routine echocardiographic screening of horses but occur so infrequently that this is not practical. In cattle, arteriosclerotic lesions are prevented by proper calcium and vitamin D supplementation.

Atrial Fibrillation

Definition and Etiology *Atrial fibrillation* is a cardiac arrhythmia characterized by a lack of coordinated atrial electrical activity. It is caused by an abnormality of impulse conduction that results from multiple small rapid and random reentrant activation of the atria. High resting vagal tone, commonly found in horses, shortens the action potential duration in atrial myocardial cells, making atrial fibrillation more likely to occur. Atrial fibrillation can occur in the presence of atrial enlargement from atrial myocardial disease, atrioventricular valvular regurgitation, ventricular failure, myocarditis, endocarditis, autonomic nervous system imbalance, electrolyte or acid-base disturbances, anesthetic drugs or tranquilizer administration, unknown causes, or in the absence of underlying cardiac disease (lone atrial fibrillation).

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Clinical Signs and Differential Diagnosis Large animals with atrial fibrillation may be asymptomatic at rest, and atrial fibrillation may be detected as an incidental finding in an otherwise normal horse. Horses that perform in rigorous athletic events usually have a history of exercise intolerance or poor performance. Other complaints may be exercise-induced epistaxis, respiratory disease, weakness, syncope, myopathy, colic, or CHF. Cattle with atrial fibrillation usually have GI disease.[249,250] Atrial premature depolarizations have also been reported in cattle with GI disease and may be a prelude to the development of atrial fibrillation.[250] Foot rot, pneumonia, and endocarditis also have been associated with atrial fibrillation in cattle. Anorexia and decreased milk production are common in cattle with atrial fibrillation. Atrial fibrillation and the clinical signs associated with it in horses and in cattle can be paroxysmal. Paroxysmal atrial fibrillation usually lasts no more than 24 to 48 hours before spontaneous conversion to sinus rhythm occurs.[251] Spontaneous conversion usually occurs in horses with small atria and an otherwise normal heart or in cattle with correction of the underlying problem. Transient potassium depletion associated with the administration of furosemide is a common cause of paroxysmal atrial fibrillation in horses. Administration of bicarbonate "milkshakes" has also been implicated in horses with paroxysmal atrial fibrillation.

Animals with atrial fibrillation have an irregularly irregular cardiac rhythm. In horses with atrial fibrillation, there is a high degree of underlying periodicity.[252] Heart sounds vary in intensity, and no fourth heart sound is audible. The heart rate may be slow, normal, or elevated. In cattle with severe abdominal disease, the heart rate usually reflects the severity of the underlying disease. In horses the resting heart rate is usually normal to slightly elevated and is rarely above 50 beats/min unless there is underlying myocardial or valvular disease. During exercise, horses with atrial fibrillation develop abnormally high heart rates that are usually 40 to 60 beats/min higher than expected for each level of exercise, far exceeding the peak heart rate of 240 beats/min at maximal exercise.[253,254] The arterial pulse varies in intensity. A pulse deficit occurs when two beats occur in rapid succession and is infrequent unless the heart rate is elevated. Cardiac murmurs of grade 3/6 or louder are present in less than 50% of the horses and in even fewer cattle with atrial fibrillation.[255-257] Signs of CHF (peripheral edema, jugular venous distention) may be present in some animals, but they are not caused by the arrhythmia. In these cases, atrial fibrillation occurs secondary to the atrial enlargement that occurs with the underlying valvular or myocardial disease.

Absence of an auscultable fourth heart sound in the presence of an irregular cardiac rhythm with no underlying regularity distinguishes atrial fibrillation from other cardiac arrhythmias. Sinus arrhythmia, which is also an irregular rhythm, has an audible fourth heart sound. Ventricular and atrial ectopic beats usually occur with a relatively regular underlying rhythm. A complicated ventricular rhythm with more than one focus of activation may have characteristics similar to those of atrial fibrillation and must be distinguished from it by an ECG. Atrial tachycardia with varying degrees of atrioventricular block has similar auscultatory characteristics, and the underlying fourth heart sounds may be missed if the animal is auscultated in a noisy environment.

Clinical Pathology In cattle with atrial fibrillation, acid-base and electrolyte disturbances occur frequently and are most likely attributable to the underlying primary disease. Most cattle with atrial fibrillation have GI disease, and the most consistent acid-base disturbance is metabolic alkalosis.[257] Hypocalcemia, hypokalemia, and hypochloremia may also be seen in cattle with atrial fibrillation. Experimental induction of metabolic alkalosis with hypokalemia in cattle has been associated with development of atrial fibrillation.[258] Most horses with atrial fibrillation have normal electrolytes, although the fractional excretion of potassium may be low, particularly in horses that sweat excessively or are routinely receiving furosemide for exercise-induced pulmonary hemorrhage.

The diagnosis of atrial fibrillation is made by ECG. The arrhythmia is characterized by an irregular R-R interval. The ventricular response rate is low, normal, or high, depending on the presence of heart disease or the severity of the primary disease. The ventricular complexes have normal polarity and amplitude but vary slightly in appearance from beat to beat. Similarly, the QT interval and the appearance of the T wave vary. P waves are absent, replaced by fine undulations of the baseline called *fibrillation* or *f waves*. In some leads the f waves are barely visible, particularly in cattle (Fig. 30-33).

The echocardiogram is used to determine whether cardiac disease is present. The most significant change associated with the arrhythmia is a mild reduction in shortening fraction (≤24%) that occurs, in part, secondary to the loss of the atrial contribution to ventricular filling.[259] Absence of the second (atrial) opening of the mitral valve, corresponding to atrial contractions, is also detected with atrial fibrillation.[260] Conversion to sinus rhythm usually results in these echocardiographic findings returning to normal within several days if there is no underlying myocardial disease.[259,261] Similar improvement occurs in horses with mitral and aortic regurgitation after conversion to normal sinus rhythm.[261] In many large animals with atrial fibrillation, no evidence of heart disease can be detected echocardiographically; these animals are often considered to have "lone" atrial fibrillation. Abnormal echocardiographic dimensions, if detected, indicate that underlying heart disease is present. Measurement of the maximal left atrial dimension in the two-chambered view of the left atrium and left ventricle from the left cardiac window should be performed in peak systole to determine whether there is left atrial enlargement. This measurement is a more sensitive indicator of left atrial enlargement than the M-mode left atrium–to–aortic root ratio. In normal horses the left atrial diameter in this view should be

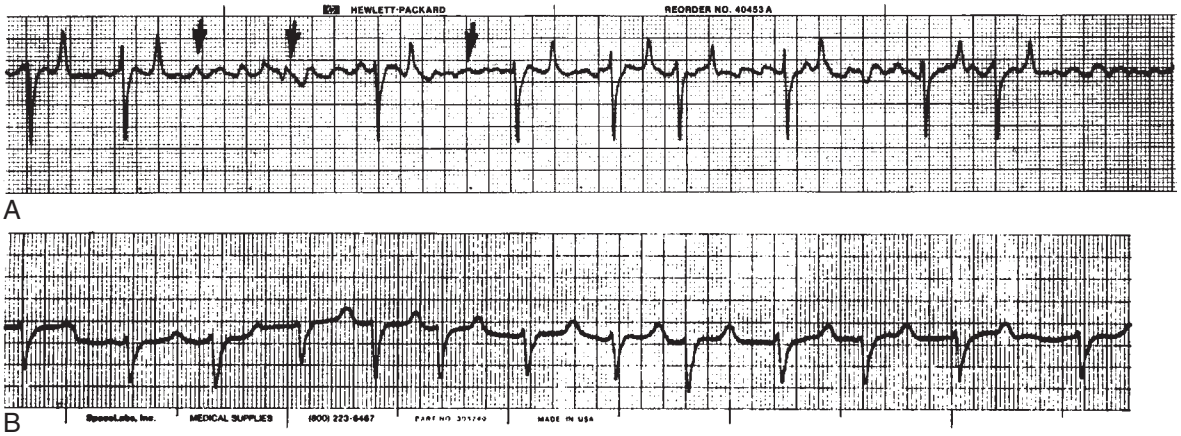


FIG. 30-33 ECGs showing atrial fibrillation in a horse **(A)** and cow **(B)**. The irregular QT intervals and absence of P waves are apparent. *Arrows* point to fibrillation waves, which are apparent only in **A.**

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13.5 cm or less. Measurement of the left atrium–to–aortic root ratio can be performed in the 2D short-axis view of the aorta across the maximal short-axis diameter of the left atrium to obtain additional information about left atrial size. Measurement of the maximal diameter of the left atrium can also be performed in the four-chambered view in peak systole if the heart can be imaged in its entirety.

Cardiac catheterization reveals normal cardiac output and blood pressure measurements in most awake horses with atrial fibrillation, but conversion to normal sinus rhythm may induce a reduction in mean right atrial, pulmonary arterial, and aortic pressures.[262] Similar studies have not been reported in cattle.

Pathophysiology

Experimentally, rapid stimulation of the atrium can initiate atrial fibrillation, which can be sustained if the animal has a large heart and sufficient vagal tone.[250,263-266] In horses and cattle the normal atria may be large enough to support atrial fibrillation once it is established. In addition, both species have a high vagal tone at rest. This combination of factors may be responsible for the large number of benign or functional cases of atrial fibrillation in large animals. The ventricular response during atrial fibrillation results from rate-dependent concealment of atrial fibrillation wavelets bombarding the AV node.[252] Cardiac diseases such as endocarditis, atrioventricular valvular regurgitation, and CHF that result in atrial enlargement and rapid stimulation of the atria provide a setting in which atrial fibrillation can develop and can be sustained naturally. Microscopic cardiac pathology might also create the proper setting for the development of conduction block and reentry.

During atrial fibrillation there is no coordinated contraction of the atria, so ventricular filling is passive. Although this might be expected to reduce cardiac output, there is no evidence this occurs in resting horses without concurrent mitral or aortic regurgitation.[262] In several horses with aortic regurgitation or aortic and mitral regurgitation, a decreased cardiac output was detected compared with horses without valvular insufficiencies before conversion.[261] The cardiac output increased significantly in warmblood horses with valvular regurgitation after conversion. During exercise, however, the heart rate of horses with atrial fibrillation exceeds normal limits, often by 40 to 60 beats/min for each level of exercise. This results in a decreased cardiac output and the resultant exercise intolerance that occurs in horses performing high-intensity athletic work.[253] Even higher heart rates were reported in warmblood horses during lungeing exercise, with the majority of these horses exhibiting QRS complexes with abnormal morphology during exercise.[267] Blood flow to other organs and viscera, although not studied, may be altered in large animals with atrial fibrillation, resulting in reduced GI motility, colic, reduced muscle blood flow, and poor milk production.

Atrial pressures are elevated in horses with atrial fibrillation.[262,268] Sustained high pressure is likely to produce dilation of the atria. With progressive dilation, secondary atrioventricular valve regurgitation may occur. During atrial fibrillation blood flow to the atrial myocardium is reduced, and progressive fibrosis can also be a consequence of chronic atrial fibrillation. Sustained atrial fibrillation may result in progressive cardiac disease, although it is usually well tolerated in the horse.

Epidemiology

Standardbred, Thoroughbred, and Draft horses have been reported to have the highest incidence of atrial fibrillation.[254-256] Racehorses have been diagnosed most frequently, but atrial fibrillation has been found in all types of horses.[255,256,261] Horses of all ages are susceptible to atrial fibrillation, but it occurs infrequently in ponies, foals, weanlings, and yearlings. Older horses, ponies, foals, weanlings, and yearlings with atrial fibrillation more frequently have underlying heart disease associated with the arrhythmia.

In cattle, atrial fibrillation is diagnosed more frequently in dairy cattle than in beef cattle, but there is no apparent breed predilection.[249,257] It is commonly associated with GI disease or abdominal pain in cattle.[249,250,257] Foot rot and pneumonia can also be associated with development of atrial fibrillation in cattle.

Necropsy Findings

Many cattle and horses have "lone" atrial fibrillation without apparent underlying heart disease, so the necropsy findings reflect the primary disease. Microscopic cardiac pathology has been found in horses with atrial fibrillation that consists of focal atrial myocardial fibrosis, microvascular alterations, and cardiac nerve abnormalities.[269-271] Multifocal or large areas of myocardial fibrosis were detected in dairy cows with idiopathic atrial fibrillation.[272] Whether these changes predisposed to the development of atrial fibrillation, were a consequence of atrial fibrillation, or were aging changes has not been established. A minority of horses and cattle have endocarditis, CHF, or valvular lesions, and the necropsy findings reflect these conditions. In horses with atrial fibrillation, mitral valve disease was the most common valvular lesion.[256] Pharmacologic and transvenous electrical cardioversion are both options for conversion of atrial fibrillation to normal sinus rhythm in horses.[256,273-284]

Treatment and Prognosis

Quinidine is the drug of choice to convert atrial fibrillation to normal sinus rhythm in horses and cattle. The drug is a negative inotrope at high dosages, causes systemic hypotension, increases the ventricular response rate, and can produce undesirable side effects and toxicity—it must be used with caution. In animals with CHF, quinidine therapy has considerable risk.[256] Because most large animals have little or no underlying cardiac pathology, treatment with quinidine is successful in restoring normal sinus rhythm. Treated animals should be monitored frequently by physical examination, with careful auscultation and ECG recording. Continuous ECG recording using radiotelemetry should be performed throughout treatment.[276] Animals should have normal acid-base balance and electrolyte concentrations before treatment. They should be adequately hydrated, allowed to drink and eat, or given additional oral fluids (horses) or IV fluids (cattle) during therapy. IV administration of quinidine gluconate is successful in converting horses with recent-onset atrial fibrillation to sinus rhythm.[277] Quinidine gluconate is most successful when administered to horses with atrial fibrillation of 2 weeks or less. However, quinidine gluconate had been successful in converting horses with atrial fibrillation of 2 to 4 weeks' duration. Horses with longer durations of atrial fibrillation should be treated with quinidine sulfate via nasogastric intubation. Quinidine is poorly absorbed after oral administration to cattle, so it must be given by IV infusion to obtain therapeutic concentrations. Cattle should be given IV fluids during quinidine infusion. Quinidine therapy should always be discontinued when conversion to normal sinus rhythm occurs.

Quinidine sulfate is the preparation most economically used in large animals, although quinidine gluconate has resulted in successful conversion of a cow with atrial fibrillation.[285] Before therapy, a baseline ECG is recorded. Horses are given a dose of 22 mg/kg of body weight (1 g/100 lb) in a suspension of water via nasogastric tube. At 2 hours (time by which blood concentration of quinidine should have peaked), they are evaluated closely for idiosyncratic or toxic reactions such as nasal edema, cutaneous reactions (urticaria or wheals), laminitis, colic, diarrhea, or ataxia. If no abnormalities are noticed, an ECG is recorded. If conversion to normal sinus rhythm has not occurred and the QRS duration is not greater than 25% of the pretreatment QRS duration, an additional dose is administered. Two hours after each dose administered via nasogastric intubation, an ECG is recorded. If there has been no conversion to normal sinus rhythm, another dose is administered, up to a maximum of four doses. A plasma quinidine concentration should be obtained 1 hour after the fourth dose administered every 2 hours to be sure the horse will be able to tolerate another dose without experiencing toxicity. If the QRS complex is prolonged by more than 25% of the pretreatment value, or if a fast (>80 to 100 beats/min) sustained supraventricular arrhythmia, ventricular rhythm, colic, diarrhea, ataxia, nasal edema or laminitis develops, therapy should be discontinued. Although laminitis is a frequently reported complication of quinidine sulfate therapy in the older literature, the actual incidence of laminitis associated with quinidine administration is rare.[276] Nasal

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mucosal edema, neurologic signs, and prolongation of the QRS duration to greater than 25% of the pretreatment value are all signs of quinidine toxicity; if detected, the drug should be discontinued. Colic associated with high dosages of quinidine should also prompt discontinuation of treatment (at least for this attempt at conversion). If conversion has not occurred after a total of four to six doses (one every 2 hours) or after a cumulative dose of 88 to 132 mg/kg of quinidine sulfate has been administered, treatment intervals should be prolonged to every 6 hours (approximate half-life of quinidine).[276] Only four doses of quinidine sulfate should be administered every 2 hours before switching to every 6 hours if plasma quinidine concentrations cannot be obtained in a timely fashion. The every-6-hour treatment can be continued until the horse converts or shows toxic or adverse side effects or the owner elects to discontinue treatment. The advantage of this treatment regimen is that steady-state plasma and myocardial concentrations of the drug are achieved. There is less quinidine toxicity, a lower total dose of quinidine sulfate is used, and horses that did not convert after the standard every-2-hour administration may convert with this treatment regimen. Digoxin at 11 µg/kg PO twice daily can then be added to the therapeutic regimen if conversion has not occurred in 24 to 48 hours; it appears to be helpful in some horses. Concurrent administration of digoxin and quinidine will result in an increased plasma digoxin concentration,[286] so to prevent digoxin toxicity, concentrations should be monitored beginning the second day of combined quinidine and digoxin therapy. If this is not possible, the horse should not receive more than 2 days of combined digoxin and quinidine therapy. Transvenous electrical cardioversion has been very successful in converting horses to normal sinus rhythm and is particularly useful in horses in which adverse or toxic reactions to quinidine prompted discontinuation of antiarrhythmic therapy with the result that conversion to normal sinus rhythm was not achieved.[281,284]

Quinidine sulfate at a dose of 48 mg/kg is suspended in 4 L of saline or lactated Ringer solution when cattle are treated for atrial fibrillation. This dose is administered at a rate of 1 L/h. IV fluids are administered simultaneously in the opposite jugular vein. Cattle should be monitored continuously during the infusion. Cattle frequently become depressed and develop diarrhea during the infusion of quinidine. These signs are side effects, and therapy can be continued. The infusion rate should be slowed if the ventricular response rate exceeds 100 beats/min. If the QRS complex is visibly prolonged or a fast (>120 beats/min) supraventricular arrhythmia or ventricular rhythm develops, therapy is temporarily discontinued. Just before conversion, some cattle have blepharospasm and are ataxic. The infusion should be discontinued as soon as conversion occurs. Therapy should be discontinued after the 4-L infusion even if conversion to normal sinus rhythm has not occurred.

During quinidine therapy the ECG shows predictable changes. The fibrillation waves become coarser and less frequent. The R-R interval becomes more regular as the heart rate increases. Before conversion there may be a rapid regular atrial rate with more than one saw-toothed flutter (F) wave or P wave for each QRS complex (atrial flutter or atrial tachycardia with atrioventricular block, respectively). At the time of conversion, a single P wave is present for each QRS complex. Frequently a large T_a wave is present and the ST segment is elevated. The ECG should be normal within 12 hours of conversion. A continuous 24-hour ECG is recommended in horses with atrial fibrillation after conversion to determine whether frequent atrial premature depolarizations are present. If the continuous ECG is normal and left atrial and ventricular function has returned to normal, the horse can be returned to training. If frequent supraventricular premature extrasystoles are detected or left atrial contractile dysfunction persists, the horse should be rested and treatment with corticosteroids considered. The horse should not be returned to work until the atrial premature depolarizations have resolved and left atrial contractile function has returned to normal. IV amiodarone and flecainide have been used to convert horses with atrial fibrillation,[279,280,282] but amiodarone is less successful than quinidine for this purpose.[279,282] Ventricular arrhythmias were common in horses given flecainide, limiting its usefulness as a treatment for atrial fibrillation in horses.[280]

Digoxin is used before quinidine therapy in horses and cattle with fast heart rates. The ventricular response rate should be less than 60 beats/min in horses and 100 beats/min in cattle before quinidine therapy. One or two doses of digoxin are administered before initiation of quinidine therapy in horses with only mild tachycardia. In horses with very labile heart rates or problems with rapid ventricular response rate during a previous conversion, digoxin is administered for up to 5 to 7 days before initiation of quinidine therapy. Digoxin should be administered at a dose of 11 µg/kg PO twice daily to horses. Cattle are given digoxin by IV infusion at 0.86 µg/kg/h or 11 µg/kg three times daily. The side effects of quinidine treatment (e.g., rapid ventricular response rate) may be decreased in animals pretreated with digoxin. Digoxin is also indicated as a pretreatment in horses with atrial fibrillation and very low FS (<24%), indicative of underlying myocardial disease. Transvenous electrical cardioversion should be considered in horses with high heart rate responses to stimulation or during prior quinidine therapy.

Because cattle with successfully treated primary GI disease frequently convert to normal sinus rhythm spontaneously—usually within 5 days of resolution of the primary problem—treatment is delayed for this period.[257] Cattle that do not convert spontaneously in 5 days, have chronic GI problems, or have atrial fibrillation with adverse hemodynamic effects (poor peripheral perfusion, weak arterial pulses, and/or pulse deficit) are selected for quinidine therapy. The prognosis for cattle with atrial fibrillation is good if the primary problem has been resolved and conversion to normal sinus rhythm occurs. Prognosis for cattle with chronic GI disease is guarded, but many show improved appetite and milk production when atrial fibrillation is resolved. Unless heart disease is present, few cattle experience a recurrence of atrial fibrillation. A small percentage of cattle fail to respond to quinidine therapy, and their prognosis is guarded to poor because milk production and appetite are intermittently poor and heart disease can be progressive.

Horses with paroxysmal atrial fibrillation have a good prognosis for return to performance, and few have a recurrence of the arrhythmia. If possible, predisposing factors such as transient potassium depletion should be removed by discontinuing furosemide administration or adding oral KCl to the diet. Oral bicarbonate milkshakes and thyroid hormone supplementation should be avoided. Horses with "lone" sustained atrial fibrillation have a good prognosis for conversion to normal sinus rhythm and a return to previous performance level.[255,256] Horses with sustained atrial fibrillation associated with mild to moderate valvular regurgitation and atrial enlargement often have a recurrence of atrial fibrillation but can usually be successfully converted when indicated. Horses with heart rates over 60 beats/min or with signs of CHF have a guarded to grave prognosis, and conversion to sinus rhythm is rarely warranted. Treatment of the underlying cardiac disease (if possible) is warranted, and the horse should be treated for CHF with digoxin, diuretics, and vasodilators as needed. Recurrence of atrial fibrillation and side effects of quinidine therapy are more frequent in horses that have had atrial fibrillation for longer than 4 months before treatment.[256] The recurrence rate for horses with atrial fibrillation of more than 4 months' duration increases from 25% to 60%. This may be the result of atrial remodeling and the associated microscopic cardiac lesions that developed with chronic atrial fibrillation.

Ventricular Tachycardia

Definition and Etiology *Ventricular tachycardia* is a cardiac arrhythmia characterized by a rapid rhythm originating in the ventricle. This rhythm originates below the bundle of His in the specialized conduction system, the surrounding ventricular myocardium, or both.[287] VT may be caused by disorders in impulse formation, impulse conduction, or a combination of the two.[287] Ventricular reentry is an important mechanism in the genesis of sustained VT,

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whereas abnormal automaticity is probably responsible for idioventricular rhythms and parasystole. Changes in autonomic tone may also be important in the genesis of VT. Early afterdepolarizations are thought to be the mechanism responsible for ventricular tachyarrhythmias associated with sympathetic stimulation. Late coupled ventricular complexes or a very premature ventricular depolarization are usually required to initiate VT. VT can occur when there is myocarditis, myocardial necrosis, fibrosis or neoplasia, bacterial endocarditis (especially involving the aortic or mitral valve), autonomic nervous system imbalance, hypoxia, ischemia, electrolyte or metabolic disturbances, anesthesia, drug administration, sepsis, endotoxemia, toxic myocardial injury, or aortic root rupture; or it may be associated with other, unknown causes.[80,206,220,288,289]

Clinical Signs and Differential Diagnosis The clinical signs detected depend on the ventricular rate, type of VT (uniform or multiform), duration of VT, and severity of the underlying cardiac disease.[289] Large animals with VT may be asymptomatic at rest if the rhythm is relatively slow and uniform, or they may have severe CHF with rapid uniform or multiform VT.[289] Exercise intolerance is common and may be so severe that the animal has frequent syncope. Other complaints include depression, weakness, colic, respiratory distress, coughing, ventral edema, and pulmonary edema. Acute viral or bacterial respiratory disease with high fever may precede development of VT in horses or may occur concurrently with it. Gastrointestinal disease and primary myocardial disease are common in horses with VT.[288,290] Horses with severe hemorrhage are also at increased risk for ventricular arrhythmias.[291] In cattle, VT occurs most frequently secondary to sepsis and toxemia. Anorexia and decreased milk production are common in affected cows.

Animals with sustained VT have a rapid heart rate with a regular (uniform) or irregular (multiform) rhythm.[292-295] Heart rates as high as 300 beats/min have been detected in horses with VT. Heart sounds vary in intensity, with some very loud booming sounds ("bruit de cannon"). Arterial pulse may be variable or uniform, with normal (slower rate) or weak (rapid rate) intensity pulses. Pulse deficits frequently occur, particularly with rapid or multiform VT. Jugular pulses are frequently detected in large animals with VT. The large pulse waves seen in the jugular vein are cannon "a" waves that occur when the right atrium and ventricle contract simultaneously. Cardiac murmurs are not commonly detected. Signs of CHF are usually present when VT is rapid and sustained but are uncommon in animals with slower or paroxysmal VT.[292-294] Signs of right-sided CHF (ventral edema, venous distention) usually predominate with sustained uniform VT and increase in severity the longer the duration and more rapid the rate of the arrhythmia. Signs of left-sided CHF (coughing, expectoration of foamy fluid, respiratory distress) usually predominate with multiform VT.

The presence of jugular pulses and bruit de cannon in an animal with a rapid regular rhythm helps distinguish VT from sinus or supraventricular tachycardia. Multiform VT can be difficult to distinguish from atrial fibrillation, because both arrhythmias have an irregular rhythm with heart sounds that vary in intensity. Jugular pulses may also be detected in large animals with atrial fibrillation but are usually less prominent than in animals with VT. Although large animals with multiform ventricular arrhythmias usually have more severe clinical signs, an ECG is necessary to distinguish these arrhythmias.

Clinical Pathology Electrolyte, metabolic, or toxic causes of VT may be present in large animals with primary GI disease. Hypomagnesemia and hypokalemia have also been associated with development of VT.[295] Serum creatinine and BUN may be elevated in horses and cattle in CHF associated with prerenal azotemia. Serum osmolality, BUN, and creatinine increase and urine osmolality decreases acutely in horses with experimental monensin toxicosis.[158] Initial decreases in serum potassium and serum calcium have also been reported in these animals. Marked elevations of cTnI have been seen in horses with VT.[171,172,290] In human beings, cTnI is a more sensitive indicator of myocardial injury and appears to have a similar sensitivity in the horse; cTnI is currently preferred for detection of myocardial injury in horses. Cardiac isoenzymes of CK and LDH are often elevated if there is recent myocardial injury associated with VT. Elevation of the myocardial fraction of CK (CK-MB) in excess of 5% of the total CK is compatible with myocardial injury in horses.[158] A neutrophilic leukocytosis and hyperfibrinogenemia may be detected in animals with infectious myocarditis or bacterial endocarditis or may be elevated owing to the primary underlying disease. In most large animals with VT, however, hematologic findings are normal.

The diagnosis of VT is made from the ECG. A series of four or more ventricular premature depolarizations is diagnostic of VT.[288,296] The electrocardiographic appearance of the ventricular premature depolarizations may be widened and bizarre, or the QRS duration and appearance of the QRS and T may be near normal, especially in horses (Fig. 30-34).[288,289] Although the duration of QRS complexes that are ventricular in origin is usually within the normal range reported for horses, it is usually longer than the QRS duration of the horse's normal sinus beats.[288] The major direction of the QRS complex is usually oriented opposite to that of the T wave. The R-R intervals may be regular or irregular. The morphology of the QRS complexes may be similar (uniform) or may vary widely with multiform VT (Fig. 30-35). Atrioventricular dissociation is usually present, with an atrial rate slower than the ventricular rate. Fusion beats and capture beats may be detected. VT can be sustained or paroxysmal.

The echocardiogram is used to determine whether cardiac disease is present. The echocardiogram is usually abnormal in large animals

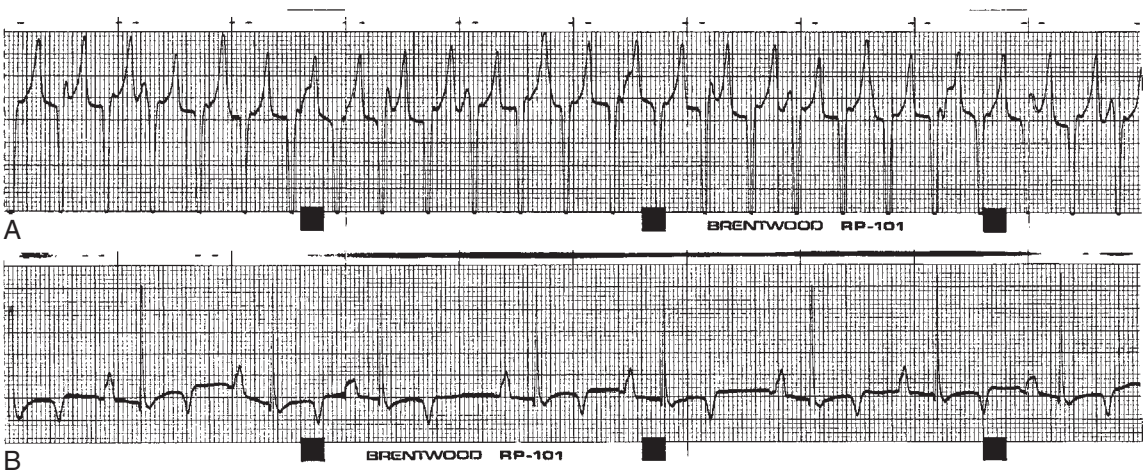


FIG. 30-34 Lead II ECG obtained from a horse with sustained uniform ventricular tachycardia and congestive heart failure before **(A)** and after **(B)** conversion to sinus rhythm. Note the abnormal QRS and T configuration and slower atrial rate during the sustained ventricular tachycardia.

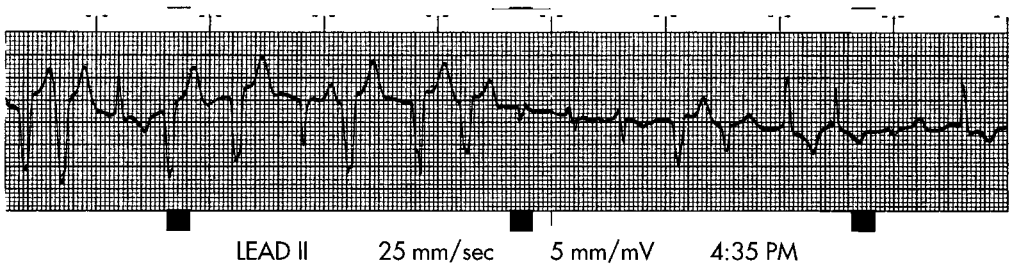


FIG. 30-35 Lead II ECG obtained from a horse with multiform ventricular tachycardia and acute onset of pulmonary edema. Note the multiple different QRS and T configurations and the elevated ventricular rate.

with primary myocardial disease and normal in large animals with secondary VT, except for the changes associated with the VT itself (see Fig. 30-15). Abnormal echocardiographic findings that may be detected in large animals with primary myocardial disease include myocardial dyskinesis, hypokinesis, and akinesis; abnormal myocardial echogenicity; decreased FS, ET, and EF; loss of the normal systolic and diastolic undulations of the aortic root; and detection of spontaneous contrast, small aortic root, and large pulmonary artery. Occasionally the echocardiographic abnormalities created by VT may be difficult to distinguish from those of primary myocardial disease. Rupture of the aortic root at the right sinus of Valsalva may be detected in horses with acute onset of uniform VT and colic.

Cardiac catheterization may reveal severe hypotension and low cardiac output. In healthy ponies with pacing-induced VT, stroke volume decreased significantly when the ventricle was paced at 150, 200, and 250 beats/min.[297] Mean left atrial pressure, mean pulmonary arterial pressure, and right ventricular systolic pressure increased significantly when the ventricle was paced at 220 and 250 beats/min. Aortic pressure and cardiac output decreased in these ponies at 250 beats/min, but the decrease from resting values was not statistically significant. Myocardial perfusion in the papillary muscles and subendocardium decreased significantly with pacing-induced VT at a rate of 250 beats/min. Decreases in cardiac output, arterial blood pressure, and myocardial perfusion are even more marked in animals with underlying myocardial disease or multiform VT, as are the changes in left atrial, pulmonary arterial, and right ventricular pressure.

Pathophysiology

VT is probably initiated spontaneously by late coupled ventricular complexes, whereas one very early ventricular premature depolarization can often initiate VT electrically.[287] Sympathetic stimulation may also provoke VT by increasing the amplitude of the early afterdepolarizations, culminating in a run of VT.[287] This may be the mechanism of some of the exercise-induced VT in horses. Reentry in the ventricle is an important cause of sustained VT, particularly in human patients with dilated cardiomyopathy and ischemic heart disease. The area of reentry is reportedly small (<1.4 cm^2).[287] Reentry is also thought to be an important mechanism in horses with sustained VT.[294,298,299] Delayed afterdepolarizations may trigger VT in humans and dogs and may be the mechanism for digitalis-induced VT.[287] Abnormal action potentials have also been demonstrated in ventricular myocardium resected from human beings with recurrent VT.[287] Depressed automaticity and afterdepolarizations have been associated with acute myocardial ischemia, whereas automaticity and afterdepolarizations are enhanced in Purkinje fibers surviving myocardial infarction. Idioventricular rhythms and parasystole may be caused by abnormal automaticity.

Cardiac diseases such as endocarditis may result in septic myocardial emboli and myocardial ischemia. Aortic root rupture and dissection of blood into the interventricular septum disrupts conduction and usually results in a uniform VT. Myocarditis, myocardial necrosis, and fibrosis also may result in abnormalities of impulse formation and conduction, leading to VT.[300] The excitement of the high-performance situation and the decreased myocardial perfusion that may occur at peak exercise may make exercise-induced VT more common in racehorses and other types of high-performance horses.

Epidemiology

VT has been reported in all large animals, although horses may have the highest incidence. VT leading to ventricular fibrillation is thought to be one of the leading causes of sudden death in horses when other causes of death cannot be found on postmortem examination.[299,301,302] Male horses are at increased risk for aortic root and sinus of Valsalva rupture and are usually at least 10 years old at the time of rupture. VT is also more likely in large animals of any age with primary GI disease and in horses following severe hemorrhage.

Necropsy Findings

If VT is not associated with primary myocardial disease, necropsy findings reflect the underlying disease. Gross and microscopic cardiac pathology has been found in horses with VT, although in some horses no cardiac pathology is found. Areas of myocardial necrosis, inflammatory cell infiltrate, fibrosis, infarction, microvascular alterations, and cardiac nerve abnormalities have been reported in horses with VT.[270,294,299,300] CHF is most likely in large animal patients with multiform VT and heart rates in excess of 180 beats/min. Bacterial endocarditis and secondary septic emboli dissemination through the coronary arteries as a result of VT occurs in a minority of large animal patients. Aortic root rupture and rupture of a sinus of Valsalva aneurysm with dissection of blood into the interventricular septum are infrequently detected in horses.

Treatment and Prognosis

Treatment and prognosis for VT depends on the suspected cause of the arrhythmia, severity of the animal's clinical signs, and electrocardiographic abnormalities detected.[288,289] Relatively slow, uniform VT often resolves or improves significantly with correction of the underlying electrolyte or metabolic imbalances, without requiring antiarrhythmic therapy. These animals usually have an excellent prognosis for conversion with correction of the underlying problem. Similarly, in large animals with sepsis or toxemia, hemodynamically and electrically stable VT often resolves with treatment of the underlying disease. Uniform, hemodynamically stable VT in animals with myocarditis may resolve with rest and/or corticosteroid therapy. A minimum of 4 to 8 weeks of rest is indicated in these patients before returning to work, once the VT has resolved.

Treatment with antiarrhythmics is indicated in any animal with hemodynamically unstable or life-threatening VT. Treatment with antiarrhythmics is indicated if clinical signs of CHF or cardiovascular collapse are present or if the rate of sustained VT is extremely high. In horses with sustained uniform VT, a heart rate in excess of 120 beats/min usually warrants antiarrhythmic therapy, whereas in cattle, antiarrhythmic therapy may not be indicated until the heart rate exceeds 140 beats/min or greater. Horses with rapid sustained uniform VT (≥120 beats/min) need antiarrhythmic therapy because signs of CHF will develop after several days or weeks with this arrhythmia, if not already present. Rapidity of CHF onset is related to heart rate and type of primary myocardial disease, if present. These horses usually have a good prognosis for conversion and return to their previous performance level with appropriate antiarrhythmic

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therapy (many times three or more antiarrhythmic drugs must be tried before conversion occurs) and rest before the horse is returned to work.

ECG findings associated with life-threatening VT include a multifocal origin for the ventricular premature depolarizations, torsades de pointes (wide ventricular tachycardia), and the presence of an R wave superimposed on the preceding T wave ("R on T"). Large animal patients with clinical signs of CHF and hemodynamic collapse with rapid (heart rate < 120 beats/min) multiform VT (±R on T) should be treated as a cardiovascular emergency; sudden death from ventricular fibrillation is likely without antiarrhythmic therapy. Large animals with multiform VT (±R on T) must be given a guarded to grave prognosis for survival, because most have severe underlying myocardial disease. Often conversion to sinus rhythm may not be successful before the animal develops ventricular fibrillation and dies. If successfully converted to sinus rhythm, many of these animals die or are euthanized because of the severity of the underlying cardiac disease.

Several antiarrhythmic choices are available to the large animal practitioner for correcting life-threatening VT (see Table 30-3). Lidocaine hydrochloride—the most readily available drug for most large animal practitioners—is rapidly acting, administered IV, and has a short duration of action and minimal hemodynamic effects. However, this drug has central nervous system side effects in horses (hyperexcitability and seizures) and must be used at a lower dosage than in cattle. Quinidine gluconate (or quinidine sulfate in cattle) is very effective in large animals but is less rapidly acting, has negative inotropic effects at large doses or if primary myocardial disease is present, causes hypotension, and can produce undesirable adverse or toxic reactions. Magnesium sulfate can cause hypotension but has no other recognized adverse cardiovascular effects. It is less rapidly acting than lidocaine, but in both normomagnesemic and hypomagnesemic patients it may be effective when other antiarrhythmics fail. IV procainamide, IV and oral propafenone, and IV flecainide have also been used successfully in horses with VT. IV propafenone is indicated for refractory VT and has been used successfully in several horses that did not respond to lidocaine, quinidine, procainamide, or magnesium sulfate. However, it is currently unavailable in the United States. Other antiarrhythmics such as propranolol have been used with less success but have converted large animals with sustained VT.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Diseases of the Respiratory System

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Diagnostic Procedures for the Respiratory System

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General Evaluation of the Patient with Respiratory Disease

History

As with any disease process, acquisition of an accurate and appropriate history is the first step undertaken in evaluating the patient with a complaint thought to be related to the respiratory tract. Animals with respiratory disease may have widely varied histories and it is important to gather as much information as possible. Age and breed may play a role in the development of respiratory disease, such as congenital defects or neoplastic disease, or in inherited or acquired immunodeficiency syndromes seen in certain breeds. The environment in which the animal is maintained can contribute to the development or severity of respiratory disease, heaves in horses for example, and respiratory disease may become manifest following a change to a new environment. The work horses are expected to perform can lead to important diagnostic clues, and recent events, such as long-distance transport, can predispose horses to diseases such as pleuropneumonia. It is important to know if certain diseases are either endemic or epidemic where the horse is kept or has recently moved from; diseases such as strangles and *Rhodococcus equi* bronchopneumonia of foals come to mind. Any recent traumatic or potentially traumatic event should be noted. If possible, a thorough vaccination history should be obtained, as should an accurate history of any administered treatments or supplements and the patient's response to those treatments.

Presenting Signs or Chief Complaints

There are many presenting signs or chief complaints that should lead to more thorough evaluation of the respiratory system, some more directly associated with either the upper or lower respiratory tract. Findings or complaints associated with respiratory disease include nasal discharge, either bilateral or unilateral. Respiratory noise at rest or during exercise is commonly associated with abnormalities of the upper airway, as may be inequalities of airflow present at the nares. Normal animals may periodically cough or sneeze, but an increase in either activity may indicate involvement of the respiratory tract. Exercise intolerance or apparent decrease in the ability of the animal to exercise should prompt evaluation of the respiratory system. Other clinical signs that indicate thorough evaluation of the respiratory tract include, but are not limited to, abnormal breathing patterns (tachypnea, hyperpnea, dyspnea), cyanosis, hemoptysis, epistaxis, unusual swellings (facial, pharyngeal, cervical), lymphadenopathy, ataxia or reluctance to move, foul smell to the breath, weight loss, and ventral abdominal, sternal, or limb edema.

Physical Examination

The initial physical examination occurs at some distance from the patient and involves evaluation of the demeanor, posture, mental status, and way of movement of the patient. It is important to note if the patient has an abnormal stance, such as standing with the head and neck extended. If the patient is unwilling to move or stands with elbows abducted, this suggests pleural pain is present. Ideally, the respiratory rate can be determined by observation as can the respiratory pattern. While some respiratory diseases are not manifest at rest, important clues can be gained from observation of the patient at rest in many others. The normal resting respiratory rate of an adult horse is between 8 and 16 breaths per minute, for adult cattle 15 to 35 breaths/min; and sheep and goats, 12 to 20 breaths/min. There is some small abdominal component during the expiratory phase, which is, along with inspiration, an active process for horses. The normal rate for neonates is up to 60 breaths/min at birth and less than 30 breaths/min by 1 month of age; respiratory rate decreases toward the adult rate with age. High ambient temperature, fever, and excitement can all increase respiratory rate. Normal breathing, which is quiet and apparently effortless, is termed *eupnea.* The term *dyspnea* is a breathing pattern that is inferred by the observer to reflect difficulty in breathing; the animal will appear distressed, and the work of breathing is obviously increased, although the actual rate may be within normal limits. Other terms used to describe breathing patterns include *tachypnea,* characterized by rapid rate and shallow depth or low tidal volume; *hyperpnea,* with increased frequency and depth of breathing (an example would be during postexercise recovery); and *apnea,* in which there is no discernible breathing. Two additional terms include *hypoventilation* and *hyperventilation,* both of which require a change in arterial carbon dioxide partial pressure as a component of their definitions. Hyperventilation is a pattern that increases alveolar ventilation and causes arterial hypocapnia, whereas hypoventilation alters gas exchange in such a way to cause arterial hypercapnia, or retention of carbon dioxide.

Closer examination can reveal some of the physical manifestations of presenting complaints listed previously. Beginning with the head, the clinician should determine that airflow is even from both nostrils, as differences can indicate either congenital or acquired abnormalities ranging from choanal atresia to the presence of upper airway masses. Abnormal respiratory sounds can sometimes be present at rest and may be heard at the nares. Abnormal breath odors

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may be prominent, particularly at the nares. The frontal and maxillary sinuses should be percussed; identification of abnormal resonance, usually dullness, may be made easier by performing this with the mouth held open. Palpation of the submandibular regions, larynx, and pharyngeal and cervical regions should be performed to identify any abnormal lymph node enlargement, masses, or areas of muscular atrophy. Both jugular veins should be checked for patency and the presence of any evidence of injection sites or infections that may contribute to abnormal upper airway function by interfering with normal recurrent laryngeal nerve or vagosympathetic trunk function.

Coughing represents a nonspecific irritation of receptors in the airway and can be induced by many mechanisms. It can be, and usually is, a normal protective reflex that allows the animal to clear material from the airway. Cough can be associated with increased mucus production, production of other respiratory secretions, or decreased mucociliary clearance. In older horses cough is most commonly associated with heaves, whereas in younger horses cough is associated with infectious diseases and small airway inflammatory disease. Normal animals should not cough when the larynx or trachea is palpated.

Nasal discharge can be unilateral or bilateral, scant or copious, clear, mucoid, mucopurulent, or even bloody. The nature and character of nasal discharge can provide some information about a possible source of the discharge, but this information should not be overinterpreted. Horses, for example, have a tendency to swallow excess airway secretions, and the volume of secretions may be underestimated. Whereas unilateral nasal discharge seems to suggest a source in front of the larynx, bilateral nasal discharge can be of either upper or lower airway origin. Skin depigmentation of the ventral nares or presence of mucoid material in feed or water containers is a clue to presence of nasal discharge.

Hemoptysis is the coughing up of blood from the airways or lungs. It is important to determine conclusively that the blood has come from the respiratory system. Epistaxis is defined as blood seen at the nares and often originates in the nasal passages, sinuses, turbinates, nasopharynx, or equine guttural pouches, although the lung can be, and is, a source on occasion, as in exercise-induced pulmonary hemorrhage (EIPH) or following lung biopsy. Bilateral epistaxis generally indicates bleeding caudal to the choanae. Because animals tend to swallow excessive respiratory secretions, bleeding can be occult and may not be seen unless the animal drops its head toward the ground. Significant blood loss can occur in this manner, unseen by owners.

Examination of the oral mucous membranes may reveal cyanosis, bluish discoloration of the oral, nasal, or vulvar mucous membranes. Cyanosis does not become apparent until 5 mg/100 mL of deoxygenated hemoglobin, about one third of the total normal hemoglobin, is present; this reflects a profound decrease in oxygen saturation of hemoglobin and is suggestive of severe hypoxemia. As it is the total quantity of deoxygenated hemoglobin that lends the mucous membranes the bluish color, very anemic patients may lack sufficient deoxygenated hemoglobin to appear blue, which makes appreciation of cyanosis impossible in these patients. One caveat is that all newborns are cyanotic for the first few breaths and only become pink when they have established neonatal, as opposed to fetal, cardiorespiratory circulation and have opened their lungs to allow for gas exchange.

It is important that auscultation of the thorax take place in as quiet an environment as possible. Additionally, auscultation of the lung fields should be performed under two breathing conditions: eupnea and hyperpnea, with hyperpnea induced by the use of a rebreathing bag. Some common misconceptions regarding the use of a rebreathing bag exist. Simply occluding the animal's nostrils is inadequate to fully examine the patient, as is using a rectal sleeve as a rebreathing bag. The purpose is to cause the animal to rebreathe its own expired carbon dioxide, not to necessarily deprive it of oxygen. Rebreathing expired carbon dioxide results in increased $PaCO_2$, which stimulates deeper and more frequent breathing efforts, making recognition of abnormal lung sounds simpler. The bag used should be large enough to accommodate 2 to 3 times the normal tidal volume of the animal and should be held in such a manner as to prevent the bag from occluding the patient's nostrils. Once the bag is removed, the animal will usually take several very deep breaths and the examiner should take advantage of these very large breaths to reexamine areas where suspicious sounds were heard during rebreathing. Animals with significant lung pathology will not tolerate the bag well, may cough when the bag is removed, and may require more time to return to baseline respiratory patterns when the bag is removed.

Normal breath sounds are those produced by turbulence within the tracheobronchial tree and may vary considerably depending on location within the lung, breathing pattern, and condition of the animal.[1] Only airways from the larynx to segmental bronchi contribute to sound generation; bronchial and vesicular sounds represent larger airway flow events. Vesicular sounds—the quietest sounds, heard over the middle and diaphragmatic lung regions—correlate best with regional ventilation and mainly represent segmental bronchial sounds; they do not represent air flow in terminal conducting airways and alveoli, which is silent due to the nature of its flow. Bronchial sounds are louder and heard best over the trachea and base of the lung. Common abnormalities found during auscultation include ventral areas of dullness if pleural effusion is significant, dorsal areas of dullness or hyperresonance with pneumothorax, and dorsal harsh lung sounds. The degree of variation in normal lung sounds is large, and auscultatory findings do not always correlate well with the degree of lung abnormality. That said, abnormal lung sounds are always potentially clinically important.

Adventitious lung sounds are divided into short discontinuous sounds called *crackles* and longer continuous sounds called *wheezes*, replacing the older terms *rales* and *rhonchi,* respectively. Crackles are most commonly generated by sudden pressure equalization when collapsed airway segments open. Although an air/fluid interface is required, crackles do not necessarily imply excessive secretions or pulmonary edema. They are often end-inspiratory and associated with reinflation of atalectatic lung. Crackles may be normal when auscultated in the previously down lung of a laterally recumbent neonate. Disease processes that generate crackles include pneumonia, interstitial fibrosis, chronic obstructive lung disease, congestive heart failure, and atelectasis.[2]

Wheezes commonly represent oscillation of airway walls before complete closing (expiratory) or opening (inspiratory). Intrathoracic airways are usually involved in expiratory wheezes and include the lower trachea, main, lobar, and segmental bronchi. Disappearance of a wheeze after coughing indicates secretory rather than tissue component origin. Disease processes responsible for wheezes include airway stenosis or external compression; airway lumen compromise by foreign body, purulent material, cyst, or neoplasm, and airway wall thickening as in chronic bronchitis; and bronchoconstriction. Expiratory wheezes are a hallmark of obstructive lung diseases such as heaves. Crackles and wheezes may be variably present. A final category of adventitious sounds is the "rubbing" or "creaking" sounds generated by sliding or stretching of inflamed pleural surfaces, commonly termed *pleural friction rubs*.

Percussion of the thorax is performed by methodical tapping over the intercostal spaces of the thorax using a variety of instruments, including plexors, pleximeters, spoons, fingers, neurologic hammers, and hands. It is an inexpensive and useful component of the physical examination and should be performed in all patients where the respiratory system is suspect. Percussion of the thorax can reveal hyporesonance (dullness) ventrally when pleural effusion is present, reveal hyperresonance dorsally in pneumothorax, and cause some patients to exhibit pleurodynia during the examination. Other conditions that can alter resonance of the thorax include, but are not limited to, diaphragmatic hernia with intrathoracic intestine, pericardial effusion, pulmonary and pleural abscessation, and consolidated lung. The point at which a change occurs from resonant to dull can be marked with adhesive tape. Thus the outline of aerated lung immediately beneath the chest wall is delineated. It is usually impossible

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to fully delineate the lung field cranially because of body fat and triceps musculature. There is a distinct region of cardiac dullness for all species on the left side.

Percussion allows delineation of pleural effusion and intrathoracic masses or consolidated lung up to 7 cm beneath the pleural surface, but cannot distinguish between them. The procedure should be performed whenever pleural effusion is suspected on the basis of auscultatory findings and in all ruminants as part of the physical examination to uncover occult pneumonia.[3]

Additional Diagnostic Evaluation of the Respiratory Tract

Endoscopy

The upper airway can be directly examined with the aid of an endoscope, the only limitations being the size of the patient, the patency of the airway, and the size of the available equipment. Standard flexible fiberoptic endoscopes, available to most practitioners and present now in virtually all referral hospitals, allow direct examination of the nasal passages, ethmoid turbinates, nasal maxillary opening of the sinuses, pharynx, guttural pouch openings, larynx, and cranial trachea (Fig. 31-1). Smaller (8 to 10 mm in diameter) endoscopes can be readily introduced into the equine guttural pouches, with the aid of a biopsy instrument, and longer endoscopes (more than 150 cm long with diameters greater than 10 mm) are commonly employed to examine main stem bronchi and their initial branches in large animals.[4] Smaller species, such as camelids, may require the use of a smaller diameter (3 to 5 mm) endoscope or bronchoscope. Small brushes, used for collecting exfoliated cells for cytologic study, and a variety of biopsy instruments can be used for sampling the airway.

Airway endoscopy in the horse has evolved to include dynamic endoscopy (e.g., treadmill, overland endoscopy) during exercise to evaluate the dynamic function of the upper respiratory tract.[3,4a] Objective measurements can be made by use of videoendoscopy with slow motion or freeze-frame features.[3] Treadmill endoscopy is available at specialty practices and typically is performed at high speed (12 to 14 m/s) using incremental standardized testing protocols. Overland endoscopy has recently become more readily available to certain specialty practices and is performed during ridden exercise in the field with endoscopy equipment that is attached to the horse.[4a] Advantages of overland endoscopy include the ability to evaluate the horse under saddle and in natural conditions. Standardizing exercise tests in the field may, however, be more challenging. Sedation/tranquilization will aid many standing endoscopic examinations, but examinations aimed at evaluating pharyngeal and/or laryngeal function are best performed without any form of chemical restraint that might alter function. Most horses will allow standing examination of the upper airway with only physical restraint, such as judicious use of a nose twitch. Introduction of the endoscope into the trachea may elicit coughing, particularly in horses but less so in cattle. Small ruminants, such as sheep and goats, may require local tracheal anesthetic administration in the form of 2% lidocaine administered through small tubing passed through the biopsy channel of the endoscope. If lidocaine is used, it must be diluted and must not reach a toxic dose in small ruminants. Diluted topical 2% lidocaine can similarly be used in horses and cattle, if need be, for evaluation of the distal trachea, main stem bronchi, and larger bronchial tree branches. Horses are more sensitive to tracheal and bronchial stimulation and are more likely to require topical anesthesia than are cattle.

Guttural pouch diseases and upper airway abnormalities, such as pharyngeal lymphoid hyperplasia, laryngeal hemiplegia, epiglottic entrapment by arytenoepiglottic folds, dorsal displacement of the soft palate, pharyngeal cysts, retropharyngeal masses, and epiglottic deformities, are best diagnosed by endoscopic examination. Direct tracheobronchoscopic examination is best for the diagnosis of EIPH if it is performed within a few hours of exercise. Bronchoscopy with a longer endoscope may be useful for evaluating additional lower airway abnormalities, such as recurrent airway obstruction in horses. The degree and nature of airway secretions accumulating in the trachea can be easily assessed with an endoscope, and accumulated secretions may be sampled by aspirating the secretions through small tubing introduced into the trachea through the biopsy channel. Because the endoscope has passed through the nonsterile upper airway, these samples are best suited for cytologic, not microbiologic, evaluation but may be fully compatible with evaluation using molecular diagnostic techniques.[5-8] Endoscopy has also been used to help remove foreign bodies from the airway, generally aided by the biopsy instrument.

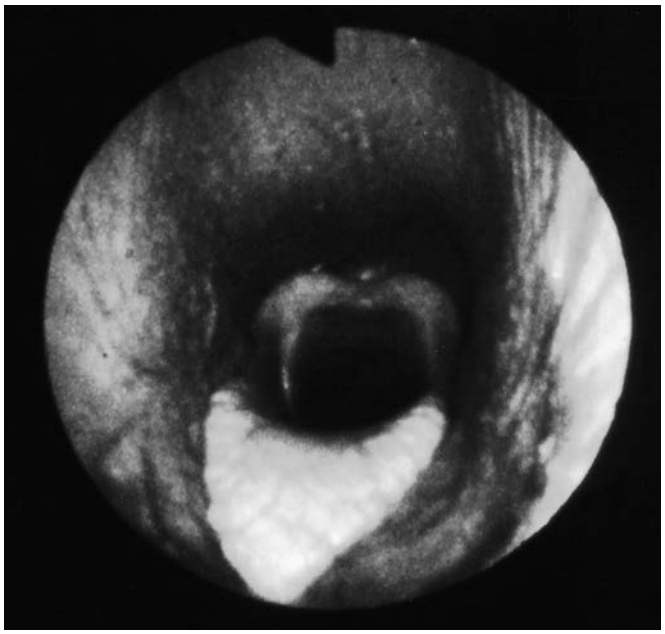


FIG. 31-1 Normal equine larynx. The larynx is directly visualized by endoscopy, with both structure and symmetry evaluated. *(Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

Radiography

Radiographs are indicated when the clinician suspects a congenital anomaly involving any thoracic structure; infectious disease of the pleura, pulmonary parenchyma, tracheobronchial tree, or mediastinum; pneumothorax or pneumomediastinum; thoracic neoplasia of any origin; or trauma. Radiographs are frequently performed along with thoracic ultrasonographic evaluation. If significant accumulation of pleural fluid is suspected based on physical examination findings, the ultrasonographic portion of the examination should be performed first and radiographs obtained following drainage of excess fluid, as fluid may obscure potentially important parenchymal disease. The equipment needed to perform radiographic evaluation of the upper airway is available in most private practices, while most large referral and university practices will have the equipment needed to perform thoracic radiography in larger patients such as adult horses and cattle. Conventional and digital radiography are available to most practitioners. Digital radiography has replaced conventional radiography in many practices and referral clinics because of recent improvements in affordability and the range of systems offered. Advantages to these systems include portability and speed of image processing along with a greater range of radiographic exposures and tools for image manipulation.[9] Because of its configuration, the thorax in adult horses and cattle is filmed as standing lateral, generally requiring a series of three to four separate but overlapping images; thus the benefit of the ventrodorsal view in which the two lungs may be compared is lost. Obtaining standing radiographs bilaterally may aid in localizing lesions to one hemothorax or the other. Neonates and small ruminants can be more readily handled and retained in recumbent positions, allowing for multiple recumbent views.

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Other imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are available at select referral practices and may aid in the characterization of certain upper airway disorders in large animal species. In horses, CT has been used in the diagnosis of sinonasal disease, particularly ethmoid hematomas,[10] and MRI has been used for the premortem diagnosis of laryngeal dysplasia associated with branchial arch abnormalities.[11] The application of CT and MRI toward routine use in the diagnosis of airway disease in large animal species is limited because of availability of equipment, cost of procedure, the need for general anesthesia in most instances, and size restrictions. Imaging of pulmonary disease is limited to immature animals or smaller species such as camelids.[12-14]

Skull and cervical radiographs offer diagnostic information for evaluation of the upper respiratory tract. For large animal species, standing lateral skull films are easily obtained, and, with practice and adequate sedation, ventrodorsal and oblique projections can be obtained in most patients. Certain difficult patients may require general anesthesia in order to obtain radiographs of diagnostic quality. Skull radiographs image the sinuses, pharynx, and larynx, allowing for assessment of anatomic dimensions of the pharyngeal and laryngeal structures. Sinuses affected by neoplasia or inflammation may show abnormal tissue density, a horizontal fluid line on a standing lateral film, bone lysis around the affected sinus, or alveolar periostitis. Thorough evaluation of the sinuses and nasal passages requires lateral, dorsoventral, and oblique views. Foreign bodies can be assessed in many cases. The equine guttural pouches are evident on lateral skull projection, and abnormal fluid accumulation, distortion by enlarged retropharyngeal lymph nodes, and emphysema can be radiographically apparent.

Radiographic assessment of the thorax of large animals remains preferable to ultrasonographic examination for detection of diffuse parenchymal diseases, such as interstitial pneumonia, pulmonary edema, equine multinodular pulmonary fibrosis (EMPF), fungal pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), chronic disorders, and deep parenchymal or mediastinal abscesses. Unfortunately, many radiographic changes in equine respiratory disorders tend to be nonspecific or, in certain diseases, such as EIPH, inflammatory airway disease, or heaves, minimal to nonexistent.

Four types of radiographic patterns are described for the thorax: alveolar (airspace), interstitial, bronchiolar, and vascular. Opaque areas coalesce and fully obliterate vessels and bronchi in the alveolar pattern, air bronchograms may be prominent, and this pattern is common in pulmonary edema, pulmonary hemorrhage, EMPF, ALI, ARDS, lung consolidation, and neoplasia. Interstitial patterns are the most common pattern noted in equine thoracic radiographs and are characterized by a blurring of the edges of pulmonary vessels, a diffuse increase in lung density, and variable reticular, linear, and nodular opacities. The reticular pattern is most commonly associated with more diffuse infectious lung diseases, pulmonary edema, interstitial pneumonia, and pulmonary fibrosis, whereas the irregular linear pattern is seen most commonly with resolving bronchopneumonia. A nodular pattern is seen with abscesses, granulomata, and neoplasms. It is rare to see a pure bronchial pattern in a horse; it is usually seen in association with an interstitial pattern. An exception is paired linear opacities or numerous small circular opacities (donuts) representing thickening of large or medium airways in equine bronchitis/bronchiolitis. The vascular pattern is seen in horses radiographed immediately after exercise or in animals with left to right cardiac shunts. Finally, extraparenchymal problems such as pleural effusions or free gas may be seen on thoracic radiographs of large animals. Thoracic radiology may be used for evaluation of potential rib fracture, but it is far less sensitive than thoracic ultrasonography in this regard.

Ultrasonography

Thoracic ultrasonography, a companion to thoracic radiography, is useful for diagnostic, therapeutic, and prognostic evaluation of the extraparenchymal thorax, the pleural space, and the peripheral (superficial) parenchyma of the lung. Unlike thoracic radiography, for which specialized equipment is needed to image the adult large animal, thoracic ultrasonography is an imaging technique readily available to most practitioners. In many instances it is superior to thoracic radiography as an imaging method; examples include evaluation of pleural effusions, assessment of thoracic trauma, evaluation of neoplasms or granulomata, detection of mediastinal masses/abscesses, and guidance of transthoracic lung biopsy.[15,16] Ultrasonography is considered greatly superior to thoracic radiography in the detection of rib fractures.[17] This imaging technique should be considered for complete evaluation of any large animal with suspected or diagnosed pulmonary disease.

Ultrasonography is generally performed with the patient standing, although in neonates lateral recumbency may be preferred or even necessary, and sound waves are generated by piezoelectric crystals, transmitted to the area of interest through a skin coupling gel with subsequently reflected echoes detected by the same crystal. Echo signals from all tissue interfaces are displayed on a screen, which can be photographed for a permanent record or stored digitally. Air trapped beneath the haired skin can interfere with the process, as can excessive skin dirt, so preparation of the acoustic window usually involves hair removal and cleansing in order to get the best image possible.

Although ultrasound waves will not penetrate the aerated portion of the lung, limiting the examination to extraparenchymal surfaces in normal horses, ultrasonography is superior to thoracic radiography for the evaluation of these areas of the chest. Small amounts of pleural fluid that would be missed on auscultation, percussion, or thoracic radiographs can be detected, and the amount and character of pleural effusion in each hemithorax can be evaluated separately.[15] Clear fluid is anechoic, but inflammatory cells, gas, and fibrin are echogenic, causing opacities that can be seen floating in pleural fluid and altering the general echogenicity of the fluid. Because of this, ultrasound is the method of choice for diagnosis and monitoring of pleural space disease. Ultrasonography should be used to guide catheter placement for drainage of accumulated fluid in the pleural space. The pleural surfaces are imaged well by ultrasound with thickened or roughened areas easily detected. Lack of normal independent movement of the visceral and parietal pleural surfaces during the respiratory cycle, suggestive of adhesion formation, can be readily monitored.[15,16]

Consolidated lung is a better acoustic medium than aerated parenchyma and can be well visualized. If there is pleuropneumonia with consolidation or atelectasis caused by compression of the ventral lung by pleural effusion, it will be evident. Pulmonary abscesses or masses extending to the lung surface can be imaged and ultrasound can be used for guidance during transthoracic biopsy.[15,16] Thoracic radiography remains superior to ultrasound in the diagnosis of pulmonary parenchymal disease and pneumothorax, but combined the two techniques will improve patient management diagnostically and therapeutically.

Nuclear Medicine Imaging

Nuclear medicine imaging is a very specialized technique available at a few university and private specialty referral practices. Gamma-emitting radioisotopes such as krypton-81m or technetium-99m can be used with an external detector (gamma camera) to assess regional pulmonary ventilation and perfusion in the horse. The procedure is safe and painless. Anesthesia is not needed, and the only requirement is that the patient stand quietly in front of the gamma camera. After the study, the patient must be kept in an isolated area to allow decay and excretion of the radiopharmaceutical (normally no more than 48 hours), and, of course, all pertinent radiation regulations must be strictly adhered to.

The radioisotope is bound to albumin aggregates of 10 to 15 micrometers in diameter. When injected into a peripheral vein, that is, the perfusion scan, the aggregates become trapped in the

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pulmonary arterial vasculature. Given even and thorough mixing in the right ventricle, the resulting image illustrates the perfusion distribution of the pulmonary arterial system. The ventilation scan is generated when the horse inhales aerosolized radioisotope particles through a closed circuit system.[18] The particles are small enough in diameter to be deposited in the alveoli and small conducting airways with the gamma camera recording the sites of deposition. Together, the ventilation and perfusion scans allow for evaluation of the ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio, important in evaluation of certain respiratory problems such as EIPH (high $\dot{V}/\dot{Q}$ areas), pulmonary thromboembolism (high $\dot{V}/\dot{Q}$ areas), and heaves (low $\dot{V}/\dot{Q}$ areas).[19] Additional uses are in the evaluation of deposition in the lung of aerosolized radiolabeled medications such as albuterol[19] and the evaluation of mucociliary clearance or tracheal mucus transport. In the latter, the time a bolus of radioisotope requires to cover a given tracheal distance is recorded in millimeters per minute and compared with normal ranges.[21]

Arterial Blood Gas Analysis

Arterial blood gas determinations are the most sensitive indicator of respiratory function readily available to the clinician. The most easily accessed arteries for sampling are the metatarsal, temporal, facial, and brachial arteries (Fig. 31-2). In cattle the coccygeal artery on the ventral aspect of the tailhead is easily accessible. Heparin is the only acceptable anticoagulant for blood gas samples, and all gas bubbles must be removed and the syringe capped to prevent equilibration of the sample with room air. Use a short (1-inch) small-gauge (25-gauge generally) needle and a 1- to 3-mL syringe for most samples. The syringe and needle can be purchased preheparinized especially for arterial blood gas samples, or regular syringes and needles may be heparinized by aspirating a small volume of heparin into the syringe via the needle and then forcefully expelling the air and heparin from the syringe three times. This minimizes the effect heparin might have on any reported values from the blood gas analyzer. Pulsation of blood from the needle, spontaneous filling of the syringe, and bright color of the blood all confirm a successful arterial puncture. If successful arterial puncture is questionable, then a comparison sample may be drawn from the jugular vein. Once the sample has been drawn, the vessel should be manually compressed for 2 to 5 minutes to prevent hematoma formation. If the sample will not be analyzed within 10 minutes, it should be placed on ice to slow metabolism of blood cells. The patient's body temperature at the time of sampling should also be recorded, as results are frequently reported at both 37° C and at the actual temperature of the patient, called *temperature-corrected values*, for pH, P_{O_2}, and P_{CO_2} as these values are known to be temperature variable. Clinically either set of values may be used for evaluating efficacy of treatment, but comparisons should only be made between samples reported similarly as either temperature corrected or not.



FIG. 31-2 Arterial blood sample drawn from temporal artery for arterial blood gas analysis. *(Courtesy Dr. Eric Birks, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

Portable arterial/venous blood gas analyzers have become relatively inexpensive. Because of their ease of use and rapid return of results, they are now making arterial blood gas analysis more practical for use in the field and the technique is no longer reserved for large institution or referral practices.[22,23] Awareness of potential device-, species-, or age-related differences in reference ranges, as well as awareness of any limitations in accuracy, is critical for proper interpretation of results. It is veritably impossible to manage severe respiratory disease without knowledge of arterial blood gas parameters. Pulse oximetry is also being more commonly employed in some institutions and referral centers. These monitors measure oxygen saturation of hemoglobin, useful for diagnosing severe hypoxemia or recognizing desaturation events, but provide no measure of actual arterial oxygen and carbon dioxide partial pressures. The most common abnormalities recognized with arterial blood gas analysis in an animal that is breathing room air are hypoxemia with normocapnia or hypocapnia and hypoxemia with hypercapnia. There are five primary means by which hypoxemia develops in any animal. For our purposes, hypoxemia is defined as decreased oxygen tension of the arterial blood (decreased Pa_{O_2}) and hypoxia is defined as decreased oxygen concentration at the level of the tissue, with or without hypoxemia. Hypoxia results from hypoxemia, decreased perfusion of the tissue bed in question, or decreased oxygen carrying capacity of the blood due to anemia or hemoglobin alteration.

Hypoxemia develops from (1) low partial pressure of oxygen in the inspired air, such as seen in high altitude or in an error mixing ventilator gas, resulting in lower than anticipated partial pressure of oxygen (altered Fi_{O_2}); (2) hypoventilation; (3) $\dot{V}/\dot{Q}$ mismatch; (4) diffusion limitation; or (5) intrapulmonary or intracardiac right to left shunting of blood. Mild to moderate hypoxemia is not an uncommon finding in neonates, but it must be evaluated in terms of the current age of the foal and its position. The difficulty in obtaining the sample must also be considered, as severe struggling can variably affect the arterial blood gas results. If the lung is significantly involved in the underlying pathology, such as with severe pneumonia, ALI, or ARDS, increased Pa_{CO_2} may very well be present, representing respiratory failure.

Hypoxemia is usually treated with intranasal humidified oxygen insufflation at 4 to 10 L/min for neonates and 10 to 15 L/min in adults. Hypercapnia is not easy to treat. It is important to try to distinguish between acute and chronic hypercapnia. Acute hypercapnia is usually accompanied by a relatively dramatic decrease in blood pH of 0.008 pH units for each 1-mm Hg increase in Pa_{CO_2}. This respiratory acidosis can promote circulatory collapse, particularly in the concurrently hypoxemic and/or hypovolemic patient. The effects of more chronic CO_2 retention are less obvious as the time course allows for adaptation. The pH change is less, about 0.003 pH units per 1-mm Hg increase in Pa_{CO_2}, as it is balanced by enhanced renal absorption of bicarbonate by the proximal renal tubule. Most patients with acute respiratory distress are in the acute stages of respiratory failure, but chronic adaptation will begin to occur within 6 to 12 hours and will be maximal in 3 to 5 days. An increase in bicarbonate will be noted, particularly if the acidosis is primarily respiratory in origin, and pH may be within the normal range.

Alveolar gas exchange is readily estimated by determining the alveolar-arterial (A-a) gradient for oxygen, computed by subtracting the Pa_{O_2} measured by the arterial blood gas from the calculated alveolar oxygen partial pressure (PA_{O_2}). The PA_{O_2} is effectively estimated using the partial pressure of inspired oxygen (Pi_{O_2}) as follows:[24]

$$PA_{O_2} = \frac{Pi_{O_2} - Pa_{CO_2}}{0.8}$$

The Pi_{O_2} equals the total barometric pressure (760 mm Hg) minus the partial pressure of water vapor (47 mm Hg) multiplied by

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TABLE 31-1

Normal Arterial pH and P_{CO_2} Values for Various Species (Nonneonate)

Species	Blood pH	P_{CO_2} (mm Hg)
Bovine	7.32-7.45	35-53
Ovine	7.32-7.54	37-46
Equine	7.32-7.44	38-46
Caprine	7.42-7.46	33-38

the fraction of room air that is oxygen (0.21) and thus equals 150 mm Hg for room air. For patients on supplemental inspired oxygen, the practitioner must remember to recalculate the P_{IO_2} with the new oxygen fraction (F_{IO_2}) (or, if at altitude, the P_{O_2} in the inspired gas), which is only possible in patients receiving inspiratory gas through a closed system. The P_{ACO_2} is obtained from the arterial blood gas measurement. The A-a gradient is normally only 4 to 10 mm Hg; an increase beyond this indicates impaired gas exchange within the lungs, most often the result of $\dot{V}/\dot{Q}$ mismatching. Only an estimate of the A-a gradient can be calculated in patients receiving intranasal insufflation of oxygen, as neither the F_{IO_2} nor the P_{O_2} is known.

A second useful measure is the P_{AO_2}/F_{IO_2} ratio, a component of most definitions of ALI and ARDS.[25] The P_{AO_2}/F_{IO_2} ratio equals the P_{AO_2} obtained from the arterial blood gas divided by the F_{IO_2}, the oxygen fraction in the inspired gases. The normal P_{AO_2}/F_{IO_2} ratio is greater than 300 mm Hg, a ratio less than 300 mm Hg is consistent with a potential diagnosis of ALI, and a ratio less than 200 mm Hg suggests ARDS, a more severe form of ALI. A consensus statement recently defined the conditions of equine neonatal acute respiratory distress syndrome and equine acute lung injury (EqNARDS and EqNALI).[26] Although similar to the definitions for ALI/ARDS in humans and adult veterinary species, the definition of EqNARDS and EqNALI account for the relative hypoxemia of normal neonatal foals compared with adults during the first week of life.[26] For this reason, over the first week of life the P_{AO_2}/F_{IO_2} increases from less than 115 mm Hg to less than 190 mm Hg in EqNARDS and from less than 175 mm Hg to less than 280 mm Hg in EqNALI.[26] The ranges of normal arterial blood gas values for various species are listed in Table 31-1.

Respiratory Function Testing

The major functions of the lungs are to transport gas from the periphery to the site of gas exchange (i.e., the "bellows" function) and to provide gas exchange with the blood, facilitating gas transport to the tissues. The first of these is assessed by means of pulmonary function tests, and the second by arterial blood gas evaluation, discussed above.

Historically pulmonary function tests have primarily been used in horses and in most cases as a research tool in veterinary teaching hospitals. Pulmonary function testing has also recently been described in awake adult llamas[27] and alpacas.[28] Portable technologies, such as flowmetric plethysmography, allow the use of noninvasive techniques in the field, and the awareness of their clinical utility to practitioners has grown.[29,30] Measurements of pressure, flow, and volume allow computation of a variety of ventilatory variables. Their ability to demonstrate airway obstruction and airway hyperresponsiveness[31] makes them clinically valuable in the diagnosis and characterization of inflammatory airway disease (IAD) and recurrent airway obstruction (RAO) in horses.[31] They may also provide an objective means with which to monitor response to therapy.[30-35] These techniques are described in greater detail in a later portion of this section.

Collection and Evaluation of Respiratory Secretions

TRACHEAL ASPIRATES AND BRONCHOALVEOLAR LAVAGE. Various spaces in the respiratory system can be aspirated or lavaged for diagnostic or therapeutic purposes. The most commonly performed procedure is the tracheobronchial aspirate. By aspirating from the airways caudal to the larynx, a sample without pharyngeal contamination is obtained.

In both the horse and the ruminant the procedure is performed with the animal standing. Sedation or restraint may be needed. A small area over the trachea in the middle third of the neck is clipped and routinely sterilely prepared. The skin is anesthetized using a local block of 2% lidocaine, generally less than 3 mL given as a "bleb" subcutaneously, and a small stab incision is made. A trocar or angiocatheter needle is introduced on the midline between muscle bundles, with the beveled edge facing ventrally to decrease the opportunity for inadvertent cutting of the tubing when it is introduced or manipulated, and the ventral tracheal wall is punctured between two cartilaginous rings. The distal end of the trocar or needle is then advanced distally in the trachea, with the bevel facing ventrally, taking care not to lacerate the dorsal tracheal mucosa. Sterile polyethylene tubing or the catheter from the angiocatheter is introduced through the trocar or needle for about 30 cm. A needle or sharp trocar should be withdrawn to prevent severing the tubing or catheter, but a cannula with rounded edges may be left in place. Approximately 20 to 30 mL of nonbacteriostatic sterile saline solution is introduced quickly. Intermittent aspiration is performed as the tubing is gradually withdrawn. The tubing can be advanced again if a guarding cannula has been left in place to prevent introduction of skin contamination. Additional saline solution aliquots can also be introduced. Once an adequate sample has been obtained, the tubing is completely withdrawn, followed by the withdrawal of any guarding catheter or trocar. Injectable antimicrobial solution or suspension can be infiltrated at the skin incision site if a septic sample is suspected, and in horses and small ruminants a sterile dressing can be applied for 24 hours if desired. Possible complications include subcutaneous emphysema (usually peritracheal but may extend into the mediastinum), local cellulitis, or cutting of the catheter at the needle and loss into the airway. The latter is usually resolved because the catheter is rapidly coughed up, but good technique should prevent this complication. If necessary, the severed catheter can be retrieved endoscopically. The sample should be cultured for aerobic bacteria. Anaerobic colonization is possible, and appropriate cultures should be made if these organisms are suspected (evidence of pleural effusion, consolidation, abscessation, fetid breath, history of aspiration). For patients with prior antimicrobial therapy, it is advised to discontinue antibiotics for 72 to 96 hours before culture, although a recent study has shown reliable recovery of bacteria using bronchoalveolar lavage fluid from foals receiving therapy.[6]

Airway aspiration can also be performed during routine endoscopy of the trachea using an aspiration catheter advanced through the endoscope biopsy channel, but there is potential for pharyngeal contamination. Results comparing culture from a protected aspiration catheter passed through an endoscope compared favorably with traditional percutaneous tracheobronchial aspirate.[5]

A direct smear and Gram stain can be used as an initial guide for antimicrobial therapy pending culture results. Cytologic evaluation can be extremely valuable in differentiating among infectious, allergic, parasitic, and neoplastic processes. Transtracheal aspirates from clinically normal horses contain columnar ciliated epithelial cells, a few neutrophils, and multiple mononuclear cells. Increased percentages of neutrophils and the presence of mast cells, eosinophils, giant cells, and hemosiderophages have been found in aspirates from normally performing Thoroughbred racehorses, indicating some airway inflammation in "normal" equine atheletes.[8] Mucus, large spores, and fungal hyphae may be found in the absence of airway disease and must not be overinterpreted. In cases of pneumonia, neutrophils may constitute 40% to 90% of the cellular sample. Bacterial pneumonia causes a more degenerate appearance of neutrophils, and intracellular bacteria may be found. Equine lungworm is characterized by the presence of large numbers of eosinophils and occasionally a larva. In ruminants the most important information gathered in patients with bronchopneumonia is usually the result of culture and antimicrobial sensitivity testing.

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Bronchoalveolar lavage (BAL) involves obtaining a sample from the terminal airways and alveolar region and is described in horses, cattle, and camelids.[28,36,37] BAL is performed using a long endoscope (2 to 3 m) or BAL (e.g., double-lumen or cuffed Bivona [Smiths Medical, Norwell, Mass.]) or MILA (MILA International, Elanger, Ky.) tubes introduced through the nares. Endoscopic BAL allows for more exact placement of the end of the endoscope, so a clear understanding of the anatomic location of the distal airway lavage is available. It also allows for the characterization of lower airway secretions and mucosal inflammation. Use of the BAL tube is a blind technique, but most frequently the dorsal lung of one hemithorax is sampled. BAL is contraindicated in horses that are expected to exercise within 24 hours of the procedure and in any animal demonstrating signs of respiratory distress, marked tachypnea, paroxysmal cough, or significant hypoxemia.

Proper sedation is critical for performing BAL. In horses, the addition of butorphanol may reduce cough that is typically associated with this procedure. Instillation of dilute 2% lidocaine, particularly when passing the tube into the trachea or past the level of the carina, may also decrease coughing associated with this procedure. Passage of the tube into the trachea can be facilitated by stretching the head horizontally. The endoscope or tube should be passed until it is wedged in the most distal bronchus. If using a cuffed BAL tube, the cuff should be inflated to seal the airway once wedged. In adult horses, it is recommended to infuse a total of 300 to 500 mL of warm (37°) sterile physiologic saline in aliquots of 60 to 250 mL. Smaller lavage volumes may be necessary in smaller animals. Fluid may be instilled via prefilled syringes or via a solution administration set using a pressure bag with fluid bag or pressure bulb with fluid bottle. The BAL sample is collected via continuous aspiration with syringes or a suction pump using low suction pressure. Aliquots should be pooled for analysis. The presence of surfactant (foam) and turbidity on gross inspection is suggestive of a properly obtained sample.

BAL has the advantage of sampling the airways nearest the parenchymal region, but only a limited area of the lung is sampled instead of the pooled secretions from a tracheobronchial aspirate. Thus bronchoalveolar lavage may be superior to tracheobronchial aspirate in evaluation of horses with diffuse chronic lung diseases of the peripheral airways, and molecular analysis of fluid is performed for identification of certain viral or bacterial species. Cytologic findings of BAL and tracheobronchial aspirates correlate poorly, and a tracheobronchial aspirate should be performed prior to a BAL if an infectious process is suspected. Bronchoalveolar lavage cytology is valuable in evaluation of fungal infections, inflammatory airway disease, and the assessment of therapeutic response. Normal cell distribution of BAL fluid in healthy horses reveals predominantly macrophages (50% to 70%) and lymphocytes (30% to 50%) with lower percentages of neutrophils (<5%), mast cells (<3%), and eosinophils (<0.1%). Macrophages are the predominant cell type (89%) in BAL fluid of healthy calves,[37] whereas alpacas may have a greater abundance of neutrophils (10%).[28]

Thoracocentesis

Aspiration from the pleural space is a simple, easily performed, inexpensive procedure that can be both diagnostic and therapeutic. In the horse with septic or neoplastic effusions, sedation is often unnecessary, because the procedure causes only minimal additional discomfort. Following ultrasonographic evaluation of the thorax, a point is chosen where drainage or fluid sampling would seem most appropriate, frequently found in the sixth or seventh intercostal space 10 cm dorsal to the olecranon and above the lateral thoracic vein. The area should be clipped, if it was not clipped for the thoracic ultrasound examination, and surgically prepared. Multiple sites may be needed in horses with loculated pockets of fluid in the pleural cavity and these sites should also be chosen using ultrasonography. The skin and intercostal tissue down to the pleura are anesthetized with lidocaine, and a stab incision is made. A sterile 2- to 3-inch teat cannula or bitch catheter is introduced immediately cranial to the rib border to avoid the intercostal nerve and vessel along the caudal aspect of the ribs. The cannula should be attached to sterile intravenous extension tubing and a three-way stopcock. While the cannula is advanced bluntly through the parietal pleura, a sudden loss of the force required to advance is felt. Aspiration should be attempted at this time. The orientation of the cannula can be varied to reach as much fluid as possible. Normally only a few milliliters of straw-colored fluid are obtained. In cases of pleural effusion, as much as 30 L may be removed from each side of the chest (Fig. 31-3). If fluid is excessive, the tubing can be extended over a bucket for gravity drainage, or a vacuum pump with a fluid trap can be attached. When the procedure is complete, a purse-string suture is placed around the stab incision and the cannula is withdrawn while the suture is tightened. In cases where the effusion is large and expected to continue forming for several days, the initial drainage can be performed by placing a chest tube instead of a puncturing the pleural space with a teat cannula. If a chest tube is to be left in place, it should be secured with a Chinese finger trap suture and the end covered by a Heimlich valve to prevent aspiration of air into the thorax through the tube. If the thorax is being drained rapidly, the patient should be watched carefully for signs of distress, as draining of large volumes can alter cardiovascular parameters significantly.

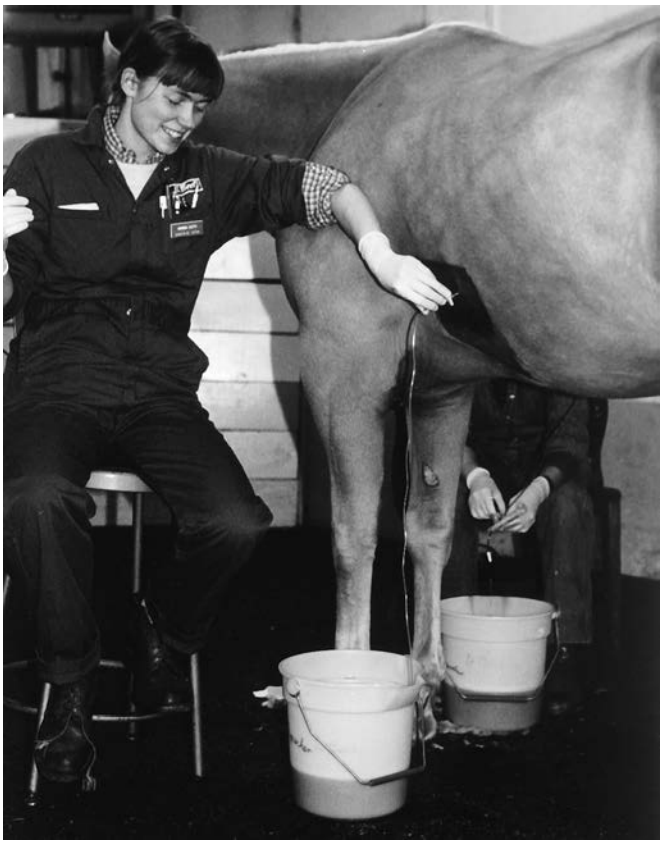


FIG. 31-3 Thoracocentesis and therapeutic drainage in the horse. Pleural effusion can be large and bilateral. Samples should be obtained for culture and cytologic examination at the time the chest is drained. *(Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

Increasing opacity, presence of fibrin clumps, and malodor of pleural fluid all suggest relative progression from transudate to septic exudate containing inflammatory cells and debris. A putrid odor suggests the presence of anaerobic bacteria. Samples should be cultured for aerobic and anaerobic organisms. A white blood cell (WBC) count of 10,000/mL or less is considered normal; fewer than 60% are normally neutrophils, the remainder being lymphocytes and macrophages. The proportion and total number of neutrophils increase with pleuritis. Erythrocytes are normally not present in the absence of a traumatic tap. The protein concentration is normally less than

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3.5 g/dL, and pH should be approximately 7.4. Additional metabolic values that give early indication of sepsis can be obtained on pleural fluid samples collected after filtration through a blood administration set to remove fibrin and debris potentially detrimental to analytic equipment. Pleural fluid pH, P_{CO_2}, and concentration of glucose, lactate, and bicarbonate can be directly compared with similar analysis of venous blood from the patient. A septic pleural exudate is acidic, with decreased glucose and bicarbonate but increased lactate and P_{CO_2} compared with venous blood concentrations or tensions, apparently reflecting metabolic activity of phagocytic cells and bacteria and development of an anaerobic environment.[38] Of these values, low pleural fluid glucose concentration (<40 mg/dL) has the best correlation with sepsis.[39]

Neoplastic cells may be found in cases of lymphosarcoma, adenocarcinoma, or other neoplasms. Equine gastric squamous cell carcinoma occasionally presents with neoplastic pleural effusion. If neoplastic effusion is suspected but diagnostic cells do not exfoliate into the pleural fluid, pleuroscopy under sedation and local anesthesia can be used directly to visualize and obtain biopsy samples of intrathoracic lesions. The technique of pleuroscopy is beyond the scope of this chapter.

Mediastinal fenestrations may be occluded by fibrin and cell debris; therefore each side of the thorax should be evaluated separately. In the horse a transtracheal aspirate for culture should also be performed because of the common association of pleuritis with bacterial pneumonia and pulmonary abscessation. Although identical organisms are generally isolated from both samples, this is sometimes not the case.

Sinus Trephination

Sinusitis is performed with some frequency in horses or ruminants. Clinical signs indicating a need for sinus trephination include foul-smelling purulent nasal discharge (the most consistent sign with dental disease or invasive tumors), facial malformation, exophthalmos, stertorous breathing, and epistaxis. Sinus cysts, neoplasms, or hematomas occur occasionally and result in serosanguineous discharge. When the physical examination, especially percussion, and radiographic findings indicate it, the sinus should be trephined for diagnostic aspiration, drainage, and flushing, if necessary. In some cases, sinoscopy may be indicated, particularly when the true extent of the disease process is difficult to determine or if biopsy samples are needed.

In the horse the frontal, sphenopalatine, and ethmoidal sinuses communicate with the posterior chamber of the maxillary sinus and drain through the nasal maxillary opening into the middle meatus. The anterior chamber of the maxillary sinus is separated by an osseous septum that often breaks down with infection, making the posterior chamber of the maxillary sinus the most productive site for diagnostic aspiration. A line is drawn from the medial canthus of the eye perpendicularly to the facial crest. After tranquilization and local anesthesia, the sinus is approached with a Steinmann pin midway on this line. Once the sinus has been entered, it should be aspirated by using a sterile 16-gauge needle or canine urinary catheter. One skin suture will suffice for closure. If purulent material or fluid within the sinus is under pressure, some leakage into the subcutaneous space may occur, with resulting cellulitis. The sample should be cultured for aerobic and anaerobic bacteria and examined cytologically for signs of septic inflammation or neoplastic cells.

The frontal sinus is trephined more often for flushing in chronic cases than for diagnostic purposes. The approach is 2.5 cm lateral to the midline of the face and 2.5 cm caudal to the point where the nasal bones begin to diverge.

In cattle the frontal sinus is most often affected with septic inflammation as a consequence of dehorning. Purulent material frequently accumulates in the postorbital diverticulum of the sinus. This site is approached for trephination 4 cm from the edge of the orbital cavity just dorsal to the temporal (lateral) canthus of the eye.

Postdehorning sinusitis in goats can be a severe condition, especially in animals dehorned when mature. The frontal sinus contains numerous septae, creating poor drainage; the bony plate protecting the brain is thin, so that septic necrosis of bone leading to meningitis may occur. Therefore, in mature goats with sinusitis, appropriate systemic antimicrobial therapy and vigorous curettage of the affected areas should be used. A bone flap similar to the technique used in chronic maxillary sinusitis may be required to expose the frontal sinuses to curettage adequately.

Guttural Pouch Catheterization

When indicated by radiography and/or endoscopy, the equine guttural pouches are easily catheterized for diagnostic sampling and lavage. Sampling can also be achieved by placing thin tubing through the biopsy channel of the endoscope, as for tracheobronchial aspiration, and directly aspirating or aspirating following introduction of sterile saline. Lavage can also be performed through the biopsy channel. The patient should be tranquilized so that the head drops, facilitating drainage of the secretions by gravity. A Chambers mare catheter can be passed through the ventral meatus into the pharynx if the endoscope is not to be used for the sampling or lavage. The curved end is directed beneath the flap of the medial lamina of the pouch ipsilateral to the nostril used for passage. Successful passage is indicated by lack of resistance while the catheter is inserted deeper than if it were in the pharynx. The position of the catheter tip in the pharynx can be observed through an endoscope placed up the opposite nasal passage. Once the catheter is within the pouch, it can be used to obtain a sample, to drain excessive secretions, or to act as a conduit for flushing. A self-retaining uterine catheter can be left in place for repeated flushing, but the Chambers catheter can be passed repeatedly with no complications.

Lung Biopsy

Lung biopsy is most often done in the horse and should be used in conjunction with other, less invasive diagnostic techniques such as ultrasonography, radiography, and transtracheal aspiration. Biopsy is indicated to obtain a histologic diagnosis or prognostic information primarily in cases of diffuse lung disease, because the sample obtained is generally very small. A more useful parenchymal sample is obtained by means of percutaneous rather than endobronchial biopsy; complications of percutaneous biopsy are uncommon but they do occur. Thoracoscopically guided pulmonary wedge resection is also an option for collection of a parenchymal sample and enables direct visualization of the lung prior to biopsy as well as collection of a larger tissue sample. The procedure is relatively safe but is more invasive and requires specialized equipment and expertise. For percutaneous biopsy a large gauge (14-gauge) 15-cm or longer biopsy needle, with a sample "slot" length of 22 mm, provides an excellent sample. Lung biopsy is easier and complications fewer with newer spring-loaded biopsy instruments than with the older hand-operated biopsy instruments. Discomfort is minimal, and sedation may or may not be needed. The site for biopsy should be determined following ultrasonographic evaluation for the thorax and should be performed away from common locations of major pulmonary vessels. Caudal and dorsal locations are generally chosen. The site should be widely clipped, surgically prepared, and infiltrated with local anesthetic down to the pleura. The biopsy needle is inserted through a stab incision just cranial to the rib, similar to catheter placement for pleural fluid sampling and drainage, and directed medially through the intercostal muscles and parietal pleura. The needle should be advanced the distance indicated by ultrasonographic measurement and then sharply advanced less than 1 cm to enter the lung parenchyma. The biopsy is obtained by "firing" the spring-loaded instrument; the biopsy instrument is then withdrawn. If no specimen is obtained, the procedure can be repeated. After sufficient biopsy specimens have been obtained and the biopsy instrument withdrawn, a single skin suture can be placed at the incision site, but no additional aftercare is needed. The specimen should be placed directly in 10% formalin or glutaraldehyde for fixation. If additional samples may be safely obtained, they should be submitted for bacterial and fungal culture, and potentially for more advanced molecular diagnostic

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techniques, and handled appropriately for the desired testing technique. Complications of lung biopsy have been reported to range from transient epistaxis or hemoptysis, which is to be expected, to more severe pleural and parenchymal hemorrhage. Lung biopsy is not indicated for pleuropneumonia cases but is generally required to differentiate between equine multinodular pulmonary fibrosis, discrete fungal lesions, and potential neoplasia, when accurate diagnosis is required for therapeutic and prognostic purposes.

Molecular Techniques

Infectious pulmonary disease represents a diagnostic challenge for the equine practitioner. A presumptive diagnosis can often be made based on the history, physical examination, clinical impression, complete blood cell count, radiography, and endoscopy. Definitive identification of the causative agent(s) is necessary to ensure that the appropriate therapeutic and prophylactic protocols are instituted.

Culture of infectious pathogens (viral or microbial) is an indispensable diagnostic technique and should be attempted in all cases of pulmonary disease. However, cultivating infectious pulmonary pathogens from clinical specimens is time-consuming and may require from days to months before an organism is identified, potentially delaying appropriate management. Molecular recognition systems that can be used for rapid identification can improve response time and reduce the number of susceptible animals exposed to the infectious pathogen.

Several technologic innovations have improved the rapidity and sensitivity with which microorganisms are identified.[40] Immunologic assays and nucleic acid–based methods for the identification of bacterial, viral, and fungal pathogens have found clinical application in the diagnosis of pulmonary disease. In addition, these techniques are widely used in research to characterize immunologic response (e.g., cytokine expression) to a variety of infectious and inflammatory respiratory diseases.

IMMUNOLOGIC TECHNIQUES. Immunologic techniques for detection of bacterial, viral, and fungal pulmonary pathogens have been developed. Immunoassays rely on interactions among the bacterial, viral, and fungal antigens and radioisotope-, enzyme-, or fluorescent-labeled antibodies. The use of polyclonal antibodies tends to increase the sensitivity of the assay as the preparation may contain antibodies to multiple epitopes on the target antigen, thus increasing the chance of antigen detection, but at the same time the use of polyclonal antibodies tends to decrease assay specificity due to their heterogeneous nature. Test specificity can be improved by the use of monoclonal antibodies as these antibodies interact with only a single well-defined epitope or very similar epitopes. Immunofluorescence, although labor intensive and time-consuming, is considered highly sensitive and specific, particularly for virus-infected cells. The enzyme-linked immunosorbent assay (ELISA) is available for the diagnosis of a wide range of infectious respiratory diseases. For certain pathogens the ELISA has the advantage of rapid turnaround of results and minimal labor; however, these tests may be subject to false-negative and false-positive results. Virus neutralization (VN) assays are also widely used and are considered highly accurate and sensitive. Unfortunately, VN is more expensive, labor intensive, and time-consuming compared with other diagnostics.

Immunohistochemistry is rapidly becoming a standard diagnostic tool for the identification of viral, bacterial, and protozoal pathogens in tissue sections. This technique depends on polyclonal or monoclonal antibodies binding to a target antigen and the demonstration of this interaction by colored histochemical reactions visible by light microscopy or by emittance of fluorescence detectable after ultraviolet light illumination. Immunohistochemistry is highly versatile, and assays have been developed to detect a variety of equine pulmonary pathogens including, but not limited to, equine herpesviruses, equine viral arteritis virus, Hendra virus, *Rhodococcus equi,* and *Pneumocystis carinii* (renamed *P. jiroveci* in humans) in tissue sections. Recent advancements in methodology have increased the ability to detect antigens in formalin-fixed tissues.

NUCLEIC ACID–BASED TECHNIQUES. Nucleic acid–based techniques for the diagnosis of equine pulmonary disease are becoming widely accepted because of the sensitivity, specificity, and speed with which results can be obtained. These assays can detect nucleic acid of both live and dead pathogens at very low concentrations, often less than 100 copies per microliter, and in a wide variety of specimens. Polymerase chain reaction (PCR) may also be advantageous compared with conventional microbiology in that it enables identification of organisms that are difficult to culture. Bacterial, viral, and fungal pulmonary pathogens can be discriminated based on nucleic acid sequences unique to that particular organism. PCR is the most widely used molecular diagnostic technique in both research and clinical laboratories. PCR involves the enzymatic replication of a target region of deoxyribonucleic acid (DNA) as defined by a set of oligonucleotide primers. DNA polymerase synthesizes each complementary strand of the target region in the 5′ to 3′ direction, and the amount of DNA that is synthesized increases exponentially.

Modifications to standard PCR, such as reverse transcriptase PCR and real-time PCR (RT-PCR), have greatly expanded its diagnostic utility. Reverse transcriptase PCR enables identification of viruses whose genome is composed of ribonucleic acid (RNA). Viral RNA is reverse transcribed into complementary DNA (cDNA) through an initial reverse transcriptase step, and the cDNA is then amplified with DNA polymerase. Commercially available single-step kits have increased the diagnostic utility of this technique.

Real-time PCR (qPCR) combines PCR amplification with simultaneous detection of the amplified products, allowing quantification of PCR products. Compared with traditional PCR, real-time PCR reduces the risk of contamination and increases sensitivity and speed of detection. DNA is detected with either nonspecific fluorescent dyes (e.g., SYBR Green I, Life Technologies Corp., Grand Island, N.Y.) that intercalate into double-stranded DNA or sequence-specific hydrolysis DNA probes (TaqMan, Applied Biosystems, Foster City, Calif.). The PCR reaction is carried out in a reaction tube to which an optical device is attached to read the fluorescent signal generated during each cycle of PCR reaction. Increases in the reported fluorescence are proportional to the increase in PCR product. By monitoring the changes in degree of fluorescence, the time in which a transition is made from exponential to log phase amplification can be determined and compared with that of a standard control to determine the initial template concentration. Real-time PCR may be combined with reverse transcriptase PCR (qRT-PCR) for the quantification of messenger RNA.

Intercalating dyes such as SYBR Green I bind to all double-stranded DNA undergoing amplification. Increases in DNA product yield proportional increases in the intensity of measured fluorescence, and thus the DNA concentration can be quantified. The use of intercalating dyes precludes the need to develop probes specific for each unique target sequence. The potential for nonspecific binding of the dye is the primary disadvantage with this technique. Hydrolysis probes, such as TaqMan, are short dual fluorophore-labeled oligonucleotides with a 5′-terminal reporter dye and 3′-terminal quencher dye. These probes can be tailored to detect specific pathogens. In the TaqMan assay, the probe binds to a nucleic acid sequence within the target region. During amplification, the *Thermus aquaticus (Taq)* polymerase hydrolyzes the probe that separates the reporter from the quenching dye and allows the emission of fluorescence. The amount of fluorescence emitted is proportional to the accumulation of specific PCR product. As these probes target only DNA containing the probe sequence, amplification of nonspecific PCR products should not result in emission of fluorescence. Because of its specificity a different probe must be provided for each unique target sequence. With the increased use of PCR as diagnostic tests, there is increased demand for standardized techniques and internal control measures. PCR is a highly sensitive test and may produce false-positive results, commonly attributed to contamination. False-negative results may occur as a result of the presence of enzyme inhibitors in the sample that suppress DNA amplification. Control

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plasmids—containing a DNA sequence that would be amplified at the same time as the target DNA but sufficiently mutated so that it could be distinguished from the target DNA sequence after PCR—are increasingly used to identify the presence of inhibitory molecules within the assay due to tissue or sample handling problems or associated with collected tissues.

Flow cytometry is a laser-based technology used to detect and quantify light scatter and fluorescence emitted by fluorescent-labeled cells suspended in liquid as they pass through a laser beam. Combinations of scattered and fluorescent light are identified by specific detectors and analyzed to derive information about the physical and chemical properties of a large number of cells at one time. Immunophenotyping of cells isolated from peripheral blood, tissues, or respiratory secretions is an important application of flow cytometry and may help to better characterize the immunologic response associated with select pulmonary diseases. Flow cytometry is currently used primarily as a research tool.

These assays do not substitute for careful clinical evaluation but can shorten the time to confirmed, accurate diagnosis and thus allow for early initiation of therapeutic strategies and prevention protocols. The continued refinement of available molecular assays, along with the development of newer technologies such as flow cytometry, will not only further our understanding of the molecular biology and immunology of pulmonary disease, but will also improve diagnosis and management.

Pulmonary Function Testing

Daniela Bedenice

Pulmonary function testing (PFT) has emerged as an essential tool in equine referral practice and is largely aimed at describing the severity, anatomic pattern, stability (reactivity), and reversibility of bronchoconstriction caused by noninfectious airway obstruction and inflammation, such as is seen in heaves and inflammatory airway disease (IAD).[1] Clinical indications for noninvasive PFT include assessment of horses with intermittent cough, exercise intolerance, abnormal breathing pattern, and excess mucus, as well as early detection of subclinical disease, evaluation of treatment response, intensive care monitoring, and prediction of outcome. PFT is generally divided into the assessment of respiratory mechanics (mechanical properties of the respiratory system) and gas exchange. Analysis of gas exchange investigates ventilation-perfusion matching, shunt, diffusion capacity, and dead space to tidal volume ratio (V_D/V_T). Lung mechanics, on the other hand, determine the static and dynamic properties of the lung, including resistance, compliance, functional residual capacity (FRC), and ventilatory parameters.[1]

Mechanics of Breathing

The mechanical function of the lung is essentially defined by static and dynamic properties. Tests that are performed with the respiratory system at equilibrium and zero flow are referred to as *static tests*. Examples include measurement of lung volume subdivisions (e.g., FRC) and compliance of the lung and chest wall.[1]

FRC is a measure of the amount of gas that remains in the lungs at end-expiration (end-expiratory volume). FRC is lower in patients with increased "lung stiffness" (reduced elastic recoil of the lung) as well as airway inflammation, whereas FRC increases in patients with expiratory airway obstruction and gas trapping.[2] This test can be easily performed in awake clinical patients via a helium dilution technique.[3] In short, the patient is connected to a reservoir bag at end-expiration to rebreathe a standard, commercial breathable gas mixture of 10% helium (He), 20% oxygen, and the remainder nitrogen for 90 seconds. The dilution of He (a nonexchangeable gas) gives a measure of end-expiratory lung volume.[3]

Measurements of static compliance or "elastic recoil of the lung" require breath holds and have applications only to the anesthetized patient. So-called pressure-volume curves are generated in the relaxed patient during lung deflation from total lung capacity (TLC), using an esophageal balloon technique. Compliance is defined as the lung volume change per unit of pressure change[2]:

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Reduced lung compliance (i.e., increased lung stiffness) may be associated with increased fibrous tissue (pulmonary fibrosis), atelectasis (e.g., underventilated lung), or an increased pulmonary venous pressure, in which the lung becomes engorged with blood. Emphysema and normal aging of the lung, which leads to alteration in elastic tissue, are causes of increased lung compliance.[2]

In contrast to static tests, tests that are performed with the respiratory system in motion (e.g., during quiet breathing) are referred to as *dynamic*. An example of a dynamic measurement is resistance, a measurement that requires flow. Resistance arises from friction of air molecules against airway walls[1]:

$$\text{Resistance} = \frac{\text{Change in pressure } (\Delta P)}{\text{Change in flow } (\Delta V)}$$

The measurement of pulmonary resistance (R_L) using a flow meter attached to a face mask and an esophageal balloon catheter to measure transpulmonary pressure changes is conventional in the horse but is rarely used in the clinical setting.[1] This technique allows computation of both R_L and dynamic compliance (C_{dyn}) at spontaneous breathing frequencies. Maximal transpulmonary pressure change (ΔPPL_{max}) and R_L both increase in cases of obstructive airway disease, whereas C_{dyn} decreases. However, this classic technique is fairly insensitive in detecting subclinical disease[4,5] and has greater utility in the diagnosis of IAD if coupled with a challenge test (i.e., histamine bronchoprovocation [see later]).[6,7]

Forced Oscillation Techniques

In contrast to the conventional methods, noninvasive measurements of total respiratory system resistance via forced oscillation techniques (FOT) are used in the diagnosis of IAD in horses. In short, oscillometry is the study of lung mechanical function via the application of external forces to the respiratory system.[8] Either a loudspeaker (e.g., impulse oscillometry system [IOS]) or air pressure (e.g., monofrequency forced oscillatory mechanics [FOM]) is used to superimpose pulses of flow (4 to 5 L/sec peak) through a face mask on the horse's respiratory system during spontaneous breathing. The generated reciprocal pressure waves are subsequently recorded at the airway opening (i.e., face mask). The magnitude and phase relationship between the input of flow and output of pressure are then used to perform the calculations of impedance (total opposition to airflow) and its components, resistance and reactance, at a variety of oscillatory frequencies (generally 1 to 7 Hz).[1] In most horses with IAD there is a frequency dependence of resistance, with higher values for resistance recorded at the lower oscillatory frequencies (1 to 2 Hz), indicative of bronchoconstriction.[9-11] Horses with moderate to severe lower airway obstruction commonly show high initial baseline values for respiratory resistance at 1 Hz (e.g., >1.0 cm H_2O/L/sec).[1] Higher frequencies (≥2 Hz) provide information concerning central airway resistance (R_{aw}). Baseline respiratory resistance measurements using FOT are often combined with bronchoprovocation tests for the early diagnosis of IAD. Additionally, the use of impulse oscillometry (IOS) has been advocated for separate analysis of inspiratory and expiratory impedance parameters, to allow the evaluation of both phases of the respiratory cycle in horses.[12]

Histamine Bronchoprovocation

Bronchoprovocation is a challenge test that assesses the response of the respiratory system to a bronchoconstrictor agonist (e.g., inhaled histamine).[1] The provocatory concentration necessary to cause a 100% increase in baseline respiratory system resistance is commonly termed *$PC100_{RRS}$*. Horses with a low $PC100_{RRS}$ (e.g., <6 mg/mL of histamine) are designated as having hyperreactive airways. Airway hyperreactivity is an exaggerated narrowing response to a bronchoconstrictive stimulus, which was first found in horses with heaves,[13]

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and is considered a hallmark of IAD. There is a correlation between airway reactivity and mast cell percentage in BAL fluid in horses with a history of exercise intolerance.[14] The clinical symptoms associated with airway hyperreactivity are thought to include coughing (increased sensitivity) and exercise intolerance, whereas bronchoconstriction causes uneven ventilation and hypoxemia.[1]

Respiratory Inductive Plethysmography

The objective assessment of respiratory function and breathing pattern may also be obtained through the concurrent application of respiratory inductive plethysmography and pneumotachography, which has been validated for use in humans,[15,16] horses,[17] and sheep.[18] In summary, two elastic bands, each containing a single sinusoidal conducting wire, are temporarily placed around the animal's thorax and abdomen (Fig. 31-4). Stretch and contraction of the bands resulting from normal respiratory movements are measured as voltage changes, which are proportional to the change in circumference and volume of the thorax and abdomen. Simultaneous measurements of nasal flow are obtained at the airway opening (face mask). This technique rapidly assesses the synchronicity of breathing pattern (e.g., thoracoabdominal asynchrony due to diaphragmatic paralysis)[19] and the individual contribution of the thorax and abdomen to respiration. It further quantifies changes in flow resulting from airway obstruction. Recently, the use of a novel respiratory ultrasonic plethysmography system was proposed to detect circumference changes of rib cage and abdominal compartments in large and small animals.[20]

Forced Maneuvers

Forced expiratory maneuvers are commonly performed in humans with suspected asthma. Simplistically, the patient is asked to blow out hard from TLC until the lung is empty. The volume of air expelled in 1 sec (FEV_1) corrected for vital capacity (FVC) is used as a measure of lower airway obstruction.[1] Couëtil and colleagues adapted the method of forced maneuvers for routine clinical application in heavily sedated, nasotracheally intubated horses.[21] They further demonstrated flow limitation in horses with early signs of obstructive airway disease (IAD) that was worse in animals with heaves. Remission from heaves showed improvement in flow limitation.[1]



FIG. 31-4 Inductance plethysmography being performed in a horse. *(Courtesy Dr. Andrew Van Eps, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

PFT is considered instrumental in the understanding of the pathogenesis, pathophysiology, epidemiology, diagnosis, and treatment of lung disease in horses.[1] The described tests are aimed at quantifying airway obstruction, airway reactivity, and lung stiffness in the clinical setting. PFT will thus facilitate the diagnosis of subclinical disease and improve the clinician's assessment with regard to aggressive management of lung disease, decisions for ventilation, intensity of monitoring, and assessment of treatment response and prognosis.

Equine Respiratory System

Pamela A. Wilkins and Kara M. Lascola, *Consulting Editors*

Disorders of the Lung

Bacterial Pneumonia and Pleuropneumonia in Adult Horses

Steeve Giguère

Bacterial infections of the lower respiratory tract are common in adult horses. Lower respiratory tract infections may be localized to the lumen of the airways (termed *bacterial bronchitis* or *septic inflammatory airway disease*) or may involve the pulmonary parenchyma (termed *pneumonia*). In equine medicine, the term *bronchopneumonia* is often used to refer to lower respiratory tract infection regardless of whether the infection is localized to the bronchi or whether the infection involves both the bronchi and the lung parenchyma. When there is subsequent extension of the infection from the pulmonary parenchyma to the visceral pleura and pleural space, the disease is referred to as *pleuropneumonia.* The spectrum of clinical signs shown by horses with bronchopneumonia is broad and reflects the severity of the disease process. Early identification of affected animals and immediate initiation of appropriate therapy are essential to prevent mortality and functional impairment of the respiratory system. Expenses incurred by owners of affected horses include cost of medical care, loss of income during the illness and the recovery period, cost of training after a prolonged period of inactivity, and financial loss due to death of some animals or diminished performance of others following recovery.

Infectious Agents Involved

Adult horses most commonly acquire bacterial pneumonia by aspiration of microorganisms that normally inhabit their nasopharynx or oral cavity.[1,2] β-Hemolytic streptococci, particularly *Streptococcus equi* subsp. *zooepidemicus,* are by far the most common bacterial pathogens isolated from adult horses with bronchopneumonia.[3] Non-enteric gram-negative bacteria such as *Pasteurella* spp. and *Actinobacillus* spp. are also frequently isolated, either alone or in combination with *S. zooepidemicus*. Enteric gram-negative bacteria such as *Klebsiella* spp., *Escherichia coli, Enterobacter* spp., and *Salmonella enterica* may also be isolated. Other aerobic gram-positive bacteria such as *Staphylococcus* spp. and *Rhodococcus equi* or gram-negative bacteria such as *Pseudomonas* spp. and *Bordetella bronchiseptica* are occasionally isolated. *Pseudomonas* spp. are rarely a primary cause of pneumonia in horses, and their presence often reflects contamination

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of equipment used for taking airway samples (such as endoscopes). *Streptococcus pneumoniae,* a common pathogen of humans, has been positively correlated with lower airway inflammation in young Thoroughbred racehorses in the United Kingdom.[4] The microorganism can also induce pneumonia in ponies following heavy intrabronchial challenge.[5] However, *S. pneumoniae* is rarely isolated from pneumonic horses in the United States.

Anaerobic bacteria are isolated from approximately one third of adult horses with severe bronchopneumonia, pleuropneumonia, or pulmonary abscessation. The most common anaerobes isolated are *Bacteroides* spp., particularly *B. fragilis, Clostridium* spp., and *Peptostreptococcus* spp.; *Fusobacterium* spp. and *Eubacterium* spp. may also be isolated.[3,6] Isolation of anaerobes from horses with pneumonia or pleuropneumonia has been associated with a less favorable prognosis in some studies. In one study, the survival rate for 221 pneumonic horses with strictly aerobic isolates from tracheobronchial aspirates was 81.4% compared with 38.3% for the 81 horses in which anaerobes were cultured.[3] Mixed bacterial infections are very common and may represent synergy between aerobic or facultative aerobic and anaerobic bacteria.

The importance of *Mycoplasma* spp. in the development of equine bronchopneumonia and pleuropneumonia is controversial. Several *Mycoplasma* species have been isolated from the respiratory tract of both diseased and healthy horses, with *M. felis* and *M. equirhinis* being the most common isolates. In one study, isolation of *M. equirhinis* was positively correlated with lower airway inflammation in a group of young Thoroughbred racehorses in the United Kingdom,[7] whereas isolation of *Mycoplasma* spp. was not significantly associated with disease in a similar population in Australia.[8] An outbreak of lower respiratory tract disease caused by *M. felis* infection has been described.[9] *M. felis* has also been isolated from horses with pleuropneumonia and, at least in one instance, experimental infection with *M. felis* has resulted in pleuropneumonia.[10,11]

Epidemiology

Bacterial bronchopneumonia may affect horses of any age or breed. In one retrospective study of 327 horses with pneumonia or pleuropneumonia, there was no sex predilection, but 82% of the horses were less than 5 years of age.[3] In a retrospective case-control study of risk factors for development of pleuropneumonia, Thoroughbred horses were at greater risk while Standardbred horses were at lower risk of developing the disease.[12] In the same study, the most significant risk factor for development of pleuropneumonia was long-distance transport within the week prior to the onset of clinical signs.[12] In another study, 24.4% of 90 horses with pleuropneumonia had recently been transported over long distances, and 12.2% had recently undergone general anesthesia.[13] Five of the postsurgical cases had undergone upper airway surgery.[13] Whether these horses had preexisting lung disease or whether they developed aspiration pneumonia as a result of surgery and general anesthesia could not be ascertained.

Other factors significantly associated with increased risk of developing pleuropneumonia include recent viral respiratory tract infection or exposure to horses with viral infections and racing within 48 hours prior to developing clinical signs.[12] One study in the United Kingdom identified a higher incidence of pneumonia and pleuropneumonia in show jumpers, presumably reflecting the greater distance over which these horses are transported compared with racehorses in that country.[14]

Pathophysiology

Colonization of the lungs by opportunistic bacteria occurs when the pulmonary defense mechanisms are compromised or are overwhelmed by massive numbers of bacteria. Several factors can contribute to causing increased numbers of bacteria in the lower airways. Dysphagia or esophageal obstruction will lead to aspiration of large numbers of pharyngeal bacteria and these disease processes often result in pneumonia. However, the vast majority of horses with bacterial pneumonia or pleuropneumonia do not have a history of dysphagia or esophageal obstruction. Other factors that have been shown to significantly increase bacterial contamination of the lower respiratory tract include confinement with the head elevated, transportation, and high-intensity exercise.[15-17] In one study, confinement of horses with the head elevated resulted in a significant increase in bacterial numbers as well as neutrophilic inflammation in the lower respiratory tract as early as 6 hours after initiating confinement.[16] *Actinobacillus* spp., *Pasteurella* spp., and β-hemolytic streptococci were the predominant bacterial isolates. Lowering the head for 30 minutes every 6 hours to facilitate postural drainage during a 24-hour confinement did not prevent multiplication of bacteria.[16] Clearance of accumulated secretions and bacteria occurred within 8 to 12 hours after release from confinement.[16] In similar confinement experiments, pretreatment with penicillin considerably reduced the number of β-hemolytic streptococci but did not reliably reduce total bacterial numbers.[18] Cilia of many other species such as dogs and humans can transport mucus effectively against gravity, and posture has no effect on tracheal mucociliary transport in these species.[19,20] In contrast, periods of lowered head posture are absolutely essential for normal mucociliary clearance in horses.[21]

In one study, long-distance transport by road over 12 hours resulted in increased bacterial contamination and neutrophilic inflammation in tracheal aspirate fluid when the horses' heads were restrained in an elevated position.[22] This is in contrast to another study in which there was no significant cytologic or bacteriologic changes in bronchoalveolar lavage fluid from mares whose heads were not restrained in an elevated position during transportation for 12 hours.[23] Collectively, these findings suggest that duration of time with a raised head position is more important than the stress of transport alone in development of airway colonization. Finally, the last factor shown to increase bacterial contamination of the large airways of horses is exercise. In one study, a single bout of high-intensity exercise resulted in a 10-fold increase in aerobic and 100-fold increase in anaerobic bacterial counts in tracheal aspirate samples compared with preexercise values.[15]

Pulmonary defense mechanisms can be compromised by numerous factors. These include stress (e.g., transport and intense exercise), viral infections, malnutrition, exposure to dust or noxious gases, immunosuppressive therapy, immunodeficiency disorders, and general anesthesia. Infections with influenza virus and EHV-4 have been shown to significantly decrease mucociliary clearance for up to approximately 30 days postinfection in horses.[24] In one study, long-distance transportation resulted in a significant reduction in phagocytosis by peripheral blood neutrophils for approximately 36 hours after transportation.[22] The effects of long-distance transport on number, viability, and function of cells in bronchoalveolar lavage fluid have given conflicting results with no clear pattern emerging.[23,25-27] Similarly, the effects of exercise on the immune system are complex and depend on a multitude of factors, including the intensity or duration of exercise, the specific immune function being analyzed, and the timing of the measurement in relation to exercise. In general, moderate exercise enhances immune function, whereas strenuous exercise tends to be detrimental to immune function.[28] High-intensity exercise in horses leads to a significant decrease in blood neutrophil and bronchoalveolar macrophage phagocytic activity, which may lead to decreased bacterial clearance from the lungs.[29-31] Exercise also affects the adaptive immune system, as lymphocyte proliferation responses and IFN-γ production are decreased following high-intensity exercise.[32-34] Strenuous exercise has also been shown to increase susceptibility to experimental influenza virus infection in ponies compared with rested animals, indicating that alterations of the immune function following exercise are a real phenomenon and not just an in vitro artifact.[32]

Regardless of the exact mechanism predisposing to bacterial colonization, the inflammatory response induced by bacterial invasion results in infiltration with neutrophils and other inflammatory cells into the airways and pulmonary parenchyma. Inflammatory cells and their mediators cause damage to the airway epithelium and capillary endothelium, leading to flooding of the terminal airways with inflammatory cells, serum cellular debris, and fibrin. This process is

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generally more severe in the ventral portions of the lung. In early stages the lungs may be simply edematous, reflecting inflammation and early exudation, whereas in chronic severe cases the airways may be filled with purulent material and necrotic debris. Affected areas may show various degrees of consolidation, although in some cases focal abscesses may develop. These lesions interfere with gas exchange and, if severe enough, the resulting ventilation-perfusion mismatch leads to hypoxemia and clinical signs of respiratory disease.

In severely affected animals, inflammation will extend to the pleural space. The first stage of bacterial pleuropneumonia is an exudative stage, which is characterized by rapid outpouring of sterile pleural fluid into the pleural space in response to inflammation of the pleura. The associated pneumonic process is usually contiguous with the visceral pleura and results in increased permeability of the capillaries in the visceral pleura. If appropriate antimicrobial therapy is initiated at this stage, the pleural effusion may not become septic and may resolve. With progression the bacteria invade the pleural fluid from the contiguous pneumonic process and the second, fibropurulent, stage evolves. This stage is characterized by the accumulation of large amounts of pleural fluid with many degenerate neutrophils, bacteria, and cellular debris. Fibrin is deposited in a continuous sheet, covering both the visceral and the parietal pleura adjacent to affected areas. As this stage progresses, there is often loculation and formation of limiting membranes. These loculations prevent dissemination of the infection but make drainage of the pleural space with chest tubes increasingly difficult. The last stage is the organization stage, in which fibroblasts grow into the exudate from both the visceral and the parietal pleura surfaces and produce a membrane called the *pleural peel.* This inelastic pleural peel encases the lung and renders it virtually functionless. At this stage the exudate is generally thick.

Clinical Signs and Physical Examination

The spectrum of clinical signs shown by horses with bacterial lung infection is broad and usually reflects the severity of the disease process. Horses with septic inflammatory airway disease and no or minimal involvement of the lung parenchyma may be completely normal at rest. Clinical signs may be limited to exercise intolerance and/or poor performance, or affected horses may cough or have bilateral nasal discharge during or immediately following exercise. Even in early cases of bronchopneumonia, clinical signs may not be obvious. As the disease progresses, clinical signs may include any combination of fever, anorexia, depression, bilateral nasal discharge, cough, weight loss, tachypnea, and respiratory distress. Nasal discharge is usually mucopurulent but may be hemorrhagic in some cases with pulmonary infarction and necrotizing pneumonia.[35] Halitosis and a foul-smelling nasal discharge may be present and has been associated with infection by anaerobic bacteria. However, the absence of a putrid odor does not rule out infection with anaerobic bacteria.

Because the parietal pleura is highly innervated and painful when inflamed, horses with acute pleuropneumonia often exhibit pleurodynia (pleural pain). Pleurodynia can often be detected by applying digital pressure to the intercostal space, resulting in grunts, intercostal muscle spasm, or even escape maneuvers by the patient when pain is present. Pleurodynia may also be manifested as pawing, stiff forelimb gait, abducted elbows, and reluctance to move. The condition may easily be mistaken for colic, exertional rhabdomyolysis, or laminitis. As more fluid accumulates in the pleural space and the disease becomes chronic, pain is less evident. A plaque of sternal edema is a common clinical finding in horses with pleuropneumonia. This is not a specific finding, as it can occur with many other disease processes.

Careful auscultation after application of a rebreathing bag (if not precluded by respiratory distress) is extremely valuable in defining the presence, and sometimes extent, of lung involvement. Horses with a large amount of secretions in the trachea often have an audible tracheal rattle. Most horses with bronchopneumonia will cough when the rebreathing bag is applied, whereas horses without bronchopneumonia will not. Occasional inspiratory or expiratory crackles and/or wheezes may be heard over affected areas, which are more commonly located ventrally. Because consolidated lung parenchyma is a good acoustic medium, mild consolidation sometimes results in only increased bronchial sounds. In contrast, the lung sounds may be diminished in areas of severe consolidation, extensive abscess formation, or pleural effusion.

Auscultation of horses with pleuropneumonia reveals normal lung sounds in the dorsal lung fields with no sound or considerably decreased lung sounds ventrally. Pleural friction rubs are often not heard because they are present only in the acute stage of the disease. If they are heard, friction rubs are present predominantly at the end of inspiration and the early part of expiration. They disappear as inflammation decreases or as pleural fluids accumulate. Cardiac sounds are often heard over a wider area of the chest than normal, probably as a result of enhanced conduction of sound through the pleural fluid. Thoracic percussion is useful to detect and delineate pleural effusion with resonant sounds dorsal and dull sounds ventral to the horizontal line of effusion.

Differential Diagnosis When physical examination and auscultation indicate pulmonary disease, the major clinical task is differentiating infectious from noninfectious causes. Among infectious causes, bacterial pneumonia is most common. Most viral infections are confined to the upper respiratory tract. The clinical presentation of equine multinodular pulmonary fibrosis may resemble that of horses with bacterial bronchopneumonia. Pulmonary aspergillosis most often follows severe gastrointestinal (GI) disease that had resulted in mucosal compromise.[36] Severe respiratory disease unresponsive to antimicrobial therapy might suggest fungal pneumonia or equine multinodular pulmonary fibrosis. Parasitic pneumonitis is rare in adult horses but may be seen in horses pastured with donkeys or mules. The two major noninfectious causes of pulmonary disease that may be confused with bacterial pneumonia are heaves and nonseptic inflammatory airway disease. Other uncommon causes of noninfectious pulmonary disease that may result in similar clinical signs are pneumothorax, pulmonary edema, smoke inhalation, neoplasia, and idiopathic interstitial pneumonia. The diagnostic tests described below aid in the differentiation between infectious and noninfectious causes of lower respiratory tract disease.

When pleural effusion is present, several differentials should be considered. Bacterial pleuropneumonia is by far the most common cause of pleural effusion in horses. In one study, 90 of 122 horses (73.8%) with pleural effusion had pleuritis secondary to bacterial pneumonia or lung abscessation.[13] Other less common causes of pleural effusion in horses include hemothorax, penetrating chest wounds, esophageal ulceration or rupture, neoplasia, fungal pneumonia, pericarditis, congestive heart failure, diaphragmatic hernia, hypoproteinemia, and chylothorax.

Diagnostic Approach Presumptive diagnosis of lower respiratory tract infection is generally based on clinical signs and careful auscultation of the lungs with a rebreathing bag. The need for additional diagnostic procedures is determined by the severity and duration of clinical signs, the number of affected animals, the value of the affected animal(s), as well as prior treatment used and response to such therapy. Bacterial pneumonia or pleuropneumonia most commonly affects an individual horse on a given farm. In horses suspected of having bacterial pneumonia, the goal of diagnostic evaluation is to rule out diseases of the upper respiratory tract and to determine the cause and severity of lung involvement.

HEMATOLOGY AND BIOCHEMISTRY. Horses with bacterial bronchopneumonia commonly have an inflammatory hematologic profile. Leukocytosis and absolute neutrophilia with or without a left shift are supportive of bacterial infection. Neutropenia with a toxic left shift may also be evident in the acute stages in severely affected animals. Increased fibrinogen concentrations, hyperglobulinemia, and mild hypoalbuminemia are common. Anemia of chronic

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inflammation may develop in chronically affected animals. There does not seem to be a good correlation between the severity of clinical signs and the presence or the magnitude of hematologic changes. When plasma fibrinogen concentrations are increased, their sequential measurement provides a useful means of monitoring response to treatment. It must be remembered that a normal hematologic profile does not rule out bacterial bronchopneumonia.

ENDOSCOPY. Endoscopy may be useful to rule out upper airway infection in situations when physical examination and auscultation of the lungs are not conclusive. Presence of mucopurulent secretions in the trachea and bronchi confirms lower respiratory tract disease. However, the presence of mucopurulent secretions does not necessarily indicate a bacterial infection, as this is also a common finding in horses with heaves and horses with nonseptic inflammatory airway disease. Bronchoscopy may also be useful in locating the affected lung segment in horses with focal pneumonia or draining pulmonary abscesses. It should be noted that exploration of the trachea and lower airways via bronchoscopy may contaminate subsequent samples taken for culture.

TRACHEOBRONCHIAL ASPIRATE FOR CYTOLOGY AND CULTURE. Tracheobronchial aspirate (TBA) for cytologic examination and bacterial culture is one of the most helpful diagnostic procedures available when bronchopneumonia is suspected. BAL is not as useful as TBA in cases of bronchopneumonia because with BAL only a small portion of a lung is sampled. In contrast to BAL, TBA samples contain a pooled sample of secretions from all portions of the lung, thus increasing chances of culturing the pathogen of interest. In one study involving 22 horses diagnosed with pneumonia or pleuropneumonia based on thoracic radiographs or ultrasonography, BAL cytology was abnormal in only 10 horses despite attempts at selectively sampling the affected area.[37] In contrast, all horses had evidence of septic inflammation based on TBA cytology.[37] Whenever possible, antimicrobial therapy should be discontinued at least 24 hours before performing TBA. TBA is preferably obtained by sterile percutaneous transtracheal aspiration to avoid contamination from the upper airway. Alternatively, the sample can be collected with a sterile guarded aspiration catheter passed through the biopsy channel of a flexible endoscope.[38,39] Endoscopy has the advantage of allowing selective aspiration of exudate when it is present, which may enhance recovery of bacteria. However, bacterial contamination of nasal or pharyngeal origin more commonly occurs in TBA samples collected via endoscopy. Airway fluid specimens should be submitted for cytology, Gram stain, and aerobic and anaerobic bacterial cultures. The fluid used for anaerobic cultures should be transferred to the laboratory immediately after collection in a manner that prevents or minimizes exposure to air. Anaerobic transport media are commercially available and should be routinely used. Specimens submitted for isolation of anaerobes should not be refrigerated, because many anaerobes are intolerant to cold. In horses with pleural effusion, a TBA should be obtained even if pleural fluid is available for bacterial culture. In one study, culture of the pleural fluid was negative in 43% of 111 horses with pleuropneumonia, whereas tracheobronchial fluid yielded growth in all cases.[3] Only approximately 5% of cases had growth from the pleural fluid but not from TBA.[3]

Macrophages and columnar ciliated epithelial cells predominate in TBA from healthy horses. The percentage of neutrophils in TBAs from apparently healthy horses can be quite variable. In one study, approximately 75% of apparently healthy Thoroughbred racehorses in training had less than 20% well-preserved neutrophils.[40] Occasional plant spores and fungal hyphae may be present, either free or in large mononuclear cells. Their presence does not necessarily indicate fungal infection and probably reflects the horse's environment. Degenerated neutrophils displaying karyolysis and cytoplasmic vacuolization are the predominant cell type in horses with bacterial lower respiratory tract infections. Bacteria may be found intracellularly or extracellularly. Presence of squamous epithelial cells indicates contamination with the upper respiratory tract or pharynx and is more common in samples obtained via the endoscope. The trachea is not a perfectly sterile site, and potentially pathogenic bacteria can be isolated from the trachea of normal horses.[38] Therefore culture results should always be interpreted in the context of clinical signs and cytologic examination. If small numbers of bacteria are cultured in the absence of cytologic evidence of sepsis, it is unlikely that they are the cause of the respiratory problem. Similarly, growth of various molds is common in TBA cultures, and the clinical signs and cytologic findings should be considered prior to initiating treatment with antifungal agents.

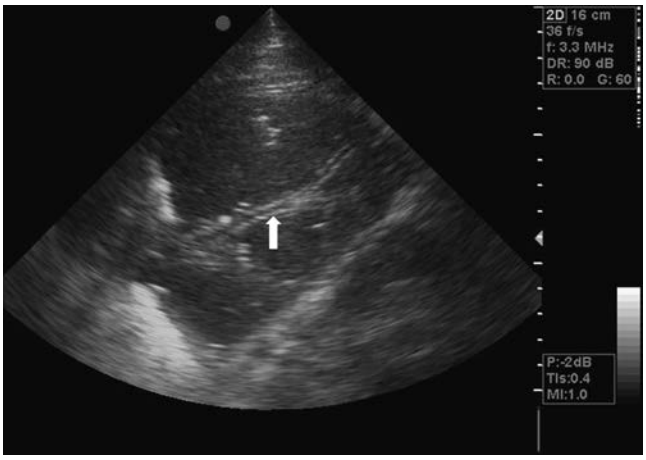


FIG. 31-5 Sonogram of the left thorax obtained from a 3-year-old Thoroughbred gelding. The ventral aspect of the lung is completely consolidated. Notice the liver-like appearance of the wedge-shaped area of the lung. Fluid bronchograms are indicated by a white arrow.

THORACIC ULTRASONOGRAPHY. Thoracic ultrasonography can be performed using a range of transducers and machine types. The normal aerated lung parenchyma is not penetrated by the ultrasound beam, rendering only the pleural space and superficial lung surface available for study. Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas, but it may not be as useful as radiography to evaluate the full extent of lung lesions since lesions with overlying aerated lung will not be detected. However, in most horses with bronchopneumonia, the periphery of the lung is affected, enabling the clinician to successfully image some of the lesions. Early ultrasonographic lesions are nonspecific and may only include irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes. Consolidated lung varies in appearance from dimples of the pleural surface to large wedge-shaped areas of sonolucent lungs (Fig. 31-5).

Ultrasonography offers a considerable advantage over radiographs in the study of the pleural surfaces and space. A small amount of pleural effusion that would otherwise be missed clinically or by radiography can be detected easily by ultrasonography. Ultrasonography can also be used to assess the nature and approximate volume of fluid, select the optimal site and depth for thoracocentesis, and detect sequelae such as fibrin deposition, pleural adhesions, abscess formation, and pneumothorax. Pleural effusion appears as hypoechoic to anechoic fluid between the parietal pleural surface and the lungs (Fig. 31-6). The echogenicity of the fluid typically reflects the degree of cellularity. Fibrin appears as filamentous strands floating in the effusion (see Fig. 31-6). The presence of small (<1 mm) bright echoes (gas echoes) often indicates anaerobic infections (Fig. 31-7).[41] Gas echoes may also be seen with gangrenous pneumonia or bronchopleural fistulas, or they may result from leakage of air during thoracocentesis.

RADIOGRAPHY. In horses with mild septic inflammatory airway disease, thoracic radiographs may be normal or may reveal only mild bronchial or bronchointerstitial patterns. In more severely affected

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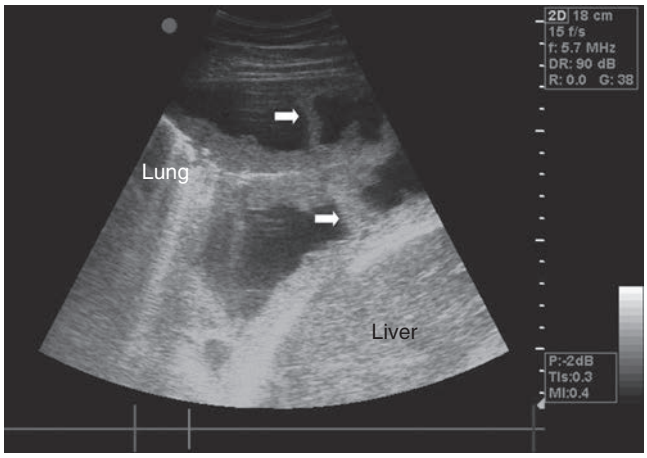


FIG. 31-6 Sonogram of the thorax obtained from a 4-year-old horse with pleuropneumonia. The ventral tip of the lung is atelectatic and covered with fibrin. There are adhesions between the tip of the lung and the diaphragm and chest wall *(white arrows)*.

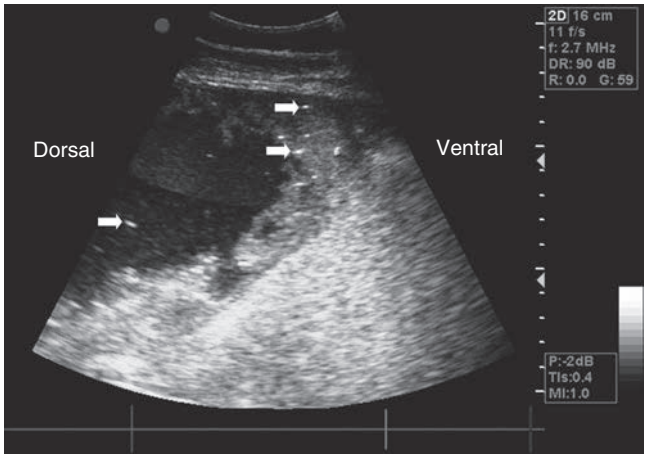


FIG. 31-7 Sonogram of the ventral thorax obtained from a horse being treated for pleuropneumonia. The sonogram shows a pleural abscess filled with fluid dorsally and with hyperechoic material ventrally. There are multiple gas echoes (some indicated by *arrows*). Multiple anaerobes were obtained on culture of an aspirate.



FIG. 31-8 Lateral thoracic radiograph of the caudoventral lung field from a 4-year-old Thoroughbred mare showing a pronounced alveolar pattern with air bronchograms. The caudal silhouette of the heart is almost completely obscured.

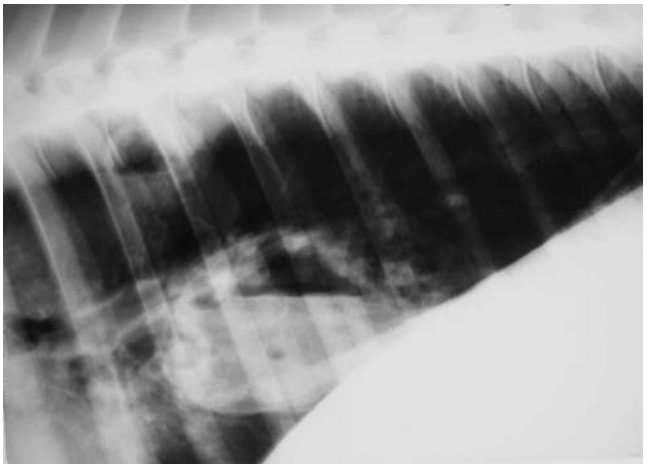


FIG. 31-9 Lateral thoracic radiograph of the caudodorsal lung field from a 3-year-old Thoroughbred filly showing two cavitary abscesses with distinct horizontal lines representing fluid-gas interface.

animals, radiographs demonstrate irregular opacities in the ventral thorax that may obscure the normal vasculature and cardiac silhouette (Fig. 31-8). Air bronchograms are sometimes visible. Abscesses are often present as circular soft-tissue opacities of varying sizes. In some cases they may be cavitated with thick walls and a distinct horizontal line representing fluid-gas interface (Fig. 31-9). Pleural effusion appears as a horizontal line demarcating a ventral soft-tissue opacity that obscures the heart and ventral lung fields (Fig. 31-10). When severe pleural effusion is present, it is most efficient to perform thoracic radiographs after the pleural fluid has been drained. Although ultrasonography is superior to radiographs in horses with pleuropneumonia, radiography should still be performed, when possible, to detect and monitor resolution of deep pulmonary abscesses that may be missed during ultrasonography.

THORACOCENTESIS FOR CYTOLOGY AND CULTURE. Thoracocentesis should be considered in horses with pleural effusion. The procedure can be of diagnostic value by allowing differentiation of septic pleuritis from effusion caused by other disease processes. It can also be of therapeutic value via removal of excessive chest fluid, which allows pulmonary reexpansion and a reduction in respiratory distress. Thoracocentesis is best performed using ultrasound guidance to determine the most appropriate site. A blunt teat cannula is typically used if a small volume of effusion is being sampled strictly for diagnostic purposes. Depending on the volume of effusion, a 16-, 24-, or 32-French chest tube is used when pleural drainage is also indicated (see below). An aliquot of pleural fluid is placed into tubes containing anticoagulant solution (ethylenediaminetetraacetic acid [EDTA]) so that cytologic evaluation may be performed. Part of the fluid should be saved in sterile containers with appropriate transport media for subsequent Gram stain and aerobic as well as anaerobic bacterial cultures.

Normal equine pleural fluid is clear to light yellow and odorless. Protein concentration is less than 3.4 g/dL (range 0.2 to 4.7 g/dL) and the nucleated cell count (NCC) is less than 8000/μL (range 800 to 12,100/μL) in approximately 95% of apparently healthy horses.[42] In horses with bacterial pleuropneumonia, the effusion is typically

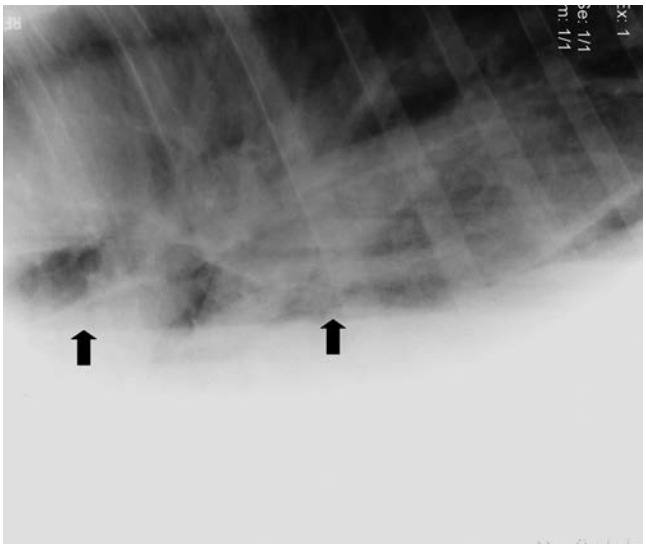


FIG. 31-10 Lateral thoracic radiographs from a 4-year-old Thoroughbred gelding with pleuropneumonia. A large amount of pleural effusion obscures the ventral lung fields. The dorsal aspect of the fluid line is indicated by black arrows. An interstitial pattern is noted in the caudodorsal lung fields.

exudative, cloudy, and yellow to red with increased NCC and protein concentration. Such effusion usually contains greater than 90% neutrophils, most of which exhibit degenerative changes. Putrid-smelling pleural fluid is a hallmark of anaerobic infection; however, the absence of odor does not exclude anaerobic infection. There is no association between the NCC count or protein concentration in pleural fluid and survival.

Biochemical analysis of the pleural fluid may also provide a rapid assessment of the likelihood of sepsis, hence the need for pleural drainage. Values for pH, P_{O_2}, P_{CO_2}, bicarbonate, lactate, and glucose in pleural fluid from horses with nonseptic pleural effusion are similar to those of concurrent venous blood samples.[43] Horses with septic pleural effusion have significantly lower pH, bicarbonate, and glucose in their pleural fluid compared with paired venous blood samples. In contrast, their pleural fluid has significantly higher P_{CO_2} and lactate concentration.[43] Pleural fluid pH less than 7.1 and glucose concentration less than 40 mg/dL are suggestive of septic effusion in horses.[44]

THORACOSCOPY. Thoracoscopy is rarely necessary in the initial evaluation of horses with pleuropneumonia. However, the technique may be of diagnostic and therapeutic value in more chronic cases in which pleural abscesses or pleural adhesions develop (see section on treatment).[45]

Treatment

SYSTEMIC ANTIMICROBIAL THERAPY. Administration of appropriate antimicrobial agents is the most important part of the therapeutic plan. The choice of the antimicrobial agent depends on the severity of the clinical signs, cost, ease of administration, and, when available, results of bacteriologic culture and susceptibility testing of TBA or pleural fluid. Dosages for commonly used antimicrobial agents are presented in Table 31-2. In early cases of mild bronchopneumonia, the practitioner is justified in suspecting *S. zooepidemicus* as the likely causative microorganism and in treating accordingly. *S. zooepidemicus* is almost invariably susceptible to penicillin, ampicillin, and cephalosporins such as ceftiofur (Table 31-3). The possibility of a mixed infection involving *S. zooepidemicus* and gram-negative microorganisms must be kept in mind when such empirical therapy is unsuccessful. Ceftiofur offers the advantage of having a good spectrum of activity against common non-enteric gram-negative pathogens (e.g., *Pasteurella* spp. and *Actinobacillus* spp.) and against many enteric gram-negative pathogens (see Table 31-3). Ceftiofur is available as a sodium salt that requires daily intramuscular administration or as ceftiofur crystalline free acid. Two intramuscular doses of ceftiofur crystalline administered 4 days apart provide therapeutic concentrations of ceftiofur- and desfuroylceftiofur-related metabolites in plasma and pulmonary epithelial lining fluid for approximately 10 days from the beginning of treatment.[46,47]

Therapy of horses with mild lower respiratory tract infections should be continued for a minimum of 10 days or until clinical signs resolve. In some cases, the duration of therapy needed may preclude continuous intramuscular therapy because of muscle soreness. Trimethoprim-sulfonamide (TMS) combinations offer the advantage of oral administration. Unfortunately, the usefulness of TMS combinations for the treatment of bacterial respiratory tract infections in horses is limited by their lack of in vivo activity against *S. zooepidemicus*. In contrast to penicillin, TMS is ineffective in eradicating *S. equi* subsp. *zooepidemicus* in a tissue chamber model of infection in horses.[48,49] This failure of in vivo response was observed despite in vitro susceptibility of the isolate and high concentrations of TMS in the tissue chamber fluid.[48,49]

In more severe cases of bronchopneumonia and in all cases of pleuropneumonia, antimicrobial therapy should ultimately be selected based on results of culture and in vitro susceptibility testing. Before obtaining these results, selection should be based on knowledge of the prevalence and susceptibility pattern of bacteria commonly isolated from affected horses (see Table 31-3). Polymicrobial and mixed aerobic/anaerobic infections are common; thus broad-spectrum antimicrobial therapy is initially required. A combination of gentamicin for gram-negative coverage and penicillin for gram-positive and anaerobic coverage is commonly used as initial broad-spectrum therapy for moderate to severe bronchopneumonia. Enrofloxacin can be used as a substitute to gentamicin for gram-negative coverage in adult horses. Advantages of enrofloxacin over gentamicin include greater activity against Enterobacteriaceae, better penetration in phagocytic cells and tissues, and better activity in purulent material. However, enrofloxacin should never be used as stand-alone initial therapy in horses with bronchopneumonia because of its lack of activity against anaerobes and variable activity against streptococci such as *S. zooepidemicus*. Ampicillin or cefazolin can replace penicillin for gram-positive coverage and offer the supplementary advantage of providing additional gram-negative coverage.

Treatment of anaerobic pleuropneumonia is usually empirical, as antimicrobial susceptibility testing of anaerobes is difficult because of their fastidious nutritive and atmospheric requirements. Thus familiarity with antimicrobial susceptibility patterns is helpful in formulating the treatment regimen when an anaerobe is suspected. The majority of anaerobic isolates is susceptible to relatively low concentrations of penicillin. However, *Bacteroides fragilis,* a frequently encountered anaerobe in horses with pleuropneumonia, is routinely resistant to penicillin. Other members of the *Bacteroides* family are known to produce β-lactamases and are potentially penicillin resistant. Metronidazole has excellent in vitro activity against a variety of obligate anaerobes, including *B. fragilis.* Oral administration rapidly results in adequate serum levels and thus is an acceptable route of administration for horses with pleuropneumonia. Therefore, if anaerobic infection is suspected, oral metronidazole is usually added to the combinations mentioned previously. Malodorous nasal discharge, halitosis, or the presence of gas echoes in pleural effusion seen on ultrasonographic examination suggests the presence of an anaerobic infection. However, the absence of these findings does not rule out anaerobic bacterial infection. Horses with extensive lung consolidation and horses with pleuropneumonia may benefit from having metronidazole added to the treatment regimen. Metronidazole is not effective against aerobes and therefore should always be used in combination therapy. Chloramphenicol is active against most aerobes and anaerobes cultured from horses with bronchopneumonia or pleuropneumonia. However, because of human health concerns, its use should be limited to the treatment of horses with severe anaerobic bacterial infections refractory to metronidazole therapy in countries

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TABLE 31-2

Antimicrobial Agents Commonly Used to Treat Bacterial Bronchopneumonia in Adult Horses

Antimicrobial*	Dose	Frequency (h)	Route
β-Lactams			
Benzyl Penicillins			
Penicillin G (Na, K)	25,000 IU/kg	6	IV
Penicillin G (procaine)	25,000 IU/kg	12	IM
Aminobenzyl Penicillins			
Ampicillin sodium	20 mg/kg	8	IV
Ampicillin trihydrate	20 mg/kg	12-24	IM
Cephalosporins			
Cefazolin	10-20 mg/kg	6	IV
Ceftiofur sodium	2.2-4.4 mg/kg	24	IM
Ceftiofur crystalline free acid	6.6 mg/kg	See note†	IM
Aminoglycosides			
Amikacin	10 mg/kg	24	IV or IM
Gentamicin	6.6 mg/kg	24	IV or IM
Fluoroquinolones			
Enrofloxacin‡	5.5 mg/kg	24	IV
	7.5 mg/kg	24	PO
Tetracyclines			
Oxytetracycline§	6.6 mg/kg	12	IV§
Doxycycline¶	10 mg/kg	12	PO¶
Minocycline	4	12	PO
	2.2	12	IV
Others			
Chloramphenicol	50 mg/kg	6	PO
Metronidazole	25 mg/kg	12	PO
	35 mg/kg	12	Per rectum
Rifampin	5 mg/kg	12	PO
Trimethoprim-sulfonamide	30 mg/kg (combined)	12	PO

*Pharmacokinetics data are available for horses, but in most cases safety studies have not been performed in the equine species.

†Two doses 4 days apart will provide 10 days of coverage. If a longer treatment period is necessary, weekly (q7days) administration is sufficient after the initial two doses.

‡Should not be used in young growing horses because of the risk of arthropathy.

§Dilute and give by slow IV infusion.

¶Administer orally only. Intravenous doxycycline has resulted in severe cardiovascular effects, including collapse and death in some horses.

where its use is allowed. Rifampin is bactericidal and active against streptococci and some species of anaerobes. It penetrates well into abscesses and may be helpful in the treatment of infections with walled-off abscesses. Rifampin should always be used in combination with another antimicrobial agent to decrease the likelihood of emergence of resistant mutants.

In cases of severe bronchopneumonia, lung abscesses or pleuropneumonia long-term antimicrobial therapy ranging from 3 weeks to sometimes several months may be required. In the initial stages of therapy, intravenous antimicrobials are preferred to achieve higher serum concentrations. Oral antimicrobial agents can be used later in the course of the disease if appropriate based on in vitro susceptibility testing. Clinical signs, lung auscultation, fibrinogen concentrations, and repeated ultrasonographic and radiographic examination are useful in assessing response to therapy and deciding when to discontinue antimicrobial therapy. Stall rest must be enforced during therapy of pneumonia, and return to exercise should be gradual and permitted only after the horse is clinically normal and antibiotic therapy has been completed.

AEROSOLIZED ANTIMICROBIAL AGENTS. Aerosolized antimicrobial agents may be a useful adjunct to oral or systemic antimicrobial agents, particularly in horses with chronic septic inflammatory airway disease and no or minimal involvement of the lung parenchyma. The rate and extent of penetration of a drug into most sites outside the vascular space such as lung tissue are determined by the drug's concentration in plasma, molecular charge and size, extent of plasma protein binding, and blood flow.[50] In other tissues such as the central nervous system, and the eye, a lipid membrane provides a barrier to drug diffusion.[50] There is a similar barrier between blood and the bronchial epithelium, restricting penetration of some drugs into bronchial secretions and epithelial lining fluid of the lower airways.[51] Aerosol administration of antimicrobial agents can result in high drug concentrations in the respiratory tract while minimizing systemic concentrations and their resulting toxicity.

Antimicrobial delivery by inhalation is greatly influenced by the product formulation and type of nebulizer. Aerosol use of intravenous formulations can lead to exposure to potentially irritant or toxic additives and inappropriate pH or osmolality ranges. In one study, the particle size distribution and particle density of gentamicin sulfate and ceftiofur sodium aerosols were affected by the antimicrobial concentration of the solution.[52] Gentamicin concentrations of 50 mg/mL or ceftiofur concentrations of 25 mg/mL produced the optimal combinations of particle size and aerosol density when a medical ultrasonic nebulizer was used.[52] Development of a silent battery-operated nebulizer for horses (Flexineb, Nortev Ltd., Galway, Ireland) has greatly facilitated delivery of antimicrobial drugs by inhalation in horses.

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TABLE 31-3

In Vitro Antimicrobial Susceptibility of Aerobic Bacterial Isolates Commonly Isolated from Horses with Bronchopneumonia or Pleuropneumonia*

Microorganisms (n)	Antimicrobials†														
	GM	AMI	CHL	TMS	TE	RIF	P	AM	TIM	CFZ	CFT	XNL	CPE	ENR	CIP
Gram-Positives															
Streptococcus zooepidemicus (192)	19	0	100	62	43	98	100	100	100	100	100	98	—	69	—
Staphylococcus aureus (43)	70	86	100	95	78	89	41	41	79	68	68	67‡	68	79	81
Other staphylococci (48)	91	100	97	85	71	97	30	30	—	65	65	85‡	65	94	97
Gram-Negatives															
Escherichia coli (127)	62	90	72	43	51	—	—	51	73	70	87	69	97	82	83
Klebsiella pneumoniae (52)	88	96	94	79	96	—	—	6	88	90	98	69	98	88	100
Enterobacter spp. (32)	40	83	41	40	57	—	—	3	43	10	53	34	80	78	80
Pseudomonas aeruginosa (48)	70	97	—	—	—	—	—	—	94	—	15	6	91	65	97
Pasteurella spp. (40)	94	94	100	91	100	—	—	100	100	94	100	95	100	100	100
Actinobacillus spp. (31)	100	87	100	93	90	—	—	95	100	100	100	97	100	100	100

*Data from the clinical microbiology laboratory, University of Florida (2003-2005). Isolates were obtained from multiple equine clinical specimens including, but not restricted to, tracheobronchial aspirates and pleural fluid.

†Percentage of susceptible isolates (number of susceptible isolates/number of isolates tested × 100).

‡In vivo, ceftiofur is rapidly metabolized to desfuroylceftiofur. Desfuroylceftiofur is as effective as ceftiofur against most bacterial pathogens, but most coagulase-positive *Staphylococcus* spp. are resistant. Therefore, despite in vitro susceptibility, ceftiofur is not the ideal choice for the treatment of staphylococcal infections.

— Not tested or testing not warranted.

AM, Ampicillin; *AMI,* amikacin; *CFT,* cefotaxime; *CFZ,* cefazolin; *CHL,* chloramphenicol; *CIP,* ciprofloxacin; *CPE,* cefepime; *ENR,* enrofloxacin; *GM,* gentamicin; *P,* penicillin; *RIF,* rifampin; *TE,* tetracycline; *TIM,* ticarcillin-clavulanic acid (Timentin); *TMS,* trimethoprim-sulfonamide; *XNL,* ceftiofur.

In healthy horses, aerosolization of 20 mL of the commercially available IV gentamicin sulfate solution (diluted to 50 mg/mL) with the use of an ultrasonic nebulizer resulted in bronchial lavage fluid concentrations approximately 12 times higher than concentrations achieved by IV administration at a dose of 6.6 mg/kg.[53] In the same study, serum concentrations following aerosol administration were below 1 µg/mL at all times.[53] Once-daily aerosol administration of gentamicin to healthy horses for 7 consecutive days did not result in pulmonary inflammation or drug accumulation in the respiratory tract.[54] The major limitation to the use of aerosolized gentamicin in horses is its lack of activity against *S. zooepidemicus,* the most common bacterial pathogen of the equine respiratory tract. Additional studies are required to assess the efficacy of aerosolized antimicrobial agents for the treatment of bacterial respiratory tract infections in horses.

ANCILLARY TREATMENTS. The need for ancillary treatments depends on the severity of the disease and is most often necessary in horses with pleuropneumonia. Nonsteroidal antiinflammatory agents such as flunixin meglumine (1 mg/kg IV or by mouth [PO] once or twice daily) or phenylbutazone (2.2 mg/kg IV or PO once or twice daily) may be beneficial to minimize inflammation, provide analgesia, and control high fevers. Additional analgesia may be necessary in horses with severe pleurodynia. Adequate hydration should be maintained in patients receiving these agents for extended periods, especially if aminoglycosides are used concurrently. Intravenous fluid therapy may be necessary to correct hypovolemia in acute stages, but it is rarely required for chronic cases. Intrapharyngeal insufflation of oxygen is indicated in horses that remain severely hypoxemic despite adequate drainage of the pleural cavity. Adequate parenteral or preferably enteral nutritional support via a nasogastric tube is beneficial in horses that remain anorectic for several days. In horses with severe systemic illness, additional therapies aimed at treating endotoxemia may be beneficial (see the section on endotoxemia in Chapter 32). In horses with severe systemic illness, distal limb cryotherapy is indicated in an attempt to prevent development of laminitis.

PLEURAL DRAINAGE. Small amounts of pleural effusion may resorb quite readily with appropriate antimicrobial therapy. Therefore, although a small sample of pleural fluid is useful diagnostically, pleural drainage is not necessarily indicated in all cases of pleuropneumonia. Drainage of pleural effusion results in removal of exudate and debris and allows for reexpansion of the lungs. Indications for drainage include a poor response to conservative therapy or the presence of pleural fluid with at least one of the following characteristics: (1) sufficient volume to cause respiratory distress, (2) emphysematous character, (3) fetid odor, or (4) cytologic or biochemical evidence of sepsis. If indicated, the procedure should be attempted as early as possible before deposition of fibrin results in loculations and impairs drainage. The ventral mediastinum is perforated in normal horses such that the left and right pleural spaces communicate. During severe inflammation, the small perforations in the ventral mediastinum may become obstructed by fibrin. Therefore, depending on the severity of the inflammatory response, draining one side of the thorax may or may not be sufficient to resolve bilateral pleural effusion. Repeat ultrasonography of the opposite hemithorax should always be performed before the placement of a chest tube to determine if draining one side has actually emptied both sides of the thorax. Pleural drainage is best performed using ultrasound guidance to determine the most appropriate site. Pleural drainage can be accomplished with either intermittent thoracocentesis or indwelling chest tubes. Thoracocentesis is easily accomplished in the field and may not need to be repeated unless considerable pleural effusion reaccumulates. Indwelling chest tubes are indicated when continued pleural fluid accumulation makes intermittent thoracocentesis impractical. If properly placed and managed, indwelling tubes provide a method for frequent fluid removal and do not exacerbate the underlying pleuropneumonia or increase the production of pleural effusion. A one-way valve must be attached to allow for continuous drainage without aspiration of air into the thorax. A Heimlich valve or an unlubricated condom with the tip cut off may be used for that purpose. As an alternative to continuous drainage, the tube can be temporarily occluded and periodically attached to a one-way valve for intermittent drainage. Heparinization of tubing after drainage may help maintain patency. The chest entry site and end of the drainage tube must be maintained aseptically. If a chest tube is placed aseptically and managed correctly, it can be maintained for several days. Local cellulitis may occur at the site of entry into the

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chest, but it is considered a minor complication. Pneumothorax is another potential complication of indwelling chest tubes. Tubes should be removed when they are no longer functional. A purse-string suture must be preplaced and tied as the tube is removed to prevent pneumothorax.

PLEURAL LAVAGE. Pleural lavage may be helpful to dilute thick viscous pleural fluid and remove fibrin, debris, and necrotic tissue. Pleural lavage is most helpful in subacute stages before loculated pockets of pleural fluid develop. However, pleural lavage may help break down fibrous adhesions and establish communication between loculae. Pleural lavage is typically performed by using the same chest tube for infusion and drainage of lavage fluid. Alternatively, lavage can be performed by infusing fluid through a dorsally positioned tube and draining it through a ventrally positioned tube. Approximately 5 L of sterile, warm isotonic fluid solution is infused by gravity flow. After infusion, the chest tube is reconnected to the unidirectional valve for drainage. Allowing the horse to walk once the continuous flow has stopped will often result in drainage of additional fluid. Pleural lavage is probably contraindicated in horses with bronchopleural communications because it may result in spread of septic debris up the airways and into normal areas of the lungs.[55] Coughing and drainage of lavage fluid from the nose during infusion suggest the presence of a bronchopleural fistula (see discussion of complications).

USE OF FIBRINOLYTIC AGENTS. The use of intrapleural fibrinolytics in the treatment of loculated pleural effusion remains controversial in human medicine.[56] Various fibrinolytic agents such as streptokinase, urokinase, and recombinant tissue plasminogen activators (rtPAs; such as alteplase and tenecteplase) have been used.[56] Numerous case series in people have shown that such therapy is fairly safe and may facilitate drainage. However, controlled trials are scarce and have given contradictory results regarding the ultimate benefit of intrapleural fibrinolytic therapy. In one study, intrapleural administration of streptokinase did not improve survival, the rate of surgery, or the length of the hospital stay among patients with pleural infection when compared with patients who had received a placebo.[57] In contrast, another study demonstrated a significant decrease in the need for surgical intervention and in the length of hospital stay with intrapleural streptokinase prior to drainage when compared with pleural drainage alone.[58]

In recent years, rtPA has largely replaced streptokinase as an adjunct therapy for selected human patients with loculated pleural effusion. Several case series indicate a potential benefit for rtPA,[59,60] but large randomized placebo-controlled clinical trials are lacking.[56,59] Fibrinolytic drugs have negligible effects on decreasing the viscosity of purulent material because the viscosity of pus is attributable mainly to its DNA content. Intrapleural recombinant human deoxyribonuclease I (rhDNase I; dornase alfa) has been used with apparent success in a single human patient who did not respond to fibrinolytic therapy.[61]

There are isolated reports of the use of rtPA in horses with fibrinous pleuropneumonia. In one report, 12 mg of alteplase was infused in volumes of 0.9% saline ranging between 250 mL and 2 L.[62] In another report, tenecteplase (12 to 30 mg in 500 mL of 0.9% saline) was administered alone or in combination with 25 mg of rhDNase I.[63] In both reports, there was a subjective decrease in the amount of fibrin in the thoracic cavity as assessed by ultrasonography. Additional studies evaluating the safety and efficacy of rtPA and rhDNase I are required before the widespread use of these agents can be recommended in the management of fibrinous pleuritis in horses.

THORACOSCOPY. Thoracoscopy allows direct evaluation of the lungs and pleural cavity. In selected cases, thoracoscopy may be a useful tool to facilitate placement of thoracic drains in abscesses, transect pleural adhesions, and disrupt loculations.[45] The technique can also be used to biopsy or aspirate specific lesions affecting the periphery of the lungs. The procedure can be performed in the standing sedated horse with local anesthesia and is usually very well tolerated.[64]

Adhesions between the lung and the diaphragm or body wall may prevent complete collapse of the lung, making insertion of the instruments more difficult and sometimes limiting the view of the pleural cavity. Adhesions are easier to disrupt during the first week after formation when the tissue is fibrinous rather than fibrous. Transection of mature adhesions is more difficult and can result in severe hemorrhage. Creation of a pneumothorax is a necessary feature of thoracoscopy, and horses should be monitored carefully throughout the procedure. Transient exacerbation in clinical signs of pulmonary disease due to pneumothorax can be alleviated by reinflation of the lungs.

THORACOTOMY. Surgical intervention in horses with pleuropneumonia is not a substitute for adequate medical management, but in carefully selected cases, it can save the lives of horses that would have to be euthanized otherwise. The criteria for surgical interventions include (1) failure to respond to antimicrobial therapy, pleural drainage, and pleural lavage; (2) stable systemic medical condition; (3) presence of a large amount of fibrin, debris, or pus in the pleural space; and (4) either a walled-off lesion or presence of a complete mediastinum to avoid creation of a bilateral pneumothorax. Surgical intervention is most beneficial in chronic cases with large unilateral localized pockets of thick debris, especially if there is resolution or at least a significant improvement of the disease in the opposite hemithorax. Before surgical exploration, the nature and location of the lesion must be thoroughly characterized by ultrasonography or thoracoscopy to determine the ideal surgical site. When there is bilateral disease, thoracotomy is performed on the most severely affected side. If necessary, a second thoracotomy can be performed on the opposite side at a later time. Thoracotomy is typically performed with the horse standing. It is common practice to place a large chest tube into the targeted cavity and leave it open to atmospheric air for at least 2 hours before thoracotomy.[55] The onset of respiratory distress indicates development of bilateral pneumothorax, in which case standing thoracotomy is contraindicated and pneumothorax must be corrected. Unilateral pneumothorax is usually well tolerated.

The standing surgical procedures most commonly performed include thoracotomy via an intercostal approach or thoracotomy and rib resection. For the intercostal approach, the surgical site is prepared and infiltrated with local anesthetic. The lateral thoracic vein must be identified to avoid inadvertent incision. A vertical incision is made through the skin, intercostal musculature, and pleura. The length of the incision is dictated by the size of the pleural abscess and consistency of its content. When necessary, partial excision of the intercostal muscles will facilitate manual exploration of the cavity and removal of fibrin and necrotic debris (Fig. 31-11). The major advantage of the intercostal approach over rib resection is preservation of thoracic wall integrity and compliance. Thoracotomy with rib resection is elected when the cavity is very large and it is anticipated that extensive manual débridement of fibrin and necrotic debris will be necessary. The advantage of the thoracotomy with rib resection over the intercostal approach is improved access to the thorax, allowing manual removal of large fibrin clumps and necrotic debris (Fig. 31-12). With both rib resection and intercostal approaches, the incision is left open and irrigated once or twice daily with a sterile isotonic fluid solution. The cavity is periodically débrided via gentle massage, taking care not to disrupt mature adhesions. After adequate formation of granulation tissue, tap water may be used. Depending on the size of the incision, it may take a few weeks to 2 to 3 months for complete closure by second intention. Complications during thoracotomy may include bilateral pneumothorax (if the cavity is not walled off and the mediastinum is not complete) and cardiac dysrhythmias (if the lesion is in close proximity to the heart). The most common long-term complication is the formation of a chronic draining fistula, but by itself, this complication does not prevent the horse from returning to its usual occupation. In a retrospective study of 16 horses that had a standing lateral thoracotomy for pleural disease,

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FIG. 31-11 Intercostal thoracotomy with partial excision of the intercostal muscles in a 7-year-old horse with a large pleural abscess. The image was obtained 3 weeks after surgery.



FIG. 31-12 Thoracotomy and rib resection in a Thoroughbred filly with a large pleural abscess in the right hemithorax communicating with another abscess cranial to the heart. In this case, a rib resection was done to facilitate manual removal of purulent material and necrotic debris from both abscesses.

14 horses (88%) survived to discharge and 46% of horses that survived returned to their previous level of athletic activity.[65]

Complications of Pleuropneumonia Several complications may occur during medical therapy of severe pneumonia and pleuropneumonia. These complications include jugular vein phlebitis or thrombosis from catheter placement, diarrhea resulting from antimicrobial therapy, pneumothorax or cellulitis secondary to thoracocentesis, endotoxemia, coagulopathy, and laminitis. In a retrospective study of 153 horses with pleuropneumonia presented to a referral hospital, complications included pleural abscesses (21.6%), cranial thoracic masses (7.2%), bronchopleural fistulas (6.5%), pericarditis (2.6%), and laminitis (1.3%).

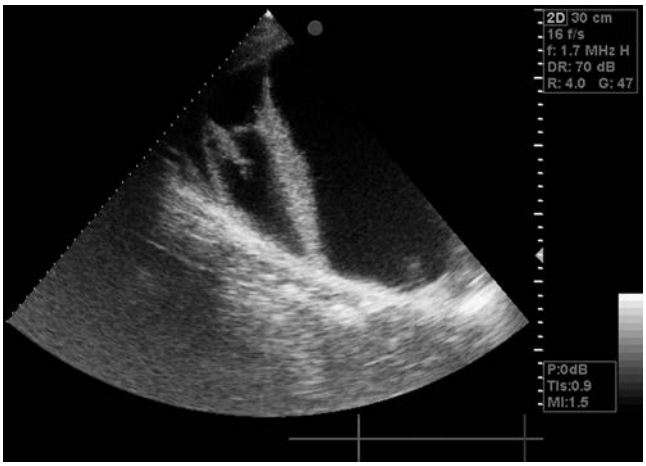


FIG. 31-13 Sonogram of the cranial thorax obtained from the third intercostal space of a 2-year-old Thoroughbred filly with distended jugular veins and pitting edema of the ventral thorax. A large fluid-filled loculated abscess was imaged.

Pleural abscesses refractory to antimicrobial therapy are treated by thoracocentesis or thoracotomy (see earlier sections). In some cases of pleuropneumonia, the heart may act as a valve to trap effusion and inflammatory debris in the cranial thorax. Small cranial thoracic masses may result in nonspecific clinical signs such as fever, tachycardia, and sternal edema. Larger abscesses may result in jugular vein distention, forelimb extension (pointing), and caudal displacement of the heart. Diagnosis is made by ultrasonography (Fig. 31-13). It is necessary to pull a forelimb forward to successfully image the cranial thorax. Most horses with cranial thoracic masses will respond to conservative therapy with antimicrobial agents.[66] Drainage of the abscess should be performed in cases refractory to medical therapy or when the mass interferes with normal cardiac function. Cranial thoracic abscesses may be sampled in the standing horse with a front limb pulled forward. However, when drainage and lavage are required, the procedure is best performed under short-term general anesthesia to avoid damage to the heart and major blood vessels present in the cranial thorax. It is not recommended to leave an indwelling tube because the triceps musculature often causes the tube to kink. Repeated drainage and lavage may be necessary in some cases.

Bronchopleural fistulas develop when necrosis of lung tissue leads to direct communication between the airways and the pleural cavity. Diagnosis may be confirmed by thoracoscopy or by injecting sterile fluorescein dye into the pleural fluid and looking for presence of dye at the nostrils or within the trachea by endoscopy. Horses with bronchopleural fistulas will often cough during pleural lavage, and lavage fluid may be noted at the nostrils. Most bronchopleural fistulas seal spontaneously as a result of adhesions to the chest wall or fibrin deposition on the visceral pleura. Sealing may take several weeks to months. In one case, partial pneumonectomy was successful at resolving a chronic bronchopleural fistula and pulmonary abscess.[67]

Prognosis The prognosis for survival and return to normal athletic function depends on the severity and duration of clinical signs prior to therapy. Horses with septic inflammatory airway disease or mild to moderate bronchopneumonia have a very good prognosis for a return to previous athletic performance. The prognosis for horses with pulmonary abscesses and without concurrent pleuritis is also good. In one study, 45 of 50 (90%) adult horses with pulmonary abscesses survived.[68] In the same study, 92% of Standardbreds and 52% of Thoroughbreds raced after treatment of pulmonary abscesses.[68] For horses that returned to racing, performance after successful treatment of lung abscesses was not significantly different from that before the illness.[68]

In a retrospective study of 327 horses with pneumonia or pleuropneumonia, the overall survival rate was 75%.[3] In the same study,

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the survival rate for 81 horses from which anaerobic bacteria were cultured was only 38.3%.[3] However, another study failed to identify an association between the presence of anaerobic bacteria and decreased survival.[69] In cases of pleuropneumonia, retrospective studies have shown survival rates ranging from 43.3% to 87.6%.[13,69,70] Differences in survival rates among studies may reflect differences in referral populations as well as advances in therapy in more recent years. Many horses that would have been euthanized because of chronicity and lack of response to medical therapy several years ago are now successfully treated with the surgical approaches described previously. This is evidenced by a retrospective of 153 horses with pleuropneumonia in which the survival rate was 95.7% when horses electively euthanized were excluded.[70]

The effect of pleuropneumonia on subsequent racing performance has not been examined extensively. In one retrospective study, 43 of 70 (61%) horses that had recovered from pleuropneumonia returned to racing, and 24 of the 43 (56%) won at least one race.[71] In the same study, horses that required placement of an indwelling thoracic drain did not have a worse prognosis for return to performance compared with horses that did require placement of a drain.[71] In contrast, horses that developed complications such as pulmonary abscesses, cranial thoracic masses, or bronchopleural fistulas were significantly less likely to return to racing.[71]

Rhodococcus equi Infections

Steeve Giguère

Rhodococcus equi, a gram-positive facultative intracellular bacterium, is one of the most common causes of pneumonia in foals between 3 weeks and 5 months of age. *R. equi* has also emerged as a significant opportunistic pathogen in immunosuppressed people, especially those infected with the human immunodeficiency virus.[1,2] Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on some farms. On farms where the disease is endemic, costs associated with veterinary care, long-term therapy, and mortality of some foals may be very high. This text reviews the clinical manifestations, pathogenesis, epidemiology, diagnosis, treatment, and control of *R. equi* infections in foals.

Clinical Manifestations

PULMONARY DISEASE. The most common clinical manifestation of disease caused by *R. equi* infections in foals is a chronic suppurative bronchopneumonia with extensive abscessation (Fig. 31-14). The slow spread of the lung infection combined with the remarkable ability of foals to compensate for the progressive loss of functional lung makes early clinical diagnosis difficult. Early clinical signs often consist of only a mild fever, occasional cough, or a slight increase in respiratory rate that may not be apparent unless foals are exercised or stressed by handling. If pneumonia progresses, clinical signs may include decreased appetite, lethargy, fever, cough, tachypnea, and labored breathing characterized by nostril flaring and increased abdominal effort. Bilateral nasal discharge is an inconsistent finding. In a recent report of 161 foals affected with *R. equi* pneumonia, the most common clinical signs were cough (71%), fever (68%), lethargy (53%), and increased respiratory effort (43%).[3] A smaller percentage of affected foals present with a more devastating subacute form. These foals may be found dead or more commonly are presented in acute respiratory distress with a high fever and no previous history of clinical respiratory disease. Foals with the subacute form of the disease have a poor prognosis despite appropriate therapy.

Because ultrasonographic screening for early detection has become routine practice at many farms endemic for pneumonia caused by *R. equi,* the most frequently recognized form of *R. equi* infection on those farms is a subclinical form in which foals develop ultrasonographic evidence of peripheral pulmonary consolidation or abscessation without manifesting clinical signs.[4,5] On those farms, the cumulative frequency of ultrasonographically visible areas of focal pulmonary consolidation or abscessation considerably exceeds the historical frequency of clinical pneumonia attributed to *R. equi,* indicating that many subclinically affected foals might spontaneously recover without therapy. In two independent studies at breeding farms endemic for *R. equi* infections, 80% to 90% of foals with ultrasonographically visible lesions recovered without antimicrobial therapy.[6,7] The proportion of such subclinically affected foals that progress to clinically apparent disease might vary by farm, geographic region, and age at which foals are examined.

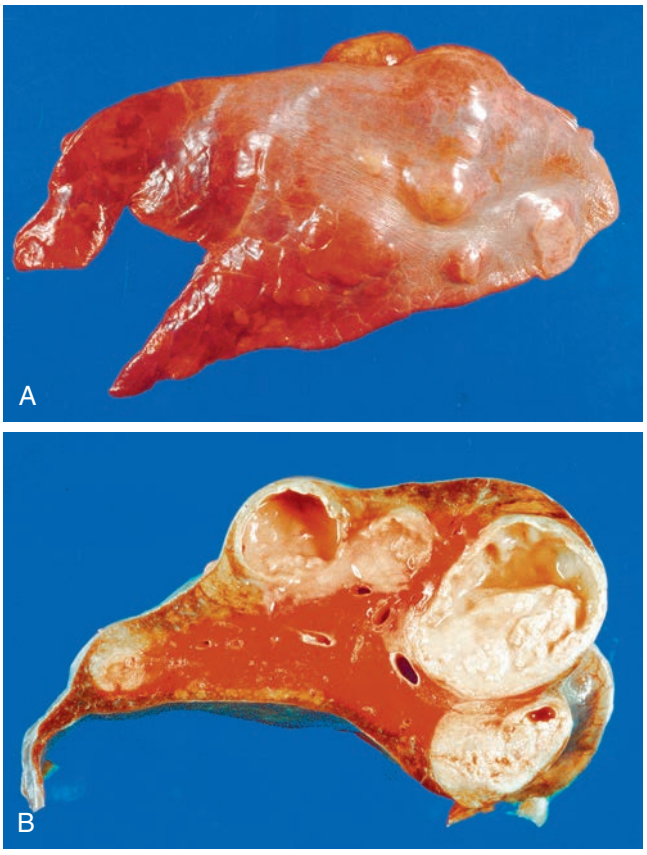


FIG. 31-14 **A,** Left lung from a foal with severe pneumonia caused by *R. equi*. There is marked consolidation of the cranial portion of the lung, and multiple abscesses are present caudodorsally. **B,** Cross-section of the same lung, showing multiple abscesses filled with caseous material. *(Courtesy Dr. William Castleman, University of Florida, College of Veterinary Medicine.)*

EXTRAPULMONARY DISORDERS. Extrapulmonary manifestations of rhodococcal infections are common.[8] In a study of 150 foals with *R. equi* infections admitted to a teaching hospital, at least 1 of 39 different extrapulmonary disorders (EPDs) were recognized in 74% of foals, although some EPDs, particularly abdominal lesions, can be difficult to recognize antemortem and were recognized only during necropsy.[8] Survival was significantly lower among foals with EPDs (43%; 48/111) than among foals without EPDs (82%; 32/39).[8] Some EPDs (e.g., polysynovitis, uveitis) might be the first clinical manifestation of *R. equi*–associated disease, detected prior to signs of pneumonia.

Intestinal lesions are present in approximately 50% of foals with *R. equi* pneumonia presented for necropsy.[9] However, the majority of foals with *R. equi* pneumonia do not show clinical signs of intestinal disease. In the same study, only 4% of the foals had intestinal lesions without pneumonia.[9] The intestinal form of *R. equi* infection is characterized by a multifocal ulcerative enterocolitis and typhlitis over the area of the Peyer patches with granulomatous or suppurative inflammation of the mesenteric and/or colonic lymph nodes.[9] In some cases, the only abdominal lesion noted may be a single large abscess (usually in a mesenteric lymph node) that often adheres to

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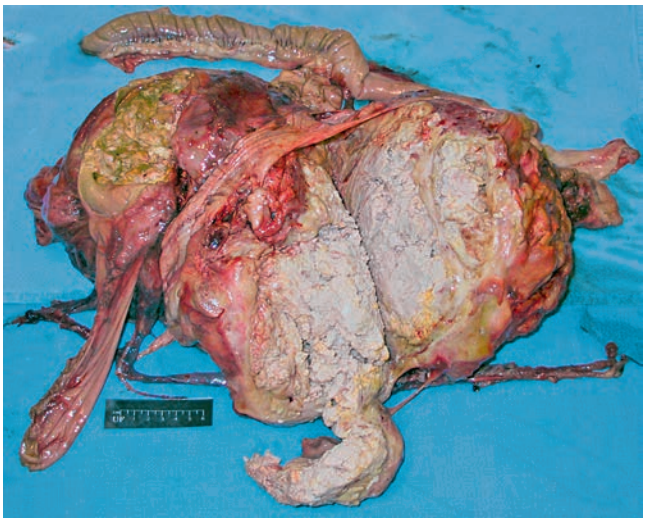


FIG. 31-15 Large abdominal abscess from a 4-month-old foal with a history of weight loss, fever, and mild intermittent episodes of colic. A portion of the small intestine and a portion of the small colon are adhered to the abscess. Culture yielded pure growth of *R. equi*.

the large or small bowel (Fig. 31-15). Foals with abdominal abscesses have a poor prognosis.[8]

Clinical signs associated with the abdominal form of the disease may include fever, depression, anorexia, weight loss, colic, and diarrhea.[8,10] Diarrhea might occur in foals infected with *R. equi* either as an EPD caused by pyogranulomatous typhlocolitis or as a result of antimicrobial treatment. Of 31 foals with ulcerative enterotyphlocolitis identified at necropsy, only 12 foals had diarrhea, whereas 9 foals had diminished growth.[8] Marked gastrointestinal lymphatic obstruction associated with increased protein concentration in the peritoneal fluid and systemic hypoproteinemia may lead to ascites, giving affected foals a pot-bellied appearance. Such foals have a poor prognosis because of the extensive granulomatous inflammation of the colonic mucosa and submucosa and mesenteric lymph nodes.

Polysynovitis is present in approximately one third to one fourth of cases with *R. equi* infections; in some cases, effusion of multiple joints may even be the presenting complaint.[11,12] The tibiotarsal and stifle joints are most commonly affected. Occasionally all joints are affected. The degree of joint effusion is variable and, in most cases, lameness is not apparent or limited to a stiff gait. Cytologic examination of the synovial fluid usually reveals a nonseptic mononuclear pleocytosis, and bacteriologic culture of the synovial fluid is negative.[12] Histologic examination of the synovial membrane of a few affected foals revealed lymphoplasmacytic synovitis.[11,13] Fluorescein-labeled antiequine immunoglobulin G (IgG) staining of the synovial membrane of three affected foals revealed evidence of immunoglobulin within the synovial membrane, and rheumatoid factors (i.e., antibodies directed against autologous or heterologous Fc portion of immunoglobulin) were identified in the synovial fluid of a foal with nonseptic joint effusion and *R. equi* pneumonia.[11,13] These findings are suggestive of an immune-mediated process. However, experimental infection with a heavy intrabronchial inoculum of virulent *R. equi* consistently results in polysynovitis without associated lameness, and culture of the synovial fluid within a few days of the onset of synovial effusion in these foals is often positive for *R. equi*.[14] Histologic examination of the synovial membrane reveals suppurative inflammation.[14] Therefore an alternative and more likely explanation is that septic polysynovitis results from bacteremia, but the infection is rapidly cleared from the synovial structures, resulting in chronic nonseptic inflammation at the time of diagnosis. Regardless of the inciting cause, local therapy of the affected joints in clinical cases of *R. equi*–associated polysynovitis is usually not indicated because the effusion resolves without any apparent consequences as the primary infection responds to appropriate antimicrobial therapy. The presence of a nonseptic polysynovitis in a foal between 3 weeks and 6 months of age is highly suggestive of *R. equi* infection and deserves further investigation (see section on diagnosis).

Intermittent or persistent bacteremia with *R. equi* might be more common than recognized and might result in metastatic spread of infection. The proportion of foals that are blood culture–positive and the stages of disease during which bacteremia is most likely to occur are poorly defined. In a retrospective study, *R. equi* was isolated from the blood of 11 of 19 foals, and foals with positive blood culture results were less likely to survive than foals that were culture-negative.[8]

Bacteremic spread of the organism from the lungs or gastrointestinal tract may occasionally result in septic arthritis and, more commonly, osteomyelitis. However, foals can occasionally develop *R. equi* septic arthritis or osteomyelitis without apparent lung involvement or other source of infection. The degree of lameness of foals with septic arthritis distinguishes them from foals with nonseptic polysynovitis. In equivocal cases, bacterial culture and cytologic examination of the synovial fluid should be performed. In addition to appropriate antimicrobial therapy (see treatment), foals with *R. equi* septic arthritis and osteomyelitis often require aggressive local therapy. *R. equi* vertebral osteomyelitis or diskospondylitis resulting in spinal cord compression has also been reported.[15-17] Clinical signs of vertebral osteomyelitis or diskospondylitis might include stiff gait, reluctance to move, palpable pain, and sometimes soft-tissue swelling associated with paravertebral abscessation.[8] If the infection or associated swelling extends to the epidural space, neurologic signs of spinal cord disease or nerve root compression might be apparent.[8] Specific neurologic signs vary according to the specific region of the spinal cord that is affected. Foals with vertebral osteomyelitis generally have a poor prognosis. However, there are reports of successful treatment with prolonged antimicrobial therapy alone or with antimicrobial therapy in conjunction with surgical débridement of infected bone.[15]

Some foals with *R. equi* infections develop ocular lesions, including uveitis, keratouveitis, and panophthalmitis.[8] Affected foals might display epiphora, photophobia, aqueous flare, hypopyon, iris discoloration, miosis, and other ophthalmic abnormalities. The pathogenesis of uveitis is often unknown but might include dissemination of bacteria to the eye or immune-mediated mechanisms. In one study, foals with uveitis were less likely to survive than foals without uveitis.[8]

Other less common EPDs associated with metastatic spread of *R. equi* include pericarditis, endocarditis, cellulitis, dermatitis, subcutaneous abscesses, peripheral lymphadenopathy, guttural pouch empyema, pleuritis, sinusitis, ulcerative lymphangitis, myositis, stomatitis, pyometra, and omphalitis.[8,18] Other immune-mediated EPDs include immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, and telogen effluvium.[8,19]

ADULT HORSES. Disease caused by *R. equi* in adult horses is rare, but there are sporadic reports of infection involving primarily the lungs or abdominal lymph nodes (similar to infection observed in foals) and, less common, of wound infection. In one adult horse, acquired combined immunodeficiency of unknown origin led to *R. equi* septicemia and lung abscessation.[20] Occasionally, the microorganism has also been isolated from infertile mares and aborted fetuses.[9,21,22]

OTHER DOMESTIC ANIMAL SPECIES. *R. equi* has been isolated from many species other than people and horses. *R. equi* is frequently cultured from the submaxillary lymph nodes of pigs with granulomatous lymphadenitis. However, *R. equi* can also be isolated from the submaxillary lymph nodes of 3% to 5% of apparently healthy pigs, and experimental infection studies in pigs have failed to reproduce granulomatous lymphadenitis.[23,23,24] The causative role of *R. equi* in granulomatous lymphadenitis in pigs thus remains unproven. Isolation of *R. equi* from other domestic animal species is rare. *R. equi* can be isolated from lymph node granulomas in 0.008% of cattle at abattoir postmortem inspection.[25] *R. equi* has also been cultured from

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rare cases of bronchopneumonia, mastitis, metritis, ulcerative lymphangitis, and septic arthritis in cattle. In goats, *R. equi* has a tendency to cause liver abscesses with concurrent bronchopneumonia or pulmonary abscessation.[26] In dogs and cats, *R. equi* has been isolated from cases of pneumonia as well as from wound infections, subcutaneous abscesses, vaginitis, hepatitis, osteomyelitis, myositis, and joint infections.[27]

Virulence

The ability of *R. equi* to induce disease in foals likely depends on both host and microbial factors. *R. equi* is a facultative intracellular pathogen and its ability of *R. equi* to persist in, and eventually destroy, alveolar macrophages seems to be the basis of its pathogenicity. Knowledge of the virulence mechanisms of *R. equi* was largely speculative until the discovery of a virulence plasmid in the early 1990s.[28,29] Unlike most environmental *R. equi,* isolates from pneumonic foals typically contain an 80- to 90-kb plasmid. Plasmid-cured derivatives of virulent *R. equi* strains lose their ability to replicate and survive in macrophages.[14] Plasmid-cured derivatives also fail to induce pneumonia and are completely cleared from the lungs of foals within 2 weeks following heavy intrabronchial challenge, confirming the absolute necessity of the large plasmid for the virulence of *R. equi*.[14,30]

Sequencing and annotation of the virulence plasmid revealed 73 coding sequences[31,32] and that it was divisible into four discrete areas based on open reading frame (ORF) amino acid sequence similarity and predicted protein function. The "backbone" sequence of the plasmid is highly similar to that of a plasmid found in the environmental microorganism *Rhodococcus erythropolis* and consists of regions for replication and partitioning, conjugation, and unknown functions.[31] The fourth plasmid region is a 21-kb pathogenicity island (PAI) that is crucial for virulence.[31,32] The 26 coding sequences of the PAI include the unique and *Rhodococcus equi*–specific virulence-associated protein (Vap) family.[32] There are six full-length *vap* genes *(vapA, vapC, vapD, vapE, vapG,* and *vapH)* and three truncated *vap* pseudogenes *(vapF, vapI,* and *vapX).*[31] To date, *vapA,* which encodes an immunodominant, temperature-inducible, and surface-expressed lipoprotein,[33,34] is the only *vap* gene with a demonstrated role in virulence,[35] whereas Vaps C, D, E, F, G, I, and X are dispensable.[35,36] VapA is required for intracellular growth in macrophages,[35] where it aids in preventing maturation of the phagosome to the stage of fusion of *R. equi*–containing vacuoles with lysosomes.[37] The functions of the other Vap proteins are unknown.

Although *vapA* is necessary for virulence, it is not sufficient.[14] Additional virulence determinants reside within the PAI.[36] Two of these, *virR* and *orf8,* each encode a regulatory protein.[38,39] Loss of either regulator results in decreased *vapA* transcription and also in attenuation of the organism.[38,39] All the *vap* genes, as well as five other ORFs within the PAI, are upregulated when *R. equi* is grown in macrophage monolayers.[40] Regulation of expression of the genes in the PAI is complex and depends on at least five environmental signals, including temperature, pH, oxidative stress, magnesium, and iron.[40-42] The precise role of each of these genes in the pathogenesis of *R. equi* infections remains to be determined. The entire virulence plasmid can be transferred by conjugation from plasmid-containing strains of *R. equi* to plasmid-free *R. equi* strains at a high frequency, and plasmid transmission restores the capacity for intracellular growth in macrophages.[43] Deletion of a putative relaxase-encoding gene *(traA)* located in the proposed conjugative region of the plasmid prevents plasmid transfer.[43]

A second major advance in the understanding of *R. equi* virulence was the recent sequencing and annotation of the genome of *R. equi*.[44] The 5.04-Mb *R. equi* genome is most similar to that of the environmental bacterium *Rhodococcus jostii* and then to *Nocardia farcinica* and *Mycobacterium tuberculosis.*[44] As with these other actinomycetes, a large number of the 4598 genes of *R. equi* appear to be involved in lipid metabolism. Like *M. tuberculosis,* lipids are a key component of the outer cell envelope of *R. equi.*[45] This mycolic acid–containing glycolipid barrier might serve to protect the peptidoglycan and plasma membrane from the damaging effects of host-generated enzymes and immune-mediated reactive intermediates. Cell envelope mycolic acid carbon chain length varies among *R. equi* isolates, and, notably, it was observed that strains with longer mycolic acids were more lethal to mice.[46] This might be explained by the fact that mycolic acid chain length plays a key role in diversion of macrophage phagosome trafficking by *R. equi*.[47]

Some of the most exciting recent data in the *R. equi* field involve the recognition of molecular "cross talk" between the virulence plasmid and the *R. equi* chromosome. Microarray analysis has shown that a gene or genes on the plasmid directly or indirectly regulate chromosomal gene expression patterns and that the two regulators in the PAI region could be involved. Although it has been firmly established that the virulence plasmid is essential for infection of foals, several chromosomally encoded genes have also been proven to play essential roles in intracellular survival and virulence, notably those involved in various metabolic functions such as fatty acid metabolism, anaerobic metabolism, aromatic amino acid biosynthesis, regulation of secreted proteins, iron acquisition, hydrogen peroxide resistance, and cholesterol catabolic pathways.[44,48-56]

R. equi isolates are often classified as virulent, avirulent, or intermediately virulent based on their ability to induce disease or death in mice. Virulent *R. equi* isolates contain the large plasmid described earlier and express VapA. Intermediately virulent *R. equi* isolates contain one of four distinct large plasmids encoding a 20-kDa antigen (VapB) that is related to, but distinct from, VapA. In contrast, avirulent *R. equi* isolates do not express Vap antigens. All three categories of *R. equi* have the ability to cause disease in immunosuppressed humans. Analysis of *R. equi* isolates from immunocompromised human patients with or without AIDS reveals that only approximately 20% of isolates contain an 80- to 90-kb plasmid and express VapA.[57,58] Therefore the pathogenesis of *R. equi* infection in immunocompromised human patients appears to be different from the pathogenesis in foals, in which the virulence plasmid is always found. Intermediately virulent isolates (expressing VapB) have never been isolated from foals with naturally acquired *R. equi* infections. Experimentally, heavy intrabronchial challenge of foals with intermediately virulent *R. equi* results in pneumonia but at a dose much higher than that required for induction of pneumonia with VapA-expressing strains.[59] Almost all isolates from the submaxillary lymph nodes of pigs produce VapB and are intermediately virulent to mice, suggesting that pigs or their environment may be the source of infection for some human cases.[60] Most isolates from cattle, goats, and dogs are avirulent and do not contain plasmids encoding *vapA* or *vapB*.[25-27] In contrast, most isolates from cats contain the virulence plasmid and express VapA.[27]

Pathogenesis Inhalation of virulent *R. equi* is the major route of pulmonary infection in foals. The incubation period following experimental intrabronchial challenge varies from approximately 9 days after administration of a heavy inoculum to approximately 2 to 4 weeks when a lower inoculum is administered.[14,61] Lung consolidation can be detected as early as 3 days following heavy intrabronchial challenge.[14] However, the incubation period under field conditions is unknown and likely varies depending on several factors, including the number of virulent bacteria in air samples in the environment, the age of the foal, and host defense mechanisms. Ingestion of the organism is an important route of exposure, and likely also of immunization, but rarely leads to hematogenously acquired pneumonia unless a foal has multiple exposures to large numbers of bacteria.[62] Indeed, intragastric administration of live virulent *R. equi* to foals on day 2 and day 7 of life is highly effective in preventing development of pneumonia following subsequent heavy intrabronchial challenge.[63] Despite conferring protection, oral vaccination with live virulent *R. equi* would not be an acceptable strategy to immunize foals since it would lead to progressive contamination of the environment with virulent bacteria. However, it undoubtedly shows that newborn foals have the ability to mount protective immune responses against *R. equi* (see section on immunity).

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Epidemiologic evidence suggests that most foals on endemic farms become infected early in life.[64] The median age at the time of diagnosis is approximately 35 to 50 days on most endemic farms.[3,65] Given the fairly long incubation period of the disease, this finding would also support the fact that many foals become infected early in life. In one study, foals aged between 3 and 13 days (mean 6.4 days) were more susceptible to experimentally induced *R. equi* pneumonia than foals aged between 14 and 36 days (mean 25 days).[66] In a recent study, foals between 3 and 42 days of age were experimentally infected with various doses of virulent *R. equi* 10^3 to 10^7.[67] Whereas the youngest foals were highly susceptible to infection, the oldest foals were resistant to 1000-fold higher challenge.[67] Collectively, these findings indicate that many foals on endemic farms become infected at a young age and that younger foals are more susceptible than older foals to infection caused by *R. equi*. However, these findings do not necessarily indicate that foals are only susceptible to *R. equi* during the neonatal period. Older foals are also susceptible to experimental infection with *R. equi,* but they require a higher inoculum. In one study, intratracheal administration of *R. equi* to 10 foals between 27 and 67 days (mean 49 days) of age resulted in disease in all foals.[30] The relative resistance of older foals to infection caused by *R. equi* compared with younger foals is likely the result of immunologic priming after natural exposure to the pathogen.

Epidemiology

Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on some farms. This probably reflects differences in environmental and management conditions, as well as differences in the virulence of isolates, but the exact basis for the difference in the prevalence of the disease among farms remain unknown. Breeding farms with a large acreage, a large number of mares and foals, a high foal density, and a large population of transient mares and foals have greater odds of being affected by *R. equi* pneumonia.[68,69] In contrast, *R. equi* pneumonia does not appear to be associated with lack of attention to routine preventive health practices.[70]

R. equi is a soil microorganism with simple growth requirements. The highest numbers of *R. equi* are found in surface soil, whereas the organism cannot be found at depths exceeding 30 cm.[71] *R. equi* can be cultured not only from the soil of all horse farms but also from the soil of areas not inhabited by horses. In one study, *R. equi* was isolated from approximately 74% of soil samples collected from 115 parks and 49 household yards in Japan. The number of *R. equi* in those samples ranged from 10 to 10^5 colony-forming units (CFUs) per gram of soil. None of the 1294 isolates from those samples expressed VapA or VapB, suggesting that the environment of people is not a significant route of exposure to virulent or intermediately virulent *R. equi*.[24]

R. equi can be isolated from the feces of most adult horses at concentrations ranging between 10 and 10^3 CFUs per gram of feces. The number of *R. equi* in the feces of mares on endemic farms does not increase in the weeks before or following foaling.[72] In one study, virulent *R. equi* could be isolated from the feces of all mares sampled; this demonstrates that mares can be an important source of virulent *R. equi* for their surrounding environment.[73] However, dams of affected foals did not shed more *R. equi* in feces than did dams of unaffected foals, indicating that heavier shedding by particular mares does not explain infection in their foals.[73] In another study, *R. equi* could be isolated from the feces of only 19% of the foals at 1 week of age and from all foals by 4 weeks of age.[72] Foals can shed high concentrations of *R. equi* in their feces, reaching numbers up to 10^5 CFUs per gram of feces.[74] Virulent *R. equi* present in the sputum of pneumonic foals will be swallowed and, as a result, the manure of *R. equi*–affected foals is likely a major source of progressive contamination of the environment with virulent organisms. Under suitable conditions of high summer temperatures, *R. equi* can multiply in the environment by 10,000-fold in only 2 weeks.[75] A single gram of soil contaminated with foal manure may therefore, under favorable conditions, contain millions of virulent *R. equi*.[76]

In a survey of the prevalence of *R. equi* at horse breeding farms in Japan, the organism was isolated from almost all soil samples, at numbers of 10^2 to 10^5 CFUs per gram of soil.[77] Although virulent *R. equi* isolates containing 80- to 90-kb plasmids and expressing VapA were cultured from 24 of the 31 farms examined, the vast majority of these isolates did not contain plasmids and were avirulent. On those farms, virulent *R. equi* represented 1.7% to 23.3% of all isolates.[77] However, neither the presence nor the concentration of virulent *R. equi* in soil is positively associated with increased cumulative incidence of *R. equi* pneumonia at breeding farms in North America or Australia.[78-80] In addition, soil geochemistry does not appear to be associated with occurrence of *R. equi* pneumonia at farms.[81]

In contrast, airborne concentration of virulent *R. equi* is correlated with disease incidence at Thoroughbred breeding farms in Australia.[80] Factors associated with increased air concentration of *R. equi* at these farms included site (holding pens and lanes relative to paddocks), warmer ambient temperature, less soil moisture, reduced grass height, and later date during the foaling season.[80] In Kentucky, concentrations of airborne *R. equi* were lower between midnight and 6 AM than later times, and the presence of horses at the sampling site appeared to increase the airborne concentrations of virulent *R. equi*.[82] These findings suggest that airborne concentrations may be increased by greater activity and density of horses at sites where foals are housed. Also in Kentucky, foals were more likely to be exposed to airborne virulent *R. equi* when housed in stalls versus paddocks and earlier (January and February) versus later (May and June) during the foaling season.[83] Similarly, the odds of detecting airborne virulent *R. equi* at three breeding farms in Ireland were approximately 17 times greater in stables (stalls) than in paddocks of a given farm, and concentrations of virulent *R. equi* were also significantly higher in stables than in paddocks.[84] In a recent study at a breeding farm in Texas, exposure of foals to airborne virulent *R. equi* during the first 2 weeks after birth was significantly associated with subsequent development of *R. equi* pneumonia.[85] The fact that exposure preceded development of *R. equi* pneumonia suggests that the higher concentration of airborne virulent *R. equi* is likely the cause of pneumonia rather than an effect.

In one study, air samples from the breathing zone of pneumonic foals had higher concentrations of virulent *R. equi* than environmental air samples collected from lanes and pens at the same farms.[86] However, concentrations of virulent *R. equi* from air samples collected from the breathing zones were not significantly different between pneumonic foals and healthy controls, indicating that affected foals do not represent a greater risk than other foals for aerosol transmission. In addition, there was no association between virulent *R. equi* in the breathing zone of foals and the subsequent diagnosis of rhodococcal pneumonia.[87] Thus, to date, there is no compelling evidence that *R. equi* infection is contagious among foals and that affected foals should be isolated from other foals.

Considerable genotypic variability has been found among isolates of *R. equi* obtained from the same farm and among isolates from various countries or continents.[88-90] Interestingly, multiple different *R. equi* strains were isolated in five of the six cases in which more than one isolate from a single foal was examined.[89] Similarly, six distinct genotypes were identified among nine *R. equi* isolates from one foal with pneumonia and concurrent abdominal lesions.[91] None of the four pulmonary isolates was identical; however, a pulmonary isolate was found to be identical to an isolate recovered from a small intestinal lymph node, and a second pulmonary isolate was identical to an isolate from a mesenteric lymph node.[91] Therefore foals can be infected with multiple strains of virulent *R. equi* and, with current techniques, it is not possible to link infections to a given geographic site or region on the basis of analysis of isolate genotyping.

Rhodococcus equi–Phagocytic Cell Interactions

Once inhaled, *R. equi* is taken up by alveolar macrophages through a process of receptor-mediated phagocytosis. One of the receptors used by macrophages to engulf complement opsonized *R. equi* is

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complement receptor 3 (CR3 or Mac-1).[92] In addition, *R. equi* might utilize the macrophage mannose receptor for entry, which might recognize lipoarabinomannan (LAM), an outer surface component of the bacterium, either directly or via mannose-binding protein or surfactant molecules adhered to LAM.[93] Once engulfed by resident macrophages, virulent *R. equi* are able to modify the phagocytic vacuole to prevent acidification and subsequent fusion with lysosomes.[37,94-96] Bacterial gene expression patterns are altered to accommodate survival in the intracellular environment and allow acquisition of essential nutrients such as iron, as well as to promote resistance to host-derived reactive oxygen intermediates.[40,41,56] Uncontrolled intracellular replication of *R. equi* leads to necrosis of the macrophage.[97] If bacteria are opsonized with *R. equi*–specific antibody, presumably promoting bacterial entry via the macrophage Fc receptor, the fate of the *R. equi*–containing phagosome is altered and lysosome fusion occurs.[98] This might explain how the presence of *R. equi* antibody might aid in the prevention of infection. Killing of *R. equi* by mouse macrophages is dependent on the presence of interferon (IFN)-γ, which activates macrophages to produce both reactive oxygen and reactive nitrogen intermediates. These two radicals combine to form peroxynitrite, which efficiently kills *R. equi*.[99] Neither reactive oxygen nor reactive nitrogen intermediates alone are sufficient to mediate killing of *R. equi*.[99] Macrophage activation and nitric oxide synthesis act, at least in part, by increasing the ability of macrophages to store iron in a way that it cannot readily be accessed by *R. equi*.[100] Additional cytokines such as tumor necrosis factor α (TNF-α) might have similar effects on restricting intracellular growth of *R. equi* in macrophages, because both IFN-γ and TNF-α are required for clearance of virulent *R. equi* in mice.[101] Neutrophils also play an important role in early host defense against virulent *R. equi*.[102] As opposed to macrophages, neutrophils from foals and adult horses are fully able to kill *R equi*.[103-105] As seen with macrophages, killing of *R. equi* by neutrophils is considerably enhanced by specific opsonizing antibody.[106,107]

Immunity

ANTIBODY-MEDIATED IMMUNITY. Immunity to *R. equi* pneumonia in foals likely depends on both the antibody and cell-mediated components of the immune system, but its exact basis remains to be determined. The strongest evidence for a role of antibody in protection against *R. equi* is the partially protective effect of passively transferred anti–*R. equi* hyperimmune equine plasma (HIP; see section on prevention). Opsonization of *R. equi* with specific antibody has been shown to promote phagocytosis and killing of *R. equi* by alveolar macrophages, identifying antibody as a critical component of HIP.[98,108] In most studies evaluating the protective effect of HIP, donors were immunized with whole cell vaccines or a mixture of several soluble antigens, making it impossible to determine the role of antibody against defined antigens of *R. equi*.

A number of studies have focused more specifically against the role of antibody against plasmid-encoded virulence-associated proteins (Vap). First, monoclonal antibody to VapA and serum from horses immunized with partially purified VapA have opsonizing activity.[109] Moreover, purified immunoglobulins obtained from horses vaccinated with partially purified VapA protected mice against intraperitoneal challenge with virulent *R. equi* compared with mice administered immunoglobulins from nonimmunized horses.[110] Finally, intravenous administration of purified immunoglobulins obtained from horses immunized with recombinant VapA and VapC to foals was found to reduce the severity of pneumonia following heavy experimental challenge with *R. equi*.[111] In the same study, the degree of protection conferred by purified anti-VapA and anti-VapC immunoglobulins was similar to that provided by commercially available HIP.[111]

In adult horses, the concentrations of *R. equi*–specific and VapA-specific IgGa and IgGb antibodies (the IgG isotypes that preferentially opsonize and fix complement in horses) are dramatically enhanced following intrabronchial challenge with virulent *R. equi*. This occurs in conjunction with clearance of the bacteria from the lungs.[112] In foals, production of antibody to VapA and VapC, but not that to other Vap proteins, increases following natural exposure to *R. equi*.[111] Characterization of the subisotype response in naturally infected foals revealed mainly an increase in IgGa, IgGb, and IgG(T).[111,113] Experimental infection of young foals with a low inoculum of virulent *R. equi* that resulted in subclinical pulmonary lesions caused a marked increase in serum IgGa and IgGb levels, resulting in concentrations that were significantly higher than those of adult horses undergoing the same challenge.[114] It is interesting to note that infection of foals of the same age with a higher inoculum leading to severe respiratory disease resulted in a switch from a predominant IgGa response to a striking IgG(T) response, indicating that the size of the *R. equi* inoculum can modulate immune responses.[115]

CELL-MEDIATED IMMUNITY. Because of the facultative intracellular nature of *R. equi,* cell-mediated immune mechanisms are thought to be of major importance in resistance to infection. A large part of the knowledge of cell-mediated immunity to *R. equi* infections comes from infection of mice. Deficiencies in the complement component C5 and in natural killer (NK) cells in mice do not impair the pulmonary clearance of virulent *R. equi*.[116] In contrast, functional T lymphocytes are absolutely required for the clearance of virulent (plasmid and VapA positive) *R. equi* in mice.[117-119] However, athymic nude mice (lacking functional T lymphocytes) clear plasmid-cured derivatives from their lungs within 1 week of infection, suggesting that, as opposed to virulent organisms, clearance of avirulent plasmid-negative strains in mice does not require functional T lymphocytes and depends mainly on innate defense mechanisms.[118]

The two major mechanisms by which T lymphocytes mediate clearance of intracellular pathogens are secretion of cytokines and direct cytotoxicity. Although both $CD4^+$ (helper) and $CD8^+$ (cytotoxic) T cells contribute to host defense against *R. equi* in mice, $CD4^+$ T lymphocytes play the major role and are absolutely required for complete pulmonary clearance.[119-121] Studies in mice have clearly shown that a type I response, characterized by IFN-γ production by T-helper lymphocytes, is sufficient to effect pulmonary clearance of *R. equi,* whereas a type II response, characterized by IL-4 production, is detrimental.[117,122]

As opposed to foals, adult horses are typically resistant to *R. equi* infections. Thus immune adult horses have been used as a relevant model to better understand what responses are necessary for immunologic protection. Clearance of virulent *R. equi* in adult horses is associated with a significant increase in bronchoalveolar (BAL) fluid $CD4^+$ and $CD8^+$ lymphocytes, lymphoproliferative responses to *R. equi* antigens, development of *R. equi*–specific cytotoxic $CD8^+$ lymphocytes (CTL), and IFN-γ induction by $CD4^+$ and $CD8^+$ lymphocytes.[112,123,124] *R. equi*–specific CTL, which are apparently present in all immune adults, are major histocompatibility complex (MHC) class I unrestricted and appear to recognize unique bacterial lipids from the cell wall.[124,125] The current thought is that these lipid antigens might be presented to T lymphocytes via the CD1 system, as has been well described in *Mycobacterium tuberculosis*.[126] How these findings in mice and adult horses relate to the foal is an area of active research.

IMMUNITY TO *R. EQUI* IN FOALS. Virtually all newborn mammals are immunologically immature and have an assortment of immunologic deficits compared with older animals. In general neonates and perinates have diminished innate immune responses and decreased antigen-presenting cell function and are less able to mount type I immune responses.[127] As a result, neonates of various species demonstrate an increased susceptibility to certain infections.

A number of relative immunologic deficits have been demonstrated in foals. In conjunction with the lack of immunologic memory in newborns, these deficits are postulated to account for the unique age-associated susceptibility of foals to rhodococcal pneumonia. Age-related deficiencies in *R. equi*–specific cytotoxic T lymphocyte (CTL) activity has been documented in 3-week-old foals.[124] Activity of CTLs is improved by 6 weeks of age and is similar to that of adult

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horses by 8 weeks.[124] Antigen-presenting cells from foals have significantly lower CD1 and MHC class II expression compared with adult horses.[126,128] In addition, several studies have demonstrated that the ability of equine lymphocytes and neutrophils to produce and/or upregulate various cytokines is strongly influenced by age.[127-132] In particular, the finding that young foals are deficient in their ability to produce IFN-γ in response to mitogens has led to the hypothesis that an IFN-γ deficiency and T-helper type 2 (Th2) bias might be at the basis of their peculiar susceptibility to *R. equi* infections.[129,130] However, recent data demonstrate that foals are also deficient in their ability to produce IL-4 in response to stimulation with mitogens, stimulation with *R. equi,* and after vaccination with a killed adjuvanted vaccine, suggesting that a clear polarization toward a Th2 response is unlikely in neonatal foals.[133-136] Consistent with these findings, experimental infection of young foals with virulent *R. equi* results in IFN-γ induction and antibody responses similar to, or greater than, those of adult horses undergoing the same experimental challenge.[114]

Recent studies have investigated various immunostimulants that might enhance host defense mechanisms during the relatively narrow period of susceptibility to *R. equi*. Inactivated *Parapoxvirus ovis*, *Propionibacterium acnes,* and unmethylated CpGs all enhance ex vivo or in vitro phagocytic cell function or cytokine induction in foals.[137-140] However, despite successfully enhancing IFN-γ production in foals, inactivated *Parapoxvirus ovis* failed to decrease the cumulative incidence of pneumonia at an *R. equi*–endemic farm. In the same study, IFN-γ and IL-4 secretion at birth was not associated with subsequent development of pneumonia.[141]

Spontaneous resolution of *R. equi* pneumonia after experimental challenge has been recognized.[66,142,143] Many foals on farms where the disease is endemic do not develop disease or develop subclinical disease that resolves without intervention. In addition, intragastric administration of live, virulent *R. equi* to newborn foals confers complete protection against subsequent heavy intrabronchial challenge.[63,144] Oral inoculation with virulent *R. equi* results in accelerated development of *R. equi*–specific CTLs,[145] providing a potential mechanism for the protection conferred by oral inoculation. Collectively, these findings unequivocally demonstrate that most foals have the ability to mount protective immune responses to *R. equi*. The basis for the peculiar susceptibility of foals to infection with *R. equi* is likely complex and multifactorial rather than involving a simple and single explanation.

Diagnosis

The distinction between lower respiratory tract infections caused by *R. equi* and those caused by other pathogens is problematic, especially at farms without previous history of *R. equi* infections. Diagnostic tests, including white blood cell (WBC) concentration, measurement of fibrinogen concentrations, ultrasonography, and radiography, may help raise the degree of suspicion that pneumonia in a given foal may be caused by *R. equi* rather than by another microorganism. However, the definitive diagnosis of bronchopneumonia caused by *R. equi* should be based on bacteriologic culture or amplification of the *vapA* gene by polymerase chain reaction (PCR) from a *tracheobronchial aspirate* (TBA) obtained from a foal with (1) clinical signs of lower respiratory tract disease, (2) cytologic evidence of septic airway inflammation, and/or (3) radiographic or ultrasonographic evidence of bronchopneumonia. Amplification of *vapA* by PCR is done preferably in conjunction with bacterial culture because it does not permit identification of other bacterial pathogens and in vitro antimicrobial susceptibility testing of *R. equi* isolates.[146] The definitive diagnosis of extrapulmonary infections (e.g., abdominal abscess, osteomyelitis) caused by *R. equi* must rely on bacteriologic culture or PCR amplification of *vapA* from samples from the site of infection. The diagnosis of extrapulmonary disorders from sites at which *R. equi* cannot be detected (e.g., uveitis or polysynovitis) should be based on isolation of *R. equi* from a TBA or other primary sites of infection. The diagnosis of enterocolitis caused by *R. equi* is problematic because isolation of *R. equi* from feces cannot be taken as evidence of enterocolitis caused by *R. equi*.[146]

CLINICAL LABORATORY TESTS. Hyperfibrinogenemia is the most consistent laboratory finding in foals with *R. equi* pneumonia, although rare cases may have normal fibrinogen concentrations. Neutrophilic leukocytosis with or without monocytosis is also common. One study showed significantly higher fibrinogen concentrations and WBC counts in nonsurvivors than in survivors,[147] whereas other studies showed no difference between the two groups.[12,148] In one study, a WBC count higher than 20,000 cells/μL, a fibrinogen concentration higher than 700 mg/dL, and evidence of pulmonary abscessation were more likely to be found in foals with pneumonia caused by *R. equi* than in foals with pneumonia caused by other bacteria.[149] However, there is a considerable overlap in distributions, which precludes the use of fibrinogen concentrations and WBC counts for diagnosis or prognosis for an individual foal.[149]

IMAGING TECHNIQUES. Thoracic radiography is useful in evaluating the severity of pneumonia and in assessing response to therapy. A prominent alveolar pattern characterized by ill-defined regional consolidation is the most common radiographic abnormality.[147] The consolidated lesions are often seen as more discrete nodular and cavitary lesions consistent with pulmonary abscessation (Fig. 31-16). Severity of alveolar pattern and number of cavitary lesions are the radiographic findings significantly associated with a poor outcome in foals with *R. equi* pneumonia.[150] Although nonsurvivors tend to have more severe radiographic lesions than survivors, many survivors have very severe radiographic lesions; thus radiographs should not be used as the sole criterion for prognostication and euthanasia.[12,148-150] Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas, but it may not be as useful as radiography to evaluate the full extent of lung lesions because abscesses with overlying aerated lung will not be detected. However, in most horses and foals with pulmonary abscessation, the periphery of the lung is affected, enabling the ultrasonographer to successfully image some of the abscesses.[151] Early ultrasonographic lesions are nonspecific and may include only irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes (Fig. 31-17, *A*). In more chronic cases, well-circumscribed, encapsulated abscesses can be detected (see Fig. 31-17, *B*). Ultrasonography is very useful in evaluating the severity of pneumonia and in assessing response to therapy, especially for equine practitioners who do not have access to thoracic radiography. Ultrasonography is also a useful tool for detection of some abdominal abscesses (Fig. 31-18) and for screening for *R. equi*–infected foals on farms where the disease is endemic (see section on control). Ultrasonographic or radiographic detection of lung abscesses raises the

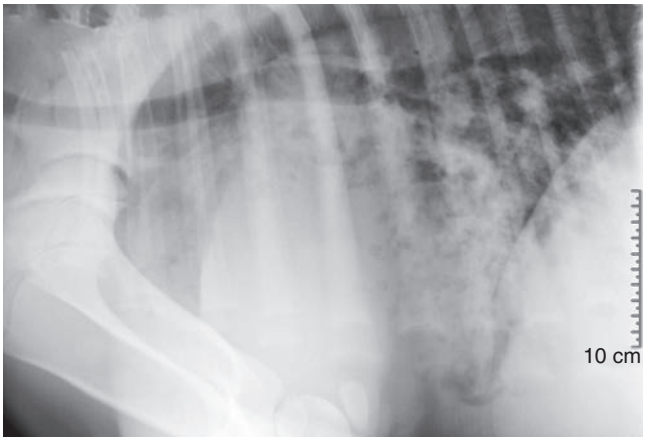


FIG. 31-16 Thoracic radiograph from a 2-month-old foal with pneumonia caused by *R. equi*. The study shows a combination of alveolar and nodular interstitial patterns as well as cavitary nodular infiltrates, primarily in the cranioventral and caudoventral thorax. A mild interstitial infiltrate is present in the caudodorsal lung. The trachea is displaced dorsally, suggesting tracheobronchial lymphadenopathy. There is slight narrowing of the tracheal lumen at the thoracic inlet, likely indicating the presence of tracheal secretions.

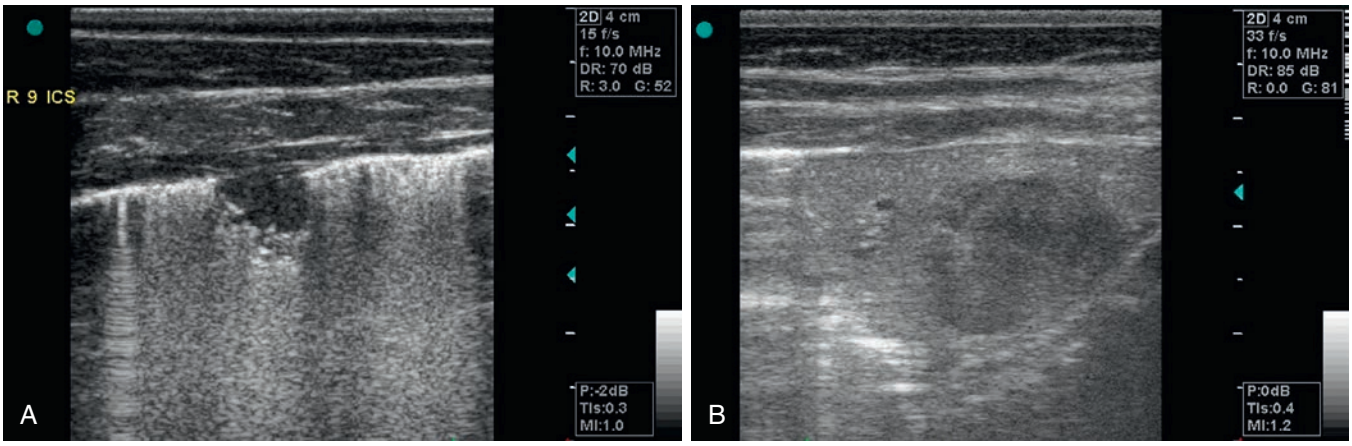


FIG. 31-17 **A,** Sonogram of the right thorax in a foal with mild pneumonia caused by *R. equi*. There is an approximately 1 cm^2 area of focal consolidation. **B,** Sonogram of the left thorax in a foal with severe pneumonia caused by *R. equi*. There is consolidation of the ventral aspect of the lung surrounding a large encapsulated abscess.



FIG. 31-18 Sonogram of the abdomen obtained from a 3-month-old Thoroughbred foal with severe pneumonia caused by *R. equi* and multiple abdominal abscesses. The sonogram shows an abdominal abscess *(arrow)*. The pneumonia resolved with therapy, but the abdominal abscesses persisted. The foal was eventually euthanized because of weight loss and intermittent episodes of colic. Postmortem examination confirmed resolution of pneumonia and the presence of abdominal abscesses caused by *R. equi*.

degree of suspicion that pneumonia in a given foal is caused by *R. equi*. However, detection of pulmonary abscesses, while commonly used as a screening test (see later), is not a definitive diagnostic test.

SEROLOGY. The current state of knowledge precludes the use of serologic tests to determine a diagnosis for *R. equi* pneumonia. Independent studies evaluating the performance of serologic tests available for diagnosis of infection caused by *R. equi* at endemic farms have demonstrated these tests have either low sensitivity, low specificity, or both.[152-155] Improving either sensitivity or specificity of enzyme-linked immunosorbent assays (ELISAs) by changing the cutoff value corresponding to a positive or negative test result could only be done to the detriment of the other. The presence of antibodies indicates exposure, subclinical infection, or maternal transfer of antibodies, but it does not necessarily indicate infection leading to clinical disease.

CYTOLOGY, CULTURE, AND POLYMERASE CHAIN REACTION AMPLIFICATION. Bacteriologic culture or PCR amplification of *vapA* from a TBA are therefore the only acceptable ways of establishing a diagnosis of *R. equi* pneumonia. In one study, only 7 (64%) of the 11 foals with positive *R. equi* culture at necropsy and 57 (64%) of the 89 foals with radiographic evidence of lung abscessation yielded *R. equi* from culture of a TBA.[156] However, in two other studies, all 17 foals in which *R. equi* was isolated from lung parenchyma at necropsy yielded the organism from culture of TBAs obtained antemortem; this suggests that culture of a TBA is a valid method for diagnosing *R. equi* pneumonia.[157,158] Larger case series are required to more accurately estimate the sensitivity of TBA culture for diagnosis of *R. equi* pneumonia in foals. Specificity of the test must also be considered. Foals without clinical disease may have *R. equi* in their trachea as a result of subclinical disease or, incidentally, from inhaling *R. equi* in contaminated environments. At a farm with endemic *R. equi* pneumonia, 77 of 216 (35%) foals sampled had positive TBA cultures but remained free of clinical signs of respiratory disease throughout the season.[159] For this reason, culture or PCR amplification of *R. equi* from a TBA should always be interpreted in the context of cytologic and clinical findings. Detection of *R. equi* from a foal without clinical signs of respiratory disease, cytologic evidence of septic airway inflammation, or ultrasonographic or radiographic evidence of pulmonary lesions is likely an incidental finding, due to the ubiquitous nature of the organism on horse farms. Amplification of *vapA* by PCR has been shown to be more sensitive than bacterial culture in most but not all studies.[160-162] However, increased sensitivity may also result in a higher incidence of false-positive results due to the detection of very small numbers of *R. equi* present as environmental contaminants. Moreover, culture offers the advantage of detecting other bacterial pathogens present and permits in vitro susceptibility testing of recovered pathogens. As a result, PCR amplification of *vapA* may be done in conjunction with, but should not replace, bacterial culture. The use of PCR assays based on genes other than *vapA* is not recommended, as these assays would also detect environmental isolates lacking the virulence plasmid, which are not known to cause disease in foals.

Isolation or detection of *R. equi* from nasal or fecal swabs cannot be taken as evidence of disease due to infection with *R. equi*. *R. equi* can be cultured from the feces of healthy horses even if they live at farms without history of *R. equi* pneumonia.[74,76,163] Quantitative culture of the feces of foals at weekly intervals has been advocated to aid in early diagnosis of *R. equi* infections because the fecal concentration of *R. equi* increased at the same time as clinical signs of respiratory disease appeared in a few foals.[76] However, a single fecal sample from a foal has no diagnostic value because of individual and farm-to-farm variation in the number of *R. equi* in feces.[74,76,163] Furthermore, a negative fecal culture may not be helpful in excluding *R. equi* infection because only 5 (17%) of 30 foals with confirmed *R. equi* pneumonia had positive fecal cultures.[159] Similarly, bacterial culture and PCR amplification of nasal swabs are insensitive for diagnosis of *R. equi* pneumonia.[160,161,164]

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Treatment A wide variety of antimicrobial agents are active against *R. equi* in vitro. However, many of these drugs are reported to be ineffective in vivo, likely because of poor cellular uptake and resulting low intracellular concentrations. For example, in a retrospective study, all 17 foals with *R. equi* pneumonia treated with the combination of penicillin and gentamicin died despite the fact that all isolates were sensitive to gentamicin.[12] The combination of rifampin and erythromycin became the treatment of choice in the 1980s and has apparently reduced foal mortality relative to historical data.[12,156] However, there are no controlled studies directly comparing the efficacy of erythromycin and rifampin to that of other antimicrobial agents. In recent years, clarithromycin or azithromycin, two newer generation macrolides, often replace erythromycin in the combination with rifampin.[165] Macrolides and rifampin are highly active against *R. equi* in vitro but only exert bacteriostatic activity.[166,167] As a result, macrolides and rifampin exert time-dependent activity against *R. equi* in vitro.[167] Of the three macrolides listed previously, clarithromycin is the most active against *R. equi* in vitro and against intracellular *R. equi* in cell culture.[167,168] The minimum inhibitory concentration at which 90% of *R. equi* isolates are inhibited (MIC_{90}) is 0.12, 0.25, and 1.0 μg/mL, for clarithromycin, erythromycin, and azithromycin, respectively.[169] The combination of a macrolide and rifampin is synergistic both in vitro and in vivo, and the use of the two classes of drugs in combination reduces the likelihood of *R. equi* resistance to either drug.[166,167,170] Rifampin and macrolides are lipid soluble, allowing them to penetrate cell membranes and caseous material.

The recommended dosages are listed in Table 31-4. Several formulations of erythromycin are commercially available. Although they all show slight differences in bioavailability and elimination, they all result in therapeutic concentrations at recommended dosages. However, the bioavailability of erythromycin in foals is considerably lower when foals are not fasted (mean ± SD: 26 ± 15% when fasted and 8 ± 7% when fed).[171] Advantages of azithromycin and clarithromycin over erythromycin in foals include enhanced oral bioavailabilities (especially in the absence of fasting), prolonged half-lives, and much higher concentrations in BAL cells and pulmonary epithelial lining fluid (PELF).[172-174] These properties of the newer generation macrolides contribute to their lower dosages and longer dosing intervals.

In general, plasma concentrations of macrolides in people and cattle are considerably lower than the MIC of the pathogens against which these drugs have been proven to be effective. Thus, plasma concentrations of macrolides are considered poor predictors of in vivo efficacy against respiratory pathogens, whereas concentrations at the site of infection provide more clinically relevant information.[175] Measurement of drug concentration in PELF and cells collected by bronchoalveolar lavage is a widely used method to estimate antimicrobial concentrations at the site of infection for antimicrobials intended to treat lower respiratory tract infections in people.[175,176] After equivalent doses, concentrations of clarithromycin in PELF and BAL cells of foals are considerably higher than concentrations reported after administration of azithromycin or erythromycin to foals.[173,174,177] However, clarithromycin concentrations at these sites decrease rapidly, whereas the release of azithromycin from cells is much slower, resulting in sustained concentrations of azithromycin in tissues for days following discontinuation of therapy.[172-174,177] There are no data from randomized prospective studies comparing the relative efficacy of erythromycin, clarithromycin, and azithromycin in pneumonic foals. In a retrospective study, the combination clarithromycin-rifampin was significantly more effective than erythromycin-rifampin or azithromycin-rifampin, especially in foals with severe radiographic lesions.[165] However, these results must be interpreted with caution because foals were not randomly distributed to treatment groups and because of biases inherent to retrospective data. Nevertheless, these data are the best available evidence to guide macrolide selection in foals with *R. equi* pneumonia. Recent studies demonstrate that concurrent therapy with rifampin considerably decreases plasma, PELF, and BAL cell concentrations of clarithromycin and potentially other macrolides.[178,179] However, there are no studies in foals comparing the clinical efficacy of the combination of a macrolide with rifampin to a macrolide alone. Until it is documented that a macrolide alone is as effective as the combination with rifampin, the combination of a macrolide (erythromycin, azithromycin, or clarithromycin) with rifampin remains the recommended treatment.[146]

Various bacteria and fungi are often isolated from TBA along with *R. equi*. The most common concurrent bacterial isolates are β-hemolytic streptococci and *Escherichia coli*.[180] However, isolation of multiple types of bacteria or fungi from a TBA does not negatively impact survival, and mixed infections are significantly more likely to be encountered in TBA than in lung tissue, suggesting that many bacteria isolated from a TBA colonize the trachea without necessarily contributing to pulmonary pathology.[180] It is common practice to add a third antimicrobial agent if heavy growth of a gram-negative pathogen resistant to macrolides and rifampin is isolated along with *R. equi*. However, recent data indicate that this practice may not be beneficial.[180] The combination of an aminoglycoside (gentamicin or amikacin) with macrolides or rifampin in vitro is antagonistic against *R. equi* compared with either drug alone.[166,167,170] However, the clinical significance of this in vitro finding has not been established.

Resolution of clinical signs, normalization of plasma fibrinogen concentrations, and radiographic or ultrasonographic resolution of lung lesions are commonly used to guide the duration of therapy, which generally ranges between 3 and 12 weeks, depending on the severity of the initial lesions and response to therapy. Foals treated based on subclinical lesions identified during ultrasonographic screening typically do not require as long a treatment period as foals

TABLE 31-4

Recommended Dosages, Oral Bioavailability, and Serum Half-Lives of Antimicrobial Agents Commonly Used for the Treatment of *R. equi* Infections in Foals

Class	Drug	Dose (mg/kg)	Route	Frequency (h)	Oral Bioavailability (%)	Serum $t_{1/2}$ (h)	References
Macrolides	Erythromycin*	25	PO	6-8	8[†]-25[‡]	1	171, 227
		5	IV	6	NA	1	226
	Clarithromycin	7.5	PO	12	57[†]	5.4	225
	Azithromycin	10	PO	24-48[§]	56[†]	18	172, 173
		5	IV	24-48[§]	NA	16	172, 173
Rifamycins	Rifampin	5	PO	12	49[‡]	15	228, 229, 230

*Erythromycin base, stearate, phosphate, estolate, or ethylsuccinate.

[†]Mean (± SD) bioavailability with ad libitum access to milk and hay.

[‡]Mean (± SD) oral bioavailability after fasting.

[§]Administration q24h for 5 days and q48h thereafter.

IV, Intravenous; *NA,* not applicable; *PO,* by mouth.

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in respiratory distress with severe pulmonary lesions. In fact, as addressed later, many foals with subclinical ultrasonographic lesions clear the infection without therapy.[6,181] Currently, there are no validated criteria to differentiate foals with subclinical ultrasonographic lesions that will clear the infection from those that will progress to clinical disease.

Although well tolerated by most foals, macrolides commonly cause diarrhea. The diarrhea is often self-limiting and does not necessitate cessation of therapy. However, affected foals should be monitored carefully because some may develop severe diarrhea, leading to dehydration and electrolyte losses that necessitate intensive fluid therapy and cessation of oral macrolides. The incidence of diarrhea in foals treated with erythromycin-rifampin has ranged between 17% and 36%.[165,182] In one study, foals treated with clarithromycin had a higher incidence of diarrhea (28%) than those treated with azithromycin (8%) although in most cases, diarrhea was mild and self-limiting.[165] In the same study, the incidence of severe diarrhea necessitating administration of IV fluids was not significantly different between groups of foals treated with azithromycin-rifampin, clarithromycin-rifampin, or erythromycin-rifampin.[165] During periods of very hot or humid weather, an idiosyncratic reaction characterized by severe hyperthermia and tachypnea has been described in foals treated with erythromycin.[182] Anecdotal reports suggest that these reactions may occasionally occur with newer macrolides as well. Administration of antipyretic drugs and placing the foal in a cool environment will treat this problem. Severe enterocolitis also has been reported in mares whose foals are treated with erythromycin, presumably by disrupting the mare's normal colonic microflora following ingestion of small amounts of active drug during coprophagia or by contamination of feeders or water buckets with drug present on the foal's muzzle. This complication seems to be rare. Enterocolitis in mares has been reproduced experimentally by administration of subtherapeutic doses of erythromycin.[183] In some cases, the severe enterocolitis in the mares of treated foals is associated with *Clostridium difficile*.[184]

Availability of a long-acting macrolide antimicrobial agent providing sustained therapeutic concentrations at the site of infection would result in less frequent administration, which in turn might improve compliance. Tulathromycin, a semi-synthetic macrolide approved for use in swine and cattle, has been shown to concentrate in the BAL cells of foals after intramuscular administration.[185] Tulathromycin was recently compared with azithromycin-rifampin for the treatment of foals with subclinical pneumonia as identified by ultrasonographic screening on a farm with a high cumulative incidence of *R. equi* infections. Although differences in survival were not statistically significant, pulmonary abscesses 1 week after initiation of treatment with tulathromycin were significantly larger and duration of therapy was significantly longer, indicating that tulathromycin is not as effective as standard therapy with azithromycin-rifampin.[5] These results might be explained by the fact that tulathromycin is poorly active against *R. equi* in vitro with a MIC_{90} higher than 64 μg/mL.[186] This concentration is more than 100-fold higher than achievable tulathromycin concentrations in BAL cells after intramuscular administration at the recommended dose of 2.5 mg/kg.[185] Tilmicosin, another long-acting macrolide approved for use in swine and cattle, is also poorly active against *R. equi* (MIC_{90} of 32 μg/mL) and administration to foals sometimes results in swelling at the site of injection.[174] Similarly, tildipirosin is also poorly active against *R. equi* in vitro with a MIC_{90} of 32 μg/mL. As a result, tulathromycin, tilmicosin, and tildipirosin are not recommended for use in foals with pneumonia caused by *R. equi*. In contrast, gamithromycin, another long-acting macrolide approved for the treatment and prevention of respiratory disease in nonlactating cattle is active against *R. equi* in vitro (MIC_{90} = 1.0 μg/mL).[168] A single intramuscular administration of gamithromycin at a dosage of 6 mg/kg maintains BAL cell concentrations above the MIC_{90} for *R. equi* for approximately 7 days.[168] However, treatment with gamithromycin is not recommended until the clinical efficacy and the safety of the drug have been established.

TREATMENT OF FOALS INFECTED WITH MACROLIDE- AND RIFAMPIN-RESISTANT ISOLATES OR TREATMENT OF FOALS WITH ADVERSE REACTIONS TO THE COMBINATION MACROLIDE-RIFAMPIN. Although the vast majority of *R. equi* isolates from foals are highly susceptible to macrolides and rifampin, strains resistant to either drug class have been encountered. Rifampin should not be used alone because this increases the chance of resistance developing,[166,187] as a result of mutations in the RNA polymerase β subunit encoded by the *rpoB* gene.[188,189] Apparent progressive development of resistance to both erythromycin and rifampin during treatment is extremely rare but has been reported.[13] In a recent study, the overall prevalence of resistant isolates in Texas and Florida over a 10-year period was 4%.[190] In the same study, the odds of death were 7 times higher in foals infected with resistant isolates.[190] In addition, the study demonstrated that isolates of *R. equi* susceptible to macrolides were sometimes misclassified as resistant; therefore it is reasonable to request retesting and/or validation of resistance by the testing laboratory. The molecular mechanisms of macrolide resistance of *R. equi* isolates have not been determined, but *R. equi* isolates resistant to erythromycin, clarithromycin, or azithromycin are almost invariably resistant to the other macrolides.

Therapy of foals that develop severe diarrhea during macrolide therapy or therapy of foals infected with resistant isolates is problematic because of the limited range of effective alternatives. Macrolide- and rifampin-resistant isolates of *R. equi* are susceptible in vitro to fluoroquinolones, aminoglycosides, oxazolidinones, and glycopeptide antimicrobials.[186,190] In one study, 18 of 24 isolates were also susceptible to chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole.[190] Currently, there are no data to indicate the preferred antimicrobial agent(s) for the treatment of foals infected with isolates resistant to macrolides and rifampin.

Although objective data regarding efficacy are lacking, several other classes of antimicrobial agents have been used to treat *R. equi* in foals. Oral doxycycline in combination with rifampin has been used with anecdotal success to treat foals with pneumonia caused by *R. equi*. Doxycycline and rifampin are highly synergistic against *R. equi* in vitro.[167] The recommended dosage for doxycycline in foals is 10 mg/kg PO q12h.[191] This dosage results in serum, PELF, and BAL cell concentrations above the MIC_{90} of *R. equi* isolates (1.0 μg/mL) for the entire dosing interval. Chloramphenicol can be administered orally and achieves high concentrations within phagocytic cells in other species. The recommended dosage regimen is 50 mg/kg PO q6h. However, the fact that only 70% of *R. equi* isolates are susceptible to this drug and the potential human health risk make this drug a less attractive alternative. High doses of a trimethoprim-sulfonamide combination (30 mg/kg of combination q8h or q12h, orally) have been used alone or in combination with rifampin in foals with mild or early *R. equi* pneumonia and for continued therapy in foals responding well to other antimicrobials.[12] Currently, there are insufficient data to recommend the use of these antimicrobial agents for treating infections caused by *R. equi*.

In an experimental model of *R. equi* infection in immunosuppressed mice, the most effective drugs in monotherapy were found to be, in order of effectiveness, vancomycin, imipenem, and rifampin.[192] Amikacin, erythromycin, ciprofloxacin, or minocycline in monotherapy did not lead to a significant decrease in bacterial counts. The most active drugs in combination were those including vancomycin or rifampin, but efficacy of these combinations was not significantly different from that of vancomycin monotherapy.[192] Vancomycin and imipenem in foals should be used only for the treatment of life-threatening *R. equi* infections caused by isolates confirmed to be resistant to all other possible alternatives.

ANCILLARY THERAPIES. Nursing care, provision of adequate nutrition and hydration, and maintaining the foal in a cool and well-ventilated environment are important. Humidified oxygen delivered by pharyngeal insufflation in moderately hypoxemic foals, or by percutaneous transtracheal oxygenation in severely hypoxemic patients, is indicated.[193] Judicious use of nonsteroidal antiinflammatory drugs

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might reduce fever and improve attitude and appetite in febrile, lethargic, anorectic foals. Nebulization with saline, antimicrobial agents, or bronchodilators has been advocated, but there are no data to either support or refute these therapeutic practices. Immune-mediated extrapulmonary disorders, such as polysynovitis, generally resolve with successful treatment of the accompanying pneumonia. Exercise should be limited but not eliminated in foals with polysynovitis. In addition to appropriate systemic antimicrobial therapy, foals with *R. equi* septic arthritis or osteomyelitis often require aggressive local therapy such as joint lavage, surgical débridement, and IV or intraosseous regional limb perfusion with antimicrobial agents. The prognosis for foals with abdominal abscesses is poor, although rare cases will respond to long-term antimicrobial therapy.[8,194] Surgical removal or marsupialization has been attempted in some foals, but abdominal adhesions usually result in inability to resect the abscess.

Prognosis Prior to the introduction of the combination of erythromycin and rifampin as the treatment of choice in the early 1980s, the prognosis of *R. equi*–infected foals was poor, with survival rates as low as 20%.[195] Using erythromycin and rifampin, Hillidge reported a successful outcome (as assessed by survival) in 50 (88%) of 57 foals with confirmed *R. equi* pneumonia.[156] Studies from referral centers, where severely affected cases are likely more prevalent, have revealed survival proportions ranging between 59% and 72%.[148,165,196] In contrast, the survival rate at farms that use a screening program to identify and treat foals with subclinical lesions has resulted in survival proportions of nearly 100%.[4,197] However, recent evidence indicates that many of these foals would have recovered without therapy. Controlled studies have shown that approximately 88% of foals with ultrasonographic lesion scores (sum of the diameter of each abscess) up to 10 cm recover without antimicrobial therapy.[6,181] In the same studies, treatment of affected foals with antimicrobial agents did not provide a clear benefit over administration of a placebo.[6,181]

The impact of *R. equi* infections on future athletic performance has been examined. No significant differences in total earnings, average earning index, or age at first race were observed when comparing 30 horses that previously had *R. equi* pneumonia with either their dams' other progeny or the North American averages.[198] In another study, 54% of 83 foals that survived *R. equi* pneumonia had at least one racing start as compared with 65% of their birth cohort, suggesting that horses contracting *R. equi* pneumonia as foals may be somewhat less likely to race as adults. However, consistent with a previous report,[198] the racing performance of those foals was not different from that of the U.S. racing population.[148] In summary, prognosis for performance after successful treatment of uncomplicated *R. equi* pneumonia should be regarded as very good.

Control and Prevention of *R. equi* Infections on Farms Where the Disease Is Endemic

Methods for control and prevention include using screening tests for early detection of *R. equi* pneumonia, environmental management, chemoprophylaxis, and prevention through use of either passive or active immunization. Currently, there is inadequate evidence to recommend environmental interventions to control or prevent *R. equi* pneumonia.[199] Further evaluation of certain practices, such as foaling at pasture and reducing either airborne concentrations of virulent *R. equi* or density of mares and foals, is merited.

SCREENING FOR EARLIER DETECTION OF AFFECTED FOALS. *R. equi* pneumonia is often not recognized until it is well advanced, and thus it is difficult to treat. Even severely affected foals may appear, to a casual observer, to suckle and behave normally. The rationale for screening is the assumption that detecting foals in the early stages of disease and implementing appropriate treatment of affected foals will improve outcomes. It is important to emphasize that screening methods are not diagnostic tests. A useful screening test is one in which the probability of disease is high with a positive test result (high positive predictive value) and very low with a negative test result (high negative predictive value). The higher the prevalence of disease is at a given farm, the higher the positive predictive value of a given test will be. Therefore, depending on the prevalence of *R. equi* infections at a given farm, a positive result of a screening test could be a basis from which to perform a diagnostic test (low to moderate prevalence) or to initiate therapy (high prevalence). Uncontrolled studies suggest that screening may reduce the mortality attributable to *R. equi* pneumonia.[4,200] Thus, in the absence of a vaccine or other effective methods for preventing this devastating disease, screening is a reasonable approach to control *R. equi* at endemic farms. Implementing screening testing at farms that are only sporadically affected by *R. equi* pneumonia may not be warranted.

A variety of screening techniques performed serially have been described, including visual inspection of foals for clinical signs of pneumonia, rectal temperature monitoring, hematologic parameters, serologic tests, and thoracic imaging using either radiography or ultrasonography, with an empirical recommendation that screening begin around 3 weeks of age.[201] Systematic comparisons of these tests have not been performed. Thus, a specific recommendation for any particular screening test cannot be made, and it is likely that the optimal approach for screening may vary among farms on the basis of cumulative incidence of disease, resources available for control and prevention, and preferences of the attending veterinarian(s) and farm management.

Studies have shown that serum concentrations of either antibodies against *R. equi,* serum amyloid A, or plasma fibrinogen are not useful screening tests.[153,155,202] WBC concentrations performed at monthly intervals had clinically acceptable sensitivity and specificity for early detection of *R. equi* pneumonia at one farm (sensitivity of 79% and specificity of 91% at a cutoff value of 15,000 cells/μL).[152] However, serial measurement of WBC or neutrophil concentrations resulted in limited performance for prediction of subsequent development of clinically apparent *R. equi* pneumonia at another farm.[203] In addition to conflicting data regarding the benefit of this approach, additional limitations of using WBC concentration for screening are the time and effort required to collect blood samples from foals, the lag from time of submission to availability of results, and the potential for false-positive results attributable to stress-associated leukocytosis or other infectious or inflammatory conditions that may be common among foals.

Over the past decade, control of *R. equi* infections at many farms where the disease is endemic has relied on early detection of subclinical pulmonary disease using thoracic ultrasonography and initiation of treatment with antimicrobial agents prior to development of clinical signs.[4,5,204] Ultrasonography of the chest offers several advantages over other screening tests: (1) results are specific for the presence of pulmonary pathology; (2) the procedure can be performed relatively quickly for an individual foal; (3) results are available immediately; and (4) the procedure may be more sensitive than radiography for detecting lesions in their early stages of development or in certain regions where soft-tissue structures are superimposed over regions of the lung.[151] Although controlled studies are lacking, periodic ultrasonography of the chest appears to result in decreased mortality due to *R. equi* pneumonia at some farms.[4,5,204]

The cumulative incidence of clinical signs of pneumonia attributed to *R. equi* on endemic farms that do not use ultrasonographic screening typically ranges between 5% and 20%,[68] whereas the cumulative incidence of foals with ultrasonographic evidence of pulmonary abscessation on *R. equi*–endemic farms is generally between 30% and 70%,[4,197,204] suggesting that many subclinically affected foals recover without therapy. Indeed, recent double-blinded randomized placebo-controlled studies documented that approximately 88% of foals with small pulmonary lesions (sum of lesion diameters [or abscess score] of 1 to 10 cm) recover without antimicrobial therapy.[6,181] In addition, antimicrobial treatment of foals with small lesions detected by ultrasonographic examination did not significantly hasten lesion resolution compared with administration of a placebo.[6,181] The use of ultrasonography for screening to detect *R. equi*

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pneumonia was recently evaluated at an endemic farm, with personnel and veterinarians blinded to screening results.[7] Of 270 foals enrolled in the study, 216 (80%) developed sonographically visible pulmonary lesions, whereas only 17% of foals developed clinically apparent *R. equi* pneumonia.[7] Resolution without clinically apparent illness or antimicrobial therapy occurred in 79% of foals with ultrasonographic pulmonary lesions.[7] In the aforementioned study, the cumulative sensitivity of ultrasonography was very good (89%) but cumulative specificity was low (62%).[7]

Because it is impossible to know which specific foal might recover spontaneously from subclinical disease, and because *R. equi* infections can cause severe disease, many breeding farms elect to treat all foals with ultrasonographic lesions. This approach has resulted in an increased number of foals treated for presumptive *R. equi* pneumonia in the absence of clinical disease. The temporal association between this widespread use of macrolides and rifampin as a result of ultrasonographic screening and a perceived increase in the frequency of detection of resistant isolates in the past decade[190] suggest that this practice may not be innocuous. Emergence of macrolide and rifampin resistance at a farm after widespread use of these drugs was instituted as part of an ultrasonographic screening program has been documented.[90] On that particular farm, 20% to 40% of *R. equi* isolates from pneumonic foals were resistant to macrolides and rifampin.[90] Currently, it is unknown if macrolide and rifampin resistance is widespread on many horse farms relying on mass antimicrobial therapy of foals with ultrasonographic lesions or if it is an isolated problem. In addition to the cost and risk for selection for resistant bacteria, unnecessary mass antimicrobial therapy of foals with pulmonary lesions might lead to development of life-threatening adverse reactions (e.g., diarrhea or hyperthermia) in some foals.

The spontaneous resolution of ultrasonographic lesions in a large proportion of foals,[6,7,181] combined with the apparent increase in macrolide and rifampin resistance at some farms,[90] support the need to stop the practice of mass macrolide treatment of all subclinically affected foals with ultrasonographic lesions. The goal should be to more accurately identify, of the many subclinically infected foals, which few are likely to go on to develop disease and hence require treatment. The degree of severity and the number of ultrasonographic lesions in a given foal that warrant therapy are unknown and may vary by farm, geographic region, and age at which lesions are detected. Additional studies are needed to establish better criteria to determine the need for therapy in subclinically affected foals and to better quantify the risks versus benefits of treating foals with subclinical ultrasonographic lesions.

PASSIVE IMMUNIZATION. Intravenous administration of HIP obtained from horses vaccinated against *R. equi* using various antigens has generally proved effective in significantly reducing the severity of *R. equi* pneumonia in foals following experimental challenge.[63,109,205] However, studies evaluating the efficacy of various HIP preparations under field conditions have given equivocal results. Although the data are conflicting and not all trials have shown a statistically significant reduction in the cumulative incidence of *R. equi* pneumonia, five of seven studies have demonstrated reduction of relative risk, suggesting some benefit of HIP.[3,65,158,206-209]

Intravenous administration of purified immunoglobulins obtained from horses immunized with recombinant VapA and VapC to foals reduced the severity of pneumonia following high-dose experimental challenge with *R. equi* to a degree similar to that provided by commercially available HIP.[111] This demonstrates that immunoglobulins, predominantly against VapA and VapC, are responsible for the protection conferred by HIP. Therefore administration of plasma obtained from horses that are not hyperimmunized against *R. equi* is not recommended for protection against *R. equi*. Because endemicity of *R. equi* at farms does not appear to be explained by farm-specific isolates and because foals may be infected with multiple strains at once,[88] there is no need to administer plasma that is produced from immunizing horses with isolates of *R. equi* obtained from a given farm; transfusion of plasma from horses that have been immunized against any virulent (i.e., VapA-positive) strain of *R. equi* should suffice.[199] Use of HIP licensed as an aid in the control of *R. equi* pneumonia is recommended (rather than plasma simply obtained from horses hyperimmunized against *R. equi*) because licensure ensures standards of potency, purity, and safety. Currently, there is insufficient information to recommend one brand of licensed antibody product over another.

The optimal amount of plasma to be transfused and the optimal age at which transfusion should occur remain to be determined. Administration of HIP 9 days after aerosol infection of foals with *R. equi* did not confer protection,[210] suggesting that administration of HIP prior to infection is important. Because of evidence that many foals become infected early in life,[64] it is commonly recommended that foals receive transfusion of at least 1 L of HIP no later than the second day of life. Because early administration may result in the decline of passively transferred antibody to a nonprotective level at a time when foals are still susceptible to *R. equi* and when environmental challenge is high, it is common practice to administer a second liter of HIP at 2 to 4 weeks of age.

Transfusion of HIP is not completely effective and therefore does not eliminate the need for careful monitoring of foals at risk. In addition to being incompletely effective, transfusion of HIP carries some risk to foals, such as trauma that may occur during handling and adverse reactions to transfusions. The process is also time intensive, labor intensive, and expensive. Thus the cost-effectiveness of transfusion depends on the value of the foals and the prevalence of disease at a given farm.

ACTIVE IMMUNIZATION. It would be convenient to control *R. equi* pneumonia on endemic farms by active immunization of mares or foals with a protective antigen. To date, however, this approach has been largely unrewarding. The role of antibody in partial protection against *R. equi* infection would suggest that vaccination of mares could confer at least some degree of protection. However, in both a field study and an experimental challenge, vaccination of mares did not provide protection against *R. equi* pneumonia despite a significant increase in colostral *R. equi*–specific antibody and transfer of these antibodies to foals.[208,211] More recently, vaccination of a small number of mares with VapA associated with a water-based nanoparticle adjuvant led to high anti-VapA IgG concentrations in mares and foals and might have conferred protection against natural challenge compared with nonvaccinated controls.[212] Large-scale studies at endemic farms will be necessary to confirm these preliminary findings before widespread vaccination of mares can be recommended.

Because cell-mediated immunity is of paramount importance for protection against *R. equi,* active immunization of foals likely will be required for complete protection. Oral immunization with *Salmonella enterica* Typhimurium expressing the VapA antigen protects mice against *R. equi* infection.[213] Preliminary studies indicate that the aforementioned vaccine also confers protection in foals.[214] Recent studies in mice indicate that DNA immunization with *vapA* protects against *R. equi* infection and that the IgG subisotype response is consistent with a Th1-based immune response.[215] A similar DNA vaccine containing the *vapA* gene has been shown to induce strong cell-mediated immune responses in adult horses, but responses were poor in foals.[216] Intrabronchial immunization of neonatal foals with a live, fully attenuated, riboflavin auxotrophic strain of *R. equi* stimulated immune responses but did not confer protection against subsequent intrabronchial challenge with live *R. equi*.[217] The fact that live, avirulent plasmid-cured *R. equi* does not elicit adaptive immunity and is cleared rapidly indicates that bacterial replication is needed for induction of strong cell-mediated immune responses.[218] Intrabronchial immunization with a deletion mutant of *R. equi* lacking the chromosomal genes isocitrate lyase *(icl)* and cholesterol oxidase *(choE)* conferred protection against subsequent challenge in three foals.[219] However, two foals developed pneumonia caused by the mutant strain.[219] More recently, oral vaccination of foals with a live attenuated *R. equi* strain lacking genes involved in the steroid

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catabolic pathway elicited substantial protection against subsequent intrabronchial challenge with live virulent *R. equi*.[53] Collectively, the aforementioned studies indicate that there is a fine line between sufficient replication of *R. equi* for induction of strong cell-mediated immune responses and development of disease from the vaccine strain. Additional challenges are that immunization in foals will need to be initiated very early in life, and an effective vaccine will have to overcome the relative immaturity of the naive neonatal immune system. Currently, there is inadequate evidence to recommend active immunization of mares or foals to control or prevent *R. equi* pneumonia, but there are promising vaccine candidates under development.

CHEMOPROPHYLAXIS. Because an effective vaccine is lacking, prophylactic administration of antimicrobial agents to all the foals during the time period when they are most susceptible to infection has been suggested as another approach for the prevention of *R. equi* infections on endemic farms. Azithromycin is an attractive choice for chemoprophylaxis because of good oral bioavailability, long half-life, and high and sustained concentrations in PELF, BAL cells, and neutrophils. Two studies have evaluated the use of azithromycin for chemoprophylaxis. In a randomized, controlled trial conducted in the United States among 338 foals at 10 farms, the cumulative incidence of *R. equi* pneumonia was reduced from 21% among untreated foals to 5% among foals that received azithromycin (10 mg/kg PO q48h for the first 14 days of life beginning on the first day of life).[220] By contrast, in a study conducted among 70 foals at a large breeding farm in Germany, the incidence of abscessing pneumonia was not significantly different between foals that received azithromycin (10 mg/kg PO q24h for the first 28 days of life) for prevention of abscessing pneumonia (cumulative incidence = 60%) and foals that did not receive azithromycin for chemoprophylaxis (cumulative incidence = 69%); however, the age at onset of abscessing pneumonia was delayed in treated foals.[197] The reason for the discrepancy between studies is unknown. Regardless, use of azithromycin is not considered an acceptable approach for chemoprophylaxis because widespread use of this drug would create greater pressure for emergence of macrolide resistance among bacteria.[146]

Gallium maltolate is a metal-based compound with antimicrobial properties that has been demonstrated to reduce replication of *R. equi* in pure culture[221] and within macrophages,[222] to reduce tissue concentrations of *R. equi* in mice following experimental infection,[221] and to be bioavailable[223] and safe in foals.[224] Unfortunately, chemoprophylaxis with gallium maltolate (30 mg/kg PO q24h for the first 14 days of life) failed to reduce the incidence of *R. equi* pneumonia in a placebo-controlled trial of 438 foals at 12 farms in the United States.[3]

Pneumonia in Foals

Daniela Bedenice

Equine pneumonia is a significant cause of morbidity and mortality in both the newborn and the older foal.[1-4] Although the causative agents and the mode of lung infection are generally different for each age group, foal pneumonia is commonly associated with a compromise in the immunologic protection of the host. The exact immunologic basis of the foal's inherent susceptibility to opportunistic respiratory pathogens needs to be further elucidated.

Failure of passive transfer of immunity (FPT) is a well-known risk factor of neonatal infection, including respiratory disease,[4] because not only are affected foals deprived of specific maternal antibody protection but their neutrophil function is also seriously impaired.[5] Although foals can respond immunologically in utero to bacterial or viral infections, their ability to do so is less than that of adults. Reduced complement values and defective chemotaxis (directed migration of neutrophils or macrophages) and killing capacity of the neonatal neutrophils contribute to a relatively decreased defense against invading bacteria. Furthermore, an immature ciliary apparatus and the presence of fewer alveolar macrophages in neonates, in comparison with adult horses, lead to decreased bacterial clearance from the lungs.[6] The number and distribution of the bronchoalveolar cells approach adult levels at approximately 3 to 6 weeks of age.[7]

It has been suggested that a natural cellular immunodeficiency may also occur in foals at 2 to 4 months of age.[8] Although the exact association between age-related cellular immunodeficiency and the defense against intracellular pathogens such as *Pneumocystis carinii* (renamed *P. jiroveci* in humans) and *R. equi* of foals still needs to be clarified, $CD4^+$ and $CD8^+$ T lymphocytopenia was documented in a filly with *P. carinii* pneumonia.[9]

Etiology

NEONATAL PNEUMONIA (<1 MONTH OF AGE). In contrast to the older foal, infectious lung disease in the neonate is usually part of a multiple-organ, systemic infection or sepsis, which may be acquired via the placenta in utero or perinatally through environmental bacteria leading to hematogenous (ascending) infection (e.g., omphalophlebitis). *E. coli, Klebsiella* spp., *Actinobacillus equuli, Salmonella* spp., and *Streptococcus* spp. are some of the more common bacteria involved in neonatal foal pneumonia.[10]

Descending lung infections may be caused by inhalation of viral, bacterial, or opportunistic fungal agents. Furthermore, iatrogenic aspiration (oil, medication, oral supplements) or aspiration of gastric reflux, milk, meconium, and contaminated amniotic fluid after placental infection may seed the foal's lung. Meconium aspiration occurs in utero in foals that experience fetal distress (perinatal asphyxia). Although meconium is commonly sterile at this time, it creates mechanical airway obstruction, surfactant inactivation, and pulmonary inflammation (caused by vasoactive mediators and chemotactic and inflammatory cytokines, including TNF-α, interleukin [IL]-1β, and IL-8).[11] The resulting edema and vasoconstriction may lead to hypoperfusion of the pulmonary parenchyma, with damage to type II pneumocytes and decreased production of surfactant.[12] This type of "secondary surfactant deficiency" may also be induced by other forms of generalized pulmonary inflammation, including diffuse bacterial and viral pneumonia. Neurologic dysfunction, severe inflammation, or structural abnormalities of the upper airways (congenital cysts, dorsal displacement of the soft palate, laryngeal paralysis, pharyngeal weakness, etc.) may predispose to aspiration pneumonia postpartum. The prognosis of foals with dysphagia due to pharyngeal dysfunction is considered favorable for life and fair for athleticism, based on a recent study by Holcombe and colleagues.[13] In the latter study, 8 of 16 (50%) affected foals were premature, diagnosed with neonatal encephalopathy, or both, and 12 of 16 (75%) had aspiration pneumonia.

Equine viral arteritis (EVA) and herpes viral infections (EHV-1 and EHV-4) have been implicated in in utero viral infections leading to lung disease.[14] Although involvement of adenovirus in the pathogenesis of pneumonia has also been reported in a Thoroughbred foal, fatal adenoviral pneumonia is primarily related to severe combined immunodeficiency (SCID) in Arabian foals.[15,16] Additionally, equine influenza virus (EIV) infection has been associated with fatal bronchointerstitial pneumonia in young foals that do not have maternal immunity.[17]

PNEUMONIA IN OLDER FOALS (1 TO 6 MONTHS OF AGE). *S. equi* subsp. *zooepidemicus* and *R. equi* are the most important pathogens associated with pneumonia in older foals, although plurimicrobial infections *(Actinobacillus* spp., *B. bronchiseptica, E. coli, Klebsiella pneumoniae, Pasteurella* spp., *Pseudomonas* spp., *Salmonella* spp., and *Staphylococcus* spp.) are not uncommon.[18,19] *S. equi* subsp. *zooepidemicus* was isolated from 87% of uncomplicated lower respiratory tract infections in foals (1 to 8 months old) on selected farms[20] and was documented as the most common cause of pulmonary abscesses in a second study.[21] In contrast, anaerobes appear to be infrequently involved in primary pneumonia of foals.[20] *Corynebacterium pneumonia* due to aerosol infection is a rare cause of

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diffusely increased interstitial and peribronchial radiographic densities, indicative of pulmonary abscesses in foals.[22] More recently, acute respiratory failure was associated with *Leptospira* spp. infection in five foals (3 weeks to 5 months of age). Pulmonary hemorrhage and interstitial pneumonia with infiltration of red blood cells, hemosiderophages, and inflammatory cells were observed at necropsy, similar to observations in people.[23]

Although respiratory viruses are often believed to be the primary offending agents that lead to secondary bacterial lung invasion, they have limited importance in nursing foals.[20,24] Equine adenoviruses (EAdVs) and EHV-2 are ubiquitous in the general equine population, with little apparent pathogenicity in immunocompetent foals. Although adenoviruses are the most common respiratory pathogens in Arabian foals with SCID, the role of EHV-2 in the respiratory disease complex of foals remains unclear. It has been suggested that EHV-2 exerts its effects on the host indirectly, through predisposition to secondary infections, such as *R. equi* pneumonia. Dunowska and colleagues recently evaluated serial blood samples from 43 foals on a single farm over a period of 10 months, where all but two foals were positive for EHV-2 on at least one occasion. The majority (88%) of foals became infected with EHV-2 within the first 2 months of life.[25]

Because of the complexity of the disease, in-depth discussions of *Rhodococcus* pneumonia and acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are presented elsewhere in this chapter.

INTERSTITIAL PNEUMONIA. Acute, severe interstitial or bronchointerstitial pneumonia is a sporadic, rapidly progressive disease in foals from 1 to 6 months of age that is characterized by a sudden onset of respiratory distress, tachypnea, fever, high mortality, and histopathologic evidence of severe, diffuse, necrotizing bronchiolitis; alveolar septal necrosis; and neutrophilic alveolitis on necropsy.[26-28] Although no definitive causative agent(s) or factor(s) of this disease have yet been identified, suspected causes include viruses, *P. carinii,* heat stroke, environmental toxins, and bacteria.[26-29] Enteric gram-negative organisms, *R. equi, Pseudomonas aeruginosa,* and *P. carinii* have all been cultured from the lungs of affected foals. The acute severe onset suggests that this disease process is a form of ALI and/or ARDS.

The reported cases are usually sporadic, affecting a single foal within a herd,[26] although rare clusters of cases have also been described.[28] The disease is generally rapidly progressive and may lead to sudden death as a result of fulminant respiratory failure. Severe respiratory distress, hypoxemia, hypercapnia, and respiratory acidosis are the most striking clinicopathologic signs. The hypoxemia of bronchointerstitial pneumonia is relatively resistant to supplemental oxygen therapy, indicating a pulmonary shunt. Thoracic radiographs commonly demonstrate caudodorsally distributed interstitial and bronchointerstitial pulmonary opacities. With advanced disease, the radiographic pattern progresses to include patches of a coalescing alveolar nodular pattern with air bronchograms.[30] As with bacterial pneumonia, many foals demonstrate hyperfibrinogenemia and neutrophilic leukocytosis on hematology.

Therapy is symptomatic, including antiinflammatory therapy, broad-spectrum antibiotics, thermoregulatory control, bronchodilation, and supplemental oxygen. In one report of this disease, survival was associated with corticosteroid treatment.[27] Surviving foals may develop a proliferative epithelial and interstitial response, including bronchiolar and alveolar epithelial hyperplasia, type II cell hyperplasia, and hyaline membrane formation.[30]

Chronic pulmonary disease (1 to 3 months' duration) with marked radiographic interstitial opacities was reported in 12 foals, age 3 to 9 months, that were examined at a veterinary teaching hospital.[31] Evaluation failed to yield a consistent pathogen from tracheobronchial aspirates. The authors proposed that chronic interstitial pneumonia occurring in foals is associated with a good prognosis and, similar to a report of acute disease, considered corticosteroid therapy as a potentially useful treatment.[27]

***PNEUMOCYSTIS JIROVECI (CARINII)* INFECTION.** Rare opportunistic fungal pathogens of the lung may include *P. carinii* (renamed *P. jiroveci* in humans), *Aspergillus, Candida,* and *Mucor* spp. *P. carinii* is a unicellular eukaryote that has been classified as a fungus after DNA studies.[32] It is most commonly seen in humans and animals that suffer from a concurrent immunodeficiency. It was first recovered in Arabian foals with SCID.[33] It has since been recovered from foals of other breeds with no specific history of immunodeficiency, although for the most part no direct testing for immunocompetence was performed in the reported cases. However, one more recently documented case demonstrated a low number of circulating $CD4^+$ and $CD8^+$ lymphocytes in a filly with *P. carinii*.[33]

In several reports the onset of clinical signs in affected foals ranged from a 3-week history of weakness, weight loss, and nasal discharge to acute dyspnea. Half of the reported non-Arabian cases had concurrent infections with *R. equi, Enterobacter cloaca, E. coli,* or *S. equi* subsp. *zooepidemicus.* A severe interstitial, sometimes miliary and alveolar pattern was seen on radiographs of the lungs. The majority of the reported foals died, and the diagnosis of *P. carinii* was obtained at necropsy.[29,33-36] On postmortem examination the lungs were uniformly heavy and consolidated, and a diffuse interstitial pneumonia was found. Trophozoites and cysts were observed in the alveolar epithelial cells and macrophages within the alveoli. Silver staining and streptavidin-biotin immunolabeling of histologic sections provide a better visualization of the organisms in the pulmonary tissue.[34] A few foals were diagnosed by visualization of the organism on a BAL sample. Two surviving foals responded to trimethoprim-sulfamethoxazole (TMS) therapy.

Clinical Presentation and Diagnosis of Foal Pneumonia

The clinical manifestation of pneumonia in the newborn foal can be variable and depends on the disease severity and underlying or associated problems. Early in life, localizing clinical signs of respiratory infection may be absent even in the presence of extensive disease. Dyspnea may be seen in severely affected foals and may manifest as an increase in respiratory rate, effort, or thoracoabdominal asynchrony (paradoxical breathing). However, signs of respiratory distress and hypoxemia are frequently vague. Some severely hypoxemic foals may show only restlessness, considerable resistance, and struggling when being handled or restrained. Abnormal respiratory sounds (crackles or wheezes) may be heard on auscultation of ill foals. However, even normal foals may show crackles on the down lung after having remained in lateral recumbency for a prolonged period of time. Furthermore, foals with no auscultable abnormalities may still have extensive pulmonary disease.[37,38] Similar to other species, cyanosis is a sign of severe hypoxemia in foals. The arterial partial pressure of oxygen (PaO_2), however, must reach very low levels (35 to 45 mm Hg) before clinical cyanosis is observed. At a minimum, 5 g/dL of unoxygenated hemoglobin needs to be present in the capillaries to generate the dark-blue color that is appreciated as cyanosis in humans. Therefore severely anemic foals may never appear cyanotic even in the face of profound hypoxemia. Weakness, depression, anorexia, weak or absent suckle reflex, dehydration, and fever may also be noted in newborn foals with respiratory disease. Cough and nasal discharge are usually absent in the early stages of neonatal pulmonary disorders.[10] The older foal, on the other hand, will generally exhibit clinical signs that focus on the respiratory tract, such as abnormal auscultation of the lungs, nasal discharge, cough, fever, tachypnea, and increased respiratory effort.

Thoracic radiographs and arterial blood gas analysis are important in confirming the presence and evaluating the extent and distribution of foal pneumonia. Because radiographic findings may precede or lag behind alteration of respiratory function, repeated diagnostic imaging is recommended. A recent study documented that radiographic abnormalities involving the caudodorsal lung region were most common in neonatal foals admitted to a referral center.[39] The presence of dyspnea, tachypnea, fibrinogen concentration greater than 400 mg/dL, systemic inflammatory response syndrome (SIRS), hypoxemia, or FPT in neonatal foals may be a predictor

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of underlying respiratory disease and should prompt an early radiographic evaluation of the thorax, even in the absence of other localizing clinical signs.[4,39] Thoracic ultrasonography has become a popular diagnostic tool for the assessment of equine lung and pleural disease and is particularly useful in determining the side(s) of the thorax affected, as well as the precise location of the lesion in most cases.[4]

Diagnostic sampling of the respiratory tract is less commonly performed in neonatal foals compared with older foals and adult horses. However, transtracheal aspirate, bronchoalveolar lavage, protected catheter brush (PCB), or protected aspiration catheter sampling (PAC) is important in stabilized patients, irrespective of age, to direct antimicrobial therapy and evaluate therapeutic efficacy. Lung biopsies are rarely performed and are limited to patients with chronic disease or suspected fungal pneumonia.[38]

Treatment The treatment goals in dealing with bacterial pneumonia in either age group are similar and directed at maintaining adequate gas exchange to ensure patient survival, limit progressive pulmonary damage, and ultimately eradicate infection. Long-term goals should aim to maintain optimal pulmonary function and conserve adult athletic performance. Specific treatment strategies for septic pneumonia may include goal-directed antimicrobial therapy, treatment of inflammation independent of antimicrobial therapy, respiratory therapy (oxygen therapy, ventilation, bronchodilation), and cardiovascular support.[37]

Broad-spectrum antimicrobial treatment, with consideration of the drugs' anticipated sensitivity and lung penetration, should be initiated before culture results are available. Third- or fourth-generation cephalosporins (ceftiofur and cefepime, respectively) show good penetration into lung tissues.[40] Ceftiofur administered intramuscularly at 6.6 mg/kg in weanling foals provided plasma and pulmonary epithelial lining fluid concentrations above the therapeutic target of 0.2 µg/mL for at least 4 days and would thus be expected to be an effective treatment for pneumonia caused by susceptible pathogens such as *S. equi* subsp. *zooepidemicus*.[41] Alveolar delivery of antimicrobials typically occurs via diffusion of a free, nonprotein-bound drug and is usually satisfactory if plasma concentrations and alveolar perfusion are adequate.[42] Aminoglycosides penetrate lung tissue at 10% to 45% of serum levels. However, the acidic environment of infected airways may reduce the drug's activity below levels sufficient to eradicate the offending bacteria in some cases.[43,44] Antimicrobial therapy should not be discontinued prematurely in neonatal foals, because pulmonary infection is commonly well established before its diagnosis.[45]

Outcome The survival of neonatal foals with septic pneumonia is contingent on the underlying disease conditions, a prompt diagnosis, and the cause and severity of lung dysfunction. Few studies have objectively evaluated the outcome of foal pneumonia.[38] One report documented that 65% of foals with radiographic evidence of pulmonary disease were discharged alive from the hospital, in contrast to 86% survival of foals without respiratory illness. The presence of diffuse radiographic infiltrates (caudodorsal, caudoventral, and cranioventral lung involvement) or concurrent alveolar patterns within the caudodorsal and caudoventral lung indicated lower survival rates.[38] Pneumonia is also considered one of the greatest causes of morbidity and mortality in foals greater than 1 month of age.[2]

The long-term effect on athletic performance has thus far been evaluated only in older foals that survived rhodococcal pneumonia. *R. equi* infection in foals was associated with a decreased chance of racing as adults. However, the performance of foals that went on to race was not significantly different from that of the general U.S. racing population.[46] It remains speculative whether severe equine neonatal pneumonia will most likely limit future peak athletic performance. Human studies have shown that many hosts develop long-lasting or permanent lung changes after recovery from neonatal pneumonia, which may significantly affect the quality of life and susceptibility to later infections. Case-based evaluations in horses have demonstrated that functional and structural pulmonary abnormalities may occur in survivors of severe neonatal pneumonia. However, the clinical significance of this finding currently remains unclear.

Fungal Infections of the Equine Respiratory Tract

Allison Jean Stewart

Definition and Etiology Fungi are eukaryotic organisms with a definitive cell wall made up of chitins, glucans, and mannans. Within the fungal cell wall, the plasma membrane contains ergosterol, a cell membrane sterol that is frequently targeted by antifungal agents. There are more than 70,000 species of fungi, but only 50 species are known to cause disease in people or animals. Pathogenic fungi can be divided into three groups: multinucleate septate filamentous fungi, nonseptate filamentous fungi, and yeasts. Dimorphic fungi are able to interchange between forms depending on environmental conditions. Examples of dimorphic organisms include *Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis,* which exist in yeast form in vertebrate host tissue and in hyphal or mycelial form in vitro. In soil and decaying matter, the mycelial form usually is present and is composed of a collection of hyphae. The mycelia produce infective spores that are capable of inoculating vertebrate tissue.

Fungal infections in horses are relatively uncommon, although geographic prevalence is highly variable. Fungi are ubiquitous, and their constant aerosol exposure to respiratory tissue is inevitable. Upper respiratory and pulmonary disease caused by fungi is frequently acquired by the inhalation route, with the sporular diameter small enough to allow penetration into the distal airways and alveoli. In most samples of stable air, more than 90% of particles visible under a light microscope are spores of fungi or actinomycetes.[1] One study found that if a horse stood quietly in its stable without access to hay, the mean concentration of dust was very low (approximately 12 particles per cubic centimeter [of particles less than 5 mm in diameter]). When the bedding was disturbed during the normal "bedding down" operation, the concentration of respirable dust increased sixfold.[2] Systemic fungal infections and some cases of fungal pneumonia are thought to arise through a compromised gastrointestinal tract, by inhalation or via open wounds.

Tissue invasion of pulmonary tissue usually occurs in the immunocompromised host, although on occasion the normal individual may be affected. Important predisposing factors for fungal pneumonia include (1) qualitative and especially quantitative granulocyte abnormalities and (2) the presence of devitalized tissue. In most cases of upper respiratory tract fungal granuloma, there are no obvious predisposing causes.

Primary pathogenic fungi such as *Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans,* and *Conidiobolus coronatus* usually infect immunologically normal horses. However, in a report of cryptococcosis in seven horses, five had a history of illness that may have predisposed them to cryptococcosis.[3] A separate group of fungal pathogens tend to infect only those equine patients with abnormal host defenses. Opportunistic fungi, including *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Emmonsia crescens,* and *Pneumocystis carinii* (renamed *P. jiroveci* in humans), have caused fungal disease in horses that are immunocompromised or neutropenic; have neoplasia, colitis, enteritis, or bacterial pneumonia; or have been treated with corticosteroids.[4-15] In vitro studies support the critical role of phagocytic cells in host defense against opportunistic fungi.

Clinical Signs Mycotic granulomas have been found in nasal passages, paranasal sinuses, nasopharynx, guttural pouch, trachea, bronchioles, lungs, and mediastinum of infected horses. The most common clinical signs of upper respiratory tract fungal infection

include unilateral or bilateral serosanguineous or mucopurulent nasal discharge, as well as inspiratory or expiratory noise. Other clinical signs include coughing, facial deformation, and dyspnea caused by partial blockage of nasal passages by granulomatous masses. Differentials for fungal granulomas of the respiratory tract include ethmoidal hematoma, squamous cell carcinoma, amyloidosis, and exuberant granulation tissue.

Fungal plaques in the guttural pouch often are located over the arterial blood supply. Horses with guttural pouch mycosis usually present with episodic serosanguineous nasal discharge that may progress to potentially fatal epistaxis if there is erosion into an artery. The duration of clinical signs can vary from days to many months. Guttural pouch mycosis is discussed in detail elsewhere.

Pulmonary fungal infections causing granulomas, diffuse pneumonia, or pleuropneumonia can present with signs similar to those of bacterial infection. There may be cough, nasal discharge, tachypnea, respiratory distress, hemoptysis, and, if chronic, weight loss. Radiographic appearance of fungal pneumonia may reveal virtually any infiltrative pattern. Although miliary patterns are occasionally seen, the most common initial finding is a patchy bronchopneumonia. Multiple focal sites are common, and lesions tend to be peripheral in distribution. Differentials include bacterial pneumonia, recurrent airway obstructive disease, silicosis, granulomatous disease complex, and neoplasia.

Systemic infections can have variable clinical signs depending on the location and extent of the infection. Fungal infections can affect multiple organ systems and body cavities. Weight loss, colic, or diarrhea can often occur with infection within the abdominal cavity.

Diagnostic Sampling Lesions in the nasal passages, nasopharynx, guttural pouch, trachea, and bronchioles usually can be observed directly during endoscopic examination. Masses in paranasal sinuses and lungs may be observed radiographically. Computed tomography or magnetic resonance imaging provide detailed imaging of the equine skull and can be used to determine the extent of lesions and bony invasion. An 8- to 20-mm trephine (Michelle 8-mm trephine or 14- to 20-mm Galt trephine, Jorgensen Laboratories, Inc., Loveland, Colo.) can be drilled into the nasal or maxillary sinus through which a sterile rigid arthroscope or flexible endoscope can then be passed to directly view some lesions within the paranasal sinuses.

For nasal and nasopharyngeal lesions, specimens for cytology, histopathology, and culture can be obtained by use of endoscopically guided biopsy instrument; however, these samples tend to be small, superficial, and often nondiagnostic. Mucosal contaminants may overgrow the organism of interest. Larger biopsy samples from the nasal passages or nasopharynx often can be obtained by use of a uterine biopsy instrument (Jorgensen Laboratories, Inc., Loveland, Colo.) passed nasally with visual guidance from a flexible endoscope. Excisional biopsy or surgical debulking may be performed through a sinus flap or via laryngotomy.

Fungal pneumonia may be diagnosed from samples obtained by tracheal wash or bronchoalveolar lavage fluid, or via a lung biopsy (Fig. 31-19). Lung biopsy is associated with significant risk if a large pulmonary vessel is accidentally punctured. The biopsy should be performed ideally after radiographic evaluation or with concurrent ultrasound guidance and should be obtained from the periphery of the lung; however, some horses have experienced fatal hemorrhage associated with puncture of a vessel only 2 cm from the periphery. The lung is rich in plasminogen, so bleeding complications may be severe. Spring-loaded biopsy needles (4-gauge × 20-cm biopsy needle, Temno Products Group International, Lyons, Colo., or Magnum biopsy needle) are safer for lung biopsy compared with Tru-Cut biopsy instruments (Cardinal Health, Dublin, Ohio).[16] Ultrasound evaluation can be used to monitor for bleeding after the procedure.

CYTOLOGY. Fungal hyphae may be identified in airway fluid or in impression smears obtained from biopsied masses. Clinicians must be careful in attributing significance to presence of fungal elements in a transtracheal aspirate. Fungal hyphae are often present either free or in large mononuclear cells in tracheal aspirates from healthy horses.[17] A study of healthy Thoroughbred racehorses showed 70% had fungal elements detected in their tracheal aspirates.[18] None of the horses from either study had other evidence of fungal pneumonia. Barn fungus such as *Alternaria* spp. are nonpathogenic and rarely incite an inflammatory response in the host. The organisms often have a block-like appearance and may be colored (Fig. 31-20). A normal predominance of macrophages, lymphocytes, and nondegenerate neutrophils (<5% to 10%) would be expected.



FIG. 31-19 Percutaneous lung biopsy from caudal periphery of lung of a weanling foal.

To be significant cytologically, large numbers of fungi should be involved in the inflammatory process within the lung. With fungal pneumonia, aspirates may contain predominantly neutrophils that often are degenerate and may contain intracellular fungal hyphae. If processing of the sample is delayed, extracellular fungi may be phagocytized, and this makes interpretation more difficult. Some fungi have characteristic morphologic features that can give an early presumptive identification (Table 31-5).

HISTOPATHOLOGY. Hyphae of certain fungi may be poorly visualized using routine hematoxylin and eosin (H&E) stains; therefore special stains such as periodic acid Schiff (PAS), Gridley fungus, and Grocott-Gomori methenamine–silver nitrate (GMS) can be useful to stain histopathologic specimens. With chronicity, there is often evidence of extensive fibrosis.

MICROBIOLOGICAL CULTURE. Fungi can be found in tracheal aspirates from healthy horses. Sixteen percent of healthy horses are reported to have fungal growth on the tracheal aspirate bacterial culture plates; therefore results of fungal culture must be interpreted with caution.[19] Some fungi have fastidious growth requirements. They may be outcompeted by contaminant bacteria and may take up to several weeks to grow on culture media. For transport of tissue for microbiological culture, the sample should be placed in a prepared culture medium (BBL Port-A-Cul Vial, Becton, Dickinson and Company, Sparks, Md.) and transported at room temperature. Specific culture media such as Sabouraud dextrose agar (Remel, Inc., Lenexa, Kans.), inhibitory mold agar, or Mycobiotic (Neogen, Lansing, Mich.) containing cycloheximide and chloramphenicol are useful.

MOLECULAR TECHNIQUES. Serologic tests that use immunodiffusion, radioimmunoassays, complement fixation, and enzyme-linked immunosorbent assays (ELISAs) are available to detect circulating antibodies against several fungal organisms (see Table 31-5). These titers often decrease with resolution of disease; therefore repeated measurements can be used to help monitor response to

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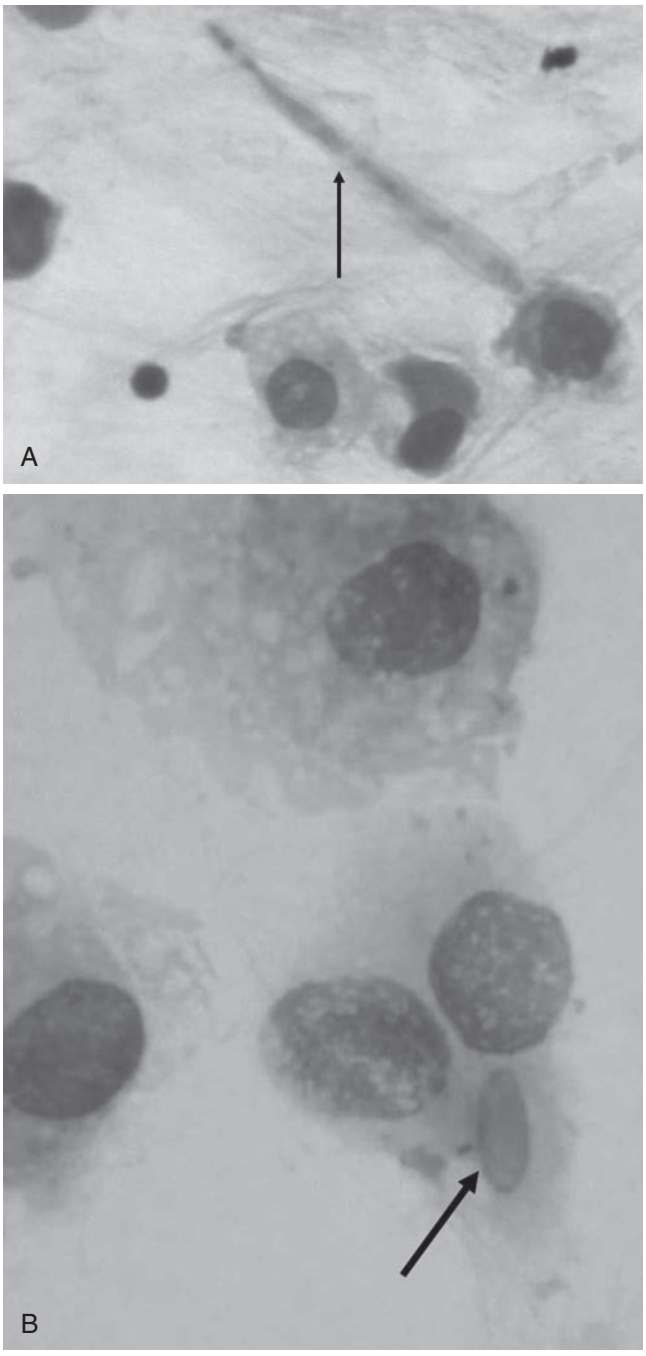


FIG. 31-20 *Alternaria* spp. from transtracheal wash specimens obtained from healthy horses. **A,** An extracellular spore *(arrow)* with several macrophages, squamous cell (indicative of pharyngeal contamination). **B,** Intracellular spores *(arrow)* within binucleated macrophage. *(Courtesy Elizabeth Welles, Auburn University, Auburn, Ala.)*

treatment. Immunohistochemistry,[10,20-22] fluorescent in situ hybridization,[21] and DNA probes[23] can be used to positively diagnose fungal organisms in histopathology sections. A panfungal real-time PCR assay (University of California, Davis, Calif.) can be used to detect a variety of fungal organisms in body fluids and fungal isolates, followed by species-specific real-time PCR to positively identify the organism.[5]

IMMUNE FUNCTION TESTING. Several fungal infections have been associated with host immune suppression caused by severe malnutrition, congenital immunodeficiency, or acquired immunodeficiency.[13-15] Blood can be tested for immunoglobulin quantification by radial immunodiffusion (Cornell University, Ithaca, N.Y.) and lymphocyte subpopulation phenotyping via flow cytometry (Kansas State University, Manhattan, Kans.).[15,24]

Treatment Treatment of fungal granulomas of the upper respiratory tract may involve surgical options (debulking, laser therapy, or cryotherapy) and/or medical therapy (systemic, topical, or intralesional). Treatment of *Aspergillus* spp. pneumonia is usually frustrating, as diagnosis is often late in the course of disease and the horse frequently has severe underlying illness. Successful therapy has been reported for other causes of fungal pneumonia.[5,25-28] Several pharmacokinetic studies on antifungal drugs have been recently performed,[29-34] and as these medications become more affordable, the success rate of therapy is likely to increase. The drug of choice depends on the site of infection, the fungus involved, and the financial resources of the owner. Specific antifungal agents used in horses have been reviewed.[35] Therapy may not be attempted because of the severity of the primary disease, the expense, or the poor prognosis.

Prevention of invasive fungal pneumonia is difficult. It is impossible for the horse to avoid large inhaled inocula, given its environmental conditions. Improving ventilation and minimizing exposure to inspired spores are most beneficial in immunocompromised patients. At present the most important methods of disease prevention are treating predisposing illnesses promptly and effectively and judiciously avoiding overuse of corticosteroids and broad-spectrum antibiotics.

ANTIFUNGAL THERAPEUTICS (Table 31-6)

Amphotericin B. Amphotericin B deoxycholate is a polyene antibiotic that combines with ergosterol in the fungal cell membrane, resulting in an increase in cell permeability. Intravenous amphotericin B can cause nephrotoxicity and phlebitis. Other possible side effects include anorexia, anemia, cardiac arrhythmias, hepatic and renal dysfunction, and hypersensitivity reactions.[36] Amphotericin B also has been used successfully to treat histoplasmosis and pulmonary aspergillosis and cryptococcosis.[25,26,37] A high dose of oral amphotericin B successfully treated mucormycosis caused by *Absidia corymbifera*.[38] Topical amphotericin B has been successful in treatment of nasopharyngeal *C. coronatus*.[39-42]

Azoles. Benzimidazole derivatives in the class *azoles,* such as miconazole, enilconazole, ketaconazole, itraconazole, fluconazole, and voriconazole, destroy fungi by inhibition of ergosterol biosynthesis in the fungal cell membrane. Azole antifungals inhibit cytochrome P450–dependent 14α–sterol demethylase, which is essential for the formation of ergosterol. Topical 2% miconazole was used in the resolution of four cases of guttural pouch mycosis[43] and as part of successful multimodal therapy against nasopharyngeal *P. boydii*.[44] Enilconazole is not commercially available in the United States but has been used topically in the successful treatment of guttural pouch mycosis.[45-47] Aerosolization of 1.2 mg/kg enilconazole q12h in 125 mL of saline resolved *Scopulariopsis* pneumonia.[28] Ketoconazole is absorbed poorly in the nonacidified form[29] but can be acidified for better absorption (30 mg/kg via nasogastric tube [NGT] q12h mixed with 0.2 N HCl).[28]

Itraconazole (Sporanox solution [Janssen, Titusville, N.J.]) is absorbed well orally (bioavailability 60%). A dose of 5 mg/kg PO q24h maintains concentrations above mean inhibitory concentration (MIC) for susceptible yeasts (*Histoplasma* spp. and *Blastomyces* spp.) and *Aspergillus* spp., with no detectable side effects.[31] The use of compounded itraconazole is not recommended. It is very unstable (requires low pH), and owing to its lipophilic nature it is difficult to formulate in aqueous solution.

Oral fluconazole at a loading dose of 14 mg/kg, followed by 5 mg/kg q24h, yields concentrations in plasma, CSF, synovial fluid, aqueous humor, and urine above the MIC reported for several equine fungal pathogens.[30] Fluconazole, however, reportedly has minimal activity against filamentous fungi (*Aspergillus* spp. and *Fusarium* spp.). Low-dose oral fluconazole (1 mg/kg PO q24h) for at least 10 to 15 days anecdotally has been successful in treatment of fungal keratitis.

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TABLE 31-5

Characteristic Morphologic Features and Availability of Serologic Tests for Fungal Organisms Reported to Cause Fungal Granulomas in Horses (January 2013)

	Cytologic Appearance	Serologic Test	
Agent	Tissue Form	Method	Veterinary Laboratory
Cryptococcus neoformans	Round, thin-walled, yeast-like fungus (5-10 µm) with a large heteropolysaccharide capsule (1-30 µm in diameter) that does not take up common cytologic stains. Capsule is best stained using the Mayer mucicarmine stain. Organisms show narrow-based budding and lack of endospores.	Capsular antigen, ELISA (antigen), or latex agglutination (antigen)[26]	$33.00 UT $21.50 CU $21.00 CSU $16.00 UGA $18.00 NMDA
Conidiobolus coronatus	Broad, thin-walled highly septate, irregularly branched hyphae (5-13 µm in diameter).[53] Often surrounded by acidophilic staining glycoprotein antigen-antibody complex known as Splendore-Hoeppli material.	Immunodiffusion is highly sensitive and specific. Decreasing titer correlated to disease resolution in horses.[51,55]	Serologic testing not widely available.
Pseudallescheria boydii	Hyaline, nonpigmented, septate, randomly branched hyphae (2-5 µm in diameter) with regular hyphal contours. Asexual form has nonbranching conidiophores with terminal conidia. Sexual form in culture has cleistothecium (large round body) and ascospores.[44]		
Coccidioides immitis	Spherules have a double-contoured wall, are variable in size, but can be large (20-80 µm, up to 200 µm). The mature spherules (sporangia) contain endospores (sporangiospores) 2-5 µm in diameter. In the environment, mycelium are thick-walled with barrel-shaped arthroconidia.	AGID (antibody) for IgM and IgG[27,76,79,81]	$30.00 UT $16.00 CSU $16.00 CU $14.00 NMDA
		MVista Quantitative EIA (antigen)	$50.00 MDL
Aspergillosis spp.	Broad (2-4 µm in diameter) septate hyphae with parallel sides and acute right-angled branching.	Platelia *Aspergillus* galactomannan EIA (sandwich immunoassay) Some reactivity to *Penicillium, Alternaria,* and *Paecilomyces*	$50.00 MDL
		AGID (antibody) *Aspergillus fumigatus* only	$20.00 UT $16.00 CSU $16.00 CU $14.00 NMDA
		Aspergillus spp. panel	$70.00 UT (send out)
Blastomyces dermatitidis	Yeasts are spherical (15-17 µm in diameter) with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic. Yeasts are often located within multinucleated giant cells.	AGID (antibody)[23]	$20.00 = UT $16.00 = CSU $16.00 CU $14.00 NMDA
		MVista quantitative EIA (antigen)	$50.00 MDL
Histoplasma capsulatum	Yeasts (2-4 µm in diameter) have a thin clear halo surrounding a round or crescent-shaped basophilic cytoplasm.	AGID (antibody)[75]	$20.00 UT $16.00 CSU $16.00 CU $14.00 NMDA
		MVista quantitative EIA (antigen)	$50.00 MDL
Acremonium strictum	Mononuclear cells contain single, spherical, intracytoplasmic encapsulated spores 3-5 µm in diameter.[5]		
Candida spp.	Ovoid budding yeast cells (2-4 µm in diameter) with thin walls, or they can occur in chains that produce septate pseudohyphae when blastospores remain attached after budding division. Filamentous, regular, true hyphae also may be visible.		
Pneumocystis carinii (renamed *P. jiroveci* in humans)	Trophozoite (yeast form) is a 2-5 µm in diameter ameboid with filopodia that attach to the surface of type I pneumocytes. Sporangia (cystic form) are encapsulated spores (4-6 µm in diameter) containing eight uninucleate spores (intracystic bodies).[85,14,15,20]		
Fungal serology panel	Antibody to *Histoplasma, Blastomyces, Coccidioides, Aspergillus* (AGID) The CU panel also includes *Cryptococcus* antigen.		$62.75 CU $39.00 NMDA

AGID, Agar gel immunodiffusion; *CF,* complement fixation; *EIA,* enzyme immunoassay; *ELISA,* enzyme-linked immunosorbent assay.

UT = University of Tennessee, College of Veterinary Medicine. P (865) 974-5639 (mycology) or -5643 (serology), http://www.vet.utk.edu/diagnostic/index.php

UGA = University of Georgia, College of Veterinary Medicine. P (706) 542-5812, F (706) 583-0843 http://www.vet.uga.edu/idl/tests

CSU = Colorado State University, Veterinary Diagnostic Laboratories. P (970) 297-1281, F (970) 297-0320 http://csu-cvmbs.colostate.edu/vdl/Pages/default.aspx

CU = Cornell University, Animal Health Diagnostic Center. P (607) 253-3900, F (607) 253-3943 http://ahdc.vet.cornell.edu

UTHSCSA = University of Texas Health Science Center at San Antonio, Center for Medical Mycology. P (210) 567-4131, F (210) 567-4076 http://www.sacmm.org/index.html

NMDA = New Mexico Department of Agriculture, Veterinary Diagnostic Services. P (505) 383- 9299 http://www.nmda.nmsu.edu/vds

MDL = Miravista Diagnostics Laboratory, Indianapolis, IN. P (317) 856-2681 F (317)-856-3685 www.miravistalabs.com

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TABLE 31-6

Pharmacokinetic Studies of Antifungal Drugs Performed in Horses

Drug and Relative Cost	Dosage	Source	Susceptible Organisms, Equine Reports, Comments
Ketoconazole $ = Moderate	30 mg/kg q12h mixed with 0.2 N HCl via nasogastric intubation[29]	LH Tablets (200 mg) (Nizoral [Janssen, Titusville, N.J.])	*Scopulariopsis,*[28] *Coccidioides, Cryptococcus, Candida, Malassezia, Histoplasma, Sporothrix, Microsporum, Trichophyton.*
Itraconazole $ = Very expensive	5-mg/kg/day solution PO[31] (bioavailability 60%, compared to 12% for capsules)	Sporanox solution (10 mg/mL oral or injectable solution) Sporanox capsules (100 mg) (Janssen)	*Aspergillus,*[45,69] *Histoplasma, Blastomyces, Coccidioides,*[80] *Cryptococcus, Candida, Paracoccidia, Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca.* Not active against *Fusarium, Mucor, Rhizopus.* Very unstable and lipophilic; therefore compounded substances are not recommended.
Fluconazole $ = Inexpensive	14 mg/kg PO loading followed by 5 mg/kg/day PO[30]	LH Diflucan (Zoetis, Florham Park, N.J.; Bedford Labs, Bedford, Ohio) Injectable solution (2 mg/mL) (Zoetis, Bedford Labs) Tablets (200 mg) (Zoetis) Generic available Powder (100 g) (Spectrum Chemicals, Mumbai, India)	*Histoplasma, Blastomyces, Coccidioides,*[27] *Cryptococcus,*[60,61] *Mucor, Rhizopus, Candida,*[12] *Conidiobolomycosis,*[54] *Paracoccidia, Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca.* Minimal activity against *Aspergillus* and *Fusarium.*
Voriconazole $ = Very expensive	4 mg/kg/day PO[32-34]	Vfend (Zoetis, Bedford Labs) Tablets (200 mg)	Drug of choice for invasive *Aspergillus,*[68] *Candida, Cryptococcus, Scedosporium apiospermum,* and *Fusarium* spp. in human patients who are unable to tolerate or are refractory to other therapeutic agents.

HCl, Hydrochloride; *LH,* local wholesaler; *PO,* by mouth.

Compounded fluconazole formulations are very stable. The cost of fluconazole has been markedly reduced since the availability of generic products.

Voriconazole, a broad-spectrum triazole antifungal agent, was approved for use in human medicine in 2002. It is now considered the drug of choice for initial treatment of invasive aspergillosis, candidiasis, cryptococcosis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. in patients that are unable to tolerate or are refractory to other therapeutic agents.[46-49] An initial single-dose pharmacokinetic study in horses recommended a dose of 4 mg/kg PO q24h.[32] Voriconazole distributes widely into body fluids and reached therapeutic concentrations in peritoneal, synovial, and cerebrospinal fluids; aqueous humor; periocular tear film; epithelial lining fluid; and urine.[33-34]

SYSTEMIC IODIDE THERAPY. The exact mode of action of iodides is unknown; however, they seem to have a beneficial effect on the granulomatous inflammatory process. Iodides have very little, if any, direct in vitro antibiotic effect.[50] Although several successful cases are reported in which iodides were used as primary or adjunctive therapy, overall efficacy is considered limited at best. Treatment is inexpensive, but toxicity and resistance can occur. Iodide toxicity is characterized by excessive lacrimation, nonproductive cough, increased respiratory secretions, and dermatitis.[50] The recommended dose of 20% sodium iodide is 20 to 40 mg/kg/day IV for 7 to 10 days.[39,42,51,52] Orally administered iodine is available in two forms. Inorganic potassium iodide (10 to 40 mg/kg/day) is available only as a chemical grade and is unstable in the presence of light, heat, and excessive humidity.[42,52] Organic ethylenediamine dihydriodide (EDDI) (0.86 to 1.72 mg/kg of EDDI is equivalent to 20 to 40 mg/kg/day of the 4.57% dextrose powdered form [Butler Co., Columbus, Ohio]) is commercially available.[52] Administration of iodine in the diet of pregnant mares may cause congenital hypothyroidism in foals and thus should be avoided.

ETIOLOGIC AGENTS

Conidiobolomycosis. *Conidiobolus coronatus* is a saprophytic fungus that causes granulomatous lesions of the upper respiratory tract in horses. Single to multiple granulomatous lesions in the nasal passages, trachea, or soft palate can be observed endoscopically (Fig. 31-21). Histologic appearance of conidiobolomycosis is similar to that of pythiosis and of basidiobolomycosis. Hyphae of *C. coronatus* are thin-walled, highly septate, and irregularly branched (see Table 31-5).[53] The lesions typically have large numbers of eosinophils and fewer macrophages, neutrophils, plasma cells, and lymphocytes surrounding hyphae. Definitive diagnosis is based on microbiological culture, immunodiffusion, or PCR.[54] Detection of serum antibodies by immunodiffusion is considered highly sensitive and specific[51,55] and can be used to monitor response to treatment.[55]



FIG. 31-21 Endoscopic image of mycotic granulomas caused by *Conidiobolus coronatus* in the nasopharynx of a horse.

Conidiobolomycosis lesions can be treated with surgical excision, laser therapy, cryotherapy, or long-term administration of iodides or antifungals.[54,39,51] Amphotericin B has been administered intralesionally or topically in combination with DMSO to treat *C. coronatus*.[39-42] It is important to remember that long-term therapy and reevaluation

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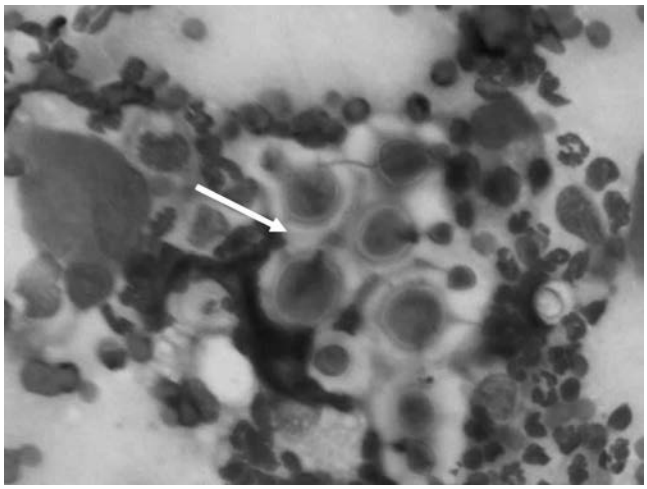


FIG. 31-22 Photomicrographs of an impression smear from a biopsy of a mass in the nasal passage of a horse. The smear is extremely cellular with abundant neutrophils and macrophages. Round yeast cells with large nonstaining capsules and occasional narrow-based budding consistent with cryptococcal organisms *(arrow)* are shown. (Modified Wright stain, ×100.) *(Courtesy Elizabeth Welles, Auburn University, Auburn, Ala.)*

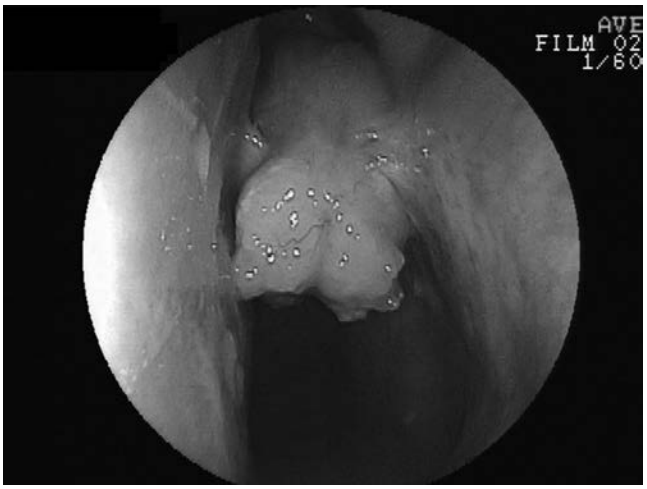


FIG. 31-23 Endoscopic image of a *Cryptococcus* granuloma in the nasal passages of a horse.

are essential, as recurrence can occur.[42] Oral fluconazole was successful in treating two pregnant mares with nasal conidiobolomycosis.[56] Fluconazole would be considered the drug of choice for the treatment of conidiobolomycosis, with treatment length varying between 4 and 16 weeks based on endoscopic reevaluation. A vaccine using *C. coronatus* antigen from broth cultures was unsuccessful in treating seven horses with conidiobolomycosis.[54]

Cryptococcosis. Cryptococcosis is caused by *Cryptococcus neoformans* (var. *neoformans* and var. *gattii*) and is a ubiquitous, saprophytic, round, basidiomycetous yeast-like fungus with a large heteropolysaccharide capsule that does not take up common cytologic stains (see Table 31-5, Fig. 31-22). The capsule forms a clear halo when stained with India ink. The capsule is immunosuppressive and antiphagocytic. A relatively high frequency of equine cryptococcosis occurs in Western Australia.[3,57] There is an epidemiologic relationship between *C. neoformans* var. *gattii* and the Australian river redgum tree *(Eucalyptus camaldulensis)*, while *C. neoformans* var. *neoformans* has historically been associated with bird (particularly pigeon) excreta.[3] Cytologic or histopathologic identification is very reliable for diagnosis because of the characteristic morphology.[58] Serologic testing with latex agglutination to identify cryptococcal capsular antigen is useful with resolution of lesions correlated with declining serum titers.[26]

Cryptococcosis in horses is associated primarily with pneumonia, rhinitis (Fig. 31-23), meningitis, and abortion. Successful medical treatment, however, has been reported rarely until the recent availability of financially viable and effective antifungal medications. Surgical removal of a localized jejunal lesion was successful in one horse.[59] A pony with multiple pulmonary cryptococcomas, from which *Cryptococcus gattii* was cultured from both transtracheal washings and lung mass aspirates, was treated successfully with daily infusions of amphotericin B over 1 month. One year after cessation of treatment, clinical signs had resolved and the cryptococcal antigen titer decreased from 4096 to 256.[26] Sinonasal cryptococcosis was successfully treated in two horses after extensive surgical débridement and long-term treatment with oral fluconazole.[60-61]

Cryptococcosis should be treated with amphotericin B, fluconazole, or voriconazole (Table 31-7).

Pseudallescheriosis. *Pseudallescheria boydii* is a saprophytic ascomycete. Infection most commonly involves the extremities, and in human patients it is known as Madura foot. Hyphae within tissue cannot be differentiated from *Fusarium* spp. or *Aspergillus* spp. unless cultured. *P. boydii* cultured from the nasal cavity and sinus of a horse with chronic, malodorous nasal discharge was susceptible in vitro to miconazole, ketaconazole, natamycin, and clotrimazole. After débriding and flushing the plaque, miconazole cream was infused twice daily for 4 weeks through lavage tubing that had been passed into the nasal passage through a hole drilled in the frontal bone and sinuses. Adjunctive iodide therapy was also administered and the lesions resolved (Fig. 31-24).[44]

Nasal mycosis caused by *P. boydii* has been reported in two other horses, both of which were euthanized.[62,63] *P. boydii* has also been isolated from the pharynx of 2 of 60 normal donkeys and from horses with chronic uterine infection.[64,65]

Aspergillosis. *Aspergillus* spp. have broad septate hyphae with parallel sides and acute right-angled branching (see Table 31-5). They have a propensity for vascular invasion. Definitive diagnosis is by culture or staining by immunohistochemistry or immunofluorescence. *Aspergillus* spp. are very common in the environment, especially in moldy feed and bedding.[37] They are opportunistic pathogens and often cause disease in horses that are immunosuppressed from debilitating disease such as enterocolitis, septicemia, neoplasia, Cushing disease, and equine protozoal myeloencephalitis (EPM), that have undergone surgery, or that have been treated with immunosuppressive drugs[4,6,8-10] (Fig. 31-25).

Infection is by inhalation of an overwhelming number of spores resulting in fungal proliferation and invasion of the small airways, or by translocation of organisms across an inflamed gastrointestinal tract leading to lesions centered around large blood vessels as a result of hematogenous spread. In two retrospective studies of invasive pulmonary aspergillosis, 41 of 49 cases were associated with enterocolitis.[4,6] *Aspergillus* spp. pneumonia is almost uniformly fatal, often with no or mild respiratory signs. Antemortem diagnosis of pulmonary aspergillosis is made rarely. In a retrospective study of 30 cases of *Aspergillus* spp. pneumonia, only 2 cases were diagnosed or suspected antemortem.[6] Transtracheal aspirates or bronchoalveolar lavages may not be helpful because hyphae and spores are often present extracellularly or within macrophages in aspirates and lavages from healthy animals.[4] False-negative results also can occur. Cytologic examination of a transtracheal wash specimen obtained from the foal shown in Fig. 31-25, *A*, 2 days prior to euthanasia failed to identify *Aspergillus* spp. hyphae. Serologic diagnosis occasionally has been useful,[66] but it is often unreliable because many horses have titers to *Aspergillus* spp. Development of a commercially available ELISA is promising.[8,37]

In human medicine, 50% to 90% of patients with invasive aspergillosis die despite treatment. Amphotericin B has been the mainstay of treatment for invasive aspergillus for decades, but it is associated with nephrotoxicity in about 50% of human patients. Nephrotoxicity is reduced with the use of liposomal amphotericin B. Voriconazole, an azole antifungal, is now considered the drug of choice against human aspergillosis, and caspofungin (in the new class

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TABLE 31-7

Treatment of Common Fungal Infections in Humans and Horses

Fungal Infection	Recommended Treatment in Humans[87]	Treatments Tried in Horses	Comments
Cryptococcosis	Induction with amphotericin B 0.7-1 mg/kg, plus 5-fluorocytosine 100 mg/kg/day for 2 weeks, then consolidation with fluconazole 400 mg/day for > 10 weeks	Daily infusions of amphotericin B (initially 0.35 mg/kg, increasing over 8 days to 0.5 mg/kg in 1 L 5% dextrose in water over 1 h IV for 1 month) successfully used to treat pulmonary cryptococcosis. Flunixin meglumine (0.25 mg/kg IV) was administered before each treatment.[26,61]	Reported dosages range from 0.3 to 0.9 mg/kg in saline IV over 1 h.
		Successful treatment with long-term fluconazole (14 mg/kg loading, then 5 mg/kg PO q24h) for sinonasal cryptococcosis after surgical débridement.[60,61]	Long-term oral fluconazole is recommended as sole treatment or after 2 weeks of IV amphotericin B.
Histoplasmosis	Amphotericin B 0.7-1 mg/kg/day for 2 weeks, then itraconazole 200-400 mg/day for 4-18 months	Successful treatment of histoplasmosis in a filly using amphotericin B (0.3-0.6 mg/kg eod IV infused over 1 h) with a total cumulative dose of 6.75 mg/kg administered over a 1-month period. After each treatment the filly became lethargic for 18-24 h. Polyuria and polydipsia occurred during week 4, but urine concentrating ability was maintained and azotemia did not occur.[25]	In vitro susceptibility to fluconazole is poor.
Blastomycosis	Amphotericin B 0.7-1 mg/kg/day to 1.5-2.5 g total or to 0.5 g total, then itraconazole 200-400 mg/day		
Aspergillosis (invasive pulmonary)	1. Voriconazole 200-400 mg PO q12h, 3-6 mg/kg IV q12h 2. Amphotericin B 1-1.5 mg/kg/day until desired response, then itraconazole 400 mg/day when disease progression slows	Voriconazole 4 mg/kg PO q24h. Successful treatment of a neonatal foal with pulmonary aspergillosis after lung lobe resection.[68]	Fluconazole has limited efficacy. Oral itraconazole or voriconazole would be the drugs of choice, possibly after 2 weeks of IV amphotericin B.
Candidiasis	1. Amphotericin B 0.7-1 mg/kg/day for 2 weeks 2. Fluconazole 6 mg/kg for 2 weeks 3. Caspofungin 70 mg × 1, then 50 mg/day for 2 weeks 4. Voriconazole	Two foals were treated with intravenous amphotericin B for 8 days (total dose, 2.6 mg/kg) and 29 days (total dose, 10.3 mg/kg), respectively. Fluconazole (5.5 mg/kg PO, q24h) for 6 weeks and (4 mg/kg PO, q24h) for 28 days was used to treat two other foals.[12]	Fluconazole is generally considered the drug of choice against *Candida* spp., although *C. krusei* is resistant to fluconazole.
Pneumocystosis	1. Trimethoprim-sulfamethoxazole 2. Pentamidine isethionate 3. Trimetrexate	Trimethoprim-sulfamethoxazole (25-30 mg/kg PO q12h) is the treatment of choice.[86] Dapsone (Jacobus, Princeton, N.J.) (3 mg/kg PO daily for 2 months) was used to successfully treat a foal with *P. carinii* that developed *Salmonella* enterocolitis after treatment with TMS.[24]	Lacks ergosterol; therefore antifungals are not effective.

eod, Every other day; *IV,* intravenous; *PO,* by mouth; *TMS,* trimethoprim-sulfamethoxazole.

of echinocandin antifungals) shows promising results in patients with refractory infections.[67] Oral voriconazole and itraconazole are currently the treatments of choice for aspergillosis in horses. In human medicine, itraconazole has shown comparable response rates to those of amphotericin B.[67] *Aspergillus* spp. are usually resistant to fluconazole. There are limited reports of horses surviving pulmonary aspergillosis.[37] A neonatal foal with pulmonary aspergillosis was successfully treated by lung lobe resection followed by treatment with systemic voriconazole.[68]

Treatment of mycotic aspergillus rhinitis and sinusitis in horses has been more successful. It is important, however, to rule out concomitant invasive pulmonary aspergillosis. Oral itraconazole,[69] topical natamycin (flushed via an endoscope or indwelling catheter placed into the sinus), nystatin powder (insufflated up the nostril), and topical enilconazole have been curative.[70,71]

Blastomycosis. Blastomycosis is caused by inhalation of conidiae of the thermally dimorphic saprophytic fungus *Blastomyces dermatitidis*. *Blastomyces* yeasts can be identified on cytologic examination, often within multinucleated giant cells. They are spherical, with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic (see Table 31-5).

Blastomycosis was reported to cause pyogranulomatous pleuropneumonia, pulmonary abscessation, peritonitis, and abscesses in a 5-year-old horse.[23] *B. dermatitidis* was positively identified from transtracheal wash fluid by use of a DNA probe, and serologic testing was strongly positive. The horse was euthanized without treatment.[23] Disseminated blastomycosis was diagnosed in a miniature horse with subcutaneous infections associated with a chronic pectoral wound. The pony had pulmonary consolidation and pleural effusion. Yeasts

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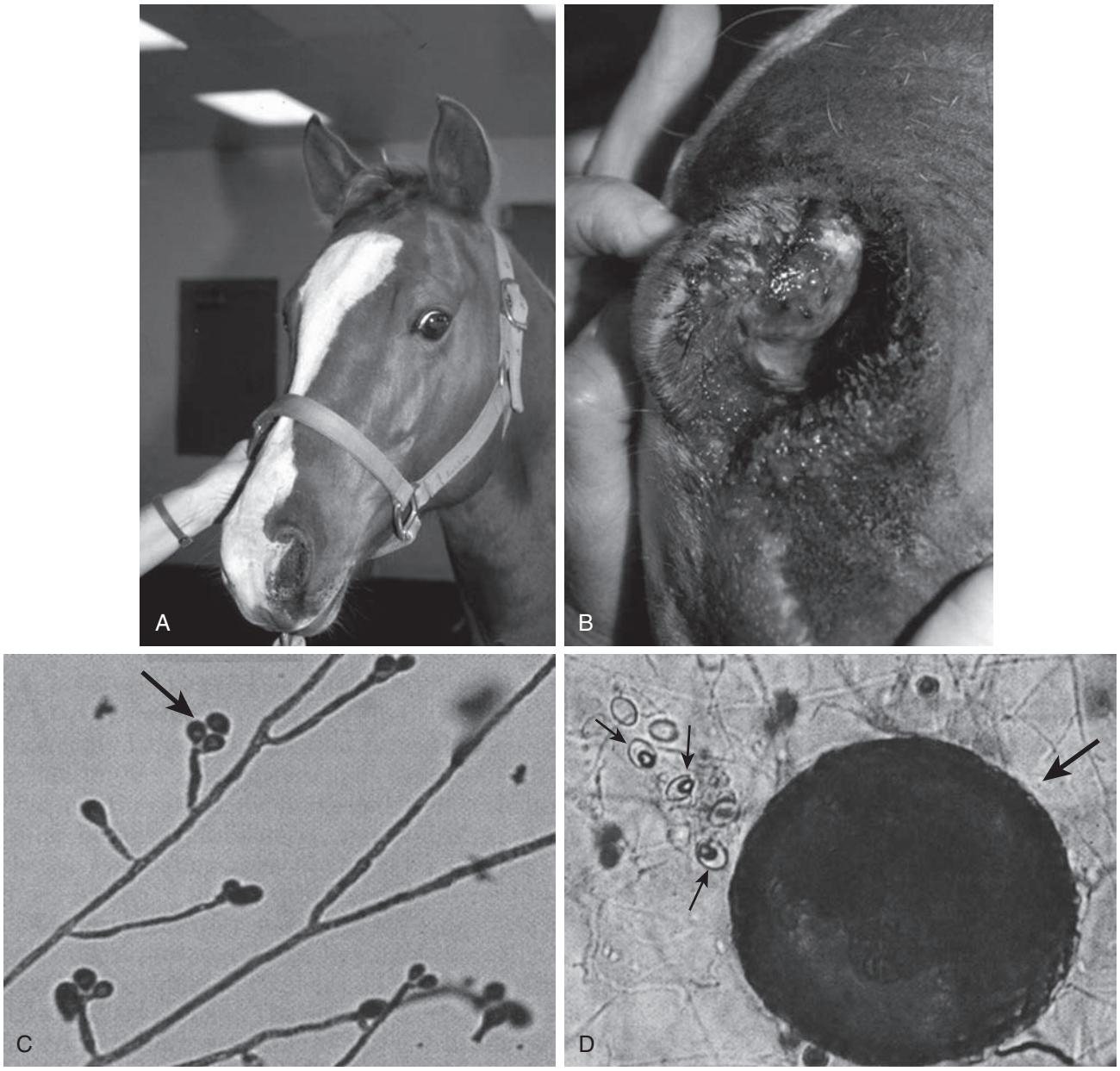


FIG. 31-24 Nasal and nasopharyngeal masses caused by *Pseudallescheria boydii* in a Quarter Horse gelding with chronic, malodorous nasal discharge. **A,** Mucosanguineous nasal discharge. **B,** Mass visible within the external nares. **C,** Asexual form of *P. boydii* in culture showing nonbranching conidiophores with terminal conidia *(arrow).* **D,** Sexual form of *P. boydii* in culture with the cleistothecium *(thick arrow)* and ascospores *(thin arrow). (Courtesy R. Reid Hanson, Auburn University, Auburn, Ala.)*

were observed histologically in many tissues, and *B. dermatitidis* was cultured after 6 weeks.[72] Disseminated blastomycosis was diagnosed in a mare with unresponsive mastitis that progressed to subcutaneous lesions on the ventrum.[73]

Treatment with amphotericin B, itraconazole, or fluconazole is recommended (see Table 31-7).

Histoplasmosis. Histoplasmosis is caused by the saprophytic, dimorphic fungus *Histoplasma capsulatum* and is most prevalent in moist soil containing bird or bat waste. Yeast organisms are 2 to 4 µm in diameter, with a thin clear halo surrounding a round or crescent-shaped basophilic cytoplasm (Fig. 31-26). Histoplasmosis has been reported in fewer than 10 equine cases,[25] and thus horses are considered to be relatively resistant to disease. *H. capsulatum* may occur in an enteric, pulmonary, or disseminated form.[25] *H. capsulatum* was identified in pulmonary granulomas in a horse dying of chronic *Yersinia* colitis.[74] It has also been associated with abortions and severe granulomatous pneumonia in neonatal foals (Fig. 31-27) and a yearling.[75] Successful treatment with amphotericin B was reported in a filly with pulmonary histoplasmosis diagnosed by cytologic identification of the organism on a tracheal wash smear and from a lung aspirate.[25] Treatment with amphotericin B or itraconazole is recommended (see Table 31-7).

Epizootic lymphangitis is caused by *Histoplasma capsulatum* var. *farciminosum* and is considered an economically important disease in the Middle East, India, the Far East, and parts of Africa. Control of the disease is gained usually by destroying infected horses and through application of strict hygiene practices to prevent spread of the organism.

Coccidiomycosis. *Coccidioides immitis* is a soil saprophyte that grows in semiarid areas with sandy, alkaline soils.[76] Inhaled arthroconidia enlarge to form nonbudding spherules, which incite an inflammatory reaction in the lungs and lymph nodes.[77] Horses infected with this fungus have weight loss, fever, abdominal pain, and signs of respiratory disease (Fig. 31-28). Localized, recurring nasal

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FIG. 31-25 One-month-old foal with *Escherichia coli* septicemia and secondary *Aspergillus* pneumonia. **A,** Dyspneic foal being supported with intranasal oxygen. The foal had eight septic joints and severe pneumonia and was subsequently euthanized because of the guarded prognosis. **B,** Photomicrograph of the pleural surface of the lung *(black arrows)* with extensive superficial and deep fungal growth. *Aspergillus* spp. characteristically have parallel-sided, regular septate hyphae with acute-angled dichotomous branching. They are seen reasonably well with hematoxylin and eosin stain. **C,** *Aspergillus* spp. hyphae within pulmonary parenchyma stained metachromatic with specific fungal stain (Gridley stain). *(Courtesy Calvin Johnson, Auburn University, Auburn, Ala.)*

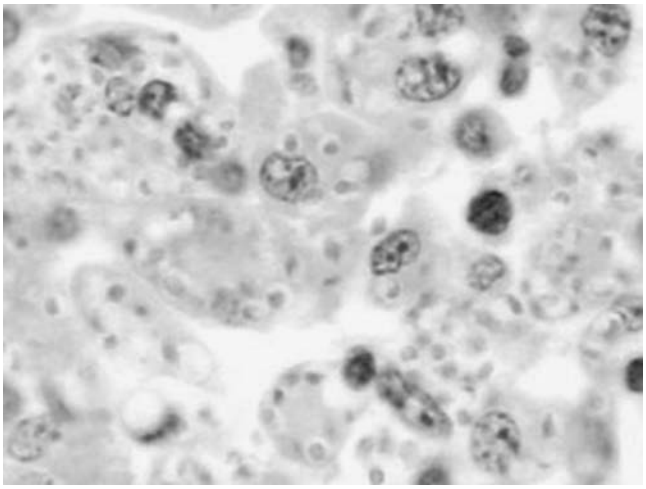


FIG. 31-26 Photomicrograph of tissue infiltrated by activated macrophages containing usually multiple yeasts of *Histoplasma* spp. These yeasts characteristically measure about 2 to 4 µm and appear as structures with a basophilic center and clear halo. (Hematoxylin and eosin stain, ×40.) *(Courtesy Arno Wünschmann, University of Minnesota, St. Paul, Minn.)*

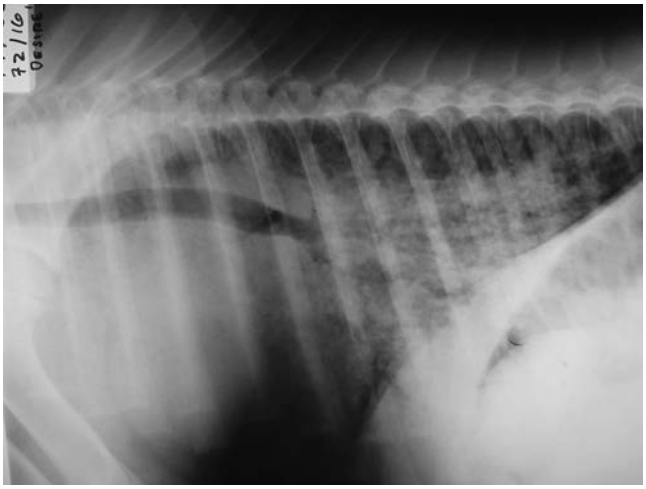


FIG. 31-27 Lateral thoracic radiographs from a foal with *Histoplasma pneumonia. (Courtesy Carol Clark, Peterson and Smith Equine Hospital, Ocala, Fla.)*

granulomas also have been reported.[77] Diffuse infections, with granulomas in the lungs, liver, kidney or spleen have a grave prognosis.[77] Przewalskii horses may be more susceptible.[78]

Coccidioides immitis is difficult to culture, and spherules may not be observed histologically from antemortem lung biopsies. However, serology is very useful for diagnosing infection, and decreasing titers are associated with clinical improvement.[27,76] Serum antibodies are detected rarely in healthy horses.[79] Higher serologic antibody titers are associated with a poorer prognosis for survival.[81] Horses with disseminated disease and pneumonia with thoracic effusion usually have severe clinical disease and frequently die (19 of 21 cases).[81] Antifungal agents successful in treatment of infected horses include itraconazole and fluconazole.[80,27]

Scopulariopsis. *Scopulariopsis* pneumonia was diagnosed by culture of bronchoalveolar lavage fluid in a 2-year-old Quarter Horse filly with pleuropneumonia. The infection resolved following

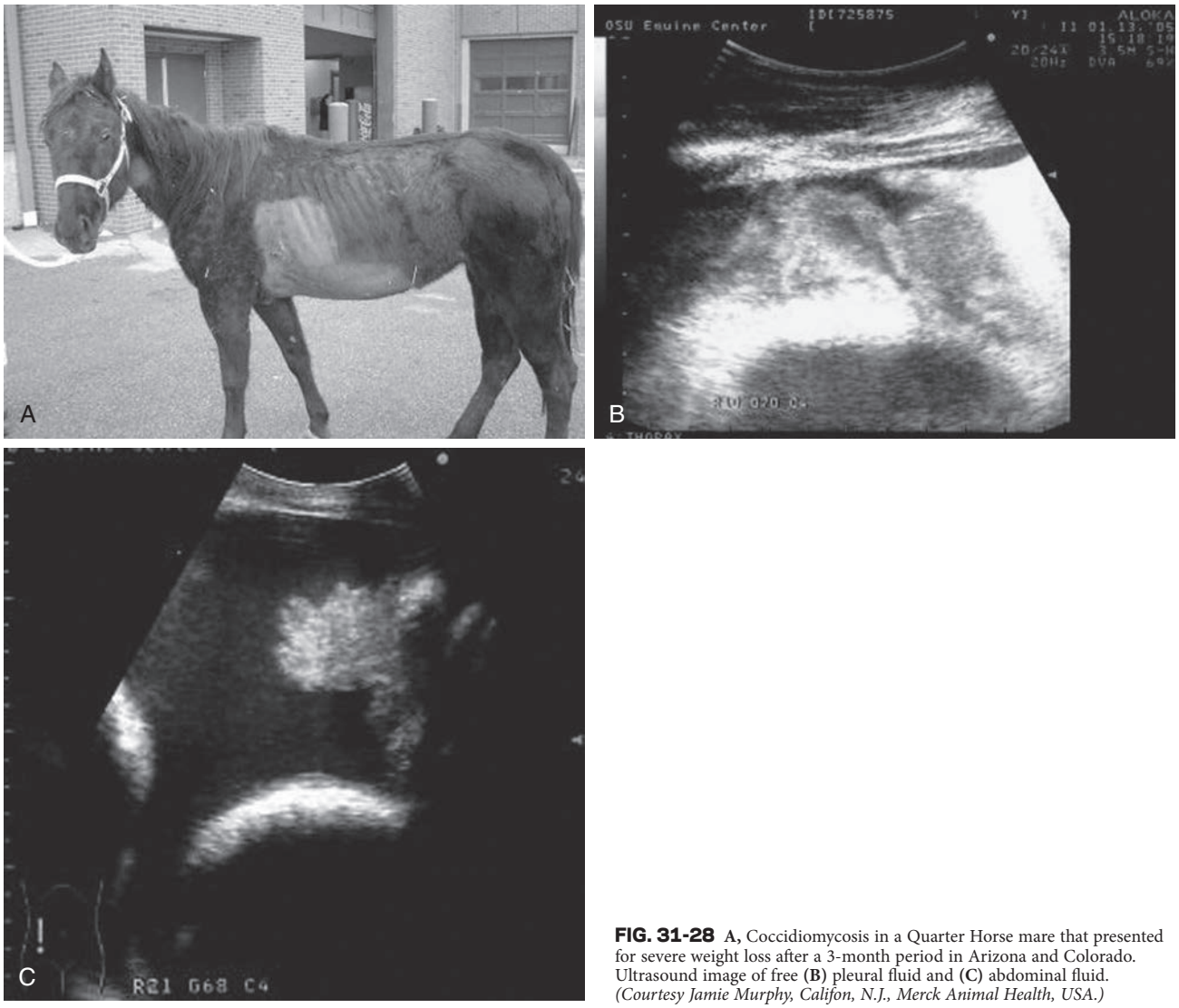


FIG. 31-28 **A,** Coccidiomycosis in a Quarter Horse mare that presented for severe weight loss after a 3-month period in Arizona and Colorado. Ultrasound image of free **(B)** pleural fluid and **(C)** abdominal fluid. *(Courtesy Jamie Murphy, Califon, N.J., Merck Animal Health, USA.)*

multimodal therapy with ketaconazole and aerosolization of enilconazole.[28]

Adiaspiromycosis. Adiaspiromycotic miliary fungal pneumonia caused by the saprophytic soil mold *Emmonsia crescens* was diagnosed in a horse by percutaneous lung biopsy. Euthanasia was performed without treatment.[11]

Acremonium strictum. A diagnosis of interstitial fungal pneumonia caused by *Acremonium strictum* was made based on cytologic evaluation, culture, and PCR testing of bronchoalveolar lavage fluid in a 10-year-old horse. The horse made an uneventful recovery with supportive treatment that included 1 month of fluconazole.[5] In general, fluconazole has been shown to have poor activity against *A. strictum* in vitro.[82] The isolate cultured from the horse was found to be resistant to fluconazole based on in vitro sensitivity testing that was performed after the course of treatment. It is therefore uncertain if the fluconazole assisted in disease resolution.[5]

Candidiasis. In human medicine, candidemia is the most common fungal infection in burn patients, neutropenic patients with malignancies, patients undergoing complex abdominal surgery, and patients receiving total parenteral nutrition and long-term corticosteroid therapy.[67] In humans, *Candida* spp. account for 8% to 10% of all blood culture isolates and rank fourth in the list of most frequently isolated pathogens from blood cultures.[67] The mortality rate in patients with candidemia is 40% to 75%.[67] Over 60% of isolates are *Candida albicans*.[67] Fluconazole is generally considered the drug of choice against *Candida* spp., although *C. krusei* is resistant to fluconazole. Itraconazole, amphotericin B, caspofungin, and voriconazole are alternative antifungal agents (see Table 31-7).[67]

Systemic candidiasis was diagnosed and successfully treated in four neonatal foals. Each foal had prior sepsis attributable to gram-negative bacteria that had been aggressively treated with numerous antibiotics and parenteral nutrition. *Candida albicans* was cultured from a transtracheal wash from one of the foals. Three of the foals had *Candida* glossitis, and one had panophthalmitis and fungal keratitis. Two of the foals were treated with intravenous amphotericin B, and oral fluconazole was used on the other two foals.[12]

Superficial *Candida* spp. infections of the mucous membranes (thrush)[83] can occur in isolation or as part of a systemic infection, and further microbiological culturing of the blood, tracheal wash, urine, or joint fluid may be indicated to rule out systemic infection.[12] *Candida* spp. glossitis can be treated by rinsing the mouth either with potassium permanganate (0.025% q24h) or nystatin (0.3 g in 10 mL of water q8h).

Pneumocystosis. *Pneumocystis carinii* (renamed *P. jiroveci* in humans) has been reclassified from a protozoan to a saprophytic fungus based on the DNA sequence of its 16S-like RNA subunit, but some researchers consider it to be a plant because it lacks ergosterol, the major fungal sterol.[84] It exists as an ameboid yeast or as a cystic sporangia. *P. carinii* cannot be cultured, and diagnosis is based on the cytologic identification of characteristic morphologic features using

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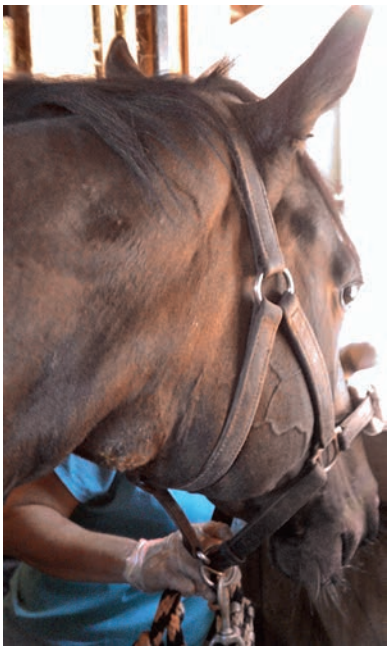


FIG. 31-29 Horse with retropharyngeal lymphadenopathy resulting in head and neck extension characteristic of *S. equi* infection.

specimens obtained by bronchoalveolar lavage rather than tracheal wash. A fluorescent in situ hybridization method with an oligonucleotide probe that targets the 18S ribosomal RNA has been developed recently to detect *P. carinii* in histologic sections.[21] Immunohistochemistry also can be used.[20]

P. jiroveci is the most common organism to cause opportunistic infection in people with HIV, and people undergoing immunosuppressive therapy after organ transplantation are predisposed. *P. carinii* causes diffuse interstitial pneumonia, especially in immunocompromised patients such as Arabian foals with severe combined immunodeficiency (SCID).[13] It also has been diagnosed in immunocompromised adult horses,[14,15] as well as an immunocompetent foal.[20] Trimethoprim-sulfamethoxazole (TMS) (25 to 30 mg/kg PO q12h) is the treatment of choice (see Table 31-7).[85,86] Dapsone (3 mg/kg PO daily for 2 months; Jacobus Pharmaceutical, Princeton, N.J.) was used to successfully treat a foal that developed *Salmonella* enterocolitis after treatment with TMS.[24]

Streptococcus equi Infection (Strangles)

Ashley G. Boyle*

The highly contagious *S. equi* subsp. *equi* infections in horses, commonly referred to as *strangles,* were first described in early veterinary science literature by Jordanus Ruffus in 1251.[1] Strangles is currently a reportable disease in at least seven U.S. states.

Clinical Signs Strangles is characterized by sudden onset of fever followed by upper respiratory tract catarrh, as evidenced by mucopurulent nasal discharge and acute swelling with subsequent abscess formation in submandibular and retropharyngeal lymph nodes (Fig. 31-29). The name *strangles* was coined because affected horses sometimes suffocated as the lymph nodes became enlarged and obstructed the airway.

Fever is the first clinical sign and remains as lymphadenopathy develops and abscesses mature. Pharyngitis makes swallowing painful, and affected animals may become anorectic or reluctant to eat and stand with the neck extended.

*Previous contributions by Corinne Sweeney are acknowledged.

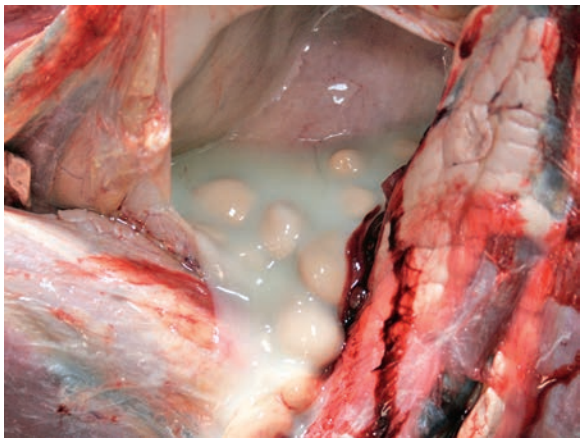


FIG. 31-30 Guttural pouch *S. equi* empyema with chondroids at postmortem. *(Courtesy Dr. Julie Engiles, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*



FIG. 31-31 Horse with the unique presentation of periorbital abscessation with concurrent ocular discharge that cultured positive for *S. equi. (Courtesy Dr. Erica Koch, Atlantic Veterinary College, University of Prince Edward Island, Canada.)*

Lymphadenopathy is a major clinical sign. The submandibular and retropharyngeal lymph nodes are about equally involved in *S. equi* infections. They usually become swollen and painful approximately 1 week after infection. Other lymph nodes of the head region (parotid, cranial, and cervical) are also frequently involved and may abscess. Retropharyngeal lymph nodes may drain into and cause empyema of the guttural pouch (Fig. 31-30). Periorbital abscesses can cause marked swelling of the eyelids and result in ocular discharge that will culture positive for *S. equi* if sampled (Fig. 31-31). Abscesses of the lymph nodes at the thoracic inlet can cause severe tracheal compression, asphyxia, and death. Clinical severity and progression varies greatly depending on the immune status of the animal.

Pathogenesis *S. equi* is of the Lancefield group C streptococcal diseases and enters via the mouth or nose and attaches to cells in the crypt of the lingual and palatine tonsils and to the follicular-associated epithelium of the pharyngeal and tubal tonsils. There is no evidence of colonization before penetration. After a few hours the organism is difficult to detect on the mucosal surface but is visible within cells of the epithelium and subepithelial follicles. Translocation occurs in a few hours to the mandibular and suprapharyngeal lymph nodes that drain the pharyngeal and tonsillar region.[2]

Complement-derived chemotactic factors attract large numbers of polymorphonuclear neutrophils (PMNs), although gross evidence of abscessation is not visible for 3 to 5 days after *S. equi* enters the

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lymph node. Failure of neutrophils to phagocytose and kill the streptococci appears to be a result of a combination of the hyaluronic acid capsule, antiphagocytic SeM protein, Mac protein, and other undetermined antiphagocytic factors released by the organism. Depending on the immune status of the patient and the degree of exposure to *S. equi* bacterial load, clinical signs may develop 3 to 14 days after exposure.[1]

Although strangles involves predominantly the upper airways, including the guttural pouches and associated lymph nodes, metastasis to other locations occasionally occurs. Spread may be hematogenous or via lymphatic channels, which results in abscesses in lymph nodes and other organs of the thorax and abdomen. This form of the disease is known as *bastard strangles.*

Nasal shedding of *S. equi* usually begins 2 to 3 days after onset of fever and persists for 2 to 3 weeks in most animals. Some animals never shed. In others, shedding may last much longer if infection persists in the guttural pouch.[3,4] Systemic and mucosal immune responses are evident 2 to 3 weeks after infection and coincide with mucosal clearance.

As long as they were not treated with antibiotics, approximately 75% of horses develop a solid enduring immunity to strangles that lasts about 5 years after recovery from the disease. A small percentage of these horses become susceptible to a second attack of the disease within months, which probably represents a failure to produce or maintain an adequate level of the appropriate mucosal and systemic antibodies. Older horses with residual immunity have limited susceptibility and develop a mild form of strangles often termed *catarrhal strangles.* These animals shed virulent *S. equi* that will produce severe disease in more susceptible, often younger horses. Colostral antibodies ingested during the first 24 hours of life have also been shown to recirculate to the nasopharyngeal mucosa, thus providing an additional source of protection to the foal during its first weeks. Foals that suckle immune mares are usually resistant to *S. equi* infection until weaning.[1]

Epidemiology

TRANSMISSION. Outwardly healthy horses that still shed organisms are a source of infection when introduced into a new population of horses. Definitive determination of carrier status requires endoscopic examination of the guttural pouches as well as culture and PCR testing of guttural pouch lavage fluid.[5,6] *S. equi* may originate from outwardly healthy horses such as the following:

- Horses that are incubating the disease and go on to develop signs themselves
- Horses that are recovering from recent disease but that continue to harbor the organism after full clinical recovery for some weeks (carriers)
- Horses that are fully recovered from the disease but continue to be potentially infectious for prolonged periods through periodic shedding of *S. equi* (carriers)

ENVIRONMENTAL PERSISTENCE OF *STREPTOCOCCUS EQUI*. Currently there is a lack of definitive field-based proof for prolonged environmental persistence of *S. equi. S. equi* is known to be sensitive to bacteriocins from environmental bacteria and does not readily survive in the presence of other soil-borne flora. Modeled environmental field conditions revealed that the organism was found to persist for less than 4 days, but moist environments (e.g., water buckets) may allow the organism to persist for extended periods.[7]

Diagnosis

Early definitive diagnosis is essential for containing this highly infectious disease. Sampling may be unsuccessful during the incubation and early clinical phases. *S. equi* is normally not present on the mucosa until 24 to 48 hours after the onset of fever, so infection in horses monitored by daily measuring of rectal temperatures during an outbreak may be recognized early and isolated to limit transmission of *S. equi*. Cytologic evaluation reveals gram-positive extracellular cocci in long chains, supporting a general diagnosis of a β-hemolytic streptococcus organism. Common hematologic findings of horses with *S. equi* are hyperfibrinogenemia, neutrophilic leukocytosis, and mild anemia.



FIG. 31-32 Infusing 50 mL of 0.9% saline for a nasopharyngeal wash on a sedated horse with a uterine pipette. The pipette is punctured through one side of the rectal sleeve.

CULTURE. Historically, the gold standard for diagnosis has been bacterial culture of abscess aspirates, nasopharyngeal swabs, and nasopharyngeal and guttural pouch washes revealing *S. equi.* Culture is the preferred method on aspirates of mature abscesses, but it takes a minimum of 24 hours to obtain results.

POLYMERASE CHAIN REACTION. The polymerase chain reaction (PCR) is designed to detect DNA sequence of *SeM,* the gene for the antiphagocytic M protein of *S. equi.* PCR can also be performed on nasopharyngeal swab, nasopharyngeal wash, and guttural pouch wash samples. Nasopharyngeal washes (Fig. 31-32) are preferable to nasopharyngeal swabs due to a larger sampling area,[1] but guttural pouch sampling is the most reliable, although most expensive, requiring aspirating the sample via polyethylene tubing through the instrument channel of a 1-meter endoscope.[5,6] The endoscope should be sterilized following and between sampling of suspect horses. PCR testing is more sensitive than bacterial culture[8] and should always be used in combination.[1]

SEROLOGY. Serologic testing involves the use of ELISA to detect the SeM protein. Serology is useful for detecting recent, but not current, infection; assessing the need for vaccination; identifying horses that may be predisposed to purpura hemorrhagica; and diagnosing *S. equi*–associated purpura hemorrhagica and metastatic abscessation (SeM titers often are =1:12,800 but have been seen as low as 1:3200 and 1:6400 in confirmed cases).[1,9] It has been suggested that horses with high serum SeM-specific antibody titers may be predisposed to developing purpura hemorrhagica when vaccinated against *S. equi*.[1] A 2009 study identified older horses, non-Thoroughbreds and non-warmbloods, and horses that had been recently vaccinated (last 1 to 3 years) with an attenuated live intranasal *S. equi* vaccine as having an increased likelihood of SeM-specific antibody titers 1:1600 or greater. Of 35 horses that had been vaccinated with intranasal strangles vaccine when SeM titer was equal to 1:1600, 26 (74%) did not have any complications associated with purpura.[10] Therefore the recommendation is to not vaccinate when the titer is 1:3200 or greater.

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The Animal Health Trust in the United Kingdom recently developed a serologic test that detects different surface antigens. This test is currently being used to identify horses with recent strangles exposure for the purposes of isolation and further examination via endoscopic guttural pouch examination.[11]

VACCINATION. Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer. This indicates that stimulation of a high level of immunity is biologically feasible given appropriate presentation of protective immunogen(s). There is evidence that immunity in horses resistant to reinfection is mediated at the mucosal level and functions to block entry of *S. equi*. However, systemic immunity after parenteral inoculation of avirulent live *S. equi* is also protective. Together, these findings indicate that optimum immunity may require both systemic and mucosal responses.

Vaccine should be administered only to healthy nonfebrile animals free of nasal discharge. Although controversial, vaccination should be considered only in horses with no known contact with animals with strangles during an outbreak.[1] The American Association of Equine Practitioners (AAEP) Infectious Disease Committee does not recommend vaccination during an outbreak. It is suggested that horses recovering from infection should not be vaccinated for 1 year.

USE OF EXTRACT VACCINES. Extract vaccines (Strepvax II [Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Mo.]) are given intramuscularly and elicit serum antibody responses 7 to 10 days later. Naive horses and foals require a schedule of two or three doses at an interval of 2 weeks. Booster doses are given once annually. Pregnant mares may be boostered a month before expected date of foaling. Extract vaccines have been associated with cases of purpura hemorrhagica.[12]

USE OF ATTENUATED LIVE INTRANASAL VACCINE. Attenuated live vaccine (Pinnacle I.N. [Zoetis, Florham Park, N.J.]) is given in a schedule of two doses at 2- to 3-week intervals. Annual booster doses are recommended. The mode of application should be such that an adequate amount of vaccine reaches the pharyngeal and lingual tonsils but does not enter the trachea. Careful handling of live vaccine is recommended to prevent inadvertent injection intramuscularly either via the vaccine directly or contamination of other vaccines given at the same time. It is not recommended in horses less than 1 year of age because of the possibility of development of vaccine-associated clinical disease.[13]

FUTURE VACCINES. It is likely that more effective and safer vaccines will eventually be developed based on genomic sequence information from *S. equi* and *S. zooepidemicus*. In Europe, clinical studies are under way evaluating a recombinant multicomponent subunit vaccine.[14]

CONTROL OF OUTBREAKS. Most outbreaks are thought to originate from introduction of an infected horse to a naive population. All new horses should be isolated for 3 weeks and monitored for any signs of disease, including fever. If cost is not prohibitive, horses should be screened for *S. equi* infection using nasopharyngeal washes. Many farms with repeated infections have resorted to screening for infection via endoscopic evaluation and PCR testing of guttural pouch lavages, a procedure considered by many as the "gold standard" for carrier detection.[5,6] A series of three nasopharyngeal swabs, collected 1 week apart, will result in detection by a positive culture on at least one of the swabs in approximately 60% of carrier animals. Concurrent testing of these swabs by PCR increases the likelihood of detection to over 90% of carrier animals.[11]

A practical disease-control strategy should then be agreed on and implemented. The general aims and measures for such a strategy are outlined in Table 31-8.[1]

Treatment

The goal of treating strangles is to control transmission and eliminate infection while providing future immunity to the disease. Appropriate treatment of horses with strangles usually depends on the stage and severity of the disease, and veterinary opinion as to whether or not to use antibiotic treatment remains markedly divided.[15]

HORSES WITH EARLY CLINICAL SIGNS. During an outbreak, immediate antibiotic therapy for new cases in the early acute phase with fever and depression may be curative and may prevent focal abscessation and shedding. Because abscesses have not developed at this early stage, the antibiotics have adequate access to the bacteria. Immediate treatment of horses that show the earliest clinical sign, fever, could be an effective way of controlling strangles outbreaks in racing stables or riding barns, although the disadvantages of treatment should be weighed.

HORSES WITH LYMPH NODE ABSCESSATION. Uncomplicated cases of strangles are often left to run their course with supportive care, providing lasting immunity. Affected horses should be isolated in a clean, dry stall and fed moist, palatable food. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used judiciously to decrease swelling and promote eating. Hot compresses or topical 20% ichthammol can be used to accelerate maturation of abscessation. Mature external abscesses should be lanced to allow drainage, followed by daily lavage of open abscesses using dilute povidone iodine solution. This speeds resolution of abscessation as well as alleviation of compression of the pharynx.

Although the use of antimicrobials for treating strangles is controversial, if the horse is febrile, depressed, anorectic, and particularly if manifesting dyspnea, antibiotic therapy is indicated to decrease abscess size and prevent complete airway obstruction. In rare cases, affected horses may require intensive supportive therapy, including IV fluids, feeding by nasogastric tube, and tracheostomy. An animal requiring a tracheostomy should be given systemic antimicrobial drugs to prevent secondary bacterial infections of the lower respiratory tract.

DRUGS OF CHOICE FOR THERAPY. Penicillin G (procaine penicillin [22,000 to 44,000 IU/kg IM q12h] or aqueous potassium penicillin [22,000 to 44,000 IU/kg IV q6h]) is generally considered the drug of choice for the treatment of nonpneumococcal streptococcal disease, with alternative drugs used depending on ease of administration or the site of infection. Other agents for therapy include cephalosporins and macrolides. Although there is evidence that trimethoprim-sulfadiazine did not eliminate *S. zooepidemicus* infection in tissue chambers implanted subcutaneously in ponies, the study did not determine its effectiveness against *S. equi*.[16] Anecdotally, trimethoprim-sulfadiazine treatment failure has been seen. Use of antibiotics during any phase of the disease may prevent the development of lasting immunity.

Complications

GUTTURAL POUCH EMPYEMA AND CARRIER STATUS. The percentage of carriers per outbreak could be as high as 10%. Endoscopic examination is required for identification of guttural pouch empyema. The SeM ELISA does not detect empyema or carrier status.[5] Elimination of guttural pouch empyema requires repeated lavage with a solution of 20% acetylcysteine in buffered saline via polyethylene tubing through an endoscope or via a chambers catheter. Chondroids are particularly difficult to remove, possibly requiring manual removal with endoscopic equipment such as a memory helical polyp retrieval basket, repeated lavage via indwelling catheters, or surgical removal. Successful elimination of *S. equi* in these carriers requires local treatment of the guttural pouch with a penicillin gel after removal of the material within the guttural pouch in addition to systemic treatment with procaine penicillin or potassium penicillin for 7 to 10 days. Eradication of this disease will not be possible until the subpopulation of carriers is eliminated.[17]

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TABLE 31-8

Aims and Measures Used to Control Transmission of *S. equi* on Affected Premises

Aim	Measure
1. To prevent the spread of *S. equi* infection to horses on other premises and to new arrivals on the affected premises	Stop all movement of horses on and off the affected premises immediately and until further notice. Horses with strangles and their contacts should be maintained in well-demarcated "dirty" (i.e., *S. equi*–positive) quarantine areas. Clustering of cases in groups should allow parts of the premises to be easily allocated as "dirty," "recovering," and "clean" areas. Perform twice-daily monitoring of rectal temperatures to identify temperature increases in horses early and move them to the "dirty" area prior to the start of shedding.
2. To establish whether convalescing horses are infectious at least 2 to 3 weeks *after* clinical recovery	*S. equi* PCR assay and culture testing of at least three nasopharyngeal lavages are performed at approximately weekly intervals in all recovered horses and their contacts, or preferably of one guttural pouch lavage with endoscopic examination. Horses that test consistently negative are returned to the "clean" area.
3. To investigate all outwardly healthy horses in which *S. equi* is detected by either culture or PCR assay	Perform endoscopy of the upper respiratory tract and guttural pouches.
4. To eliminate *S. equi* infection from the guttural pouches	Remove pathology through a combination of flushing and aspiration with saline, and remove chondroids using endoscopically guided instruments. Perform topical and systemic administration of antimicrobials to eliminate *S. equi* infection. A minimum of 3 weeks should pass before retesting a treated, previously positive guttural pouch via PCR.
5. To prevent indirect cross-infection by *S. equi* from horses in the "dirty" area to those in the "clean" area of the premises	Personnel should use dedicated protective clothing when dealing with infectious animals and should not deal simultaneously with susceptible animals. If this is unavoidable, infectious horses should be dealt with *after* susceptible animals. Strict hygiene measures are introduced, including provision of dedicated clothing and equipment for each area and disinfection facilities for personnel and use of thorough stable cleaning and disinfection methods. When cost is not a factor, consideration should be given to destruction of the dedicated equipment after eradication of the infection. After removal of organic material from stables, all surfaces should cleaned first with detergent and then be thoroughly soaked in an appropriate liquid disinfectant (phenols, quaternary ammonium compounds) and allowed to dry. Manure and waste feed from infectious animals should be composted (disinfected by heat) in an isolated location. Pastures used to hold infectious animals should be rested for 4 weeks. Care should be taken to clean and disinfect water troughs at least once daily during an outbreak. Horse vans should be cleaned with detergent and then disinfected after each use.

PCR, Polymerase chain reaction.

COMPLICATIONS ASSOCIATED WITH METASTATIC SPREAD OF INFECTION. In as many as 20% of cases, *S. equi* spreads hematogenously or lymphatically. This results in metastatic abscessation, which can affect any organ system. Aspiration of mucopurulent discharge or hematogenous or lymphatic spread to the lungs can cause pneumonia. Abscessation in the mesentery, liver, spleen, and kidneys is common, leading to peritonitis and clinical signs of colic. Abscessation of the cranial mediastinal lymph nodes can cause tracheal compression and respiratory distress. Neurologic signs are present when abscessation occurs in the brain.[1] The mortality rate of horses with strangles is less than 2%, but the presence of bastard strangles can increase the mortality rate to as high as 62%.[18,19] Attempted culture and sensitivity from the affected body cavity provides direction for the appropriate antibiotic treatment, which has included penicillin, ceftiofur, chloramphenicol, and doxycycline. An average of 2.5 months of antibiotic treatment was needed for resolution.[18] Some horses have been treated via surgical drainage along with systemic antibiotics.[19]

PURPURA HEMORRHAGICA. Purpura hemorrhagica is an aseptic necrotizing vasculitis that can occur in mature horses after repeated natural exposure to infection or after vaccination of horses that have had strangles. The actual incidence of this type III hypersensitivity response secondary to strangles or vaccination is unknown. Clinical signs range from mild to life-threatening, including pitting edema of the head, trunk, and distal limbs, as well as petechiae and ecchymoses. In some cases, antigen-antibody complexes affect other sites, including the gastrointestinal tract, muscles, lungs, myocardium, and kidneys. In addition to prolonged treatment with penicillin, cases of purpura hemorrhagica also require the use of systemic corticosteroids (dexamethasone, 0.1 to 0.2 mg/kg IV or IM q12-24h; prednisolone, 0.5 to 1 mg/kg PO q24h) for an average of 3 weeks to reduce systemic vasculitis.[12] Significant rhabdomyolysis with progressive atrophy has been identified in some Quarter Horses, after exposure to *S. equi,* without other signs of purpura.

Acute Respiratory Distress Syndrome and Acute Lung Injury (Acute Bronchointerstitial Pneumonia)

Bettina Dunkel

Definition and Pathophysiology Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) comprise a syndrome of severe pulmonary dysfunction and respiratory failure caused by physical or chemical injury or an exaggerated pulmonary immune response. In human medicine, ALI and ARDS are defined by an acute onset, bilateral pulmonary infiltrates, a ratio of partial arterial oxygen pressure (PaO_2) to fraction of inspired oxygen (FiO_2) of less than 300 mm Hg for ALI (the less severe form) and less than 200 mm Hg for ARDS, and no clinical evidence of left atrial hypertension or a pulmonary arterial occlusion pressure of less than 18 mm Hg.[1] Recently, a further stratification based on the PaO_2/FiO_2 ratio into mild (201 to 300 mm Hg), moderate (101 to 200 mm Hg), and severe (up to 100 mm Hg) disease has been introduced.[2] During

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a consensus meeting, definitions for veterinary ALI and veterinary ARDS were developed (Box 31-1).[3] Because of lack of available data, no species-specific definitions were established, but the physiologic differences in arterial oxygenation in foals less than 1 week of age were addressed by introducing different inclusion criteria for this age group (Table 31-9). The consensus definition also acknowledged the disease presentation in neonatal foals with presumed pulmonary surfactant deficiency (termed *neonatal equine respiratory distress syndrome; NERDS*) secondary to very early gestational age, induction of parturition, or caesarean section as a distinct entity different from VetALI/VetARDS.[3]

ALI or ARDS arises as a complication after major infectious or noninfectious bodily injury. During injury or infections, the body mounts a protective response that involves controlled activation of the inflammatory and coagulation system.[4,5] In ALI and ARDS an imbalance of proinflammatory and antiinflammatory factors, combined with activation of the pulmonary endothelium and derangement of the coagulation cascade, favors the development of a fulminant, uncontrolled pulmonary inflammatory response and a widespread procoagulant environment in alveoli and the pulmonary microcirculation.[5,6] The triggering event can be an intrapulmonary insult (viral or bacterial pneumonia, smoke inhalation, near drowning, or food aspiration) or an extrapulmonary insult (trauma, multiple transfusions, systemic inflammatory response, or sepsis). In people, variants of several genes regulating inflammation, coagulation, and endothelial cell function, as well as genetic polymorphism predisposing individuals to the pathogenic effects of specific bacteria and viruses, are thought to influence the development of ALI and ARDS and also the outcome.[5]

The pathophysiology of ALI and ARDS is centered around dysregulation of pulmonary inflammation and coagulation, leading to accumulation and activation of leukocytes and platelets, altered permeability of the endothelial and epithelial barrier, and ultimately accumulation of extravascular protein-rich edema fluid.[5,7] Although not temporally distinct and largely overlapping, the pathophysiologic events can be divided into an initial exudative phase, a fibroproliferative phase, and, if the patient survives, a recovery phase.[8] The exudative phase is characterized by uncontrolled release of inflammatory mediators and influx of inflammatory cells into the pulmonary tissue. Activated platelets, neutrophils, and alveolar macrophages marginate in the microcirculation and extravasate into the pulmonary tissue, where they release oxidants, reactive oxygen species, proteases, and cytokines, amplifying and perpetuating inflammation and coagulation.[9] A variety of mediators, pathways, and molecular systems ultimately contribute to the breakdown of the alveolar endothelial and epithelial barrier, causing flooding of the alveoli once the edema safety factors have been exhausted. The barrier tends to collapse suddenly, resulting in rapid filling of the alveoli with proteinaceous exudate, leukocytes, and red blood cells, and destruction of the surfactant layer.[6] The fast onset of pulmonary edema may correspond with the clinically observed acute onset of respiratory distress in foals. The prothrombotic and antifibrinolytic environment favors formation of thrombi in the pulmonary microvasculature and deposition of intraalveolar fibrin-rich hyaline membranes.[10] The fibroproliferative response, which can begin within 24 hours of the onset of ALI and ARDS, is characterized by type I pneumocyte necrosis and proliferation of the more resistant type II pneumocytes in an attempt to restore the epithelial surface.[6,11] Fibroblasts invade the

BOX 31-1

Veterinary Acute Lung Injury (VetALI) and Acute Respiratory Distress Syndrome (VetARDS)

At least one each of the first four criteria must be met; criterion 5 is recommended but optional (Wilkins et al, 2007).

1. Acute onset (<72 hours) of tachypnea and labored breathing at rest
2. Exposure to a known risk factor
3. Evidence of pulmonary capillary leak without increased pulmonary capillary pressure* (any one or more of the following):
   a. Bilateral/diffuse infiltrates on thoracic radiographs (>1 quadrant/lobe)
   b. Bilateral dependent density gradient on computed tomography
   c. Proteinaceous fluid within the conducting airways
   d. Increased extravascular lung water
4. Evidence of inefficient gas exchange (any one or more of the following):
   a. Hypoxemia without PEEP or CPAP and known FiO_2
      i. PaO_2/FiO_2 ratio
         1. <300 mm Hg VetALI ($PaO_2 \leq 63$ mm Hg at room air†)
         2. <200 mm Hg VetARDS ($PaO_2 \leq 42$ mm Hg at room air†)
      ii. Increased arterial-alveolar (A-a) gradient
      iii. Venous admixture (noncardiac shunt)
   b. Increased "dead-space" ventilation
5. Evidence of diffuse pulmonary inflammation
   a. Transtracheal wash/bronchoalveolar lavage cytologic neutrophilia
   b. Transtracheal wash/bronchoalveolar lavage biomarkers of inflammation
   c. Molecular imaging (positron emission tomography)

Adapted from Wilkins PA, Otto CM, Dunkel B, et al. 2007. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. J Vet Emerg Crit Care 17:333; with permission.

*No evidence of cardiogenic edema (one or more of the following):

Pulmonary arterial occlusion pressure < 18 mm Hg (adult horse)

No clinical or diagnostic evidence supporting left heart failure, including echocardiography

†FiO_2 room air: 21%.

CPAP, Continuous positive airway pressure; *FiO_2,* fraction of inspired oxygen; *PaO_2,* partial arterial oxygen pressure; *PEEP,* positive end-expiratory pressure.

TABLE 31-9

Equine Neonatal Acute Lung Injury/Respiratory Distress Syndrome (Eq NALI/NARDS)*

Postnatal Age	Normal PaO_2	Normal PaO_2/FiO_2 Ratio	Eq NALI	Eq NARDS
60 min	60.9 ± 2.7 mm Hg	>300 mm Hg	<175 mm Hg	<115 mm Hg
12 hours	73.5 ± 3.0 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
24 hours	67.6 ± 4.4 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
48 hours	74.9 ± 3.3 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
4 days	81.2 ± 3.1 mm Hg	>400 mm Hg	<250 mm Hg	<160 mm Hg
7 days	90.0 ± 3.1 mm Hg	>430 mm Hg	<280 mm Hg	<190 mm Hg

Adapted from Wilkins PA, Otto CM, Dunkel B, et al. 2007. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. J Vet Emerg Crit Care 17:333; with permission.

*As for VetALI/VetARDS but adhering to the following age-dependent adaptation of the PaO_2/FiO_2 ratio in term foals in lateral recumbency breathing room air ($FiO_2 = 0.21$) based on age-dependent normal values for PaO_2 under similar conditions (Wilkins et al, 2007).

FiO_2, Fraction of inspired oxygen; *PaO_2,* partial arterial oxygen pressure.

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pulmonary interstitium and alveolar walls and deposited collagen, which can result in fibrosis and significant impairment of pulmonary mechanics and gas exchange. The extensive pulmonary pathology leads to severe hypoxemia with hypocapnia or hypercapnia caused by ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch and decreased pulmonary compliance. Alveolar edema creates areas of a low $\dot{V}/\dot{Q}$ ratio (adequate perfusion but no ventilation), causing hypoxemia, whereas areas with deceased perfusion generate hypoxemia and eventually hypercapnia by increasing dead space ventilation (high $\dot{V}/\dot{Q}$ ratio; adequate ventilation with minimal perfusion).[6] The coexistence of areas with high and low $\dot{V}/\dot{Q}$ ratios adjacent to normal lung tissue makes mechanical ventilation of patients with ALI and ARDS extremely challenging and predisposes the patient to ventilator-induced lung injury.

The resolution of ALI and ARDS requires repair of endothelial and epithelial barriers, reabsorption of alveolar edema, and removal of inflammatory exudate and cellular debris.[5] Sodium and chloride ions are actively transported via ion channels on the apical surface and Na+/K+-ATPase on the basolateral membrane of alveolar epithelial cells while water follows the created osmotic gradient through aquaporin-5 channels located on type I epithelial cells. If damage to the pulmonary epithelium is minor, pulmonary edema can be cleared swiftly, pulmonary function improves rapidly, and chances of survival increase. If large areas of alveolar epithelium are destroyed, gradual reepithelialization by proliferation of type II cells, and potentially also by recruitment of progenitor cells, must occur first.[5,12] Severe damage to the epithelium corresponds with prolonged respiratory failure, slow recovery, and high mortality.[13] Recovering patients may have complete resolution of pulmonary compromise or may suffer from residual functional impairment, such as muscle weakness, decreased pulmonary function, restrictive or obstructive changes, and low diffusion capacities.

VetALI/VetARDS, in earlier reports also referred to as *acute interstitial* or *bronchointerstitial pneumonia,* has been described in foals and weanlings up to 7 months of age.[14-20] Extensive searches for a common pathogen were conducted until, with increasing understanding of the pathophysiology, it became evident that multiple infectious and noninfectious agents are capable of initiating the inflammatory response.[14-17] In foals the most common risk factor appears to be intrapulmonary injury, namely bacterial or, in rare cases, viral pneumonia.[14-17,19-21] There are no clinical reports of VetALI or VetARDS in adult horses, although descriptions in case reports and small studies suggest its occurrence. Buergelt and colleagues[14] reported respiratory distress in six adult horses; however, the description they give better fits the heterogeneous group of interstitial pneumonias than it does VetALI and VetARDS. Two adult horses with respiratory distress after near drowning met the criteria for ALI,[22,23] and two horses affected by smoke inhalation experienced fulminant pulmonary inflammation and, most likely, VetALI.[24] Experimentally, VetARDS has been induced by intravenous (IV) injection of perilla mint ketones[25,26] and was observed after experimental gram-negative sepsis.[27] However, most of the animals in the latter study were in an agonal state, making interpretation of the observed pulmonary changes difficult.[27] Further risk factors recognized in other species that might also occur in the horse include systemic inflammation, severe trauma, multiple transfusions, aspiration of stomach contents, drugs, and toxins.[3] The discovery of genetic predispositions to dysregulation of inflammation and coagulation in people is intriguing, as a similar predisposition in equids could potentially explain why, of many foals affected by infectious pneumonia, very few develop VetALI and VetARDS.

Clinical, Diagnostic, and Postmortem Findings

It is almost impossible to clinically differentiate foals with VetALI and VetARDS from foals with severe bacterial, chiefly advanced *Rhodococcus equi,* pneumonia, particularly as the syndrome can be triggered by an underlying bacterial infection. Clinical signs include profound depression, fever, and respiratory distress with tachycardia, tachypnea, nostril flare, and cyanotic mucous membranes. Auscultation of the lungs can reveal a variety of abnormal sounds or complete silence over nonventilated areas. Laboratory findings include severe hypoxemia with hypocapnia or hypercapnia and, depending on the underlying disease process, leukocytosis or leukopenia and hyperfibrinogenemia. Signs of disseminated intravascular coagulation were present in two foals with VetALI and VetARDS in one report,[16] and abnormal coagulation parameters may be observed. Transtracheal lavage fluid demonstrates neutrophilic inflammation with or without signs of infection, depending on the underlying cause. Thoracic radiographs show a diffuse, dense bronchointerstitial pattern often coalescing to a focal or diffuse alveolar pattern with prominent air bronchograms. The initial radiographic appearance of the lungs may worsen dramatically within hours as a result of rapid progression of pulmonary edema. On the other hand, absorption of the alveolar fluid may result in impressive improvement of the radiographic appearance within days.[16,17] A thoracic sonogram is useful in foals that cannot be safely transported to a radiography unit and reveals multiple coalescing comet-tail artifacts, predominantly in the caudodorsal lung field.

On gross pathologic examination, the affected lungs are wet and firm and fail to collapse; airways contain variable amounts of pink, foamy liquid. Histologically, necrosis of alveolar and terminal bronchial epithelium is observed, with extensive filling of the alveolar spaces with neutrophils, macrophages, hemorrhage, protein-rich edema fluid, or hyaline membranes. Occasionally, microthrombi can be detected in interstitial capillaries. In more chronic cases, diffuse proliferation of cuboidal pneumocytes and fibroblasts and beginning fibrosis may be present.[14-17]

Diagnosis

The diagnosis can be established if the criteria outlined in Box 31-1 and, depending on the age, Table 31-9 are met; cardiac disease is absent; and the extent of the respiratory distress cannot solely be attributed to a primary disease process (e.g., almost complete destruction of the pulmonary parenchyma by a primary disease process). Presence of bacterial or viral pneumonia does not rule out concurrent VetALI or VetARDS.

Treatment and Prognosis

A recent reduction in mortality rates in human ALI and ARDS has largely been attributed to more widespread use of lung-protective ventilation with lower tidal volumes (6 mL/kg) and airway pressures and conservative fluid therapy.[28] Antiinflammatory, antioxidant, anticoagulant, and surfactant therapy and treatment to enhance alveolar edema removal (aerosolized or intravenous β-adrenergic agonists such as salmeterol, terbutaline, or epinephrine to stimulate active transepithelial ion transport) have largely failed to improve survival.[5] However, considering that, in contrast to human medicine, most equine patients die as a direct result of respiratory failure, some of those therapeutic options may still benefit equine patients. As mechanical ventilation is, with few exceptions,[29] feasible only in neonates, the most important treatment remains intranasal insufflation of humidified oxygen via unilateral or bilateral intranasal cannulas. Large-bore tubing systems minimize the resistance to airflow, and Fi_{O_2} as high as 70% and 75% has been measured at the carina in adult horses and foals, respectively, using bilateral flow rates of 15 L/min (10 L/min in foals; combined 30 L/min in adults or 20 L/min in foals).[30,31] Alternatively, use of intratracheal oxygen insufflation has been described, achieving results similar to high bilateral intranasal flow rates.[32] Although controversial, administration of methylprednisolone at 1 to 2 mg/kg/day is still occasionally recommended in acute cases of human ALI and ARDS for up to 2 weeks, followed by a gradual decrease of the dose.[33] Considering that ventilation is rarely an option and that in two reports all but two foals surviving ALI and ARDS received corticosteroids, anecdotal evidence is in favor of steroid administration (IV prednisolone sodium succinate or methylprednisolone at 1 to 2 mg/kg/day divided in 2 to 4 doses). Antimicrobial treatment, if required, should be directed against the underlying disease process. Bronchoconstriction is not a prominent feature of ALI and ARDS, and bronchodilators are therefore most likely of limited use. Care should be

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taken when administering bronchodilators as they can induce sudden worsening of $\dot{V}/\dot{Q}$ mismatch and can lead to acute decompensation of the severely hypoxic patient. Judicious IV fluid therapy may be necessary in dehydrated patients, but overhydration or rapid changes in circulating blood volume should be avoided as capillary hydrostatic pressure is the main determinant of pulmonary edema formation when endothelial and epithelial permeability is increased. On the other hand, a suboptimal hydration status decreases cardiac output and worsens oxygen delivery to the peripheral tissue. Measurement of central venous pressure may aid in determination of the patient's hydration status. If foals are too depressed to nurse or eat, nutritional support is essential.

Based on the limited information available, the prognosis for survival and future athletic performance is guarded, with survival rates ranging from 60% to 69% in two clinical reports.[16,17] It is difficult to extrapolate long-term outcomes of pulmonary function from human patients because of the extensive use of mechanical ventilation with associated injury and frequent presence of preexisting comorbidities such as smoking.[34] Experimental induction of ARDS in horses did not result in any lasting histologic changes or fibrosis despite severe clinical signs.[25] The few long-term reports of equine survivors have so far suggested little noticeable lasting respiratory compromise, and successful careers as racehorses have been reported even in severely affected animals.[17] More information is clearly needed to determine the long-term effects of severe pulmonary injury in horses.

Interstitial Pneumonia

Pamela A. Wilkins • Kurt Williams • Fabio Del Piero

Interstitial pneumonia is an uncommon cause of acute or chronic lower respiratory tract disease in horses.[1-7] Because of the potential severity of the process, it becomes important to recognize and definitively diagnose interstitial pneumonia as early as possible in its clinical course. Unfortunately, its onset is often insidious and subclinical. By the time it clinically manifests itself, there is often considerable involvement of the lungs, with chronic remodeling of the gas exchange regions with extensive fibrosis, resulting in altered mechanical properties of the lung typical of restrictive lung disease.

Etiology A variety of agents have been implicated in the genesis of interstitial pneumonia in animals, although fewer than 20 have been confirmed in horses (Box 31-2). Chief among these are infectious agents and ingested and inhaled toxins. Because of the frequently insidious onset of interstitial pneumonia, the causative agent(s) is(are) often not identified, leading to a diagnosis of idiopathic interstitial pneumonia. Because the lung response to injury, especially in long-standing cases of interstitial pneumonia, is often nonspecific relative to the initial insult, and the cause may no longer be present, it is often difficult to identify the inciting cause. Therefore all efforts should be made to identify a causative agent early in the course of the disease, if possible, but the practitioner needs to be aware that treatment frequently will be nonspecific and supportive.

INFECTIOUS AGENTS. Infectious causes of interstitial pneumonia in horses and foals include viral, bacterial, parasitic, protozoal, and fungal agents. Typically the pneumonia is acute and severe, characterized by severe damage to the lung parenchyma (alveolar region).

Viral agents are frequently implicated or suspected but rarely identified by the usual serologic, histopathologic, and virus isolation methods. The advent of more sensitive and specific techniques, such as in situ PCR and monoclonal antibody immunohistochemistry, may partially resolve the current diagnostic challenge.

Since 2008 the equine gammaherpesvirus EHV-5 has been associated with a nodular form of interstitial pneumonia of horses characterized by pulmonary interstitial fibrosis, suggesting that these rather unusual cases may have an underlying infectious cause.[8] This disease has been termed *equine multinodular pulmonary fibrosis* (EMPF) by the authors describing the pathology of the disease. Horses affected by the disease generally have a history of fever, cough, and weight loss, accompanied by exercise intolerance and, finally, respiratory distress. They can be acutely affected or have a more chronic progressive disease. Typical radiographs reveal multiple discreet to coalescing nodular densities overlying a diffuse interstitial pattern (Figs. 31-33 and 31-34). Histologic appearance is diagnostic of this disease (Fig. 31-35). EHV-5 has been identified in both BALF and lung biopsy samples from affected patients by both PCR assay and immunohistochemistry. Preliminary efforts to reproduce the disease through lung inoculation of horses with isolates of EHV-5 obtained from animals with EMPF have shown that similar nodular pulmonary fibrosis can be induced in such infected animals, providing strong evidence that the virus is the cause of the disease.

BOX 31-2

Causes of Interstitial Pneumonia in Horses

Acute

Infections (systemic viral, bacterial, parasitic)
Inhaled chemicals
  Oxygen (Fio_2 > 50%)
  Smoke
Ingested toxins or precursors
  Perilla mint (*Perilla frutescens*), Crofton weed (*Eupatorium adenophorum*), *Crotalaria* spp., *Senecio* spp.
Adverse drug reactions
  Uncertain
Hypersensitivity
  Acute hypersensitivity pneumonitis
Endogenous metabolic or toxic conditions
  Shock—particularly endotoxic (ARDS)
  Disseminated intravascular coagulation (DIC)
  Uremia
Idiopathic or cryptogenic

Chronic

Infections (systemic viral, bacterial, parasitic)
Inhaled inorganic dust (pneumonoconioses)
  Silicosis
Hypersensitivity
  Hypersensitivity pneumonitis
Ingested toxins or precursors
  Perilla mint (*Perilla frutescens*), Crofton weed (*Eupatorium adenophorum*), *Crotalaria* spp., *Senecio* spp.
Collagen-vascular disorders
  Uncertain
Idiopathic or cryptogenic

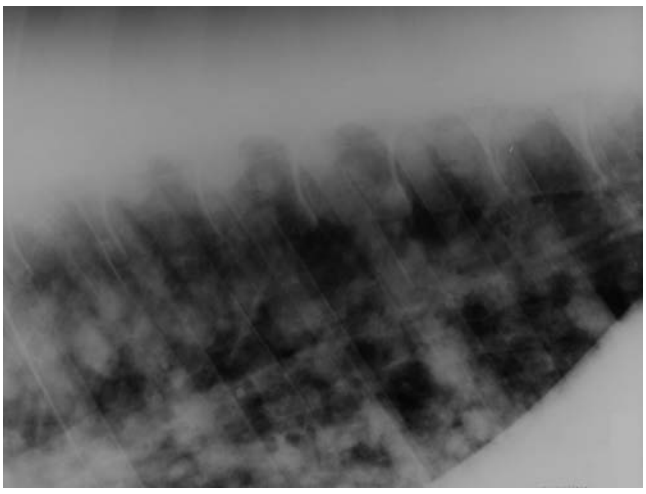


FIG. 31-33 Thoracic radiograph of horse with equine pulmonary nodular fibrosis. Note diffuse interstitial pattern and multifocal areas of soft-tissue density distributed throughout the lung. *(Courtesy Dr. David Wong, Iowa State University, Ames, Iowa.)*

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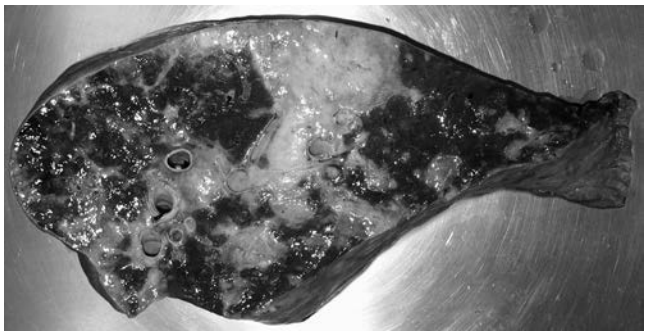


FIG. 31-34 Cut section of lung from horse with equine multinodular pulmonary fibrosis. Note large areas of fibrosis within the pulmonary parenchyma. *(Courtesy Dr. Perry Habecker, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

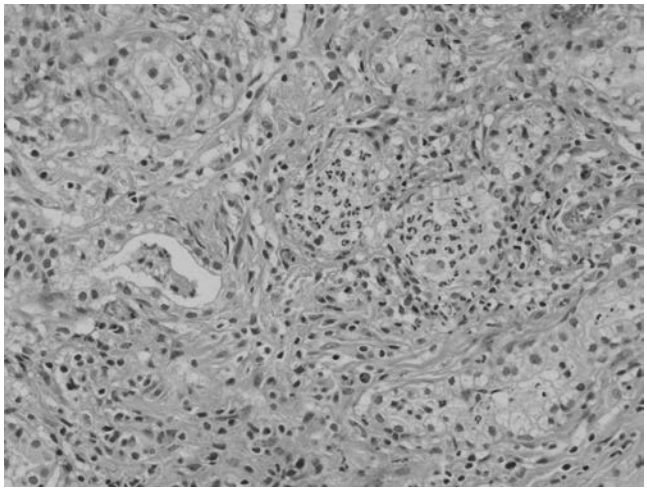


FIG. 31-35 Lung histopathology from a horse with equine multinodular pulmonary fibrosis. Note the cuboidal epithelial cells lining the remodeled airspaces in the regions of fibrosis. Within the airspace lumen there is a mix of neutrophils and macrophages. An intranuclear viral inclusion body is visible within one of the cells. *(Courtesy Dr. Fabio Del Piero, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

In some horses with bronchointerstitial pneumonia of unknown cause, bacterial agents have been isolated from the lung. The usual distribution of bacterial bronchopneumonia in the horse is cranioventral, whereas the distribution in interstitial pneumonia is often nearly diffuse. In the latter cases the bacteria most likely represent contaminants or possibly opportunistic agents and do not represent the primary cause. An exception is *R. equi* pneumonia of foals, which has been associated with ARDS-like disease in older foals. *R. equi* has been cultured from foals with severe, acute bronchointerstitial pneumonia with a diffuse pulmonary distribution.[4] Interstitial pneumonia associated with *P. carinii* has been described in the foal, and *Mycoplasma* spp. have been isolated from the respiratory tract of adult horses.[9] *Mycoplasma* isolates in horses should usually be considered incidental to the disease, as their significance in equine respiratory disease is unproven. *P. carinii* pneumonia is thought to occur primarily in immunocompromised foals as a complication of some other serious disease, such as infectious pneumonia *(R. equi)* or SCID. It is characterized by a severe plasmacytic lymphocytic interstitial pneumonia with flooding of alveoli with foamy acidophilic material.

Parasitic pneumonia, an uncommon cause of chronic bronchointerstitial pneumonia, usually occurs in young foals secondary to migration of *Parascaris equorum* larvae through the pulmonary parenchyma.

INGESTED CHEMICALS. Ingested chemicals rank second only to infectious agents as potential causes of interstitial pneumonia in horses. Ingestion of pyrrolizidine alkaloids from a variety of plants (mostly genera *Crotalaria, Trichodesma,* and *Senecio*) can cause interstitial pneumonia in horses.[10] This toxicity is associated with production of a toxic metabolite that is activated in the liver and then circulates to the lung. The toxic alkylating agents damage capillary endothelial cells, although the amount of alkaloid required to damage the lung is generally less than that required for hepatotoxicity. Crofton weed *(Eupatorium adenophorum),* a poisonous plant found primarily in Australia and Hawaii, produces interstitial pneumonia in horses. Toxicity is associated with ingestion of the flowering plant, but the nature of the toxin is not known. Perilla ketone, derived from the plant *Perilla fructans,* experimentally produced acute respiratory distress with a week of ingestion in ponies. The lesions include diffuse alveolitis and type II pneumocyte proliferation with sparing of the bronchioles. Toxicity depends on additional metabolism of the 3-substituted furan by the mixed function oxidase system, which occurs directly in the lung of the horse.

INHALED CHEMICALS. Direct pulmonary injury by inhaled chemicals is an uncommon cause of interstitial pneumonia in horses. In people this type of pneumonia is primarily related to occupational exposure. Smoke inhalation causes acute, diffuse interstitial pneumonia in horses, frequently followed within a few days by opportunistic bacterial pneumonia. Oxygen toxicity can theoretically produce interstitial pneumonia and alveolar type II cell proliferation. This problem is more likely to be seen in neonatal foals mechanically ventilated with increased levels of oxygen ($Fi_{O_2} > 50\%$) for several days, although this may in fact be a form of ventilator-associated lung injury (VALI) associated with mechanical stretch of the airspaces. Damage is thought to be due to production of reactive oxygen metabolites, which attack a lung that may already have been injured by barotrauma resulting from a ventilator-driven increase in airway pressure. Agrichemicals or herbicides, such as paraquat, may cause acute interstitial pneumonia (AIP) in horses and should be considered in horses with a history of possible exposure. Silicate pneumoconiosis is a specific chronic granulomatous pneumonia of horses associated with inhalation of silicates. This syndrome has been described in horses originating from the Carmel Valley region of California. The inhaled particles are ingested by alveolar macrophages and result in lysis of the macrophage, chronic alveolitis, and fibrosis. Multiple granulomas are present, and intracytoplasmic crystalline particles can be identified in macrophages.

HYPERSENSITIVITY REACTIONS. In the most specific sense, *hypersensitivity pneumonitis* refers to pulmonary disease caused by inhalation of organic antigens. Lymphocytic, plasmacytic bronchitis and bronchiolitis, combined with lymphocytic interstitial pneumonia, characterize the disease in horse lung. Granuloma formation and fibrosis can be observed. Chicken dust and fungi have been implicated as causes of severe, chronic bronchointerstitial pneumonia, but the syndrome itself is quite rare.

Endogenous Metabolic and Toxic Conditions

Various conditions cause acute pulmonary injury with inflammatory edema or severe alveolar wall damage and serofibrinous exudation similar to that described for AIP. Acute uremia, shock, burns, and trauma can produce an acute pulmonary injury termed *acute lung injury* (ALI) or *acute respiratory distress syndrome* (ARDS), depending on severity. Although endotoxin does not directly injure the lung, endotoxemia in the horse initiates inflammatory and metabolic cascades that can lead to pulmonary injury. Activation of these pathways produces vasoactive and chemoattractant molecules that increase vascular permeability, activate complement, produce proinflammatory cytokines, and release neutrophil enzymes that can adversely affect the lungs of horses. Horses as a species are quite sensitive to the negative effects of endotoxemia, and their lungs are particularly sensitive, perhaps because of the presence of intravascular macrophages, which further amplify the inflammatory cascade. Both ALI and ARDS have recently been defined for veterinary patients.

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Pathophysiology Interstitial pneumonia progresses through four phases. During the first, the initial insult causes parenchymal injury and alveolitis. This is followed by a proliferative phase characterized by cellular and parenchymal alterations in tissues of the lung. Chronic cases progress to the development of interstitial fibrosis, and the final stage results in end-stage irreparable fibrosis of the lung.

The structural changes that occur in the lung reduce the number of functional alveoli, adversely affecting ventilatory function of the lung and altering ventilation-perfusion relationships. Reduced lung compliance is associated with the loss of distensible alveoli, the presence of pulmonary edema, and fibrosis. Total and vital lung capacities are decreased in association with the loss of functional gas exchange units and reduced lung compliance. The work of breathing is increased, resulting in exercise intolerance and difficulty in breathing. Pulmonary hypertension and cor pulmonale may be complications of severe chronic interstitial pneumonia and fibrosis. Although the origin of pulmonary hypertension is unclear, hypoxic vasoconstriction and generation of vasoactive compounds (such as endothelin-1) that alter pulmonary vascular resistance acutely, and vessel anatomy chronically, may play a role.

Clinical Signs Horses affected with interstitial pneumonia frequently have fever, cough, weight loss, nasal discharge, exercise intolerance, severe dyspnea, cyanosis, and a restrictive breathing pattern. A "heave line" is frequently present; nostril flare and an anxious expression are usual. The history can be acute or chronic. Although affected foals are frequently depressed and anorectic, adults may be bright and alert with a variable appetite. The disease proceeds toward death in many cases, with progressive respiratory compromise, although some patients may also slowly improve with time. More than one foal at a farm may be affected.

Diagnosis In older horses the primary differential diagnosis of heaves may be excluded by the leukocytosis and hyperfibrinogenemia that commonly occur in horses with interstitial pneumonia and fibrosis but do not occur in horses with heaves. However, these abnormal features are common in horses with infectious bronchopneumonia, and thoracic radiography is of paramount importance in the establishment of a definitive diagnosis. Typically, thoracic radiographs reveal extensive interstitial and bronchointerstitial pulmonary patterns.[11] Nodular infiltrates may be present, either large or miliary, but always diffusely distributed.

Culture of transtracheal or BAL aspirates often yields no significant growth of bacterial or fungal pathogens. Cytologic evaluation of tracheal or BALF shows increased numbers of neutrophils and macrophages. If *P. carinii* is involved, BALF may reveal trophozoites or intracystic bodies with special stains, such as toluidine blue or methenamine silver. Using PCR, EHV-5 has been found in BALF from horses with EMPF.

Histologic examination of a transthoracic lung tissue biopsy specimen is the definitive diagnostic test for chronic interstitial pneumonia and fibrosis and for EMPF. Care must be taken to ensure the tissue biopsy is obtained from a representative area, and ultrasound guidance can be useful. Clinically important complications from this technique are uncommon but can occur. Biopsy can both define the causative agent and confirm the clinical diagnosis in EMPF when the sample is evaluated for EHV-5.

Additional diagnostic procedures could include arterial blood gas analysis, abdominocentesis and thoracocentesis to rule out metastatic neoplastic disease, PFT, viral isolation, serologic testing for antibody to fungi and chicken serum if hypersensitivity pneumonitis is suspected, and immunohistochemical evaluation of lung tissue for suspected infectious agents. A complete cardiac evaluation should also be conducted, as pulmonary hypertension and cor pulmonale are not uncommon sequelae.

Treatment Treatment of these cases is often unrewarding. Therapeutic goals are treatment of any underlying or secondary infection; suppression of inflammation; maintenance of tissue oxygen delivery within appropriate limits; relief of any associated bronchoconstriction; and prevention or treatment of complications. Environmental control, with appropriate temperature and humidity control and good ventilation, is beneficial.

Parenteral corticosteroid therapy is the mainstay of treatment, with early and aggressive therapy providing the best long-term outcome, particularly in foals. In one report of 23 foals affected with acute bronchointerstitial pneumonia, 9 of 10 treated with corticosteroids survived, but none of those not receiving steroid treatment lived.

Broad-spectrum antimicrobial treatment should be instituted initially, particularly in foals, as described for the treatment of infectious bronchopneumonia. The choice of antimicrobial agent and duration of therapy should be dictated by the culture and sensitivity results from the transtracheal aspirate (TTA) and by the patient's clinical course. Anecdotally, horses with EMPF have responded to treatment with acyclovir and corticosteroids. The course of therapy is generally prolonged (6 to 12 weeks); clinical and radiographic improvement has been noted in a few cases to date.

Foals, in particular, and adults with severe respiratory distress may benefit from nasal insufflation of humidified oxygen, with flow rates of 10 L/min for foals and 15 L/min in adults. If necessary, as determined by persistent hypoxemia in the face of intranasal insufflation at the rates given, a second nasal cannula can be placed in the opposite nostril to increase the FiO_2. Care must be taken to avoid obstruction of the nasal passages. Alternatively, intratracheal or transtracheal insufflation can be considered to further increase FiO_2 and improve oxygenation.

Systemic bronchodilator therapy may or may not be indicated in these cases. If used, bronchodilators may worsen ventilation-perfusion inequalities. Therefore bronchodilator therapy should be accompanied by supplemental oxygen, and the effects should be monitored with serial blood gas measurements and discontinued if hypoxemia worsens. Nebulized or aerosolized bronchodilator therapy may be more judicious, and beneficial effects are evident in some foals with respiratory distress. Aminophylline and theophylline should not be used, owing to their narrow therapeutic range. Furosemide may be appropriate for its bronchodilator effect and its effect on reducing pulmonary artery pressure, particularly if cor pulmonale develops.

Prognosis The prognosis for horses with interstitial pneumonia is uniformly poor to guarded. Affected foals, treated early and aggressively with corticosteroid and antimicrobial therapy, have the best outlook for life. The disease is usually progressive in adults and eventually results in the demise of the horse, although the occasional horse recovers sufficiently to return to previous performance levels. A fair number of adult horses, with continuous intense management, will live for a period of time but will be severely compromised, which limits their usefulness. Exceptions to the poor prognosis may be seen in cases of *P. carinii* pneumonia in foals if they are treated early and aggressively and possibly also in cases of idiopathic interstitial pneumonia or EMPF in adult horses that are treated early with corticosteroids and antiviral drugs. A trial of treatment for peracute interstitial disease for 48 hours is warranted, and patients with chronic interstitial pneumonia should be treated for a minimum of 6 weeks before the possibility of recovery is discarded.

Equine Respiratory Viruses

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Viral respiratory infections in horses are major causes of respiratory disease resulting in impaired pulmonary function and reduced performance. Although vaccines are available for many of the causative agents, the respiratory viruses have remained a major concern in the horse industry. Infection with equine respiratory viruses can lead to serious respiratory illness with potentially fatal consequences. The incidence and severity of viral respiratory disease varies from year

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to year and is dependent on the attack rate, virulence of the circulating virus, infectious dose, management and environmental conditions, and the degree of immunity of individual animals in the population.

With the exception of Hendra virus infection, in a group of susceptible horses, equine viral respiratory infection generally is characterized by the rapid spread of an acute, febrile respiratory disease accompanied by a dry cough and nasal discharge. Therefore a presumptive diagnosis of viral respiratory disease can often be made based on history and clinical signs. However, to confirm and differentiate among the potential causative agents, laboratory diagnosis is required.

Diagnosis of Equine Respiratory Viruses

The basic approaches for the laboratory diagnosis of equine viral respiratory disease are the isolation of the causative agent (virus isolation), demonstration of the virus or viral product in clinical specimens (detection of virus particles by electron microscopy; detection of viral antigens by immunofluorescence, enzyme-linked immunosorbent assay [ELISA], or immunoperoxidase; detection of the viral genome), and the detection of virus-specific antibodies (serology). Because each of these methods has its merits as well as disadvantages (e.g., lack of sensitivity, long turnaround time, high costs), it may be necessary to combine several of them to identify the causative agent accurately and rapidly. The World Organization for Animal Health (OIE, http://www.oie.int) publishes the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals,* which provides an in-depth review of current diagnostic testing strategies.

VIRUS ISOLATION. Virus isolation from clinical samples is crucial for epidemiologic investigation and for vaccine production and generally is carried out in cell culture. The notable exception is equine influenza virus for which embryonated chicken eggs have remained the culture system of choice. As virus shedding in secretions of the respiratory tract is greatest within the first few days after infection, the best results for virus isolation are often achieved by culturing nasal or nasopharyngeal swab samples collected in the first 24 to 48 hours after onset of clinical disease. As the duration of nasal virus shedding is often brief in partially immune animals, it may prove useful to sample immunologically less protected individuals in a group (e.g., younger horses, poorly vaccinated or unvaccinated animals) to increase the likelihood of demonstrating infectious virus. Nasopharyngeal or nasal swab samples are best collected using polyester-tipped swabs instead of cotton swabs because certain viruses (e.g., influenza A virus) have been found to adhere to the cotton fibers. The swabs should be placed in a sterile viral transport medium and kept on ice until further analysis.

ANTIGEN DETECTION. The most important advantages of diagnostic tests aimed at the detection of viral antigen over traditional virus isolation are the faster turnaround time as well as the ability to detect virions that have lost their infectivity. Immunofluorescence (fluorescent antibody [FA] test) is based on the detection of virus-infected cells employing virus-specific fluorochrome-labeled antibodies. The technique is used to detect viral antigen in a broad range of clinical samples (e.g., frozen sections of tissues, tissue imprints, cells obtained from nasal scrapings or tracheal washes) and has been shown to be highly sensitive. A number of antigen-capture ELISA-based assays have been developed for the detection of equine respiratory viruses.[1-5] Frequently, a solid-phase system is used for virus detection. Specific antibody is first adsorbed to the surface of a microtiter plate, and the sample containing the suspected virus is then added. If the virus is present, it binds to the adsorbed antibody. After washing, specific enzyme-labeled antibodies are added. Detection of virus in the sample is achieved by addition of the enzyme substrate, which results in a color reaction. Commercially available ELISA-based test kits (e.g., Flu OIA assay [Biostar, Boulder, Colo.]; Directigen Flu-A assay [Becton Dickinson Microbiology Systems, Cockeysville, Md.]) have been validated for the rapid, stall-side detection of equine influenza virus. Many investigators found these commercial diagnostic kits to be highly specific and rapid, and their sensitivity approaches that of egg isolation.[6-10] Since the discovery of the polymerase chain reaction (PCR), the technique has found wide application in diagnostic laboratories. By choosing appropriate oligonucleotide primers, a selected region of the viral genome can be amplified. PCR-based assays are extremely sensitive and theoretically can detect a single copy of the target nucleic acid in a sample.[11-13] Because of the assay's high sensitivity, the greatest challenge facing the diagnostic application of PCR is the production of false-positive results. Nevertheless, PCR-based techniques offer a more sensitive tool for the diagnosis of equine respiratory viruses than conventional techniques such as culture or immunoassays. To increase the diagnostic capacity of PCR, multiplex PCR assays have been developed. By including more than one pair of primers in the reaction mixture, these assays are designed to simultaneously detect a panel of respiratory pathogens. For example, multiplex PCR assays designed to detect nucleic acid of influenza A and B viruses, respiratory syncytial virus, adenovirus, and parainfluenza virus have been developed for screening of human clinical samples.[14-17] In equine diagnostics, assays capable of simultaneously detecting and differentiating EHV-1 and EHV-4[18-20] as well as EHV-2 and EHV-5[21] have been published. More recently, real-time PCR-based assays have been used for the detection and quantification of equine respiratory pathogens.[22-24] By employing a target-specific fluorescent probe, real-time PCR-based assays eliminate the need to distinguish the target by PCR fragment size on electrophoresis or hybridization with probes post-PCR. The advantages of real-time PCR include high specificity, sensitivity, and a rapid turnaround time.

ANTIBODY DETECTION. Detection of virus-specific antibodies has been, and continues to be, a key tool in the diagnosis of equine viral respiratory disease. Detection of specific antibody can provide support that an animal has been exposed to a given antigen. Although this is often used as circumstantial evidence of infectious disease, a diagnosis of active infection requires the demonstration of at least a fourfold increase in antibody titers (seroconversion) in samples collected during acute infection and during convalescence. Therefore serology typically provides only retrospective information. Yet, as most serologic assays are fairly easy to perform, are cost-effective, and large numbers of samples can be collected and tested simultaneously, serologic testing is particularly useful for large-scale herd surveillance. Commonly used techniques for antibody detection include ELISA-based assays, virus neutralization tests, single radial hemolysis, complement fixation tests, and hemagglutination inhibition assays. Because of the inherent variability of immunoassays, paired samples always should be run by the same laboratory. Lastly, it is important to recognize that antibody is not always detected in the presence of active infection. The most common reason for a negative result despite infection is that insufficient time has passed between infection and measurement of an antibody response. Alternatively, immunocompromised horses may fail to produce a detectable antibody response despite active infection.

Treatment

The treatment of horses suffering from viral respiratory disease is primarily symptomatic. It is important to ensure that sick animals are kept in a clean, well-ventilated, and stress-free environment. Morbidity caused by pyrexia and myalgia may be reduced by administering NSAIDs. It is important to monitor affected horses for development of complications such as pneumonia and myocarditis, and animals exhibiting signs of respiratory disease beyond 10 days should be reevaluated to rule out secondary bacterial infections.

Antiviral drugs, such as amantadine, rimantadine, oseltamivir, and the chain-terminating nucleoside analogs (e.g., acyclovir, valacyclovir, valganciclovir) have been evaluated for prophylaxis and treatment of horses during outbreaks of equine influenza and EHV-1, respectively. Clinical trials with the influenza virus M2 ion channel blockers amantadine and rimantadine have shown that both drugs

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appear to be equally effective in reducing the severity and duration of clinical illness.[25,26] In addition, oral administration of rimantadine (30 mg/kg, q12h) was shown to reduce the virus load in nasal secretion, although the duration of nasal virus shedding was similar to that in the untreated controls.[25] However, the therapeutic and prophylactic benefits of M2 ion blocker antiviral therapy during outbreaks of equine influenza may be limited because of the potential for the rapid development of drug resistance. In vivo and in vitro studies have demonstrated that drug-resistant influenza virus mutants can develop as early as 1 day after start of treatment.[27] Subsequent isolation of the drug-resistant virus from susceptible contacts showing signs of clinical disease indicates that acquisition of drug resistance is not associated with attenuation of the virus.[28,29] Lastly, treatment of horses with amantadine has also been associated with adverse effects and poor oral bioavailability.[30] Oseltamivir, a neuraminidase inhibitor with demonstrated antiviral activity against equine influenza in vitro, was also found to reduce the magnitude of nasal virus shedding and severity of clinical signs in horses following experimental inoculation.[31] In addition, oseltamivir administration reduced the counts of *Streptococcus equi* subsp. *zooepidemicus* in bronchoalveolar fluid samples collected 7 days after influenza infection compared with the untreated controls.[31] Despite these findings, the use of antivirals during an equine influenza outbreak should be carefully deliberated, as their use can result in the development of antiviral resistance among influenza A viruses.[32-34] Hence, the indiscriminate use of these drugs can possibly reduce the effectiveness of treatment during an outbreak.

Acyclovir, valacyclovir, ganciclovir, valganciclovir, and other chain-terminating nucleoside analogs have been shown to be efficacious against various strains of abortigenic and neuropathogenic EHV-1 viruses in vitro.[35-38] Although there are no controlled studies reporting on the efficacy of acyclovir in the treatment and prevention of EHV-1 infection in horses, anecdotal reports suggest a potential benefit of acyclovir administration (10 mg/kg PO 5 times daily; 20 to 30 mg/kg PO 2 or 3 times daily) in horses with clinical signs of EHV-1 infection (e.g., EHM, neonatal infection).[39-41] Two studies evaluating the pharmacokinetics of a single oral dose of acyclovir in adult horses revealed that intragastric administration of the drug was associated with high variability in serum drug concentrations as well as poor oral bioavailability.[42] Studies examining the effectiveness of oral valacyclovir, a prodrug of acyclovir, in the treatment of horses infected with EHV-1 have demonstrated controversial results. While administration of valacyclovir (27 mg/kg q8h followed by 18 mg/kg q12h), either prior to experimental EHV-1 inoculation or at the onset of fever, reduced the severity of clinical signs in one study,[43] another study found no effect on clinical signs, nasal virus shedding, or viremia in ponies treated (40 mg/kg q8h) compared with the untreated control ponies.[44]

Equine Influenza Virus

Equine influenza is the most frequently diagnosed cause of viral respiratory disease in horses.[45,46] It is a highly infectious disease that affects horses, donkeys, mules, and zebras. Outbreaks of a disease resembling influenza have been reported as early as 1751; however, the causative agent was not isolated until 1956.[47,48]

Etiology Equine influenza viruses are members of the family Orthomyxoviridae, which contains enveloped viruses with segmented, single-stranded, negative-sense RNA genomes.[49] The Orthomyxoviridae comprise five genera; influenza A, B, and C viruses; thogotoviruses; and isaviruses.[49] Equine influenza viruses are influenza A viruses. In contrast to influenza B and C viruses, which appear to have a fairly narrow host range, influenza A viruses can infect a wide variety of species (e.g., horses, humans, wild and domestic birds, pigs, sea mammals, dogs, and cats). It has long been recognized that influenza A viruses exhibit partial restriction of their host range,[48] indicating that viruses from one host species occasionally can transmit to infect another host. Although horses have often been regarded as isolated or "dead-end" hosts for influenza,[48] events of recent years clearly indicate that the species barrier for viruses jumping either to or from horses is not absolute. For example, the severe influenza epidemic in horses occurring in 1989 in the Jilin and Heilongjiang provinces in the northeast region of the People's Republic of China was caused by a virus with avian-like genetic features, suggesting that the virus had spread directly to horses from birds.[50] Another, more recent example is the transmission of an equine-lineage H3N8 virus to dogs in the United States.[51]

Although the viral and host factors that determine the host range of influenza viruses, and the mechanisms by which species barriers are overcome, are not completely understood, a large body of research highlights the importance of the viral hemagglutinin (HA) glycoprotein in determining host specificity.[48,52,53] The HA serves as the viral receptor-binding protein and is embedded, along with the neuraminidase (NA) and the ion channel M2 protein, in a host cell–derived lipid envelope. Mediated by binding of the HA to sialic acid residues on the host cells, the virion envelope and the host cell membrane fuse. This interaction subsequently promotes the release of the viral genome into the cytoplasm of the host cell. The NA is responsible for the cleavage of the α-ketosidic linkage between a sialic acid molecule and an adjacent sugar D-galactose or D-galactosamine. Biologically, the NA facilitates the mobility of the influenza virus virion by assisting in the release of the budding virus particle from the host cells.[54,55] Both HA and NA are major surface antigens of the influenza virus virion. Partly because of the host immune pressure, these proteins can undergo substantial antigenic variation (antigenic drift), which allows the mutant viruses to escape neutralizing antibodies.

Based on antigenic properties of the HA and NA, influenza A viruses are divided into subtypes. To date, 17 HA subtypes (H1 to H17) and 10 NA subtypes (N1 to N10) have been described.[56] With the exception of one HA and one NA subtype, all other subtypes have been isolated from wild waterfowl.[56-59] In contrast, only a limited number of subtypes have been associated with infection of mammals. For example, in humans, only viruses of H1, H2, H3, N1, and N2 subtypes have circulated widely in the population,[48,60] and only H1, H3, N1, and N2 subtypes have been consistently isolated from pigs.[61-63] In horses, influenza infections have been caused mostly by viruses of H7N7 (A/equine/1) and H3N8 (A/equine/2) subtypes.[47,64,65] Although serologic evidence suggests that H7N7 viruses may still be circulating at low levels in the equine population of Central Asia[48] and Eastern Europe,[47,66] these viruses have not been isolated from horses since the late 1970s.[10,57,67] In contrast, despite intensive vaccination programs, equine H3N8 viruses continue to circulate in large parts of the world. Since the 1980s, a number of severe, widespread influenza outbreaks in horses have occurred in South Africa,[68] in India,[69] in the People's Republic of China,[50,70] and in the United Kingdom.[71] The causative agent of the South African outbreak was identified as an H3N8 virus, which was most likely introduced by importation of infected horses from the United States or Europe.[10,72] In 2007, an equine influenza outbreak occurred for the first time in Australia, a country previously considered to be free of the disease.[73] The outbreak was caused by an equine-lineage H3N8 virus that was thought to have been introduced by importation of influenza-infected horses from Japan.[73,74] Stringent control measures, consisting of movement restrictions and vaccinations, allowed for the eradication of the virus from the Australian horse population, and Australia regained its equine influenza–free status in December 2008.[75,76]

Since the early to mid 1980s, the equine H3N8 viruses have diverged into two distinct evolutionary lineages, Eurasian and American. Although the circulation of both lineages initially centered largely on their geographic origin,[77] introduction and apparent maintenance of American-lineage viruses in horses in Europe initially resulted in the co-circulation of both lineages in Europe. In contrast, only a few reports support sporadic infection of horses in North America with viruses originating in Europe.[78-80] Continued genetic divergence of the American-lineage viruses resulted in the formation of three antigenically distinct American-like sublineages (a South American lineage, a Kentucky lineage, and a Florida lineage)[80] with

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further evolution of the Florida sublineage into two antigenically distinct groups, referred to as Florida sublineage clades 1 and 2. Whereas clade 1 viruses circulate in North America and parts of Europe, clade 2 viruses have only been identified in Europe and parts of Asia. Despite the fact that the rate of genetic diversion of equine viruses is small compared with human and swine influenza viruses, this sustained genetic and antigenic evolution continues to have an impact in terms of immunization.

Epidemiology Experimentally, horses of all age groups are susceptible to infection.[81] However, whereas sporadic infection in foals has been described, there exists only one published report of a widespread influenza outbreak in foals less than 6 months of age.[82] The lower incidence of disease in young foals is most likely due to the presence of maternally derived antibodies. Influenza-specific serum antibody concentration is an accurate correlate to protection against infection and disease, and animals with high concentrations of homologous antibody are by and large protected against experimental challenge.[83,84] After natural infection, ponies were reported to be protected from infection for 8 months, with partial protection persisting for more than 1 year.[85] Although vaccination does not always provide full protection against clinical disease, immunization has reduced the frequency of influenza outbreaks and the frequency and severity of clinical signs when influenza occurs among vaccinated animals.[81,86,87]

Equine influenza outbreaks occur most often when susceptible animals are congregated and housed in close contact with each other (e.g., horse shows, racetracks, sale barns). Virus transmission is thought to occur through direct contact with infected animals, contact with virus-contaminated fomites (e.g., feed buckets, tack), or airborne droplets of respiratory tract secretions.[88] Depending on the prevailing environmental conditions (humidity, temperature, exposure to sunlight, etc.), the virus can remain infectious for days on contaminated surfaces.[89] Once the virus has been introduced into a group of immunologically naive animals, disease can spread rapidly (in a matter of hours to days). Such effective spread is enhanced by a short (≈2 days) incubation period, high concentrations of virus shed in nasal secretions, an explosive cough, as well as the practice of housing horses in confined spaces.[89] In partially immune animals, the spread of disease is often considerably slower and outbreaks may last as long as 3 to 4 weeks.[90] Following experimental infection, horses typically shed virus for 6 to 7 days.[91-94]

Pathogenesis Influenza A viruses replicate and induce pathologic changes throughout the entire respiratory tract with the most significant lesions typically occurring in the lower airways. After inhalation of the virus, the virion attaches to sialic acid receptors on the surface of the respiratory epithelial cell and enters the cell by receptor-mediated endocytosis. Following replication and release from the host cell, the virus spreads quickly throughout the respiratory tract. Largely through apoptosis,[95-97] influenza virus replication leads to cell death. The loss of the ciliated respiratory epithelium in the trachea and bronchial tree[98] results in the impairment of tracheal mucociliary clearance.[64,99,100] In addition, the disruption of the superficial layers of the respiratory epithelium allows opportunistic bacteria to invade the deeper tissues of both the upper and the lower respiratory tract. The combination of reduced airway clearance and erosion of the respiratory epithelium predisposed affected horses to the development of secondary bacterial complications such as bacterial bronchopneumonia.[98,101] In uncomplicated cases, regeneration of the respiratory epithelium begins about 3 to 5 days after onset of illness,[101] but resolution of the epithelial damage takes a minimum of 3 weeks.[100,102]

Clinical Presentation Clinical signs of influenza virus infection in horses are often seen 48 hours after exposure to the virus. In vaccinated animals, the disease is rarely fatal, but deaths have been reported during some epidemics, particularly in donkeys and, rarely, in neonatal foals.[47,103] The typical clinical presentation of equine influenza consists of pyrexia, anorexia, lethargy, nasal discharge, and cough. Pyrexia is often the first symptom present, with body temperatures peaking somewhere between 48 and 96 hours after infection. In some cases, a second peak of pyrexia may occur around 7 days after infection. Nasal discharge is typically serous in the first few days of illness but may become mucopurulent 72 to 96 hours after infection. Concurrently, a dry, hacking cough develops. Coughing tends to persist long after pyrexia and nasal discharge have resolved and may still be present 3 weeks postinfection. The majority of affected animals are anorexic during the initial pyrexia. Whereas uncomplicated cases of equine influenza can resolve within 7 to 14 days postinfection, complications of equine influenza can be severe and include secondary bacterial pneumonia, myositis, myocarditis, and limb edema.[65,99,100] It has also been speculated that influenza infection may predispose horses to the development of inflammatory airway disease (IAD), recurrent airway obstruction (RAO), and exercise-induced pulmonary hemorrhage (EIPH).[65,98,99] Furthermore, the effects of influenza virus infection can be significantly exacerbated by even moderate exercise.[104]

Hemogram abnormalities associated with equine influenza infection can include a moderate normocytic, normochromic anemia and a leukopenia, which may result from both neutropenia and lymphopenia. Monocytosis during early convalescence is a variable finding.

Control Vaccination against equine influenza virus infection remains the foundation of equine influenza control. Although a wide variety of vaccine formulations, including modified live and recombinant vaccines, are commercially available, inactivated vaccines remain the most common type of vaccine used. Many challenge studies have demonstrated the ability of inactivated vaccines to protect against homologous virus challenge.[83,84,105,106] However, the value of inactivated vaccines is critically dependent on the type of adjuvant, quality, quantity, and strain of virus used for vaccine preparation.[107]

Based on the finding that the H7N7 viruses have not been isolated from horses since the late 1970s,[67] the inclusion of A/equine/1 virus is no longer thought to be necessary for equine influenza vaccines. In the recent past, vaccine manufacturers were encouraged to include strains representative of both American and Eurasian H3N8 lineages. However, because there has been an absence of any isolation of Eurasian viruses in recent years, the 2010 OIE Expert Surveillance Panel on equine influenza vaccine composition recommended that there is no longer a need to include these viruses in vaccines. In contrast, with the divergence of the Florida sublineage viruses into two antigenically distinct clades, the 2010 OIE panel recommends that killed vaccines should include strains representative of Florida clades 1 and 2. As the sustained genetic evolution of the equine H3N8 viruses will likely continue to result in failure of killed vaccines in the future, inclusion of viral antigens representative of contemporary circulating viruses has to remain a priority.

Studies have demonstrated that an intranasal, cold-adapted, modified live virus vaccine (FluAvert I.N., Intervet, Millsboro, Del.) was able to confer protection for up to 12 months after a single administration. Despite this, only a 6-month claim is made on the product data sheet.[94,108] Although the vaccine contains only one modified life virus strain, which is based on the H3N8 A/Eq/KY/91 isolate, the vaccine appears to protect against both European and American lineage isolates.[109] Lastly, the recombinant canary pox vector-based vaccine (Proteq-Flu, Merial, Duluth, Ga.) has also shown excellent performance against recent influenza virus strains.[110]

Because of the presence of maternal antibodies, recommendations for vaccination generally state not to vaccinate foals less than 6 months of age.[111-113] For inactivated vaccines, initial vaccination should include three doses (even when the data sheet only recommends two initial doses). The timing of the first three doses is critical. As such, the recommended interval between the first and second dose is 3 to 4 weeks. The third dose should be administered when the antibody response to the second dose has waned, which is thought to occur at 3 to 4 months after the administration of the second dose.

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Regardless of the recommendations provided by the manufacturer, this vaccination regimen is preferred, and contemporary inactivated vaccines are likely to perform well if this approach is taken. Following the initial vaccination series, subsequent booster vaccinations should be given at 6-month intervals in high-risk populations. The modified live cold-adapted intranasal vaccine requires only a single initial dose, followed by booster doses at 6-month intervals. If a higher risk of infection is anticipated (e.g., horse show), booster doses may be administered, even to well-vaccinated horses, 1 to 2 weeks prior to potential exposure.

Equine Herpesviruses

Equine herpesvirus (EHV) infection is a common infection of equids throughout the world, with at least nine herpesviruses identified to date.[114,115] The most important equine herpesviruses are the Alphaherpesvirinae EHV-1 and EHV-4, which cause respiratory disease. EHV-1 commonly infects horses, donkeys, other equids, and occasionally infects domestic cattle, captive camelids, cervids, and zebras; EHV-4 is restricted to horses.[114] EHV-3, also a member of the subfamily Alphaherpesvirinae, is the cause of equine coital exanthema, a venereally transmitted disease characterized by superficial lesions on the epithelium of the external genitalia of mares and stallions. Both EHV-2 and EHV-5, which are members of the subfamily Gammaherpesvirinae, can be associated with respiratory disease, although their pathogenicity is still under investigation.[116] Recently, potential associations between EHV-5 infection and equine multinodular pulmonary fibrosis (EMPF), as well as equine lymphoma, have been suggested.[117-119] EHV-2 is distributed throughout the world and is a ubiquitous infection of the horse, which increasingly appears to be the case for EHV-5.[120-122]

Etiology

Both EHV-1 and EHV-4 are members of the Alphaherpesvirinae subfamily of herpesviruses, in the genus Varicellovirus. These two viruses have very similar antigenic, genetic, and pathogenetic characteristics, although they are quite distinct from the gammaherpesviruses EHV-2 and EHV-5.[114] Both viruses are easily inactivated by solvents, detergents, disinfectants, and other common veterinary means of decontamination, but in favorable environmental conditions they can persist for as long as a month and in refrigerated liquids for much longer.

EHV-1 and EHV-4 have a linear double-stranded DNA genome of 145 and 150 kbp encoding 79 and 80 open reading frames (ORFs), respectively,[123-124] which can code for 77 proteins. Amino acid homology of EHV-1 and EHV-4 is 55% to 96%.[123] The gene products of EHV-1 and EHV-4 are classified as immediate early, early, or late (which include the major glycoproteins).[125-129] In recent years, a single nucleotide polymorphism (N752/D752) in the EHV-1 ORF 30, encoding the catalytic subunit of the viral DNA polymerase, was suggested to be significantly associated with the neuropathogenic potential of EHV-1 strains.[130,131] The link between the substitution of asparagine (N) and aspartic acid (D) at position 752 and its neuropathogenic potential may be due to the higher magnitude and duration of viremia that was found after experimental infection of horses with virus carrying this mutation.[132] The discovery of this mutation and its association with neuropathogenic potential led to the development of PCR-based diagnostic assays that are able to detect strains carrying the N752D mutation. Despite this, it should be taken into consideration that infection with an EHV-1 strain encoding D at position 752 does not inevitably result in neurologic disease. Likewise, although D752 is present in the large majority of EHV-1 viruses causing neurologic disease, EHM has also been caused by strains with N at position 752.

Epidemiology

EHV-1 infection causes significant suffering in horses and extensive economic losses through frequent outbreaks of respiratory disease, abortion, neonatal foal death, equine herpesvirus myeloencephalopathy (EHM), and chorioretinopathy.[114] EHV-4 can cause respiratory disease outbreak but only sporadic cases of abortion rather than abortion storms. Infections caused by EHV-1 and EHV-4 are particularly common in young performance horses and frequently result in establishment of latent infection within the first weeks or months of life.[133] Establishment of latency with subsequent viral reactivation resulting in clinical disease and viral shedding during periods of stress is a characteristic of herpesviruses in general, including EHV-1 and EHV-4,[114] and makes elimination of these pathogens from the equine population a difficult if not impossible endeavor. Latency and reactivation are critical features of the epidemiology of EHV-1 and EHV-4 infections, allowing the virus to persist for lengthy periods and in all likelihood as a lifelong infection in the majority of previously infected horses before reactivating. Reactivation and subsequent nasal virus shedding can result in infection of newly susceptible horses and possibly in disease in the latently infected horse itself. Although the true prevalence of latent equine herpesvirus infection is unknown, as more sophisticated methods of detecting latent infection with EHV-1 and EHV-4 are developed,[134] the detectable prevalence of infection continues to rise with the implication that EHV-free horses are a very rare occurrence.

Pathogenesis

The pathogenesis of EHV-1 infection has been comprehensively reviewed.[114,135,136] Primary EHV-1 infection occurs at the respiratory epithelium, resulting in erosion of the upper respiratory mucosal surface and viral shedding for 4 to 7 days postinfection; shedding can occur for longer at lower levels, and possibly beyond 14 days. Cell-to-cell spread results in the presence of virus in respiratory tract lymph nodes within 12 to 24 hours postinfection. In contrast to EHV-4 infection, which is mostly limited to the respiratory tract, EHV-1 establishes a lymphocyte-associated viremia, which is responsible for the delivery of virus to the pregnant uterus and other tissues. Spread of virus from leukocytes to endothelial cells at these secondary sites results in vascular injury (vasculitis) with potential hemorrhage, thrombosis, and ischemic necrosis. Viremia can persist for up to 21 days and is a prerequisite for abortion, chorioretinopathy, and EHM. Moreover, there appears to be a positive correlation between the development of EHM and the magnitude as well as the duration of viremia.[137] Despite this, only a small percentage of horses with viremia develop EHM, indicating that the clinical outcome of infection in the individual animal is influenced by other factors (e.g., age, sex, breed, and virus strain).[131] In pregnant mares, EHV-1 infection can result in abortion subsequent to vasculitis of the small arteriolar branches of the glandular layer of the endometrium with subsequent thrombosis, microcotyledonary infarction, perivascular cuffing, and transplacental spread of virus.[114] Abortion typically occurs in the last 4 months of pregnancy but has been reported to occur as early as the second trimester. There are usually no signs of impending abortion, and the foal is typically expelled in the amniotic membrane having just died from asphyxia caused by placental separation. Some fetuses survive initially but then die as a result of respiratory failure due to infection of the lungs. EHV-1 myeloencephalopathy results from widespread vascular injury after damage to the vascular endothelium of the blood-brain barrier and thromboischemic necrosis in the spinal cord and the brain. It is possible that the immunopathologic response to EHV-1 infection of the vascular endothelium of the CNS may play a part in the etiology of the thromboischemic necrosis. EHV-1 chorioretinopathy is also caused by a vascular endotheliopathy with subsequent ischemic injury to the chorioretina, and it is characterized clinically by focal or multifocal "shotgun" lesions.[138] Although the incidence of ocular lesions has been reported to be over 50% following EHV-1 infection, most ocular infections remain subclinical.[138] Moreover, these lesions are typically not detectable in acute disease and take weeks following infection to become visible. Latency is established in the lymphoreticular system and/or in the trigeminal ganglion, and it remains unclear which tissue is more commonly the home of latent EHV-1 virus.[114,139,140] Reactivation of latent virus frequently results in reinfection of the upper respiratory tract and shedding of virus in nasal secretions.

Immunity to EHV-1 and EHV-4 has been extensively reviewed.[141] The protective immune response following infection is short lived

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(3 to 6 months), although this may increase with age and repeated exposure. High titers of virus-neutralizing (VN) antibody before infection can reduce the amount and duration of virus shed from the nasopharynx[142] but fail to prevent infection or the development of EHM or abortion.[141] The reason for this failure is likely to be related to the rapid intracellular translocation of the virus,[143,144] thereby escaping the effects of VN antibody. However, intracellular virus is susceptible to cytotoxic T lymphocytes (CTLs), which can lyse virus-infected cells. This CTL activity is MHC class I restricted and mediated by CD8+ lymphocytes.[145] Ponies with high frequencies of CD8+ CTLs show a reduction in the clinical and virologic outcome of infection[146] and are protected against abortion.[147] Control of EHV-1 infection requires an immune response that not only limits primary infection but also controls reactivation of latent infections.[141] While circulating and mucosal antibodies each play some role in protection,[142,148] the most important component of a protective immune response to EHV-1 is the CTL response.[147,149,150]

Another important aspect of EHV-1 pathogenesis and immunity is the capacity of the virus to evade the immune response.[151] Strategies of immunoevasion employed by EHV-1 virus include modulation of cytokine responses with subsequent effects on T- and B-cell responses, interference with antigen presentation by downregulation of MHC-1 expression, alteration of NK-cell lysis, and loss of efficient chemoattraction of professional antigen-presenting cells.[152-155]

Clinical Presentation Clinical diseases associated with EHV-1 and, to a lesser extent, EHV-4 infection include respiratory disease, abortion, EHM, chorioretinopathy, and neonatal foal death. Infection with both EHV-1 and EHV-4 causes respiratory signs, but clinical signs are likely more severe for EHV-1, as is the likelihood of viremia. Clinical signs of EHV-1 and EHV-4 respiratory tract infection include pyrexia, which may be biphasic, with a first peak at 24 to 48 hours associated with upper respiratory tract infection and a second peak occurring at 4 to 8 days if viremia develops. Lethargy and anorexia are often mild, and nasal discharge, serous at first, becomes mucopurulent by days 5 to 7. Conjunctivitis, lymphoadenopathy of the submandibular lymph nodes, and edema or vasculitis of the distal limbs are variable findings. Respiratory disease, particularly affecting a large number of animals, is uncommon in horses over 2 years of age, presumably because of recurrent exposure to the virus and development of sufficient immunity to suppress clinical signs of airway disease.

Neonatal foals infected with EHV-1 in utero may be normal at birth, but they quickly become weak and lethargic and develop profound respiratory distress. Prognosis is poor for survival. The abortion and EHM forms of EHV-1 are discussed elsewhere under the appropriate system.

The clinical signs resulting from infection with EHV-2 and EHV-5 remain poorly described and established, although these viruses may be a cause of acute respiratory tract disease with clinical signs of nasal discharge, reactive submandibular lymph nodes, and coughing.[116,156] There is mounting support of a potential association between EHV-5 infection and equine multinodular pulmonary fibrosis (EMPF). However, despite findings of EHV-5 in pulmonary macrophages within the fibrotic portions of the lungs of horses suffering from EMPF, the exact nature of the relationship between the virus and the disease has not yet been elucidated.[117,118,157-159]

Prevention Because of the ability of the equine herpesviruses to establish latency within their host, the elimination of these pathogens from the equine population is not a feasible approach to infection control. Therefore strategies must be used that prevent dissemination of the virus from horses with active infection. Vaccines are an attractive tool for this, but currently there are no products that can provide comprehensive protection against equine herpesvirus infection and its potential sequelae. Inactivated EHV-1 vaccines are capable of eliciting circulating VN antibody responses, which can limit respiratory disease and nasal viral shedding, and the use of some of these vaccines has been associated with a reduction in the incidence of abortion storms.[141,142,160] Vaccines containing higher antigen loads, and typically those licensed for control of abortion, can generate high-titered VN antibody responses and even EHV-1–specific IFN-γ responses.[160] Such vaccines are likely to outperform other inactivated products with lower antigen loads. The one commercially available modified live EHV-1 vaccine (MLV) generates limited EHV-specific cellular immunity[161] and has been demonstrated to reduce respiratory disease and viral shedding.[162] The use of current commercial vaccines of proven efficacy is recommended at 6-month intervals for control of respiratory disease and shedding of EHV-1 and EHV-4. Generally, vaccines effective against EHV-1 will cross-protect against EHV-4. There is no evidence that any commercial or experimental vaccine can prevent the occurrence of EHM.

No attempts are made to control infection caused by EHV-2 or EHV-5 with vaccination. However, the proposal that concurrent EHV-2 infection may play a role in the etiology of *Rhodococcus equi* pneumonia has led some clinicians to attempt vaccination of foals with killed EHV-2 vaccines.[163]

Biosecurity measures following detection of outbreaks of EHV-1 and EHV-4 infection should include the use of strict hygiene and barrier precautions as well as isolation of affected and in-contact horses for periods of up to 28 days. The virus is thought to spread primarily through contact, with limited airborne droplet spread compared with equine influenza virus. Extensive codes of practice have been described for control of the spread of EHV-1 in facilities, both in publications[114] and in online resources (http://www.hblb.org.uk; http://www.aaep.org).

Equine Arteritis Virus

Equine viral arteritis (EVA), named after the characteristic inflammatory changes found in the walls of small arteries, is a contagious disease of horses caused by equine arteritis virus (EAV).[164] Although EVA is a disease with worldwide distribution, the seroprevalence varies substantially between countries and equine populations. Despite the fact that the vast majority of EAV infections are subclinical, occasional outbreaks occur that result in respiratory disease in adult horses, abortion, and fatal pneumonia in foals. These disease outbreaks have significant costs in terms of animal suffering and economic loss. Recent examples of larger scale outbreaks with substantial impacts on animal health and economic losses include a multistate EAV outbreak in 2006/07 in the United States as well as a 2007 disease outbreak in the Normandy region of France.[165-167]

Etiology EAV is an enveloped positive-strand RNA virus and is a member of the family Arteriviridae, order Nidovirales.[168] The Arteriviridae currently comprise four members: EAV, porcine reproductive and respiratory syndrome virus (PRRSV), lactate dehydrogenase-elevating virus (LDV) of mice, and simian hemorrhagic fever virus (SHFV). The polycistronic genome of EAV is approximately 12.7 kb and contains 10 known functional ORFs.[169-171] ORF1a and ORF1b encode two replicase polyproteins that are post-translationally processed by three proteinases to produce at least 13 nonstructural proteins. The remaining eight ORFs encode eight structural proteins, two (M and GP5) of which serve as the major viral envelope proteins. The GP5 envelope glycoprotein carries the major neutralization determinants of the virus and four neutralization sites (A through D) have been identified.[172] Based on phylogenetic analyses of the EAV-ORF5, the viruses are divided into two distinct clades: a North American clade and a European clade that share approximately 85% nucleotide identity.[173,174] Only one serotype has been identified, which is the Bucyrus strain isolated during the 1953 disease outbreak of abortion and respiratory disease in Standardbreds that first led to the definition of EVA as a clinical viral disease of horses and the identification of EAV as the causative agent.[164] Despite the fact that there is only one serotype, there are extensive variations in virulence of different isolates of the virus. Although the molecular determinants of EAV virulence have not been fully elucidated, recent data suggest that amino acid

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substitutions in the replicase and/or the structural proteins (GP2, GP4, GP5, and M) result in attenuation of a virulent strain of EAV.[175] The virus is readily inactivated by lipid solvents and disinfectants, although it can survive for years at subfreezing temperatures.

Epidemiology EAV is spread by the respiratory and venereal routes, and the persistently infected carrier stallion is central to the persistence of the virus in the horse population.[164] As a consequence, disease outbreaks frequently follow the importation of carrier stallions or their semen. With the increasing internationalization of the horse industry, this has been become an important factor in the spread of the virus throughout the world in recent years and highlights the fact that identification of the carrier stallion is a key component of EVA control programs.[165,176]

Following infection, a variable percentage (30% to 70%) of stallions infected can become carriers and shed the virus for months to years in their semen. The virus persists primarily in the ampulla of the vas deferens, and the carrier state has been shown to be testosterone dependent, as castration resolves infection.[176] In addition, some carrier stallions may also spontaneously eliminate the virus from their reproductive tract. During replication of the virus in the carrier stallion, genetically and phenotypically distinct variants of the virus can emerge and these variants can be found subsequently in the semen of these stallions.[166,177,178] When one of these variants is transmitted to a mare through breeding, or occasionally through contaminated fomites, a new outbreak can occur.[164] Transmission by the venereal route is associated with infection rates in mares as high as 85% to100%, and disease outbreaks often result from breeding a seronegative mare with EAV-containing semen.[168] Subsequent spread of the virus to other horses on the premises is by respiratory droplets and the airway route.[168] During these outbreaks the EAV strain remains stable with minimal genetic change.[164] Seroprevalence varies among breeds and between countries and geographic regions, with a reported seroprevalence of up to 85% of Standardbreds but less than 5% of Thoroughbreds in the United States.[179] Because there is no variation in breed susceptibility to EVA, this difference is probably a consequence of the number of actively shedding carrier stallions in different breeds. The virulence of strains in specific breeds can vary, however, and the strains shed by Standardbreds are typically highly attenuated, causing minimal disease.[164] Recent research suggests a correlation between the host's genotype (i.e., CD3(+) T-cell susceptibility to EAV infection) and the clinical outcome of infection, including the potential to become a carrier of the virus.[180-182]

The immune response to infection is strong, leading to protective immunity with a duration of several years.[168] Foals born to immunized mares are protected by colostral antibodies for 2 to 6 months.

Pathogenesis Virus transmission occurs by both venereal and respiratory routes. After respiratory infection the virus invades the respiratory epithelium and infects bronchial and alveolar macrophages, reaching bronchial and other regional lymph nodes by 48 hours postinfection.[168] The establishment of viremia then leads to dissemination of the virus throughout the body and further replication of the virus in the adrenals, thyroid, liver, and testes. Following infection, virus can be detected in the buffy coat for 2 to 21 days and in the plasma and serum for 7 to 9 days. The virus infects and replicates in endothelial cells, causing direct injury to the vascular endothelium and adjacent muscularis media, and subsequently gains access to the media of affected vessels. Vasculitis is characterized by fibrinoid necrosis of small muscular arteries, leukocyte infiltration, and perivascular hemorrhage and edema. With the exception of the carrier stallion, virus is eliminated by 28 days postinfection, although reports have been made of the virus being recovered for up to 180 days postinfection from the accessory sex glands of prepubertal colts.[168,183,184]

Clinical Presentation The great majority of infected horses are asymptomatic. When disease does occur, the clinical signs of EVA infection can vary from fever and leukopenia to severe disease and death. In general, the severity of EVA tends to be greater in very young and old horses. The incubation period is 2 to 14 days (6 to 8 days following venereal exposure). Horses may show some of the following signs. Typically the affected animals are pyrexic, with temperatures reaching 40.5° C (105° F) for 1 to 5 days. Anorexia, lethargy, serous nasal and ocular discharge, and coughing may occur. Conjunctivitis ("pinkeye") with ocular discharge and periorbital as well as supraorbital edema; dependent edema of the limbs, prepuce, scrotum, and mammary glands; and urticaria, localized to the sides of the neck and face or generalized, have also been reported.[168]

In stallions, acute infection can cause short-term subfertility characterized by reduced libido, decreased sperm motility, decreased sperm concentration, and abnormal sperm morphology. These changes in semen quality are transient but can persist for up to 16 weeks.[165] In contrast, persistent infection does not appear to have an effect on sperm quality in carrier stallions.[165]

Abortions in pregnant mares occur in the acute or early convalescent phases of infection and are often not preceded by premonitory signs. Abortion can occur from 2 to 10 months of gestation, with abortion rates from 10% to 70%. Comingling of pregnant mares with mares recently bred by an infected stallion is a common scenario leading to abortion.

Neonatal foals infected with EVA show severe respiratory signs and a high mortality rate. In foals that survive more than 24 hours, fever and leukopenia or thrombocytopenia are present. Interstitial pneumonia, lymphocytic arteritis or periarteritis, renal tubular necrosis, and fibrinoid necrosis of the tunica media are seen on pathologic examination.[164]

Prevention EVA control programs should be directed at eliminating the risk of abortion and neonatal foal death and establishing carrier status in stallions. The prevention of the development of carrier status in future stallions can be accomplished through vaccination of all colts with breeding potential in the first year of life and annual revaccination thereafter.[168] If carrier status has been identified, these stallions should be managed separately and under strict hygiene protocols to prevent spread of virus to naive in-contact animals.[165,176] Mares being bred to carrier stallions should be vaccinated against EVA. Fresh and frozen semen from carrier stallions is also infective, and EVA-negative mares receiving this semen should be vaccinated. Extensive codes of practice have been produced by both the U.S. Department of Agriculture (USDA; http://www.aphis.usda.gov) and the Horserace Betting Levy Board (http://www.hblb.org.uk) to assist in control of EVA. Moreover, guidelines for vaccination of horses against EAV have been established by the American Association of Equine Practitioners (AAEP; http://www.aaep.org).

Both a modified live and a killed vaccine against EVA have been developed.[164,168] In the United States, the modified live virus (MLV) vaccine has been available since the mid-1980s. The vaccine was derived from an experimental vaccine that had been created by serial passage of the virulent Bucyrus strain in primary horse kidney and primary RK cells. The MLV vaccine provides complete or partial protection against the clinical signs of EVA, but viral replication still occurs after challenge. The duration of vaccinal protection appears to be as long as 2 years, although annual revaccination of breeding stallions is recommended before the start of the breeding season. The MLV vaccine has been used successfully to limit outbreaks of infection in racehorses after initial diagnosis.[168] The manufacturer does not recommend the use of this vaccine in pregnant mares, and vaccination of pregnant mares during the last 2 months of gestation has been associated with the risk of abortion.[185]

Equine Rhinitis Virus

Etiology Equine rhinitis viruses (formerly equine rhinoviruses) are a known cause of clinical and subclinical respiratory infections in horses worldwide. The viruses are classified as members of

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the family Picornaviridae, which includes small ("pico"), nonenveloped, single-stranded RNA viruses. Among the equine rhinitis viruses, at least two serotypes have been isolated from horses: equine rhinitis A virus (ERAV; formerly equine rhinovirus 1 [ERV-1]) and equine rhinitis B virus (ERBV; formerly equine rhinovirus 2 [ERV-2]).[186,187]

Considerable uncertainty has surrounded the classification of the equine rhinitis viruses. As the illness caused by these viruses resembles the common cold brought about by rhinoviruses in humans, they initially were included in the genus *Rhinovirus*. However, subsequent studies demonstrated that ERAV differed from other members of the *Rhinovirus* genus as well as from ERBV.[187-190] For example, whereas rhinoviruses generally demonstrate a narrow host-cell range in vitro and in vivo, ERAV can infect and replicate in a broad range of cell types and host species. For instance, intranasal inoculation of a human volunteer with ERAV resulted in pharyngitis, lymphadenitis, fever, and viremia.[191] Furthermore, the presence of systemic signs and viremia during ERAV infection, the occurrence of persistent infections, and the physical properties of the virus are all more reminiscent of foot-and-mouth-disease virus (FMDV). Based on these characteristics, along with similarities in protein sequences, ERAV was placed alongside FMDV in the *Aphthovirus* genus of the Picornavirus family. Subsequently, ERBV has been reclassified as the sole member of the new genus *Erbovirus*. To date there are three known serotypes of ERBV: ERBV1, ERBV2, and ERBV3 (acid-stable equine picornavirus).

Epidemiology First isolated from horses in the United Kingdom,[192] ERAV infection occurs worldwide and is a recognized cause of acute respiratory disease.[186,193-195] The incidence of neutralizing antibody to ERAV varies according to the age of the horse, and most horses appear to become infected during their second year of life. In a study by Studdert and Gleeson, only 16% of horses between the age of 6 and 12 months were seropositive.[189] However, studies conducted in older horses found that a high percentage (50% to 90%) of horses 5 years of age have antibodies to equine rhinitis virus.[193,196-198] As is the case with many other respiratory pathogens, young horses entering a large population in frequent contact with other horses are most susceptible to infection.[194] In addition, there appears to be a seasonal distribution with most of the ERAV infections occurring in late winter and spring.[199,200] Stress (e.g., transportation and training) and concurrent disease resulting in immunosuppression may predispose to infection.[201] The virus is fairly resistant to inactivation and is thought to survive in the environment for a considerable amount of time. The spread of human rhinoviruses occurs most likely through direct and indirect contact (fomites).[202]

The clinical significance of ERBV-1, ERBV-2, and ERBV-3 is not well defined. Several recent surveillance studies indicate that the prevalence of ERBV-1 and ERBV-2 neutralizing antibodies is between 24% and 80% of horses.[156,197,198,203] However, the consequence of infection with ERBV-1 and ERBV-2 are unclear, as these viruses have been isolated from horses with and without signs of acute respiratory illness.[197,204,205]

Clinical Presentation Although ERAV is generally considered a respiratory pathogen, the clinical signs associated with infection may be quite variable. Following experimental infection with ERAV, horses may develop pyrexia, anorexia, nasal discharge, pharyngitis, and lymphadenitis involving at least the submandibular and pharyngeal lymph nodes.[206] On rare occasions, laryngitis or mild bronchitis can develop.[196] Based on serologic studies, subclinical ERAV infection may also occur and may be important in the dissemination of the disease.[189,199,202,206,207]

An important distinction of ERAV, compared with other members of the genus *Rhinovirus* (e.g., human or bovine rhinoviruses), is the finding that horses infected with ERAV may develop viremia. On average, viremia lasts 4 to 5 days, and the disappearance of virus from the blood coincides with the appearance of neutralizing antibodies.[206] Although the relationship between antibody levels and protection against disease has not been established, immunity is thought to be solid and antibodies persist for a long time.[202]

Infection with ERAV may be accompanied by long-term urinary and fecal shedding as well as virus persistence.[206,208] The recognition of the potential for ERAV persistence has important implications for disease diagnosis. Highly sensitive diagnostic methods (e.g., immunofluorescent antibody [IFA] or RT-PCR) may be able to detect persistent ERAV in horses suffering from respiratory disease, which may not be associated with the observed illness. This notion is underlined by the recent finding that the ERAV genome was detected by RT-PCR in nasopharyngeal swab samples obtained from two clinically healthy horses 1 year after acute ERAV infection.[187]

Control There is currently no vaccine available to control ERAV infection. As the capsid protein VP1 participates directly in viral receptor binding[209] and is a major surface antigen, it could serve as a potential target for vaccines.

Equine Adenovirus

Etiology Adenoviruses (family Adenoviridae) comprise a group of nonenveloped, icosahedral DNA viruses. Whereas most vertebrate species harbor an adenovirus, the viruses are highly species specific. In humans, adenoviruses are extremely prevalent and represent a significant cause of acute respiratory, ocular, and gastrointestinal disease. Infections of immunocompetent individuals usually stay localized and often take a mild or subclinical course.[210] Similarly, equine adenoviruses have been isolated from clinically healthy adult horses[211] and foals.[212,213] Equine adenovirus 1 (EAdV-1) has been implicated as the cause of acute respiratory tract disease[214,215] and conjunctivitis, as well as a progressive, fatal pneumonia in Arabian foals with severe combined immunodeficiency (SCID).[216-218] A second serotype, equine adenovirus 2 (EAdV-2) has been incriminated as a cause of intestinal infection[219,220] and diarrhea in immunocompetent foals.[221,222]

Epidemiology First isolated in 1969 from a foal with respiratory disease,[223] equine adenoviruses have a worldwide distribution.[224,225] Although serologic evidence from Australia, the United Kingdom, the United States, the Netherlands, and Nigeria indicates that adenovirus infection occurs at a high frequency in the general horse population,[225-228] the role of equine adenovirus in respiratory disease in adult horses remains unclear. In this regard it is interesting that a number of studies found no apparent association between clinically apparent respiratory disease in young adult horses and infection with adenovirus, as diagnosed by subsequent seroconverison.[205,207,229]

In contrast, fatal and nonfatal adenovirus pneumonia has been well documented in foals, particularly of the Arabian breed. Fatal respiratory disease is seen predominantly in foals with SCID. Other foals may develop respiratory disease but usually do not succumb to disease.

In general, adenovirus transmission is thought to occur via direct contact with secretions from infected animals or indirect contact via fomites or infected premises. In adult horses, the virus can persist in the upper respiratory tract, and these animals can act as a reservoir host for the virus. Adenoviruses are highly stable and have been found to remain infectious at 4° C for up to 1 year.

Clinical Presentation The clinical signs recorded after experimental intranasal infection of a Thoroughbred yearling were confined to a serous nasal discharge that lasted from 4 to 12 days postinoculation. Peak levels of serum antibodies were found at 13 days after inoculation and dropped by approximately 2 months after experimental infection.[230]

In foals, clinical signs generally occur between 10 and 35 days of age.[231] After experimental inoculation at 24 hours of age, clinical signs appeared 3 to 5 days after infection and consisted of intermittent pyrexia, nasal and ocular discharge, tachypnea, and cough. All

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foals recovered by day 10 postinoculation. The majority of foals developed a mild and transient lymphopenia that was followed by lymphocytosis. Typically, about 25% of infected foals also develop diarrhea.[231] Gross pulmonary lesions found in animals euthanized at 14 to 21 days postinoculation included atelectasis, involving up to 25% of the pulmonary parenchyma, and suppurative bronchopneumonia. Histologically, swelling and hyperplasia of the airway epithelium, as well as intranuclear inclusion bodies in the respiratory epithelial cells, were a consistent finding up to 11 days postinfection.[232]

Foals with SCID show a progressive decline in health despite intensive therapy. In necropsy, conjunctivitis, rhinitis, tracheitis, and bronchopneumonia are present. Intranuclear inclusion bodies are readily demonstrated in the respiratory epithelial cells. Areas of interstitial pneumonia surround affected bronchi. Acute pancreatitis characterized by inclusion bodies in acinus and ductal cells, as well as adenoviral sialoadenitis involving labial and parotid salivary gland, can often be demonstrated.[220,233]

Control No vaccine is available to control adenovirus infection in horses. However, except in immunocompromised animals, the virus appears to be of little clinical importance.

Hendra Virus

In August 1994, two horses died suddenly on a property in Mackay, Queensland, Australia. Ten days after the death of the second horse, the owner of the animals was admitted to the hospital with meningitis. One month after the incident in Mackay, 13 horses housed at a stable in Hendra, Queensland, died or were euthanized because of severe respiratory illness. Subsequently, the trainer and one of the stable workers developed an influenza-like illness, to which the trainer succumbed 6 days later. Although exotic to Australia, potential diagnoses included African horse sickness and equine influenza. Yet, during postmortem examination, a novel paramyxo-like virus was isolated from tissues of the affected horses and the trainer.[234] The virus, first referred to as *equine morbillivirus,* was subsequently named *Hendra virus* (HeV). Sporadic HeV infections of horses, and occasionally of humans, have since been reported in Queensland and northern New South Wales in Australia. Since 2006 there has been a marked increase in the frequency of equine HeV infections, with an unprecedented rise of equine cases occurring in 2011.[235,236]

Etiology HeV is a member of the genus *Henipavirus* (that also contains Nipah virus) within the Paramyxoviridae virus family. Paramyxoviruses, like orthomyxoviruses (see equine influenza), are enveloped viruses that contain a negative-sense, single-stranded RNA genome. HeV has unique morphologic characteristics that are useful for diagnostic purposes.[237] Electron microscopy reveals a pleomorphic enveloped particle, which contains a helical nucleocapsid that is characteristic for paramyxoviruses. The envelope is covered with spikes of 10 and 18 nm length, which gives the particle a unique "double-fringed" appearance.[238] Due to the fact that HeV contains a host-cell–derived lipid envelope, inactivation of the virus is possible using compounds that disrupt the lipid envelope (e.g., Lysol, sodium dodecyl sulfate [SDS], acetone, methanol).[239]

Epidemiology HeV can cause natural disease in humans and horses[234] and experimentally induced disease in cats, guinea pigs, and mice.[240,241] The virus infects pteropid bats (fruit bats or flying foxes). These bats are considered to be the reservoir host of HeV, and infection of these animals with virus does not seem to cause clinical disease.[242,243] However, experimental infection of flying foxes results in the appearance of virus in blood, saliva, urine, feces, as well as in fetal tissues and fetal membranes.[244] Transmission of virus between bats has been thought to occur within the roost by exposure of naive animals to virus-contaminated urine or feces.[245] The mode of transmission of HeV from bats to horses (the spillover host) is unknown. Whereas the virus transmits readily between bats, it does not appear to spread easily between horses or from horses to humans. Horse-to-horse transmission has been observed to occur during two disease outbreaks and was most likely due to direct contact with virus-contaminated urine, saliva, and blood or nasal secretions or contaminated fomites.[240] Despite these findings, horse-to-horse transmission in the experimental setting has not been documented to date.[246] Transmission of the virus from horses to humans has been recognized but appears to occur in only rare instances.[245] To date, seven human HeV infections have been reported, all of which were associated with close contact with infected horses.[234,247,248] In contrast, direct bat-to-human or human-to-human transmission of HeV has not been reported.[247]

Despite the fact that intermammalian transmission of HeV appears to be relatively rare, the virus has the potential to cause lethal zoonotic infection and poses a serious public health and occupational safety risk for veterinarians.[249]

Pathogenesis Experimentally, horses can be infected following parenteral and oronasal challenge.[234,246] Infection is characterized by the systemic distribution of the agent. After experimental infection of horses and cats, the virus was isolated from the buccal cavity, blood, brain, spleen, lungs, bronchial lymph nodes, kidneys, and urine.[240,241,246] Based on the finding that the virus is shed in the urine of experimentally infected animals, it has been speculated that consumption of food contaminated with the urine of infected horses may serve as a method of transmission under natural conditions. However, although the virus was present in the urine of horses that had died of natural HeV infection, investigators failed to recover HeV from the floor of the stalls where the animals had been housed.[246]

Clinical Presentation In horses, HeV infection is characterized by an acute, febrile respiratory illness that is sometimes accompanied by facial swelling, ataxia, head pressing, and recumbency.[250] Experimentally, the incubation period is 6 to 12 days. Frothy nasal discharge and tachycardia are considered to be indicators of imminent death. The course of disease in infected horses is short, with animals dying within 36 hours after onset of clinical signs. On necropsy, the most significant lesions are the severely congested, firm, and fluid-filled lungs. In some cases, fibrin tags are present on the pleural surface. Histologically, HeV infection is associated with vasculitis and fibrinoid degeneration and necrosis in major organs such as the lungs, brain, spleen, lymph nodes, and kidneys.[250] Pulmonary lesions identified at necropsy include necrotizing alveolitis, proteinaceous alveolar edema, and hemorrhage. Possibly the most remarkable histologic finding is the presence of syncytial giant cells in the endothelium of pulmonary blood vessels.[250] If examined under the electron microscope, these giant cells contain cytoplasmic inclusion bodies with the characteristic nucleocapsid structure of paramyxoviruses.[239]

As only seven cases of human HeV infection have been reported, the disease syndrome associated with infection is not well defined. In six patients, infection was initially characterized by an influenza-like illness. Whereas two of these patients recovered clinically, the other four patients succumbed after having developed more severe illness characterized by either encephalitis (three patients) or pneumonitis and multiorgan failure (one patient).[245,251,252] One patient developed fatal encephalitis without prior signs of influenza-like illness.[245]

Control Although a number of drugs (e.g., ribavirin, chloroquine) have been tested for their activities against HeV,[245,253] no approved antiviral drug is available to date. As horses appear to serve as an intermediate host in the transmission of HeV from bats to humans, an equine vaccine preventing virus replication and shedding would have the potential to protect horses and humans alike. Experimental testing of such a vaccine has been performed in mammals and has shown promising results.[254,255] To date, however, HeV control continues to be based on education, stringent infection-control measures, quarantine of infected premises, segregation of in-contact

horses, control of animal movement in defined zones, and serologic surveillance.

Equine Lungworm

Kara M. Lascola

The equine lungworm, the nematode *Dictyocaulus arnfieldi,* has a worldwide distribution particularly in temperate areas.[1] *D. arnfieldi* can infect all equid species with donkeys and mules considered to be the natural reservoir hosts.[1-3] Overt clinical disease associated with *D. arnfieldi* infection is typically not observed in reservoir species even in the face of prolonged patent infections or very high parasite burden.[1,2] In contrast, clinical signs of respiratory disease caused by *D. arnfieldi* infection are observed in horses and ponies.[1,4-6] The primary source of infection for horses is believed to be exposure to larvae that have developed from parasite eggs shed in feces by donkeys. Evidence for horse-to-horse transmission exists in cases of *D. arnfieldi* infection in horses with no known history of exposure to donkeys or other reservoir hosts.[1,4] Although less common than in donkeys, patent infections have also been identified in both adult and immature horses and ponies under natural and experimental conditions.[3-8] Under experimental conditions pony foals exposed to *D. arnfieldi* larvae shortly after birth more readily established patent infection compared with adults or foals exposed at an older age.[3] In addition, clinical signs of *D. arnfieldi* infection may be less common in pony foals infected when less than a year of age.[1,3,9]

Reported estimates of prevalence of *D. arnfieldi* from the 1980s and 1990s are 51% to 80%, 30%, and 2% to 11% for donkeys, mules, and horses, respectively.[1,3,4,6,10] In these studies considerable variability in prevalence was noted among horse farms surveyed and was attributed to differences in management or parasite control programs.[4,7] More recent estimates of prevalence have not been performed; however, it has been suggested that it has decreased, particularly in areas with effective anthelmintic administration.[11] The true prevalence of *D. arnfieldi* infection in horses and ponies is difficult to establish as infection is usually nonpatent.[6,8] A study of 488 Thoroughbred horses examined postmortem confirmed *D. arnfieldi* infection in 11% of horses with only 3% of horses demonstrating patent infection (documented via a modified Baermann technique).[7] These values are similar to estimates of prevalence based on patent infection in live horses from other studies[3,10] and are much lower than what has been observed in donkeys. A study of 5437 live equids revealed a prevalence of patent *D. arnfieldi* infection of 68% and 30% in donkeys and mules, respectively, compared with only 2% in horses and no infection in ponies.[4]

The direct life cycle of *D. arnfieldi* has been previously described and is thought to be similar to the life cycle of *Dictyocaulus viviparus,* the bovine lungworm.[8] L1 hatches almost immediately after eggs are passed in the feces, and the larvae undergo two molts before they enter a free-living, infective form (L3), which migrates to the surrounding vegetation. The development of L3 can occur in as little as 4 days. L3 has a limited survival time in the environment (49 days in warm soil) and cannot overwinter on pasture.[1] L3 that are ingested by the host penetrate the intestinal mucosa before passing to the mesenteric lymph nodes where they molt to L4. The L4 then travel via the lymph and blood to the lungs, where they migrate though the walls of the capillaries into the alveoli. The final molt from L4 to L5 occurs in the bronchioles, and maturation to the adult form occurs in the small bronchi.[1,6,8] Eggs are laid in the bronchi and then transported via mucociliary clearance to the pharynx where they are swallowed and eventually passed in the manure. The prepatent period of *D. arnfieldi* is 2 to 4 months.[1,8] In horses and ponies with nonpatent infection, larval development is arrested at the L5 stage.

Clinical disease has been documented as early as 12 days after infection in severe cases, but often it takes several weeks to develop.[1,6,12] Infected donkeys pass eggs throughout the year; however, fecal larval production increases through the spring and summer months and environmental conditions may favor larval development to the infective L3 stage during the summer in temperate climates.[1,5,12] As with *D. viviparus, Pilobolus* fungi may play a role in the dissemination of *D. arnfieldi* larvae from feces. L3 larvae travel to the fungal sporangia and are dispersed with the fungal spores when the sporangia rupture.[8,13]

The most common clinical signs attributed to *D. arnfieldi* infection in horses include cough, increased expiratory effort, tachypnea, audible wheezes and crackles on auscultation, and mucoid or mucopurulent nasal discharge.[3,5,6,10] Clinical signs described less frequently include dyspnea, paroxysmal cough, and abnormal tracheal auscultation.[5,10] Most reports of lungworm infection describe a chronic disease process of several weeks' duration[5,6,10]; however, acute onset of clinical signs is possible with severe infection or concomitant bacterial or viral respiratory disease. Although clinical disease is rare in donkeys, *D. arnfieldi* infection has been associated with increased susceptibility to respiratory viruses (e.g., influenza).[14]

A presumptive diagnosis of *D. arnfieldi* infection may be made in horses with clinical signs of nonpyrexic, chronic respiratory disease and a history of contact with donkeys once other causes of respiratory disease have been ruled out and if clinical signs resolve with appropriate anthelmintic treatment. In adult horses clinical signs of *D. arnfieldi* infection are similar to those observed in horses with recurrent airway obstruction. In young animals, similar clinical signs may be observed during transient migration of *Parascaris equorum*. Fecal examination using a modified Baermann technique frequently delivers false-negative results in horses but can be used to identify animals with patent infection and should be performed in suspect cases.

Endoscopic examination may reveal lymphoid hyperplasia and increased tracheal or bronchial exudate, but these signs are not specific for *D. arnfieldi* infection.[5,10] Examination of tracheobronchial fluid or bronchoalveolar lavage may reveal eosinophilia,[5,6,14] and *D. arnfieldi* larvae have been identified in respiratory secretions and in centrifuged tracheal mucus prior to fixing and staining.[5] Tracheobronchial aspirates and bronchoalveolar lavage fluid obtained from normal horses are expected to contain few (<3%) eosinophils[15,16]; however, eosinophilia has been identified in horses with no apparent respiratory disease[17] as well as in those with eosinophilic pulmonary disease,[14,18] inflammatory airway disease,[16,19] and during transient migration of *P. equorum*. Eosinophilia in respiratory secretions is therefore suggestive but not pathognomonic for *D. arnfieldi* infection. Repeat evaluation of respiratory secretions posttreatment should reveal a marked improvement in eosinophilia in lungworm cases.[5,20] Peripheral eosinophilia has not been definitively correlated with lungworm infection.[5,21] A definitive diagnosis can be made at necropsy by identifying larval or adult worms within the airways. A modified Baermann technique can be applied to diced lung tissue to aid in the identification of larvae.

Treatment for *D. arnfieldi* includes effective anthelmintic treatment, removal from contact with donkeys, and moving horses and ponies to a pasture not grazed by donkeys since the previous autumn. Moxidectin (0.4 mg/kg) and ivermectin (0.2 mg/kg) are active against larval and adult parasites and have been associated with 99.9% and 100% efficacy in donkeys and horses, respectively.[3,9,22] Mebendazole (15 to 20 mg/kg/day for 5 days) was effective in significantly reducing patent infection in donkeys.[23] Fenbendazole has been shown to improve clinical signs of presumed *D. arnfieldi* infection in horses; however, suppression of fecal shedding was maintained for less than 4 weeks with doses up to 30 mg/kg.[21] The pharmacokinetics and efficacy of pour-on eprinomectin against *D. arnfieldi* infection have recently been evaluated in donkeys.[24,25] Treatment of naturally infected donkeys with 0.5 mg/kg eprinomectin was found to be 100% effective in eliminating fecal larvae up to 28 days post administration.[24] Treatment of donkeys should be instituted to decrease transmission to horses and ponies and potentially to decrease the donkey's susceptibility to other respiratory diseases.[12]

Necropsy findings in donkeys and horses with *D. arnfieldi* infection are similar.[2,26] Gross findings include circumscribed areas of raised pulmonary tissue (3 to 5 cm), typically in the caudal lung

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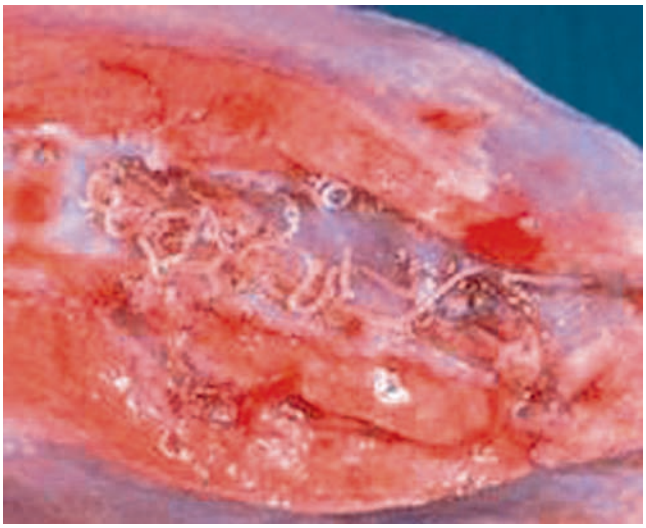


FIG. 31-36 Overinflated pulmonary tissue surrounding small bronchi that are packed with mature *Dictyocaulus arnfieldi*.

lobes. Section of these areas reveals overinflated pulmonary tissue surrounding small bronchi that are packed with mature *D. arnfieldi* nematodes (Fig. 31-36). Small airways in these areas tend to be occluded with exudate. Histologic examination of the pulmonary tissue reveals diffuse eosinophilia throughout the pulmonary tissues, especially around the airways. A marked inflammatory reaction is found around parasitized bronchi, with heavy lymphoid cell infiltration of the epithelium, lamina propria, and peribronchial tissue. The epithelium is often hyperplastic with an increase in size and number of mucus-secreting cells. Little cellular or mucoid reaction is seen in the bronchial lumen surrounding adult parasites; however, free larvae in the lumen result in an intense mucopurulent reaction. Bronchioles in affected areas of the lung usually show evidence of bronchiolitis with free mucus present in the lumen of bronchioles and hyperplastic, columnar epithelium. Bronchioles are most commonly surrounded by discrete lymphoid nodules. Pulmonary pathology in donkeys tends to be very localized, with much of the lung appearing normal on histologic examination.[2]

Prevention of *D. arnfieldi* infection in horses and ponies involves effective anthelmintic treatment and pasturing horses and ponies separately from donkeys, or treating donkeys with appropriate anthelmintic treatment to avoid patent infection. Anthelmintic treatment is especially important in the spring. Regular removal of manure from pasture can also help to decrease the parasite load in the environment.

Thoracic Trauma

Jane E. Axon • Pamela A. Wilkins

Thoracic trauma results from blunt or penetrating injuries to the chest wall, axillary, and pectoral regions. Trauma can result in thoracic wounds (penetrating and nonpenetrating), hemothorax, pneumothorax, pneumomediastinum, pleuritis, fistula of the sternum or ribs, fractured ribs, lameness, osteomyelitis, or diaphragmatic hernia, and a combination can occur in the same horse.[1-3] Prompt assessment and implementation of emergency procedures in injured horses presenting with respiratory distress is vital to optimize their chances of survival.

Clinical signs associated with injury to the thorax can vary from mild musculoskeletal pain and a stiff gait (lameness) to severe respiratory distress and hypovolemic shock (pneumothorax, hemothorax, diaphragmatic hernia). Signs of respiratory distress include anxiety, tachycardia, cyanotic mucous membranes, tachypnea, nostril flaring, and an altered respiratory pattern. Auscultation and percussion of the thorax may assist with locating and identifying the lesions. Percussion and palpation will need to be performed carefully in horses that are in pain and may reveal areas of tenderness, subcutaneous emphysema, and crepitus associated with fractures. Palpation of subcutaneous emphysema in the absence of an external wound may be associated with a lacerated lung or tracheal trauma and, in a dyspneic horse, should raise the suspicion of a concurrent pneumothorax.[2-4] Injured horses may also show signs of weak pulses, pale mucous membranes, and tachycardia due to acute hemorrhage from lacerated intercostal or pulmonary parenchymal vessels. Evaluation of the abdomen should also be undertaken. On expiration the cranial portion of the diaphragm extends to the sixth rib; thus an abdominocentesis should be performed on a horse with a wound caudal to the sixth rib or with a deep penetrating wound to assess abdominal involvement.[1] Further evaluation of the injured horse will include thoracic radiographs, ultrasonographic examination, thorough exploration of the wound and, in cases of lameness, nuclear scintigraphic examination. Arterial blood gas analysis will assist in determining the extent of hypoventilation and hypoxemia.



FIG. 31-37 Emergency stabilization of a horse with an open thoracic wound and subsequent pneumothorax. Plastic wrap has been wrapped around the chest to prevent air entering the thoracic cavity. Air has been removed from the thoracic cavity and a Heimlich chest drainage valve has been attached to the dorsally placed chest tube. The horse is on intravenous fluids and intranasal oxygen.

Emergency stabilization may be required prior to a full evaluation of the horse. The aim is to stabilize the cardiovascular system, providing respiratory support, preventing further air entering the thorax, and, whenever possible, controlling hemorrhage. Sedatives and tranquillizers should be used judiciously as most cause respiratory depression, but they may have to be used if the horse's anxiety precludes instituting treatment. Open thoracic wounds should be covered immediately to prevent further air entering the chest cavity.[2-4] Plastic food wrap can be placed over the wound and around the thorax, or a gauze roll or towel can be used (Fig. 31-37). A tension pneumothorax, which may occur with sucking thoracic or axillary wounds, can be alleviated by inserting a trocar into the dorsal pleural space so that pleural and atmospheric pressures can equilibrate and result in a less compromising pneumothorax.[1,2] Intranasal oxygen therapy and removal of air from the thorax may be necessary to improve alveolar ventilation and oxygenation in the horse. Circulatory support may be necessary until hemorrhage has stabilized.[1-3] Analgesics, antiinflammatory therapy, broad-spectrum antimicrobial therapy, and tetanus prophylaxis may also need to be instituted.

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Hemothorax

Thoracic trauma, by causing lacerations to pleural or pulmonary vessels or rupture of large thoracic vessels, may result in hemothorax. Other causes of hemothorax include rupture of lung parenchymal bullae, vessel erosion by severe lung abscessation or neoplasia, hemangiosarcoma, spontaneous hemorrhage at maximal excursion, and coagulopathy.[5,6] Iatrogenic causes include tube thoracostomy and lung biopsy. Hemothorax has recently been reported as a complication of phenylephrine administration for treatment of left dorsal displacement of the large colon (nephrosplenic ligament entrapment) and should be suspected if the history is appropriate.[7] Hemothorax can be unilateral or bilateral depending on the cause and whether the mediastinum is complete.

Diagnosis is based on clinical signs, radiographic and ultrasonographic findings, and laboratory evaluation of fluid obtained from thoracocentesis.[2-5] Dyspnea and tachycardia may be present, depending on the volume of blood loss into the pleural cavity. On auscultation there is a decrease in audible breath sounds ventrally and heart sounds are often muffled and radiate over a wider area.[2-5] Percussion reveals a change from normal resonance of aerated lung to dullness over the hemothorax.[5] Thoracic radiographs show opacity of ventral lung fields with an associated horizontal fluid line and a loss of diaphragmatic and cardiac silhouettes.[2,3,8] Ultrasonography shows fluid within the pleural cavity with a characteristic hypoechoic to echogenic smoke swirling pattern.[2,9] Fluid collected by thoracocentesis should be submitted for cell count, packed cell volume, and total protein. A cytologic evaluation should also be performed to determine whether there is evidence of infection or neoplasia, and the sample should be cultured if an infection is suspected. A clotting profile and platelet count should be performed if a coagulopathy is suspected. Hematology and biochemistry should also be performed as the horse may develop anemia and hypoproteinemia associated with the blood loss. Systemic antibiotics, tetanus prophylaxis, and NSAIDs are indicated in most cases.

Treatment is aimed at stabilizing the cardiopulmonary function and treating the underlying cause.[1-3] Horses with hemothorax from nonpenetrating thoracic trauma or noninfectious causes can be managed conservatively with intranasal oxygen insufflation, analgesics, intravenous fluids, or whole blood transfusion if the blood loss is severe. If the horse is not hypoxemic or in respiratory distress, rest alone and close monitoring may suffice. Even if respiratory distress is evident, a tube thoracostomy and drainage of blood may not be necessary.[2,6] Drainage of the thorax is not recommended in horses with a coagulopathy unless severe respiratory distress is present.[6] If there is a penetrating wound or evidence of infection, drainage should be attempted by ultrasound-guided ventral placement of chest drains. This, however, should not be undertaken until the hemorrhage has stopped and circulating blood volume has been restored.[2,10] All horses, even without evidence of infection, should have broad-spectrum antimicrobial coverage, as blood is an excellent medium for bacterial growth.[2,5]

The prognosis for horses with uncomplicated trauma and hemothorax is good. If the hemothorax is the result of a penetrating wound, the prognosis is poor.[2,3]

Pneumothorax

Traumatic causes of pneumothorax include puncture or laceration of the trachea, ruptured esophagus, penetration of foreign objects into the thoracic cavity, external wounds resulting in subcutaneous emphysema and pneumomediastinum, or direct penetrating or blunt trauma to the lung parenchyma.[2,3,12-14] Pleuropneumonia also causes pneumothorax; in one study, 17 of 40 horses had pneumothorax resulting from pleuropneumonia.[11] Air can escape into the pleural cavity through slow leaks from necrotic lung or through formation of bronchopleural fistulas. Additional causes of pneumothorax include ruptured emphysematous lung bullae, maximal exercise, and iatrogenic causes such as tube thoracostomy, lung biopsy, mechanical ventilation, and transtracheal aspiration.[5,6]

Pneumothorax can be described as closed, in which air from the lung is trapped in the pleural space, or open, in which there is free communication between the pleural space and external environment and air is sucked into the pleural space with inspiration.[14] Tension pneumothorax occurs when air accumulates in the thorax until intrapleural pressure exceeds atmospheric pressure. This is usually seen with a sucking pleurocutaneous wound as air moves into the chest cavity with inspiration and, because of a valve effect of the wound, cannot escape during expiration.[2-4] Intrapleural pressure may increase to an extent that the thorax becomes fixed in maximal extension. This leads to severe cardiopulmonary effects, thoracic tamponade, with decreased venous return to the heart from vena cava compression and consequent hypoxemia.[15] Pneumothorax is usually bilateral because of the incomplete mediastinum of horses; however, it may be unilateral if the fenestrations in the mediastinum are blocked as a result of inflammation or collapsed lung.

Diagnosis is based on clinical signs, aspiration of air from the pleural cavity, and radiographic and ultrasonographic findings.[2-4] Clinical signs that can be associated with pneumothorax are dyspnea, tachypnea, cyanosis, and evidence of trauma. Characteristic findings on auscultation are a decrease or lack of audible breath sounds dorsally and tympany and hyperresonance on percussion; however, these clinical signs can vary and are not reliable.[11] Concurrent subcutaneous emphysema may complicate interpretation. However, if a horse with subcutaneous emphysema is dyspneic or distressed, pneumothorax should be suspected, unless the emphysema is causing airway compression.[5] Thoracic radiographs show lack of pulmonary vasculature in the dorsal aspect of the caudal lung fields and ventral displacement of the dorsal lung margin (Fig. 31-38, *A*). On

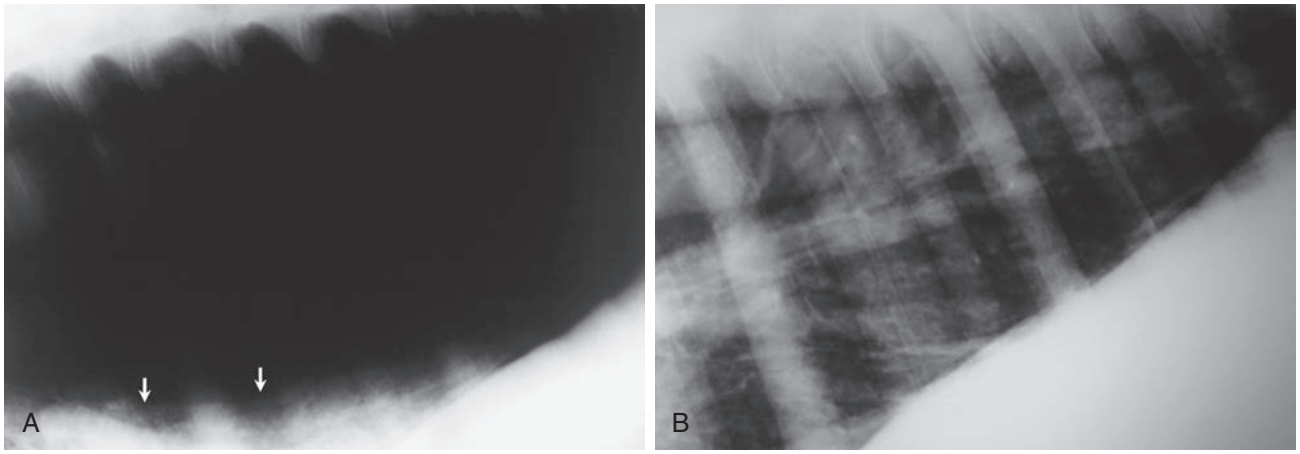


FIG. 31-38 **A,** Lateral radiographic view of the caudal dorsal portion of the thorax of a horse with bilateral pneumothorax. The dorsal borders of the lung margin are marked by arrows. **B,** Same view as **A** after thoracocentesis and resolution of the pneumothorax.

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ultrasonographic examination there are parallel horizontal lines of air artifact reverberation without the pattern of pleura and "comet tail" artifacts. The dorsal air image also moves ventrally with inspiration over underlying collapsed lung or pleural fluid, creating a "curtain" image.[9] Subcutaneous emphysema in tissue and fascial planes may prevent accurate sonographic imaging. Aspiration of air from the thorax is also diagnostic, as is the associated improvement in clinical signs (see Fig. 31-38, *B*).

Treatment is aimed at improving alveolar ventilation by correcting the pneumothorax, if the horse is showing signs of respiratory distress, and treating the underlying cause. Treatment of simple pneumothorax requires rest and close observation while gradual reabsorption of air occurs. If hypoxemia (Pa_{O_2} < 80 mm Hg, percentage oxygen saturation [$\%O_2$sat] < 90%) or dyspnea is present, nasal insufflation of oxygen (5 to 15 L/min) should be administered.[2,3,10] Open sucking wounds should be occluded. Air is removed from the pleural space by inserting a teat cannula or thoracostomy tube into the dorsal thoracic cavity in or near the twelfth intercostal space and attaching a suction device. If a suction machine is not available, repeated aspiration can be accomplished with a 60-mL syringe through a three-way stopcock valve and/or tubing attached to the teat cannula and run into a container of water.[2,4] The latter acts as a simple water trap allowing air to be expelled during inspiration while preventing air movement back into the chest with expiration. If the pneumothorax reoccurs or continues, tubes should be left in place to allow constant air removal. A Heimlich chest drainage valve (Bard Parker, Division of Becton-Dickinson, Rutherford, N.J.) provides continual drainage and, if correctly placed, is effective for long periods. In long-standing cases, gradual reexpansion of the lungs is recommended to avoid reexpansion pulmonary edema.[5] Prophylactic broad-spectrum antimicrobial therapy is recommended as long as the tube is in place. If the cause of pneumothorax requires correction under general anesthesia, ventilation should be improved prior to induction by removing air from the pleural cavity and correcting lung atelectasis.

The prognosis for horses with pneumothorax is good, providing infection can be successfully treated and air leaks are sealed. Pneumothorax associated with pleuropneumonia and parenchymal lesions resulting in air leakage carry a poor prognosis; esophageal rupture and penetrating thoracic trauma carry a poorer prognosis.[3,5,11]

Pneumomediastinum

Pneumomediastinum can result from physical trauma with direct penetration into the region from wounds to the axilla, caudal neck, or thorax. Extensive subcutaneous emphysema that often occurs with large wounds to the axilla region may also result in air tracking into the mediastinum, and potentially into the thoracic cavity. Pneumomediastinum has also been reported with tracheal rupture, perforation of the thoracic esophagus, and pulmonary bulla formation.[2] No clinical signs may be evident unless the horse develops complications such as pneumothorax or infection. Diagnosis is based on classic radiographic findings of visualization of the esophagus, greater vessels, and outer margin of the trachea.[2] Treatment is aimed at treating the primary cause and monitoring for complications.

Rib Fractures

Fractured ribs are most often a result of an accident, fall, or kick. In neonates fractured ribs are commonly associated with birth trauma.

ADULTS. Fractured ribs can be detected on physical examination either through exploration of the wound or eliciting pain on palpation over the affected area, although not all fractures will be discovered in this manner. Crepitus associated with a closed fracture is often not detected. Shallow breaths and guarded thoracic movements may be seen as a result of pain from the fracture; however, these signs may also be indicative of complications such as hemothorax, pneumothorax, or pleuropneumonia. Soft-tissue swelling and subcutaneous emphysema may also be present. Ultrasonographic examination of the cortical surface of the rib is a sensitive method of detecting fractures and enables evaluation of the pleural cavity, underlying lung parenchyma, and the surrounding soft tissue. Fractured ribs in adults usually heal without fixation; however, if there is pain and excessive movement of rib ends, surgical correction may be warranted. True flail chest (fractures at two points, dorsal and ventral of a rib or neighboring ribs, resulting in paradoxical movement of that section of ribs with breathing) requires some type of stabilization. Analgesic therapy (including opioids and nonsteroidal antiinflammatories), circumferential bandaging, and intercostal nerve blocks with a long-acting anesthetic along the caudal border of the rib provide some pain relief. Open fractures should be explored and débrided, and soft tissue should be repaired.[2-4] The horse should be closely monitored for respiratory distress or hemorrhage because a closed pneumothorax or hemothorax may result if a fractured rib end lacerates underlying lung parenchyma or vessels.[1] Lameness has been reported as the only consequence of rib injury in adult horses and thus thoracic trauma, particularly if there is an appropriate history, should be considered in some occult lameness cases.[16]

FOALS. Blunt thoracic trauma during parturition resulting in costochondral dislocation or rib fracture is more common in foals from primiparous mares and dystocias.[17] The majority of fractures are subclinical; however, sudden death, hemothorax, hemopericardium, lacerated myocardium, pneumothorax, diaphragmatic hernia, and severe respiratory distress can occur.[17,18] The incidence of fractured ribs in newborn foals on one farm was 21% (55 of 263) and none of the affected foals had clinical signs associated with the fracture after a 6-month period.[17] However, in other reports, rib fractures accounted for 13% of life-threatening fractures in foals less than 7 days of age, and 19 of 67 (28%) foals in a necropsy study with fractured ribs died as a direct result of rib fracture.[18,19] The most common site of injury is at the costochondral junction or adjacent dorsal area.[18] Clinical signs are variable and include pain on rib palpation; "clicking" or crepitation on auscultation; edema localized over, or ventral to, the fractured ribs; and signs of pain, including grunting or groaning when manipulated or lying on the affected side. Palpation of crepitus over the fractured site is not a consistent finding. If the foal is systemically stable, asymmetry of the thoracic cage can be evaluated if the foal is positioned in dorsal recumbency.[17] In severe cases involving multiple consecutive ribs, the foal can be in respiratory distress, particularly with true flail chest. Foals may also exhibit respiratory distress with pneumothorax, hemothorax, or diaphragmatic hernia. Pale mucous membranes can be indicative of internal hemorrhage and abdominal hemorrhage, and diaphragmatic hernia should be considered if the diaphragm has been lacerated. Radiographs for detection of fractured ribs in neonates is not reliable although visualization is improved if radiographs are taken using a horizontal beam with the foal in lateral recumbency, injured side up (author's experience).[18,20] Ultrasonographic examination is more reliable and also assists in evaluating the adjacent structures and presence of hemothorax, pneumothorax, or diaphragmatic hernia (Fig. 31-39). Conservative treatment with box rest and supportive care is successful in the majority of uncomplicated rib fractures; however, surgical repair has been performed in cases with multiple rib fractures or those with potential for severe internal injury and is considered lifesaving in many cases.[20-22] Specific treatments based on the internal injuries should also be implemented.

Diaphragmatic Hernia

Diaphragmatic hernias occur sporadically in horses. Occurrence is usually associated with a history of trauma or sudden increase in abdominal pressure and exertion, as may be experienced by stallions during breeding or mares during parturition.[23-25] In one study, 48% of 50 horses diagnosed with diaphragmatic hernia had a history of recent trauma.[23] In some cases no history of injury or predisposing cause can be identified.[24] Congenital diaphragmatic hernia can occur as a result of incomplete fusion of any of the four embryonic components of the diaphragm or as a result of abdominal compression

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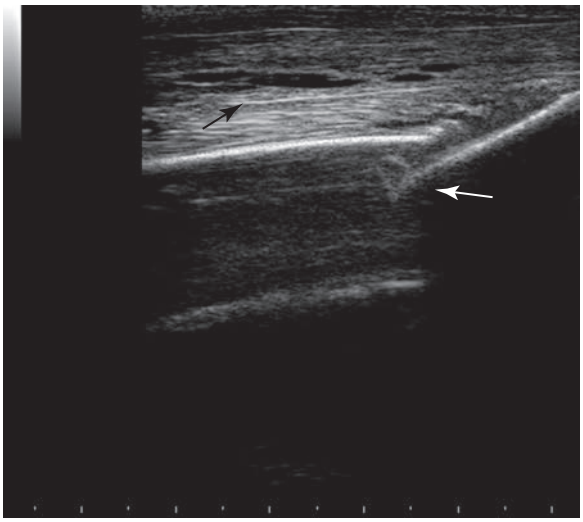


FIG. 31-39 Fractured rib *(white arrow),* sagittal view. Left is dorsal view. Note edema around surrounding tissues *(black arrow)* and around fracture site.

during parturition.[26] A congenital peritoneopericardial hernia has been reported.[27] Congenital hernias are typically located in the ventral-most portion of the diaphragm, whereas diaphragmatic defects from trauma are usually located at the junction of muscular and tendinous portions of the diaphragm.[26] The size and position of the defect are important in determining whether herniation of abdominal viscera occurs.[24,25,28] Any segment of intestine can be involved, although the small intestine is the most frequent.[26]

Clinical signs usually relate to intestinal obstruction or respiratory compromise, but less specific signs of exercise intolerance and weight loss also have been reported.[24,25] A diaphragmatic hernia may also initially be clinically silent if there is minimal pulmonary or bowel compromise. Gastrointestinal clinical signs are variable and depend on the segment and amount of intestine herniated and whether it is simply displaced, incarcerated, or strangulated.[24,25] Frequently reported clinical signs are colic, moderate to severe tachypnea, and endotoxic shock. Respiratory signs of tachypnea can be attributed to pain at the site of injury or gastrointestinal tract, shock, and lung compression and decreased ventilation.[24,25,29,30] Acute tearing of the diaphragm may be associated with hemorrhage into both thoracic and abdominal cavities.

Diagnosis can be challenging, and thoracic radiographs showing gas-filled intestine or abdominal viscera within the thoracic cavity are considered most diagnostic.[24,25,29,30] Ultrasonographic examination may show abdominal organs in the thoracic cavity; however, viscera may not be seen if located away from the thoracic wall and covered by aerated lung.[9] Rectal examination often suggests a relative lack of normal abdominal viscera in horses with extensive migration of abdominal organs into the thoracic cavity. Auscultation of the thorax may reveal gastrointestinal sounds; auscultation usually does not clearly differentiate sounds referred from the abdomen. There may also be an absence of breath sounds ventrally and associated dullness on percussion; however, these findings are not reliable. Abdominal paracentesis is usually normal and can be misleading as the compromised intestine is in the thorax, and thus thoracocentesis may be more representative.[24] Thoracoscopy may also assist visualization of the hernia, but partial deflation of the lungs is necessary to visualize the diaphragm, which may further compromise the patient.[15,28] Because of these difficulties in diagnosis, a definitive diagnosis, in some cases, may be obtained only at the time of surgery or necropsy.

The prognosis for survival is poor, with reports from recent retrospective studies of 16% (7 of 44) and 23% (7 of 31).[25,31] Surgical repair also carries a poor prognosis with complications associated with anesthesia, resection of devitalized bowel, anatomic location and repair of the defect, possible fractured rib repair, and breakdown of the hernia repair site.[24,25,31] Survival in one study was significantly associated with the age of the horse (2 years old), location (ventral) and size (<10 cm) of the diaphragmatic tear, and the amount of compromised viscera at surgery (<50% small intestine).[31] Foals and adult horses that survive can return to their previous level of activity, including those of a broodmare.[25,29,31] In chronic cases with few or no clinical signs, repair does not appear to be necessary, although complications associated with herniated viscera may eventually occur.[26,28]

Pulmonary Edema

Pamela A. Wilkins

Pulmonary edema rarely occurs as a primary event in the horse and, when present, is usually secondary to some other pathologic process. Extravascular fluid accumulates within the lung after events that alter hydrostatic and colloid osmotic interstitial and vascular forces, change the surface area and pore size of the blood-gas barrier, or diminish lymphatic drainage.[1] Pulmonary edema can be classified as cardiogenic or noncardiogenic. Pulmonary capillary pressure can be increased by any increase in left atrial or pulmonary artery pressure. In horses, this can occur secondary to acute renal failure, left heart failure, or very high cardiac output conditions, such as extreme exercise. Increases in microvascular permeability may occur with sepsis, disseminated intravascular coagulation, hypoxic acidosis, allergic responses such as transfusion reactions or primary pulmonary pathology, resulting in the release of mediators of inflammation that increase vascular endothelial or alveolar epithelial permeability. Pulmonary edema associated with airway obstruction has been termed *negative-pressure pulmonary edema* (NPPE) and has been reported in horses.[2-7] NPPE occurs secondary to inspiratory efforts against a closed glottis that result in a precipitous fall in intrathoracic pressure. The large decrease in intrathoracic pressure increases the transmural pressure gradient for all intrathoracic vascular structures, favoring movement of water into the extravascular space. Transient pulmonary obstruction may be a root cause of fatal exercise-induced pulmonary hemorrhage (EIPH) in racehorses and other horses performing at maximal exercise; these horses are predisposed because of already large transmural pulmonary vascular pressures and large intrathoracic pressure swings associated with breathing (Wilkins and Del Piero, unpublished data) (Fig. 31-40).

Diagnosis is based on clinical examination, history of predisposing causes, and radiographs. Horses have a shallow rapid respiratory pattern and may be dyspneic. Arterial blood gas analysis may reveal hypoxemia and hypercapnia. Fine crackles or wheezes may be audible on auscultation. Patients with volume overload (associated with renal failure or, rarely, too-rapid fluid administration) or primary cardiac problems may have an increased central venous pressure with pronounced venous distention. Fluid (clear or slightly yellow or pink-tinged) may drip from the nostrils and can increase in volume without necessarily becoming frothy. Continuous coughing and production of frothy blood-tinged or bloody fluid production warrants a very grave prognosis. Radiographic findings are nonspecific but include peribronchial and perivascular cuffing, increased prominence of vessels, and a hazy reticular interstitial pattern (Fig. 31-41). Underlying pulmonary disease may obscure signs of edema, and radiographs of sufficiently high quality to show relatively subtle changes may not be obtainable in mature horses. Diffuse numerous comet-tail artifacts are seen with thoracic ultrasound examination (Fig. 31-42). Noncardiogenic pulmonary edema (capillary leak) is a component of the definition for VetALI and VetARDS.

Treatment Treatment consists of correcting the cause, reversing hypoxemia, decreasing plasma volume and left atrial pressure, and increasing plasma colloid osmotic pressure. Intranasal oxygen and even positive ventilation may be needed in severe cases. Improvement in oxygenation can be monitored by sequential arterial blood gas analysis or by using transcutaneous oxygen saturation monitoring equipment (pulse oximetry) applied to the nasal mucosa, tongue,

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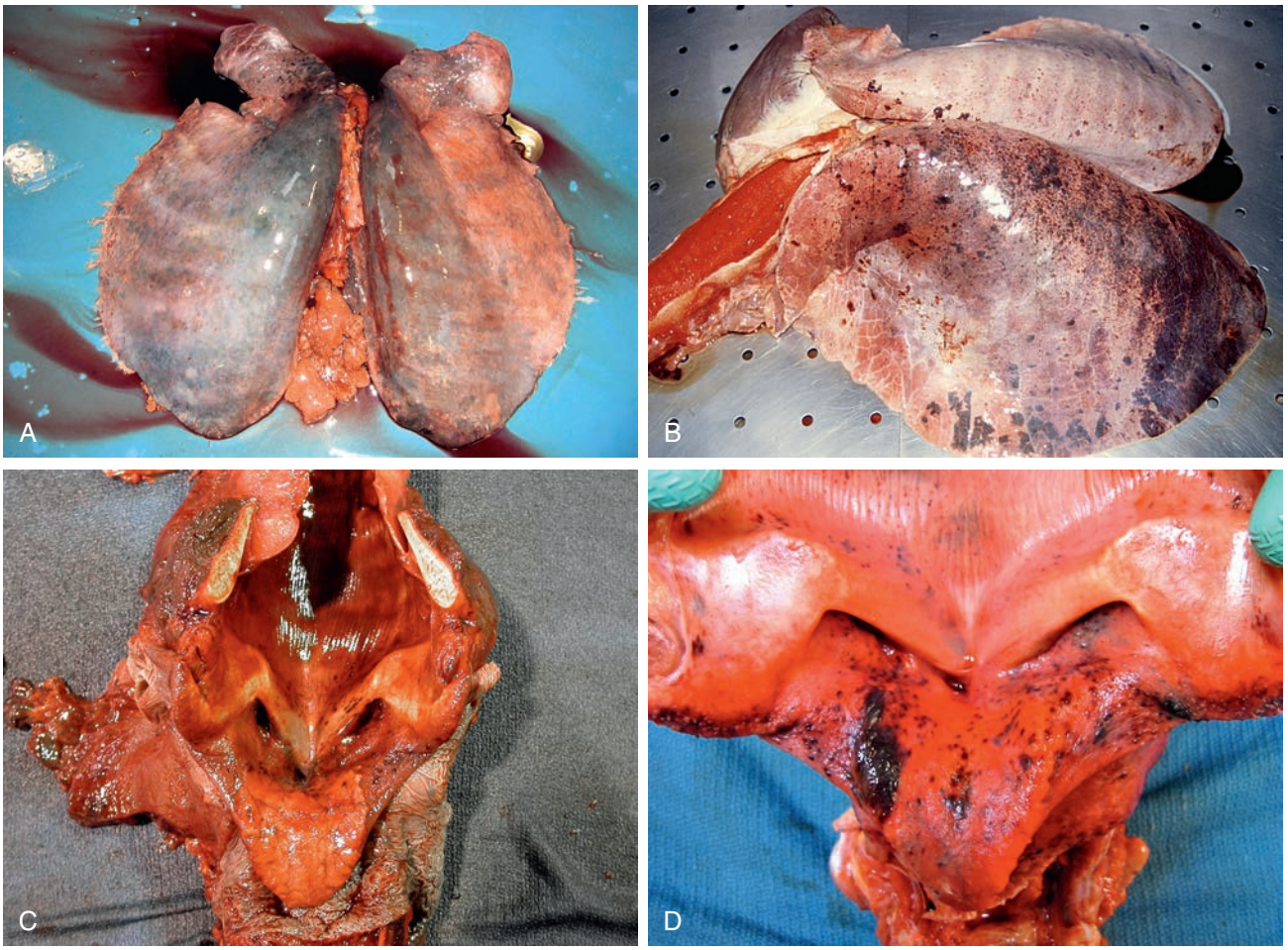


FIG. 31-40 **A,** Lung from a horse that suffered sudden death on the racetrack caused by "fatal exercised-induced pulmonary hemorrhage" (EIPH). Note the dorsal acute hemorrhage, diffuse edema, and the rib impressions present on the dorsal surface of the lung. *(Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)* **B,** Lung from a horse that suffered documented upper airway obstruction at maximal exertion on a treadmill. This horse experienced fatal EIPH. Note severe pulmonary edema with hemorrhage, bloody froth in trachea, and ecchymotic hemorrhages in trachea. *(Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)* **C,** Larynx of a horse that suffered from fatal EIPH. Note widespread diffuse subepithelial hemorrhage, ecchymoses, and petechia, supporting negative airway pressure as the cause. Upper airway occlusion due to left laryngeal hemiplegia is supported by the significantly decreased muscle mass of the left cricoarytenoideus dorsalis muscle bodies. *(Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)* **D,** Larynx from a horse found dead in stall with evidence of hemorrhagic pulmonary edema. Negative pressure pulmonary edema secondary to airway occlusion is supported as the cause of death because of its presence throughout the larynx and upper airway. *(Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)*

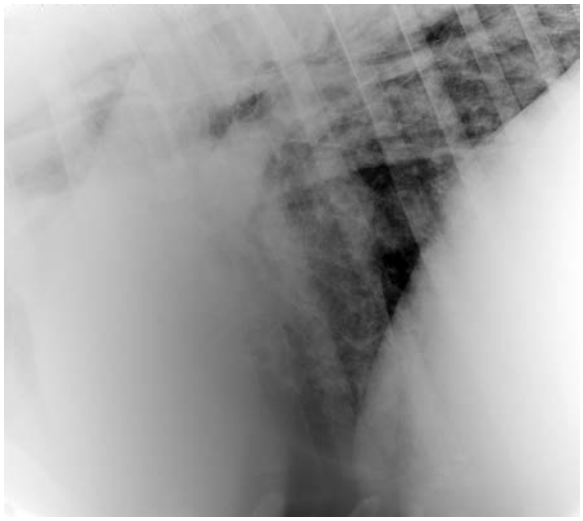


FIG. 31-41 Radiograph of caudal ventral lung of a horse with pulmonary edema. Note mixed hazy reticular interstitial pattern. Bronchiolar cuffing is also evident. *(Courtesy Dr. Midge Leitch, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)*

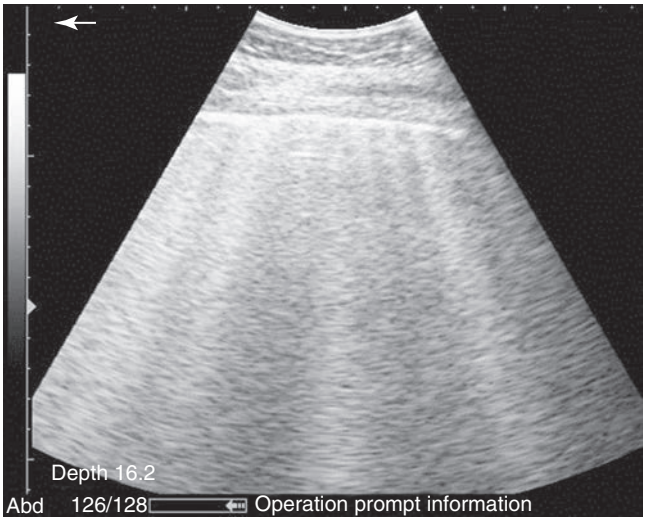


FIG. 31-42 Ultrasound image of lung of horse with pulmonary edema. Note multiple diffuse comet-tail artifacts. *(Courtesy Dr. Kim Sprayberry, California Polytechnic State University, San Luis Obispo, Calif.)*

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TABLE 31-10

Pharmacologic Treatments for Pulmonary Edema in Horses

Treatment	Reason	Route	Dose/Rate	Comments
Oxygen	Hypoxemia	Intranasal insufflation	5-15 L/min	Aim for PaO_2 > 85 mm Hg, O_2sat > 90%
Furosemide	Diuresis	Intravenous	1 mg/kg	Repeat as needed; monitor acid-base status, hydration, and electrolyte concentrations
Furosemide	Bronchodilation	Nebulization		Will not be effective with concurrent NSAID administration
Bronchodilators (various)	Bronchodilation	Nebulization Oral Intravenous	See section on obstructive pulmonary disease	Many will be effective, described in depth elsewhere in Chapter 31
Flunixin meglumine	Antiinflammatory	Intravenous	1 mg/kg	BID; monitor renal function
Diphenhydramine	Antihistamine	Intravenous	0.1-1 mg/kg	BID; monitor for excessive drowsiness
Epinephrine	Anaphylaxis	Intravenous	3-5 mL IM for 450-kg horse	Use ONLY for treating anaphylaxis

bid, Twice a day; *IM,* intramuscularly; *NSAID,* nonsteroidal antiinflammatory drug; *O_2sat,* percentage oxygen saturation; *PaO_2,* partial arterial oxygen pressure.

or other available nonpigmented mucous membrane. In cases of NPPE, maintaining an adequate, low-resistance airway is very important to prevent further damage, and tracheostomy may be necessary. IV fluid therapy should be guided by the patient's needs and monitored by serial measurement of central venous pressure if necessary. Furosemide may be given intravenously or intramuscularly at a dose of 1 to 2 mg/kg and repeated in 1 hour (Table 31-10). If helpful, the dose can be titrated for each patient. At a dose of 1 mg/kg, approximately 8 L of urine is produced in approximately 1 hour.[8] A few studies have been conducted on the effects of furosemide on pulmonary hemodynamics in the horse.[8-12] Furosemide provides some relief to recurrent airway obstruction (RAO)–affected horses within 20 minutes of administration, increasing dynamic compliance without affecting PaO_2.[13] The beneficial effects appear to be mediated by prostaglandin E_2, derived from either the renal or airway epithelium, resulting in bronchial smooth muscle relaxation. Prior treatment with flunixin meglumine prevents the furosemide-induced bronchodilation.[14] The effect in horses with pulmonary edema has not been reported. Colloid solutions should be administered cautiously or in conjunction with use of diuretics because they can initially increase vascular pressure. Plasma may be safer than other colloid preparations such as dextrans or hetastarch. Colloid solutions may be of little benefit in raising intravascular osmotic pressure in patients with increased microvascular permeability.

Antiprostaglandin drugs (flunixin meglumine, phenylbutazone) and antihistamines may help and are indicated particularly in cases of anaphylactic reaction, as are diphenhydramine and epinephrine (see Table 31-10). Bronchodilators may be of benefit (see Table 31-10). The use of corticosteroids remains controversial; if they are used, antimicrobial coverage is advisable, as pulmonary edema has been shown to impair pulmonary bacterial defense mechanisms.

Smoke Inhalation

Peggy S. Marsh

Smoke inhalation injury is typically associated with exposure to fires, and there are often concurrent problems in other body systems from thermal injury. Extensive or severe burns can magnify the severity of the injuries. Thermal injury, along with smoke inhalation, leads to both local and systemic lesions. Diffuse tissue edema may occur; this is a challenge to manage and can create organ dysfunction. To further complicate the problem, severely affected patients may develop problems, including life-threatening sepsis, hypermetabolism, or both. Depending on the severity of the lesions, smoke and fire injuries often lead to systemic inflammatory response syndrome and, in some cases, multiple organ system failure.[1]

Insult to the respiratory system by smoke inhalation depends on the fuels that burned, the completeness of combustion, and the generated heat intensity. In general, lesions are initiated by three mechanisms. The first is direct thermal injury, which is often limited to the upper respiratory tract by laryngeal reflexes and efficient heat exchange within the nasal passages.[2] Second, toxic chemicals in the smoke can cause damage, both directly and indirectly, through inflammatory mediators. Carbon monoxide intoxication is commonly associated with human injuries from smoke and is a product of incomplete combustion.[3] Finally, with combustion there is consumption of oxygen, and the resulting low PAO_2 can lead to pulmonary vasoconstriction as well as generalized hypoxia.

Three phases of pulmonary dysfunction have been described in the horse.[4,5] The first stage is acute pulmonary insufficiency caused by several mechanisms. Carbon monoxide may be present in sufficiently high concentration to cause toxicity within a short time after exposure. Carbon monoxide combines with hemoglobin to form carboxyhemoglobin. Hemoglobin has a 200 to 250 times greater affinity for carbon monoxide as compared with its affinity for oxygen.[3] High levels of circulating carboxyhemoglobin result in a shift of the oxyhemoglobin dissociation curve to the left, thereby decreasing oxygen release at the tissue level and leading to tissue hypoxia. Other processes occurring during this acute phase include progressive edema and necrosis in the upper respiratory tract, leading to airway obstruction; bronchoconstriction in the lower respiratory tract, caused by the irritating effects of noxious products; and altered pulmonary blood flow.[6]

These insults produce the second stage: formation of pulmonary edema, lower airway obstruction, and pulmonary parenchymal lesions. Within 48 to 72 hours after exposure, driven by pulmonary macrophages, neutrophils are called into the area of insult. They release cytokines, proteolytic enzymes, and oxygen-derived free radicals. Expression of the inflammatory cascade in excess of balance causes microvascular damage, leading to increased extravascular lung water. Local insult also results in the release of tissue factor, initiating the coagulation cascade to produce fibrin. Debris from the inflammatory cascade, along with fibrin and material directly deposited from smoke inhalation, create pseudomembranous casts, which may obstruct the small airways. Widespread plugging of the airways may significantly increase airway pressure, causing barotrauma and alveolar damage.[6] The last stage, bronchopneumonia, occurs as a result of the impaired host immune system, both locally and systemically. This phase may occur up to 1 to 2 weeks after the initial injury.

As the saying goes, "Where there's smoke, there's fire"; it is common for horses with smoke inhalation injury to also have burn injury. A complete description of this process in horses has been

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reported.[7] Thermal injury causes a local response that includes microvascular insult and direct tissue coagulation leading to inflammation, local edema, and, finally, necrosis. Extensive local injuries will drive a systemic response. An initial decrease in systemic organ blood flow is followed by the formation of generalized edema. The pathophysiology of edema formation is complex and involves protein shifts, endothelial damage, and alteration of the interstitial architecture, all leading to a net accumulation of fluid in the interstitial spaces.[8] Over time major thermal injury is characterized by high cardiac output, increased oxygen consumption, and protein and fat wasting, all of which may create a hypermetabolic state.[9,10] Loss of skin as a barrier, release of inflammatory mediators, and hypermetabolism play a role in the development of immunosuppression. Other features noted with burn injury in the horse include acute hemolysis, renal failure, laminitis, and myositis.[11]

Horses exposed to fire with smoke will have a variety of clinical signs depending on the duration and type of exposure and the length of time from the insult. The extent of damage to the skin may be very difficult to ascertain initially. Acutely, within the first 6 hours, signs of carbon monoxide toxicity and shock may occur. The patient shows signs of severe hypoxemia and may be depressed, disoriented, irritable, ataxic, or even moribund and comatose. As edema and necrosis progress in the upper respiratory tract, dyspnea and stridor may develop. Auscultation of the thorax may reveal decreased air movement, crackles, or wheezes, but these may not become apparent for 12 to 24 hours. If edema of the airways is sufficiently severe, airflow may be severely restricted. Edema fluid may be visible at the nostrils and, later, may be replaced by inflammatory exudate. Concurrent edema formation may be occurring systemically. Hypoxia and generalized edema may lead to dysfunction of distant organs such as the kidneys and muscles. Signs of infection may be difficult to ascertain from other signs. All that may be noticed is a fever and a worsening of respiratory signs after initial improvement.

Diagnosis is typically based on history and physical examination. A normal initial examination does not rule out exposure because the onset of clinical signs may be delayed several days. Within a short time after exposure, carboxyhemoglobin concentration in venous blood can be measured. A level above 10% is consistent with carbon monoxide toxicity.[3] Various diagnostic tests are useful in determining the extent of respiratory injury. These tests include endoscopy of the upper respiratory tract and tracheobronchial tree, thoracic radiographs, blood gas analysis, hematology, and cytologic evaluation of tracheal aspirates. Any or all of these tests can be performed on a serial basis as prognostic aids. Diagnostic tools for other organ injury include blood pressure monitoring, measurement of central venous pressure, serial hematologic and serum chemistry analyses, and monitoring of urine production.

Treatment depends on stage of injury. Initially, oxygen support is of benefit. It is a treatment for carbon monoxide toxicity and helps reduce hypoxemia.[12] Humidified oxygen can be supplied by nasal insufflation or via transtracheal catheter. Upper respiratory tract obstruction may necessitate a tracheostomy. Attention should be paid to keeping the airways clear, and nebulization may be useful, especially when pseudomembranous casts are suspected. Bronchodilators may be useful in counteracting reflex bronchoconstriction. Decreasing inflammation and pulmonary edema may necessitate the use of diuretics and NSAIDs. Use of corticosteroids is controversial because of the potential for immunosuppression and laminitis.[4] Novel therapies may include use of hyperbaric oxygen chambers and inhalation treatment with medication to inhibit inflammatory mediators, coagulation factors, or oxidative stress.[13]

Secondary complications require attention. Cardiovascular compromise and burn-induced edema may necessitate the judicious use of intravenous fluids. To prevent infection, strict hygiene, meticulous nursing care, and optimal nutritional support should be provided.[1,7,13] Prophylactic antimicrobial use is not recommended in human patients. Documented infection should be treated with appropriate antimicrobial agents based on results of culture and sensitivity patterns.[1,7]

Recurrent Airway Obstruction

Dorothy M. Ainsworth

Definition and Etiology Recurrent airway obstruction (RAO) is an inflammatory condition of the lower respiratory tract of mature horses that is characterized by excessive mucus production, neutrophil accumulation, bronchial hyperreactivity, and (in most cases) reversible bronchospasm. Because etiopathogenesis of the equine disease differs from that of chronic obstructive pulmonary disease (COPD) in humans, it is recommended that the equine disorder no longer be called COPD. The preferred name is RAO or "heaves."[1]

RAO typically develops in adult horses residing in the northeast and midwest regions of the United States and Canada as well as in Great Britain and Switzerland, where the climate is wet and cool and horses are stabled and fed hay. RAO can also occur in horses that are pastured outdoors but fed dusty hay, especially from round bales. RAO rarely occurs in horses maintained in warm, dry climates such as those found in California or in Australia.[2] In North America the prevalence of RAO diagnosed at veterinary teaching hospitals has been positively correlated with rainfall, minimum temperatures, and total pollen and mold counts occurring 1 to 3 months previously.[3] These findings suggest that environmental conditions are integral to the development of the disease in genetically susceptible horses.

RAO is considered to be a hypersensitivity to inhaled molds and organic dusts contained in the feeds, hay, and straw. It is similar to occupational (neutrophilic) asthma that develops in human workers exposed to organic dusts.[4] Identifying the *specific* causative agents within the hay dust that induce the disease has been a challenge, as stable dust contains more than 50 species of molds, large numbers of forage mites, endotoxins, and other inorganic components.[5] Inhalation challenge with endotoxin, a component of hay dust, induces airway neutrophilia but not all of the changes in pulmonary function that are characteristic of RAO.[6,7] Inhalation challenge with aqueous extracts of *Aspergillus fumigatus, Faenia rectivirgula (Micropolyspora faeni),* or *Thermoactinomyces vulgaris* partially induces RAO in susceptible horses.[8-10] Complete experimental induction of RAO in susceptible horses requires inhalation of hay dust particulates either by natural challenge (hay feeding) by nebulization of a hay dust solution or a solution containing fungal spores, endotoxin, and silica microspheres.[11-15]

ROLE OF THE INNATE IMMUNE SYSTEM. Within hours of hay dust exposure, neutrophilia and excessive mucus production are evident endoscopically and cytologically[16,17] and reflect the response of a multitude of pulmonary cell types that initiate innate and adaptive immune responses. Alveolar macrophages isolated from RAO-susceptible horses just 6 hours following nebulization of a hay dust solution[18] exhibit an upregulation in the gene expression of tumor necrosis factor (TNF)–α, interleukin (IL)-1β, and IL-8. Pulmonary intravascular macrophages (PIMs) may also play a pivotal role in airway inflammation, as temporary depletion of PIMs alone in RAO-susceptible horses (by intravenous [IV] gadolinium chloride) significantly reduces airway neutrophilia and airway cell IL-8 and TLR4 gene expression normally induced by moldy hay challenge.[19] The "trigger" for transcription of proinflammatory genes in macrophages (or other pulmonary cells) may reflect activation of Toll-like receptor (TLR) 2 and TLR4, or both, by fungal wall components, endotoxin, or other bacterial cell products leading to nuclear factor κB (NF-κB) activation and gene transcription.[20-22] Recently, hypoxia-inducible factor 1α (HIF-1α) has been proposed to play an essential role in the innate responses of RAO.[23] Although HIF-1α is a known regulator of energy homeostasis and cellular adaptation to hypoxia, it also regulates expression of proinflammatory genes such as TNF-α, IL-8, and vascular endothelial growth factor (VEGF), and engages in cross-talk with the NF-κB pathway.[23] HIF-1α expression in bronchoalveolar lavage fluid (BALF) cells is significantly increased in symptomatic but

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not asymptomatic RAO-affected horses or controls.[23] However, the relative importance of these receptors and transcription factors requires further investigation.

The initial upregulation of macrophage-derived proinflammatory genes is transient, with mRNA levels returning to preexposure levels 24 hours after hay dust challenge.[18,24] However, with continuous hay dust exposure, both the protein and the gene expression levels of IL-8 in the airway cells (neutrophils) and bronchial epithelium, as well as the gene expression levels of IL-1β and TNF-α in the BALF cells (probably neutrophils) remains upregulated in chronically affected horses.[25-28] In addition to these chemokines there is evidence that airway neutrophilia in the chronic phase of RAO (disease that has lasted longer than 2 weeks) may also be propagated by IL-17.[28-29] Secreted by lymphocytes and neutrophils, IL-17 promotes maturation, chemotaxis, and activation of neutrophils. IL-17 has the capacity to upregulate the gene expression of IL-8 in the airway epithelium, further promoting the inflammatory cycle, but this remains to be confirmed in horses.[28]

The net effect of proinflammatory cytokine production is to enhance the chemokinetic gradient existing within the airways and to promote neutrophilic extravasation.[25,30] The neutrophil intracellular signaling pathways required for extravasation into the airways involve mitogen-activated protein kinases (MAPKs) and/or phosphoinositide-3-kinase (PI3K): in vitro inhibition of MAPK or PI3K significantly attenuates neutrophil chemokinesis.[30]

ROLE OF THE ADAPTIVE IMMUNE SYSTEM. The role of the adaptive immune system in the development of RAO remains controversial. Data that support the hypothesis that RAO is an IgE-mediated (T-helper type 2 [Th2]) disorder include the findings of elevated allergen-specific IgE concentrations in the serum[31] and in the BALF of RAO-susceptible or affected horses,[32,33] increased numbers of IL-4 and IL-5 (mRNA-positive) BALF cells (detected by in situ hybridization techniques) in RAO-affected horses,[34,35] and the results of genetic studies that suggest a phenotypic association (at least in one family of Swiss warmblood horses) with a locus on equine chromosome 13 that contains the IL-4 receptor gene.[36] Although Th2 disorders are typically characterized by eosinophilic infiltrates, it has been hypothesized that IL-4 activates its receptor on neutrophils to inhibit neutrophil apoptosis, to increase protein synthesis, and to upregulate the expression of the IL-9 receptor.[37] It has been further hypothesized that activation of the IL-9 neutrophil receptor then enhances IL-8 production and neutrophil influx.[37,38] Although the gene expressions of IL-4 and IL-9 receptors are indeed upregulated in peripheral blood neutrophils isolated from RAO-prone and RAO-affected horses, the existence of this pathway, linking the Th2 limb with the development of neutrophilia, requires additional investigation and confirmation.

Other data suggest that RAO is not simply a Th2 immune response. For example, Van der Haegen and colleagues were unable to demonstrate a significant difference in IgE-protein–positive cells in the lung tissue samples of RAO-affected horses compared with control horses.[39] Second, cytokine profiles of BALF cells[26,27] or of pulmonary $CD4^+$ and $CD8^+$ cells[40] isolated from RAO-affected horses during the first 24 or 48 hours after hay dust exposure fail to demonstrate an upregulation of IL-4, IL-5, or IL-13. Furthermore, chronic (3-week) hay dust exposure is associated with an increase in the gene expression of IFN-γ in the BALF cells,[26,27] although in one trial, but not in the second trial, of the same chronically affected horses, the gene expression of IL-4 was upregulated.[26] Fourth, GATA-3, the transcription factor required for IL-4 gene expression, is not upregulated in the bronchial cells of RAO-affected horses.[41] These data *do not* provide unequivocal evidence that RAO is a Th1 immune response because (1) concomitant increases in the gene expression of T-bet, the transcriptional factor for IFN-γ expression in $CD4^+$ cells, is not upregulated concurrently with IFN-γ,[27] and (2) multiple signaling pathways may stimulate the production of IFN-γ. In other species, TLR stimulation leads to the production of proinflammatory factors, including IL-12, and subsequent IFN-γ synthesis.[42,43]

OTHER INFLAMMATORY MEDIATORS. With the accumulation of intraluminal neutrophils and peribronchiolar lymphocytes and with the activation of alveolar macrophages, it is not surprising that numerous other inflammatory mediators are released and may contribute to the inflammatory response of RAO. For example, histamine that is released by degranulated mast cells increases vascular permeability and produces bronchoconstriction. (Although mast cell degranulation is typically attributed to IgE-mediated cross-linking of high-affinity receptors [FceRI] on mast cells, leukotrienes, prostaglandin E, acetylcholine, substance P, endothelin, and peptidoglycan also induce mast cell degranulation.)[44,45] Despite the finding of increased histamine concentrations in the BALF of RAO-affected horses, histamine-1 receptor antagonists provide little therapeutic relief for affected horses; this finding suggests that histamine may not be the predominant mediator responsible for the airway inflammation.[46] The potential role of prostaglandins, with their bronchoconstrictive (PGF_{2a}, PGD_2, TXA_2) and/or bronchodilatory capabilities (PGE_2, PGI_2), has also been examined. In a differential gene expression study of peripheral lung tissue, Lavoie and colleagues[47] reported an upregulation in RAO-affected horses of (1) PGF synthase (an enzyme that reduces PGD_2 and PGH_2 to PGF_{2a}) and (2) PTGDR, a PGD_2 receptor. In diseased horses, increases in BALF, PGE_2, PGF_{2a},[48,49] and serum TXB_2 (a metabolite of TXA_2) are found.[50] However, although administration of a cyclooxygenase inhibitor prevents the increase in the serum TXB_2 in RAO-affected horses, it does not inhibit the development of airway hyperresponsiveness or bronchospasm in susceptible horses; this finding suggests that eicosanoids are not the major contributor to clinical signs.[50] The contribution of lipoxygenase metabolites to the airway disease has also been investigated in RAO-affected horses. In humans, LTB_4, LTC_4, and LTD_4 are considered to be bronchoconstrictors; LTC_4 and LTD_4 are also mucus secretagogues; and LTB_4 (through its action on NF-κB) is a chemotactin, promoting the upregulation of adhesion molecules and cytokines that facilitate neutrophil extravasation.[51] Inhalation of LTB_4 or LTD_4 induces airway neutrophilia and bronchoconstriction, respectively, in normal and RAO-affected horses.[52] BALF cells isolated from RAO-affected horses during the first 48 hours of hay dust exposure and stimulated ex vivo produce increased concentrations of LTB_4 and LTC_4.[51] However, actual BALF concentrations of LTB_4 and LTC_4 are not elevated in chronically affected horses[49] despite the finding that the gene expression of LTA_4 hydrolase (which metabolizes LTA_4 to LTB_4) is upregulated in RAO-affected horses.[47] Pretreatment of RAO-susceptible horses with either a 5-lipoxygenase inhibitor or a LTD_4 receptor antagonist before hay dust exposure does not prevent the development of airway neutrophilia or alterations in lung mechanics.[53,54] Treatment of clinically affected horses with a leukotriene receptor antagonist montelukast (LTC_4, LTD_4, LTE_4 antagonist) also fails to improve pulmonary function test results, clinical scores, or arterial blood gas tensions.[55]

There is increasing evidence that reactive oxygen species, derived from pulmonary macrophages and granulocytes, contribute to the inflammatory process of RAO.[56] Oxidative stress occurs when enzymatic (superoxide dismutase, glutathione peroxidase, glutathione-*S*-transferase) and nonenzymatic antioxidants (glutathione [GSH], ascorbate, α-tocopherol, bilirubin, albumin, and transferrin) are depleted.[57] Evidence of an oxidant stress within the airways of RAO-affected horses is based on the findings of (1) increased levels of oxidized glutathione (GSSG), (2) increased glutathione redox ratios (GSSG/GSSG + GSH), and (3) decreased ascorbic acid concentrations in the pulmonary epithelial lining fluid of RAO-affected horses.[56-58] Tan and colleagues[57] also reported that both red blood cell and white blood cell glutathione peroxidase activities were significantly increased in RAO-affected horses during exacerbation compared with controls, suggesting a systemic response to the pulmonary inflammation.[57] Changes in these indices of oxidant stress are also correlated with lung dysfunction parameters (total lung resistance, dynamic lung compliance, and arterial oxygen tensions) in RAO-susceptible and RAO-affected horses.[59] Although reactive oxygen species are well recognized for their microbicidal activities, they

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also upregulate proinflammatory gene expression by activating NF-κB.[60] It is likely that reactive oxygen species generated during the inflammatory process of RAO also contribute to the NF-κB activation in bronchial epithelial cells and in BALF cells of RAO-affected horses.[61,62]

Proteases derived from airway phagocytes, lymphocytes, and epithelial cells may also propagate the inflammatory reaction of RAO. Although many matrix metalloproteinases (MMPs) with gelatinolytic and collagenolytic activities have been identified in the respiratory tract secretions of RAO-affected horses,[63,64] the gelatinase MMP-9 is markedly increased in BALF and in tracheal epithelial lining fluid of diseased horses.[65] It has been suggested that the degradative effect of MMP-9 on the basement membrane and on the extracellular matrix components facilitates the extravascular movement of neutrophils into the airways. In vitro, tetracycline derivatives effectively inhibit MMP activity detected in tracheal epithelial lining fluid,[66] but the efficacy of these compounds in ameliorating or preventing the inflammatory response of RAO-susceptible horses exposed to hay dust remains to be determined.

Epidemiology and Genetics RAO occurs in both ponies and horses, but no gender or breed predisposition has been identified.[67,68] The prevalence of RAO is dependent on the geographic region examined. Bracher reported that 60% to 80% of Swiss horses older than 8 years of age suffer from some degree of this disease. In North America and in Europe the prevalence of RAO is estimated to range from 12% to 50%.[67] Although it has been clearly demonstrated that hay particulates are integral to the development of the disease, the role of a prior viral (or bacterial) infection in inducing susceptibility to hay dust hypersensitivity remains to be established. Furthermore, even though horses with inflammatory airway disease (IAD) share many of the clinical features of RAO,[69] the relationship of IAD to the development of RAO is unknown. Currently there is no evidence that IAD progresses to RAO.[1]

A heritable component of RAO disease susceptibility has long been suspected. Marti and colleagues examined families of RAO-affected warmblood and Lipizanner horses and found that the risk of developing RAO was 3.2 times higher when one parent (dam or sire) had the disease and 4.6 times higher when both parents did.[70] Marti and colleagues concluded that the clinical manifestations of RAO are the result of the interactions of genetic and environmental factors. More recently, results of segregation and genomic analyses performed on two families of Swiss warmblood horses suggest that the mode of inheritance of RAO is characterized by major gene effects but that potential candidate genes differ between the two families.[36,71] In one family of Swiss warmblood horses, RAO was transmitted in an autosomal recessive mode with the major association of microsatellites or single nucleotide polymorphisms and affected cases being found on equine chromosome 13 (ECA 13). In the other family of Swiss warmblood horses, an autosomal dominant mode of inheritance was found with the major association found on equine chromosome 15.[71] Potential candidate genes on ECA 13 include IL-17, IL-4 receptor, and integrin alpha X gene (ITGAX). On ECA 15, a gene of interest is SOCS5 (suppressor of cytokine signaling 5), a gene whose protein product negatively regulates IL-4–dependent pathways and Th2 cell differentiation.[36,71-75] The investigators suggested that the observed genetic heterogeneity between the two families of Swiss warmblood horses may reflect etiologically distinct subgroups of RAO that are not distinguished phenotypically. Although the results are intriguing, it remains to be determined if RAO genetic susceptibility maps to loci on ECA 13 and ECA 15 in other horse breeds.

Clinical Signs and Differential Diagnosis The severity of clinical signs in RAO-affected horses is variable and is exacerbated by stabling; exposure to dusts, hay, and ammonia fumes; and hot, humid weather. In a study of 148 cases of RAO presented for evaluation to a veterinary referral hospital in the United Kingdom, the chief complaints (median duration of which was 7 months) included coughing (84% of cases), bilateral nasal discharge (54%), exercise intolerance (51%), and postexercise breathing difficulty (23%).[76] In a review of 16 cases presented to a veterinary teaching hospital in western Canada, the most common historical complaint (88% of the cases) was coughing,[77] whereas the predominant clinical complaints in 65 cases presented to a veterinary teaching hospital in the northeastern United States were abnormal breathing effort (68%), nasal discharge (50%), and a spontaneous cough (46%).[78]

On physical examination, mildly affected horses are typically afebrile and exhibit a bright demeanor and a normal or slightly accentuated (abdominal) breathing effort, respiratory rate, and heart rate. Nasal discharge may not be evident in all cases, but the horse may be observed to swallow excessively because of expectorated exudate. When the horse is exercised, a thick white nasal discharge and a cough become apparent. The frequency of coughing increases when horses are stabled, often exceeding 10 to 15 coughs per hour.[79] More severely affected horses exhibit tachypnea (respiratory rates > 40 breaths/min), nostril flaring, and a markedly accentuated expiratory effort (heave). The thoracic expiratory component may precede that of the abdominal compartment, producing a "double effort."[80] Abdominal pressure swings may be large enough to cause the anus to protrude with expiration. Paroxysmal coughing, bilateral nasal discharge, anxious facial expression, flatulence during coughing, reluctance to move, inappetence, and weight loss occur in the most severely affected cases.

Although RAO is a diffuse lung disease, auscultation of mild cases may not reveal abnormal lung sounds unless a rebreathing bag is used to induce a hyperpnea. In one survey, thoracic auscultation was abnormal in 47% of the cases, whereas tracheal auscultation was abnormal in 63% of the cases.[76] In the latter, abnormal lung sounds and "mucus clicks" (tracheal exudate) were detected by tracheal auscultation. In mildly affected horses, only regional areas of adventitious lung sounds (crackles or high-pitched expiratory wheezes) may be detected. In contrast, in severely affected horses, wheezes and mucus clicks may be heard at the horse's nostrils without the use of a stethoscope. Depending on the severity of the disease, thoracic percussion may be normal or may reveal expansion of the caudal lung fields beyond the normal line of pleural reflection.

Researchers have developed a clinical scoring system to categorize the severity of RAO. In one system the total clinical score is based on the magnitude of nostril flaring (1 to 4) and the abdominal breathing effort (1 to 4).[81] RAO in horses with a clinical score of 3 or 4, 5 or 6, or 7 or 8 was diagnosed as mild, moderate, or severe, respectively. In moderately to severely affected horses, there is a very good correlation between the clinical signs and alterations in pulmonary resistance or dynamic compliance.[82] For mildly affected horses, clinical scores underestimate the severity of changes in the pulmonary function tests resulting in an underdiagnosis of RAO. Another clinical scoring system—based on the respiratory rate (graded 0 to 2), the respiratory effort (0 to 2), and lung auscultation findings (0 to 2) in affected horses—was found to more closely correlate with histopathologic changes obtained by lung biopsy (and, in particular, the presence of peribronchiolar neutrophil and/or mast cell infiltration) than with the degree of BALF neutrophilia.[77] (Pulmonary function tests were not performed.) However, Tilley and colleagues, in a study of 30 RAO-affected horses and 10 controls, found that the severity of some clinical signs (e.g., cough, nostril flare, and abdominal lift but not breathing frequency, thoracic auscultation, or exercise intolerance) correlated with tracheal mucus scores, BALF neutrophil percentages, and thoracic radiographic evidence of bronchial and tracheal thickening.[83]

In rare cases, horses with long-standing RAO develop cor pulmonale, which is evidenced by jugular distention, pulsation, ventral edema, and tachycardia, in addition to the clinical signs of RAO.[84-85] Although RAO-susceptible horses develop evidence of echocardiographic alterations during acute episodes of RAO (characterized by an increase in pulmonary artery diameter, a decrease in left ventricular diameter [and estimated stroke volume], and an abnormal septal motion), serum troponin measurements remain normal.[86] As the echocardiographic parameters return to normal when horses are in

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remission, it is likely that the reversibility of the airway disease reduces the risk of permanent myocardial disease.

Laboratory Aids and Diagnostic Tests The diagnosis of RAO is based on the history, the clinical signs, demonstration of the reversibility of airway obstruction following bronchodilator administration, and the response to therapy. It may be difficult to arrive at a definitive diagnosis in asymptomatic horses or in horses that are exhibiting mild signs at the time of the examination, thus necessitating the use of additional diagnostic tests such as cytologic analysis of lower respiratory tract secretions. During periods of clinical remission, BALF cell populations obtained from RAO-susceptible horses consist predominantly of mononuclear cells (90% macrophages and lymphocytes), and the cell differential counts do not differ from those found in healthy horses.[87] However, when horses develop RAO, aspirates of tracheal and bronchoalveolar fluid contain increased numbers of nondegenerative neutrophils (>25%). The BALF neutrophil percentages may be as great as 90%, far exceeding the normal 5% to 15% found in healthy horses that are stabled and fed hay. The extent of pulmonary neutrophilia alone is not correlated with severity of clinical signs.[88] There also is no regional difference (left versus right lung) in neutrophil percentages in affected horses.[88] In most cases the percentage of eosinophils or mast cells is not increased in affected horses. Therefore cytologic analysis of respiratory secretions in RAO-affected horses reflects a suppurative nonseptic inflammation, distinguishing this disorder from lungworm infections (pulmonary eosinophilia) or pneumonia (degenerative neutrophils, intracellular bacteria). In rare cases, infectious bronchitis may complicate RAO; microbial cultures yield low growth of the bacterial isolate, but the predominant cell type in the tracheal secretions is a nondegenerative neutrophil.

Endoscopic examination of the respiratory tract of RAO-affected horses demonstrates excessive amounts of tracheobronchial secretions that originate from most of the bronchial segments. Distal airways are edematous and inflamed, and airways easily collapse during expiration. Expectorated secretions from the lower respiratory tract coat the pharynx, larynx, and other structures of the upper respiratory tract.

In general, the complete blood cell count, serum biochemistry profile, and serum fibrinogen concentrations are usually normal in RAO-affected horses.[78] In severely stressed horses, a mature neutrophilia and lymphopenia may be evident on the leukogram. Recently, Lavoie-Lamoureux and colleagues reported significant increases in serum haptoglobulin and serum amyloid A concentrations in symptomatic RAO-affected horses, challenging the conventional thinking that RAO is a compartmentalized inflammatory response.[89]

Arterial blood gas analyses are normal in approximately 25% of the cases,[90] but other cases exhibit hypoxemia (Pa_{O_2} < 85 mm Hg) with or without evidence of arterial hypercapnia.[91] In affected horses that are exercised, at a given work effort the arterial oxygen tensions are reduced compared with blood gas values obtained from the same horses during clinical remission.[92] Prognostic value of arterial blood gases in RAO-affected horses has not been examined.

In a study of digital thoracic radiographs of 22 warmblood horses affected with RAO, an unstructured interstitial pattern was found in all cases; a bronchointerstitial pattern occurred in 21 cases, and an alteration in the diaphragmatic silhouette (flattened or concave presumably due to lung hyperinflation) was noted in 10 cases. None of the thoracic radiographs demonstrated evidence of hilar opacity or concavity.[93] Nevertheless, radiographs may be of limited value in diagnosing RAO because the accentuated bronchointerstitial pattern can often be detected in healthy aged horses. Radiographs can be useful in ruling out thoracic neoplastic or infectious (interstitial or bronchopneumonia pneumonia, equine multinodular pulmonary fibrosis) disorders in horses that have clinical signs resembling RAO (cough, nasal discharge, abnormal breathing effort). In severely affected horses with RAO that repeatedly fail to respond to medical interventions, radiographs should be taken to determine if bronchiectasis (dilation or deformation of the bronchi or bronchioles) exists.[94] Bronchiectasis is a relatively uncommon complication of RAO but, when it occurs, it causes irreversible airway obstruction as a result of collapse of the affected airways.

Ultrasound evaluation of RAO-affected horses confirms a shift of the caudal lung border caused by alveolar hyperinflation.[95] However, gas in the large colon (left side) or in the cecum (right side) may preclude complete imaging of the most caudal extent of the lung fields at the sixteenth intercostal space. Thoracic ultrasonography of RAO-affected horses may demonstrate small hypoechoic areas of irregularity on the lung surface, but in general ultrasonography is not useful in detecting airway inflammation. In horses with cor pulmonale, ultrasonography confirms the presence of pulmonary hypertension and right ventricular hypertrophy.[85]

Lung biopsies, although not typically performed to diagnose RAO, demonstrate bronchiolar goblet cell metaplasia, bronchiolar luminal exudate, peribronchiolar lymphoplasmacytic cell infiltration, and accumulations of neutrophils within the airways.[77] The potential disadvantages of performing a lung biopsy include the risk of inducing hemorrhage (hemothorax, epistaxis) and the chance of obtaining a nonrepresentative tissue sample.

Intradermal skin testing of RAO-affected horses has been investigated by many with the aim of diagnosing RAO and identifying the offending allergens. Evans and colleagues found that in RAO-affected horses the total number of positive intradermal skin tests evaluated at 0.5, 4 to 6, and 24 hours after allergen injection exceeded that in control horses. Positive responses were detected for two pollens (English plantain, goldenrod), three molds *(Rhizopus* spp., *Monilia* spp., and *Alternaria tenuis),* and one insect extract (*Tabanus* spp.). However, this difference in skin reactivity, which involved only 3% of the possible extract reactions, did not permit discrimination between a diseased horse and a healthy horse.[96] Similarly, in a retrospective study of cases examined at a veterinary teaching hospital over a 10-year period, Jose-Cunilleras and colleagues found that the percentage of RAO-affected horses that had positive skin reactions exceeded that of the control horses at each time point examined (0.5, 4, and 24 hours).[97] In contrast, others have failed to find a significant difference between RAO-affected and control horses in either the number of positive skin responses to a variety of molds in the titers developed at the early (0.5, 4 hours) or late (24 hours) phases.[98-100] Wong and colleagues, evaluating the skin responses to intradermal histamine and *Aspergillus* antigens, found that compared with the controls the RAO-affected horses had a heightened response to histamine (evaluated at 0.5 hours post injection) and a delayed resolution of the skin wheal (after 24 hours) to the *Aspergillus* antigens.[101] Thus positive skin tests and serum precipitins to fungal and thermophilic actinomycete antigens are found in many normal as well as RAO-affected horses, reflecting a level of exposure of the horse rather than a susceptibility to disease. In general, skin testing does not allow identification of RAO-susceptible or RAO-affected horses or the specific inhaled particulate that is inciting the pulmonary inflammation.[102]

Serum allergy tests such as the radioallergosorbent test (RAST) or IgE-based enzyme-linked immunosorbent assay (ELISA), which aim to identify the allergen that is inciting the hypersensitivity, are of limited value in the diagnosis of RAO. Lorch and colleagues compared the results of three serum IgE quantitation assays (the spot test, a RAST; Allercept [Heska, Loveland, Colo.], an ELISA that uses a recombinant human FcεRIα chain as the IgE readout reagent; and equine ELISA, which uses a polyclonal antiserum to detect equine IgE) with intradermal skin test responses in RAO-affected horses. They concluded that based on the poor performance of all three tests, none should be used as a screening test for allergen hypersensitivity.[103] Similar conclusions were reached by Tahon and colleagues (2009) who compared the Allercept test and the CAST (Alpco, Salem, N.H.) test (which measures IgE-mediated release of sulfidoleukotrienes from peripheral blood basophils) with intradermal testing in RAO-affected horses and controls. None of the tests showed a significant difference in responses between diseased and control horses and thus did not support an IgE-mediated basis for RAO.[104]

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Conventional pulmonary function tests, which require measurements of pleural pressure (obtained via an intrathoracic esophageal balloon catheter system) and airflow (detected by a flow meter attached to a sealed face mask worn by the horse), are typically reserved for experimental investigations and are not routinely performed on clinical patients. The characteristic alterations in the pulmonary function test results of horses with RAO are a decrease in dynamic lung compliance or lung distensibility (C_{dyn}), an increase in pulmonary resistance (R_L), an increase in maximum pleural pressure changes (ΔP_{plmax}), and an increase in peak inspiratory and expiratory flow rates.[105] In general, C_{dyn} reflects peripheral airway function, whereas R_L reflects central, larger airway function. RAO-affected horses also exhibit bronchial hyperreactivity: the dose of aerosolized histamine or methacholine required to reduce C_{dyn} to 65% of its baseline value is much less in diseased horses than in controls.[106] These alterations in lung function that develop in affected horses are repeatable on reexposure to hay dust.[107,108] During periods of clinical remission the pulmonary function test results return to normal and are not significantly different from those of healthy age-matched horses. However, an inability to detect a difference in R_L or C_{dyn} between healthy horses and RAO-susceptible horses during periods of disease remission may reflect a relative lack of sensitivity of these tests.[109] For example, some researchers have found that in RAO-susceptible horses during periods of clinical remission, some degree of bronchial hyperreactivity and airflow obstruction remains.[110,111] In some tertiary care centers, pulmonary function testing using impulse or forced oscillation methods aids in the diagnosis of RAO. (See Inflammatory Airway Disease section).

Pathophysiology The changes in respiratory mechanics and the development of clinical signs are consequences of the influx of inflammatory cells (mechanisms discussed earlier), the contraction of smooth muscle in the airways, and the production and accumulation of mucus. Bronchoconstriction probably results from the cumulative effects of (1) released inflammatory mediators (histamine, serotonin, eicosanoids, leukotrienes, endothelin) and (2) activation of muscarinic receptors on the smooth muscle by released acetylcholine.[112] In addition to their direct effects on smooth muscle tension, histamine and serotonin also augment the release of acetylcholine from parasympathetic nerves.[113] Based on in vitro muscle bath studies, there is also evidence that RAO-affected horses lack inhibitory nonadrenergic-noncholinergic innervation of the peripheral (but not central) airways, further contributing to the development of bronchospasm.[114] The expression or distribution of airway muscarinic receptor subtypes (M_1, M_2, M_3) is, however, unaltered in RAO-affected horses.[115] The magnitude of airway narrowing that occurs in response to smooth muscle contraction is a function not only of the thickness of the smooth muscle layer but also of the width of the mucosal layer between the muscle and airway lumen. Thus thickening of the airway by peribronchial infiltrates and by epithelial metaplasia amplifies the airway narrowing induced by bronchospasm.[116]

As noted earlier, excessive mucus is evident endoscopically and cytologically in RAO-affected horses. Mucus consists of a liquid sol layer, which surrounds the ciliated epithelium, and an overlying viscous gel layer, which contains water, electrolytes, lysozymes, cells, and the mucin glycoproteins. In RAO-affected horses the excessive mucus formation may be the result of an upregulation of a mucin-producing gene, responding to released elastases, reactive oxygen species, and other inflammatory mediators. However, Gerber and colleagues were unable to demonstrate an upregulation of two mucin-producing genes, MUC5AC and MUC2, in airway tissues of RAO-affected horses.[117,118] Increased viscosity of the mucus[119] may be a consequence of alterations in the side chain glycoproteins[120] and/or formation of mucin aggregates from DNA and actin released by airway neutrophils. Delayed clearance of the mucus from the lower respiratory tract contributes to the accumulation of the exudate and may reflect an impairment of the mucociliary apparatus as a result of epithelial cell destruction.[121,122]

Airways that are narrowed, obstructed, or both (as a result of inflammatory exudate, alterations in pulmonary surfactant, or both[123,124]) increase R_L and fail to participate in efficient gas exchange. Low ventilation-perfusion lung regions contribute to a widening of the alveolar-arterial oxygen-difference ($AaDO_2$) gradient and the development of arterial hypoxemia.[125,126] High ventilation-perfusion regions (dead space) also increase in affected horses, but normal arterial $PaCO_2$ levels can be maintained in some horses through increases in the total minute ventilation.[127] Changes in minute ventilation are usually due to an increase in breathing frequency, as tidal volume changes little with the disease. In general, there are no significant changes in cardiac output, heart rate, and mean systemic arterial pressure, but pulmonary artery systolic and mean pressures and pulmonary vascular resistances are significantly increased in diseased horses.[127] The combination of airway inflammation and hypoxemia, if severe enough, stimulates the respiratory controller in the ventral medulla to increase the respiratory drive and to activate inspiratory and expiratory muscles (abdominal heave). Recruitment of respiratory muscles increases the maximum pleural pressure excursion (ΔP_{plmax}), the work of breathing, and the total body oxygen consumption.[128] However, much of the increased expiratory effort (and increased intrathoracic pressures) collapses the noncartilaginous airways, further compounding gas trapping and impairing gas exchange.

Pathology The lungs obtained from RAO-prone horses that are asymptomatic at the time of death macroscopically appear normal.[125] In symptomatic horses, the lungs are pink, soft, hyperinflated, and imprinted with rib impressions. Lungs fail to collapse when the chest is opened because of gas trapping distal to occluded airways.[98] Emphysematous bullae are usually lacking, but accumulations of mucus and cellular debris occlude the small airways, forming spiral-shaped casts known as *Curschmann spirals.* Light and electron microscopic examinations of lung segments from diseased horses demonstrate that the peripheral airways are the most severely affected, although pathologic alterations do occur in the central airways.[121,122] Histologic changes include goblet cell hyperplasia, epithelial cell damage, bronchial and bronchiolar epithelial cell hyperplasia, smooth muscle hypertrophy and hyperplasia, and overinflation of the alveoli.[129-131] It is interesting to note that the extent of the bronchiolar epithelial cell hyperplasia is correlated with the increase in dead space ventilation that occurs in RAO-affected horses.[127] Peribronchiolar infiltrates consist of lymphocytes and plasma cells, along with collagen deposition[132]; eosinophils are rarely observed either within the airways or in the lung parenchyma. In the peripheral airways, the type and location of collagen I and III, examined by immunohistochemical techniques, is not increased in RAO-affected horses compared with controls.[133]

Despite these pathologic changes, the clinical signs are usually considered to be reversible. Increases in airway smooth muscle mass due to hyperplasia and hypertrophy, evident following 30 days of continuous allergen exposure in RAO-susceptible horses,[134] are reversed after long-term allergen avoidance or following inhaled corticosteroid administration.[135] In rare instances bronchiectasis may develop in RAO-affected horses. In a single case study of one such affected horse, histopathologic alterations of the affected airway demonstrated separation of the cartilaginous plates of the dilated bronchus, disorganization of the chondrocytes, reduction in the elastic fibers surrounding the perichondrium and lamina propria, and a lymphoplasmacytic infiltrate.[94]

In RAO-affected horses with cor pulmonale, reductions in the circumferential ratio of the aorta to the pulmonary artery and in the mass ratio of the left ventricle and septum to the right ventricle can be found.[85,136]

Treatment and Prognosis

ENVIRONMENTAL MANAGEMENT. Environmental management remains the single most important therapeutic and prophylactic intervention. Whenever possible, RAO-prone and RAO-affected

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horses should be kept outside at all times, blanketed during inclement weather as needed, and provided access to a well-ventilated three-sided shelter from which manure and urine are frequently removed. Horses should be provided with pasture access and supplemented with complete pelleted feed or hay cubes as needed. Some horses will tolerate hay that has been soaked in water, but this practice reduces the nutrient value of the hay and is often forsaken when the weather becomes cold. Preliminary data suggest that steamed hay may be helpful in preventing exacerbations of RAO in susceptible horses.[137] Reducing dust exposure is critical, as inhaling organic dusts for as little as 1.5 hours causes a significant increase in R_L. By 5 hours, horses exhibit significant decreases in C_{dyn} and PaO_2 and have evidence of pulmonary neutrophilia.[16,138] The ensuing inflammation from a single 5-hour dust exposure takes approximately 4 days to resolve.[139] For chronically affected horses that have been turned out to pasture, clinical remission and normalization of pulmonary function test results usually take 4 to 8 weeks depending on weather conditions.[2,140] However, owners should be warned that acute exacerbations of RAO may occur in susceptible horses turned outside during periods of hot (dusty) weather.[141]

Horses for which optimal management changes cannot be implemented should be fed pellets, hay cubes, or both and kept in well-ventilated stalls that are bedded with a material that has a low respirable dust particle count and mold concentration. Cardboard bedding has a significantly lower particulate concentration (dust, *A. fumigatus, F. rectivirgula,* and *T. vulgaris*) than do wood shavings, wheat, or flax straw, although cardboard may be difficult to obtain and store.[140,142] Horses should be removed from the barn when stalls or other areas are being cleaned. Typically, when affected horses are bedded on shavings and fed pelleted rations, significant improvements in the pulmonary function test results occur within 3 days.[143] Complete resolution of clinical signs may take 30 days, although not all horses may respond to only allergen reduction measures.[144] When RAO-susceptible horses that are in clinical remission are fed low dust–containing forages and bedded on low dust–containing materials or turned outside in a low dust environment, they can remain clinically normal for months. However, even though BALF neutrophil percentages, and indices of airway inflammation such as exhaled ethane, are normal, bronchial hyperreactivity and forced expiratory airflow in RAO-prone horses remains abnormal.[110,145-147] Therefore these horses will always be more susceptible to disease development than healthy horses when dust levels increase in the environment.

Environmental management considerations should also be implemented when horses are transported. Their heads should not be tied in close proximity to the hay net, as this practice places their breathing zone near a concentrated source of organic dusts and molds and restricts their head position so as to further decrease mucociliary clearance of respiratory secretions.[148]

BRONCHODILATORS. During acute exacerbations of RAO, bronchodilators can be very effective in improving lung mechanics and in establishing the reversibility (and thus diagnosis) of RAO. Three main classes of bronchodilators have been used in RAO-affected horses: these are the anticholinergics (muscarinic antagonists), the β_2-agonists, and the phosphodiesterase (PDE) inhibitors.

The muscarinic antagonists, of which atropine, ipratropium, and n-butyl scopolammonium bromide are examples, block the smooth muscle–constricting effects of acetylcholine. These actions have the greatest effects in the central as opposed to the peripheral airways. IV administration of 0.01 to 0.02 mg/kg of atropine sulfate decreases ΔP_{plmax} and respiratory rate and induces a clinical improvement usually within 30 minutes of administration.[149,150] Its short duration of action (2 hours) and its undesirable side effects (mydriasis, ileus, tachycardia, dry airway secretions) preclude its routine use in the treatment of RAO.[151] In contrast, ipratropium bromide is poorly absorbed from either the respiratory or gastrointestinal tract, minimizing the development of systemic effects. The powder form is nebulized (2 to 3 µg/kg) and exhibits an onset of action within 30 minutes with effects lasting from 4 to 6 hours.[152] When given to RAO-affected horses before an incremental exercise test, ipratropium reduces R_L and ΔP_{plmax} and increases C_{dyn} in resting horses but produces no significant improvement in exercise pulmonary function tests or oxygen consumption.[153] N-butyl scopolammonium bromide, when administered at 0.3 mg/kg intravenously, improves clinical scores and pulmonary function tests of RAO-affected horses within 10 minutes of its administration, with effects lasting for approximately 1 hour. No adverse effects were noted following its use in a research trial.[154]

The β_2-adrenergic agonists—clenbuterol, albuterol, fenoterol, pirbuterol, and salmeterol—produce relaxation of smooth muscle by increasing the intracellular levels of cyclic adenosine monophosphate (cAMP). The bioavailability of clenbuterol is greater than 90%, and when administered orally at a dose of 1.6 µg/kg of body weight twice per day (bid), a significant improvement in the clinical signs of horses with RAO can occur.[155] However, the effective dosage of clenbuterol may vary among horses: Traub-Dargatz and colleagues[156] found that 400 µg of oral clenbuterol hydrochloride administered twice daily failed to improve the severity of clinical signs, the BALF or tracheal cytologies, or the arterial blood gases in RAO-affected horses. During the treatment, horses were maintained outside but still fed hay. Erichsen and colleagues[155] recommended increasing the dose of clenbuterol stepwise if clinical improvement is not observed within 3 days of initiating treatment (e.g., 2.4 µg/kg for 3 days, 3.2 µg/kg for 3 days). Adverse side effects (anxiety, shivering, sweating, and tachycardia) occur at higher dosages but appear to be minimized when clenbuterol is increased in a stepwise manner. Reports of fatal overdoses of clenbuterol have been reported in horses estimated to have received 100 µg/kg orally of a compounded product.[157] In addition to its bronchodilatory effect, clenbuterol also exerts an antiinflammatory effect. When administered intravenously (0.75 µg/kg bid) to RAO-susceptible horses before hay dust exposure, there is a significant attenuation of the BALF neutrophilia and the transcription of the proinflammatory genes, TNF-α and IL-1.[158] Prolonged administration of clenbuterol (0.8 µg/kg bid for 3 weeks) may result in tachyphylaxis[159] due to downregulation of β-adrenoceptors, but this phenomenon may be reversed with concurrent corticosteroid administration.[160]

Other β_2-agonists have been administered as aerosolized drugs to RAO-affected horses. Inhalation therapy allows direct delivery of the drug to the respiratory tract, minimizes the total amount of drug needed to be delivered, and reduces the prevalence of unfavorable systemic effects. The metered dose inhaler containing the drug is attached to a delivery system such as a mask (Aeromask, Trudell Medical, Inc., London, Ontario, Canada) or other device (Equine Haler [Equine Health Care, Inc., Hørsholm, Denmark] or Aerohippus [Trudell Medical, Inc.]). The systems contain spacers to optimize the drug particle size that is inhaled (larger sized particles drop out) and deposited in the lower respiratory tract. Both the Equine Haler and Aerohippus exhibit similar efficacy in drug delivery and clinical improvement.[161] The inhaled rapidly acting β_2-agonists pirbuterol, albuterol sulfate, and fenoterol improve pulmonary function by 60% to 70% in RAO-affected horses for approximately 1 to 3 hours, necessitating frequent administration of the drugs.[162-164] They are poorly absorbed, so systemic effects are uncommon. The recommended dose of albuterol for a 450-kg horse is 600 to 720 µg q4-6h, for fenoterol it is 2 mg q4-8h, and for pirbuterol it is 16 µg/kg q4-6h. More frequent administration may be necessary in some horses. Salmeterol, a longer-acting β_2-agonist, is administered at a dose of 0.5 µg/kg q6-8h. Clinical improvement develops within 2 hours of administration, but significant decreases in pulmonary resistance last for only 6 hours.[165]

The PDE inhibitors are the third class of bronchodilators and are represented by aminophylline and pentoxifylline. These drugs inhibit the breakdown of intracellular cAMP, thus maintaining smooth muscle relaxation. PDE inhibitors also exert antiinflammatory properties.[166] The clinical efficacy of aminophylline (the soluble salt of theophylline) was evaluated by Pearson and Riebold in 18 clinical cases of RAO. Administration of 12 mg/kg IV in 1 L of 5% dextrose

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achieved blood levels of 10 µg/mL, improved clinical signs in 50% of the cases, and reduced ΔP_{plmax} in 41% of cases. Horses also became hyperesthetic and hyperexcitable and trembled.[150] Because of the narrow range between therapeutic efficacy (serum concentrations = 10 µg/mL) and toxicity (serum concentration = 15 µg/mL), aminophylline is not routinely used for the treatment of RAO. Pentoxifylline is well absorbed after oral administration (16 g bid, 32 mg/kg), improves pulmonary function test results (effects are similar to those produced with atropine), and lacks adverse side effects. It does not improve BALF neutrophilia.[167]

ANTIINFLAMMATORY DRUGS. Whereas most corticosteroids are efficacious in the treatment of RAO, NSAIDs have not proven to be beneficial.[50] Oral prednisone also does not improve the clinical signs, the BALF cytologic alterations, or the pulmonary function test results in RAO-affected horses.[143,168,169] Its therapeutic failure is attributed to its poor absorption and the lack of conversion to the active metabolite, prednisolone.[169] In contrast, both liquid and tablet forms of prednisolone are rapidly absorbed from the equine gastrointestinal tract (bioavailability is approximately 50%), achieve peak prednisolone concentrations 45 minutes post-administration, and exert pharmacologic effects (based on changes in serum cortisol levels) for 8 hours.[169] Oral prednisolone (2 mg/kg PO once per day [sid] for 7 days) improved pulmonary function test results (R_L, elastance E_L, and ΔP_{plmax}) within 3 days of its administration to RAO-affected horses stabled and continuously exposed to dusty hay[170] but was less efficacious than oral dexamethasone (0.05 mg/kg PO q24h) treatment.

The beneficial effects of dexamethasone in the treatment of RAO-affected horses have also been investigated by several different research groups.[168-173] Within 2 hours of its IV administration to RAO-affected horses (0.1 mg/kg), there is a 37% decrease in ΔP_{plmax} that is further reduced 59% by 4 hours post treatment.[169] Oral administration of the IV formulation of dexamethasone (0.164 mg/kg q24h to account for bioavailability) produces a significant improvement in lung function parameters within 6 hours of treatment, with peak effects occurring 24 hours later.[169] For horses that are maintained in dusty environments during a 10-day treatment period, IV dexamethasone (0.1 mg/kg q24h) or dexamethasone isonicotinate (0.04 mg/kg IM every 3 days for three treatments) improves pulmonary function within 3 days of initiating therapy[168] and reduces airway inflammation (BALF neutrophilia) within 10 days of treatment.[172] As might be predicted, a single dose of dexamethasone isonicotinate (0.06 mg/kg IM) administered to RAO-affected horses maintained in a dusty environment fails to provide discernible improvements in the clinical score, the pulmonary function test results, the BALF cytologic findings, or the activities of the transcription factors NF-κB or AP-1 evaluated 10 days post treatment.[173] In general, the rapid onset of action of IV dexamethasone makes this an antiinflammatory of choice in horses exhibiting respiratory distress caused by RAO.[174]

The therapeutic efficacy of triamcinolone acetonide and isoflupredone has also been evaluated in RAO-affected horses maintained in a dusty environment.[175,176] A single IM dose of triamcinolone acetonide (0.09 mg/kg) markedly improved lung mechanics evaluated 7 and 14 days post treatment, and this effect lasted for 4 weeks. Cytologic changes were also evaluated 14 days post treatment and demonstrated a reduction in airway neutrophilia (neutrophil percentages decreased from 62% to 32%), but this improvement was not statistically significant.[175] Adverse effects of triamcinolone administration were not reported. In another study, RAO-affected horses received isoflupredone acetate for 14 days (0.03 mg/kg IM q24h) while being maintained in a dusty environment. Significant increases in C_{dyn} and reductions in R_L and ΔP_{plmax} occurred within 3 days of initiation of the treatment[176]; beneficial effects continued 7 days beyond the cessation of drug therapy. The only adverse effect noted was the development of hypokalemia.

The effectiveness of a 3-week course of inhaled fluticasone on pulmonary function, BALF cytologies, and BALF cell gene expression was examined by Giguère and colleagues.[26] RAO-affected horses that received 2 mg of fluticasone propionate bid for 21 days while still being fed hay demonstrated marked (and significant) improvements in ΔP_{plmax}, C_{dyn}, and R_L by day 21 of the treatment period. Furthermore, BALF neutrophil counts became normal and IL-8 copy numbers in the BALF cell were reduced to levels equivalent to those found during remission.[26] In an experimental trial, Robinson and colleagues[174] compared the therapeutic and preventive efficacies of inhaled fluticasone (6 mg bid) and IV dexamethasone (0.1 mg/kg q24h) on pulmonary function and BALF cytologies in RAO-affected horses. They found that (1) no adverse effects, including laminitis, were associated with a 3-day course of fluticasone at 6 mg bid; (2) greater reductions in ΔP_{plmax} in RAO-affected horses were achieved with dexamethasone than with fluticasone treatment; and (3) prophylactic (3-day) and continual (4-day) administration of fluticasone (6 mg bid) to RAO-susceptible horses subjected to stabling and dusty hay exposure is more efficacious in preventing the disease than is dexamethasone. The investigators concluded that dexamethasone should be used for "rescue" therapy, whereas fluticasone is best used as a preventive agent. Fluticasone is approximately 18 times more potent than another inhaled corticosteroid, beclomethasone dipropionate. Nasal or oral administration of fluticasone has no effect on circulating glucocorticoid levels, suggesting that the bioavailability across nasal and intestinal epithelium is poor.[177] However, daily aerosolization of fluticasone (dose of 1.5, 3, or 6 mg bid) significantly reduces serum cortisol measured 72 hours after initiating therapy.[174,177] The effect of long-term fluticasone administration on innate and immune responses has also been investigated. Administration of 2 mg bid for 11 months to RAO-affected or susceptible horses had no significant effect on (1) peripheral blood leukocyte, neutrophil, or lymphocyte numbers; (2) percentages of lymphocyte phenotypes; (3) blood neutrophil chemokine (IL-8, TNF-α) and glucocorticoid receptor gene expression; (4) IgG vaccine titers induced by immunization against tetanus toxoid or an inactivated IBR vaccine; or (5) mitogen-induced lymphocyte proliferative responses.[178] These data suggest that fluticasone is a relatively safe drug for use in the treatment of RAO.

Another inhaled corticosteroid that has been widely investigated in RAO-affected horses is beclomethasone diproprionate. When administered at a dose of 1320 to 1500 µg bid for 7 to 10 days to diseased horses continuously stabled and fed dusty hay, investigators noted that by day 7 of treatment there was a significant improvement but not a complete normalization of pulmonary function test results and BALF neutrophil percentages.[81,179]

Inhaled steroids are often used in conjunction with inhaled bronchodilators for maximal therapeutic effects. When separate formulations are used, it is recommended that the bronchodilator be administered first so as to improve subsequent glucocorticoid deposition in the peripheral airways.[180] As suggested earlier, when administering glucocorticoids, adrenal gland atrophy, immunosuppression, and precipitation of laminitis remain a concern. All of the previously discussed parenteral and inhaled glucocorticoids reduce endogenous serum cortisol levels but despite prolonged treatment protocols with glucocorticoids, adrenal gland responsiveness to adrenocorticotropic hormone administration remains.[175,176,181] Finally, despite the improvement in clinical signs and in pulmonary function tests achieved with glucocorticoid therapy, BALF neutrophilia remains evident until environmental management changes are implemented.

OTHER THERAPIES. In horses that develop respiratory distress because of the bronchospasm and airway inflammation, additional therapies are required. Administering nasal oxygen at flow rates as low as 5 L/min improves arterial oxygen tension by as much as 30 mm Hg in some severely affected horses.[182] As the total nasal oxygen flow increases, so too should the mean arterial oxygen tension, although not to the same degree that occurs in healthy horses. Flow rates of 30 L/min (delivered by 2 nasal cannulae at 15 L/min) are associated with coughing and gagging in horses. Nasal oxygen supplementation does not reduce breathing frequency,

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suggesting that stimulation of vagally mediated afferents (perhaps responding to inflammatory mediators) is responsible for the tachypnea.

Furosemide (1 mg/kg IV or nebulized) provides beneficial effects to RAO-affected horses within 20 minutes of its administration, decreasing R_L and increasing C_{dyn} without affecting PaO_2.[183] The beneficial effects appear to be mediated by prostaglandin E_2, derived from either the renal or the airway epithelium, which promotes smooth muscle relaxation. Prior treatment with the cyclooxygenase inhibitor flunixin meglumine prevents the furosemide-induced bronchodilation.[184]

Additional therapeutic approaches that have *not* been found to be efficacious in the treatment of RAO-affected horses include a single acupuncture treatment,[185] the oral administration of an herbal preparation containing thyme and primula,[186] the rapid IV administration of 30 L of isotonic saline,[187] a constant rate infusion of IV lidocaine,[188] and sound-wave physiotherapy.[189]

Prognosis RAO-prone horses are likely to develop acute exacerbations of the disease when husbandry practices lapse or when weather conditions become adverse. Horses do not "outgrow" the disorder, and, in fact, some clinicians believe that the inflammation becomes more difficult to manage as the horse ages. The basis for the lack of clinical response is unknown but may be the result of lung remodeling—development of fibromuscular hyperplasia in the alveolar septa,[85] excessive smooth muscle hyperplasia,[131] bronchiectasis,[94] or potential downregulation of the glucocorticoid receptor.

If proper environmental management changes are implemented and if the appropriate therapy is initiated, then clinical remission occurs in most cases. In a follow-up survey conducted by Naylor of RAO-affected horses that had been examined and treated at a referral center 2 to 4 years previously, it was found that 20% of the original cases (3 of 15) had been euthanized, that 33% were still receiving bronchodilators on an as-needed basis, and that the athleticism had not decreased in 92% of the horses.[77] Similarly, in a follow-up survey conducted by Aviza and colleagues,[78] 13% of the horses that had been diagnosed with RAO 3 to 4 years earlier had been euthanized. However, in contrast to Naylor's findings, Aviza noted that more than 50% of the respondents in that survey stated that the athletic performance of the horse had been compromised by the disease. Perhaps this difference between the two surveys simply reflected a failure of the owners to comply with environmental management recommendations. When queried about the husbandry practices, 77% of the respondents still stabled the horse for part of the day, and 84% still fed the horse dry hay.[78]

Because the effects of repetitive episodes on the development of irreversible changes in lung structure have yet to be determined, clients should be encouraged to implement effective husbandry changes that minimize the recurrences of RAO.

Summer Pasture–Associated Obstructive Pulmonary Disease

Dorothy M. Ainsworth

Definition and Etiopathogenesis In the southeastern United States a condition clinically similar to RAO called *summer pasture–associated obstructive pulmonary disease* (SPAOPD) develops in mature horses that are kept outdoors on pasture. Clinical signs typically occur between the early summer and early autumn (June through September) when the weather is warm and humid.[1] Clinical signs partially or completely resolve during the winter or when the horse is removed from the pasture; thus the pulmonary inflammatory condition is considered reversible. The temporal pattern of clinical signs parallels increases in environmental fungal spore *(Basidiospore, Nigrospora,* and *Curvularia)* and grass pollen counts (Bermuda grass and Johnson grass).[2] Thus it is thought that these aeroallergens (and potentially others) trigger the disease. SPAOPD has also been reported to occur in horses in the United Kingdom although some of those cases may represent horses with underlying (subclinical) recurrent airway obstruction (RAO) whose condition is exacerbated by hot weather and airborne particulates.[3-5]

Investigators have sought to determine if SPAOPD reflects a T-helper type 2 (Th2) or T-helper type 1 (Th1) immune response to the airborne particulates by examining antibody and cytokine profiles in the pulmonary secretions of affected horses. In one study, neither the total nor the antigen-specific immunoglobulin E and G (IgE and IgG) titers to certain fungi (*Aspergillus* spp., *Cladosporium herbarum, Penicillium* spp.), thermophilic actinomycetes species *(Faenia rectivirgula, Saccharomonospora viridis, Thermoactinomyces thalpophilus),* or to the forage mite *Lepidoglyphus destructor* in the tracheal lavage fluid were increased in SPAOPD-affected horses relative to controls.[6] During the winter months, when the horses are free of clinical signs, *A. fumigatus*–specific (IgG) titers in the SPAOPD group exceeded those in controls, but it was not known if this increase reflected ongoing production or decreased consumption.

Cytokine profiles in bronchoalveolar lavage (BAL) cells and peripheral blood mononuclear cells (PBMCs) (or lymphocytes) isolated from SPAOPD-affected and control horses fail to provide consistent support for a Th2 response. Increased gene expression of interleukin (IL)-4 and interferon (IFN)-γ in BAL cells and PBMCs isolated from symptomatic horses relative to controls was reported in one study.[7] In another investigation by the same group,[8] the gene expression of IFN-γ and IL-13 (but not IL-4) in BAL cells and peripheral blood lymphocytes isolated from symptomatic horses exceeded that of controls. Only when horses were asymptomatic (winter) did BAL cell or peripheral lymphocyte IL-4 gene expression exceed that of controls.

Venugopal and colleagues performed differential display polymerase chain reaction on lung samples obtained from symptomatic horses and controls.[9] Of the 88 genes that were differentially expressed, 18 genes were eventually identified and assigned functional roles such as lung protection; defense; mediation of proinflammatory or antiinflammatory responses; promotion of, or protection from, oxidative stress; cell recovery and repair; and mitogenesis. Of the 18 genes, only secretoglobin was downregulated in diseased horses. This gene encodes a family of proteins that blocks the activation of phospholipase A_2 so that its decreased expression would be expected to enhance arachidonic acid metabolism and the formation of inflammatory and vasoactive leukotrienes and prostaglandins. Venugopal also reported upregulation of eight genes that encode proteins associated with cell repair and proliferation[9] involved in lung repair and airway remodeling, supporting histopathologic changes previously described in affected horses.[10] Differential expression of immune cytokines (IL-4, IFN-γ, IL-17, TGF-β) was not reported in their study.

Because of the role of endothelin-1 (ET-1) in the pathophysiology of human obstructive pulmonary disorders, investigators have evaluated ET-1 concentrations in horses with SPAOPD. This 21-amino acid peptide induces bronchoconstriction; enhances mucus secretion; promotes DNA syntheses and cell proliferation in airway smooth muscle cells; and facilitates airway inflammation by upregulating IL-1, IL-4, IL-8, TNF-α, and IFN-γ expression.[11,12] Compared with control horses, symptomatic SPAOPD horses have increased ET-1 protein concentrations in the venous blood, bronchoalveolar lavage fluid, and pulmonary epithelial lining fluid.[12] This finding, coupled with the observation that endothelin receptors A and B in the bronchial smooth muscle of affected horse are increased,[11] suggests that ET-1 is just one mediator involved in the pathophysiology of SPAOPD.

Epidemiology Based on a survey of large animal veterinarians practicing in Louisiana who had examined horses with SPAOPD,[13] the median age of affected horses was 12 years, and male and female horses were equally affected. Quarter Horses were overrepresented in the affected group. Nearly 61% of the affected horses were on pasture at all times, and 99% of the cases were kept on pasture more

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than half of each day. In an earlier retrospective study[1] Seahorn and Beadle reported the mean age of clinical cases was 13.7 years and that 79% of cases developed SPAOPD on a recurring basis over the horse's lifespan.

Clinical Signs and Differential Diagnoses The clinical signs of SPAOPD are seasonal and reversible and vary in severity depending on the duration of disease. Initial signs may be subtle and include exercise intolerance, intermittent cough, intermittent nasal discharge (serous or mucoid), and tachypnea. As the disease progresses, accentuated expiratory efforts (heave line), nostril flaring, frequent coughing, and even respiratory distress become evident.[1] Crackles, wheezes as well as silent areas, suggesting the absence of air movement, may be auscultated.[1,10] Horses are usually afebrile. Differential diagnoses include concurrent bacterial, viral, or fungal respiratory infections (ruled out by evaluation of blood work and culture/examination of tracheal aspirates) and anhidrosis (ruled out by assessing sweat production in affected animals).

Diagnosis Historical and physical examination findings, along with the temporal development of clinical signs, support the diagnosis of SPAOPD. As with RAO, endoscopy of the lower respiratory tract reveals an accumulation of mucopurulent exudate within the tracheobronchial tree and evidence of bronchial epithelial hyperemia (in some horses). During bronchoscopic examination, dynamic collapse of the airway during expiration may be evident. Cytologic analysis of tracheobronchial secretions or of bronchoalveolar lavage fluid demonstrates neutrophilia (15% neutrophils), the absence of intracellular bacteria, and excessive mucous production.[10] Microbial culture of pulmonary secretions is typically negative. Thoracic radiographic examination may reveal mild to moderate bronchointerstitial patterns with evidence of lung field hyperexpansion (flattened diaphragm). Ultrasonographic findings, although not specifically described in SPAOPD-affected horses, would be expected to be similar to those in horses with RAO. Postmortem examination of the lungs from affected horses reveals overinflation, the presence of rib impressions, and a failure to collapse. Histopathologic changes include accumulation of mucus and neutrophils in the small airways, peribronchiolar smooth muscle hypertrophy, epithelial hyperplasia, and peribronchial neutrophilic and lymphocytic infiltrates. There is usually minimal evidence of emphysema and fibrosis.[10]

Treatment The most important management change to implement is to move the horse from the offending pasture to either another pasture or to a cool, dust-free stall that is bedded with shavings. Hay should be moistened and fed to the horse from the ground to reduce inhalation of organic dusts. When stalls and barn areas are being cleaned, the horse should be removed from these areas. Medical therapies include administration of glucocorticoids and bronchodilators, as described for horses with RAO (see Treatment of RAO).

Prognosis Recurrence of the condition is likely to develop when susceptible horses are exposed to environmental triggers. Longitudinal studies have not been conducted to ascertain the risk of permanent (irreversible) lung remodeling in recurring cases. The heritability of SPAOPD has not been established.

Inflammatory Airway Disease in the Horse

Melissa Mazan

What Is Inflammatory Airway Disease? *Inflammatory airway disease (IAD), small airway inflammatory disease, small airway disease,* and *allergic airway disease* are names that are often used interchangeably, but the once-fluid definition of IAD is slowly taking form. Although low-grade inflammation of the small airways is recognized as a common cause of poor performance in young to middle-aged athletic horses, it is only recently that the clear distinction has been made between heaves, or recurrent airway obstruction (RAO), and IAD. Workers in the field continue to debate whether IAD is a discrete disease entity[1] or whether it is merely a part of the continuum of airway inflammation that, if left untreated, will progress inexorably to the better characterized syndrome of RAO.[2] Horses with IAD are generally young, although middle-aged horses may also be affected[3]; have impaired performance that may go unnoticed at rest or during light work[4-6]; have mild to moderate airway inflammation that may involve neutrophils,[6,7] mast cells,[4,8,9] eosinophils,[2] or lymphocytes[6]; have variable clinical signs, including cough, nasal discharge, and abnormal lung sounds[2,8,10]; may have endoscopic evidence of tracheobronchial mucus accumulation[2,8,11]; and may have normal lung function at rest but show evidence of airway hyperresponsiveness on exposure to nonspecific agents such as histamine[12] or evidence of low limitations on forced expiratory maneuvers.[5] These observations were confirmed by a consensus agreed on in October 2002,[13] which also stated that the clinical picture of horses with IAD includes poor performance or exercise intolerance, coughing, and excessive tracheal mucus (although not all of these need be present) and nonseptic inflammation as detected by bronchoalveolar lavage cytology. In addition, these horses may have lung dysfunction, as evidenced by airway obstruction, airway hyperresponsiveness, or abnormal blood gas exchange. This definition specifically excludes horses that appear systemically sick or that have overt evidence of respiratory dysfunction, such as flaring nostrils or excessive thoracic or obvious abdominal breathing efforts.

The prevalence of IAD is somewhat of a guessing game. One study involving 965 Standardbreds in active racing founding that 22% had evidence of mucopus at the trachea or bronchial bifurcation when examined endoscopically, although these were diagnosed as horses with chronic obstructive pulmonary disease (COPD); undoubtedly these horses properly belong in the IAD group.[14] Similarly, 27% of actively racing Thoroughbreds in one study had IAD.[15] A remarkable 55% of 2-year-old Thoroughbreds in training could be classified as having lower airway disease on the basis of finding mucus in the trachea on endoscopy and inflammation on examination of tracheal aspirate fluid,[16] and abattoir studies have shown up to 37% of horses with histopathologic evidence of airway inflammation.[17] Because a standard definition of IAD has only recently been agreed on, the prevalence of IAD has varied according to the individual researcher's case definition. Nonseptic airway inflammation, regardless of whether it causes overt signs of respiratory disease, appears to be very common in performance horses. This discussion adheres to the definitions of IAD and RAO as developed by the International Workshop on Equine Chronic Airway Disease,[13] the Havemeyer Workshop, and the recent American College of Veterinary Internal Medicine (ACVIM) consensus statement on IAD. With RAO, horses have demonstrable lower airway obstruction, characterized by peak pleural pressures of at least 15 cm H_2O, induced by an environmental challenge of moldy hay, largely reversible by use of a bronchodilator or return to nonchallenge environment, and accompanied by an increase in BALF neutrophils during challenge. In contrast, IAD refers to a nonseptic airway disease in athletic horses that does not have a clearly defined allergic cause. The data from the many studies involving horses with what was traditionally known as COPD and is now more properly referred to as RAO, or heaves, did not conform with these guidelines, and many of the horses would more properly be characterized as having IAD.

Clinical Findings Although most investigators agree that IAD is a disease of younger horses expected to do athletic work, and as such is distinct from the picture of the dyspneic horses with overt RAO, there remains a plethora of clinical signs and case definitions for IAD. One of the most common findings in IAD is exercise intolerance, with or without overt signs of respiratory disease. Of 25 horses referred either for routine physical examination or for poor performance, and without any clinical signs or history of respiratory disease, 76% had evidence of airway inflammation according to an inflammation scoring system based on endoscopy and tracheal wash findings.[18] Subclinical airway disease may result simply in mild

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abnormalities on auscultation and endoscopy, and occasionally in coughing.[19] Signs such as nostril flaring and excessive abdominal effort at rest, however mild, are usually associated with horses that have true RAO, as clinical signs that can be reliably detected using clinical scoring systems usually are accompanied by significant mechanical dysfunction of the respiratory system.[20] The prevalence of cough in horses with IAD is hard to estimate, as many studies use the presence of cough as an inclusion criterion.[5,8,21] Other studies have shown that cough may be seen less than 16% to 50% of the time.[6,21,22] On endoscopic examination, excessive airway mucus is often seen, ranging from multiple specks to streams of mucus.[23] Other clinical signs that are frequently noticed include prolonged respiratory recovery,[3] respiratory embarrassment at exercise,[11] worsening of signs during hot, humid weather, and inability to perform work during collection. Racehorses with IAD are typically described as fading during the last quarter of the race (Mazan, personal observation). It is interesting to note that horses with dorsal displacement of the soft palate (DDSP) have a higher prevalence of IAD than do control horses. This brings into play a chicken-or-egg argument, as it cannot be determined whether IAD is a risk factor for DDSP, or if DDSP is a risk factor for IAD.[24]

How does IAD affect performance? The answer depends on the use of the horse and the expectations of the owner. A practitioner with a primarily pleasure-horse practice or with show-hunter clientele might report a very low incidence of IAD in younger horses, primarily because the level of exercise in these horses is not likely to force a diagnosis through signs of exercise intolerance. A racetrack practitioner, on the other hand, would be far more likely to detect exercise intolerance resulting from lower airway disease in young horses because the level of expected athletic output is much higher and the horses have a greater likelihood of being examined endoscopically. Indeed, in a National Hunt racing population, excessive mucus was detected endoscopically in 68% of horses,[25] and IAD was one of the top two reasons cited for horses not running.[26] As might be expected, cough is more common in sport horses than in racehorses, as is an elevated respiratory rate, reflecting the generally earlier diagnosis in racehorses.[22] Indeed, racehorses with excessive tracheal mucus performed at a lower level than those with no mucus found on endoscopic examination.[14,11] Persson, looking at Standardbred trotters and saddle horses, found that low-grade nonseptic airway inflammation does have a negative impact on ventilatory capacity but that this is more pronounced in racehorses.[27] Moreover, using bronchiolar biopsy, this group also demonstrated that oxygen uptake and pulmonary ventilation correlated inversely with the morphologic grade of small airway disease and the height of the bronchiolar epithelium—the last finding suggesting that the extent of obstruction may determine the extent of exercise impairment. Racehorses with IAD have impaired gas exchange during exercise.[28,29] However, other studies have found that horses with obvious evidence of airway inflammation do not necessarily have a history of exercise intolerance.[15,30] This may reflect the difficulty of diagnosing low-grade respiratory impairment and the trainer's failure to recognize poorer performance than nature intended, however, rather than the benign nature of the underlying disease.

Diagnosis

BRONCHOALVEOLAR LAVAGE. Varying levels of specificity are used when documenting the presence of airway inflammation. The least specific is the documentation of mucus in the trachea, although it is the method that best lends itself to large studies in the field.[4,31] Visualization of mucus in the trachea gives little information, however, as to the nature and the exact origin of the inflammation. Many workers have used and continue to use tracheal aspirate cytology to describe the nature of inflammation in IAD. Although tracheal aspiration can be used to explore the presence of inflammation and has been used to document neutrophilia, mastocytosis, and eosinophilia in young performance horses,[32,15] the question of the nature and exact origin again presents itself. Studies have shown poor correlation between tracheal aspiration and bronchoalveolar lavage (BAL) cytology in horses.[33,34] Whereas tracheal aspiration harvests primarily neutrophils and epithelial cells, BAL yields primarily alveolar macrophages and lymphocytes in normal horses. Moreover, there is no evidence of correlation between tracheal wash findings and performance. Consequently, to avoid the problem of neutrophil count sensitivity to the collection method, the recent International Workshop on Equine Chronic Airway Disease recommended use of BAL to characterize horses with chronic airway disease; this recommendation was seconded by the Havemeyer Workshop on IAD.

Different pictures of inflammation emerge from various BAL studies, leading to speculation that different genetic predispositions and environmental exposures are important to the inflammatory phenotype. In comparison with healthy horses, BAL cytology in horses with IAD has shown, variably, neutrophils,[6,7] mast cells,[4,8,9] eosinophils,[2] or lymphocytes.[6] In general, horses with IAD have airway inflammation that may involve increases in nucleated cells or may also involve lymphocytosis. This is distinguished from RAO by the relatively low percentage of abnormal cells in IAD; whereas horses with RAO may exhibit almost entirely neutrophils in the BALF, horses with IAD seldom have greater than 2% to 15% neutrophils. The Havemeyer consensus has established that horses with IAD will have airway inflammation characterized by BAL cytology with any one of the following: mast cells greater than 2%, PMNs greater than 5%, or eosinophils greater than 1%.

HISTOPATHOLOGY. Histopathologic studies of IAD are sparse, but useful information can be teased from COPD studies that on inspection included horses with what would more appropriately be termed *IAD*. Bronchiolar biopsies of athletic young horses with lower airway inflammation have shown inflammatory mucosal cellular infiltrates and luminal exudates, bronchiolar hyperplasia, and goblet cell metaplasia.[2] It is interesting to note that 80% of supposedly normal horses had minimal evidence of peribronchiolitis; this raises the question of what constitutes normal. O'Callaghan, while directing his concern to exercise-induced pulmonary hemorrhage (EIPH), nevertheless found plentiful evidence of multifocal, small airway-centered disease on postmortem examination of young racehorses. These findings included thickened walls caused by increased quantities of mucosal and peribronchiolar connective tissue, mononuclear bronchiolar cuffs, and extension of nonciliated bronchiolar epithelial cells into alveolar ducts.[35] Lakritz,[36] looking at lung tissue of clinically normal, young Thoroughbred horses in training, found evidence of increased collagen, disruption of the epithelial basement membrane, and duplication of the epithelial basement membranes, suggesting previous airway inflammation and epithelial injury, which correlate with an increased interstitial pattern on radiographs. An ultrastructural study of young horses with "mild COPD" in one study found a decreased number of typical Clara cell granules and goblet cell metaplasia before the bronchioles began to show signs of inflammation typical of RAO.[37] Although the authors state that there was good correlation between histopathology and the results of a battery of pulmonary function tests, auscultation, bronchoscopy, blood gas analysis, and BAL in these horses, it is a lasting disappointment that the results of the ancillary testing remain unpublished. These data, in sum, suggest that the histopathologic lesion of IAD is not only local bronchiolar inflammation but also remodeling and thickening of the bronchioles themselves, which lends itself to at least low-grade airway obstruction.

LUNG FUNCTION TESTING. The esophageal balloon and pneumotach method for measuring lung function tends not to detect airway obstruction even in horses with RAO in remission.[38] However, use of the forced oscillatory technique[4] and forced expiratory maneuvers has shown the existence of low-grade obstruction of the small airways of some horses with IAD. The mechanical behavior of the respiratory system has been shown to differ with sampling frequencies in asthmatic humans,[39] and a pattern of decreasing respiratory system resistance (RSR) with increasing frequency has been termed *negative frequency dependence of resistance* and has been interpreted

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as evidence of underlying small airway obstruction despite baseline measurements within the expected range. Similarly, horses with IAD as a group have significantly higher values for RSR at the lower frequencies (1 to 3 Hz) and mild frequency dependence of resistance compared with controls,[40,41] although the baseline measurement of RSR may still frequently fall within the normal range. A study finding that lower oxygen uptake capacity and tidal volume correlated to a reduced diameter of the bronchiolar lumen owing to epithelial hyperplasia is strongly supportive of the existence of airway obstruction in IAD.[27] Likewise, lung resistance decreases with increasing minute ventilation in control horses but not in horses with IAD.[42] Consequently, without dynamic, frequency-dependent tests of lung function, forced maneuvers, or bronchoprovocation, it seems that researchers are simply failing to document a common feature of small airway obstruction in horse with IAD because testing devices are not sufficiently sensitive to these changes.

AIRWAY RESPONSIVENESS. Horses with clinical signs compatible with IAD also exhibit signs of airway hyperresponsiveness when they are exposed to nonspecific agents such as histamine aerosol.[12,40,43] The basis for airway hyperresponsiveness remains hotly debated among pulmonary physiologists. It is likely a multifactorial phenomenon that has been associated with airway wall thickening undetectable by conventional lung function testing,[44] airway inflammation, and autonomic nervous system dysfunction.[1] There is a paucity of information concerning the mediators of airway hyperresponsiveness in horses with IAD, although the presence of elevated levels of leukotriene C4 levels has been documented.[40,45] In our laboratory, horses with a clinical history and signs compatible with IAD have significantly greater airway reactivity than controls, although some control horses display airway hyperresponsiveness as well. This nonspecific airway hyperresponsiveness has been seen in humans and is associated with a greater risk of eventual development of asthma.[46,47] Although nonspecific airway hyperresponsiveness has been noted both in adult horses without signs of respiratory disease and in foals, the significance of this finding remains unclear.

RADIOGRAPHY. Although radiography can be useful in helping to exclude septic causes of lower respiratory tract disease, such as pneumonia, lung abscess, or pleuropneumonia, its sensitivity in IAD is too low for it to be useful for identification of this disease. Moreover, no correlation exists among thoracic radiographs, airway hyperresponsiveness, and BAL cytology.[48] However, the more frequent finding of a bronchial pattern on thoracic radiographs supports the existence of airway obstruction in these horses.

Etiology

No single cause of IAD has been identified, although there has been plentiful speculation about the role of environment, viral disease, bacterial infection, air pollution, and genetic predisposition. Although horses with IAD do not seem to experience bouts of overt airway obstruction on exposure to an allergenic environment, organic dust associated with stabling likely contributes to the initial inflammation. Sweeney noted that the racehorses in her study lived in conditions of poor ventilation, and she speculated that covert IAD may be instigated by the organic dusts, especially mold, in hay.[15] Others have noted that there is more mucopus in the tracheas of horses kept in poorly ventilated conditions, and in one study Thoroughbred racehorses in training, housed on straw, were found to be twice as likely to suffer from lower airway disease as those kept on shredded paper.[23] More recently, Holcombe and coworkers[49] showed that yearlings had a significantly higher number and percentage of neutrophils (polymorphonuclear neutrophils as high as 18%) in BALF when they were stabled versus when they were at pasture. In support of this finding, endotoxin concentrations are, as expected, higher in stables than at pasture.[50,51] Although none of these horses had any clinical signs of respiratory disease or evidence of exercise intolerance, they were not in work, and subtle signs of performance impairment could easily have gone undetected. Dust levels in the horse's breathing zone can be as high as 25 mg/m^3 (a level that would be considered unacceptable in any human workplace), which can explain the development of airway neutrophilia as a nonspecific response to high levels of particulates.[52] It is also likely that increased levels of endotoxin in hay and grain dust contribute to the development of airway neutrophilia,[53-55] which is supported by the finding that hay eating is a risk factor for increased tracheal mucus in pleasure horses.[30] In addition, the horse's position in the stable may affect development of IAD. In one study, there was a significant association between the presence of visible accumulation of mucus in the trachea and the stable, stall, and particulate concentration and numbers.[56] Moreover, even when unaffected horses are exposed to stable dust, the neutrophil chemoattractant, IL-8, increases in the BALF.[57]

Although previous viral disease is commonly invoked as a predisposing factor in the development of IAD, little evidence exists to implicate viral disease. As in humans with asthma, viral respiratory disease has been shown to cause airway hyperresponsiveness for a period of time after infection, perhaps because of denuding of the respiratory epithelium. However, no known virus was associated with poor performance and respiratory disease in 68% of cases in the United Kingdom,[23,47] although in one study various equine herpesviruses were found with greater frequency in the tracheal aspirate of poorly performing horses with signs compatible with IAD.[58]

The role of bacterial infection in IAD, particularly in young racehorses, is unclear. In several studies there was a strong relationship between inflammation of the lower respiratory tract and the presence of streptococcal species; horses with greater evidence of airway inflammation on tracheal aspiration and endoscopy had higher mean bacterial counts in tracheal aspirate,[23] and horses with bacteria found in the tracheal aspirate had a greater tendency to cough.[16] However, it is important to remember that association is not necessarily causation, and increased numbers of bacteria may reflect impaired airway clearance rather than a causative role for bacteria. The role of bacterial and viral infection in IAD remains unclear at this time.

Because horses sample the ambient air on a continual basis, it seems logical that air pollution might contribute to the development of IAD. In one study, clinically normal horses exposed to ozone had a significant increase in the glutathione redox ratio as well as total iron levels in the pulmonary epithelial lining fluid (both markers of exposure to oxidizing agents), and there was a strong correlation between airway inflammation score and the glutathione redox ratio in horses examined for poor performance but without overt airway disease.[18] In contrast, horses living in urban environments have been shown to have less airway reactivity, although greater levels of iron in the BALF, than do horses living in rural environments.[59]

There are multiple other possible contributors to the development of IAD. Cold air exposure is an important risk factor for the development of asthma in human athletes, and cold air exposure has been shown to be a risk factor for development of tracheal mucus accumulation in some horses.[30] In support of this observation, exposure of equine airways to cold air resulted in altered immunologic responses for at least 48 hours.[60] Exercise may also play a role in the development of IAD, in that neutrophils are increased in the BALF for at least 48 hours after exercise, and there is a corresponding increased late phase expression of IL-8 and TNF-α in the BALF.[61] Finally, in vitro studies showed that equine bronchial epithelial cells produce IL-8 in excess when they are exposed to blood,[62] raising the idea that EIPH may be a contributing factor in the development of IAD.

Although heaves has been shown to be at least partially allergen mediated, in which horses manifest a Th2-type cytokine response,[63] and although environmental challenge can produce a consistent exacerbation of disease,[54] there is no such convincing evidence of an allergic response in horses with IAD. However, the presence of elevated numbers of mast cells in the BALF of horses with poor performance,[64] the association of BAL mastocytosis with airway hyperresponsiveness,[65] and immunohistochemistry studies showing more IgA-containing cells and occasionally increased numbers of IgM- and IgG-containing cells are suggestive of a degree of allergic response and a heightened immune response. Anyone looking at recent studies of gene expression profiles in the BALF of horses with

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IAD should take note of whether the horses were diagnosed as having IAD on the basis of a generalized increase in inflammatory cells or if the study group was parsed more thoroughly into horses with increased mast cells or horses with increased neutrophils. One study of horses with a generalized increase in inflammatory cells revealed an upregulation of IL-1β, IL-23, and TNF-α but no evidence of a polarized cytokine response.[66] On the other hand, when horses are stratified into mast cell versus neutrophil groups, mRNA for IL-4 correlated with mast cells but not neutrophils, whereas for all groups, similarly to the previous study, TNF-α and IL-1β were increased.[67,68] It is most likely that multiple factors contribute to the development of IAD in individual horses; a critical level of risk factors or exposure is probably necessary for the disease to manifest itself.

Differential Diagnoses

The diagnosis of IAD often requires the exclusion of other diseases that may have a similar clinical picture. Whereas horses with RAO (heaves) or summer pasture–associated RAO (SPARAO) in remission may be very difficult to distinguish from horses with IAD, horses with RAO or SPARAO have a history of episodes of obvious breathing difficulty associated with exposure to either moldy hay or summer pasture. Upper airway disease, such as sinus infection or guttural pouch infection, may cause cough and nasal discharge, and both static and dynamic upper airway obstructions may cause poor performance and poor recovery from exercise. These may be largely ruled out by endoscopy. Horses with pneumonia, bronchopneumonia, or lung abscess commonly have abnormalities suggesting systemic disease, such as abnormal findings on complete blood cell count, recent history of fever, weight loss, or inappetence. In these cases tracheal wash can be very helpful in determining a septic cause of disease. Thoracic radiographs or ultrasound will also aid in the detection of these septic respiratory diseases. EIPH may be seen in conjunction with IAD, but the presence of epistaxis, blood on endoscopy of the trachea, or red cells or hemosiderophages on BAL confirm the diagnosis of EIPH. Overt viral respiratory disease is difficult to confuse with IAD, as it usually manifests with fever and malaise, but horses with viral respiratory disease may exhibit prolonged cough and airway hyperresponsiveness for weeks to months after resolution of the primary disease.

Therapy

There is remarkably little evidence-based support for any particular therapy in treating IAD. However, the mainstay of treatment has become a combination of environmental remediation, corticosteroid therapy, and bronchodilators.

ENVIRONMENTAL REMEDIATION. The barn environment is a hotbed of particulate matter, respirable endotoxin, molds, and volatile gases such as ammonia. The worst offenders appear to be hay and straw. A study looking at different management systems showed that when hay and straw bedding were replaced by pelleted feed and wood shavings, the respirable particulate levels were remarkably reduced.[51] Further improvements can be made by using cardboard bedding to reduce dust and mold levels.[69] Indoor arenas present another high dust challenge to the horse, with respirable particulate levels 20 times the level recognized to cause respiratory dysfunction in humans.[70] Other fairly commonsense strategies can be used. I make the following recommendations to owners in addition to the suggestion to change to low-dust feeds and beddings:

- Sprinkle aisles with water before sweeping.
- Avoid storing hay overhead. If unavoidable, lay a tarp under the hay to avoid dust raining down on the horses.
- Use a humectant or hygroscopic agent to reduce dust in the indoor and outdoor arenas.
- Remove horses from the barn while cleaning stalls or moving hay.
- Do not use blowers to clean aisles.
- Wet hay before feeding or use Dengie or other baked hay products.
- Remove cobwebs and other dust collectors routinely.

A recent study demonstrated that environmental control was by far the most important means of treating airway inflammation and dysfunction in horses with heaves (RAO), a more severe disease than IAD.[71] It is logical, therefore, to suppose that environmental management is equally important in the treatment of IAD.

CORTICOSTEROID THERAPY. Either parenteral or inhaled corticosteroids form the mainstay of drug therapy for IAD. Although the utility of corticosteroids for preventing or ameliorating airway remodeling in human asthma is debated,[72] corticosteroids have recently been demonstrated to prevent airway smooth muscle thickening in mice with experimental asthma.[73] The degree of efficacy in decreasing BAL neutrophilia is not completely known. Some studies show an obvious benefit of dexamethasone in improving clinical signs and lung function and reducing BAL neutrophilia,[74] whereas others show improvement primarily in lung function with little effect on BAL cytology.[71,75] Corticosteroid treatment certainly causes adrenocortical dysfunction, but this is less pronounced with inhaled therapy versus systemic.[74] Although concerns about precipitating laminitis with corticosteroid therapy are frequently expressed, the actual risk of laminitis with corticosteroid therapy is completely unknown. Prednisone has been used in the past, but studies have shown lack of effect in horses with RAO.[76] In our clinic we frequently treat with an initial course of parenteral corticosteroids, typically a 4-week decreasing course of prednisolone followed by inhaled corticosteroids. A recent study demonstrated that fluticasone propionate is detectable in blood and urine after delivery by inhalation.[77]

BRONCHODILATOR THERAPY. Bronchodilators, especially the inhaled form, appear to be efficacious in treating IAD in conjunction with corticosteroids. The most commonly used bronchodilators in IAD include aerosolized β-adrenergics, such as albuterol, and aerosolized parasympatholytics, such as ipratropium. β-Adrenergic drugs such as albuterol also increase mucociliary transport. The use of systemic β-adrenergics such as clenbuterol is not advised, as the extent of bronchoconstriction in IAD does not warrant risking the adverse effect of cardiovascular remodeling, which has been shown to occur in horses.[78] Moreover, a recent study demonstrated that when clenbuterol is given to horses with airway hyperresponsiveness, tachyphylaxis associated with increased airway reactivity develops by 21 days of treatment.[79]

MAST CELL INHIBITORS. Sodium cromoglycate can be efficacious in treating known mast cell–mediated IAD[9] but will not be of use for treating the majority of horses with neutrophil-mediated disease. The use of sodium cromoglycate requires considerable owner compliance, as the maximum response to this drug occurs at 1 to 2 weeks after beginning treatment.

AEROSOLIZED THERAPY. Aerosolized therapy using a combination of inhaled corticosteroids and bronchodilators is well established clinically in the treatment of IAD; however, there are no clinical trials establishing the efficacy of these drugs. When using inhaled drugs, we use a spacer and mask in order to improve delivery of the drug. Regardless of the type of mask and spacer device used, actual delivery of particles to the lower airways is poor in horses, as indeed it is even in humans, and the least efficacious means of delivering aerosolized drugs is by nebulization.[80-82] Unfortunately, strategies that we know improve lung deposition of aerosolized drugs in humans, such as slow deep breathing and breath holding, are not practical in horses. Devices currently on the market include the Aeromask and the Equine Haler. Individual horse and owner preference determines which device should be used. Inhaled corticosteroids commonly used in the treatment of IAD include beclomethasone and fluticasone.

Although there are no reported clinical trials using corticosteroids in horses with IAD, horses with RAO treated with 3750 μg of beclomethasone dipropionate twice daily using the Aeromask showed improvement in both clinical signs and lung function.[83] Smaller doses (500 to 1500 μg twice daily) administered with a device that is no longer on the market were shown to be efficacious in horses with

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heaves.[74] I commonly use small doses (500 to 1000 µg twice daily) using the Aeromask with good clinical effect in horses with IAD.

Fluticasone is a more potent corticosteroid than beclomethasone and has been shown to be efficacious when administered in conjunction with the Aeromask in treating horses with heaves, as well, using doses of 2000 µg twice daily. Unlike beclomethasone, in this study fluticasone did not cause adrenocortical dysfunction.[84] I use a decreasing-dose regimen, starting at 1500 to 2000 µg twice daily, working down to 1000 µg once daily or every other day. The lowest dose is reached over a 3- to 4-week period. Although we previously advised use of a short-acting bronchodilator, such as inhaled albuterol, 5 to 15 minutes before treatment with inhaled corticosteroid to increase deposition of the latter by fully opening the small airways, the accepted practice in human medicine currently is to avoid this practice. The logic behind this is that it is important to get the most useful and costly drug administered first before compliance decreases. It is important that the owner understand that even with the higher doses of inhaled corticosteroid, it may require 1 to 2 months for the best therapeutic effects to be achieved.

The most commonly used inhaled bronchodilator is albuterol, a β_2-specific adrenergic drug. The onset of effect with albuterol is quite rapid, with maximum bronchodilation being seen within 15 minutes. However, it is important to note that the maximum effect lasts in some horses for only an hour, and there are side effects (such as anxiety, nervousness, trembling, and tachycardia) with higher doses of the drug, even in the inhaled form. There is no evidence to suggest that the oral form of albuterol is even absorbed in the horse, and it is not suggested as appropriate therapy. Longer-acting β_2-adrenergic agonists, such as salmeterol and formoterol, can also be used, with bronchodilation lasting 6 to 8 hours. Parasympatholytic drugs such as ipratropium have a slower onset of action but longer duration than albuterol (at least 6 hours) and lack the severe side effects of parenteral use of drugs such as atropine. It is important to remember that these bronchodilators are symptomatic drugs only; they do not treat the underlying inflammation and therefore are unsuitable for single-drug therapy.

Mast cell inhibitors that can be administered by metered dose inhaler include Intal (cromolyn) and Tilade (nedocromil sodium). They are discussed in earlier sections.

In summary, IAD is a disease characterized by nonseptic inflammation, visible on BAL cytology as excessive neutrophils, mast cells, or eosinophils, and involving low-grade airway obstruction and airway hyperresponsiveness. Clinical signs include variable cough, nasal discharge, and poor performance. Excessive amounts of mucus may also be visualized in the trachea during endoscopic examination. The cause of IAD is unknown, but the disease is probably best avoided by achieving a low-dust and low-endotoxin environment. Treatment logically begins with environmental remediation and is supplemented by antiinflammatory drug therapy using systemic or inhaled corticosteroids and inhaled bronchodilators. IAD that involves an excess of mast cells in the airways can be further treated with inhaled mast cell inhibitors.

Tuberculosis

Peggy S. Marsh

Tuberculosis refers to any infectious disease caused by *Mycobacterium* spp. and associated with the formation of focal granulomatous lesions. In humans many forms of the disease exist, with the primary site of infection most commonly being the lungs. *M. tuberculosis* is the typical causative agent in humans, whereas *Mycobacterium avium* or *Mycobacterium bovis* is usually implicated in animal cases. Tuberculosis is extremely rare in horses, especially in the United States. Most cases in horses have reported isolation of *M. avium*[1-4]; however, there are reports of infection with *M. bovis*[5,6] and *M. tuberculosis*.[7] In equine cases it appears the organism is usually ingested, although primary respiratory infection may occur. Spread is hematogenous, and the organism frequently settles in lymph nodes and the spleen.

The most frequent presenting complaint is chronic weight loss with ensuing weakness and lethargy. Terminally ill horses with the pulmonary form are febrile and dyspneic and have a cough. Radiographic or sonographic evaluation of the thorax may be helpful in defining the pattern and distribution of lesions. Other clinical signs may be noted depending on the organ systems affected; these signs include intestinal tract abnormalities, hepatitis, and osteomyelitis of the cervical vertebrae.[1-7]

Diagnosis, usually made after the horse's death, is based on the presence of tubercles and isolation of the organism. The intradermal skin test is not reliable in the horse because a majority of clinically normal horses may have positive test results.[7,8] Cytologic or histologic evaluation of a wash or aspirate of a lesion may reveal acid-fast bacilli. Biopsy of the lesion(s) is necessary for a definitive diagnosis. When tuberculosis is suspected, culture of an appropriate sample, such as a tracheal aspirate with primary pulmonary involvement, is advisable. However, this is a very slow-growing organism, and isolation may take multiple weeks. More recently polymerase chain reaction technology has proven a useful tool.[5,7]

Treatment is not usually attempted, because of public health concerns. If treatment is undertaken, the horse should be isolated, with precautions taken to prevent spread of disease and in consultation with the public health officials and/or the horse handler's physician. Tuberculosis is a reportable disease in other species. Drugs used in other species (rifampin, isoniazid, and streptomycin) could be considered, but there are no guidelines for their use in horses with this condition. Isoniazid has been used in horses for other conditions at a dose of 5 to 15 mg/kg PO twice daily.[9] A study on rifampin pharmacokinetics in horses recommended using 10 mg/kg PO twice daily.[10] In humans, treatment periods are very prolonged, frequently a year or more. Because treatment is usually not a viable option in horses, prognosis is very poor.

Bacillus Calmette-Guérin vaccine has been used in humans with potential exposure, but the benefit of its use in horses to provide increased resistance after exposure to a tuberculosis infection is unknown.

Pneumoconiosis (Silicosis)

Peggy S. Marsh

Pneumoconiosis refers to lower respiratory tract disease associated with deposition of small particles (dust) within the lungs. In human medicine the majority of cases are related to occupation and include coalworker's lung, silicosis, and asbestosis.[1] There are two related reports of horses with silicosis.[2,3] The majority of the horses originated from the Monterey-Carmel Peninsula in California. Silicosis is a disease caused by inhalation of crystalline silica. There are several clinical forms of silicosis in humans, including simple and complicated chronic forms as well as acute silicosis (silicoproteinosis). Silicosis has been associated with mycobacterial diseases, airway obstruction, and pulmonary neoplasia.[4] Freshly fractured silica is more toxic to alveolar macrophages than aged silica. Crushing silica leads to the formation of reactive radials.[5] The small (0.5 to 5 mm) particles are deposited in small airways and alveoli and subsequently phagocytosed, initiating a cycle of granulomatous inflammation, oxidative stress, and apoptosis leading to chronic fibrotic interstitial disease.[1,4,5]

The clinical signs reported in horses are similar to those of chronic obstructive pulmonary disease and include weight loss, cough, exercise intolerance, and, sometimes, exercise-induced respiratory distress (sweating, nostril flaring, abducted elbows, reluctance to move, and shaking). Resting respiratory rates are often increased. Physical examination revealed a restrictive pattern of breathing. Auscultation revealed harsh breath sounds and some wheezing, which was exacerbated by exercise.

Diagnosis was based on the presence of birefringent crystalline inclusions within pulmonary macrophages.[3] Samples were obtained via tracheal aspiration, BAL, or lung biopsy or at necropsy. In some

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cases repeated tracheal sampling was required. Radiographs of the thorax revealed a variety of findings, including, most commonly, an interstitial pattern (miliary, reticulonodular, and linear) that was most severe in the caudodorsal lung fields. Other radiographic abnormalities noted were lymphadenopathy, pleural effusion or thickening, hyperinflation, and pulmonary consolidation.[3]

Gross pathologic analysis revealed interstitial granulomatous pneumonia and fibrosis. Histologic examination with both light and electron microscopy revealed peribronchitis, perivasculitis, and cellular infiltrates consisting of mostly macrophages and giant cells, with refractile inorganic dust particles noted both intracellularly and extracellularly.[2,3]

In general the horses reported to have silicosis had a poor prognosis. The original study discussed postmortem findings of nine horses.[2] In a related paper, a total of 19 horses were identified.[3] Short-term (2 to 12 months) follow-up evaluation was available in eight of these individuals, with a progressive loss of respiratory function noted in four of the cases, leading to euthanasia. Treatment consisted of environmental change and glucocorticoid therapy. Novel forms of therapy, including inhibition of inflammatory mediators as well as inhibition of apoptosis, may be seen in the future.[5]

Recent work has revealed a systemic osteoporosis in a group of horses associated with fibrosing pulmonary silicosis.[6] Also, there are reports of pneumoconiosis in other domestic species that was caused by environmental contamination.[7] It may be prudent to keep environmental contamination in mind when investigating chronic non-infectious forms of lower respiratory tract disease in the horse.

Mycoplasma

Peggy S. Marsh

Mycoplasma spp. are a group of bacteria that differ from other bacteria because they lack a cell wall, are much smaller than most bacteria, and need cholesterol to survive. These organisms are proven to cause respiratory disease in humans, cattle, and pigs. *M. felis* has been isolated as a pathogen causing pleuritis and pericarditis in the horse.[1-3] Experimental infection with *M. felis* in ponies induced pleuritis.[3] The relative importance of *Mycoplasma* spp. as a pathogen in acute respiratory disease of the horse has been debated. Several species of mycoplasma can be isolated from the respiratory tract of healthy and diseased animals, both adults and foals. A report from Australia did not yield growth of mycoplasmas in any of the samples from young racing horses with coughs.[4] However, a similar case control–type study from the United Kingdom showed an association between *M. felis* and inflammatory airway disease in young racehorses.[5] Also, a Canadian report demonstrated growth of *Mycoplasma equirhinis* and *M. felis,* along with other bacteria commonly thought of as respiratory pathogens, in horses with acute lung disease.[6] *M. felis* has been reported as a potential cause of an outbreak of acute respiratory disease in a stable of young racehorses, as well as of respiratory disease in foals.[7,8]

Clinical signs of pleuritis caused by mycoplasma infection, including fever, depression, and pleurodynia, mimic other bacterial pleural pneumonia cases. Auscultation of the thorax may reveal pleural friction rubs and dull lung sounds over the cranioventral thorax. Sonographic examination of the thorax reveals pleural effusion, often bilateral. Thoracocentesis should be performed for both diagnostic and, if necessary, therapeutic purposes. The fluid is most often an exudate, lacking any odor. Cytologic examination reveals large numbers of neutrophils within the pleural fluid.

Crucial to diagnosis of mycoplasma infection is the elimination of more common pathogens, such as streptococcal infections. Thus routine cultures for aerobic and anaerobic bacteria should be performed in any case of pleuritis. Culture for the presence of *Mycoplasma* bacteria is difficult to obtain. Immediate centrifugation of pleural fluid is ideal, because supernatants are the preferred culture samples.[9] These samples should then be placed in mycoplasma-specific media. Seroconversion can also be an aid in diagnosis, with seroconversion occurring in a large number of the reported cases of *M. felis* infection.[1,2,7] Experimental infection revealed that once seroconversion has occurred, the organism can no longer be isolated from culture samples.[3] Seroprevalence in the United States is not known. Diagnosis may be aided by the use of newly devolved real-time polymerase chain reaction methods for the detection of *M. felis*.[11]

Experimentally infected ponies recovered without treatment in one study, so the requirements of treatment specific for mycoplasma are unclear.[3] Although sensitivity testing should be performed on any isolate, *Mycoplasma* spp. have been found to be sensitive to gentamicin, tetracyclines, and erythromycin.[10] The role these organisms play in equine respiratory disease is still unclear, and investigation continues.

Glanders (Farcy)

Faisal Ghazi Habasha

Glanders is serious zoonotic bacterial disease that primarily affects horses, mules, and donkeys. Some animals die acutely within a few weeks. Others become chronically infected and can spread the disease for years before succumbing. Without antibiotic treatment, the case fatality rate can be as high as 95%. Glanders also occurs in other mammalian species, particularly members of the cat family, dogs, sheep, goats, camels, and humans. Swine and cattle appear to be resistant.[1,2] The term *farcy* is limited to the visible appearance of external lesions, but in the latter case, internal lesions always exist, although they may not be evident.[3]

Glanders is one of the oldest diseases of horses described. Absyrtus, a Greek veterinarian in the army of Constantine the Great (AD 300), described the disease with considerable accuracy and recognized that it was contagious.[4]

Etiology Glanders is caused by *Burkholderia mallei,* a nonmotile, nonsporulating, facultative intracellular gram-negative bacillus in the family Burkholderiaceae. The organism name comes from the Greek *melis* ("severe disease") and its Latin derivative *malleus* ("depicting a malignant disease"). The organism was first identified in Germany by Loeffler and Schutz in 1882 and confirmed as the cause of glanders in 1886.[3] The organism was formerly known as *Pseudomonas mallei* before being reclassified into the new genus *Burkholderia* in 1992. Traditionally the *Burkholderia* species are known as plant pathogens and soil bacteria, with two important exceptions, *B. mallei* and *Burkholderia pseudomallei,* the latter of which causes melioidosis. These two organisms differ in their survival in the environment. *B. mallei* is subject to inactivation in the environment, and it is not thought to persist outside equine hosts for long periods of time. Limited environmental survival, particularly in wet, humid, or dark conditions, may be possible for 3 to 5 weeks, and the organism can remain viable in 20° to 25°C (68° to 77°F) water for as long as a month.[4] It is inactivated by heat, direct sunlight, and commonly used disinfectants, including hypochlorites.[1-3]

GENOME STRUCTURE. The genome of *B. mallei* consists of two circular chromosomes. Chromosome 1 contains 3,510,148 base pairs (bp) and chromosome 2 contains 2,325,379 bp. A total of 5,535 predicted protein-encoding open reading frames are identified in the genome.[5] The genome of this organism carries a large number of insertion sequences as compared with the related *B. pseudomallei,* with a large number of simple sequence repeats that may function in antigenic variations of cell surface proteins (National Center for Biotechnology Information [NCBI] genome project).

GEOGRAPHIC DISTRIBUTION. Glanders is thought to be endemic in parts of the Middle East, Asia, Africa, Central America, and South America. Between 1998 and 2012, cases were reported from Brazil, Turkey, Russia, Eritrea, Ethiopia, Iran, Iraq,[6] United Arab Emirates, India, Pakistan, Afghanistan, and Mongolia, with suspect cases in other parts of Africa.[1] The disease was eliminated from

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horses in the United States during the 1940s, although one human case of glanders was reported in a laboratory worker in 2000.[7] This was the first human case reported in the United States since 1945.

Transmission Glanders is mainly transmitted by contact with skin exudates and respiratory secretions from infected equids. Latently infected as well as clinically ill animals can spread the disease.[1,2]

Horses, mules, and donkeys often become infected when they ingest *B. mallei*–contaminated food or water. The organism can also be spread in aerosols and entry through skin abrasions and mucous membranes. Carnivores usually become infected when they eat contaminated meat. *B. mallei* is readily spread by fomites such as harnesses, grooming tools, and food and water troughs. Humans are infected by contact with sick animals, contaminated fomites, tissue, or bacterial cultures. Rare cases of person-to-person transmission have been reported in family members who nursed sick individuals. *B. mallei* has been weaponized and was used as a biological weapon against military horses and humans during the first and second world wars. Aerosols may be the major route of infection in bioterrorist attacks.[8]

INCUBATION PERIOD. The incubation period varies with the form of disease from a few days to several weeks. Septicemia or localized disease usually becomes apparent after 1 to 5 days, while the pulmonary form typically becomes clinically apparent after 10 to 14 days.[1,2]

Clinical Signs and Differential Diagnosis In equids, glanders is traditionally categorized into nasal, pulmonary, and cutaneous forms (farcy).[1,2] In the nasal form, deep ulcers and nodules occur inside the nasal passages, resulting in a thick, purulent, yellowish discharge. This discharge may be unilateral or bilateral and can become bloody. Nasal perforation is possible. The regional (submaxillary) lymph nodes become enlarged and indurated and may suppurate and drain. Healed ulcers become star-shaped scars. In the pulmonary form, nodules and abscesses develop in the lungs. Some infections are inapparent whereas others vary from mild dyspnea to severe respiratory disease. In more severe cases, the clinical signs include coughing, dyspnea, febrile episodes, and progressive debilitation. Diarrhea and polyuria may also be seen. Discharges from pulmonary abscesses can spread the infection to the upper respiratory tract.

In the cutaneous form, the skin contains nodules that rupture and ulcerate, discharging an oily, purulent yellow exudate (Fig. 31-43). The regional lymphatics and lymph nodes become chronically enlarged and are filled with purulent exudates. There may also be swelling of the joints and painful edema of the legs. Orchitis is a common symptom in males. Clinical cases are usually a combination of these forms and can occur as acute, chronic, or latent disease. Donkeys and mules, as a general rule, manifest the acute symptoms, which progress rapidly, whereas horses usually have the chronic or latent disease.



FIG. 31-43 Typical cutaneous form of glanders (known as farcy) showing skin nodules.

Nasal and pulmonary signs are usually seen in the acute form. The symptoms include a high fever, decreased appetite, coughing, progressive dyspnea, nasal discharge, and ulcers and nodules on the nasal mucosa. Bloody crusting may be seen on the nostrils, and there may be a purulent ocular discharge. The submaxillary lymph nodes are usually swollen and painful. Central nervous system signs have been reported in experimentally infected horses, possibly as the result of secondary bacterial infection from a compromised blood-brain barrier.[9] Animals with the acute form of glanders usually die in a few days to a few weeks.

The chronic form develops insidiously and results in progressive debilitation. The symptoms may include coughing, dyspnea, intermittent fever, enlargement of the lymph nodes, a chronic nasal discharge, and ulcers, nodules, and stellate scars on the nasal mucosa. The skin and lymphatics may also be involved. The chronic form is often fatal, but affected animals may live for years before succumbing to the disease.

In the latent form, there may be few symptoms other than a nasal discharge and occasional labored breathing. Lesions may be found only in the lungs.

The differential diagnoses for glanders include strangles caused by *Streptococcus equi;* epizootic lymphangitis, which is a chronic granulomatous and suppurative fungal infection caused by *Histoplasma farciminosum;* sporotrichosis, a chronic subcutaneous lymphatic mycosis caused by a gram-positive fungus *Sporotrichum schenckii;* ulcerative lymphangitis, a bacterial disease caused by *Corynebacterium pseudotuberculosis;* and melioidosis (Whitmore disease), which is caused by *B. pseudomallei.* Melioidosis is particularly difficult to differentiate because *B. pseudomallei* and *B. mallei* cross-react in many serologic and hypersensitivity tests.[1,2]

Diagnosis A diagnosis of glanders based on clinical signs can be made when *B. mallei* is isolated from samples or an immunologic reaction to the organism is detected serologically or on the basis of hypersensitivity test results. Isolation and identification of *B. mallei* in cultures of samples from lesions or various exudates, including respiratory secretions, is regarded as a gold standard for the diagnosis of glanders. *B. mallei* can be stained with methylene blue, Wright, or Gram stain, but the staining can be weak or irregular, and bipolar staining of the gram-negative organism may be observed. They can be pleomorphic in older cultures, but in clinical samples and young cultures they typically form straight or slightly curved rods that are 0.3 to 0.8 µm in width and 2 to 5 µm in length. Some authors report that, in tissues, the organism is identified best with Giemsa stain.[10]

B. mallei can be grown on routine culture media, including nutrient, blood, and MacConkey agars; growth is slow, but colonies are usually visible within 48 hours. Optimal growth occurs at 37°C (98.6°F).

Automated bacterial identification systems do not always correctly identify this organism. All isolations must be performed in biosafety level 3 laboratories. Inoculation into laboratory animals, particularly guinea pigs (the Strauss reaction) or hamsters, was used for identification of *B. mallei* in the past, but this technique is now rarely practiced.

A cell-mediated hypersensitivity reaction test (mallein intradermal skin test) was used extensively to screen horses for glanders. This test is still used to certify horses as negative for glanders during importation to some countries. It may also be used in the diagnosis of clinical cases. The mallein test is based on hypersensitivity reaction to mallein, a commercially available, purified protein derivative of *B. mallei.* The test is performed most often by intradermal palpebral injection. Reactors are identified by marked eyelid swelling that develops within 24 to 48 hours, accompanied by fever and occasionally by purulent ocular discharge. No reaction or minimal swelling

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of the eyelid develops in unsensitized animals. False-positive reactions can occur in animals that are sensitized to other closely related *Burkholderia* spp. including *B. pseudomallei,* and cross-reactions with *Streptococcus equi* have been described.

Serologic tests are sometimes used to screen horses for importation to glanders-free countries or to identify clinically affected animals. Measurable titers of serum antibody against *B. mallei* develop approximately 1 week after infection. Complement fixation was the preferred serologic test in past eradication programs because of its ability to detect subclinically or chronically infected animals. This test was most useful when the prevalence of disease was high. Complement fixation is still used by some countries to assess imported equids for glanders. Enzyme-linked immunosorbent assay tests are also used to screen animals for international trade. Other serologic tests include indirect hemagglutination,[11] counterimmunoelectrophoresis, immunoblotting, and indirect fluorescent testing, but these tests are not approved by the World Organisation for Animal Health (OIE) for use in international trade.[1,2] Rapid DNA tests, such as polymerase chain reaction assays, are now also used.

Treatment

Treatment of glanders is often not advised because infected animals may remain subclinically infected and shed *B. mallei*.[1,2] The risk of zoonotic transmission also discourages treatment. Systemic treatment with antibiotics, including penicillin and streptomycin, is usually ineffective in controlling the disease. Some evidence has accumulated that enrofloxacin, erythromycin, ampicillin, sulfonamide, gentamicin, and tetracycline might be effective against *B. mallei.* This evidence has emerged from in vitro antibiotic sensitivity testing and from treatment studies in experimentally infected guinea pigs. Experimentally, in lab animals effective treatments also include doxycycline, ceftazidime, gentamicin, and trimethoprim sulfas.[1]

Prevention and Control

Cases of glanders in animals must be reported to the OIE.[1] The occurrence of this disease in any country can result in restrictions on international trade in horses and other affected animals. The mallein test and complement fixation test are approved assays recommended by the OIE for international trade purposes.[1]

If glanders is detected, control measures include strict quarantine of all infected and exposed animals, diagnostic testing of animals with clinical signs indicative of glanders, and assessment of apparently normal equids with the elimination of those that react positively in screening tests. Ill animals and those with positive results of mallein tests are euthanized. Horses exposed to *B. mallei* that yield negative results in mallein tests are isolated and retested 2 to 3 weeks later. Carcasses and contaminated bedding and feed should be burned or buried. Equipment or other items in contact with infected animals should be disinfected.

People who handle tissues from infected animals, bacterial cultures, or contaminated fomites should implement strict precautions to prevent infection. Protective clothing, including surgical masks, gloves, face shields, and gowns, should be worn. In clinical and research laboratories, *B. mallei* requires biosafety containment level 3 accommodation. Precautions are indicated for activities that are likely to produce aerosols, droplets, or concentrations of bacteria. Currently, there is no commercial vaccine against glanders for use in humans or any other animal species.

Exercise-Induced Pulmonary Hemorrhage

Pamela A. Wilkins[†]

EIPH is a pervasive disorder of horses that perform strenuous exercise and is best recognized in Thoroughbred and Standardbred racehorses. The disorder is associated with reduced performance of Thoroughbred racehorses, and probably in other breeds, and costs the Thoroughbred and Standardbred racing industries in the United States and Canada between $100 million and $225 million (U.S. dollars [USD]) annually.[1] The disease occurs commonly in horses; less commonly in camels and greyhound dogs; and rarely in human athletes.[2-4]

Etiology

Epistaxis and hemorrhage into airways can occur as a result of a number of diseases, including disorders of the upper airways and lungs. Hemorrhage into trachea or bronchi can be a result of EIPH, pulmonary abscess, fungal granuloma, trauma, pneumonia, pulmonary foreign body, or hemangiosarcoma or other pulmonary neoplasia. Epistaxis can be associated with all of these causes of hemorrhage into the lower airway and with diseases of the upper airway, including guttural pouch mycosis, ethmoidal hematoma, trauma, and neoplasia of the upper airways and associated structures. Thrombocytopenia can cause epistaxis.

The likely proximate cause of hemorrhage in horses with EIPH is rupture of alveolar capillary membranes, with subsequent extravasation of blood into interstitial and alveolar spaces.[5] The source of blood in such instances is the pulmonary circulation. Bleeding from bronchial circulation during exercise has been suggested based on histologic evidence of bronchial angiogenesis in horses that have experienced previous episodes of EIPH,[6] but contribution of the bronchial circulation to EIPH has not been demonstrated. Regardless of the contribution of bronchial circulation to blood in the airways, the likely initial lesion is in capillaries associated with the pulmonary circulation. Recently alteration within the pulmonary venous circulation has been postulated as a contributor to EIPH.[7] Hemorrhage into the interstitial space and alveoli, with subsequent rostral movement of blood in the airways, results in blood in the trachea and bronchi, which, in rare instances, results in epistaxis.

Clinical Signs and Differential Diagnosis

HISTORY AND PRESENTING COMPLAINT. Poor athletic performance and epistaxis (Fig. 31-44) are the most common presenting complaints for horses with EIPH. Although poor performance may be attributable to any of a large number of causes, epistaxis associated with exercise is almost always secondary to EIPH.

Epistaxis caused by EIPH occurs during or shortly after exercise and is usually first noticed at the end of a race or similar period of maximal exercise, particularly when the horse is returned to the paddock or winner's circle and is allowed to lower its head. It is usually bilateral and resolves within hours. Epistaxis can occur on more than one occasion in the same horse.

EXERCISE-INDUCED PULMONARY HEMORRHAGE AND PERFORMANCE. Failure of racehorses to perform to the expected standard (poor performance) is often, accurately or not, attributed to EIPH. Many horses with poor performance have cytologic evidence of EIPH on microscopic examination of tracheobronchial aspirates or BALF or have blood evident on endoscopic examination of the tracheobronchial tree performed 30 to 90 minutes after strenuous exercise or racing.[8,9] However, it is important to recognize that EIPH is very common in racehorses and should be considered the cause of poor performance only after other causes have been eliminated. Severe EIPH undoubtedly results in poor performance and, on rare occasions, death of Thoroughbred racehorses.[10-13] A relationship between finishing position and incidence of EIPH, diagnosed by bronchoscopic examination, was not detected for 191 Thoroughbred racehorses that finished in first, second, or third place.[11] Furthermore, there was no relationship between the proportion of horses with EIPH and placing (first, second, or third versus other) in another 98 horses.[12] Similarly, there was no relationship between finishing position and proportion of horses with EIPH in 191 Thoroughbreds examined after racing.[13] There was no relationship between severity of EIPH, assessed on tracheobronchoscopic examination, and race performance in 258 Thoroughbreds or 296 Standardbred racehorses.[14] Together, these studies do not demonstrate a clear

[†]Previous contributions by K.W. Hinchcliff are acknowledged.

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FIG. 31-44 Horse with exercised-induced pulmonary hemorrhage and epistaxis.

relationship between the presence of EIPH, or its severity, and race performance.

In contrast to the studies just discussed, among 452 Thoroughbred horses examined after racing in Hong Kong, those finishing in the first three positions had less severe EIPH than did horses finishing in lower positions.[15] Of horses finishing in the first three places, 43.9% had evidence of EIPH on tracheobronchoscopic examination after racing, whereas 55.9% of horses finishing in fourth to fourteenth place had evidence of EIPH.

A recent study demonstrated that Thoroughbred horses with EIPH racing in Victoria, Australia, had impaired performance compared with unaffected horses. Horses were assessed as having no EIPH or grades 1 to 4 EIPH on the basis of endoscopic examination performed within 2 hours of racing. After statistical correction of other factors that could influence performance, there was a clear association between EIPH higher than grade 1 (i.e., grades 2 to 4) and impaired performance.[16] Horses with EIPH lower than grade 1 were 4 times more likely to win, 1.8 times more likely to finish in the top three positions, and 3 times as likely to be in the 90th percentile for earning as horses with EIPH higher than grade 2. Horses with EIPH finished farther behind the winner than did horses that did not have EIPH.[16]

Results of studies in Standardbred racehorses indicate either a lack of effect of EIPH on performance or an association between EIPH and superior performance. There was no relationship between the presence of EIPH and finishing position in 29 Standardbred racehorses with intermittent EIPH examined on at least two occasions[17] or in 92 Standardbred racehorses examined on one occasion.[18] However, of 965 Standardbred racehorses examined after racing, those finishing first or second were 1.4 times more likely (95%, confidence interval 0.9 to 2.2) to have evidence of EIPH on tracheobronchoscopic examination than were horses that finished in the seventh or eighth position.[19]

Physical Examination

Apart from epistaxis in a small proportion of affected horses, there are few abnormalities detectable on routine physical examination of horses with EIPH. Rectal temperature and heart and breathing rates may be increased as a consequence of exercise in horses examined soon after exercise, but values of these variables in horses with EIPH at rest are not noticeably different from those in horses with no evidence of EIPH. Affected horses may swallow more frequently during recovery from exercise than do unaffected horses, probably as a result of blood in the larynx and pharynx. Coughing is common in horses recovering from strenuous exercise, and after recovery from exercise horses with EIPH are no more likely to cough than are unaffected horses.[20] Other clinical signs related to respiratory abnormalities are uncommon in horses with EIPH. Respiratory distress is rare in horses with EIPH and, when present, indicates severe hemorrhage or other serious lung disease such as pneumonia, pneumothorax, or rupture of a pulmonary abscess. Lung sounds are abnormal in a small number of EIPH-affected horses and, when present, are characterized by increased intensity of normal breath sounds during rebreathing examination.[21] Tracheal rales may be present in horses with EIPH but are also heard in unaffected horses.[22] Cardiac dysrhythmias, such as atrial fibrillation, should be ruled out as contributors to EIPH, particularly in nonracing breeds.

Horses that have experienced one episode of epistaxis, the most severe form of EIPH, are more likely to have a second episode. For this reason most racing jurisdictions do not permit horses with epistaxis to race for a period of weeks to months after the initial instance, with more prolonged enforced rest after a subsequent episode of epistaxis and retirement from racing after a third bout. The recurrence rate after one episode of epistaxis in Thoroughbred horses is approximately 13.5% despite affected horses not being permitted to race for 1 month after the initial episode of epistaxis.[23] This high rate of recurrence suggests that the inciting pulmonary lesions have not healed.

Diagnostic Approach

DIAGNOSTIC TESTS. Various techniques are available for determining the presence and severity of EIPH, including direct examination of the airways through a flexible endoscope or examination of bronchial lavage fluid or tracheal aspirates for evidence of hemorrhage. The utility of these diagnostic tests varies, and choice of examination technique depends on the time between the racing of the horse and the examination and on the desired sensitivity of the test. For instance, tracheobronchoscopic examination is most appropriate if a horse is examined within 1 to 2 hours of exercise, whereas examination of airway washings is most appropriate if the examination is days to a week after strenuous exercise. Radiography, pulmonary scintigraphic examination, and lung function tests are useful in eliminating other respiratory diseases as causes of poor performance but are minimally useful in confirming a diagnosis of EIPH or in determining the severity of hemorrhage.

TRACHEOBRONCHOSCOPY. Observation of blood in the trachea or large bronchi of horses 30 to 120 minutes after racing or strenuous exercise provides a definitive diagnosis of EIPH. The amount of blood in the large airways varies from a few small specks on the airway walls to a stream of blood occupying the ventral third of the trachea (Fig. 31-45). Blood may also be present in the larynx and nasopharynx. If there is a strong suspicion of EIPH and blood is not present on a single examination conducted soon after exercise, the examination should be repeated in 60 to 90 minutes. Some horses with EIPH do not have blood in the rostral airways immediately after exercise but do so when examined 1 to 2 hours later. Blood is detectable by tracheobronchoscopic examination for 1 to 3 days in most horses, and some horses have blood detectable for up to 7 days.

Bronchoscopic examination can be used to estimate the severity of EIPH through use of a grading system.[11,24] The interobserver repeatability of tracheobronchoscopic assessment of severity of EIPH using a 0 to 4 grading scale has been demonstrated[24] (see Fig. 31-38).

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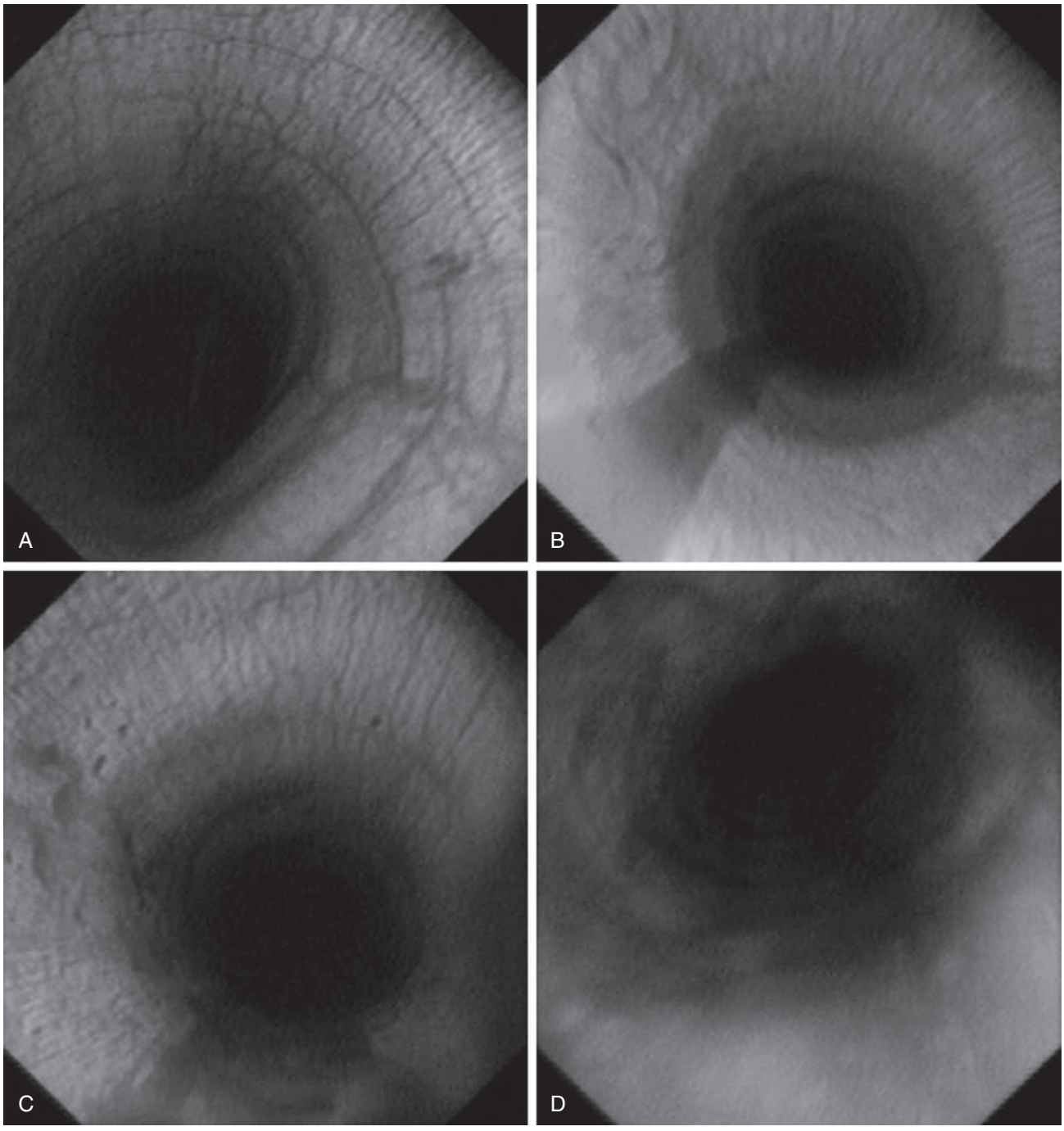


FIG. 31-45 Tracheobronchoscopic findings in horses with exercise-induced pulmonary hemorrhage. **A,** From a horse with grade 1 hemorrhage. **B,** From a horse with grade 2 hemorrhage. **C,** From a horse with grade 3 hemorrhage. **D,** From a horse with grade 4 hemorrhage.

- Grade 0: No blood detected in the pharynx, larynx, trachea, or main stem bronchi.
- Grade 1: Presence of one or more flecks of blood or <2 short (<1/4 length of the trachea) narrow (<10% of the tracheal surface area) streams of blood in the trachea or main stem bronchi visible from the tracheal bifurcation.
- Grade 2: One long stream of blood (>half the length of the trachea) or >2 short streams occupying less than 1/3 of the tracheal circumference.
- Grade 3: Multiple distinct streams of blood covering more than 1/3 of the tracheal circumference. No blood pooling at the thoracic inlet.
- Grade 4: Multiple coalescing streams of blood covering >90% of the tracheal surface with pooling of blood at the thoracic inlet.

It is assumed that a higher score represents more severe hemorrhage, but although the repeatability of this scoring system has been established, the relationship between the amount of blood in the large airways and the actual amount of hemorrhage has not been established.

TRACHEAL ASPIRATION AND BRONCHOALVEOLAR LAVAGE. The presence of red cells or macrophages containing either effete red cells or the breakdown products of hemoglobin (hemosiderophages) in tracheal fluid or BALF provides evidence of EIPH. Detection of red cells or hemosiderophages in tracheal aspirates or BALF is believed to be both sensitive and specific in the diagnosis of EIPH.[9,25] Examination of airway fluids indicates the presence of EIPH in a greater proportion of horses than does tracheobronchoscopic

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examination after strenuous exercise or racing. The greater sensitivity of examination of airway fluid is likely attributable to the ability of this examination to detect the presence of small amounts of blood or its residual products and the longevity of these products in the airways. Whereas endoscopic examination may detect blood in occasional horses up to 7 days after an episode of EIPH, cellular evidence of pulmonary hemorrhage persists for weeks after a single episode.[9,25,26] Red blood cells (RBCs) and macrophages containing RBCs are present in BALF or tracheal aspirates for at least 1 week after strenuous exercise or instillation of autologous blood into airways, and hemosiderophages are present for at least 21 days and possibly longer.[9,26]

Studies have reported on the use of RBC numbers in BALF as a quantitative measure of EIPH.[27-30] However, this indicator of EIPH severity has not been validated or demonstrated to be more reliable or repeatable than tracheobronchoscopic examination and visual scoring. Furthermore, considerable concern exists over the suitability of RBC counts in BALF for assessment of severity of EIPH given that an unknown area, although presumably small, of the lung is examined by lavage and there is a risk that this area of lung may not be representative of the lung as a whole, similar to the situation of examination of BALF of horses with pneumonia.[31] BAL of sections of both lungs, achieved using an endoscope, may obviate some of these concerns.

Tracheal aspirates may be obtained any time after exercise by either aspiration during tracheobronchoscopic examination or aspiration through a percutaneous intratracheal needle. Aspirates obtained through an endoscope may not be sterile, depending on the collection technique. BALF can be obtained through either an endoscope wedged in the distal airway or a cuffed tube inserted blindly into a distal airway. Collection of fluid through an endoscope has the advantage of permitting examination of the distal airways and selection of the area of lung to be lavaged. However, it does require the use of an endoscope that is longer (2 m) than those readily available in most equine practices. A commercial BAL catheter does not require use of an endoscope and can be performed readily in field situations, the disadvantage being lack of knowledge of the final location of the portion of lung that is lavaged.

RADIOGRAPHY. Thoracic radiography is of limited use in detecting EIPH in horses. Radiographs may demonstrate the presence of densities in the caudodorsal lung fields of some horses, but many affected horses have minimal to undetectable radiographic abnormalities.[32] Examination of thoracic radiographs of horses with EIPH may be useful in ruling out the presence of another disease process, such as a pulmonary abscess, that is contributing to the horse's pulmonary hemorrhage or poor athletic performance.

Pathophysiology

Rupture of alveolar capillaries occurs secondary to an exercise-induced increase in transmural pressure (pressure difference between the inside of the capillary and the alveolar lumen). If the transmural stress exceeds the tensile strength of the capillary wall, the capillary ruptures.[33] The proximate cause of alveolar capillary rupture is the high transmural pressure generated by positive intracapillary pressures that are largely attributable to capillary blood pressure and the lower intraalveolar pressure generated by the negative pleural pressures associated with inspiration.

During exercise the absolute magnitudes of both pulmonary capillary pressure and alveolar pressure increase, with a consequent increase in transmural pressure. Strenuous exercise is associated with marked increases in pulmonary artery pressure in horses.[28,34,35] Values for mean pulmonary arterial pressure at rest of 20 to 25 mm Hg increase to greater than 90 mm Hg during intense exercise because of the large cardiac output achieved by exercising horses. The increases in pulmonary artery pressure, combined with an increase in left atrial pressure during exercise, likely result in an increase in pulmonary capillary pressure. Combined with the increase in pulmonary capillary pressure is a marked decrease (more negative) in pleural, and therefore alveolar, pressures during exercise. Pleural pressures of normal horses during inspiration decrease from approximately −0.7 kPa (−5.3 mm Hg) at rest to as low as −8.5 kPa (−64 mm Hg) during strenuous exercise.[36] Together, the increases in pulmonary capillary pressure and decrease (more negative) in intrapleural (alveolar) pressure contribute to a marked increase in stress in the alveolar wall. Although the alveolar wall and pulmonary capillary of horses are stronger than those of other species, rupture may occur because the wall stress in the alveolus exceeds the mechanical strength of the capillary.[37]

Other theories of the pathogenesis of EIPH include small airway disease, upper airway obstruction, hemostatic abnormalities, changes in blood viscosity and erythrocyte shape, intrathoracic sheer forces associated with gait, and bronchial artery angiogenesis.[6,38] It is likely that the pathogenesis of EIPH involves several processes, including pulmonary hypertension, lower alveolar pressure, and changes in lung structure, that summate to induce stress failure of pulmonary capillaries.

Obstruction of either the upper or lower airways has been proposed as a cause of EIPH.[39] Inspiratory airway obstruction results in more negative intrapleural, and therefore alveolar, pressures. This effect is exacerbated by exercise, with the result that alveolar transmural pressure is greater in horses with airway obstruction.[40,41] The higher transmural pressure in such horses may increase the severity of EIPH, although this has not been demonstrated. Moreover, although inspiratory airway obstruction may predispose to EIPH, the prevalence of this condition is much less than that of EIPH, indicating that it is not the sole factor inducing EIPH in most horses.

Horses with moderate to severe EIPH have histologic evidence of inflammation of the small airways,[42,43] and there is a clear association between presence of EIPH and inflammatory changes in bronchoalveolar or tracheal aspirate fluid.[44] However, instillation of autologous blood into the airways induces a marked inflammatory response in normal horses,[45] and it is therefore unclear if inflammation alone induces or predisposes to EIPH or if the inflammation is a result of EIPH. Theoretically, small airway inflammation and bronchoconstriction have the potential to produce intrathoracic airway obstruction and therefore a more negative alveolar pressure. Given that small airway disease is common in horses, there is the potential for an important effect of factors, such as viral infections, air pollution, and allergic airway disease, to contribute to the initiation or propagation of EIPH.[46]

Exercise is accompanied by marked changes in blood flow characteristics attributable to an increase in hematocrit and decrease in RBC deformability.[47,48] These changes cause an increase in microvascular shear stress and thus could conceivably contribute to capillary rupture. However, there is at present no direct evidence that indicates that this is an important feature of development of EIPH.

The characteristic location of lesions of EIPH in the caudodorsal lung fields has led to the proposal that hemorrhage is a result of tissue damage occurring when waves of stress, generated by forelimb foot strike, are focused and amplified by the narrowing cross-sectional area of the caudal lung lobes.[38] According to the theory, the locomotory impact of the forelimbs results in transmission of forces through the scapula to the body wall; from there they pass into the lungs and caudally and dorsally. As the wave of pressure passes into the narrower caudodorsal regions of the lungs, it generates progressively greater shearing forces that disrupt tissue and cause EIPH. However, studies of intrapleural pressures have not demonstrated the presence of a systemic pressure wave passing through the lung and do not provide support for this hypothesis.[49] The observation that horses competing in hurdles or steeplechase events on hard ground have increased incidence of epistaxis lends support to the suggestion that locomotory impact, thought of as an "abdominal piston," might influence the development of EIPH.[50]

Horses with EIPH have been suspected of having defects in either hemostasis or fibrinolysis. However, although exercise induces substantial changes in blood coagulation and fibrinolysis,[51] there is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis.[52,53]

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Regardless of the cause, rupture of pulmonary capillaries and subsequent hemorrhage into airways and interstitium causes inflammation of both airways and interstitium, with subsequent development of fibrosis and alteration of tissue compliance. Heterogeneity of compliance within the lungs, and particularly at the junction of normal and diseased tissue, results in development of abnormal shear stress with subsequent tissue damage. These changes are exacerbated by inflammation and obstruction of small airways with resulting uneven inflation of the lungs.[54] The structural abnormalities, combined with pulmonary hypertension and the large intrathoracic forces associated with respiration during strenuous exercise, cause repetitive damage at the boundary of normal and diseased tissue with further hemorrhage and inflammation. The process, once started, is lifelong and continues for as long as the horse continues to perform strenuous exercise.[6]

Epidemiology EIPH occurs in horses throughout the world. It is a disorder of horses that run at high speed, such as Thoroughbred or Standardbred racehorses, Quarter Horses (racehorses and barrel racing horses), and polo ponies. The disorder is apparently uncommon in endurance horses and is very uncommon in draft breeds, such as Clydesdales, Percherons, or Belgians, after participation in weight-pulling competition.[55] As a general rule, the more intense the exercise is or the higher the speed attained, the greater the proportion will be of horses with EIPH.

The prevalence of EIPH varies with the method used to detect it and the frequency with which horses are examined, as discussed later in this section. Almost all Thoroughbred racehorses in active training have hemosiderophages in BALF, indicating that all have some degree of EIPH.[9] The prevalence of EIPH decreases when diagnosis is based on endoscopic examination of horses after exercise or racing.

Risk Factors

BREED. EIPH is very common in Thoroughbred racehorses, with estimates of prevalence, based on a single endoscopic examination of the trachea and bronchi, of 43% to 75%.[13,15,56] The prevalence increases with the frequency of examination, with over 80% of horses having evidence of EIPH on at least one occasion after examination after each of three consecutive races.[57] The prevalence of EIPH in Standardbred racehorses is assumed to be lower, with 26% to 34% of horses reported to have blood in the trachea after racing.[18,58] However, these studies were based on a single examination, and one study[58] reported as positive only those horses with blood covering more than one half of the tracheobronchial tree. When examined after each of three races, 87% of Standardbred racehorses showed evidence of EIPH on at least one occasion,[17] suggesting that EIPH is as common in Standardbred racehorses as it is in Thoroughbred racehorses.

EIPH occurs in approximately 62% of racing Quarter Horses and has been observed in Quarter Horses used for barrel racing.[59] The disorder occurs in racing Appaloosa horses.[60] Approximately 11% of polo ponies are affected with EIPH[61] and the disorder occurs in Chilean Criollo horses.[62]

AGE. Age is considered an important risk factor for EIPH, with the prevalence of the disorder being higher in older horses.[11,12,63,64] There is no consistent effect of sex on prevalence of EIPH.[13,15,18,56]

Among Thoroughbred racehorses the prevalence of EIPH increases with increasing speed,[13,42] being greater in Thoroughbreds after racing than after breezing (galloping). Lesions of EIPH are not detected in young Thoroughbred racehorses that have trained at speeds less than 7 m/sec.[13,42]

Epistaxis associated with exercise is almost always attributable to pulmonary hemorrhage but occurs only in a small proportion of racehorses.[23,65,66] The prevalence of epistaxis in racehorses varies between 0.1% and 9%, with the frequency depending on the breed, age, and sex of horses selected for study, the type of racing, and the timing and frequency of observation of horses after racing. Epistaxis is more common in older horses.[23,65] There are conflicting reports of a sex predisposition, although epistaxis may be more common in female Thoroughbreds.[23,65] Epistaxis is more common after races of less than 1600 m than in longer races,[23] although not all sources agree on this point.[65] However, horses in steeplechase races, which are typically longer than 2000 m, are at greater risk of epistaxis than are horses in flat races.[23,50] In addition, horses racing in hurdle or steeplechase races over hard ground in Britain are more likely to have epistaxis.[50]

The effect of genetics on the incidence of EIPH has been examined only minimally, with one study of horses with epistaxis, which is characteristically associated with severe EIPH, suggesting a hereditary predisposition among Thoroughbred racehorses in South Africa.[67] The heritability of the predisposition to epistaxis was considered low.[67]

Necropsy EIPH is a cause of sudden death of horses during racing and training[68-70] and in most studies is secondary to musculoskeletal injury as the cause of death. Necropsy examination reveals that approximately 60% of horses that die during racing or training or are euthanized because of acute injury during racing or training have evidence of EIPH.[70] Necropsy examination of affected horses is usually but not always incidental to examination for another cause of death.

Pertinent abnormalities detected on necropsy of horses with EIPH are restricted to the respiratory tract. Grossly, horses examined within hours of strenuous exercise, such as horses examined because of catastrophic musculoskeletal injuries incurred during racing, often have severe petechiation in the caudodorsal lung fields. Horses that die of EIPH also have pulmonary congestion and edema.[70] Horses with chronic disease have blue-gray or blue-brown discoloration of the visceral pleural surfaces of the caudodorsal lung fields that is often sharply demarcated, especially on the diaphragmatic surface.[70,71] The discoloration affects both lungs equally, with 30% to 50% of the lung fields being discolored in severe cases. Affected areas do not collapse to the same extent as unaffected areas and, in the deflated lung, have a spleenlike consistency. On the cut surface the discolored areas of lung are predominantly contiguous with the dorsal pleural surface and extend ventrally into the lung parenchyma. Areas of affected lung may be separated by normal lung. There is proliferation of bronchial vessels, predominantly arteries and arterioles, in affected areas.[72] In cases where upper airway obstruction might have played a role in the acute death, petechiae and ecchymotic hemorrhages are commonly present throughout the trachea and laryngeal region (Wilkins and Del Piero, unpublished data). Histologically, affected areas exhibit bronchiolitis, hemosiderophages in the alveolar lumen and interstitial spaces, and fibrosis of interlobular septa and pleura and around vessels and bronchioles.[43]

Therapy, Prevention, and Control Therapy for EIPH is usually a combination of attempts to reduce the severity of subsequent hemorrhage and efforts to minimize the effect of recent hemorrhage. Treatment of EIPH is problematic for a number of reasons. First, the pathogenesis of EIPH has not been determined, although the available evidence supports a role for stress failure of pulmonary capillaries secondary to exercise-induced pulmonary hypertension (see later). Second, there is a lack of information using large numbers of horses under field conditions that demonstrates an effect of any medication or management practice (with the exception of bedding) on EIPH. There are numerous studies of small numbers of horses (fewer than approximately 40) under experimental conditions, but these studies often lack the statistical power to detect treatment effects, and, furthermore, the relevance of studies conducted on a treadmill to horses racing competitively is questionable. Treatments for EIPH are usually intended to address a specific aspect of the pathogenesis of the disease and will be discussed in that context.

PREVENTION OF STRESS FAILURE OF THE PULMONARY CAPILLARIES. There is interest in reducing the pressure difference across the pulmonary capillary membrane in an effort to reduce

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EIPH. Theoretically, this can be achieved by reducing the pressure within the capillary or increasing (making less negative) the pressure within the intrathoracic airways and alveolus.

Furosemide apparently reduces pulmonary capillary pressure in exercising horses. Furosemide administration as prophylaxis against EIPH is permitted in a number of racing jurisdictions worldwide, most notably Canada, the United States, Mexico, and most of the South American countries.[73] Within the United States and Canada, almost all Thoroughbred, Standardbred, and Quarter Horse racing jurisdictions permit administration of furosemide before racing. The vast majority (>90%) of Thoroughbred horses racing in the United States receive furosemide before racing, at an estimated annual cost of between $6 million and $20 million (USD).[1] Although accurate numbers are not available, it appears that a smaller proportion of Standardbred and Quarter Horse racehorses receive furosemide before racing. Furosemide is administered to 22% to 32% of Standardbred racehorses and 19% of racing Quarter Horses in two racing jurisdictions.[74-76]

The efficacy of furosemide in treatment of EIPH is uncertain. Although field studies of large numbers of horses do not demonstrate an effect of furosemide on the prevalence of EIPH,[57] studies of Thoroughbred horses running on a treadmill provide evidence that furosemide reduces the severity of EIPH.[29,30,77] Under field conditions, based on tracheobronchoscopic evaluation of the severity of bleeding, furosemide has been reported to reduce, or have no influence on, the severity of bleeding.[78] This apparent inconsistency may be attributable to measurement of RBC counts in BALF of horses that have run on a treadmill not being representative of effects of furosemide under field conditions. The weight of evidence, albeit unconvincing, from field studies does not support a role for furosemide in preventing, or reducing the severity of, EIPH.

The mechanism by which furosemide may reduce the severity of EIPH is unknown, although it is speculated that furosemide, by attenuating the exercise-induced increase in pulmonary artery and pulmonary capillary pressure of horses, reduces the frequency or severity of pulmonary capillary rupture.[35,79,80]

Furosemide is associated with superior performance in both Thoroughbred and Standardbred racehorses.[74,81] Thoroughbred horses treated with furosemide are 1.4 times as likely to win the race, earn more money, and have a standardized 6-furlong race time 0.56 to 1.09 seconds less than that of untreated horses.[81] Similarly, furosemide reduces 1-mile race times of Standardbred pacers by 0.31 to 0.74 seconds.[74]

Enalapril inhibits angiotensin-converting enzyme activity in horses but does not affect pulmonary artery pressure of exercising horses.[82] Similarly, the efficacy of enalapril in preventing EIPH has not been demonstrated.

Nitric oxide is a potent vasodilator in many vascular beds. Administration of nitroglycerin (a nitric oxide donor) reduces pulmonary artery pressure of standing horses but does not affect pulmonary artery pressure of horses during intense exercise.[83] L-Arginine is a nitric oxide donor with no demonstrated efficacy in reducing pulmonary capillary pressure or EIPH in horses. The effect of L-NAME, an inhibitor of nitric oxide synthetase, on pulmonary artery pressure during maximal exercise is controversial, with either no effect or a decrease in pulmonary artery pressure reported.[84,85] It is interesting to note that L-NAME administration has been reported to cause an increase in severity of EIPH.[84] Sildenafil, a phosphodiesterase (PDE) inhibitor that accentuates the effect of nitric oxide and is used in the treatment of erectile dysfunction in men, has been administered to horses in an apparent attempt to reduce EIPH. However, its efficacy in preventing EIPH or reducing pulmonary capillary pressure has not been demonstrated.

An increase in pulmonary capillary pressure secondary to altered rheostotic properties of blood during exercise has been suggested as a possible contributing factor for EIPH.[47] Furosemide increases blood viscosity, whereas pentoxifylline increases RBC deformability and may attenuate the increase in blood viscosity that occurs during exercise.[86-88] However, pentoxifylline does not affect the pulmonary capillary pressure of exercising horses and did not affect the prevalence of EIPH in a small experimental study.[89]

Airway obstruction, either intrathoracic or extrathoracic, increases airway resistance and results in a more negative intrathoracic (pleural) pressure during inspiration to maintain tidal volume and alveolar ventilation. Causes of extrathoracic airway obstruction include laryngeal hemiplegia and other abnormalities of the upper airway, whereas intrathoracic obstruction is usually a result of bronchoconstriction and IAD. Horses with partial extrathoracic inspiratory obstruction or bronchoconstriction and airway inflammation associated with recurrent airway obstructive disease (heaves) have pleural (and hence alveolar) pressures that are lower (more negative) than those in unaffected horses or in horses after effective treatment.

Partial inspiratory obstruction, such as produced by laryngeal hemiplegia, exacerbates the exercise-induced decrease in intrapleural pressures, with a consequent increase in transmural capillary pressures.[40,41,90] These changes may exacerbate the severity of EIPH, although an association between upper airway obstructive disease and EIPH has yet to be clearly demonstrated. Surgical correction of airway obstruction is expected to resolve the more negative intrapleural pressure, but its effect on EIPH is unknown.

Recently the role of the nares in contributing to upper airway resistance, and therefore lowering inspiratory intrapleural pressure, during intense exercise has attracted the attention of some investigators. Application of nasal dilator bands (FLAIR strips; http://flairstrips.com/flair-strips/) reduces nasal resistance by dilating the nasal valve[91] and reduces RBC of BALF collected from horses after intense exercise on a treadmill.[29,30] Furthermore, application of the nasal dilator strips to horses in simulated races reduces red cell count in BALF of some, but not all, horses.[92]

The role of small airway inflammation and bronchoconstriction in the pathogenesis of EIPH is unclear. However, horses with EIPH are often treated with drugs intended to decrease lower airway inflammation and relieve bronchoconstriction. β-Adrenergic bronchodilatory drugs such as clenbuterol and albuterol are effective in inducing bronchodilation in horses with bronchoconstriction, but their efficacy in preventing EIPH is either unknown or, in very small studies, is not evident. Clenbuterol neither alters the hemodynamic responses of horses to exertion nor attenuates exercise-induced arterial hypoxemia in normal horses.[93,94] Ipratropium, a parasympatholytic drug administered by inhalation, showed promise in a very small study (two horses) of preventing EIPH.[95] Corticosteroids, including dexamethasone, fluticasone, and beclomethasone administered by inhalation, parenterally, or enterally reduce airway inflammation and obstruction but have no demonstrated efficacy in preventing EIPH. Cromolyn sodium (sodium cromoglycate) has no efficacy in preventing EIPH.[96]

Water vapor treatment (inhalation of water-saturated air) has been proposed as a treatment for EIPH because of its putative effect on small airway disease. However, water vapor treatment has no effect on EIPH.[97]

The use of bedding of low allergenic potential (shredded paper) to prevent EIPH has no apparent effect on prevalence of the condition.[98] Although it is suggested that preventing or minimizing small airway disease may reduce the severity of EIPH, studies to demonstrate such an effect have not been reported. However, optimizing the air quality in barns and stables and preventing infectious respiratory disease appear to be sensible precautions.

INTERSTITIAL INFLAMMATION AND BRONCHIAL ANGIOGENESIS. Hemorrhage into interstitial tissues induces inflammation, with subsequent development of fibrosis and bronchial artery angiogenesis.[45,72,99] The role of these changes in perpetuating EIPH in horses is unclear but likely is of some importance. Treatments to reduce inflammation and promote healing with minimal fibrosis have been proposed. Rest is an obvious recommendation, and many racing jurisdictions have rules regarding enforced rest for horses with epistaxis. Although the value of rest is intuitive, there is no

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information that rest reduces the severity or incidence of EIPH in horses with prior evidence of this disorder.

Similarly, corticosteroids are often administered by inhalation, enterally, or parenterally in an attempt to reduce pulmonary inflammation and minimize fibrosis. Again, the efficacy of this intervention in preventing or minimizing the severity of EIPH has not been documented.

EXCESSIVE BLEEDING. Exercise induces substantial changes in blood coagulation and fibrinolysis.[51] However, there is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis.[52,53,100] Regardless, aminocaproic acid, a potent inhibitor of fibrin degradation, has been administered to horses to prevent EIPH. Although appropriate doses of aminocaproic acid inhibit fibrinolysis in stationary horses,[100] the efficacy of aminocaproic acid in preventing EIPH has not been demonstrated. Tranexamic acid is similarly administered to horses in the hope of preventing or mitigating EIPH. Estrogens are given to horses with the expectation of improving hemostasis, although the effect of estrogens on coagulation in any species is unclear. There is no evidence that estrogens prevent EIPH in horses.

Vitamin K is administered to horses with EIPH, presumably with the expectation that it will decrease coagulation times. However, because EIPH is not associated with prolonged bleeding times, it is unlikely that this intervention will affect the prevalence or severity of EIPH.

Herbal preparations are marketed for treatment of EIPH. The only scientific study of these products examined the efficacy of Yunnan Paiyao or Single Immortal on RBC count in BALF of horses that had run on a treadmill. Neither product affected RBC count or coagulation variables.[101]

Aspirin inhibits platelet aggregation in horses and increases bleeding time.[102] Seemingly paradoxically, aspirin is sometimes administered to horses with EIPH because of concerns that increased platelet aggregation contributes to EIPH.[103] There is no evidence that aspirin exacerbates or prevents EIPH.

CAPILLARY INTEGRITY. Capillary fragility increases the risk of hemorrhage in many species. Various bioflavonoids have been suggested to increase capillary integrity and prevent bleeding. However, hesperidin and citrus bioflavonoids have no efficacy in prevention of EIPH in horses.[104] Similarly, vitamin C is administered to horses with EIPH without scientific evidence of any beneficial effect.

SUMMARY OF TREATMENT OPTIONS. Selection of therapy for horses with EIPH is problematic. Given that most horses have some degree of pulmonary hemorrhage during most bouts of intense exercise, the decision must be made not only as to which type of treatment to use and its timing but also which horses to treat. Moreover, the apparent progressive nature of the disease with continued work highlights the importance of early and effective prophylaxis and emphasizes the need for studies of factors such as air quality and respiratory infections in inciting the disorder.

The currently favored treatment for EIPH is administration of furosemide before intense exercise. Its use is permitted in racehorses in a number of countries. Increasingly persuasive laboratory evidence of an effect of furosemide to reduce RBC count in BALF collected from horses soon after intense exercise supports the contention that furosemide is effective in reducing the severity of EIPH in racehorses. However, it should be borne in mind that neither the relationship between severity of EIPH and RBC count in BALF in racehorses in the field has been demonstrated. Only recently has there been solid evidence that furosemide reduces the prevalence of EIPH under field conditions.[105] The association between furosemide administration and superior performance in Standardbred and Thoroughbred racehorses should be borne in mind when recommending use of this drug.

Rest is an obvious recommendation for horses with EIPH, but the hemorrhage is likely to recur when the horse is next strenuously exercised. The duration of rest and the optimal exercise program to return horses to racing after EIPH are unknown, although some jurisdictions require exercise no more intense than trotting for 2 months. Firm recommendations cannot be made on duration of rest because of a lack of objective information.

Although a role for lower airway disease (either infectious or allergic) in the genesis of EIPH has not been demonstrated, control of infectious diseases and minimization of noninfectious lower airway inflammation appear prudent. Horses with evidence of upper airway dysfunction, such as laryngeal hemiplegia, with concurrent evidence of EIPH may benefit from appropriate treatment.

Prognosis The prognosis for racing for horses with clinically significant EIPH is guarded because of the progressive nature of the disease. Horses that have experienced severe EIPH on one occasion are likely to do so again regardless of treatment. However, the risk of horses experiencing a repeated bout of severe hemorrhage and the effect of EIPH on career longevity and long-term health are currently unknown.

Equine Thoracic Neoplasia

Fabio Del Piero • Pamela A. Wilkins

Surveys of equine neoplasms indicate a low prevalence of thoracic neoplasia in the horse. In an abattoir survey in London of 1308 horses, only 2 horses had pulmonary tumors: one granular cell tumor and one bronchiolar adenoma.[1] Two other necropsy surveys of 155 and 687 equines reported no thoracic neoplasms.[2,3] A report on chronic pulmonary disease in the horse states that the practical importance of lung tumors in this species is negligible.[4] University of Pennsylvania researchers examined 5629 horses between 1968 and 1987. Thirty-five horses had neoplasia involving the thoracic cavity, corresponding to a prevalence of 0.62%.[5]

The prevalence of primary lung neoplasms of any type is reported to be less than 1% of all reported neoplasms in domestic animals.[6] The lungs are susceptible to tumor emboli because of the filter action of the capillary bed associated with small capillary diameter and, perhaps, specific adhesion factors. It can sometimes be difficult or even impossible to distinguish metastatic disease from primary pulmonary neoplasia; thus, an important part of the diagnosis is exclusion of possible primary sites elsewhere in the body. Primary pulmonary tumors reported in the horse include granular cell tumor, bronchial myxoma, adenoma, adenocarcinoma, anaplastic bronchogenic carcinoma, and pulmonary carcinoma (Fig. 31-46). Other primary thoracic tumors reported in the horse include pulmonary chondrosarcoma, pleural mesothelioma, thymoma, and lymphosarcoma. The majority of these neoplasms generally occurs in the mature or aged horse. The exception is lymphosarcoma, which may also be observed in young animals.

Antemortem diagnosis of thoracic neoplasia depends first on recognition of thoracic disease. Most of the reported cases of thoracic neoplasia involve metastatic disease. The horses' clinical signs are generally related to the primary site of the neoplasm; therefore the clinician often has no reason to suspect thoracic involvement. When respiratory signs such as dyspnea, tachypnea, hemoptysis, cough, cyanosis, nasal discharge, and epistaxis are present, relevant diagnostic tests are more likely to be performed. Ultrasonography and bronchoscopy increase the frequency of antemortem diagnosis of thoracic neoplasia.

Granular cell tumors are the most frequently reported primary pulmonary neoplasm of the horse. They are usually confined to the lungs and are characterized by single to multiple well-defined whitish dense nodules associated with a major bronchus, often protruding into the bronchial lumen or more distally within the parenchyma. Most granular cell tumors have been diagnosed only at postmortem examination, often as incidental findings. These homogeneous growths of granular eosinophilic cells express S-100 and occasionally neuron-specific enolase.[7] The ultrastructural morphology of this

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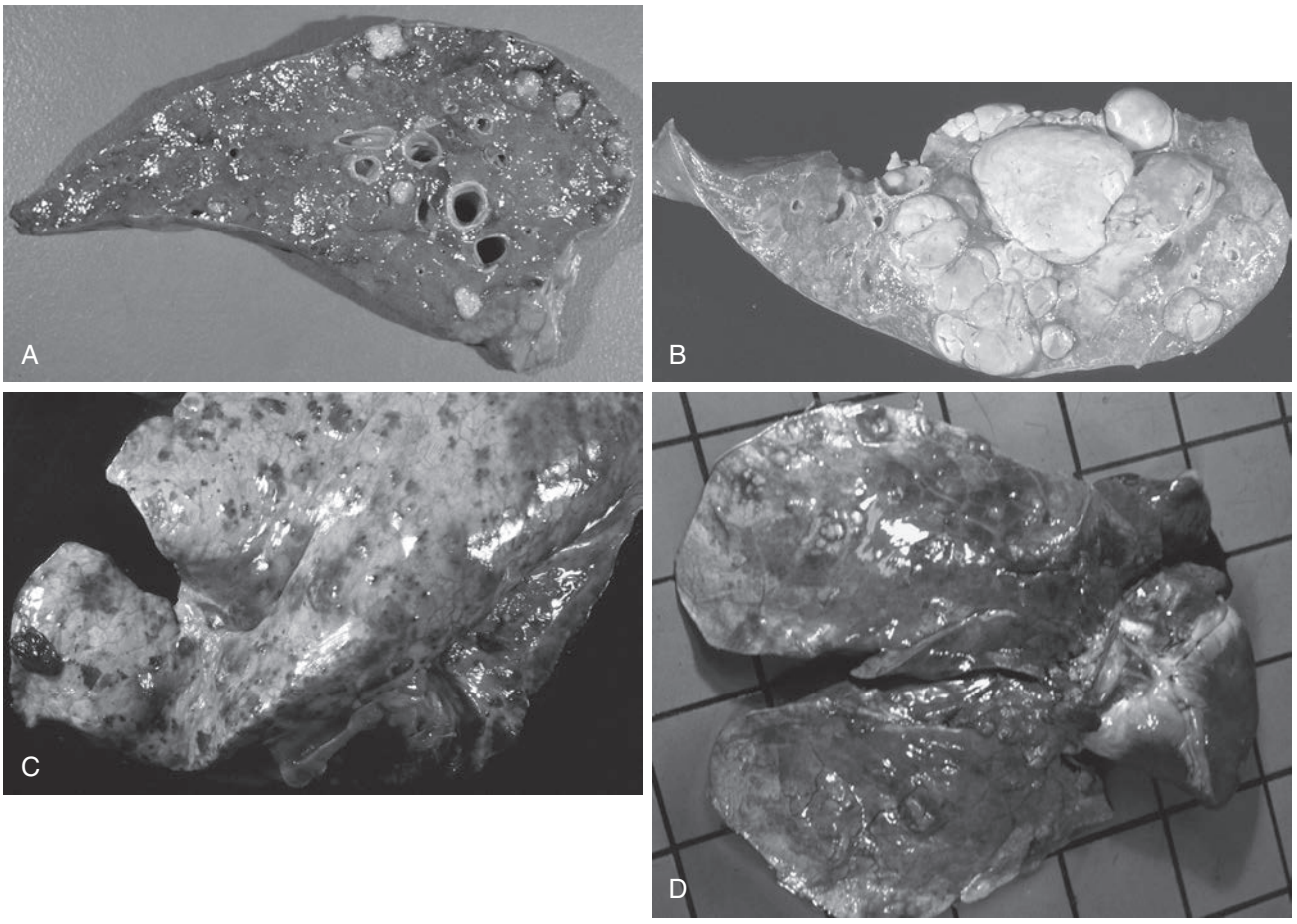


FIG. 31-46 **A,** Metastatic undifferentiated sarcoma. **B,** Granulosa cell tumor. **C,** Metastatic hemangiosarcoma. **D,** Metastatic squamous cell carcinoma.

tumor may suggest a neural origin as well. Primary pulmonary chondrosarcoma has been reported in the horse.[8] Cytologic examination of pleural fluid and antemortem needle aspirate of the pulmonary mass revealed neoplastic chondrocytes. Another report describes metastatic chondrosarcoma in the lungs of a horse with a primary tumor in a rib.[9] A primary bronchial myxoma, characterized by loose spindloid mesenchymal cells, was reported in a 25-year-old Arabian mare with a history of intermittent coughing, hyperpnea, and respiratory disease of 2 years' duration.[10]

Primary pleural tumors are also rare. The type reported in the horse is pleural mesothelioma. The tumor is frequently associated with a large volume of pleural effusion. Cytologic examination of the pleural effusion revealing numerous pleomorphic mesothelial cells may aid in the antemortem diagnosis.

Thymomas are neoplasms of thymic epithelial cells, regardless of the presence or absence of lymphocytes. They are infrequently reported in the horse.[11-13] Equine lymphosarcoma occurs in mediastinal, alimentary, multicentric, cutaneous, and generalized forms; combinations of one or more of these are not infrequent.[14,15] In a 1973 review of 54 cases of equine lymphosarcoma,[3] the lung was involved in 16.6% of the cases, whereas the thoracic lymph nodes were involved in 35.2%.[16] In the University of Pennsylvania survey, thoracic lymphosarcoma was the single most common neoplasia of the thorax and was present in 19 (54%) of the cases.[3] Pleural fluid cytologic evaluation was diagnostic in six (75%) of the eight horses. Diagnosis was made by biopsy of a peripheral lymph node in several cases. In a report from the University of Bristol, thoracic malignant lymphoma accounted for 74% of the cases of thoracic neoplasia.[16] Metastatic adenocarcinoma accounted for 20% of the cases in the University of Pennsylvania study[5] and 11% of the cases in the University of Bristol study.[16] The primary sites of the tumor were thought to be kidney, uterus, thyroid, and ovary.

Gastric squamous cell carcinomas commonly metastasize to the thoracic cavity. Cytology of pleural fluid with identification of neoplastic epithelial squamous cells has allowed for antemortem diagnosis of the carcinoma in several cases. Metastatic squamous cell carcinoma of the thorax was found in 14% and 5% of the cases in the University of Pennsylvania[5] and University of Bristol[16] surveys, respectively. Neoplastic epithelial cells may also be identified in biopsy specimens via indirect immunohistochemistry using antibodies recognizing cytokeratins of various molecular weights.

Hemangiosarcoma with pulmonary involvement was found in 9% of the horses in the University of Pennsylvania survey.[5] Hemothorax, anemia, and dyspnea were commonly seen with this type of neoplasm. Tentative antemortem diagnosis of the hemangiosarcoma can be made by transcutaneous direct thoracoscopy and observation of hemorrhages over the visceral and parietal pleural surfaces as well as tissue biopsy of these sites. Identification of neoplastic endothelial cells demarcating irregular, sometimes blood-filled cavities allows diagnosis from the biopsy specimen. Neoplastic endothelium expresses a variable amount of immunohistochemically identifiable factor VIII.

Malignant melanoma in a 20-year-old gelding had widespread infiltration of many organs, including the lungs and pleura.[16] This pattern of distribution is not uncommon in malignant, less pigmented melanomas. Amelanotic melanomas are rare in the horse, and microscopic identification of melanin simplifies the diagnosis of these tumors. Equine melanocytes express S-100 and PNL2 proteins, and their detection can be used to diagnose melanocytic neoplasms.

Other pulmonary metastatic tumors reported are mammary carcinoma,[17] seminoma,[18] and malignant pheochromocytoma.[19] Pulmonary hamartomas are occasionally observed in the newborn foal. Although they are nonneoplastic growths, they appear as tumorlike

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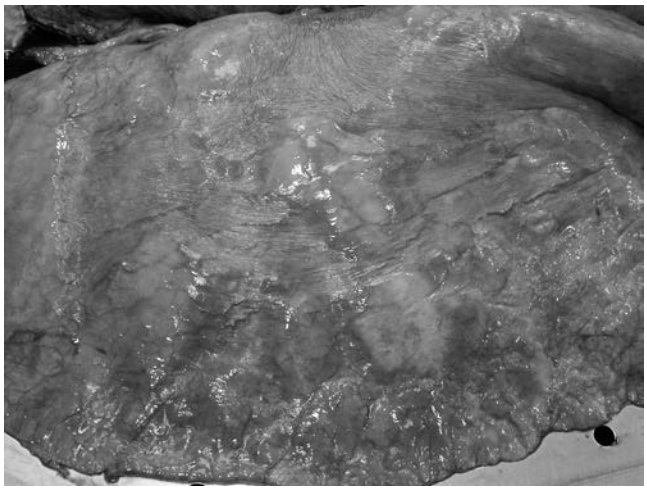


FIG. 31-47 Equine multinodular pulmonary fibrosis.

masses that can compress the surrounding parenchyma and cause systemic passive congestion and hydrops of the amnion in the fetus. Their histologic characterization is that of bronchiolar-like structures lined by cuboidal epithelium with lack of alveolar development or by normal alveoli, bronchi, and blood vessels but with an alveolus : artery ratio greater than normal. Generally they are not compatible with a long period of extrauterine life.

An unusual progressive idiopathic multifocal granulomatous pneumonia of adult horses may resemble neoplasia behaviorally and morphologically during clinical examination.[20,21] Pulmonary biopsy may allow the identification of equine multinodular pulmonary fibrosis (EMPF), which has been associated with EHV-5 infection[21] (Fig. 31-47).

Clinical signs of thoracic neoplasia are often inapparent or nonspecific—for example, depression, inappetence, weight loss, and pyrexia. More specific signs include cough, epistaxis, and dyspnea. Cytologic examination of tracheobronchial aspirate, bronchoalveolar lavage fluid, or pleural fluid and histologic examination of a thoracic mass tissue biopsy with ancillary histochemistry and indirect immunohistochemistry may allow for antemortem diagnosis of the neoplasm. Occasionally, electron microscopy may provide additional information. In equine patients with respiratory signs, all causes of infectious or allergic lung disease should be eliminated before neoplasia is considered in the differential diagnosis.

Diseases of Lymph Nodes, Vasculature, and Pharynx

Retropharyngeal Lymph Node Abscessation

John R. Pascoe

Definition and Etiology In horses, the retropharyngeal lymph nodes consist of medial and lateral lymphoid chains. The lateral chain (8 to 15 nodes) is located ventral to the atlas and along the lateral sides of the guttural pouches. These lymph nodes are covered by the parotid gland and are not clearly distinguishable from the medial retropharyngeal lymph nodes (20 to 30 nodes). The medial retropharyngeal lymph nodes are located ventral to the lateral chain on the dorsolateral aspect of the pharynx and the caudoventral aspect of the guttural pouches.[1]

Retropharyngeal lymph node abscesses in horses are generally caused by *Streptococcus equi* subsp. *equi* infection (see section on Strangles) or are secondary to trauma.[2,3] Other bacterial isolates have included *S. equi* subsp., *Streptococcus zooepidemicus, Corynebacterium pseudotuberculosis,* and *Actinobacillus* spp., including *A. denticolens*.[4,5] An unusual case of granulomatous infection of the guttural pouch caused by *M. avium* complex was believed to have originated from the retropharyngeal lymph nodes.[6] Extension of guttural pouch infections into the retropharyngeal space has been suggested as another source of infection.[7] Lymphadenopathy of the retropharyngeal nodes may also occur during viral respiratory infections, including equine herpesvirus (EHV) infection, influenza, and viral arteritis.[8] Retropharyngeal abscesses not associated with regional lymph nodes can result from perforation of the oropharynx or nasopharynx by ingested foreign bodies,[9] passage of a nasogastric tube,[10] or use of a balling gun.

In ruminants, the medial retropharyngeal lymph nodes are located on the dorsolateral aspect of the pharynx, one on each side of the midline. One to three lymph nodes may be present in cattle. The lateral retropharyngeal lymph nodes are located caudal to the medial retropharyngeal lymph nodes in the cranial neck region and are caudal to the retropharyngeal space.[11]

Abscessation of the medial retropharyngeal lymph nodes in cattle may result from pharyngeal actinobacillosis, foreign body penetration, or traumatic perforations by balling guns or dose syringes.[12-14] *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) or *Actinobacillus* spp. are frequently isolated.[8] Cattle with abscessed pharyngeal lymph nodes often have a small ulcer in the mouth, most frequently at the junction of the base and shaft of the tongue. This is more likely to occur when cattle are eating dry scabrous roughage. In addition to traumatic perforations and foreign bodies, caseous lymphadenitis (CLA) caused by *C. pseudotuberculosis* frequently results in abscessation of these lymph nodes in sheep and goats.

Clinical Signs and Differential Diagnosis Clinical signs associated with retropharyngeal lymph node infection or abscessation in horses include dysphagia, odynophagia (painful swallowing), nasal or oral regurgitation, excess salivation, difficult and often noisy breathing, painful throatlatch swelling, mucoid to mucopurulent nasal discharge, extension of the head and neck, and weight loss. In 46 horses with retropharyngeal lymph node abscessation, common clinical signs were fever and increased heart and respiratory rates (80%); unilateral or bilateral throatlatch swelling (65%); respiratory stertor or distress (35%); purulent nasal discharge (20%); inappetence and signs of depression (15%); and dysphagia (9%).[2] Other signs observed endoscopically include reduction in size or collapse of the pharyngeal lumen, asymmetry of the dorsal pharyngeal wall, and deviation of the laryngeal aperture away from the retropharyngeal mass.[2,3] Differential diagnosis for a retropharyngeal mass should include abscess, cellulitis, guttural pouch empyema or tympany, parotiditis, lymphadenopathy, neoplasia, and hematoma.

Clinical signs observed in cattle with infection or abscessation of the medial retropharyngeal lymph nodes include difficult breathing, excessive salivation, extension of the head and neck, anorexia, enlarged submandibular lymph nodes, nasal discharge, and swelling in the retropharyngeal space.[12] Other disease conditions that affect the oropharynx and surrounding lymph nodes should be considered in the differential diagnosis. These include actinobacillosis, lymphosarcoma, sialolithiasis, and necrotic laryngitis, laryngeal edema, or severe tracheitis caused by infectious bovine rhinotracheitis (IBR) virus.[8,12]

Affected sheep and goats may exhibit excessive salivation, increased respiratory rate, stertorous breathing, mucopurulent nasal discharge, regurgitation, gagging, depression, subcutaneous crepitation, weakness, and fetid breath. A false carotid aneurysm in the retropharyngeal space has been reported; on external examination it may be confused with abscessation of the medial retropharyngeal lymph nodes.[15] Enlarged retropharyngeal lymph nodes are usually easily palpated and identified in sheep and goats. CLA (see Chapter 37) is the most frequent cause of enlarged retropharyngeal lymph nodes in these species.

Clinical Pathology Collection of purulent material from abscessed lymph nodes may assist in identification of the causal

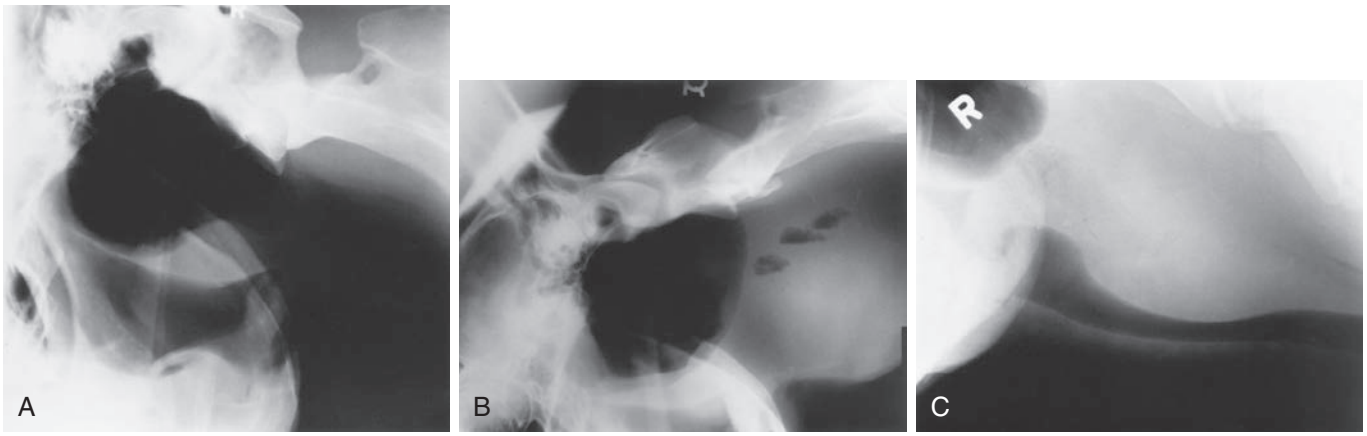


FIG. 31-48 **A,** Lateral radiograph. A soft-tissue density (retropharyngeal abscess) is distorting the floor of the guttural pouch. **B,** Lateral radiograph. There is increased soft-tissue density with gas shadows ventral to the cervical vertebrae. These changes are consistent with abscessation of the retropharyngeal lymph nodes. **C,** Lateral radiograph. There is increased soft-tissue density ventral to the cervical vertebrae, with compression of the dorsal border of the trachea. These changes were caused by cellulitis and abscessation of the retropharyngeal lymph nodes.

agent. Leukocytosis may be evident on the hemogram, with neutrophilia peaking as the lymph nodes abscess.

Laboratory Aids and Definitive Diagnostic Tests

Lateral radiographs of the pharynx, diagnostic ultrasound, and endoscopy aid in the diagnosis of retropharyngeal infections or abscesses. In horses, radiography may reveal a large soft-tissue mass impinging on the guttural pouch from a caudoventral direction (Fig. 31-48, *A*), as well as thickening of the pharyngeal roof. The soft-tissue swelling may contain gas (see Fig. 31-48, *B*). Compression of the larynx and trachea with ventral displacement may also be evident (see Fig. 31-48, *C*).[2] Observation of a gas-fluid interface on radiographs of the pharynx generally indicates abscessation, but care should be taken to distinguish a retropharyngeal abscess from guttural pouch empyema.[6] Foreign bodies associated with pharyngeal trauma are not usually radiopaque and therefore are not visible radiographically unless outlined by contrast medium. Exceptions include small wire foreign bodies likely ingested from baled hay that can perforate the tongue or oropharynx and cause cellulitis and dysphagia[9] and, in cattle, magnets that have been inadvertently placed retropharyngeally.

On endoscopy, asymmetry or collapse of the pharyngeal lumen or both signs suggests a retropharyngeal space-occupying mass. Recognition of drainage from the guttural pouch openings or examination of the guttural pouches may be necessary to differentiate between guttural pouch empyema and retropharyngeal lymphadenopathy or pharyngeal neoplasia. Occasionally the pharyngeal wall ruptures, allowing endoscopic observation of retropharyngeal drainage into the pharynx, usually near the esophageal entrance. Percutaneous needle aspiration may yield a definitive diagnosis if purulent material is obtained. Ultrasonography improves diagnostic precision by permitting more accurate identification of the abscess and highlighting its anatomic relationships as an aid to surgical drainage.[16]

Clinical examination, radiography, ultrasonography, endoscopy, and percutaneous centesis may all prove helpful in making a diagnosis of medial retropharyngeal lymph node infection or abscessation in ruminants. In cattle, localized swelling cranial to the larynx may be detected by digital palpation of the oropharynx.[12] Oropharyngeal examination must be performed carefully in animals with respiratory distress to prevent further airway compromise.

Pathophysiology

Upper respiratory tract disease, trauma, and foreign body penetration with resulting infection and drainage to local lymph nodes result in clinically apparent infection and abscessation of the retropharyngeal lymph nodes. In horses, the retropharyngeal space is occupied primarily by the guttural pouches. Because the vagus, glossopharyngeal, hypoglossal, spinal accessory, and sympathetic nerves traverse this area, their function can be affected by infectious or inflammatory processes involving the retropharyngeal space.[2] If such infections are contained within the lymph nodes or are confined within the fibrous capsule of the abscess, cranial nerve dysfunction is not usually evident.[2] Clinical evidence of dysphagia or odynophagia such as the presence of feed and saliva at the external nares may result from angina and from inflammation or injury of the glossopharyngeal nerve or pharyngeal branch of the vagus nerve, compression, or obstruction of the pharynx or esophagus. It has been suggested that retropharyngeal lymphadenitis may result in neuritis of the pharyngeal branch of the vagus nerve in young horses and contribute to the pathogenesis of dorsal displacement of the soft palate.[17]

Respiratory distress may result when enlargement of the retropharyngeal lymph nodes compresses or obstructs the nasopharyngeal, laryngeal, or tracheal lumen, and the disease caused by *S. equi* subsp. *equi* in horses is appropriately named *strangles*.

The most common cause of pharyngeal inflammation and infection in cattle is pharyngeal trauma associated with balling guns, dose syringes, paste wormer guns, esophageal feeders, or nasogastric tubes. A careful history to determine whether any of these devices were used is important in ascertaining the source of pharyngeal abscessation. Such infections usually involve mixed bacterial flora, because they are directly connected with the oropharynx.

Epidemiology

Infection with *S. equi* usually results from contact (inhalation or ingestion) with pasture, feed, or water contaminated with nasal discharge from infected horses. Asymptomatic carrier horses have also been implicated as source of infection.[18] The likely bacterial reservoir in carrier horses is the guttural pouch, particularly if chondroids are present in one or both pouches[18-20] or if swollen or discharging lymph nodes are present in the floor of the medial compartment of the guttural pouch. Infection of the pharyngeal and nasal mucosa results in an acute pharyngitis and rhinitis, and drainage to regional lymph nodes results in lymphadenopathy and possibly abscessation.[8]

CLA is spread through the discharges from ruptured lymph nodes. The causal agent *C. pseudotuberculosis* may persist in the environment for long periods, and infection results from contact of shearing, docking, or castration wounds with contaminated soil, equipment, or freshly ruptured abscesses. Sheep dips have been reported as another important source of infection.[8] Spread of infection from skin wounds often leads to involvement of local nodes and abscess formation. The mode of spread in goats is not well understood, but the disease usually spreads in a low-grade contagious manner, often involving most of the herd over a period of years.

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Necropsy Findings Fatalities are rare and most likely result from respiratory compromise or septicemia. Necropsy lesions include cellulitis with compression and ventral displacement of the larynx and cranial aspect of the cervical trachea. Abscesses are variable in size and may contain either caseous *(C. pseudotuberculosis)* or liquid material *(S. equi* subsp. *equi)*. A thick, fibrous capsule may occur in response to the infectious process and may account for the surrounding tissue compression. Occasionally, draining tracts may connect the abscess to the pharynx, guttural pouch, or skin.[10,21]

Treatment and Prognosis Treatment goals are relief of respiratory distress and control of infection. Temporary tracheotomy may be needed for relief of respiratory distress and may be prudent, especially in foals with singular, large, or multiple abscesses, before percutaneous drainage is attempted. After surgical drainage, appropriate systemic antibiotics are administered and supportive therapy to further reduce swelling may be beneficial.

Surgical approaches include percutaneous drainage, intraoral drainage, and marsupialization.[2,12] In horses, an intraoral approach is very difficult because of the long narrow oral cavity, and for this reason percutaneous drainage is commonly used. For abscesses visible through the mucosal lining of the guttural pouch, endoscopically assisted drainage into the pouch can also be considered. Surgical access to the retropharyngeal space has been described, including dorsal and ventral approaches, an approach through Viborg triangle, and a lateral approach.[3] A ventral surgical approach is recommended because of the relative lack of vital structures encountered and the excellent ventral drainage achieved. A less invasive drainage technique can be accomplished in standing sedated horses, by ultrasound-guided percutaneous needle placement into abscessed lymph nodes. Affected nodes can have a wall thickness of 1 to 2 cm and a diameter of 5 to 11 cm.[16] Aspiration of purulent matter and cavity lavage with antiseptic solutions and concurrent administration of parenteral antibiotics may be sufficient for resolution. If aspiration is not possible because the purulent material is too viscous, incision directly along the needle shaft, after careful consideration of regional anatomy, provides adequate exterior drainage and access for cavity lavage with antiseptic solutions or use of a seton or gauze packing. If the abscess is endoscopically visible beneath the guttural pouch mucosa, drainage into the guttural pouch and subsequent lavage of the purulent material can be accomplished. Before, or at the time of, abscess drainage or excision, the horse should be started on broad-spectrum antimicrobials, followed by the appropriate specific antimicrobial drug when results of the microbial culture and susceptibility testing are known.

Occasionally, medical management alone may resolve infection; however, this is less likely if abscessation has occurred. Because the most common bacterial isolate in the horse is *S. equi,* parenteral antimicrobial therapy with procaine penicillin G (22,000 IU/kg IM twice daily) or potassium penicillin (22,000 IU/kg IV four times daily) is recommended. Systemic NSAIDs are useful to reduce inflammation and swelling, and fluid and electrolyte therapy may be necessary if there is odynophagia or dysphagia. Aspiration pneumonia can occur with dysphagia or if there is oral or nasal regurgitation associated with painful swallowing.

In cattle with pharyngeal trauma, an existing wound is often draining from the retropharyngeal area into the oropharynx, making surgical drainage unnecessary, and response to parenteral broad-spectrum antimicrobial therapy is typically favorable.[22] Parenteral antimicrobial therapy alone has been ineffective in treating retropharyngeal abscesses when there is no draining tract.[12] Intraoral or percutaneous drainage has been used successfully in conjunction with broad-spectrum, parenteral antimicrobial therapy. After drainage, the abscess cavity is flushed daily with an antiseptic or antibiotic solution.[12] Surgical drainage into the oral cavity must be handled with caution. The head should be lowered so that exudate or flush solution is not aspirated; inspection of the granulating abscess cavity is necessary if feed impaction is suspected.[2,12] Aspiration pneumonia may be a serious complication when dysphagia is present.

In sheep and goats, walled-off *C. pseudotuberculosis* abscesses may often be most safely drained by suturing the skin to the thick abscess capsule (a procedure known as *marsupialization*) before opening the capsule. Marsupialization prevents contamination of other retropharyngeal structures with infected material and markedly reduces postsurgical cellulitis. Although *C. pseudotuberculosis* is susceptible in vitro to a number of antimicrobial agents, abscesses associated with the condition have not been well controlled by antimicrobial therapy. Walled-off *C. pseudotuberculosis* abscesses are difficult to eliminate solely with antimicrobial therapy, and drainage or removal of the entire lymph node gives the best results.

Prevention and Control Preventive measures to limit infection and abscessation of retropharyngeal lymph nodes include correct administration of therapeutic agents with balling guns and dose syringes, isolation of horses affected with viral or bacterial upper respiratory tract disease, vaccination against strangles, and vigorous treatment in the early stages of streptococcal infection. Reducing environmental sources of contamination and preventing contamination of shearing equipment, dipping vats, and feeders with *C. pseudotuberculosis* are important to limiting spread in sheep. Culling affected sheep and goats may also help to reduce the incidence of CLA.

Pharyngitis

John R. Pascoe

Definition and Etiology Pharyngitis is inflammation of the pharyngeal tissues. It is not generally considered to be a specific disease entity but a response to other diseases, particularly viral and bacterial respiratory disease, and to a lesser extent to local physical, chemical, or allergic causes. Acute and chronic forms are recognized.

Although physical and chemical causes of pharyngitis may be identified with certainty, the role and specificity of microbial pathogens as causative agents remain controversial. In horses, *Streptococcus* spp. and various viral respiratory diseases have been incriminated as specific causes of pharyngitis, but given the ubiquitous nature of some virus groups in horses, a direct causal association remains unsubstantiated.[1,2] In cattle, *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Actinobacillus* spp., and *Fusiformis necrophorus* are frequently isolated.[3]

Synonyms for chronic pharyngitis in horses include *pharyngeal lymphoid hyperplasia (PLH), chronic pharyngitis, chronic lymphoid follicular hyperplasia, follicular pharyngitis,* and *follikelkatarrh.*[4-6]

Clinical Signs and Differential Diagnosis In acute pharyngitis, signs are associated with pharyngeal pain (odynophagia, dysphagia), nasal discharge (serous, seromucous, mucopurulent, purulent, feed-contaminated), regional lymphadenopathy (submandibular, retropharyngeal nodes), ptyalism (especially in cattle), respiratory noise (often inspiratory), pharyngeal swelling, and cough. Mouth breathing may occur in cattle when there is increased resistance to breathing associated with excessive exudate, diphtherous membranes, and lymphadenopathy or lymph node abscess. Pharyngitis from local pharyngeal trauma or incarcerated foreign bodies may also be associated with odor of either the breath or nasal discharge. Calves with necrotic laryngitis, pharyngitis, and stomatitis have a characteristic malodorous breath. Acute laryngeal inflammation and edema of unknown cause can occur in horses and ruminants and is characterized by marked inspiratory difficulty and stertor without malodorous breath. Treatment of acute edema with dexamethasone (0.05 mg/kg IM; avoid in pregnant heifers or cows) and broad-spectrum antimicrobials or penicillin has produced rapid clinical improvement.

Signs observed on endoscopic or oropharyngeal examination in cattle include pharyngeal hyperemia and edema, lymphonodular swelling, and either a moist appearance of the pharyngeal surface

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or the presence of exudate or a diphtherous membrane adhering to the pharyngeal surface. Focal necrosis or ulceration of the mucous membrane and tonsillar tissue may occur; signs associated with rhinitis and laryngitis may be evident. Signs of chronic pharyngitis are similar. In horses, there may be endoscopic evidence of more marked hyperplasia of the lymphonodular follicles within the pharyngeal mucosa, and single or multiple lymphonodular masses may be within, or protrude from, the pharyngeal mucosa. Biopsy and cytologic evaluation are recommended to rule out neoplasia, particularly squamous cell carcinoma, lymphoma, and lymphosarcoma. Differential diagnostic possibilities include rhinitis and laryngitis, and in cattle, rabies should be strongly considered before oropharyngeal examination. If the predominant sign is dysphagia (see Chapter 7), other diagnostic ruleouts include foreign bodies in the tongue, fractures of the hyoid apparatus or jaws, and, in the horse, diseases of the guttural pouches. If exercise intolerance is the primary complaint in a horse, pharyngitis should be considered only after other possible causes of impaired performance have been eliminated (see Chapters 5 and 6).[7-11] Pharyngitis is not a risk factor for poor racing performance in racing Thoroughbreds[12] or Standardbred trotters.[10] More severe PLH grades were found in poorly performing endurance horses (primarily Arabian horses); however, more definitive causes for poor performance were identified in these horses.[11]

Upper airway inspiratory pressures recorded during strenuous exercise in horses with grade IV PLH are not different from those of normal horses under the same exercise conditions.[8] Assuming that airflow in both groups of horses was comparable, severe PLH does not appear to cause functional upper airway obstruction. It is conceivable that pharyngeal pain associated with PLH may contribute to bronchoconstriction and impaired performance; however, this effect remains unproven.



FIG. 31-49 Endoscopic view showing the nodular appearance of pharyngeal lymphoid hyperplasia.

Clinical Pathology

Changes in the hemogram and serum biochemical profiles are likely to result from concurrent respiratory disease (increases or decreases in absolute or differential leukocyte counts, hyperfibrinogenemia, anemia) or to reflect abscess formation (neutrophilia, hyperfibrinogenemia) or dehydration and fasting associated with dysphagia.

Laboratory Aids and Definitive Diagnostic Tests

Although a presumptive diagnosis can be made from clinical signs, definitive diagnosis requires observation of the pharynx (Fig. 31-49) and, more important, exclusion of other conditions that have similar signs. Radiography of the pharynx can provide information on pharyngeal anatomy, radiodense foreign bodies, soft-tissue masses, fractures, and, in horses, guttural pouch disorders. Ultrasonography of the pharyngeal region and, if indicated by the clinical examination, both radiographic and ultrasound examination of the thorax may help define the extent of concurrent pulmonary disease.

Microbial culture of pharyngeal secretions can be considered, but interpretation is difficult because (1) the pharynx normally has resident microflora with considerable individual variation, and (2) many of the microorganisms isolated are capable of opportunistic infection. In horses with grades III and IV PLH, the number of bacteria recovered per gram of pharyngeal secretion was almost 100-fold greater than in normal horses.[9] The pattern of microbial isolation was not consistent among horses, suggesting that these organisms were not the source of the pharyngitis but rather other factors had made conditions for colonization more favorable.

Biopsy and cytologic examination are indicated in refractory cases and when abnormal masses are present to rule out neoplasia.

Pathophysiology

Acute pharyngitis occurs as a sequela to inflammation of regional lymphoid tissue (see Kumar and colleagues[13] for a description of the morphologic and histochemical features of the normal equine nasopharyngeal tonsil).[14] In horses, the pharyngeal tonsil consists of discrete lymphoid follicles diffusely distributed in the dorsal and lateral walls of the pharynx. In ruminants, the pharyngeal tonsil is located caudal to the pharyngeal septum in the caudodorsal wall of the pharynx and is bounded by long ridges and grooves into which mucous glands open. In response to local or lymphogenous spread of infection, the tonsillar tissue becomes inflamed and the tonsillar crypts become filled with desquamated epithelium, leukocytes, and bacteria. Clinically this is seen as hyperemia and edema of the pharyngeal tonsil with diffuse white or yellow tips to the lymph nodules. The edematous appearance is associated with hyperplasia of the lymph nodules and sequestration of perinodular inflammatory fluid.

If extensive destruction of the lymphoid cells or subsequent invasion of the nodules or supporting soft tissue is evident, the result is focal or diffuse necrosis, which may be seen as pinpoint areas of follicular necrosis or diffuse necrosis with associated purulent or fibrinonecrotic exudate. With resolution, atrophy of some follicles and increased fibrosis are present. Follicular atrophy also occurs with aging.

Epidemiology

No specific epidemiologic data are available. When pharyngitis occurs as a sequela to respiratory tract infection, the population demographics should be similar to those known for the specific respiratory disease. For example, grade II PLH was identified in 60% of foals with distal respiratory tract infection and in only 13% of control foals.[15] Because physical and chemical injury to the pharynx occurs sporadically, no universal epidemiologic characteristics would be anticipated.

PLH is prevalent in horses less than 5 or 6 years of age, and the severity of PLH grades[5] is inversely correlated with age.[4,12,16,17] In endoscopic surveys of primarily Thoroughbreds in race training, prevalence of PLH ranges from 29% to 34%, with grade II PLH observed in 45% to 63% of 2-year-olds and less than 12% to 20% of horses older than 5 years affected.[16] Similar results are reported from Japan for racing Thoroughbreds with a history of cough or abnormal respiratory noise[18] and in a mixed population of horses in Calgary, Canada.[17] Pharyngeal mucus scores are not correlated with PLH, transtracheal wash aspirate, or bronchoalveolar lavage fluid variables, suggesting that PLH is not directly a manifestation of lower airway inflammation or disease.[17,19]

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Treatment and Prognosis Approach to treatment is largely symptomatic and directed at palliation of pharyngeal pain and maintenance of unobstructed breathing until the initiating disease process has abated. In many instances, the signs are sufficiently mild that treatment is unnecessary. When pharyngeal angina is causing inappetence or dysphagia, administration of NSAIDs should be considered. Dehydration should be corrected by either parenteral or enteral fluid administration. Enteral fluid therapy may be difficult because passage of a nasogastric tube may elicit too much pain. For inappetent animals, nutritional support may be necessary until pharyngeal pain subsides sufficiently for normal eating to resume. Soft feeds, especially green grass, should be offered when available to encourage animals with pharyngeal discomfort to eat.

Antimicrobial therapy is probably not indicated, but it is often given to limit development of secondary bacterial infection. Infections caused by foreign body injury should be treated with antibiotics that have a broad aerobic and anaerobic spectrum of activity. Daily lavage of any cavitary wounds, débridement, and removal of feed material may be necessary to prevent additional abscess formation and hasten healing.

Custom topical preparations, usually containing an antibiotic, an antiinflammatory drug, and a hygroscopic agent (glycerin) or DMSO, are often used for palliation of clinical signs, especially in horses with PLH. These preparations are usually administered two or three times daily and sprayed onto the pharyngeal surface through a transnasal catheter. Despite frequent use, the efficacy of this therapy is unknown and response may reflect natural resolution of the predisposing cause.

Treatment of PLH is empirical and generally palliative. Rest from training for 4 to 8 weeks is commonly recommended, and although some horses have recurrence when training resumes, this enforced rest is beneficial as convalescence for any concurrent subclinical respiratory disease. Horses kept in training are often initially treated empirically with sulfa compounds and topical throat preparations. With continued clinical signs, penicillin or broad-spectrum antibiotics are often administered. If PLH does not improve or resolve after therapy, pharyngeal cautery may be used. Techniques for pharyngeal cautery include topical application of trichloroacetic acid, electrocautery, freezing with liquid nitrogen or Freon, and photoablation by neodymium:yttrium aluminum garnet (Nd:YAG) laser with either a contact or a noncontact technique.[20] Although cauterization techniques have received considerable testimonial support, it is likely that cautery does not effect a cure but simply obliterates reactive tissue so that it is no longer clinically evident.

Routine immunization at frequent intervals for known viral respiratory pathogens is also recommended for treatment and prevention of PLH.[21]

Prevention and Control Methods used to control and prevent most of the common viral and bacterial respiratory diseases (see Chapter 48 for vaccines) should limit herd problems with acute pharyngitis. Non–respiratory disease-related causes such as trauma from balling guns, nasogastric tubes and dose syringes, foreign objects, and chemical burns can be minimized by improved husbandry practices.

Prevention of PLH in horses by prophylactic immunization against common equine viral respiratory agents at regular intervals has been discussed at length, but there is no evidence to support this practice. Nevertheless, racetrack veterinarians maintain that frequent immunization (60-day intervals) against influenza and rhinopneumonitis markedly reduces the severity of PLH and improves exercise tolerance.[21] Considering the mobility of racing and show horse populations, this approach should at least be beneficial for limiting outbreaks of viral respiratory disease and consequently perhaps limiting chronic PLH. Until more is understood about the clinical appearance of the pharyngeal tonsil in horses, along with normal variations that occur with aging in exercised and nonexercised horses, and these findings can be correlated with immunopathologic events and indices of performance, it will remain difficult to treat, control, and prevent pharyngitis in a systematic manner.

Guttural Pouch Diseases

John R. Pascoe

Definition and Etiology The guttural pouches are paired air-filled diverticula of the eustachian tubes that communicate between the middle ear and the pharynx. They are located ventral to the atlas, dorsocaudal to the pharynx, and rostrodorsal to the retropharyngeal lymph nodes and occupy a large part of the retropharyngeal space. Each pouch is divided into medial and lateral compartments by a stylohyoid bone that courses through the caudolateral aspect of each pouch. The medial compartments appose each other on the midline. The lateral walls of each guttural pouch contain cranial nerves VII (facial), IX (glossopharyngeal), X (vagus), XI (spinal accessory), and XII (hypoglossal); the cranial sympathetic trunk; the internal carotid artery; and branches of the external carotid artery.[1] The intimate relationship of these vessels and nerves with the mucous membrane lining the guttural pouches explains why epistaxis and nerve dysfunction frequently accompany guttural pouch disease. Each pouch has a capacity of approximately 300 mL, with the medial compartment accounting for approximately two thirds of this volume. Communication with the pharynx occurs through a slitlike opening situated rostral and ventral to the pharyngeal recess. The pharyngeal opening of the guttural pouch is funnel shaped and wider rostrally than caudally. The plica salpingopharyngea is a fold of mucous membrane that contributes to the caudal narrowing of the pharyngeal opening and makes catheterization of the guttural pouch difficult. Redundancy of this fold of tissue may contribute to guttural pouch tympany.[1]

The guttural pouch is lined with pseudostratified ciliated epithelium containing goblet cells.[2] As an extension of the pharynx, the guttural pouches are not a sterile environment. In 30 normal horses, 59% of percutaneous guttural pouch lavage aspirates had bacterial growth, although only 7% were considered to have bacteria considered to be pathogenic; no fungi were isolated.[3] Inflammatory cell counts and distribution were correlated with recovery of bacteria. Aspirates were considered normal if they contained less than 5% neutrophils; typical cell distribution was primarily ciliated columnar epithelial cells, a few nonciliated cuboidal epithelial cells, and less than 1% monocytes, lymphocytes, and macrophages.[3] Horses exercised strenuously on a regular basis had lower total cell counts, lower neutrophil counts, and fewer bacteria isolated.[3] Preventing horses from head lowering for 12 to 24 hours increases the frequency of bacterial isolation, especially at 24 hours, including an increase in neutrophil counts, and likely indicates reduced ability to clear guttural pouch secretions.[4] Interpretation of microbial isolates from guttural pouches requires correlation with cytologic characteristics of guttural pouch fluid and clinical signs.[5]

Three disease conditions commonly affect the guttural pouches: tympanitis, empyema, and mycosis. Less common conditions include neoplasia,[6] fractures of the hyoid bone, foreign bodies,[1] and cystic structures.[7]

Guttural Pouch Tympany

Tympany of the guttural pouch occurs infrequently and is recognized in foals after birth up to 1.5 years of age[8-10]; affected foals are usually identified within the first 2 weeks of life. Fillies are more commonly affected, with the ratio of females to males ranging from 2:1 to 4:1. Familial and complex inheritance of guttural pouch tympany occurs in Arabian horses and German warmblood horses and sex-specific quantitative trait loci have been identified.[11-13]

Tympany is characterized by unilateral or bilateral distention of the guttural pouch with air. The exact cause is unknown, but congenital redundancy of the plica salpingopharyngea has been suggested. This mucosal fold acts as a one-way valve apparently permitting airflow into but not out of the pouch. Upper airway infection or inflammation has been postulated to result in neuromuscular dysfunction of the plica or enlargement contributing to air trapping.

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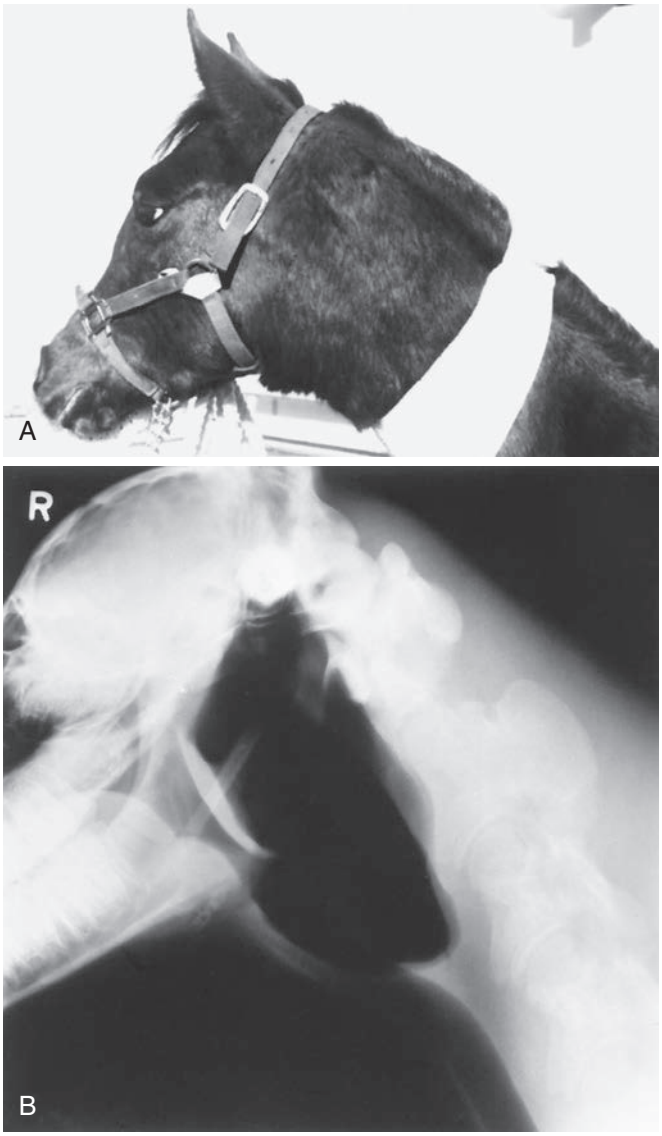


FIG. 31-50 **A,** Foal with guttural pouch tympanitis. Note the protrusion of the soft tissues over the lateral and ventral aspects of the throatlatch. **B,** Lateral radiograph of a foal with tympanitis of both guttural pouches.

Clinical Signs and Differential Diagnosis Affected foals usually have a nonpainful, soft, fluctuant swelling in the retropharyngeal space (Fig. 31-50, *A*) with variable respiratory distress, extension of the head and neck, nasal discharge, signs of dysphagia, and possible development of aspiration pneumonia.[8,9] Guttural pouch fluid accumulation and empyema can occur. Mild tympany may not result in signs other than swelling of the throatlatch (retropharyngeal) region. Respiratory distress occurs when continued distention of the pouch compresses the pharyngeal area. The differential diagnosis for throat latch regional swelling should include guttural pouch empyema and retropharyngeal abscesses or cellulitis.

Clinical Pathology Stress leukocytosis may occur if there is marked respiratory distress.

Diagnostic Aids Diagnosis of guttural pouch tympany is based on recognition of characteristic swelling in the retropharyngeal space and confirmation by physical examination. Although the distention is most often unilateral, extreme distortion of a single pouch may give the impression of bilateral involvement. Differentiation between unilateral and bilateral involvement can be difficult and may require deflation of the affected guttural pouch by catheterization or percutaneous needle aspiration combined with external compression. Other adjunctive diagnostic procedures include radiographic demonstration of gas distention of one or both pouches (see Fig. 31-50, *B*) and endoscopic observation of pouch distention and pharyngeal distortion.

Treatment and Prognosis Guttural pouch tympany and respiratory distress can be alleviated temporarily by aspiration of air from the affected pouch by means of either percutaneous decompression at the point of greatest distention through Viborg triangle or introduction of a catheter through the pharyngeal opening of the guttural pouch. These measures are palliative, and the pouch rapidly refills when decompression is discontinued. Treatment methods of choice include surgical excision of the plica salpingopharyngea and part of the medial lamina of the eustachian tube, partial resection of the plica, or photoablation of the plica; fenestration of the median septum between the two pouches by excision, electrosurgery, or photoablation; and creation of a salpingopharyngeal fistula by photoablation and temporary stenting of the fistula.[8-10,14-17] The latter technique is similar to an older, successful approach that involved incising the floor of the guttural pouch into the pharynx.[18] If the condition is bilateral, fenestration of the median septum alone does not successfully resolve the condition, and excision of one or both plica salpingopharyngea, in combination with septal fenestration or septal fenestration and salpingopharyngeal fistula formation, must be performed. After surgery the prognosis for resolution of guttural pouch tympany is generally considered favorable[10] unless complicating factors such as aspiration pneumonia exist.[9] Early recurrence after surgery can range from 15% to 30%, but further resection of the plica salpingopharyngea or refenestration of the mesial septum or enlargement of the fenestration typically results in resolution of signs.[9,10]

Guttural Pouch Empyema

Guttural pouch infections are introduced either directly through the pharyngeal opening or by lymphatic spread. Accumulation of purulent material (empyema) is considered to be a secondary, chronic, localized manifestation of a more generalized ascending respiratory infection. Empyema is usually unilateral and is often a sequela to an infectious respiratory disease, especially infection by *S. equi* subsp. *equi*.[19-21] Typically a horse with guttural pouch empyema displays continued nasal discharge after recovery from streptococcal infection.[21] In a case control study of foals with lower respiratory tract infection, 21% had concurrent mucopurulent drainage from the pharyngeal openings of the guttural pouches.[22] *S. equi* subsp. *zooepidemicus* was isolated from respiratory secretions of most infected foals and from exudate collected from guttural pouches.[23] Rupture of retropharyngeal abscesses into the guttural pouch has also been associated with empyema, suggesting that strangles or other upper respiratory tract infections may have an important role in the development of guttural pouch infection in horses.[19]

Clinical Signs and Differential Diagnosis Clinical signs include intermittent nasal discharge that may worsen when the head is lowered, retropharyngeal swelling, cough, fever, parotid swelling and pain, dysphagia, difficult breathing, dysphagia, and pneumonia.[24] Nasal discharge can be unilateral or bilateral, even if only one pouch is affected, because the pharyngeal openings of the guttural pouches are located caudal to the nasal septum. Nasal discharge is generally nonodorous, white, and opaque. Signs of dysphagia may be observed secondary to pharyngeal compression or paresis. Labored breathing may result from gradual collapse of the pharynx as the guttural pouch distends. Inspissation of the purulent material results in chondroids (hard concretions of inspissated pus). Differential diagnosis of guttural pouch empyema should include diseases with chronic mucopurulent nasal discharge such as pneumonia, sinusitis, upper respiratory tract infections, and guttural pouch tympany.

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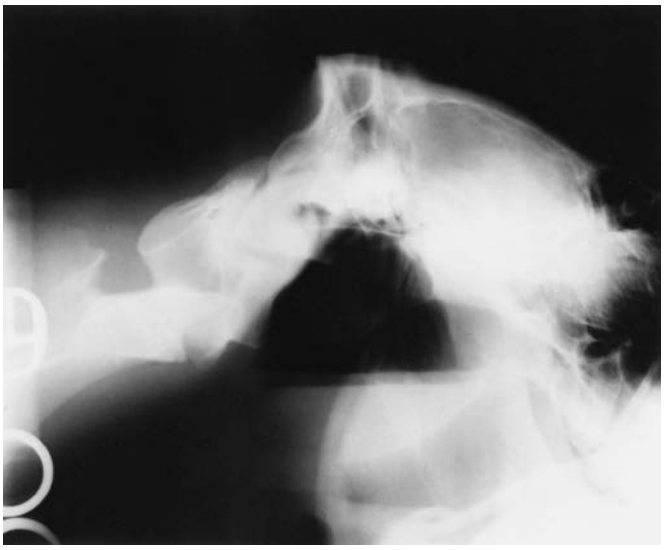


FIG. 31-51 Lateral radiograph demonstrating distinct fluid lines in both guttural pouches.

Clinical Pathology Leukocytosis is often present. Plasma fibrinogen levels are often increased,[24] and these changes generally parallel development of leukocytosis, pyrexia, and clinical signs of strangles or primary guttural pouch empyema. Analysis of fluid obtained by catheterization of the guttural pouch often yields a β-hemolytic *Streptococcus* spp.,[19] although other bacterial species have been isolated.[24]

Diagnostic Aids Guttural pouch empyema should be considered when there is a chronic, nonresponsive nasal discharge. Diagnostic aids include radiography, endoscopy, percutaneous centesis, and aspiration of material from the pouch through the pharyngeal opening. Recognition of fluid (Fig. 31-51) or radiodense masses (chondroids) within the pouch on standing lateral radiographs supports a diagnosis of empyema. Physical and endoscopic examination or oblique radiographic projections may be needed to identify which pouch is involved. Endoscopic examination permits identification of the affected pouch and evaluation of the character of the fluid. Endoscopic examination of the lateral compartment is important to avoid missing sequestered fluid or chondroids.[25] Absence of fluid at the pharyngeal ostium does not preclude the possibility of guttural pouch empyema, if the fluid is inspissated or the ostium is sealed.[26] Fluid identified on radiographs should be characterized by endoscopic examination of the pouches or aspiration of the fluid with cytologic and microbial analysis. Fluid samples can be aspirated through the pharyngeal ostium using a sterile artificial insemination pipette, a Chambers catheter, or tubing advanced through the biopsy channel of an endoscope. Alternately, fluid can be aspirated percutaneously, but this may lead to cellulitis along the needle tract if pathogenic bacteria are tracked through tissues on needle withdrawal.

Pathophysiology Strangles is a common upper respiratory tract disease affecting young horses. Primary clinical signs of strangles usually develop after a short incubation period of 2 to 6 days and include depression, pyrexia, coughing, and ocular and nasal discharges that become mucopurulent as the disease progresses. Lymph nodes of the head and neck become enlarged and painful and often form abscesses. Guttural pouch empyema may result from extension of the upper respiratory tract infection with *S. equi* (strangles) to the guttural pouches or from rupture of retropharyngeal lymph node abscesses into the guttural pouch.[19] Commonly isolated bacteria from guttural pouch empyema include *S. equi, S. zooepidemicus, E. coli,* and *Klebsiella* spp.[24] Not all horses with empyema have a history of strangles or previous respiratory infection, and empyema seemingly can occur by many of the same mechanisms as middle ear infection: that is, fluid accumulates in the area, and uncontrolled growth of bacteria normally present results in inflammation and exudation. Most streptococcal isolates are resistant to potentiated sulfonamides and sulfadimethoxine.[24]

Treatment and Prognosis Treatment of guttural pouch empyema is complicated by poor drainage from the affected pouch. The pharyngeal opening of the guttural pouch is located rostrodorsal to the floor of the guttural pouch, and drainage can be achieved only by lowering the horse's head. In horses with empyema, lowering the head may not achieve adequate drainage if there is ventral distortion of the pouch. Inflammation of the lining mucosa may result in swelling of the tissue surrounding the pharyngeal opening, further compromising normal drainage.

Choice of medical or surgical treatment depends on the duration and nature of the empyema and the presence of chondroids. Parenteral antimicrobial therapy may reduce the quantity of the nasal discharge, but relapse often occurs after cessation of treatment.[24] The early stages of empyema may respond to daily lavage of the affected guttural pouch. Because of the thin nature of the mucosal lining and the proximity of cranial nerves VII and IX-XII and the cranial sympathetic trunk, it is important to use physiologic solutions, saline antibiotic solutions, or nonirritating solutions to avoid neural inflammation or neuritis. Large volumes have caused guttural pouch rupture. Typically, 500 mL should be flushed into the pouch under moderate pressure to create contact with as much of the interior of the guttural pouch as possible. During lavage the head should be lowered to prevent aspiration of fluid. Purulent fluid from the affected guttural pouch should be aspirated on initial catheterization and submitted for bacterial culture and antimicrobial susceptibility testing. This can be accomplished with most flexible uterine culturettes under direct endoscopic observation. Parenteral antimicrobial drugs should be administered on the basis of susceptibility testing results; although medication may be of benefit in treating empyema, adequate drainage and local therapy are of primary therapeutic importance.

Indwelling catheters in normal guttural pouches have caused increasing purulent discharge with time; nasal discharge diminished after catheter removal and was absent after 3 days. Although indwelling catheters are convenient, daily catheterization and irrigation with an artificial insemination pipette or Chambers catheter should be considered to diminish the inflammatory response associated with indwelling catheters in an already inflamed guttural pouch. However, consideration of daily catheterization must be weighed against stress, possible tissue trauma, and time requirements for intermittent catheterization.

Treatment with parenteral antimicrobials and local lavage is successful and requires a patent opening for adequate drainage, but the course of treatment may be protracted. Povidone iodine (1% available iodine) diluted to a 10% solution (0.1% available iodine) for lavage of the guttural pouch caused considerable reaction, including inflammatory infiltrates, hemorrhage, necrosis, and lymphoid reaction.[27] Likewise, antimicrobial concentrations of chlorhexidine gluconate are not recommended.[28] Although acetylcysteine, a mucolytic, was used successfully to resolve inspissated empyema,[29] subsequent reports have shown lack of efficacy and concern for added mucosal inflammation.[30] If response to lavage is poor or if secretions reaccumulate and empyema returns, surgical drainage of the guttural pouch should be considered.

Surgery is generally indicated when purulent material becomes inspissated or chondroids have formed,[31] although resolution has been reported in one horse after prolonged lavage (14 days) through an indwelling catheter.[32] Surgical approaches include percutaneous drainage through standard approaches to the guttural pouches in anesthetized recumbent or standing sedated horses and creation of a nasopharyngeal fistula by use of an Nd:YAG laser.[33] Other approaches when chondroids are present include removal by retrieval snares passed endoscopically, standing removal through a modified Whitehouse approach,[34] and removal from the contralateral pouch after

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fenestration of the mesial septum when the ipsilateral ostium is closed.[26]

The prognosis for guttural pouch empyema is generally favorable if it is recognized promptly and treated appropriately.[24] Likewise, removal of chondroids typically carries a good prognosis.[24]

Guttural Pouch Mycosis

Guttural pouch mycosis is a fungal disease of the guttural pouch that typically affects the dorsocaudal region of the medial compartment, although lesions affecting larger areas, including the lateral compartment, occur.[35-37] Fungal invasion of neurovascular structures coursing through the walls of the guttural pouches results in clinically apparent disease. The exact cause is unknown, although a number of fungi, especially *Aspergillus (Emericella) nidulans* and *Aspergillus fumigatus,* have been isolated from lesions.[37-41]

Clinical Signs and Differential Diagnosis Lesions are usually unilateral but can occur bilaterally. The wide spectrum of clinical signs that can occur with guttural pouch mycosis reflects the degree of fungal invasion and subsequent inflammation of vascular structures or nerves beneath the lining mucous membrane of the guttural pouch; however, the size of the lesion apparently is not correlated with the severity of clinical signs. Intermittent spontaneous epistaxis and dysphagia are the common clinical signs that stimulate owners to seek veterinary care; however, the earliest clinical sign in most affected horses is nasal discharge (serous to mucopurulent).[42] Epistaxis generally results from fungal erosion of the wall of the internal carotid artery in the roof of the medial compartment and, less commonly, from erosion of the external carotid artery (or its branches, e.g., caudal auricular artery) and maxillary artery in the lateral compartment. Epistaxis is usually unilateral from the ipsilateral nostril, but it can be bilateral because the pharyngeal openings of the guttural pouches are located caudal to the caudal border of the nasal septum.[36] Episodes of epistaxis typically occur at rest and vary from mild to severe, with several premonitory bleeds that generally culminate in a fatal episode of epistaxis.[36,37] Occasionally a horse dies of a single episode of epistaxis without previous clinical signs. Epistaxis may recur at intervals varying from 24 hours to 3 weeks.[36]

Dysphagia, the second most common clinical sign, likely results from damage to the pharyngeal branches of the vagus and glossopharyngeal nerves and generally occurs later than epistaxis in the course of the disease.[36] Horses with dysphagia cough during attempts to eat solid food, and, in addition to food material in the nasal discharge, a considerable quantity of food is coughed out the mouth. Recovery from dysphagia may occur,[36] but in general the prognosis for full recovery is poor.

Other clinical signs include parotid pain, abnormal head posture, unilateral or bilateral nasal discharge, head shyness, abnormal respiratory noise from pharyngeal paralysis or laryngeal hemiplegia, sweating and shivering, Horner syndrome, visual disturbances, colic, and facial paralysis.[36,37] These signs are the result of angina and dysfunction of cranial nerves and the sympathetic nervous system.

The differential diagnosis for a horse with epistaxis should include EIPH, ethmoid hematoma, guttural pouch or pharyngeal neoplasia, tracheobronchial foreign bodies, and guttural pouch mycosis.[36] Differentiation of these diseases is aided by a thorough history and endoscopic examination. Differential diagnosis for dysphagia should include fractures of the hyoid apparatus; pharyngeal and guttural pouch fistula; cleft palate; esophagitis; pharyngeal paralysis; foreign body entrapment in the mouth or esophagus; pharyngeal neoplasia; lead poisoning; bacterial, viral, and mycotic central nervous system infections; and guttural pouch mycosis.[36]

Clinical Pathology If epistaxis is the presenting complaint, moderate to severe anemia with accompanying hypoproteinemia may also be present. Differential white cell distributions may be normal or may indicate a stress response. If dysphagia becomes a dominant clinical sign, other hematologic changes indicative of infection secondary to aspiration pneumonia may be evident.

Diagnostic Aids Clinical signs of epistaxis or cranial nerve dysfunction are suggestive of a diagnosis of guttural pouch mycosis. A thorough physical examination may reveal abnormal sensitivity on digital palpation of the parotid area on the affected side.[35] A definitive diagnosis of guttural pouch mycosis requires endoscopic observation of the characteristic diphtheritic lesion in the dorsocaudal aspect of the medial compartment, typically covering over the temporohyoid joint and internal carotid artery, or elsewhere within the guttural pouch.[36] Aneurysm of the internal carotid artery is rarely present. A healed lesion may be identified by presence of scar tissue within the mucous membrane.[36] Lesions vary in color (brown, yellow, black, or white) and size (from discrete nodules to diffuse irregular patches covering the roof of both the medial and lateral compartments)[37]; erosion with fistula formation can occur into the opposite guttural pouch or pharynx. Occasionally the characteristic lesion is obscured by clotted blood, so that the diagnosis is based on the clinical signs of epistaxis correlated with blood present in the guttural pouch. Because hemorrhage may originate from the internal carotid, external carotid, or maxillary arteries, it is important to identify the source of bleeding before therapy, particularly if surgical intervention is being considered. Care should be taken not to dislodge a thrombus and produce further hemorrhage. If dysphagia is apparent, food and saliva may be identified during endoscopy of the pharynx and nasal passages.

In guttural pouch mycotic infections, radiographs are of limited value because only minimum suppuration is associated with mycotic infections; however, a lateral projection may allow assessment of the degree of fibrous reaction and loss of normal air space. Radiography may also aid in diagnosing some of the long-term sequelae, such as fibrous deposits in the pouch and associated bony changes.

Serum titers to *A. fumigatus* are not diagnostic; however, reactivity to 22-kd and 26-kd serum antigens measured by immunoblot analysis may be diagnostic for guttural pouch mycosis.[39]

Pathophysiology The pathogenesis and predisposing factors leading to guttural pouch mycosis and arterial erosion are unknown, but it is believed that the disease is initiated by some stress (inflammation, trauma, vascular insult) to the soft tissues where the mycotic plaques are generally found.[37] Aneurysm formation is not well correlated with the severity of the plaque formation. Although the nature of the initiating lesion remains unclear, it is generally agreed that the later stages are associated with deep fungal infections.[37] *A. nidulans* and other *Aspergillus* spp. have been isolated and may be the causative agents[37-41]; *A. nidulans* is rarely pathogenic but may grow as an opportunist in the warm humid environment of the guttural pouch.[37] The mycotic lesions show no predilection for either the right or the left guttural pouch.[36] Fungal infection of the pouch, erosion of major blood vessels, and involvement of nerves (IX, X, XI, XII, cranial cervical ganglion, and postganglionic sympathetic fibers) that traverse the area explain the epistaxis, local pain, and neurologic signs associated with guttural pouch mycosis.[36,37]

Epidemiology No apparent age, sex, breed, or geographic predispositions have been observed. Guttural pouch mycosis is a sporadic disease that tends to arise during the warmer months of the year and rarely affects more than one horse in a particular stable.[36] Affected horses are afebrile; infection is diagnosed when clinical signs such as epistaxis and dysphagia occur, although nasal discharge is often the earliest reported sign.[36]

Necropsy Findings Lesions are confined to the pharyngeal muscles, guttural pouch, and bones of the skull.[35] Gross findings may include large blood clots in the nasal passages and at the pharyngeal opening of the guttural pouch. Unilateral denervation atrophy of the ipsilateral pharyngeal or laryngeal muscles may occur if there is involvement of the pharyngeal and recurrent laryngeal branches of

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the vagus nerve.[35] Examination of the guttural pouch generally reveals clotted blood and a diphtheritic plaque in the dorsocaudal aspect of the medial compartment that is firmly adherent to the underlying tissue and is clearly demarcated from surrounding tissue.[37] The lesion may be localized or may affect the entire roof of the pouch. If hemorrhage has occurred, the lesion may be obscured by clotted blood, pus, or mucus.[37] An intense inflammatory reaction may be evident in response to acute fungal infection, whereas the inflammation may subside with chronic healing lesions so that scar tissue is evident.[37] Active inflammation may also predispose to osseous lesions of the petrous temporal and stylohyoid bones.[35,37] Some cases of guttural pouch mycosis may not have associated clinical signs and may only be diagnosed on necropsy.[36]

Treatment and Prognosis Without treatment a poor prognosis is warranted, because affected horses are at risk for a fatal episode of epistaxis. Both medical and surgical treatments have been recommended, with variable results; however, surgical treatment by an intraarterial occlusion technique is generally considered to yield the best prognosis.[43-45] Spontaneous regression of guttural pouch mycosis can occur and must be considered when the various medical or surgical treatments are being evaluated.[36]

Medical treatment is topical therapy of the mycotic lesion through the pharyngeal opening of the guttural pouch by means of a catheter. Bathing the lesion may be facilitated by anesthetizing the horse and positioning it in dorsal recumbency. Instilling fungicidal and fungistatic drugs, topical enzymes, and organic iodine compounds into the guttural pouch has been attempted with variable success.[46,47] The necessity and efficacy of these treatments are unknown, and systematic treatment is hampered by a lack of knowledge of the pathogenesis of guttural pouch mycosis.[48] Parenteral administration of antibiotics, corticosteroids, thiabendazole, ketoconazole, and iodine compounds also has questionable efficacy.[48] The response of guttural pouch mycosis to local and parenteral treatment is protracted; thus the risk of fatal hemorrhage exists long after initiating treatment.[49,50]

Surgical treatment of guttural pouch mycosis appears to offer the best prognosis for eventual cure. The internal carotid artery is not an end artery, and blood can enter this vessel from the bifurcation of the common carotid or return from the cerebral arterial circle. Various surgical techniques have been described,[1] and use of a balloon-tipped catheter inserted into the distal internal carotid artery combined with proximal ligation of the internal carotid artery,[49-51] transarterial coil embolization,[44,52,53] or transarterial nitinol vascular plugs[54] induces thrombus formation and prevents hemorrhage from normal and retrograde blood flow. Thrombosis sufficient to prevent hemorrhage may develop in the distal internal carotid artery within 10 days of catheter placement.[51] Mucosal healing and complete regression of the fungal plaque have been reported to occur as early as 5 weeks after arterial catheterization[49] and as early as 15 days after coil embolization.[44] Insertion of a balloon-tipped catheter successfully prevented fatal epistaxis in 13 horses.[49] Topical or systemic treatment of the mycotic plaque is considered unnecessary after arterial catheterization.[49] Intraarterial insertion of latex balloons, embolization coils, or nitinol vascular plugs also results in lesion resolution,[54-57] although progression of a mycotic plaque after coil embolization and subsequent development of neurologic signs have been reported.[58] Complications associated with each of these arterial occlusion techniques have been reported.[59]

Diseases of the Paranasal Sinuses

Sinusitis

John R. Pascoe

Definition and Etiology *Sinusitis,* inflammation of the paranasal sinuses, results from primary microbial infection or from secondary bacterial infection associated with dental or other sinus disease. Lined by respiratory mucosa, the paranasal sinuses are at risk for developing diseases affecting the respiratory tract. Sinus empyema, accumulation of pus within a sinus cavity, may result from bacterial or viral infection.

Incidence of sinusitis is relatively low, likely less than 0.5% of disease in equine practice.[1] In two longitudinal retrospective studies, covering 25 years, of 477 horses referred with sinonasal disease, the distribution of causes was primary sinusitis (subacute or chronic; 33%), dental-associated sinusitis (21%), sinus cysts (13%), sinonasal neoplasia (7%), ethmoid hematoma (6%), sinonasal trauma (6%), mycotic lesions (4%), dental-related oromaxillary fistula (3%), and miscellaneous causes (6%).[2,3] The caudal maxillary, rostral maxillary, ventral conchal, and conchofrontal sinuses are more commonly involved, and the sphenopalatine sinus is affected less often.[4] The median age of horses affected with sinonasal disease is 7 to 11 years.[2]

Acute or chronic upper respiratory tract infections of viral or bacterial origin can result in primary sinusitis; *Streptococcus* spp. infection is the most common. Maxillary sinusitis caused by disease of the third (caudal roots) through sixth cheek teeth (modified Triadian numbers 109 to 111, 209 to 211) often results from alveolar periostitis, patent infundibula, fractured or split teeth, or deep diastemata between caudal maxillary teeth. Dental defects can permit access of food material or bacteria to the tooth root and sinus cavity, with extension to the frontal sinus likely through the frontomaxillary opening. Reported neoplasms include osteoma, osteosarcoma, adenocarcinoma, lymphosarcoma, squamous cell carcinoma, neuroendocrine tumors/neuroblastoma, fibroma, and chondrosarcoma.[5-7]

Clinical Signs and Differential Diagnosis Signs vary depending on cause, location, and extent of sinus involvement, with unilateral nasal discharge (serous, mucoid, mucopurulent, purulent) being the most frequent sign.[2,3] Physical examination of a horse with sinusitis should include observation for epiphora, facial asymmetry, altered nasal airflow, abnormal breath odor, mandibular lymphadenopathy, and sinocutaneous fistula.

Nasal discharge is typically unilateral because the nasomaxillary opening is located rostral to the caudal edge of the nasal septum. Intermittent or continuous nasal discharge need not be related to a previous upper respiratory tract infection. Although malodorous discharge is commonly associated with dental sinusitis and sinonasal mycosis, it has been reported to occur in 14% to 27% of primary sinusitis cases.[2,3] Mucopurulent discharge is more commonly associated with sinus cysts.[2] Sanguineous discharge is common with ethmoid hematoma and sinonasal trauma; however, guttural pouch mycosis, pulmonary hemorrhage, nasal turbinate necrosis, and neoplastic or granulomatous lesions should also be considered. Other differential diagnoses of nasal discharge should include guttural pouch empyema or mycosis, acute pharyngitis (strangles, rhinopneumonitis, influenza, trauma), neoplasia or necrosis of the turbinates, ethmoid hematoma, and pulmonary disease.

After nasal discharge, submandibular lymphadenopathy is the most common sign, particularly when microbial infection is a component of sinusitis.[3] Facial swelling occurs with frequency similar to that of lymphadenopathy, typically when sinus drainage is obstructed, there is an expansile mass within the sinus, or as an acute sign after facial trauma. Occasionally exophthalmos can occur with marked sinus distortion.

Patency of the nasomaxillary opening generally precludes facial distortion. Loss of patency occurs when inspissated exudate accumulates or mucosal lining tissue reaction obstructs the opening. Expansion of the sinus may result in reduced ipsilateral nasal airflow caused by distortion of the architecture of the nasal passages. In these cases abnormal respiratory noise rather than nasal discharge may be the primary presenting sign.

Epiphora occurs if there is nasolacrimal duct involvement from trauma, compression, or destruction of the duct from underlying sinus disease. Approximately 20% to 50% of horses with dental sinusitis, sinus cyst, or sinonasal trauma have epiphora as a presenting sign.[2,3]

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Percussion of the affected sinus may reveal dullness or pain, although normal resonance does not preclude the possibility of sinusitis. If there is bone thinning over gas above a fluid line (as can occur with some maxillary sinus cysts), percussion may elicit increased resonance.

Careful examination of the oral cavity for signs of dental or periodontal disease should be performed when any of these signs are present. Particular attention should be paid to examination of the occlusal surface of the teeth with a very fine dental pick (e.g., 22-gauge needle); however, it should be recognized that periapical abscess formation can occur without defects in the occlusal surface. Accuracy of diagnosis of dental disease is substantially enhanced by use of intraoral endoscopy and computed tomography.

Clinical Pathology The hemogram generally remains within the normal range, although acute sinusitis of infectious origin may be associated with neutrophilia. With chronic sinusitis there may be concurrent hyperfibrinogenemia. Sinus fluid obtained by percutaneous centesis should be examined cytologically (including a Gram stain) and submitted for microbial culture and susceptibility testing to differentiate among bacterial, fungal, and neoplastic disease. Flecks of feed material indicate sinusitis secondary to dental abnormalities.

Laboratory Aids and Definitive Diagnostic Tests A presumptive diagnosis of sinusitis can be made from the physical examination and associated clinical signs.[2,3,8] Procedures most helpful in establishing a diagnosis are sinonasal endoscopy, oral cavity examination, imaging (radiography, computed tomography [CT], scintigraphy, magnetic resonance imaging [MRI]), sinus centesis, and sinoscopy.[4,8]

Nasal cavity endoscopy may permit identification of exudate draining from the nasomaxillary opening or, in advanced cases, may reveal distortion of the nasal cavity secondary to sinus enlargement. Middle meatus examination is an important component of endoscopic examination. Diagnosis beyond recognition of the potential source of the nasal discharge is limited unless an obvious mass or abnormal tissue is observed. Sinoscopy can be accomplished by using an arthroscope[9] or flexible endoscope[10] inserted through small trephine holes in either the maxillary or the frontal sinus. Examination of the rostral compartment of the maxillary sinus requires a separate portal unless the bony septum between the rostral and caudal compartments has been destroyed. Observation may be limited by fluid or tissue, especially in the rostral compartment of the maxillary sinus, but can potentially be enhanced after sinus lavage and aspiration. Alternately, fenestration of the ventral conchal bulla can be used to facilitate endoscopy of the rostral compartment of the maxillary sinus.[4]

Standard radiographic projections include standing lateral, dorsoventral, and right and left oblique views.[11,12] Radiographic findings include fluid lines within the sinus, space-occupying soft-tissue densities, areas of decreased bone density, fractures, or dental abnormalities. Dental root disease is identified radiographically by a loss of continuity of the lamina dura and lysis of the tooth root or surrounding bone, combined with new bone formation and cement deposition.[11] Anatomy of normal equine skulls as demonstrated by CT and MRI has been described.[13-15] Diagnostic accuracy, especially determination of the extent of involvement of structures within the skull, can be enhanced by CT.[16,17] MRI may be useful in some sinonasal disorders.[18]

Findings associated with dental caries include hypoattenuation of cementum, destruction of enamel, and filling of the infundibular cavity with gas, whereas with dental decay there is gas accumulation in the root area or fragmentation of the root, and sinus mucosal thickening. Additional changes with sinusitis typically involve the maxilla with endosteal sclerosis, thickening, periosteal reaction, and deformation, especially involving the facial crest.[17] Scintigraphic examination may improve specificity in identification of dental involvement in sinusitis.[19]

Percutaneous sinus centesis may provide a definitive diagnosis and allow an avenue for subsequent therapy. Cytologic evaluation, with concurrent microbial culture and antibiotic susceptibility testing, may elucidate the cause of the sinusitis. Isolation of a single organism such as *Streptococcus* spp. generally indicates a primary sinusitis, whereas polymicrobial infection is more compatible with sinusitis of dental origin. Visual examination of the oral cavity, especially intraoral endoscopy, and careful probing of the occlusal surfaces with a dental pick may help practitioners identify dental abnormalities.

Necropsy Findings Affected sinuses contain fluid or tissue of variable color and consistency. Fluid character ranges from clear and odorless with cystic sinus disease to white, yellow, or green purulent fluid with a variable, but often putrid, odor in sinusitis resulting from other causes. Sinusitis of dental origin has a characteristically pungent and unpleasant odor. Granulomatous lesions often appear as large lobular gelatinous masses filling the sinus cavity. The gross appearance of neoplastic lesions within the sinus cavity depends on the type of neoplasm. Neoplasia may cause surrounding soft-tissue and bony destruction, whereas large, benign space-occupying lesions may result in distortion of the nasal turbinates and nasal septum, as well as external facial bone distortion.

Treatment and Prognosis Not infrequently, horses with a chronic mucopurulent nasal discharge from sinusitis have a history of response to antimicrobial therapy, followed by recurrence of the discharge after antibiotic therapy ceases. Definitive diagnosis of sinusitis can be accomplished using the techniques described earlier. Sinoscopy permits examination of the paranasal sinuses and, in some instances, facilitates treatment.[20-22]

Suggested treatment for primary sinusitis or empyema involves daily lavage of the sinus through a percutaneous centesis site with 1 L of saline, to which a broad-spectrum antibiotic or antiseptic has been added. Once the results of culture and susceptibility testing are available, the appropriate antibiotic should be administered locally in the flush solution, as well as systemically, for 14 days. Resolution or reduction in the volume of nasal discharge is an indication of successful therapy. Sinus lavage often fails to remove inspissated material, which is often the nidus for continuing sinusitis and must be removed for resolution.[8] If little progress is made after 10 to 14 days of lavage or if drainage recurs, sinusotomy (trephination or bone flap technique, standing or recumbent anesthetized) is recommended to remove inspissated material[22] or identify other causes. The prognosis is generally favorable if primary sinusitis is not chronic and if the mucous membrane is not markedly thickened.[21,22] Chronic sinus disease (longer than 6 months) carries a poor prognosis, and, for resolution to occur, surgical removal of the thickened, infected mucous membrane is required; creation of sinonasal drainage by sinus fenestration is also recommended.

Sinusitis that results from secondary factors is generally not responsive to medical management. Such conditions include diseased teeth, granulomas, or neoplasia; surgical removal of the inciting cause is required, and adjunctive treatment may be required. The prognosis for sinusitis associated with dental abnormalities is usually favorable once the diseased tooth has been removed.[21,22] Complications are lower with oral extraction rather than repulsion of diseased teeth.[22] Generally, failure of oral extraction and subsequent tooth or tooth fragment repulsion results in lower morbidity than initial repulsion.[22] If the periodontal ligament is intact, endodontic therapy can be used to save the tooth. This is accomplished by surgical apicoectomy and retrograde occlusion of the root canal after débridement of the pulp. In geriatric horses with dental-associated sinusitis, when economic constraints limit surgical options, sinusotomy and periodic sinus lavage and antibiotic therapy have been used successfully to manage nasal discharge.

The prognosis for resolution of granulomatous lesions is generally guarded and depends on surgical access and extent of the lesion. Neoplastic lesions are often well established and have metastasized,

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either locally or regionally, by the time they become clinically apparent; the prognosis for resolution is generally guarded to poor.[4]

Prevention and Control Prevention of sinusitis in horses is difficult because of the variety of causes. Isolation of horses from those with upper respiratory bacterial or viral diseases may be of benefit in preventing primary sinusitis. Regular dental care and a proper diet may help circumvent sinusitis caused by dental abnormalities, although many cases most likely result from a variety of causes not yet defined or over which the owner or veterinarian has no control.

Ethmoid Hematoma

John R. Pascoe

Definition and Etiology Ethmoid hematomas (*progressive ethmoidal hematoma*[1]; *hemorrhagic nasal polyps*[2]) are slowly expanding angiomatous masses (median dimensions: 3.8 × 9 × 13 cm)[3] originating principally from the mucosal lining of the ethmoid conchae. Smaller hemangiomas arising from the mucosal lining of the frontal, maxillary, and sphenopalatine sinuses have been recognized, but the relationship between these benign endothelial tumors and ethmoid hematoma remains uncertain. Ethmoid hematoma is a relatively uncommon condition of unknown cause. Distinctly different histologic features characterize ethmoid hematoma and paranasal sinus cysts,[4] which makes it unlikely that these lesions are variants of each other with a common cause.[5] Although ethmoid hematomas have been reported in a 4-week-old foal and in 3-year-old horses, most affected horses are older than 8 years and are generally Thoroughbred, Arabian, or warmblood horses[6,7]; males (geldings) seem to be more commonly affected.[3]

Clinical Signs A blood-tinged nasal discharge with intermittent epistaxis from one or both nostrils is the most common clinical sign. Unilateral or bilateral, epistaxis varies from blood-tinged mucoid or mucopurulent discharge to blood spots or a trickle of blood; fulminant or fatal epistaxis is uncommon. If the hematoma occupies the choana(e) or nasal cavity, a mucopurulent, occasionally malodorous nasal discharge with some blood discoloration is more commonly seen. Typically there is a history of abnormal respiratory noise, both inspiratory and expiratory, especially during exercise. With nasal cavity involvement, airflow may be reduced or absent on the affected side. Facial distortion or asymmetry is uncommon and more likely to occur with involvement of the frontal and maxillary sinuses. Secondary mycotic infections and empyema may be associated with intraparanasal sinus ethmoid hematoma.[8] Less commonly there may be an associated history of coughing, choking, ptyalism, increased respiratory effort during resting breathing, and either head shyness or headshaking.[1] If the hematoma has expanded into the paranasal sinuses, percussion yields a dull sound.

Laboratory Aids and Definitive Diagnostic Tests Confirmation requires endoscopy of the ethmoid conchae and diagnostic imaging (Figs. 31-52 and 31-53). Although survey radiography is useful to identify the mass, its origin and extent are delineated more accurately with CT, which is also more reliable than a combination of clinical examination, endoscopy, and conventional radiography.[3] Limited information is available to assess the value of magnetic resonance imaging for diagnosis of ethmoid hematoma.[9] In the absence of CT, sinoscopy may be of diagnostic value when the ethmoid hematoma involves the paranasal sinuses without nasal cavity protrusion. Rarely, ethmoid hematoma infiltrates the nasal conchae; these lesions, identifiable by CT, may be missed on sinoscopy. Definitive localization of ethmoid hematoma involving the sphenopalatine sinus is not likely to be achieved through use of radiography or sinoscopy.[3]

Ethmoid hematomas are bilateral in 30% to 50% of affected horses, so it is prudent to examine both ethmoidal conchae. The

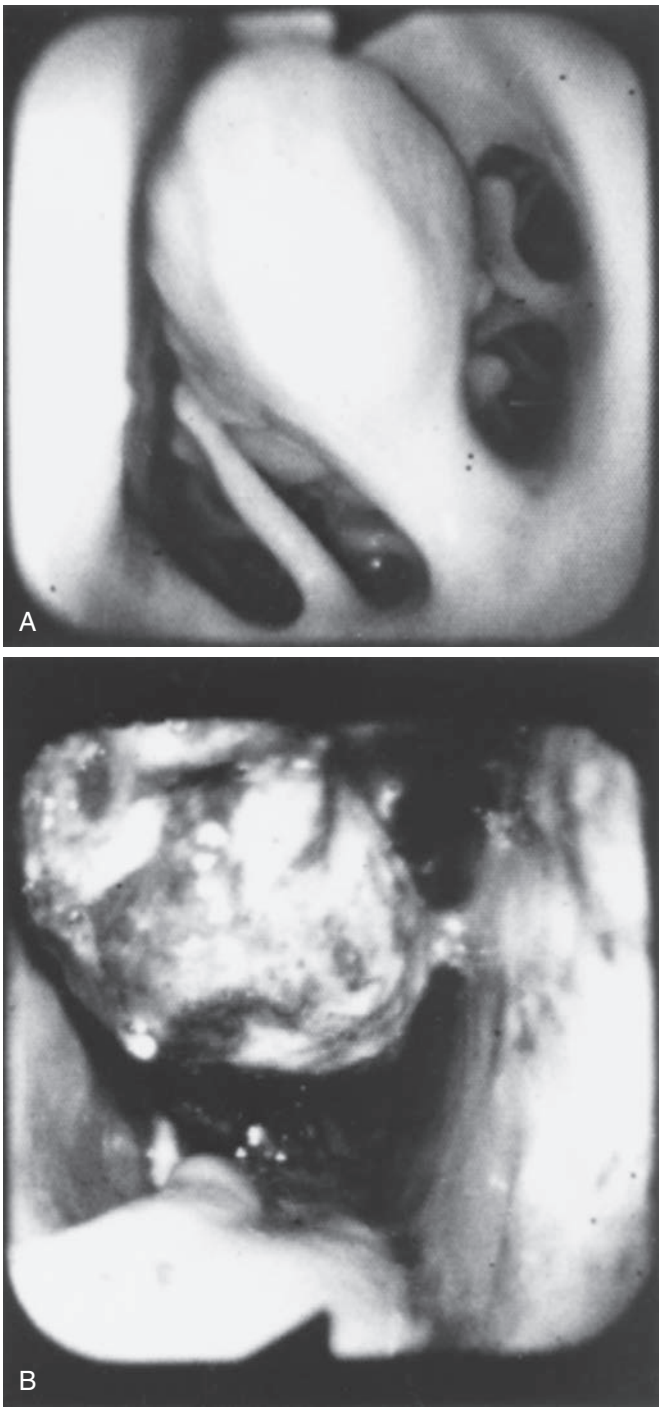


FIG. 31-52 Endoscopic view of left ethmoturbinate. **A,** Normal appearance. **B,** Ethmoturbinate obscured by an ethmoid hematoma.



FIG. 31-53 Lateral radiograph demonstrating an ethmoid hematoma.

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ethmoidal labyrinth is visible approximately 25 cm from the nares, with the endoscope positioned in the ventral nasal meatus and the viewing tip deflected dorsally. The rostral surface of the ethmoidal concha does not protrude beyond the caudal aspect of the nasal cavity; it has a bulbous shape and a moist pink to pale red mucosal covering. Distal to the rostral surface are numerous pillars that form the ethmoidal conchae and separate the ethmoidal spaces (cellulae ethmoidales). Ethmoid hematomas that project into the ventral meatus or through the choana into the nasopharynx often obscure the ethmoidal concha. Unilateral ethmoid hematomas that expand into the nasopharynx may extend into the contralateral ventral meatus and obscure that ethmoidal labyrinth.

The origin of hematomas that expand dorsally into the frontal sinus may not be visible on endoscopy, but hemorrhage that originates deep to the visible portion of the ethmoidal conchae may be evident or noticed from the region of the nasomaxillary opening in the middle meatus. Visible ethmoid hematomas vary in color from deep red to red-purple or may have a yellow-brown or yellow-green-brown to bronze color. The surface is irregularly rounded, with small punctate hemorrhages or erosions, and may be partially covered in yellow-white mucopurulent material that may be admixed with blood. Often the floor of the ventral meatus and regions of contact with the nasal cavity have pooled exudate (blood and mucopurulent matter). Manipulation of the hematoma surface with the endoscope may cause bleeding or oozing.

Radiographic recognition of a discrete, often smooth-surfaced homogeneous radiodensity originating from the ethmoidal conchae and extending into the frontal, maxillary, or sphenopalatine sinuses, or into the pharynx or nasal cavity, is suggestive of ethmoid hematoma. Precise definition of the hematoma origin is difficult to determine from radiographic projections, and small hematomas contained within the ethmoid labyrinth may not be visible.

CT examination allows more accurate assessment of the origin of the ethmoid hematoma,[3] allows determination of the extent of involvement of the paranasal sinuses (especially the sphenopalatine sinus) and conchae, and facilitates surgical planning. On CT scans, masses are often associated with bone destruction, especially of the ethmoturbinates and infraorbital canal, and typically abut the cribriform plate in 50% of cases. Masses commonly have mild to moderate signal heterogeneity and a hyperdense swirling appearance consistent with recent hemorrhage or mineralization, which are also common morphologic features.[3]

Necropsy Findings Morphologic features have been described from surgical specimens, but few skulls with intact ethmoid hematomas have been examined.[2,3] Except in regions with necrosis or secondary infection associated with contact with the sinus or nasal cavity walls, the hematoma is a smooth-surfaced saclike structure containing blood in various stages of organization. The sac lining is generally healthy respiratory mucosa originating from a pedunculated region of the mucosal covering of the ethmoturbinate or sinus wall. On section, contents are amorphous red-black to chocolate brown, and in larger masses some evidence of irregular compartmentalization by fibrous tissue exists, especially on the inner surface of the sac.

Morphologic features include an outer covering of respiratory epithelium (flattened columnar or cuboidal ciliated epithelium containing glands, and occasionally stratified squamous epithelium[4]) overlying an irregular zone of submucosal fibrous tissue, containing hemosiderophages, occasional plasma cells, and lymphocytes, less commonly neutrophils, that forms a pseudocapsule around hemorrhage in varying states of organization. There is variable organization of the fibrous tissue components. Endothelial cells do not show evidence of neoplasia. Thin endothelium-lined sinuses are often present within the myxomatous stroma. The respiratory epithelium is sometimes focally ulcerated and infiltrated with neutrophils, and occasionally there are squamous metaplastic changes. Ethmoid adenocarcinoma with a similar gross appearance to that of ethmoid hematoma has been reported.[3,10]

Treatment and Prognosis Ethmoid hematomas slowly and progressively increase in size and can cause skull distortion if there is paranasal sinus involvement, so removal is recommended. Treatment method depends on location and size. Surgical ablation has been the preferred method; however, destruction of the hematoma by intralesional injection of formaldehyde solution is associated with less morbidity, although recurrence rates are similar to those achieved through other methods.[6-8,11,12] Surgical access is achieved by sinusotomy and then hematoma ablation by curettage, cryosurgery, or use of an Nd:YAG laser[12]; photoablation can be achieved through the biopsy channel of an endoscope. After sinusotomy, the pedunculated origin of the hematoma is identified by digital palpation and then dissected, frozen, or photoablated, and the hematoma removed. If the hematoma is friable, intact removal may not be possible, and hemorrhage may make observation of the origin of the mass difficult. After removal, the paranasal sinuses and nasal cavity are packed with gauze to control postoperative hemorrhage.

Surgical curettage can be associated with marked intraoperative blood loss typically from the turbinates or sinus mucosa rather than the hematoma. Temporary occlusion of both carotid arteries[13] can reduce blood loss until the sinus cavity is packed with gauze. Blood loss is minimized with cryosurgical extirpation and photoablation techniques, but these approaches are not always practical with large hematomas. Although blood loss is minimal with transnasal photoablation, this technique requires multiple procedures to destroy large masses but can be performed in the standing sedated horse. Photoablation (Nd:YAG laser, 100 W in noncontact technique) is effective in controlling remnants after surgical extirpation or subsequent regrowth.[14]

Destruction of ethmoid hematomas by endoscopically guided intralesional injection of formalin in standing sedated horses may reduce the need for surgical ablation.[11,15] A catheter passed through the endoscope biopsy channel is advanced through the rostral surface of the mass toward its origin, then 10% formalin (4% formaldehyde solution) is injected intralesionally. Commercially available catheters with a beveled needle tip are available, but relatively stiff plastic tubing that slides through the biopsy channel will penetrate the hematoma capsule. Sufficient volume (10 to 100 mL) is injected until fluid leaks back alongside the catheter or from the mass. For visibly pedunculated masses, formalin should be injected at the origin or neck of the mass. Tissue necrosis and slough occur within 5 to 10 days and may be associated with nasal discharge. Repeat injections, typically at no longer than 10- to 14-day intervals, may be needed to destroy the mass. Removal of necrotic tissue can be facilitated by use of long grasping forceps and hydropulsion. Mycotic plaques may cover the treated site during healing but typically resolve without treatment; endoscopically delivered topical natamycin has been used if mycotic plaque is extensive and associated with malodorous, purulent discharge.[16] If the hematoma has a paranasal sinus extension, necrosis of that tissue within the sinus, after destruction of the ethmoturbinate origin of the hematoma, may result in sinus empyema, mycotic infection, or both,[9] requiring ancillary treatment.

Occasionally progression of the ethmoid hematoma may result in weakening or loss of the cribriform plate or roof of the sphenopalatine sinus.[16] During mass removal, loss of this protective bony covering may result in intraoperative or postoperative neurologic complications. Recognition of loss of the integrity of these bony plates may not occur until sinus lavage. In a rare complication, death occurred following intralesional formalin injection in a horse where the cribriform plate had been eroded by the ethmoid hematoma.[17] Erosion of calvarial bone is rare, but careful computed tomographic evaluation of these regions in horses with extensive hematoma formation involving the frontal or sphenopalatine sinuses is warranted.[3]

Irrespective of treatment method, recurrence of the hematoma occurs in 17% to 50% of cases from several months to years after the initial surgery.[2,3,6-8,11,12,16] Increased use of CT to guide surgical planning and for postoperative evaluation is likely to contribute to a reduction in recurrence rates.

Disorders of the Equine Soft Palate

Safia Z. Barakzai • Padraic Martin Dixon

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Anatomy and Physiology of the Soft Palate The equine soft palate extends caudally from the hard palate and completely divides the pharynx into nasal and oral compartments. Because the horse is an obligate nasal breather, the caudal border of the soft palate normally fits snugly around the base of the epiglottis and the palate remains in this subepiglottic position at all times except during deglutition. The soft palate consists of the oral mucous membrane, palatine glands, palatine aponeurosis, palatal muscles, and nasopharyngeal mucosa. The soft palate is relatively thick (>2 cm) rostrally and tapers caudally as the amount of glandular tissue within it reduces considerably.[1] The paired muscles that control palatal position include the palatinus muscles (running rostrocaudally on either side of midline); the palatopharyngeus muscles (running from the palatine aponeurosis and lateral aspect of the palatinus, sweeping laterally up the walls of the nasopharynx); the tensor veli palatini muscles, which tense the rostral aspect of the soft palate; and the levator veli palatini muscles, which elevate the soft palate during deglutition.

Endoscopically, the dorsal aspect of the soft palate forms the floor of the nasopharynx and has longitudinal ridges that become more apparent when the palate is flaccid. Horses that resent endoscopic examination of the respiratory tract often tense their soft palate, giving its rostral aspect a dorsally "domed" appearance.

Dysfunction of the soft palate presenting as dorsal displacement of the soft palate or palatal instability at fast exercise is by far the most frequent palatal abnormality that clinicians are presented with in equine practice. Other palatal disorders are relatively uncommon.

Dorsal Displacement of the Soft Palate and Palatal Instability

Palatal dysfunction, which includes the two syndromes of dorsal displacement of the soft palate (DDSP) and palatal instability (PI), is the most commonly diagnosed cause of upper airway obstruction in racehorses (reported prevalence around 10% to 20%[2,3]). It also occasionally affects other types of horses, particularly those that are exercised with their head and neck in a flexed position, such as dressage horses, showjumpers, and Saddlebreds.[4,5] Intermittent DDSP is a disorder that characteristically occurs in horses toward the end of fast work, when the caudal border of the soft palate becomes displaced dorsal to the epiglottis (Fig. 31-54). A definitive diagnosis of intermittent DDSP or palatal instability can be made only with the use of exercising endoscopy. Palatal instability is seen as wavelike dorsal billowing of the rostral and caudal soft palate but without actual displacement of the caudal border of the soft palate dorsal to the epiglottis. Palatal instability commonly precedes DDSP.[6-9] Swallowing may temporarily halt PI, but instability usually recurs within a few seconds in affected horses and may progress to true DDSP. As the soft palate billows dorsally, it may lift the epiglottis, changing the epiglottic conformation and cause the aryepiglottic folds to deviate axially.[9,10] It is unclear what degree of soft palate instability is "normal" and what percentage of horses diagnosed with PI would experience DDSP under different conditions, such as racing. When PI is observed in isolation, it has been described as equivalent to a "presumptive" diagnosis of DDSP[11] and has also been suggested as a "prodromal" sign of impending DDSP.[9,12]

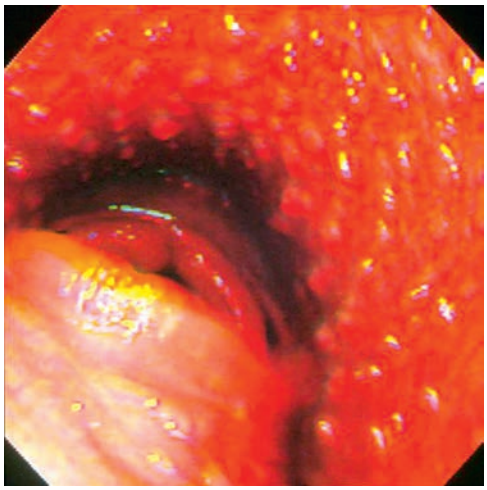


FIG. 31-54 Dorsal displacement of the soft palate seen in a horse undergoing exercising endoscopy, with marked airflow obstruction.

Rostral palatal instability is another form of palatal instability that has been reported in horses and ponies and is associated with neck flexion during exercise.[13,14] As the name suggests, the condition is characterized by dorsoventral billowing confined to the rostral soft palate. Rostral palatal instability causes inspiratory nasopharyngeal obstruction and respiratory noise. This condition has been produced experimentally by bilateral tensor veli palatini tenectomy.[15]

Pathophysiology Horses that have other abnormalities of the palate or larynx, such as epiglottal entrapment, pharyngeal paralysis, or palatal cysts, are predisposed to DDSP. The cause of the disorder in horses without such abnormalities is currently unknown. Research efforts have focused on determining the pathophysiology of DDSP in an attempt to improve understanding of the condition, with the ultimate goal of developing more effective treatments.[15-20] Current theories include neuromuscular dysfunction of the intrinsic soft palate muscles,[20-22] variations in positioning of the laryngohyoid apparatus,[19,23] and the role of the distal hypoglossal nerve in maintaining nasopharyngeal stability.[24] Epiglottic hypoplasia or flaccidity was previously thought to be associated with intermittent DDSP. However, clinical and experimental data show that the epiglottis is not required to maintain the palate in a normal position and that the majority of horses that experience DDSP during treadmill endoscopy have an epiglottic length that is within normal limits.

Clinical Signs Most horses with DDSP make a "gurgling" noise during exercise and may either pull up abruptly or slow down significantly after the palate has displaced. DDSP results in a flow-limiting expiratory obstruction leading to decreased airflow, increased tracheal expiratory pressure and impedance, reduced minute ventilation and subsequent hypoxia, hypercapnia, and impaired athletic performance.[17,25,26] Conversely, once the palate has displaced, minimal obstruction is observed during inspiration, as the upper airway inspiratory pressure maintains the soft palate in close apposition to the dorsal aspect of the epiglottis. During expiration, because a proportion of the exhaled air is directed ventral to the displaced palate and into the oral cavity, some horses are reported to exhibit "fluttering" of the cheeks during exhalation. Palatal instability has also been shown to have a negative effect on ventilatory parameters if moderate to severe.[27] Low frequency fluttering of the caudal border of the palate is believed to be the source of the loud expiratory and inspiratory gurgle or "snore" reported in 70% to 80% of affected horses[28]; however, up to 30% of horses can experience DDSP yet make no audible abnormal respiratory noise (these cases are referred to as "silent displacers").[29-31]

Diagnosis An accurate history, including details of reduced exercise performance, abnormal noise production, type of noise made, and stage of exercise when the noise occurred, can be very helpful. A thorough resting endoscopic examination of the nasopharynx should be performed to rule out other causes of palatal dysfunction, such as pharyngeal or palatal cysts, epiglottic entrapment, or pharyngeal paralysis. DDSP and PI are dynamic conditions, and findings of resting endoscopy have been shown to correlate poorly with

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dynamic endoscopic findings.[12,30,31] Horses that displace their soft palates at rest are often normal during exercising endoscopy, and conversely, many horses that are normal during resting endoscopic examination can develop DDSP at exercise.[30] One study reported that use of a characteristic history and findings at resting endoscopy alone resulted in a 35% misdiagnosis rate of palatal dysfunction as compared with findings of treadmill endoscopy.[31]

High-speed treadmill videoendoscopy has been the gold standard for diagnosis of DDSP and PI for the past 20 years.[6-8,12,31] The recent development of portable telemetric endoscopic systems used in horses undergoing ridden exercise provides an alternative method of visualizing the upper respiratory tract during exercise.[3,32,33] Clinically normal horses may transiently displace their soft palates during exercise, particularly when pulling up. However, a normal horse typically swallows and replaces the palate to its normal subepiglottic position within a few breaths, whereas DDSP is typically diagnosed if the palate remains dorsal to the epiglottis for a longer period of time, or if DDSP occurs repeatedly.

Sound analysis has been used as a research tool for diagnosis of DDSP[29]; however, given that up to 30% of horses are known to be silent displacers, the level of false-negative diagnoses made using sound analysis may be reasonably high. A significant relationship has recently been reported between the depth of the basihyoid bone measured using percutaneous ultrasonography at the caudal aspect of the lingual process at rest and the occurrence of DDSP at exercise.[34] A more ventrally located basihyoid at rest was associated with an increased probability of DDSP occurring during treadmill endoscopy. This test had a high negative predictive value (89%) but a low positive predictive value (36%), meaning that DDSP could be ruled out with reasonable certainty using laryngeal ultrasound, but care should be taken when making a positive diagnosis of DDSP using this method.

Treatment Many treatments are available for horses with DDSP, and this probably reflects both the unknown cause(s) of the disorder and the fact that most treatments have a similar success rate. Concurrent respiratory disorders, including upper or lower airway inflammation or infections, should be addressed fully before resorting to surgical remedies. The use of systemic corticosteroids, nonsteroidal antiinflammatory drugs, and topical antiinflammatory nasopharyngeal ("throat") sprays have been advocated to try to reduce upper airway inflammation.[2,30] Tack changes, including use of a tongue tie,[35] dropped or crossed noseband,[35-37] and "W" or Serena Song bits, have also been reported to be of benefit in affected racehorses. The laryngohyoid support device (Cornell collar) has been advocated as a nonsurgical "tie-forward" procedure for horses with DDSP and was effective in 100% (7 of 7) of horses with experimentally induced DDSP.[38] Results of the Cornell collar in horses with naturally occurring DDSP are not available.

Surgical treatments for DDSP are numerous and include insertion of a thyrohyoid prosthesis (the tie-forward or laryngohyoid reduction procedure), staphylectomy, myectomy of the sternothyrohyoideus muscles, epiglottic augmentation with Teflon, tension palatoplasty, thermocautery of the oral surface of the palate, laser cautery of the nasopharyngeal surface of the palate, in addition to multiple combinations of these procedures. A systematic review of treatments for palatal dysfunction in the horse concluded that there currently is no clearly superior treatment for DDSP.[39] The use of combinations of surgeries usually represents a "belt and braces" approach, but it may be argued that this provides a multimodal approach to a disorder with a multifactorial etiology. The use of multiple treatments in scientific studies means that researchers are often left unsure as to which of the reported treatments, if any, may have had a beneficial effect.[39]

Persistent Dorsal Displacement of the Soft Palate

Persistent DDSP, where the soft palate is permanently positioned dorsal to the epiglottic cartilage is rare, compared with intermittent DDSP. It is observed in the resting horse and is usually secondary to underlying structural abnormalities such as subepiglottic cysts, epiglottitis, epiglottic entrapment, intrapalatal cysts, pharyngeal paralysis, pharyngeal neoplasia, or pharyngeal foreign bodies,[13,40] but it can also be idiopathic. Persistent DDSP may also be observed following epiglottic or laryngeal surgery, particularly after surgery to release epiglottal entrapment[41,42] if a large fold of the subepiglottic mucosa is resected. Horses affected with persistent DDSP make a loud gurgling noise at exercise, have poor exercise tolerance, and are often mildly dysphagic.

Diagnosis Diagnosis is easily made by endoscopic examination of the nasopharynx in the resting horse where the epiglottis is not visible because the soft palate lies dorsal to it. Ulceration of the caudal border of the soft palate can sometimes be observed. Observation of persistent DDSP with the scope passed *per nasum* (through the nose) is an indication to perform endoscopy of the oropharynx (with a full dental speculum in place) to examine the epiglottis and associated structures for abnormalities.

Treatment In most cases, persistent DDSP is secondary to some other disorder, and treatment should therefore be directed at the initiating cause. If no primary disorder is found, the tie-forward procedure (laryngohyoid prosthesis) can be done, as it has been reported to be effective in alleviating idiopathic persistent DDSP in 7 of 15 horses in a recent case series.[40] In the same case series, 8 of 15 horses required laser staphylectomy after the tie-forward procedure to resolve persistent DDSP.[40]

Congenital Palatal Defects

Congenital defects of the palate (cleft palate of palatal hypoplasia) are rare in horses, having a reported prevalence of 0.01% to 0.02%.[13] These defects arise from incomplete embryologic closure of the palatal folds and may involve only the caudal aspect of the soft palate (Fig. 31-55), or both the hard and soft palates. Affected foals should be examined carefully for other congenital defects such as cardiac, gastrointestinal, or nasal septum abnormalities.

Clinical Signs and Differential Diagnosis Clinical signs of cleft palate include nasal regurgitation of milk (in foals) or other feed material in older horses, coughing, poor growth, and signs indicative of aspiration pneumonia. If the defect is small, abnormal respiratory noise due to palatal instability or DDSP may be the only presenting sign. Endoscopic examination of the nasopharynx (using a small-diameter endoscope) reveals an abnormal outline to the caudal border of the soft palate and food material within the nasopharynx, larynx, and trachea. Differential diagnoses for dysphagia with aspiration of food material in foals includes subepiglottic cysts,



FIG. 31-55 Congenital midline defect ("cleft") of the soft palate.

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pharyngeal paralysis or dysfunction (which can be transient in neonatal foals[43]), and in older horses, esophageal obstruction (choke), guttural pouch mycosis, severe arytenoid chondritis, complications of laryngeal surgery (e.g., laryngoplasty or arytenoidectomy), and large pharyngeal cysts or pharyngeal/laryngeal foreign bodies or neoplasms.

Treatment Surgical repair is possible for foals with less than 30% of the palatal tissue missing, but this is generally a salvage procedure only, and they may be unable to perform athletically when older, even if surgery is successful.[2] Surgical repair of soft palate defects is challenging and has a high prevalence of complications and failure; therefore, if signs of severe aspiration pneumonia are present, euthanasia of affected foals should be considered as an alternative. Surgical approaches to the soft palate include transoral, pharyngotomy, and mandibular syphysiotomy.[44,45] If signs of the palatal defect are confined to occasional coughing after eating, nasal discharge, or both (i.e., there are minimal or no systemic signs), some affected foals can survive to adulthood and may be capable of ridden work if left untreated or treated symptomatically.[46]

Palatal Cysts

These rare lesions usually occur in young horses and may be a cause of abnormal respiratory noise and airway obstruction if they become large or if they disrupt the normal palatoepiglottic relationship. Palatal cysts probably form as the result of the obstruction of mucus-secreting glands within the soft palate, or they may have a traumatic etiology.[13,47] The presence of palatal cysts predisposes horses to DDSP.

Clinical Signs and Diagnosis Clinical signs include respiratory noise (at rest or during exercise), coughing, exercise intolerance, nasal discharge, dysphagia, and signs of aspiration pneumonia. Diagnosis is made by endoscopic examination of the nasopharynx where a raised intrapalatal mass can be seen. Obtaining an open-mouthed straight lateral radiograph (with the incisors held apart with a gag) will cause the soft palate to move dorsally away from the tongue and allows focal thickening of the palate to be visualized more easily than on a closed-mouth lateral view. Differential diagnoses include palatal neoplasia and intrapalatal abscesses, the latter being usually associated with intrapalatal foreign bodies or strangles infection. Transendoscopically guided aspiration of the cyst should yield clear viscous fluid.

Treatment Treatment involves surgical excision or laser ablation of the cystic structure, if it is large enough to cause abnormal respiratory noise or airway obstruction. If the cyst is simply drained and some of the lining is left in situ, it is likely to recur.

Neoplasia

Neoplasms of the soft palate are rare. Lymphosarcoma and squamous cell carcinoma (Fig. 31-56) occur most frequently, and lesions may vary markedly in appearance. Surgical excision of pharyngeal neoplasms is rarely successful, because total excision with wide margins is almost impossible to achieve. Radiotherapy may provide an alternative for treatment of pharyngeal neoplasms, but it is not widely available for horses.

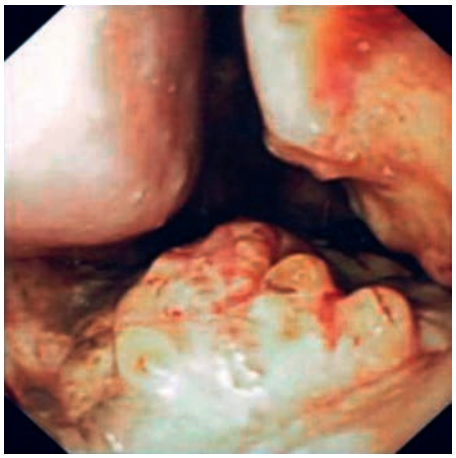


FIG. 31-56 Squamous cell carcinoma of the soft palate viewed at the caudal edge of the nasal cavity, where the hard palate meets the soft palate.

Disorders of the Trachea

Anatomy of the Trachea

The equine trachea extends from the caudal larynx to the carina, where it divides into the two main stem bronchi at the level of the fifth and sixth intercostal spaces. It is about 75 to 80 cm long in a 500-kg horse.[48] The trachea occupies a midline position in the neck and also in the rostral thorax, where it lies in a fold of mediastinum, but at its termination, it becomes slightly displaced to the right by the adjacent aortic arch.[49] It is composed of 48 to 60 individual tracheal rings of hyaline cartilage, which are incomplete dorsally.[48] In the cervical trachea, the free ends of the tracheal rings usually overlap, but in the thoracic trachea, they rarely meet.[49] Each individual tracheal ring is 10 to 12 mm wide, being 2 to 3 mm thick dorsally and 5 to 7 mm thick ventrally. The dorsal tracheal ligament completes the dorsal aspect of the tracheal lumen, attaching to the inner surface of the tracheal rings. The cartilage rings vary a little in shape in the normal horse: the first few rings are slightly dorsoventrally flattened, but as the trachea is traced distally, the rings become more circular in shape. Finally, at the level of the aortic arch, the rings can become slightly laterally flattened, particularly on the left side.[48] The tracheal ligament contains the transversely oriented trachealis muscle; this elastic structure allows the trachea to expand slightly during times of increased respiratory effort.

Each tracheal ring is covered by and connected to adjacent rings by an intimately attached fibroelastic ligament, termed the *annular ligament.* This arrangement of semi-rigid cartilaginous rings and elastic annular ligaments, along with the loose attachment of the tracheal adventitia to other tissues, allows much flexibility of the trachea during head and neck movement while retaining its cross-sectional shape. The cricotracheal ligament, which attaches the first tracheal ring to the cricoid cartilage, is of similar structure to the annular ligaments but is wider (craniocaudally) and under less tension.

Running bilaterally along the dorsolateral aspects of the trachea are many vital structures, including the carotid artery, vagus and recurrent laryngeal nerves, sympathetic truck, tracheal lymph ducts, and cervical lymph nodes. The trachea is lined by a pale mucosa, containing numerous mucus and serous glands and possibly fine longitudinal folds. Ciliated epithelial cells are the predominant cell type,[50] with each cell containing about 200 cilia that beat 15 to 20 times per second. These cilia transport mucus from the lungs proximally to the nasopharynx. In the equine trachea, mucus is transported at a velocity of 13 to 20 mm/min.[51,52] The "sump-like" depression in the rostral thoracic trachea is a common place for respiratory secretions to accumulate in horses.[53]

Primary tracheal disorders are relatively uncommon in horses, but abnormal pooling of respiratory secretions in the "sump" of the trachea is often seen as a consequence of lower airway inflammation or exercise-induced pulmonary hemorrhage. Primary lung disorders are not discussed further in this section.

Cricotracheal Ligament Prolapse

A limited number of clinical reports describe this disorder in Thoroughbred racehorses during fast exercise.[53-55] The cricotracheal membrane is normally longer (rostrocaudally) and under less tension than

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the tracheal annular ligaments. It is suggested that a congenitally abnormally long and/or slack cricotracheal ligament may prolapse dorsally, ventrally, or circumferentially into the airway lumen as a result of the very negative inspiratory airway pressures that are generated during fast exercise. Concurrent upper and lower airway disorders may increase the severity of cricotracheal ligament prolapse by further increasing the negative pressure generated within the upper respiratory tract.

Clinical Signs and Diagnoses Clinical signs are reported to be abnormal respiratory noise during exercise and reduced exercise performance[53-55] due to the dorsally displaced ligament causing turbulent airflow and obstructing the airway. Differential diagnoses must include all forms of dynamic upper airway collapse, in particular those that are associated with inspiratory noise, including recurrent laryngeal neuropathy, axial deviation of the aryepiglottic folds, vocal fold collapse, collapse of the apex of the corniculate cartilages, epiglottic retroversion, and nasopharyngeal collapse. Diagnosis requires exercising endoscopy, either over ground or on a high-speed treadmill, with a specific effort made to examine the caudal laryngeal area. In the most recent report concerning two horses,[55] both horses had concurrent dynamic upper airway abnormalities. Presumably, cricotracheal collapse is exacerbated with head and neck flexion as this position will reduce tension on the cricotracheal ligament; however, this has not been discussed in any of the case reports to date. Ultrasonography of the ventral aspect of the cricotracheal ligament with the horse's head extended may be useful to measure the length and thickness of the ligament, but the range of these ultrasonographic measurements in normal horses has not yet been reported.

Treatment The reported treatment of cricotracheal membrane prolapse is to imbricate the ventral aspect of this ligament; one surgeon has suggested that the residual cricotracheal membrane should be left approximately 1.5 cm wide rostrocaudally.[54] However, the use of videoendoscopy during exercise has shown other aspects of the cricotracheal membrane can also collapse and these areas would also need treatment. In conclusion, there is little factual evidence regarding either the significance of cricotracheal membrane collapse in exercising horses or the response of affected horses to treatment.

Tracheal Collapse

Tracheal collapse is commonly recorded in many breeds of toy dogs[56-58] and can also occur in goats[59] and sheep and cattle (Dixon, personal observations). In equidae, this developmental disorder is often reported in small ponies and miniature horses[60-65] but also occurs in larger breeds of ponies[66] and donkeys.[63,67] In many small ponies, the disorder remains undiagnosed because of their low workload. There is a high prevalence of tracheal deformities in donkeys; in one postmortem study, 68.8% of tracheal rings did not have an oval or circular shape. Affected donkeys are usually asymptomatic, unless severe tracheal deformity or intercurrent pulmonary disorders, such as advanced pulmonary fibrosis, are present.[67]

Pathophysiology Tracheal collapse is usually caused by a cartilage ring deformity, including where the normal rounded or oval tracheal ring is replaced classically by a flatter tracheal ring with a greatly reduced dorsoventral diameter (Fig. 31-57). In some cases, a slack and elongated dorsal tracheal ligament can exacerbate the dynamic collapse.[60,61,66] A more recent study also showed most cases of tracheal collapse in donkeys were caused by structural cartilage abnormalities other than those previously mentioned[67]; thus perhaps a term other than *tracheal collapse* should now be used.

Many ponies and donkeys with tracheal collapse will have some dorsoventrally flattened tracheal rings (especially in their lower cervical trachea) but will also have other types of ring deformities (Fig. 31-58) at more caudal sites.[63,67] In other affected cases with relatively normal-shaped tracheal rings, there appears to be separation of the dorsal ligament from the dorsal aspect of the tracheal rings (Fig. 31-59). This defect usually involves the mid and distal cervical, as well as the intrathoracic trachea, and may occasionally involve the main stem bronchi. Some affected equids may also have some degree of tracheal rotation, with the dorsal aspect of the trachea facing dorsolaterally (authors' personal observations).

Most ponies and miniature horses develop clinical signs of tracheal collapse in middle age,[65,68] thus indicating that some degenerative process of the tracheal cartilage or connective tissue may play a role in the pathogenesis of this disorder. In one case series of 13

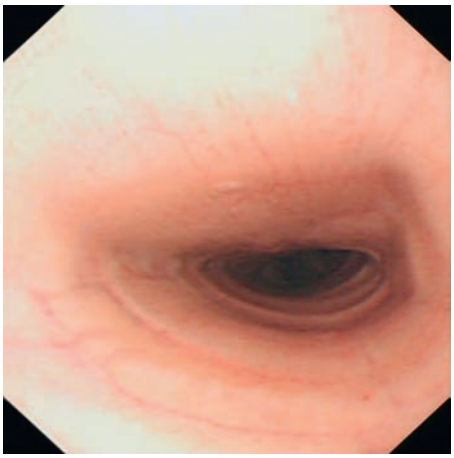


FIG. 31-57 Endoscopic view of dorsoventrally collapsed trachea



FIG. 31-58 Severe structural abnormality of an equid trachea.

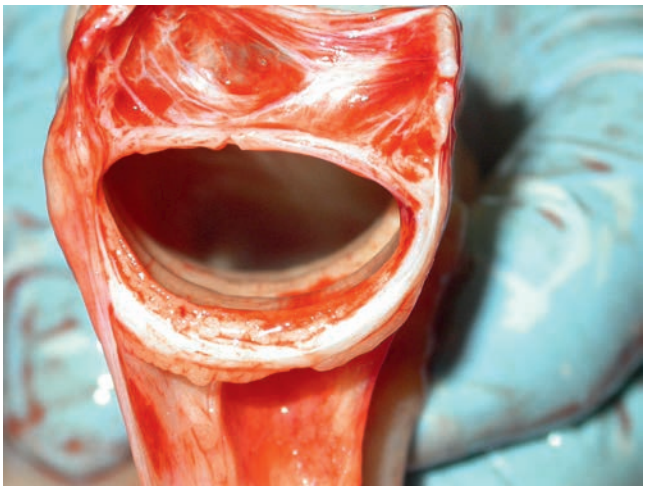


FIG. 31-59 This tracheal ring is a normal C shape, but the dorsal tracheal ligament has separated from the dorsomedial aspect of the tracheal rings.

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American Miniature Horses, all four horses, which had histopathology performed, had tracheal chondromalacia that varied from mild multifocal hyalinization of the extracellular matrix to marked multifocal coalescing areas of chondromalacia characterized by complete degradation of the cartilaginous matrix and loss of chondrocytes.[65] The presence of chronic respiratory disease that may cause tracheal mucosal thickening and also increase intrapleural pressure swings and neuromuscular problems causing loss of tone of the trachealis muscle have also been implicated in the pathogenesis of this disorder in donkeys.[67]

Temporary Tracheal Collapse

Horses with severe expiratory dyspnea caused by pulmonary disease have increased positive intrathoracic pressure during expiration, which can cause a temporary collapse of the intrathoracic trachea, particularly of its dorsal ligament. Such temporary and often near total tracheal collapse can also be seen transiently in all horses if they cough during bronchoscopy.

Clinical Signs and Diagnosis The typical clinical signs in affected equids are dyspnea and stridor, which commonly occur in hot or humid weather and may regress in autumn. Aleman and colleagues[65] report that clinical signs were initially intermittent and often associated with stressful events, exercise, dusty environment, and eating but that all owners reported increasing severity of clinical signs with age. Stridor may be very loud, with Delahanty and Georgi[60] reporting a pony that made sounds like a truck horn that could be heard over 800 meters away! The stridor is loudest when auscultated directly over areas of tracheal obstruction. Severe dyspnea may occur even at rest, because hyperventilation will exacerbate the partial tracheal obstruction in a self-perpetuating cycle. Affected horses can also exhibit tachycardia (60 to 130 bpm) and hyperthermia (38.2 to 40° C).[65]

Exercise-induced pulmonary hemorrhage may occur in severe cases, presumably because of increasingly subatmospheric intrathoracic pressures. Coughing may also occur and it is unclear if this is due to tracheal inflammation caused by abnormal contact of dorsal and ventral tracheal mucosa, or due to underlying pulmonary disease that may have precipitated the clinical problem.

Diagnosis Palpation of a collapsed cervical trachea may reveal lateral protrusion of cartilage rings. However, palpation of the lateral edges of the flattened trachea can be difficult, as the deeper, distal cervical trachea is most commonly affected. Additionally, some small ponies such as Shetlands have very thick skin and much subcutaneous fat, which makes tracheal palpation difficult.[48]

Endoscopy of affected cases will show the normal circular or oval appearance of the tracheal lumen to be replaced by a wider, flatter, or otherwise restricted lumen. Additionally, excessive dynamic movement of the dorsal tracheal wall and even airway occlusion may be observed during deep breathing, with inspiratory narrowing of the cervical tracheal lumen and expiratory narrowing of the intrathoracic tracheal lumen. The mucosa may be red and inflamed.

Lateral radiographs of the distal cervical and thoracic trachea may be diagnostic, demonstrating the flattened appearance of the trachea,[61,65] but radiographs must be taken during inspiration for the cervical trachea and during inspiration for the intrathoracic trachea. Radiography can be misleading in cases where tracheal rotation is present along with collapse, where the trachea may actually appear wider than normal on lateral radiographs.

Treatment and Prognosis Treatment of such cases should initially be conservative, by restricting exercise, keeping affected cases indoors in cool boxes in hot weather, and treating any concurrent pulmonary disease. Acutely affected horses will benefit from intranasal oxygen therapy that reduces hyperventilation and thus decreases the degree of tracheal collapse. Tracheostomy usually does not provide relief because it does not bypass the affected region (usually distal cervical and intrathoracic trachea). Therefore insertion of an endotracheal tube via the tracheotomy to keep the collapsed trachea patent is usually necessary to provide a functional airway in severely affected animals. Hyperthermia, if present, increases the metabolic rate and thus increases the respiratory demand further, causing a vicious cycle of events. Cooling down such ponies with a cold-water hose can be beneficial. Parenteral corticosteroids are also indicated in severely affected cases to reduce the secondary tracheal mucosal inflammation/edema that is likely to be present. The long-term prognosis for severely affected miniature horses with such conservative therapy appears to be poor, with 10 of 13 horses in the largest case series to date either dying or requiring euthanasia.[65]

Surgical correction of affected cartilaginous cervical tracheal rings (as is commonly performed in miniature dogs)—such as placing external stents over deformed tracheal rings[62,69] or inserting stainless steel sutures into every third tracheal ring along with imbrication of the slack dorsal membrane[60]—has been performed in ponies with limited success. The use of a metallic intraluminal stent has also been reported to have been successful in one miniature horse; however, intratracheal granulation tissue formation and lower airway infection was associated with the stented area.[64] In some ponies, altering the shape of the tracheal rings may not be successful, because separation of the dorsal ligaments from the cartilage rings is the primary problem. Additionally, careful evaluation will usually reveal involvement of the intrathoracic trachea and, because only three or four intrathoracic rings can be exteriorized rostrally to the distal cervical area for surgical correction, this may be of limited benefit to the horse. Although intrathoracic surgery to correct more caudal tracheal deformities is technically feasible, it is not practical.

Other Congenital Defects of the Trachea

Congenital defects of the trachea, other than tracheal collapse, are rare in horses. Only a few other types of deformities have been recorded, including a few reports of accessory or ectopic pulmonary tissue, such as that by Davis and colleagues,[70] who recorded an accessory cervical tracheal bronchus in a 3-day-old foal. The foal presented with a large, air-filled sac in its cervical region caused by a rudimentary accessory lung that contained cartilaginous tissue and ciliated epithelium. Peek and colleagues[71] reported a combined tracheal and esophageal duplication cyst in a 4-month-old Arabian foal with a slowly developing cervical swelling that was successfully resected.

EXTERNAL TRACHEAL TRAUMA. Tracheal trauma is usually caused by blunt trauma, such as kicks to the neck region that can cause severe tracheal damage, particularly if the trachea is compressed between a hoof and the overlying cervical vertebral body. Tracheal trauma can cause tearing of the mucosa (Fig. 31-60), tearing of the overlying annular ligaments, and fracture of tracheal rings. Penetrating tracheal injuries occur less commonly.



FIG. 31-60 Tracheal trauma: oval-shaped tear in the tracheal mucosa showing separation of the underlying tissues.

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Clinical Signs and Diagnosis A common presenting sign in horses with tracheal rupture is extensive subcutaneous emphysema and swelling over the cranioventral aspect of the neck.[72-74] External skin wounds are not always present. The emphysema may later spread to involve the head, trunk, mediastinum, and even limbs. Horses will later become stiff, and possibly febrile from secondary infection, and epistaxis and coughing may occur.[73] In addition to possibly having a ruptured trachea, horses with emphysematous cervical swellings should always be suspected of suffering from a ruptured esophagus[75] (authors' personal observations). Because the esophagus may lie ventrolateral, or even ventral to the trachea at around the level of the sixth cervical vertebra in some horses, it is prone to trauma at this site.[48]

Cervical radiography of horses with tracheal or esophageal rupture will show extensive gas infiltration along the fascial planes of the neck, in addition to variable soft-tissue or fluid-filled swellings of the cranial and ventral neck regions. Thoracic radiography may also reveal pneumomediastinum and possibly pneumothorax. Endoscopy (tracheoscopy) will confirm if tracheal trauma has occurred, by evidence of mucosal tears, prolapse of submucosal tissue into tracheal lumen, distortion or partial occlusion of the lumen caused by cartilage ring fractures, and/or local inflammation.[73,74] Esophageal endoscopy to examine the integrity of the esophagus should also be performed with the greatest of care in horses with neck swelling and emphysema.

Treatment and Prognosis If the esophagus is ruptured, the prognosis is poor, as compared with tracheal rupture, where the prognosis is usually good. Small tears of the tracheal mucosa will usually heal spontaneously. In addition to tetanus prophylaxis, NSAIDs should be administered to such cases to decrease the traumatic inflammation, along with broad-spectrum antibiotics to reduce the potential spread of pathogenic bacteria with entrapped air along the fascial planes of the neck and into the mediastinum. The emphysema present in such cases will usually resolve in 1 to 2 weeks but may remain for up to a month in some horses.[73] Large rents in the tracheal mucosa with extensive herniation of soft tissue into the tracheal lumen can be sutured, as described by Fubini and colleagues.[74]

Fractures of the cartilaginous tracheal rings with gross distortion of the trachea may also occur, and it may be difficult to evaluate the degree of the cartilage ring damage in the presence of severe local inflammation and emphysema. If available, computer tomography or magnetic resonance imaging of such lesions are the optimal methods of assessing cartilage damage. If life-threatening tracheal obstruction occurs, a temporary tracheostomy may be performed with insertion of an uncuffed endotracheal tube through the tracheostomy to open up the collapsed section of trachea if the obstruction is distal to the mid-cervical region.

Intraluminal granulation tissue and subsequent development of fibrotic bands of tissue can be long-term sequelae of tracheal trauma. Occasionally such rings of tissue may eventually (months later) reduce the tracheal lumen to a significant extent, leading to respiratory obstruction with stridor. Transendoscopic laser resection of the protruding stricture can be attempted, but the site should be monitored postoperatively for recurrence of the lesion. The use of topical corticosteroid after laser surgery may help to prevent a recurrence of strictures. Complete resection of the affected cervical tracheal ring(s) (up to 4 rings maximum) with end-to-end tracheal anastomosis can also be attempted, but such procedures can be very challenging. If the stricture is in the cranial cervical trachea, then a permanent tracheostomy can be placed at a more distal site.

Focal Intraluminal Tracheal Lesions Including Neoplasia

Apart from granuloma formation post tracheostomy (Fig. 31-61) or after tracheal trauma, focal intraluminal tracheal lesions are rare in horses (although many horses and especially ponies have multiple small cartilaginous nodules that are of no clinical significance). Charlton and Tulleners[76] reported infected/necrotic mid-cervical tracheal proliferative lesions in two adult horses, following intratracheal antibiotic administration in one and following a transtracheal aspiration in the other. The masses were resected using a transendoscopic laser in one horse and combination of transendoscopic laser and conventional surgery in the other.

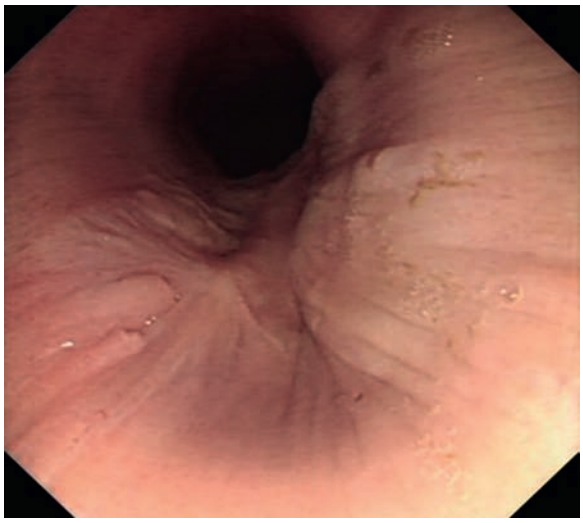


FIG. 31-61 Intraluminal scar tissue formation and cartilage deformity after tracheostomy tube removal.

Malignant tracheal tumors are rare in horses, but squamous cell carcinomas have been reported in the trachea of aged horses.[77] Benign lesions, including papillomas, fibromas, eosinophilic polyps, chondromas, and adenomas, are more common.[78,79] Benign lesions can often be successfully resected using a distal cervical tracheostomy and/or a transendoscopic laser (although transnasal retrieval of excised masses can be difficult if the lesion is at a distal site).

Extramural Tracheal Compression

Occasionally, enlarged lymph nodes compress the trachea, causing stridor. Severe lymphadenopathy is usually associated with *Streptococcus equi* subsp. *equi* (strangles) infection[80] and may involve the upper cervical chain, compressing the proximal cervical trachea. The distal cervical chain that compresses the trachea at the thoracic inlet may also be involved.[48,80-82] Diagnosis can usually be made from the history and clinical signs indicative of strangles, and confirmation can be made by needle aspiration and/or ultrasonography of cervical swellings. The abscessed lymph nodes should be drained and then lavaged with dilute povidone iodine solution.[81]

Mediastinal tumors (mainly lymphosarcomas), other cranial thoracic tumors (including primary lung tumors), or grossly abscessed mediastinal lymph nodes can cause compression of the intrathoracic trachea (Fig. 31-62) or of one or both main stem bronchi, leading to stridor and dyspnea. Such an endoscopic finding should lead to a careful thoracic examination, including radiography and ultrasonography. Thoracic tumors are usually untreatable in the horse.

Tracheobronchial Foreign Bodies

Inhaled foreign bodies are common in humans and dogs but less common in horses because of their height. O'Connor[83] described a range of laryngeal and tracheal foreign bodies in horses and stated that a fatal bronchopneumonia could develop if the foreign body is not expelled by coughing. Inhaled foreign bodies seldom bypass the larynx, but if they do, they will usually become entrapped at the carina or in the main stem bronchi,[84-87] predominantly the right main stem bronchus.[68]

A history of sudden onset of persistent coughing is a very prominent finding in these cases, and malodorous breath will often be present. Other signs of pulmonary disease, such as increased

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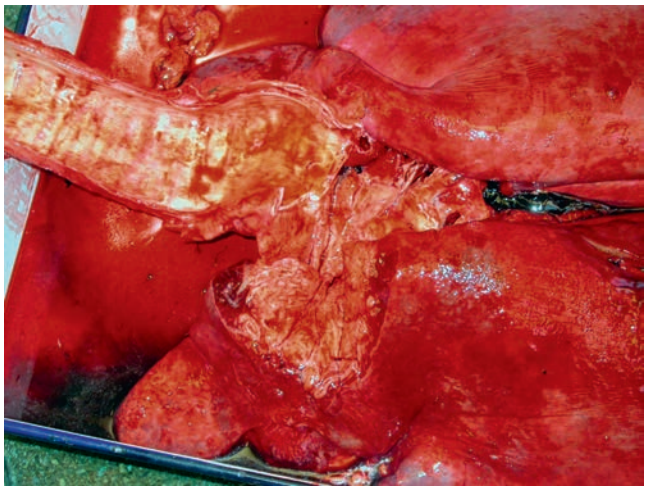


FIG. 31-62 Intrathoracic tracheal deviation and lateral collapse caused by extramural pressure from a mediastinal tumor.

respiratory rate or the presence of abnormal lung sounds, are usually absent, at least initially, unless secondary lung infection occurs. If significant pulmonary infection develops, abnormal lung sounds and possibly purulent or blood-tinged nasal discharge may occur. No response or only a temporary response (decreased nasal discharge) may occur following antibiotic therapy. Radiography may show a localized interstitial pattern caudal to the vena cava.[86]

Endoscopically, local airway inflammation and purulent respiratory secretions may obscure a foreign body. Even small foreign bodies may significantly obstruct airflow if they become lodged in the bronchii, and the induced local bronchial inflammation may also obstruct normal drainage of respiratory secretions from the affected bronchus, inducing severe, focal pulmonary infection. Transendoscopic lavage of the area may help determine if a bronchial foreign body or tumor is present. When identified, bronchial foreign bodies may be removed using transendoscopic grasping or basket forceps. Cranially facing branches and thorns will make the recovery of such vegetation difficult, but with persistence, most bronchial foreign bodies will eventually become loose and retrievable. If this is unsuccessful, a distal cervical tracheostomy can be performed and long, rigid grasping instrumentation (such as a bronchoesophageal grasping forceps) can be used under endoscopic guidance to retrieve the foreign body.[85,86]

Epiglottic Entrapment

Santiago D. Gutierrez-Nibeyro

Definition and Etiology Epiglottic entrapment, persistent or intermittent, refers to the dorsal displacement of the aryepiglottic folds and subepiglottic mucosa over the epiglottis. The aryepiglottic folds attach to the free margins of the epiglottis and blend with both the dorsal epiglottic and subepiglottic mucosa. Normally, the subepiglottic mucosa is loosely attached to the epiglottis to allow movement of the cartilage during swallowing. The cause of the disease is unknown, but inflammation of the subepiglottic mucosa and submucosa, redundant subepiglottic mucosa, and epiglottic hypoplasia or flaccidity have been reported as predisposing factors.[1-4] Epiglottic entrapment is typically a disease of Thoroughbred and Standardbred racehorses,[4] although it has been reported in nonracing Thoroughbreds and other breeds.[5] Epiglottic entrapment is often an incidental finding in weanlings and yearlings.[6]

Clinical Signs and Differential Diagnoses Clinical signs are variable and depend on the severity of the entrapment and the presence of other diseases of the upper respiratory tract. Some Thoroughbred and Standardbred racehorses can be asymptomatic



FIG. 31-63 Endoscopic image of the nasopharynx of a 3-year-old Standardbred racehorse with a history of increased respiratory noise and chronic epiglottic entrapment. The entrapping membrane was thick, wide, and mildly ulcerated, and the epiglottis had moderate hypoplasia once the entrapment was corrected surgically. As in this case, most epiglottic entrapments are persistent and thick, and approximately half are ulcerated.

and compete successfully with an entrapped epiglottis.[7] However, affected horses most commonly have a variable degree of abnormal respiratory noise, exercise intolerance, or both, because of partial airflow obstruction.[1,2,8] Severe inflammation and ulceration of the entrapping tissue can exacerbate airway obstruction and noise production; in rare cases, it may also cause cough and dysphagia.[1,8] Potential endoscopic differential diagnoses include subepiglottic cysts, epiglottitis, epiglottic granulomas, and dorsal displacement of the soft palate.[5,9,10]

Definitive Diagnostic Tests Endoscopic examination of the nasopharynx with the horse at rest is frequently diagnostic. Typically, the scalloped edge of the epiglottis and the vessels on its surface are not evident on endoscopy because they are obscured by the entrapping aryepiglottic fold (Fig. 31-63). Most epiglottic entrapments are persistent and thick, and approximately half are ulcerated.[2,8] If the epiglottis is not entrapped during the initial endoscopic evaluation but intermittent entrapment is suspected, endoscopy during a high-speed treadmill stress test may be necessary for diagnosis.

Although radiography is not used to diagnose the disease, an epiglottic entrapment can be detected with this diagnostic technique.[4] Epiglottic hypoplasia can be determined with both subjective endoscopic evaluation and radiographic measurement of the epiglottic length (determined by thyroepiglottic length).[4,11]

Treatment and Prognosis Intermittent epiglottic entrapment may be treated conservatively with topical and systemic antiinflammatory therapy and exercise restriction. Persistent epiglottic entrapment is typically treated surgically.[2,8] There are several surgical techniques to correct epiglottic entrapment: transendoscopic axial division using a Nd:YAG or diode laser,[2] transnasal or transoral axial division using a curved bistoury,[1,8,12-14] transnasal axial division using a shielded curved bistoury,[15] transendoscopic axial division using monopolar electrocautery,[16] and surgical excision via a laryngotomy.[3] Currently axial division of the entrapping aryepiglottic folds and subepiglottic mucosa is the preferred technique because the tissues are simply transected, avoiding "debulking" of the epiglottis and excessive scarring postoperatively, which can cause dorsal

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displacement of the soft palate.[17] Resection of the entrapping tissues through a ventral laryngotomy is typically reserved for excessively thickened, ulcerated, or fibrotic-appearing entrapping membrane.[3] Postoperative care consists of topical and systemic antiinflammatory therapy and exercise restriction.

The prognosis is typically good; however, postoperative complications include recurrence of the entrapment, intermittent or persistent dorsal displacement of the soft palate, and epiglottis deformity.[2,8,13,18] The recurrence rate after surgical correction of an entrapped epiglottis using laser axial division is 5%[2]; it is up to 15% using a curved bistoury,[8,12,14,15] and it is as high as 40% using electrosurgical division.[16]

Pharyngeal Cysts in Horses

Santiago D. Gutierrez-Nibeyro

Definition and Etiology Pharyngeal cysts are uncommon in the horse[1-3]; however, they are occasionally diagnosed in young Thoroughbreds, Standardbreds, and Quarter Horses.[4-8] Pharyngeal cysts occur most commonly in the subepiglottic region (Fig. 31-64) and occasionally in the soft palate or dorsal wall of the nasopharynx (Fig. 31-65).[4,6,8] Some authors believe subepiglottic cysts are embryonic remnants of the thyroglossal duct (precursor of the thyroid gland), but others believe these cysts are secondary to inflammation and obstruction of the mucus-secreting glands that line the pharynx.[5] Cysts formed within the dorsal nasopharyngeal wall are thought to be embryonic remnants of the craniopharyngeal duct (precursor of the adenohypophysis).[4] The origin of soft palate cysts has not been elucidated; however, histopathologic examination of these cysts is consistent with a mucocele.[6]

Clinical Signs In foals subepiglottic cysts are frequently asymptomatic,[3] but many cause increased respiratory noise, cough, nasal discharge, persistent dorsal displacement of the soft palate, dysphagia, and aspiration pneumonia.[5,6] The most common presentation in the adult performance horse is partial obstruction of the upper respiratory tract, abnormal respiratory noise, exercise intolerance, coughing, dysphagia, and, in rare cases, complete obstruction of the upper respiratory tract.[4,7-9]

Clinical Pathology Complete blood cell count and biochemistry profiles are typically within normal limits unless concurrent inflammatory airway disease, pneumonia, or acute upper respiratory tract obstruction exists.

Definitive Diagnostic Tests Endoscopic examination of the nasopharynx confirms the diagnosis and may also detect concomitant pathology such as epiglottic entrapment.[4,5,8] Occasionally, a lateral radiographic view of the pharynx or transoral endoscopic examination of the oropharynx with the patient anesthetized is needed if the cyst is within the soft palate or beneath the epiglottis protruding into the oropharynx. Although contrast pharyngography has been described to help delineate cysts in the oropharynx,[6] in the authors' opinion the use of contrast is unnecessary if digital radiography is available. The use of ultrasound has been described to delineate the cyst from the adjacent structures before surgery, if necessary.[10]

Treatment and Prognosis Pharyngeal cysts can be surgically removed, ensuring complete removal of the secretory lining without excessive excision of surrounding pharyngeal mucosa in the case of a subepiglottic cyst, which may lead to cicatrization and epiglottic dysfunction.[8] Subepiglottic cysts can be removed via a ventral laryngotomy,[4] via an oral or transnasal approach using an endoscopically guided laser, electrocautery snare, or a cyst snare constructed with obstetrical wire loop threaded through a Chambers catheter.[8,9] More recently, intralesional administration of 10% formalin has been reported, which provides an economically suitable alternative to surgical treatment[11]; however, multiple treatments may be required for complete resolution of the cyst.[11] Postoperative care consists of topical and systemic antiinflammatory therapy and exercise restriction. The prognosis following removal of subepiglottic cysts is good, and most horses return to full athletic function.[4,8] Less information is available regarding the prognosis after removal of other pharyngeal cysts.

Nasopharyngeal Cicatrix Syndrome

Ben Buchanan

The nasopharyngeal cicatrix syndrome is an inflammatory condition that was first described in 1987 in horses from south Texas[1] and



FIG. 31-64 Endoscopic image of the nasopharynx of a 2-year-old Standardbred horse with a small smooth and rounded subepiglottic cyst. The horse had a history of abnormal respiratory noise during training.



FIG. 31-65 Endoscopic image of the nasopharynx from a 1-week-old foal with a large cyst attached to the dorsal wall of the pharynx and a nasogastric tube in place. The cyst was resected with a cyst snare under endoscopic control.

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continues to be a common finding of horses grazing pastures in certain areas of Texas. It is also sporadically reported in other Gulf Coast (U.S.) states. The syndrome is a combination of inflammation and scarring of the nasal passage, pharynx, larynx, arytenoid cartilages, and proximal trachea. Severity ranges from incidental findings during endoscopy to airway obstruction that requires permanent tracheostomy.[2,3]

Clinical Signs Clinical signs include abnormal respiratory noise, nasal discharge, exercise intolerance, coughing, respiratory distress, and abnormal vocalization.[4] The character of the nasal discharge is frequently clear and mild. When compared with a case-controlled population in a retrospective study, affected horses made up 118 of 1236 horses examined endoscopically for any reason.[4] Of these affected horses, 97% had some degree of pharyngeal inflammation or scarring, of which 50% had a circumferential scar. In addition, 91% of affected horses had some inflammation or scarring of the larynx, and 39% had an airway obstruction with the majority being at the level of the larynx. In this same study, horses with endoscopic evidence of acute nasopharyngeal cicatrix syndrome were more likely to have nasal discharge and respiratory distress, whereas horses with endoscopic evidence of chronic nasopharyngeal cicatrix syndrome were more likely to make respiratory noise or suffer from respiratory distress.

Endoscopic Signs A scoring system used by the author is presented in Fig. 31-66 and builds on a system previously proposed by Rakestraw.[5] This system was developed to provide practitioners with a concise, simple, and complete system to document any abnormality of the upper respiratory tract seen on standing endoscopy.

NASAL PASSAGE. Both nasal passages should be examined. Lesions in the nasal passage appear as ulcerations and occur in less than 10% of cases.[4]

PHARYNGEAL SCAR. Schumacher and Hanselka first proposed a scoring system for this syndrome that focused on the pharyngeal scar.[1] This system has been adapted into a 7-point scale with 0 indicating no visible scarring. A score of 1 indicates a scar just forming on the ventral floor. A score of 2 indicates a consistent ventral scar. A score of 3 indicates a prominent ventral ridge with scarring just evident on the lateral walls of the pharynx. A score of 4 indicates a ventral scar with evidence of a dorsal scar just forming. A score of 5 indicates a complete ring with less than 25% reduction in the size of the airway. A score of 7 indicates a severe case with a complete ring that has reduced the airway over 75% (Fig. 31-67).

GUTTURAL POUCH PLICA. Occasionally scarring of the external guttural pouch plica is observed as a deformity to the guttural pouch openings.

PHARYNGEAL INFLAMMATION. The overall appearance of the pharyngeal walls should be graded with attention to degree of redness, edema, and chronic scarring. Acute/active is indicated by erythematous edematous tissue with or without discharge and no areas of scarring noted (Fig. 31-68). The level of inflammation should be graded as mild, moderate, or severe. Chronic/active is similar, with areas of active inflammation mixed with areas of previous scarring (Fig. 31-69). The degree of inflammation should be graded as mild, moderate, and acute. A chronic description is indicated when there are areas of scarring with no active inflammation (Fig. 31-70). Any level of pharyngeal lymphoid hyperplasia should be noted.

DORSAL PHARYNGEAL RECESS. The dorsal pharyngeal recess should be examined for inflammation and areas of previous scarring. Occasionally this area is the only area of inflammation noted in the pharynx. The recess should be graded as mild, moderate, severe, and chronic.

EPIGLOTTIS. The epiglottis should be examined for swelling, scarring, displacement, occlusion of the airway, and cysts. Mild changes of the epiglottis include diffuse swelling with some curling of the margins. Moderate changes, although more severe, do not occlude the airway. Severe changes are noted as scarring of the epiglottis with occlusion of the airway. Any displacement of the soft palate or epiglottic cysts should be recorded.

ARYEPIGLOTTIC FOLD. The aryepiglottic fold should be examined for edema and entrapment of the epiglottis. The abnormalities should be described as mild, moderate, or severe. Mild abnormalities are noted as minimal edema just making the fold visible. Severe changes are noted as significant edema causing the fold to overlap the arytenoid cartilages.

ARYTENOIDS. The left and right arytenoid cartilages should be evaluated for swelling, reddening, scarring, and abnormalities of abduction. Each cartilage is graded separately as having mild, moderate, or severe changes. Mild changes are noted as minimal edema/inflammation with or without reddening of the cartilage, with complete abduction. Moderate changes are noted as significant edema/inflammation with or without scarring, causing altered abduction of the cartilages. Severe changes are noted as obvious scarring of the cartilage that cannot be abducted from midline. Any laryngeal hemiplegia should be recorded.

VOCAL FOLDS. The vocal folds should be evaluated for edema and scarring. Changes in this area are common and should be recorded as present or absent.

PALATOPHARYNGEAL ARCH. The palatopharyngeal arch should be examined for edema and rostral displacement. The abnormalities should be described as mild, moderate, and severe. Mild abnormalities are noted as minimal edema causing minimal displacement. Moderate changes are noted as significant edema causing a prominent rostral displacement. Severe changes are noted as significant edema causing overlap of the palatopharyngeal arch over the apex of the arytenoids. Rostral displacement of the palatopharyngeal arch was noted in 36% of cases.[4]

TRACHEA. The proximal trachea should be evaluated for areas of edema, inflammation, and scarring, as lesions in the proximal 6 to 10 rings of the trachea are common. Changes in this area should be graded as mild, moderate, and severe. A mild change is focal to multifocal areas of inflammation not reducing the size of the airway. A moderate change is areas of inflammation causing a reduction in the airway less than 25%. A severe change causes airway reduction greater than 25%. Abnormalities in the trachea have been reported in 75% of cases.[4]

Progression This syndrome is rarely seen in horses under 4 years of age, and the length of time for an acute case to develop respiratory distress is unknown. In the author's experience the most severe cases occur in older horses.

Pathogenesis To date no specific etiology has been identified, although some risk factor analysis has been completed. A retrospective case-control study of 121 horses[2] with the nasopharyngeal cicatrix syndrome found a high association with housing on pasture or part time on pasture and with increased age. Cases of nasopharyngeal cicatrix syndrome were more likely to be presented in the summer months with acute cases also being seen in the spring and fall. No breed or sex risk factor was noted. Cases seem to be more prevalent in years with higher rainfalls, although a few new cases may be seen during times of drought.

Inhalation of larger sized particulate matter (>5 microns) is suspected to be the inciting cause as these particulates are deposited in the nasal mucosa, pharynx, larynx, and proximal trachea. This corresponds to the anatomic areas where the inflammation and

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Pharyngeal/Laryngeal Evaluation

PICTURES ON FILE
REPEAT EXAM

Name: Date:

Nasal Passage – Are lesions present?
Left nasal passage ☐ YES ☐ NO **Right** nasal passage ☐ YES ☐ NO

Pharyngeal Scar – Describe pharyngeal scar / cicatrix according to the scale below.
0. No scarring visible
1. Scarring just visible on floor of pharynx
2. Scarring on floor of pharynx w/ prominent ventral ridge
3. Prominent ventral ridge with scarring evident on lateral walls of pharynx
4. Prominent ventral ridge with scarring evident on walls and forming dorsally
5. Complete circular scar with prominent ventral ridge and just starting to constrict <25% of airway
6. Complete circular scar constricting 25-50% of airway
7. Complete circular scar constricting >50% of airway

Guttural Pouch Plica – Are alterations to plica of guttural pouch opening present?
Left plica ☐ YES ☐ NO **Right** plica ☐ YES ☐ NO

Pharyngeal Inflammation – Describe the overall inflammation of the pharynx.
None
Acute/Active – Tissue inflamed with no areas of chronic scarring noted. Score changes as mild, moderate, or severe.
Mild – Diffuse reddening with or without some yellow discharge and minimal edema
Moderate – Edema present in mucosal tissue with diffuse reddening and/or yellow discharge and plaques
Severe – Significant edema present in mucosal tissue
Chronic/Active – Areas of previous scarring visible with new areas of acute inflammation. Score changes as mild, moderate, or severe.
Mild – Diffuse reddening with or without some yellow discharge and minimal edema
Moderate – Edema present in mucosal tissue with diffuse reddening and/or yellow discharge and plaques
Severe – Significant edema present in mucosal tissue
Chronic – No edema, reddening, or yellow discharge present. Areas of scarring may be visible.
Is there lymphoid hyperplasia? ☐ YES ☐ NO

Dorsal Pharyngeal Recess – Describe the inflammation / scarring of the dorsal pharyngeal recess.
Normal
Mild – Minimal edema of tissue
Moderate – Significant edema of tissue
Severe – Severe edema of tissue obliterating the recess
C **Chronic Scarring** – No inflammation but obvious scarring present

Epiglottis – Describe changes to epiglottis. Score changes as mild, moderate, or severe.
Normal
Mild – Inflamed w/ diffuse swelling +/– curling of margins
Moderate – Scarring of epiglottis not occluding airway
Severe – Scarring of epiglottis occluding airway
Is there dorsal displacement of soft palate (DDSP)? ☐ YES ☐ NO Is there an epiglottic cyst? ☐ YES ☐ NO

Aryepiglottic Fold – Describe changes to aryepiglottic fold. Score changes as mild, moderate, or severe.
Normal
Mild – Minimal edema of fold just making it visible
Moderate – Significant edema of fold making it prominent
Severe – Severe edema of fold causing overlapping of the arytenoid cartilages
Is there an epiglottic entrapment? ☐ YES ☐ NO

Arytenoid – Describe changes to left and right arytenoid cartilages. Score changes as mild, moderate, or severe.

Left	**Right**
Normal	**Normal**
Mild – Minimal edema/inflammation with or without reddening. Maintains complete abduction	**Mild** – Minimal edema/inflammation with or without reddening. Maintains complete abduction
Moderate – Significant edema/inflammation with or without scarring. Altered but not complete abduction	**Moderate** – Significant edema/inflammation with or without scarring. Altered but not complete abduction
Severe – Obvious scarring of cartilage that cannot be abducted from midline	**Severe** – Obvious scarring of cartilage that cannot be abducted from midline
Is there laryngeal hemiplegia? ☐ YES ☐ NO *I, II, III, IV, V*	*Is there laryngeal hemiplegia?* ☐ YES ☐ NO *I, II, III, IV, V*

Vocal Folds – Are alterations to vocal folds present?
Left ☐ YES ☐ NO **Right** ☐ YES ☐ NO

Palatopharyngeal Arch – Describe changes to the palatopharyngeal arch. Score changes as mild, moderate, or severe.
Normal
Mild – Mild rostral displacement of palatopharyngeal arch
Moderate – Prominent displacement and inflammation of palatopharyngeal arch
Severe – Prominent displacement and inflammation of palatopharyngeal arch overlapping arytenoid cartilages

Trachea – Describe changes to the proximal trachea. Score changes as mild, moderate, or severe.
Normal
Mild – Focal to multi-focal areas of edema/inflammation
Moderate – Multi-focal coalescing areas of inflammation constricting airway <25%
Severe – Areas of inflammation/cicatrix constricting airway >25%

FIG. 31-66 Pharyngeal/laryngeal scoring system.

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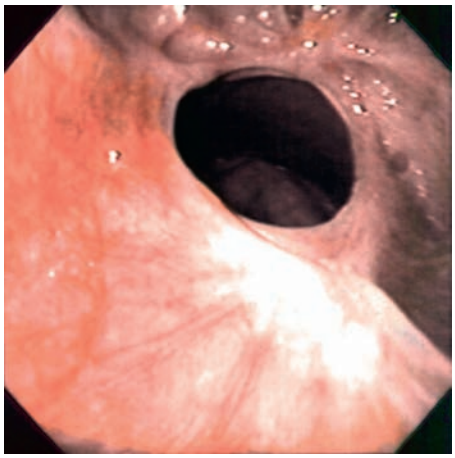


FIG. 31-67 Endoscopic image of nasopharyngeal cicatrix. This is an example of a grade 7 cicatrix.



FIG. 31-68 Endoscopic image of acute pharyngeal inflammation and swelling consistent with nasopharyngeal cicatrix syndrome.

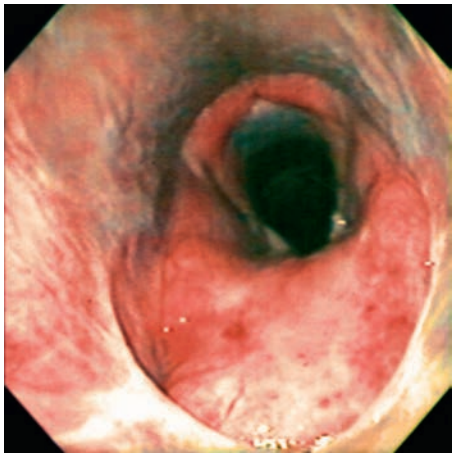


FIG. 31-69 Endoscopic image of chronic/active nasopharyngeal syndrome. There is both inflammation and swelling with a grade 3 cicatrix.

subsequent scarring are noted. Whether these particulates include bacteria, fungus, allergen, or some other irritant is not known. There is some discussion of pythium insidiosum as a possible cause, although in the author's experience this is not likely a primary pathogen in these cases.

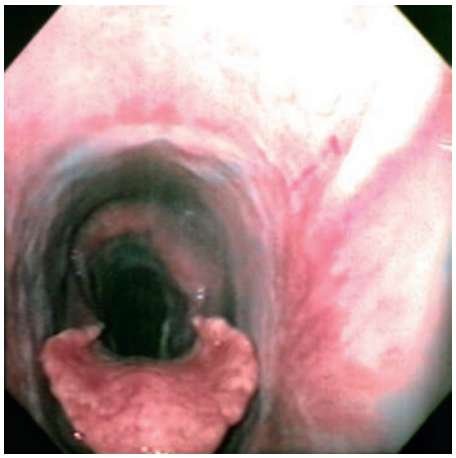


FIG. 31-70 Endoscopic image of chronic nasopharyngeal syndrome. There is scarring of the epiglottis and left arytenoid cartilage and a grade 3 cicatrix.

Treatment Because the agent or combination of agents causing this syndrome has not been identified, a single effective therapy has not been found. In addition, identification of effective treatments is complicated by the chronicity of the syndrome when it is typically first identified, the cyclical/seasonal nature of the clinical signs, and the response to changes in environmental factors. Current therapy consists of reducing exposure to pasture and reducing inflammation. No treatment has been effective if the horse remains on pasture. Surgical resection of affected areas frequently leads to excessive granulation tissue, especially after arytenoidectomy. If the airway is compromised, a permanent tracheostomy is the therapy of choice. If surgical reduction of the affected tissue is elected and the horse is not moved to a new environment, the lesions will recur.

Outcome In acute cases, simply removing the horse from pasture and feeding in a dry lot or stall resolves most of the condition. It is believed that repeat or continual exposure of acute cases lead to the chronic scarring. Once the chronic scarring has developed, it will not resolve.

Equine Influenza in Australia

James R. Gilkerson • Charles Mark El-Hage • Brett Tennent-Brown • Andrew W. Van Eps

Until 2007, Australia was one of a small number of countries that had never experienced an outbreak of equine influenza (EI). Equine influenza has never been reported in New Zealand. In August 2007 a consignment of horses was admitted into the quarantine station in Sydney, all of which had been vaccinated in accordance with Australian quarantine requirements. At least one of these horses was subclinically infected with EI. The virus spread among horses within the quarantine station and, following a breakdown of quarantine procedures, escaped into the general horse population. Because the Australian general horse population was highly susceptible to EI, the virus spread rapidly, affecting more than 76,000 horses on 10,600 premises in New South Wales and Queensland. Control of the outbreak and eradication of the virus from Australia had an estimated cost of approximately US$1 billion.

As soon as EI had been confirmed in the general population, a control and eradication program based on movement restrictions and, subsequently, vaccination was initiated. Although only two states were affected, a complete national ban on all horse movements was put in place immediately. All race meetings and other horse events were cancelled. Horses already at events were not permitted to leave until cleared by government veterinarians. Whereas movement restrictions proved highly effective in preventing the spread of virus beyond those areas affected in the first week of the outbreak,

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these restrictions were financially extremely damaging to horse-related businesses. To alleviate some of the economic concerns, especially those of the breeding industry, some movement restrictions were eased to allow the breeding season to proceed.

At the time of the outbreak in August 2007 there were no EI vaccines registered for use in the Australian general horse population. When additional measures were required to contain the outbreak, an emergency use permit was issued in September 2007 for a canarypox-vectored recombinant EI vaccine (ProteqFlu, ProteqFlu-TE [Merial, Lyon, France]). This vaccine was selected for several reasons, including rapid onset of immunity[1]; the ability to differentiate vaccinated horses from those naturally infected; and reports of efficacy in the South African 2003/2004 outbreak.[2] Vaccination was initially employed to create buffer zones around infected areas to contain spread of the epidemic. Horses inside the infected areas on unaffected properties were subsequently also vaccinated. Most horses received a primary course booster at 4 weeks (the recommended interval); however, some horses received an accelerated primary course schedule with the interdose interval reduced to 14 days.[3,4]

Approximately 4 months after the outbreak commenced, the last reported infected premise was reported. Provisional freedom from disease was declared in March 2008, and EI-free status was confirmed by the OIE (World Organisation for Animal Health) the following year.

The EI virus isolated from horses in the quarantine station and horses in the general population was named A/equine/Sydney/2888-8/2007 (H3N8).[5] Following molecular characterization, the virus was classified as an American lineage, Florida sublineage, Clade 1 type[6] and is phylogenetically similar to the EI viruses that were circulating in Japan and the United States at the time.[7]

Clinical disease caused by the EI virus in adult horses was considered mild in the vast majority of cases; however, secondary bacterial bronchopneumonia was described as a complication and occasional cause of death in predominantly mature horses.[8] Infection of late gestation mares was associated with increased severity of clinical signs and neonatal morbidity.[8,9] A fatal bronchointerstitial pneumonia associated with EIV infection was reported in several foals from infected properties.[10]

Hendra Virus

Andrew W. Van Eps • Brett Tennent-Brown • Charles Mark El-Hage

Hendra virus (HeV) was first identified in September 1994 following the deaths of 14 Thoroughbred horses and 1 human during an outbreak of respiratory disease at racing stables located in Hendra, Queensland, Australia.[1] Severe, acute respiratory disease due to HeV occurred sporadically over the subsequent 14 years; however, neurologic signs have predominated in cases since 2008. In 2011 there was a marked increase in HeV incidence (18 separate incidents in total) occurring over a wider geographic area than previously reported. At the time of writing, infection has been confirmed in a total of 56 horses, 7 humans (with 4 human fatalities), and 1 dog (seroconversion without clinical signs) in the states of Queensland and New South Wales.

Epidemiology

Hendra and the closely related Nipah viruses together form the genus *Henipavirus* in the family Paramyxoviridae. The natural hosts for HeV are fruit bats (flying foxes or *Pteropodidae* spp.), which are widely distributed throughout northern and eastern Australia.[2] Hendra virus infection of fruit bats is asymptomatic and apparently widespread. Serologic surveys indicate a high prevalence of HeV antibodies in fruit bats, including those in areas where equine or human disease has not been documented. In infected bats, HeV can be detected in urine, uterine fluids, placental tissues, and aborted pups.[3]

The majority of equine cases have occurred between June and December, although the reason for this apparent seasonality is unclear. On many occasions, the index case has been a horse that is kept outdoors in an area attractive to fruit bats. The mechanism of virus transmission to horses is not completely understood but likely follows ingestion of contaminated feed or water.[3] Horse-to-horse (and horse-to-human) transmission requires close contact with body fluids (particularly respiratory secretions) and appears to occur infrequently in horses kept at pasture but more efficiently in stabled horses.[4] HeV uses the cell surface receptors ephrin-B2 and ephrin-B3 that are widespread on vascular endothelium.[5] As a consequence, HeV infection of horses results in a vasculitis that affects, in particular, the respiratory and central nervous systems.

Hendra virus poses a serious zoonotic risk to animal caretakers and attending veterinarians. Although the risk of viral transmission increases as the disease progresses, virus is shed at low levels prior to the appearance of clinical signs in experimental infections. Horse-to-human transmission is thought to require direct physical contact with nasopharyngeal secretions; however, the virus can survive for several hours in the environment, and transmission by fomites might be possible. The risk of transmission to humans is particularly high in the terminal stages of disease and postmortem. Postmortem examinations should be postponed in suspect cases until HeV infection has been ruled out by appropriate testing.

Clinical Signs

In experimental infections, the incubation period ranges between 5 and 16 days in horses and 5 and 21 days in humans.[4,6,7] Prior to 2008, signs of acute severe respiratory disease predominated in HeV infections. However, since 2008, neurologic signs have been described more commonly and might be the result of a minor genetic change to the virus. Approximately 75% of cases are fatal, and these typically progress rapidly. Sudden death of one or more horses without obvious signs of illness should raise suspicion of HeV infection. Clinical signs in animals that survive beyond the peracute stages include pyrexia, depression, and signs of respiratory and/or neurologic disease. Signs related to respiratory tract involvement include tachypnea, respiratory distress, and a frothy nasal discharge. Commonly described neurologic signs include weakness, collapse, and an inability to rise; ataxia; altered mentation; central blindness; head tilt and circling; and urinary incontinence. Additional clinical signs might include tachycardia, frequent weight shifting or restlessness, muscle fasciculation, colic, and facial swelling or edema.

Pathology

Gross changes at postmortem include edematous (submandibular and bronchial) lymph nodes, dilated pulmonary lymphatics, subpleural hemorrhages, and pulmonary consolidation and edema. Edema of other tissues might also be apparent. Histologically, HeV infection is characterized by a systemic vasculitis, particularly of the respiratory tract, brain, and meninges. In addition to edema, syncytial cells, viral inclusion bodies, and alveolitis can be seen in pulmonary tissues. Perivascular lymphocyte cuffing, neuronal necrosis, and focal gliosis have been observed in the brain.

Diagnosis

In regions where the virus is known to occur, HeV infection should be considered in any horse exhibiting a high fever and signs of acute lower respiratory tract or neurologic disease. Hendra virus infection should also be considered in cases of sudden death. Differential diagnoses for HeV infection include plant (e.g., Crofton weed, avocado) or ionophore toxicity; bacterial pneumonia; and viral encephalitis/meningoencephalitis (e.g., equine herpesvirus 1 [EHV-1], flavivirus infection).

Laboratory testing is essential for confirmation or exclusion of HeV infection and includes virus isolation, detection of viral nucleic acid in body fluids or tissues, and demonstration of specific serum antibodies. Blood, nasal swabs, oral swabs, or rectal mucosal swabs are suitable for quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) testing of both living and dead horses. However, samples collected very early in the disease incubation period can produce a negative result by qRT-PCR testing. Detailed guidelines for sample collection, handling, and submission

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are available from local Australian government sources (e.g., the Department of Primary Industries). Appropriate personal protective equipment (protective eyewear, particulate mask, impervious gloves, and gown) must be worn when collecting samples from suspect horses. Postmortem examinations pose the highest transmission risk for humans, and necropsies of suspect cases should be postponed until HeV infection has been ruled out.

Treatment and Prevention In regions where HeV occurs, owners are advised to reduce contact between fruit bats and horses. Recommendations include the following: avoid placing feed or water beneath trees in which fruit bats might roost, limit horse access to flowering or fruiting trees that might attract fruit bats, and stable horses at dusk and overnight when fruit bats are most active.

In November 2012, a subunit, adjuvanted vaccine containing soluble HeV G-proteins was released under a "minor permit" requiring strict conditions for its use.[8] All vaccinated horses must be identified by microchip prior to vaccination and the two doses of vaccine must be administered exactly 21 days apart. Effective antibody levels were present 21 days after administration of the second dose and prevented infection in limited experimental trials. The duration of protection is currently unknown. At present, treatment of confirmed cases is not permitted and all horses infected with HeV must be euthanized.

Crofton Weed Poisoning (Numinbah Horse Sickness, Tallebudgera Horse Disease)

Andrew W. Van Eps • Brett Tennent-Brown

The plant *Eupatorium (Aregatina) adenophora* is native to Central America but now appears as an intractable weed in many countries, including Australia and New Zealand.[1] Ingestion of large quantities of *E. adenophora* causes a pneumotoxicosis characterized by increased respiratory effort and rate. Outbreaks of respiratory disease caused by *E. adenophora* were reported in Southern Queensland and New South Wales in the 1940s and have occurred periodically since then.[1] Respiratory disease caused by *E. adenophora* has also been reported in New Zealand. The related species *Eupatorium riparium* is a perennial weed in Queensland and New South Wales and causes a similar syndrome in feeding trials. However, field cases of disease caused by *E. riparium* have not been reported.[2]

Epidemiology Respiratory disease caused by *E. adenophora* has been described in horses aged between 18 months and 12 years with no gender predilection. Horses appear to be the only large animal species affected. Flowering stages are more toxic than non-flowering stages and most cases occur during the summer following ingestion of the plant in spring.[1,3] There is typically a minimum of 2 months between plant ingestion and the appearance of clinical signs.[2]

Clinical Signs The earliest clinical sign noted in affected animals is coughing that is exacerbated by exercise.[1,3] Respiratory rate and effort are markedly increased and, in some cases, a double expiratory effort is apparent. Affected horses have reduced exercise tolerance and adventitial sounds may be appreciated on thoracic auscultation. Severely affected horses experience weight loss and may be cyanotic. Cardiac arrhythmias that can result in sudden death develop in some horses.[1,3]

Pathology The toxic principle of *E. adenophora* is unknown.[2] Pyrrolizidine alkaloids are suspected because of the condition's similarity to *Crotalaria*-associated lung disease ("jaagsiekte") seen in South African horses. The toxin (or toxins) appears to be absorbed from the gastrointestinal tract, and inhalation of plant material (e.g., pollen) is not required for disease.

At necropsy, the lungs are firm and do not collapse on opening the thorax. Pulmonary fibrosis is widespread, and there may be cavities containing necrotic material within the parenchyma. The visceral pleura are often thickened and white in appearance with focal adhesions to the parietal pleura. Hydrothorax, pulmonary edema and emphysema, hydropericardium, and cardiac dilation may be found in horses dying suddenly.[1,3]

Sheets of epithelial-like cells lining the alveoli are apparent on histologic examination. Accumulations of inspissated protein are present within the alveoli of most chronic cases, and eosinophils and neutrophils commonly fill the bronchioles and surrounding alveoli.

Treatment No effective treatment is known; once diagnosed, the condition is irreversible although antimicrobials and corticosteroids have improved clinical signs in some cases.

Ruminant Respiratory System

Amelia R. Woolums, *Consulting Editor*

Upper Respiratory Tract Diseases

Amelia R. Woolums[‡]

Diseases of the Nasal Cavity

Amelia R. Woolums

Mycotic or Bacterial Nasal Granuloma

Infectious granulomas in the nasal cavity of ruminants are not common. Documented causes include the fungal organisms *Rhinosporidium seeberi* and other *Rhinosporidium* spp. (which cause rhinosporidiosis), *Helminthosporium* spp. (which cause maduromycosis), *Drechslera rostrata, Aspergillus* spp., *Phycomycetes* spp., *Stachybotrys* spp., and *Bipolaris* spp. Nasal granuloma caused by *Nocardia* spp. bacteria has also been reported.[2] There is no apparent age, breed, or seasonal predilection, and cases are sporadic. The major clinical signs are upper respiratory noise (stridor), dyspnea, and mucopurulent nasal discharge, sometimes with epistaxis. Affected animals may rub the nose, suggesting pruritus or irritation. Nasal airflow may be reduced, and open-mouth breathing may occur in advanced cases. Hot or dusty weather may accentuate the signs, giving the appearance of seasonal exacerbation, but the lesions are progressive. The granulomas may be single or multiple, unilateral or bilateral, and located anywhere in the nasal cavity. They consist of 0.5- to 5-cm yellow to yellow-green or red nodules or polyps, which may be sessile or pedunculated. Rhinosporidiosis tends to be a single unilateral polyp in the posterior nasal cavity, and maduromycosis tends to occur in

[‡]Previous contributions by John C. Baker and John A. Smith are acknowledged.

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the anterior cavity, but these distinctions are not consistent. Red and black spots (spores) may occur on the masses, and some may become secondarily infected with bacteria and ulcerate. Differential diagnoses include allergic rhinitis, foreign bodies, tumors, nasal actinobacillosis, nasal actinomycosis, and *Oestrus ovis* infection in small ruminants.

Endoscopy, biopsy, and culture of the lesions aid in the diagnosis. Histopathologic analysis reveals granulation tissue containing eosinophils, mononuclear cells, round sporangia, and sometimes hyphae or filamentous bacteria.[1,2] The pathogenesis of the disease involves inoculation of eroded nasal mucosa with fungal spores or filamentous bacteria from the environment. The infectious agent causes a chronic delayed (type IV) hypersensitivity reaction, which eventually leads to the formation of a granuloma. Fungal granulomas can be more common in warm, wet climates. The granulomas can be difficult to treat and, although rarely fatal, the disease is chronically debilitating, with salvage often being the most practical solution.

Recommended treatments include surgical removal of the granulomas when possible and long-term sodium iodide (NaI) therapy. NaI can be administered at a dose of 66 mg/kg IV as a 20% solution, repeated at 10- to 14-day intervals until remission or iodism occurs. Iodism is characterized by lacrimation, cough, and scaling of the skin. The use of antifungal drugs to treat this condition in ruminants has not been reported.

Allergic Rhinitis and Enzootic Nasal Granuloma

Allergic rhinitis occurs in cattle and in its chronic stages may lead to the formation of granulomas. A similar condition may occur in sheep.[3] The inciting antigen is frequently a plant pollen or more likely a fungal spore.[4] Once homocytotropic antibody (immunoglobulin E or possibly other classes in cattle) to the allergen has developed, subsequent exposure results in a localized, ongoing, immediate (type I) hypersensitivity reaction.[4-6] If recurrent exposure to the allergen occurs, repeated tissue damage by mast cell factors results in chronic epithelial, duct, and goblet cell hyperplasia and metaplasia, as well as mucous hypersecretion and granulomatous inflammation, suggesting that a type IV hypersensitivity reaction contributes to the chronic lesion.[4,5,7]

Any breed may be affected, but Channel Island breeds and Friesians seem most susceptible.[4] The disease occurs sporadically in the United States. A familial predisposition has been reported.[8] Most affected animals are between 6 months and 2 years of age. The signs are initially seasonal, usually occurring in warm, moist conditions; they include rhinorrhea, sneezing, nasal pruritus, a sudden onset of dyspnea, and stertorous inspiration.[8,9] There is a profuse bilateral nasal discharge. Intense pruritus is characteristic and associated with sneezing, headshaking, and nose rubbing.[9] In severe cases facial swelling, tachypnea, hyperpnea, and ulceration of the nasal mucosa may occur.[5,9] Nasal foreign objects may result from the animal's attempts to scratch the nasal mucosa. Lacrimation, chemosis, and blepharitis may also be present. In the chronic stages (the "enzootic nasal granuloma"), the signs are more constant, with seasonal exacerbations.[5,7,9] The granulomas tend to be multiple, firm, white, raised nodules 1 to 2 mm in diameter with an intact mucosa or pale pink flat plaques scattered throughout the nasal cavity. Differential diagnoses include fungal granulomas, foreign bodies, respiratory viruses, nasal actinomycosis or actinobacillosis, tumors, *O. ovis* infection (small ruminants), and irritation caused by inhalation of hot or irritant gases.

Endoscopy, biopsies, cultures, antigen detection tests for viruses, bacteria, or fungi, and serologic analysis can be used to rule out these differential diagnoses. Eosinophil counts in nasal secretions correlate with the susceptibility of the animal and activity of the disease, but no absolute level is diagnostic.[4] Intradermal allergen testing has been suggested to aid in diagnosis, but interpretation of results needs to be done in conjunction with historical and clinical findings.[6] This condition should be differentiated from fungal or bacterial granuloma because the therapy is different.

Treatment and control entail removal of the allergen, or removal of the animal from the allergen, and therapy to block the hypersensitivity reaction. Recommended drugs include various antihistamines, meclofenamic acid, and corticosteroids at standard antiinflammatory doses (0.05 to 0.2 mg of dexamethasone per kilogram IM or IV or 1 to 2.2 mg of prednisolone per kilogram IM or IV daily). Topical corticosteroid therapy can be considered in severe, acute occurrences of the disease. The adverse effects of corticosteroids on milk production and their potential to induce abortion or parturition should be considered before their use. Antihistamine therapy has had equivocal results.[6]

Nasal Foreign Bodies

Cattle are more prone than small ruminants to the acquisition of nasal foreign bodies. Foreign objects may be acquired as a result of attempts to scratch the nose in cases of allergic rhinitis or because of the cow's aggressive eating habits. Depending on the size and duration of residence of the object, signs may include headshaking, stridor, sneezing, snorting, frequent nose licking, unilateral decreases in airflow, foul odors, and serous, mucopurulent, or hemorrhagic discharges. Differential diagnoses include fungal granulomas, allergic rhinitis, tumors, nasal actinomycosis or actinobacillosis, and *O. ovis* (small ruminants). Many objects can be visualized on careful examination of the nasal cavity with an adequate light source, whereas some may require endoscopy for diagnosis and removal.

Nasal Trauma and Fractures

Trauma to the facial bones, sinuses, and turbinates may result from fighting, accidents caused by improper restraint, farm machinery accidents, human maliciousness, and passage of excessively large nasogastric tubes. Severe fractures can lead to facial swelling, subcutaneous emphysema, obstruction of airflow, stertor, and epistaxis. Secondary infection causes foul odors and mucopurulent nasal discharge. Differential diagnoses for the acute external swelling of the head with stertor include snakebite, actinobacillosis, actinomycosis, and phlegmon (*Fusobacterium, Clostridium* spp.). Unless the development of severe depression fractures, formation of sequestra, or severe obstruction of airflow occurs, surgery is usually not indicated. Radiographs confirm the diagnosis and help determine the need for surgical removal of potential sequestra or elevation and fixation of large displaced segments. Prophylactic antibiotics (typically penicillin G procaine, 22,000 IU/kg IM q12-24h) are recommended to prevent fracture infection and sinusitis, and nonsteroidal antiinflammatory drugs (aspirin, 100 mg/kg PO q12h; flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help relieve pain, swelling, and stridor. The prognosis is usually good.

Nasal Tumors and Polyps

Tumors and polyps of the nasal cavity and sinuses are rare in ruminants. Nasal tumors reported in cattle include osteomas and osteosarcomas of the sinuses, squamous cell carcinomas,[10] neuroblastomas, and adenocarcinomas of the ethmoid mucosa. Ethmoid adenocarcinomas are speculated to be caused by viruses on the basis of an endemic pattern in some cases.[11] They tend to occur in cattle 6 to 9 years of age and are frequently unilateral. Metastasis occurs to the lymph nodes and lungs. There is a report of a hemangiosarcoma involving the external naris of a cow.[12] Signs common to all nasal tumors include mixed or inspiratory dyspnea, stridor, nasal discharge, epistaxis, foul breath odors, unilateral decreases in airflow, open-mouth breathing, and distortion of the facial bones. Differential diagnoses include fungal granulomas, atopic granulomas, foreign bodies, sinusitis, fractures, and nasal actinobacillosis and actinomycosis. Treatment has not been investigated.

The majority of nasal neoplasms in sheep and goats are adenopapillomas, adenomas, or adenocarcinomas.[13] Squamous cell carcinoma[14] has also been reported. An enzootic form of nasal adenocarcinoma occurs in both sheep and goats and is associated with ovine nasal adenocarcinoma virus (ONAV)[15,16] or caprine nasal adenocarcinoma virus (CNAV),[17] respectively. These agents are

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β retroviruses that are closely related to, but distinct from, jaagsiekte sheep retrovirus (JSRV), the cause of ovine pulmonary adenocarcinoma (OPA).[17,18] Although nasal adenocarcinoma has been difficult to consistently reproduce experimentally, inoculation of kids with concentrated cell-free and bacteria-free filtrate containing virus from naturally infected goats has resulted in disease.[19] Neoplastic transformation is limited to secretory epithelial cells of the nasal turbinates, but CNAV appears to have a wider tissue tropism than ONAV; in one study viral provirus incorporated into host DNA was found in many tissues of infected goats but was largely confined to tumor tissue of infected sheep.[17] There is no breed or sex predisposition for enzootic nasal adenocarcinoma; affected animals are most commonly young adults, but the tumor has been identified as early as 4 months of age.[15] Signs include progressive inspiratory dyspnea; stridor; exercise intolerance; mouth breathing; serous, mucoid, or mucopurulent nasal discharge, which is typically profuse; tachypnea; decreased airflow; headshaking; sneezing; exophthalmos; and facial asymmetry. The lesions may be unilateral or bilateral, originating in the olfactory region of the ethmoid turbinates. The neoplasia arises either from Bowman glands or serous glands of the nasal mucosa. The tumor begins as a small nodule that can grossly resemble the mucoid polyps that occur in animals with chronic rhinitis. Over time the adenocarcinoma grows into a soft, gray to grayish pink, mucoid, nodular, cystic mass. The tumor is benign but locally expansive, often entering the sinuses and eroding overlying bone. Histologically the tumor is typically classified as a low-grade adenocarcinoma, but it may also be identified as an adenopapilloma or adenoma. In the initial stage, affected animals eat and drink normally and maintain body condition, but as the tumor expands the animal begins to lose condition, and death eventually occurs as a result of inanition, asphyxia, or aspiration pneumonia. Necrosis or secondary bacterial infection of the tumor can occur and may lead to the production of foul-smelling, purulent discharge and systemic signs related to bacterial infection, such as fever, depression, and hyperemic mucous membranes.

Differential diagnoses for nasal neoplasia in small ruminants include nasal fungal or bacterial granuloma, actinobacillosis, actinomycosis, *O. ovis* infection, and sinusitis. Endoscopy and radiology are helpful in establishing an initial diagnosis of a nasal mass. Preoperative or antemortem punch biopsies and exfoliative cytologic analysis frequently are nondiagnostic, and findings may be misleading.[13,14] Identification of tumors in multiple animals in a herd or flock supports a diagnosis of enzootic nasal adenocarcinoma. Definitive identification of infection with ONAV or CNAV can be difficult. Serologic tests are not reliable because animals do not consistently produce antibody to the viruses,[20] possibly because of the presence of endogenous retroviruses[21] that share epitopes with ONAV and CNAV and induce the development of immunologic tolerance. Polymerase chain reaction has been used to specifically identify and differentiate ONAV, CNAV, and JSRV in tissues of affected animals.[22] Surgical management of nasal adenocarcinoma in sheep has been described.[23]

Oestrus ovis Infestation

Amelia R. Woolums

Definition and Etiology *O. ovis* is parasite of the nasal passages and sinuses of sheep and, less commonly, goats. Goats are relatively resistant to infection and, even when housed with sheep, tend to have a lower prevalence of infection.[1] Occasionally humans and other animals are accidentally infected, with conjunctival infection the most common form of disease in humans.[2,3] The pathogenic stage of the parasite is the larval stage. The first instar larvae are deposited near the nostrils of sheep by the adult female fly and migrate into the nasal and ethmoid turbinates; in the ethmoids the larvae molt to second instars, which migrate to the sinuses before molting again and becoming third instar larvae. Third instar larvae, which are yellow-white in color and have a dark dorsal stripe with rows of spines on the ventrum of each segment, return to the nasal passages and are sneezed out onto the ground, where they pupate and eventually develop into adult flies.[4,5] The adult is active during warm months, and the parasite may overwinter either as a first instar larva in the host or as a pupa in the ground. Larvae can persist in the upper airways for weeks to months and appear to be able to arrest development for a period of time if necessary to avoid climate extremes.[6] Adult flies have a rudimentary mouthpiece and are not able to feed; thus the larvae must ingest adequate nutrients while in the host to support the life of the adult fly.[7]

Clinical Signs The larvae cause irritation of the nasal passages and sinuses, leading to mucoid to mucopurulent and sometimes blood-tinged nasal discharge, sneezing, nose rubbing, and inspiratory stridor. Adult flies cause annoyance by flying around the heads of animals; thus both stages can lead to decreased productivity by decreasing the time spent grazing by affected animals. Occasionally the larvae may cause sinusitis or pneumonia owing to secondary bacterial infection associated with irritation caused by the larval infestation. Differential diagnoses to consider include nasal foreign bodies, allergic rhinitis, nasal adenocarcinoma, fungal rhinitis, trauma, sinusitis, actinobacillosis, or actinomycosis.

Pathogenesis The larvae cause direct irritation to the nasal passages and sinuses, and this irritation may predispose animals to the development of secondary bacterial rhinitis, sinusitis, and/or pneumonia. Interstitial pneumonia has also been seen on occasion in affected sheep, presumably induced by inhalation of parasite antigens and inflammatory mediators from the upper respiratory tract.[8]

Epidemiology Infection is more common in warm climates. European surveys have identified *O. ovis* in 35% to 91% of sheep surveyed,[9,10] with seroprevalences of 46% to 69%.[1,10,11] A majority of flocks surveyed had at least one infected animal.[1,9] No North American reports describing the prevalence of *O. ovis* infestation have been published in recent decades.

Diagnosis Diagnosis is usually presumptive, based on typical clinical signs. The larvae can also be identified via radiographs of the head or by endoscopy, but these tests may not be practical for field use. Serologic diagnosis has been used for research studies of the epidemiology of *O. ovis* infection, but these tests are unlikely to be available at most diagnostic laboratories.

Treatment and Prevention The larvae are susceptible to ivermectin at 200 µg/kg PO.[12] Moxidectin at 0.2 mg/kg as a 0.1% oral drench was not effective against *O. ovis*[13]; these investigators found that the same dose given as a 1% injectable solution was effective, but this route is not approved in the United States. Pour-on eprinomectin at 0.5 mg/kg (applied immediately after shearing)[14] and injectable doramectin at 200 µg/kg IM[15] have also been shown to be effective in sheep, but these treatments are also not approved for use in sheep or goats in the United States. Because the adult fly should be killed by freezing weather, in areas with a season of freezing weather it is logical to treat after the first hard freeze, when sheep will no longer be susceptible to infection until warm weather returns. Prevention is aimed at regular strategic treatment with effective anthelmintics to prevent long-term infection with the larvae.

Congenital Cystic Nasal Turbinates in Cattle

An apparently developmental anomaly that results in signs of nasal obstruction has been reported in cattle.[1] The nasal conchae lack the normal communication with the nasal cavity and become filled with a thick white fluid, which may account for the enlargement. Signs are evident at or near birth and include progressive stridor, tachypnea, decreased airflow, exercise intolerance, mouth breathing, and short, convex nasal bones. Digital, radiographic, and endoscopic examinations of the nasal cavity reveal large, smooth, bilateral cystic ventral nasal conchae, often bilobate. Differential diagnoses include foreign

bodies, trauma, and tumors. Surgical removal of the conchae with bilateral dorsolateral nasal bone flaps relieves the obstruction. Transnasal removal using obstetric wire has been described.[2]

Diseases of the Sinuses

John R. Pascoe

Sinusitis

Definition and Etiology Inflammation of the paranasal sinuses is most common in cattle and occurs infrequently in sheep and goats. Typically the frontal or maxillary sinuses are involved, and a variety of bacteria may be isolated. The proximate cause for infection is usually dehorning (frontal sinusitis) or infected teeth (maxillary sinusitis). Other causes include extension of actinomycosis or nasal neoplasia into the sinus, injuries to the horn, facial fractures, respiratory viruses (including malignant catarrhal fever, infectious bovine rhinotracheitis [IBR], and parainfluenza viruses), sinus cysts,[1] lymphosarcoma,[2] and *O. ovis* (in sheep).

Clinical Signs and Differential Diagnosis Sinusitis associated with dehorning may be acute or may occur weeks to months later; typically only one sinus is affected. Nonspecific clinical signs include anorexia, lethargy, reluctance to move, and fever. When sinusitis occurs acutely after dehorning, the portal of entry is frequently open and discharging pus, and the animal is often febrile (39.5° C to 40.5° C). In chronic sinusitis, signs may include unilateral or bilateral nasal discharge, mild stridor, changes in airflow, and foul breath odors that are frequently unilateral; fever is not common. The animal may hold its head at an odd angle (extended up or down, tilted) and may squint the eyelids as if in pain.[3,4] With chronicity, frontal bone distortion, exophthalmos, and neurologic signs may occur.[4,6] In one report of 12 cattle with frontal sinusitis, 4 cattle had abnormal posture, with an extended head and neck, partially closed eyes, and a tendency to head-press or to rest the head on a stationary object; the other 8 cattle were apprehensive and intolerant of head manipulation.[4] Extension of infection may involve the central nervous system.

Occasionally sinusitis irritates the animal sufficiently that it may rub its head on the ground, driving more debris into the sinus. Maxillary sinus cysts have been observed in cattle.[1] Typical signs included unilateral facial swelling over the affected sinus; mucopurulent, nonfetid nasal discharge; and radiographic evidence of septal deviation. One cow had stertorous respiration with diminished airflow. Differential diagnoses for sinusitis include facial fractures, nasal tumors, actinomycosis, actinobacillosis, retrobulbar abscess, and lymphosarcoma.

Diagnosis Diagnosis can usually be made based on clinical signs. Diagnostic aids may be useful in selected cases, particularly when there is no recent history of dehorning, or in cases of maxillary sinusitis. The hemogram is quite variable and is of little assistance in diagnosis. Percussion of the sinus may reveal a dull, full sound and may elicit pain. If the bone has been greatly thinned and has gas underlying it, percussion may produce a hyperresonant sound. Fractures, soft-tissue masses, dental disease, fluid in the frontal sinus, or lysis of bony septa may be evident on radiographs.[4] Sinus centesis may yield purulent material, which should be cultured and examined cytologically. A small area over the affected sinus is clipped and surgically prepared, and local anesthetic is infiltrated subcutaneously. Then a small stab incision is made through the skin and periosteum, and a Steinmann pin is used to drill a small hole. Polyethylene tubing is inserted, and attempts are made to aspirate material. A small amount of sterile isotonic fluid can be injected and aspirated to obtain a washing. The stab incision is closed unless sinusitis is confirmed.

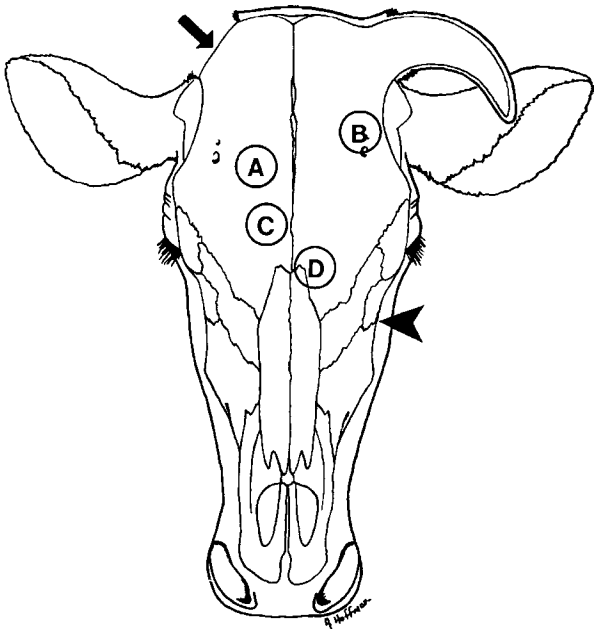


FIG. 31-71 Trephine sites for sinusotomy. **A,** Dorsal frontal sinus. **B,** Postorbital diverticulum. **C,** Rostral frontal sinus. **D,** Turbinate portion of frontal sinus. The maxillary sinus is trephined ventral to a line from the infraorbital foramen to the medial canthus *(arrowhead)*. If draining tracts are present at the poll, an additional sinusotomy can be made in the cornual portion of the frontal sinus *(arrowhead)*.

Treatment and Prognosis Trephine sites for sinusotomy (Fig. 31-71) are as follows:

1. Dorsal frontal sinus
2. Postorbital diverticulum
3. Rostral frontal sinus
4. Turbinate portion of the frontal sinus
5. Maxillary sinus

Cattle that have frontal sinusitis after dehorning should be treated by sinusotomy and drainage of the sinus.[7] Sinusotomy sites should be based on anatomic landmarks[4] and modified as needed to accommodate any frontal bone distortion or wounds related to dehorning.[4] Sinusotomy should be performed 3 to 4 cm from midline, intersecting a line drawn between the caudal aspect of the orbits. If draining tracts are present at the poll, an additional sinusotomy can be made in the cornual portion of the frontal sinus.[4] Sinusotomy is performed after sedation and local anesthetic infiltration of the centesis site(s). A 2-cm-diameter circular piece of skin is excised, and a 19-mm (¾-inch) trephine used to create an opening into the sinus, through which purulent fluid should be evacuated and the sinus lavaged.

Additional trephine sites that permit access to other regions of the frontal sinus include the postorbital diverticulum, which is trephined approximately 4 cm caudal to the dorsal rim of the orbit, just above the temporal crest of the frontal bone; the rostral frontal sinus, which is trephined just caudal to a line between the centers of the orbits and to either side of the midline; and the turbinate portion of the frontal sinus, which is trephined just rostral to the line described and to either side of the midline.

Access to the maxillary sinus is achieved by trephining ventral to a line from the infraorbital foramen to the medial canthus. If an infected tooth is the cause of maxillary sinusitis, a sinusotomy is created with a trephine over the affected tooth to repel it; otherwise, the hole is usually made just dorsal and caudal to the facial tuberosity. The trephine site should be higher in the sinus of younger animals because the tooth roots are longer.

If the frontomaxillary and nasomaxillary openings are still patent, one trephine site may be sufficient, with the natural opening providing ventral drainage. In more chronic cases, two trephine sites (for

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ingress and egress) are needed. Another alternative in chronic sinusitis is the use of a curved steel sinus probe (1 cm diameter × 55 cm long), which is forcefully driven through the septal plates of the frontal sinus into the nasal meatus for ventral drainage.[8] The frontal sinus is very compartmentalized in mature sheep and goats, and effective drainage is difficult. Therapy should therefore be aggressive in these species, even in early cases, and double trephination or bone flaps for exposure and curettage should be considered.

If a tooth has been repelled, a roll of gauze or dental impression material should be used to occlude the alveolar socket to prevent feed material from entering the sinus. A strip of umbilical tape tied around the gauze roll or a wire in the dental material is passed through socket, sinus, and trephine hole and secured to the face by tying around another roll of gauze as a stent. These gauze packs are replaced each time the sinus is flushed. The sinus is lavaged daily with dilute antiseptic solutions such as 0.1% povidone iodine or chlorhexidine in saline. Lavage is continued until infection is resolved. Enzymes (papain or 200,000 U of streptokinase and 50,000 U of streptodornase in at least 10 mL of normal saline solution) may help remove thick exudate.

Parenteral antibiotics and NSAIDs (aspirin, 100 mg/kg PO q12h or flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) are indicated if systemic signs are present. In the absence of microbial culture and susceptibility results, penicillin G procaine (22,000 U/kg IM q12h) is recommended as the antibiotic of choice because *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is the most common organism isolated from cattle with chronic frontal sinusitis resulting from dehorning. *Pasteurella multocida* is the most common organism isolated from infections of the frontal sinus not associated with dehorning.[4] Penicillin may be effective against some isolates of *P. multocida;* alternatively, oxytetracycline can be administered if *P. multocida* is suspected (11 mg/kg IV or SC q24h, or 20 mg of long-acting oxytetracycline per kilogram SC q72h). If bacterial culture and susceptibility results are available, antimicrobial therapy should be modified accordingly. Early cases often resolve in 10 to 14 days, with a good prognosis. Long-term therapy (weeks) is frequently needed in chronic cases; the prognosis is more guarded, and salvage is often the best option.

Prevention and Control Dehorning ruminants as neonates, particularly if a "closed" method such as a dehorning iron is used, is the most effective way to prevent frontal sinusitis. In larger cattle, surgical dehorning with primary skin closure achieved under aseptic conditions minimizes the likelihood of sinusitis.[9] When this is not practical, dehorning should be avoided in rainy, windy, or dusty conditions, and fly control must be used. The dehorning of mature sheep or goats leaves massive wounds that typically take 4 to 6 weeks to close by second intention and so are susceptible to infection; special care, such as bandaging for the initial 7 to 10 days, must be taken.[10] Sinusitis did not occur in goats aged 2 to 24 months dehorned with a technique in which primary skin closure was achieved.[11]

Diseases of the Pharynx, Larynx, and Trachea

Amelia R. Woolums[§]

Pharyngeal Trauma, Abscesses, Cellulitis, and Granulomas

Definition and Etiology Pharyngeal trauma may result in hematomas, foreign body granulomas, cellulitis, or abscesses. Trauma usually results from careless use of balling guns, dose syringes, paste-type anthelmintics or calcium preparations, specula, and stomach tubes. Rough, stemmy feeds (especially when chopped), grass awns, briars, and foreign objects (e.g., nails, baling wire) may also cause punctures. Migrating foreign objects or medications (e.g., mineral oil, anthelmintics) may cause pharyngeal granulomas. Hematomas and puncture wounds often result in abscess formation. Diffuse cellulitis may also result. Common bacteria involved include *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Actinobacillus* spp., *Pasteurella* spp., *Bordetella* spp., *Fusobacterium necrophorum,* and *Streptococcus* spp. In cases of particularly virulent bacterial invasion, the condition can become rapidly fatal. *C. pseudotuberculosis* (caseous lymphadenitis) may localize in the pharyngeal nodes of sheep and especially goats. Caseous lymphadenitis is discussed later in this chapter and also in relation to the hemolymphatic system in Chapter 37.

Clinical Signs and Differential Diagnosis Signs of pharyngeal trauma vary with the severity of the resulting reaction (e.g., peracute cellulitis vs. chronic abscess or granuloma). Prominent signs include inspiratory dyspnea with stertorous inspiratory sounds and a prolonged inspiratory phase; extended head and neck; ptyalism, which is often profuse; quidding; evident pain on swallowing or reluctance to swallow solid feed but willingness to drink liquids; prolonged chewing of boluses; regurgitation of food or saliva through the nostrils caused by pharyngeal paresis; mucopurulent to bloody nasal discharge and fetid odors, usually bilateral; cough; bloat; and visible or palpable swelling in the pharyngeal area.[1,2] Megaesophagus has been reported subsequent to pharyngeal trauma.[3] Palpation of the pharynx may increase the stertor and cause pain. In severe cases, systemic signs of fever, anorexia, depression, dehydration, and forestomach stasis may be present. Aspiration pneumonia may be a secondary complication.

Differential diagnoses include pharyngeal tumors; lymphosarcoma; sialoliths; rabies; botulism; actinobacillosis; necrotic laryngitis; laryngeal abscesses, trauma, edema, or paralysis; and laryngeal tumors.

Diagnosis A thorough manual examination of the oropharynx or a visual examination with an adequate speculum and light source usually confirms the diagnosis of a pharyngeal swelling and often reveals a puncture that is discharging pus. Cases in which the infection is diffuse can be more difficult to recognize, and endoscopy or radiography can be particularly helpful.[1] Restraining the jaws with a McAllum speculum allows a guarded needle attached to a length of tubing and a syringe to be inserted into the swelling for aspiration of any swelling identified. This helps to differentiate localized abscesses from granulomas, hematomas, cellulitis, and tumors; allows culture and sensitivity determinations on abscesses; and may aid in cytologic diagnosis of granulomas or tumors. Radiographs may reveal foreign bodies (Fig. 31-72) or air densities (Fig. 31-73) in the pharyngeal tissues. The complete blood cell count (CBC) usually reflects an inflammatory process, with a neutrophilic leukocytosis and a left shift, or a neutrophil-lymphocyte reversal. Dehydration is frequently evident. If the animal is unable to swallow, large amounts of bicarbonate may be lost through the saliva, which may lead to evidence of metabolic acidosis on blood gas analysis or serum biochemical profile.

Treatment and Prognosis Discrete pharyngeal abscesses are usually best drained into the pharynx. Whenever possible, the procedure should be done on the standing animal without sedation to preserve the cough reflex and prevent aspiration. A good oral speculum and excellent restraint are needed. The head should be kept lowered. A guarded blade such as a hook blade from a fetotomy set is introduced into the pharynx, and the abscess is lanced. The cavity is flushed with a mild antiseptic such as 0.2% povidone iodine in saline solution, again taking care to prevent aspiration. Other options include drainage to the exterior, drainage and flushing with a large-gauge needle and tubing, and extirpation.[2] Removal of a

[§]Previous contributions by John C. Baker and John A. Smith are acknowledged.

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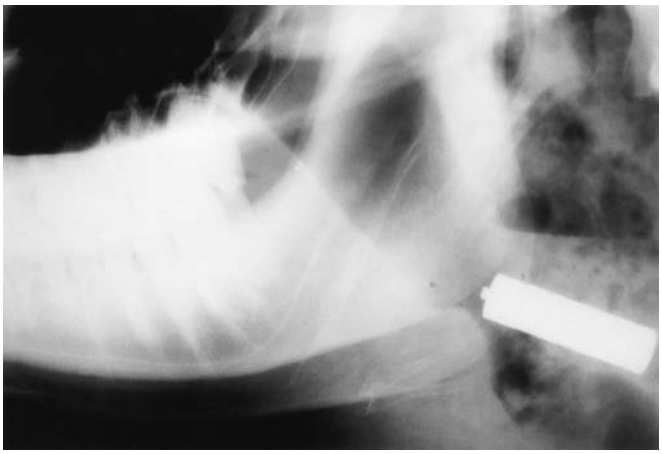


FIG. 31-72 Radiograph of the pharyngeal area of a cow. Note magnet located in the retropharyngeal tissue.

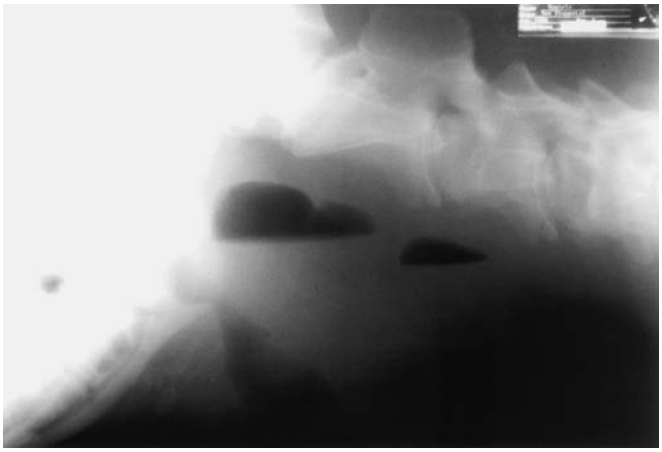


FIG. 31-73 Radiograph of the pharyngeal area of a cow. Note air densities in the tissue, suggestive of abscess formation.

bacterial granuloma from the pharynx of a cow via electrocautery has been described.[4] Systemic antibiotics are administered in accordance with culture and sensitivity results, or, in their absence, procaine penicillin G (22,000 U/kg IM q12-24h), tetracyclines (11 mg/kg IV or SC daily, or 20 mg/kg of long-acting oxytetracycline SC q72h), or sulfadimethoxine (55 mg/kg IV loading dose followed by 27.5 mg/kg IV q24h) are used. Nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin (100 mg/kg PO q12h) or flunixin (1.1 to 2.2 mg/kg IV daily or divided twice daily) help relieve pain, swelling, and stertor. In animals with severe persistent dyspnea, tracheostomy may be necessary. Granulomas and diffuse cellulitis are likewise treated medically with appropriate antimicrobials and antiinflammatory drugs. Supportive therapy such as IV fluids or feeding through a rumenostomy site may be necessary if the animal refuses to eat or drink. The prognosis for most pharyngeal abscesses, hematomas, cellulitis, and granulomas is usually good with appropriate therapy.

Dorsal Displacement of the Soft Palate

Although rare, dorsal displacement of the soft palate has been reported in cattle.[5] Respiratory noise is apparent on inspiration and expiration but is loudest on inspiration. Diagnosis can be made by endoscopic examination. Treatment is similar to that used in horses and can include conservative therapy, which consists of antiinflammatory drug therapy and rest, or the condition can be surgically corrected.

Subepiglottic Cyst

Although rare, a subepiglottic pharyngeal cyst causing upper airway obstruction has been reported in cattle. Surgical removal by a peroral approach has been described.[6]

Necrotic Laryngitis (Calf Diphtheria, Laryngeal Necrobacillosis)

Definition, Etiology, and Epidemiology Acute to chronic infection of the laryngeal mucosa and cartilage of young cattle is very common, particularly in feedlots. Laryngeal contact ulcers[7] probably provide a damaged mucosal surface, which then allows invasion of the cartilage by *F. necrophorum,* which is the proximate cause of the lesions. It has also been suggested that *Histophilus somni* is the primary agent inducing a perilaryngeal vasculitis and that *F. necrophorum* represents a secondary bacterial invader.

The disease is most common where cattle are housed in dirty or crowded conditions and in feedlots. Most feedlot cases occur in animals on feed for longer than 30 days. The incidence is sporadic. Cases occur year round, but there appears to be a higher incidence in fall and winter. The disease has a worldwide distribution.

Clinical Signs and Differential Diagnosis The problem occurs most commonly in calves from 3 to 18 months of age, up to about 24 months. It is characterized by an acute onset of a moist, painful cough, which the animal may attempt to suppress because of pain. Frequently a severe inspiratory dyspnea with a loud guttural stertor and open-mouth breathing with the head and neck extended are observed. The animal may salivate, make frequent painful swallowing movements, and stand and sip water continually. Signs of systemic disease include anorexia, depression, and fever (as high as 106° F [41.1° C]), and hyperemic mucous membranes are present. There is often a bilateral nasal discharge and a fetid odor to the breath. The larynx may be visibly or palpably swollen, and palpation may elicit a cough, cause pain, and markedly increase the dyspnea and stertor. If untreated, many calves will die in 2 to 7 days as a result of systemic effects of bacterial toxins and upper airway obstruction. Recovered cases may have a chronic roaring respiration and a harsh, dry cough because of the misshapen larynx. Aspiration pneumonia and chronic "poor doers" are common sequelae. Differential diagnoses include pharyngeal trauma (abscess, cellulitis), severe viral laryngitis (e.g., infectious bovine rhinotracheitis [IBR]), actinobacillosis, and laryngeal edema, abscesses, trauma, paralysis, and tumors.

Diagnosis The diagnosis is usually made presumptively based on clinical signs alone. A laryngoscopic or endoscopic examination can help confirm the diagnosis, but care must be taken to prevent further stress and respiratory embarrassment. Acute cases show changes in the CBC consistent with any acute septic condition: leukopenia caused by neutropenia with a left shift. In chronic or ongoing cases, leukocytosis with neutrophilia, monocytosis, and hyperfibrinogenemia may be present.

Pathophysiology *F. necrophorum* normally does not penetrate intact mucous membranes. Laryngeal contact ulcers are thought to provide the portal of entry for *F. necrophorum,* which is ubiquitous. Laryngeal contact ulcers are also very common in slaughter cattle and are speculated to be caused by the following combination of factors: (1) an acute mucositis from mixed upper respiratory tract infections (such as IBR virus, bovine respiratory syncytial virus [BRSV], parainfluenza virus type 3 [PIV-3], mycoplasma, and bacteria, including *Mannheimia, Pasteurella,* and *Histophilus* spp.); (2) reflex coughing and swallowing, which accelerate the rate of laryngeal closure; and (3) resulting erosion of the swollen membranes over the vocal processes and medial angles of the arytenoid cartilages.[8] It has also been proposed that necrotic laryngitis results from

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a perilaryngeal vasculitis initiated by *H. somni* with secondary invasion by *F. necrophorum*.[9] Necrotic laryngitis can alter pulmonary function such that the growth rate is impeded, and it also predisposes to secondary bacterial pneumonia.[10]

Necropsy Lesions The lesions are typically located over the vocal processes and medial angles of the arytenoid cartilages. Acute lesions consist of marked edema, hyperemia, and swelling of the mucous membrane around a necrotic ulcer, with accumulated exudate. The lesions spread along the vocal processes and vocal folds and may extend into the cricoarytenoideus dorsalis muscles. In chronic cases the lesions consist of a focus of necrotic cartilage surrounded by purulent exudate, with a tract extending to the mucosal surface. The tract opening is surrounded by granulation tissue and may drain pus. The arytenoid cartilage may be rotated into the lumen or may contain mucosal cavities lined with thin, hyperemic epithelium.[8]

Treatment, Prognosis, Prevention, and Control Oxytetracycline (11 mg/kg IV or SC q24h, or 20 mg/kg of long-acting oxytetracycline SC q72h) or procaine penicillin G (22,000 U/kg IM q12-24h) is appropriate; sulfonamides are also usually effective. NSAIDs (aspirin, 100 mg/kg PO q12h, or flunixin, 1.1 to 2.2 mg/kg IV once daily or divided twice daily) reduce swelling, inflammation, and fever. Cases with severe respiratory distress may benefit from one or two doses of steroids (dexamethasone 0.05 to 0.2 mg/kg IV or IM once or twice), but repeated doses of steroids are not recommended. A tracheostomy may be necessary in severe cases to relieve dyspnea and rest the larynx. Good nursing and supportive care are also important, including shelter, adequate ventilation, easy access to feed and water, and oral or intravenous fluids if needed. The prognosis is good when the condition is detected very early and treated vigorously; when extensive cartilage necrosis occurs, a fatal outcome or chronic ill-thrift with stertorous breathing is expected. There are no specific control measures. The proposed pathogenesis would suggest that measures to control other respiratory diseases may reduce the incidence of necrotic laryngitis.

Laryngeal Granulomas

Laryngeal granulomas have been described in cattle.[11] They may originate from laryngeal contact ulcers that have been described in feedlot cattle at slaughter (see the previous section on necrotic laryngitis for more information).

Laryngeal Papillomatosis

Papillomas of the larynx are common in feedlot cattle. They are caused by a papovavirus, which is thought to enter laryngeal contact ulcers (see the previous section on necrotic laryngitis). Characteristic signs of laryngeal papillomatosis are stertorous respiration and cough. Differential diagnoses include necrotic laryngitis; pharyngeal trauma, abscess, or granuloma; actinobacillosis; and laryngeal abscesses, trauma, edema, paralysis, and tumors. The lesions are sessile to pedunculated, yellow, frondlike, 1- to 10-mm growths over the vocal processes of the arytenoid cartilages.[8] Treatment usually is not indicated but involves surgical removal. Measures to decrease other respiratory infections and thereby decrease contact ulcers may lower the incidence of papillomas.

Laryngeal Abscesses

Abscessation of the arytenoid cartilages caused by *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) has been reported in calves[12] and sheep.[13] Clinical signs include tachypnea, extension of the head and neck, cyanosis, and a severe progressive dyspnea with marked stertor that can be localized to the larynx. Many affected animals remain alert and afebrile and continue to eat until the terminal stages of severe dyspnea. Endoscopy reveals generalized edema and hyperemia of the laryngeal mucosa and obstruction of the rima glottidis by swelling of one or both arytenoids. Radiographs may demonstrate soft-tissue swelling of the larynx. The condition has been speculated to be initiated by grass awns, trauma, hereditary predisposition, or congenital cavitations in the cartilages. In sheep, rams appear to be more commonly affected than ewes, and two reports found a breed predisposition in Texels and Southdowns, although other reports have indicated that various breeds are affected.[13] The necropsy lesions consist of encapsulated abscesses containing pus and necrotic debris in the arytenoid cartilage, usually in the vicinity of the vocal cord. A tract from the abscess typically opens in an area of granulation tissue in the laryngeal mucosa. Treatment consists of tracheostomy, antibiotics (usually penicillin G procaine at 22,000 U/kg IM q12-24h), and NSAIDs (aspirin, 100 mg/kg PO q12h, or flunixin, 1.1 to 2.2 mg/kg IV daily or divided twice daily). The prognosis for recovery is considered guarded unless the condition is detected in the earliest stages and treated vigorously; however, one affected heifer lived for at least 1 year and was bred successfully after permanent surgical tracheostomy for chronic arytenoid abscessation.[14]

Other Laryngeal Obstructions (Laryngeal Trauma, Edema, Paralysis, and Foreign Objects)

Other laryngeal obstructions are all sporadic and may manifest with similar signs. Trauma to the larynx may result from roping or injury in restraint devices. Inappropriate placement of an endotracheal tube can potentially damage the larynx. The respiratory system is the main target organ for anaphylaxis in ruminants, and laryngeal edema can be a prominent component of this syndrome. Inhalation of smoke or other noxious gases also may cause laryngeal edema. Paralysis of the larynx was reported in a sheep with a false carotid aneurysm[15]; presumably other lesions of the neck or anterior mediastinum could cause laryngeal paralysis through involvement of the recurrent laryngeal nerves. Laryngeal hemiplegia has been reported in association with *Sarcocystis* spp. infection of the muscles of the larynx and pharynx in a ram.[16] Foreign objects more commonly lodge in the pharynx, but sharp objects and food materials may be aspirated and lodge in the larynx. Signs common to these laryngeal obstructions include inspiratory dyspnea, prolongation of the inspiratory phase, mouth breathing, stertor, cyanosis, salivation, and extension of the head and neck. Palpation of the larynx may reveal swelling and may exaggerate the dyspnea and stertor. Differential diagnoses include necrotic laryngitis, laryngeal abscesses, severe viral laryngitis, actinobacillosis, and tumors. Endoscopy and radiology are required in most cases to differentiate these conditions. Hematologic analysis may give some indication of the presence of bacterial infection; a stress leukogram may also be seen. Tracheostomy is indicated in all severe cases. Surgical correction of laryngeal obstruction by tracheolaryngotomy has been described in cattle.[17]

Laryngeal trauma and paralysis may resolve spontaneously or may require reconstructive surgery. Foreign objects should be removed surgically or endoscopically. NSAIDs (aspirin, 100 mg/kg PO q12h, or flunixin, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help reduce swelling, edema, and respiratory embarrassment in all forms of obstruction. If anaphylaxis is suspected, corticosteroids may be useful.

Tracheal Collapse and Stenosis

Definition and Etiology Tracheal collapse or stenosis is infrequently reported in cattle and goats.[18-21] The cause is usually unknown, but the problem may result from cranial thoracic trauma, roping, tracheostomies, or possibly congenital defects. In cattle the majority of reports have described tracheal collapse in calves in which signs were usually first evident at several weeks of age.[18,19] The

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FIG. 31-74 Radiograph demonstrating collapse of the thoracic trachea in a calf.

majority of these cases also involved the thoracic trachea (Fig. 31-74), suggesting a congenital lesion. However, in most calves with tracheal collapse the condition has been a result of dystocia at birth, especially breech presentations, which suggests a traumatic cause.[22] In contrast to reports in cattle, tracheal collapse has been reported in a mature goat that showed no previous signs of respiratory abnormality.[21]

Tracheal collapse has also been reported in Texel-cross lambs with inherited chondrodysplasia[23]; affected lambs were normal at birth but developed exercise intolerance as early as 1 week of age. Severely affected lambs developed fatal respiratory compromise when exercised. Tracheal stenosis can also occur in lambs born to ewes that ingest *Veratrum californicum* root and rhizome material at days 31 through 33 of gestation.[24]

Clinical Signs and Differential Diagnosis

Clinical signs of tracheal collapse may include fever, tachycardia, tachypnea, cyanosis, and mucosal hyperemia with vessel engorgement, but affected animals may have normal vital signs and are otherwise alert and in good condition. Dyspnea is usually induced or exacerbated by excitement or exercise or may be severe at rest. Stertorous respiration is usually evident, is frequently worse on inspiration, and can often be localized to the trachea on auscultation. The inspiratory phase is prolonged, and a "honking" cough is characteristic, especially with intrathoracic collapse. Palpation may reveal or induce the collapse when the cervical trachea is involved. Tracheal palpation or elevation of the head may increase the stertor or induce the honking cough. In some cases there may be other evidence of trauma (fractured ribs, sternebrae), and in some animals pneumonia may be present. There is no response to antibiotics, steroids, or tracheostomy.

Texel-cross lambs with tracheal collapse resulting from inherited chondrodysplasia also exhibited retarded growth, forelimb varus, and reluctance to walk. Severity of signs varied among affected individuals; some died or were euthanized within weeks because of respiratory compromise, whereas others survived to breeding age.[23] Animals that survived for several months often developed arthritis characterized by severe erosive lesions of the articular cartilage of major joints, including the shoulder, hip, and stifle. Lambs with congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* died within 5 minutes of birth after signs of severe respiratory distress.

Other possible disorders with signs similar to those seen in animals with tracheal collapse or stenosis are tracheal foreign bodies, tracheal actinobacillosis, neoplasms, bronchopneumonia, necrotic laryngitis, and extratracheal compressive lesions (e.g., abscesses, tuberculosis, hematomas).

Diagnosis

Any deviation of the hemogram from normal is probably a reflection of associated pneumonia or stress. Endoscopy and radiography are the most helpful ancillary aids. Care must be taken when restraining, sedating, and passing the endoscope in these animals; oxygen should be available. In cattle with idiopathic tracheal collapse, radiography (see Fig. 31-74) and endoscopy usually reveal a dorsoventral flattening, most typically in the caudal cervical and cranial thoracic trachea, although lateral collapse and collapse in other locations (cranial cervical, intrathoracic) are occasionally encountered.

Pathophysiology

Proposed causes of tracheal collapse in other species include congenital malformations, genetic or nutritionally induced weakness of cartilage, deficient innervation of the trachealis muscles, trauma, ischemic lesions from endotracheal tube cuffs, and primary pulmonary disease. No histologic differences were noted in tracheal rings from collapsed and normal segments when this has been assessed.[18]

As previously mentioned, most calves with tracheal collapse have a history of dystocia at birth. During delivery, compression of the chest wall with fracture of the first pair of ribs may cause injury at the thoracic inlet.[25] Signs of tracheal collapse are not immediately evident at birth but rather develop over time.

Lambs with tracheal collapse associated with inherited chondrodysplasia had clinical signs most similar to a condition in humans that results from a mutation in the diastrophic dysplasia sulfate transporter gene,[26] but the causative mutation in sheep has not yet been reported. Preliminary data indicated that the chondrodysplasia was inherited via a recessive mode of inheritance.[23] Tracheal stenosis in lambs born to ewes fed *V. californicum* was presumed to be caused by cyclopamine, a steroidal alkaloid that is the toxic principle in highest concentration in *V. californicum*. It was notable that lambs developed tracheal stenosis when ewes were fed *V. californicum* at 31 to 33 days of gestation, whereas craniofacial defects typically recognized in lambs born to exposed dams are seen when the ewe ingests the toxic plant by day 14 of gestation.[24]

Necropsy Lesions

At necropsy, affected animals may have either a laterally or a dorsally compressed trachea; typically several centimeters of the trachea are affected. Necropsy of sheep with inherited chondrodysplasia reveals a trachea that is flaccid, flattened, and sometimes irregularly kinked. Tracheal rings are markedly thickened, and the lumen is narrow, possibly extremely so. Diffuse pulmonary congestion and edema, with epicardial ecchymoses, may occur as a result of terminal anoxia and respiratory distress. Other lesions include exaggerated convex curvature of the ribs, angular limb deformities, and erosive arthritis with exposure of the subchondral bone in one or more joints. Histologically, hyaline cartilage in affected organs is hypercellular and disorganized, with foci of apparent chondrolysis. Chondrocytes are larger than normal, although shrunken, apparently necrotic chondrocytes are also seen. Necropsy of lambs with congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* reveals pronounced lateral flattening of the trachea. Tracheal rings are reduced in number, with abnormal size and shape and irregular spacing. Histologically the cartilage rings in affected lambs were flattened and thin and had a thinner zone of proliferating chondrocytes on their outer surface compared with normal age–matched controls.[24]

Treatment and Prognosis

Mild cases may respond to confinement sufficiently to be fed out for slaughter. A number of surgical treatments have been proposed in other species, including anastomosis, bisection of tracheal rings, internal and external prostheses, and plication of the dorsal membrane.[18] External prostheses have been used successfully in calves,[18,22,25] adult cattle,[27] and a goat.[21] A favorable prognosis for surgical correction is estimated at approximately 30%.[22] A detailed description of surgical repair in calves by external prostheses has been published.[23] Successful management of lambs with congenital tracheal collapse or stenosis has not been reported, although mildly affected lambs with congenital chondrodysplasia survived into adulthood. Because of the apparent genetic basis for the disease, breeding of affected animals should not be recommended.

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Tracheal Foreign Bodies and Masses

Ruminants may occasionally inhale foreign objects that lodge in the trachea. There are also two reports of tracheal actinomycosis that resulted in signs of tracheal obstruction.[29] Signs include a chronic cough, inspiratory dyspnea, audible stridor that can be localized to the trachea, extension of the head and neck, open-mouth breathing, and salivation. Differential diagnoses should include pharyngeal trauma; necrotic laryngitis; laryngeal abscesses, trauma, edema, or paralysis; tracheal collapse; and extratracheal compressive lesions. Endoscopy and radiology are important aids to diagnosis. Care must be exercised in restraint and in passage of the endoscope. Some small objects may be retrieved by a snare passed through an endoscope; others may require tracheostomy. When possible, the tracheostomy should be performed below the object. The actinomycotic masses are soft, pedunculated lesions with a granular surface containing small yellow foci. Of the two reported cases of tracheal actinomycosis, one died of asphyxiation and the other responded initially to partial surgical removal of the masses, tracheostomy, and therapy with sodium iodide, penicillin, and streptomycin but relapsed some months later.

Tracheal Edema Syndrome of Feedlot Cattle

Tracheal edema syndrome has also been referred to as *tracheal stenosis* in feedlot cattle. In this condition extensive edema and hemorrhage in the dorsal wall of the trachea result in coughing, dyspnea, and stertor, which has given rise to the term "honker cattle."[30] Tracheal edema syndrome occurs in two forms, characterized by either acute dyspnea or a chronic cough. It is not known whether the two forms are related. Although the syndrome has been recognized for years, no controlled research has been undertaken to determine the cause or risk factors of this syndrome, and the cause is unknown. Theories regarding possible causes include infections with upper respiratory viruses or bacteria such as *P. multocida* or *H. somni,* trauma to the trachea from feedbunks, passive congestion and edema from excessive fat accumulation in the thoracic inlet, hypersensitivity reactions, and mycotoxins.[31]

The acute dyspnea syndrome occurs mainly in heavy feedlot cattle in the latter two thirds of the feeding period and is most common in southern plains feedlots. It is sporadic and more common in summer, possibly because of exacerbation by hot weather. At one extreme, sudden deaths without the onset of noticeable clinical signs have been reported, and at the other extreme subclinical disease was evidenced by lesions in animals at slaughter that did not have clinical signs. Other factors that increase respirations also may cause signs to appear. Signs include an acute onset of dyspnea and loud guttural inspiratory sounds that can be localized to the lower trachea. Open-mouth breathing, extension of the head and neck, and cyanosis, leading to recumbency and death by asphyxiation, are present. Differential diagnoses for this form include pharyngeal trauma or abscess; necrotic laryngitis; IBR; laryngeal abscess, tumor, foreign object, edema, or paralysis; tracheal foreign object, mass, or collapse; and acute interstitial pneumonia.

The chronic form occurs in lighter cattle (135 to 400 kg [300 to 900 lb]) and is more common in western plains feedlots. It is also sporadic but less seasonal. Affected animals may have a history of IBR or pneumonia. The main sign is a continuous, frequent, deep, hacking, nonproductive cough. The animal may be unthrifty but is otherwise normal in appearance. The main differential diagnoses are necrotic laryngitis or mild, chronic suppurative pneumonia. Endoscopy and visualization of the lesions subsequently described aid in the diagnosis. Necropsy of the acute form reveals an edematous thickening of the submucosa and mucosa of the dorsal trachea (Color Plate 31-1) as much as 5 cm thick and extending 20 to 30 cm from the midcervical area to the thoracic inlet or tracheal bifurcation. There is also extensive mucosal, submucosal, and peritracheal edema and/or hemorrhage, possibly related at least in part to agonal breathing. There may be no other lesions of the airway or lungs, and abnormalities (e.g., pulmonary edema, bronchitis, interlobular edema and emphysema, alveolar hemorrhage) may not be seen. Lesions in the chronic form consist of hyperemia of the mucosa of the caudal third of the trachea, with a thin layer of mucopurulent exudate. The mucosa may have a cobblestone appearance or even large, fiber-like projections and polyps. No effective treatment exists for the chronic form. Corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV; prednisolone, 1 to 2.2 mg/kg IM or IV daily) are recommended for the acute form, as well as such practices as preventing stress, providing shade, and cooling with water sprays and fans. Broad-spectrum antibiotics have been recommended by some,[30,31] whereas others have not found them to be necessary.[32] However, because animals with tracheal edema syndrome may be difficult to distinguish clinically from animals with conditions that could respond to antimicrobials (such as necrotic laryngitis), antimicrobials are often administered. Because withdrawal times associated with antimicrobial administration could delay shipment of affected animals to slaughter, drugs with a short withdrawal time should be used if salvage is an option. Tracheostomy may not be helpful if placed proximal to the obstruction, and relief of dyspnea via tracheostomy may require insertion of an endotracheal tube to the tracheal bifurcation. Oxygen administration could be beneficial if available. Recovered patients tend to relapse and should be salvaged.

Lower Respiratory Tract Diseases

Amelia R. Woolums[‖]

Clinical Classification of Pneumonia

Amelia R. Woolums

In an effort to simplify the differential diagnosis of the array of lower respiratory tract diseases of cattle, a classification system based on pathophysiology and clinical signs has been suggested.[1] Three classifications were proposed:

1. Bronchial pneumonia (bronchopneumonia) is characterized pathophysiologically by invasion of pathogenic organisms that gain access to the lung through the pulmonary tree. It is characterized clinically by depression, fever, and other signs of sepsis (such as hyperemic mucous membranes or scleral injection), and an anterior-ventral distribution of abnormal lung sounds and lesions. Bronchopneumonia is the final outcome of the respiratory disease complex of ruminants, and because viruses play an important role in this disease complex, viral causes of respiratory tract disease in ruminants are placed in this category.
2. The interstitial pneumonias are a very diverse group of (usually) noninfectious diseases. Although it is difficult to make generalizations, these diseases are characterized pathophysiologically by an interstitial reaction that usually results from ingestion or inhalation of toxins or allergens. Clinically affected animals tend not to be as depressed and septic, the abnormal lung sounds and lesions are diffusely distributed, and there is little or no response to antibiotic therapy.
3. Metastatic pneumonia is characterized pathophysiologically by septic embolization of the lungs from other foci in the body, classically liver abscesses and postcaval thrombi. Clinically, cases of metastatic pneumonia exhibit signs of sepsis, as with bronchopneumonia, but with widespread pulmonary lesions and abnormal lung sounds and the eventual development of hemoptysis (see descriptions of vena caval thrombosis and metastatic pneumonia in this chapter).

[‖]Previous contributions by John C. Baker and Trevor R. Ames are acknowledged.

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The Bronchopneumonias (Respiratory Disease Complex of Cattle, Sheep, and Goats)

Amelia R. Woolums

The respiratory disease complex of ruminants consists of the single clinical entity of bronchopneumonia or pleuropneumonia but is caused by numerous combinations of infectious agents, compromised host defenses, and environmental conditions. Bronchopneumonia causes greater economic losses than any other disease of feedlot cattle or lambs and is one of the most common causes of dairy calf mortality.

In dairy calves, bronchopneumonia, sometimes called *enzootic pneumonia,* is most common in housed calves. It is called *shipping fever* in beef calves because the greatest incidence of bronchopneumonia occurs after shipment to stocker operations or feedlots; the term *bovine respiratory disease* (BRD) is also used to describe bronchopneumonia in cattle. Bronchopneumonia also occurs in nursing beef calves and in mature beef or dairy cows, sometimes in outbreaks that can have significant morbidity or mortality. Less is known about which factors are specifically the most important for putting these populations at risk for bronchopneumonia, but they are likely similar to risk factors described for housed dairy calves or feedlot cattle. The infectious agents and risk factors of bronchopneumonia of sheep and goats are similar to those of calves.

Bronchopneumonia of ruminants is a disease of multifactorial causation that occurs when a certain combination of host, environment, and infectious agent characteristics (risk factors) is active. The numerous infectious agents (Boxes 31-3 and 31-4) that are associated with bronchopneumonia are ubiquitous in ruminant populations, and the bacteria most often associated with pneumonic lesions are part of the normal resident flora of the ruminant nasopharynx. In addition to recognition of the microbial agents that contribute to the development of bronchopneumonia in ruminants, understanding of the management practices that also play a role is necessary for developing successful programs of prevention. Management practices and other risk factors for bronchopneumonia are discussed in the section Host and Environmental Risk Factors for Undifferentiated Ruminant Respiratory Disease (see p. 611).

Infectious Agents Associated with the Respiratory Complex of Cattle, Sheep, and Goats

Etiology Numerous infectious agents have been isolated from cases of bronchopneumonia in ruminants (see Boxes 31-3 and 31-4). Although infectious bronchopneumonia of ruminants is usually caused by two or more infectious agents acting together, some agents can also cause significant disease alone. Therefore the clinical and epidemiologic characteristics, means of diagnosis, and treatment and prevention of the infectious agents will be first considered individually. A description of epidemiology, diagnosis, and treatment of "undifferentiated" bronchopneumonia (bronchopneumonia with no specific causative diagnosis attempted) will then follow. The clinical signs, gross pathologic lesions, and recommended methods of diagnosis for the major infectious causes of ruminant respiratory disease are listed in Table 31-11.

Viral Agents

Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis Virus)

Definition and Etiology Bovine herpesvirus type 1 (BHV-1) is an enveloped DNA virus that is classified in the family Herpesviridae, subfamily Alphaherpesvirinae, genus *Varicellovirus*. It is associated with multiple, distinct disease syndromes of cattle that include

BOX 31-3

Viral Agents Associated with Respiratory Tract Diseases in Ruminants

Bovine

Viruses of Major Importance (Commonly Isolated or Generally Accepted to Be Important Contributors to Ruminant Respiratory Disease)

Bovine herpesvirus type 1 (BHV-1, aka infectious bovine rhinotracheitis virus [IBRV])
Bovine respiratory syncytial virus (BRSV)
Bovine viral diarrhea virus (BVDV)
Bovine parainfluenza virus type 3 (PIV-3)
Bovine respiratory coronavirus
Alcelaphine herpesvirus types 1 and 2/ovine herpesvirus type 2 (malignant catarrhal fever)

Viruses of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

Bovine herpesvirus type 4 (BHV-4)
Bovine adenovirus
Bovine rhinitis virus
Bovine reovirus
Calicivirus
Influenza virus

Ovine and Caprine

Bovine respiratory syncytial virus (BRSV)
Parainfluenza virus type 3 (PIV-3)
Adenovirus
Bluetongue virus
Ovine progressive pneumonia (maedi-visna) virus of sheep*
Pulmonary carcinoma of sheep*

*Cause of chronic progressive respiratory disease.

BOX 31-4

Bacteria, *Mycoplasma, Ureaplasma,* and *Chlamydophila* Species Associated with Bronchopneumonia of Cattle, Sheep, and Goats

Bacteria of Major Importance (Commonly Isolated or Generally Accepted to Be Important Contributors to Ruminant Respiratory Disease)

Mannheimia haemolytica
Pasteurella multocida
Histophilus somni
Mycoplasma bovis
Bibersteinia trehalosi
Mycoplasma dispar
Ureaplasma spp.
Mycoplasma ovipneumoniae (sheep and goats only)
Mycoplasma mycoides subsp. *mycoides,* large colony variant (goats)
Trueperella pyogenes (formerly *Arcanobacterium pyogenes*) (secondary opportunistic pathogen)

Bacteria of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

Pseudomonas aeruginosa
Escherichia coli
Streptococcus spp.
Staphylococcus spp.
Moraxella spp.
Salmonella spp.
Bacteroides spp. (anaerobe)
Peptococcus indolicus (anaerobe)
Fusobacterium spp. (anaerobe)
Chlamydophila spp.

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TABLE 31-11

Clinical and Gross Pathologic Characteristics of Common Infectious Agents That Cause Respiratory Disease in Ruminants

Agent	Species	Clinical Signs*	Gross Pathology*	Diagnosis
Viruses				
BHV-1 (IBR)	Cattle	Fever, depression, anorexia, serous to mucopurulent nasal discharge, muzzle hyperemia, nasal plaques, coughing, inspiratory stridor (conjunctivitis ± keratitis, abortion)	Congestion; fibrinopurulent exudate of nasal passages, larynx, trachea; in young calves, pneumonia and involvement with other organs	VI or IFA nasal swabs, conjunctival scrapings PS VI, IFA, or IHC of tissue from upper airways or lungs collected at necropsy
BRSV†	Cattle, sheep, goats	Fever, depression, anorexia, tachypnea, nasal discharge (±), coughing, expiratory dyspnea, harsh bronchovesicular sounds over cranioventral lung, crackles and wheezes rarely, quiet lung sounds caused by pneumothorax, subcutaneous emphysema	Lobules in cranioventral lung collapsed, firm, dark red; caudodorsal lung fails to collapse, rubbery texture (suggestive of acute interstitial pneumonia); dorsocaudal emphysema	IFA or RT-PCR of nasal swabs (VI unreliable) PS IFA or IHC of lung at necropsy (most reliable in acute stage of disease)
PIV-3	Cattle, sheep, goats	Like BRSV but milder, commonly asymptomatic; contributes with other agents to enzootic calf pneumonia or shipping fever	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI or IFA of nasal swabs PS VI, IFA, or IHC of lung at necropsy
BVDV	Cattle	Fever, depression, anorexia, nasal discharge, tachypnea, coughing (±); contributes with other agents to enzootic calf pneumonia or shipping fever (diarrhea, abortion, congenital defects, PI calves, hemorrhagic syndrome)	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI, ELISA, or PCR of peripheral blood buffy coat PS VI, IFA, or IHC of lung at necropsy
Respiratory coronavirus†	Cattle	Contributes with other agents to enzootic calf pneumonia or shipping fever	Not yet well characterized, probably as for PIV-3	VI (need special cells) or RT-PCR of nasal swabs PS VI or IFA of lung at necropsy
Bacteria				
Mannheimia haemolytica	Cattle, sheep, goats	Fever, depression, anorexia, signs of endotoxemia, tachypnea, evidence of pleural pain, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles (coughing not prominent)	Cranioventral lung lobes firm, dark red to gray-brown; fibrin on pleura; yellow pleural fluid that may be gelatinous; infarct-like (wedge-shaped) lesions sometimes seen	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Pasteurella multocida	Cattle, sheep, goats	Fever, tachypnea, cough, depression, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles	Cranioventral lobules (sometimes lobes) firm, dark red to purple; purulent exudate in airways; fibrin on pleura not expected	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Histophilus somni†	Cattle, (uncommon in sheep, goats)	As for *P. multocida*; possibly also evidence of pleural pain (joint effusion, infertility or abortion, otitis, conjunctivitis, neurologic signs)	As for *M. haemolytica*, although fibrinous pleuritis not as consistent; fibrinopurulent arthritis, myocarditis often seen in respiratory cases	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Mycoplasma bovis‡	Cattle	Fever, anorexia, tachypnea, cough, nasal discharge; chronic or ongoing pneumonia that fails to respond as expected to therapy (joint or tendon sheath effusion, otitis, conjunctivitis)	Cranioventral lobules collapsed, firm, dark red; multiple grossly visible raised nodules filled with caseous material (abscesses or caseous necrosis); (fibrinopurulent arthritis, tenosynovitis, or otitis common in respiratory cases; myocarditis or pericarditis)	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret; more meaningful if several in group have positive culture from characteristic lesions at necropsy)

*Clinical signs not related to the respiratory system but possibly also prevalent are listed in parentheses. Note that respiratory disease is often caused by two or more agents, so clinical signs and gross pathology in an individual or herd may be any combination of those listed for individual agents.

†Agent does not survive transport well or can be difficult to isolate; requires special handling or culture techniques to maximize likelihood of isolation.

‡Usually need to specifically request tests to isolate mycoplasmas and to specifically identify the species *M. bovis*.

BVDV, Bovine viral diarrhea virus; *BHV-1,* bovine herpesvirus type 1; *ELISA,* enzyme-linked immunosorbent assay; *IBR,* infectious bovine rhinotracheitis; *IFA,* immunofluorescent assay; *IHC,* immunohistochemistry, most commonly used on formalin fixed lung tissue collected at necropsy; *PCR,* polymerase chain reaction; *PIV-3,* parainfluenza virus type 3; *PS,* paired serology; *RT-PCR,* reverse transcriptase–PCR; *TTA,* transtracheal aspirate; *VI,* virus isolation.

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infectious bovine rhinotracheitis (IBR), conjunctivitis (see Chapter 39), infectious pustular vulvovaginitis, balanoposthitis, abortion (see Chapter 43), encephalomyelitis (see Chapter 35), and mastitis. Although only a single serotype of BHV-1 is currently recognized, two subtypes have been identified on the basis of restriction endonuclease cleavage patterns. These subtypes are referred to as BHV-1.1 and BHV-1.2; BHV-1.2 can be divided further into 1.2a and 1.2b. Either subtype can cause respiratory or genital disease; only the respiratory manifestations of infection with BHV-1 are discussed here. The respiratory form is characterized by rhinitis, tracheitis, and pyrexia and is referred to as IBR. BHV-1 can also cause pneumonia as part of a severe generalized infection in newborn calves.[1] The virus is also of great importance in the BRD complex because of its role in enhancing secondary bacterial bronchopneumonia by causing respiratory injury and immunosuppression,[2] as discussed later.

Clinical Signs Clinical signs vary and range from mild to severe. Genetic factors also appear to be an important determinant of the severity of BHV-1 infection, specifically the type-I interferon genotype.[3] Clinical signs include pyrexia, anorexia, a dramatic drop in milk production in dairy cattle, increased respiratory rate, a slight degree of hyperexcitability, ptyalism, coughing, and nasal discharge that progresses from serous to mucopurulent. Dyspnea characterized by open-mouth breathing may appear if the larynx or trachea becomes partially blocked with mucopurulent material. Auscultation of the lungs may reveal harsh bronchovesicular sounds and referred tracheal sounds. Clinical signs of lower respiratory tract infection may be exacerbated by secondary bacterial pneumonia, which is a common sequel to BHV-1 infection. Severe hyperemia and reddening of the muzzle can occur, which is the reason for the common name of "red nose" to describe BHV-1 infection. Pustules may develop on the nasal mucosa and later form diphtheritic plaques. Conjunctivitis with excessive ocular discharge may be present. Conjunctivitis with corneal opacity can also occur as the principal manifestation of BHV-1 infection and may be misdiagnosed as infectious bovine keratoconjunctivitis (pinkeye). Abortions may occur concurrently with respiratory disease, but they can also occur as late as 100 days after infection.[4] Abortions may also occur in cattle that escape serious respiratory disease.

On rare occasions, neonatal calves may suffer from both an acute respiratory and a systemic form of BHV-1 infection. The infection is characterized by rhinitis, marked lacrimation, inflammation and necrosis of the soft palate, laryngotracheitis, and ulceration of the gastrointestinal tract.[1] Vaccination of calves within 3 days of age with modified live viral vaccines has also been associated with severe fatal systemic BHV-1 infection.[5] The severity of disease in vaccinated calves was suspected to be caused by lack of maternal antibody and resultant widespread multiplication of the vaccine virus.

Pathogenesis The route of infection is by direct contact with infected cattle or aerosol; apparent transmission by aerosol has been recognized among calves separated by as little as 4 m.[6] At least three of the surface glycoproteins of BHV-1, gC, gD, and gB, mediate host cell attachment and entry through interaction with heparan sulfate proteoglycans and other host cell proteins.[7,8] Epithelial cells of the respiratory tract are the initial target of infection after respiratory exposure, and after initial infection the virus can spread intracellularly to neighboring epithelial cells via intracellular bridges. Lymphocytes and monocytes are also susceptible to infection; although infection with these cells produces little virus, they appear to be a means by which the virus reaches extrarespiratory sites after respiratory infection. In severe field cases of BHV-1 infection, the virus can be found in multiple organs, including the esophagus, spleen, and liver.[9,10]

Respiratory disease caused by BHV-1 is mediated by two major mechanisms: (1) direct injury and destruction of infected epithelial cells in the upper respiratory tract and bronchi, with resultant inflammation and increased susceptibility to infection with secondary opportunistic pathogens, and (2) immunosuppression resulting from dysfunction of neutrophils, lymphocytes, and macrophages. Immunosuppressive actions of BHV-1 include decreased neutrophil chemotaxis and mitogen-induced blastogenesis of lymphocytes,[11] decreased expression of MHC class I molecules,[12] and induction of apoptotic death of lymphocytes and monocytes.[13] BHV-1 infection modifies expression and activity of cell surface receptors in ways that can be harmful; binding of the adhesion molecule ICAM-1 (CD18/CD11a) on bovine leukocytes to *Mannheimia haemolytica* leukotoxin was increased after BHV-1 infection of cattle, leading to enhanced leukocyte death.[14]

Another important mechanism of pathogenesis of BHV-1 is the ability to establish latent infection in neural tissue.[8] After acute infection, BHV-1 can be found in a latent state in the trigeminal ganglia; the virus may also persist latently in the tonsil.[15] During latent BHV-1 infection, virus is not actively produced in infected cells; thus latently infected cattle do not shed virus. However, an RNA molecule termed the *latency related transcript* (LRT) is abundantly produced in latently infected cells. Research indicates that the LRT prevents apoptosis in cells receiving signals that should trigger apoptosis, suggesting that the LRT functions, at least in part, to promote survival of infected cells.[8] One or more proteins encoded by the LRT appear to be required for the virus to reactivate from latency.[16] Stress or administration of glucocorticoids causes reactivation of the latent virus, leading to shedding of virus and the possibility of infection of in-contact susceptible animals. Latency appears to occur in effectively all cattle that are infected with BHV-1, thus ensuring that the virus can be spread during times of stress by animals that have been free of clinical disease from BHV-1 infection for months to years. Modified live BHV-1 vaccines are also capable of causing latent infections.[17] Calves that are exposed to BHV-1 when they have moderate levels of circulating maternal antibody can develop latent infection while never showing signs of clinical disease.[18] Latency of BHV-1 is thus an important mechanism by which the virus can persist and spread in a group of cattle.

Epidemiology Studies of antibody prevalence to BHV-1 indicate that infection is widely distributed in the cattle population.[4] Adult cattle are thought to be the principal reservoirs of infection.[4] Infections of the respiratory tract by BHV-1 are prevalent when large concentrations of beef or dairy cattle are assembled, although BHV-1 does not appear to have an important role in enzootic pneumonia of calves.[19,20] Feedlot cattle appear to have higher attack rates, more severe disease, and higher case fatality rates than do range or dairy cattle. This is likely because of the stressful conditions experienced by feeder calves at the time of entry into feedlots. Entry into feedlots may also coincide with decline of passive immunity. The case fatality rate is generally low unless complicated with secondary bacterial pneumonia. Historically, disease caused by BHV-1 infection was most commonly recognized within the first few weeks after feedlot entry. However, since the 1990s, disease resulting from BHV-1 has sporadically been recognized in cattle that have been in feedlots for several months; these "late breaks" of disease are noteworthy in that they often occur in cattle that have been previously vaccinated against BHV-1.[21,22] Although BHV-1 is a relatively genetically stable virus, there is evidence that mutations are occurring in BHV-1 isolates currently circulating in cattle populations, which may help the virus escape host immunity.[22] Studies have shown that, although commercially available vaccines can still prevent disease resulting from experimental challenge with modern BHV-1 isolates, viral shedding is increased relative to cattle challenged with older BHV-1 isolates that are more similar to the strains of virus included in vaccines.[22,23] Repeat vaccination later in the feeding period has been recommended to decrease risk of late BHV-1 breaks,[21] although the efficacy of this practice has not been confirmed in clinical trials.

Necropsy Findings IBR is rarely fatal in mature cattle unless it occurs during periods of severe stress or is complicated by secondary bacterial infection of the lung. Lesions caused by BHV-1 infection

include rhinitis, laryngitis, and tracheobronchitis. The mucosa of the nasal passages and trachea can be congested or hemorrhagic. Pustular lesions (sometimes referred to as "plaques") may be observed, and these lesions may coalesce to form adherent necrotic material on respiratory (Color Plate 31-2), ocular, and reproductive mucosa. Usually the inflammatory lesions induced by BHV-1 do not extend into airways contained within the lung, but secondary bacterial bronchopneumonia with the expected pathology is common. Conjunctivitis and, less commonly, keratitis may be present. Esophageal erosions have been identified in severe natural outbreaks.[9] Perinatal infection of calves can lead to fatal systemic disease, with necrotic foci found in the liver, adrenal glands, kidneys, and other organs.[5] Although intranuclear inclusion bodies are a feature of herpesvirus infections, they are not a common histologic feature of BHV-1.

Diagnosis BHV-1 can be diagnosed by virus isolation, immunofluorescent antibody (IFA) testing, or polymerase chain reaction (PCR) to identify virus or viral nucleic acid in nasal swabs or conjunctival scrapings antemortem or from samples collected postmortem. Infection can also be diagnosed by paired serology, with tests for serum neutralizing antibody most commonly done.

Treatment and Prevention Cattle infected with BHV-1 should receive supportive care. Good-quality feed and water should be made easily available, and additional stressors such as transport, castration or dehorning, or introducing new cattle to the group should be avoided or postponed. NSAIDs such as aspirin or flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) may help severely affected individuals maintain water and feed consumption. Administration of antimicrobials appropriate to prevent infection with bacteria likely to cause secondary bronchopneumonia (Table 31-12) may be appropriate. Steroids should not be administered. Because protective immunity develops rapidly after either intranasal or intramuscular vaccination,[24-28] BHV-1 vaccination in the face of an outbreak may help limit disease, although the efficacy of this practice has not been tested in a controlled study.

Efforts to prevent BHV-1 infection should include practices that optimize host immunity and avoid management practices that put cattle at risk, such as mixing newly introduced cattle with established populations. Many brands of inactivated and attenuated BHV-1 vaccines for subcutaneous or intramuscular administration are commercially available; products are available that contain BHV-1 alone or in combination with other pathogens. Modified live vaccines are also available for intranasal administration; intranasal vaccines also include parainfluenza virus type 3 (PIV-3) with or without bovine respiratory syncytial virus. Numerous reports confirm that either parenteral or intranasal BHV-1 vaccines can protect cattle from disease after experimental challenge with virulent BHV-1[24-28] or BHV-1 followed by *M. haemolytica*[29]; only a few are referenced here. Unfortunately, there are few studies of BHV-1 vaccine efficacy in field trials, which better reflect the impact of vaccination in the "real-life" setting. In one older trial, vaccinated feedlot cattle were more likely to develop respiratory disease than unvaccinated cattle[30]; in a more recent trial there was no difference in respiratory disease between vaccinated and unvaccinated cattle, but vaccinated cattle had improved feed efficiency over the first 28 days after entering the feedlot.[31] The lack of field trials confirming vaccine efficacy may result in part from reluctance on the part of veterinarians or producers who perceive the vaccines to be useful to allow the inclusion of control groups of animals that are not vaccinated; researchers have admitted to being thwarted by this obstacle when organizing a field trial of BHV-1 vaccine efficacy.[32] In spite of the lack of published field trials supporting efficacy of BHV-1 vaccines to prevent respiratory disease, they are widely used; over 90% of feedlot cattle are reported to receive BHV-1 vaccines.[33] Historically it was thought that vaccination with modified live BHV-1 leads to protective immunity for years, or perhaps even the life of the animal, but recent evidence of infection and disease in feedlot animals within months of vaccination[21,22] indicates that this is not the case.

Although both modified live and inactivated BHV-1 vaccines are available, modified live vaccines are preferable when it is safe to use them because they are more likely to stimulate a cell-mediated immune response similar to that induced by infection. Few studies to date have compared modified live to inactivated vaccines in the same trial. When this comparison has been made, it has been to compare protection against experimental BHV-1 infection, with modified live vaccines providing superior protection in some[34] but not other[35] studies. Improved efficacy of inactivated vaccines in more recent studies[35] may be a result of inclusion of more advanced adjuvants, which can greatly improve the immune response to inactivated vaccines. Modified live BHV-1 vaccines are capable of causing latent infections, which could theoretically lead to shedding and spread of the vaccine strain of virus to in-contact naive animals.[17] Because modified live BHV-1 vaccines can induce abortion, the manufacturer's label recommendations regarding administration to pregnant cattle should be closely followed. Modified live vaccines may also lead to severe disease if administered to calves within a few days of birth[5]; intranasal modified live BHV-1 vaccines may be safer than parenterally administered modified live virus vaccines in very young calves.[36]

If a modified live vaccine is to be used, the veterinarian must then decide whether to use a product for intranasal or for parenteral administration. Both have been shown to provide protection rapidly; in one study, intranasal vaccination protected calves challenged within 48 hours of vaccination,[24] whereas other studies have shown that intramuscularly or subcutaneously administered modified live vaccine can protect cattle challenged 72 hours after vaccination.[25,28] Both types of vaccines can induce protection in cattle before serum neutralizing antibodies are evident,[27,28] indicating that cell-mediated rather than humoral immunity is responsible for protection soon after vaccination. In one trial that compared the protection afforded by intranasal versus parenteral BHV-1 vaccine, feedlot cattle that received intranasal vaccine had improved feed efficiency over cattle that received parenteral vaccine, but there was no difference in morbidity or mortality attributable to respiratory disease between the two groups.[31] Intranasally administered BHV-1/PIV-3 vaccines are theoretically preferable to parenteral vaccines because they induce a better mucosal immune response; they may also have an advantage when calves are vaccinated in the presence of passive immunity.[26,37] It appears that intranasal modified live vaccines are more likely to be spread to in-contact animals than are parenteral modified live vaccines; two studies confirmed BHV-1 shedding by nonvaccinated cattle in contact with cattle vaccinated intranasally with modified live BHV-1,[38,39] although two different studies could not identify evidence that modified live virus vaccine given intramuscularly spread to nonvaccinated cattle.[40,41]

Vaccines that have gene deletions have been developed and used in Europe.[42] These vaccines allow serologic differentiation of vaccinated from naturally infected animals and have application for BHV-1 control or eradication programs.

Herpesviruses in Sheep and Goats

Herpesviruses have been isolated from sheep and goats. The importance of herpesviruses in respiratory disease of small ruminants in North America has not been well defined.

Respiratory Syncytial Virus of Cattle, Sheep, and Goats

Definition and Etiology Bovine respiratory syncytial virus (BRSV) is an enveloped RNA virus that is classified in the family Paramyxoviridae, subfamily Pneumovirinae, genus *Pneumovirus*. This virus is named for the characteristic cytopathic effect it produces in vitro and in vivo, which is the formation of syncytial cells. BRSV shares many similarities in its biology and epidemiology with the human respiratory syncytial virus (HRSV), a common respiratory pathogen of humans with particular importance in disease of young children and the elderly. Although BRSV and HRSV are closely related, they are distinct viruses.[1] Respiratory syncytial virus (RSV) has also been isolated from sheep and goats with respiratory disease.

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TABLE 31-12

Antimicrobials Approved by the FDA for Treatment of Bronchopneumonia of Beef Cattle

Antimicrobial	Label Dose	Route of Administration	Treatment Interval (Hours)	Slaughter/Milk Withdrawal	Approved for BRD Control (Metaphylaxis)?	Approved for Sheep and Goats?
Standard Preparations						
Amoxicillin	11 mg/kg	IM, SC	24	25 days/96 hours	No	No
Ampicillin	2-5 mg/kg (22 mg/kg)*	IM	24	6 days/48 hours	No	No
Ceftiofur (sodium)	1.1-2.2 mg/kg	IM, SC (cattle) IM (sheep and goats)	24	4 days/0 days	No	Sheep and goats
Ceftiofur (HCl)	1.1 mg/kg	IM, SC	24	3 days/0 days	No	No
Enrofloxacin†	2.5-5.5 mg/kg multiday therapy	SC	24 or once	28 days/not approved	No	No
Erythromycin	8.9 mg/kg	IM	24	14 days/72 hours	No	Sheep
Oxytetracycline	11 mg/kg	IV,‡ IM,‡ SC‡	24	15-22 days‡/not approved	No	Not for injection§
Procaine penicillin G	6600 U/kg (22,000 U/kg)*	IM	24	10 days (cattle), 9 days (sheep)/ 48 hours	No	Sheep
Spectinomycin	10-15 mg/kg	SC	24	11 days/not approved	No	No
Sulfadimethoxine	55 mg/kg, initial treatment 27.5 mg/kg thereafter	IV, PO	24	7 days/60 hours	No	No
Tylosin	17 mg/kg	IM	24	21 days/not approved	No	No
Long-Acting Preparations						
Ceftiofur crystalline free acid	6.6 mg ceftiofur equivalent per kg (1.5 mL/45 kg)	SC in the ear	Once	13 days/0 days	Yes	No
Danofloxacin†	6 mg/kg	SC	48 for 2 treatments total	4 days/not approved	No	No
	8 mg/kg	SC	Once	4 days/not approved	No	
Enrofloxacin†	7.5-12.5 mg/kg	SC	Once	28 days/not approved	Yes	No
Florfenicol	20 mg/kg	IM	48	28 days/not approved	No	No
	40 mg/kg	SC	Once	38 days/not approved	Yes	No
Gamithromycin	6 mg/kg	SC	Once	35 days/not approved	Yes	No
Oxytetracycline (product formulated at 200 mg/mL)	20 mg/kg	IM, IV, SC	48-72	28 days/96 hours	No	No
Oxytetracycline (product formulated at 300 mg/mL)	30 mg/kg	IM, SC	Once	28 days/not approved	No	No
Sulfadimethoxine (sustained-release bolus)	138 mg/kg	PO	7 days	21 days/not approved	No	No
Tilmicosin	10 mg/kg	SC	72	28 days/not approved	Yes	Sheep Toxic to goats
Tildipirosin	4 mg/kg	SC	Once	21 days/not approved	Yes	No
Tulathromycin	2.5 mg/kg	SC	Once	18 days/not approved	Yes	No

*Dose that has been shown to be more effective than label-approved dose. Higher dose can be given by the same route of administration and with the same treatment interval, but use of extralabel dosages must comply with the Animal Medicinal Drug Use Clarification Act (AMDUCA), and withdrawal times must be extended.

†Extralabel use in food animals prohibited by law.

‡Varies with preparation.

§Oxytetracycline is labeled for administration to sheep in feed; not a recommended route for treatment of respiratory disease.

BRD, Bovine respiratory disease; *FDA,* Food and Drug Administration; *IM,* intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

Note: Many of the drugs listed in this table are not approved for use in veal calves; some are not approved for use in lactating dairy cattle.

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Research suggests that ovine RSV may be distinct from HRSV and BRSV, whereas caprine RSV may be more closely related to BRSV.[2,3] The possibility of interspecies transmission has not been well defined. However, a European serologic survey undertaken to determine whether nonbovine species were likely to harbor BRSV infection found that only goats, in addition to cattle, were commonly seropositive.[4] These results indicate either that goats are commonly infected with BRSV or that antigenic similarities between caprine RSV and BRSV led to production of cross-reactive antibodies in many goats. Although two major antigenic subtypes, A and B, of HRSV have been clearly defined, research has shown that BRSV is less variable than HRSV at the genetic level.[5] However, in spite of minimal to moderate differences among BRSV isolates at the genetic level, isolates can differ notably in their reactivity with monoclonal antibodies directed against individual BRSV proteins[6,7]; this indicates that apparently minor genetic differences could lead to changes that allow the virus to evade host immunity. Differences in molecular weights of viral proteins also divide isolates into two major groups.[8] A study of genetic variability in BRSV isolates collected over several decades showed that genetic change occurred over time[9,10] and that BRSV isolates commonly included in commercial vaccines differed a relatively large amount from some isolates collected from recent natural outbreaks.[9] Studies have also shown that genetic differences in BRSV isolates can be grouped by geographic origin, with some European isolates differing to a notable degree from isolates from the United States or Japan.[9,10] It is important to note that European research identified genetic changes in a region of the BRSV G glycoprotein (the viral attachment protein) that was previously thought to be highly conserved and difficult or impossible for the virus to change.[9] These changes appear to be driven by vaccination, indicating that antigenic pressure induced in cattle by vaccination can lead BRSV to change in unexpected ways. These data indicate that commercial vaccines may need to be reformulated periodically to include isolates of the virus that are similar to isolates currently circulating in natural populations.

Clinical Signs

Clinical signs of BRSV infection can vary from inapparent to severe in an infected group of cattle.[11-13] Signs of disease are limited to the respiratory system. Infected animals may display elevated rectal temperature of 40°C to 42.2°C (104°F to 108°F), depression, decreased feed intake, elevated respiratory rates, ptyalism, cough, and nasal and lacrimal discharges. Signs of disease may progress rapidly, and early signs may be missed. Thoracic auscultation may reveal increased bronchial and bronchovesicular sounds; fine crackles or wheezes may be heard, particularly in the middle or dorsocaudal lung fields. Absence of bronchovesicular sounds may be noticed in the dorsal or dorsocaudal lung fields if an emphysematous bulla is present, or if a bulla has ruptured, leading to pneumothorax. In later stages of the disease, dyspnea can become pronounced and is characterized by increased expiratory effort and mouth breathing. Subcutaneous emphysema and intermandibular edema are sometimes noted. Dramatic reduction in milk production has been reported in dairy cattle. Duration of disease is variable (1 to 2 weeks). A biphasic clinical course has been described but does not appear to be a consistent finding. Experimental infections of lambs with ovine RSV caused a mild primary pneumonia and was also capable of causing lower respiratory tract lesions in calves and deer.[14]

Pathogenesis

The means of transmission appears to be contact with infected cattle and aerosols. Fomites such as bottles and buckets are also a likely means of transmission, as fomites are an important source of HRSV transmission to children. The incubation period is 3 to 5 days. Infection with BRSV can cause bronchitis, bronchiolitis, alveolitis, and interstitial pneumonia.[11-13] After experimental infection, BRSV is found in cells of the nasal, tracheal, and bronchial epithelium by 2 days post infection and in bronchiolar and alveolar epithelial cells by day 4 post infection.[15] The virus causes epithelial cells to fuse, resulting in the characteristic multinucleated cells, or syncytia, which are seen in airways and alveoli. Epithelial cells, which may undergo apoptosis after BRSV infection,[15] slough into the lumen of airways and are phagocytized by neutrophils or alveolar macrophages.[15] Infection of alveolar macrophages and circulating peripheral blood mononuclear cells occasionally occurs,[16,17] and BRSV infection of macrophages decreases important functions of these cells, including Fc receptor expression, phagocytosis, phagosome-lysosome fusion, and production of factors that induce neutrophil chemotaxis.[18,19] Infection leads to bronchitis, bronchiolitis, alveolitis, and sometimes acute interstitial pneumonia (AIP); these changes lead to clinical signs referable to small airway and alveolar disease, including expiratory dyspnea, auscultable wheezing, and hypoxemia.[20]

The severity of disease after BRSV infection is related to host immunity. Both humoral and cell-mediated immunity contribute to protection. Clinical signs of infection are less severe in animals with moderate to high levels of serum antibody against BRSV,[21,22] and more extensive pathology is seen in calves depleted of $CD8^+$ T cells before infection.[23] Protection after intranasal vaccination is related to rapid onset of BRSV-specific immunoglobulin (Ig) A production in nasal secretions,[24] indicating that mucosal immunity is likely also important in protection against naturally occurring disease. Host immunity after exposure to BRSV can minimize disease, and clinical signs are usually the most noticeable in calves under 6 months of age.[12,25] However, very young calves are not necessarily most likely to have the most severe disease; clinical signs after experimental infection were less severe in 1-day-old calves than 6-week-old calves, apparently because of a less robust inflammatory response in younger calves.[26] Ruminants appear to be susceptible to reinfection with BRSV throughout their lives, and adult cattle can develop severe disease after BRSV infection.[12,13] Because genetic variability among BRSV isolates is not great, reinfection does not seem to be largely due to viral strain variation. Although data investigating the duration of BRSV immunity after natural infection are limited, it appears that natural infection does not confer lifelong immunity, and some cattle may be reinfected annually,[27] although clinical signs are not always apparent.

Although host immunity can protect ruminants from severe disease after BRSV infection, the host immune response can also contribute to disease. Evidence for BRSV immunopathogenesis comes from both natural outbreaks and experimental challenge studies. Cattle with severe disease after natural infection have a higher proportion of degranulated mast cells in their lungs than less severely affected cattle,[28,29] indicating that mast cell mediators contribute to physiologic and pathologic changes seen in severe cases. In experimentally challenged cattle, BRSV-specific IgE has sometimes been associated with disease severity.[30,31] Exposure to the fungus *Saccharopolyspora rectivirgula* (formerly *M. faeni*), the spores of which induce pulmonary hypersensitivity in cattle and other species, enhanced BRSV-specific IgE production in calves, indicating that environmental allergens can also affect the nature of the immune response to BRSV infection.[31] Calves infected with BRSV before infection with *Histophilus somni* developed higher levels of *H. somni*–specific serum IgE than did calves infected with *H. somni* alone.[32] Thus BRSV infection can lead to production of virus-specific IgE, which may be enhanced by coexposure to allergens; and BRSV infection may also increase IgE production in response to infection with other agents. In these cases, cross-linking of IgE bound to mast cells by binding of BRSV or other specific antigen is expected to lead to mast cell degranulation and subsequent bronchoconstriction, pulmonary edema, and other sequelae of mast cell mediator release and immediate hypersensitivity.

Other evidence that BRSV can trigger immunopathogenesis is the fact that certain BRSV vaccines have, on rare occasion, been shown to cause enhanced disease when vaccinated animals are subsequently infected with BRSV. Vaccine-enhanced disease has been seen after both natural[33,34] and experimental[35,36] infection. Vaccine-enhanced disease has also occurred in human infants vaccinated with a formalin-inactivated RSV vaccine,[37] and formalin-inactivated BRSV vaccines have caused enhanced disease in cattle in some[35,36] but not

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all[20] studies. Inactivated BRSV vaccines have also been shown to prevent disease after infection[38,39]; therefore not all inactivated BRSV vaccines enhance disease. It appears that the dose of BRSV protein, the adjuvant included in the vaccine, and probably additional factors related to the formulation of the vaccine and the genetics of vaccinated cattle determine whether enhanced disease is likely after infection of cattle given a particular BRSV vaccine.[40] Apparent vaccine-enhanced disease has also been reported in cattle that received a modified live vaccine in the early stage of a natural BRSV outbreak, which suggests that BRSV vaccination in the face of a BRSV outbreak could be harmful.[33] It is important to note that BRSV vaccines are commonly used and that vaccine-enhanced disease is rarely reported; thus vaccination is still recommended as part of any plan to control disease caused by BRSV. Many gaps exist in our understanding of what aspects of the immune response contribute to disease severity after BRSV infection or vaccination. Most research completed to date has focused on enhanced disease in calves that received formalin-inactivated BRSV. The data suggest that when enhanced disease occurs in calves vaccinated with formalin-inactivated BRSV, it is related to a relatively strong response by T-helper type 2 (Th2) cells, as evidenced by decreased production of the Th1 prototype cytokine interferon gamma,[41] increased production of BRSV-specific IgE,[42] and pulmonary eosinophil infiltration.[35] The association of BRSV-specific IgE production with disease severity in some experimental studies indicates that at least some individual ruminants will produce IgE after BRSV vaccination or infection, which may contribute to severe disease in these individuals.

The presence of co-infection with other pathogens such as *M. haemolytica*[43] or bovine virus diarrhea virus (BVDV)[44] can also increase the severity of disease after BRSV infection. Although genetic variation among BRSV isolates is not extensive, experimental challenge with certain isolates of BRSV can lead to serious disease,[20,45] whereas challenge with other isolates leads to only minimal disease.[46,47] This indicates that, in spite of limited differences among viral isolates at the genetic level, variation among BRSV isolates may still contribute to variations in disease severity.

Epidemiology

Prevalence of antibodies to BRSV in the cattle population of the United States ranges from approximately 60% to 80%.[48] The virus has been recognized in association with respiratory tract disease in nursing beef calves, dairy calves, adult dairy cows, and cattle entering into feedlots. BRSV was demonstrated to be involved in 14% to 71% of respiratory disease outbreaks in North American and European studies of calf pneumonia outbreaks involving several farms.[49] Seroconversion to BRSV has been significantly associated with treatment for respiratory disease in feedlot cattle,[50,51] and cattle with low antibody titers to BRSV at feedlot entry have increased risk of developing disease.[50] Although feedlot cattle are commonly infected with BRSV after arrival, a survey of necropsy findings at 72 Canadian feedlots found BRSV at postmortem of only 11% of the cattle that died or were euthanized because of pneumonia.[52] The low rate of isolation at necropsy suggests that if the virus contributes to the development of pneumonia in feedlot cattle, it is often no longer present by the time the animal dies or is euthanized.

BRSV therefore represents an important virus in the BRD complex on the basis of its frequency of occurrence and predilection for causing infection of the lower respiratory tract. In general, morbidity rate tends to be high in outbreaks of BRSV, whereas case fatality rate is variable, ranging from no fatalities to as high as 20%.[49]

Cattle are most likely the principal reservoirs of infection, although a European serologic survey of different species found that goats were also often seropositive,[4] indicating that goats may be a source of BRSV infection for cattle, and vice versa. The mechanism by which BRSV persists in the cattle population is not known. Possibly a similar epidemiologic pattern to that described for HRSV also exists for BRSV. HRSV is capable of reinfecting the host throughout his or her life, with the most severe disease occurring in the very young or elderly. Subsequent exposure results in mild upper respiratory tract disease. Similarly, adult cattle may periodically undergo subclinical to mild infections and serve as a source of infection for susceptible young stock. However, one study concluded that transmission among seropositive cattle was not a plausible mechanism of BRSV persistence in a dairy herd.[53] These authors suggested that persistent BRSV infection in individuals is a more plausible explanation of population persistence of BRSV. BRSV has been identified in B lymphocytes in tracheobronchial and mediastinal lymph nodes of calves 71 days after experimental infection,[54] so it may be that individual cattle harbor the virus long term and periodically begin shedding it, allowing it to periodically reappear in herds even if they are closed to new introductions. However, more research is needed before persistent infection is clearly proven to be a means by which BRSV remains established in herds.

Necropsy Findings

Grossly, BRSV infection can cause signs of AIP; therefore differential diagnoses for the typical gross lesions include other causes of AIP. Signs of AIP are most evident in the dorsocaudal lung; the affected lung is heavy, with a rubbery texture, and fails to collapse when the thorax is opened. Individual lobules may appear dark, and interstitial or bullous emphysema is often present in the dorsocaudal lung in severe cases (Color Plate 31-3). Pathologic emphysema must be differentiated from that sometimes caused by agonal breathing of cattle. Cranioventral lobes or lobules are often dark red and collapsed (Color Plate 31-4). Histologic lesions depend on the stage of infection. Neutrophilic and later mononuclear bronchitis, bronchiolitis, and alveolitis are present in infected animals. Syncytial cells may be seen in the airways or alveoli; intracytoplasmic inclusion bodies are rarely present.[12,22,45] Signs of AIP, including alveolar epithelial hyperplasia, hyaline membrane formation, and interstitial inflammatory cell infiltrate, hemorrhage, and edema, are seen in severe cases. Later, evidence of chronic bronchitis and bronchiolitis obliterans can be found.[12]

Diagnosis

Infection is diagnosed by identification of the virus in nasal secretions, tracheal aspirates, or lung lavage fluid from live calves or in lung tissue collected postmortem. BRSV is difficult to isolate, as it does not survive transport well; thus methods of identification that do not require the virus to be alive (such as immunofluorescence, immunohistochemistry [IHC], and real-time PCR [RT-PCR]) are preferable to virus isolation for the identification of BRSV. IHC of formalin-fixed tissue is convenient because the virus can be identified in tissue processed for histopathologic evaluation. If virus isolation is to be attempted from samples collected in the field, it is recommended that the veterinarian contact his or her diagnostic laboratory before collecting samples to confirm the method of sample handling to optimize the likelihood of success. Although virus is readily identifiable in lung tissue of cattle early in the course of disease (within approximately 7 days of infection), it is less likely to be found in lung tissue by 10 to 15 days post infection, even when IHC is used.[15,35]

Seroconversion as evidenced by paired serology also supports a diagnosis; virus-neutralizing or enzyme-linked immunosorbent assays (ELISAs) are most commonly used to identify BRSV-specific antibody. Identification of BRSV-specific IgM in a single acute sample is also diagnostic, but testing for BRSV-specific IgM may not be available at most diagnostic laboratories.

Treatment and Prevention

Treatment of BRSV is supportive and aimed at limiting the inflammatory response in bronchioles and alveoli and preventing secondary bacterial infection. Antiinflammatory therapy with NSAIDs (such as flunixin meglumine at 1.1 to 2.2 mg/kg IV daily or divided twice daily) is considered appropriate, but controlled studies of these drugs in animals with disease caused by BRSV are limited. Administration of one or two doses of steroid therapy (dexamethasone 0.05 to 0.2 mg/kg IV or IM once or twice) is appropriate in selected individuals with severe respiratory distress or evidence of AIP. Antimicrobials appropriate for preventing

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secondary bacterial infection are listed in Table 31-12. Insufflation with intranasal oxygen, if available, and diuretic therapy with furosemide (0.5 to 1 mg/kg IM or IV once or twice daily) may be helpful for animals suspected of having AIP. Although the prognosis for animals with uncomplicated BRSV infection is good, the prognosis for animals with AIP is guarded. Animals with severe respiratory distress should be handled with care, as even careful manipulation to administer treatment can lead to rapid respiratory decompensation and death.

Both modified live and inactivated BRSV vaccines for IM or SC administration are commercially available, and a modified live vaccine for intranasal (IN) administration which contains BRSV with BHV-1 and PIV-3 was recently released in the United States and Canada. Reports have confirmed that commercially available vaccines for IM or SC administration can protect calves against virulent experimental challenge.[38,39,55] Intranasal (IN) vaccination can also protect calves from disease following experimental BRSV challenge.[56,57] Results of some well-designed field trials testing the efficacy of parenteral (IM or SC) BRSV vaccines have been published.[58-61] In some of these trials the effect of BRSV vaccination on all clinical respiratory disease (i.e., not only disease caused specifically by BRSV) was evaluated, whereas in other trials, protection against disease caused by BRSV was specifically evaluated. Vaccination decreased all respiratory morbidity in some but not other groups of cattle evaluated. Vaccination decreased disease specifically caused by BRSV in large groups of calves if all calves in the group were vaccinated but not if half of the calves in the group were vaccinated.[59] A large clinical trial evaluating the effect of vaccination of feedlot cattle with a modified live vaccine containing BHV-1, PIV-3, and BVDV, with or without BRSV, found that pens of cattle that received the vaccine including BRSV had lower overall morbidity and mortality and lower numbers of respiratory deaths than pens of cattle that received the vaccine that did not include BRSV.[61] In summary, there is some evidence from well-designed field research that BRSV vaccines can improve resistance of cattle to respiratory disease, although this is not invariably the case. More research comparing IM/SC to IN BRSV vaccination is needed; currently data are lacking to clarify whether one route is superior to the other, particularly in field trials.

There is no RSV vaccine licensed for use in small ruminants, although these vaccines are sometimes administered to sheep or goats in an extralabel manner. However, controlled studies of the effects of extralabel administration of BRSV vaccines licensed for cattle on respiratory disease in sheep or goats have not been published.

Bovine Viral Diarrhea Virus

BVDV is an enveloped RNA virus of the genus *Pestivirus* in the family Flaviviridae. A wide spectrum of disease has been associated with BVDV infection, including subclinical infection, bovine virus diarrhea and mucosal disease (see Chapter 32), immunosuppression, repeat breeding problems, abortion, fetal mummification (see Chapter 43), congenital defects, immunotolerance, and persistent infections. Only the contribution of this virus to respiratory disease is discussed here.

Historically the role of BVDV in the BRD complex was controversial,[1-3] but more recent research provides good evidence that the virus contributes to BRD and related decreased productivity of cattle in the field in at least some cases.[4,5] Experimental challenge of cattle with BVDV alone leads to mild pneumonia,[6,7] and occasionally herd outbreaks of BVDV are first identified by the presence solely of signs that are likely to be interpreted as evidence of respiratory disease, such as fever, tachypnea, and loud bronchovesicular sounds.[8] Experimental infection studies have also shown that respiratory disease caused by *M. haemolytica*,[6] BHV-1,[9] or BRSV[10] is significantly more serious when cattle are co-infected with BVDV. This synergistic effect of BVDV with other respiratory pathogens is believed to be a result of immunosuppression caused by BVDV. The ability of BVDV to cause respiratory disease appears to depend in part on the strain of infecting virus.[7,11]

Although the results of experimental challenge studies show that BVDV can cause mild respiratory disease alone and can contribute to the development of more serious disease in combination with other pathogens, data from field cases of respiratory disease are generally considered to be of greatest relevance. Studies of naturally occurring BRD have shown that in some situations BVDV can be isolated from a majority of cattle affected with shipping fever pneumonia, particularly in association with *M. haemolytica*,[12,13] or in association with *Mycoplasma bovis* in animals with chronic pneumonia.[14,15] Seroepidemiologic studies have indicated an association of BVDV with respiratory disease in some but not all cases. The most convincing data linking BVDV to respiratory disease has come from studies of calves purchased and assembled at sale barns for shipment to feedyards across several states.[5] In 2 consecutive years BVDV was significantly more likely to be isolated from calves that were treated for respiratory disease than calves in the same group that were not treated; calves treated for respiratory disease were also significantly more likely to seroconvert to BVDV than penmates who were not treated for respiratory disease.

In addition to contributing directly to BRD by infecting the respiratory tract and enhancing the pathogenicity of co-infecting bacteria or viruses, BVDV may also contribute to respiratory disease by impairing the ability of cattle to respond properly to vaccination against other respiratory pathogens. Calves infected with BVDV before BHV-1 vaccination shed BHV-1 longer after subsequent BHV-1 infection than calves that were not co-infected with BVDV.[16] In another study, calves persistently infected with BVDV failed to develop a serologic response to a *M. haemolytica* vaccine, in contrast to control animals not infected with BVDV.[17]

In summary, although the importance of BVDV in the BRD complex has previously been debated, recent research indicates that BVDV is significantly associated with the development of BRD in at least some cases. Whereas experimental challenge studies indicate that BVDV can cause at least mild respiratory disease when acting alone, the virus appears to contribute most importantly by impairing the host's ability to resist infection and limit disease caused by other pathogens that infect the animal at the same time or soon after BVDV infection occurs.

Bovine Parainfluenza Virus 3 of Cattle, Sheep, and Goats

Definition and Etiology

Bovine PIV-3 is an enveloped RNA virus classified in the family Paramyxoviridae, subfamily Paramyxovirinae, genus *Respirovirus*. The virus has been associated with respiratory tract disease in cattle, sheep, and goats. It hemagglutinates and hemadsorbs red blood cells of certain species, which means that serum antibodies can be identified by hemagglutination inhibition assays. Variation in virulence among strains of PIV-3 has been reported.[1] Significant similarities between bovine PIV-3 and human PIV-3 have led to efforts to use bovine PIV-3 as a modified live intranasal vaccine for humans; bovine PIV-3 was found to be safe and immunogenic in a clinical trial in human infants.[2]

Clinical Signs

Uncomplicated PIV-3 infections result in subclinical to mild signs. Clinical signs, if present, may include fever, cough, nasal and ocular discharge, increased respiratory rate, increased bronchovesicular sounds, and wheezes.[3-5] The most important role of PIV-3 is in predisposing the respiratory tract to subsequent infection by other viruses and bacteria such as *Mannheimia (Pasteurella) haemolytica*. Severity of signs increases with the development of secondary bacterial pneumonia, and if death occurs it is usually the result of secondary bacterial infection. Infection with PIV-3 is widespread in sheep and goats.[6,7] Only one serotype of ovine PIV-3 has been identified, and it is related to, but distinct from, the bovine strain. Most infections are inapparent to mild.

Pathogenesis

Infection with PIV-3 can lead to signs referable to both upper and lower respiratory tract infection. After experimental infection of calves, clinical signs are evident by 2 days

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post infection, and signs peak 4 days post infection. Virus is found in the nasal passages, trachea, and bronchiolar and alveolar epithelial cells. The virus damages the pulmonary mucociliary apparatus[8] and depresses several important functions of alveolar macrophages such as Fc receptor expression, phagocytosis, and microbicidal activity,[9] which are important in predisposing infected animals to secondary bacterial pneumonia.

Epidemiology The widespread prevalence of antibodies to this virus indicates that it commonly circulates in ruminant populations.[7,10,11] This finding suggests the possibility of repeat infections or at least the persistence of antibodies after infection. Inapparent or subclinical infections with PIV-3 are common; in one report, 28 groups of calves seroconverted to PIV-3 over 8 months, but respiratory disease was seen in association with PIV-3 infection in only four of these groups.[12] Although infection can often be inapparent, if environmental and managerial practices are suboptimal, PIV-3 may become an important initiator of respiratory tract disease. Infection appears to spread rapidly in susceptible cattle housed at high population densities and in close contact. In seroepidemiologic surveys evaluating groups of calves in herds experiencing outbreaks of respiratory disease, seroconversion to PIV-3 has been associated with 14% to 38% of outbreaks evaluated.[13,14] In some surveys PIV-3 is the virus most commonly isolated from the lungs of calves that die or are euthanized because of pneumonia.[15] Feedlot cattle commonly seroconvert to PIV-3 soon after feedlot arrival, and seroconversion has been associated with treatment for respiratory disease in some[16] but not all[17] cases. In spite of the fact that feedlot cattle frequently become infected with PIV-3 after feedlot entry, a recent survey of necropsy findings at 72 Canadian feedlots found PIV-3 at postmortem examination of only 4% of the cases with pneumonia.[18] The low rate of isolation at necropsy suggests that if the virus contributes to the development of pneumonia, it may no longer be present by the time the animal dies or is euthanized.

Necropsy Findings Lesions of PIV-3 infection alone are rarely seen during postmortem examination. Experimental PIV-3 infection results in congestion of the respiratory mucosa, swelling of lymph nodes associated with the respiratory tract, and lobular consolidation concentrated in the cranioventral lung.[5] Bronchiolitis and alveolitis are seen histologically with both proliferative and degenerative changes in the epithelial cells of the bronchioles and alveoli. Syncytia and intranuclear and intracytoplasmic inclusion bodies may be seen.[5] In many respects, pathologic features of PIV-3 infection are similar to those caused by BRSV, although the lesions produced by the latter are generally more extensive and pronounced.

Diagnosis PIV-3 can be identified by virus isolation or RT-PCR of nasal swabs from infected animals. Unlike BRSV, which is also a paramyxovirus, PIV-3 is not particularly difficult to isolate. Diagnosis can also be confirmed with paired serology, with virus neutralizing or hemagglutination inhibition assays most commonly used.

Treatment and Prevention There is no specific treatment for infection with PIV-3; as for other respiratory viruses of ruminants, administration of appropriate antibiotics to prevent secondary infection with likely bacteria may be appropriate. As for any viral respiratory tract infection, supportive care is indicated, such as providing readily available good-quality feed and water and avoiding or postponing additional stressors such as movement or mixing of animals. Both inactivated and modified live PIV-3 vaccines are available for parenteral administration, and modified live PIV-3 vaccines are available in combination with BHV-1 with or without BRSV for intranasal administration; these vaccines are labeled for use in cattle but not in sheep or goats. Experimental challenge studies have shown that both parenteral and intranasal vaccines can decrease viral shedding and clinical signs after challenge.[3-5] No field trials have specifically evaluated the effect of PIV-3 vaccines to decrease respiratory disease. One study reported that a modified live BHV-1/PIV-3 vaccine licensed for use in cattle decreased clinical signs and viral shedding when administered before experimental challenge of sheep, but the vaccinated sheep also appeared to become latently infected with BHV-1.[19] The investigators noted that induction of latent BHV-1 infection could be an important negative side effect of vaccination, as sheep could theoretically spread BHV-1 to other in-contact ruminants, such as cattle. Although the practice appears to occur commonly, administration of BHV-1/PIV-3 vaccines to sheep or goats constitutes an extralabel use of these products.

Bovine Coronavirus

Coronaviruses are enveloped, single-stranded positive sense RNA viruses of the family Coronaviridae. Bovine coronavirus is a major cause of calf diarrhea and has also been implicated as a cause of winter dysentery in cattle. Although it has been known for some time that bovine coronavirus can infect the respiratory tract of calves,[1] the practical relevance of this agent as a respiratory pathogen has been debated. However, evidence is accumulating that bovine coronavirus may be an important contributor to outbreaks of respiratory disease in some cases.

One reason for the lack of awareness regarding a role for coronavirus in respiratory disease may be the fact that standard cell lines used for isolation of other respiratory viruses are often not permissive to bovine respiratory coronavirus infection. Thus, coronavirus may not be isolated if only standard cell lines are used to attempt to isolate viruses from cattle experiencing respiratory disease. Bovine respiratory coronavirus can readily be recovered by using human rectal tumor-18G cell lines.[2] An antigen-capture ELISA and a sensitive RT-PCR assay have also been developed for identification of the virus.[3] It is not yet clear whether the coronaviruses that have been associated with respiratory disease in cattle are different in important ways from the coronaviruses that cause enteric disease; studies comparing biological and antigenic properties of enteric and respiratory isolates have yielded mixed results.[4,5]

An association of coronavirus with two naturally occurring outbreaks of shipping fever was described in a well-detailed report.[6] In these outbreaks, which were characterized by high morbidity and mortality, coronavirus was isolated from the nasal passages of over 80% of the cattle in the early stages of the outbreaks. No other respiratory viruses were identified in most of the cattle, but *M. haemolytica* was also isolated from a majority of cattle as the two epizootics progressed. However, a clear causative role for coronavirus was difficult to identify because so few cattle remained healthy that it was apparently not possible to find a difference in viral shedding or seroconversion in animals that had respiratory disease versus those that did not. In a separate report the researchers used Evans's criteria of causation, which have been suggested as more appropriate than Koch's postulates for evaluation of causative factors in complex diseases such as the BRD complex, to support a causative role for coronavirus in the outbreaks they studied.[7] A more recent study found that calves with low antibody titers to bovine coronavirus at feedlot entry were more likely to be subsequently treated for respiratory disease than calves entering the feedlot with higher titers.[8] Other researchers attempting to confirm or refute an important causative role for coronavirus in BRD have nearly always found the virus when calves are sampled soon after feedlot entry.[3,8,9,10] Moreover, it is very common for a majority of cattle to have antibody titers to the virus at feedlot arrival or to seroconvert soon after feedlot entry; therefore it is clear that cattle are often infected with the virus at times when respiratory disease is likely to occur.[3,9,11] However, the importance of the virus in causing respiratory disease has still been debated[11] because seroconversion has not always been significantly associated with treatment for respiratory disease or with decreased weight gain during the feeding period.[11-13]

Although vaccines labeled for the prevention or control of respiratory disease due to bovine coronavirus are not currently marketed in

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the United States or Canada, a research trial tested the value of a modified live bovine coronavirus and rotavirus vaccine commercially marketed to decrease diarrhea caused by these viruses (i.e., an extra-label use of the vaccine). In this study, vaccination significantly decreased the subsequent rate of treatment for respiratory disease in cattle that had relatively low serum antibody titers against coronavirus at feedlot arrival.[10]

In summary, some of the currently available data support an important role for coronavirus in contributing to the BRD complex, but other data do not. In this regard coronavirus is similar to other infectious agents, which can be identified as important players in some outbreaks studied but not identified at all in others.

Malignant Catarrhal Fever Virus

The African (wildebeest-associated) form of malignant catarrhal fever virus (MCFV) is caused by alcelaphine herpesvirus types 1 and 2. A causative agent for the American (sheep-associated) form is believed to be ovine herpesvirus type 2. The occurrence of MCFV in the cattle population is sporadic. There is multisystemic involvement, including involvement of the respiratory tract. MCFV is discussed in Chapter 32.

Bovine Herpesvirus Type 4

Bovine herpesvirus type 4 (BHV-4) is in the subfamily Gammaherpesvirinae, genus *Rhadinovirus;* therefore it is serologically distinct from BHV-1. Although the seroprevalence of BHV-4 is high in the cattle population of the United States, it has been implicated in several disease conditions of cattle, including reproductive disorders (abortions and metritis), mammillitis, and enteric disease. Several of these viruses (DN-599, Movar 33/36, FTC-2) have been isolated from cattle with respiratory tract disease, and experimental inoculation of calves with some strains can cause respiratory disease.[1] However, BHV-4 can also be isolated from apparently healthy cattle. The role of BHV-4 in BRD has not been well defined.

Adenoviruses of Cattle, Sheep, and Goats

Adenoviruses are nonenveloped double-stranded DNA viruses of the family Adenoviridae. At least 10 serotypes of bovine adenovirus (BAV) have been identified. BAV infection is widespread and frequently subclinical[1,2]; adenoviruses are also often isolated in association with other viruses and bacteria,[1] making it difficult to assign causation in naturally occurring disease outbreaks. Adenoviruses have been associated with pneumonia, enteritis, conjunctivitis, keratoconjunctivitis, and "weak calf syndrome."[3] When calves develop pneumonia and enteritis at the same time, adenoviral infection in particular should be considered as a possible cause.

At least six antigenic types of ovine adenovirus and two types of caprine adenovirus have been identified. Little information concerning the incidence and distribution of adenovirus infection in the sheep and goat population is available; however, it appears likely that this virus causes widespread infection.[4] A study in Iowa reported that adenovirus infections were widespread in the sheep population and that the prevalence of active infection based on seroconversion rates was approximately 45%.[4] The majority of isolations of this virus have been from young lambs, and it has been isolated in association with respiratory and enteric disease. Experimental infections result in mild disease with anorexia, pyrexia, increased respiratory rates, coughing, and diarrhea. Gross lesions observed include atelectasis, edema, and consolidation of the lungs.[5] Ovine adenovirus serotype 6 has been shown under experimental conditions to act synergistically with *Mannheimia (Pasteurella) haemolytica* in the production of pneumonia in lambs.[6]

Bovine Rhinitis Virus

Bovine rhinitis virus is a nonenveloped single-stranded RNA virus in the family Picornaviridae. There are two serotypes of bovine rhinitis virus, bovine rhinitis virus A and bovine rhinitis virus B. Little information is available that characterizes the relative importance of rhinitis virus in the BRD complex.

Bovine Reovirus

Bovine reovirus is a nonenveloped, double-stranded segmented RNA virus in the family Reoviridae. Reoviruses have been isolated from the respiratory and digestive tracts of apparently healthy cattle. Infections appear to be common in cattle, and bovine isolates are antigenically identical to human serotypes. The importance of reovirus infections in bovine respiratory tract disease is unclear. Subclinical infections appear to predominate under field conditions.

Calicivirus

A calicivirus has been isolated from dairy calves from a herd with a persistent respiratory disease problem.[1] This virus caused only minimal disease in experimentally infected calves, but a persistent infection was produced.

Influenza Virus

Influenza virus has not historically been considered to cause naturally occurring respiratory disease in ruminants in North America. However, it is possible to experimentally infect cattle with influenza,[1] and a report from England described several cattle that seroconverted to human influenza A virus during outbreaks of clinical respiratory disease and decreased milk production in dairy cattle.[2] Antibodies from the cattle reacted most strongly with a human H1N1 virus (A/England/33/80) and a human H3N2 virus (A/England/427/88). Retrospective analysis of banked serum samples also identified measurable antibody titers to human influenza in 49% to 59% of samples tested, with several sets of paired sera taken from animals during respiratory disease outbreaks showing evidence of seroconversion, with relatively high virus neutralizing antibody titers.[2,3] Attempts were made to isolate influenza virus from cattle with signs of respiratory disease but were not successful.[3] It was not possible to rule out other more recognized causes of BRD in the outbreaks in which cattle seroconverted to influenza, so it has not been proven conclusively that influenza is a significant contributor to naturally occurring BRD. However, the relatively high rate of seropositivity seen in cattle in England suggests that the virus may commonly circulate among cattle in at least a subclinical form, and thus cattle may be a significant reservoir of virus that could infect other species. More research is necessary to determine the significance of influenza infection in cattle and other ruminants.

Bacterial and Chlamydial Agents

Mannheimia haemolytica

Definition and Etiology *M. haemolytica* (formerly *Pasteurella haemolytica*) is a gram-negative aerobic bacterium of the family Pasteurellaceae. There are at least 12 serotypes of *M. haemolytica,* and some ruminant isolates are untypable with currently available laboratory tools. Some serotypes of *M. haemolytica* are pathogenic, whereas others are nonpathogenic commensals of the ruminant nasopharynx, and the serotypes that are pathogenic for cattle are not the same as those that are pathogenic for sheep or goats. Serotype A1 is the most common isolate from pneumonic lungs of cattle, and serotype A6 is the next most common[1,2]; serotype A2 is the most common isolate from the nasopharynx of normal cattle.[3] Serotype is also relevant to pathogenicity of isolates from sheep and goats; serotype A2 is the most common isolate from sheep and goats with pneumonia, and serotypes A7, A9, and several others have also been associated with disease.[4-6]

Clinical Signs Cattle, sheep, or goats infected with *M. haemolytica* display a dull or depressed attitude and lose interest in eating. Fever, tachypnea, and depression are often the only abnormal signs early in the course of infection[7-9]; coughing is not a prominent sign in the acute stage of disease[8,9] unless co-infection with another agent such as BHV-1 or BRSV is present. Animals may display evidence of thoracic pain, such as standing with elbows abducted or catching the

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breath before expiration; these signs are a result of the painful fibrinous pleuritis caused by *M. haemolytica*. Because *M. haemolytica* is a gram-negative organism, endotoxin (lipopolysaccharide) is produced by the agent, and thus cattle with mannheimiosis may show signs of endotoxemia, including fever, tachycardia, tachypnea, salivation, respiratory distress, pale or dark mucous membranes with prolonged capillary refill time, and cool extremities. Thoracic auscultation may reveal harsh or loud bronchovesicular sounds consistent with pulmonary consolidation,[8] particularly over the cranioventral lung. Disease after *M. haemolytica* infection can be fatal, particularly if it is not treated; it can also lead to chronic pneumonia associated with secondary invasion with agents such as *P. multocida, Mycoplasma bovis,* or *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*).

It is important to remember that naturally occurring disease caused by *M. haemolytica* is commonly preceded by infection with a viral agent such as BHV-1, BRSV, or BVD; therefore the clinical signs described previously for these and other respiratory viruses may also be present in animals infected with *M. haemolytica*.

Pathogenesis *M. haemolytica* is a normal inhabitant of the nasal and pharyngeal mucosa,[10] but not the lung, and is considered an opportunistic pathogen. Calves and lambs become infected at an early age and carry *Mannheimia* as a minor part of the upper respiratory tract flora. Only a small percentage of nasal swabs yields positive results for *M. haemolytica* serotype A1 in healthy, unstressed calves,[11] but if several areas of the nasal mucosa are cultured at necropsy, it is often possible to isolate *M. haemolytica* from animals that previously had negative findings on nasal swabs.[12] The stress of transportation or viral infection causes a breakdown of the defense mechanisms that limit normal bacteria flora, resulting in a rapid proliferation of virulent *M. haemolytica* serotype A1. A greater number of calves will yield positive nasal swab *M. haemolytica* culture during and after transport, and there is a large increase in the numbers of *M. haemolytica* in positive samples.[11,12] BHV-1 and PIV-3 have been shown to have the same effect as transportation on *Mannheimia* populations of the nasal mucosa. *M. haemolytica* has been demonstrated in the tracheal air of stressed, healthy calves harboring the organism on their nasal mucosa. Some of these inhaled organisms are deposited deep within the lung and normally are cleared within hours. But under conditions of impaired pulmonary defenses caused by insults to the upper respiratory tract, nutritional deficiencies, or preexisting viral infection, *M. haemolytica* is able to proliferate rapidly within the lung and, with the aid of its virulence factors and toxins, to produce a severe lobar necrotizing fibrinous pleuropneumonia. Calves infected with respiratory viruses, including BHV-1, PIV-3, BVDV, and BRSV, or *Mycoplasma* spp. have increased susceptibility to severe bronchopneumonia when exposed to *M. haemolytica*. Similarly, infection of lambs with PIV-3 or adenovirus followed in several days by *M. haemolytica* causes severe pneumonia.[13]

Once *M. haemolytica* becomes established in the lungs, interactions between the bacteria and the host defenses result in tissue damage and elimination of the invader.[14] A major virulence factor of *M. haemolytica* is an exotoxin that is lethal to ruminant leukocytes, the leukotoxin. Leukotoxin, which is produced by *M. haemolytica* during the logarithmic phase of growth, causes cytolysis of ruminant platelets, lymphocytes, macrophages, and neutrophils.[15] There is diversity in the gene encoding the leukotoxin molecule among *M. haemolytica* serotypes, and genetic diversity is related to differences in toxicity. For example, the leukotoxin encoded by some pathogenic bovine serotype A1 strains differs from the leukotoxin encoded by ovine A1 strains by only one amino acid but is substantially more toxic for bovine leukocytes than for ovine leukocytes.[16] Leukotoxin binds to cells via CD18, the beta subunit of the β_2 integrins CD11a/CD18 (LFA-1), CD11b/CD18 (Mac-1), and CD11c/CD18 (CR-4),[17,18] and although leukotoxin can bind to cells from nonruminant species, only ruminant cells are killed by the toxin.[15] Contact with leukotoxin increases expression of LFA-1 on ruminant leukocytes, making the cells even more sensitive to injury by leukotoxin.[19] At low concentrations, leukotoxin induces leukocyte death by apoptosis, whereas at higher concentrations the toxin causes cell lysis.[20] *M. haemolytica* expressing a mutant nontoxic leukotoxin induced less lung pathology in calves as compared with *M. haemolytica* producing functional toxin, but clinical signs were not different between the two groups of calves, indicating that leukotoxin is not the only virulence factor of importance in causing disease.[21]

Another virulence factor that contributes to disease resulting from *M. haemolytica* is lipopolysaccharide, or endotoxin. As in other species, exposure of ruminants to endotoxin from gram-negative bacteria induces a multitude of responses leading to inflammation, including initiation of the complement and coagulation cascades, activation of endothelial cells and recruitment of neutrophils, and activation of neutrophils and alveolar macrophages, leading to their production of proinflammatory cytokines, which further amplify the inflammatory response. The proinflammatory cytokines TNF-α, IL-1β, and IL-8 are expressed in the lungs of cattle within 48 hours of *M. haemolytica* infection.[22] Calves exposed to a preparation containing *M. haemolytica* endotoxin develop leukopenia, fever, tachypnea, diarrhea, and dyspnea as early as 2 hours after exposure.[23] Endotoxin potentiates the effects of leukotoxin by inducing increased expression of β_2-integrins on leukocytes, which contain CD18, the receptor for leukotoxin.[19,24] Bovine alveolar macrophages first exposed to endotoxin were susceptible to death induced by concentrations of leukotoxin too low to cause cell death alone, and macrophages exposed to both endotoxin and leukotoxin produced more of the proinflammatory cytokines IL-8 and TNF-α than did macrophages exposed only to leukotoxin.[24] These data indicate that leukotoxin and endotoxin work in synergy to cause disease in ruminants. The production of IL-8 is of particular importance, because IL-8 is a major inducer of neutrophil chemotaxis.[25] The massive influx of neutrophils induced by IL-8 and other inflammatory mediators is a key factor in lung tissue destruction caused by *M. haemolytica*. Calves experimentally depleted of neutrophils are completely protected from gross and microscopic lesions of the severe fibrinonecrotic bronchopneumonia that is induced by intratracheal inoculation of *M. haemolytica* in calves with normal neutrophil levels.[26] Lysis of neutrophils results in the release of lysosomal products, including elastase, collagenase, and reactive oxygen intermediates. These chemicals are bactericidal but also capable of destroying the neutrophils themselves and surrounding tissues. Neutrophil-mediated damage to the endothelial cells results in exudation and thrombosis, which produce the classic lesions of necrosis and fibrinous exudation.[27]

In addition to leukotoxin and endotoxin, *M. haemolytica* possesses other factors that contribute to its virulence. The bacteria have a polysaccharide capsule that aids in attachment and prevents phagocytosis by neutrophils,[28] and iron-regulated outer membrane proteins (IROMPs) that bind transferrin and alter the function of neutrophils.[29,30] The bacteria produce adhesions that mediate attachment to host cells,[31] and neuraminidase produced by the bacteria may aid in host colonization by decreasing the viscosity of respiratory mucus[32] and decreasing the repellant negative charge on host cells by cleaving sialic acid residues.[33]

Epidemiology In many studies over several decades, *M. haemolytica* has been found to be the most common bacterial isolate from feedlot cattle with fatal fibrinous bronchopneumonia.[34-37] *M. haemolytica* was isolated postmortem from 25% to 30% of cattle that died or were euthanized because of pneumonia in two studies evaluating causes of mortality in feedlot cattle.[34,37] Seroconversion to *M. haemolytica* or *M. haemolytica* leukotoxin has been significantly associated with treatment for respiratory disease or "undifferentiated fever" in feedlot cattle in some[38,39] although not all[40] studies. Booker and colleagues found that the odds of developing undifferentiated fever (case definition similar to that usually used for undifferentiated respiratory disease) was 2.8 times greater for cattle that developed a fourfold rise in antibody titer to *M. haemolytica* leukotoxin, as compared with cattle that did not seroconvert to leukotoxin.[39] And whereas O'Connor and coworkers found no association between seroconversion to *M. haemolytica* and treatment for undifferentiated

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respiratory disease, they did find that vaccination against *M. haemolytica* was significantly associated with protection against the development of undifferentiated respiratory disease in feedlot cattle in their study, which indirectly indicated a role for *M. haemolytica* in the development of respiratory disease.[40] Although *M. haemolytica* is recognized as the bacteria most commonly contributing to fibrinous pneumonia in feedlot cattle, one study that used bronchoalveolar lavage (BAL) to identify bacteria present in the lungs of feedlot cattle before antimicrobial treatment for acute pneumonia found that *M. haemolytica* was not identified more frequently in the lungs of cattle with pneumonia than normal controls, whereas *P. multocida* was significantly associated with bronchopneumonia.[41] In this study, none of the calves died or were euthanized because of the naturally occurring disease, indicating that disease was not severe. Because *M. haemolytica* is relatively more likely to cause acute fatal pneumonia than other bacterial pathogens of the ruminant lung, it may be overrepresented in necropsy surveys in which only fatal cases of disease are sampled.

In contrast to the situation in feedlot cattle, *M. haemolytica* is not commonly associated with outbreaks of pneumonia in dairy calves. At postmortem examination of 43 calves from 34 outbreaks of respiratory disease, *M. haemolytica* was isolated from only two calves[42]; in another study, *M. haemolytica* was isolated from calves in 4 of 14 outbreaks of respiratory disease.[43] Although *M. haemolytica* is not as commonly isolated from calves as are other bacterial pathogens, it can be a cause of fatal disease; in one study, only *M. haemolytica* was significantly more often isolated from calves with fatal pneumonia as compared with calves with subclinical pneumonia.[44]

Necropsy Findings Infection with *M. haemolytica* causes fibrinopurulent bronchopneumonia or pleuropneumonia (Color Plate 31-5). The infection is aerogenous, so disease occurs primarily in the cranioventral lung, but in severe cases, a majority of the lung may be affected. Affected areas of lung are dark red to purple or gray-brown (Color Plate 31-6), firm, and heavy; discolored areas may be wedge-shaped owing to thrombosis of a vessel supplying the affected region during the severe inflammatory response. The interlobular septa are expanded by clear to yellow gelatinous material that represents proteinaceous fluid that has leaked from blood vessels in the lung. The inflamed areas of lung are covered with yellow fibrin that may adhere to the pleura of the thoracic wall, and the pleural cavity usually contains straw-colored fluid, which may be voluminous.[7-9] In cases that have been ongoing for a few days, firm, gritty lumps that are dry and crumbly on sectioning may be identified; these represent areas of necrotic tissue.[9] Bronchial lymph nodes may be swollen, wet, and dark red. Histologically, alveoli are filled with edema and fibrin, and there is massive infiltration of neutrophils and macrophages. "Oat cells" can be seen, which are necrotic leukocytes with streaming of the chromatin.[34] Foci of coagulative necrosis are often found rimmed by a basophilic border of leukocytes; coagulative necrosis may expand to fill entire lobules. Hemorrhage is often present both within and between alveoli, and an occasional vessel may be found to contain a thrombus. Interlobular septa and lymphatics can be found dilated with edema and fibrin. Bronchioles are filled with leukocytes and may have foci of epithelial necrosis.[8,9,34] *M. haemolytica* may also produce pneumonia characterized by firm, dark red pulmonary consolidation without fibrinous pleuritis; this is especially common in dairy calves or sheep and goats. Animals that survive the acute stage of pneumonia caused by *M. haemolytica* may have multiple abscesses and pleural adhesions; in these cases other bacteria such as *P. multocida, Mycoplasma bovis,* or *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) may be contributing to pathology.

Diagnosis Diagnosis of pneumonia caused by *M. haemolytica* is most reliably made by culture of lungs with typical gross pathology at postmortem evaluation of animals that die or are euthanized as representative cases in outbreaks. Antemortem diagnosis in individual animals can be made by collecting fluid by transtracheal aspiration (TTA) or BAL and submitting the fluid for aerobic bacterial culture. These methods are not practical for widespread use in the field, but they may be warranted for valuable individual animals or to identify the cause of an outbreak of respiratory disease in several animals. Cytologic evaluation of TTA or BAL samples would be expected to reveal septic purulent inflammation characterized by large numbers of neutrophils that may be degenerate, exhibiting toxic change, and possibly containing intracellular bacteria. Deep nasopharyngeal swabs may accurately indicate involvement of *M. haemolytica* in a respiratory disease outbreak in a group of cattle, but the results of deep nasopharyngeal swabs collected from individual cattle are hard to interpret because *M. haemolytica* can be found in the normal bovine nasopharynx. Thoracocentesis can be a useful diagnostic procedure for identifying fluid accumulation in the thorax; fluid collected shows a high percentage of neutrophils with a high (>3 g/dL) total protein content if bacterial pleuropneumonia is the cause of fluid accumulation. Pleural fluid collected by thoracocentesis can also be submitted for aerobic bacterial culture to confirm infection with *M. haemolytica*. In a hospital with the necessary equipment, transthoracic ultrasound evaluation can be used to confirm the presence of consolidated lung tissue and pleural effusion with fibrin.[45] Thoracic radiography, if possible, is expected to show evidence of consolidation of the cranial lung and possibly pleural fluid accumulation.[46] Evidence of pneumonia identified by either radiography or transthoracic ultrasound evaluation has been shown to correlate strongly with findings on postmortem examination of calves with bacterial bronchopneumonia.[45,46]

Serologic tests can be used to identify serum antibodies to *M. haemolytica,* and seroconversion identified by paired serologic testing could be used to confirm infection with *M. haemolytica* in one or more ruminants. However, these tests are most commonly used for research applications, and they may not be available at all diagnostic laboratories.

Treatment and Prevention Treatment of *M. haemolytica* requires administration of an antimicrobial effective against the organism. Many antimicrobials are currently labeled for the treatment of *M. haemolytica* (see Table 31-12). The decision to choose any one of the many approved products is based on multiple factors, including regional susceptibility of *M. haemolytica* isolates, the number of times it is possible to treat animals, withdrawal times, and cost.

In addition to appropriate antimicrobial therapy, treatment to prevent the adverse effects of endotoxin should be considered for ruminants suspected or confirmed to have pneumonia caused by *M. haemolytica.* The NSAID flunixin meglumine can ameliorate the inflammatory response to endotoxin, and treatment with flunixin meglumine has been shown to improve outcome in individual animals infected with *M. haemolytica.* However, administration of NSAID drugs such as flunixin meglumine has not been shown to be reliably cost-effective in the treatment of large numbers of feedlot cattle with respiratory disease. Thus a consideration of the value of the animals treated may be necessary before NSAID therapy can be justified in an entire group of calves.

Prevention of infection and disease caused by *M. haemolytica* is approached by three avenues: administering antimicrobials prophylactically to animals at high risk of disease; increasing host immunity by ensuring adequate passive transfer and administering vaccines against *M. haemolytica;* and minimizing factors such as viral respiratory tract infection, mixing of animals from various sources, and long-distance shipment, which increase the susceptibility of animals to disease caused by pathogenic serotypes of *M. haemolytica.*

Prophylactic or metaphylactic administration of antimicrobials effective against *M. haemolytica* is a reliable means of decreasing morbidity and mortality associated with respiratory disease in calves at high risk for disease because of recent weaning, uncertain immune status, mixing with cattle from a variety of sources, and long-distance shipment. In one study, administration of tilmicosin to groups of such high-risk calves either before shipment or on arrival at feedlots

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decreased the proliferation of *M. haemolytica* serotype A1 in the nasopharynx of calves and was associated with decreased treatment for respiratory disease as compared with calves not treated with tilmicoson.[47] In a later study, administration of florfenicol at arrival decreased colonization of the nasopharynx with *M. haemolytica* A1 and delayed treatment for respiratory disease.[11] Further discussion of the role of metaphylactic administration of antimicrobials to control BRD can be found elsewhere in this chapter.

Mixing recently weaned calves from multiple sources and shipping them long distances is a well-known precursor to outbreaks of fibrinous pneumonia[48]; and because *M. haemolytica* is the species of bacteria most commonly associated with fatal fibrinous pneumonia, it follows that efforts to minimize stresses and improve immunity for calves moving through the marketing chain should lessen disease caused by *M. haemolytica.* Recent studies have indicated that preconditioning, wherein vaccination and stressful procedures such as weaning and castration are carried out well in advance of mixing and shipment, can decrease costs associated with fibrinous pneumonia in feedlot cattle.[49] However, preconditioning should not be considered a guarantee against all respiratory disease; disease that is sometimes severe can occur in preconditioned calves. Further discussion of the role of preconditioning to prevent BRD is continued elsewhere in this chapter.

Vaccination can be used as part of a plan to decrease disease caused by *M. haemolytica.* Many experimental and commercially marketed vaccines have been tested for efficacy in preventing either disease resulting from experimental infection with *M. haemolytica* or naturally occurring respiratory disease, and the published literature is too extensive to describe in detail here. In summary, some research indicates that vaccination can lessen disease, other research shows that vaccination has no effect, and a few older reports show that *M. haemolytica* vaccination can enhance disease after infection.[50] Although commercially marketed vaccines are tested for safety, and no published reports exist that describe enhanced disease caused by currently available products, the fact that *M. haemolytica* bacterins historically caused enhanced disease is a reason to avoid the use of autogenous products that are not thoroughly tested for safety before administration. To induce protective immunity, a vaccine against *M. haemolytica* must contain leukotoxin; additional benefit may be gained by including other antigens associated with the bacterial cell wall.

Experimental challenge studies have shown that currently available commercial vaccines can lessen disease caused by infection with *M. haemolytica.*[51-53] However, data from well-designed field trials, which are a more relevant measure of the value of vaccination in the field, have reported mixed results. Recently a meta-analysis of 18 clinical trials testing the efficacy of *M. haemolytica* vaccines to prevent respiratory disease in feedlot cattle was published.[54] The 18 trials included were selected from a larger number of published trials based on the quality of their design and the fact that they evaluated the effect of vaccination on naturally occurring disease in feedlot cattle. The summary relative risk for respiratory morbidity in vaccinated cattle was 0.93 (95%, confidence interval 0.89 to 0.98), indicating that *M. haemolytica* vaccination was associated with a statistically significant decrease in morbidity when considering all the trials included in the meta-analysis. However, the summary relative risk for mortality was not significantly different for vaccinated cattle. Thus this assessment of the current research indicated that respiratory morbidity in feedlot cattle is decreased by *M. haemolytica* vaccination, but total mortality is not. Because *M. haemolytica* vaccines can be relatively expensive, they may be most cost-effective in cattle at high risk for respiratory disease.

Vaccination of sheep or goats using commercially available vaccines labeled for use in cattle is not likely to provide reliable protection against disease, as serotypes of *M. haemolytica* that most commonly cause disease in sheep and goats are not included in vaccines for cattle. Moreover, although vaccination with sheep-associated serotypes can provide protection against infection, cross protection among different serotypes is not reliable,[5] indicating that an effective vaccine will likely need to contain antigens from multiple serotypes.

Pasteurella multocida

Definition and Etiology *P. multocida* is a gram-negative aerobic bacterium of the family Pasteurellaceae. Like *M. haemolytica, P. multocida* can be found in the nasopharynx of healthy ruminants. Although *P. multocida* is regularly isolated from the lungs of ruminants with bronchopneumonia, there has been debate over the years as to whether this species is a primary pathogen—that is, capable of causing disease alone—or whether some other primary stressor or insult is required to occur before this agent can participate in disease. As with *M. haemolytica,* experimental challenge of calves with *P. multocida* alone does cause clinical signs and pathologic change in the lung similar to that seen in natural outbreaks of disease,[1-3] but large numbers of the bacteria must be administered in a way that bypasses the upper respiratory tract (most commonly by intratracheal instillation). Alternatively, prior administration of a viral respiratory pathogen makes ruminants more susceptible to disease caused by experimental *P. multocida* infection. These findings indicate that some insult that weakens the ability of the respiratory tract to resist advancement of these bacteria into the lower airways is necessary for most if not all cases of naturally occurring disease to occur. However, because *P. multocida* can cause lung lesions that can be severe,[2] and because the bacteria can exacerbate disease caused by primary viral infection, it is logical to consider this agent when planning strategies to treat and control ruminant respiratory disease.

P. multocida is a diverse species of bacteria that is classified into five serogroups (A, B, D, E, and F) based on antigenic differences in the bacterial capsule. Serogroups B and E cause hemorrhagic septicemia, a disease predominantly seen in Asia and Africa; these serogroups are rarely isolated in the United States. Serogroup A is by far the predominant serogroup associated with ruminant respiratory disease,[4,5] although serogroups D and F may be common in some regions, particularly in sheep.[6] In addition to the alphabetic serogroup designation, isolates may also receive a numeric designation based on cell wall antigen types (e.g., *P. multocida* A3 has been commonly isolated from cases of bovine pneumonia). A report characterizing 153 *P. multocida* isolates from cases of pneumonia and mastitis in cattle in England and Wales indicated that relatively few strains of *P. multocida* cause the majority of disease in cattle. Moreover, although a few strains isolated from cattle had also been associated with disease in swine and poultry, the majority of strains were uniquely associated with their host species of origin.[5] Other research indicated that certain strains of *P. multocida* had a predilection for the respiratory tract of sheep, whereas other strains were associated with the reproductive tract.[6] Taken together, these data suggest that differences among strains of *P. multocida* are related to the type of disease caused and the host likely to be affected. Therefore merely isolating *P. multocida* without further characterizing the isolate could make it difficult to know with confidence whether the type of bacteria isolated was actually contributing to disease. It has been suggested that strain variation is related to differences in severity of respiratory disease occurring in ruminants infected with *P. multocida.*[2]

Clinical Signs Calves infected with *P. multocida* alone display clinical signs of fever, increased respiratory rate, and sometimes depression, coughing, and mucoid to mucopurulent nasal discharge.[1-3] Loud or harsh bronchovesicular sounds may be heard over the cranioventral lung fields owing to pulmonary consolidation, and coarse crackles may be heard as a result of air moving through exudate in large airways. Because *P. multocida* is a gram-negative organism that produces endotoxin, signs of endotoxemia (tachypnea, tachycardia, fever) may also contribute to signs that accompany infection with the organism. Compared with calves infected with *M. haemolytica,* calves infected with *P. multocida* tend to have less severe signs, and signs of disease last for a shorter time.[1-2] *P. multocida* is more commonly isolated from young calves with pneumonia[7,8] than with other

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bacterial respiratory pathogens such as *M. haemolytica,* but it is less commonly isolated from feedlot cattle with acute bronchopneumonia.[9] Thus *P. multocida* is considered to be of relatively greatest importance in contributing to calf pneumonia. *P. multocida* has been found to overgrow *M. haemolytica* in the lungs of calves experimentally challenged only with *M. haemolytica*[1]; therefore *P. multocida* may also be an important contributor to cases of subacute to chronic pneumonia in feedlot cattle initiated by other organisms.

Pathogenesis Little is known about the pathogenesis of *P. multocida* in ruminant respiratory disease. In addition to lipopolysaccharide (LPS), the organism also has a capsule that allows it to resist phagocytosis. Outer membrane proteins, particularly iron-regulated outer membrane proteins, are likely to contribute to the ability of the bacteria to establish and proliferate within the host.[10,11] The prominent role of *P. multocida* in dairy calf pneumonia and the rather minor role in acute bronchopneumonia of feedlot cattle suggests that prolonged impairment of the respiratory defense mechanisms is necessary for this organism to establish in the lungs in sufficient numbers to create bronchopneumonia. It is likely that the organism is chronically inhaled in small numbers into the lungs of calves with persistent damage to the respiratory defenses from infectious agents such as viruses or mycoplasmas and environmental insult from inadequate housing and ventilation, allowing it to colonize and produce an expanding lesion. This proposed pathogenesis agrees with the insidious onset that is commonly observed with enzootic calf pneumonia (ECP) and would also fit the association of *P. multocida* with chronic or ongoing pneumonia in feedlot cattle. It is important to remember that culture of *P. multocida* from pneumonic lung does not exclude the possibility of other bacteria such as *M. haemolytica* being the primary pathogen, because *P. multocida* has been shown to overgrow *M. haemolytica* in challenge studies using large doses of pure cultures of *M. haemolytica.*[1]

Epidemiology *P. multocida* is commonly isolated from the lungs of calves that die or are euthanized because of bronchopneumonia, with mycoplasmas being the only bacteria isolated more often in surveys involving multiple farms experiencing outbreaks of calf pneumonia.[7,8] In contrast, *M. haemolytica* is more frequently isolated postmortem from feedlot cattle with fibrinous pneumonia than is *P. multocida.*[9,12] However, one study of bacterial isolates from BAL of feedlot cattle found that *P. multocida* was the only species isolated more frequently from cattle with clinical signs attributed to acute pneumonia as compared with normal cattle.[13] A notable aspect of this study was that animals were sampled before treatment with antimicrobials; in surveys of bacteria identified postmortem, animals have usually received antimicrobial treatment before death, which may bias the microbiological findings.

Necropsy Findings *P. multocida* produces a purulent bronchopneumonia with plum-colored cranioventral consolidation and purulent exudate on cut section within the airways; when calves are experimentally infected with *P. multocida* alone, the lesion is usually not extensive and is typically confined to the cranioventral lung lobes.[1-3] Histologically, bronchopneumonia characterized by infiltration of neutrophils and macrophages into alveoli and airways is seen. Microscopic evidence of abscesses may be present. Fibrin deposition with expansion of lymphatics and interlobular septa with edema, and focal areas of coagulative necrosis, has been reported in calves infected with *P. multocida,*[2,3] but this lesion is more typical of infection with *M. haemolytica.*[1]

Diagnosis Bronchopneumonia caused by *P. multocida* is diagnosed as described for *M. haemolytica.* The species is most commonly identified by culture of lung lesions identified at postmortem examination of affected animals. Because of the association of *P. multocida* with chronic or ongoing pneumonia, identification of this agent may indicate that the animal has been affected with bronchopneumonia for several days to weeks.

Treatment and Prevention Treatment of *P. multocida* is as described for *M. haemolytica.* Several antimicrobials are labeled specifically for the treatment of *P. multocida,* and products labeled for the treatment of *M. haemolytica* are also likely to be effective against this organism (see Table 31-12). Because *P. multocida* seems to be associated with chronic or ongoing pneumonia, effective treatment of infection with this species may require longer therapy than the 3 to 5 days historically recommended for ruminants with bronchopneumonia, but this recommendation has not been tested in controlled studies and would be an extralabel use of some antimicrobials.

Because prior insult to respiratory defense mechanisms appears necessary for infection with *P. multocida* to cause disease, prevention of disease is likely to be aided by undertaking efforts to prevent other primary respiratory injury. This would include efforts to prevent infection with viral respiratory pathogens and to establish management practices that help minimize respiratory tract disease (see more discussion of management-related risk factors for respiratory disease at the end of this section).

As compared with *M. haemolytica,* relatively little is known about protective immunity to *P. multocida.* Modified live vaccines can protect calves from disease caused by experimental challenge.[14,15] Antibody responses to several outer membrane proteins were associated with protection in one study, and these were induced by live but not killed vaccine.[15] Several commercial vaccines are marketed that contain *P. multocida* in combination with *M. haemolytica*. There are currently no vaccines marketed that contain only *P. multocida.* A recent meta-analysis evaluated clinical trials testing the efficacy of *M. haemolytica, P. multocida,* and *H. somni* vaccines to decrease morbidity and mortality due to BRD.[16] This meta-analysis included three trials testing vaccines including both *M. haemolytica* and *P. multocida;* no clinical trials were found to be suitable for inclusion that tested only the effect of *P. multocida* vaccines. Of the three trials testing vaccines containing *P. multocida,* one trial found a statistically significant decrease in respiratory morbidity in vaccinated cattle. More data from properly designed clinical trials are needed to clarify the value of *P. multocida* vaccination to prevent or limit respiratory disease in different cattle populations.

Histophilus somni

Definition and Etiology *H. somni* is a gram-negative aerobic bacterium of the family Pasteurellaceae. *H. somni* can be found on the genital and upper respiratory mucosa of normal ruminants,[1-4] but it can also cause a variety of diseases, including septicemia, thrombotic meningoencephalitis (TEME), endometritis, abortion and infertility, pneumonia, pleuritis, laryngitis, otitis, conjunctivitis, myocarditis, mastitis, and polyarthritis.[5] Only pneumonia and pleuritis resulting from this organism are considered here. Two bacteria very similar to *H. somni, Haemophilus agni* and *Haemophilus ovis,* have been isolated from sheep with septicemia, meningitis, mastitis, and reproductive abnormalities; DNA hybridization studies have indicated that these three organisms should all be classified as *H. somni.* Although specific serotypes of *H. somni* have not been associated with disease as is the case for *M. haemolytica* and *P. multocida,* differences in virulence among different strains have been demonstrated in experimental challenge studies.[6] Moreover, differences in expression of molecules considered to be virulence factors have been demonstrated when strains from healthy animals are compared with strains from diseased animals.[7] Thus it appears that some isolates of *H. somni* are more likely to cause disease than others, but more research is needed to confirm the characteristics that define a pathogenic isolate.

Clinical Signs As mentioned earlier, *H. somni* can cause disease in a variety of organ systems, and the clinical signs of infection will depend on the organ system affected. The possibility of concurrent infection of multiple systems should be considered in patients suspected to have disease caused by *H. somni.* In a Canadian retrospective study from the early 1990s, the majority of animals

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presented to a regional diagnostic laboratory for necropsy as a result of haemophilosis had disease in more than one organ system.[8] Signs of respiratory tract infection can range from mild to severe and can include fever, tachypnea, cough, nasal discharge, and depression. Severe cases of the disease can be fatal.[6,9] Harsh or loud bronchovesicular sounds may be heard on thoracic auscultation because of pulmonary consolidation, particularly over the cranioventral lung fields. Affected animals may have signs of pain owing to fibrinous pleuritis,[9] including reluctance to move, standing with elbows abducted, and catching the breath before expiration. The cell wall of *H. somni* contains lipooligosaccharide (LOS), which induces inflammatory responses identical to those induced by LPS from *E. coli*[10]; therefore animals with pleuritis or pneumonia caused by *H. somni* could also have clinical signs referable to endotoxemia, including tachypnea, tachycardia, dark or pale mucous membranes with prolonged capillary refill time, salivation, or dyspnea.

Pathogenesis *H. somni* can live on respiratory or genital mucous membranes without causing disease, and it is not entirely clear what factors related to the pathogen or host must change for disease to occur. The physical and immunologic barriers presented by the upper respiratory tract are apparently of major significance; calves exposed to *H. somni* by aerosol did not develop disease,[11] whereas instillation of the bacteria directly into the trachea or bronchi led to disease that could be severe.[6,9] As has been shown for *M. haemolytica* and *P. multocida,* primary infection by a viral respiratory pathogen is likely a predisposing factor that allows *H. somni* to advance and establish in the lower respiratory tract in many cases. Calves infected with BRSV before infection with *H. somni* had disease of greater severity than that seen in calves infected with either BRSV or *H. somni* alone.[9,12]

H. somni has many features that help the bacteria escape the immune response.[13] The bacteria have outer membrane proteins that bind to the Fc region of antibody, allowing them to escape opsonization.[7] When the bacteria are ingested by neutrophils or macrophages, they are able to resist being killed.[14] The bacterial LOS induces inflammatory responses similar to the LPS of other gram-negative bacteria,[10] and *H. somni* is able to periodically change the structure and antigenicity of its LOS, which is likely to be important in evading the host immune response.[15]

An important aspect of the pathology caused by *H. somni* is the formation of vasculitis and vascular thrombi; this was first recognized in the context of the neurologic lesion caused by the bacteria, which is known as *thrombotic meningoencephalomyelitis* (TME), but vascular thrombi are also identified histologically in the lungs of animals with pneumonia caused by *H. somni*.[9] For some time the exact cause of the vascular thrombosis typical of *H. somni* infection was not known, but research now indicates that the bacteria cause the death of vascular endothelial cells by inducing apoptosis (programmed cell death).[16] Apoptotic death of endothelial cells is mediated in part through the bacterial LOS, which interacts with the P2X7 purinergic receptor on endothelial cells, inducing activation of certain caspases, enzymes that activate the apoptotic pathway and initiate a cell suicide program.[2] Although the entire pathway leading to vasculitis and thrombosis has not been completely elucidated, thrombosis is no doubt mediated in part by exposure of the vascular basement membrane on endothelial cell death, which leads to exposure of the basement membrane, activation of platelets and the coagulation cascade, and thrombosis.

Another important aspect of *H. somni* is the propensity of infection to induce IgE production by the host.[12,17] Infection with BRSV before infection with *H. somni* led to production of high levels of *H. somni*–specific IgE, which was associated with disease of increased severity as compared with control calves.[12] Cattle vaccinated with four different *H. somni* bacterins were all found to develop serum levels of *H. somni*–specific IgE that were significantly higher than levels seen in control unvaccinated cattle.[17] Because IgE mediates type I (immediate) hypersensitivity, animals that produce IgE against *H. somni* after vaccination or primary infection could have signs of an allergic or anaphylactic response on subsequent revaccination or reinfection. Such IgE-mediated hypersensitivity reactions have been proposed to contribute to the adverse reactions sometimes seen in cattle after vaccination for *H. somni*.[17] In addition to inducing IgE production, *H. somni* directly produces histamine,[18] which could further contribute to the development of hypersensitivity-like signs during *H. somni* infection. Among other actions, histamine increases permeability of the bronchial epithelium; this may aid the bacteria in moving out of the airway and into the lung parenchyma.

Epidemiology Exposure to *H. somni* is common, with 25% to 100% of cattle in various populations having serum antibodies.[19] A retrospective study of bovine carcasses submitted to a regional diagnostic laboratory in western Canada from 1970 to 1990 indicated that cases affected with the neurologic form of haemophilosis were decreasing, whereas cases with respiratory and/or myocardial disease caused by *H. somni* were increasing.[8] The reason for the apparent shift in type of disease caused in cattle could not be determined from the study, and a similar study has not been repeated to see if the trend is continuing.

It is common for feedlot cattle to have measurable antibody titers to *H. somni* at feedlot entry,[20,21] indicating that cattle are commonly exposed on the farm of origin or in transit to the feedlot. Seroconversion is also common in the first few weeks after feedlot entry,[21,22] indicating that cattle also continue to be exposed to *H. somni* in the feedlot. Several Canadian reports have indicated that *H. somni* can be a significant contributor to the development of respiratory disease or undifferentiated fever in feedlot cattle,[23-25] although studies of feedlot respiratory disease do not always find the bacteria involved. A causative association is typically inferred either by the association of seroconversion with respiratory morbidity and mortality during the period of study or by the association of *H. somni* vaccination with decreased respiratory morbidity and mortality. By these measures it appears that most disease resulting from *H. somni* occurs within the first 2 months of the feeding period[25] and perhaps even within the first 2 weeks.[22] In some cases the association of seroconversion or vaccination with all morbidity and mortality is also evaluated, but one study found that when causes of mortality were separated into those in which it was biologically plausible for *H. somni* to be involved and those in which it was not (e.g., cattle with musculoskeletal injuries), vaccination was associated with decreased mortality attributable to *H. somni* but not with a decrease in all causes of mortality.[25] A causative association for *H. somni* (or any respiratory pathogen) is sometimes assumed when animals with high antibody titers to the organism at feedlot entry ultimately have lower respiratory morbidity and mortality,[21] although the case has been made that this is not a reliable marker of causation.[22] A decreasing antibody titer to *H. somni* was associated with decreased likelihood of disease in one study[21] and increased likelihood of disease in another[20]; this demonstrates that it is not always easy to develop a unified theory regarding the role of infectious agents and the immune response from the available data. It is also noteworthy that high-quality field research on the role of *H. somni* in feedlot respiratory disease in recent years has come almost entirely from Canada; it is not clear whether this indicates that *H. somni* is a less significant contributor to disease in the United States or whether the research has just not been done.

H. somni is uncommonly isolated in surveys of the causes of pneumonia in young calves,[26,27] but it can cause bronchopneumonia that is significant; one necropsy survey found pneumonia in 12 of 15 calves under 8 weeks of age submitted because of disease resulting from *H. somni,* and in 8 of the 15 calves, pneumonia was the only lesion found.[8]

Necropsy Findings *H. somni* produces lesions similar to those of *P. multocida,* and it may rarely produce lesions that resemble those of *M. haemolytica,* creating a fibrinous pleuropneumonia.[5,6,9] Grossly, plum or red to brown consolidated lobules are seen in the cranioventral lung, sometimes with abscesses containing brown-red fluid material. Interlobular septa can be distended with edema and

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fibrin (Color Plate 31-7), and hemorrhage may be grossly visible.[6] Purulent material is seen within airways on the cut surface of lung. The surface of the pleura may be flecked with fibrin, or in some cases fibrin deposition may be extensive, with varying amounts of straw-colored fluid in the pleural cavity. Bronchial lymph nodes may be enlarged, with ecchymotic hemorrhages on the cut surface.

Histologically, inflammatory cells predominantly made up of neutrophils infiltrate the alveoli and airways. Edema, hemorrhage, and fibrin can be seen in alveoli and interstitial spaces, and areas of coagulation necrosis surrounded by inflammatory cells may be found. Interlobular septa are expanded with fibrin, and thrombi are seen in blood vessels.[6,9]

A massive fibrinous pleuritis with pleural effusion sometimes results from septicemic spread of *H. somni.* This condition can be differentiated from the fibrinous necrotizing lobar pleuropneumonia of shipping fever caused by *M. haemolytica* because the *H. somni* lesion involves only the pleural surface, not the lung.

Diagnosis Bronchopneumonia or pleuropneumonia caused by *H. somni* is diagnosed as described for *M. haemolytica.* The bacteria can be difficult to isolate, so samples collected for culture should be transported to the diagnostic laboratory without delay, and the diagnostic bacteriology laboratory should be specifically requested to attempt to isolate *H. somni* if involvement of the agent is suspected. Samples are ideally taken from animals before antimicrobial treatment, as *H. somni* is susceptible to a wide variety of antimicrobials and treatment makes it difficult to isolate the bacteria.[5] Serologic tests have been used to identify antibodies to *H. somni* for studies of the epidemiology of *H. somni* infection,[21,22] and seroconversion as measured via paired serology could be used to confirm infection in a group of cattle, but these assays may not be available at all diagnostic laboratories. IHC has been used to identify *H. somni* in association with lesions in formalin-fixed tissues,[28] and this may be an additional test available at some diagnostic laboratories.

Treatment and Prevention *H. somni* is susceptible to a variety of antimicrobials, including tetracycline, penicillin, sulfonamides, and erythromycin, as well as more recently developed antimicrobials, many of which are labeled for use in the treatment of *H. somni* (see Table 31-12). In a feedlot with unusually high morbidity and mortality because of haemophilosis, prophylactic treatment with oxytetracycline was administered at different time points within the first 2 weeks of the feeding period in an effort to decrease haemophilosis morbidity or mortality, to no avail (although morbidity from all causes of respiratory disease was decreased).[29]

Several *H. somni* vaccines are commercially available; all are killed whole bacteria preparations (bacterins). Vaccination can prevent disease caused by experimental challenge; in one study, vaccination of 10-week-old calves with a commercial bacterin significantly decreased clinical signs and pulmonary pathology resulting from *H. somni* challenge.[6] Clinical trials of *H. somni* bacterins in the 1980s gave mixed results, with evidence that vaccination decreased respiratory morbidity and/or mortality in some trials but not in others,[25,30,31] and very little research has provided more information since then. In a cow-calf herd with a high incidence of calf pneumonia, vaccination of calves at 3 and 5 weeks of age with an *M. haemolytica* and *H. somni* bacterin in combination with a modified live BRSV vaccine led to a trend toward statistically significantly decreased treatment rates as compared with calves not vaccinated or calves vaccinated with either the bacterin or the BRSV vaccine alone.[32] Because of the trial design, the effect of *H. somni* vaccination could not be separated from the effect of *M. haemolytica* vaccination. A recent meta-analysis evaluated clinical trials testing the efficacy of *M. haemolytica, P. multocida,* and *H. somni* vaccines to decrease morbidity and mortality due to BRD.[33] Three trials testing the efficacy of *H. somni* vaccines to decrease respiratory morbidity were included in this meta-analysis—a summary relative risk of 0.97 (95%, confidence interval 0.61 to 1.54), indicating that vaccination has a statistically significant impact on respiratory morbidity. However, the authors noted that the small number of published trials testing *H. somni* vaccines gave their meta-analysis low power to detect an effect of vaccination.

The fact that *H. somni* vaccines induce cattle to produce IgE against the bacteria[17] indicates that vaccinated cattle may be at increased risk for a hypersensitivity reaction after a booster vaccine or infection. Although some older clinical trials showed a benefit associated with vaccination in terms of decreased respiratory morbidity and/or mortality, *H. somni* vaccination may also put cattle at risk for adverse reactions. Therefore it may be most prudent to recommend vaccination only for groups of cattle on operations in which significant morbidity or mortality caused by infection with *H. somni* has been confirmed.

As described for *M. haemolytica* and *P. multocida,* preventing primary injury to the respiratory tract by viral infection and limiting other causes of stress that suppress the host immune response are expected to help animals resist disease caused by *H. somni.*

Mycoplasma bovis

Definition and Etiology *Mycoplasma bovis* is a member of the genus *Mycoplasma* of the class Mollicutes, and as such it is among the smallest free-living organisms. The first known mycoplasma, identified in 1898, was the causative agent of contagious bovine pleuropneumonia, *Mycoplasma mycoides* subsp. *mycoides,* small colony variant. Mycoplasmas have since been recognized to cause disease in humans and a wide variety of animal and plant hosts. Mycoplasmas are small (approximately 200 nm) and pleomorphic, with a genome of only approximately 500 to 1000 kD. They are bounded by a single membrane, and because they lack a cell wall they are naturally resistant to antimicrobials such as penicillins and cephalosporins that work by impairing cell wall synthesis. *M. bovis* was first identified in 1961 in the United States, where it was isolated from a case of mastitis.[1] It has since spread worldwide. The bacterium was originally considered a subspecies of *Mycoplasma agalactiae,* and the two agents can be difficult to distinguish. However, *M. agalactiae* is a pathogen of sheep and goats and is rarely isolated in the United States, whereas *M. bovis* is regularly isolated in cases of pneumonia, respiratory disease, arthritis, tenosynovitis, and other disorders of cattle. *M. bovis* can cause disease in sheep, goats, and other species, but this is a rare occurrence. An overview of the clinical syndromes associated with *M. bovis* and the approach to their treatment and prevention was recently published.[2]

Clinical Signs Respiratory infection with *M. bovis* causes fever, tachypnea, inappetence, and sometimes respiratory distress.[3] Coughing and nasal discharge are reported in some outbreaks.[4,5] Respiratory disease caused by *M. bovis* can occur in outbreaks; in young calves, a subset of calves affected often develops otitis, characterized by unilateral or bilateral drooping of ears with purulent aural discharge, possibly with facial paralysis caused by cranial nerve VII involvement, and vestibular signs such as head tilt, nystagmus, and ataxia.[4-6] In weaned beef calves and cattle entering feedlots, a subset of affected animals may develop arthritis and tenosynovitis[7-9]; this syndrome is sometimes referred to as *chronic pneumonia and polyarthritis syndrome* (CPPS).[9,10] Young calves can also develop arthritis or tenosynovitis.[5] A typical complaint by the producer experiencing a respiratory disease outbreak involving *M. bovis* is that cattle do not respond to therapy as expected, and a significant proportion of affected animals remain chronically ill and unthrifty for weeks after the onset of disease.[7,8] In addition to respiratory disease, *M. bovis* can also cause mastitis, arthritis and tenosynovitis, conjunctivitis, otitis, sinusitis, and myocarditis and/or pericarditis. The bacteria can also be isolated from aborted fetuses and from semen, linking the agent to reproductive failure. North American bison *(Bison bison)* can develop severe and sometimes fatal disease following *M. bovis* infection, with mature adults often being predominantly affected.[11]

The ability of *M. bovis* to act as a primary respiratory pathogen has been debated. Classically the agent has been understood to be an opportunist, establishing itself after primary infection with viral pathogens or other bacteria. However, experimental challenge of

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gnotobiotic calves with *M. bovis* alone induced respiratory disease with clinical signs of fever, tachypnea, and inappetence in four of seven calves and grossly evident lung lesions in all seven.[3] These findings indicate that *M. bovis* can cause disease while acting alone, but, as for other bacterial respiratory pathogens described earlier, it is likely that natural disease often follows other primary insult. A survey of causes of death in cattle in Ontario feedlots identified caseonecrotic pneumonia caused by *M. bovis* as a cause of more fatalities within the first 60 days of the feeding period than acute fibrinosuppurative pneumonia typical of disease caused by *M. haemolytica* or *H. somni*.[12] This study indicates that *M. bovis* is an important contributor to mortality in some feedlots, but more research is needed to determine whether the factors that predispose cattle to fatal disease resulting from *M. bovis* are different from the factors known to predispose cattle to fibrinous bronchopneumonia caused by *M. haemolytica.*

Pathogenesis Although *M. bovis* has been recognized to cause respiratory disease in cattle for some time, little is known about the mechanisms by which the agent causes disease. In disease caused by other mycoplasmas, attachment has been shown to be a key factor in pathogenesis. In vitro studies of *M. bovis* suggest that pathogenicity is likewise associated with the ability to attach, as isolates from cases of clinical disease were better able to attach to embryonic bovine lung cells than were isolates from asymptomatic animals or high passage laboratory isolates.[13] Antibodies against several of the variable surface proteins (Vsps) expressed by *M. bovis* were able to partially but not completely block attachment, indicating that the Vsps play a role in attachment.[13] Invasiveness is another pathogenic mechanism of *M. bovis; M. bovis* was found to be capable of migration between ciliated respiratory epithelial cells, whereas *Mycoplasma dispar,* another mycoplasma commonly isolated from cases of bovine pneumonia, remained on the surface of ciliated epithelial cells.[14] The ability of *M. bovis* to invade allows the organism to cause disease in organs outside the respiratory tract, such as joints and tendon sheaths.

Available data indicate that *M. bovis* may cause disease in part through evading or impairing host immune function. Although not yet well characterized, a feature of *M. bovis* that is likely important in enabling the bacteria to escape the host immune response is the expression of Vsps. The ability to vary surface protein expression has been shown to be an important pathogenic mechanism in certain mycoplasmas.[15] *M. bovis* expresses at least three Vsps (VspA, VspB, and VspC), and isolates have been found that express some or all of these proteins.[16] A study of 50 *M. bovis* isolates, including many field isolates, showed extensive variability in Vsps at both the genetic and the antigenic level.

Evidence indicates that *M. bovis* can directly impair the activity of neutrophils. In one study *M. bovis* was found to adhere to bovine neutrophils, but adherence did not elicit an expected activation response by the neutrophils. Moreover, adherent *M. bovis* inhibited normal neutrophil microbicidal activity.[17] The bacterium is also able to kill lymphocytes by inducing them to undergo apoptosis (programmed cell death).[18] Induction of proinflammatory cytokine production by the host may also contribute to disease caused by *M. bovis.*[19]

Other research suggests that *M. bovis* may induce an immune response that is not optimally protective. Vanden Bush and Rosenbusch showed that in calves experimentally infected with *M. bovis,* serum titers of *M. bovis*–specific IgG1 increased significantly after infection, whereas titers of *M. bovis*–specific IgG2 did not increase as markedly.[20] Because IgG2 is considered superior in opsonizing ability as compared with IgG1, the authors speculated that preferential induction of IgG1 by *M. bovis* infection may be related to the apparent inability of the immune response to rapidly clear the organism.

Epidemiology *M. bovis* can be isolated from the respiratory tracts of normal cattle[21,22] and from cattle with respiratory disease.[23-25] Surveys of nasopharyngeal swabs taken from dairy calves with no clinical signs of respiratory disease found *M. bovis* in up to 34% of the animals sampled.[25,26] A survey of multiple source weaned beef calves sampled soon after arrival at nine different backgrounding or stocker operations identified nasal shedding of *M. bovis* in up to 6% of animals at each operation.[27] *M. bovis* can also be found in bovine lungs without evidence of disease at postmortem examination.[12] The fact that *M. bovis* can be isolated from animals with no clinical or pathologic signs of pneumonia has led some to question whether the agent is a true respiratory pathogen. However, a consistent association of *M. bovis* with a clinical syndrome of chronic nonresponsive pneumonia with or without otitis, arthritis, or tenosynovitis and a pathologic syndrome of bronchopneumonia with multifocal caseous necrosis visible histologically and/or grossly has led to general acceptance that *M. bovis* can contribute to significant morbidity and mortality in some situations.

Currently available data support the concept that *M. bovis* can spread from a few animals carrying the bacteria to others until a large proportion of a group is infected; transmission in these cases is most likely via respiratory infection by direct contact or short-distance aerosol.[7,8,21] Feeding milk infected with *M. bovis* appears to be another important source of infection for dairy calves.[5-7] The fact that *M. bovis* infection can be widespread in some populations was illustrated by a case-control study of cattle in the first 4 weeks after feedlot entry. *M. bovis* was found in bronchoalveolar lavage fluid of 52% of controls that were not treated for respiratory disease in the first 28 days on feed, versus 61% of cases that were treated for respiratory disease within 28 days.[28] Two weeks later *M. bovis* was found in BAL fluid from over 80% of the controls and in 100% of animals who ultimately were treated for respiratory diseases by 28 days, indicating that colonization of the respiratory tract of all cattle sampled was widespread within a short period after feedlot entry.[21] More recent work has confirmed that a large proportion of cattle can be infected with *M. bovis* over the first weeks after feedlot entry[29,30] and that infection is associated with decreased weight gain.[29] *M. bovis* infection of the respiratory tract appears to persist for weeks in feedlot cattle, but data are mixed in terms of whether cattle clear one infection only to be infected with a new isolate[30] or whether a single isolate persists for several weeks.[31] More than one genetic lineage of *M. bovis* can be involved with outbreaks; in one report, a single genetic lineage was associated with disease in a closed herd, whereas multiple genetic lineages were associated with disease in a calf ranch where animals were frequently brought on-site from multiple sources.[32]

M. bovis has been isolated from both dairy calves and feedlot cattle with respiratory disease in multiple studies, with particularly high prevalence occurring in animals with chronic pneumonia nonresponsive to antimicrobial therapy. In a survey of cattle subjected to necropsy within 60 days of arrival at 72 feedlots, lung lesions were categorized as either fibrinosuppurative (typical lesion caused by *M. haemolytica* or *H. somni*) or caseonecrotic, which were characterized grossly by the presence of multiple foci of dry caseous material and histologically by areas of eosinophilic necrotic cellular debris (caseous necrosis) surrounded by inflammatory cells and fibrous tissue. *M. bovis* was isolated in 53 of 54 cases (98%) with caseonecrotic lesions and in 52 of 58 of cases (89%) with fibrinosuppurative lesions; it was also isolated from 6 of 13 animals (46%) with normal lungs in this study.[12] In 49 chronically sick cattle from a single feedlot, *M. bovis* was identified in the lungs of 82% of the cases and in the joints of 45% of the cases.[33] BVDV was also present in 39% of the cases from which *M. bovis* was isolated. A later retrospective study by the same authors found BVDV in the lungs of 44% of cattle subjected to necropsy with a final diagnosis of pneumonia caused by *M. bovis;* these data led the authors to suggest that immunosuppression resulting from BVDV may predispose a subset of animals to chronic pneumonia and/or arthritis caused by *M. bovis*. In contrast, others found that BVDV infection was not more common in feedlot cattle with caseonecrotic lesions typical of *M. bovis* infection.[24]

Necropsy Findings Grossly, lungs of cattle with pneumonia caused by *M. bovis* have dark red, firm consolidated lobules of the

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cranioventral lung. In some cases, raised white to yellow, firm nodules that range from 0.5 to several centimeters in diameter, or that may coalesce, are seen clustering in the cranioventral lung (Color Plates 31-8 and 31-9).[3,10,34] These nodules may appear to be abscesses, but in most cases they are actually foci of coagulation necrosis.[3,24] Differential diagnoses for gross lesions of abscessing pneumonia in cattle include infection with *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *F. necrophorum,* or *Mycobacterium bovis* (tuberculosis). Other gross lesions include enlargement of interlobular septa by edema and fibrin; fibrinous or fibrous pleural adhesions are unusual but could be present if the animal is or has been co-infected with *M. haemolytica* or *H. somni*. Animals with pneumonia typical of *Mycoplasma bovis* may also have arthritis in one or more joints, characterized by abundant yellow fluid with fibrin and sometimes purulent material, and tenosynovitis, characterized by extensive caseous exudate and pyogranuloma formation in the tendon sheaths.[8,10] Fibrin, purulent material, and caseous material may be present in the tympanic bullae.

Histologically there is purulent pneumonia and bronchiolitis, with extensive infiltration of neutrophils in airways, and peribronchiolar cuffing with lymphocytes and mononuclear cells. Foci of eosinophilic coagulation necrosis are surrounded by a rim of dark pyknotic inflammatory cells and, farther out, a region of primarily macrophages and some plasma cells.[3,10] Immunohistochemical staining for the organism often shows large numbers surrounding the periphery of areas of coagulation necrosis, as well as in association with bronchiolar and alveolar epithelial cells.[10,35] Histologic evaluation of joints, tendon sheaths, and the tympanic bullae and petrous temporal bone will reveal changes consistent with the gross lesions. Close inspection may also reveal foci of mononuclear cell accumulation with positive staining for *M. bovis* by IHC in the liver and kidney[35] or in the pericardium.[36]

Diagnosis Confirmation of respiratory disease caused by *M. bovis* is best made by identification of the agent by culture or IHC in conjunction with typical gross and histopathologic lesions. Thus, in order to reliably confirm a role for *M. bovis* in an outbreak of BRD, postmortem of representative affected cases is necessary. Identification of the bacteria in nasal swabs is less reliable; the agreement between the results of nasal swab culture and the presence of lung disease caused by *M. bovis* was good in one study[23] and only moderate to poor in two other studies.[28,37] Deep nasopharyngeal swabs may accurately indicate involvement of *M. bovis* in a respiratory disease outbreak in a group of cattle if swabs from multiple animals are positive. Therefore, if diagnosis is to be attempted via nasopharyngeal swabs, multiple animals should be sampled. The results of deep nasopharyngeal swabs collected from only one or two cattle are hard to interpret because *M. bovis* can be found in the normal bovine nasopharynx. It is important to request that the diagnostic laboratory specifically identify *M. bovis;* in many cases diagnostic laboratories characterize mycoplasmas only to the level of the genus. Because other mycoplasma such as *Mycoplasma bovirhinis, Mycoplasma dispar,* and *Mycoplasma alkalescens* can also be isolated from the respiratory tract of cattle with pneumonia, a report of "*Mycoplasma* sp." is not equivalent to a diagnosis of disease caused by *M. bovis*. Species-specific identification of *M. bovis* can be made by antibody-based tests such as IHC or immunofluorescence (available at the Iowa State University Veterinary Diagnostic Laboratory, and possibly others) or PCR (available at many laboratories, including the University of Georgia Athens Veterinary Diagnostic Laboratory).

Although available data suggest that *M. bovis* is less commonly isolated from healthy cattle than are other mycoplasmas, because the organism can be found in nasal swabs and lung tissue of apparently normal animals, an isolation of the bacteria in the absence of evidence of disease is of uncertain significance. Serologic assays have been used to characterize seroconversion in epidemiologic studies, but the tests are not widely available, and their results have not been shown to reliably indicate active infection.[38] If serology is attempted, paired serology with evidence of rising titers in association with outbreaks of respiratory and/or joint disease is likely to be more useful than measurement of titers on a single occasion.

Treatment and Prevention Multiple authors report that cattle with pneumonia or arthritis caused by *M. bovis* respond poorly to antimicrobial therapy.[8,9,38] Early studies indicated that tilmicosin had good effect against experimentally induced[38] disease caused by *M. bovis* in cattle; however, recent studies of in vitro susceptibility profiles of panels of *M. bovis* isolates reveal evidence of widespread resistance to tilmicosin, as well as to erythromycin, ampicillin, and ceftiofur.[39,40] Susceptibility to oxytetracycline and chlortetracycline has been variable; most isolates have been susceptible to fluoroquinolones such as enrofloxacin or danofloxacin.[40-42] Several antimicrobials are currently labeled in the United States for treatment of disease caused by *M. bovis,* including tulathromycin (Draxxin, Zoetis, Florham Park, N.J.); florfenicol (Nuflor Gold, Merck Animal Health, Summit, N.J.); enrofloxacin (Baytril 100, Bayer Healthcare LLC, Animal Health Division, Monheim, Germany); and gamithromycin (Zactran, Merial, Duluth, Ga.).

Although clinical trials and data from well-controlled experimental studies under conditions typical of U.S. and Canadian cattle operations are lacking, reports suggest that in vitro minimum inhibitory concentration (MIC) data may not always predict antimicrobial efficacy in the field.[38,43] If in vitro susceptibility tests fail to predict clinical efficacy, the reason for this failure is not certain. Because *M. bovis* can be seen in association with foci of coagulation necrosis in lungs of affected cattle,[10,24] it may be that antimicrobials are not maximally effective in this environment, or it may be that insufficient duration of treatment is carried out in at least some cases. Controlled trials indicating the duration of antimicrobial therapy needed for effective treatment of pneumonia caused by *M. bovis* are lacking, but anecdotal reports suggest that early treatment is critical for success[5,44] and that treatment should be continued for at least 7 to 10 days. Failure of antimicrobials that are predicted to be efficacious against *M. bovis* may also be related to inability of the immune response to effectively clear the organism, due to immunosuppressive mechanisms described previously. Some veterinarians report that outbreaks of *M. bovis* cannot be stopped with any treatment but that outbreaks are eventually terminated when chronically affected animals die or are shipped to slaughter.

Research indicates that vaccination can afford some protection against experimental challenge with *M. bovis.*[45,46] Autogenous vaccines have been used for years, but no reports with large numbers of animals and appropriate controls are available to provide information about efficacy. Vaccines for control of disease caused by *M. bovis* are licensed for sale in the United States; for vaccines to be fully licensed, evidence of safety and efficacy in experimental challenge studies must be presented. However, properly designed field trials provide better evidence of usefulness of vaccines in the field, and reports of field trials to test the efficacy of currently licensed *M. bovis* vaccines are sparse. Results from two trials testing the effect of *M. bovis* vaccines on respiratory disease in dairy or veal calves were recently reported.[47,48] In one trial, there was no difference in respiratory morbidity or mortality in the first 90 days of life for vaccinated calves, as compared with unvaccinated controls.[47] In the second trial, which evaluated the effect of two different commercially available *M. bovis* vaccines on lung lesions at harvest of veal calves at approximately 145 days of age, lung lesions were decreased in one vaccine group but not the other group, as compared with unvaccinated controls.[48] More properly designed field trials are needed to determine the value of *M. bovis* vaccination as used in the field in different types of cattle populations.

It is not yet clear why some cattle develop chronic disease typical of *M. bovis* and others do not when it can be found in the respiratory tracts of animals in both populations. Certainly the primary insults known to put cattle at increased risk for infection with other bacterial respiratory pathogens—insults such as primary viral infection, mixing of animals from multiple sources, inadequate host immunity, and environmental stressors—may all play a role, but the relative

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importance of these and other factors in predisposing animals to disease caused by *M. bovis* are not yet known. One group presented data suggesting that disease resulting from *M. bovis* has increased in severity since the early 1980s,[24] so it may be that factors such as increasing virulence of currently circulating isolates or changes in certain management practices are involved. Because of the chronic nature of disease often associated with *M. bovis,* the syndromes described warrant control from both a financial and an animal welfare perspective. Anecdotal reports indicate that some producers with at-risk cattle have more problems with chronic nonresponsive disease caused by *M. bovis* than other producers with similarly at-risk cattle.[9] More research is needed to clarify the factors that put animals at specific risk for chronic disease associated with *M. bovis* infection.

Mycoplasma mycoides Subsp. *mycoides*, Large Colony Type

Definition and Etiology Caprine pneumonias that are not contagious among adults can be caused by several species of *Mycoplasma*. However, *M. mycoides* subsp. *mycoides* Large Colony type (MmmLC) can be a very serious cause of mortality among goat kids and does in North America.[1,2] It has been proposed that MmmLC be reclassified as a serotype of *Mycoplasma mycoides* subsp. *capri* (Mmc), as the two organisms can only be distinguished serologically.[3] *Mycoplasma mycoides* subsp. *mycoides* Small Colony type (MmmSC), which is more distantly related to MmmLC and Mmc, is the causative agent of contagious bovine pleuropneumonia, a serious cause of sickness and death in cattle in Africa. MmmSC has been eradicated from North America.

Clinical Signs In herds with MmmLC infections, goat kids usually appear clinically normal until 2 to 8 weeks of age, when any of the following three clinical syndromes occur[1,2]:

1. A peracute illness characterized by high fevers (41.1°C to 42.2°C [105.8°F to 107.9°F]) and death within 12 to 24 hours
2. A central nervous system syndrome with opisthotonos and death within 24 to 72 hours
3. An acute to subacute syndrome with high fevers, multiple hot swollen joints, and pneumonia

The most common manifestations are swollen joints, lameness, and recumbency. About one half of affected kids have increased lung sounds on expiration and elevated respiratory rates. During an outbreak, 80% to 90% of kids die or are euthanized because of permanent recumbency. MmmLC infection in adult does is also life-threatening. Forty-six does died in 1 week on a 600-goat dairy during an acute outbreak of arthritis and polyarthritis, mastitis, and interstitial pneumonia caused by MmmLC infection.[4]

Necropsy Findings The most common necropsy finding in goat kids that die of MmmLC infections is a fibrinopurulent polyarthritis.[1,2] Approximately one half of field cases have pneumonia. One or more lung lobes have areas of patchy to diffuse red consolidation that is sometimes covered with a fibrinous exudate. Clear, golden yellow to serosanguineous fluid is found in the thorax in half of the cases. In some patients there are fibrinous adhesions between the lungs and thoracic wall. Affected lungs have microscopic evidence of bronchopneumonia or interstitial pneumonia. Other common lesions include pericarditis, peritonitis, and enlargement of the kidneys, liver, and spleen.

Diagnosis The definitive diagnosis of MmmLC infection in individuals requires isolation of the agent from milk, joint fluid, blood, urine, or tissue. Infected goat herds can be readily identified by culturing bulk tank milk because infected does shed up to 10^{10} MmmLC organisms per milliliter of milk.[1] Inapparent carriers can be identified by milk culturing, but false-negative results are a risk because organisms are shed intermittently. Goats can carry MmmLC in their external ear canal, and PCR of auricular swabs has been shown to be a sensitive means of diagnosis of chronic carriers.[5]

Treatment and Prevention Conventional antibiotic therapy for goats with MmmLC infections is almost always unsuccessful.[1,2] Tylosin or tetracyclines have been used; newer generation antibiotics effective against *Mycoplasma bovis* could also be tried, although this would be an extralabel use of these drugs. A low percentage of kids make a clinical recovery from the septicemic illness but often have arthritis by the time they freshen. Does that recover from mastitis become chronic carriers.

Prevention is based on maintaining herds free of MmmLC infection. Purchased does should originate only from herds that have no history of mortality in kids from arthritis and pneumonia and that have negative bulk tank cultures for MmmLC. Purchased individuals should be held separate from the milking herd until they have an MmmLC-negative milk culture result; treatment for ear mites may also be prudent. A vaccine is not commercially available.

Control of MmmLC outbreaks is centered on prevention of the systemic infection in kids and mastitis in milking does. Rapid prevention of new cases in kids can be expected from a program of feeding heat-treated goat colostrum (56°C [132.4°F] for 1 hour) or cow colostrum at birth, pasteurized milk up to 1 month of age, and pasteurized milk or a high-quality milk replacer from 1 month to weaning.[1] All kids with swollen joints should be culled. Milking hygiene should be improved to prevent transmission of infection during milking. Udders should be dried with individual cloths or paper towels, teats should be dipped with an organic iodine base preparation, and teat cups should be backflushed. Milk samples from all does in the milking herd should be cultured to identify carrier does. Infected does should be kept in a separate string and milked last or culled, depending on production. Colostrum of dry does should be cultured as they freshen, and the does should be hand-milked separately until their milk is found to be free of Mmm. Monthly cultures of the bulk tank milk from the noninfected string should be performed to ensure that it is free of Mmm infection. The goal of control procedures is eradication of Mmm from the herd.

Other Mycoplasmas

Mycoplasmas are isolated, usually in combination with other pathogens, from 50% to 90% of beef and dairy cattle pneumonias.[6-9] Mycoplasmas have been associated with peribronchial and peribronchiolar lymphoid hyperplasia, which is sometimes referred to as a "cuffing pneumonia," a common lesion in calves that die or are euthanized because of pneumonia.[10,11] Mycoplasmas have also been recovered from lesions of acute and chronic bronchopneumonia in which a cuffing pneumonia was not apparent.

Other than *Mycoplasma bovis,* the species of mycoplasmas (see Box 31-4) prevalent in North America are generally considered to be mild respiratory pathogens, mainly causing subclinical infections unless coupled with environmental stresses or infections by other pathogens. Tracheobronchial aspiration performed on dairy calves at random found that calves with both *Mycoplasma* spp. and *Pasteurella* spp. present in the aspirate were at significantly greater risk of developing pneumonia than calves with only one organism or no organisms. A study of feedlot cattle found seroconversion to *M. alkalescens* to be significantly associated with undifferentiated fever, a clinical definition similar to undifferentiated respiratory disease.[12] Effects such as immunosuppression and inhibition of the mucociliary transport mechanism, which can be mediated by mycoplasmas, suggest that they may play an important contributory role in the pathogenesis of bovine pneumonia. *Mycoplasma ovipneumoniae* is often isolated from pneumonic lungs of sheep and goats, usually accompanied by *M. haemolytica.* On its own, *M. ovipneumoniae* is capable of causing mild, subacute to chronic bronchiolitis or bronchopneumonia that probably predisposes to *M. haemolytica* infections.

Bibersteinia trehalosi

Bibersteinia trehalosi (formerly *Pasteurella trehalosi* and before that *Pasteurella haemolytica* biotype T) causes pneumonia or systemic disease with multiorgan infection in sheep. Recently *B. trehalosi* was isolated from the lungs of cattle or recently weaned calves with severe

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peracute to acute bronchopneumonia.[1] Affected cattle described in this report often died before they were noticed to be ill, and antimicrobial therapy did not seem to be very effective in spite of the fact that *B. trehalosi* isolated from lungs of affected cattle were susceptible to many antimicrobials in vitro. Vaccines against *Mannheimia haemolytica* may help limit disease caused by *B. trehalosi,*[1] but the efficacy of this has not been confirmed in field trials.

Trueperella pyogenes (formerly *Arcanobacterium pyogenes*)

Trueperella pyogenes[1] (formerly *Arcanobacterium pyogenes,* before that *Actinomyces pyogenes,* and before that *Corynebacterium pyogenes*) is a gram-positive rod-shaped species of bacteria that is a common cause of internal or subcutaneous abscesses in ruminants. *T. pyogenes* is occasionally isolated from the lungs of ruminants with pneumonia, typically from animals that have chronic pneumonia, especially with grossly visible abscesses. This species is viewed as an opportunist that contributes to respiratory disease as a secondary or possibly "tertiary" invader after viral pathogens and other bacterial respiratory pathogens have become established. *T. pyogenes* has a variety of virulence factors including a cytolytic toxin termed *pyolysin,* as well as several molecules that aid in adherence to host cells.[2] Diagnosis of this pathogen is usually made as an incidental finding at necropsy of an animal with significant respiratory disease from other primary causes. Finding *T. pyogenes* during a respiratory necropsy should not induce efforts to directly treat or prevent this pathogen, but rather should induce efforts to prevent other primary or secondary causes of pneumonia and to treat animals in a timely manner with appropriate therapy for an adequate duration in order to prevent chronic pneumonia.

Chlamydial Agents (*Chlamydophila* Species)

Chlamydial agents, most commonly *Chlamydophila abortus, Chlamydophila psittaci,* or *Chlamydophila pecorum,* have been associated with a variety of disease syndromes in cattle and small ruminants, including abortion and infertility, conjunctivitis, polyarthritis, encephalomyelitis, and enteritis. These agents are also occasionally identified in pneumonic ruminant lungs. Because chlamydial agents can also be identified in ruminants with no signs of disease, and because seroprevalence is high, the importance of chlamydial agents in ruminant respiratory disease has been debated.[1] Whereas experimental infection of calves with high numbers of *C. psittaci* via a route that bypasses the upper respiratory tract can lead to clinically evident respiratory disease that may be severe,[2] in the natural setting, these agents are most likely to participate as one of multiple factors necessary to induce important ruminant respiratory disease. Research indicates that calves are infected with chlamydial agents relatively early in life and that crowding enhances the likelihood of a high proportion of animals being infected.[3]

Approach to Diagnosis and Treatment of Respiratory Disease of Undetermined Cause (Undifferentiated Ruminant Respiratory Disease)

Amelia R. Woolums[¶]

Information regarding diagnosis and treatment of individual infectious agents that can cause ruminant respiratory disease was described earlier. However, it is common for multiple agents to be involved when a group of cattle, sheep, or goats has an outbreak of respiratory disease. Moreover, when a veterinarian is called to make an initial evaluation of a group of ruminants with respiratory disease, the infectious agents involved are not yet known. The term *undifferentiated respiratory disease* has been applied to respiratory disease of undetermined cause. Thinking of an outbreak as "undifferentiated respiratory disease" before one or more specific etiologic agents are identified is helpful to ensure that the veterinarian considers all possible infectious agents and management factors that may be contributing to disease in the animals in question, rather than immediately focusing on one agent or factor that is guessed to be of importance. A plan to diagnose and treat the current problem and prevent future respiratory disease can then be made by administering treatments and instituting management changes appropriate for any of the agents likely to affect the class of animals involved.

History Successful management of one or more ruminants with respiratory disease will require identification and alteration of the risk factors associated with occurrence of the disease; this is particularly true when multiple animals are affected in an outbreak or when endemic disease occurs at an unacceptable rate. Evaluation of the problem begins with collection of a thorough history and is followed by examination of affected animals and the environment. The history questions are directed at management practices that predispose to respiratory disease. It is important to observe personally as many management practices as possible to ensure that what is described is actually implemented. Examination of the environment includes evaluation of animal housing to determine whether poor ventilation, crowded or dirty housing, or temperature extremes are likely increasing the disease susceptibility of animals. The nutrition program should be assessed to determine whether nutritional deficiencies are likely contributing to disease susceptibility.

Clinical Signs Once a thorough history is collected, several animals involved in the outbreak should be examined. The degree of fever and severity of abnormal lung sounds were correlated with risk for retreatment for respiratory disease in feedlot cattle[1]; thus clinical examination may be important not only for accurate identification of sick cattle but also for improving estimates of outcome for cattle with respiratory disease. A scoring system has been developed to aid in the assessment of clinically evident respiratory disease in individual dairy calves and in groups of dairy calves.[2]

Ruminants affected by bronchopneumonia exhibit signs of respiratory tract inflammation and, sometimes, systemic inflammatory response. In early stages, animals stand off by themselves and do not readily approach feed. They hold their heads and ears low, appear depressed, and move slowly. Respirations become rapid and shallow, there may be frequent licking of the muzzle, and a moist cough is often present. Animals may have a fever of 40° C to 41° C (104° F to 105.8° F), and as the disease progresses they appear gaunt, have deep labored respirations, and may hold the head extended. Dyspnea may be both inspiratory and expiratory. Ocular and nasal discharges progress from serous to mucopurulent. The heavy chest wall of larger cattle may make it difficult to hear normal airway sounds. Auscultable lung changes may include increased harshness or loudness of inspiratory sounds ("large airway sounds" or "bronchial tones"). Auscultation of the anterior ventral lung fields may reveal crackles and wheezes. When ventral consolidation occurs, harsh breathing is still audible ventrally, but percussion reveals ventral dullness. Percussion is best accomplished on young calves and goats of any age. Recently shorn sheep can be readily percussed, but heavy wool makes percussion difficult. Animals in which a fibrinous pleuritis develops are reluctant to move (because of pain), have shallow respirations, and sometimes have pleural friction rubs detectable on auscultation.

Nasal discharge, dyspnea, abnormal lung sounds, cough, and high fevers are cardinal signs of bronchopneumonia. Other respiratory tract conditions that must be considered as differential diagnoses include acute bovine pulmonary edema and emphysema (ABPEE), interstitial pneumonia, pulmonary edema, pleuritis, laryngitis, tracheitis, and lungworms. Rare conditions include thoracic neoplasia and diaphragmatic hernia. Nonrespiratory diseases that may result in abnormal respiratory signs include septicemia, heart failure, acid-base imbalances, and poisonings such as nitrate toxicity. In sheep

[¶]Previous contributions by John C. Baker, Trevor R. Ames, and Steven E. Wikse are acknowledged.

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and goats, ovine progressive pneumonia (OPP), caprine arthritis-encephalitis (CAE), and lung or mediastinal abscesses caused by *Corynebacterium pseudotuberculosis* or other bacteria are additional differential diagnoses.

Because ruminants are often housed in groups and are often not acclimated to individual handling, signs of respiratory disease in one or more individuals are often first noticed from a distance rather than from "hands-on" examination. Early signs of bronchopneumonia include mildly depressed attitude and appetite; thus caretakers may first identify animals with bronchopneumonia when they are offered feed, at which time affected animals fail to come forward to consume feed with normal enthusiasm. Groups at particularly high risk for respiratory disease, such as animals that have been recently weaned and/or transported by truck or trailer, should be evaluated two or three times per day for at least the first week or two after weaning or transport. Frequent evaluation of animals at high risk is important because the early signs of respiratory disease are nonspecific and subtle, and severe bronchopneumonia can advance rapidly, sometimes leading to death that is sudden and unexpected in as little as a few hours. For this reason, it is preferable to feed groups of ruminants at high risk for bronchopneumonia relatively small amounts of feed frequently, providing only what they will consume in 12 to 24 hours, rather than providing enough feed for several days in a self-feeder or via large round bales of hay. It is important to remember that once obvious signs of bronchopneumonia (such as coughing, profuse mucopurulent nasal discharge, and dyspnea) are evident from a distance, disease is often advanced and animals are less likely to respond well to therapy.

Diagnostic Evaluation of Undifferentiated Ruminant Respiratory Disease If clinical examination of a group of cattle, sheep, or goats indicates that respiratory disease is present, it is not always necessary to immediately submit samples for diagnostic testing. Occasional outbreaks of respiratory disease occur in groups of ruminants, and such occasional outbreaks can often be managed successfully with administrative symptomatic therapy alone. However, if recurrent outbreaks occur, or if animals do not respond appropriately to symptomatic therapy, then diagnostic tests are warranted so that more information is available to better characterize the nature of the problem. In such situations a careful evaluation of management practices and facility design is also warranted to ensure that all practices possible are in place to maximize the ability of animals to resist respiratory infection. Management practices that may help decrease respiratory disease are described in the section Prevention and Control of Undifferentiated Ruminant Respiratory Disease (see p. 613).

Clinical Pathology and Assessment of Immune Status Complete blood cell counts or serum biochemical analyses are rarely of much value in diagnosis of respiratory disease in ruminants. Some viruses, such as BVDV, may cause leukopenia, but when bacterial pneumonia is superimposed the white blood cell (WBC) count is most often in the high-normal range to mildly elevated with a left shift. Animals with bacterial pneumonia may have an inflammatory leukogram characterized by a leukocytosis with a mature neutrophilia, possibly with a left shift; hyperfibrinogenemia is likely to occur. Animals with chronic pneumonia may have a normal WBC count even when there is significant pulmonary pathology.

Failure of passive transfer is an important risk factor for disease in calves, so investigation of respiratory disease outbreaks in calves should include an evaluation of passive transfer status by measurement of immunoglobulins or total solids in the serum of a subset of calves 1 to 7 days of age. The zinc sulfate turbidity test, sodium sulfite test, and measurement of total serum protein with a refractometer are alternative procedures for estimation of serum immunoglobulin concentrations in groups of calves.

Necropsy Findings The value of necropsy findings to confirm the cause of death, particularly in animals that die unexpectedly, cannot be overemphasized. If producers can be convinced to allow animals that die to be subjected to necropsy, much valuable information may be gained before a disease outbreak causes excessive mortality. On a herd level, establishing a practice of subjecting all animals that die to at least gross necropsy can aid greatly in maintaining management practices that limit animal disease and death; this is because the actual cause of death identified at necropsy can sometimes be unexpected. For example, if an animal is assumed to have died of pneumonia, but it actually died of acute enterocolitis, then inappropriate control measures may be undertaken.

The cost of having animals sent to the local diagnostic laboratory for full necropsy may dissuade some owners from allowing necropsies. However, much useful information can be gained simply by gross necropsy evaluation performed on the farm by the local veterinarian. With some practice, veterinarians can develop confidence in identifying the major differentiating gross features of common diseases, and they can thus ensure that management is aimed at control of disease of the correct organ system. Moreover, there are some identifiable characteristics typical of the major infectious causes of bronchopneumonia. Gross necropsy can help the veterinarian make a more accurate list of differential diagnoses for outbreaks of bronchopneumonia, allowing the development of a more appropriate plan for treatment and prevention. Gross pathologic features of disease caused by infectious respiratory agents are described elsewhere in this chapter and are summarized briefly below. Recent reviews of the pathology of common pulmonary diseases of cattle are available for additional information.[3,4]

A respiratory necropsy should include assessment of the upper airways and trachea. Fibrinopurulent material in the larynx is evident in cattle with necrotic laryngitis. Infection with BHV-1 (IBR virus) causes generalized reddening (congestion) and small, raised, red or pale plaques on the mucosa of the nasal passages and trachea; more severe cases have dark red, hemorrhagic changes, possibly with yellow-brown exudate adherent to the mucosa (fibrinopurulent tracheitis) (see Color Plate 31-2).

Bronchopneumonia in recently transported cattle (shipping fever pneumonia) is most commonly a fibrinopurulent bronchopneumonia or pleuropneumonia. The infection is aerogenous; it begins in the bronchioles and extends into the surrounding parenchyma. The cranioventral areas of affected lungs are swollen, dark red to gray-brown in color, firm, and heavy. Bronchial lymph nodes are swollen, wet, and dark red. The inflamed lung and parietal pleura are sometimes covered with variable amounts of white or yellow fibrin, and the pleural cavity may contain straw-colored or red-tinged fluid (see Color Plate 31-5). Fibrinous pleuritis usually indicates the presence of *M. haemolytica* or *H. somni,* or possibly *Bibersteinia trehalosi*. These species can also cause necrosis of the lung, which will be firm and brown to gray (see Color Plate 31-6) and which may contain dark red wedge-shaped lesions (infarcts) that are caused by thrombosis of an artery supplying the region. The dorsal regions of the caudal lobes often are mottled by interspersed patches of inflammation and normal parenchyma. In some bronchopneumonia cases, forced respirations result in vesicular to bullous pockets of emphysema in the dorsal areas of the caudal lobe (see Color Plate 31-3). These changes can also be seen with primary BRSV infections or with AIP. Focal or multifocal areas of firm white to yellow material that look like abscesses may actually be caseous necrosis caused by *Mycoplasma bovis* (see Color Plate 31-9); the chronic phase of pneumonia resulting from *M. haemolytica* may also cause similar lesions. Abscesses containing caseous or liquid purulent material may also be caused by *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) or anaerobic bacteria. Sheep or goats that die of bronchopneumonia caused by *M. haemolytica* may have swollen lungs with reddish purple cranioventral consolidation. An extensive fibrinous pleuritis with large amounts of straw-colored exudate is often present. Chronic cases have multiple abscesses and pleural adhesions. As much as 60% to 80% of the lung tissue is often involved in fatal cases of severe bacterial pneumonia.

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Bronchopneumonia in housed dairy calves is less often fibrinous; rather it is characterized by the presence of firm, collapsed, dark red lobules in the cranioventral and possibly the caudoventral lung (Color Plate 31-10); in severe cases whole lobes of the lung may be affected. Firm dark red lobules without fibrin on the pleura are common in pneumonia caused by *P. multocida, M. bovis,* or other mycoplasmas. Infection with BRSV and PIV-3 can also cause lobular consolidation of the ventral lung. Less commonly *M. haemolytica* or *H. somni* organisms are isolated from such lesions in the absence of fibrinous pleuritis.

Animals that die after chronic persistent coughing, dyspnea, and weight loss often exhibit lesions of chronic suppurative pneumonia. Bronchi and bronchioles are filled with purulent exudate, there are multiple mature lung abscesses, and greatly dilated bronchioles contain malodorous exudate. When bronchiectasis is severe, the lung lobes have a nodular appearance.

Although gross necropsy alone can be very helpful in generating an accurate list of differential diagnoses, histopathologic and microbiological findings may add valuable information. Gross necropsy findings alone are not always definitive; for example, in one study of AIP in feedlot cattle, only 67% of the cases that were diagnosed with AIP based on clinical and gross pathologic findings were confirmed by histopathology.[5] Therefore, in outbreaks with relatively high mortality or in cases in which long-term and possibly expensive therapy is not yielding expected results, the cost of full necropsy of two or three typical cases is likely to be well worth the expense.

If full necropsy at a local diagnostic laboratory is to be undertaken, two or more animals showing signs that are typical of the early stages of the disease outbreak should be sent for euthanasia and necropsy. Although the producer may be reluctant to euthanize animals that may recover, and would rather send animals with chronic, nonresponsive disease, the chronic cases are unlikely to yield information relevant to the primary problem.

Microbiological Tests

Samples for identification of viral and bacterial pathogens associated with cases of respiratory disease can be collected antemortem from live animals or at necropsy of animals that have died or been euthanized. Appropriate samples to collect from live animals include nasal swabs, deep nasopharyngeal swabs, TTA, or BAL. Each of these samples has benefits and drawbacks. Nasal swabs are usually collected with a 6-inch (13.5-cm) swab that is not guarded (protected) from contamination. After sampling, the swab is put into transport medium that may come with the swab or may be obtained from a veterinary diagnostic laboratory. Deep nasopharyngeal swabs are usually collected using a longer swab guarded by an outer sheath, such as is used for mare or cow uterine culture. Although these swabs are unwieldy for use in sampling young calves, they allow the swab to be protected from contamination by commensal bacteria in the outer nasal passage, providing a theoretically more representative sample of viruses and bacteria in the nasopharynx that are more likely contributing to respiratory disease. Identification of common respiratory viruses such as BHV-1, BRSV, or BVDV from either a nasal or nasopharyngeal swab is significant. Although these viruses can be shed by cattle without signs of respiratory disease, if these viruses are identified in animals with respiratory disease, they should be considered contributing factors. Identification of bacterial respiratory pathogens such as *M. haemolytica, P. multocida,* or *H. somni* from nasal or deep nasopharyngeal swabs is of less certain significance. These bacteria can all be found in the upper respiratory tract of normal cattle and are thus considered part of the normal flora. However, these bacteria can cause disease if they become established in the lung. Therefore identification of these bacteria in samples collected from the respiratory tract distal to the nasopharynx (e.g., TTA or BAL) is more likely to signify lower respiratory tract infection. However, TTA or BAL samples are more time-consuming to collect than are nasal or deep nasopharyngeal swabs, particularly if multiple animals are to be sampled in an outbreak investigation. The results of bacterial culture of deep nasopharyngeal swabs and TTA or BAL have been compared.[6-8] Taken together, these studies indicate that, for individual animals, the results of a deep nasopharyngeal swab do not predict the bacteria identified in the lower respiratory tract with a high level of accuracy. However, the results of deep nasopharyngeal swabs taken from multiple animals do appear to accurately represent the status of the group. Therefore the use of deep nasopharyngeal swabs to identify bacterial pathogens likely causing a respiratory outbreak appears to be reliable if multiple animals are sampled and the same bacteria are found in a majority of the animals sampled. Because deep nasopharyngeal swabs are not reliable for identifying bacterial pathogens causing lower respiratory tract infection in an individual animal, TTA or BAL should be used to obtain a representative sample for identification of bacterial pathogens in the lung if only one or two animals are to be sampled.

Proper handling and transport of the specimens collected from live animals or at necropsy is critical to maximizing the chance of an accurate diagnosis. The veterinarian is encouraged to contact the diagnostic laboratory if he or she is uncertain about the proper methods of sample collection and transport; most laboratories now post this information on their websites. Recent reviews of diagnostic sample collection and submission in the diagnosis of respiratory disease of cattle are available for additional information.[4,9] See Table 31-11 for guidelines for identification of common infectious respiratory pathogens.

Viruses

A specific viral diagnosis requires laboratory confirmation. Most laboratories direct their diagnostic efforts toward the viruses for which vaccines are available. Diagnosis of other respiratory viruses may require the assistance of specialized laboratories.

VIRUS ISOLATION. Virus isolation is time-consuming and expensive, but it can be a sensitive method for identifying some viruses. Virus isolation is performed in cell culture. A variety of specimens can be tested, including nasal, nasopharyngeal, conjunctival, and tracheal swabs, TTA, BAL, and a variety of respiratory tract tissues that can be obtained at postmortem examination. Fluids, tissues, and swabs may be frozen; however, freezing may kill some of the virus in the sample. Alternatively, swabs and tissue specimens may be placed in a viral transport medium and kept refrigerated or on ice packs until arrival at the diagnostic laboratory, preferably within 24 hours. In general, better success at virus isolation is obtained when specimens are collected in the acute phase of disease. Chances of successful isolation may be improved by sampling asymptomatic animals that are in close contact with affected animals. These animals may be in an incubation phase of infection. Some viruses appear to be more difficult to isolate than others. For example, BRSV can be difficult to isolate by routine procedures, and other diagnostic procedures should be performed in conjunction with attempts at virus isolation to confirm BRSV infection.

DETECTION OF VIRAL ANTIGENS. IFA staining is a rapid method for identification of specific respiratory viruses. Antemortem identification can be made in cells in material obtained from nasal, nasopharyngeal, or conjunctival swabs or from cells obtained by TTA or BAL. Postmortem identification can be made from frozen tissue sections prepared from a variety of respiratory tract tissues.

Another technique that is used to detect viral antigen in tissues is immunohistochemical (IHC) testing, which is most often carried out on formalin-fixed tissue. This is a very useful procedure that allows histologic examination of tissues in conjunction with specific identification of the causative agent.

Antigen capture enzyme immunoassay (EIA) provides a rapid means for detection of respiratory viruses. These tests can be performed on fluids or homogenates of tissues obtained from the respiratory tract. Commercially available antigen capture EIAs are available for diagnosis of HRSV infections in infants and young

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children that are also capable of detecting BRSV,[10] and these are in use in some veterinary diagnostic laboratories. The same technique has been developed for the detection of BVDV and is in use for screening serum samples to detect cattle persistently infected with BVDV.

DETECTION OF VIRAL NUCLEIC ACIDS. Testing of material from swabs, fluids, or tissues for viral nucleic acid by PCR (for DNA viruses) or reverse transcriptase (RT)-PCR (for RNA viruses) is widely available at veterinary diagnostic laboratories. One benefit of using nucleic acid detection to identify pathogens is that the pathogen does not have to be viable to be identified; this can be a particular benefit for relatively labile viruses such as BRSV.

SEROLOGIC DIAGNOSIS. Retrospective diagnosis of viral infections can be made by determination of antibody titers in paired sera from individual animals. The first sample is collected in the acute phase of the disease (the "acute" sample), and the second is collected 2 to 4 weeks later (the "convalescent" sample). In a respiratory disease outbreak, multiple animals should be tested to achieve a serologic diagnosis; it is typical for seroconversion to be identified in only a subset of animals tested in any outbreak. Serologic diagnosis is made by demonstrating a fourfold increase in antibody titer in the convalescent sample as compared with the acute sample; a fourfold fall in titer from the acute to the convalescent sample also indicates recent infection. Because day-to-day variation in results of tests used for serologic diagnosis is typical, the acute and convalescent samples should be run by the laboratory on the same day. Thus the acute serum samples should be processed and stored in the freezer by the local veterinarian and later shipped together with the convalescent samples.

Because infections in young ruminants can occur in the presence of passively derived antibodies, seroconversion might not always occur during outbreaks of bronchopneumonia involving young animals.[11] This problem may be overcome by inclusion of older individuals in contact with the younger animals in the population sampled, which are likely to have lost passively derived antibodies to these viruses and will be more likely to seroconvert. A wide variety of serologic procedures is available for antibody determinations, but most laboratories use a serum neutralization (SN) test (also known as a virus neutralization [VN] test) for identification of antibodies to viruses. It is important to remember that SN tests take several days to run. Some laboratories use more rapid procedures such as ELISA or IFA for determination of virus-specific serum antibody titers. A hemagglutination-inhibition test can also be used for PIV-3 and respiratory coronavirus.

Bacteria

A wide variety of bacteria have been isolated from the respiratory tract of ruminants in association with respiratory disease. However, the most frequent and most important isolates are *M. haemolytica, P. multocida, H. somni,* and *M. bovis*. The isolation of *T. pyogenes,* coliforms, or anaerobic bacteria often is indicative of chronic pneumonia or aspiration pneumonia and may be associated with lung abscessation.

Before bacterial culture is attempted, the status of any recent antibacterial therapy should be determined, and, if possible, specimens from untreated cattle should be collected. It is important to remember that *M. haemolytica, P. multocida, H. somni,* and mycoplasmas are normal inhabitants of the nasal passages of cattle and may be cultured from respiratory tissue in the absence of respiratory disease. Not all laboratories will identify the species of mycoplasmas cultured; thus an isolate may be identified only as "*Mycoplasma* sp." If involvement with *Mycoplasma bovis* is to be confirmed, the veterinarian will likely need to specifically request species identification for any mycoplasmas isolated. Specific identification of *M. bovis* is most often done by IFA, IHC, or PCR. Some mycoplasmas are hardier or easier to grow than others; for example, it is not unusual for *M. bovis* to overgrow *M. dispar* when both are present in the same sample. Culture of mycoplasmas typically takes at least 1 week, and laboratories often call a sample negative only after the sample has been subcultured at least once, which usually requires at least an additional week.

As discussed earlier, although isolates obtained from nasal or deep nasopharyngeal swabs may reflect the bacteria causing pneumonia on a group level, accuracy may be improved by obtaining specimens from the lower respiratory tract.[8] When sampling lung tissue for bacterial infection at necropsy, contamination of the sample with environmental agents can best be prevented by first searing the lung surface with a heated spatula or knife, then making an incision with a sterile scalpel, followed by sampling with a swab through the incision. However, it may not be practical to sear the surface of the lung in the field setting. Alternatively, sections of lung and other tissue samples can be sent in sterile sealed containers on ice to the diagnostic laboratory for appropriate sampling for bacteria there.

DETECTION OF BACTERIAL ANTIGENS OR NUCLEIC ACIDS. It is common for diagnostic laboratories to use IHC for identification of bacteria in formalin-fixed tissues. This technique offers many advantages, including correlation of the pathogenic organism with the lesion and detection of pathogens not found on bacterial culture because of overgrowth of other organisms such as *T. pyogenes* or *P. multocida*. The use of PCR for identification of bacterial agents in a variety of samples is also increasingly available. The veterinarian is encouraged to contact the diagnostic bacteriologist at the local diagnostic laboratory or check the laboratory website for information regarding which tests are available.

SEROLOGIC TESTING FOR BACTERIAL PATHOGENS. Diagnosis of infection with bacterial pathogens can be attempted retrospectively through use of serologic testing as described earlier for viral pathogens. However, the use of serologic tests for identification of infection by bacterial respiratory pathogens has mostly been limited to use in research. Thus these tests are not likely to be widely available in veterinary diagnostic laboratories.

Treatment of Undifferentiated Ruminant Respiratory Disease

Amelia R. Woolums[#]

ANTIMICROBIAL THERAPY. The basic principles of antimicrobial therapy for bacterial bronchopneumonia are to treat early enough, treat long enough, and treat with the appropriate antimicrobial agent. Because there are currently many effective antimicrobials marketed for the treatment of important bacterial respiratory pathogens in cattle (see Table 31-12), failure to treat early enough is more likely an important cause of treatment failure than failure to choose the correct antibiotic. If lung lesions becomes too advanced before treatment is initiated, it may not be possible to reverse lung pathology with a practicable course of any antimicrobial.

Treating early enough requires timely identification of animals with clinical signs of respiratory disease. Because individual ruminants in production agriculture settings often receive their first treatment for undifferentiated respiratory disease from a layperson caretaker and not from a veterinarian, it is appropriate for caretakers to be taught by the supervising veterinarian to recognize signs of respiratory disease. Caretakers should be trained to watch for these signs whenever they are in contact with ruminants in their care. A clinical scoring system for use in evaluating individual and groups of dairy calves has been developed[1]; this system may help improve timely identification of calves with clinical signs of respiratory disease. Similarly, in cattle feedlots clinical signs are assessed by lay caretakers, including the pen riders who evaluate cattle in the feedlot pens and the "hospital crew" who examine individual cattle "pulled"

[#]Previous contributions by John C. Baker, Trevor R. Ames, and Steven E. Wikse are acknowledged.

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or removed from feedlot pens by the pen riders and sent to a treatment area for individual assessment and treatment by the hospital crew. It is imperative that lay caretakers evaluating animals for clinical signs of disease receive training from the supervising veterinarian and that training be reviewed regularly so disease identification and treatment is as accurate and timely as possible. Additionally, treatment of affected animals by lay caretakers should be based on written protocols established by the supervising veterinarian and maintained for easy review on the farm or feedlot.

It is often the case that ruminants with undifferentiated bronchopneumonia are identified and treated presumptively based on clinical signs, without diagnostic testing to identify specific viral or bacterial causative agents. However, if animals fail to respond as expected to nonspecific therapy, diagnostic tests are warranted, as they may reveal an unexpected pathogen, a bacterial pathogen with unexpected antimicrobial resistance pattern, or another underlying disease that must be addressed. (See page 606 for a discussion of appropriate sample collection for bacterial culture and susceptibility testing.)

Because bacteria often contribute to bronchopneumonia in ruminants, appropriate presumptive treatment includes an antimicrobial effective against the most common causes of bacterial bronchopneumonia. Selection of the appropriate antimicrobial tends to be what most veterinarians focus on when treating respiratory disease because this is the aspect of therapy over which they have the greatest control. Factors such as cost, route of administration, treatment interval, drug label restrictions, necessity of extralabel doses, and withholding times may exclude a number of antimicrobials, leaving a short list of suitable alternatives for use as a first-line antimicrobial agent. Antimicrobials that are associated with severe injection site reactions, such as erythromycin, or those associated with complications of administration, such as balling gun injuries with oral boluses, are often avoided. Only antimicrobials that are licensed and effective at label doses should be considered for routine use in food animals. Table 31-12 lists antimicrobials currently approved in the United States for the treatment of respiratory disease in cattle, sheep, and goats. If data regarding the MIC of bacteria isolated from untreated animals are available, the dose or duration of therapy can be rationally modified, but it is imperative that proper withdrawal times be observed when antimicrobials are used in an extralabel fashion. At the time of this writing, the Food Animal Residue Avoidance Databank (FARAD; www.farad.org or 1-888-USFARAD) is an invaluable resource for veterinarians who need to identify withdrawal times for drugs administered to food animals in an extralabel manner. The use of MIC data requires some understanding of the pharmacokinetics and pharmacodynamics of the drugs to be considered; published information is available regarding interpretation of MIC data, or veterinarians can contact FARAD, the diagnostic bacteriologist at their local diagnostic laboratory, or a veterinary clinical pharmacologist for assistance.

A decision regarding which antimicrobial to use to treat bronchopneumonia may be based on the results of antimicrobial susceptibility testing or MIC data for bacteria isolated antemortem or postmortem from animals in the group. However, such results must be interpreted carefully. The most relevant information is gained from bacterial culture and susceptibility testing of samples collected from diseased lung at postmortem from animals that have not yet received any antimicrobial therapy. However, because animals are often treated presumptively before they die or are euthanized, it may be difficult to obtain diseased lung from postmortem of animals that have not already been treated. Once an animal has been treated, bacteria later cultured from the animal may be resistant to antimicrobials given in the past. Many bacteria, including *M. haemolytica,* can develop plasmid-mediated multiple antimicrobial resistance by bacterial conjugation so that they can become, with acquisition of a single plasmid, resistant to multiple antimicrobials.[2] Anecdotal reports indicate that bacteria recovered from the respiratory tract of cattle that have been treated with multiple antimicrobials (e.g., cattle with chronic, poorly responsive bronchopneumonia) can be resistant to multiple antimicrobials. However, bacteria isolated from the lungs of cattle that have been treated with antimicrobials are not always resistant to these drugs.[3] If bacteria resistant to certain antimicrobials are isolated from cattle that have been treated with multiple antimicrobials, it is not clear how such results should be interpreted. It may not be true that the bacteria with the same resistance profile are present in cattle in the group that have not yet been treated. Therefore treatment decisions based on bacterial culture and susceptibility results from animals that have been treated multiple times may be incorrect if applied to animals that have not yet been treated.

In situations where animals have failed to respond to therapy and a new antimicrobial choice is being considered for first-line treatment, it would seem appropriate to collect samples for culture and susceptibility testing from new cases before they are treated. However, researchers in one study that evaluated the response of cattle to treatment with tilmicosin when *M. haemolytica* or *P. multocida* resistant to tilmicosin were isolated from nasopharyngeal swabs before treatment found no difference in subsequent response to treatment by cattle with resistant pathogens isolated from the nasopharynx and cattle with no resistant pathogens isolated.[4] More research is needed to provide evidence-based guidance for interpretation of antimicrobial susceptibility data in the treatment of cattle in groups with BRD.

The choice of which antimicrobial to use can also be based on records of efficacy for animals treated in the past. Producers who keep accurate records of drugs used, with results of treatment responses, relapses, and proportion of treated animals that become chronic cases, may select first-line antimicrobials based on historical performance of a drug. This may be the best approach to antimicrobial selection. Guidelines for response to antimicrobial therapy for feedlot cattle with BRD have been suggested: 70% to 80% of animals should respond to the first treatment they are given, the case fatality rate should be between 4% and 7%, and the ratio of chronic cases to cases that die should be 0.5 to 1.0.[5]

A final method of choosing a first-line antimicrobial drug is reliance on published treatment trials. Published trials give comparisons among responses for various antibiotics in cattle with naturally occurring bacterial bronchopneumonia. The outcomes for these trials are often expressed as both health and production values. When evaluating published treatment trials that use cases of naturally occurring bacterial bronchopneumonia, it is important to realize that the results may not be applicable to the cattle and pathogens outside the operation where the trial was carried out.

Mass medication of an entire group of cattle during an outbreak can curtail the daily number of new cases and improve outcomes. In the acute stages of an outbreak, whatever drug is chosen should be given by injection; therapeutic levels are not likely to be reliably maintained by administering drugs in feed or water because of suppressed feed intake by sick cattle. It is important to base a decision to mass-medicate on measurable criteria. Some feedlot veterinarians implement mass medication when the pull rate of sick animals is 10% on each of 3 consecutive days, or 25% on a single day.[6]

Although little research has been undertaken to determine optimal duration of therapy for undifferentiated respiratory disease of ruminants, a general recommendation is that therapy should be continued for at least 48 hours after clinical signs of fever, dyspnea, and systemic inflammatory response have abated. Many of the antimicrobial drugs labeled for use in the treatment of pneumonia in cattle provide multiple days of therapeutic drug concentrations in lung tissue after only a single injection. These products decrease the time and stress associated with daily treatment; in feedlots, they also make it easier for caretakers to return animals to home pens rather than keeping them in hospital pens, which may be associated with poorer responses by treated animals. Although a 3-day course of antimicrobial therapy for undifferentiated bronchopneumonia was considered adequate in the past, the view is increasingly held that treatment for a longer duration may be more appropriate. This is particularly true for pneumonia caused by *M. bovis* in dairy calves or feedlot cattle, which may respond better to treatment for at least 7 to 10 days.[7,8] Although treatment for 7 to 10 days would be

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extralabel for some antibiotics, multiple drugs currently marketed have been shown to provide therapeutic drug levels for at least 7 days when used at dosages recommended on the label.

In some cases clinical signs of bronchopneumonia do not resolve following treatment with the first-line antimicrobial. In such cases, veterinarians must decide when to give a new drug and which drug to choose for second-line therapy. In the past, a standard recommendation was to administer a second antimicrobial if the animal was still febrile 72 hours after treatment with the first-line antimicrobial. However, recent research has suggested that, for cattle given a long-acting antibiotic as a first line of treatment, it may be acceptable to wait longer than 72 hours before administering a second antibiotic. For example, it has been recommended that cattle not responding to treatment with long-acting (200 mg/mL) oxytetracycline should be treated with a second drug after 2 to 3 days, whereas cattle treated with ceftiofur crystalline free acid (Excede, Zoetis) should be treated with a second drug if not responding after 5 to 7 days, and cattle treated with tulathromycin (Draxxin, Zoetis) should be treated with a second drug if not responding after 7 to 14 days.[9] It can be difficult for a veterinarian to withhold treatment with a second or even third drug if cattle are not improving quickly, but administering a different long-acting product every 3 days may not improve outcomes, although the practice will increase cost of treatment and may also increase opportunities for the development of bacteria resistant to the antimicrobials. More research is needed to provide evidence-based guidelines regarding when a second or third drug should be given to nonresponding cattle. At this time, veterinarians often make recommendations based on past experience. A typical decision tree for treating feedlot cattle with antibiotics is shown in Fig. 31-75, but protocols such as these may be modified as more information about the use of long-acting antimicrobials is obtained from field research.

The same principles of therapy described previously apply to the treatment of sheep and goats. Unfortunately, fewer drugs are labeled for the treatment of sheep and goats as compared with products used for cattle. Drugs labeled for use in sheep and goats are listed in Table 31-12. Note that whereas tilmicosin (Micotil 300, Elanco Animal Health, Indianapolis, Ind.) is labeled for use in sheep, fatal reactions to tilmicosin have occurred in goats treated with this drug. Goats should not be treated with tilmicosin. It is imperative to ensure that producers are given an appropriate meat and milk withdrawal time when antimicrobials are administered to sheep and goats at extralabel dosages; this is a particular concern in feedlot lambs or goats and in lactating dairy sheep or goats, from which products may enter the food chain in a relatively short time after treatment.

ANTIINFLAMMATORY THERAPY. Viral or bacterial infection that leads to bronchopneumonia can cause significant tissue injury and inflammation. Moreover, many of the bacteria that cause bronchopneumonia are gram-negative bacteria that produce endotoxin, which can cause a systemic inflammatory response that can be harmful and even fatal. Treatment with NSAIDs could mitigate these effects; treatment should also decrease fever and discomfort, which should lead to improved feed intake and improved growth or milk production. For these reasons, it is rational to consider treatment of ruminants with bronchopneumonia with NSAIDs. A recent review critically evaluated the published evidence for the use of NSAIDs in treatment of BRD.[10] Whereas NSAIDs often decrease fever and improve clinical appearance in cattle with BRD in the first few days after administration, a positive impact of NSAID treatment on other outcomes has not been as consistent. For example, average daily gain was improved for cattle with BRD given an NSAID as well as an antimicrobial in one study[11] but not in another.[12] Mortality was not decreased by NSAID treatment,[12,13] but lung consolidation at slaughter or necropsy was decreased in cattle receiving certain NSAIDs.[11,13] The number of properly designed studies attempting to quantify the impact of NSAID therapy on BRD is quite small; thus more research is needed to provide strong support for their use. Therapy with NSAIDs might be justified on the grounds that they should improve animal comfort and therefore animal welfare, but the degree to which they actually improve comfort and welfare has not been quantified. It has also not been well established that NSAIDs are cost-effective; this will likely vary in different settings depending on the number of animals to be treated and the cost of the drug administered. If NSAIDs are to be used for BRD treatment, in the United States and Canada flunixin meglumine (Banamine, Merck Animal Health, Summit, N.J.) is approved for control of pyrexia associated with BRD (1.1 to 2.2 mg/kg IV either as a single dose or divided into two doses at 12-hour intervals for up to 3 days). It is important to remember that flunixin meglumine is labeled only for IV use; administration via the IM or SC route can result in violative residues in tissues if longer withdrawal times are not observed. Phenylbutazone, which has been used in the past for antiinflammatory effect in ruminants, is now illegal to use in lactating dairy cattle in the United States, and because of prolonged tissue levels found in treated cattle, its use is discouraged in all food animals. Aspirin (100 mg/kg PO q12h) is sometimes used for antiinflammatory effect in cattle; however, in the United States it is not specifically approved for treatment of BRD and thus use of aspirin for BRD therapy would be extralabel. Recently meloxicam has received significant attention in North America for the control of pain and inflammation in cattle (1 mg/kg PO[14] or 0.5 mg/kg IM[15]). Like aspirin, at the time of this writing meloxicam is not specifically approved for the treatment of BRD in the United States or Canada; it is approved in Canada for treatment of calves with diarrhea or for pain control associated with disbudding. At the time of this writing no NSAID is labeled in the United States or Canada for the treatment of respiratory disease in sheep or goats.

Because NSAIDs can be nephrotoxic and because nephrotoxicity is exacerbated by dehydration, dehydrated animals should be rehydrated before administration of these drugs. Care should also be taken not to overdose NSAIDs or use them for prolonged periods, because they may also result in abomasal ulceration.

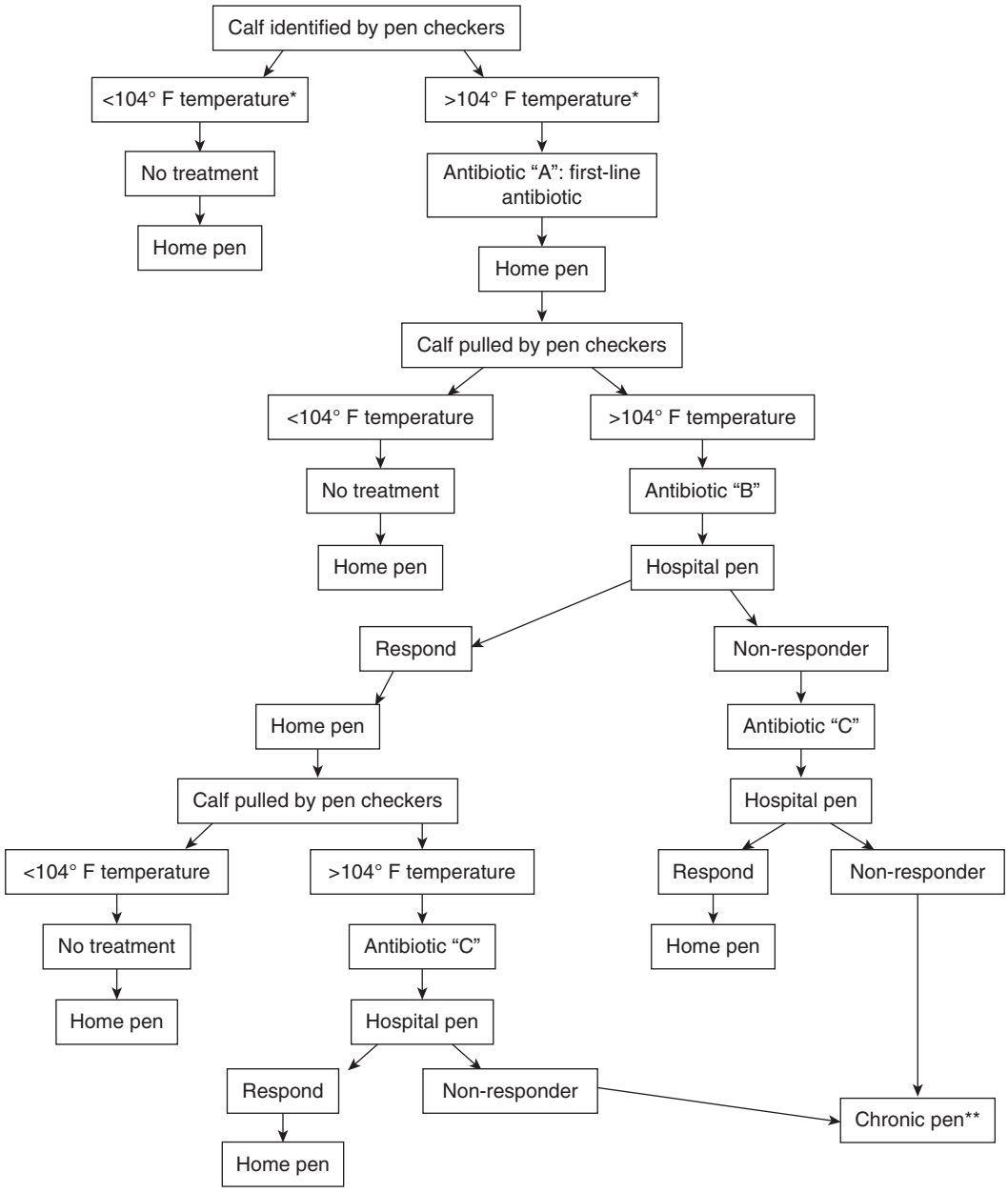
Although corticosteroids have a potent antiinflammatory effect and are sometimes used for treatment of severe inflammation associated with an infectious disease, they should not be used indiscriminately in the treatment of respiratory disease because of the potential for immunosuppression. Corticosteroids may have a place in treatment of respiratory diseases such as necrotic laryngitis or tracheal edema syndrome of feedlot cattle because edema of the larynx or trachea can cause life-threatening airway narrowing. The dose for dexamethasone in cattle is 0.05 to 0.2 mg/kg IM or IV, and the dose for isoflupredone acetate is 10 to 20 mg IM for an adult bovine animal. Treatment with corticosteroids may cause recrudescence of BHV-1 infections.

There has been little or no properly designed research to support the use of antihistamines, expectorants, or other adjunct therapies for ruminant respiratory disease.

ANTIVIRAL AND IMMUNOMODULATING THERAPY. Although antiviral drugs, in theory, could be beneficial treatment for ruminants with undifferentiated bronchopneumonia, they are not routinely used. Levamisole and isoprinosine have been used in attempts to stimulate the bovine immune system with equivocal success.[16] It is important to recognize that the immunostimulatory benefits of levamisole occur at doses in the 2- to 3-mg/kg range, compared with the anthelmintic dose of 6 mg/kg. A decreased immune response has been observed after an 8-mg/kg dose of levamisole. Vitamin C (1 g/45 kg; 1 g/100 lb) has been shown to enhance the activity of bovine neutrophils and reverse dexamethasone-induced suppression of neutrophil activity.[17] However, a recent critical review of published research testing ancillary therapies such as immunostimulants for BRD treatment[10] did not find quality evidence to support their use at this time.

SUPPORTIVE THERAPY. Supportive treatment may foster recovery of patients with respiratory disease. Sick animals should be provided shelter that protects them from rain, cold, wind, and hot sun. They should not be crowded, and good-quality feed and clean water should be easily accessible. Mineral and vitamin deficiencies

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*Temperature at which cattle are treated can vary from 103.5° F to 104.5° F; cutoff is selected at discretion of supervising veterinarian.
**Calves in chronic pen should be monitored for weight gain, suffering, and withholding times, so that appropriate action can be taken (i.e., euthanize, sell, continue feeding).

FIG. 31-75 Decision tree for antibiotic treatment of feedlot cattle. *(Input contributed by Dr. Robert A. Smith, VRCS LLC, Greeley, Colo.)*

should be corrected with the use of injections or oral preparations if necessary.

Epidemiology of Undifferentiated Ruminant Respiratory Disease

Amelia R. Woolums**

RESPIRATORY DISEASE IN DAIRY CALVES. Respiratory disease in dairy calves has been described to occur both in epizootics (outbreaks), and also in an endemic (enzootic) pattern ("enzootic calf pneumonia"). At the farm level, the occurrence of producer-identified calf respiratory disease is skewed, with few or no calves being identified with respiratory disease on many farms, and many calves being identified with respiratory disease on a few farms.[1-3] The median farm-level incidence of producer-identified respiratory disease is 3% to 17% (range: up to 91%).[3-5] Reported case fatality rates for respiratory disease in dairy calves are 2.2% to 9.4%.[2,5,6] Respiratory disease accounts for a significant proportion of the total mortality (proportionate mortality) in dairy calves, with proportionate mortality rates of 30% to 52% reported.[2,7] Respiratory disease in dairy calves can be identified as early as the first week of life.[2,5] The median age at which calves are first identified by producers to have respiratory disease is between 25 and 37 days of life,[6,8] and the age at which the highest proportion of calves are treated ranges from 35 to 70 days (5 to 10 weeks) of life.[2,5,9] In a study following a large number of calves until they were 18 months old, the highest proportion of calves were treated for respiratory disease at 4 months of life.[10]

**Previous contributions by John C. Baker and Trevor R. Ames are acknowledged.

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The agreement between producers and veterinarians in identification of dairy calf respiratory disease was evaluated in two studies. Van Donkersgoed and colleagues[4] found that the risk of respiratory disease in Saskatchewan dairy calves was 39% as diagnosed by the farmer and 29% when the disease was veterinarian diagnosed. Virtala and colleagues[5] found that the risk of respiratory disease was 11% in New York dairy calves when diagnosed by producers and 26% when diagnosed by a veterinarian. In both studies the agreement between veterinarian and producer diagnosis was poor at the level of the individual calf but moderate at the level of the herd. Agreement of diagnosis in these studies was likely influenced at least in part by the fact that producers see their calves daily, while veterinarians examined calves every 1 or 2 weeks in these studies. Sivula and colleagues[2] evaluated the accuracy of producer diagnosis by subjecting 52 of the 64 calves that died to necropsy. For calves subjected to necropsy, and using necropsy as the gold standard, the antemortem diagnosis of respiratory disease by producers was determined to have a sensitivity of 56% and a specificity of 100%. Therefore producers commonly failed to identify calves with respiratory disease, but no producer incorrectly identified a calf as having respiratory disease when it did not. Although the number of cases evaluated was small, this study supports the value of necropsy for calves that die in order to ensure the correct identification of causes of death that might otherwise be missed.

Respiratory disease in dairy calves can have a negative impact on their subsequent growth and productivity. Calves treated for respiratory disease in the first 90 days of life were 2.5 times more likely to die before weaning than calves that were not treated.[11] Multiple investigators have shown that calfhood respiratory disease decreases calf growth.[12-14] Dairy heifers treated for respiratory disease weighed 10.6 kg less at 6 months of age than untreated calves.[14] Calves without signs of respiratory disease in the first 3 months of life were twice as likely to calve in the herd and calved 6 months earlier as compared to calves with signs of respiratory disease.[13]

RESPIRATORY DISEASE IN PREWEANING BEEF CALVES. As in dairy calves, respiratory disease can occur in preweaning (nursing) beef calves. Respiratory disease was reported to be the leading cause of preweaning death for beef calves 3 weeks of age or older on U.S. cow-calf operations.[15] Sixteen percent of deaths in calves born alive are attributed to BRD.[16] However, as compared with dairy calves, much less research has characterized the epidemiology of preweaning beef calf respiratory disease. Two reports described the pattern of respiratory disease occurring over several years in nursing calves in a single large herd.[17,18] In 110,412 calves over 20 years, the annual incidence of preweaning calf BRD in the herd varied from 3% to 24%, with an average annual incidence of 11%. Annual mortality among calves with preweaning respiratory disease varied from 7% to 17%, with an annual average of 13%. In some years the incidence of preweaning BRD was higher than the incidence of respiratory disease after calves were weaned and transferred to the feedlot. Calves identified with preweaning respiratory disease weighed 7.7 kg less at weaning than calves not identified with preweaning respiratory disease. A mail survey of cow-calf producers in Québec found that 16% of respondents with fewer than 40 cows recognized calves with BRD, as compared with 36% of respondents with 40 cows or more.[19] In a mail survey of producers in six U.S. states, 21% of operations reported observing one or more calves with preweaning respiratory disease. Of these, 89% treated one or more calves and 46% reported one or more calf deaths attributed to preweaning respiratory disease.[20]

RESPIRATORY DISEASE IN FEEDLOT AND STOCKER CATTLE. In the U.S. and Canadian cattle production systems, weaned beef calves are typically transported from the farm where they are born (cow-calf operation) to feedlots where they are fed and managed until they have reached the appropriate weight for slaughter. Calves may enter feedlots directly from their cow-calf operation of origin, although they often are sold by the farmer (cow-calf operator) to the feedlot "order buyer" at local or regional auction markets. Alternatively, after they are sold by the cow-calf operator, calves may not enter a feedlot directly but instead they may be sent for temporary management to a "backgrounding" (aka "conditioning") operation, where they may receive vaccinations or other treatments such as anthelmintics and growth implants, with dehorning and/or castration if necessary. At this time they may be sorted based on their size, breed type, and/or gender into new groups before being sent on to feedlots. Similarly, after sale, weaned calves are sometimes transported to "stocker" operations, where they are housed or "stocked" on pasture for weeks to months with supplemental feed given as needed, along with vaccinations and other treatments, before being transported to a feedlot at a later date. Undifferentiated BRD is the most common cause of morbidity and mortality in feedlot and stocker cattle. The disease is also known as "shipping fever" because it commonly occurs after cattle have been transported. The pattern of BRD in North American feedlot cattle has been well characterized. Jensen and colleagues described the diseases identified in feedlot cattle that died in a population of 407,000 yearling cattle in 1974.[21] Approximately 5.1% of the total population became sick, and 1% died. Of the cattle that died, approximately half were subjected to necropsy, which revealed that respiratory disease was the cause of death in 64% of the cases. Bronchopneumonia or pleuropneumonia was the type of respiratory disease present in 75% of the cases of BRD, and 72% of the bronchopneumonia/pleuropneumonia cases that ultimately died occurred within the first 45 days of the feeding period.

Another detailed report described health outcomes and necropsy findings in cattle from over 60 feedlots in Bruce County, Ontario, over a 3-year period.[22] The Bruce County study was noteworthy because it was the first large-scale study to prospectively evaluate management practices to determine which were associated with feedlot BRD. Mortality was approximately 1% over the course of the study, and the majority of cattle that died were subjected to necropsy. The most common cause of death was BRD, which caused 50% of the deaths in the first year of the study.

Two studies occurring approximately 10 years later also evaluated the epidemiology and risk factors associated with BRD.[23,24] In the study by Alexander and colleagues,[23] data from 17,696 cattle in a single feedlot were evaluated, and factors related to respiratory disease morbidity were evaluated (rather than BRD mortality, as in the Jensen[21] and Martin[22] studies). Respiratory disease was the cause of treatment for 50% of the cattle treated, with 58% of BRD cases developing in the first 40 days on feed. In the study by Ribble and colleagues,[24] data were collected on all 58,885 spring-born calves entering a single western Canadian feedlot over a 4-year period. Across the 4 years of the study, total (crude) mortality was fairly consistent, ranging from 2.4% to 4.8%, whereas the mortality caused specifically by BRD varied more than tenfold (0.25% to 2.73%). Across years proportionate mortality caused by BRD ranged from 10% to 57%. Epidemic curves constructed for each of the 4 years showed that peak mortality occurred approximately 16 days after arrival at the feedlot and that at least 50% of BRD mortalities occurred within 3 weeks of arrival. Similar results were found in the Alexander study,[23] where 58% of BRD cases were found to develop in the first 40 days on feed. The consistent onset of fatal disease in cattle within days of their arrival at the feedlot indicates that the disease process is often well under way in affected animals before feedlot entry. Ribble and colleagues[24] demonstrated that when the incidence of fatal BRD was high (greater than 2%), the disease clustered within truckload groups of calves and also, in 1 year, within pens.

A recent epidemiologic study evaluated patterns of BRD in the first 100 days after feedlot entry in lots (cohorts) of cattle entering 10 U.S. feedlots over 8 years.[25] For 1.2 million cattle in 7553 lots, the cumulative within-lot BRD morbidity ranged from 0.3% to 84.3%, with a median of 4.2% and a mean of 8.8%. This study demonstrated that the pattern of BRD occurrence in the first 100 days on feed can vary greatly among lots of cattle. For some lots, 80% of BRD cases occurred within the first 10 days on feed, whereas in other lots, 80% of BRD cases had not occurred until the cattle had been on feed for more than 90 days. For some lots the proportion of cattle treated for

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BRD increased rapidly over relatively few days, and for others, the proportion treated increased slowly over several weeks. For some lots a rapid increase in the proportion of cattle treated for BRD occurred relatively late, between 60 and 100 days on feed. The reasons for the different patterns of BRD occurrence that were observed in different lots of cattle were not determined, but they are likely related to a combination of factors related to the cattle and their environment.

Feedlot BRD has a significant negative impact on productivity of cattle. Numerous reports have demonstrated that BRD can decrease average daily gain, final weight at slaughter, and carcass quality, with these impacts decreasing producer profit.[26-30] Feedlot BRD has been shown to decrease average daily gain during the entire feeding period by 0.06 to 0.08 kg.[29,30] In one study, cattle treated once, twice, or three times for BRD yielded $41, $58, or $292 less, respectively, than cattle not treated for BRD.[26] Although the negative impacts of BRD are well established, affected cattle sometimes exhibit compensatory growth in the later phase of feeding period, so that cattle with BRD do not always perform more poorly than unaffected cattle when the entire feeding period is considered.[28] Therefore the exact impact of BRD on the performance and profit returned by a group of feedlot cattle will vary substantially depending on numerous variables, including the specific risk factors the cattle have encountered; the management of health and nutrition in the feedlot; the cost of feed, medications, and labor; and the value of the cattle at the time they are purchased and marketed.

Although little is published that specifically describes the epidemiology of BRD in stocker and backgrounding operations, an informative summary has been presented by Smith and Gill.[31] These authors estimate that respiratory disease accounts for 88% of the disease in stocker and backgrounding operations.

RESPIRATORY DISEASE IN ADULT DAIRY OR BEEF CATTLE. Although anecdotal reports indicate that adult beef or dairy cows can experience outbreaks of respiratory disease with high morbidity and an important impact on milk production in dairy herds, the epidemiology of respiratory disease in adult cows has not been well characterized. Surveys of U.S. producers indicated that respiratory disease is the cause of 3.4% of the deaths that occur in adult beef cattle[15] and 11.3% of deaths that occur in adult dairy cattle.[32] The lack of data regarding respiratory disease in adult cows is likely due to the fact that other diseases that affect reproductive performance and milk yield are of greater economic significance in this class of cattle. However, the few published descriptions of respiratory disease outbreaks confirm that the problem can be of major importance to individual herds.[33,34]

RESPIRATORY DISEASE IN SHEEP AND GOATS. Little information is available regarding the epidemiology of respiratory disease in sheep and goats in North America. A survey of U.S. producers indicated that 7% of death in adult sheep is due to respiratory disease, whereas 12% of lamb deaths are due to respiratory disease.[35] Feedlots reported that shipping fever pneumonia accounted for 13% of feedlot lamb deaths, and other respiratory disorders accounted for 29% of lamb deaths.[35]

Host and Environmental Risk Factors for Undifferentiated Ruminant Respiratory Disease

Amelia R. Woolums[††]

In general, risk factors for respiratory disease in all ruminants are related to (1) factors that impair the host physiologic and immunologic responses that defend against respiratory infection, and (2) characteristics of the environment that overwhelm the ability of these physiologic and immunologic responses to prevent respiratory infection. More specifically, host risk factors are related to (1) mechanical respiratory defense by the anatomic features of the upper respiratory tract and the mucociliary elevator; (2) innate immune defense provided by soluble factors, such as lysozyme and defensins, and cells, such as granulocytes, macrophages, and natural killer cells; and (3) acquired immune defense provided by antibodies on mucosal surfaces and in serum, and cells such as T-helper lymphocytes and T-cytotoxic lymphocytes. Characteristics of the host that can impair these mechanisms include other concurrent disease, nutritional deficiency, pronounced or chronic stress related to events such as mixing animals from various sources, crowding, and/or long-distance transport. In young animals, failure of passive transfer is a cause of transient immunodeficiency that may contribute to respiratory disease.

Environmental factors can also contribute to the development of respiratory disease in ruminants. High concentrations of airborne particulates, infectious agents, or noxious gases impair the function of host respiratory defense mechanisms or enhance the transmission of infectious respiratory pathogens. Inadequate housing can lead to cold or heat stress, which may increase nutritional requirements beyond what is available and lead to increased disease susceptibility. Crowding or mixing animals of different age groups can increase opportunities for transmission of infectious respiratory pathogens. Long-distance transport is well known to predispose animals to respiratory disease; this is due to close contact with other animals, which enhances transmission of infectious agents, as well as inhalation of particulates and noxious gases in truck exhaust. Mixing animals from multiple sources, such as occurs when animals are sold through livestock auctions, increases risk for respiratory disease by increasing opportunities for exposure to respiratory and other types of pathogens; psychological stress associated with establishment of new hierarchies may also contribute to immune suppression and increased rates of disease.

When respiratory disease occurs in any group of ruminants, a systematic evaluation of host and environmental factors that may increase risk of respiratory disease should be undertaken. The purpose of this evaluation is to identify modifications in management and husbandry that should help to limit ongoing respiratory disease and that should decrease the risk of future respiratory disease. Although this approach is logical, there is unfortunately little research that confirms that management modifications decrease respiratory disease in ruminants; it is hoped that future work will address this knowledge gap. Specific risk factors relevant to various classes of ruminants are discussed below.

DAIRY CALVES. In young calves, adequate passive transfer of antibody (and possibly also cells from colostrum) is very important to improve the defense against respiratory and other infections. Nutritional deficiency, stress associated with weaning, mixing of calves from different sources, castration and/or dehorning, concurrent disease, and temperature extremes may all impact host defense mechanisms. Environmental risk factors are related to (1) air quality, including humidity and the concentration of bacteria, other particulates, and noxious gases in air; (2) ambient temperature extremes; and (3) opportunities for exposure of calves to respiratory pathogens through new introductions or through contact with older animals in the same herd. When dairy calves are affected by either epizootic respiratory disease (outbreaks) or enzootic calf pneumonia, careful evaluation of management practices that influence both host and environmental risk factors may help prevent future disease.

Specific risk factors for respiratory morbidity and mortality in dairy calves have been evaluated in many research studies.[1-10] It is noteworthy that factors significantly associated with respiratory morbidity and/or mortality in some studies are not always associated with disease in other studies; this is likely because of differences in the populations studied or in methods of collection or analysis of data. Factors identified as significant in more than one study may be relatively more important. Knowledge of factors associated with dairy calf respiratory disease can help veterinarians focus efforts to modify management to limit or prevent respiratory disease in herds where calf respiratory disease is a problem. Calf-level and farm-level factors

[††]Previous contributions by John C. Baker, Trevor R. Ames, and Steven E. Wikse are acknowledged.

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TABLE 31-13

Factors Associated with Respiratory Disease in Dairy Calves

Risk Factors Associated with Increased Respiratory Disease Morbidity in Dairy Calves

Calf-Level Factors

Having diarrhea[2]
Serum total IgG ≤ 1200 mg/dL[27]
Being fed mastitic colostrum[27]
Certain sires[1]
Calfhood in fall or winter[1,6,27]

Farm-Level Factors

Shared housing with cows[9,27]
Larger herd size[3,5,9]
More than 8-week age range among calves in same pen[9]
Leaving calves with dams for more than 24 hours after birth[9]
Housing calves in group pens with 6 to 30 calves and automatic feeders (vs. hutches or group pens with 3 to 8 calves individually fed)[6,28]
Diarrhea occurring in calves[2,9]

Risk Factors Associated with Decreased Respiratory Disease Morbidity in Dairy Calves

Calf-Level Factors

Being housed individually in outdoor hutch (vs. any other housing)[2]
Having supervised calving[7]
Serum total IgG > 800 mg/dL[5]
Receiving antibiotic preventively[2]

Farm-Level Factors

Decreased total bacterial counts in calf pen air[29]
Solid barriers between individual calf pens[29]
Bedding deep enough for calves to nest[29]
Antibiotics in feed or milk replacer[2]

that have been found to be significantly associated with dairy calf respiratory disease (morbidity) are presented in Table 31-13.

PREWEANING BEEF CALVES. As compared with dairy calf respiratory disease, less is known regarding factors that increase risk for respiratory disease in preweaning beef calves. Calf-level factors associated with preweaning respiratory disease over several years in a large U.S. herd included the year of the calf's birth, the location of the calf's group on the operation, whether or not the calf experienced dystocia requiring major assistance, the calf's sex (with male calves being at greater risk), and the age of the calf's dam (with calves born to heifers being at greater risk).[11]

A survey of Canadian cow-calf producers in the province of Québec[12] found that farms with fewer than 40 cows were less likely to report a problem with preweaning calf pneumonia than farms with 40 or more cows (16% vs. 36% of producers recognizing nursing calf pneumonia). There were regional differences in the rate of recognition of preweaning calf pneumonia, with producers in the northern regions of the province reporting treatment of a larger proportion of their calves for preweaning pneumonia. The rate of preweaning calf pneumonia was associated with calving season length, with a longer calving season being associated with more cases of calf pneumonia. Another study in Québec found that the incidence of preweaning calf respiratory disease in the first month of life was decreased if the producer vaccinated cows for respiratory viruses, with a 13% incidence in herds with nonvaccinated cows versus a 6% incidence in herds with vaccinated cows.[13]

More recent research has evaluated herd-level risk factors for preweaning calf respiratory disease in U.S. cow-calf herds. An analysis of USDA NAHMS data collected by producer survey found that introduction of steers from outside sources, herd breed makeup, number of visits to the herd by outsiders, administration of antibiotics in feed to prevent calf respiratory disease, and the herd being the primary source of income for the producer were factors associated with preweaning calf respiratory disease treatment rate.[14] A mail survey of cow-calf producers in three eastern U.S. states and three Plains states found that occurrence of preweaning calf respiratory disease was significantly associated with larger herd size, respiratory disease in cows, and diarrhea in calves.[15] Calving season length was associated with calf respiratory disease in Plains but not eastern U.S. herds. Cumulative treatment incidence was negatively associated with larger herd size and checking cows for pregnancy, and positively associated with winter calving, bringing calves into the herd from outside sources, giving calves supplemental feed, and using a heat synchronization program. Common features of risk factors identified to date may be that they increase opportunities for introduction of respiratory pathogens new to the herd, and they increase opportunities for close contact between calves and among cows, older calves, and younger calves. This increased contact may lead to more opportunity transmission of infectious doses of respiratory pathogens to calves when passive or active immunity is inadequate to resist disease.

FEEDLOT AND STOCKER CATTLE. Risk factors for respiratory disease in feedlot and stocker cattle are active in three areas: at the farm of origin, during transit, and in the stocker operation or feedlot.[16-18]

On the farm (cow-calf operation) of origin, management practices can have an impact on subsequent occurrence of respiratory disease in stocker operations or feedlots. Weaning, creep feeding, and performance of routine surgeries at least 3 weeks before shipment ("preconditioning") have been shown to reduce morbidity rates by 20% to 25%.[18] Vaccination on the farm against respiratory pathogens would be expected to reduce the incidence of stocker and feedlot cattle pneumonia, but the practice is not always beneficial. For example, Step and colleagues[19] found that calves kept on the farm for 45 days after weaning and prior to shipment had significantly decreased respiratory morbidity in the first 42 days after feedlot entry, as compared with calves shipped immediately at weaning. However, administration of a multivalent modified live viral respiratory vaccine and an *M. haemolytica* vaccine to the calves that had been weaned for 45 days prior to shipment did not significantly improve resistance to respiratory disease at the feedlot. Thus, this study suggested that, to limit feedlot respiratory disease, weaning 45 days in advance of shipment was more important than vaccination prior to shipment. Nevertheless, preconditioning programs that include vaccination have been associated with improved resistance to feedlot respiratory disease when morbidity and mortality rates and total profit for calves managed in such programs are evaluated over several years.[18] (Preconditioning is discussed in more detail on page 614.)

Risk factors that are active during transport from the farm to the feedlot include sale through auctions, feeding of low-energy diets before shipping, and prolonged time in market channels (sales barns, transport vehicles). Excessive dehydration or "shrink" from transport has been shown to account for significant morbidity and mortality in the feedlot. Movement through multiple auctions greatly increases the risk of respiratory disease.

Risk factors that influence morbidity and mortality rates at the stocker operation or feedlot include processing procedures, numbers of calves and number of different origins of calves per pen, diet, on-arrival surgeries (e.g., dehorning), and environmental conditions. In a Canadian study of risk factors for feedlot respiratory disease from the 1980s,[20] the administration of respiratory vaccines at arrival, feeding of corn silage in the first weeks after arrival, and mixing cattle from various sources were consistently associated with higher mortality in groups of cattle. The negative effect of vaccination at arrival was decreased if vaccination was delayed for 2 weeks. The results of this study led many to question the value of vaccination on arrival for control of feedlot respiratory disease. A relevant finding was that infectious bovine rhinotracheitis virus (IBRV) was more often

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associated with respiratory disease in cattle that were not vaccinated for IBRV, indicating that IBRV vaccination was protective against disease specifically caused by IBRV.

More recent studies have confirmed that mixing cattle from multiple sources prior to or at feedlot entry is an important risk factor for feedlot respiratory disease.[19,21,22] Shipment for longer distances prior to feedlot entry has been associated with increased rates of respiratory disease in some studies[22,23] but not others.[24] Changes in weather have been associated with respiratory disease; Alexander and colleagues[21] found that a wide range between the high and low environmental temperatures in the first 2 weeks after feedlot entry was associated with increased respiratory disease. Cernicchiaro and colleagues[25] found that several weather-related variables such as maximum wind speed, mean wind chill, and temperature range were significantly associated with increased daily BRD incidence in the next 7 days, although the effect of weather was dependent on various characteristics of the cattle, such as their average weight, risk category, month of arrival, and the number of cattle in the group. Heavier weight at entry has been shown to decrease feedlot BRD risk.[22] Metaphylactic antibiotic administration at arrival has been shown in multiple studies to decrease risk for subsequent respiratory disease (see more discussion of metaphylaxis later in this chapter).

Although vaccination of cattle to prevent respiratory disease when they are first received by feedlot or stocker operations is a common practice, published research evaluating risk factors for feedlot respiratory disease have not found the practice to be consistently associated with decreased risk.[20,22] Failure of vaccination at arrival to protect cattle against later respiratory disease may be because cattle are already infected at the time of vaccination or because they are not capable of mounting an adequately protective immune response because they are immunologically naive or they are immunosuppressed by a variety of possible factors. Because of this, cattle sometimes are given a second dose of respiratory vaccine 7 to 21 days after the initial dose at feedlot entry, although few data from properly designed trials are available to support the practice of revaccination. Many large feedlots carry out private research trials to determine whether practices such as vaccination at arrival are beneficial; because the practice is still quite prevalent, it may be that some feedlots have confirmed vaccination on arrival to be beneficial but have not published the data supporting it. It should be noted that clinical trials evaluating vaccines for specific agents, such as BRSV or *M. haemolytica,* have found vaccination at arrival to be associated with decreased rates of respiratory disease in feedlot cattle in some cases. (For more information, see earlier sections on specific infectious agents.)

Calves that arrive in the feedlot with moderate concentrations of serum antibodies against respiratory viruses have sometimes been shown to have a decreased incidence of BRD, indicating that natural exposure or vaccination prior to arrival can be protective. Starting calves on diets containing 75% concentrate or greater or feeding corn silage as a major dietary component during the first month is associated with higher mortality and morbidity rates, possibly because of inhibition of certain immune functions by systemic acidosis. Feeding of nonprotein nitrogen, such as urea, is associated with increased rates of respiratory disease. The addition of antibiotics to the drinking water of newly arrived feedlot cattle has been shown to be detrimental to their health, possibly because of decreased water consumption.

Smith and Gill[26] have presented a helpful summary of risk classification of cattle in stocker and backgrounding operations. Stocker and backgrounding cattle can be grouped into one of three categories: (1) high risk, exposed: cattle with little or no history of vaccination, adaptation to hay or concentrate diet, or other preventive health management, and with a history of mixing with cattle from multiple sources; (2) high risk, not exposed: as for high risk, exposed, but with no history of mixing with cattle from multiple sources; and (3) low risk: cattle that have been vaccinated, weaned, and turned out for a period of time before shipment. By nature most backgrounding/stocker cattle are in categories 1 or 2 and thus are at risk for respiratory disease because of various factors, including inadequate immunity, stress of recent weaning, and suboptimal nutritional history. Cattle may require dehorning, castration, or both, when entering the facility, which will further impact their health and productivity. Respiratory disease in high-risk, exposed calves is likely incubating when these calves reach the backgrounding or stocker facility, because they may have been accumulated from several different locations over several days before arrival. The impact of commingling cattle from multiple sources to increase respiratory disease has been shown clearly in a recent study that identified 42% respiratory morbidity in auction market–derived cattle entering a feedlot versus 11% respiratory morbidity in calves entering the same feedlot directly from their ranch of origin without mixing with other cattle.[19] If such calves are not sick on arrival, then BRD can be expected to peak within the first week after arrival. Respiratory disease in high-risk, not exposed calves often peaks at 2 weeks post entry, because these calves are not mixed with calves from other sources before they reach the backgrounding or stocker operation.

ADULT DAIRY AND BEEF CATTLE. Studies confirming risk factors for respiratory disease of adult dairy and beef cattle in modern North American production systems are lacking, but it is assumed that factors are similar to those described previously for calves and for cattle entering stocker operations and feedlots.

SHEEP AND GOATS. Many of the risk factors that have been found to predispose sheep and goats to undifferentiated respiratory disease are similar to those affecting cattle. Respiratory disease is more common in younger animals, after shipping or storms, and under crowded conditions. In addition, cold stress is an important risk factor for respiratory disease in young lambs and recently shorn adult sheep and goats. In contrast, heat stress may predispose to respiratory disease in unshorn sheep that do not have access to shade. Respiratory disease is also associated with semiconfinement or total confinement of sheep in poorly ventilated barns.

Prevention and Control of Undifferentiated Ruminant Respiratory Disease

Amelia R. Woolums[‡‡]

MANAGEMENT PRACTICES TO MINIMIZE DAIRY CALF RESPIRATORY DISEASE. Efforts to minimize respiratory disease in calves should begin with assessment of factors that may be impairing host defense mechanisms, which were outlined earlier. Ensuring adequate transfer of maternal antibodies to newborn calves by appropriate colostrum handling and administration is one of the practices most important to ensuring calf health. On farms with high rates of calf respiratory disease, particularly in calves in the first month or two of life, efforts to address respiratory disease should include assessment of passive antibody transfer in calves within the first week of life. If rates of failure of passive transfer are unacceptably high, management practices should be corrected to address the problem.

Although passive antibody transfer is important to ensuring calf health, groups of dairy calves with adequate passive antibody transfer can still have high rates of respiratory disease. Thus, other risk factors must also be assessed on dairies with unacceptable rates of calf respiratory disease. The method of calf housing has an important impact on risk for respiratory disease. Commonly used dairy calf housing includes individual calf hutches outdoors, super-hutches for small groups of calves outdoors, individual calf pens inside a building, and group calf pens inside a building. Respiratory disease is less common in calves housed in individual hutches outdoors, as compared with calves housed in individual pens indoors or in group pens indoors.[1,2] In spite of this, many producers house calves in individual pens or group pens indoors because of the negative impact of weather

[‡‡]Previous contributions by John C. Baker, Trevor R. Ames, and Steven E. Wikse are acknowledged.

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extremes for calves housed outdoors in hutches and for their caretakers. Group pen housing also facilitates use of automatic self-feeders to allow calves to nurse milk more frequently, and group pen housing allows calves to interact socially with other calves. These benefits of group pen housing must be weighed against the likelihood of increased rates of respiratory disease for group housed calves. If calves are housed in group pens, respiratory disease is less common when the pens contain smaller numbers of calves (9 or fewer per pen)[3,4]; however, on large dairies it may not be practical or cost-effective to house calves in such small groups.

Standards for ventilation of calf housing have been reported.[6-8] A study evaluating respiratory disease prevalence in calves housed in individual pens in naturally ventilated barns[5] found that respiratory disease prevalence was decreased on farms where pens had lower total airborne bacterial counts, solid barriers between calves, and bedding that was deep enough for calves to nestle into (so that their legs could not be seen when they were lying down). Airborne bacterial counts in the alleys between the calf pens were not related to calf respiratory disease in that study. Because having four or more solid partitions around a calf increased total bacterial counts in pen air, solid partitions should be placed between calves but on no more than three sides; on the front, back, and top of calf pens, mesh barriers should be used.

Calf housing with overcrowding of calves or excessive stocking densities results in increased transmission of pathogens, especially if there is mixing of calves of wide age range. Overcrowding also puts additional stress on the building ventilation through buildup of noxious gases and pathogens. Cleaning of calf crates with high-pressure water sprayers is associated with new cases of pneumonia several days later. Sivula and colleagues[7] found that 80% of calf barns provided housing that failed to meet adequate standards of ventilation and housing regardless of whether calves were housed individually or in groups. In addition, calf housing in which calves shared the same air space as adults never met the adequate standards of ventilation and housing. A much higher percentage of calf housing that used calf hutches met these adequate standards of ventilation and housing, and virtually 100% would have been adequate housing if the hutches had been positioned correctly. Calves raised in inadequate housing have significantly poorer growth rates than do calves raised in housing that is considered adequate, which emphasizes the importance of adequate housing. A review of factors relevant to adequate ventilation of calf housing was recently published.[8]

After weaning, calves need to move to housing that allows small groups to be segregated from older age groups. Sharing air space or having direct contact with older calves or adult cattle is an important risk factor for calf respiratory disease. Super-hutches or pens in pole sheds separated by barrier walls can effectively provide this post-weaning housing. Calves should be fed proper nutrition for protein, energy, minerals, and vitamins and should be vaccinated appropriately. Vaccination programs are often used in dairy calves beginning at 1 to 2 months of age in situations where housing or mixing of postweaning calves results in a high incidence of respiratory disease. More information regarding the use of vaccines for preventing infectious respiratory disease is presented in the following sections. Historically it has been recommended that vaccination be delayed until maternal immunity has waned, but recent research indicates that calves can often be primed for a protective immune response by vaccination in the face of maternal antibodies (see further discussion in Chapter 48).

Nutritional problems that predispose to calf pneumonia include deficiencies of energy, protein, vitamins, or the minerals necessary for the immune response. Deficiencies of copper, selenium, zinc, manganese, iron, and vitamins A and E are of special concern. Dairy managers sometimes create energy and protein deficiencies by feeding calves a low volume of milk during the first few weeks of life to minimize the incidence of neonatal diarrhea. Therefore it is important to evaluate feeding practices to determine whether nutritional deficiencies are likely when attempting to limit dairy calf respiratory disease.

Ambient temperature is an important factor affecting dairy calf health. Cold weather is especially detrimental to young calves, which have little body insulation. Increased humidity or precipitation in the calf's environment exacerbates the impact of cold weather on the calf's ability to maintain thermoneutrality. Warm weather can also be undesirable, because young calves are capable of greater perspiration per pound of body weight than are adults, and warm weather may predispose young calves to dehydration.

Veal calves are at great risk for respiratory disease because they are often reared in rooms that are filled to high stocking density with calves from multiple dairies that may put minimal effort into ensuring that the calves are fed adequate amounts of high-quality colostrum. Similar problems occur on "calf ranches" or dairy heifer rearing operations where hundreds to thousands of very young dairy calves are raised to the point at which they are old enough to be returned to dairies or sent on to feedlots. A high proportion of calves that enter calf-rearing operations may have failure of passive antibody transfer unless the managers uphold standards for passive antibody transfer status for dairies that are the source of their calves. Also, the accumulation of a large number of calves with a variety of histories and from a variety of sources causes problems similar to those encountered with older animals in feedlots.

MANAGEMENT PRACTICES TO MINIMIZE PREWEANING BEEF CALF RESPIRATORY DISEASE. Relative to dairy calves, less is known regarding management practices that should prevent preweaning respiratory disease in beef calves. Risk factors identified include a longer calving season, concurrent neonatal calf diarrhea, and practices that increase opportunities for introduction of respiratory pathogens to the herd, or that increase opportunities for close contact among calves and between cows, older calves, and younger calves. Thus, in herds where preweaning calf respiratory disease is a problem, it may be helpful to shorten or prevent situations where preweaning calves and/or cows are brought together in close proximity. Improving immunity of preweaning calves by addressing factors that can lead to failure of passive antibody transfer from colostrum (such as dystocia and hypothermia) may help mitigate preweaning calf respiratory disease, particularly in herds with a high incidence of respiratory disease in calves in the first month or two of life. Because occurrence of calf diarrhea has been associated with preweaning calf respiratory disease, efforts to control calf diarrhea, which usually precedes respiratory disease, should be undertaken in herds with both problems. Administration of vaccines for viral and bacterial respiratory pathogens to preweaning calves may help decrease disease; if vaccination is attempted, two doses of vaccine should be administered, with the second dose timed to occur at least 2 weeks before the expected onset of respiratory disease. More information about vaccination of calves in the face of maternal antibodies follows. Once an outbreak is under way, anecdotal reports suggest that vaccination with intranasal or injectable modified live vaccines containing IBRV, PIV-3, and/or BRSV may be helpful to shorten the outbreak, but this is not yet supported by controlled research. Moreover, BRSV vaccination in the face of a BRSV outbreak has been associated with apparent disease enhancement[9]; thus there is a possibility that administration of BRSV vaccine could make an outbreak of undifferentiated calf respiratory disease worse if BRSV is the cause of the outbreak.

MANAGEMENT PRACTICES TO MINIMIZE FEEDLOT AND STOCKER RESPIRATORY DISEASE

Preconditioning. Preconditioning of calves is an attempt to eliminate certain risk factors that influence the occurrence of BRD in feedlot cattle. Preconditioned calves are weaned well in advance of shipment to feedlots. They are trained to eat some grain from feed bunks and drink water from tanks (this is especially important for calves raised on rangeland where feed bunks or water tank may not be seen). Calves are castrated and dehorned, treated for internal and external parasites, and vaccinated against respiratory pathogens, with one dose of vaccine administered before weaning and the second

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dose administered at or after weaning. The exact details of a preconditioning program can be tailored to the needs and characteristics of the individual herd of cattle. A variety of preconditioning protocols have been described, and most of the major companies that sell vaccines have recommended standardized preconditioning programs. Also, in many areas of the United States and Canada, state, provincial, or regional groups may offer a standardized preconditioning program for local cattle producers. Some sort of validation that calves have received preconditioning typically is available through these organizations. Some of these groups also help the participating producers market the preconditioned calves in large, relatively uniform groups, which may help the calves bring better prices. In some cases, producers can retain ownership of their cattle after they enter the feedlot and receive data regarding health and performance of their animals throughout the feeding period and at slaughter. Information about local preconditioning programs can usually be obtained from agricultural extension agents or from faculty members who specialize in beef cattle management and health at colleges of animal science or veterinary medicine.

The value of preconditioning has been debated over the decades. A summary of eight studies comparing the health of preconditioned calves with that of control calves indicated that, on average, preconditioning reduced morbidity rates by 23% and mortality rates by 50% in the feedlot.[10] However, preconditioned cattle do not always escape disease once they enter feedlots, and they sometimes experience outbreaks of high morbidity and mortality not unlike those seen in high-risk calves that are not preconditioned. Moreover, even when preconditioned calves experience less disease, their performance in the feedlot is not always better than that of nonpreconditioned calves,[11] or they may not always perform well enough that a profit is returned that is greater than the cost of preconditioning.[12] An evaluation of data collected over 8 years by the Texas A&M Ranch to Rail program showed that preconditioned cattle returned, on average, $90 more per head than nonpreconditioned cattle. However, in some years the return was better for preconditioned cattle than in other years. These data emphasize that preconditioning is likely to be cost-effective in the long run, but it may not always be cost-effective for an individual group of cattle in a single year. Also, while cattle that develop BRD in the feedlot often have decreased weight gain and/or feed efficiency and reduced carcass quality at slaughter,[13-15] they sometimes exhibit compensatory gain after they recover from BRD, which allows them to "catch up" to cattle that do not develop BRD.[16] For this reason, some feedlot operators elect not to specifically purchase preconditioned cattle, which can cost more to purchase and which may not consistently yield higher profits. Because of year-to-year uncertainty in the economic advantage of preconditioned cattle, producers who sell preconditioned calves may not always be able to sell calves at a price that provides a profit over the cost of preconditioning. If an individual producer or producer organization develops a good reputation for generating reliably healthy preconditioned calves, marketing these calves directly to cattle buyers may be the best way for the producer to realize a profit from preconditioned calves. Retaining ownership of calves sent to feedlots may also allow the producer to realize better profits, but this requires a relationship with a feedlot that will manage the calves in ways that will continue to optimize health once the calves enter the feedlot. It has also been shown that preconditioning can help the producer net greater returns simply because preconditioned calves weigh more when they are sold.[17]

Backgrounding. Another practice similar to preconditioning is the practice of backgrounding. In backgrounding, weaned beef calves from a variety of sources (often purchased from multiple sale barns) are accumulated and processed in a manner similar to that carried out for high-risk calves at feedlot entry (Box 31-5). Calves are then sorted by size and type and sold to feedlots, usually within a few days of arriving at the backgrounding operations. Backgrounding operations are sometimes referred to as "conditioning" operations. A variation of the backgrounding operation is the stocker operation; in stocker operations calves are processed and then "stocked" onto pastures, often with supplemental concentrate feeding, to graze and grow for a few weeks to months before shipment to feedlots. The difference between preconditioning and backgrounding is that preconditioning occurs on the farm where the calf is born, or at least before the calf is mixed with other calves from different sources, with some aspects of treatment such as the first dose of vaccines ideally being administered before weaning. Calves that enter backgrounding or stocker operations often have uncertain health histories, they have often been weaned immediately before purchase, and when they arrive they have been mixed with calves with similar uncertain backgrounds from a variety of sources. Because of these factors, disease outbreaks of high morbidity and mortality are not uncommon on backgrounding and stocker operations, and respiratory disease is the leading cause of morbidity and mortality.[18] The backgrounder or stocker operator is thus taking on some of the risk of high-risk calves and is theoretically providing the feedlot with animals more likely to grow well with minimal disease than if the cattle entered the feedlot straight from the auction market.

BOX 31-5

Examples of Processing Protocols for High- and Low-Risk Cattle Entering Feedlots

Processing Protocol for High-Risk, Fall-Weaned, Auction Market Calves

1. Modified live BHV-1 (IBRV), BVDV-1, BVDV-2, BRSV, and PIV-3 vaccines
2. Eight-way clostridial bacterin
3. Antiparasitic
4. *Mannheimia haemolytica* ± *Pasteurella multocida* vaccine
5. *Histophilus somni* vaccine (if significant problem in past)
6. Growth implant
7. Ear tag identification
8. Bulls castrated (if needed)
9. Tip dehorning (if needed)
10. Metaphylactic antimicrobial treatment

Processing Protocol for Healthy Yearlings Previously Fed in Backgrounding Operations

1. Modified live BHV-1 (IBRV), BVDV-1, BVDV-2, BRSV, and PIV-3 vaccines
2. Eight-way clostridial vaccine
3. Antiparasitic
4. Growth implant
5. Ear tag identification

Management at Feedlot Entry. It is not surprising that preconditioning does not always influence the occurrence of respiratory disease in cattle after they enter the feedlot, because it has no effect on many risk factors active during transit and in the feedlot. Therefore optimal control of feedlot respiratory disease should begin with preconditioning and continue with avoidance of auction yards, minimization of transport time to the feedlot, limited mixing of calves from different sources, limited number of calves per pen, control of dust, and careful diet management in the feedlot. Correction of vitamin and/or mineral deficiencies (if known or detected) with vitamin injections in entering calves may be helpful to decrease disease associated with immunodeficiencies of nutritional origin.

Processing procedures on arrival at the feedlot affect the incidence of pneumonia. General recommendations for handling incoming cattle can be made that are appropriate for any category of animals.[18-20] In a receiving program, rest, rehydration, and ruminal restoration need to be addressed because cattle are physically and psychologically stressed by the marketing and transportation processes. It is recommended that these cattle be rested for 12 to 24 hours and that in the summer they should be processed before the hottest part of the day. Prolonged holding before processing is associated with increased illness, and holding times over 48 hours should be avoided. Holding pens should be clean and dry or have dry bedding, because this

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allows all cattle to lie down and rest. Shelter from wind, sun, rain, and dust should also be present in the receiving pen.

It is important that incoming cattle have access to clean, fresh water. Raised spigots have been suggested as a way to teach incoming cattle to drink out of automatic watering devices because cattle will be attracted to the sound of splashing water. Incoming cattle should also be offered good-quality, long grass hay on arrival. Hay is the best foodstuff for restoring or refilling the rumen. Hay can be put in the feed bunks as well as in feeders in the pen as a way of teaching cattle to eat out of bunks. Hay feeders may also be put along the pen perimeter to decrease walking the fence line and encourage eating. The starter ration is an important source of energy and should be highly palatable. The proportion of the starter ration dry matter that is forage is not usually less than 50%; this will prevent problems of acidosis. Starter rations often contain a coccidiostat, because coccidiosis can occur in calves after commingling.

Processing protocols may be tailored to the category of the incoming cattle. Pharmaceutical processing options include vaccination (respiratory and nonrespiratory), vitamin injections, growth hormone implanting, deworming for internal parasites and acaricides for external parasites (may be the same product for both), long-acting antibiotic therapy, drugs for aborting pregnant heifers, and probiotic administration. Management procedures for processing include ear tagging, branding, tail trimming, castration, and tip dehorning. Some management procedures such as castration and dehorning could be left for a later time—for example, at reimplanting at 70 to 90 days on feed (if cattle are expected to be on feed for more than 150 days). Taking the rectal temperature of cattle at initial processing can be very useful, because even cattle that look bright can have very high temperatures and thus can be identified as "sick" by this procedure. Examples of processing protocols for high- and low-risk cattle are shown in Box 31-5.

Metaphylactic Antimicrobial Therapy. The term *metaphylaxis* refers to the administration of an antimicrobial to a group of animals that may be in the early stages of bacterial pneumonia or that are at significant risk of developing bacterial pneumonia. Thus the antimicrobial drug administered may have either a therapeutic or a prophylactic effect, depending on the state of each animal treated. Metaphylactic administration of antibiotics to feedlot cattle on arrival, in order to prevent bacterial bronchopneumonia, has been shown in many studies to decrease morbidity and mortality in groups of high-risk cattle.[21,22] Long-acting antibiotics have been reported to significantly alter the number of calves from which *M. haemolytica* can be cultured.[23,24] An additional rationale for metaphylaxis on arrival is based on the epidemic curve of fatal disease onset for bacterial bronchopneumonia, which shows that feedlot calves dying from fatal fibrinous pneumonia are already sick on arrival or become ill within days of arrival. Although metaphylaxis through feed and water was used in the past, it is currently recommended that metaphylaxis be administered by use of injectable antimicrobial agents. The ability of these drugs to reach therapeutic levels quickly in all animals gives them a clear advantage given the previously discussed rationale for bacterial bronchopneumonia metaphylaxis.

A number of trials have been published that examine various antimicrobial agents and their effectiveness for bacterial bronchopneumonia metaphylaxis. Most of these studies have examined both health and production values, and a variety of products have been shown to be efficacious in decreasing respiratory morbidity and mortality and sometimes in improving production parameters. At the time of this writing, several antimicrobials are approved for administration to control BRD (metaphylaxis; see Table 31-12).

Similar use of long-acting antimicrobials in dairy calves may also be of value. The disease process does not have the same narrow windows of therapeutic intervention that occur in calves entering the feedlot. Dairy calves properly managed in maternity facilities and raised in hutches are typically relatively protected against respiratory disease until they are moved to postweaning group housing. Injectable mass medication is often used at the time calves are moved as a means of controlling postweaning BRD.[25]

MANAGEMENT PRACTICES FOR PREVENTING RESPIRATORY DISEASE IN SHEEP AND GOATS. Prevention of pneumonia in sheep and goats is also based on altering the risk factors that predispose to pneumonia. Minimizing cold and heat stress, providing properly ventilated housing, avoiding overcrowding, and avoiding long transports in adverse weather aid in prevention. Mass medication can be used to control outbreaks of pneumonia in flocks. Injectable long-acting oxytetracycline is often used; tilmicosin can also be used for mass medication therapy for sheep, but tilmicosin should never be administered to goats, as it can result in fatal reactions. Feedlot lambs are sometimes administered metaphylactic therapy (long-acting oxytetracycline) on arrival. See Table 31-12 for a list of antimicrobials approved for administration to sheep and goats.

Vaccination to Prevent Undifferentiated Ruminant Respiratory Disease

Amelia R. Woolums

Impact of Maternal Antibody on the Response to Vaccination

Historically veterinarians were taught that young animals cannot be effectively vaccinated when they have circulating maternal antibodies obtained through passive transfer after birth. This was based on numerous research studies that showed that vaccination of young animals with maternal antibodies did not lead to the expected increase in serum antibodies to the agent in the vaccine. However, an important finding is that some vaccines appear to prime calves for an improved response to subsequent challenge, even when vaccination occurs in the presence of maternal antibodies. In such cases vaccination may not induce an increase in serum antibody titer within 2 weeks of vaccination, but when calves are vaccinated or challenged at a later date, they respond with what appears to be an anamnestic response as measured by increased serum antibodies, or protection against disease resulting from experimental or natural challenge, as compared with unvaccinated calves.[1-4] In general and based on research to date, a response is most reliably induced when modified live vaccines are administered and when the calves receive at least two doses of vaccine at an appropriate (at least 2- to 4-week) interval. Similarly, calves exposed to live pathogens in the face of maternal antibody can develop a protective immune response, even though they do not seroconvert after exposure.[5,6] It has been shown that a cell-mediated immune response can be measured even when there is no evidence of humoral response in calves infected in the face of maternal antibodies.[6] Although multiple studies show that calves can be primed for an anamnestic immune response in the face of maternal antibodies, if very high titers of maternal antibody are present, priming by the vaccine can be blocked, as traditionally understood.[4] Intranasal (IN) vaccination may be more effective than intramuscular or subcutaneous vaccination when calves have moderate concentrations of circulating maternal antibody to antigens in the vaccines.[7] In a recent study, 10- to 13-week-old calves with maternal antibodies that were vaccinated IN with modified live multivalent vaccine containing BRSV had significantly higher serum neutralizing titers to BRSV after they were boosted subcutaneously 3 months later, as compared with calves that did not receive the IN vaccine.[8] This indicated that IN vaccination in the face of maternal antibodies primed the calves for an anamnestic serum antibody response when they were later boosted. However, another recent study indicated that IN vaccination of 3- to 8-day-old calves did not lead to protection at challenge 4.5 months later,[9] indicating that IN vaccination is not invariably effective in calves with maternal antibodies.

This information suggests that, at least in some cases, a protective immune response can be initiated in calves when the first dose of vaccine is given in the face of maternal antibodies; a cell-mediated response may occur even if calves do not have an increase in serum antibody titer after vaccination. This is particularly useful in the

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context of pneumonia in nursing dairy or beef calves, as it supports the concept that vaccination can improve the immune response to challenge even if calves have some level of maternal antibodies at the time of vaccination. More research is needed to confirm which vaccines have this effect and to determine how this information should be used to guide vaccination recommendations for calves. It is also not known if this information can be extrapolated to sheep and goats.

Efficacy of Vaccines for Preventing Ruminant Respiratory Disease

Information regarding the use of vaccines for individual agents that cause ruminant respiratory disease was presented earlier, in the section describing the individual infectious agents. There has been considerable debate over the years regarding whether vaccines have any impact on ruminant respiratory disease. The literature on the subject is extensive, and interpretation of the data is complicated by the fact that there is much variation among research studies in the type and number of animals studied, the nature of animal management, and the outcomes measured as evidence of efficacy. There are three major types of research studies by which vaccine efficacy can be measured: (1) studies that measure production of antibodies or in vitro cell-mediated immune responses in vaccinated animals; (2) studies that measure the resistance of vaccinated animals to experimental challenge with viral or bacterial pathogens; and (3) studies that measure the impact of vaccination on health and productivity of animals in a conventional field setting (field trials). Of the three methods, field trials are the most meaningful, but they are also the most expensive and difficult to undertake. When they are undertaken, it is often in small numbers of animals under management practices that may not be representative of practices in other regions. Moreover, they rely on the natural occurrence of the disease in question in the animals under study. A well-designed field trial can be very expensive and time-consuming, and the results can be useless if no animals in the study contract the disease naturally.

In spite of these limitations the results of some field trials testing the efficacy of respiratory disease vaccines have been published. For some important pathogens (e.g., BVDV), there are still no large-scale field trials published that show evidence of efficacy in preventing respiratory disease. One trial showed an economic advantage to administering a modified live vaccine containing BHV-1, BVDV, PIV-3, and BRSV over the use of a modified live vaccine containing only BHV-1 in feedlot cattle,[10] but it was not possible to determine which component of the multivalent vaccine was responsible for efficacy. Multiple field trials have been published that tested currently available vaccines against *M. haemolytica* and BRSV; these are discussed further in earlier sections on these specific pathogens. In general, some of these studies found that vaccination could prevent disease and sometimes improve productivity, and some of these studies could not find a beneficial effect of vaccination. It is important to remember that in nearly all of these field trials, the effect of vaccination to decrease *all* respiratory disease was measured. That is, in most cases, no effort was made to determine whether disease specifically caused by the agent included in the vaccine was affected by vaccination. Therefore the apparent lack of efficacy of vaccines in some studies may have been because animals developed disease caused by other respiratory pathogens.

Occasionally, in addition to evaluating the impact of vaccination on morbidity, mortality, and measures of productivity, investigators calculate the economic advantage or disadvantage of vaccination. When such calculations are made, it is important that the reader assess the assumptions made and determine whether they are appropriate. It has been noted that when the economic advantage of using a given vaccine is calculated, various scenarios should be considered that might prove the vaccine to be economically advantageous in some situations and disadvantageous in others.[11]

The mixed results of clinical trials published to date indicate that vaccines decrease respiratory disease, improve animal productivity, and save money for the producer in some cases, and in some cases they do not. This should not be a surprise when the multitude of factors that can converge to cause an outbreak of respiratory disease is considered. Vaccination should be seen as one component of a multifactorial approach to minimize animal disease; it should not be seen as a guarantee against all disease, all the time. Thus the value of vaccination will depend on the risk of disease in the population in question, and the risk of disease will depend on the likelihood of pathogen exposure and the likelihood that other host and management factors can be modified to maximize the ability of the host to respond to vaccination and resist disease.

No single, simple recommendation for vaccination of ruminants for the control of respiratory disease can be made. The veterinarian must individualize each vaccination program to the situation at hand. Many factors need to be considered in formulating recommendations for vaccination, including type of production unit, age of animals, system of management, housing facilities, amount of stress imposed on animals, open or closed herd, type of ration, and level of sanitation. In addition, some infectious agents such as BHV-1, BVDV, and *H. somni* can cause other disease problems not associated with the respiratory tract. Thus the complete spectrum of disease caused by these agents must be considered in formulation of a vaccination program. Examples of respiratory vaccination protocols that could be used in a cow-calf operation and in a dairy are presented in Boxes 31-6 and 31-7.

BOX 31-6

One Example of a Respiratory Vaccination Protocol for Use in a Cow-Calf Herd

Replacement Heifers

Modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 with boost 4 weeks later, before breeding

Cows

Modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 before breeding
Boost with killed or approved modified live* BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 at pregnancy check
Consider *M. haemolytica/P. multocida* vaccine at pregnancy check with boost 4 to 8 weeks before calving in herds with history of problems with pneumonia in nursing (preweaning) calves.

Calves

Consider killed or approved modified live* BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 and *M. haemolytica/P. multocida* vaccine at 1 to 4 months of age with boost 4 to 8 weeks later. If herd has a history of nursing calf pneumonia, time boost to occur approximately 4 weeks before expected onset of calf pneumonia.

To Minimize Pneumonia in Calves Postweaning

Killed or approved modified live* (preferable) BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 4 weeks before weaning with boost at weaning
Consider *M. haemolytica/P. multocida* vaccine preweaning with boost at weaning in herds with a history of postweaning pneumonia, or if required for participants in defined preconditioning programs.

*Certain modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 vaccines are approved for use in pregnant cattle and in calves nursing pregnant cattle when administered in accordance with label directions.

The Interstitial Pneumonias

Amelia R. Woolums[§§]

Understanding of the interstitial pneumonias of ruminants has undergone considerable evolution over several decades. Unfortunately, lack of clarity still exists, particularly with regard to

[§§]Previous contributions by Daniel L. Grooms and John A. Smith are acknowledged.

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BOX 31-7

One Example of a Respiratory Vaccination Protocol for Use in a Dairy

Replacement Heifers

Modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 with boost 4 weeks later, before breeding

Cows

Modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 before breeding, OR killed or approved modified live* BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 at dry off

Consider *M. haemolytica/P. multocida* vaccine at 8 weeks before calving, with boost 4 weeks later, in herds with history of problems with pneumonia in calves under 6 months of age.

Calves

In herds with significant calf pneumonia, consider modified live† BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 and *M. haemolytica/P. multocida* vaccine at 1 to 4 months of age with boost 4 weeks later, timed so the boost occurs approximately 4 weeks before expected onset of calf pneumonia.

To Minimize Pneumonia in Calves Postweaning

Modified live† BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 4 weeks before weaning with boost at weaning

Consider *M. haemolytica/P. multocida* vaccine 4 weeks before weaning with boost at weaning in herds with a history of postweaning pneumonia.

*Certain modified live BHV-1/PIV-3/BRSV/BVDV-1/BVDV-2 vaccines are approved for use in pregnant cattle when administered in accordance with label directions.

†Injectable modified live BHV-1 and BVDV vaccines can occasionally induce disease in very young (<1 month of age) or very debilitated calves. In such calves, intranasal modified live vaccines or inactivated vaccines may be safer.

terminology. Terms such as *acute bovine pulmonary emphysema, atypical interstitial pneumonia* (AIP), *fog fever, pulmonary adenomatosis, farmer's lung,* and *acute respiratory distress syndrome* (ARDS) have been used interchangeably for all of the conditions that follow. This text uses a classification presented by Breeze,[1] which places the interstitial pneumonias into four groups: (1) ARDS, (2) hypersensitivity diseases, (3) chronic conditions that may be sequelae of ARDS or hypersensitivity diseases, and (4) parasitic diseases. Bovine respiratory syncytial virus (BRSV) infection can also cause AIP; this disease was discussed earlier in this chapter in relation to the respiratory disease complex of cattle, sheep, and goats.

Acute Respiratory Distress Syndromes

ARDS is any respiratory condition characterized clinically by a sudden onset of (usually severe) dyspnea (Fig. 31-76) with gross and histopathologic findings consistent with AIP. The characteristic gross findings of AIP are lungs that fail to collapse when the thorax is opened (Color Plate 31-11) and that are heavy and have a firm, rubbery texture on palpation. Interlobular or bullous emphysema is usually present (see Color Plate 31-3), and sometimes the cut surface of the lung has a shiny or wet appearance because of edema. In some cases affected lobules, which are dark red to purple, or sometimes grayish, are interspersed with normal-looking lobules, giving the lung a "patchwork" appearance. Although the gross findings are suggestive and often characteristic, other lung diseases can cause similar changes, so a diagnosis of AIP can be confirmed only by histopathologic evaluation. The histopathologic changes that confirm a diagnosis of AIP include alveolar hyaline membrane formation and fibrin deposition, alveolar and interstitial edema, and type II pneumocyte proliferation. Hemorrhage, emphysema, and interstitial inflammatory cell infiltrate can also be seen.



FIG. 31-76 Heifer exhibiting respiratory distress typical of acute respiratory distress syndrome (ARDS). Note extended head, frothing at mouth, and wide-set front legs.

The term *atypical interstitial pneumonia* has often been applied to describe the changes characteristic of AIP, but it has been pointed out that the clinical and pathologic changes in affected cattle are not "atypical" but are rather "typical" of acute lung injury.[1,2] Use of the term *acute interstitial pneumonia* to describe the characteristic pathologic changes and the term *acute respiratory distress syndrome* to describe the clinical picture in an animal with AIP of as-yet-undetermined cause is both accurate and all-encompassing. A diagnosis of AIP should be understood as a pathologic diagnosis rather than a causal diagnosis, because a variety of insults can lead to AIP.

Acute Bovine Pulmonary Edema and Emphysema

Definition and Etiology Acute bovine pulmonary edema and emphysema (ABPEE), classically known as *fog fever,* is an ARDS of adult (over 2 years old) cattle that occurs when they are changed from dry, sparse forages to lush green pastures. It is caused by the conversion of L-tryptophan ingested in the lush forages to a pneumotoxic compound (3-methylindole [3-MI]), which leads to the development of pulmonary edema, alveolar epithelial hyperplasia, hyaline membranes, and emphysema.

Clinical Signs Adult brood cows are most commonly affected because this is the type of animal most likely to be subjected to the abrupt pasture change required to produce the condition. No breed is resistant. The type of pasture appears to be unimportant, as long as it is lush; ABPEE has been reported on a wide variety of grasses, alfalfa, rape, kale, and turnip tops.[3] Signs usually occur within 2 weeks of the pasture change. In severe cases there is an acute onset of very severe dyspnea with a loud expiratory grunt, frothing at the mouth, mouth breathing, and tachypnea. The animals are obviously distressed (as opposed to exhibiting the typical depression that occurs with infectious respiratory diseases) and stand with the head and neck extended and elevated and the nostrils dilated. Temperature and heart rate may be elevated secondary to the severe dyspnea and hypoxia. On auscultation the breath sounds are usually surprisingly soft in view of the gross dyspnea and tachypnea; a few crackles may be heard. Even mild exercise increases the dyspnea and may precipitate collapse and death. As many as 30% of severely affected patients may die, usually within 2 days. Those that survive typically show a dramatic improvement after 3 days. Recovering patients and those that are less severely affected exhibit tachypnea, harsh breath sounds, and crackles and wheezes, particularly in the caudal lung fields. Subcutaneous emphysema may develop. The demeanor of the entire group tends to become more tranquil. In cattle that have repeated episodes of nonfatal ABPEE, a chronic respiratory condition characterized by diffuse pulmonary fibrosis and alveolitis may develop.[4] For

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purposes of differential diagnosis, it is important to note that coughing is not prominent in the individual or the group. The main differential diagnoses are those diseases that cause ARDS in pastured adult cattle, usually in outbreak form. The association of ABPEE with typical management conditions (e.g., changes of pasture) and the absence of coughing, signs of sepsis, and adventitious lung sounds in early cases are also very important features. Primary considerations should include the other plant toxicities (moldy sweet potatoes, perilla mint, and possibly others) that can be differentiated only by identifying the source. An outbreak of BRSV infection or parasitic bronchitis could cause similar clinical signs and pathology, but these are characterized by more coughing, signs of depression, and more prominent adventitious sounds; fever is common in animals with acute BRSV infection.

Pathophysiology L-Tryptophan in lush forages is converted by ruminal microorganisms to indole acetic acid and eventually to 3-MI, which is rapidly absorbed from the rumen into the blood. Metabolism of 3-MI by the cytochrome P-450 mixed function oxidase system in the nonciliated bronchiolar epithelial (Clara) cells and type I pneumocytes results in one or more highly reactive intermediates that bind to intracellular proteins or other macromolecules and thus lead to damage or death of the cells. These intermediates are detoxified by conjugation with glutathione.[5] Cellular damage results in degeneration, necrosis, exfoliation of type I pneumocytes and Clara cells, and edema. These lesions in turn cause hyaline membrane formation, proliferation of type II pneumocytes, and, to a lesser extent, proliferation of Clara cells.[6] The proliferation of type II cells is also known as *adenomatosis*.

Epidemiology As indicated, ABPEE is consistently related to management practices in which hungry adult cattle are suddenly moved from sparse, dry grazing to lush green pastures. The British name *fog fever* arose from the association of the disease with "fog" pastures, which are the lush green regrowth pastures after hay or silage has been cut. The problem usually occurs in the fall. In the typical pattern in the western United States, cattle are moved from dry summer range onto irrigated or fertilized aftermath pastures. The disease usually appears as a herd outbreak, but individuals may be affected to widely varying degrees[7]; the morbidity rate commonly approaches 50%, with a case fatality rate as high as 30%.[8] Nursing calves are typically not affected.

Necropsy Findings In animals that die of ABPEE, ecchymotic to petechial hemorrhages occur in the larynx, trachea, and bronchi, and frothy fluid is present in the airways. The gross and histopathologic lung lesions are consistent with AIP. Congestion, edema, and hyaline membranes cause deep red to purple coloration of the cranial lung lobes and a smooth, glistening appearance to the cut surface. Interstitial emphysema with large bullae and gelatinous yellow interlobular edema is common. Histologically, eosinophilic hyaline membranes line alveoli and alveolar ducts, and there edema and proliferation of type II alveolar epithelial cells are present. In animals that are killed after 3 to 4 days, emphysema and edema are less obvious, and the lungs tend to be light brown, firm, heavy, and rubbery. There is severe diffuse alveolar epithelial hyperplasia (adenomatosis), and large mononuclear cells, multinucleated giant cells, and hyaline membranes are present in alveolar spaces. Edema, eosinophils, and inflammatory cells occupy the septa.

Diagnosis Diagnosis is usually presumptive based on the history of recent exposure to lush green forage, typical clinical signs, and gross and histopathology in fatal cases. Measurement of metabolites of 3-MI in blood or urine can be diagnostic, but this test is typically reserved for research applications.[9] Thoracic radiographs could be used to identify changes consistent with interstitial pneumonia in valuable individual animals. The results of TTA or BAL cytology have not been reported for cattle with ABPEE, but a nonseptic mixed inflammatory cell response would be expected. There are no unique hematologic or biochemical changes. A stress leukogram may be seen.

Treatment and Prevention The stress of handling cattle can precipitate further deaths; because there is no specific treatment for ABPEE, moving cattle to attempt treatment may cause more deaths than it prevents. Some authors maintain that most cases in an outbreak occur within 4 days, that removing the herd from the pasture does not prevent additional cases, and that leaving the herd on the pasture does not result in additional cases; consequently the recommendation has been to handle severely affected cattle only if necessary to remove them to shade or to slaughter. Others recommend careful removal from the offending pasture. Antihistamines, corticosteroids, epinephrine, atropine, diethylcarbamazine, and diuretics are alleged to be of palliative value, but none of these has been confirmed to be effective in a properly designed trial. Recovery often occurs without therapy in the less severe cases. In view of the dangers of handling affected cattle, the questionable efficacy of medical treatment, the probable irreversible nature of severe lesions, and the probability of spontaneous recovery in less severe cases, the best treatment may be no treatment. If treatment must be attempted, affected cattle should be handled very cautiously, and furosemide (0.5 to 1 mg/kg IM or IV once or twice daily) and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or steroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV once daily) may be given. Most fatalities occur in the first 2 days. Severely affected animals that survive may develop chronic emphysema or heart failure secondary to cor pulmonale. Moderate to mild cases often show marked improvement after day 3, with recovery over about 10 days; relapses do not typically occur.

Prevention is based on modification of management and prophylactic drugs. Management strategies that have been recommended to prevent the exposure of susceptible cattle to potentially toxic pastures include the following[5-8,10]:

1. Place the cattle in a dry lot, feed the cattle palatable hay for several days, and turn them onto the lush pasture for 2 hours the first day. Gradually decrease the amount of hay fed and increase the time on pasture over a period of 10 to 12 days.
2. Delay use of lush pastures until after a hard frost.
3. Mow and windrow the pasture before turning cattle out.
4. Use the pasture for young stock (less than 15 months old) or sheep or other livestock; turn adult cattle out only after the pasture has been thoroughly grazed over.
5. Use the pasture before it becomes particularly lush.
6. Use continuous strip-grazing.

Because such management changes are frequently not feasible, prophylactic medication is a useful alternative. Monensin or lasalocid at 200 mg/head/day PO reduces the conversion of tryptophan to 3-MI.[3] Treatment with monensin should be started at least 1 day before pasture change and should be continued an additional 10 days, whereas lasalocid requires a longer pretreatment period of 6 days.[11] Monensin or lasalocid is not expected to be beneficial after the onset of signs. Future possibilities include blockers of the mixed function oxidase system and enhancers of intracellular glutathione levels.

Feedlot Acute Interstitial Pneumonia

Definition and Etiology In feedlot cattle an ARDS occurs that is commonly referred to as *feedlot AIP*. The exact cause of this syndrome is unknown; it is probably multifactorial. Feedlot management practices typically do not include exposure of cattle to lush forages similar to those that cause ABPEE, and the feeding of moldy sweet potatoes has not been associated with feedlot AIP.[12] A variety of causes have been proposed[13,14]; unfortunately, the amount of research to confirm or refute the various hypotheses ranges from small to nonexistent. The most commonly suggested possible causes or predisposing factors are (1) feed-associated pneumotoxins such as 3-MI[9,15,16] or dietary factors related to protein metabolism,[17] (2) chronic bacterial pneumonia,[18,19] (3) gender[9,15] and hormonal influences,[20,21] (4) chronic small airway injury,[18,19,22] (5) BRSV

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infection,[19,23] (6) heat or dust exposure,[22,24] and (7) hypersensitivity reactions.[22,25,26] These possible causes could also work together in various combinations to cause feedlot AIP.

Support for 3-MI as a cause of feedlot AIP comes from research that showed that levels of a stable metabolite of 3-MI, 3-methyleneindolenine (3-MEIN), were significantly higher in the blood of cattle with AIP than in control cattle.[9,15] Increased levels of 3-MEIN may be a result of decreased clearance of the toxin.[15] Loneragan and colleagues also found that 3-MEIN levels were higher in lung tissue of AIP cases as compared with animals without lung disease, but they were not higher than 3-MEIN levels in the lung tissue of cattle with bronchopneumonia; this suggested that 3-MI may contribute to the pathogenesis of both AIP and bronchopneumonia.[15] The mechanism by which 3-MI is generated and leads to lung damage was discussed earlier, in the section describing ABPEE. If 3-MI does contribute to the pathogenesis of feedlot AIP, it is not clear what about the feedlot diet predisposes cattle to produce high levels of 3-MI. Normal cattle produce some 3-MI through metabolism of dietary proteins. It may be that the protein composition (e.g., the tryptophan concentration) of feedstuffs sometimes added to feedlot rations can lead to spikes in 3-MI production. Cattle with feedlot AIP have been found to have higher ruminal pH values than expected for cattle adapted to a high concentrated diet. Ruminal pH in AIP cases ranged from 5.6 to 7.2 in one study[19] and from 4.9 to 7.4 in another,[27] whereas the ruminal pH of cattle adapted to a high concentrate diet is typically about 5.5 to 5.6.[28] Many proteins are relatively basic; therefore the high ruminal pH could be related to abnormal protein metabolism. However, the relatively high ruminal pH could also be caused by anorexia. The concept that abnormal ruminal protein metabolism could contribute to feedlot AIP was also supported by a small study that found increased ammonia levels in the ruminal gas cap of cattle with AIP.[29] An interaction between digestive health and AIP was also suggested by the finding that in feedlot pens in which at least one animal had died from digestive disease, the incidence of AIP was approximately 70% greater than in pens in which digestive disease deaths did not occur.[17]

The hypothesis that bacterial bronchopneumonia contributes to feedlot AIP is supported by the finding by multiple authors that cattle with AIP frequently have superimposed gross and histopathologic lesions consistent with bacterial bronchopneumonia.[18,19,30] In a study evaluating the bacteria isolated from the lungs of cattle with feedlot AIP that had not received antimicrobial therapy, *Pasteurella multocida* and *Mycoplasma* spp. were significantly more likely to be isolated from the lungs of cattle with AIP than from the lungs of normal penmates.[19] An earlier study found that bacterial respiratory pathogens were not more likely to be isolated from cases of AIP as compared with controls, but the samples in this study were collected at necropsy of animals that received antimicrobial treatment before death in at least some cases.[31] No study has yet been able to confirm whether, in cases with both lesions, the bacterial bronchopneumonia was present before AIP occurred or the bacterial bronchopneumonia developed after the animals had AIP. If bacterial bronchopneumonia leads to the development of AIP, it is not clear how this happens. In humans with ARDS, bacterial infection is often a predisposing factor that appears to lead to ARDS through the induction of high local or systemic levels of proinflammatory cytokines.[32] The role of proinflammatory cytokines in cattle with feedlot AIP has not been investigated.

A role for gender and/or hormonal influences in the pathogenesis of feedlot AIP is related to the frequent (although not inevitable)[18] finding that the majority of affected animals are heifers.[15,17,19] Feeding of melengestrol acetate (MGA), which is fed to heifers to control estrus, has been suggested to contribute to AIP by some authors,[20] but others have not found evidence of any association between MGA and AIP.[33] Although one research study indicated that MGA could exacerbate experimentally induced AIP in sheep,[20] a well-controlled experimental study to determine the effect of MGA on AIP in cattle in the field is needed to clarify the involvement of MGA with AIP. It has also been suggested that growth hormone implants may contribute to development of feedlot AIP, although a survey of feedlot managers did not find data to support this.[33]

Infection with BRSV was linked to feedlot AIP in an early study.[23] Because BRSV infection can sometimes cause AIP, the possibility that a ruminant with lesions of AIP is simply a case of BRSV infection must always be considered. However, cattle with feedlot AIP do not always have a fever,[19] which is expected in animals with acute BRSV infection. Moreover, feedlot AIP can occur in outbreaks, but cases often occur sporadically, which would be less consistent with BRSV infection. Neither Sorden and colleagues nor Loneragan and colleagues found BRSV significantly more often in animals with feedlot AIP than in controls.[18,31] In another study the difference in frequency of identification of BRSV in feedlot AIP cases as compared with normal penmates approached significance ($P = .07$).[19] Although AIP is by definition "acute," it is interesting that several authors have reported histopathologic evidence of chronic airway injury (particularly, bronchiolitis fibrosa obliterans) in the lungs of animals with AIP.[18,19,22] In one study, the presence of bronchiolitis fibrosa obliterans was identified significantly more often in cattle with AIP than in penmates with no history of treatment for respiratory disease; this was in spite of the fact that AIP cases in the study also had no history of previous treatment for respiratory disease.[19] It is not known how past airway injury is related to the development of AIP, although chronic airway injury could be linked to the occurrence of chronic bacterial pneumonia, which has also been associated with feedlot AIP, as described previously. It may be that the chronic airway injury is related to dust exposure, although it is not clear why animals with AIP would be more likely to have airway injury caused by dust exposure than other penmates. Dust exposure has been anecdotally related to AIP,[22,24] and feedlot managers often report that efforts to control dust, such as spraying water lightly onto the surface of pens, decreases AIP occurrence when the disease is a problem. However, repeated exposure to feedlot dust or to fungal organisms from feedlot dust did not induce AIP in sheep or goats in experimental studies.[34,35] One study of the effect of dust on feedlot respiratory disease found only a weak association between airborne dust particles and respiratory disease.[36]

High ambient temperatures are thought to contribute to feedlot AIP because several investigators have found that the majority of cases occur in the summer,[17,22] but no mechanism by which hot weather might exacerbate AIP has been researched. Hypersensitivity reactions are often suggested to cause AIP. It is true that anaphylaxis can cause pulmonary edema, hemorrhage, and emphysema, with microscopic evidence of hyaline membrane formation.[37] However, animals that survive longer than a few hours after an episode of anaphylaxis do not have lung changes consistent with AIP, such as type II pneumocytic proliferation and interstitial inflammatory cell infiltrate.[38] Therefore an anaphylactic reaction may cause an occasional case of sudden death with lung changes typical of AIP, but anaphylaxis does not explain the majority of feedlot AIP cases. Other types of hypersensitivity-mediated lung diseases have pathology that is unlike that seen in feedlot AIP, also making other types of hypersensitivities unlikely causes of the majority of feedlot AIP cases.[1]

In summary, the cause of feedlot AIP is unknown, but the strongest support currently exists for some role for (1) factors related to feed, or ruminal metabolism, including 3-MI; (2) infectious respiratory disease, especially chronic bacterial pneumonia, and possibly BRSV; (3) gender and/or other hormonal influences; and (4) chronic airway injury, which may be related to infectious respiratory disease. It seems likely that multiple factors can contribute to the development of feedlot AIP, and the factors may act in some as-yet unidentified combination in at least some cases. It is also possible that some causes predominate in some feedlots or individual cases, whereas other causes predominate in other feedlots or individual cases. A study evaluating the occurrence of bacterial respiratory pathogens in cattle with feedlot AIP found bacterial respiratory pathogens in the lungs of the majority of cases in one feedlot, and in almost none of the cases in a second feedlot,[19] suggesting that bacterial infection

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played a role in the development of AIP cases in the first feedlot but not the second.

Clinical Signs Feedlot cattle with AIP may be found dead in the pen. Clinical presentation includes rapid onset of expiratory dyspnea and tachypnea, although if the respiratory effort is great, the actual respiratory rate may not be greatly elevated. Cattle typically exhibit open-mouth breathing and stand with their heads extended and front legs spread apart (see Fig. 31-76). Frothing from the mouth may also be observed. Rectal temperatures are variable, ranging from normal to elevated.[19] Physical examination may reveal cyanosis, tachycardia, and subcutaneous emphysema that extends from the cervical to dorsal thoracic area. Auscultation of lungs reveals dull areas throughout the lungs, along with some crackles. Differential diagnoses of bronchopneumonia, tracheal edema, tracheal obstruction, and hypersensitivity pneumonitis should be considered.

Pathogenesis Because the cause of feedlot AIP is unknown, the pathogenesis is also uncertain. If feed-related pneumotoxins cause at least a subset of cases with AIP, the pathogenesis will be similar to that described for ABPEE, 4-ipomeanol toxicity, and perilla ketone toxicity. If bacterial infection is a cause of some cases of feedlot AIP, as is true for some human cases of ARDS, then proinflammatory cytokine production and the resultant inflammatory cascades they initiate are likely involved. More research is necessary to determine the cause and the pathogenesis of feedlot AIP.

Epidemiology In the 1999 NAHMS survey of feedlots, AIP was identified as the second leading cause of feedlot mortality, behind bronchopneumonia (shipping fever).[39] Mortality rates resulting from AIP of 0.03% to 0.15% have been reported.[17,22,30,33] An important feature of AIP is the tendency of the disease to occur most often in cattle on feed more than 60 days,[15,19,22,31] as opposed to shipping fever, in which mortality peaks by 45 days after feedlot entry. This means that losses due to AIP deaths are amplified by the fact that relatively more resources in feed and labor have been invested in cattle that die of AIP, as compared with cattle that die of shipping fever. Most cases of feedlot AIP occur in the summer,[17,33] but the disease can occur in any season of the year; and most studies report that heifers are disproportionately affected.[15,17,19] One survey found the odds of an animal with AIP being a heifer were 3.1 times greater than the odds of the animal being a steer.[17] In feedlot pens in which an animal died from a digestive disorder, the relative risk of AIP occurring was about 1.7, indicating that pens with a digestive disorder death were about 70% more likely to also have an AIP death, as compared with pens with no digestive disorder deaths.

Necropsy Findings The gross pathology of feedlot AIP is essentially the same as that described for ABPEE. If there is concurrent bacterial bronchopneumonia, there may be cranioventral consolidation, with fibrin deposition on the pleura, but in cases with no concurrent bacterial pneumonia, the pleura is free of fibrin. Grossly it is common to see a "patchwork" appearance of dark and light colored lobules interspersed, and the lobules are freely movable (see Color Plate 31-11). Histologically, the most acute cases will have only hyaline membrane formation and alveolar edema, possibly with hemorrhage in the alveoli or interstitium; cases that have been going on longer will have proliferation of type II alveolar epithelial cells and inflammatory cell infiltrate into the interstitial space (septa). It is not unusual to find evidence of chronic airway injury, such as peribronchiolar lymphoid cuffing, peribronchiolar vascular fibrosis, and bronchiolitis fibrosa obliterans.[18,19] Whether the chronic airway injury is related to the pathogenesis of AIP or whether it is an incidental finding is unknown.

Diagnosis Diagnosis of feedlot AIP can be confirmed only by histopathologic evaluation of lung from animals that die or are euthanized because of the disease. Clinical signs and even gross pathology are not definitive; only 65% to 80% of cases identified based on clinical signs were confirmed by histopathologic evaluation to have AIP in two studies.[6,15]

Treatment and Prevention Treatments recommended are similar to those recommended for ABPEE. However, feeding monensin does not preclude development of feedlot AIP, as cattle that die of AIP are often consuming feed including monensin when they contract AIP.[15] Treatment is supportive and typically includes administration of antiinflammatory drugs such as steroids (dexamethasone at 0.05 to 0.2 mg/kg once or twice) or flunixin meglumine (1.1 to 2.2 mg/kg IV q24h), and diuretics such as furosemide (1 mg/kg IM or IV q12-24h). Antimicrobial drugs are appropriate given the fact that cases often have superimposed bacterial pneumonia (see Table 31-12). There are no studies evaluating the response of cattle with AIP to any treatment, and such studies would be difficult because there is no perfect method of making an antemortem diagnosis of the disease. However, anecdotal reports indicate that the prognosis is guarded even with treatment. It is important to note that simply moving cattle out of the pen could lead to death from severe respiratory compromise. Because of the risks and uncertainties of treatment and the expected high case fatality rate, immediate salvage slaughter may be the most economic course to take; if salvage slaughter is attempted, remember to observe proper drug withdrawal times.

Because the cause of feedlot AIP is unknown, it is difficult to recommend control measures. Administration of aspirin and of vitamin E have been suggested as rational preventive strategies to counteract inflammatory pathways suspected to be involved in feedlot AIP; however, two trials showed no clear effect of these therapies on levels of 3-MI in treated cattle.[40,41] No cattle in these trials developed AIP, so an effect on disease could not be identified. The risk factors identified suggest that management strategies to minimize abrupt dietary changes and to control infectious respiratory disease may be helpful; anecdotal reports also suggest that efforts to control feedlot dust may be helpful.

4-Ipomeanol (Moldy Sweet Potato) Toxicity

Definition and Etiology Moldy sweet potato toxicity is caused by the ingestion of a furanoterpenoid toxin produced by sweet potatoes *(Ipomoea batatas)* in response to infestation with the fungus *Fusarium solani (javanicum).* It should be emphasized that this disease is an intoxication and not an allergic response to the fungus.

Clinical Signs There is an acute onset of tachypnea, tachycardia, hyperpnea, and dyspnea, with loud expiratory grunting, frothing at the mouth, extension of the head and neck, flaring of the nostrils, and frequent deep coughing. Crackles and harsh bronchial sounds are heard on auscultation. Signs usually occur within 1 day of exposure, and deaths may occur 2 to 5 days later. Differential diagnoses are as for ABPEE (see earlier discussion), which this condition closely resembles, except for the history of exposure and the more prominent cough and adventitious lung sounds.

Pathogenesis When *F. solani* (or closely related species) grows on sweet potatoes, the potato produces several 3-substituted furans, including 4-hydroxymyoporone, which is hepatotoxic. This is converted by the fungus to a series of pneumotoxins, the most abundant of which is 4-ipomeanol. When ingested by cattle in sufficient amounts, this toxin is absorbed, carried to the lungs in the blood, and converted to a highly reactive metabolite by a cytochrome P-450–dependent mixed function oxidase system. From this point the pathogenesis is similar to that of ABPEE—that is, the toxin binds to intracellular macromolecules in the cell, causing cellular damage, particularly in Clara cells, type I pneumocytes, and endothelium; edema, hemorrhage, cellular necrosis, hyaline membrane formation, and proliferation of cuboidal epithelium result, with secondary emphysema.

Epidemiology The disease usually occurs in outbreak form when groups of cattle are fed damaged sweet potatoes. Morbidity

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and case fatality rates are high. Calves nursing affected cows are unaffected.[42]

Necropsy Findings The lungs are wet, firm, and large and fail to collapse. Hemorrhages, yellow gelatinous edema fluid, and emphysema with bullae occur throughout. Lobules are dark red and firm. Microscopic lesions include edema, emphysema, hyaline membranes, hemorrhage, mixed interstitial infiltrates, alveolar epithelial hyperplasia, peribronchiolar fibrosis, and bronchiolitis obliterans.

Diagnosis Diagnosis is made based on history of feeding sweet potatoes and identification of clinical signs and pathology consistent with AIP. Other diagnostic tests as described for ABPEE could also be attempted in valuable individual animals.

Treatment and Prevention Treatment has not been investigated. Because the pathophysiologic mechanisms are similar to those of ABPEE, similar recommendations are suggested: handle affected animals with extreme care; if treatment is attempted, furosemide (0.5 to 1 mg/kg IM or IV q12-24h) and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or dexamethasone (0.05 to 0.2 mg/kg IV or IM q24h) may be given. The prognosis for moderate to severe cases is grave, regardless of management. Because toxicity is difficult to predict and is usually severe and irreversible when it occurs, the feeding of mold-damaged sweet potatoes should be strictly prevented.

Perilla Ketone *(Perilla frutescens)* Toxicity

Definition and Etiology Perilla ketone toxicity is an ARDS caused by ingestion of a pneumotoxin found in the leaves and seeds of *Perilla frutescens,* a common weed in the southeastern United States. This plant is also known as purple mint, perilla mint, wild coleus, and beefsteak plant.[43] It is an erect herbaceous annual about 2 m high, with characteristic square stems, an aromatic odor, and opposite, coarsely serrated ovate leaves 5 to 10 cm long and 4 to 8 cm wide, with a purplish tint at maturity. The seed and flower stage, which occurs in August to October, appears to be most toxic. The flowers are small, white to purple blooms on a long raceme. The plant prefers semishade, such as damp, open wooded areas.

Clinical Signs Animals are often found dead.[43] Signs observed include a sudden onset of moderate to severe dyspnea, wheezing, frothing at the mouth, and an expiratory heave or grunt. In less severe cases the cow may pant. Exertion worsens the signs and may precipitate death. Mature cows are most often affected, but deaths have been reported in yearlings and calves.[43] Death occurs in 3 to 7 days in experimental toxicity.[43] Differential diagnoses are as for ABPEE, which this condition closely resembles and from which it can be differentiated only by history of exposure.

Pathogenesis The volatile oils of *P. frutescens* contain a number of 3-substituted furans that are chemically similar to 4-ipomeanol, the moldy sweet potato toxin. One of these, perilla ketone, predominates in the later growing season (when most toxicities occur) and has been shown to be pneumotoxic when given parenterally to mice, hamsters, goats, calves, and sheep.[43] The toxin is absorbed from the rumen, carried to the lungs through the blood, and probably metabolized to the toxic form by the mixed function oxidase system, as for 4-ipomeanol and 3-MI. The pathogenesis from this point parallels that of ABPEE or moldy sweet potato toxicity.

Epidemiology *P. frutescens* seems to thrive in late summer, when pastures in the southeastern United States are frequently dry and dormant. This also corresponds with the more toxic stage of the plant. Cattle normally avoid the plant when other pasture is available but may be forced to consume it during this critical period. However, under experimental conditions calves were noted to prefer the mint.[43] The preseed stage appears to be of relatively low toxicity; the green seed–stage plant is most toxic, especially the seed parts; dried hay from seed-stage plants is less toxic than green plants but is still potentially lethal; and frosted plants appear to have relatively low toxicity.[43] The exact toxic dose is unknown, but 2.3 kg of green seed–stage plant and 11.2 kg of hay were lethal for cattle in one trial.[43]

Necropsy Findings The lungs are distended (often bearing the impressions of the ribs), fail to collapse, and are moist, heavy, edematous, and emphysematous. There are often bullae, pleural effusions, and froth in the airways. Histologic characteristics are edema, extensive alveolar epithelial hyperplasia, emphysema, and congestion.

Diagnosis Diagnosis is based on history of exposure to perilla mint and characteristic clinical signs and lung pathology.

Treatment and Control Treatment has not been investigated. On the basis of the similar pathophysiologic mechanisms, the recommendations for ABPEE should be followed. The prognosis for severe cases is grave, regardless of management. Cattle should be provided sufficient forage that they do not seek out perilla mint; once they have begun to eat it, they should be fenced away from stands of the plant, and other forage should be provided.

Other Toxic Plants

As mentioned in relation to ABPEE, *Brassica* spp. (rape, kale, turnip tops) are one of the types of pastures that can precipitate the 3-MI–associated disease. The possibility that other specific toxins may be identified in these species has not been excluded. Morbidity and mortality rates appear to be much higher on *Brassica* spp. pastures than on other lush forages.[1] The hepatotoxic effects of pyrrolizidine alkaloids, which are found in certain toxic plants, are well known; pyrrolizidine alkaloids also cause lung lesions. Lung lesions develop only in animals with chronic liver lesions, and the minimum dose necessary to produce lung lesions is never less than that which is hepatotoxic; therefore signs of liver disease usually predominate. *Crotalaria* and *Trichoderma* spp. are the most common offenders; to a lesser extent, *Senecio* spp. are a cause. Horses, sheep, cattle, and pigs have been affected. Pulmonary lesions include edema, congestion, hemorrhage, proliferation of bronchiolar and alveolar epithelial cells with megalocytosis, and interstitial fibrosis and cellular infiltration. As with 3-MI, 4-ipomeanol, and perilla ketone, the toxicity of the pyrrolizidine alkaloids depends on activation by the mixed function oxidase system.

Toxic Gases

Ruminants may be exposed to a variety of toxic gases in the environment. The most important are ammonia, hydrogen sulfide, carbon dioxide, and methane from excreta and respiration; these can be especially important when excreta is collected in pits or tanks. Other gases include nitrogen dioxide from silos; carbon monoxide from machinery exhausts and heaters; zinc oxide from welding of galvanized metal in barns; and chlorine, formaldehyde, insecticides, and other fumes from agricultural chemicals and cleaners. Smoke from fires can also cause pulmonary damage. In most cases concentrations usually remain below overtly toxic levels, and effects are very subtle. Such chronic low-level exposure may result in decreased disease resistance and depression of growth rates. Slightly higher levels of chronic exposure may cause clinically vague syndromes of lethargy, mild dyspnea, anorexia, depressed growth, excessive lacrimation and salivation, low incidence of sudden deaths over weeks or months, and stillbirths. Acute, severe outbreaks usually occur in tightly enclosed facilities and are related to accidents, power outages, agitation or pumping of manure pits, or other combinations of unusual circumstances. Such outbreaks are characterized by an ARDS of variable morbidity and frequently a high case fatality rate.

NITROGEN DIOXIDE. Nitrogen dioxide (NO_2) is a yellow-orange to brown gas with an acrid odor that is produced by anaerobic fermentation of green plant material. It is a major component of "silo

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gas." Acute exposure of farm workers to high concentrations of NO_2 causes a respiratory condition known as "silo-filler's disease," characterized by severe acute edema and congestion and followed by bronchiolitis obliterans and progressive interstitial pulmonary fibrosis. A similar condition has been induced experimentally in cattle,[44] and apparent spontaneous field cases have been reported.[45,46] Clinical signs in experimental and apparent field cases include cough, tachycardia, tachypnea, respiratory grunting, depression, anorexia, hypogalactia, extension of the head, open-mouth breathing, fever, salivation, lacrimation, and subcutaneous emphysema. Auscultation reveals decreased breath sounds and crackles. The primary differential diagnoses should include other ARDSs of housed cattle that occur in outbreak form, especially exposure to other toxic gases (manure pit gases, zinc oxide, chlorine, carbon monoxide), and hypersensitivity pneumonitis from moldy hay. Nitrate toxicity should also be considered. Clinical pathologic evaluation is of limited benefit. Leukocyte counts remained normal in experimental cases; methemoglobin levels increased to a peak at 30 minutes after exposure and returned to normal in 12 to 24 hours.[44] The pathophysiologic mechanism probably involves the dissolution of the NO_2 in the water of the respiratory tract to form nitric acid. Nitrates and nitrites are also formed; these are irritating, and the nitrites cause methemoglobinemia. NO_2 is also an oxidant itself and may contribute directly to the injury. The disease occurs as an outbreak, usually in housed cattle in proximity to a silo chute in a tight or poorly ventilated barn.[45,46] NO_2 is heavier than air and layers on the top of silage or spills out around the bottom of the silo. Corn silage produces more gas than hay, and a high nitrate content increases the danger. The levels are highest in the first 48 hours after filling the silo but may remain dangerous for 2 to 3 weeks.

Necropsy findings in experimental disease include hyperemia of the upper airways; hemorrhages, fibrinous membranes, and froth in the trachea; distended, noncollapsing lungs with rib imprints; a patchwork appearance caused by consolidated lobules alternating with emphysematous lobules; and bullae. Microscopic lesions include alveolar epithelial hyperplasia, large foamy alveolar macrophages, hyaline membranes, hyperemia, hemorrhage, and edema.

Treatment involves the establishment of adequate ventilation; cows should be completely removed from closed buildings if necessary. Corticosteroids have apparently been beneficial in field cases,[45,46] but no controlled studies have been performed to confirm efficacy. Because of the obvious differences in pathophysiologic characteristics, it would be unwise to extrapolate treatment regimens from those of ABPEE. Suggested empirical therapy might include corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice daily), and appropriate antibiotics to prevent secondary bacterial infections.

ZINC OXIDE. Zinc oxide (ZnO) fumes have been associated with ARDS in cattle.[47] Oxyacetylene cutting or arc welding of galvanized pipe results in production of white fumes of ZnO containing colloidal particles 0.3 to 0.4 mm in diameter, which can reach the terminal alveoli when inhaled. Construction activities in closed barns containing animals may result in toxicity in animals in close proximity or in the path of ventilation. All ages may be affected.

Clinical signs in severe cases include acute onset of anorexia, frothing at the mouth, anxiety, extension of the head and neck, mouth breathing, expiratory grunting, tachypnea, tachycardia, mild fever, subcutaneous emphysema, and crackles on auscultation of the lungs. Death may occur within 12 hours. Less severely affected animals exhibit depression, mild fever, and tachypnea. Differential diagnoses include other ARDS of housed cattle that occur in outbreak form, such as exposure to other toxic gases (nitrogen dioxide, manure pit gases) or hypersensitivity pneumonitis. The pathophysiologic process presumably involves direct damage to cells by the ZnO and its products dissolved in the fluid lining the respiratory tract. Necropsy findings include purulent conjunctivitis; subcutaneous emphysema; congestion of the airways; tracheal hemorrhages; stiff, noncollapsing lungs; and pulmonary congestion, edema, and emphysema with bullae. Histologic lesions include pulmonary congestion, emphysema, edema, and mixed cellular infiltrates with a prominent eosinophil component. Treatment of severe cases with epinephrine, antihistamine, atropine, and corticosteroids had no effect in one outbreak, whereas mild cases recover spontaneously. Suggested empirical therapy could include ventilation of the area, dexamethasone (0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice), and appropriate antibiotics to control secondary bacterial invaders.

CHLORINE. Chlorine is a greenish yellow gas widely used in manufacturing. Animal exposure is usually the result of industrial accidents. Exposed animals may be found dead. Signs include depression, profuse nasal discharge, lacrimation, and dyspnea; crackles may be heard on auscultation.[48] The toxic effects are the result of the formation of hydrochloric and hypochlorous acids; the latter breaks down to hydrochloric acid and oxygen, both of which are toxic to tissues. Necropsy findings include congestion of the nasal mucosa, tracheitis, and pulmonary edema, hemorrhage, and emphysema. Histologic lung lesions include edema, emphysema, hemorrhage, atelectasis, hyaline membrane formation, and lymphocytic bronchitis. Treatment is empirical; suggestions include corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily to twice daily), and appropriate antibiotics to prevent secondary bacterial infection.

MANURE GASES. Manure gases include mixtures of hydrogen sulfide, ammonia, carbon dioxide, methane, and carbon monoxide.[1] Accumulation of these gases can result in asphyxiation of animals in enclosed barns over manure pits.

Hypersensitivity Pneumonitis

Definition and Etiology Hypersensitivity pneumonitis, also known as *extrinsic allergic alveolitis* (EAA) or "bovine farmer's lung," is an allergic respiratory disease caused by inhalation of organic dusts. Several such conditions are recognized in humans, differing only in the nature of the antigen and the circumstances under which exposure occurs. The classic example, of which the bovine disease is probably the counterpart, is "farmer's lung." EAA is caused by exposure to the dust from moldy hay, grain, or other plant matter containing spores and products of thermophilic actinomycetes such as *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*) and *Thermoactinomyces vulgaris*.[1,2] Other unidentified forms of hypersensitivity pneumonitis probably occur in cattle.

Clinical Signs EAA is a disease of confined adult cattle; consequently it is more common in dairy than in beef breeds. Typically a succession of acute cases occurs during the winter housing period, so the clinician is presented with a group problem in which animals are in varying stages of the disease. The acute form is indicative of recent exposure and is characterized by a sudden onset of dullness, decreased appetite, hypogalactia, coughing, expiratory tachypnea, dyspnea, and cranioventral crackles on auscultation of the lungs.[1-3] There is a moderate transient fever, which is frequently missed. The chronic form is insidious at onset and may not be detected until there is considerable fibrosis. Animals with the chronic disease may have acute exacerbations as a result of heavy antigen exposure; some may not be detected until turned out in the spring, when increased exercise causes an acute crisis. There is a history of weight loss and coughing for several winters, with remission in the grazing season. Chronic signs include hypogalactia, weight loss, productive coughing, tachypnea, obvious hyperpnea, and widespread crackles and wheezes on auscultation of the lungs, especially in the rostroventral areas. Differential diagnoses should include respiratory diseases affecting groups of housed adult cattle in winter. Infectious diseases (viral and bacterial pneumonias) can usually be differentiated from farmer's lung by careful evaluation of factors such as

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clinical signs of fever and pulmonary consolidation. Therefore the main differential diagnoses are the toxic gases. It should be emphasized that hypersensitivity pneumonitis is not considered an ARDS and that no evidence exists for the involvement of hypersensitivity in the pathogenesis of the ARDS described previously. However, severe cases of EAA with prominent dyspnea and moderate, nonfatal cases of gas intoxication may appear clinically similar. If the group outbreak aspect of EAA is ignored, the clinician who examines one individual may be unable to distinguish this condition from fibrosing alveolitis.

Pathogenesis The spores of the thermophilic actinomycetes are 0.7 to 1.3 mm in diameter and can easily reach the alveoli, where they induce both humoral (precipitating) and cellular immune responses. It is thought that repeated exposure results in the activation of a number of immunologically specific and nonspecific cellular and humoral effector mechanisms at the alveolar level, which results in tissue damage.[1,2]

Epidemiology EAA is a problem in areas with wet summers and severe winters, a situation characterized by the combination of moldy hay and housing of cattle in winter. In North America, EAA occurs primarily in the Great Lakes region of the United States and the eastern provinces of Canada.[3] Baling and stacking of hay with a high moisture content (over 30%) results in overheating of the stacks. Thermophilic molds become dominant and produce billions of spores, which are released when the hay is distributed for feeding. A similar situation can occur in stored grains. Affected hay is usually dry, friable, discolored, and dusty; however, it is not necessary for hay to be grossly dusty and poor in quality to release large numbers of spores.[2]

Necropsy Findings In acute cases the lungs are superficially grossly normal. Closer inspection reveals small gray spots in many lobules, which represent interstitial and peribronchiolar accumulations of lymphocytes. Other lobules exhibit dark red centers of atelectasis surrounded by pale pink, raised edges of trapped air that are caused by narrowing of airways with lymphocytic infiltrates. Histologic evaluation confirms the presence of these lymphocytic infiltrates and aggregations, as well as epithelial granulomas, bronchiolitis, and bronchiolitis obliterans. The gross appearance in chronic cases is similar, with the addition of focal areas of interalveolar fibrosis and epithelial hyperplasia; epithelioid granulomas are absent unless a recent acute exposure has occurred.[1,2]

Diagnosis Precipitating antibodies to *S. rectivirgula* are found in the serum in most cases.[1,2] However, two precautions are necessary. First, the presence of precipitating antibodies only indicates exposure to the antigen; many normal animals also have antibodies. Second, it is possible that other as yet unidentified antigens may cause allergic respiratory disease in cattle. The presence or absence of titers is therefore not necessarily diagnostic of the clinical status of the animal, and the magnitude of the titer does not reflect the extent of disease.

Treatment and Prevention Treatment and control center on removal of the offending antigen, which is frequently difficult from an economic and management standpoint. Corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IV or IM daily) may be beneficial in acute cases. Suggestions to decrease the molding of hay or degree of exposure include making silage instead of hay, ensuring proper drying before baling, and feeding hay outside. If the condition can be arrested before significant fibrosis occurs, the prognosis is good.

Anaphylaxis

In ruminants the lung is the major target organ in immediate (type I) hypersensitivity reactions. Precipitating antigens include vaccines, drugs, blood, *Hypoderma bovis* or *Hypoderma lineatum* larvae, insect bites, and bee stings. Signs of anaphylaxis usually develop in 10 to 20 minutes and include severe acute dyspnea, with flaring of the nostrils, extension of the head and neck, open-mouth breathing, frothing of the mouth, hyperpnea, and abduction of the elbows. Pharyngeal and laryngeal edema cause stertor and inspiratory dyspnea. Urticaria may occur in some cases, such as milk allergy in Jersey cows. Shivering, salivation, lacrimation, pruritus, diarrhea, fever, edema (eyes, muzzle, anus, and vulva), collapse, nystagmus, cyanosis, and discharge of froth from the nostrils also may occur. On auscultation there are harsh breath sounds, large airway sounds, and crackles. The primary differential diagnosis is peracute interstitial pneumonia. The pathogenesis involves an initial exposure to the antigen, which results in a genetically determined production of immunoglobulin E (IgE); IgG may also be involved. This antibody attaches to receptors on mast cells and basophils. On subsequent exposure to the antigen, bridging of the Fab parts of the antibody on these cells results in degranulation, with release of a variety of mediators such as histamine, bradykinin, 5-hydroxytryptamine, serotonin, slow-reacting substance-anaphylaxis (SRS-A), eosinophil chemotactic factor A, platelet-activating factor, kinins, and prostaglandins. These mediators result in a cascade of vascular events, notably increased vascular permeability, which in turn results in acute severe edema. Pulmonary venous constriction, pulmonary artery hypertension, splanchnic pooling, increased mucus secretion, and bronchospasm also occur. Ruminants that die of anaphylaxis have severe pulmonary congestion and edema, laryngeal edema, and froth in the airways. Lung lesions of ARDS may be present.

The treatment of choice is epinephrine, 4 to 8 mg (4 to 8 mL of 1:1000 solution) IV or SC or 1 to 5 mg IV for an average 500-kg cow and 1 to 3 mg IV or SC for an average adult sheep or goat. Epinephrine has a short half-life, and animals should be observed closely for relapse. Ancillary therapy includes corticosteroids (dexamethasone, 0.1 mg/kg IM or IV; prednisolone, 2.2 mg/kg IM or IV daily). Other supportive therapies include shock doses of IV fluids (40 mL/kg/h), aminophylline, diuretics such as furosemide, oxygen therapy, and tracheostomy if necessary.

Miscellaneous Chronic Pneumonias

At least two chronic interstitial pneumonias of uncertain cause have been identified in cattle: fibrosing alveolitis and bronchiolitis obliterans. These are typically chronic diseases of individual animals.

Fibrosing Alveolitis

Fibrosing alveolitis is, by definition, a chronic disease of unknown and possibly multiple causes, characterized by diffuse inflammation of the lung beyond the terminal bronchiole. Approximately 50% of cases produce positive results for precipitating antibody to *M. faeni,* and it is possible that these cases represent chronic farmer's lung, whereas others (that have negative *M. faeni* results) may be the chronic stage of hypersensitivity to other unidentified antigens.[1] Field investigations have failed to substantiate any connection between fibrosing alveolitis and repeated episodes of ARDS such as ABPEE. Furthermore, recovery from a single dose of 3-MI does not result in lesions typical of fibrosing alveolitis. However, repeated doses of 3-MI at weekly intervals experimentally cause fibrosing alveolitis–like lesions. Fibrosing alveolitis occurs in individual adult cattle (usually over 6 years of age) in both housing and pasture conditions. The history is usually that of a chronic progressive respiratory disease several weeks to 2 years in duration. Affected cattle remain bright and alert and continue to eat until the terminal stages of cor pulmonale and heart failure intervene. Signs include marked weight loss; consistent coughing; tachypnea; very marked hyperpnea, even at rest; and dyspnea after mild exertion. Auscultation may reveal crackles in the rostroventral lung field and widespread wheezes. Fever is not apparent. The primary differential diagnoses to consider are other chronic respiratory conditions of individual adult cattle. Chronic suppurative pneumonia and metastatic pneumonia can usually be differentiated from fibrosing alveolitis by careful physical examination and detection of depression, anorexia, shallow respiration,

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thoracic pain, and hemoptysis. ARDS caused by feed-associated pneumotoxins and lungworms are typically group problems, with at least some severe cases in the group. Differentiation from EAA may be impossible if the group outbreak nature of farmer's lung is not apparent; in fact, at least some cases of fibrosing alveolitis may represent chronic farmer's lung. At necropsy the lungs are very pale, firm, and heavy throughout. Scattered lobules are gray-red, slightly collapsed, and edematous. Thick mucus may be found in the airways, and there is frequently right ventricular hypertrophy as a result of cor pulmonale. Histologic changes are diffuse and include interalveolar fibrosis and infiltration with plasma cells, lymphocytes, mast cells, and interstitial cells; obliteration of alveolar spaces; mononuclear exudates in alveoli; alveolar epithelial hyperplasia; bronchitis; and bronchiolitis. The epithelioid granulomas characteristic of acute farmer's lung are absent. No treatment exists, and the lesions are irreversible.

Bronchiolitis Obliterans

Bronchiolitis obliterans is a chronic respiratory condition of yearling or young adult cattle characterized by a deep infrequent cough, tachypnea, hyperpnea, and an exaggerated expiratory effort. There is no fever. The cause is unknown; the condition is speculated to be a sequela to viruses (respiratory syncytial virus [RSV], parainfluenza virus type 3 [PIV-3], infectious bovine rhinotracheitis [IBR]), parasites such as *Dictyocaulus viviparus,* or hypersensitivity pneumonitis. The lungs appear grossly normal at necropsy, except that they do not collapse. Histologic examination reveals extensive bronchiolitis and bronchiolitis obliterans, with epithelium-covered polyps with a connective tissue core projecting into and obstructing the lumen.[1]

Parasitic Bronchitis and Pneumonia

Dwight D. Bowman • Anne M. Zajac

There is only a single lungworm, *Dictyocaulus viviparus,* which matures to the adult stage within the lungs of cattle. In sheep, the three main lungworms that may occur are *Dictyocaulus filaria, Muellerius capillaris,* and *Protostrongylus rufescens;* some other species mature in the lungs of sheep and goats around the world, but they are fairly rare compared with these other species. *Toxocara vitulorum* of cattle larvae undergo a liver to lung migration on their way to the intestine after infective eggs are ingested, and they can induce a transient pneumonitis during lung passage. In cattle, *Ascaris suum* of pigs can also cause signs similar to larval toxocariasis if cattle ingest large numbers of eggs; these infections do not develop to patency. In sheep and goats, *Toxocara canis* (and perhaps other species from carnivores) can cause transient pneumonitis as the larvae migrate through the liver and lungs on their way to arrest as larvae in other tissues such as muscle and nervous tissues.

Lungworms of Cattle: *Dictyocaulus viviparus*

Definition and Etiology *Dictyocaulus viviparus* is a trichostrongylid nematode that is found in the bovine trachea and bronchi. These are robust white worms that can reach lengths of 8 cm; the slightly smaller males have very dark brown stubby spicules that can often be visualized within the body of the worm just anterior to the copulatory bursa. The life cycle of *D. viviparus* is direct. The female produces larvated eggs that hatch in the lungs, and the larvae make their way up the respiratory tract, are coughed up, and swallowed to be passed in the feces. The larvae on pasture ultimately develop to an infective third stage without feeding and can develop in the laboratory in aerated water into double-sheathed infective stages. The larvae take 5 days or longer, depending on environmental conditions, to develop to the infective stage on pasture. The larvae then migrate onto grass where they are ingested by the feeding cattle. After ingestion, the larvae migrate through the intestinal wall and make their way into the mesenteric lymph nodes where they molt to the fourth stage. It is the fourth-stage larvae that make their way to the lungs via the blood and lymph systems and initially are found in the terminal capillaries of the ventral parts of the caudal lobes. About 7 days after ingestion, the fourth-stage larvae enter the alveoli and then molt to the immature adult stage. The adults develop and mate. Eggs will first appear in the bronchi, and subsequently larvae in the feces, some 3 to 4 weeks after the animal was initially infected. Clinically evident infection with *D. viviparus* typically occurs in young, nonimmune stock (less than 12 months old) or in previously unexposed yearling or adult cattle. A reinfection syndrome can also occur when previously infected (and therefore immune) adults are subjected to massive challenge with infective larvae.[1,2]

Clinical Signs and Differential Diagnosis Primary infection with *D. viviparus* can be broken down clinically into a prepatent phase, a patent phase, and a postpatent phase.[3] No signs are associated with the initial penetration of larvae until they reach the alveoli, where they provoke an eosinophilic exudate that blocks small airways. During the prepatent phase (approximately 7 to 25 days after ingestion), there is a gradual onset of coughing and tachypnea (35 to 60 breaths/min), which becomes increasingly apparent from day 14 to day 25. The severity of signs in this stage is proportional to the number of larvae ingested, the rate of ingestion, and the proportion reaching the lungs. Severe illness and death can occur in cases of heavy infection. In the patent phase (approximately 25 to 55 days after ingestion), a parasitic pneumonia with consolidation develops in the ventral areas of the caudal lung lobes as a result of aspiration of eggs and larvae into these areas. Tracheitis and bronchitis associated with the adult worms also develop. Clinical signs vary in severity and range from intermittent to marked coughing, tachypnea (respiratory rate may increase to more than 70 breaths/min), dyspnea, anorexia, and weight loss. Fever may develop with secondary bacterial infection. Auscultation reveals harsh breath sounds and widespread crackles and wheezes. In severe cases animals may exhibit open-mouth breathing, extended head and neck, protrusion of the tongue, and an expiratory grunt. Death is common in untreated, heavily infected animals.[2,3]

Recovery begins in the late patent phase, and the signs gradually resolve, sometimes over several months. During the postpatent phase (about days 55 to 90), adult parasites are expelled by a self-cure phenomenon. In approximately 25% of severe cases the postpatent phase is characterized by a sudden exacerbation of dyspnea at days 45 to 60 that is often fatal, after secondary bacterial infection or alveolar epithelialization.[1,3] The reinfection syndrome occurs 14 to 16 days after adult cattle are placed on heavily contaminated pastures. Signs include acute hypogalactia; severe, frequent coughing; marked tachypnea; and depression. Auscultation reveals only harsh breath sounds with no crackles or wheezes.[1,3]

Relative to *D. viviparus,* an ancillary finding occurred as part of a 3-year study in Sweden that examined the effects of different parasite control strategies administered to cattle during their first grazing season on their weight gain during the three second grazing seasons when they were all handled equivalently.[4] Basically, during the second season of grazing, deficits acquired within each management group the first year were maintained during the second year, but the first season of treatment had no effect on weight gain the second season. During the second and third second-season grazing period, *D. viviparus* entered the groups when additional contaminated pastureland was added to the grazing area in the last 2 years. The work then clearly showed that the presence of *D. viviparus* had a detrimental effect on all animals both seasons, and during the second such season, signs of dictyocauliasis appeared in August and the cattle underwent dramatic weight loss (the trial precluded treatment without more serious signs of induced disease). Thus, it was fairly clear that the larvae had overwintered on pasture, increased in number within the herd, and was there in sufficient numbers to cause significant effects the second year.

Differential diagnosis should be straightforward if both the clinical signs and epidemiologic characteristics of the disease are taken into account, especially in endemic areas. This is a disease of groups of cattle at pasture, typically in late summer or fall in northern

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temperate climates; the situation thus resembles ABPEE, which differs in clinical signs (i.e., less coughing and fewer adventitious lung sounds). The signs associated with lungworm infection are reminiscent of those of farmer's lung, which occurs in quite different circumstances. In typically nonendemic areas, outbreaks associated with climatic changes are frequently mistaken for acute bacterial bronchopneumonia.[1]

Diagnosis Classically, diagnosis has been through the detection of the characteristic larva passed in the feces. In cattle, this is the only nematode parasite routinely producing larvae found in the feces, and thus, if the fecal sample is fresh, the finding of larvae is fairly diagnostic. Rectal fecal samples are preferred for parasite examination because samples picked up off the ground may contain free-living nematodes that can be difficult to differentiate from lungworm larvae. Recovery of larvae from fecal samples is substantially diminished if the sample is stored at room temperature for more than a few hours. The larvae are best detected by the Baermann test[5] and may be seen on a transtracheal wash. The larvae themselves are large (390 to 450 μm × 25 μm), have a somewhat pointed tail (compared with *Dictyocaulus filaria* of the sheep), and an intestine is filled with dark granules. The esophagus appears clear compared with the intestine under the microscope and is about one fourth of the total length of the larva. If the Baermann test cannot be set up soon after fecal collection, the sample can be safely refrigerated for 24 to 48 hours without serious larval loss.[6] No larvae are detected in the reinfection syndrome. In some European countries, enzyme-linked immunosorbent assay (ELISA) tests are used within various diagnostic laboratories to detect antibodies in cattle that have been exposed to infection.[7] An increase in eosinophils in the peripheral blood may also occur approximately 2 weeks after infection, peaking at 4 to 7 weeks after infection.[8]

In Europe, ELISA technology has now been developed to detect antibody in the milk and serum of cattle that is based on an antigen that is a recombinant product representing a major sperm protein of the adult male.[9,10] Examination in experimentally infected dairy cows revealed that the ELISA detected antibodies in the serum and milk some 30 to 32 days after infection and remained elevated for 112 to 138 days postexposure even though the cows had been treated for their infections with eprinomectin 49 days after infection and had ceased larval shedding.[9] However, if the cattle were treated during the prepatent period, larvae were never shed in the feces, and the animals remained antibody negative. This technique has now been adapted to determine the presence of antibodies in bulk milk and has been used for the collection of epidemiologic data. Of 810 dairy farms in Germany that were tested in January, September, and November, some 18% were positive on one occasion, and most positive samples were detected in January.[11] It was not known what percentage of zero-grazing herds were included in the bulk-milk samples.

Pathophysiology Once the fourth-stage larvae enter the alveoli, they incite an eosinophilic exudate that blocks small bronchi and bronchioles, resulting in atelectasis and causing the cough and tachypnea of the prepatent phase. As these larvae mature and migrate up the airways, these lesions may resolve. However, the adult worms produce an inflammatory response in the larger airways, and aspirated eggs and larvae cause a marked macrophage and giant cell response, with consolidation of the ventral caudal lobes; these lesions are the cause of the signs in the patent phase. At any point in the pathogenesis (prepatent, patent, or postpatent stage), complications may occur that account for acute exacerbation and death. These complications are as follows:

- Development of pulmonary edema caused either by heart failure or by extensive alveolar epithelial damage and hyaline membrane formation
- Severe interstitial emphysema from the severe dyspnea
- Alveolar epithelial hyperplasia
- Secondary bacterial infection (relatively uncommon)

In the reinfection syndrome the immune response cannot completely overcome a massive challenge, and a small number of larvae reach the lungs. The signs are caused by the immune reaction to the migrating larvae. Lymphoid nodules develop around dead larvae in the bronchioles.[1-3]

Epidemiology Parasitic bronchitis and pneumonia in cattle occur most often in temperate areas with high rainfall or intense irrigation. In the United States, lungworm infection is widely distributed, but disease outbreaks are uncommon, probably because periods of dry summer weather limit larval survival and accumulation on pasture.[2] In the southern United States, lungworm transmission is probably greatest in the cool winter months,[12] whereas autumn is probably the season of most intense transmission in the northern United States.[13,14]

Dictyocaulus infections have been studied extensively in Europe, where the parasite is an important pathogen. Disease outbreaks occur most frequently in first-season grazing animals. If large numbers of larvae are present on pasture at spring turnout of calves, disease may develop at that time. Often, however, levels of pasture larvae are too low to cause disease but lead to low-level primary infections in calves that result in the accumulation of additional larvae on pasture. This second wave of infection may lead to clinical lungworm disease when the primary infection did not produce adequate levels of immunity. If infection levels remain low, disease may not be observed until a third generation of parasites occurs. Immunity develops beginning about 10 days after heavy infection, and patent infections usually persist for only a few months. In the absence of continued exposure to parasites, immunity to reinfection will begin to decline after several months.[2,15]

Older animals without immunity also develop lungworm disease when exposed to high levels of pasture contamination with larvae. This can occur when animals from a nonendemic area are moved to an endemic area. In recent years outbreaks of primary parasitic bronchitis have become an important cause of respiratory disease in adult dairy cows in Europe. The increased prevalence of disease in this older age group is likely the result of decreased levels of immunity after the widespread use of powerful suppressive anthelmintic regimens in first- and second-season grazing animals. Other management factors, such as isolation of calves from adult carrier animals and increased movement of livestock, may also contribute to a decline in levels of immunity.[7,16] Beef animals are less often affected than dairy cattle because management practices are more extensive and levels of infective larvae on pastures are generally lower.[2] The reinfection syndrome occurs in immune adult animals when, for example, immune cows are placed on a pasture previously contaminated very heavily by calves with patent disease.[1,2]

In northern temperate climates, the infection is carried from year to year by overwintering of larvae on pasture in some areas, by spreading of manure from infected housed calves in the spring, and by carrier cattle. Lungworm larvae also may be inhibited in the lungs of calves in winter (as with *Ostertagia* spp. in the abomasum) and mature in the spring.[1,3]

Necropsy Findings In the prepatent phase the lungs are largely normal, with a few atelectatic lobules in the ventral caudal lobes; adult worms are not present until late in this phase, but larvae may be detectable by microscopic examination of smears of bronchial exudate. In the patent phase there is usually bilaterally symmetric red consolidation of the ventral caudal lobes. Adult worms can be recognized on necropsy by their relatively large size and location in the trachea and bronchi. The lesions of the postpatent phase are similar, but no adult worms or larvae are present. In those animals that die of an acute exacerbation, there is extensive pulmonary edema and emphysema, with hyaline membranes and alveolar epithelial hyperplasia.

In the reinfection syndrome the pulmonary lymphoid nodules may be 3 to 4 mm in diameter and thus grossly visible as raised, gray-red to greenish yellow nodules under the pleura. Initially these

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TABLE 31-14

Anthelmintics Approved for Treatment of *Dictyocaulus viviparus* in the United States

Anthelmintic	Formulation	Efficacy of a Single Treatment	Approved for Dairy Cattle of Breeding Age
Levamisole	Drench, bolus, injection		
Fenbendazole	Paste, suspension, medicated feed, mineral		+
Oxfendazole	Suspension		
Albendazole	Paste, suspension		
Ivermectin	Injection, pour-on	28 days	
Eprinomectin	Pour-on	28 days	+
Doramectin	Injection, pour-on	Injection: 28 days Pour-on: 21 days	
Moxidectin	Pour-on, injection	42 days	+ Pour-on only

are composed of a core of eosinophilic parasitic debris surrounded by macrophages, multinucleated giant cells, hyperplastic bronchiolar epithelium, eosinophils, and plasma cells. The lesions eventually mature to lymphoreticular nodules with a germinal center. There is also greenish mucus in the airways and a greenish discoloration to the tissues, both caused by eosinophil infiltration. There is no edema or emphysema, and the rare lungworms that may be found are small and stunted.[1]

Treatment, Prognosis, Prevention, and Control *D. viviparus* infection can be treated with a number of bovine anthelmintics available in the United States and other countries (Table 31-14). Macrocyclic lactone products also have residual efficacy against *D. viviparus*.[17] Animals with only cough and tachypnea respond well, whereas those with dyspnea, fever, anorexia, and depression have a more guarded prognosis; some of these can be expected to die or remain chronically unthrifty.[1] Control (see also Chapter 49) involves appropriate pasture management and the strategic use of anthelmintics to prevent buildup of infection in the herd and on pastures. Several strategic deworming programs have been developed in Europe, which effectively suppress lungworm infection throughout the grazing season. These programs include use of ivermectin at 3, 8, and 13 weeks after turnout and use of doramectin or eprinomectin at 0 and 8 weeks. Use of an oxfendazole pulse release bolus (not available in the United States) also provides strategic treatments. Alternatively, use of a continuous-release ivermectin or fenbendazole bolus (not available in the United States) will prevent development of lungworm infection during its period of efficacy.[16] A long-acting moxidectin injection product that provides protection from lungworm infection for 120 days is also now available in some countries.[18] Anthelmintic treatment with moxidectin or fenbendazole followed by movement of calves to safe pasture 9 weeks after turnout was also effective in controlling lungworm.[19] None of these control programs has been extensively tested under the variety of grazing conditions found in the United States.

Despite concern that suppressive programs may limit exposure to larvae and interfere with the development of immunity to lungworm, several studies conducted in Europe have shown that stimulation of the immune response still occurs, although relative levels of immunity may vary with different management systems and with annual variation in the intensity of lungworm challenge.[7,20-22] In Europe, methods of control also include an effective irradiated larval vaccine.

Delay of spring turnout is an adjunct to control but should not be relied on as the sole means of control.[21] A targeted selective deworming program was successful in controlling lungworm infection in a dairy herd in Sweden. Only cattle testing positive for lungworm by the commercial ELISA test were treated at each sampling date.[23] In an attempt to eradicate *D. viviparus* from two farms in the Netherlands that had had lungworm-associated disease outbreaks, both herds were mass treated with eprinomectin at turnout.[24] From August to November of the first year after treatment, all first-year heifers remained lungworm negative as determined both by fecal examination and by monitoring for *D. viviparus*–specific antibodies. However, in the second year following treatment, one of the herds developed signs of parasitic bronchitis that was confirmed serologically. The other herd remained negative until at least the fourth year after treatment, but at that time signs of parasitic bronchitis were observed and the cattle were treated. The authors believe that in both cases, either the *D. viviparus* was reintroduced into the herd from an outside source or the reuse of pastures that may have lain fallow for an extended period provided the source of the new infections.

TOXOCARA VITULORUM. This parasite seems to be reemerging in prevalence within the developed world; there have been recent reports from a bison herd in western Canada, suckling beef calves in the Netherlands, suckling Simmental cattle in the United Kingdom, and in a closed cow-calf beef operation in north central Florida, 17.6% of 105 calves under 3 months of age were found infected.[25-28] Infections in neonatal calves are acquired by fairly large larvae (0.75 to 1.5 mm in length) that are passed from cow to calf in the milk. In cows that ingest eggs, the larvae undergo a liver-lung migration before they make their way to the various tissues of the cow where they are known to persist for at least 5 months.[29] There typically do not appear to be any signs associated with the lung migration of the larvae, but repeated passage of the larvae through the lungs on contaminated pasture could perhaps produce respiratory signs in older calves or adult animals.

ASCARIS SUUM. Cattle exposed to large numbers of *Ascaris suum* eggs in areas contaminated by swine may have an interstitial pneumonia. Animals are typically affected approximately 10 days after exposure. Signs include depression, anorexia, fever, tachycardia, tachypnea, dyspnea with an expiratory grunt, variable coughing, ruminal stasis, and bloat. Auscultation of the lungs reveals increased breath sounds without adventitious sounds. Some deaths may occur. Differential diagnosis is difficult. Differentiation from the other interstitial pneumonias depends more on history of exposure to the causative agents (e.g., lush pastures, moldy sweet potatoes, *P. frutescens,* toxic gases, moldy hay). Differentiation from viral pneumonia (such as that caused by RSV) and *D. viviparus* reinfection syndrome requires necropsy and demonstration of larvae. Ascarid larvae have characteristic lateral alae in histologic sections. Patent *D. viviparus* infection can be differentiated by Baermann examination of the feces. In fatal cases the lung lobes are firm and mottled blue, red, and gray. The cut surface oozes thin yellow exudate. There is emphysema in the dorsal diaphragmatic lobes and subpleural hemorrhage with neutrophil infiltration and necrosis of bronchiolar and alveolar epithelium. In chronic cases the cellular infiltrate is lymphocytic, bronchiolar epithelium proliferates, and peribronchial fibrosis is present. Recommended treatments include corticosteroids (dexamethasone, 0.04 mg/kg IM or IV, or prednisolone 1 mg/kg IM or IV daily) and antibiotics to control secondary bacterial infection.[30] Clinical signs

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resolved after treatment with oxfendazole in one outbreak of suspected *A. suum* migration.[31] Cattle should not be exposed to areas heavily contaminated by swine.

Lungworms of Sheep and Goats

Three species of lungworms are of primary importance in sheep and goats: *D. filaria* and the two metastrongylid nematodes, *M. capillaris* and *P. rufescens*. Other genera of metastrongylid lungworms of minor pathogenic importance in sheep and goats include *Cystocaulus, Spiculocaulus,* and *Neostrongylus*. These parasites are rare or absent in North America.[32]

DICTYOCAULUS FILARIA. *D. filaria* has a life cycle essentially identical to that of *D. viviparus;* the time from ingestion to the appearance of larvae in the feces is about 4 weeks. Mainly young animals are affected, but disease can also occur in adults. Dyspnea, tachypnea and coughing, and loss of condition occur in clinical cases.[32,33] Differential diagnosis includes the progressive viral pneumonias. Diagnosis is made by finding larvae in fresh feces by the Baermann test.[5] Samples should be tested soon after collection because larval recovery is significantly reduced in stored samples.[6] Larvae of *D. filaria* are similar in size and appearance to those of *D. viviparus* but also have a distinctive knob on the anterior end. The pathogenesis is similar to that of *D. viviparus* (see earlier discussion). The adults are found largely in the dorsal-caudal regions of the diaphragmatic lobes. Bronchitis and peribronchitis, along with cone-shaped areas of pneumonia and atelectasis, and emphysema are present. Secondary bacterial infections may also occur.[32,33] Levamisole (8 mg/kg), fenbendazole (5 to 10 mg/kg), ivermectin (0.2 mg/kg PO),[33] and moxidectin (0.2 mg/kg, PO or SC)[32-36] can be used for treatment. When outbreaks occur, all animals should be treated and moved to fresh pasture when possible. Clinical *D. filaria* infections seem to occur most frequently in areas with warm climates. In temperate areas the parasite overwinters either as arrested larvae in ewes or as larvae on pasture.[32]

MUELLERIUS CAPILLARIS. *M. capillaris* is probably the most common of the lungworms of sheep and goats. Infection is more pathogenic in goats than in sheep. Surveys in Maryland and Georgia detected the parasite in 64% and 68% of goats, respectively.[37,38] The life cycle is indirect. First-stage larvae are coughed up, swallowed, and passed in the feces. These larvae are relatively resistant and may survive for several months in the environment. After penetration of an appropriate molluscan intermediate host, the infective third stage develops in a minimum of about 12 days, is ingested with the snail, and passes to the mesenteric lymph nodes. The fourth-stage larva proceeds to the lungs, where adults develop in the alveoli. The prepatent period of *M. capillaris* infection is about 6 weeks.[39] Although many infections are subclinical, clinical disease may develop. Goats appear to be more likely than sheep to develop unthriftiness, coughing, and dyspnea. Infection may also predispose to secondary bacterial infection.[33,40] The difference in clinical signs between sheep and goats probably results from a difference in the pathogenesis of infection. The adult worms live in the pulmonary parenchyma, particularly the subpleural tissue. In sheep they produce grayish nodules typically 2 to 3 mm in diameter. On palpation at necropsy, these nodules have been described as feeling like "lead shot."[39] Each nodule contains a worm and necrotic leukocytes and pulmonary tissue surrounded by a connective tissue wall and giant cells.[32] They may calcify or become secondarily infected with bacteria. Reports of lesions in goats indicate that *M. capillaris* causes an interstitial pneumonia. The lungs are resilient and firm, fail to collapse, and have tan, yellow, or gray patches located especially in the dorsal diaphragmatic lobes. The histologic lesion in goats is a diffuse thickening of alveolar septa, with a mononuclear cell infiltrate and alveolar epithelial hyperplasia that extends far beyond the area immediately around the parasite. The local reaction around the worm is quite variable and does not appear to produce the nodules seen in sheep.[40] Diagnosis is made by Baermann examination of the feces. The larvae are smaller than those of *D. filaria* and have a kink at the end of the tail with a characteristic subterminal accessory spine.[5]

Several anthelmintics have been used in the treatment of *M. capillaris* infections. Moxidectin (0.2 mg/kg in oral or injectable formulation) is effective in treating sheep infected with M. capillaris and other small lungworms *(Cystocaulus ocreatus, Neostrongylus linearis,* and *P. rufescens)* and may be equally effective in goats.[41] Although larvae may initially disappear in the feces after treatment, they often reappear in fecal samples again after 1 to 2 months, either because anthelmintics are ineffective against immature worms and/or because of resumption of development by inhibited larvae. Treatments that appear to eliminate adult parasites in goats include fenbendazole (15 to 30 mg/kg),[39,40,42-44] albendazole (10 mg/kg),[44] oxfendazole (7.5 to 10 mg/kg),[45] and ivermectin (0.3 mg/kg).[42,46] *M. capillaris* is largely resistant to levamisole.[33] Better control of immature or inhibited larvae with fenbendazole was achieved by administering the drug (1.25 to 5 mg/kg) for 7 to 14 days, although a regimen of 1 week on/1 week off/1 week on appeared to provide the most effective treatment. Albendazole (1 mg/kg PO daily) for 7 to 14 days was also effective.[44] Possible teratogenic effects of extended benzimidazole treatment in goats have not been thoroughly investigated, and albendazole should be used cautiously in the first 35 days of pregnancy.[42] Administration of ivermectin (0.3 mg/kg) or fenbendazole (15 mg/kg) two or three times at 35-day intervals has also been suggested for treatment.[33] Control methods include avoiding wet pastures and treating animals before the start of the grazing season to reduce infection levels in the intermediate host.[33]

PROTOSTRONGYLUS RUFESCENS. *P. rufescens* also uses molluscan intermediate hosts, and adults develop in the small bronchioles of sheep and goats.[39] Most infections are probably subclinical or produce only mild signs of chronic bronchitis or bronchopneumonia with nasal discharge and cough. Occasionally *P. rufescens* may produce severe or even fatal disease.[47] The diagnosis of *Protostrongylus* spp. infection is made by finding larvae in the feces via the Baermann technique. The larvae are similar to those of *Muellerius* except *Protostrongylus* larvae lack the subterminal accessory spine on the tail.[5] Fenbendazole, levamisole,[47] and moxidectin[41] can be used for treatment at the dosages used for *Dictyocaulus*. Other macrocyclic lactone products may also be effective but have not been tested. Control strategies are identical to those for *M. capillaris*. Few cases of infection have been reported in the United States, but nonspecific clinical signs, presence of subclinical carriers, and need for a special diagnostic technique may produce an underestimation of the prevalence of *P. rufescens* infection in sheep and goats.[47]

LARVAL TOXOCARIASIS. The dog ascaridoid, *Toxocara canis,* will infect and persist in the tissues of sheep and goats following the ingestion of infective eggs from pasture.[48-50] Although migration of the larvae through the lungs results in diffuse pulmonary inflammation, there do not seem to be any clinical pulmonary signs that have been noted accompanying the experimental infections.[51,52] Serologic examination of sheep through use of antibody detection tests shows the prevalence of infection increases with age, with overall prevalences being 50% or more in the older animals that were sampled in Wales and Brazil.[53,54]

Progressive Viral Pneumonias of Sheep and Goats

Jeanne Lofstedt

Chronic progressive pneumonias are diagnosed with some frequency in mature small ruminants. In sheep, ovine progressive pneumonia (OPP) and *Corynebacterium pseudotuberculosis*–induced mediastinal lymph node and lung abscesses are the chief causes of chronic progressive pneumonia. Chronic progressive pneumonia in goats has

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been associated with the pneumonic form of caseous lymphadenitis (CLA) and occasionally with caprine arthritis-encephalitis virus (CAEV)–induced lung lesions. Additional differential diagnoses that should be entertained in small ruminants exhibiting signs of chronic pneumonia include ovine pulmonary adenomatosis (OPA) in the case of sheep and chronic bacterial pneumonia, verminous pneumonia, mycotic pneumonia, tuberculosis, and pulmonary neoplasia in sheep and goats.

Ovine Progressive Pneumonia (Maedi-Visna)

Definition and Etiology

OPP and *maedi-visna* (MV) are North American and European names, respectively, for multisystemic diseases of adult sheep characterized by chronic, progressive, debilitating pneumonia; wasting; indurative mastitis; arthritis; and, occasionally, neurologic signs.[1-6] Synonyms are *Marsh progressive pneumonia, Montana sheep disease, zwoegerziekte, la bouhite,* and *Graaff-Reinet disease*.[2,4] The OPP virus (OPPV) and MV virus (MVV) are nononcogenic exogenous retroviruses that belong to the genus *Lentivirus,* which includes the human, simian, feline, and bovine immunodeficiency viruses, equine infectious anemia (EIA) virus, and CAEV.[4-6] These enveloped, single-stranded RNA viruses contain the enzyme RNA-dependent DNA polymerase or reverse transcriptase (RT). With this enzyme the viruses use cellular machinery to transcribe a segment of DNA from a template of single-stranded viral RNA; the DNA strand or provirus is then incorporated into the host genome. Close similarity of causal viruses, clinical signs, and lesions produced in tissues permits discussion of OPP and MV as a single disease entity.[3] Extensive mutation of the gene encoding for envelope glycoproteins occurs in all lentiviral infections; this allows the mutated virus to escape elimination by the host immune response. Antigenic variation in the MVV has been documented.[4] The ovine lentiviruses (OvLVs) are closely related to the CAEV of goats and cross-species transmission is possible through feeding of infected milk and colostrum.[5,8] These two viruses are now often referred to as *small ruminant lentiviruses* (SRLVs).[4,5]

Clinical Signs and Differential Diagnosis

The incubation period of OvLV infections is prolonged and most infections are subclinical.[4,5] Approximately 25% to 30% of infected sheep eventually exhibit clinical symptoms.[1] Clinical disease is usually not evident until at least 50% of a flock is seropositive.[1] Conditions in sheep attributed to infection with OvLV include progressive emaciation ("thin ewe syndrome"), progressive respiratory failure, indurative lymphocytic mastitis ("hard bag"), posterior paresis, and chronic nonsuppurative arthritis.[1,4,5]

In North America, progressive pneumonia and aseptic indurative mastitis are the most common clinical manifestations of OvLV infections.[3] Clinical signs of disease are usually first observed in 2- to 3-year-old sheep, but most affected animals are 4 or 5 years old before they exhibit signs.[3,7,8] Emaciation, despite a good appetite, is one of the earliest symptoms. Tachypnea and respiratory distress develop gradually and initially are evident only on exertion.[4-6] Flared nostrils, neck extension, and open-mouth breathing are seen in advanced cases. Thoracic auscultation may reveal increased breath sounds, but crackles and wheezes are typically absent.[6] Pyrexia and purulent nasal discharge are uncommon and, if present, usually indicate concurrent secondary bacterial pneumonia.[5] Wool loss may be seen in advanced cases.[4] Affected ewes may give birth to small, weak lambs.[5] Death from anoxia or secondary bacterial infection ensues within 6 to 12 months of first appearance of clinical signs. In some flocks the disease appears to persist virtually unrecognized, whereas in flocks kept under harsh environmental conditions, mortality rates are quite high.[4]

The neurologic form of OPP is accompanied by weight loss and neurologic signs such as hindlimb ataxia, stumbling, and proprioceptive deficits, which progress over a period of months to paralysis or occasionally quadriplegia[5,6] (see Chapter 35). This form of the disease is encountered sporadically in heavily infected flocks and may occur separately or concurrently in sheep with respiratory distress.[4,5] Indurative mastitis is often encountered in heavily infected flocks. The somatic cell count (SCC) in affected ewes is increased but the milk is grossly normal; a firm udder may be detected with careful palpation.[4] The main consequence is poor weight gains in lambs suckling affected ewes, particularly if there are twins or triplets.[4] Arthritis, primarily affecting the carpal joints, is a rare manifestation of OvLV infection.[4,5]

Chronic pneumonias of sheep that have to be differentiated from OPP include chronic bronchopneumonia caused by *Mannheimia (Pasteurella) haemolytica,* OPA, verminous pneumonia, and pulmonary and thoracic lymph node abscesses caused by *C. pseudotuberculosis.*[1,2] Thoracic radiographs, culture of tracheal wash material, and fecal examination by the Baermann technique are useful for antemortem differentiation. Gross and histopathologic evaluations of pulmonary tissues obtained at necropsy are helpful for diagnosing a flock problem.

Clinical Pathology and Diagnosis

Hematologic changes in sheep with OPP are nonspecific and may include lymphocytosis early in the course of disease and mild hypochromic anemia and hypergammaglobulinemia in advanced cases.[6,8] A presumptive diagnosis of OPP can be made on the basis of clinical signs of progressive weight loss and chronic pneumonia or, in rare cases, neurologic disease in adult sheep,[4,5] but the diagnosis is often overlooked if mildly affected sheep are culled for other reasons.[4] The majority of sheep infected with OvLV do not show obvious clinical signs and are essentially asymptomatic virus carriers serving as a reservoir of virus for other sheep in the flock.[4,5] For disease control purposes it is important to identify such animals as soon as possible after infection. Several tests, based on detection of antibodies or virus, have been used to identify subclinically infected sheep.

Serologic tests include the agar gel immunodiffusion (AGID) test, several ELISAs, and the Western blot assay.[4,6] The time period from infection to seroconversion typically ranges from 3 weeks to several months but can take up to a year.[4] Some infected sheep never seroconvert, whereas others with advanced disease become transiently seronegative.[5] The AGID test has been the preferred serologic test for many years. It has good specificity but has gradually been replaced by a variety of ELISAs.[4,5] ELISAs are more sensitive than the AGID test and are useful when large numbers of samples need to be screened.[4-6] The use of ELISAs to detect antibodies in milk offers the option of low-cost screening in milking sheep flocks.[4] The Western blot test is used on occasion to confirm ELISA results.[5]

Tests for virus include virus isolation in cell culture or viral genome detection by polymerase chain reaction (PCR).[5,9,10] These tests are usually reserved for select cases—for example, when infection is suspected in a seronegative animal or in young lambs that have received colostrum from seropositive ewes.[5] Milk or lung lavage samples are useful substrates for this purpose. Virus isolation, which is time-consuming and expensive, is accomplished by coculture of infected fresh or frozen tissue with indicator cell lines. In culture, retroviruses form characteristic multinucleated syncytia.[8] Viral antigens can be detected in these syncytia by use of immunofluorescent staining.[8] PCR testing is more cost-effective than virus isolation.[4,6]

Pathophysiology

OvLVs gain access to the body via ingestion of milk or colostrum or through inhalation of aerosolized infectious particles. Infection is then established in the monocyte or macrophage cell line and spreads via these infected cells to the lungs, lymph nodes, choroid plexus, spleen, bone marrow, mammary glands, and kidneys.[8] The virus is able to persist in the face of humoral and cellular immunity through (1) latent infection of host cells by DNA provirus, (2) long-term nonproductive infection of blood monocytes (virus replicates only on differentiation of monocytes into macrophages), and (3) virus mutation with emergence of new antigenic variants that are not neutralized by preexisting antibody.[8] Because of the interaction of the virus with the macrophage

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monocyte series, a progressive multisystem chronic inflammatory process is initiated, primarily, but not exclusively, in the lungs and mammary gland.[4] Variations in genetic susceptibility, virus genotype, and the immune response of individual sheep influence target organ involvement and disease progression.[4]

Epidemiology OPP and MV are present in many sheep-rearing countries but has not been diagnosed in Australia or New Zealand.[5] The seroprevalence of OPP in cull ewes in the United States has ranged widely and increases with advancing age.[2] With the exception of West Texas, with an infection rate of 0.5%, serologic surveys in cull ewes in other states have revealed infection rates of 30% to 67%. The low seroprevalence in Texas has been attributed to the hot dry climate and extensive grazing practices.[8] Limited studies in large mixed-breed flocks have provided evidence that some sheep breeds may be more resistant to infection than other breeds.[2] Additional research is required before a particular breed or line of sheep can be viewed as resistant to OvLV infection. The lung and mammary gland are believed to be the main sources of excreted virus.[2] Studies conducted in Europe and Iceland have shown that transmission from the ewe to her lambs commonly occurs through the ingestion of infected colostrum and milk.[2] In other studies, close confinement of diseased or seropositive sheep with healthy or seronegative sheep resulted in disease or seroconversion in the previously healthy or seronegative animals; these infections were presumed to have occurred via the respiratory route.[2] Concurrent OPA is believed to have a synergistic effect on disease transmission via the respiratory route.[4] OvLV transmission has been shown to occur through fecal contamination of drinking water.[2] Blood contaminated placentas, contaminated milking equipment, and poor biosecurity practices have also been implicated as playing a role in the spread of infection.[2,4] Transmission through the uterine wall, or via germ cells, can occur but is of minor importance compared with other routes.[2,4]

Necropsy Findings Lesions may develop in any or all of the following tissues of OPPV-infected sheep: lungs and regional lymph nodes, brain, joints, mammary glands, and blood vessels.[4] Changes are most obvious in the lungs, which do not collapse on opening of the thorax.[4,5,8] Vertical rib impressions may be seen on the exterior lung surface. Affected lungs are heavy and, after removal of any visible trachea, weigh more than 1 kg (normal lung weight is up to 500 g) and have a mottled to uniform pink-brown to gray-blue discoloration.[5] Secondary bacterial pneumonia may cause anterior-ventral pulmonary consolidation. Tracheobronchial and mediastinal lymph nodes are markedly enlarged (up to 10 times normal size), bulge on cut surfaces, and are homogeneous, gray-white throughout.[4,5] Histologic examination reveals a diffuse lymphoproliferative pneumonia characterized by prominent lymphoid follicle formation adjacent to bronchioles and small vessels; discrete nodules of lymphocytes, unrelated to vessels or airways, are also found in the lung parenchyma.[8] Lymphocytes, plasma cells, and macrophages infiltrate into interalveolar septa, and hyperplasia of alveolar epithelium and terminal bronchial smooth muscle may be seen.[4] In some flocks uncomplicated OPP is the norm. In other flocks it may occur as a mixed infection with lungworm, bacterial bronchopneumonia, or pulmonary adenomatosis, which may result in the OPP lesions being overlooked on routine necropsy.[4]

Treatment and Prevention OPP is not treatable. Antimicrobials can be used to control secondary bacterial pneumonia, but most sheep die within a year of first exhibiting clinical signs.[2,7] No effective vaccines are presently available for control of the disease.

OPPV is difficult to eradicate from a flock once infection has been established. Uninfected flocks should maintain strict biosecurity measures to avoid introduction of the disease. This may include not sharing rams, not mixing sheep with other flocks, and maintaining segregation at shows.[4] Breeding stock should be purchased from known OPP-free herds and quarantined and tested to ensure that they are seronegative before being introduced into the flock. Control methods that may be economically feasible for purebred flocks with a low seroprevalence rate include (1) a "test-and-cull" practice and (2) isolation of infected adults and artificial rearing of their offspring.[3] With the first method, all sheep are tested annually for antibody, and seropositive animals and their progeny younger than 1 year of age are culled or isolated from the negative flock; culling is preferred because of the risk of cross-contamination. New additions should be seronegative and originate from seronegative flocks. Annual testing should be performed until two consecutive negative test results are obtained to be reasonably confident that the flock is virus free. With the second approach, progeny are removed from their dams before they nurse and are fed cow's colostrum or colostrum from seronegative ewes and raised in isolation. The clean herd should be kept isolated from infected sheep and goats and from humans and equipment in contact with infected sheep. Herd additions and annual testing should be handled as described for method 1. In flocks with well-established infections and a high seroprevalence rate, control options are limited.[4] The test-and-cull procedure and removal of lambs are impractical under commercial conditions. Increasing the flock replacement rate by strict culling of suspect cases and not keeping ewes beyond 4 to 5 years of age will assist in keeping the flock seroprevalence down and in reducing the incidence of clinical disease.[4]

Ovine Pulmonary Adenocarcinoma

Definition and Etiology OPA, also known as jaagsiekte (South Africa), sheep pulmonary adenomatosis (United Kingdom), or pulmonary carcinoma (United States),[11] is a naturally occurring retrovirus-induced bronchioloalveolar carcinoma of sheep and, in rare cases, goats that has been associated etiologically with a betaretrovirus named jaagsiekte retrovirus (JSRV).[12,13] OvLVs and herpesviruses have been isolated from OPA tumors; however, they are not consistently present and do not induce OPA when inoculated experimentally.[14] One theory is that these viruses may act as cofactors in tumor induction. Defining the role of JSRV in OPA has been complicated by the presence of 15 to 20 endogenous jaagsiekte retroviruses (enJSRVs) that are stably integrated into the genomes of sheep and goats.[15,16] Recent research has indicated that exogenous JSRV is likely not of endogenous origin. There has been speculation that the endogenous viruses may modify the genome of exogenous JSRV, either by inducing the expression of an oncogene or by inactivating a tumor suppressor gene.[13] Sequence analyses of exogenous JSRV and enJSRV suggest that endogenous viruses do not directly contribute to the pathogenesis of OPA through large-scale recombination events, but small-scale recombination or complementation of gene function has not been definitively excluded.[15] There has been speculation that expression of enJSRV in the fetal or neonatal period may influence expression of OPA through induction of immunologic tolerance.[12,15]

Clinical Signs and Differential Diagnosis Symptoms normally appear in mature sheep between 2 and 4 years of age, although lambs as young as 3 months of age and sheep as old as 11 years have occasionally been diagnosed with OPA.[11] Signs include exercise intolerance, weight loss despite a good appetite, tachypnea, dyspnea, occasional cough, and high-pitched crackles on thoracic auscultation. A characteristic feature of OPA is the accumulation of abundant fluid in the respiratory tract that is frothy, clear, milky, or at times pink-tinged and may flow from the nostrils of affected sheep when the rear limbs are raised and the head is lowered ("wheelbarrow test").[11-13] Up to 400 mL of nasal secretions may be collected in a day, although 10 to 40 mL/day is more usual. Rectal temperature is usually normal unless secondary bacterial infection is present. Sheep with OPA typically succumb within a few weeks to months after first exhibiting clinical signs.

Chronic pneumonias of sheep that have to be differentiated from OPA include chronic bronchopneumonia caused by *M. haemolytica*, OPP, verminous pneumonia, and pulmonary and thoracic lymph node abscesses caused by *C. pseudotuberculosis*.[1,2] Thoracic radio-

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graphs, culture of tracheal wash material, and fecal examination by the Baermann technique are useful for antemortem differentiation. Gross and histopathologic evaluations of pulmonary tissues obtained at necropsy are helpful for diagnosing a flock problem.

Clinical Pathology and Diagnosis The only reported clinical pathologic abnormality in sheep with OPA is hypergammaglobulinemia. Advanced clinical cases in mature sheep can be presumptively diagnosed based on clinical signs of weight loss and respiratory distress accompanied by copious nasal secretions, but in many cases the disease is subclinical.[11,12] To date, sensitive and specific tests for identifying apparently healthy animals that may be infectious are lacking. The absence of JSRV-specific antibodies in infected sheep have precluded the use of serologic tests for diagnosing infection.[12,13] PCR tests, capable of demonstrating viral nucleic acids of endogenous JSRV tissues in OPA-infected animals, have been developed but have a high false-negative rate and are not useful for identifying individual animals for eradication purposes.[12] The most successful approach for early diagnosis of OPA is PCR testing of bronchoalveolar fluid collected from live animals, but this is impractical for widespread testing and saliva and nasal secretions of infected sheep often test negative for JRSV.[12]

Epidemiology OPA has been reported in sheep-rearing countries throughout the world but not in Australia, New Zealand, or the Falkland Islands.[12,13] Iceland is currently free of OPA as a consequence of implementing an aggressive slaughter policy in endemic areas in the 1950s.[12] The prevalence of OPA varies among countries in which the infection occurs; it is endemic in Scotland, Peru, and South Africa, where annual losses range from 2% to 10%. In contrast, OPA is infrequently diagnosed in the United States and Canada, where totals of 11 and 43 cases, respectively, have been reported.[13]

OPA has been reproduced experimentally by intratracheal inoculation of lung homogenates or pulmonary lavage fluids obtained from infected animals.[17] Lambs between birth and 5 weeks of age have been shown to be more susceptible to experimental infection than 10-week-old lambs.[17] This age-related susceptibility to OPA suggests that natural virus transmission occurs in the neonatal period.[12] Aerosol transmission and contamination of feed and water by respiratory secretions are likely methods of disease spread, particularly in confined sheep.

Necropsy Findings OPA lesions in the lungs are categorized as classical OPA or atypical OPA based on their appearance.[11,12] In classical OPA the lungs are heavy (two to three times normal weight) and exude clear fluid from the cut surface.[11-13] The trachea and bronchi often contain clear, foamy fluid. Large, firm, gray masses are commonly encountered in the cranioventral regions of one or both lungs. Smaller (1- to 2-cm) nodules are occasionally visualized in the caudodorsal lung regions. In atypical OPA the tumors consist of solitary or aggregated hard white nodules that are clearly demarcated from normal lung tissue and have a dry cut surface.[11,12]

Metastasis to regional lymph nodes occurs in approximately 10% of cases, resulting in pulmonary lymph node enlargement.[11,12,18] Metastases to cardiac and skeletal muscles are infrequently reported.[11,12,18] Secondary bacterial pneumonia caused by *M. haemolytica* may mask the lesions of OPA.[12]

OPA is classified by the World Health Organization (WHO) as a bronchioloalveolar carcinoma arising from alveolar type II pneumocytes or nonciliated bronchiolar cells.[18] Histologic lesions in the lungs consist of columnar or cuboidal cells arranged in an acinar or papillary pattern and are similar for classical or atypical OPA but with an exaggerated inflammatory response and fibrosis in the atypical form of the disease.[11]

Treatment, Prevention, and Prognosis There are no known treatments for this disease. Antibiotics may prolong the life of OPA-affected sheep through control of secondary bacterial pneumonia.[13]

There are no vaccines for OPA at this time.[12] Prompt culling of ewes suspected to be infected, as well as their offspring, has been employed to decrease disease prevalence in endemic flocks.[11,12] OPA was eradicated from Iceland by slaughtering all sheep in endemic areas.[11-13] Contaminated areas where infected sheep were held should be left vacant for 2 months.[12] OPA has reportedly been eliminated from two flocks by removing the lambs at birth, depriving them of maternal colostrum, and raising them in isolation or by using embryo transfer.[11,12] This approach is impractical for commercial flocks. Until reliable diagnostic tests for subclinically affected sheep are developed, control will remain problematic.

Caprine Arthritis-Encephalitis

CAE is a persistent lentiviral infection of goats with four possible clinical presentations: leukoencephalomyelitis in kids 2 to 6 months of age and chronic, hyperplastic polysynovitis, indurative mastitis, and interstitial pneumonia in mature goats.[19-21] Mild interstitial pneumonia, which is silent clinically, is a common postmortem finding in goat kids infected with CAEV.[22] Occasional kids with the leukoencephalomyelitis may have diffuse involvement of one or more lung lobes.[21] In one study, 60% of adult goats serologically positive for CAEV had lesions of severe chronic interstitial pneumonia at slaughter.[22] In addition, chronic interstitial pneumonia, accompanied by exercise intolerance and dyspnea, was described in dairy goats originating from herds that had clinical cases of arthritis and leukoencephalomyelitis.[23] The lung lesions in these goats resembled those of OPP and MV and were positive for CAEV.[23,24] However, CAEV has been recovered from the lungs of goats with advanced arthritis but without interstitial pneumonia. In addition, goats inoculated intratracheally with purified CAEV did not develop pulmonary lesions.[23] This may indicate that there is no causal relationship between CAEV and interstitial pneumonia in goats, or that an additional agent such as a helper virus is required for the lesions to develop.[21] The first signs of chronic progressive pneumonia associated with CAEV infection appear at times of stress such as kidding and include exercise intolerance, dyspnea, weight loss, and occasionally a cough.[21] Enlarged carpi may be present in some of the affected goats.[21] Radiographs in advanced cases demonstrate large areas of lung consolidation and sometimes bullous emphysema in the cranioventral or caudal lung lobes.[23] Histopathologic examination of lung biopsy samples may assist with an antemortem diagnosis.[21] Serologic testing is of no diagnostic value other than identifying the presence of CAE in the herd of origin. Lesions in the lungs at postmortem are as for sheep with the pneumonic form of OPP.[21] CAE is discussed in detail in Chapter 38.

Caseous Lymphadenitis

CLA, caused by *C. pseudotuberculosis* (previously known as *C. ovis*), is a chronic disease of sheep and goats characterized by the development of pyogranulomatous abscesses in lymph nodes and internal organs.[25-30] The disease affects small ruminants worldwide.[30] CLA most commonly presents as an external form characterized by abscesses in superficial lymph nodes.[28,30] The internal, or visceral, form of CLA manifests as internal abscesses in the mediastinal and mesenteric lymph nodes as well as internal organs, primarily the lungs, but also the liver, kidneys, and central nervous system.[30] Small ruminants with the visceral form of the disease rarely have concurrent abscessation of external lymph nodes.[29] Goats are more commonly afflicted with external abscesses, whereas the visceral form of CLA appears to be more common in sheep.[25] Visceral CLA may be asymptomatic but is typically associated with progressive weight loss.[25,29,30] Specific clinical signs that may implicate visceral CLA of the lungs and associated lymph nodes include exercise intolerance, tachypnea, dyspnea, and chronic cough. Because of the encapsulated nature of pulmonary abscesses and the lack of exudate in airways, pulmonary crackles are rarely auscultated.[29,30] Nonspecific laboratory findings in sheep and goats with CLA include leukocytosis,

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hyperfibrinogenemia, hyperproteinemia, and hypergammaglobulinemia; however, laboratory findings are frequently normal in animals with chronic abscesses.[27,28] A definitive diagnosis of visceral CLA with pulmonary involvement may be achieved by thoracic radiographic and ultrasonographic findings of abscesses in the lungs and mediastinal lymph nodes or by isolating *C. pseudotuberculosis* from a transtracheal aspirate (TTA).[25,29] Failure to isolate the organism from tracheal wash fluid, however, does not rule out CLA as the cause of pulmonary disease. Characteristic postmortem findings of the respiratory form of CLA are one or more thick-walled, laminated, encapsulated, caseopurulent abscesses in the bronchial lymph nodes, mediastinal lymph nodes, and/or lung parenchyma.[27] Serologic tests have been developed for the detection of asymptomatically affected animals or those with internal abscess. They include the synergistic hemolysis inhibition (SHI) test and several ELISAs.[27,28] Most serologic tests are not specific enough to justify their use in culling programs. However, an ELISA test developed in the Netherlands for disease eradication purposes has recently been improved to increase sensitivity (94%) and specificity (98%).[31] CLA is discussed in more detail in relation to the hemolymphatic system (see Chapter 37).

Other Pneumonias

Amelia R. Woolums[III]

Aspiration Pneumonia

Aspiration pneumonia is caused by inhalation of large amounts of foreign material, often liquids. The most common cause is careless drenching or passage of stomach tubes during administration of milk or liquid medication. It also occurs occasionally in pail-fed calves, animals with pharyngeal paresis, animals with necrotic laryngitis, lambs with nutritional myodegeneration, anesthetized animals, sheep that are dipped, cattle that have parturient paresis, and cattle that ingest crude oils or fuel oils. Meconium aspiration secondary to fetal distress has been recognized as a possible risk factor of neonatal calf mortality.[1]

If large quantities of fluid are aspirated, death may be almost instantaneous, but generally a gangrenous bronchopneumonia develops as a result of infection and the irritating properties of the inhaled material. Affected animals exhibit depression, tachypnea, dyspnea, coughing, and fever and may have putrid breath. Crackles, wheezes, and occasionally pleural friction rubs can be heard on auscultation.

A presumptive diagnosis is based on the history and clinical evidence of bronchopneumonia; definitive diagnosis can be confirmed by gross or histopathologic identification of feed, milk, or other aspirated material in airways. Differential diagnoses include acute bacterial bronchopneumonia and septicemia. Necropsy reveals consolidation of the anterior ventral areas of the lungs. Affected areas are severely hemorrhagic in acute cases and contain suppuration and liquefactive necrosis in subacute cases.

The prognosis is guarded in all cases of aspiration pneumonia, but some animals can be successfully treated. Antibiotics combined with antiinflammatory agents should be promptly administered, and long-term antimicrobial therapy (weeks) is required. Prevention of aspiration pneumonia centers on careful administration of medication and avoidance of other risk factors that may promote inhalation of foreign materials.

Mycotic Pneumonias

Fungal pneumonia is a rare occurrence in ruminants. The clinical presentation is typically one of poor response to antimicrobial therapy. Cases of fungal pneumonia with metritis or placentitis have been reported.[2,3] Diagnosis is confirmed by identification of fungal organisms with an inflammatory reaction in tracheal aspirate or bronchoalveolar lavage, or at postmortem, with fungal culture to confirm the identity of the agent. Little information is available regarding successful treatment of ruminants with fungal pneumonia. In other species such as horses, treatment requires weeks to months of therapy with antifungal agents such as ketoconazole or itraconazole; these drugs may be cost-prohibitive for many ruminant cases, and their disposition in the rumen has not been described. Therapy with oral potassium iodide is an inexpensive alternative that might be attempted for some cases, but the efficacy of this therapy has not been confirmed. Prognosis for fungal pneumonia in all species is guarded to poor, depending on the severity of disease and the feasibility of treatment. Given these restrictions, treatment of fungal pneumonia in ruminants is likely reserved for valuable individuals. More guidelines regarding treatment for fungal pneumonia are presented in the section on equine respiratory diseases.

Vena Caval Thrombosis and Metastatic Pneumonia

Definition and Etiology Metastatic or embolic pneumonia in cattle, also called *caudal vena caval thrombosis, pulmonary thromboembolism,* or *embolic pulmonary aneurysm,* is a distinct syndrome associated with multifocal abscessation of the lungs caused by septic thromboembolism of the pulmonary arterial system. The septic emboli arise from septic thrombi of the caudal vena cava (Fig. 31-77) or, less commonly, the cranial vena cava. Vena caval thrombi are, in turn, a sequela to various septic conditions such as jugular phlebitis, mastitis, metritis, foot rot, or, most often, liver abscesses secondary to rumenitis.[1] A variety of bacteria may be involved; those most frequently encountered include *Fusobacterium necrophorum, Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), staphylococci, streptococci, and *Escherichia coli.*

Clinical Signs Because of its association with rumenitis, this condition is most commonly seen in feedlot cattle, but any age, breed, sex, or class of cattle may be affected. The problem is unusual in cattle less than 1 year of age. Cattle with metastatic pneumonia usually exhibit respiratory disturbance or weight loss or, occasionally, thoracic pain. The clinical signs in affected cattle have been described.[2,3] The classic presentation includes tachycardia, tachypnea, dyspnea, coughing, heart murmurs and pale mucous membranes (caused by anemia), widespread wheezes, epistaxis, and hemoptysis. The duration of signs is quite variable, ranging from acute respiratory distress



FIG. 31-77 Postmortem photograph of thrombus in caudal vena cava, which leads to embolic pneumonia. *(Courtesy Feedlot Health Management Services, Okotoks, AB, Canada.)*

[III]Previous contributions by Steven E. Wikse are acknowledged.

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to a chronic history of weight loss and coughing for weeks to months. Other signs, which are more variable, include fever, thoracic pain on deep palpation of the sternum and intercostal spaces, hepatomegaly (indicated by the ability to palpate the caudal edge of the liver in the right paralumbar fossa), subcutaneous emphysema, froth at the muzzle, and melena caused by coughing up and swallowing blood. Nonspecific accompanying signs include depression, anorexia, ruminal stasis, scant feces, and decreased milk production. In chronic cases, cor pulmonale may lead to signs of right ventricular failure, such as jugular distention and brisket edema. The combination of respiratory signs with anemia, widespread wheezes, and especially hemoptysis is generally regarded as pathognomonic for this syndrome. Animals usually deteriorate rapidly once hemoptysis becomes evident, and death despite treatment is typical. Many patients die suddenly with an acute episode of severe intrapulmonary hemorrhage or hemoptysis after a variable course of respiratory disease. Some of these cases in which the respiratory signs were overlooked may account for the reports of sudden death attributed to vena caval thrombosis. Caudal vena caval thrombosis can also lead to hepatomegaly and extensive ascites, but most of these animals also have respiratory signs.[3] Sudden erosion of a large hepatic abscess into the caudal vena cava may also result in a massive embolic shower, with acute respiratory distress and death.

In patients with the pathognomonic signs (the majority of cases), other differential diagnoses are unlikely. However, many patients are examined before the onset of hemoptysis, and a few may die without exhibiting these signs.[3] Differential considerations in such cases, which usually manifest as acute dyspnea, should include anaphylaxis, various causes of ARDS, hypersensitivity pneumonitis, lungworms, and acute bronchopneumonia. Patients with right ventricular failure should be differentiated from those with pericarditis, lymphosarcoma, cardiomyopathy, and endocarditis.

Pathogenesis The pathogenesis of this disease begins with the development of rumenitis secondary to lactic acidosis caused by highly fermentable diets such as those used in feedlots, some dairies, and some growing rations. Bacteria such as *F. necrophorum* and *T. pyogenes* are then able to penetrate the damaged ruminal epithelium and are transported to the liver in the portal drainage system, where they are filtered out and result in abscesses. If an abscess is located next to the caudal vena cava (where the vessel is closely applied to the left border of the liver), a septic thrombus may form in the vena cava as a result of infiltration of its wall by the abscess (see Fig. 31-77). Septic emboli detach from the thrombus and reach the lungs through the pulmonary arterial system. Alternatives to this classic pathway are rare; they include the following: thrombosis of the cranial vena cava from primary lesions such as jugular phlebitis; thrombosis of the caudal vena cava from other subdiaphragmatic abscesses; right-sided endocarditis; and emboli arising from other septic foci, such as mastitis, metritis, and foot rot. Large emboli may block lobar or larger arteries, causing an acute crisis and death. More typically, smaller emboli lodge in arterioles, where they cause arterial thromboembolism, arteritis, endarteritis, and pulmonary abscesses (Color Plate 31-12). The widespread arterial embolism also results in pulmonary arterial hypertension. Arteritis and endarteritis weaken the vessel walls and, in combination with pulmonary hypertension, lead to the formation of aneurysms. In some cases, a perivascular abscess not only erodes an arterial wall to produce an aneurysm but simultaneously erodes a bronchial wall; when the aneurysm ruptures, the abscess cavity channels the blood into the bronchus, resulting in massive hemoptysis. In other cases, rupture of aneurysms results in large interstitial hematomas. Both processes result in anemia; when coughed-up blood is swallowed, melena may result. Coughing and wheezes are probably caused by blood clots in airways, peribronchial aneurysms and abscesses, and suppurative pneumonia. Pain results from dissecting aneurysms and hematomas.[2]

Epidemiology Metastatic pneumonia accounted for 1.3% of necropsy diagnoses in one large feedlot survey, with a rate varying between 1.6 and 7.3 cases per 100,000 head on feed. Cases occurred year round and during all stages of fattening, although 68% of cases occurred during the first 90 days on feed.[4] The case fatality rate is usually 100%.

Necropsy Almost all patients with significant hemoptysis have a thrombus in the posterior vena cava between the liver and the right atrium. There is usually an adjacent hepatic abscess, varying degrees of venous congestion of the liver, and hepatomegaly. The lungs are large, uncollapsed, and firm. Aneurysms may occur in either lung or both. Hematomas associated with ruptured aneurysms are frequently 3 to 10 cm in diameter.[4] Large blood clots may be found in the airways, aspirated blood in the alveoli, and swallowed clots in the rumen. Areas of suppurative pneumonia and multiple abscesses are present (see Color Plate 31-12).

Diagnosis The complete blood cell count (CBC) may reveal anemia and a neutrophilic leukocytosis with a regenerative left shift. Hyperglobulinemia is frequently present. Serum chemical analysis may reflect chronic passive congestion of the liver, with elevation of liver enzymes. Radiographs often reveal only an irregular increase in lung density. Small discrete densities (areas of embolic infarction and collapse); large, discrete, spherical opacities (hematomas); cavitating nodules, sometimes with gas-fluid interfaces (abscesses); bullae; and areas of consolidation may be observed in some cases.[2,3]

Treatment and Prevention The prognosis is grave, so treatment is rarely indicated, and salvage is the most feasible recommendation. In valuable individuals, antibiotics and supportive therapy may be attempted. Penicillin, oxytetracycline, or florfenicol may be effective; treatment should be administered for extended periods (weeks to months). Supportive therapy for cases with acute severe dyspnea includes furosemide (0.5 to 1 mg/kg IV or IM once or twice daily) and flunixin meglumine (1.1 to 2.2 mg/kg once or divided twice daily). One or two doses of corticosteroids (dexamethasone at 0.05 to 0.2 mg/kg IV or IM q24h) may be helpful in cases with severe respiratory distress.

On the basis of the assumption that rumenitis and liver abscesses are the first steps in the pathogenesis of most cases, measures to reduce the incidence of these problems are appropriate. Recommendations include slow adaptation of animals to high-energy rations and feeding of antibiotics to reduce the incidence of liver abscesses.

Bovine Tuberculosis

W. Ray Waters

Definition, Etiology, and Epidemiology Tuberculosis (TB) in animals and humans may result from exposure to bacilli within the *Mycobacterium tuberculosis* complex (i.e., *M. tuberculosis, M. bovis, M. africanum, M. pinnipedii, M. microti, M. caprae,* or *M. canetti*).[1] *M. bovis* is the species most often isolated from tuberculous cattle, and it is infectious to humans (zoonotic). Within the United States, bovine tuberculosis is nearly eradicated in cattle; however, sporadic cases are detected primarily because of ongoing importation of tuberculous cattle from Mexico, spillover from a wildlife reservoir host (i.e., white-tailed deer, *Odocoileus virginianus*) in the northeast region of the lower peninsula of Michigan, and transmission from captive cervids infected with *M. bovis.* From 1998 to 2011, there were 114 TB-affected herds within the United States (62% beef, 27.5% dairy, 1.5% mixed, and 9% captive cervids). In Great Britain, the prevalence of bovine TB has been steadily rising despite continuous compulsory testing, with 10% of cattle herds in England (22.7% in the South West region) under movement restriction and nearly 25,000 cattle slaughtered at a cost of £91 million.[2] This dramatic and steady rise in TB prevalence in Great Britain is most likely due to the failure of the tuberculin skin test and slaughter strategy and the presence of a wildlife reservoir (Eurasian badgers, *Meles meles*[2]). Wildlife

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reservoirs also hinder eradication efforts in New Zealand and Spain with continual spillover from brushtail possums *(Trichosurus vulpecula)* and wild boar *(Sus scrofa)*/red deer *(Cervus elaphus),* respectively. In Latin American and Caribbean countries, bovine TB is relatively common, with estimates of 70% of cattle being held in regions with *M. bovis* prevalence rates higher than 1%.[3] In underdeveloped regions of Africa and Asia, bovine TB is endemic and is causing significant economic losses for producers and public health concerns as a result of the close contact of humans and animals and the frequent consumption of raw milk. Bovine TB in African free-ranging species (e.g., African buffaloes *[Syncerus caffer]* and lions *[Panthera leo]*) threatens wildlife conservation efforts and ecotourism, thereby impacting the balance of entire ecosystems.[4] Tuberculosis in goats and sheep, primarily caused by *M. bovis* or *M. caprae,* is uncommon in the United States but may occur in other regions of the world (e.g., Spain, Italy, New Zealand, Ireland, United Kingdom, and Sudan and other African countries).[5,6]

In most countries with active control programs, affected cattle herds contain few infected animals; this suggests low rates of cattle-to-cattle transmission and a slowly progressive course of disease.[7] Transmission is generally by direct contact with TB-infected animals, as the organism may occur in exhaled droplets, saliva, feces, milk, urine, vaginal discharges, semen, or exudate from tuberculous lesions (e.g., lymph nodes with draining tracts that communicate to the exterior). Infection of the upper respiratory tract, pharyngeal area, and gastrointestinal tract may also result from ingestion of infected feeds.[8] Housing (e.g., milking parlors and cattle sheds) and crowding increase contact between naive animals and infected animals and enhance the spread of this disease. *M. bovis* is also transmitted by indirect contact through contaminated feed and water, feeding and watering equipment, cleaning equipment, or movements of personnel—anything that mechanically transfers the organism between locations. Movement of infected animals resulting from transfer of ownership, sharing of breeding animals, and fence-line contact with other herds is a common means of transferring the disease between herds and regions. Additionally, global trade agreements are increasingly being implemented to promote international trade of livestock, thereby significantly increasing risks for interregional spread and distribution of TB over great distances.

Primary control strategies for bovine TB include diagnosis via tuberculin skin test and/or interferon-gamma (IFN-γ) release assays, isolation of affected herds, subisolation of infected animals within affected herds (i.e., Bang method), slaughter of infected animals, slaughter surveillance, and movement/border testing policies.[9] In addition to these traditional methods, antibody-based tests have recently emerged for use in the detection of *M. tuberculosis*–infected elephants[10,11] and *M. bovis*–infected captive cervids.[12] In addition, molecular-based tools such as mycobacterial interspersed repetitive-unit-variable number tandem repeat (MIRU-VNTR), spoligotyping, and restriction fragment length polymorphism (RFLP) analysis of mycobacterial DNA are used to characterize mycobacterial isolates for epidemiologic investigations to determine potential links between new cases and prior outbreaks as well as the likely origin of infection. Most recently, high throughput whole genome sequencing and rapid sequence analysis tools have been developed for a more thorough comparison of relatedness between *M. tuberculosis* complex isolates obtained from livestock, wildlife, humans, and zoo species.

Clinical Signs and Diagnosis

In most animals, the disease is slowly progressive; however, bovine TB occasionally follows a more rapid, fulminating course with early dissemination. Most animals do not show clinical signs of *M. bovis* infection until late in the course of the disease. Clinical signs, when present, are often nonspecific (e.g., weight loss, inappetence, and a low-grade fluctuating fever) and vary according to organs involved. Respiratory signs are generally mild and may include a soft, moist cough more noticeable during cold weather and after exercise. In advanced stages, animals may exhibit obvious dyspnea, emaciation, and respiratory distress. Enlarged lymph nodes may rupture and drain. Enlarged mediastinal lymph nodes may cause bloat. Enlarged retropharyngeal lymph nodes, a frequent sequela in cervids, may cause dysphagia, stridor, and salivation. Enlarged mesenteric lymph nodes may cause intestinal obstructions. Lesions occur less frequently in peripheral lymph nodes, the reproductive tract (causing infertility, abortion, metritis, and vaginitis), and the mammary gland. Particularly with chronic cases, tuberculous mastitis may occur with the potential for transfer of *M. bovis* to humans, calves, cats, or other animals through ingestion of nonpasteurized milk or processed dairy products.

The tuberculin skin test remains the primary tool for the diagnosis of bovine TB. Specific applications of the tuberculin skin test, however, vary according to regional and country directives.[9] Primary screening tests may use a single injection of *M. bovis* purified protein derivative (PPD) applied either to the skin fold at the base of the tail (e.g., caudal fold test used in New Zealand, United States, Canada, and Mexico) or skin of the mid-cervical region (e.g., many European Union member states). Alternatively, a dual injection of *M. avium* and *M. bovis* PPD may be applied to separate mid-cervical sites as the primary screening test (Great Britain, Ireland, and Portugal) or as a confirmatory test (United States, Canada). An IFN-γ release assay (i.e., Bovigam, Prionics, Schlieren, Switzerland) is also used as a confirmatory test in many countries.[9,13] Test specificity varies regionally, most likely because of application techniques (including differences in PPD usage), environmental factors, and co-infection (e.g., parasite burden[14]). In particular, it is widely recognized that exposure of cattle to various nontuberculous *Mycobacterium* spp. may confound interpretation of PPD-based tests. The use of dual injection of *M. avium* and *M. bovis* PPDs at separate sites was developed to address this issue, and comparative tests improve test specificity with only a slight loss in test sensitivity when compared with single injection tests (e.g., caudal fold test). Recently, *M. tuberculosis* complex–specific antigens such as ESAT-6, CFP10, and Rv-3615c have been developed for use with IFN-γ release assays and skin test.[15] These antigens are generally not produced by nontuberculous *Mycobacterium* spp., including *M. avium* subsp. *paratuberculosis;*[16] thus, they afford greater specificity with only minimal loss in test sensitivity.

Potential pathogens for differential diagnosis consideration are nontuberculous *Mycobacterium* spp., *Nocardia* spp., *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Corynebacterium pseudotuberculosis* (caseous lymphadenitis in goats/sheep), and mycotic infections. In particular, nontuberculous mycobacteria (e.g., *M. avium* subsp. *paratuberculosis, M. avium* subsp. *avium, M. kansasii,* and many others) are common isolates within tissues obtained from domestic livestock and wildlife. Johne's disease, caused by *M. avium* subsp. *paratuberculosis,* is common in domestic livestock and causes a mild to severe granulomatous enteritis. Other nontuberculous mycobacteria occasionally cause clinical disease that results in granulomatous lesions in lymph nodes, lungs, and visceral organs.

Pathophysiology and Necropsy Findings

Although often viewed as a pulmonary disease in humans, TB is primarily a disease of the lymphatic system. With ruminants, tuberculous lesions are most commonly detected within the pulmonary and cranial lymph nodes as well as the lungs. A survey of naturally infected cattle revealed that 67% of tuberculous lesions are detected within the lungs and pulmonary lymph nodes, 39% in cranial lymph nodes, and 8% in mesenteric lymph nodes.[17] Lesions are most commonly detected in the medial retropharyngeal lymph nodes of infected white-tailed deer[18]; lungs, pulmonary lymph nodes, and pleura are other common sites of lesions in deer. In pigs (i.e., Eurasian wild boar and free-ranging domestic black pigs), tuberculous lesions are most commonly detected in the cranial lymph nodes, and dissemination is common.[19,20] Infectious doses affect disease severity and progression: animals exposed to high doses develop an earlier onset of lesions with greater severity than animals exposed to lower doses. The infectious dose of *M. bovis* for ruminants is quite low. Experimentally, intratracheal administration of one colony-forming unit may cause disease.[21]

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Mycobacterium tuberculosis complex bacilli (including *M. bovis*) infect cells primarily of monocyte/macrophage lineage and may also be associated with type II alveolar epithelial cells, dendritic cells, neutrophils, and a few others. The pathognomonic lesion of *M. bovis* infection is the granuloma. Tuberculous granulomas form in response to pathogen virulence factors and chronic antigen stimulation (caused by persistent infection). Granulomatous inflammation is thought to limit the spread of tuberculous bacilli within the host by walling off the infection. The combination of the initial site of infection and the regional (i.e., draining this site) lymph node constitutes the primary complex commonly referred to as the *Ghon complex* with pulmonary *M. tuberculosis* infection of humans. Dissemination from the primary complex occurs via both lymphatic and hematogenous spread. Particularly in cases of prolonged or severe disseminated disease, determination of the primary complex may be impossible, confusing speculation on the initial route of infection. When infection occurs across mucous membranes, such as the oropharynx or intestine, the initial lesion in the mucous membrane may not be visible, whereas lymph node lesions are generally obvious.[22] From the initial site of entry, the organism invades local lymph nodes, where it causes necrosis surrounded by granulomatous inflammation consisting of primarily mononuclear cells. Localized lesions stimulate development of a fibrous capsule that varies in severity depending on the rate of development and chronicity of infection. Postprimary dissemination may occur, leading to spread of the organism and resulting in discrete nodular lesions in various lymph nodes and organs. Diffuse miliary tuberculosis may occur in severe cases. Latency, although a common sequela with *M. tuberculosis* infection of humans, is typically not considered a common stage of disease with *M. bovis* infection of cattle; however, *M. bovis* may be isolated from tissues without visible gross lesions, indicating a potential for "latent" infection.

Postmortem diagnosis is based on (1) gross and microscopic evaluation for tuberculous lesions, (2) detection of the organism by mycobacterial culture of tissues with follow-up confirmation/characterization using molecular techniques, and (3) detection of *M. tuberculosis* complex–specific DNA by PCR on histologic sections. Often, multiple lesions are detectable on examination, but it is possible that infected cattle will display no grossly visible lesions or only a single visible lesion. Macroscopic lesions appear as firm encapsulated nodules and vary in size from barely visible to more than 100 mm in diameter. Lesions may contain thick, white to yellow/orange, creamy to caseous purulent material. Lesions may be calcified. Lymph nodes, organs, and pleural/peritoneal serosa may be riddled with small miliary tubercles, and in the lungs these lesions may coalesce into a suppurative bronchopneumonia. Granulomas, along the pleural serosa (i.e., pearl disease), often appear glossy. Chronic lesions are characterized by a discreet, thickened fibrous to calcified capsule, often containing thick caseous material. Lesion cavitation caused by *M. bovis* infection in cattle is rare. Microscopically, lesions in lymph nodes or organs are granulomatous, generally consisting of caseous necrosis surrounded by infiltrates of epithelioid macrophages, Langhans-type multinucleated giant cells, and lymphocytes. Lesions with necrotic cores may contain dystrophic calcification. Detection of acid-fast bacilli within granulomatous lesions in tissue sections provides a preliminary diagnosis of mycobacterial infection that must be confirmed by mycobacterial culture and PCR. Acid-fast bacilli are often few in number and most commonly detected within the caseum of the necrotic core. Resolving lesions are rare. Lesion development can be divided into four different stages primarily based on the level of necrosis, fibrous encapsulation, and mineralization: stage 1 (no necrosis), stage 2 (minimal central necrosis, thin connective tissue capsule), stage 3 (central caseous necrosis with complete fibrous encapsulation), and stage 4 (extensive multicentric caseous necrosis with mineralization).[23] Differentiation between the thickness of the fibrous capsule and the histopathologic stage of development may assist in determining the chronicity of the infection.

Mycobacterial culture is the gold standard for TB diagnosis. *M. bovis* grows slowly, and cultures are incubated for 8 weeks; growth usually becomes visible within 3 to 6 weeks. The identity of the organism in cultures is confirmed with biochemical tests, colony morphology, and *M. tuberculosis* complex–specific PCR.

Treatment, Prevention, and Control Bovine TB is rarely, if ever, treated in domestic livestock. Particularly in developed countries, affected animals are slaughtered to limit potential transmission to other animals and to limit the duration and/or severity of regulatory restrictions. Antimycobacterial therapy may be indicated for rare or endangered animals or for those considered valuable as zoologic exhibits.[10] Antituberculous first-line chemotherapies include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. These are agents with the greatest activity and the least undesirable side effects. Second-line agents include capreomycin, ethionamide, cycloserine, and thiacetazone. The fluoroquinolones (moxifloxacin, ciprofloxacin, levofloxacin, and enrofloxacin), although not considered as first-line agents, have significant bactericidal activity against *M. tuberculosis* complex species. Outside of these rare cases, treatment for TB in animals is generally not considered practical on a cost basis.

Many countries have official bovine TB eradication and/or control programs including uniform methods and rules for application. Prevention and control efforts are designed to identify affected herds and remove infected animals or depopulate the entire herd (stamping out). These efforts are generally achieved via routine slaughter surveillance to identify affected herds, targeted testing schemes to remove TB test–positive animals (reactors), movement restriction of affected herds, thorough epidemiologic investigations of reported cases to determine risks for other impacted herds, and depopulation of affected herds. Additionally, movement testing with certification of a negative TB test(s) may be required prior to entry of animals into certain countries or regions, particularly with animals entering from bovine TB–affected regions. In certain instances, entry of animals from known TB-affected regions may not be allowed. Specific regulations and rules concerning bovine TB control are provided within specific country and regional directives.[2,24,25] Because of limitations in the sensitivity of antemortem diagnostic tests for tuberculosis, depopulation of infected herds is thought to be the most effective means to ensure eradication of the disease from the target population. Surveillance and control of *M. bovis* infection in wildlife reservoirs, as well as mitigation efforts to limit spread from wildlife to livestock, is also critical for bovine TB control.

In instances where herds are depopulated and the owner intends to repopulate in the future, it is important to remove or thoroughly clean and disinfect facilities and equipment potentially exposed to the organism. The ability of *M. bovis* to survive for an extended period in the environment, and the ineffectiveness of disinfection of organic materials, necessitates that pastures and fields to be used in repopulation schemes be left vacant for a period of time prior to use. Instances of infection that are thought to originate from wildlife sources may precipitate changes in facilities, management and feeding practices, or wildlife control to prevent reinfection. Current experience with endemic *M. bovis* infections in wildlife in numerous countries has demonstrated that eradication of TB in free-ranging wildlife is difficult and is a long-term proposition. Vaccines are rarely used for the control of bovine TB in regions with official control programs, primarily because of the potential for interference with traditional antemortem testing strategies using PPD as antigen (i.e., tuberculin skin test and IFN-γ release assays).[26] Bacillus Calmette-Guérin (BCG) is an attenuated *M. bovis* developed by Albert Calmette and Camille Guérin circa 1911 at the Pasteur Institute in Lille, France. Field efficacy trials performed in the early twentieth century demonstrated the partial effectiveness of BCG for the control of bovine TB.[26] Recent experimental trials with cattle have demonstrated that (1) subunit vaccines may boost immunity elicited by BCG in cattle, (2) BCG is particularly protective when administered to neonates, and (3) differentiation of infected from vaccinated animals is feasible in cattle through use of in vitro or in vivo methods.[15,26] With regard to wildlife reservoirs, the efficacy of BCG delivered orally has been

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demonstrated for brushtail possums (in field trials) as well as Eurasian badgers, wild boar, and white-tailed deer (each in experimental challenge studies). The most practical route of vaccine delivery to wildlife reservoirs of *M. bovis* is via oral-delivered baits, although a parenteral route is being deployed for badgers in England. Additional research is needed in the areas of diagnostic testing, environmental sampling, vaccine development, and management practices that may decrease the risk of disease spillover from wildlife reservoirs to cattle.

Diseases of the Thoracic Wall and Cavity

Amelia R. Woolums[¶]

Pleuritis and Pleural Effusions

Definition and Etiology Acute, primary pleuritis is rare in ruminants. It is almost always a secondary condition. The most common primary cause is most likely bronchopneumonia caused by *Mannheimia haemolytica* or *Histophilus somni*. Other possible causes of pleuritis and pleural effusions include traumatic reticulopericarditis, extension from other causes of peritonitis, tuberculosis, liver abscesses, tumors (especially lymphosarcoma), external trauma, fractured ribs, gunshot, perforating injuries, various septicemic conditions, acorn toxicity and other causes of uremia, uroperitoneum, right ventricular failure, hypoproteinemia, ruptured thoracic duct, and hemothorax from trauma or hemangiosarcoma.

Clinical Signs The signs depend on, and may be overshadowed by, the primary disease process. Pleuritis is a painful, septic process, whereas the signs associated with nonseptic effusions depend largely on the cause. Signs referable to pleuritis itself include anorexia, depression, fever, weight loss, decreased milk production, progressive dyspnea, and a characteristic stance and respiratory pattern, with the head and neck extended, elbows abducted, restricted excursion of the thorax, abdominal breathing, tachypnea, and a grunting or groaning with respiration. The animal may be reluctant to move. If a cough is present, it is often soft and suppressed because of pain. Jugular distention and pulsation may result from interference with venous return. Auscultation may reveal creaking or rubbing noises in dry pleuritis or a cranioventral masking of sounds caused by effusion. Percussion may reveal dullness ventral to the fluid line and may elicit pain. Differential diagnoses for dyspnea with abnormally quiet lung fields may include acute interstitial pneumonia, pneumothorax, and space-occupying lesions such as large abscesses, tumors, and diaphragmatic hernia. Once pleuritis or pleural effusion has been identified, the main differential diagnostic consideration is the determination of the underlying cause, as listed previously.

Diagnosis A CBC helps to separate infectious from noninfectious causes and distinguish relatively acute conditions (with significant left shifts) from those of a more chronic nature (with mature neutrophilia, hyperglobulinemia, and nonregenerative anemia of chronic disease). Serum chemical determinations and urinalysis identify hypoproteinemia and azotemia. A thoracocentesis should be performed and submitted to cytologic and cultural examination for bacteria, mycoplasma, and chlamydia. Nonseptic transudates indicate conditions such as neoplasia, heart failure, hypoproteinemia, and uremia. Septic exudates high in both cells and protein occur with pleuropneumonia, hardware, peritonitis, abscesses, penetrating trauma, and septicemias. A transtracheal wash is usually indicated because of the common association with pneumonia. Pericardiocentesis, abdominocentesis, and radiographs may indicate the primary source of an infection. Tuberculosis tests, leukemia virus titers, electrocardiography, echocardiographic examinations, ultrasonographic examination of the liver, and exploratory laparotomy may also help to detect other primary processes.

Treatment The primary problem should be treated. Effusions should be drained, either periodically or continuously through a Heimlich valve or a suction device fashioned from a syringe with the plunger transfixed with a pin. Effective drainage can be difficult in ruminants because of their propensity for fibrin formation and loculation of the fluid. Intermittent drainage is as effective as continuous drainage and simpler to maintain. Attempts at lavage have rarely been successful because of adhesions. Appropriate antibiotics are indicated in the presence of sepsis. NSAIDs (aspirin, 100 mg/kg PO twice daily; flunixin meglumine, 1.1 to 2.2 mg/kg IV or divided twice daily) are useful to relieve pain, ease respiration, and improve appetite. Rest and good nursing care are essential. The prognosis obviously depends on the extent and duration of the disease.

Pneumothorax

Pneumothorax is not common in ruminants. Most cases result from the rupture of an emphysematous bulla associated with pneumonia, straining, or coughing or from puncture of the lung by a fractured rib. The bullae that occur in pneumonia induced by bovine respiratory syncytial virus (BRSV) are a common source. Trauma to the pharynx or larynx can also lead to pneumothorax, presumably caused by air traveling from the cranial cervical regions through soft tissues and into the thoracic cavity. Penetration from the exterior is possible but less common. A case has been described in a postparturient cow with no other underlying cause found.[1] A retrospective study of 30 cattle with pneumothorax presented to a referral hospital found that 18 of the cases (60%) were associated with bronchopneumonia, 7 cases were associated with interstitial pneumonia, 3 cases were associated with laryngeal or pharyngeal trauma, and 2 cases were associated with neonatal respiratory distress.[2] Of interest was the finding that 13 of the 18 cases with bronchopneumonia were chronic, based on history and diagnostic findings; an association between pneumothorax and chronic bronchopneumonia had not been previously reported. The rate of survival for cattle with pneumonia and pneumothorax was lower than for cattle with pneumonia but no pneumothorax, with an overall survival rate of 60% for cattle with pneumothorax.

Clinical signs of pneumothorax include inspiratory dyspnea, sometimes severe, with open-mouth breathing sometimes present.[1] One side of the thorax may be relatively collapsed and immobile, with a compensatory increase in the size and excursion of the other side; however, this latter finding is often subtle and difficult to appreciate. Ruminants have a complete mediastinum; thus, when pneumothorax occurs it is usually unilateral, and the animal is able to ventilate adequately using the opposite lung. Unless an infectious disease is responsible, affected animals are often alert and anxious. They may attempt to stand with the forefeet elevated. There is a pronounced abdominal component to the respirations. Cyanosis may occur, and airflow may be markedly reduced in severe cases. On auscultation there is an obvious disparity between the two sides; bronchovesicular sounds will be diminished dorsally on the affected side or may be entirely absent. Those lung sounds that are audible have a harsh, high-pitched, large airway character similar to those of a consolidated lung, especially over the carina; these sounds seem to be distant, as if the animal were breathing in a barrel. The point of maximum intensity of the heart may be displaced, and tachycardia is often present. Percussion may reveal an abnormal resonance when compared with that of the normal side, and simultaneous auscultation and percussion may produce a "ping" over the thorax. Subcutaneous emphysema is a fairly common feature, and pleuritis is often a sequela. Differential diagnoses of the inciting cause should include the various causes of ARDS, bronchopneumonia, viral pneumonias (especially BRSV), pleural effusions, diaphragmatic hernia, other space-occupying lesions (large abscesses, tumors), and clostridial

[¶]Previous contributions by John A. Smith are acknowledged.

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infections. Pneumothorax can be diagnosed with radiographs, transthoracic ultrasound, or thoracocentesis; radiographs and ultrasound will also be useful to characterize the extent of any underlying lung disease. Other diagnostic tests to characterize underlying lung disease as described for infectious bronchopneumonia or interstitial pneumonia are appropriate.

If the affected animal shows signs of significant distress, the air in the pleural space should be evacuated. Evacuation can be accomplished by aseptically placing a teat cannula into the thoracic cavity at the dorsal aspect of the thorax at the tenth intercostal space and withdrawing air by use of an extension set, three-way stopcock, and syringe. In some cases this method can be successfully used to intermittently remove air; in other cases, continuous removal with a pleural evacuation device (Pleur-evac A-8000, Teleflex, Research Triangle Park, N.C.) has been more effective.[3] If continuous evacuation is attempted, the animal must be adequately restrained; this is likely to be possible only with hospitalized animals. Other treatment includes therapy appropriate for underlying acute or chronic pneumonia, as described previously for infectious bronchopneumonia or interstitial pneumonia. External wounds allowing air to enter the thorax should be closed.

Diaphragmatic Hernia

Definition and Etiology Diaphragmatic hernias are uncommon in ruminants. Hernias may be congenital, but most appear to be acquired, including those occurring in neonates. A congenital weakness in the diaphragm may predispose to some cases. Causes include difficult parturition, external trauma, and, by far the most common cause, traumatic reticuloperitonitis (TRP).

Clinical Signs and Differential Diagnosis Affected animals can be asymptomatic for a prolonged period.[4] Most affected cattle are in late gestation or have calved recently. The history may include decreased milk production, weight loss, capricious appetite, difficulty in swallowing or regurgitation, previous signs of abdominal pain (possibly associated with acute TRP), vomiting, and abnormal posturing of the head and neck on swallowing or regurgitation. Respiratory signs are actually fairly uncommon, with the exception of large congenital hernias, in which there is obvious severe dyspnea and abdominal respiration from birth. Occasional cough and dyspnea have been reported, and auscultation may reveal asymmetric sounds, with lack of lung or heart sounds in the affected area, or splashing sounds similar to those heard with pericarditis. Gastrointestinal signs are actually more common and include bloat, signs consistent with TRP, difficulty or pain on passage of a stomach tube, diarrhea, constipation, and ruminal hypomotility. Some cows may retch or vomit on regurgitation. Pain is evidenced by odontoprisis or grunting on regurgitation. The primary differential diagnoses are TRP, pericarditis, esophageal stricture, esophageal foreign body (choke), neoplasia, and abscessation.

Diagnosis Radiographs can be used to confirm the diagnosis. The normal outline of the diaphragm and heart may be obscured, and the honeycombs or foreign objects in the reticulum may be seen in the thorax[4] because this organ is most commonly involved. Oral barium may also aid in the radiographic interpretation, particularly in early small hernias that will be missed on plain films. Pleuritis and other masses such as tumors and abscesses can also mimic hernias on plain films.[4] If TRP is involved, the CBC, pleural effusions, and abdominocentesis may reflect the septic process. In cases not associated with TRP, the pleural effusion may be hemorrhagic in acute cases and normal in chronic cases.

Necropsy The hernial ring is usually located at the junction of the musculotendinous portion of the diaphragm, about 12 cm ventral to the vena cava and slightly lateral to the midline. The ring is usually round to oval, with a diameter of 7 to 20 cm. The reticulum is usually herniated, most frequently to the right side of the chest. The liver, spleen, rumen, omasum, abomasum, intestine, and omentum may also be involved. Extensive adhesions usually develop between the herniated organs and the thoracic organs, and evidence of hardware can often be found.

Treatment and Prognosis Treatment is surgical. A two-stage approach is usually used. First, a standing left flank laparotomy and rumenotomy are performed; the defect is identified, foreign bodies are removed, and the ruminoreticulum is emptied. Because of the complete mediastinum, ventilatory assistance is rarely needed during this stage. Next, the animal is placed under general anesthesia with positive pressure ventilation. Various approaches have been used for this portion, including ventral midline, paramedian, semilunar postxiphoid, paracostal, and transthoracic with rib resection. The hernia is reduced, and the rent is repaired with sutures or mesh grafts. Mesh grafts are contraindicated if infection is present.

Pleural Mesothelioma

Mesotheliomas have been reported in cattle and goats,[5] including a congenital form in calves.[6] Most are peritoneal, but pleural mesotheliomas also occur.[7] Mesotheliomas result in the accumulation of large amounts of fluid in the involved body cavity; signs of pleural mesothelioma are therefore related to pleural effusion. They include dyspnea, tachypnea, decreased lung and heart sounds (sometimes unilateral, with a concomitant increase in sounds on the normal side), dullness on percussion, exercise intolerance, cyanosis, tachycardia, anorexia, weight loss, decreased production, cough, and weak pulses. If peritoneal lesions are also present, as is common but not universal, ascites is also present. Radiographs confirm the pleural effusion, and thoracocentesis yields a serous, sometimes blood-tinged or gelatinous fluid. Cytologic examination may reveal reactive mesothelial cells. At necropsy the pleura is thickened and contains multiple nodules of gray to yellowish white tissue measuring several millimeters to several centimeters in diameter. Metastasis is uncommon. The tumor can be difficult to diagnose histologically and may resemble inflammation, pleural tuberculosis ("pearl disease"), or metastasis of another tumor.[6] There is no treatment.

Miscellaneous Conditions

Amelia R. Woolums[##]

Lung Tumors

Lung tumors are uncommon in ruminants. Those reported include pulmonary alveolar carcinomas, pulmonary adenomas, pulmonary adenocarcinomas, bronchogenic carcinoma, and pulmonary blastoma.[8,9] Malignant forms metastasize to regional lymph nodes and occasionally to other organs. Lymphosarcoma is the most frequent neoplasm to become metastatic to the lung, and uterine and ovarian adenocarcinoma may undergo metastasis to the lung. Because many lung neoplasms in cattle are incidental findings at slaughter or necropsy, clinical signs are therefore not well documented. The lesions are typically discrete, round, yellow to gray masses distributed throughout the lung tissue. Tumors are most likely to be detected antemortem by radiographic examination. Differential diagnoses in such cases include pulmonary abscesses, mycotic pneumonias, and tuberculosis.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

[##]Previous contributions by John C. Baker and John A. Smith are acknowledged.

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Equine Respiratory System

Disorders of the Lungs

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• CHAPTER 32

Diseases of the Alimentary Tract

SAMUEL L. JONES and BRADFORD P. SMITH, *Consulting Editors*

Diseases of the Equine Alimentary Tract

Samuel L. Jones, *Consulting Editor*

Diagnostic Procedures in the Examination of the Equine Alimentary System

Samuel L. Jones

A thorough physical examination is compulsory, and tests that provide a minimum database (complete blood count [CBC], serum chemistries, and urinalysis) are often indicated in horses with suspected alimentary tract disease. Once a list of differential diagnoses is compiled, a number of ancillary diagnostic tests are available to narrow the possibilities. Each diagnostic test or procedure is limited in the type and extent of information that can be obtained, and therefore the clinician should select the complement of procedures that is most likely to provide the information required to make a proper diagnosis and determine the appropriate therapy.

Rectal Examination

A systematic approach to examining the abdominal and retroperitoneal viscera should be established and applied during each examination to ensure that all pertinent regions and structures are examined. When feasible and if required, the patient should be sedated to allow a more thorough examination. In some cases, epidural anesthesia is required to obtain adequate access to structures during rectal examination. The principal goal of a rectal examination is to identify changes in size, texture, shape, or location of visceral organs, peritoneum, mesentery, vasculature, or objects that are normally not present. Rectal examination is often performed with ultrasonographic examination, and information derived from each must be considered in order to draw conclusions. Ultrasonographic examination will be described in a later section.

In the pelvic region of the normal horse, the urethra and accessory sex glands (male) or the vaginal vault and cervix (female) can be palpated. The urethra is usually not discernible in the female, but abnormalities such as uroliths may be felt. In the caudal abdominal cavity, the bladder, the uterus in females, and the pelvic flexure and small colon typically should be felt. The pelvic flexure and left ventral and left dorsal colons are normally located ventrally, on midline, or toward the left side of the abdomen. The small colon, with formed fecal balls palpable, courses throughout the caudal abdomen, mostly on the left side. In females the left ovary can be felt in the left dorsal, caudal region of the abdomen. Both ovaries should be palpated in conjunction with palpation of the uterus. The peritoneal surface should be felt along the surface of the abdominal wall and the surfaces of the viscera. It should feel smooth, with no crepitus or irregularities. Advancing along the left side of the abdomen, the spleen can be felt as a smooth structure, with the caudal border having a well-delineated, tapered border. The size and location of the spleen are variable, because it can extend from the left body wall to the right ventral region of the abdomen. Advancing cranially and dorsally, the left kidney can be palpated. The kidney should feel smooth with the renal pelvic fissure discernible, although in the overweight horse extensive perirenal fat may obscure this detail.

From the left kidney, moving toward midline and extending from the abdominal aorta, the cranial mesenteric and ileocecocolic arteries may be felt. Palpation of fremitus in these arteries may be associated with arteritis and thrombus formation secondary to *Strongylus vulgaris* larval migration, although this association has been very inconsistent. Fremitus is frequently absent when severe arteritis exists, or the arteries may be entirely normal and fremitus felt. Fremitus can often be elicited by compressing the wall of the normal artery, thus accelerating flow through the compressed lumen. The mesenteric root of the colon can be felt ventral to the cranial mesenteric artery. This should palpate as a mildly taut band of tissue extending from the dorsal midline ventrally. Excessive tension, displacement, thickening, or masses within the mesentery should be considered abnormalities. It may be possible to palpate an enterolith, fecalith, or gravel impaction in the transverse colon, although this may be beyond the reach of the examiner because the transverse colon is located cranial and medial to the left kidney.

Sweeping to the right side of the abdomen, the base and cupola of the cecum can be felt. The body of the cecum can be followed partially by sweeping along the medial aspect of the cecum, cranially toward midline. The cecum has a prominent ventral band and sacculations. Gas, together with ingesta that is soft and mainly of a fluid consistency, can be felt within the cecum. Firm or excessive ingesta suggest an abnormality.

Findings that are different from normal often must be differentiated as being variations of normal or truly abnormal. Some common abnormal findings include abnormalities of the peritoneal surface. Crepitus, or a "plastic wrap" texture, is indicative of gas secondary to trauma or infection. An irregular or rough surface may be indicative of fibrin on a visceral surface or neoplasia, or with a perforated intestine there may be ingesta adhered to a visceral surface. There are many abnormal presentations of the large colon, most of which are associated with signs of colic. Thickening of the wall of the colon may

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be appreciated on rectal palpation and is indicative of edema or cellular infiltration of the colon. Palpation of abnormal masses in the wall of the colon or associated with the colonic mesentery is indicative of infection, infarction, granulomatous colitis, or neoplasia.

Normally the small intestine is not discerned by palpation. Occasionally, though, peristaltic contractions may be felt in the small intestine as it courses across midline toward the base of the cecum. In some cases this will cause the small bowel to palpate as a firm, tubular structure. Relaxation of the peristaltic contraction should be discerned in such cases. Distention of the small intestine is abnormal. In some cases the bowel may feel thickened, which can occur with ileal muscular hypertrophy, edema, or inflammatory disorders of the small bowel.

Other abnormal findings that may accompany disorders of the abdominal alimentary system include masses, adhesions, enlarged and thickened mesenteric arteries, and caudal displacement of the spleen (secondary to gastric distention or neoplasia).

Paracentesis

Abdominal paracentesis is performed routinely in patients with suspected disorders of the abdominal viscera. Cytologic examination of peritoneal fluid; white blood cell (WBC) and red blood cell (RBC) counts; protein, fibrinogen, lactate, phosphate, and glucose concentrations; lactate dehydrogenase (LDH), creatine kinase (CK), and alkaline phosphatase (ALP) activity; and pH can be quantitated. The results of peritoneal fluid analysis may help establish a specific diagnosis but, more important, may reflect inflammatory, vascular, or ischemic injury to the intestine, requiring surgical intervention.

Endoscopy

There are two basic types of endoscopic equipment available: equipment based entirely on a fiberoptic system and equipment based on a video chip system. A wide array of affordable endoscopes is now available, and endoscopic examination of the proximal alimentary tract is now common. A typical endoscope found in many private practices is a fiberoptic endoscope that has an insertion tube that is 100 to 110 cm in length and 10 to 14.5 mm in outer diameter. The larger-diameter tube can be inserted only through the nasal passages of older yearlings and adults and is not suitable for alimentary endoscopy, whereas a diameter of 10 mm allows passage through the turbinates of young foals. An insertion tube of 100 cm is sufficient for esophagoscopy in foals up to approximately 3 months of age. For older animals, an insertion tube length of 150 to 180 cm is required for esophagoscopy.

An insertion tube length of 110 cm is sufficient to reach the stomach of foals up to 30 to 40 days of age. A length of 150 to 180 cm is required for weanlings, and 200 cm is usually required for yearlings and adults. An insertion tube length of 200 cm is sufficient to reach the stomach of all adults of warm-blooded breeds, although 280 to 300 cm is required to examine the pylorus in adult horses. A 280- to 300-cm-long insertion tube permits duodenoscopy in adult horses.

Before a gastroscopic examination, suckling foals up to 20 days of age are not routinely kept from nursing for more than 1 hour. Older foals and mature horses should not have solid feed for 6 to 10 hours so that ingesta from the stomach may be adequately emptied. Longer duration of feed deprivation (12 to 18 hours) is desirable to view the antrum and pylorus of horses. Many foals less than 30 days old do not require sedation for gastroscopy, although sedation with 0.5 mg of xylazine per kilogram may facilitate the procedure. Sedation is required if the foal is to be placed in a recumbent position so that the entire glandular portion of the stomach can be examined. Sedation of older foals and horses is required. Xylazine (0.5 mg/kg given intravenously [IV]) usually provides adequate sedation. For greater sedation, detomidine (0.005 to 0.05 mg/kg IV) or a combination of xylazine and butorphanol (0.01 mg/kg) is effective.

After insertion of the endoscope, the stomach is distended with air until the nonglandular and glandular regions of the gastric surface can be observed. Distention with air is tolerated by foals and horses and has been associated only rarely with adverse effects. Occasionally, sick neonates with poor intestinal motility developed small intestinal distention and experienced discomfort after gastroscopy.

More complete descriptions of techniques of gastroduodenal endoscopy can be found elsewhere.[1,2]

Endoscopy of the rectum and distal small colon can be performed with most flexible endoscopes in use in equine practice and should be preceded, as much as possible, by evacuation and saline lavage of the rectum and distal small colon. The mucosal surface should appear pink to pale red and should have a smooth, "velvety" appearance. Mucosal edema or thickening, hyperemia, irregularities, defects, tears, and intraluminal masses are abnormal findings. Because of the concern for trauma to the rectum and small colon, the horse should be adequately sedated and restrained before preparation and examination of the distal alimentary tract.

Laparoscopy

Laparoscopy can offer valuable diagnostic information regarding the abdominal cavity and is only minimally invasive.[3,4] It should always be preceded by a thorough physical examination, including abdominal palpation per rectum, and abdominal ultrasonographic examination, paying particular attention to the sites for trocar insertion to ascertain that there are no adherent masses or viscera in the area. If abdominocentesis is to be part of the diagnostic workup, it should be performed before laparoscopy because of the effect of laparoscopy on abdominal fluid values. In experimental animals undergoing diagnostic laparoscopy with carbon dioxide insufflation, both the abdominal WBC count and the abdominal total protein increased.[5]

The indications for laparoscopy include palpable abdominal masses, enlarged viscera, adhesions, acute or chronic colic, weight loss, or the need to obtain visceral biopsy specimens. Contraindications include adherent viscera or masses at the site of laparoscopic trocar insertion, diaphragmatic hernias, or extreme bloating. Horses with acute colic can be safely examined laparoscopically if one is careful when inserting the trocars and telescopes.

The basic instruments for laparoscopic examinations include a laparoscopic telescope, laparoscopic cannula and trocar assembly, fiberoptic light source and cable, insufflator, and biopsy and manipulation instruments. The 30-degree laparoscope allows better visualization of the less accessible areas compared with the 0-degree telescopes. Video cameras make visualization easier with less eyestrain but require more powerful light sources. The cost of laparoscopic instrumentation has decreased recently as a result of the explosion of popularity of laparoscopy in humans, increasing the supply and availability of used instruments.

Horses should be fasted for 18 to 24 hours before most laparoscopic procedures; water is allowed on an ad libitum basis. Fasting increases intraabdominal visualization and decreases the possibility of penetrating a gas-distended viscus. The animal is restrained in standing stocks if the procedure is to be done while it is standing. Preoperative antibiotics, antiinflammatory drugs, tetanus prophylaxis, and a sedative analgesic combination are administered. It is important to administer the analgesics before abdominal insufflation. The flank areas are prepared for aseptic surgery. Local anesthetic agents are infiltrated subcutaneously (SC) and intramuscularly (IM) in the middle of the paralumbar fossa slightly above the crus of the internal abdominal oblique muscle for the insertion of the laparoscopic telescope. If additional instruments are to be used, their insertion sites are similarly anesthetized.

It is preferable to begin the laparoscopic procedure on the left side of the abdomen to minimize the chance of penetrating the cecal base. The horse is then draped and a stab incision is made. The laparoscopic cannula and trocar assembly are inserted through the musculature and into the abdominal cavity. It is useful to orient the trocar toward the opposite coxofemoral joint when inserting it. The trocar is exchanged for the telescope, and confirmation of entry into the abdominal cavity is made before insufflation is commenced. If the

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abdominal cavity has not been penetrated, a quick thrust with the telescope will usually penetrate the peritoneum. Insufflation of the abdomen with CO_2 to 8 to 10 mm Hg will usually be sufficient for most examinations.

Systematic examination of the abdominal cavity is then carried out. On the left side of the abdomen, the spleen, left kidney, nephrosplenic ligament (Fig. 32-1), stomach, left side of liver, diaphragm, and ventral colon may be visualized cranially. Looking caudally, the examiner will see the root of the mesentery, the isolated small intestinal and small and large colon sections, the urogenital tract, the bladder, and the terminal rectum. The procedure is repeated on the right side of the abdomen. Looking cranially, the examiner will see the liver, epiploic foramen, right kidney, descending duodenum, cecal base, and large colon. Caudally, the urogenital tract, root of mesentery, and isolated pieces of intestine are visible. Liver biopsies and right kidney biopsies are taken from the right side. Left kidney and spleen biopsies are taken from the left side of the abdomen. Mesenteric lymph node biopsies are usually obtained via the left flank. Other masses are biopsied from the more accessible side. At the end of the procedure the abdomen is deflated, and the skin is closed with skin sutures only. Closure of the skin incision should wait until examination of both sides is completed in order to minimize subcutaneous emphysema.

In some horses with ventral or cranial abdominal masses as determined with ultrasound, it is useful to anesthetize the animal in dorsal recumbency for better characterization of the mass. Biopsies may be readily obtained. In horses with acute colic but without obvious signs indicating the necessity for surgery, laparoscopy can help in making the decision to continue medical therapy or proceed to surgery. Strangulated sections of small intestine can be seen, proximal enteritis can be diagnosed, and edema and vascular compromise to the large colon can be seen. No abnormalities may be detected in some animals with very localized lesions, or lesions may be inaccessible, depending on location.

Laparoscopic complications are similar to those of any other abdominal exploratory procedure. Inadvertent penetration of a viscus may occur. The left kidney may be perforated if the laparoscope is inserted too far dorsally. The spleen may be penetrated if the laparoscope is inserted too far ventrally or is not aimed toward the opposite coxofemoral joint. The cecum may be perforated when entering from the right side. Fasting the horses and carefully inserting the laparoscopic trocars will minimize the occurrence of these problems. Subcutaneous emphysema occurs commonly but has not caused any clinical problems. The peripheral WBC count increased but stayed within normal limits in experimental animals undergoing laparoscopy.[5]

Transcutaneous Ultrasonography of the Mature Equine Alimentary Tract

Michelle Henry Barton

Technique

One of the most innovative, practical, affordable, and portable diagnostic tools introduced into the field of equine internal medicine in the past two decades is transcutaneous ultrasonography. Although several different types of ultrasound transducers exist, adult equine abdomens are most completely imaged using a 2- to 5-MHz curvilinear array transducer, although a high-frequency (6- to 8.5-MHz) linear array transducer can be used to optimize resolution of superficial intraabdominal structures. Ideally, before getting started, the patient's hair should be clipped, the skin cleaned, and coupling gel applied. If clipping the hair is not an option, removing debris with grooming aids and soaking the hair with isopropyl alcohol will often suffice. Most horses tolerate transabdominal ultrasonography without sedation. In patients sedated with α_2-adrenergic agonists, small intestinal and cecal motility can be transiently reduced, especially in fasted horses, and the luminal diameter of the small intestine may appear more dilated than in unsedated patients.[6,7] Detailed review of the physics of ultrasonography is beyond the scope of this section; however, there are several general principles that should be kept in mind when transabdominal ultrasonography is performed. First, to ensure that all structures are properly assessed, it is essential to have a consistent and systemic approach for covering the entire area to be evaluated—for example, scanning one side at a time, dorsal to ventral, cranial to caudal. Using seven discrete locations in horses being evaluated for acute abdominal pain, the FLASH (fast localized abdominal sonography) method can be completed in less than 15 minutes and is highly effective in correctly assisting diagnosis.[8] The seven locations evaluated in the FLASH method are ventral, gastric, splenorenal, left middle third of the abdomen, duodenal, right middle third, and thoracic.

Next, being mindful of the position of the transducer and its orientation marker on the patient relative to the "default" method for display of the image on the monitor greatly facilitates correct orientation to the anatomy being imaged (Fig. 32-2). Because abdominal

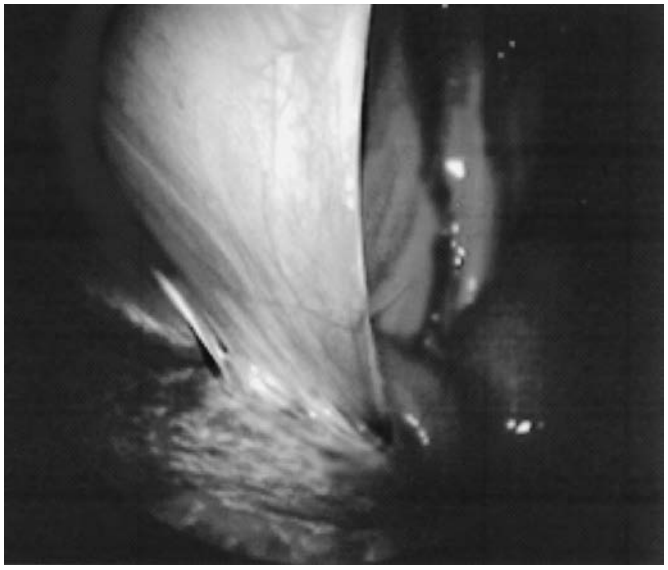


FIG. 32-1 Laparoscopic view of nephrosplenic ligament in a horse.

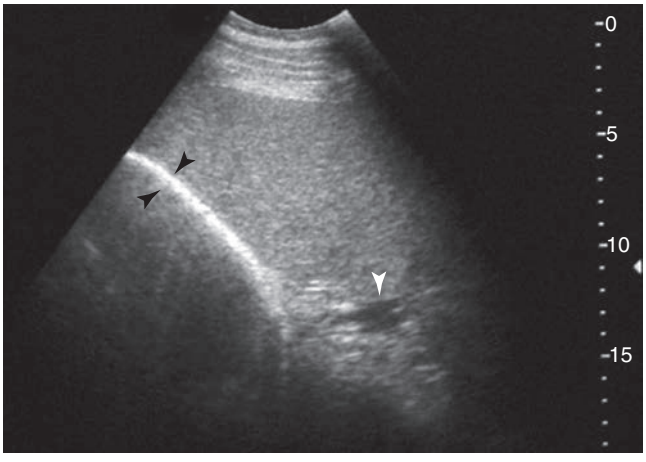


FIG. 32-2 This image is from the gastric window at the left eleventh intercostal space at the level of the shoulder. The left side of the image is dorsal. The black arrowheads mark the serosal layer to mucosal-luminal interface of the stomach wall, which appears as a curved hyperechoic line. The spleen is located in the near field between the stomach wall and the body wall. The white arrow is the splenic vein. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 19 cm.

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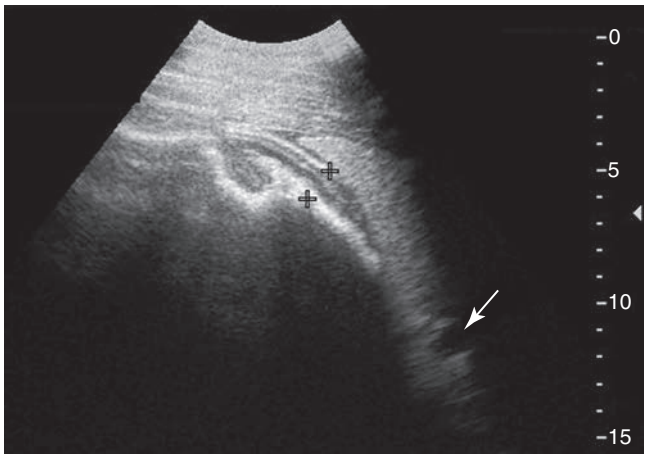


FIG. 32-3 Layers of the stomach wall. This image is from the gastric window with the left side of the image dorsal. The white arrow marks the splenic vein. The electronic calipers (+) are placed at the serosal layer and mucosal-luminal interface and mark the stomach wall. The five ultrasonographic layers of the wall are visible, and it is abnormally thickened at 1.34 cm. On follow-up gastroscopy, this horse had severe gastric ulceration.

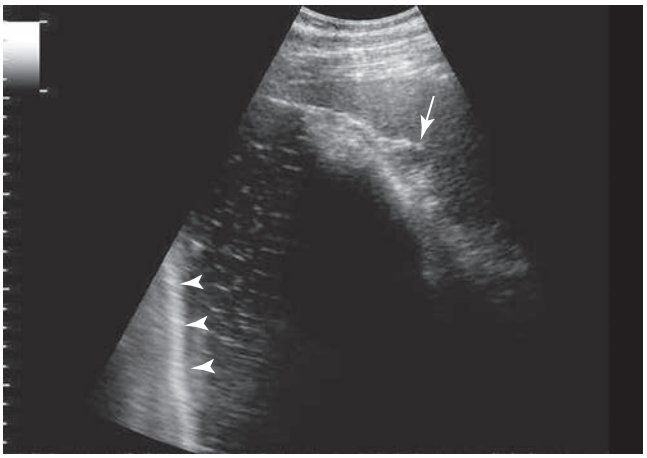


FIG. 32-4 This image is from the gastric window with the left side of the image dorsal. The white arrow marks the splenic vein. The white arrowheads mark the interface between hyperechoic fluid in the dependent portion of the stomach *(right)* and gas dorsally. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 23 cm.

ultrasonography is often performed with the footprint of the transducer in an intercostal space, most imaging of the abdomen is performed with the transducer oriented in a slightly oblique transverse plane (i.e., slicing across the long axis of the body). Careful attention should be paid to the spatial relationship of the viscera because this may be the only key feature distinguishing normal from abnormal.[9] Furthermore, the walls of some sections of the gastrointestinal tract appear strikingly similar and cannot be distinguishable unless information is provided about the probe's exact location on the patient.[10]

Third, in any ultrasonographic examination, it is important to be aware of the depth of the field of view. Selecting the appropriate frequency for the transducer is the key to producing high-quality images that are suitable for the depth of display. High-frequency probes provide sharp images, but the resolution is compromised as the depth of the viewing field increases.

A final general and helpful principle of ultrasonography is that more sound waves reflect to the transducer if two adjacent interfaces have markedly different acoustic impedances. The more sound that reflects to the transducer, the "whiter" the interface appears on the monitor; these tissue interfaces are called *echogenic* or *hyperechoic*. In contrast, less dense tissues reflect less sound, appear darker, and are referred to as *anechoic* or *hypoechoic* structures. The soft tissue of the walls of the gastrointestinal tract have an acoustic impedance that is several thousand-fold greater than that of the free gas inside the adjacent lumen.[11] Consequently, the image at this soft tissue–to-gas interface appears as a fuzzy hyperechoic border (see Fig. 32-2). Because most of the sound waves at this interface are reflected and the free gas in the lumen has extremely low impedance, the rest of the lumen is obscure as sound is neither penetrating nor reflecting from the lumen. Gas within a large luminal viscus is one of the greatest limitations to gastrointestinal ultrasonography in the horse, as it impedes visualization of deeper structures. While imaging a patient, the ultrasonographer should remember that gas rises to the nondependent portion of the abdomen and fluid and heavier structures fall to the dependent locations. When using a 3.5- to 5-MHz curvilinear transducer, identification of the anatomic layers of the intestinal wall in healthy horses is less distinct, with the wall typically appearing as a single hyperechoic line. Depending on the surrounding tissue and the contents of the lumen, three to five layers of the gastrointestinal wall may be visible when a high-frequency transducer is used; these five layers are the hyperechoic serosa, hypoechoic muscularis, hyperechoic submucosa, hypoechoic mucosa, and the hyperechoic mucosal interface with the lumen (Fig. 32-3).[12]

Ultrasonography of the Left Side of the Abdomen

In the following sections, transabdominal ultrasonography of the gastrointestinal tract will be reviewed with a systematic approach of scanning the left side of the abdominal cavity, cranial to caudal, followed by scanning the right side of the abdominal cavity. For the gastrointestinal tract, the ultrasonographer should be careful to document the following key elements: motility, presence of luminal distention, wall thickness and morphology, luminal contents, and viscera position.

STOMACH. When imaging is started on the left rostral side of the abdomen, the stomach should be located deep to the spleen between the ninth and thirteenth intercostal spaces at approximately the level of the shoulder. In this location, the only part of the stomach that can usually be seen is the wall of the greater curvature, which can be reliably identified as a smooth curved hyperechoic line adjacent to the spleen and the splenic vein (see Fig. 32-2).[13] The motility of the stomach is sluggish and the ultrasonographer may get the impression that the greater curvature of the stomach remains stationary.[7] The stomach has the thickest wall in the gastrointestinal tract, measuring approximately 7 mm thick from the serosal layer to the mucosal-luminal interface.[14] When the stomach is empty, the wall measures up to 1 cm thick, ill-defined loops of small intestine may appear between the stomach and the spleen, gastric rugal folds may be visible, and the gastric wall may be found only below the costochondral junction.[7,14]

Gastric Impaction and Ulceration. Because only the dorsal portion of the greater curvature can be seen and the lumen generally contains gas at this location, transcutaneous ultrasonography of the stomach is not a sensitive diagnostic tool for gastric ulceration, intramural gastric masses, or gastric impaction. However, if the wall of the greater curvature of the stomach extends beyond the fourteenth intercostal space in a horse that has not recently drunk or eaten, gastric distention should be suspected.[15] Furthermore, if excessive gastric fluid is present ventrally, a distinct hyperechoic gas–fluid interface may be apparent in the lumen (Fig. 32-4). If the stomach wall appears irregular or thickened, follow-up gastroscopy is indicated for a more definitive diagnosis (see Fig. 32-3).

SPLEEN AND LEFT KIDNEY. Although the focus of this section is gastrointestinal ultrasonography, the proximity of the spleen and left kidney to the gastrointestinal tract warrants brief review. Caudad from the stomach, the spleen should be identifiable immediately adjacent to the body wall, from the left ventral eighth intercostal

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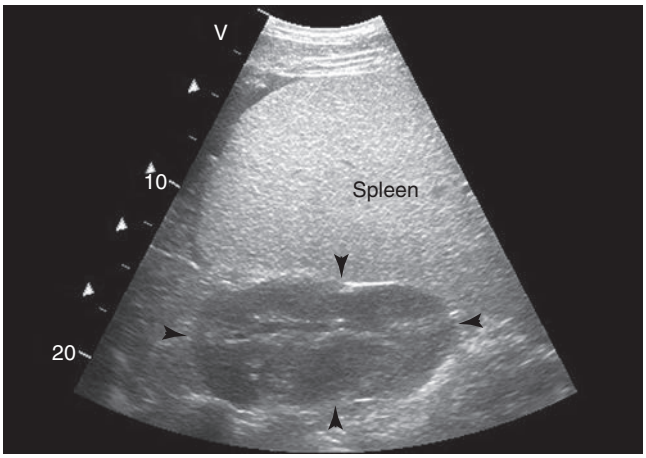


FIG. 32-5 This image was obtained at the left dorsal fifteenth intercostal space and shows the normal adjacent orientation of the spleen to the left kidney *(black arrows).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm. Left is dorsal.

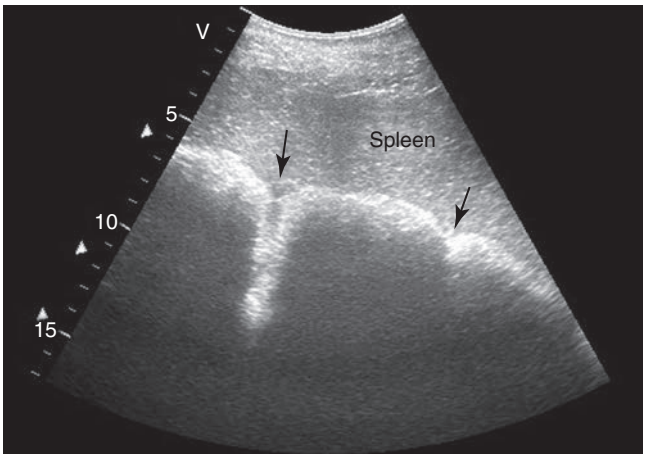


FIG. 32-6 This image was obtained from the left flank and shows the spleen adjacent to left ventral colon, identifiable by its location and the presence of sacculations *(black arrows).*

space to the paralumbar fossa. The size and location of the spleen vary greatly: the spleen can be left of the midline or extend slightly right of the ventral midline. In the rostral ventral left abdomen of some horses, the most rostral aspect of the spleen can be seen either lateral or medial to the liver.[9] The spleen's ultrasonographic architecture is usually homogeneous, with vessels that are rarely visible. The echogenicity of the spleen is greater than that of the liver or kidneys.

The left kidney can be found between the fifteenth and seventeenth intercostal spaces and the first to third lumbar vertebrae, medial or deep to the spleen (Fig. 32-5), between the level of the tuber coxae and the tuber ischii.[16,17] Rarely, the left kidney can directly appose the left body wall.[9] Gas in the small colon, left colon, or lung can normally preclude transabdominal viewing of the left kidney, though colonic gas obscuring visualization of the left kidney may be adjunct evidence of dorsal displacement of the left colon.[18] The ultrasonographic dimensions of the left kidney vary according to the location from which the measurements are obtained. The longitudinal axis for craniocaudal length (i.e., the dorsal plane parallel to the spine) is difficult to measure because of interference by the ribs.[17] In Thoroughbred horses, the length of the left kidney varies from 9.6 to 15.6 cm.[16] The dorsoventral height in the slightly oblique transverse plane varies from 3.1 to 8.1 cm and the lateromedial thickness varies from 6.6 to 9.1 cm.[16] The corticomedullary junction should be distinct, with the cortex being more echogenic. The adrenal glands are not usually identifiable via transabdominal ultrasonography.[9]

LEFT COLONS. Many disorders of the large colon can be palpable by rectal examination, and thus transabdominal ultrasonography is an ancillary tool. Ventromedial to the spleen, the left ventral colon can be identified by its sacculated wall (Fig. 32-6) and sluggish but visible motility, normally contracting two to six times per minute.[7,10,12] Precise measurement of the colonic wall can be difficult because of the indistinct mucosal-luminal interface; in general, however, the wall of the colon should measure less than 4 mm.[10,12,14] The left dorsal colon is not sacculated and can be located dorsal, lateral, medial, or even ventral to the left ventral colon. Gas in the left ventral colon often precludes distinct identification of the left dorsal colon when the latter lies medial or dorsal to the left ventral colon. Gas in the colon typically generates a hyperechoic wall with an indistinct luminal border and intraluminal acoustic shadowing that precludes identification of the contents and the medial walls.

Colitis. When visualized through ultrasonographic exam of the left colon, wall thickness and morphology, orientation of the colon, and its contents, are useful diagnostic characteristics. For example, thickening of colon wall can be caused by inflammation, infiltration by neoplastic cells, hemorrhage, or edema. Inflammation of the colon wall (i.e., colitis) can result in mural widening, but the mucosal

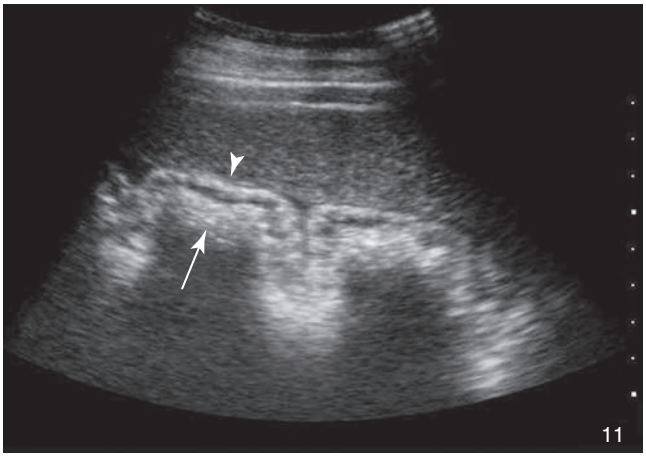


FIG. 32-7 This image was obtained from the same location as Fig. 32-6 from a patient with colitis. The left ventral colon is identifiable by its location medial to the spleen and by its sacculations. The wall of the colon was thickened to approximately 1 cm with three distinct layers: hyperechoic serosa *(white arrowhead),* hypoechoic muscularis, and submucosal, hyperechoic mucosal-luminal interface *(white arrow).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 11 cm. Left is dorsal.

border often appears shredded, undulating, or wavy (Fig. 32-7). These later findings may be particularly helpful in identifying horses in the prodromal phase of colitis, prior to the onset of diarrhea. The contents of the colon can change from characteristic acoustic shadowing to that of swirling mixed echogenic fluid that may enable visualization of the distal colonic wall. With colitis, colon motility can be increased, decreased, or remain unaffected.

Colon Volvulus. Colonic edema resulting from a volvulus of the colon will also result in uniform hypoechoic mural thickening that is best identified with imaging along the ventral midline behind the xyphoid. In one study that evaluated colon wall edema by transcutaneous ultrasonography using a ventral abdominal window, a colon wall thicker than 9 mm had a sensitivity of 67% and specificity of 100% for colon volvulus.[19] In addition, in some cases of colonic volvulus, nonsacculated colon replaces sacculated colon in the left ventral abdomen.[20] Furthermore, the blood supply to the ascending colon is located in the mesentery along its medial aspect, and thus there are normally no major blood vessels visible ultrasonographically on the lateral surface (adjacent to the body wall) of the ascending colon. The ultrasonographic finding of distended vessels with reduced blood flow in colonic mesentery adjacent to the body wall implies that the colon is rotated along its long axis and would be

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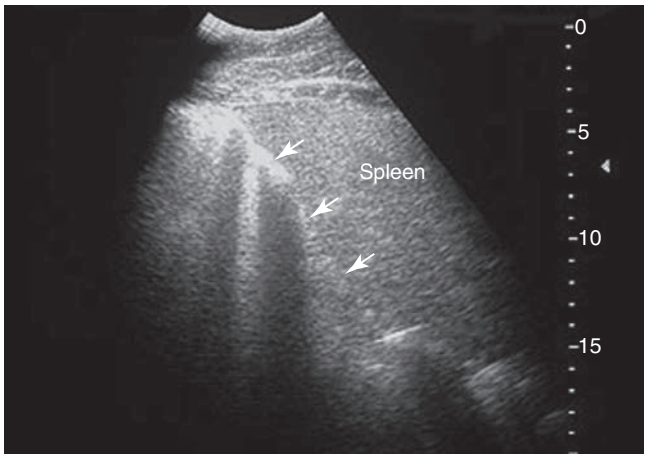


FIG. 32-8 This image was obtained from the same location as Fig. 32-5 using a 3.5-MHz curvilinear probe set to a depth of 20 cm. This horse had a left dorsal displacement of the colon into the renosplenic space. The gas-distended colon *(arrows)* obscures visualization of the left kidney. *(Courtesy Science In 3D, Inc. and © 2002—University of Georgia Research Foundation, Inc.)*

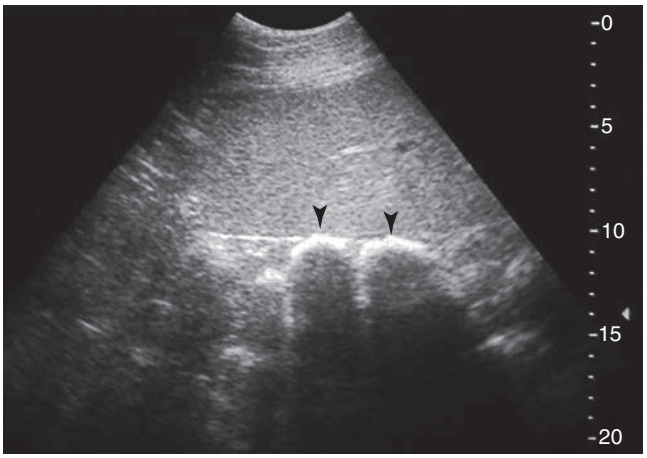


FIG. 32-10 This image was obtained from the left dorsal paralumbar fossa. The spleen is in the near field. The serosal surface *(black arrowheads)* of two adjacent loops of small colon are visible. Note the anechoic shadowing that precludes visualization of the distal small colon wall. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm. Left is dorsal.

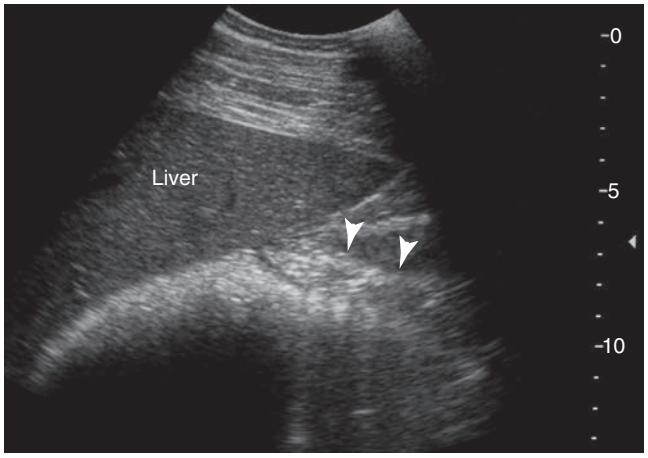


FIG. 32-9 This image was obtained from the same location as Fig. 32-23 using a 3.5-MHz curvilinear probe set to a depth of 13 cm. The left side of the image is dorsal. Sand and gravel in the dependent portion of the right dorsal colon (*white arrowheads* on serosal surface) create reverberation artifacts in the lumen. The colon wall is thickened. *(Courtesy Science In 3D, Inc. and © 2002—University of Georgia Research Foundation, Inc.)*

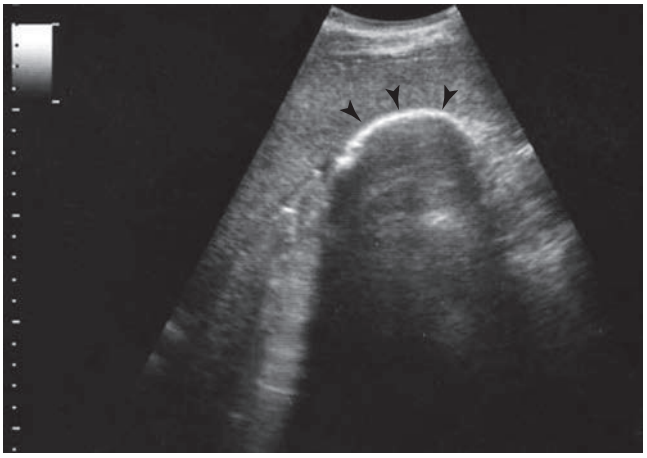


FIG. 32-11 This image was obtained from the left dorsal paralumbar fossa. The spleen is in the near field. The serosal surface *(black arrowheads)* of the small colon is visible and is bulging. Note the dramatic anechoic shadowing that was created by an intraluminal enterolith. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm. Left is dorsal. *(Courtesy Science In 3D, Inc. and © 2002—University of Georgia Research Foundation, Inc.)*

consistent with a diagnosis of displaced colon or a colon volvulus.[21] Colonic motility would be reduced with a volvulus.

Left Colon Displacement. On the left side of the abdomen, dorsal displacement of the left colon over the nephrosplenic ligament may obscure ultrasonographic visualization of the dorsal aspect of the spleen or left kidney, or the colon may appear lateral to the spleen (Fig. 32-8).[18] However, if gas is not present in the entrapped colon, the ultrasonographic diagnosis can be missed. Likewise, gas within the left colon can obscure the left kidney without the colon being entrapped. When ultrasonographic and other clinical findings support the diagnosis of left dorsal displacement of the colon, serial ultrasonography of the area can be a useful noninvasive method to determine if the colon has relocated to its ventral position upon successful ultrasonographic visualization of the left kidney.

Colon Impaction. Gas within the colon often precludes accurate ultrasonographic diagnosis of colonic impaction. An impaction should be suspected in the ventral colon by the presence of a hyperechoic border at the mucosal surface that casts a strong acoustic shadow and flattened sacculations. Sand impactions are best seen in the ventral abdomen and often compress the mucosal surface, create excessive acoustic shadowing or reverberation artifacts (Fig. 32-9), and significantly reduce visible motility of sacculations.[22]

SMALL COLON. The small colon is located in the left paralumbar fossa medial or ventral to the spleen. Because of its small diameter, sacculations, and packed serpentine loops that suspend from the dorsal mesocolon, often only small sections of the surfaces are visible ultrasonographically as short, sharply curving, hyperechoic lines (Fig. 32-10). As with the large colon, the motility of the small colon is slow (no more than 3 contractions per minute) and luminal surface gas typically prevents visualization of the contents and the distal walls.[12] Likewise, the dense content of fecal balls in the small colon often generate anechoic shadows from the near wall that precludes visualization of the distal wall (see Fig. 32-10).

Small Colon Impaction. Impactions or enteroliths obstructing the lumen of the small colon can usually be readily diagnosed by transrectal examination; however, transabdominal ultrasonography may reveal loss of, or enlargement of, sacculations and intense anechoic shadowing (Fig. 32-11).

SMALL INTESTINE. In fed healthy horses, the jejunum can only be identified in approximately 10% of horses.[7] One must carefully watch for peristaltic activity that creates transient expansion of the lumen from movement of ingesta. The medial location of the ileum precludes distinct identification by transcutaneous ultrasonography.

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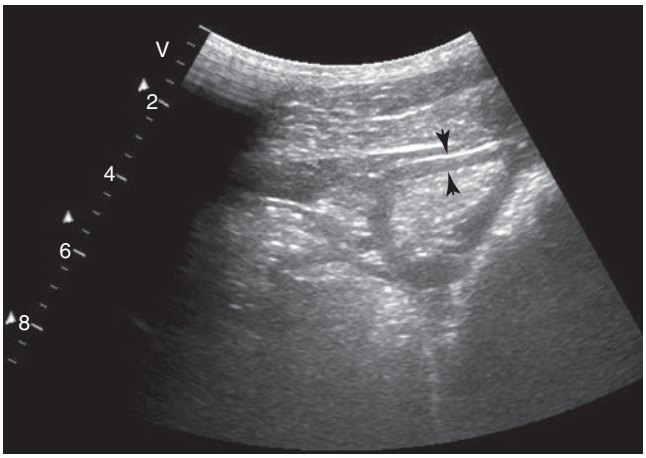


FIG. 32-12 This image was obtained from a healthy unsedated horse in the left flank using a 3.5-MHz curvilinear probe set to a depth of 8 cm. A single loop of small intestine is present between the body wall and the left ventral colon. The serosal to mucosal surfaces are most distinct in the near wall and are marked by the black arrowheads.

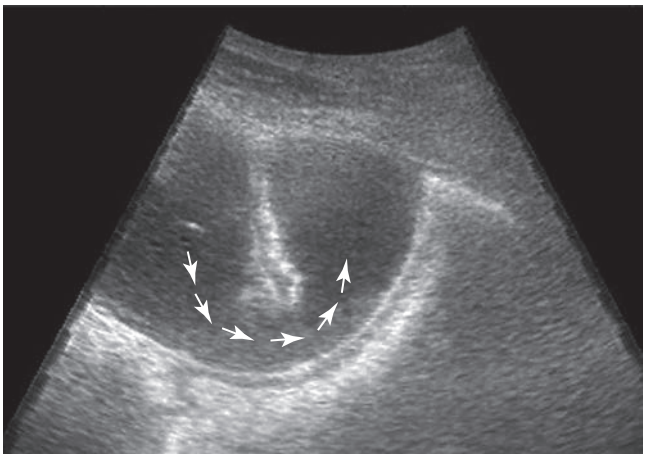


FIG. 32-13 This image was obtained from the left flank and depicts a segment of distended small intestine that is folding back on itself, creating the appearance of a "U turn" *(arrows).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 10 cm.

The jejunum is most consistently found in the left inguinal area, medial to the spleen and the left ventral colon (Fig. 32-12). The small intestine has the most visible motility of any part of the gastrointestinal tract, with peristaltic waves producing frequent rhythmic contractions. Fluid luminal contents typically enable accurate measurement of the wall (<3 mm) and visualization of the far wall along its long or short axis.[14] In healthy horses, jejunal luminal diameters rarely exceed 3 cm.[14] Following complete contraction with peristalsis, a distinct lumen becomes difficult to discern. Fasting and/or sedation with an α_2-adrenergic agonist decreases motility of the small intestine, thereby significantly increasing the likelihood of visualization.[6,7]

Distended Loops of the Small Intestine. Distended loops of small intestine often look the same on ultrasound, despite the underlying cause. Recalling that normal duodenum and jejunum are difficult to visualize in healthy fed horses, if the small intestine is found easily by ultrasonographic exam, the luminal diameter of small intestine exceeds 3 cm, or peristaltic contractions are notably reduced, it should be considered abnormal. Small intestinal distention can result from paralytic causes, in which there is reduced motility without physical luminal blockage or from mechanical reasons, in which there is a distal luminal or extraluminal obstruction impeding peristalsis. With either paralytic or mechanical ileus, small intestinal distention can progress to the point where the dilated segments of small intestine must fold back on themselves, creating the appearance of turns or curves within the lumen when caught in long axis (Fig. 32-13). As ileus progresses, denser ingesta will settle to the dependent portion of the affected segments (Fig. 32-14). In general, if small intestinal distention progressively increases and motility decreases over serial examination, mechanical causes of obstruction that require surgical intervention should be considered.[23,24] Scrutiny of the patient's clinical signs, ancillary diagnostic findings, and some distinguishing ultrasonographic features can be helpful in discriminating paralytic versus mechanical causes of small intestinal distention. In particular, the ultrasonographer should pay close attention to the small intestinal wall thicknesses and morphology, progression of distention, degree of motility, and appearance of the intestinal contents.

Acute Enteritis. The wall of the small intestine can be thicker than normal (i.e., >3 mm) from inflammation, edema, hypertrophy, or neoplasia. Some causes of inflammation and edema are acute in nature, such as proximal or anterior enteritis, and some causes are chronic or insidious in nature, such as the inflammatory bowel syndromes or idiopathic intestinal hypertrophy. In addition to the clinical signs and other diagnostic features of proximal enteritis (low-grade fever, gastric reflux, inflammatory leukogram, pain followed by

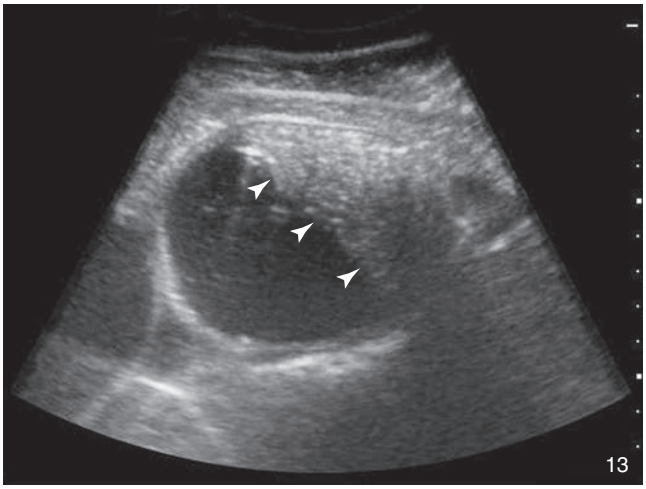


FIG. 32-14 This image was obtained from the left flank and depicts a segment of distended small intestine with hyperechoic ingesta settled dependently *(arrowheads).* The left side of the image is dorsal. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 13 cm.

depression after gastric decompression), on ultrasonographic exam, the mucosal wall of the small intestine may appear shredded, [14] corrugated, or wavy, resembling the edge of a lasagna noodle (Fig. 32-15). The proximal portions of the small intestine, especially the duodenum (see duodenum section below; Fig. 32-16), and the stomach may be distended with fluid. The motility of these loops can vary from low to apparently no movement to hypermotile. For horses with enteritis, the expected response to medical therapy varies, but lessening degrees of luminal distention with progressive improvement in motility are expected. If hyperechoic gas sounds are seen within the wall of the small intestine, it is indicative of either necrosis or anaerobic bacterial infection.

Inflammatory Bowel Disease and Ileal Hypertrophy. If the signs of abdominal pain are more insidious, if there is weight loss despite a good appetite, or if panhypoproteinemia is present, symmetrically and diffusely or regionally thickened small intestine may be a sign of infiltrative or hypertrophic disease, such as inflammatory bowel disease, neoplasia (especially lymphosarcoma), or idiopathic ileal hypertrophy.[25] In these circumstances, the wall can be either uniformly or irregularly thickened, often with a narrow or obscure lumen (Fig. 32-17). Motility is usually preserved, unless mural thickening results in secondary mechanical obstruction. Definitive

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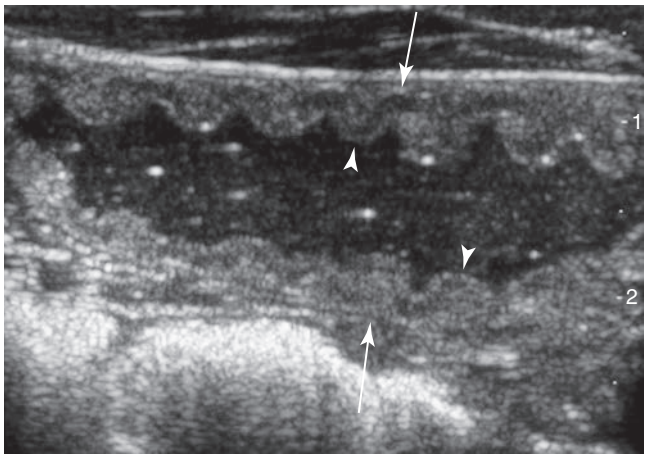


FIG. 32-15 A linear probe set to a depth of 3 cm was used to capture this image of enteritis, obtained from the ventral left flank. The small intestinal wall is thickened (up to 6 mm in some areas) and the mucosa has a "wavy" or corrugated appearance. The white arrows mark the serosa and the arrowheads mark the mucosal-luminal interface.

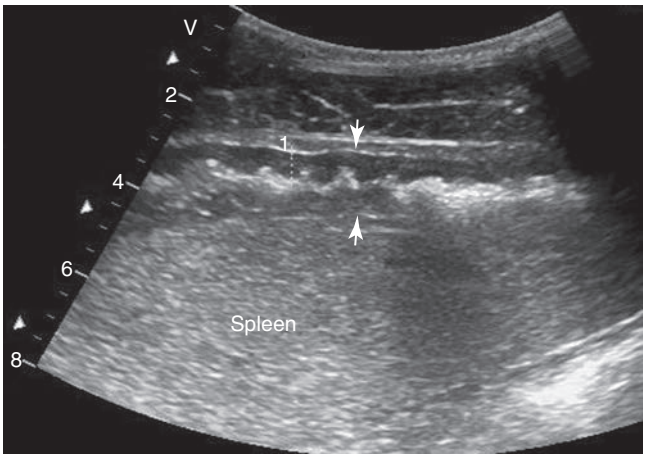


FIG. 32-17 This image was obtained from the left flank adjacent to the spleen, revealing the thickened and wavy wall of a longitudinally oriented segment of small intestine from a horse with chronic inflammatory bowel disease. The white arrows mark the serosal surfaces. The thickened walls are predominantly hypoechoic. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 8 cm.

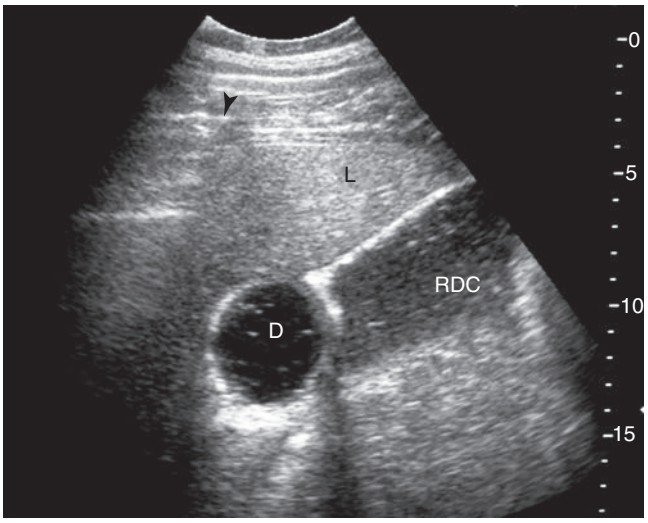


FIG. 32-16 This image was obtained from the right twelfth intercostal space using a 3.5-MHz curvilinear probe set to a depth of 18 cm. This patient has proximal enteritis. The duodenum *(D)* was distended to approximately 4 cm with reduced motility. The duodenal wall was mildly thickened at 4 mm. The black arrowhead marks the ventral tip of the lung. *L,* Liver; *RDC,* right dorsal colon.

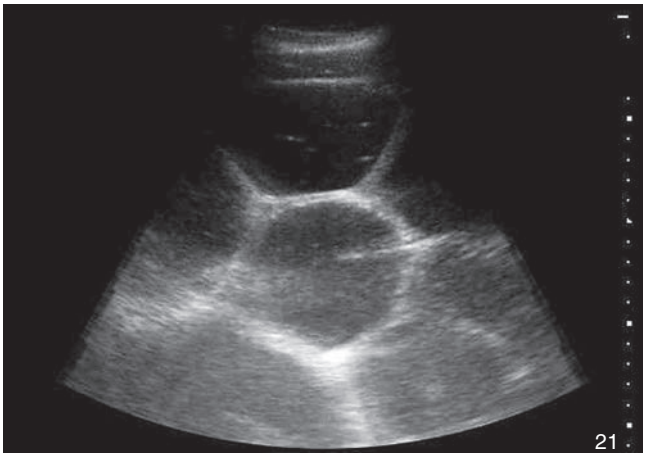


FIG. 32-18 This image was obtained from the left flank from a horse with a nonstrangulating obstruction that required an exploratory celiotomy for correction. Note the numerous turgidly round and distended loops of small intestine. In real time, these distended loops had no appreciable motility. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm.

diagnosis of inflammatory bowel disease or idiopathic hypertrophy requires histopathologic evaluation.

Nonstrangulating Obstructive Lesions of the Small Intestine. Mechanical obstruction of the small intestine in which the adjacent blood supply remains intact, such as an ileal impaction, adhesions, mural hematoma, or severe chronic infiltrative disease of the intestinal wall, would be expected to cause variable degrees of luminal distention proximal to the site of obstruction. In general, lack of significant changes in wall thickness or morphology would be helpful features for distinguishing simple nonstrangulating lesions of the small intestine from strangulating or severe inflammatory lesions. If serial ultrasonography reveals progressive severity of distention and lack of motility (see Fig. 32-17), surgical intervention should be considered.[23,24]

Strangulating Obstructive Lesions of the Small Intestine. Progressive pain with poor response to medical intervention, lack of fever, and serosanguineous peritoneal fluid with increased or increasing lactate concentrations are clinical features that might help distinguish strangulating lesions of the small intestine from simple obstructions and enteritis. As with nonstrangulating obstructive lesions of the small intestine, ultrasonographically, the intestine proximal to strangulating obstructions will be distended with either gas or fluid. The degree of distention and motility will vary with the duration of strangulation, although the presence of progressive distention of preobstruction segments to turgidly circular and completely amotile loops of small intestine is highly correlated with mechanically obstructive lesions that require surgical intervention (Fig. 32-18).[23,24] An important distinguishing feature of strangulated small intestine is the appearance of focally and usually uniformly thickened walls at the site of the strangulation (Fig. 32-19). Thus, when regional uniformly thickened small intestine is identified ultrasonographically, with other evidence of obstruction (hypomotile, hairpin turn stacks of turgidly round and distended loops of small intestine with dependent ingesta), a strangulating obstruction should be the top consideration. Frequently the strangulated loops are identified in the ventral portions of the abdomen. In one study, focally thickening and distended small intestine with no motility was 100% sensitive and 100% specific evidence for strangulating lesions of the small intestine.[23] If the affected segments are most readily visualized adjacent to the spleen and stomach on the left side of the abdomen (Fig. 32-20) or between the liver and right dorsal colon on the right side of the abdomen (Fig. 32-21), these respective locations are areas

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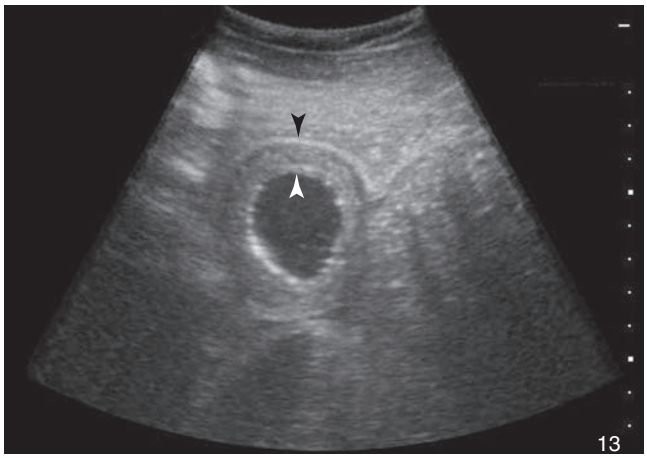


FIG. 32-19 This image was obtained from the left flank from a horse with a strangulating obstruction using a 3.5-MHz curvilinear probe set to a depth of 13 cm. Depicted is a single distended loop of small intestine with a uniformly thickened wall of approximately 8 mm (between *arrowheads*). In real time, this segment had no discernible motility.



FIG. 32-22 This image was obtained along the caudal ventral midline from a horse with a jejunojejunal intussusception. The arrowhead marks the inner loop telescoped into the outer loop of jejunum *(arrow),* creating the classic "bull's-eye" appearance. This image was obtained using a 3.5-MHz curvilinear probe set to a depth of 10 cm.

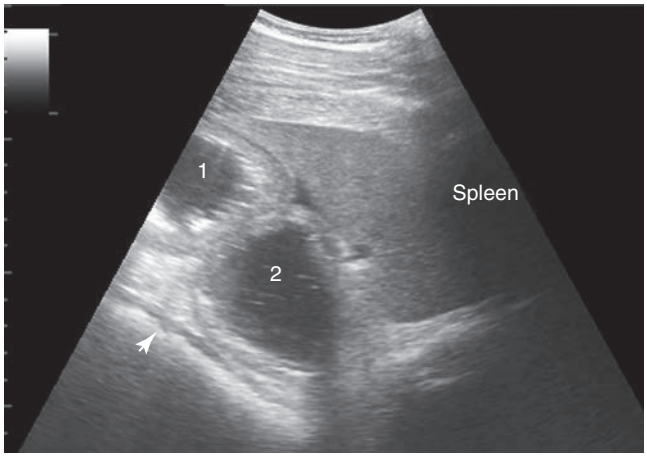


FIG. 32-20 This image was obtained from the gastric window from a horse with a strangulating gastrosplenic ligament entrapment, using a 3.5-MHz probe set to a depth of 17 cm. Two loops (labeled *1, 2*) of thickened, distended, and amotile loops of small intestine were found between the spleen and the stomach *(arrowhead).* Dorsal is to the left.

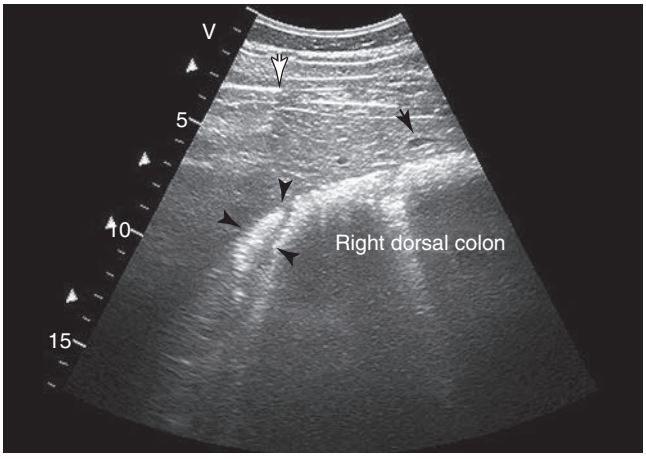


FIG. 32-23 This image was obtained at the eleventh right intercostal space at approximately the level of the shoulder, using a 3.5-MHz curvilinear probe set to a depth of 17 cm. Dorsal is to the left. The white arrow marks the ventral tip of the lung. The black arrowheads mark the serosal surface of the duodenum with a hyperechoic lumen, located between the liver and the right dorsal colon. Short hyperechoic parallel lines in the liver are the walls of portal veins *(black arrow).*

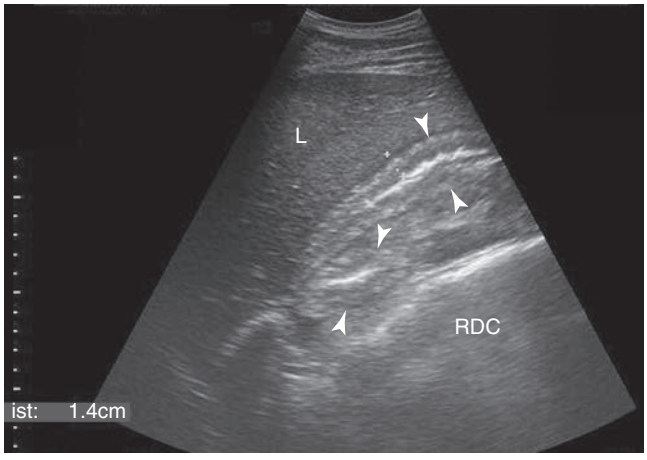


FIG. 32-21 This image was obtained from the right twelfth intercostal space from a horse with an epiploic foramen entrapment. Arrowheads mark the serosal surfaces of two thickened (14-mm wall) and compressed loops of amotile small intestine located between the liver *(L)* and the right dorsal colon *(RDC).* This image was obtained using a 3.5-MHz curvilinear probe set to a depth of 24 cm.

in which gastrosplenic and epiploic foramen incarcerations are readily found.

Intussusception. Finally, intussusceptions of the small intestine are most common in foals and young horses and have a characteristic "bull's-eye" or target lesion appearance of the affected segments when imaged across the short axis of the small intestine (Fig. 32-22).[26] The intussuscepted intestine tends to fall toward the dependent portion of the abdomen. Like other mechanical obstructive diseases, the proximal small intestine will have normal wall thickness but will be distended, with reduced motility and hairpin turns, depending on the degree of obstruction.

Ultrasonographic Anatomy of the Right Side of the Abdomen

LIVER AND PANCREAS. The liver, descending duodenum, and right dorsal colon have characteristic proximity of location and can be identified in the right rostral abdomen at the level of the shoulder (Fig. 32-23). The liver is located from the sixth to the fourteenth intercostal spaces between the diaphragm and the right dorsal colon (see Fig. 32-23). Gas in the lung or the right dorsal colon can obscure identification of the liver dorsally and ventrally, respectively; thus

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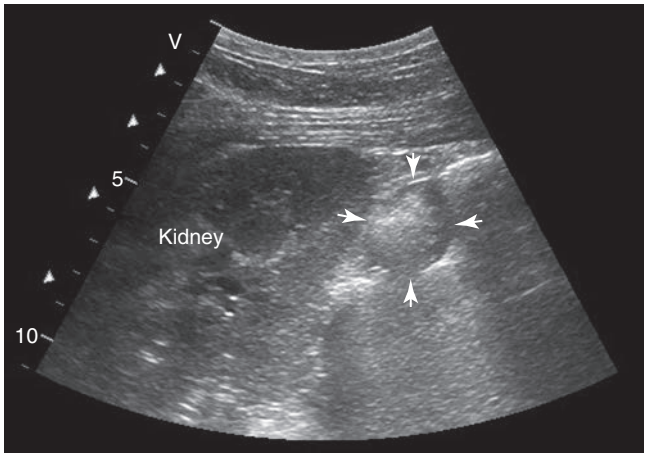


FIG. 32-24 This image was obtained from the right fifteenth intercostal space using a 3.5-MHz curvilinear probe set to a depth of 11 cm. Dorsal is to the left of the image. The duodenum *(arrows)* can be seen ventral to the right kidney. This still image was captured when a peristaltic wave distended the luminal diameter to approximately 2.5 cm.

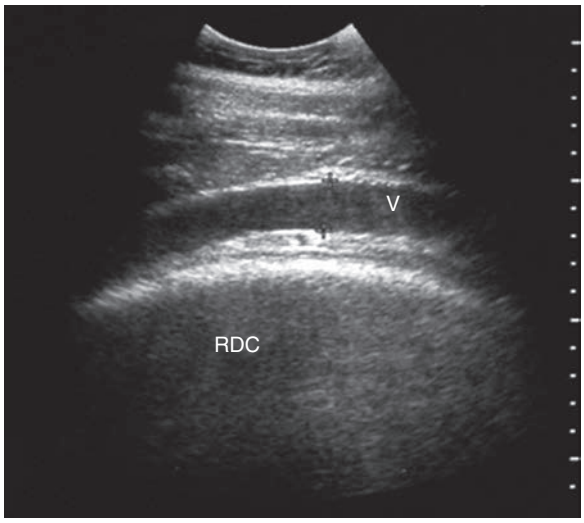


FIG. 32-25 This image was obtained from the right fifteenth intercostal space using a 3.5-MHz curvilinear probe set to a depth of 17 cm. A distended vein *(V)* is visible lateral to the wall of the right dorsal colon *(RDC)*. This horse had a colon volvulus. *(Courtesy Science In 3D, Inc. and © 2002—University of Georgia Research Foundation, Inc.)*

ultrasonographically, the liver may only be visible over a few intercostal spaces. Only a small portion of the right side of the liver can be imaged, so its size is estimated based on its expanse across the intercostal spaces.[9] It is unusual for the liver to be seen beyond the fifteenth intercostal space or in the same transverse plane as the right kidney, except at the most rostral aspect of the kidney. The ventral edges of a normal liver are distinctly sharp. As with the spleen, the architecture of the liver is relatively homogeneous, but more vessels are visible in the liver and the general echogenicity of the liver is less than that of the spleen.[14] Portal veins have more connective tissue in their walls and thus have more echogenic walls than the hepatic veins.[9] Short segments of smaller portal veins often appear as hyperechoic parallel lines (see Fig. 32-23). In some small horses, the portal vein can be seen entering the hilus deep on the medial side of the image. The common bile duct and its branches within the liver are not normally visible.[9] The pancreas is not usually identifiable via transabdominal ultrasonography.[9]

DUODENUM. The position of the duodenum is fixed by its suspending mesoduodenum; thus the duodenum can reliably be found descending the right middle abdomen at approximately the level of the shoulder and is located between the liver and the right dorsal colon (see Fig. 32-23), where it can be imaged transversely along its short axis. As with the jejunum, to locate the descending duodenum, the ultrasonographer must wait for a peristaltic contraction to deliver ingesta through the lumen, thereby expanding the lumen. Otherwise, the duodenum typically appears as a hyperechoic flattened or crescent-shaped line to flattened oval shape. It is unusual for the duodenal diameter to exceed approximately 3 cm in healthy horses during peristaltic propulsion of ingesta.[27] The duodenum contracts one to four times per minute in fed horses,[27] but contractions are less frequent in anorectic, fasted, or heavily sedated horses. The duodenum can be followed to the level of the ventral right kidney (Fig. 32-24), where it crosses medially into the abdomen and is no longer distinguishable. The wall of the duodenum is less than 3 mm thick.[14]

RIGHT COLONS. The right dorsal colon, which has no sacculations, is immediately ventral to the liver and duodenum and is usually found from the right tenth to twelfth intercostal space, although it can extend to the fourteenth intercostal space.[28] The wall of the right dorsal colon consistently appears as a hyperechoic curved line, adjacent to the liver (see Fig. 32-23), that measures less than 4 mm, although a range up to 5.9 mm has been reported in healthy horses.[28] If the ultrasonographer locates the right dorsal colon and slides the transducer ventrally, the interface between the right dorsal and right ventral colon is often identifiable as what appears to be an indentation in the wall between the nonsacculated right dorsal colon dorsally and the sacculated right ventral colon ventrally. The right ventral colon has sacculations, and its contractions and wall thickness are similar to those of the left colon, although a wall thickness up to 5.1 mm has been reported in healthy horses.[28] The contents of the right colons and their medial walls are normally obscured by luminal gas. The transverse colon is not usually identifiable via transabdominal ultrasonography.[9]

Right Dorsal Colitis. When diarrhea in a horse is accompanied by panhypoproteinemia and a history of nonsteroidal antiinflammatory drug (NSAID) use, transabdominal ultrasonography of the right dorsal colon can be a useful diagnostic aide.[28] In patients with NSAID-induced right dorsal colitis, the wall of the right dorsal colon will often appear thickened with mixed echogenicity and an irregular mucosal-luminal interface.

Right Dorsal Colon Displacement. Identification of a large gas-distended viscus in the right caudal abdomen by transrectal palpation with accompanying taut colonic bands is consistent with a diagnosis of right dorsal displacement of the colon. The only major blood vessels normally visible ultrasonographically in the right caudal abdomen are those associated with mesentery of the lateral cecal band.[12] Thus the ultrasonographic finding of distended vessels with reduced blood flow in colonic mesentery adjacent to the body wall implies that the colon is rotated along its long axis and would be consistent with a diagnosis of right dorsally displaced colon or a colon volvulus (Fig. 32-25).[21]

CECUM. The cecum has a sacculated wall that extends from the right paralumbar fossa to ventral midline and has motility that is similar to that of the colons.[7,12] A unique characteristic that can be useful to distinguish the cecum from the right ventral colon is that the lateral cecal band is oriented dorsoventrally and contains an associated artery and vein, whereas the lateroventral band of the right ventral colon is oriented caudocranially and does not have associated vasculature.[12] The cecal wall is less than 4 mm thick, and gas in the lumen precludes imaging the contents and far wall. Most diseases affecting the cecum can be sufficiently identified by transrectal palpation; however, transcutaneous ultrasonography can be helpful in confirmation of the diagnosis.

Typhlitis. With acute inflammatory disease of the cecum, the wall may be thickened, the mucosal surface may appear irregular or wavy, and motility will vary from hypomotile to hypermotile. Gas

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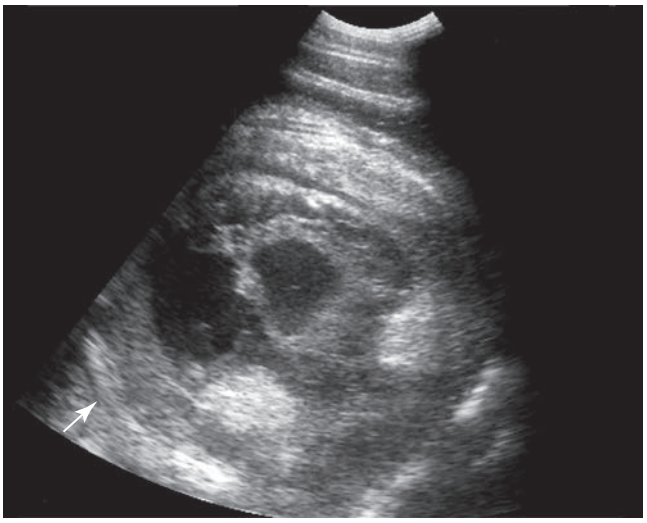


FIG. 32-26 This image was obtained from the right mid flank using a 3.5-MHz curvilinear probe set to a depth of 24 cm. This horse had a cecocolic intussusception that appears as a large mass. The appearance of a "wall within a wall" is most apparent in the near field.

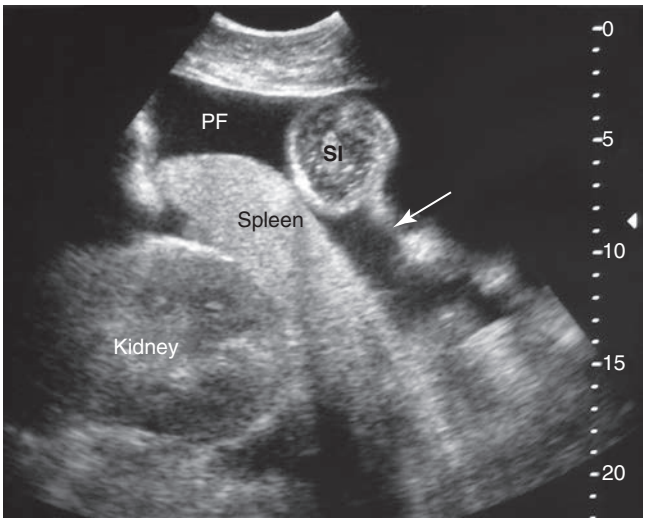


FIG. 32-27 This image was obtained from the left dorsal sixteenth intercostal space using a 3.5-MHz curvilinear probe. The left side of the image is dorsal. Excessive hypoechoic peritoneal fluid *(PF)* has displaced the spleen from the left body wall and enabled distinct visualization of a single loop of small intestine *(SI)* and its supporting mesentery *(arrow),* appearing as a "balloon on a string." This horse had metastatic mesothelioma.

normally present in the body or base of the cecum precludes visualization of its contents and distal wall; however, with typhlitis, the cecum is often distended with fluid that is readily seen swirling inside of the lumen and can enable visualization of the distal wall, especially toward the cecal apex.

Cecal Impaction. Transrectal palpation is a better method to diagnose cecal impactions, but transabdominal ultrasonography of cecal impactions may reveal loss of characteristic sacculations.

Cecocolic and Cecocecal Intussusception. Intussusceptions involving the cecum are often palpable on transrectal evaluation as indistinct large, firm masses in the right or mid caudal abdomen. Like small intestinal intussusceptions, the characteristic "target lesion" of the wall of the cecal apex or body within the lumen of the cecum or right ventral colon can be seen. In chronic intussusceptions, the walls are very thick and may appear abscessed or mass-like (Fig. 32-26).

RIGHT KIDNEY. Gas in the cecum, right dorsal colon, or lungs sometimes obscures visualization of the right kidney, which can normally be found in the rostral fifteenth to seventeenth intercostal space[17] (see Fig. 32-24). In Thoroughbred horses, the right kidney is 6.5 to 9.1 cm dorsoventrally (the slightly oblique transverse plane), 12.1 to 16.2 cm in length craniocaudally (the dorsal plane), and 6.5 to 8.4 cm lateromedially.[16] The ureters are usually difficult to identify, but the proximal right ureter sometimes appears as a hyperechoic circular structure at the hilus. The architecture of the right kidney is similar to that of the left kidney.

PERITONEAL CAVITY. In the healthy horse, only minute pockets of peritoneal fluid should be identifiable in the rostroventral area of the abdominal cavity or adjacent to sacculations of the ventral colons. The abnormal presence of excessive peritoneal fluid displaces organs and greatly facilitates visualization of structures not normally seen on ultrasonographic exam, such as the mesentery of the small intestine (Fig. 32-27).

PERITONITIS. Peritonitis should be suspected if there is increased volume or echogenicity of peritoneal fluid. In some cases, free-floating or adherent fibrin or fibrous tags may be visible (Fig. 32-28). An abdominocentesis would be an integral step to further characterize the etiology of peritonitis.

HEMOABDOMEN. Excessive blood in the peritoneal cavity will displace organs off the body wall. Blood in the peritoneal cavity

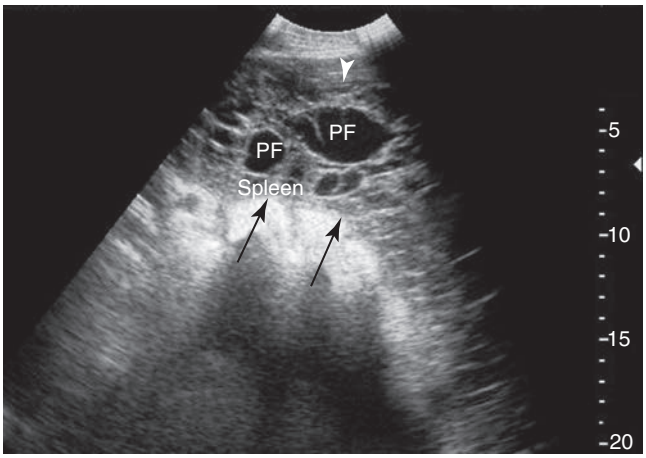


FIG. 32-28 This image was obtained from the lower right flank using a 3.5-MHz probe set to a depth of 21 cm. The left of the image is dorsal. Numerous hyperechoic fibrinous and fibrous adhesions trapping pockets of hypoechoic peritoneal fluid *(PF)* are present between the body wall *(white arrowhead)* and the serosal surface of the right ventral colon *(black arrows).* This horse had septic peritonitis.

appears as a mixed echogenic fluid that, in real time, often appears to "swirl" as it mixes with less echogenic peritoneal fluid (Fig. 32-29).[12] Abdominocentesis will confirm the presence of blood.

INTRAABDOMINAL MASSES. Abscessation, hematoma, and neoplasia are the top differential diagnoses for intraabdominal space-occupying lesions, each of which can be located just about anywhere in the peritoneal cavity, in or attached to bowel, other intraabdominal viscera (i.e., spleen, kidney, liver), or the peritoneum. Space-occupying lesions appear as soft tissue densities of variable shapes and acoustic properties that distort normal sonographic architecture (Fig. 32-30). Although the definitive cause of an intraabdominal mass is often not discernible ultrasonographically, both abscesses and hematomas appear as either uniform echogenic or loculated space-occupying masses of mixed echogenicity. Chronic abscesses may be characterized by the presence of a thick echogenic capsule. An abscess or hematoma more commonly is isolated to a single location, whereas metastatic neoplasia should be considered if variable sized space-occupying lesions that distort normal ultrasonographic

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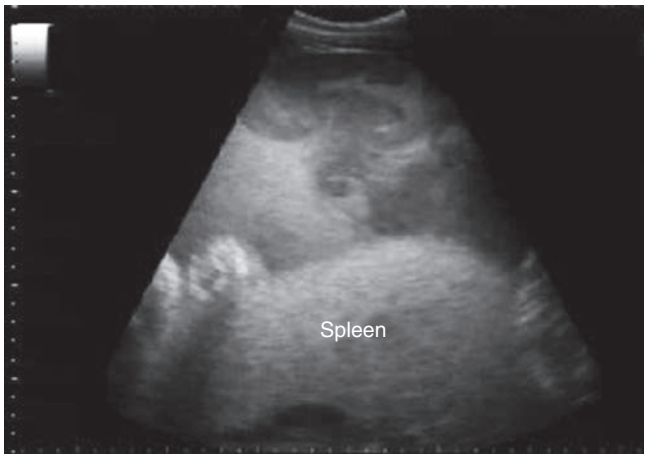


FIG. 32-29 This image was obtained from the lower left flank of a horse with hemoabdomen using a 3.5-MHz curvilinear transducer set to a depth of 24 cm. The left of the image is ventral. Blood displaces the spleen from the left body wall and appears as swirls of mixed echogenicity between the spleen and left body wall.

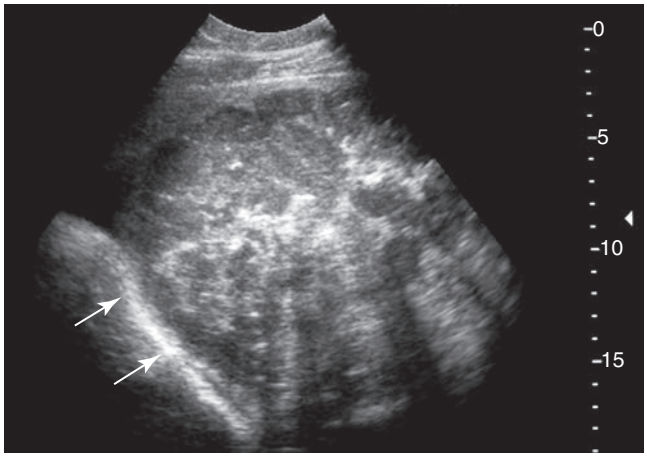


FIG. 32-30 This image was obtained from the gastrosplenic window using a 3.5-MHz curvilinear probe set to a depth of 19 cm. The left of the image is dorsal. A large mixed echogenicity mass occupies the space adjacent to the stomach wall *(arrows)* in the location normally occupied by the spleen. This horse had abdominal lymphosarcoma.

anatomy are present in multiple locations. Although the ultrasonographic appearance of a space-occupying lesion may not help determine the cause, ultrasonography can be a useful guide to biopsy or aspiration of the affected tissue.

Other Imaging of the Alimentary Tract

Radiography

In the horse the alimentary tract is a dynamic and complex environment to evaluate with any modality. Because of the size of the animal, as well as the distinct difference between air and soft tissue, radiographs are a useful diagnostic tool for evaluating the teeth, pharynx, esophagus, stomach, and intestinal tract. Portable x-ray units with maximal kilovolt peak (kVp) settings up to 100 and the upper limits of the milliampere-second (mAs) settings at 30 make it possible for ambulatory practitioners to obtain diagnostic images of the head and cranial esophagus. However, to obtain images of the thoracic esophagus and abdomen, a referral clinic with a more powerful x-ray generator is usually required.

For the average foal, abdominal radiographs have been described using exposures ranging from 80 to 88 kVp and 20 to 26 mAs for the

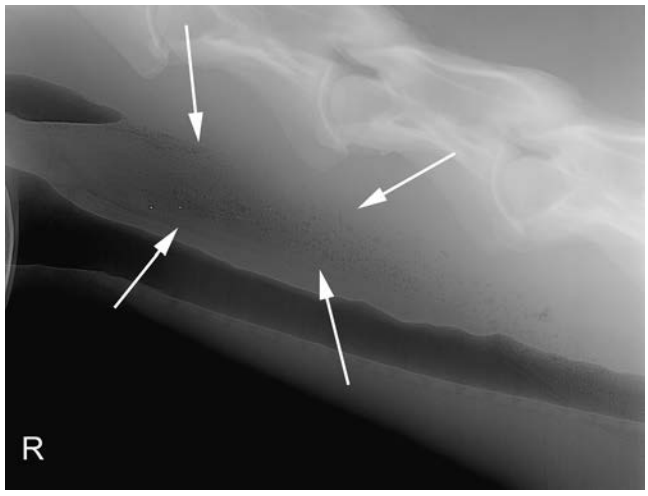


FIG. 32-31 Standing lateral radiograph of a 13-year-old Morgan gelding with an esophageal tear. Note the tubular region of small gas opacities caused by air trapped around the outer border of the esophagus *(arrows)*. An esophageal perforation secondary to an ingested foreign body was confirmed with endoscopy.

standard abdomen.[29] In adult horses, exposures range from 60 to 140 kVp and 20 to 70 mAs.[30,31] To do a complete evaluation of the abdomen, it is recommended that the abdomen be divided into four quadrants (cranioventral, midabdominal, caudodorsal, and caudoventral).[30] Large cassettes (35 cm × 43 cm) and fast screens are also needed to ensure a diagnostic image is obtained. Because of the large amount of scatter radiation produced from the high exposure and thickness of tissue penetrated, an 8:1 to 10:1 grid should be used.[29-33] Alternatively, an air gap technique can be used to prevent image degradation.

Availability of computed radiography (CR) and digital radiography (DR) has greatly increased the diagnostic capabilities of conventional radiographic examinations. Both of these systems, available to equine practitioners, are considered indirect imaging modalities in which the x-ray photon interacts with an intensifying screen to convert the x-ray photons to light. This light then interacts with an imaging plate: film, as with a conventional radiographic system; within a photostimulable phosphor, as with CR; or within a flat-panel detector, as with DR. Regardless of the method, these images are considered "indirect" because the x-ray photon is first changed to light and then detected by the imaging medium.[34] The main benefits of CR and DR are the increased latitude of the film. It is possible to change the contrast and grayscale levels after the exposure if an adequate number of photons is available to the detector. The DR systems also offer a rapid evaluation of the image because the cassette is directly connected to the computer. This allows the portable systems to show radiographic images within 10 seconds after the exposure is made. In contrast, the CR system requires the cassette to be placed into a reader in order to display the image. Finally, because both CR and DR are generally Digital Imaging and Communications in Medicine (DICOM) compliant, this allows any specialists with standard medical imaging software to view the images via a compact disk (CD) or via the Internet.

Survey radiography is generally helpful in evaluating the cervical esophagus for evidence of rupture as well as to evaluate the abdomen. Esophageal ruptures secondary to an obstruction or vigorous placement of a nasogastric tube result in a small volume of gas that tracks just dorsal to the trachea (Fig. 32-31). This can be confused with a tracheal laceration; however, with tracheal lacerations, generally the gas accumulation will surround the trachea and the volume of gas within the subcutaneous tissues and the cranial mediastinum will be severe. In addition, esophageal obstructions, also called *choke,* can sometimes be identified on survey radiographs depending on the material that is causing the obstruction and the amount of air or

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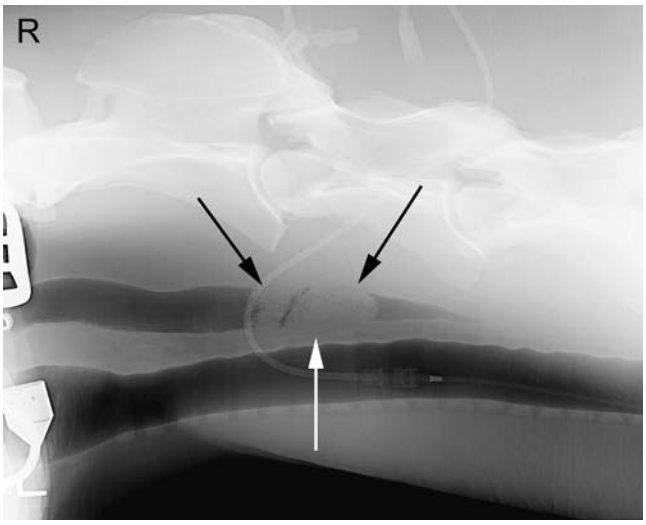


FIG. 32-32 Standing lateral radiograph of a 12-year-old Quarter Horse mare. Note the ovoid mass surrounded by gas just dorsal to the trachea *(arrows)*. This lesion was a mixture of hay and grass.



FIG. 32-33 Standing lateral radiograph of a 4-year-old Arab mare with a history of colic. Note the large amount of opaque material within the ventral colon, likely secondary to sand accumulation.

contrast medium that is able to surround the structure (Fig. 32-32). Although the nature of the obstruction cannot be determined, the extent of the abnormality can sometimes be identified.

Abdominal radiography is useful for evaluating the small and large intestines for sand accumulation, enterolithiasis, impactions, or small intestinal disorders in foals. When sand is ingested, it generally will accumulate within the large colon along the ventral abdomen[8] (Fig. 32-33). Radiography has been found to be a useful method for monitoring the resolution of sand impactions after medical management; however, sequential examinations are needed to verify that the

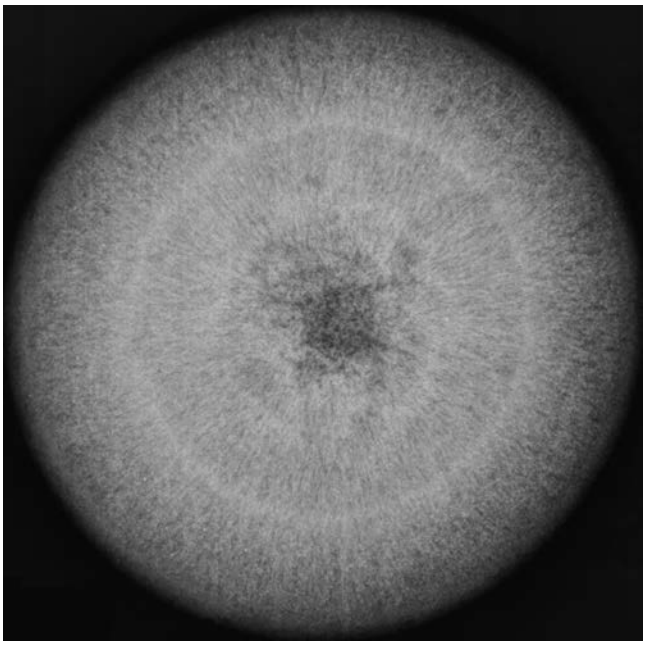


FIG. 32-34 Radiograph of enterolith obtained after surgical removal from the small colon. Note the variation in opacities caused by the various types of minerals that are contained within the enterolith.

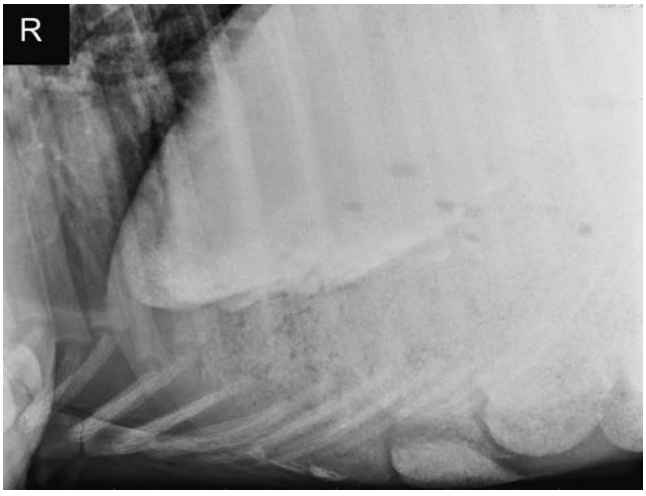


FIG. 32-35 Standing lateral radiograph of a 3-year-old Paint Horse gelding with a pelvic flexure impaction. The radiograph shows the sternal flexure with a large amount of granular material and a small amount of sand accumulation in the ventral colon.

volume of sand has reduced.[31] If the volume of sand is large enough, it is difficult to determine if an enterolith is present because of summation of the two lesions. Enteroliths are solid concretions of mineral that usually form around a nidus, such as a metallic foreign body (Fig. 32-34). The mineral composition is varied, as illustrated by the different opacities present within the enterolith. Radiographs have a 96.4% positive predictive value to detect enteroliths in high-prevalence areas. These enteroliths were generally found to be within the midabdominal radiograph, and 67% of small colon enteroliths caused large colon distention, which was also identified on radiographs.[30] Impactions are more difficult to diagnose because usually there is just increased feed accumulation within the abdomen. Although no enterolith or obstruction is identified, granular material can be seen, usually within the ventral colon near the sternal flexure. This is because pelvic flexure impactions will cause the feed material to accumulate orad, causing distention of the left ventral colon (Fig. 32-35). Intestinal disorders such as functional ileus secondary to

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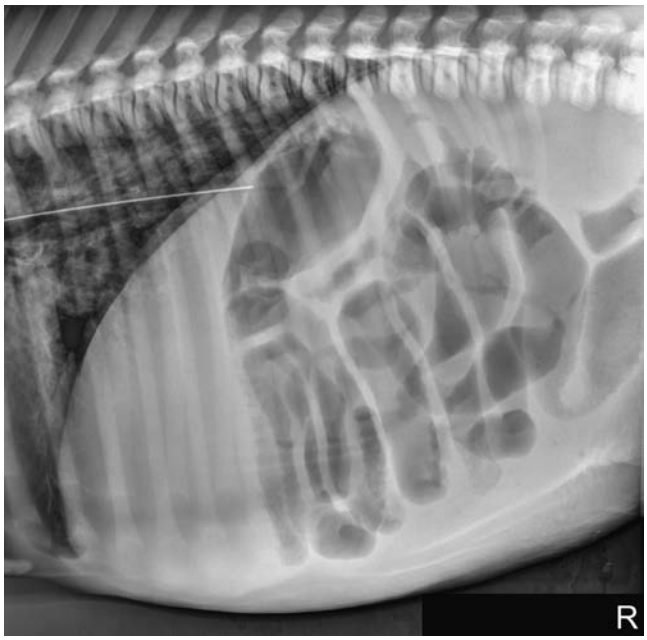


FIG. 32-36 Standing lateral radiograph of a 1-day-old, premature Quarter Horse filly. Note the large amount of gas-distended intestine. Because of the large amount of small intestinal distention, functional ileus is the primary differential diagnosis.

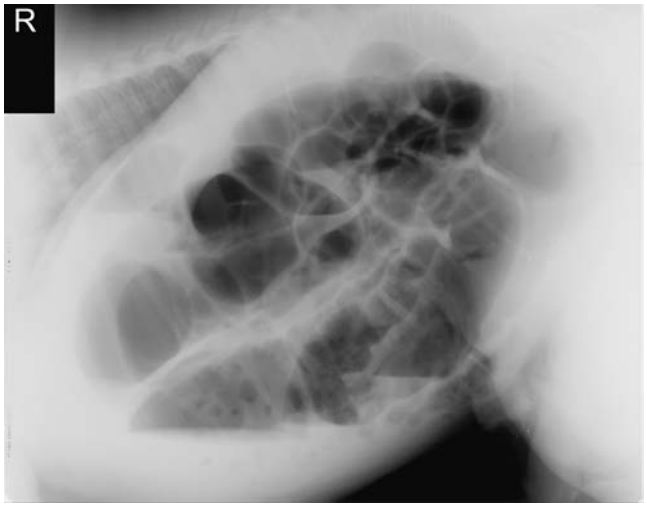


FIG. 32-37 Standing lateral radiograph of a 2-day-old Thoroughbred colt with a meconium impaction. Note the large amount of gas distention of the colon.

enteritis (Fig. 32-36) or obstruction secondary to intussusception or meconium impaction (Fig. 32-37) in foals can also be identified on abdominal radiographs. These images show large dilation of the small intestine, and differentiation between functional and mechanical ileus in foals is generally based on the size of the intestine and the volume of gas that is present.[32] Evaluation of the abdomen using ultrasound may aid in qualifying the small or large intestinal motility as well as identifying the source of an obstruction if the determination on radiographs cannot be made.

Radiography also allows for the use of contrast medium administration to further outline the alimentary tract as well as evaluate pharyngeal function and esophageal motility.[35-37] First administering approximately 60 mL of barium sulfate paste or liquid orally via a 60-mL dosing syringe and obtaining radiographs of the laryngeal region and esophagus provides useful information about swallowing as well as large obstructions. If the barium liquid is identified dorsal to the soft palate, within the larynx or trachea, abnormal pharyngeal

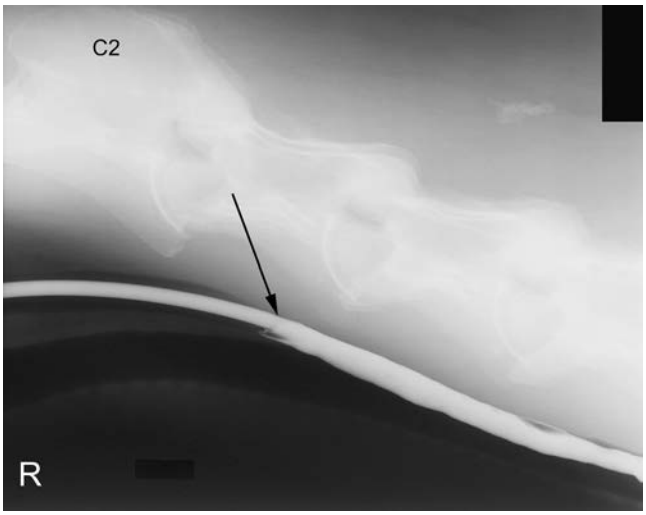


FIG. 32-38 Standing lateral radiograph showing a normal esophagram using barium liquid. The *arrow* marks the region where the nasogastric tube ends. This is approximately at the level of C3.

function is likely present.[35] The barium paste will coat the pharynx and esophagus and is useful in identifying any ulcerations or irregularities in the mucosal surface. After those procedures have been performed or if there is no evidence of an oropharyngeal dysphagia, then an esophagram is performed. This procedure is done using approximately 200 to 500 mL of barium sulfate liquid diluted 1:1 or 2:1 with water to bring the total volume to 500 to 1000 mL. This liquid is administered through a nasogastric tube or cuffed endotracheal tube placed within the cranial esophagus to the level of C2 to C3. If a cuff is available, the cuff can be inflated with approximately 10 mL of room air. A radiograph is then made to verify that the tube is not within the trachea, and when it has been confirmed that the tube is within the esophagus, the dose of barium is administered using a stomach pump. Toward the end of the dose, while still pumping the liquid, radiographs of the cranial, mid, and caudal esophagus are obtained (Fig. 32-38). The use of the pump provides distention of the esophagus to help identify strictures or irregularities in the esophageal wall.

Positive (barium sulfate) and negative (room air) contrast medium radiography have also been used to evaluate the stomach and intestinal tract through oral administration of contrast medium,[29,38,39] and the rectum and colon have been evaluated via retrograde administration of contrast medium.[39] These methods allow for the evaluation of the stomach, intestinal tract, and rectum for regions of obstruction as well as ulcerations, tumors, motility disorders, and/or malformations. Although these methods have been described, ultrasound has virtually eliminated the need to expose personnel and patients to the repetitive, high doses of radiation needed to obtain sequential radiographs of the abdomen.

Computed tomography (CT) and magnetic resonance imaging (MRI) are of little use for evaluation of the alimentary tract (except for the head). This is mainly because of the size of the patient compared with the size of the gantry and bore in CT and MR units, respectively. Dental disorders such as abscesses and fractures can be clearly seen on CT images, especially after three-dimensional reconstructions (Fig. 32-39), and CT is also useful to detect pharyngeal and esophageal masses that may not be fully identified with conventional radiographs. CT and MRI can be used in foals that can be placed within the gantry or bore of the magnet; however, because of the motion of the gastrointestinal tract and the long acquisition times used with respiratory gating sequences, MRI has not been used widely to evaluate the thorax or abdomen. A single case report has been published that described the use of contrast esophagography and CT to aid in the surgical planning of a persistent right fourth and left sixth aortic arch that caused a vascular ring anomaly in a foal.[40]

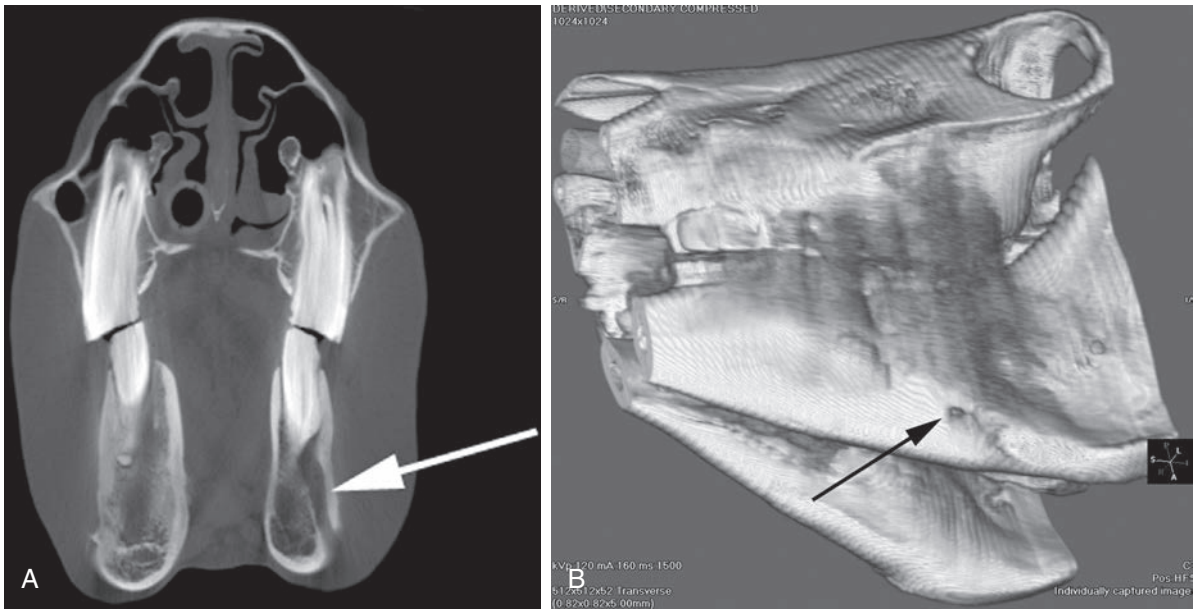


FIG. 32-39 These are transverse **(A)** and three-dimensional **(B)** reconstructed computed tomography images of the head of a 4-year-old pony mare with chronic draining tracts from the mandible. The *arrows* illustrate the tract through the mandible that communicates with the apical portion of the left mandibular first molar (tooth #309).

However, the applications for these technologies have yet to be realized.

Scintigraphy

Nuclear medicine is a widely used modality for imaging the gastrointestinal tract in humans and animals. Although physical obstruction can be assessed with endoscopy, ultrasound is unable to identify the pylorus in the normal horse because of the peripheral nature of the colon and colonic gas. Nuclear medicine provides a functional evaluation of the pylorus to determine if delayed gastric emptying compared with normal horses is present. This modality works better than gastric emptying with barium sulfate because of the minimal invasive nature and ease of acquisition of images. However, the need for a gamma camera to generate the images and the licensing requirements to handle radioactive material make this modality less universally available. The primary use for evaluating the gastrointestinal tract with scintigraphy is to evaluate gastric emptying time.[41-44] Two protocols have been outlined in the references provided. The first uses the readily available technetium-99m pertechnetate (^{99m}Tc) bound to disofenin or sulfur colloid.[42,45,46] This combination of radioisotope and radiopharmaceutical is fed in a pelleted ration alone or mixed with radiolabeled eggs. The normal range for the $t_{1/2}$ gastric emptying has been reported to be 1.49 ± 0.17 hours[23] and 1.56 ± 1.08 hours.[22] The other method is the carbon-13 (^{13}C) bound to octanoic acid breath test (^{13}C-OABT). This method was validated compared with the ^{99m}Tc sulfur colloid and found to have similar results compared with the solid phase gastric emptying $t_{1/2}$.[40] The main difference is that the ^{13}C-OABT is measured in the exhaled breath of the horse and with spectroscopy rather than with a gamma camera. The rationale for ^{13}C-OABT is that because a gamma camera is not needed, this test may be more portable and useful for field investigations.[45]

Another nuclear medicine procedure in the realm of alimentary tract evaluation involves the use of ^{99m}Tc hexamethyl propyleneamine oxime (^{99m}Tc-HMPAO). This procedure allows for radiolabeling WBCs in order to determine areas of inflammation.[47,48] The use of ^{99m}Tc is a matter of convenience because it is also used in equine bone imaging. Detection equipment, such as a low-energy, all-purpose collimator, is readily available in many practices. HMPAO is used because it binds to granulocytes and therefore should travel to areas of increased inflammation.[48] HMPAO also associates with the reticuloendothelial system, enabling localization within the lungs, liver, spleen, kidneys, and urinary bladder. The main drawback is that with the activity bound to WBCs there is a general lack of anatomic information, which can cause lesion localization to be difficult.[48] Although this technique is expensive and labor-intensive, the results from the limited studies available appear encouraging.

Biopsy

The decision about whether to obtain a biopsy is often based on the ease of obtaining a sample and the relative value of the evaluation that can be made. Very small samples, such as those obtained with an endoscope biopsy instrument, are relatively easy to obtain, but they provide limited information. Full-thickness bowel specimens, obtained by means of ventral midline or flank laparotomy, are more difficult to obtain, but they provide much more information. Laparoscopic techniques to safely obtain full-thickness intestinal biopsies are described and may be more practical than laparotomy.[49]

Taking a biopsy sample by endoscopy allows the practitioner to choose the biopsy site on the basis of the appearance of the mucosal surface, which most frequently reflects an inflammatory disorder. Conversely, when a biopsy sample is obtained through laparotomy, the serosal surface of the bowel may not reflect a disorder within the bowel wall. In such instances it may be useful to obtain several biopsy specimens. Rectal mucosal biopsies are easily performed. Many instruments can be used to obtain the biopsy specimen, and a uterine biopsy forceps works well. A fold of mucosa can be pinched readily between two fingers, and a sample of this tissue is obtained this way. The size of the sample is adequate for histologic or bacteriologic examination.

Fecal Examination

Cytologic, biochemical, bacteriologic, immunologic, and electron microscopic evaluations can be performed on fecal samples. In addition, observation of the consistency and color, the presence of foreign material such as sand or gravel, and the presence of parasites should be included in the examination of the alimentary system. In addition to fecal consistency, fecal particle size can be used to evaluate the efficiency of mastication or the colonic transit time. Increased particle size, with loose or watery stool, is suggestive of decreased colonic transit time.

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Cytologic examinations are used primarily to evaluate the parasite burden of the animal. Ova of large and small strongyles, tapeworms, round worms, and *Strongyloides westeri* are most common. Coccidia are observed occasionally but are clinically unimportant. Examination of fecal WBCs has been advocated in the evaluation of horses and foals with enterocolitis. Because these cells are very labile, their presence in large numbers indicates that an inflammatory process is present and that the inflammation is in the distal colon or is associated with decreased transit time.

Determination of fecal occult blood has been recommended to diagnose gastric ulcers, duodenal ulcers, and other potentially hemorrhagic disorders of the alimentary tract. However, the usefulness of this test has been shown to be quite limited, because negative results can be obtained when blood is present in the proximal portion of the gastrointestinal tract.[50] The sensitivity of most commercially available tests is poor, giving negative results in the face of severe gastric bleeding.

Fecal culture is an essential component in the evaluation of many patients. In bacteriologic culture techniques for fecal samples, selective media that are designed to isolate *Salmonella* are routinely used. These media include selenite broth, tetrathionate broth, brilliant green agar, XLD agar, and *Salmonella-Shigella* agar. Less selective media, McConkey and eosin methylene blue agars are desirable to culture other potential gram-negative bacterial pathogens such as *Escherichia coli,* but the mere presence of *E. coli* in the feces does not determine its pathogenicity. Enterotoxigenic *E. coli* have been isolated from foals with diarrhea, but special tests, such as polymerase chain reaction (PCR) assays, must be performed to determine whether an isolate produces enterotoxin. Rapid enzyme-linked immunosorbent assays (ELISA) for detection of enterotoxins of *Clostridium difficile* (*C. difficile* Tox A/B Test, TechLab, Blacksburg, Va.) and *Clostridium perfringens* (*C. perfringens* enterotoxin test, TechLab, Blacksburg, Va.) in fecal specimens are available at diagnostic laboratories.

The presence of rotavirus in a fecal sample can be determined by use of an ELISA or an agglutination test. Both assays test for the presence of viral antigen in the feces. PCR assays are also available to detect rotaviral nucleic acids. The ELISA is reported to be more sensitive than the agglutination test but is less specific. Therefore the agglutination test is likely to give more false-negative results, and the ELISA test is likely to give more false-positive results. The ELISA test is more time-consuming and inconvenient to perform than the agglutination test. When rotavirus is a concern, particularly as a farm problem, a reasonable approach is to screen fecal samples with the agglutination test and repeat testing of samples that yield negative findings with the ELISA or PCR.

Some diagnostic laboratories have developed sensitive and specific multiplex PCR tests for panels of gastrointestinal pathogens (equine coronavirus and rotavirus, *Lawsonia intracellularis, Cryptosporidium, Rhodococcus equi, Neorickettsia risticii, Salmonella* spp., and *Clostridium difficile* toxins A and B), that provide relatively rapid diagnostic information that can be used alone or in combination with culture or antigen detection methods.

Absorption and Digestion Tests

Tests that evaluate the ability of the equine intestinal tract to digest and absorb nutrients have a more limited clinical application than in human or small animal medicine, but they can be useful in the evaluation of horses with chronic weight loss, suspected small intestinal inflammation or neoplasia, gastric and small intestinal partial obstruction, and postoperative small intestinal malabsorptive disorders. For absorption tests to be diagnostic, the intestinal disorder must either be diffuse or affect the delivery to and transit through the small intestine.

Maldigestion tests are performed to evaluate exocrine pancreatic function and small intestinal mucosal brush border disaccharidase activity. Pancreatic exocrine deficiencies have not been described in the horse, probably because equine pancreatic secretions consist primarily of water and bicarbonate and have less enzymatic activity than in monogastric omnivorous species. Mucosal brush border disaccharidase-related maldigestion is relevant in viral and bacterial enteritides of foals, particularly rotavirus and coronavirus enteritides. As a result of these viral infections, there is loss of the superficial villous epithelial cells of the small intestine, in which the disaccharidases lactase, cellobiase, maltase, sucrase, and trehalase are located.[51] Lactase levels are greatest in young suckling foals, and loss of this enzyme activity, secondary to loss of the mucosal villous cells, leads to lactose maldigestion. Lactose tolerance can be tested by administering a 20% solution of D-lactose at a dose of 0.5 to 1 g/kg. This dose should result in an approximate doubling of the serum glucose level within 60 minutes of administration.[52]

Clinically applicable absorption tests include the D-glucose and D-xylose absorption tests. The glucose absorption test has the advantage of being relatively easy and inexpensive to perform. However, cellular uptake and metabolism of glucose, as well as intestinal absorption, influence the results and thus are undesirable variables. The xylose absorption test is therefore advantageous because it more directly measures intestinal absorptive capacity. The results of both tests, however, are affected by gastric emptying rate and small intestinal transit time. In the United States, D-xylose is available only through chemical suppliers and only for research purposes; its availability for clinical diagnostic use is restricted.

The D-glucose and D-xylose tests are performed similarly. After an 18- to 24-hour fast, a 10% solution of D-glucose or D-xylose, 0.5 to 1 g/kg, is administered through a nasogastric tube. For the measurement of glucose, blood is collected in sodium fluoride tubes, and for the measurement of D-xylose, blood is collected in heparinized tubes. Samples are taken at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after administration. Peak levels, which normally range from 20 to 25 mg/dL, occur 60 to 120 minutes after administration, and levels thereafter should decrease. The normal curve resembles an inverted V. Variability in absorption curves occurs as a function of age and type of feed the horse is given.[53] Delay or flattening of the absorption curve may reflect delayed gastric emptying, increased intestinal transit time, or impaired intestinal absorption.[54] Accurate interpretation of the results of these tests depends on the results of other diagnostic evaluations. In addition, different types of diets have been shown to affect the height, although not the shape, of the absorption curves significantly. In general, diets that have higher digestible energy content result in a lower peak in the curve.

Breath Tests

In humans, dogs, and cats, breath tests are used to assess a variety of intestinal disorders. The urea breath test is used as part of an assessment of *Helicobacter* status of the patient,[55] but this is not an issue for horses. The hydrogen breath test is used in assessments of intestinal bacterial overgrowth and in determination of carbohydrate digestion and absorption in the intestine. In patients with an abnormal intestinal bacterial population or carbohydrate malabsorption, there will be excessive bacterial fermentation of carbohydrate, with one by-product being hydrogen. Because hydrogen is freely diffusible from the bowel into the blood, and from the blood into the alveoli, measurement of exhaled hydrogen gas can be used to assess the status of intestinal bacterial fermentation of carbohydrates. In horses, the hydrogen breath test is most applicable to conditions in which there is carbohydrate malabsorption and thus increased delivery of soluble carbohydrate to the large intestine for bacterial fermentation to occur. There are two reports of this technique in horses, one in which different carbohydrate substrates were evaluated in ponies[56] and another in which the hydrogen breath test was used in conjunction with D-xylose absorption in nine horses with a variety of clinical disorders.[57] In the study with ponies ($n = 7$), fasting resulted in negligible levels of breath hydrogen excretion. Sustained increases in breath hydrogen concentration greater than 10 parts per million (ppm) were observed for all ponies after the ingestion of oats or the administration of wheat flour, for three ponies after the

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administration of glucose and xylose, and for two ponies after the administration of lactulose and lactose. The pattern of breath hydrogen excretion was subject to variation among animals after the ingestion of identical test meals. In the clinical study the diseased horses showed higher fasting breath hydrogen (H_2) levels (range 7.5 to 61.5 ppm) than normal horses (range 0 to 5 ppm). After xylose administration, none of the healthy animals showed an increase in breath H_2 production, and five of diseased animals showed increases in breath hydrogen. In this group of patients, abnormalities in hydrogen breath measurement were more apparent than abnormalities in D-xylose absorption.

Dentistry and Oral Disease

Jack Easley

The equine species has evolved as a continuously grazing animal, developing its own dental form and function over millions of years. Its oral and dental structures provide the horse with the ability to detect, prehend, masticate, and begin the digestion of mixed grass forage. As humans have domesticated and confined the horse, we have altered its diet to consist of grazing improved pastures and more interval feedings of dry hay, grain, processed forages, and concentrates. Selective breeding and domestication practices have increased the incidence of equine dental and oral disease in modern equine populations.

Anatomy and Function

The structures the horse uses in eating include tactile and prehensile lips, hypsodont incisors, premolars and molars, the facial bones, muscles of mastication, tongue, hard palate, buccal mucosa, cheeks, olfactory organs, taste buds, salivary glands and ducts, and the blood vessels and nerves that support them. The equid oral cavity is long and cylindrical and is the entrance to the alimentary canal. The muscular lips form the entrance to the mouth, which is bound laterally by the cheeks, dorsally by the palate, and ventrally by the body of the mandible and the mylohyoid muscles. The caudal aspect of the mouth is composed of the soft palate, root of the tongue, and epiglottis and is continuous with the oropharynx.[1-2]

The blood supply to the mouth is derived from the maxillary, mandibular, labial, and sphenopalatine arteries. The venous drainage is chiefly through the linguofacial veins. Nerve sensation to the mouth, cheeks, and lateral aspect of the tongue is derived from the mandibular and maxillary branches of the trigeminal nerve (cranial nerve [CN] V). The sublingual and mandibular salivary glands, lacrimal glands, and facial and labial muscles receive motor function from the facial nerve (CN VII). The hard palate has a central raphe, dividing the surfaces into right and left halves. The portion of the palatal mucosa just caudal to the upper incisors may appear swollen in the young horse when permanent incisor teeth erupt. This normal mucosal enlargement seen in 2- to 5-year-old horses has historically been referred to as *lampas*. Further caudal, the hard palate becomes more concave and contains paired transverse ridges that traverse the cavity. These ridges are instrumental in moving a food bolus caudally in a spiral fashion as the horse masticates forage. The muscular tongue sits in the bottom of the mouth between the paired hemimandibular rami. The tongue is supported in a sling formed by the mylohyoideus muscles. The root of the tongue is attached to the lateral aspect of the soft palate, the pharynx, and the hyoid bone. The lingual muscles receive their motor innervation from the hypoglossal nerve (CN XII) and sensory innervation from the lingual and glossopharyngeal nerves (CN IX).

The mandible is the largest bone of the face and is formed by the paired hemimandibles, which fuse rostrally at the mandibular symphysis when the horse is approximately 2 to 3 months of age. Each hemimandible is composed of a horizontal and a vertical ramus. The horizontal ramus contains the alveoli of the teeth in the lower jaw. The vertical ramus terminates with the coronoid process rostrally and the mandibular condyle caudally. The temporalis muscle inserts on the coronoid process.

Between the incisors and the rostral aspect of the mandibular cheek teeth in the horizontal rami of the mandible, is a large diastema; the interdental space or "bars" of the mouth. Canine teeth, if present, are located in this area. In the young horse, the central border of the mandible is wide and round. Eruption swellings or bumps are often seen on the ventral border of the mandible of young horses as the permanent mandibular cheek teeth erupt. As the horse ages and eruption of the mandibular cheek teeth continues, the ventral border of the mandible takes on a sharper, angled appearance.

The paired incisive (premaxillary) bones form the rostral part of the upper jaw and contain the alveoli of the upper incisors. Caudally, the incisive bone becomes thinner and forms the rostral part of the hard palate. The suture line between the incisive bones and the maxillary bones is an anatomically weak area and a common site of facial fractures. The upper canines (if present) are situated just caudal to this suture line.

The paired, large maxillary bones extend from the incisive bone rostrally to the nasal bones dorsally and lacrimal bones caudally. The facial crest is a prominent ridge of bone on the lateral aspects of the maxillae. This crest continues caudally as the zygomatic process and joins the molar and temporal bones to form the zygomatic arch. The ventromedial aspects of the maxillary bones join to form a horizontal shelf that provides rigid support to the majority of the hard palate. The alveoli of the upper canines, premolars, and molars are embedded in the maxillae. The positions of the upper cheek teeth alveoli are somewhat variable, but usually the alveoli of the first two cheek teeth lie rostral to the maxillary sinuses. The third and fourth cheek teeth lie within the rostral maxillary sinus in the young to middle-aged horse. The caudal two cheek teeth lie within the caudal maxillary sinus. Each alveolus is separated by transverse interalveolar bony septa.

The horse has seven paired paranasal sinuses: ventral conchal, dorsal conchal, frontal, sphenopalatine, caudal maxillary, rostral maxillary, and ethmoidal sinuses. The rostral and caudal maxillary sinuses are contained within the maxillae and are usually separated by a thin bony septum, although this septum often breaks down with sinus disease. The long infraorbital canals (one on each side of the head) traverse longitudinally through the maxillary sinuses, encasing the large paired infraorbital nerves.

Sinusitis can occur secondary to disease of the third, fourth, fifth, and sixth upper cheek teeth and classically results in a unilateral, malodorous nasal discharge. In a young horse, virtually the entire maxillary sinuses are occupied by dental alveoli. Therefore, as the facial bones grow and reserve crowns of the upper cheek teeth erupt, the cheek teeth move forward and ventral in the sinus compartments. The maxillary sinuses drain into the back of the nasal cavity via a slit-like aperture, the nasomaxillary opening. The medial compartment of the rostral maxillary sinus is called the *ventral conchal sinus*. This compartment has poor drainage and is a common site for inspissated pus to accumulate. Its secretions must drain dorsally over the infraorbital canal into the lateral compartment of the rostral maxillary sinus. Drainage from both sinuses courses into the caudal middle meatus adjacent to the drainage angle of the caudal maxillary sinus.

The temporomandibular joint is a synovial joint formed by the articulation of the squamous temporal bone and the condylar process of the mandible. The joint lies approximately 15 cm above the level of the occlusal surface of the cheek teeth. The joint cavity is large and divided in two by a cartilaginous intraarticular disc. The joint is bound by a tight capsule and lateral and caudal ligaments. The equine temporomandibular joint has a wide range of lateromedial movements (allowing the medial directed power stroke of mastication) but limited vertical and rostrocaudal movements.

As a result of the wide lateromedial range of the temporomandibular joint, motion associated with the power stroke of chewing,

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the masseter and pterygoid muscles are the most highly developed muscles of mastication in the horse. The powerful masseter muscle originates along the full length of the facial crest and zygomatic arch and has wide insertions along the caudolateral aspect of the mandible. The superficial masseter muscle fibers run almost vertically while the deep fibers course in a ventrocaudal direction. The masseter pulls the jaw to the ipsilateral side and also contributes to closure of the jaw. The medial and lateral pterygoid muscles have origins and insertions similar to those of the masseter and these lie on the medial aspect of the mandible. The digastricus muscle originates on the occipital bone and attaches to the caudal aspect of the mandible and is small as a result of the minimal effort required to open the jaw with gravity assistance. The temporalis muscle, whose function is jaw closure, is also small and poorly developed in the horse due to limited vertical opening of the temporomandibular joint. The muscles of mastication are innervated by the motor branch of the mandibular nerve, which originates from the trigeminal nerve (CN V).

Teeth

At approximately 6 months of age, the foal has erupted 24 deciduous teeth. Development of the cranial and facial bones during the first 2 to 3 years of life allows room for the expansion of the dental formula from 24 deciduous to between 36 and 44 permanent teeth in the mature horse. The mature mouth of the horse contains six incisors each in both the upper and lower jaws and six permanent upper and lower cheek teeth on each side of the mouth (Fig. 32-40). The rostral three cheek teeth are premolars, and the caudal three cheek teeth are molars. Incisors and premolars have deciduous and permanent sets. Molars erupt at an older age and do not have deciduous counterparts. The cheek teeth of the upper jaw are broad and square, whereas the lower cheek teeth are narrower and rectangular shaped. The cheek teeth in each quadrant of the horse's mouth are commonly referred to by number, from rostral to caudal (1 to 6). The inconsistent and vestigial first premolar, often referred to as a "wolf tooth," is not included in the 1 to 6 nomenclature. To help avoid confusion, the American Veterinary Dental College Nomenclature and Classification Committee has endorsed use of the Modified Triadan Tooth Numbering System for the horse.[3] This three-digit tooth numbering system is based on a full phenotypic dentition composed of 44 total teeth. The first digit designates the quadrant and arcade location and whether the dentition is deciduous or permanent. The numbering sequence starts with 1 for the permanent upper right, 2 for the upper left, 3 for the lower left, and 4 for the lower right. As the permanent dentition is designated using numbers 1 to 4, the deciduous teeth quadrants are numbered 5 to 8. In each dental quadrant, the first central incisor is always 01 with incisors numbered 01 to 03. The canines, whether present or not, make up the 04 position in this formula. The premolars are numbered 05 to 08 and the molars 09 to 11.

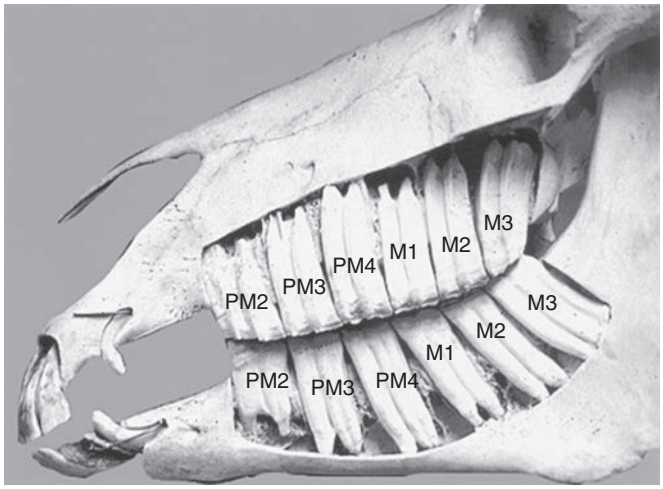


FIG. 32-40 Lateral view of equine cadaver skull. *M,* Molar; *PM,* premolar.

The equine incisor and molarized cheek teeth are hypsodont and have long anatomic crowns, which erupt throughout the life of the animal by a dynamic process of periodontal ligament and alveolar bond remodeling. The tooth crown is the enamel-containing portion of the tooth. When these hypsodont teeth first erupt, the occlusal surface is covered with cementum and enamel. As the teeth are subjected to masticatory forces and abrasive forage, the thin layers of occlusal cementum and enamel wear away, exposing the true or functional occlusal surface of the tooth. This process is termed *coming into wear.* The functional occlusal surface of hypsodont teeth is composed of thin, brittle sheets of hard enamel, sandwiched between softer but more stress-resistant layers of cementum and dentin. This three-textured occlusal surface is self-sharpening and very wear- and fracture-resistant. At the time of eruption, there are no true roots, and teeth are divided into apical and coronal regions, but most of the crown (reserve crown) lies within the alveolus. True roots are formed gradually over a period of 2 to 3 years after eruption.

The incisors and upper cheek teeth have enamel crown invaginations termed *infundibula.* These invaginations partially fill with cementum that receives its blood supply from the occlusal soft tissues covering the tooth prior to eruption. This shallow infundibulum presents on each incisor tooth and has a wide opening at the occlusal surface referred to as a "cup." As the tooth wears down over time, the small bottom portion of the infundibulum is exposed at the occlusal surface and is called the "spot." The upper cheek teeth have a rostral and caudal infundibulum. These extra enamel cones give the central area of these teeth a hard chewing surface. The center of the cement lake that fills the infundibulum contains a hole of variable diameter. This channel is a remnant (ghost) of the central blood vessel that supplied nutrition to the now dead infundibular cementum.

The interior of the tooth is composed primarily of dentine with primary dentine lining the common pulp chamber of the newly erupted hypsodont tooth. The pulp chambers of hypsodont teeth are active throughout the horse's life with primary and secondary dentine continually produced within the pulp cavity. This process of continuous secondary dentine production prevents pulp exposure at the occlusal surface as the tooth wears. The depth of secondary dentine at the occlusal surface of the pulp horns (seen as a brownish area on the occlusal surface of the tooth) varies in horses but is usually 5 to 7 mm thick. No age-related increased thickness of occlusal secondary dentine has been found in recent studies, which supports the theory that secondary dentine deposition is at least partially regulated by occlusal stimulation.[4-5] The pulp cavity in the young equine permanent cheek tooth is very large. With increasing age, it divides into smaller pulp chambers (or horns) as dentine deposition increases. From 2 to 4 years after eruption, mandibular cheek teeth have a distinct, apically located, common pulp chamber that communicates with the pulp horns. The number of pulp horns has been well described with five pulp horns present in the 07s to 10s, six pulp horns in the 06s, and six or seven pulp horns typically present in the 11s (Fig. 32-41). Two to four years after tooth eruption, the dentine divides the endodontic system of most of the mandibular cheek teeth into two distinct compartments or roots. Each compartment consists of a root canal, a pulp chamber, and two or three pulp horns. The maxillary cheek teeth, as well as the 311 and 411, have three roots: one palatal and two buccal. Because of the continuous production of cementum around the apical or root portion of the tooth and continuous crown wear, old equine teeth are primarily composed of dentine and cementum. When most of the crown enamel has worn away, the softer dentine and cementum are quickly worn flat, leading to the condition known as "smooth mouth."

Innervation of the dental structures is supplied by the trigeminal nerve (CN V), which exits the skull just below the ear. This nerve traverses rostrally and divides into the ophthalmic, maxillary, and mandibular branches. The maxillary nerve enters the caudal maxilla

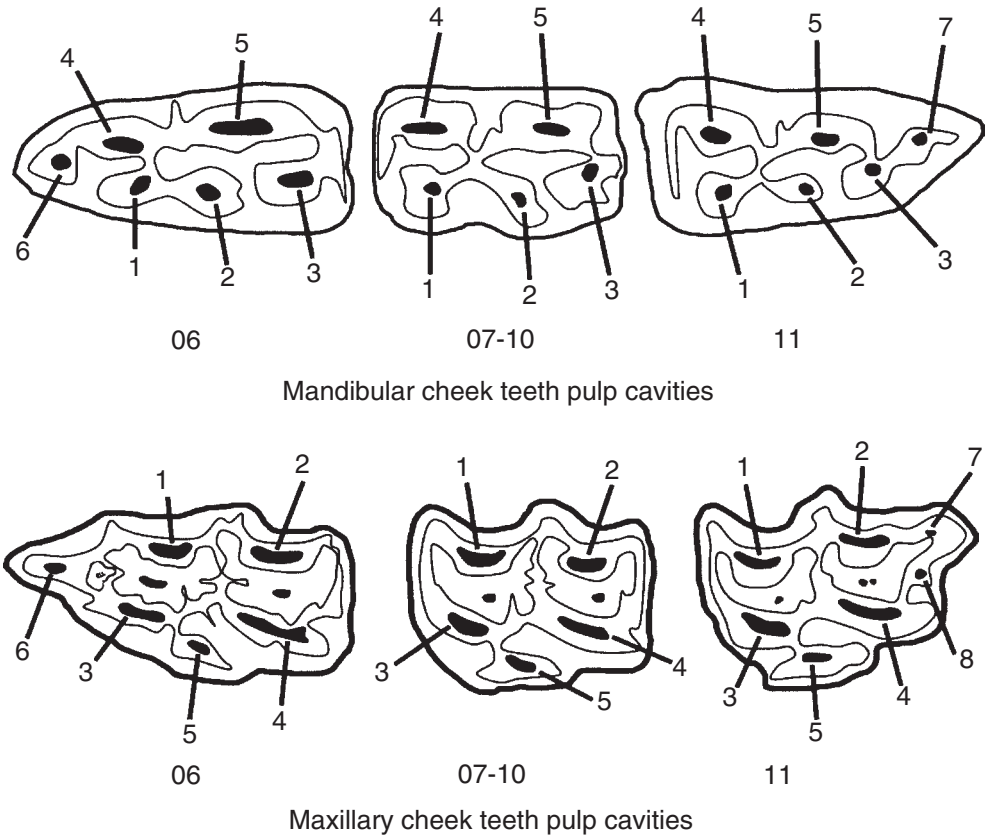


FIG. 32-41 Diagram of the premolar and molar pulp horns seen as areas of dark stained secondary dentine on the occlusal surface.

ventral to the orbit via the maxillary foramen and runs through the maxilla in the infraorbital canal, giving off branches to supply the maxillary cheek teeth. A branch of the infraorbital nerve exits the maxilla at the infraorbital foramen, just rostral and dorsal to the facial crest. The mandibular nerve runs medially along the mandible, with the lingual and inferior alveolar nerves arising as a common trunk and passing rostrally between the pterygoideus medialis and the ramus of the mandible. The inferior alveolar nerve enters the mandibular canal on the caudomedial aspect of the mandible, innervating the mandibular teeth. The mental nerve exits the mandibular canal via the mental foramen at the rostrolateral aspect of the mandible just rostral to the mandibular cheek teeth and supplies the ipsilateral soft tissues over the incisive portion of the mandible.

Rudimentary first premolars (wolf teeth) are constant in fetal life in both upper and lower jaws. Many never develop to the point of eruption but instead degenerate and become incorporated in the maxilla or mandible. The uppers erupt in 20% to 80% of horses; the lowers rarely erupt (1% to 5%).

Equine males normally have two upper and two lower canine (bridle) teeth. The upper canine erupts just caudal to the suture between the incisive and maxillary bones. Lower canines are forward, producing a long lower diastema or interdental space. Canines are absent or rudimentary in most mares.

The horse is anisognathic, meaning the bottom jaw is narrower (by about 25%) than the upper jaw. The lateral excursion of the jaw during mastication favors occlusal wear of the buccal aspect of the lower and the lingual aspects of the upper molar arcades. The horse's jaw anatomy and jaw motion have an effect on the angle of the molar tables.[7] As the horse chews, the jaw moves in rotational motion from side to side with limited rostral-caudal excursion. The construction of the molars with interdigitations of enamel, cementum, and dentine allows for uneven, continuous wear with a sharp, serrated surface when the horse is grazing. The extent of lateral excursion of the mandible during normal mastication is affected by the length of the stem or roughage in the horse's ration. A horse on pasture or hay has a full or wide area of mandibular excursion. However, horses eating pellets or concentrates have a limited range of lateral jaw excursion. Horses with limited lateral jaw excursion have incomplete wear of the molar surface, which predisposes the arcades to sharp enamel edges, a vaulted ceiling of occlusion, or the serious problem of shear mouth. Malocclusion of the incisor or molar arcades perpetuates abnormal wear patterns that will eventually predispose to diastema and secondary periodontal disease.

Rostral or caudal molar malocclusions or eruption problems (displaced, deformed, delayed eruption, missing or supernumerary teeth) lead to uneven dental wear. Horses with asymmetry between the upper and lower molar arcades (due to mandibular fracture, facial injury, congenital deformities such as brachygnathism [parrot mouth] and prognathism [sow mouth] or an abnormally narrow mandible in relation to the maxilla) often have abnormal tooth wear in the form of sharp enamel points, dental overgrowths (hooks or ramps), shear mouth, step mouth, or wave mouth.

The dynamic change that takes place in the mature horse's head continues at a slower rate throughout life, with continual eruption and crown wear of the hypsodont premolar, molar, and incisor teeth with their large reserve crowns and slowly forming short root structures. With continuous eruption and wear of the equine hypsodont teeth, all horses eventually wear their teeth smooth to the root.

Equine Dental Developmental Abnormalities

Equine dental developmental abnormalities can involve tooth number, morphology, or position in the dental arcades. Abnormalities of dental development and eruption occur quite commonly in the horse and result in a wide range of clinical conditions. A congenital/developmental problem that presents at the time of tooth eruption often leads to acquired dental problems as the teeth continue to erupt and wear. Some developmental abnormalities of the

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teeth of the very young horse may not cause it to exhibit clinical signs until middle age. Consequently, several different dental abnormalities, whose pathogenesis may be interrelated, are often present at the time of clinical presentation.[8-9]

Supernumerary Teeth

Supernumerary teeth are teeth in excess of the normal expected number in any of the dental arcades. This disorder has been referred to as *polydontia* or *hyperdentition*. Supernumerary teeth can be loosely categorized morphologically into two categories: (1) supplemental teeth that resemble teeth of the normal series in crown and root morphology but not always in size, and (2) rudimentary or dysmorphic teeth that are abnormally shaped and smaller in size than normal teeth.

In general, these extra teeth are encountered at the caudal aspects of the molar arcades, but supernumerary teeth can also occur lingual, buccal, or rostral to the normal arcades. Clinical signs most commonly associated with supernumerary cheek teeth are dental overgrowths and diastemata, which often cause secondary periodontal disease.

Supernumerary incisors are reported more often in horses than are supernumerary cheek teeth. The main differential diagnosis for supernumerary incisors or cheek teeth is retained deciduous teeth. In some cases, it may be clinically difficult to determine whether an extra tooth is a retained deciduous tooth or a supernumerary tooth. Examination with a radiograph that encompasses the entire affected dental arcade is often necessary to diagnose this condition. Radiographic examination of the affected jaw is often indicated to determine the identity of an extra tooth. A retained deciduous tooth has a more mature root and a shorter reserve crown than the adjacent permanent teeth. Such distinguishing characteristics are visualized with radiographs.

Management of horses with supernumerary teeth is generally limited to regular assessment of the dentition, coupled with aggressive dental floating to minimize the opportunity for soft tissue damage by unopposed elongations or sharp enamel points. If complications such as severe periodontal disease or maxillary sinusitis occur, the supernumerary tooth or displaced adjacent tooth should be extracted and appropriate therapy undertaken to manage associated pathology.

Oligodontia

Oligodontia is the congenital absence of a tooth germ or retention and inclusion of a tooth within the jaw. It is difficult to differentiate developmental oligodontia from acquired tooth loss caused by damage to, or displacement of, a dental bud from injury. It is possible for permanent tooth germs of a young horse to be damaged, displaced, or removed when deciduous teeth or jaw bones are injured. Absence of a tooth in the dental arcade leads to dental drift or tipping of adjacent teeth. Lack of wear of the antagonist to the missing tooth can lead to dental elongations and abnormal mastication. Radiographic examination is often necessary to confirm a diagnosis of true oligodontia. Oligodontia may be associated with other epidermal defects such as poor development of hair and hooves.

Dental Dysplasia or Hypoplasia

Dental dysplasia (i.e., abnormal growth and/or development of a tooth or teeth) may result in an irregularly shaped tooth that does not fit well into a dental row. The poor fit may lead to food entrapment and periodontal disease. Enamel hypoplasia has been associated with certain drugs or chemicals administered to the dam during gestation, or it may be idiopathic in origin. Dental dysplasia can involve the abnormal formation of the entire tooth structure or only a single tissue type. Abnormal enamel morphology, such as branched pulp horns or abnormally shaped teeth, has been observed. Enamel acts as the scaffolding and template for the deposition of dentine and cementum. These tissues follow the abnormal enamel pattern, and consequently all three calcified tissues are dysplastic. Cemental hypoplasia usually involves the infundibular portion of the tooth, but it can also be seen as a defect of the peripheral, coronal, or reserve crown or root cement.

Abnormal Dental Eruption

Abnormal dental eruption, or maleruption, is often seen following trauma to developing teeth or surrounding bones, but it has also been reported to be congenital or idiopathic in origin. Cheek teeth can become vertically impacted when dental buds are developing in abnormal or crowded areas in the dental arcades. Teeth may become rotated or otherwise displaced as a result of developmental malpositioning of tooth buds or overcrowding before, during, or after eruption.

Dixon reported that 70% of cheek tooth displacements were developmental in origin as a result of overcrowding of the cheek tooth row at the time of eruption.[6] This research team frequently found that if a cheek tooth was displaced in an arcade, the same tooth in the contralateral arcade was also displaced. The remaining 30% of tooth displacements were believed to be due to abnormal tooth positioning, which may result in non-eruption of the displaced teeth if they are sufficiently horizontal to the adjacent teeth. Developmental diastemata or abnormal spaces or gaps between cheek teeth are often due to insufficient angulation of teeth to achieve food compression between adjacent teeth. Another cause for diastemata is embryonic teeth developing too far apart.

A detailed oral examination includes checking teeth for proper number and position. Only the exposed crown of the equine tooth can be visualized in the oral cavity. Because many developmental defects may not be recognized simply by oral examination, the dentition should be examined radiographically to further delineate abnormalities.

Malocclusions of incisors are congenital, developmental, or acquired in origin. Mandibular brachygnathism (parrot mouth) is a congenital incisor malocclusion, the origin of which is usually genetic. Many horses have some degree of overjet of the premaxillary incisors, but the overjet rarely causes a problem with prehension, unless the premaxillary and mandibular incisors totally lack occlusion. If brachygnathism is discovered when the foal is young, treatment may correct, or at least improve, the functional outcome for the animal.

A main consideration with an incisor overjet in the adult horse is the cheek teeth malocclusions that accompany this condition. The maxillary cheek teeth arcades are usually positioned rostral to the mandibular cheek teeth, causing a rostral overgrowth of the 106 and 206 and a caudal overgrowth of the 311 and 411. Those check teeth malocclusions must also be reduced to allow for proper lateral jaw excursion and mastication.

Prognathism or undershot jaw occurs with less frequency in the horse and is seen most commonly in miniature or dwarf breeds. Early detection and correction of the malocclusion in the foal may prevent the condition from worsening with age. The cheek teeth should be evaluated for malocclusion caused by overgrowths of the 111, 211, 306, and 406.

Bony malformations of the head can result in malocclusion of the incisors and cheek teeth. These bony skull curvatures or asymmetries usually result in an offset or diagonal incisor bite. Some bony malformations, such as campylorrhinus lateralis (wry nose) are obvious, but subtle changes to the large bony plates in the head can be difficult to recognize. Care must be taken with correcting dental overgrowths associated with malocclusions. Overgrowths should be corrected gradually to prevent damage to pulp horns (which can lead to apical infection), dysphagia, and pain. Often, incisor malocclusion remains, but regular maintenance may prevent it from worsening.

Acquired Dental Disease

Dental disease is grouped into four basic categories or groups:

1. Type 1 dental malocclusions and abnormal occlusal wear patterns
2. Diastema and periodontal disease

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3. Infundibular or peripheral dental caries
4. Disease of the dental pulp

All of these basic dental disease types are interrelated, and in most clinical cases, the horse suffers from a combination of varying degrees of dental disease types.[8-11]

Alignment of the dental arcades is critical to the normal wear of equine dentition. Historically, abnormal dental wear patterns have been described as dental crown elongations, descriptive terms for which include *hooks, ramps, waves, steps,* and *transverse ridges.* These elongations usually involve a normal tooth that is out of occlusion with an abnormality in the opposite arcade. This opposite diseased, damaged, misplaced, or missing tooth and/or jaw should be evaluated when elongations are found. Most dental elongations are treated by reducing the crown height of the long tooth or portion of a tooth with a rasp or grinding instrument. Care should be exercised in dental reductions not to cause iatrogenic damage to the tooth, such as pulp horn exposure, thermal injury, or crown fracture. The viable pulp is usually 7 to 10 mm deep but may be as close as 2 to 4 mm below the occlusal secondary dentine. Therefore crown reductions should be carried out in stages, reducing no more than 3 to 4 mm of occlusal crown in a session.

Periodontal disease is often a painful dental condition and is described as the leading cause of "quidding" in horses. Gingivitis is the mildest form of periodontal disease and is often associated with local irritants such as plant awns or bristles, bot fly larvae, traumatic injury, or chemical exposure. Oral ulceration can be a reflection of systemic disease, such as vesicular stomatitis. Another mild form of periodontal disease affects primarily young horses 2.5 to 5 years of age when deciduous teeth (caps) are shed and permanent incisors and premolar teeth are erupting. A more progressive form of periodontal disease is seen in older horses as a result of the chronic effects of diastema or spaces that develop between teeth that are not aligned properly in the arcade. Diastema can form during tooth development when dental buds are spaced too far apart or abnormally angulated so that the teeth in a dental row are not properly compressed, allowing forage to become trapped between teeth. This is usually a progressive condition that, when left untreated, becomes worse over time. Spaces between teeth or teeth out of alignment in the dental row also predispose to abnormal wear patterns on the affected and opposing dental arcades.

Treatment of periodontal disease involves treating both the cause and the effect of the problem. Diastema with feed trapped in the gingival margin often responds to thorough cleaning with dental picks, irrigation, or both. Reduction of any associated abnormal wear patterns is also indicated. In more refractory cases, it may be necessary to open or widen the diastema with a special burr or a right angle grinder. This procedure may allow the horse's masticatory actions to more easily channel food in and out of the gap, thus preventing or reducing entrapment of feed or stagnations and decay. This procedure is not without risk of pulp exposure and should only be performed by a professional with the proper equipment and training.

Some practitioners have had positive results using high-pressure irrigation to clean out periodontal pockets, followed by packing the area with a perioceutic agent such as doxycycline gel or a powdered antibiotic. This technique packs a high concentration of antibiotic in contact with the infected and inflamed tissues and acts as a temporary barrier to recontamination. This form of therapy may need to be repeated on a regular basis (every 4 to 6 months) in order to achieve long-term positive results. Severe periodontal disease that has resulted in bone loss and tooth mobility will only respond positively to extraction of the involved teeth.

Dental caries usually involves the cemental layer of the tooth. Peripheral cemental caries is seen secondary to periodontal disease. The most common type of cemental caries involves the infundibular portion of the incisor and maxillary cheek teeth. All incisor infundibula show some evidence of cemental decay in the cup or open portion of the infundibula. The upper cheek teeth have two infundibula, each with a cup or open portion incompletely filled with cementum.[10] As the tooth wears, the infundibulum that is filled with cementum (except for the small central vascular channel) is exposed at the occlusal surface (referred to as the "spot" in the incisor teeth). Feed and other products of mastication can be compressed into a ghost of a vascular canal, and some degree of decay is always present. The infundibulum contains dead cementum and is lined with a layer of enamel. Therefore this decay does not usually lead to an inflammatory response or dental infection. True dental disease secondary to infundibular decay can occur only if this protective enamel layer is penetrated. Developmental malformations of the infundibulum may weaken this enamel and predispose to dentine exposure and pulp disease. In upper cheek teeth with very large vascular channels or deformed infundibula, decay may weaken the tooth and predispose the tooth to excessive crown attrition or midsagittal crown fracture. Infundibular caries lesions are innocuous in most cases, but the length of infundibulum and dental wear can predispose to dental elongations on the opposite occlusal arcades (wave mouth). The abnormal wear patterns need to be reduced on a regular basis. To help strengthen the tooth and delay the progression of infundibular decay, some practitioners advocate cleaning out abnormally enlarged infundibular vascular channels and partially packing and sealing them with a dental composite material. As advanced diagnostic methods such as CT become more readily available to equine practitioners, these abnormal appearing infundibula can be better evaluated and treated.

Disease of the dental pulp is seen primarily in younger horses between the ages of 4 and 10 years. The type of dental disease usually presents as an infection and associated inflammatory changes at the apical region of the tooth. The clinical presentation will be different depending on the structures adjacent to the apex of the affected tooth. Infections of the lower first four cheek teeth present as ventral mandibular swellings with a draining tract. The last two lower cheek teeth are embedded in the portion of the mandible surrounded by the large muscles of mastication. These muscles are often enlarged or swollen and, on ultrasound evaluation, exudate may be seen accumulating between the mandible and muscle. The upper rostral two or three cheek teeth apices are closely associated with the facial bones and nasal passages. The caudal three or four upper cheek teeth are in the maxillary sinuses and can be associated with secondary sinusitis. Unilateral nasal discharge is often seen when the upper cheek teeth are affected. Because pulp disease compromises the tissue responsible for the production of secondary dentine, the pulp horns and root canals on the affected teeth do not fill with secondary dentine as they should. In the later stages of pulp disease, the affected tooth usually shows some degree of pulp horn decay on the occlusal surface. This weakened, decayed area may predispose to crown fracture.[11-12] Medical therapy has been successful in the management of apical disease in the early stages of disease. Chronic apical infections are usually treated by surgically removing the tooth and treating any associated bone or sinus disease. Equine teeth have been removed surgically by three methods:

1. Extraction via oral approach
2. Repulsion via apical approach
3. Elevation via lateral buccotomy approach

More recently, minimally invasive procedures using small radiographic guided pins for repulsion or an oral trocar approach to teeth through the cheek have been developed.

Salivary Glands and Ducts

Saliva hydrates and lubricates the oral cavity, facilitates swallowing, prevents tooth demineralization, and regulates the oral flora.[13] Diseases of the salivary glands and ducts, including sialoadenitis, salivary calculi, salivary mucocele, trauma, and neoplasia are uncommon in the horse. During oral examination, the openings of the salivary ducts should be noted. The parotid salivary duct communicates with the oral cavity via a flap-like, dorsally directed papilla, opposite the upper third of fourth check tooth. The mandibular salivary duct opens into the mouth on the lateral aspect of the sublingual caruncle.

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The sublingual salivary ducts (approximately 30 in number) are seen as small pores in the sublingual recess.

Slobbering or drooling may indicate excessive accumulation of saliva in the mouth (sialism, ptyalism, or dysphagia). Heavy metal toxicity, parasympathomimetic poisoning, cholinesterase inhibiting insecticides (organophosphates or carbamates), neurologic disease, and stomatitis may cause ptyalism. A cholinergic agonist (slaframine) can cause "slobbers" in horses consuming forages, mostly commonly clover, contaminated with rhix. Dysphagia can be caused by esophageal obstruction (choke), oral foreign body, rabies, or other neurologic disease.

Sialoadenitis may be the result of salivary duct obstruction from accumulation of exudate or mucus or an ingested foreign body or sialolith. Sialoliths occur in the parotid duct and can cause duct obstruction and salivary retention, which can lead to glandular atrophy or acute sialoadenitis, swelling, and rupture. On palpation, sialoliths are usually hard, smooth, and painless enlargements over the course of the parotid duct on the lateral aspect of the jaw. The diagnosis of sialolith is straightforward and should differ from that of trauma, tooth abscess, or facial tumor. Surgical removal, usually orally, and primary closure often yield good results.

Salivary mucocele is an accumulation of salivary secretions in a single or multiloculated cavity adjacent to a ruptured salivary duct. A ranula is a type of mucocele that occurs secondary to obstruction of the sublingual salivary duct. Treatment consists of creating a salivary fistula into the oral cavity or excising the mucocele and associated salivary gland.

Laceration or iatrogenic injury to the salivary ducts can lead to salivary cutaneous fistula. These injuries can be surgically repaired by reapposing the severed duct and creating an oral opening for the duct or resecting the salivary gland. Oblation and sclerosis of the gland has been achieved by flushing 1% formalin solution into the duct. Wounds involving the salivary glands can usually be handled by cleansing, débridement, and primary skin closure.

Benign mixed tumors, adenocarcinomas, and acinar cell tumors of the salivary glands have been reported in horses. Local invasion of a salivary gland by tumor originating in adjacent tissues and metastasis of melanomas to the parotid salivary gland in older gray horses are more common.

Equine Oral Tumors

Equine oral tumors are rare, making up a very small percentage of the facial or mandibular swellings. These tumors can be divided into three basic types: odontogenic, osteogenic, and secondary.[14]

Odontogenic tumors are derived from remnants of dental epithelium. Five types have been recorded in the maxilla and mandibles of horses. They are ameloblastomas, ameloblastic odontomas, complex odontomas, compound odontomas, and cementomas. Because of their rarity, ill-defined biological behavior, and poorly defined radiographic features, diagnosis can be difficult. Histopathology can be confusing because of variation in appearance at different sampling sites and age-related changes in tumor appearance.

Primary bone tumors are rare in the horse and if present, they are usually benign. More than 80% of equine osteosarcomas occur in the head region. As is the case with odontogenic tumors, disagreement remains on histologic classification, terminology, and nature of tumor. In addition to gross and histologic examination, correlation of history clinical, radiologic, and some biochemical findings by clinicians and pathologists is often essential to establish a diagnosis.

Secondary tumors of the head include extensions of oropharyngeal squamous cell carcinoma, lymphosarcoma, papilloma, and melanoma. Squamous cell carcinoma is the most frequently reported oral tumor in the horse. Generally, these tumors are seen in older horses and there is no gender or breed predilection. There are many treatment options and methods of controlling the progression of oral tumors. Radiotherapy, hyperthermia, chemotherapy, cryosurgery, immunotherapy, autogenous vaccines, photodynamic therapy, laser therapy, and surgical resection have been used with variable success.

Dental Examination

Biannual dental examination of the horse should be performed as part of a routine health maintenance program. Improved eating efficiency and oral hygiene are the most important considerations from a medical standpoint. However, often owners are more enthusiastic about dental care because of its positive effects on the horse's sensitivity to the bit and athletic performance. Written documentation of dental examination findings is necessary to formulate a problem-oriented treatment plan and follow age-related dental changes and progress after maintenance, treatment, or both. A consistent routine on the part of the examiner increases the efficacy and quality of the examination (Box 32-1).

Several signs may be obtained from history or observed in a horse suffering from dental problems. A history of abnormal head carriage or head tossing when being ridden or eating, longer time taken to eat, halitosis, dysphagia, drooling or hypersalivation, dribbling feed (quidding), or eating hay before grain suggest that a dental problem exists. Indicators of dental problems in performance horses include tail wringing, headshaking, lunging in or out on the track, and fighting the bit (refusing to collect the head). Chronic colic or choke can result from improper mastication of feed. Reluctance to drink cold water may be a result of dental pain.[8,9,15]

Good dental health is extremely important to the equine digestive system. Proper mechanical digestion of feed allows better carbohydrate absorption in the small intestine and improved fiber fermentation in the cecum and large colon. Improperly masticated roughage and concentrate leads to poor digestibility in the small and large intestine because of large feed particles with decreased surface area per mass. This decreased surface area does not allow proper enzyme degradation or bacterial fermentation. Findings of whole grain or stem particles longer than 5 mm during manure examination indicate improper mastication.

As a routine aspect of the dental examination, a horse's overall condition should be evaluated in light of its use and dietary intake. A body score should be assigned, as this is a more accurate way to subjectively record body condition[16] (Table 32-1). Objective assessment of body condition using a scale, weight tape, or photographs is also beneficial and provides good data to assist in proper documentation and management.

The age of the horse should be considered during evaluation.[17] Different conditions need to be addressed for each stage of the horse's growth, development, and maturity. The use of the horse should be considered during evaluation, because horses that wear a bit might require dental care that differs from dental care required by horses that don't wear a bit. Stable surroundings should be carefully observed for evidence of vices (such as cribbing) or poor eating habits (such as quidding or dribbling grain).

The physical examination begins with observation of the horse's body condition, attitude, and temperament. The horse should be approached from the left side of the shoulder. Body and head conformation should be considered during evaluation of the masticatory system. Horses with small heads have more of an angle in the curve of the mandibular ramus (i.e., curvature of Spee) and are predisposed to dental crowding and ramps on the lower dental arcades. Observe the head from both sides and the front, noting any asymmetries, protuberances, or swellings. Check the tongue for proper movement, abnormal swellings, or signs of trauma or injury; also check the horse's ability to swallow. Lacrimation should be noted as well as any nasal discharge. Neurologic evaluation should be considered if any cranial nerve deficits are detected. Finally, examine the head by palpating the mandibular rami, masticatory muscles, temporomandibular joints, and submandibular lymph nodes to detect enlargements or asymmetry.

The frontal and maxillary sinuses should be percussed with the horse's mouth open. The width between the mandibular ramus should be noted as this correlates with the room in the mouth for the bit. The sides of the head lateral to the upper dental arcade should be compressed from the orbit, moving forward to the first cheek tooth

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BOX 32-1

Recommended Timetable for Routine Dental Examinations and Common Corrective Procedures

Birth

1. Examine for congenital defects of lips or palate.
2. Assess tongue motion and strength.
3. Identify dental malocclusions.
4. Evaluate all body systems.

Recommended Procedures

1. Provide genetic and orthodontic consultation and perform corrective surgery if necessary.
2. Look for other problem signs such as underdeveloped carpal or tarsal bones, ruptured extensor tendons, hernias, etc.

6 to 8 Months of Age

1. Check incisor and premolar occlusions.
2. Check to see that all incisors have erupted.
3. Check for sharp enamel points or hooks.
4. Check tongue and buccal mucosa for ulcers.

Recommended Procedures

1. Provide orthodontic consultation, and float teeth if necessary.

16 to 24 Months of Age

1. Check for expanded lower wolf teeth eruption.
2. Check points and hooks on premolars.
3. Look for bit lesions.

Recommended Procedures

1. Float teeth and round off rostral corner of premolar 2.
2. Extract wolf teeth.

2 to 3 Years of Age

1. Look for upper and lower wolf teeth.
2. Check corners of mouth and interdental space for bite injuries.
3. Evaluate incisors and molars for eruption and premolars for points and loose or retained deciduous teeth.

Recommended Procedures

1. Float outside of upper and inside of lower cheek teeth.
2. Remove caps if present and ready.
3. Extract wolf teeth.

3 to 4 Years of Age

1. Check corners of mouth and interdental space for bit injuries.
2. Evaluate incisors for retained deciduous teeth or supernumerary teeth.
3. Evaluate molars for eruption and premolars for points and retained or loose deciduous teeth.
4. Evaluate size and shape of lower jaw and percuss sinuses.
5. Check for blind wolf teeth.

Recommended Procedures

1. Remove caps if present and loose.
2. Float teeth.
3. Remove wolf teeth.

4 to 5 Years of Age

1. Check all incisors for eruption and wear occlusion.
2. Check canine teeth for sharp edges or eruption delays.
3. Evaluate entire molar arcade for proper eruption and alignment (third cheek tooth).
4. Visually check upper rostral and lower caudal cheek teeth for hooks from malocclusion.
5. Digitally check for points on sharp edges of cheek teeth.
6. Percuss sinuses.

Recommended Procedures

1. Remove deciduous teeth if loose and ready.
2. Reduce hooks if present.
3. Float teeth.
4. Remove mucosa over canines if gingival cysts are present.

5 Years and Older

1. Examine mouth visually and digitally, especially noting hooks and uneven wear.
2. Evaluate canines for sharp edges and tartar.
3. Percuss sinuses.
4. Use olfactory senses to detect evidence of oral decay or gingivitis.
5. Observe incisors for even wear.
6. Evaluate lateral jaw excursion.

Recommended Procedures

1. Float teeth.
2. Remove hooks.
3. Level or shorten incisors if indicated.

at the level of the nasal notch; note any protuberances, depressions, asymmetry, or evidence of pain.

The commissures of the lip should be observed and palpated for signs of trauma from sharp teeth or improperly fitting bits. A loose-fitting halter is necessary to properly evaluate the mouth and oral cavity. If the horse is fractious or resists examination, sedation should be administered before proceeding with the oral portion of the examination. Sedation should be given after a medical assessment of the animal (i.e., consideration of temperament, breed, age, body condition, mucous membranes appearance, CRT, heart rate and rhythm, and rectal temperature).

The mouth should be rinsed thoroughly with clean water. Impacted or trapped feed in the mouth should be removed manually or by using a dental pick and irrigation. Horses with sharp buccal points on the upper dental arcade often resist the full-mouth speculum. Floating the upper arcades before applying the speculum may decrease the horses' resistance. With a full-mouth speculum in place and the head properly restrained, a detailed visual and tactile oral examination can be carried out. A bright light source is necessary to illuminate the entire oral cavity for complete visual inspection. An examiner should manually inspect all hard and soft tissue in the oral cavity. A dental mirror and pick are often necessary to see and probe the occlusal surfaces and pickets between the cheek teeth. An oral endoscopic camera can aid in the completeness of the oral examination.

Dental Imaging

Diagnostic radiology is a valuable aid in the diagnosis and management of equine dental disease. The excellent contrast among air, bone, soft tissue, and tooth substance make the head an excellent area for radiologic evaluation. Good-quality films can be obtained with portable x-ray machines and rare-earth intensifying screens without a grid. Digital and computed radiology have improved radiograph image quality and allow for high-quality images to be shared electronically for consultation with colleagues.

Indications for radiographic examination of the head include a suspicion of dental infection, maleruption, diastema, or oral pain of unknown origin. Radiographs should be obtained before, during, and after dental extraction. Any facial swelling, deformity, neoplasm, trauma, or fracture may warrant a radiograph to aid in diagnosis and management.

Radiographs can be taken in the standing, sedated horse. The head and radiographic cassette can be placed on a stand to decrease motion distortion. A lateral view centered over the rostral edge of the facial crest will demonstrate fluid line in the sinuses. The lateral view

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TABLE 32-1

Henneke Body Condition Scoring System

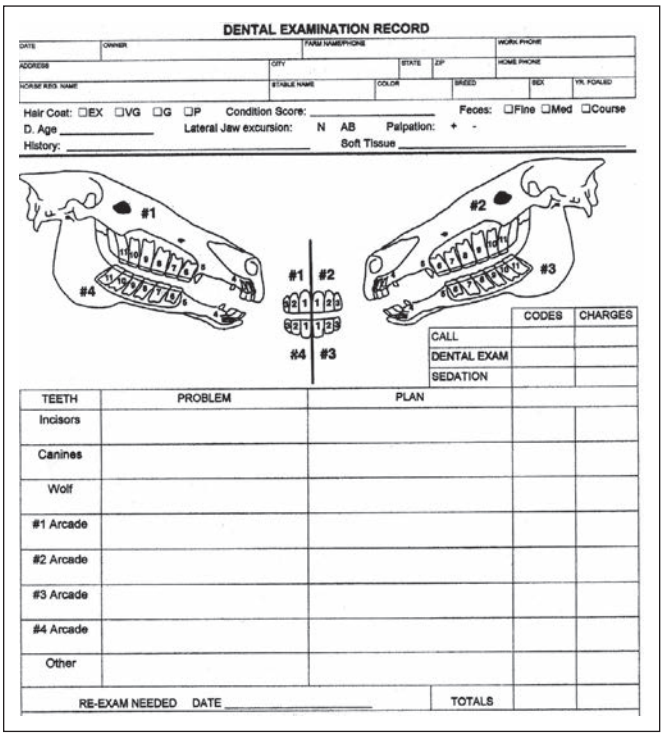
Condition	Neck	Withers	Shoulder	Ribs	Loin	Tailhead
1 Poor	Bone structure easily noticeable	Bone structure easily noticeable	Bone structure easily noticeable	Ribs protruding prominently	Spinous processes projecting prominently	Tailhead, pinbones, and hook bones projecting prominently
2 Very thin	Bone structure faintly discernible	Bone structure faintly discernible	Bone structure faintly discernible	Ribs prominent	Slight fat covering over base of spinous processes Transverse processes of lumbar vertebrae feel rounded Spinous processes are prominent	Tailhead prominent
3 Thin	Neck accentuated	Withers accentuated	Shoulder accentuated	Slight fat cover over ribs Ribs easily discernible	Fat buildup halfway on spinous processes, but easily discernible Traverse processes cannot be felt	Tailhead prominent, but individual vertebrae cannot be visually identified Hook bones appear rounded, but are still easily discernible Pin bones not distinguishable
4 Moderately thin	Neck not obviously thin	Withers not obviously thin	Shoulder not obviously thin	Faint outline of ribs discernible	Negative-crease (peaked appearance) along back	Prominence depends on conformation Fat can be felt; hook bones not discernible
5 Moderate (ideal weight)	Neck blends smoothly into body	Withers rounded over spinous processes	Shoulder blends smoothly into body	Ribs cannot be visually distinguished but can be easily felt	Back is level	Fat around tailhead beginning to feel soft
6 Moderately fleshy	Fat beginning to be deposited	Fat beginning to be deposited	Fat beginning to be deposited	Fat over ribs feels spongy	May have a slight positive crease (a groove) down back	Fat around tailhead feels soft
7 Fleshy	Fat deposited along neck	Fat deposited along withers	Fat deposited behind shoulder	Individual ribs can be felt with pressure, but noticeable fat filling between ribs	May have a positive crease down the back	Fat around tailhead is soft
8 Fat	Noticeable thickening of neck	Area along withers filled with fat	Area behind shoulder filled in flush with body	Difficult to feel ribs	Positive crease down the back	Fat around tailhead very soft
9 Extremely fat	Bulging fat	Bulging fat	Bulging fat	Patchy fat appearing over ribs	Obvious crease down the back	Bulging fat around tailhead

superimposes the dental arcades and should not be relied on to diagnose diseases involving the dental reserve crown and roots. Lesion-oriented oblique films demonstrating the root or apical portion of the upper or lower cheek teeth are helpful in diagnosis of periapical disease. Open-mouth oblique films are beneficial in evaluating the exposed crown of the dental arcades. Special 4- by 8-inch flexible dental cassettes can be used to obtain intraoral radiographs of the maxillary dental arcades. Dorsoventral views centered over the tooth in question or area of concern can demonstrate periodontal disease on the buccal aspect of the upper cheek teeth, fractured teeth, or large area of infundibular decay. Intraoral occlusal films are useful in demonstrating incisor lesions or fractures rostral to the bars of the mouth. Other imaging techniques, such as ultrasonography, nuclear scintigraphy, computed tomography, and magnetic resonance imaging are useful in the diagnosis of many oral and dental-related diseases.[18]

Treatment

A plan for treatment based on the results of history, clinical findings, and oral examination should be outlined before proceeding with any dental work. This problem-oriented approach ensures that the owner and/or trainer is informed of any abnormalities and is given a plan for treatment, as well as an estimate of the cost, before any corrective procedure is taken.

Therapy must be planned to ensure all equipment is present to complete the prescribed task. The horse should be properly restrained and adequate help present to assist in performing and completing the


DENTAL EXAMINATION RECORD

DATE | OWNER | FARM NAME/PHONE | WORK PHONE
ADDRESS | CITY | STATE | ZIP | HOME PHONE
HORSE REG. NAME | STABLE NAME | COLOR | BREED | SEX | YR. FOALED
Hair Coat: ☐EX ☐VG ☐G ☐P Condition Score: _____ Feces: ☐Fine ☐Med ☐Course
D. Age _____ Lateral Jaw excursion: N AB Palpation: + -
History: _____ Soft Tissue _____

#1 #2 #3 #4

	CODES	CHARGES
CALL		
DENTAL EXAM		
SEDATION		

TEETH	PROBLEM	PLAN		
Incisors				
Canines				
Wolf				
#1 Arcade				
#2 Arcade				
#3 Arcade				
#4 Arcade				
Other				
RE-EXAM NEEDED DATE _____			TOTALS	

FIG. 32-42 Dental record form used to document dental examination findings and treatments performed.

corrective or surgical procedures. A dental record form should document examination findings, treatment plan, and procedures performed (Fig. 32-42).

Routine Dental Maintenance

FLOATING (ODONTOPLASTY OF ENAMEL POINTS AND DENTAL CROWN ELONGATIONS). Dental floating is an age-old and routine method to correct the abnormal wear patterns associated with equine dental eruption and occlusal wear. Floating is also a procedure that allows the sculpting of the teeth to accommodate the bit. The main purpose of molar floating (leveling) is to remove points or sharp edges from the buccal aspect of the upper and lingual aspect of the lower molar arcades. Floating may also entail removing minor hooks or ramps from the rostral or caudal aspect of the arcades or leveling minor elevations on the occlusal surface of the arcades.

Proper equipment is required to reach all aspects of the cheek teeth molar surfaces completely, regardless of horse size. Smaller instruments are often needed to access the oral cavity of a miniature horse or pony. Longer, heavier instruments are often used to work in the mouths of large, warmblood, or draft horse breeds. Sharp float blades made of carbide chips or tungsten carbide planning blades make the work of floating more efficient and less strenuous than in the past. The outward curve of the upper arcade makes the central buccal area involving premolar 3 (PM3) through molar 2 (M2) the easiest to reach with the float. The area around PM2 and M3 requires an offset or angled head on the rasps to reach all extremities. In most cases the lower arcade can be floated to remove the lingual enamel points with a flat, long-handled rasp. To correct rostral and caudal hooks, specialized tools such as carbide planning blades or power burrs may be required. The use of all dental equipment requires special training and skill to prevent iatrogenic injury to the horse's mouth.

Use of a full-mouth speculum aids in the oral examination and floating procedures. Use of a speculum ensures the horse's mouth is kept in an open, safe (for the examiner as well as the animal) position for floating. In horses with slightly ramped back teeth caused by a greater curvature of Spee, a mouth speculum and a slightly curved or swivel-head float may be required to reach the table of the last molar.

In bitted horses, the rounding of the first upper and lower cheek teeth and lowering of the buccal cusps from upper PM2 and PM3 is referred to as a "bit seat" and usually requires an offset float or an S-shaped rasp. In theory, a bit seat is fashioned to prevent the soft tissue of the mouth from pressing against sharp points on the first premolars. To prevent pulp cavity exposure, care should be taken not to "overfloat" the occlusal surface of a tooth when forming bit seats or correcting overgrowths, as this could lead to a direct pulp horn exposure.[5] Routine floating and other corrective measures in the mouth may require the added physical restraint of a dental halter and mild chemical sedation.

WOLF TEETH. Wolf teeth are the first premolars to erupt and are present in 20% to 80% of horses. They are most often located in the upper arcade and seldom present in the lower arcade. Horses that are worked with a bit in their mouth benefit from having the wolf teeth extracted. Some wolf teeth are naturally exfoliated at about 3 years of age when the first cheek teeth (or 06 caps) are shed and the permanent tooth erupts. Although not all wolf teeth cause problems, a loose or sharp wolf tooth can be a distraction or even cause pain of such severity as to lead to bad bitting habits. In some instances, diagnosis of wolf tooth problems is difficult and confusing. Sometimes they do not erupt in a normal downward path, penetrating the gum but rather migrating rostrally under the gum and causing a subgingival enlargement, which in turn, is irritating to the horse. Such unerupted first premolars have been referred to as "blind" wolf teeth and should be removed. Most wolf teeth are easily elevated with the horse sedated and/or after infiltrating a small volume of local anesthetic around the tooth.

CANINE TEETH. Canine teeth are present in most male horses over 4 years old. Their unopposed position in the bars of the mouth make them unlikely to cause problems. Some mares have small or rudimentary canines that do not seem to cause a problem but can become loose or accumulate tartar and necessitate removal. Long or sharp canines in a stallion or gelding can interfere with bitting, be a nuisance or a danger to the groomer/handler, or become an area of tartar accumulation. Erupting canine teeth in the 4- to 6-year-old horse may cause an operculum to form and lead to subgingival pain and bit irritation, which may manifest as headshaking or other bad habits. The thin layer of tender mucosa should be removed over the canine if the gingival operculum is present. Severe calculus accumulation can be present on the lower canines, which predisposes to periodontal disease. Scaling calculus and frequent brushing of lower canines can control this problem in most horses.

The canine roots are long and curved, making this tooth extremely difficult to extract in the male. If the canine becomes injured, infected, or involved in painful odontoclastic tooth resorption, surgical removal through a bone flap is indicated.[19]

DENTAL CAPS. As the developing permanent tooth (incisor or premolar) pushes toward the surface, it presses on the roots of the worn down deciduous tooth, gradually cutting off that tooth's nutrition. The deciduous tooth becomes loose, its blood supply diminishes, dies, and the tooth is displaced occlusally. The osseous alveolar wall adjusts to these changes by bone production and resorption, thereby providing a new socket for the embedded portion of the newly formed permanent tooth. The remaining cap portion of the deciduous tooth has up to four "legs" (root slivers) that cover the crown of the permanent tooth. If these slivers are broken off and remain subgingivally after the cap has shed, gingivitis and periodontal disease often result.

The eruption pattern of permanent molarized dentition follows a sequence that predisposes to entrapment of deciduous PM3 and PM4.[20] Delayed shedding of deciduous premolars can predispose to gingivitis, periodontal irritation, or apical infection. Retained, split, or displaced deciduous premolars can be distracting to the training

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process of a young horse and may have been a factor in dorsal displacement of the soft palate.

Retained caps can cause displacement or delayed eruption of permanent teeth. Clinically, they present as bony enlargements on the ventral mandibular ramus or on the maxilla, rostral to the facial crest. Often, such swellings are benign. However, they can become diseased if eruption is severely inhibited or blood-borne bacteria inhabit the inflamed dental pulp, leading to anachoretic pulpitis and bony swelling with a draining tract. Caps should be evaluated visually as well as by manual palpation. A crease or indentation can be felt just above the gum line at the juncture of the separating deciduous and permanent tooth. Radiographs may be necessary to diagnose retained deciduous premolars.

Disorders of the Esophagus

Samuel L. Jones

Anatomic and Physiologic Considerations

The most cranial aspect of the esophagus is located on the median plane immediately dorsal to the trachea. However, at approximately the midcervical region (C4 to C5), the esophagus typically shifts to the left of the trachea and lies just deep to the external jugular vein.[1,2] It is here that intraluminal obstructions or the tip of a stomach tube may be visualized, and this is the region where trauma can readily result in esophageal perforation. When a stomach tube is passed, it is critical that the tube be palpated to ensure the tube is in the esophagus because jugular pulses can be confused with the appearance of the tip of the tube. In addition to its proximity to the external jugular vein, the esophagus is also located adjacent to the vagosympathetic trunk and the common carotid artery.[1] The esophagus is innervated by branches of the vagosympathetic trunk, and blood is supplied to the cervical esophagus by branches of the carotid arteries. The thoracic esophagus, which lies ventral to the trachea until it reaches the tracheal bifurcation, where it resumes a dorsal position, receives its blood supply from the bronchoesophageal artery. Venous drainage is via the external jugular veins in the cervical esophagus and the esophageal vein in the thoracic esophagus.

The muscular wall of the esophagus increases in thickness as the esophagus courses distally, while the lumen gets smaller.[1] The esophagus is not covered by a serosa except for a very short segment that traverses the abdominal cavity between the diaphragm and the stomach.[2] Instead, the outer wall of the esophagus is composed of adventitia that is loosely attached to surrounding tissues. This loose connection allows movement of the esophagus during swallowing and during movement of the neck. The cranial two thirds of the esophageal wall consists of skeletal muscle, whereas the distal third of the esophagus is composed of smooth muscle. Although the muscular layers are composed of an outer and an inner layer, similar to the remainder of the gastrointestinal tract, the skeletal muscle layers are oriented obliquely to one another.[1] This, and an abundant submucosa, enables extensive dilation of the esophagus as a bolus of food moves toward the stomach. In addition, the velocity of esophageal contraction is faster in the skeletal muscle segment of the esophagus compared with the distal smooth muscle segment.[3] The muscle layers become oriented in more of an outer longitudinal and inner circular configuration in the caudal esophagus.[1] In the resting collapsed state, redundant esophageal mucosa and submucosa become oriented in longitudinal folds. The mucosa is composed of stratified squamous epithelium that is continuous with the stratified epithelium of the cardiac portion of the stomach.[1]

The cranial esophageal sphincter is formed by the cricopharyngeus muscle and maintains a resting intraesophageal pressure of approximately 85 mm Hg and a postdeglutition pressure as high as 200 mm Hg. Although the caudal esophageal sphincter is anatomically indistinct, resting intraesophageal pressure in this region is maintained at approximately 13 mm Hg, and postdeglutition pressure in the caudal esophagus may be as high as 100 mm Hg. The pressure in the caudal esophagus is maintained at approximately 10 mm Hg higher than the intraluminal pressure of the stomach.[3,4] Although the higher pressure in the distal esophagus has been implicated as the cause for the inability of most horses to vomit and for gastric rupture, other factors such as a poorly developed vomiting reflex may be more important.[5]

Diagnostic Considerations

Esophageal disease should be a differential diagnosis in any horse that demonstrates excessive salivation. Such signs also indicate the need to assess hydration, electrolyte levels, and acid-base status. In a study in which horses had continual loss of saliva via an experimentally placed esophagotomy, abnormalities included hypochloremia, hyponatremia, and hypokalemia.[6] This results from the relatively high levels of these electrolytes in saliva. Furthermore, because horses depend on dietary intake of potassium, hypokalemia would be exacerbated in a horse that was also unable to eat because of esophageal obstruction. Loss of salivary fluid and bicarbonate also results in dehydration and metabolic acidosis. However, metabolic alkalosis subsequently occurs, presumably as a result of renal compensation for electrolyte loss, particularly chloride.[6]

Further examination of horses with esophageal disease may reveal evidence of swelling or emphysema in the region of the cranial or cervical esophagus that should prompt a thorough oral examination and further diagnostics such as radiography and endoscopy to define the nature of any esophageal abnormalities. If the esophagus has been perforated or ruptured, subcutaneous emphysema is usually evident. The lungs should be carefully auscultated for evidence of aspiration pneumonia. Radiographs of the chest are required for a full pulmonary assessment.

Radiographs of the esophagus should initially include plain films that may reveal evidence of an obstruction or areas of gas opacity within facial planes indicative of esophageal perforation.[7] However, facial and subcutaneous emphysema must be differentiated from other causes, including tracheal perforation.[5] The esophagus is often gas-distended cranial to an obstruction up to the cranial esophageal sphincter. Plain films may be diagnostic, but contrast radiographs are frequently required to fully define the nature of esophageal abnormalities.[7] Administration of barium paste or liquid will reveal linear opacifications as a result of the linear mucosal folds and may help outline intraluminal obstructions or strictures (Fig. 32-43).[7] A double-contrast study is a useful radiographic technique for defining esophageal wall abnormalities, particularly postobstruction mucosal ulceration. It is performed by placing a cuffed nasogastric tube in the cranial esophagus and injecting 300 to 500 mL of liquid barium



FIG. 32-43 Barium contrast esophagram outlining esophageal luminal structure. *(Courtesy Dr. K.E. Sullins.)*

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followed by a similar volume of air. Care should be taken when evaluating such radiographs, because swallowing can create the false impression that there is a stricture.[8] The incidence of swallowing can be decreased by administration of xylazine. Liquid barium is preferable if swallowing function is compromised because it is less harmful to pulmonary tissues than paste, and water-soluble iodinated contrast material is particularly damaging to the lung because of its hypertonicity.[5] However, if an esophageal perforation is suspected, water-soluble contrast material is preferable.[5]

Ultrasonographic examination of the cervical esophagus is often helpful to identify the exact location of obstructions and to determine whether abnormalities of the esophagus are present. Perforations can be identified by periesophageal gas patterns. Whereas intraluminal contents cannot often be examined with ultrasonography because of the presence of air, abnormalities of the mucosal or muscularis layers can be identified. Intramural or extramural causes of esophageal problems (particularly obstructions) may be discovered using ultrasonography. The location and characteristics of masses (neoplasia, granulomas, abscesses, etc.) may be evaluated more readily with ultrasonography versus radiography or endoscopy. The thoracic esophagus cannot be evaluated using ultrasonography.

Endoscopic evaluation of the esophagus should be performed as part of a complete evaluation of esophageal injuries and abnormalities. After the patient is sedated, the endoscope should be passed all the way into the stomach before the esophagus is examined; the esophagus is viewed more easily as the endoscope is withdrawn.[7] Inflation of the esophagus must also be performed intermittently as the wall of the esophagus collapses around the end of the endoscope. The longitudinal folds of the esophageal mucosa will be readily appreciated and can be flattened out as the esophagus is distended to more clearly view the entire circumference of the esophagus. Swallowing may create artifacts such as the appearance of strictures, so the esophagus should be carefully reinflated after each swallow to carefully evaluate such findings.[8]

A recent study evaluated structures via thoracoscopy of the mediastinum, including the thoracic component of the esophagus. Although this procedure caused pneumothorax, a 15-minute period of evaluation allowed observation of numerous structures, including the esophagus.[9] Portals placed at the eighth, tenth, and twelfth intercostal spaces were useful for completion of this procedure and could provide additional information aside from radiographic and endoscopic evaluation of the thoracic esophagus.

Esophageal Obstruction

Esophageal obstruction, either primary (simple choke) or secondary to other disease processes, is the most common esophageal disorder seen in horses. Although primary obstructions may be caused by foreign bodies (including corncobs, potatoes, apples, carrots, medicinal boluses, stones, riding crops, or wood fragments), primary obstructions are most often caused by roughage, particularly leafy alfalfa hay, coarse grass hay, bedding, and even grass.[10-20] Prior esophageal trauma or poor mastication caused by dental abnormalities may predispose horses to esophageal impaction. Obstructions from roughage may be precipitated by wolfing or gulping food, particularly if the horse is exhausted or mildly dehydrated (such as after a long ride) or weakened from chronic debilitation. Secondary impactions are caused by intramural or extramural abnormalities that mechanically impede food passage. Examples of intramural obstructions include tumors (squamous cell carcinomas), strictures, diverticula, cysts, and vascular ring anomalies.[21-27] Mediastinal or cervical masses (tumors or abscesses) may cause extramural obstructions.

The clinical signs associated with esophageal obstructions are similar whether they are classified as primary or secondary and are rarely specific. Horses with esophageal obstruction are often anxious and stand with the neck extended. Gagging or retching may be noted, particularly with acute proximal obstructions. Bilateral frothy nasal discharge containing saliva and food material, coughing, odynophagia, ptyalism, and dysphagia are usually the primary clinical signs, the severity of which varies with the degree and location of the obstruction. Distention of the cervical esophagus may be evident at the site of obstruction. Other clinical signs may be observed related to complications stemming from the obstruction, such as dehydration, weight loss, aspiration pneumonia, or esophageal rupture.

Thorough physical examination, including a complete oral examination, must be performed to rule out other causes of hypersalivation, dysphagia, and nasal discharge. Palpation of the jugular furrow may reveal a mass associated with the impaction. In most horses the esophagus is located in the left jugular furrow, but it may be found in the right furrow in some animals. Crepitus or cellulitis may be evident, suggesting rupture of the esophagus. Auscultation of the lungs can determine whether pneumonia or pleural fluid is present because of aspiration or intrathoracic esophageal rupture. Passage of a nasogastric tube is a good way to determine whether and where an obstruction is present, but it provides little information about the nature of the obstruction or the condition of the esophagus.

Ultrasonography of the cervical region is extremely useful not only to confirm the presence of a cervical esophageal impaction but also to provide critical information about the location and extent of the impaction and esophageal wall thickness and integrity. Ultrasonography may also provide information about the cause of the obstruction. Radiography, particularly air or barium contrast studies, may be useful to assess an esophageal impaction but may be more useful for evaluating the esophagus after, rather than before, relief of the impaction to demonstrate stricture, dilation, diverticula, esophageal rupture, or masses.[28,29] Care should be taken when interpreting radiographic studies in sedated horses, particularly after passage of a nasogastric tube or other esophageal manipulations that may contribute to esophageal dilation.[30] Impacted food material can be detected in the esophagus by a typical granular pattern, and gas is often observed to accumulate proximal to the obstruction. Foreign bodies may be identified by contrast radiographic studies.

Definitive evaluation of esophageal obstructions often requires endoscopic examination. Most cases of esophageal obstruction occur at sites of natural narrowing of the esophageal lumen, such as the cervical esophagus, the thoracic inlet, the base of the heart, or the terminal esophagus; therefore an endoscope longer than 1 meter may be required. The endoscope can be used to localize and investigate the nature of the impaction if a foreign body is suspected. Foreign bodies may be retrievable via transendoscopic tethering.[18] Critical diagnostic and prognostic information is obtained after resolution of the impaction to determine whether mucosal ulceration, esophageal rupture, masses, or strictures are present.

The primary goal of treatment for esophageal impaction is to relieve the obstruction. Parenteral administration of acepromazine (0.05 mg/kg IV), xylazine (0.25 to 0.5 mg/kg IV) or detomidine (0.01 to 0.02 mg/kg IV), oxytocin (0.11 to 0.22 IU/kg IM), and/or esophageal instillation of lidocaine (30 to 60 mL of 1% lidocaine) may help reduce esophageal spasms resulting from pain or increased esophageal tone.[15,30-32] However, recent conclusive studies revealed that detomidine, acepromazine, or a combination of xylazine and butorphanol had the greatest effect on esophageal motility when evaluated by a monomer in conscious horses.[33] In vitro studies revealed a relaxant effect of oxytocin on esophageal muscle, suggesting it may be useful for relief of esophageal obstruction.[34]

Resolution of an impaction may require physical dispersal of the material. A nasogastric tube can be used to displace the impacted material in conjunction with external massage if the obstruction is in the cervical region. Often it is necessary to carefully lavage the esophagus with water via an uncuffed or a cuffed nasogastric tube while the head is lowered to aid in breaking up the impaction. Some clinicians advocate a dual tube method whereby a tube is placed through each nasal passage into the esophagus for ingress and egress of the lavage fluid. Because of the risk of aspiration of water, food, or both, esophageal lavage is sometimes done under general anesthesia with a cuffed nasotracheal tube.

In refractory cases, intravenous administration of isotonic fluid containing 0.9% NaCl and KCl (10 to 20 mEq/L) for 24 hours at a

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rate of 50 to 100 mL/kg/day, in conjunction with an esophageal relaxant such as oxytocin, may promote hydration and softening of the impaction and will help prevent or alleviate any electrolyte or acid-base imbalances resulting from salivary losses of chloride, sodium, and potassium. Refractory cases may require esophagotomy to relieve the impaction. Restriction of access to food, water, and bedding material must be enforced until the obstruction is resolved and the esophagus has regained function.

Dilation proximal to the site of obstruction, mucosal injury from trauma, and esophagitis are sequelae to esophageal impaction that predispose patients to reobstruction (Color Plates 32-1 and 32-2). The rate of reobstruction may be as high as 37%. Depending on the duration of the obstruction and the degree of trauma or dilation, the risk of reobstruction is high for 24 to 48 hours or longer; therefore food should be withheld for at least 24 to 48 hours after resolution of the obstruction. After 48 to 72 hours or when the esophageal mucosa has recovered as assessed by endoscopy, soft food (moistened pellets and bran mashes) can be fed. The patient can be returned to a high-quality roughage diet over a period of 7 to 21 days depending on the degree of esophageal damage induced by the impaction and the nature of any underlying disease. The prognosis for survival is good (78%), but some horses may require permanent dietary modification if persistent chronic obstruction is a problem.[17]

Complications of esophageal impaction include metabolic alkalosis from prolonged loss of salivary chloride and sodium, esophageal ulceration, stricture, perforation, aspiration pneumonia, and megaesophagus. Esophageal endoscopy, ultrasonography, or both should be performed immediately after the impaction is relieved to determine whether any complications of the impaction have developed or if an inciting cause of the obstruction is present. Endoscopic evaluation is critical to determine the postobstruction treatment and follow-up. Reevaluation should be performed intermittently every 2 to 4 weeks after resolution of the impaction if esophageal dilation or mucosal injury is noted. Additional evaluation via radiography may be warranted to assess motility and transit times.

If the obstruction was present for 48 hours or longer, dehydration, hyponatremia, hypochloremia, and hypokalemia may occur and should be corrected via oral electrolyte solutions or intravenous administration of 0.9% NaCl and KCl (10 to 20 mEq/L). If aspiration is suspected, administration of broad-spectrum antibiotics that are effective against gram-positive and gram-negative organisms, including metronidazole for anaerobes, is advisable. Sucralfate (20 mg/kg orally [PO] q6h) may hasten healing if esophageal ulceration is evident, but this is controversial. Some clinicians suggest that administration of a nonsteroidal antiinflammatory drug such as flunixin meglumine (1 mg/kg PO or IV q12h) or phenylbutazone (1.1 mg/kg PO or IV q12h) for 2 to 4 weeks after resolution of the impaction may reduce the development of strictures.

Esophagitis

Inflammation occurs during many conditions of the esophagus. *Esophagitis* refers to a clinical syndrome of esophageal inflammation, which may or may not be ulcerative. Causes of esophagitis in horses include trauma (foreign bodies, nasogastric tube), infection (mural abscesses), and chemical injury (medicines, cantharidin).[35,36] An important category of esophagitis is reflux esophagitis, caused by reflux or delayed clearing of gastric contents into the distal esophagus and subsequent chemical injury to the mucosa (Fig. 32-44). Similar to ulceration of the squamous portion of the stomach in horses, a major cause of ulcerative esophagitis is epithelial damage resulting from exposure to acid, which is synergistically exacerbated by bile salts.[11,37] The major protective mechanisms of the esophageal mucosa include salivary and food material buffers, normal peristaltic motility, and the barrier formed by the gastroesophageal sphincter. Thus esophagitis may be seen in conjunction with gastric ulcer disease, motility disorders, increased gastric volume from gastric outflow obstructions, gastric paresis, intestinal ileus, or impaired lower esophageal sphincter function.

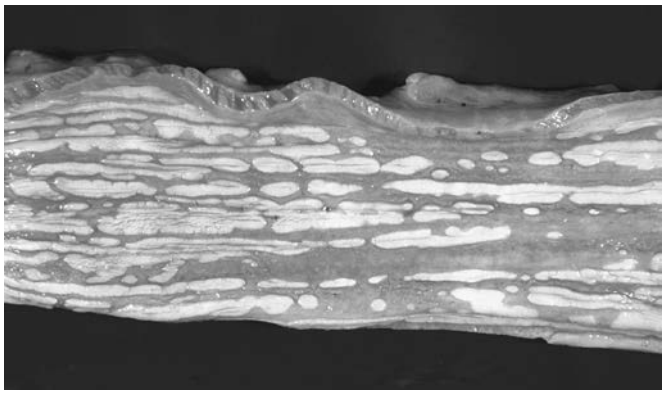


FIG. 32-44 Severe ulceration of the esophagus in a weanling foal that had severe duodenitis and gastric outflow obstruction. *(Courtesy Dr. M.J. Murray.)*

The clinical signs of esophagitis are nonspecific and similar to those of esophageal obstruction and gastric ulcer disease. In fact, esophagitis may occur concurrently with esophageal obstruction or gastric ulcer disease, so clinical signs may overlap extensively with these diseases. Gagging, or discomfort when swallowing, may be evident, and hypersalivation and bruxism are signs of esophageal pain. Partial or complete anorexia may be noted such that horses with chronic esophagitis may have significant weight loss. Motility dysfunction secondary to esophagitis may cause recurrent esophageal impaction. Clinical signs of underlying disease that predispose to esophagitis may predominate or mask the signs of esophagitis. Horses with gastrointestinal motility disorders such as anterior enteritis are at high risk for developing reflux esophagitis because of the presence of both gastric acid and bile salts in the fluid reflux. However, signs attributable to esophagitis secondary to ileus may not be noted because of the profound signs caused by the intestinal disorder. Foals with gastric outflow obstructions commonly have reflux esophagitis.

Diagnosis requires endoscopic examination of the esophagus. Diffuse, patchy, linear, or coalescing erosion or ulcerations may be noted. Significant edema or hyperemia may also be observed. It is important to determine whether underlying disease, such as infection, neoplasia, diverticula, or esophageal stricture is present. In addition, the stomach must be examined because reflux esophagitis is commonly accompanied by gastritis or gastric ulcer disease. Contrast radiography may be helpful if endoscopy is not available to detect esophageal ulceration and can be used to assess esophageal motility and transit time.

The principles of therapy for reflux esophagitis include control of gastric acidity and correction of any underlying disorder that is contributing to gastroesophageal reflux. Thus treatment with histamine-2 (H2)–receptor antagonists such as ranitidine or proton pump antagonists such as omeprazole is important for resolution of the disease. Some clinicians advocate sucralfate administration to aid healing of esophageal ulcers. However, the efficiency of sucralfate binding to ulcerated mucosa in the squamous epithelium of the gastrointestinal tract has recently been brought into question since low pH is optimal for the sucralfate polymers to bind ulcerated tissues. It is not clear whether reflux esophagitis provides the right pH environment for binding.

Foals with reflux esophagitis secondary to delayed gastric outflow caused by gastroduodenal ulcer disease or gastric paresis may benefit from prokinetic drugs that act on the proximal gastrointestinal tract. Metoclopramide (0.02 to 0.1 mg/kg SC q4-12h) reduces gastroesophageal reflux by increasing lower esophageal sphincter tone, gastric emptying, and gastroduodenal coordination. Caution should be exercised when giving metoclopramide to horses because they are prone to extrapyramidal neurologic side effects. Continuous rate infusion of metoclopramide (0.04 mg/kg/h) is one way to administer the drug to reduce the risk or severity of neurologic side effects. The rate

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can be reduced if side effects appear. Cholinergic drugs such as bethanechol (0.025 to 0.035 mg/kg SC q4-24h or 0.035 to 0.045 mg/kg PO q6-8h) may improve gastric emptying and are effective for treating reflux esophagitis. For esophagitis from trauma or pressure injury after esophageal impaction, judicious use of nonsteroidal anti-inflammatory drugs may be warranted to reduce esophageal inflammation and pain.

Dietary modification may be necessary in patients with esophagitis, depending on the degree of ulceration or if motility is impaired. Horses with less severe esophagitis should be fed frequent small meals of moistened pellets and fresh grass. Severe esophagitis may necessitate withholding food and complete esophageal rest for several days. Although the prognosis for esophagitis is good in the absence of underlying disease, the risk of stricture formation is high if severe circumferential or coalescing ulcerations are present. Animals with esophagitis from severe trauma or infection also may be prone to stricture formation.

Motility Disorders of the Esophagus

Esophageal hypomotility is the most common motility dysfunction of the equine esophagus and results in esophageal dilation or megaesophagus. Although megaesophagus in horses is most commonly acquired, there are reports of idiopathic megaesophagus in young horses that is likely congenital (Fig. 32-45 and Color Plate 32-3).[38-41] Acquired megaesophagus in adult horses is usually caused by either primary or secondary esophageal obstruction. Esophageal impactions of relatively short duration cause proximal dilation of the esophagus that is generally reversible. However, if the duration of the obstruction is long, the motility of the esophagus may be permanently impaired. Acquired megaesophagus in foals is often secondary esophagitis resulting from gastric outlet or duodenal obstruction. Other causes of acquired megaesophagus include extraesophageal obstruction by tumors or abscesses, pleuropneumonia, and vascular ring anomalies. In addition, acquired megaesophagus may result from neurologic, neuromuscular, or muscular disorders. Neurologic diseases that cause vagal neuropathy, such as equine protozoal myeloencephalitis, equine herpesvirus myeloencephalitis, and idiopathic vagal neuropathy, have been associated with megaesophagus in horses. Pleuropneumonia may be associated with vagal neuropathy, resulting in megaesophagus. Megaesophagus is also an early sign of equine dysautonomia[42] and may be noted in patients with botulism. Myasthenia gravis is a well-known cause of megaesophagus in other species but has not been reported in horses. Also in other species, electrolyte disorders, cachexia, primary myopathies, myositis, and Addison disease may affect esophageal motility, but these have not been associated with megaesophagus in horses.

Esophageal inflammation, particularly reflux esophagitis, may affect motility and cause megaesophagus. However, because esophageal hypomotility may predispose to reflux esophagitis, it may be difficult to determine whether the esophagitis or the megaesophagus is the causative disorder (see Color Plate 32-3). Iatrogenic megaesophagus can be induced by the α_2-adrenergic agonist detomidine, but this is transient and reversible.[43] However, the use of this drug may complicate clinical evaluation of esophageal motility. Because esophageal hypomotility is a functional obstruction, the clinical signs of esophageal hypomotility or megaesophagus are similar to those of esophageal obstruction. These clinical signs include ptyalism, dysphagia, and nasal discharge of saliva and food material. The cervical esophagus may be sufficiently dilated to be evident externally. Weight loss is a common sign, and clinical signs attributable to an underlying disease may be evident.

Diagnosis of esophageal hypomotility requires transit studies. Transit time of a bolus from the cervical esophagus to the stomach can be measured by fluoroscopy or contrast radiography.[7,42] Other signs of esophageal hypomotility and megaesophagus include pooling of contrast material and an absence of peristaltic constrictions. Endoscopy may reveal a dilated esophagus and an absence of peristaltic waves. Evidence of underlying disease causing obstruction or esophageal dilation may be observed. The esophagus should be evaluated for evidence of esophagitis that is either causing esophageal motility dysfunction or is a result of impaired esophageal clearance of gastric fluid. Esophageal manometry may be useful to document abnormal postdeglutition contraction pressures, contraction time, and propagation times.[4,38] Other diagnostic tests such as a CBC and chemistry to help identify an underlying cause should be performed. A careful neurologic evaluation should be performed. Signs of neurologic disease and abnormal cerebrospinal fluid analysis suggest an underlying neurologic disorder. Myopathy may be detected by electromyography.

Treatment of esophageal hypomotility or megaesophagus should be aimed at the underlying cause. Dietary modification should be aimed at improving esophageal transit of food. Slurries of pellets should be fed. In addition, it may be beneficial to feed from an elevated position to promote transit. In patients with reflux esophagitis associated with megaesophagus, metoclopramide or bethanechol may be beneficial to increase lower esophageal tone, promote gastric emptying, and reduce gastroesophageal reflux. The prognosis depends on the underlying cause and the degree of dilation. Although many cases of megaesophagus associated with reflux esophagitis respond well to treatment, many other forms of megaesophagus, including congenital megaesophagus, have a poor prognosis.

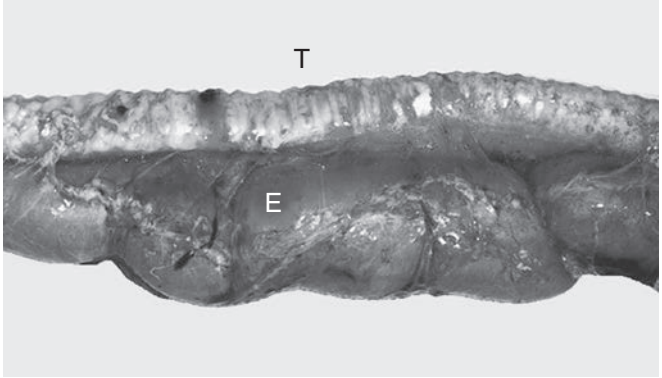


FIG. 32-45 Megaesophagus in a 10-month-old Paint Horse foal that had two duodenal strictures that appeared to have been present for several months. The trachea *(T)* lies dorsal to the dilated esophagus *(E). (Courtesy Dr. M.J. Murray.)*

Congenital Disorders

Congenital disorders of the esophagus are rare. Reported congenital abnormalities include congenital stenosis,[44] persistent right aortic arch, congenital strictures, esophageal duplication cysts,[45,46] and idiopathic megaesophagus.[47] In the one report on congenital stenosis, double-contrast radiography revealed concentric narrowing of the thoracic esophagus in the absence of any vascular abnormalities at the base of the heart. Successful treatment included having the foal stand with the forelimbs elevated off the ground after each feeding.

Persistent right aortic arch is a congenital anomaly in which the right fourth aortic arch becomes the definitive aorta instead of the left aortic arch, which results in constriction of the esophagus by the ligamentum arteriosum as it extends between the anomalous right aorta and the left pulmonary artery.[24] Clinical signs may include dysphagia, drooling of saliva, and distention of the cervical esophagus as a result of partial obstruction of the thoracic esophagus.[48] Endoscopic examination typically reveals dilation of the esophagus cranial to the obstruction with evidence of diffuse esophagitis. In addition, evaluation of the thorax usually reveals the presence of aspiration pneumonia. Successful surgical treatment of persistent right aortic arch has been reported in one foal.

Esophageal duplication cysts cause typical signs of esophageal obstruction, including salivation, dysphagia, and swelling of the cervical esophagus as they enlarge. Such signs can make them difficult to differentiate from simple obstruction (choke). However, an

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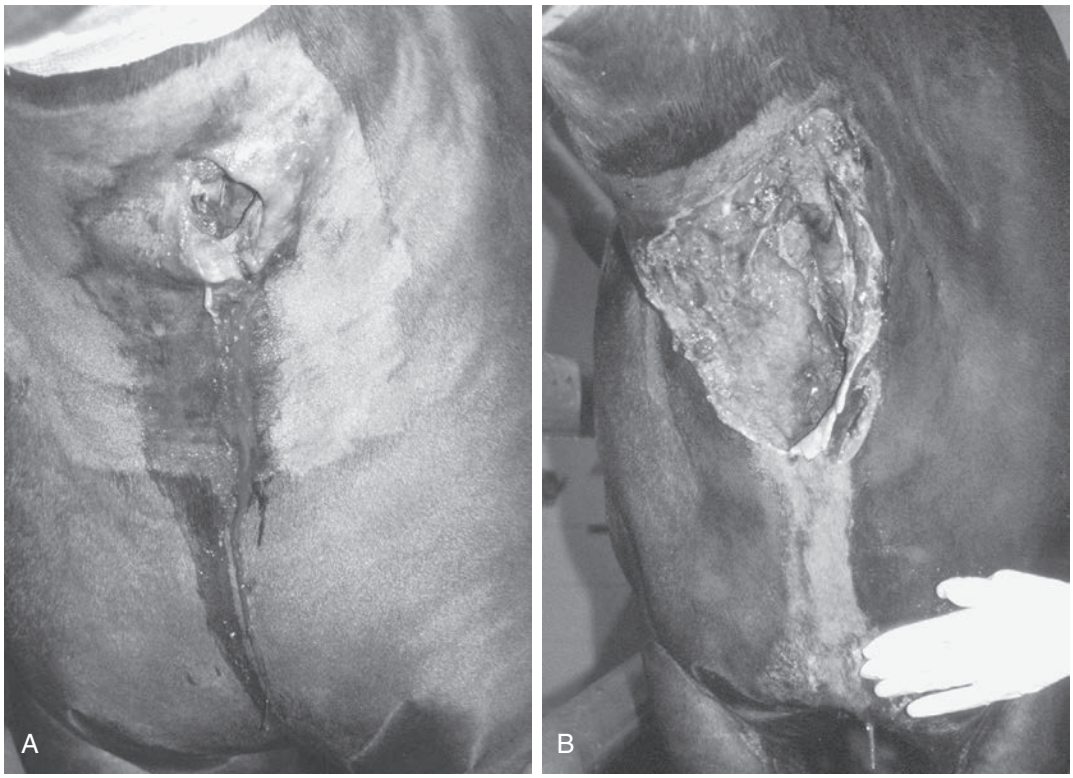


FIG. 32-46 Esophageal perforation in a horse. **A,** An open esophageal laceration was detected on presentation in the midcervical region. The wound was treated by lavage and débridement, and the horse was fed via a tube inserted into the esophagus through the wound. **B,** Approximately 14 days later, dissection of esophageal contents within surrounding fascial planes resulted in extensive sloughing of tissue.

aspirate of the mass may aid in the diagnosis by revealing the presence of keratinized squamous cells.[49] Cysts may communicate with the lumen of the esophagus. Surgical treatments have included complete surgical resection and surgical marsupialization. The latter appears to be more successful and to result in fewer complications. Complications of surgical resection have included (1) laryngeal hemiplegia secondary to surgical trauma to the recurrent laryngeal nerve in the region of the esophagus and (2) esophageal fistula formation.

Esophageal Perforation

Perforation typically occurs in the cervical region in response to external trauma or rupture of an esophageal lesion such as an impacted diverticulum. The esophagus is particularly vulnerable to external trauma in the distal third of the neck because it is covered by only a thin layer of muscle at this location.[50] Iatrogenic perforation may occur in response to excessive force with a stomach tube against an obstruction or a compromised region of the esophagus. Esophageal perforations may be open or closed and tend to cause extensive necrosis of tissues surrounding the wound because of drainage of saliva and feed material within fascial planes (Fig. 32-46). This may lead to extensive cellulitis and endotoxemia. Closed perforations of the esophagus are particularly troublesome, as wound discharge may migrate all the way to the mediastinum and pleural space via fascial planes and may cause abscessation (Fig. 32-47). In addition, extensive subcutaneous and fascial emphysema frequently develops and is usually evident on cervical radiographs.

Treatment should include conversion of closed perforations to open perforations if possible,[51] extensive débridement and lavage of affected tissues, broad-spectrum antibiotics, tetanus prophylaxis, and esophageal rest. The latter may be achieved by placing a feeding tube into the esophagus via the wound. Alternatively, a nasogastric tube should be placed using a small tube (12-French diameter). For open perforations, once the wound has granulated and contracted to a small size, oral feeding may be attempted. Extensive loss of saliva via esophageal wounds may lead to hyponatremia and hypochloremia. In addition, transient metabolic acidosis occurs because of salivary bicarbonate loss, followed by progressive metabolic alkalosis. Although there are reports of esophageal wounds healing well by second intention, it takes a prolonged period of time.[52] In addition, some perforations never completely heal and form permanent esophagocutaneous fistulas that may require surgical correction. The development of esophageal strictures is not common because wounds are usually linear and not circumferential. However, traction diverticula may develop. Other complications of esophageal wounds include Horner syndrome and left laryngeal hemiplegia.

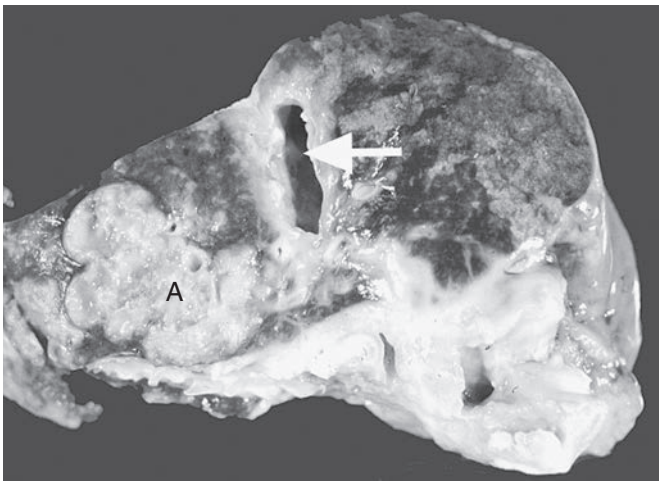


Fig. 32-47 Esophageal abscess *(A)* and cellulitis that developed secondary to an esophageal obstruction. The esophageal lumen is indicated by the *white arrow*. *(Courtesy Dr. M.J. Murray.)*

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In a retrospective study on esophageal disorders, only 2 of 11 horses with esophageal perforations survived long term,[17] and in a report on esophageal trauma secondary to nasogastric intubation, 4 of 5 horses were euthanized.[35] The prognosis is therefore poor in horses with esophageal perforations, largely because of the extent of cellulitis, tissue necrosis, shock, and local wound complications.

Esophageal Stricture

Strictures most commonly occur as sequelae to esophageal obstructions that result in circumferential erosion or ulceration of the esophageal mucosa, although strictures may result from oral administration of corrosive medicinal agents and trauma to the neck.[53] Congenital strictures have also been reported. Strictures that result from mucosal and submucosal trauma are termed *esophageal webs* or *rings*. Strictures may also originate in the muscular layers and adventitia of the esophagus (mural strictures) or in all of the layers of the esophagus (annular stenosis).[54] Horses with these lesions have a presentation similar to that of horses with simple obstructions because strictures result in partial obstruction and accumulation of feed material in the lumen. Esophageal webs or rings can be observed endoscopically, whereas mural strictures or annular stenosis may require double-contrast esophagrams to confirm their presence.

In one study on esophageal stricture after simple obstruction, maximal reduction in esophageal lumen occurred within 30 days of esophageal obstruction. Although surgery has been employed to reduce such strictures, initial medical management is warranted because strictures may resolve with conservative therapy, and the esophagus continues to remodel for up to 60 days after ulceration. In one report, seven horses with esophageal obstruction-induced stricture were treated conservatively by feeding a slurry diet and administering antiinflammatory and antimicrobial medications, and five of seven were clinically normal within 60 days. One of the five successfully treated horses had a 10-cm area of circumferential ulceration, suggesting extensive mucosal injury may resolve without permanent stricture formation. If there is insufficient resolution of strictures within 60 days, other methods to increase esophageal diameter should be investigated. Bougienage has been used successfully in small animal patients and human beings. The technique involves passage of a tubular dilatable instrument down the esophagus and stretching of the stricture. Some authors have suggested that this may be accomplished by passing a nasogastric tube with an inflatable cuff (Fig. 32-48).[55] However, the procedure has to be performed frequently to have any success and is often not well tolerated by horses. Alternatively, several surgical techniques have been used to resolve strictures, including resection and anastomosis,[56,57] temporary esophagostomy with fenestration of the stricture, esophagomyotomy for strictures of the muscularis and adventitia,[58,59] and patch grafting with local musculature.[60] However, such surgeries are fraught with complications, largely because of the propensity of the traumatized esophagus to restricture. The esophagus lacks a serosal layer and does not rapidly form a fibrin seal, as does the remainder of the intestinal tract, so anastomoses tend to leak. In addition, tension on the esophagus during swallowing and movement of the neck impairs healing of anastomoses.

Esophageal Diverticula

There are two types of diverticula: traction (true) diverticula and pulsion (false) diverticula. Traction diverticula result from wounding and subsequent contraction of periesophageal tissues, with resultant tenting of the wall of the esophagus. Pulsion diverticula arise from protrusion of esophageal mucosa through defects in the muscular wall of the esophagus and usually result from trauma or acute changes in intraluminal pressure (Fig. 32-49). Traction diverticula appear as a dilation with a broad neck on contrast esophagography, whereas pulsion diverticula typically have a flask shape with a small neck on an esophagram.[61] Whereas traction diverticula are usually asymptomatic and of little clinical significance, pulsion diverticula may fill with feed material, ultimately leading to esophageal obstruction.[62] However, a movable mass in the midcervical region may be noticed before onset of complete obstruction.[5] Pulsion diverticula may be surgically corrected by inverting or resecting prolapsed mucosa and closing the defect in the wall of the esophagus.[26,61,62] Inversion of excessive mucosa may predispose horses to esophageal obstruction and should therefore be reserved for small diverticula.



FIG. 32-48 Attempted dilation of esophageal stricture using bougienage. In this case, a cuffed Silastic tube (Dow Corning, Midland, Mich.) was passed to the site of stricture aided by endoscopy, and the cuff was then inflated to distend the site of stricture. *(Courtesy Dr. M.J. Murray.)*

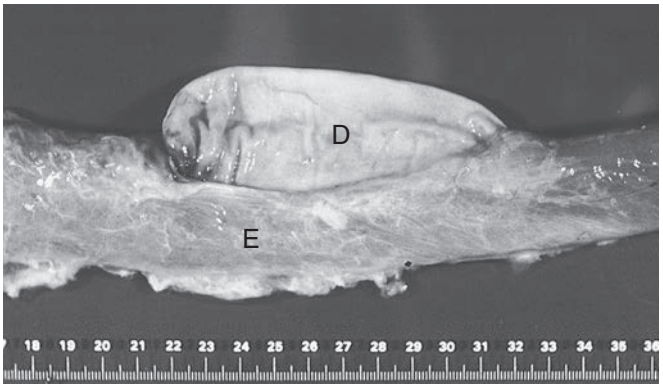


FIG. 32-49 Pulsion diverticulum *(D)* of the esophagus *(E)* in a horse that had intermittent episodes of esophageal obstruction. *(Courtesy Dr. M.J. Murray.)*

Neoplasia

Neoplasia of the esophagus is rare, but squamous cell carcinoma[63,64] and leiomyosarcoma[65] have reportedly affected the esophagus either as the primary site or in association with a lesion in the squamous portion of the stomach. The predominant clinical signs are weight loss, colic, and recurrent esophageal obstruction. The tumor is typically detected antemortem on esophagoscopy and radiography, but a definitive diagnosis may require a biopsy during laparotomy.[21,65] When neoplasia affects the lower esophageal sphincter, gastroesophageal reflux may contribute to ulceration of esophageal mucosa. The prognosis for malignant neoplasia of the esophagus is grave.

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Disorders of the Stomach

Ben Sykes

Equine Gastric Ulcer Syndrome

Gastric ulceration is the most common disease condition of the equine stomach. The term *equine gastric ulcer syndrome* (EGUS) was first adopted in 1999 to describe the gastric ulceration in the horse.[1] By definition the term EGUS refers to a syndrome, within which numerous disease entities exist. Recently an attempt has been made to clarify the terminology to recognize this distinction.[2] The distinction is important, as the proposed pathophysiologies of the diseases are different, different risk factors have been described for squamous[3-7] and glandular[8] disease, the presence of squamous and glandular ulcerations within an individual are unrelated,[9-11] and the response of glandular ulceration to treatment with omeprazole is inferior to that of squamous ulceration.[12-14] As such, the direct extrapolation of findings from the squamous mucosa, which is by far the more thoroughly studied of the two, to the glandular mucosa is inappropriate. Instead, disease of the squamous mucosa should be considered as a distinct entity to disease of the glandular mucosa.

For the purposes of this discussion, diseases of the squamous and glandular mucosa will be discussed separately. The term *equine squamous gastric ulcer syndrome* (ESGUS) will be used to discuss diseases of the squamous mucosa, while the term *equine glandular gastric ulcer syndrome* (EGGUS) will be used to discuss diseases of the glandular mucosa.

Diagnosis

Gastroscopy remains the only reliable method of diagnosis for gastric ulceration; however, the advent of smaller portable units and a dramatic reduction in price has meant that gastroscopy is no longer the domain of referral centers only. Adequate patient preparation, plus some operator skill and patience, is required for a complete diagnostic evaluation of the entire stomach. A fasting period of at least 16 hours is required in most horses, and even small amounts of residual food make accessing the pyloric antrum difficult. In horses on low-roughage diets (e.g., racehorses), shorter durations of starvation may be acceptable. Removal of water 1 hour prior to examination is advantageous but not mandatory. A complete examination of the stomach is important and the presence or absence of squamous ulceration cannot be used as a predictor for the presence or absence of glandular ulceration.[9-11] Observation of the squamous mucosa is relatively easy, whereas passage through to the pyloric antrum is more technically demanding. However, observation of the pyloric antrum is critical as the majority of glandular ulceration occurs in this region.[8,11-14] Observation of the most ventral portion of the fundus is typically not possible because of the presence of fluid; however, ulceration in this region is rare.[15] The squamous and glandular mucosa should be scored separately and, although a variety of scoring systems have been described, the author prefers the system first described by the EGUS council[1] shown in Table 32-2. Examples of the normal appearance of the gastric and duodenal mucosa and lesions encountered in horses and foals undergoing gastroscopy are shown in Color Plates 32-4 through 32-12.

In the absence of gastroscopy, various other methods have been proposed for diagnosis. The presence of clinical signs, including recurrent colic, poor appetite, weight loss, hair coat and behavioral changes, pain on tightening of the girth, and diarrhea,[15-17] can be useful with a significantly greater prevalence of ESGUS in symptomatic horses compared with asymptomatic controls.[16] The link between colic and EGUS is controversial, but the author believes that EGUS should be considered as a differential in all cases of idiopathic colic and that investigation is warranted, especially in recurrent cases. Further, clinical experience tells us that many horses will have relatively severe gastric ulceration with no apparent clinical signs. However, treatment of the ulceration in these horses often results in a change in behavior or appetite of the horse, suggesting that the symptoms displayed by many animals are mild and readily overlooked.

TABLE 32-2

Scoring System for Equine Gastric Ulcer Syndrome

Grade	Squamous Mucosa	Glandular Mucosa
0	The epithelium is intact and there is no appearance of hyperkeratosis (yellow appearance to the mucosa)	The epithelium is intact and there is no hyperemia (reddening) of the mucosa
I	The mucosa is intact, but there are areas of hyperkeratosis	The mucosa is intact, but there are areas of hyperemia
II	Small single, or multifocal lesions	Small single, or multifocal lesions
III	Large single, or multifocal lesions, or extensive superficial lesions	Large single, or multifocal lesions, or extensive superficial lesions
IV	Extensive lesions with areas of apparent deep ulceration	Extensive lesions with areas of apparent deep ulceration

The presence of overt clinical signs increases the clinical index of suspicion, while their apparent absence does not discount EGUS as a differential. If gastroscopy is not readily available, then a therapeutic trial with omeprazole can be useful. A positive response to treatment with omeprazole confirms the diagnosis of EGUS but does not differentiate between ESGUS and EGGUS. Such a distinction is important because the treatment recommendations for ESGUS and EGGUS vary and as such, in the author's opinion, a positive response to treatment should be viewed as a clear indication to conduct a gastroscopic exam to obtain a definitive diagnosis. A negative response to trial therapy with omeprazole reduces the likelihood of EGUS but does not completely discount it, as some animals are slow to respond clinically and symptoms may not completely resolve until healing has occurred, especially with EGGUS. As such, in light of a negative response to omeprazole, other more likely differentials should be discounted first, but gastroscopic examination is indicated if no specific diagnosis is made.

Fecal occult blood testing is appealing in terms of ease of use and cost, and kits specifically designed for the equine market are available. However, its accuracy has not been validated in the peer-reviewed literature, and several theoretical reasons exist as to why fecal occult blood is likely to be of limited use in the horse. As such, the use of fecal occult blood cannot be recommended as a diagnostic test until further validated. The use of sucrose as a marker of gastrointestinal permeability has been reported and a blood test developed for the purpose[18,19]; however, the test has not found favor and gastroscopy remains the diagnostic of choice because of its accuracy and ability to distinguish ESGUS from EGGUS.

Equine Squamous Gastric Ulcer Syndrome

Squamous ulceration can be a primary problem or, occasionally, a secondary problem that results from obstruction of gastric outflow with subsequent backflow of acid gastric juices. For the purposes of this discussion, the focus will be on primary squamous disease with the understanding that management of secondary squamous disease is largely dictated by treatment of the primary disease causing delayed gastric outflow.

Pathophysiology

Squamous ulceration occurs, fundamentally, as a result of increased exposure of a tissue with limited defense mechanisms to highly acidic gastric contents. Horses are constant secretors of gastric acid[20,21] with HCl primarily responsible for the damage to the squamous mucosa. Damage occurs rapidly with evidence of acid injury within 30 minutes of exposure in vitro.[22] The

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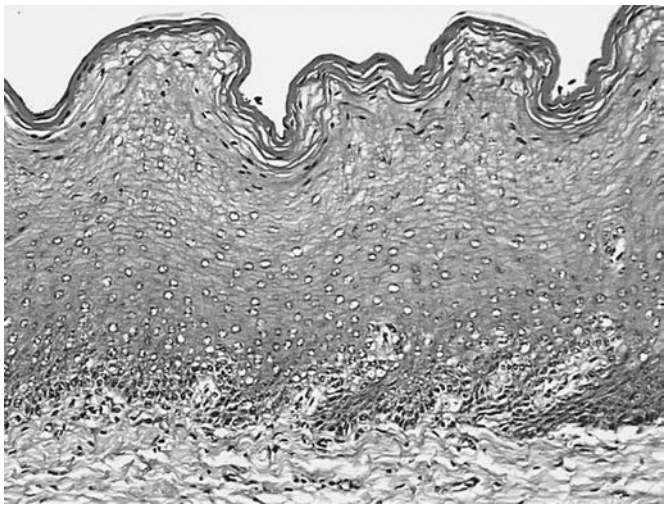


FIG. 32-50 Photomicrograph of equine gastric squamous epithelial mucosa. There are multiple layers of epithelium arranged in parallel with the luminal surface. The most superficial layers of cells are cornified, and superficial to these cells are layers of keratin. (Hematoxylin and eosin stain.)

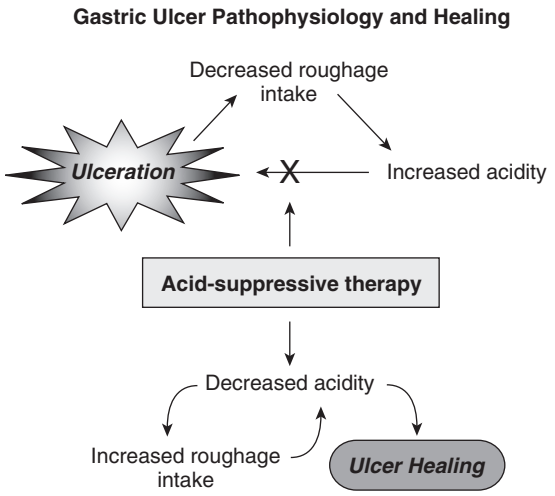


FIG. 32-51 Diagram representing the pathophysiology of ulceration of the equine gastric squamous mucosal epithelium and the permissive effect of acid suppression on ulcer healing.

horse has evolved as a constant grazer, and under pasture conditions the consumption of roughage creates a basketball-sized bolus of feed in the stomach that acts as a buffer to absorb gastric acidity and physically prevents the splashing of highly acidic gastric contents into the dorsal region of the stomach that is lined by squamous mucosa (Fig. 32-50). Any disruption in normal feeding or behavior results in breakdown of this protective mechanism and a resultant increase in the risk of ESGUS. Short-chain fatty acids released during fermentation of soluble carbohydrates consumed in the diet are likely also to directly contribute to squamous mucosal injury[23] and disrupt the physical protective effect of a predominantly roughage-based diet. As such, ESGUS is largely a disease that results from the management changes imposed on horses for a variety of purposes.

Prevalence and Risk Factors

The prevalence of ESGUS mirrors exercise intensity with the risk of disease increasing as the intensity of work increases. The highest prevalences have been reported in Thoroughbred racehorses with more than 70% of animals affected across a wide range of studies.[9,24-26] However, it is the author's opinion that these studies overstate the prevalence of clinically significant ulceration because many of the "affected" animals are likely to have had only small focal lesions that are unlikely to be of clinical significance but by definition meet the criteria of ulceration. This overrepresentation of the rate of the ESGUS has led many clinicians to dismiss ESGUS as a "normal" finding in the performance horse. Along these lines the author proposes that mild (grade II/IV) ESGUS maybe an incidental finding and that, although it may be associated with clinical signs, typically horses with grade III-IV/IV ESGUS are more likely to be clinically affected. As such, discussions on the prevalence and significance of ESGUS should be conducted in context with the relative severity of lesions observed.

The Thoroughbred racehorse is the best studied of horse breeds and the focus on this group in both developing an understanding of the disease and validating various treatments has led to a misconception that ESGUS is solely a disease of racehorses. On the contrary, ESGUS is seen across a wide range of other horse types. In a recent Danish study, ESGUS was observed in 69% of horses ranging from horses at pasture to horses in hard work, and there was no apparent association between presence of ESGUS and horse use.[10] Similar prevalences of ESGUS have been reported in Standardbred (63% to 87%[3,27]), endurance (67% to 93% during competition[28,29]), show (58%[30]), and western performance (40%[31]) horses. The prevalence of ESGUS in horses at rest is variable but typically lower and, when observed, tends to be less severe. However, in selected cases, severe (grade III-IV/IV) ESGUS can be observed in horses at pasture, and ESGUS should not be discounted as a differential simply because a horse does not meet the "typical" risk profile.

The commencement of training, with the multitude of management changes imposed, including exercise[32] and high-concentrate/low-roughage diets,[33] can result in the development of ESGUS within 7 days.[7,34] In addition to the overall risk associated with the induction of training, specific risk factors that have been identified for ESGUS include fasting,[21] transport,[7] stabling,[21] and time in work.[8] Although nonsteroidal antiinflammatory drugs (NSAIDs) may induce ESGUS experimentally, epidemiologic study results[25] and the lack of a direct link to the pathophysiology of squamous ulceration make it unlikely that they contribute to ESGUS in the clinical setting.

Treatment

Treatment of ESGUS focuses on suppression of acid production and, where possible, changing management practices that may have contributed to the disease (Fig. 32-51). Acid suppression therapy does not directly contribute to healing, but the squamous mucosa has an enormous proliferative capacity and the removal of ongoing insult is sufficient for the tissues to heal. Theoretically, removal of the horse from the risk factors that caused disease in the first place and reestablishment of a normal pH gradient in the stomach should result in healing. However, a reduction in workload is not possible in many cases, and treatment is required in the face of ongoing exposure to risk factors. Further, even when removal from the risk factors is possible (i.e., resting of the horse), acid suppression therapy is often required to restore a normal appetite so that enough roughage is consumed to reestablish the pH gradient in the stomach allowing healing to occur. If removal from work is used to manage ESGUS, then follow-up gastroscopy 4 to 6 weeks later is indicated to ensure that healing has occurred.

Because the ability to remove risk factors, such as exercise and concentrate diets, is often limited, the use of acid suppression therapy remains a cornerstone in the management of ESGUS. Various drugs have been used for this purpose, but omeprazole remains the most effective and best studied. Omeprazole impairs the H^+, K^+-ATPase (proton) pump that secretes HCl. It is most commonly registered at a dose of 4 mg/kg PO q24h for 28 days, and its efficacy at this dose for treatment of squamous ulcer disease is well documented by several clinical trials.[35-39] Recently, the use of lower doses has been evaluated and, under certain conditions, doses as low as 1 mg/kg have been shown to be as efficacious as 4 mg/kg in the treatment of ESGUS.[13] Based on experimental studies,[40-46] it is widely believed that once-daily administration of omeprazole results in 24 hours of acid suppression; however, a recent study has suggested that the duration of acid suppression following dosing at 4 mg/kg may be as short as

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12 hours.[47] Considering this, the timing of administration may be important, with exercise considered to be the peak risk period for ESGUS development[32]; however, a recent study found no advantage of administration of omeprazole 1 to 4 hours prior to exercise compared with administration after exercise.[12] Reported healing rates at 28 days for horses that stay in work are typically around 70% to 80%.[12,35,36,39] As such, although the majority of animals will have improved by 28 days,[12-14,35] control gastroscopy is recommended before therapy is terminated to ensure that healing has occurred.

Other drugs have been used in the treatment of ESGUS, most commonly the H2 receptor antagonists ranitidine and cimetidine. Both drugs work by competitively blocking the H2 receptor on the parietal cell, and their efficacy is dependent on maintaining plasma concentrations. Ranitidine, most commonly used at 6.6 mg/kg PO q8h, has been shown to effectively suppress gastric acidity in experimental studies[20,48-50] and provides an option for acid suppressor therapy where omeprazole is not available or is cost prohibitive. However, in a study directly comparing the efficacy of ranitidine versus omeprazole, ranitidine was shown to be inferior[37]; thus omeprazole remains the treatment of choice. Cimetidine is relatively poorly studied and its use is not justified.

Nonpharmaceutical methods, such as feed supplements and antacids, of treating ESGUS are popular among owners, typically because of low cost and availability. Although antacids can effectively reduce gastric acidity, their effect is short lived (2 hours)[48,51] and, as such, their use beyond short-term symptomatic control cannot be recommended. Mucosal protectants, such as pectin-lecithin complexes, may play a role in providing a physical barrier between the mucosa and acid, and symptomatic relief as a result of their use is often reported. Their use in selected cases may be sufficient for control of ESGUS, but the author's opinion is that they are more likely to be effective as preventive, and alongside omeprazole in the treatment of EGGUS, than as a primary treatment for ESGUS.

Prevention The approach to prevention of ESGUS is similar to treatment. The instigation, where possible, of management changes such as increased roughage and decreased concentrate in the diet and increased turnout are likely to decrease the risk of disease. However, in most cases, ongoing use of the horse results in ongoing exposure to risk factors, and the risk of recurrence is typically moderate to high. Prevention should be approached on a case-by-case basis, wherein the greater the ability is to affect risk factors, the lower the need will be for additional therapy. When additional therapy is required, the use of mucosal protectants such as the pectin-lecithin complexes may be adequate in low- to moderate-risk environments, whereas omeprazole is indicated in cases where the risk of recurrence is deemed to be high. Omeprazole is typically used at 1.0 mg/kg PO q24h for prevention,[52] but 0.5 mg/kg PO q24h has been shown, under specific conditions, to be as effective.[53]

Equine Glandular Gastric Ulcer Syndrome

The advent of gastroscopy as a diagnostic tool in the 1990s created an enormous wave of publications on EGUS but, despite awareness of gastric ulceration as a disease for more than 20 years, it is only recently that a real emphasis has begun to be placed on distinguishing ESGUS from equine glandular gastric ulcer syndrome (EGGUS). A key reason for this is that when the original endoscopes were developed for use in the horse, they were only 2.5 meters in length and, as such, the pyloric antrum, where the majority of glandular ulceration occurs,[8,10,12-14,54] was rarely observed in clinical cases.

However, interest in distinguishing EGGUS as a separate entity from ESGUS has increased,[2] and a series of recent studies have clearly demonstrated that the risk factors for,[8] and response to treatment of,[12-14,54] EGGUS differ dramatically from those of ESGUS. This is not surprising given the differences in the anatomy of the glandular mucosa (Fig. 32-52) and pathophysiology of the conditions.

Pathophysiology The glandular mucosa differs fundamentally from the squamous mucosa in that under normal physiologic conditions it is exposed to highly acidic gastric contents with the pH in the ventral portion of the stomach relatively stable at between 1 and 3.[47] As such, whereas ESGUS results from exposure of mucosa unaccustomed to acidity, EGGUS is believed to result from a breakdown of the normal defense mechanisms that protect the mucosa from acidic gastric contents. Under normal conditions the glandular mucosa of the stomach is lined by a continuous layer of gastric mucus

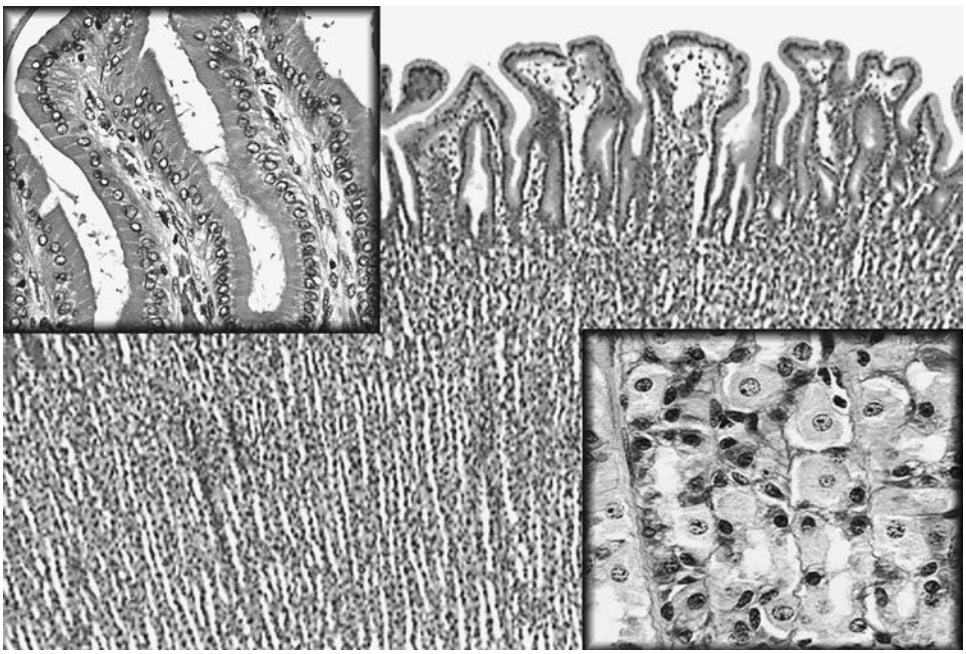


FIG. 32-52 Photomicrograph of equine gastric glandular mucosa. In contrast to the squamous mucosa, the glands are parallel to one another and perpendicular to the luminal surface. There are multiple cell types within the mucosa, with surface epithelial cells and mucus-secreting cells toward the lumen, and parietal cells, chief cells, enterochromaffin-like cells, G cells, and D cells deeper in the mucosa. The insert at the top left shows a high-power magnification of cells lining gastric pits on the surface of the epithelium. The insert at the lower right shows a high-power magnification of cells lining the gastric glands deeper in the mucosa. (Hematoxylin and eosin stain.)

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that is a complex mixture of glycoproteins, water, electrolytes, lipids, and antibodies.[15] The factors that contribute to breakdown of this protective layer are yet to be elucidated in the horse, but in humans bacterial agents and NSAIDs are the predominant causes of gastric ulceration with *Helicobacter pylori*–negative NSAID-negative gastric ulceration rare.[55] As such, current research in the horse is focused primarily on these two mechanisms.

To date there remains significant conflict in the literature as to the role of bacteria in EGGUS. A recent study demonstrated that both gastric-adapted bacteria and opportunistic pathogens may play a role in squamous ulceration,[56] but whether the situation is similar in the glandular mucosa is unknown. *Helicobacter*-like organisms have been identified in horses affected with EGGUS in some studies,[57-59] whereas other studies have failed to identify such organisms.[60,61] Pending further investigation of the subject, the author believes that the potential exists in the individual patient for bacteria to be significant, and it is likely that, in some patients, bacterial infection, either primary or secondary, plays a role in the establishment or perpetuation of disease.

The potential for NSAIDs to cause EGGUS under clinical conditions is controversial. An ulcerogenic capacity has been demonstrated for flunixin, phenylbutazone, and ketoprofen at doses only 50% higher than typically recommended,[62] whereas at clinical doses phenylbutazone and suxibuzone did not induce gastric ulceration when administered for 15 days.[63] Further, the administration of NSAIDs was not identified as a risk factor in a recent study.[8] The author believes that, at clinically used doses in otherwise healthy animals, the risk of EGGUS associated with short-duration NSAID therapy is negligible, but in animals receiving NSAIDs for long durations (>2 weeks), or in animals that are systemically compromised, EGGUS should be considered as a potential side effect.

Prevalence and Risk Factors

Prevalences of 47%[9] and 62.5%[8] have been reported in Thoroughbred racehorses in Australia, whereas the prevalence in Thoroughbred racehorses in the United Kingdom is significantly lower (8%).[8] However, the low prevalence reported among UK horses should be interpreted with caution as only a small number of horses (n = 25) were examined. A mixed population of horses in Denmark had an overall EGGUS prevalence of 57%,[10] endurance horses have reported prevalences of 27%[28] and 33%,[29] whereas abattoir studies have reported rates of 57%[60] and 67%[61] in a variety of horse types.

In a study of Thoroughbred racehorses,[8] the risk factors identified for EGGUS were gender (colts are at reduced risk), trainer, no grass turnout, horses in direct contact with each other, horses not fed haylage, horses fed unprocessed grain, horses that were infrequently fed a complete diet, horses that underwent fast exercise on fewer days of the week, and horses that went swimming. In contrast to ESGUS, where the risk of ulceration increases with time in work,[8] time in work was not a significant risk factor; similarly, a Danish study found that horses in work were no more likely to have EGGUS than were young horses, breeding mares, or mature horses at pasture.[4] The results of these studies suggest that whereas diet may influence the risk of EGGUS in a manner similar to that of ESGUS, with high-concentrate/low-roughage diets increasing the risk of disease, the relatively direct relationship between intensity of, and duration in, work and the prevalence of ESGUS is not observed in horses with EGGUS. As such, while the clinical index of suspicion for ESGUS is relatively low for horses at rest and increases with the intensity of work, EGGUS should be a differential in horses demonstrating clinical signs of the disease regardless of the intensity of work.

Treatment

Until recently, treatment recommendations for EGUS have not differentiated between squamous and glandular disease. However, in three recent studies only 25% of glandular ulcers healed with 28 to 35 days of omeprazole therapy at 4.0 mg/kg PO q24h in direct contrast to an ESGUS healing rate of 78%[12-14]; these findings suggest that specific treatment recommendations for EGGUS are needed. In humans, the duration of therapy for glandular ulceration is dependent on the primary cause of the lesion and, although acid suppression remains a cornerstone of treatment, its duration and the use of adjunctive agents depend on the primary cause.[55] In the horse it is widely believed that once-daily dosing of omeprazole results in 24 hours of acid suppression[64]; however, a recent study has suggested that the duration of acid suppression may be less than 12 hours.[47] As such, it is possible in the horse that the duration of acid suppression required, either within each 24-hour period or over the total course of treatment, for squamous healing may be less than that required for glandular healing and that the primary reason for failure of omeprazole to work on glandular ulcers might be that the duration of acid suppression, although adequate for squamous healing to occur, is inadequate for glandular healing to occur. Given the slow rate of healing the author typically recommends a minimum of 6 weeks of therapy prior to control gastroscopy for EGGUS.

An alternative explanation, as discussed earlier, is that bacteria may play a role in the development or perpetuation of glandular ulceration and that acid suppression therapy alone may be inadequate. Antimicrobial therapy is commonly recommended as an adjunct to acid suppression therapy in refractory EGGUS[64,65]; however, in a recent study the addition of trimethoprim-sulfadimidine at 30 mg/kg PO q24h to omeprazole at 4.0 mg/kg PO q24h failed to improve the treatment response compared with omeprazole therapy alone.[54] Based on these results, and in line with the principles of responsible use of antimicrobials, the author does not believe that antimicrobial therapy is justified as a first-line treatment for EGGUS. However, as a potential role for bacteria cannot be ruled out, antimicrobials may be considered in refractory cases. Consistent with this, the author does not use antimicrobials until at least 6 weeks of omeprazole and mucosal barrier therapy have failed to resolve the condition at which point doxycycline at 10 mg/kg PO q12h administered concurrently with sucralfate at 20 mg/kg PO q12h may be beneficial. Doxycycline is chosen for its relatively broad spectrum, and the concurrent administration of sucralfate prolongs contact of the antimicrobial at the site of the ulcer bed.[66]

Give the proposed role of failed mucosal defenses in the pathogenesis of EGGUS, the use of mucosal protectants as a component of therapy is logical. It is unlikely that mucosal protectants alone will result in significant healing, but they may serve as an important adjunct to omeprazole therapy. The two most commonly used agents are sucralfate and pectin-lecithin complexes. The mechanism of action of sucralfate is likely a combination of adherence to ulcerated mucosa, stimulation of mucous secretion, prostaglandin E synthesis, and enhanced blood flow, all of which are likely to be beneficial in horses with EGGUS.[17] Anecdotally superior healing has been reported with the addition of sucralfate over omeprazole therapy alone[66] and its use at 20 mg/kg PO q12h in addition to omeprazole therapy as a front-line treatment is logical. Alternatively, pectin-lecithin complexes may be of benefit. Apolectol (Boehringer Ingelheim, Ingelheim en Rhein, Germany), a unique pectin-lecithin complex, has been shown to increase the total mucus concentration in gastric juice,[67] and another study suggested that it may have a role in the treatment of EGUS in clinical patients.[68] Its use has been suggested in cases where reduced mucosal barrier integrity is suspected,[66] and the author believes that its use as a adjunctive front-line treatment at 150 g q12h is warranted.

Prevention

Prevention of EGGUS, either as primary disease or recurrence, is problematic. In a series of recent studies, worsening of EGGUS grade was observed in 23% of horses despite omeprazole therapy at doses ranging from 1 to 4 mg/kg PO q24h.[12-14] Further, it has been suggested that gastric hyperplasia may be present in a percentage of EGGUS cases and that in such cases omeprazole therapy is contraindicated.[66] At the time of writing, the exact role of omeprazole for prevention is unclear; however, use as per the recommendations for ESGUS is logical until further defined. Gastric mucosal biopsy is indicated in patients that develop EGGUS in the face of omeprazole therapy in order to individually tailor treatment.

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Given the risk factors associated with the feeding of low-roughage and high-concentrate diets that have been identified for horses with EGGUS,[8] the use of dietary modification similar to that for treating ESGUS is logical. However, such changes are often difficult to achieve and the author has observed numerous cases of EGGUS in horses with "good" management strategies (i.e., free choice hay, pasture turnout, and reduced concentrate feeding). In one study, the addition of corn oil at 0.3 to 0.45 mL/kg/day (150 to 225 mL/day for a 500-kg horse) decreased gastric acid output and increased prostaglandin E_2,[69] both of which are, in theory, beneficial for the treatment and prevention of EGGUS. As such, the addition of corn oil at 0.5 mL/kg/day may be beneficial. Last, given the fundamental role of failed mucosal defenses in the pathogenesis of EGGUS, the use of mucosal barrier protectants is logical and the use of Apolectol at 150 g q12h as a follow-up in clinical cases of EGGUS has been suggested[66] and is logical.

Gastric Impaction

Gastric impaction is a relatively common presentation. Clinical signs are diverse, with inappetence the most common presentation and representing 50% of cases in one study.[70] Affected horses typically eat small amounts but have a significantly decreased total daily intake. Acute and recurrent colic are also common presentations.[70,71] The causes of gastric impaction are unclear and although poor dental care has been proposed as a predisposing factor,[17] cases commonly occur in horses with no dental abnormalities. The author has recognized three types of gastric impaction: type I is impaction of feed material where the stomach size is not increased; type II is impaction of feed material where the stomach size is significantly increased and, although difficult to prove, there is commonly a suspicion of an underlying motility disorder in these cases that is reflected in the poor response to treatment and prognosis; type III impactions occur following the formation of a phytobezoar secondary to persimmon seed ingestion.[71,72] Classification of the type of gastric impaction is important because treatment and prognosis vary depending on the type. Distinguishing between types I and II can be difficult.

Diagnosis of gastric impaction in the field is difficult, but it should be considered as a differential in any horse that presents with mild colic symptoms that dramatically worsen following the administration of fluids via a nasogastric tube, horses with unexplained inappetence, and horses with colic that appears to resolve with fasting only to relapse with the reintroduction of feed and recurrent colic cases. The presentation of type I impactions is typically mild with a normal heart rate.[70] Symptoms may be slightly more pronounced in type II impactions, and displacement of the spleen may be palpable on rectal examination. Type III impactions more commonly present with mild to severe colic and/or weight loss.[71,72] Definitive diagnosis is made when, after an appropriate period of starvation, entry to the stomach with a gastroscope is obstructed by feed material. Alternatively, in type I cases the stomach can often be entered and distended with air, but a clearly defined ball of feed material extending above the level of the margo plicatus is visible. In type III impactions a phytobezoar is typically visible once the stomach has otherwise emptied of feed material. Ultrasonography can be useful to distinguish between type I impactions, where visualization of the stomach is difficult or limited, and type II impactions where the distended stomach will often extend for several rib spaces.

Treatment and prognosis are dependent on the type of impaction present. In all cases, correction on any concurrent systemic abnormalities such as dehydration and/or electrolyte imbalances is indicated, and resolution of the impaction should be confirmed by gastroscopic examination before reintroducing food.

- Type I. The use of enteral fluids is highly effective in this population with 1 L/100 kg of isotonic electrolyte solution given q2h via an indwelling large-bore nasogastric tube. Depending on the response, the rate and volume can be increased or decreased. The author routinely uses flunixin at 1.1. mg/kg IV/PO q12h until resolution of the impaction, as mild symptoms of abdominal discomfort are not uncommon. The use of indwelling, small-bore nasogastric tubes for the administration of enteral fluids has been described[73]; however, theoretically the bolus administration of fluids should result in a more pronounced stimulation of the gastro-colic reflex. Other treatments such as dioctyl sodium succinate (DSS) and gastric lavage have been proposed[17] but given the good prognosis reported for enteral fluid therapy alone (90% survival to discharge),[70] alternative therapies appear to offer little advantage.
- Type II. Treatment of type II impactions is similar to that of type I impactions, but caution should be exercised in the volume of fluids administered as the stomach wall is often friable and gastric rupture can occur. Concurrent intravenous fluid therapy should be considered if fluid requirements cannot be met with enteral therapy alone. The response of type II cases to treatment is often poor and the addition of prokinetics may be beneficial in some cases; however, the response to prokinetic therapy is often disappointing. Bethanechol at a dose of 0.025 mg/kg SC q4-6h is the prokinetic of choice,[17] although it is often difficult to obtain, and erythromycin at 1 mg/kg IV q6-8h is a reasonable alternative. Surgery should be considered in impaction types I and II if the animal is showing signs of systemic deterioration or if medical therapy has not resolved the impaction within 5 to 7 days with successful treatment by gastrotomy reported.[74] The prognosis for type II impactions has not been reported but in the author's opinion is guarded as gastric rupture is a relatively common occurrence (even without enteral fluid therapy) and reoccurrence is common. The use of low-bulk diets during the refeeding stage is logical.
- Type III. Persimmon seed phytobezoars are generally refractory to standard enteral and intravenous fluid therapy. The use of carbonated cola drinks has been reported with a variety of techniques ranging from constant infusion of 1 L/h for 1 to 3 days to bolus administration via nasogastric tube at 700 mL q12h with the mechanism believed to be a combination of the mucolytic effects of sodium bicarbonate, the acidifying effects of the cola, and mechanical disruption of the fibers of the phytobezoar by the carbon dioxide bubbles.[71] Constant infusion via a small-bore nasogastric tube appears to be the treatment of choice and the use of caffeine-free, diet cola is recommended to reduce the risks of caffeine toxicoses or laminitis secondary to carbohydrate overload. The prognosis for type III impactions appears good with five of eight horses responding to medical therapy in one report.[71] In the same report two additional horses were successfully treated surgically via laparotomy with manual manipulation of the phytobezoar without gastrotomy while the horse in which a gastrotomy was attempted was euthanized at surgery because of extensive contamination of the abdominal cavity.[71]

Miscellaneous Diseases of the Stomach

A variety of miscellaneous disease conditions also affect the stomach of the horse, including, but not limited to, gastric rupture, tumors, abscesses and pyloric stenosis. Gastric rupture most commonly occurs secondary to obstruction of the small intestine or chronic gastric impaction. Idiopathic rupture accounted for 17% of cases in one report,[75] suggesting that a variety of other causes can result in rupture. Squamous cell carcinoma (Fig. 32-53) is the most commonly reported of the tumors that affect the stomach, representing nearly 80% of cases in a recent report,[76] although a variety of other neoplastic conditions occur. No breed or sex predilection exists, and a wide range of ages are affected. Clinical signs of abdominal neoplasia and abscesses are typically nonspecific, although weight loss, inappetence, and lethargy are common, and the diagnosis is typically made based on gastroscopic examination.

Pyloric stenosis is an uncommon condition that typically affects foals and young horses,[77] although horses of any age can be affected. The presentation is thought to most commonly result from chronic gastric ulceration, although other space-occupying lesions may be

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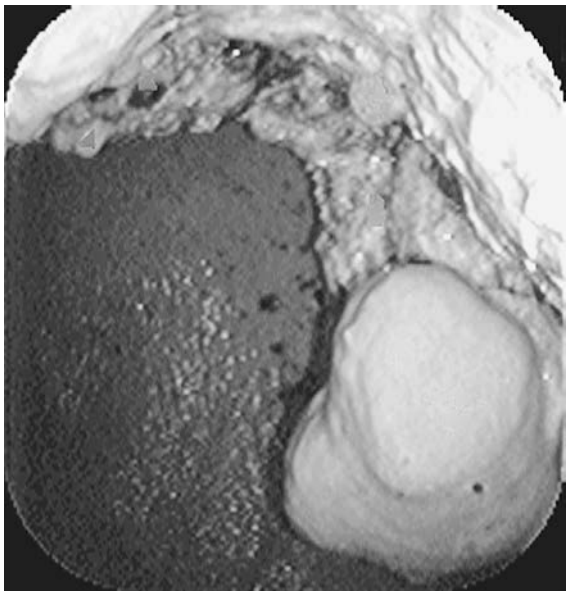


FIG. 32-53 Endoscopic view of a gastric squamous cell carcinoma.

the cause. Affected animals typically have a history of weight loss, poor appetite, and postprandial colic or recumbency.[77] Excessive ptyalism or spontaneous reflux of gastric contents from the nasal passages is common. Diagnosis is typically made on gastroscopy, although ultrasonography and contrast radiography are useful adjunctive tests. Conservative management involves acid suppression therapy, with omeprazole at 4 mg/kg PO q24h effective in less severe cases. Intravenous therapy is indicated in patients with spontaneous reflux of gastric contents or where gastric emptying is significantly delayed. Omeprazole at 0.5 mg/kg IV q24h is highly effective at acid suppression, but the availability of intravenous preparations of omeprazole is limited and the instability of the solution limits shelf life to a few hours. Ranitidine at 2 mg/kg IV q6h is a reasonable alternative. The response to medical therapy is often disappointing and early surgical intervention is indicated in such cases. Long-term survival rates of 50% to 69% have recently been reported for gastrojejunostomy,[78,79] further supporting early surgical intervention in nonresponsive cases.

Intestinal Injury and Healing in the Horse

Nathaniel A. White, II

There are numerous causes of intestinal injury in animals with equine acute abdomen. Classic pathophysiologic explanations use ischemia, ulceration, and inflammation from infection, parasites, trauma, toxins, or immune complexes to categorize and explain intestinal injury. For the clinician, understanding the underlying pathophysiology of injury is important for recognition and treatment of horses with colic. For many of these intestinal disorders, the signs can be similar, making clinical differentiation difficult.

Cellular injury was once characterized by the morphologic change it caused. However, dysfunction caused by cellular injury is more important when considering the resultant clinical signs and morbidity. The response to a stimulus is mediated by numerous autocrine and paracrine messengers, which include cytokines, chemokines, prostaglandins, neuropeptides, and proinflammatory substances such as interleukins (ILs), tumor necrosis factor alpha (TNF-α) complement, histamine, bradykinin, serotonin, and interferon (IFN).[1-3] In the intestine, inflammatory responses to these messengers can be orchestrated by mucosal cells, fibrocytes, macrophages, mast cells, endothelial cells, neurons, muscle cells, and polymorphonuclear cells.[1] The chain of events is complex, and the relationship of the different cell responses is not yet fully understood. It is clear that the inflammatory response from any insult initiates a multitude of chemical and immune reactions, which, depending on the severity of the insult, can cause both local and systemic effects.

Several mechanisms can stimulate an inflammatory response, including ischemia, reperfusion after ischemia, inflammation from bacterial or viral infection, and inflammation from parasites, trauma (surgical), or toxins. The resulting tissue injuries vary and may be differentiated by their effect on the different layers of the intestine and by the vascular and nervous response. Although the mucosa and serosa are often affected first, the inflammatory response frequently involves the remaining layers of the intestine, the submucosa, and smooth muscle.[4,5] The inflammatory response may also vary depending on the specific cause. For example, ischemia can be caused by strangulation of the blood supply, distention of the intestinal wall, or poor perfusion resulting from systemic shock. Although the response of individual intestinal cells may be similar for each, each stimulus appears to evoke different sequences of cell response, thereby causing different clinical signs and varying responses to treatment. In some instances injury to the intestine may be secondary to another disease process, but the damage to the intestine can still initiate a systemic response resulting in systemic inflammatory response syndrome (SIRS) with multiple organ failure.[6]

Intestinal Inflammation: General Concepts

The cascade of events initiated by infection or ischemia has been studied extensively. Inflammatory mediators increased during bowel inflammation are released from numerous cell types, including mucosal cells, endothelial cells, fibrocytes, myocytes, mesothelial cells, and neurons.[1] There is also evidence that the compounds making up the tissue ground substance and cytoskeleton can also initiate an inflammatory response and help transmit signals or cells between immunocytes and afferent neurons.[7] Theoretically all cells in the intestine can act as effector cells, both producing cytokines to send messages to other cells and being activated to respond to the insult by chemokines.[1,3,8] Cytokines, growth factors, and adhesion molecules can all initiate an inflammatory response.[1,3] This response also alters cell apoptosis, resulting in delayed removal of mucosal cells and neutrophils or turnover of immunocytes or specific cells in organs.[6,9] Cytokines such as IL-1β and TNF-α, platelet-activating factor (PAF), complement (C5a), IFN-γ, and histamine are all reported to be involved in inciting intestinal inflammation.[10] Describing all the effects and interactions of the inflammatory cytokines and eicosanoids is beyond the scope of this chapter, but it is apparent these substances can stimulate and inhibit the inflammatory reaction by directing cell communication and cell response to injury. As a result the disease process should be viewed as a sequence of altered cell functions, which are integrated and designed to protect the intestine from permanent injury.

Most intestinal cells—including mucosal cells, endothelial cells, neurons, fibroblasts, mast cells, eosinophils, neutrophils, and macrophages—initiate a response associated with inflammation. Rather than responding independently, these cells appear to respond to the initial insult, each with its inherent cytokine production or cell activation, which stimulates or suppresses other cell responses. Envisioned as a group acting simultaneously, the sequence can proceed from an initial stimulus to mucosal or serosal cells or, in the case of ischemia, the vascular endothelium or enteric neurons.

Mucosal cells react by releasing cytokines to activate macrophages and lymphocytes in the lamina propria.[8] These cells release cytokines and adhesion molecules, which in turn activate other cells while initiating local defenses. Simultaneously, endothelial cells respond to the cytokine message by releasing chemokines to attract neutrophils and eosinophils and subsequently enable them to migrate through the endothelium into the interstitium.[3,7] Afferent neurons detect

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cytokine increases and initiate neuropeptide, cytokine, or eicosanoid release from the efferent neurons, resulting in activation of numerous cells, including those already activated by the initial cell messengers.[11-13] Fibrocytes, responding to the initial cytokine messages and growth factors, subsequently release cytokines and growth factors such as IL-1α, IL-1β, TNF-α, transforming growth factor, and platelet-derived growth factor. All can be proinflammatory or can help to repair the mucosa.[14,15] Metalloproteinases released in response to inflammatory cytokines alter the basement membranes and collagen in the different layers, allowing migration of cells to the extracellular space and stimulating other cells to release chemoattractants.[1,16] Muscle cells, once thought to be neutral in the inflammatory cycle, appear to be able to release cytokines, thereby participating in the inflammatory reaction.[17] Increased adhesion molecule production in the muscle after surgical manipulation has been linked to neutrophil infiltration and subsequent bowel dysfunction.[4,18-20]

Although all the cells in the intestine participate in the inflammatory response as effector cells, they can also act as suppressors. Each appears to communicate with other cells locally to cause or suppress the inflammatory response. Production of nitric oxide by endothelial cells can reduce neutrophil adhesion, whereas increased release of growth factor by fibroblasts and the vascular endothelium speeds healing of the mucosa.[14] The response to receptor activation can take only seconds to minutes to upregulate cytokine production. Lack of suppression, perhaps because of chronic or overwhelming stimulation or severe damage to cells, which release the inhibitor messengers, allows amplification of inflammation and permanent cell damage.

The role of each cell type as effectors and messengers is slowly being unraveled. The role of some cells is better understood than that of others. Reperfusion, cytokines, and complement initiate endothelial cell changes. Subsequent production of cytokines and prostanoids by endothelial cells attracts neutrophils and macrophages.[21] Endothelial cells also stimulate the inflammatory response by altering capillary permeability, promoting neutrophil adhesion, and altering blood flow.[22] The interaction between the endothelial cells and neutrophils or eosinophils is a pivotal response in causing intestinal injury. This response is made possible by PAF, leukotrienes (LTB_4), and adhesion molecules produced by endothelial cells and neutrophils.[3,21] Neutrophil migration into affected tissues subsequently causes severe damage, including damage to cells and tissue ground substance, which further promotes the inflammatory response.[6]

Although all intestinal cells can be involved in the inflammatory process, the nervous system is now known to be integral in the inflammatory response. Release of potassium, adenosine triphosphate (ATP), bradykinin, and prostaglandin E_2 all stimulate afferent neurons.[11,23] Neuropeptides are released from neurons in response to afferent signals caused by products of cell injury, including cytokines, eicosanoids, and histamine.[11,23] Substance P, neurokinin, calcitonin gene-related protein (CGRP), and vasoactive peptide (VIP) have all been found in increased levels in inflamed tissues, suggesting that they act as messengers to histiocytes or immunocytes, which subsequently release cytokines.[11,12] The paracrine response differs in different tissues, but inflammatory responses by mast cells, neutrophils, T cells (cytokine release), B cells, macrophages, fibroblasts, and muscle cells are in part caused by neuropeptide stimulation. The coordination of this response is not totally understood, but it is known that neuropeptides serve as proinflammatory mediators or suppressors.[24,25] This system allows for immediate response of cells to a stimulus without humoral involvement and likely can cause persistent inflammatory reactions in response to inflamed tissue.

Local inflammation of the intestine is known to cause changes in other organs distant to the intestinal damage, specifically the lung. Circulating cytokines and activated neutrophils rapidly initiate an inflammatory response in the lung after intestinal inflammation.[26] This response is well known in experimental models and humans but has not been reported during intestinal disease in the horse. Other organs are likely affected, creating signs of multiple organ involvement as part of SIRS.

Ischemia and Reperfusion

Ischemia is a deficiency of blood flow in tissue or an organ. The lack of energy production in the cell starts a degenerative process. Within 5 minutes there are alterations in mitochondria, characterized by swelling and disorganization of cristae. Mitochondrial changes precede cytoplasmic and membrane changes, which occur in the first 30 minutes by activation of phospholipases, cytokine production, and accumulation of arachidonic acid. If ischemia persists, the cell degradation continues with failure of the membrane ion pumps, allowing calcium to move into the cytoplasm.[27] This calcium accumulation within the cell activates proteases, which cause cell membrane damage and nuclear clumping. Calcium uptake in the mitochondria is increased, which inhibits oxidative phosphorylation, thereby decreasing the cell's source of energy.

During ischemia, microscopic changes become evident at 30 minutes when the mucosal epithelial cells and serosal mesothelial cells separate from their basement membranes.[28] This appears to be a mechanical separation caused by water movement from the vasculature into the subepithelial space. Metalloproteinases may also be involved in altering the basement membrane. The space, created by the initial separation, named *Gruenhagen space,* occurs at the tip of the villus in the small intestine (Fig. 32-54).[28] If ischemia continues, the cell damage progresses as the mucosal cells progressively slough off the lamina propria toward the intestinal crypts (see Fig. 32-54). The change is similar in the colon, with epithelial cells sloughing off the surface of the mucosa (Fig. 32-55). However, the slough is somewhat slower in the colon as it proceeds into the crypts. The serosa reacts in a similar fashion, with mesothelial cells lifting off the basement membrane before there is visible cell membrane or cytoplasmic change. Other than vascular congestion, there is minimal change in the architecture of the supporting tissues in the mucosa or the serosa for the first 60 minutes of total ischemia. After 180 minutes of ischemia the lamina propria and mucosal vascular tuft have lost their architecture. The tissue is necrotic and becoming homogeneous, with lack of nuclear definition and cell structure.

Estimating the time required to create ischemic lesions depends on the experimental methods used. Different types of anesthesia in the horse and other animals have resulted in different rates of mucosal degeneration during ischemia. For example, experiments using animals anesthetized with inhalant anesthetics are different from those that require animals breathing air, most likely from higher tissue oxygen concentrations.[28-30] Also, some cell types, such as muscle, appear more resistant to ischemia, which probably depends on the intracellular energy reserves of the cells. There are also differences in the response to low-flow ischemia versus total arteriovenous obstruction. Nevertheless, lesions caused by ischemia progress with reperfusion.

If reperfusion—either resumption of blood flow or increased flow after low-flow conditions—occurs while cells are still viable, a cascade of events is set in motion by the delivery of oxygen to the previously ischemic tissue.[21,31] The resultant injury is called *reperfusion injury* and relies on renewed oxygen in the tissue, with participation of endothelial cells and afferent receptors to create the subsequent inflammatory response. Although it makes sense that oxygen is needed to resuscitate the previously ischemic cells, the innate defense system in many cell types is to respond to the ischemic change with an inflammatory response. This response appears to help initiate a defense against bacterial invasion and is aimed at removing the damaged cells from the system. If enough cells have been damaged, the reperfusion effect can cause enough inflammation to prevent cells from surviving, thereby delaying healing.

Reperfusion injury starts as a change in intracellular metabolism in previously ischemic tissue. It does not require exposure to a microbe or toxin, but it does rely on cell production of complement, cytokines, and leukotrienes as signals to numerous blood and tissue cells required to complete the process.[32] One primary initiator of reperfusion injury in the intestine is the production of oxygen (O_2) radicals. Oxygen has the ability to take on an extra electron during

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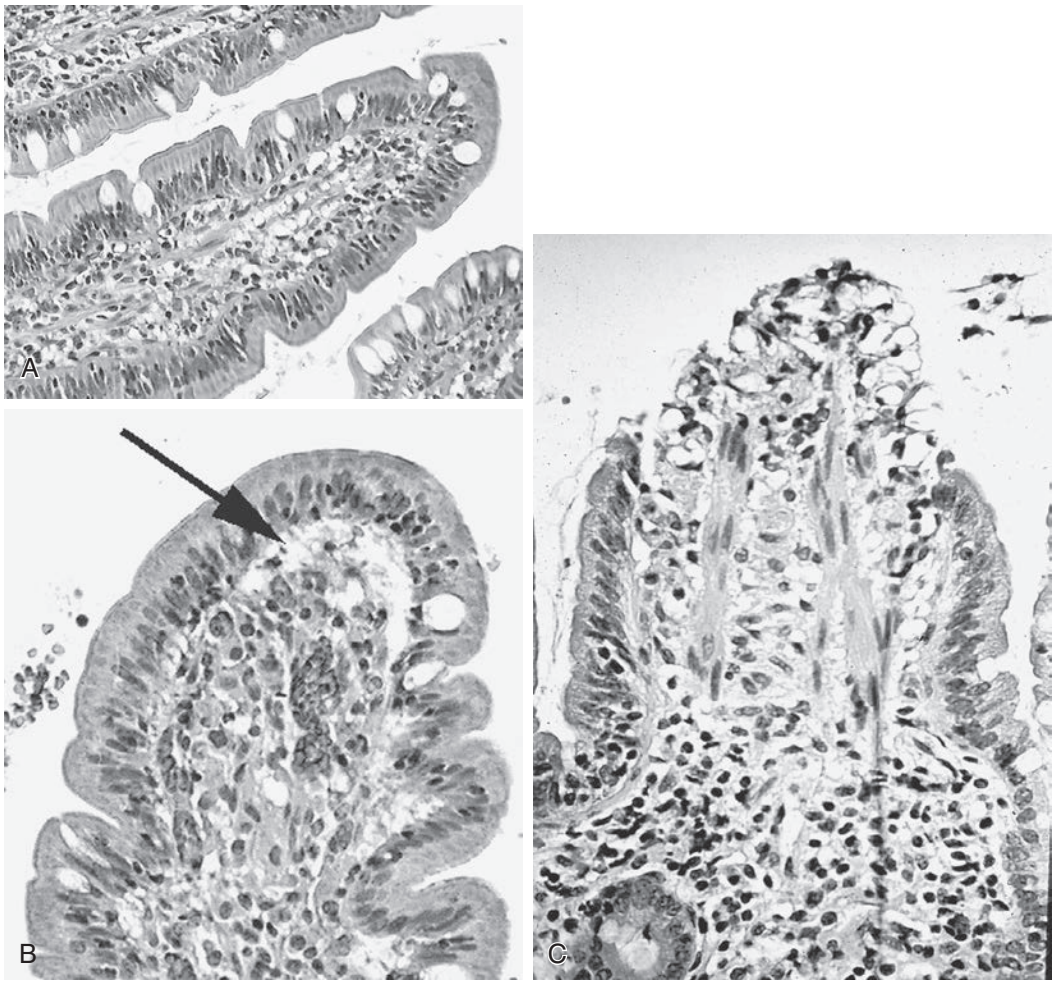


FIG. 32-54 Photomicrographs of normal small intestinal villus **(A),** grade I epithelial lesion with formation of Gruenhagen space *(arrow)* at the top of the villus **(B),** grade III lesion with mucosal slough off the sides of the villus **(C).** (Hematoxylin and eosin stains.)

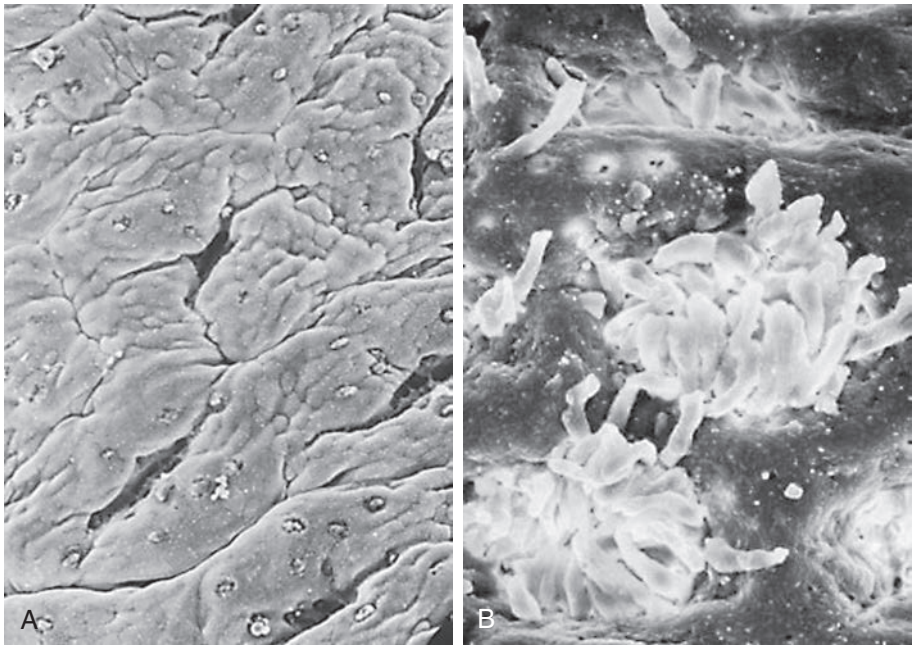


FIG. 32-55 Scanning electron photomicrographs of normal large colon mucosal surface **(A)** and ischemic large colon mucosal surface with loss of the surface mucosa and mucosal cell slough with the openings of the crypts **(B).**

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enzymatic processes in the cell. Most cells, including endothelial cells and the small intestinal mucosal cells, contain xanthine dehydrogenase, which, when converted to xanthine oxidase, catalyzes hypoxanthine to xanthine.[31] Hypoxanthine is increased in the cytoplasm of cells during ischemia. Calcium and proteases initiate xanthine dehydrogenase conversion to xanthine oxidase, a process that can be stimulated in endothelial cells by IL-1, TNF-α, and C5a, as well as neutrophil adherence. Oxygen is used in the reaction and ends up with an extra electron, making an O_2 radical or superoxide.

Once released, O_2 radicals can initiate a number of chemical reactions that cause cell membrane damage directly and by stimulating phospholipase activity. During O_2 radical production, nitric oxide (NO) production is decreased, thereby allowing neutrophil adhesion and migration. Superoxide interaction with iron or catalase causes production of hydroxyl (OH) radicals or hydrogen peroxide (H_2O_2) respectively. Both are cytotoxic. The OH radicals alter or destroy cell membranes. Affected cells rapidly express cytokines and leukotrienes, which act as chemoattractants for neutrophils. After the initial free radical production, cell injury progresses as two main events. Calcium, already increased in the cell, increases further, effectively blocking further energy production in the mitochondria and activating proteases, causing further degradation of the cell nucleus and cytoplasm.[27] Second, radicals formed from molecular oxygen can cause cell membrane damage, thereby initiating a similar cellular response. The formation of chemical mediators takes only seconds to minutes after reperfusion and rapidly sets the inflammatory cascade in motion.

Although the mucosal cells and serosal mesothelial cells are damaged early in ischemia and are able to release cytokines to alert other cells locally, endothelial cells appear to be the primary initiators of reperfusion injury.[2] They participate in cytokine production and are involved with neutrophil adhesion and migration from blood into tissues. Endothelial cells are also involved with the changes in blood flow after reperfusion.[22,24,33] The platelets and neutrophils accumulate in and obstruct capillaries, altering blood flow (Fig. 32-56). Endothelial cell swelling or contraction causes constriction of blood vessel lumens. Changes in endothelial cells in response to histamine, complement, leukotrienes, and PAF increase capillary permeability, allowing fluid and protein to move into the interstitium.[24] Even though the metabolic state of the tissue during initial reperfusion initially results in overall increased blood flow, the increased vascular permeability increases interstitial pressure, causing capillary collapse. Combined with endothelial cell change, plugging of capillaries with neutrophils, vascular constriction, and capillary collapse result in a "no-reflow phenomenon," promoting further tissue ischemia.

Endothelial cell membrane changes allow expression of adhesion molecules and receptors, which are necessary for neutrophil adhesion and migration through the capillary and venule endothelium (Fig. 32-57). This migration of neutrophils causes the most prominent inflammation in the tissue, because activated neutrophils release elastase, oxygen radicals, and other serine proteases, which attack collagen, ground substance, and cell membranes.[34] The respiratory burst, a buildup of oxygen free radicals in neutrophils during activation, is responsible for most of the inflammation and tissue damage seen during reperfusion. It is also apparent that reperfusion injury can expand the initial injury into the surrounding viable tissue and that it can cause irreversible tissue damage.[4,35] Reperfusion injury can also cause injury distant from the local damage and has been observed in the lung because of cytokine and activated neutrophil circulation.[36] Although not reported in the literature, the resulting lesion can be seen in the lungs of horses that succumbed to severe intestinal strangulation, obstruction, and shock.

Cell necrosis is recognized as a pathologic feature during ischemia and reperfusion. Recently, however, alterations in apoptosis (programmed cell death) have been found to increase during ischemia and reperfusion in experimental studies of the heart, brain, liver, adrenal glands, kidney, and intestine.[37-39] Alternatively, epithelial cells undergoing hypoxia and reoxygenation modulate neutrophils to delay apoptosis, suggesting a role in initiating SIRS.[6] A significant

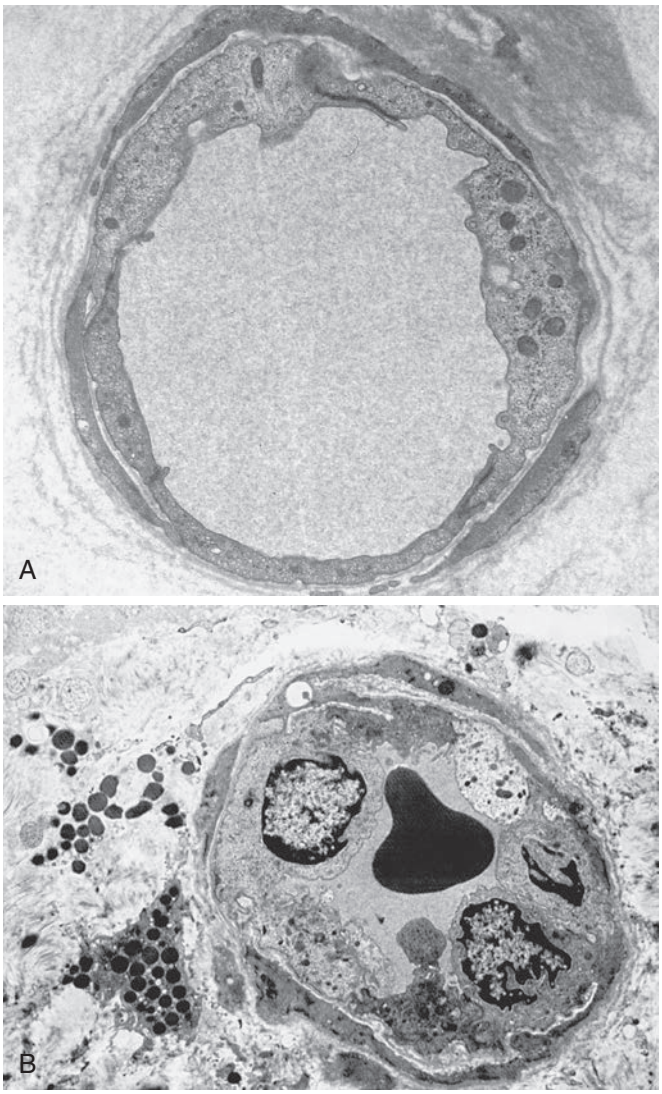


FIG. 32-56 Transmission electron photomicrographs of small vessels in the serosa, with normal endothelial cells prior to ischemia **(A)** and with plugging of the vessel with adherent neutrophils during reperfusion **(B).**

increase in the number of apoptotic cells in muscle, mucosa, neurons, and glia in naturally obstructed or strangulated equine intestine suggests apoptosis is stimulated by, and may promote, the inflammatory response (Fig. 32-58).[40,41]

Apoptosis is also increased in intestine distant to the primary lesion, supporting systemic stimulation by cytokines.[40] The amount of apoptosis observed in experimental animals and in horses with intestinal obstruction suggests this process is excessive during reperfusion and may result in both morphologic and functional changes.

The importance of oxygen radical generation as a mechanism of injury in strangulating lesions has been questioned in the horse.[42] However, both clinical signs and lesions from clinical cases suggest that intestinal damage progresses after reperfusion. In a low-flow to no-flow model of ischemia with subsequent reperfusion, treatment to counteract injury from superoxide production and neutrophil accumulation decreased intestinal injury.[43] This suggests that free radical production is part of the cascade of events causing an inflammatory response in the small intestine after bowel strangulation. Lack of malondialdehyde and conjugated diene production in the large intestine suggests less of a role for tissue-generated oxygen radicals and that reperfusion injury is caused primarily by the oxygen radical release from migrating neutrophils as seen in xanthine oxidase–deficient rats.[34,44]

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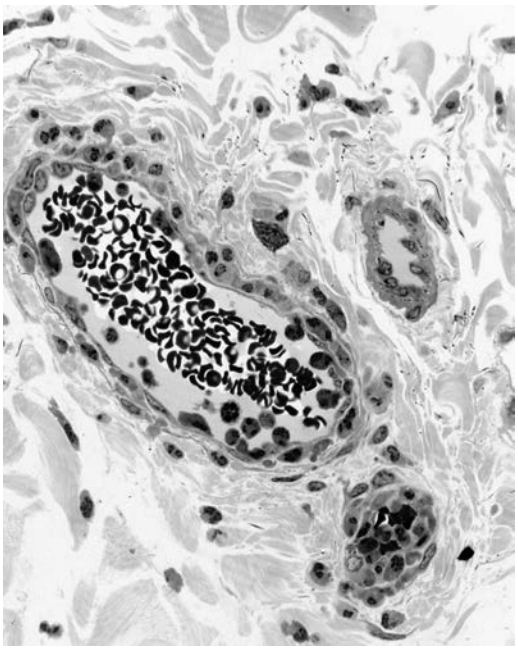


FIG. 32-57 Photomicrograph of serosal vessels with adhesion of neutrophils to endothelial cells and migration into the interstitium. (Hematoxylin–basic fuchsin stain.)

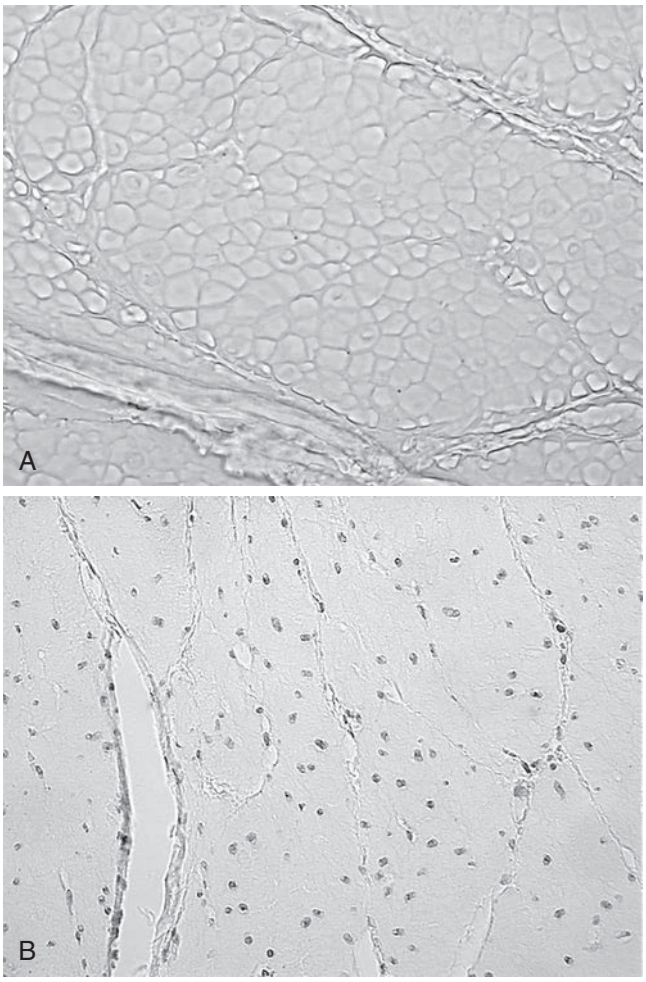


FIG. 32-58 Photomicrograph of tissue stained to detect apoptosis in normal circular muscle with no evidence of apoptosis staining **(A)** and circular muscle in which the dark staining nuclei indicate apoptosis of smooth muscle cells **(B)**.

Recent research suggests that endothelial cells are not the only cells that act as "local effectors" of inflammation during reperfusion. Signs of inflammation are present in all parts of the intestine, including the muscle and myenteric plexus.[17,45-47] Alterations in muscle mitochondrial morphology have been identified in equine jejunum after low-flow ischemia.[22] Similarly, during large colon volvulus, the neurons in the myenteric plexus undergo degeneration and decrease in number compared with normal conditions.[46] Evidence of ischemic injury and inflammation occurs in both muscle and myenteric plexuses. This is relevant in horses with colon volvulus, in which survivors had significantly more neurons than nonsurvivors.[46] Perhaps of greater importance is the long-term effect of the inflammation in the myenteric plexus after ischemia and reperfusion. One can speculate that the high rates of repeat colic episodes in horses after colon torsion or large colon obstruction are related to damage to the enteric nervous system.[48]

Reperfusion injury occurs after low-flow and no-flow ischemia. These models appear to emulate the clinical event, although the onset of ischemia in strangulation obstruction most likely starts as low-flow progressing to no-flow ischemia. Although the time frame of reperfusion injury is somewhat understood from the experimental models, the functional effects of dynamic events set in motion by reperfusion such as "no reflow," as well as persistent inflammation in the serosa and around the intestinal nerve ganglia, are not well understood.

Functional effects of reperfusion are elucidated in intestine undergoing experimental ischemia and reperfusion. Lidocaine treatment for ischemia and reperfusion injury inhibited cyclooxygenase type 2 (COX-2) expression, and when combined with flunixin meglumine neutrophil migration was decreased.[49] Ischemic muscle treated with lidocaine in vitro improved contractility compared with untreated muscle.[50] Treatment of experimentally created intestinal ischemia with Carolina rinse solution significantly decreased neutrophil migration and subsequently resulted in less serosal fibrosis.[51] These responses suggest that ischemia-reperfusion injury stimulates intestinal inflammation and decreases motility and that the effects can be decreased with treatment.

Low-Flow Ischemia

The effect of ischemia-reperfusion differs with the type of ischemia. Low-flow ischemia is defined as flow less than 25% of normal blood flow. At this flow rate, vascular and cell damage is minimal, and degeneration occurs over a long time period. When normal flow is returned by increasing vascular volume or by release of the arterial obstruction, there is a hyperemic response doubling the normal blood flow to the affected intestine.[22] Cell damage accelerates during reperfusion, with marked changes in vascular permeability, mucosal damage, serosal damage, and signs of fluid accumulation in the submucosa, muscle, and serosa.[22,52,53] Edema in the submucosa and serosa causes vascular collapse, leading to decreased blood flow and eventually a "no-reflow" phenomenon in the serosa and mucosa, resulting in decreased flow to the affected segment.[33,54,55] The decreased flow is partially caused by endothelial cell swelling and neutrophil margination in the vasculature. Neutrophils migrate into all intestinal layers but predominantly the mucosa and serosa. As neutrophils migrate through the capillary or venule, they accumulate around the vessels. As reperfusion progresses, the greatest injury is observed in the serosa, with marked accumulation of neutrophils beneath the serosal basement membrane. This type of low-flow ischemia is rarely documented in equine abdominal disease, but it likely exists in distended intestine in which there is low flow to the affected bowel wall. The flow is directly related to the intraluminal pressure, with pressures causing greater than 50% reduction in blood flow common in severe small intestinal distention.[55]

When examined in experimental models or when observed in clinical cases, most of these changes from acute low-flow ischemia are reversible and the affected intestine survives and heals. The effect varies greatly and is dependent on the length of ischemia. It is suspected that function is compromised temporarily, resulting in ileus,

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endotoxin absorption, or enteritis with excess secretion. In the small intestine, serosal scarring and adhesions are the most common long-term result and may increase the risk of colic episodes in the future. Even if lesions are not grossly evident and appear minor on microscopic examination, horses with colic, particularly those requiring surgery, likely have intestinal injury, which can ultimately result in temporary or permanent intestinal dysfunction. Hypothetically this is one possible reason for increased risk of colic after previous colic episodes or previous surgery for colic.[48,56]

Nonstrangulating infarction is the classic example of low-flow ischemia. In the horse, thromboembolic colic is reported to be caused by thrombosis of the mesenteric artery and its branches in horses infected with fourth-stage larvae of *Strongylus vulgaris*.[57] The mechanism of infarction is most likely reduction of blood flow from a thrombus in the artery or thromboembolism obstructing the peripheral vasculature. In nonstrangulating infarction the intestinal injury most likely results from long-term low-flow ischemia or low-flow ischemia with episodes of reperfusion injury. In clinical cases the injury is severe, often resulting in necrosis in all layers of the bowel, with obvious infarction.

Low-flow ischemia may also occur during shock.[58] In horses with obstructing or strangulating lesions, biopsies from nonaffected, grossly normal intestine have evidence of some degree of bowel injury, including neutrophil infiltration.[4,59,60] This injury can also be caused by endotoxemia with loss of mucosa and neutrophil infiltration in the mucosa. This may be relevant to assessing horses in shock.

Total Arteriovenous Occlusion

Total ischemia caused by arteriovenous occlusion causes total vascular stasis. The most common cause of this form of ischemia is incarceration of bowel in hernias or constricted spaces. Early in the occlusion, capillary congestion is observed in all layers of the intestine. The intestine undergoes degeneration as previously described for ischemia. When total ischemia exceeds 2 hours in the small intestine and 3 hours in the large colon, the tissue changes during blood flow occlusion are extensive, and cell necrosis may preclude a response to reperfusion.[28,61,62] If the capillary damage is not too extensive during total ischemia, reperfusion causes further degeneration, including mucosal cell loss, increased edema, and neutrophil migration.[59] However, oxygen radical production seen with low-flow ischemia and reperfusion may not be responsible for the continued damage during total arteriovenous occlusion.[63] Furthermore, these events cannot be separated from systemic shock or circulation of cytokines, which can cause secondary lesions seen in intestine distant to the lesion.[26] Despite the questions about the validity of reperfusion in the total ischemic event, continued intestinal injury during reperfusion is seen in both the small intestine and the large colon after total ischemia.[35,60,64] The epithelial cell loss after reperfusion is progressive and is likely caused by either countercurrent exchange creating a decreased oxygen concentration in the distant mucosa or by inflammation resulting from oxygen radical–induced inflammation from neutrophil activation.[45,65] The response in the serosa includes marked edema with initiation of neutrophil migration. Eventually a massive collection of neutrophils fills the outer border of the serosa.[54,64] During this type of ischemia and reperfusion, the damage from the inflammatory reaction can continue for days and, if severe enough, can prevent healing of the mucosa and serosa and is consistent with persistent ileus and shock.

Venous Occlusion

Venous obstruction without arterial obstruction causes increased pressure at the capillary, resulting in decreased blood flow with red blood cell (RBC) and fluid extravasation into the interstitium. The result is separation of the tissues with an increased diffusion distance for oxygen and nutrients. The RBC accumulation causes tissue damage, and if it is severe enough a continuation of cell hypoxia becomes irreversible even with reperfusion. Injury during venous obstruction appears more severe than observed during subsequent reperfusion.[66] Small intestine can survive 2 hours of venous obstruction, although the resultant degeneration is severe and the intestine is permanently scarred after healing.[29] The gross lesion is marked with obvious thickening of the bowel, which at first is red and eventually turns purple. With time and subsequent necrosis the color turns black or green as a result of alterations in hemoglobin.

For the surgeon, venous occlusion is the most difficult type of lesion to assess, as intestinal thickness or amount of hemorrhage may not correlate with viability.[67] Recent reports of survival of horses with hemorrhagic lesion at surgery suggest that this injury can be reversed more readily than a lesion caused by total arteriovenous occlusion. The sequence of mucosal degeneration remains the same in this type of ischemia, making the biopsy the most reliable method for determining if the intestine can survive and heal.[67]

Distention

Although distended intestine may appear to have normal color and motility after decompression, alterations in blood flow in the intestinal wall create low-flow ischemia. During intestinal distention, intraluminal pressure causes collapse of the veins and capillaries, thereby decreasing the vascular capacity. This occurs even when blood pressure is normal. When small intestinal pressure is increased to 18 cm of water, as previously measured in clinical disease,[68] mesenteric blood flow to the intestine is decreased by at least 50%.[55,69] Increasing capillary back pressure while maintaining arterial pressure alters Starling forces in the intestinal wall. The result is secretion of fluid from the vasculature even with an increase in wall tension. Water and some protein escape into the interstitium, causing submucosal and serosal edema. At higher intraluminal pressures there is more secretion than absorption of water, creating a cyclic increase in intraluminal pressure after bowel compliance has reached its limit.[69a] Fluid and eventually protein leak through the serosa into the intestinal lumen and peritoneal cavity.

If the pressure is maintained, intestinal compliance allows blood flow to gradually increase, acting as a form of reperfusion.[55] Serosal and submucosal edema progresses during the period of distention. The mucosal and serosal lymphatics dilate, and RBCs and white blood cells (WBCs) migrate into the mucosa, submucosa, and serosa (Fig. 32-59). There is minimal injury to the mucosal epithelium at pressures seen in clinical cases during simple obstruction of the small intestine or colon.

Subsequent decompression of the bowel causes reperfusion with a hyperemic response similar to that seen after low-flow or total ischemia. Blood flow to the affected bowel can initially double, but this effect is temporary, with subsequent blood flow decreasing below normal.[55] The mucosa appears relatively resistant to short-term distention, whereas the edema in the serosa causes capillary closure and increased vascular permeability. Serosal edema increases and more neutrophils migrate into the serosa, causing destruction of collagen and ground substance.[54] Intestinal smooth muscle is also affected with edema, and neutrophil migration is evident in the fascial planes around the myenteric plexuses (Fig. 32-60). Although bowel can frequently heal after this type of ischemic insult, the serosa is often thickened by fibrous tissue with the possibility of adhesion formation and mesenteric constriction.[51,70] The mucosa appears relatively resistant to the low-flow ischemia created by bowel distention, but the response is time dependent. Rarely does prolonged distention cause bowel necrosis. Bowel wall necrosis is more common when foreign bodies or impactions cause focal distention. Because the response to distention is both time and pressure dependent, the time frame for permanent damage is difficult to determine. The small intestine is more susceptible to distention injury compared with the large colon. Clinical measurement of intraluminal pressure during obstruction indicates that the large colon can tolerate at least twice the distention pressure with no adverse effects.[71,72]

Intestinal dysfunction occurs after decompression of previously obstructed bowel. Ileus with gastric reflux is common in horses with previously distended small intestine, and the bowel pressure measured at surgery can predict the severity.[71,72] Abnormal motility with lack of response to prokinetic drugs is also observed after small

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intestine distention in vitro.[73] Although the injury from distention cannot be separated from conditions in the peritoneal cavity or failure of the cardiovascular system, the correlation of increased intraluminal pressures and survival indicates the importance of intestinal distention in causing injury.

The enteric nervous system also appears to respond to intestinal distention. Chronic obstruction caused by impaction of the colon or cecum or colon displacement has been associated with a significant decrease in the number of neurons in the myenteric plexuses of the large colon, whereas the number of myenteric plexuses was similar to that in normal horses.[46] This change in neuron number was also associated with increased thickness of the longitudinal muscle in the pelvic flexure or both circular and longitudinal muscle hypertrophy in the cecum.[74] This appears similar to pseudoobstruction in humans and to experimental denervation of intestinal segments in rats. The lack of nervous inhibition is hypothesized to allow constant and uncoordinated muscular contractions with resulting hypertrophy and eventually poor transit of ingesta.

Myenteric plexuses from distended or obstructed large colons also had an increase in the number of glial cells (Fig. 32-61).[46] This appears to be an inflammatory response by the enteric nervous system to the conditions involved with bowel distention.[47] Alternatively the inflammation and neuron dropout may have been responsible for colon dysfunction in these horses examined because of colon obstruction.



FIG. 32-59 Photomicrograph of edema, lymphatic dilation *(L),* and white blood cell *(arrows)* accumulation in a small intestinal villus after 18-cm H_2O distention for 2 hours and reperfusion for 1 hour. (Hematoxylin–basic fuchsin stain.)

Infection

Enteritis caused by infection is frequently a result of *Salmonella* spp., *Clostridia* spp., *Neorickettsia risticii, Lawsonia intracellularis,* or virulent *E. coli.* Viruses such as rotavirus can also cause infection in foals with subsequent clinical signs. These agents adhere to and attack mucosal cells. When bacteria bind to the mucosal cells, the release of endotoxins or exotoxins causes the mucosal cells to release cytokines, which signal immunocytes and neutrophils of impending invasion. The gut has a large number of lymphocytes and

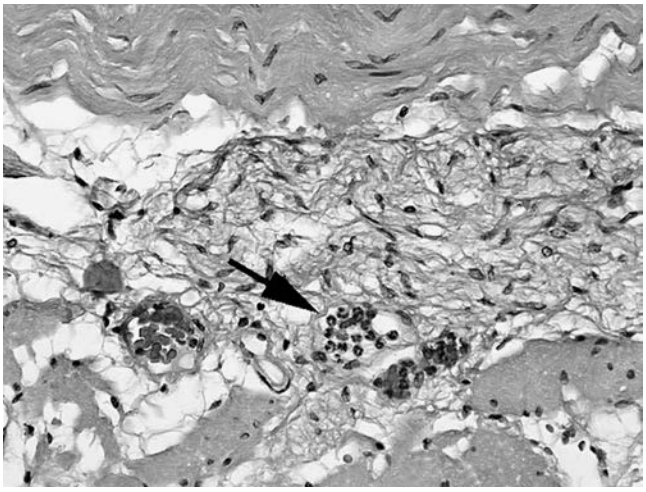


FIG. 32-60 Photomicrograph of neutrophil infiltrate *(arrow)* in the muscle and around a myenteric plexus after low flow ischemia and reperfusion. (Hematoxylin and eosin stain.)

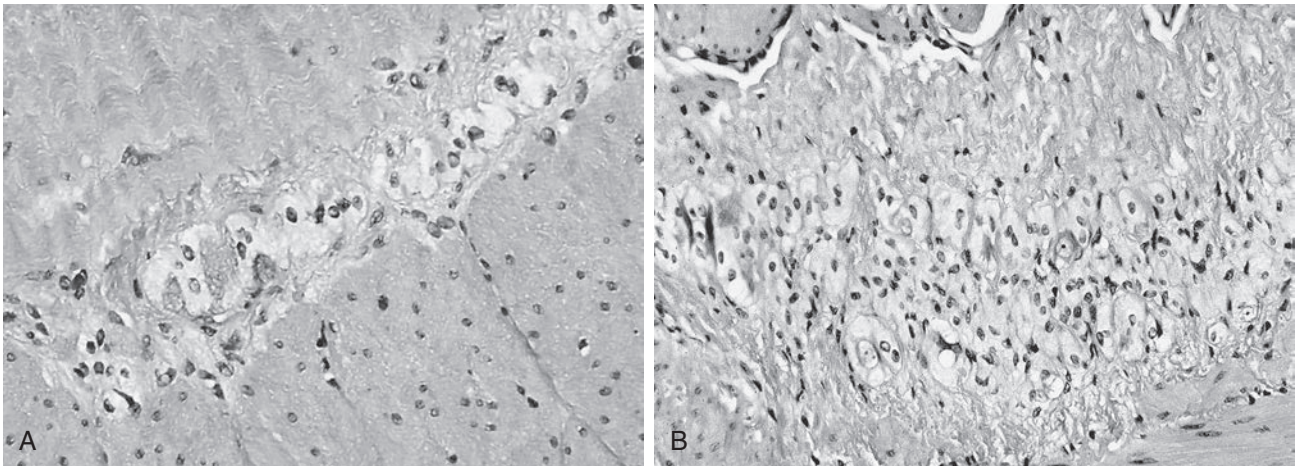


FIG. 32-61 Photomicrographs. **A,** A normal myenteric plexus with connective tissue surrounding an accumulation of neurons. **B,** Increase in glial cells in the myenteric plexus from a horse with chronic obstruction of the large colon. (Hematoxylin and eosin stain.)

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macrophages in the lamina propria, suggesting constant stimulus by agents or substances.[10,75] Although the mucosal cell has an innate ability to resist infection, the communication between the immunocytes and the mucosa is likely the chief defense. The infection can change mucosal function without destroying the mucosal barrier; increased TNF-α concentration has been shown to impair barrier function at the tight junctions.[76] The change can cause lack of absorption and/or massive secretion of fluid into the bowel, causing diarrhea.

Interaction of neutrophils with the apical membrane of epithelial membrane after paracellular migration stimulates adenosine receptors by production of 5′ adenosine monophosphate (5′-AMP).[77] Subsequent functional secretion is caused by stimulation of adenyl cyclase and guanyl cyclase, which catalyze formation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), respectively. These cyclic nucleotides subsequently activate protein kinases, which block the sodium chloride (NaCl) absorptive process in the absorptive mucosal cell and stimulate chloride (Cl) secretion in the crypt cell.[78] Inflammation with release of eicosanoids and bradykinin can also initiate the secretory process. The enteric nervous system can also induce inflammation and secretion in the bowel, which can be inhibited by nerve-blocking agents or indomethacin.[79] Neuropeptides from efferent nerves are hypothesized to initiate this response by affecting mucosal cells, fibroblasts, and endothelial cells.[1]

When bacteria cause injury by adhering to the mucosal surface and invading the mucosa, the response of the mucosal cells stimulates both the afferent nervous system and an immediate local immune reaction. Cytokines from local macrophages or injured epithelial cells serve as the messengers of recognition, which stimulate macrophages, neutrophils, and eosinophils to migrate to the region of invasion. Lymphocytes are also activated, releasing cytokines, including IFN-γ. After an initial delay in mucosal cell apoptosis during bacterial adhesion and invasion, apoptosis is increased, theoretically to increase cell turnover and healing. TNF-α and nitric oxide appear to control mucosal cell apoptosis.[6]

The inflammatory response to invasion often causes massive mucosal necrosis, with loss of mucosal cells and a massive infiltrate of neutrophils and lymphoid cells. Fibrin exudate creates a "cast" on the mucosal surface of the bowel. The vasculature is exposed to the bowel lumen, allowing subsequent invasion of the bacteria, both pathogens and others, as well as bacterial toxins. The remaining mucosal cells are stimulated to secrete water via the stimulation of cAMP within the crypt cells. Water is also retained in the bowel because of the lack of absorptive cells; the result is diarrhea.

The infection can involve the other layers of the intestine, although it rarely involves the serosa. Still, some diseases such as hemorrhagic fibrinonecrotic duodenitis–proximal jejunitis (DPJ) affect all layers of the intestine. The cause of DPJ is unknown, but the lesion is similar to that seen with clostridial disease in young swine.[80] Similar to reperfusion injury, the inflammatory process creates dysfunction that can last for days. Although long-term complications from DPJ have not been reported, animals with severe cases have not survived because of the lack of healing and severe residual inflammation in the bowel wall.

Peritoneal Inflammation

The serosal layer is made of a single-cell mesothelial layer mounted on a layer of connective tissue. This layer is important for maintenance of a lubricated barrier at the bowel surface, necessary for normal intestinal motility and peritoneal cavity fluid exchange. The mesothelial layer attaches to a basement membrane, which is adjacent to an elastic layer. The mesothelial cells vary in type. Some are short and have channels linking the peritoneal surface to the serosa. Others have long microvilli, which appear to help trap fluid on the surface of the peritoneum, providing the chief mechanism of lubrication on the bowel surface. Mesothelial cells react to circulating or intraperitoneal lipopolysaccharide (LPS), infection, and surgery by releasing TNF-α, IL-1β, IL-6, and macrophage inflammatory protein (MIP).[81] The response in the serosa is attraction and migration of neutrophils into the serosal connective tissue.

The initial response to serosal injury has been studied in laboratory animals using predominantly scarification of organs or fecal contamination of the peritoneal surface. The response to ischemia or distention of the equine small intestine is similar, although often more severe. During ischemia the mesothelium is rapidly lost, with subsequent serosal swelling with edema. During reperfusion the serosal vasculature becomes more permeable, and polymorphonuclear cells and mononuclear cells migrate through capillaries or venules and infiltrate into the serosal connective tissue layer. Neutrophils accumulate at the basement membrane around vessels and within lymphatics. Fibrin accumulates within the serosa layer and on the surface. WBCs release oxygen radicals and proteolytic enzymes, resulting in disruption of collagen, the primary ground substance of the serosa. The denuded serosal response includes increased vascular permeability, which allows the surface to be covered with a fibrin clot. After 24 to 48 hours there is massive accumulation of cells, which are predominantly neutrophils, within the serosa and at its new surface.

Cytokines are involved in the response to serosal injury and the subsequent healing. [82,83] After intestinal anastomosis in rabbits, macrophages increased in number until about day 4. Superoxide levels in these cells are high in the first 24 hours. Prostaglandins, cytokine secretion, and plasminogen activator inhibitor activity are known to increase during the first 3 days after peritoneal injury.[82] IL-1 and TNF-α are secreted by peritoneal macrophages after injury and appear to modulate peritoneal healing.[84] Peritoneal macrophages also secrete plasminogen activator. The secretion of both plasminogen activator and plasminogen activator inhibitor is stimulated by IL-1. After intestinal anastomosis there is a decrease in fibrinolytic activity for the first 5 days. Thereafter, plasminogen activator returns to the normal preoperative level. Normally fibrin will be dissolved by plasmin after plasminogen is activated by tissue plasminogen activator (TPA). The severity of the serosal injury is also related to the reduction of TPA and to the suppression of plasminogen activator normally produced by macrophages. If plasminogen is not activated or is absent, adhesions have a greater likelihood of becoming fibrous and permanent.

As healing progresses, fibroblasts migrate into the fibrin and a layer of granulation tissue forms both beneath and on top of the original basement membrane (Fig. 32-62). Mesothelial cells produce connective tissue growth factor in response to IL-1β, which simulates fibroblast proliferation.[15] During this stage IL-1β stimulates and prostaglandin E_2 inhibits fibroblast activity in the injured serosa.

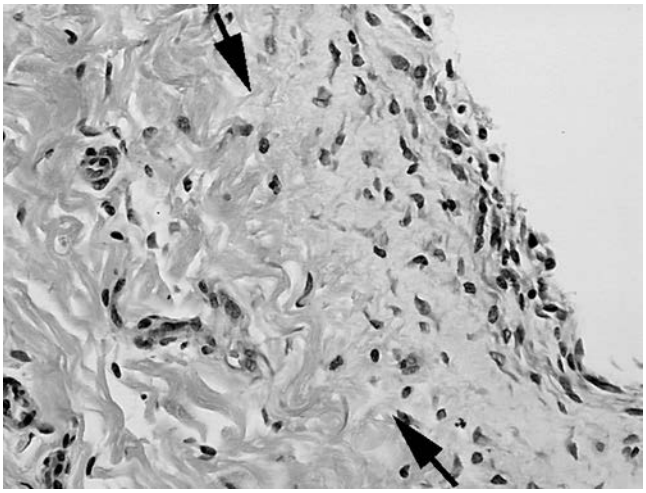


FIG. 32-62 Photomicrograph of the serosa with addition of a fibrous layer extending beyond the original level of the basement membrane *(arrows)* 10 days after bowel ischemia and reperfusion (hematoxylin and eosin stain). The new serosal surface has yet to heal with a new mesothelial layer.

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Primordial stem cells migrate to the surface and change to form a new mesothelium, a metaplasia likely under the control of growth factor from fibroblasts. The greater the inflammatory reaction is within the serosa and on the surface, the more fibroplasia occurs, thereby delaying mesothelium resurfacing and increasing the chance for adhesion formation or bowel scarring. Under experimental conditions the severity of adhesions is correlated with increasing concentrations of TNF-α in peritoneal fluid, and antibodies against TNF-α can decrease adhesion formation.[85] Healing of the serosa may not result in bowel-to-bowel adhesions but can still cause bowel and mesenteric scarring, which can cause luminal narrowing or kinking. The serosa also becomes thickened, which may result in bowel dysfunction or may interrupt the vascular supply, resulting in chronic obstruction.

In the horse the serosal injury is frequently caused by bowel distention. The cellular injury is similar to an inflammatory model except for the vascular sequelae. After small intestinal ischemia there is an initial vascular hyperemia in most of the bowel but a reduction of perfusion to the serosa.[33] This same effect occurs during bowel distention and is even greater after alleviation of distention. The edema formation in distended bowel takes place immediately and increases serosal tissue pressure, which exerts extravascular pressure and closes capillaries and venules.[33] This continues after bowel decompression, resulting in ischemic injury during reperfusion of the serosa. Reperfusion after decreasing bowel distention also causes serosal endothelial cell swelling and capillary plugging. This helps to explain the adhesions seen in bowel that was distended only proximal to an obstruction or strangulating lesion but was otherwise not involved in an ischemic lesion.

Decreasing the inflammatory response, including neutrophil migration in bowel after experimental ischemia and reperfusion, is associated with a marked decrease in subsequent fibroplasia and gross adhesion formation. Use of flunixin combined with antibiotics or depressing the initial inflammatory response to reperfusion using rinse solutions suggests that controlling septic serositis is required to decrease scarring of the serosa.[51,86]

Adhesions resulting from septic peritonitis occur in response to a massive inflammatory response in the serosa. Similar to the response to ischemia, neutrophil migration and fibrin deposition occur in and on the serosa.[83] The inflammatory response may be so great that the proteolytic enzymes may prevent adhesion between bowel loops by breaking down fibrin. However, in most cases there is massive fibrin production, and bowel-to-bowel adhesions occur frequently.

Bowel Healing

After ischemic damage, the mucosa heals rapidly.[87] Enterocytes migrate along the lamina propria, covering the surface within 24 to 38 hours. In the mucosa the crypt cells are responsible for rapid multiplication and physically forcing the older cells to the mucosal surface. Delayed healing is associated with a massive inflammatory response, which can stimulate delayed epithelial apoptosis and lack of cell replacement.[9,88] Connective tissue growth factor stimulates mucosal growth and may be responsible for excessive fibrosis in chronic inflammatory disease.[89]

Common use of nonsteroidal antiinflammatory drugs (NSAIDs), in particular flunixin meglumine, delays mucosal cell function during reperfusion.[87] Although replacement of the mucosal cell lining after ischemia is rapid, in vitro application of flunixin meglumine delays normal return of mucosal barrier function. Increased permeability to endotoxin in flunixin-treated bowel compared with the control intestine may lead to shock or delayed healing of intestine.[90]

Lidocaine administration has been shown to decrease the bowel injury in response to experimental ischemia and reperfusion.[91] When lidocaine was added to horses treated with flunixin meglumine mucosal barrier function was preserved. COX-2 inhibitors such as meloxicam administered to bowel did not increase bowel permeability; this suggests that total COX inhibition affects mucosa healing after ischemia and reperfusion.[92] In a similar manner, firocoxib inhibited lipopolysaccharide permeability across ischemic-injured mucosa.[93]

The serosal mesothelium also heals rapidly after loss from abrasion, although it takes longer than the mucosa to heal with a functional cell boundary. The mesothelial cells come from multipotent stem cells in the serosal connective tissues. These migrate to the serosal surface and form an initial layer of cuboidal cells before transforming to the more characteristic flattened mesothelial cells. The healing time appears to be dependent on the amount of inflammation and subsequent production of fibrous tissue on the serosal surface.

Although healing is thought to be successful when clinical signs of colic, obstruction, or peritonitis are no longer observed, the latent effect of serosal fibrosis, residual mucosal inflammation, and ganglionitis with loss of neurons may increase the risk of future colic episodes. Horses that have had a colic episode or previous abdominal surgery are three to four times more likely to have a second colic episode than horses that have never had colic.[56] Whether chronic inflammation or intestinal scarring is responsible for recurrent colic has not been determined.

Endotoxemia and Sepsis

Kelsey A. Hart • Robert J. MacKay

Definitions

The term *endotoxin* was originally coined to describe toxic bacterial components that were contained within or on the bacterial cell rather than "exotoxins" that were secreted from bacterial cells. The heat-stable endotoxic activity of *Vibrio cholerae* identified by Pfeiffer more than 100 years ago resides in lipopolysaccharide (LPS), the principal component of the outer leaflet of the outer membrane of all gram-negative bacteria[1] (Fig. 32-63). Today, the terms *endotoxin* (the activity) and *LPS* (the molecule) are used synonymously to refer to this specific gram-negative bacterial membrane component, except when purified LPS is being referenced.[2] Each LPS molecule has three structural domains: a polar polysaccharide O-region, which projects into the aqueous extracellular environment; a hydrophobic lipid A-region, which is largely buried in the bacterial outer membrane; and a core acidic oligosaccharide region connecting the two. The O-region is highly variable, consisting of repeating units each of one to eight glycosyl residues, and contains antigens specific for each bacterial strain; the core glycolipid region is relatively constant among bacteria and mediates most of the toxic effects of endotoxin. On bacterial death or during bacterial proliferation, large (>10^6-dalton molecular mass) aggregates of LPS and membrane protein are released. It is these protein-lipid micelles that constitute native endotoxin.

Endotoxemia literally is the presence of endotoxin in the blood. However, when the term is used clinically, it implies only the presence of clinical signs typically caused by the inflammatory response to circulating endotoxin. Endotoxemia—actual circulating endotoxin or related clinical signs—can occur with gram-negative bacterial infection in any tissue or through exposure to gram-negative enteric bacteria any time the intestinal mucosal barrier is compromised.

The ability to respond to minute local concentrations of endotoxin by mounting vigorous inflammatory responses is well conserved across species.[3] Endotoxemia as a clinical syndrome in equine patients was first recognized more than 45 years ago.[4] The potential clinical importance of equine endotoxemia is clear from reports that intravenous infusion of LPS into horses reproduced many of the adverse clinical signs of diseases such as colitis, metritis, and strangulating intestinal obstruction.[5-10] Further evidence for the importance of endotoxemia is the detection of circulating endotoxin in some horses with experimentally induced laminitis[11] or intestinal strangulation obstruction[12] and in horses with naturally occurring

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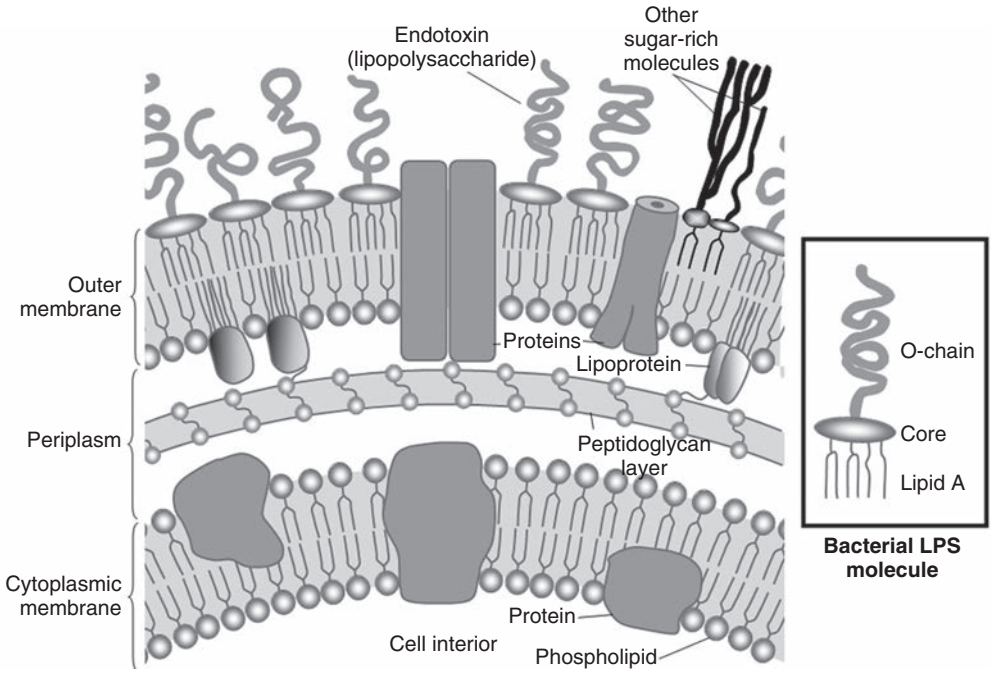


FIG. 32-63 Cross-section of the double lipid bilayer that forms the cell membrane of gram-negative bacteria. As is shown in this figure, lipopolysaccharide *(LPS)* is the principal component of the outer leaflet of the outer membrane. The insert shows a single LPS molecule with an O-polysaccharide chain, a two-part core oligosaccharide, and a hydrophobic lipid A phospholipid. R-mutant bacteria lack the O-chain ± varying amounts of the core oligosaccharide.

gastrointestinal diseases or septicemia,[13-17] hemostatic disorders,[16] and exhaustion associated with endurance[18] or racing[19] events. Since these original descriptions were published, a large body of review literature has documented the efforts that have been made to understand and, more important, treat equine endotoxemia.[20-23]

Endotoxemia should not be confused with either *bacteremia,* which refers only to the presence of viable circulating bacteria and can occur without clinical signs, or *septicemia,* which refers to systemic disease caused by any circulating microorganisms and/or their products. *Sepsis* is a related term that is best defined as clinical evidence of an infection (documented or suspected) coupled with the presence of a *systemic inflammatory response syndrome* (SIRS) that is characterized by alterations in body temperature, heart rate, respiratory rate, and leukogram parameters.[24,25] A scheme showing increasingly severe stages of SIRS and sepsis, from local infection to death, and adapted definitions for SIRS and organ dysfunction adapted for horses is shown in Fig. 32-64 and Table 32-3. In general, *severe sepsis* includes sepsis (infection + SIRS) and evidence of organ dysfunction, and *septic shock* includes severe sepsis plus acute circulatory failure (usually manifested by persistent hypotension after appropriate volume resuscitation).[25] Dysfunction of two or more organs in severe sepsis/septic shock is termed *multiple organ dysfunction syndrome* (MODS) and is associated with increased mortality in human beings.[25a] The lethality of each grade increases from the base to the apex (see Fig. 32-64), with reported mortality rates among humans of 10% to 20% for sepsis, 20% to 50% for severe sepsis,[25b] and 40% to 80% for septic shock.[26] Comparable mortality data are not currently available for horses.

It is important to note that endotoxemia—as the clinical manifestation of a systemic inflammatory response to circulating endotoxin—is a subset of sepsis and can manifest at all stages of disease. Note also that sepsis is defined as *suspected* infection plus SIRS; therefore a horse with a strangulating intestinal obstruction and clinical evidence of SIRS (tachycardia, tachypnea, leukopenia) but no easily identifiable infection is still classified as septic or endotoxemic. Horses with signs of mild endotoxemia (e.g., leukopenia and fever) also fit the definition for sepsis.

The fundamental difference between serious sepsis in humans and the syndromes seen in equids is the propensity for the latter to be associated with laminitis. In the context of sepsis, laminitis is often life-threatening. Because an organ is defined here as "a dispersed or solid tissue that performs a specialized function," it is probably inappropriate to classify the hoof as an organ as part of an equine MODS definition. It is clear from recent data, however, that the same types of global inflammatory and coagulation disorders that lead to MODS in patients with sepsis also are involved in the pathogenesis of both carbohydrate- and black walnut–induced laminitis.[27-31] In light of their likely common pathogenesis, MODS and laminitis (MODS/L) are presented together in Fig. 32-64. With the exception of laminitis, the definitions listed in Table 32-3 are not validated for horses, but they are reasonable extrapolations from accepted human criteria. Several recent studies have used these or similar criteria for SIRS, MODS, or septic shock in horses or foals.[32-37]

The extraordinary ferocity of SIRS as triggered by endotoxin was nicely captured by Thomas[38]:

The gram-negative bacteria … display lipopolysaccharide … in their walls and these macromolecules are read by our tissues as the very worst of bad news. When we sense lipopolysaccharides we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all tissues in the area …. Cells believe that it signifies the presence of gram-negative bacteria, and they will stop at nothing to avoid this threat.

Although this picture still accurately describes modern concepts of the early immune response to endotoxin, it has become clear that a variety of other pathogen-derived molecules set off similar or identical host responses. For example, toxic shock syndrome resulting from *Staphylococcus aureus* infection[39] and streptococcal toxic shock[40] are examples of hyperinflammatory septic syndromes in horses that resemble diseases characterized by true endotoxemia (circulating LPS). Thus, in sepsis, including putative endotoxemia in horses, it is likely that the clinical presentation is an aggregate of responses to multiple or varied microbial signals as well as to certain "danger" signals generated by the host itself. Circulating endotoxin is not always detectable in horses described as "endotoxic"; in fact, it is typically found in less than 30%[41,42] of these horses; this suggests that other microbial components and host inflammatory molecules

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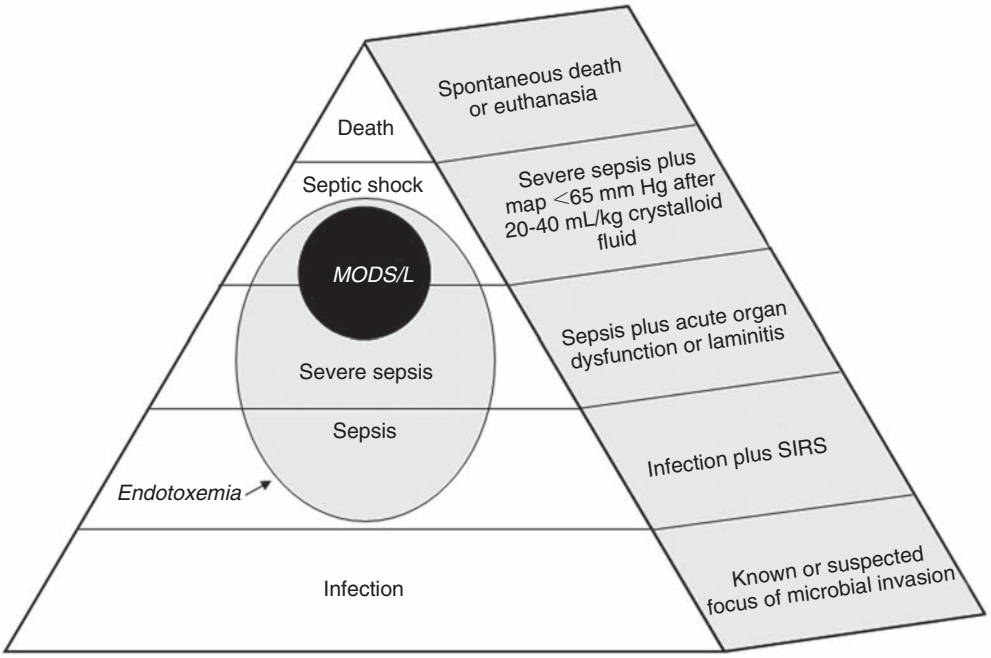


FIG. 32-64 Scheme for sepsis classification. Definitions for systemic inflammatory response syndrome, organ dysfunction, and laminitis are given in Table 32-3. *MODS/L,* Multiple organ dysfunction syndrome/laminitis; *SIRS,* systemic inflammatory response syndrome.

TABLE 32-3

Criteria for Systemic Inflammatory Response Syndrome, Organ Dysfunction, and Laminitis

SIRS Criteria (Two or More of the Following)	
Hypothermia	<98° F or hyperthermia >101.5° F
Leukopenia	<5000/μL or leukocytosis >14,500/μL
Tachycardia	>50 beats/min
Tachypnea	>25 breaths/min or Pa_{CO_2} < 32 mm Hg
Organ Dysfunction and Laminitis Criteria	
Neurologic	Severe obtundation (stupor, semicoma, coma)
Renal	Creatinine >2 mg/dL after ≥20 mL/kg IV crystalloid fluids, or increase of ≥0.5 mm Hg since last measurement
Hemostatic	Platelet count < 100,000/μL or aPTT > 70 seconds
Respiratory	Pa_{O_2} < 65 mm Hg, or <75 mm Hg with oxygen supplementation or mechanical ventilation
Intestinal	Absent gut sounds, or absent motility on ultrasound examination
Hemodynamic	Mean arterial pressure <65 mm Hg after ≥20 mL/kg IV crystalloid fluids
Hepatic	Bilirubin concentration > 6 mg/dL; GGT > 60 U/L with no other explanation
Laminitis	Bounding digital pulses, sensitivity to digital pressure over the coronary band, sensitivity to hoof tester pressure over the sole, Obel grade >1

aPTT, Activated partial thromboplastin time; *GGT,* γ-glutamyltransferase; *IV,* intravenous; *SIRS,* systemic inflammatory response syndrome.

likely trigger similar clinical signs. Thus, the terms *sepsis* and *SIRS* might be more appropriate than *endotoxemia* to accurately describe the clinical signs usually attributed to endotoxin in horses (e.g., hyperemic or toxic mucous membranes, fever, tachycardia, tachypnea, leukopenia). In this section, sepsis will be used to imply SIRS in response to any microbial infection, and endotoxemia will be used to refer specifically to the presence of endotoxin in the blood or to the specific clinical signs related to documented circulating endotoxin. However, our understanding of the molecular basis of sepsis in the horse via mechanisms other than endotoxemia is limited at best, so the majority of the following discussion will center on endotoxemia as an important component of equine sepsis.

Pathophysiology

Endotoxin or Other Microbial Products Enter the Circulation

Although endotoxin and other microbial components are ubiquitous in the environment (both free and as a component of intact bacteria), these components normally are excluded from the body by the skin and mucous membranes. If the protective integument or mucosae are subjected to bacterial infection or otherwise damaged, bacteria or bacterial components such as endotoxin may reach the blood in a sufficient amount (<1 μg of purified LPS in experimental situations) to cause clinical signs. Gram-negative bacterial enterocolitis (e.g., salmonellosis), metritis, pleuropneumonia, wound infection, and neonatal septicemia are common pathways to endotoxemia in horses. Because gram amounts of free endotoxin normally are safely sequestered within the intestine of the adult horse, damage to the gut wall—as a result of local (e.g., intestinal volvulus, infarction, incarceration) or systemic (e.g., hypovolemic shock) causes of tissue hypoxia; inflammation (e.g., duodenitis–proximal jejunitis [DPJ] or clostridial enteritis); mechanical trauma (e.g., rectal perforation, prolonged exercise); or intraluminal acidification (e.g., grain overload)—is particularly likely to result in endotoxemia. In highly contaminated environments, potentially harmful amounts of endotoxin can be introduced into the lungs via inhalation.[43] Endotoxin may even be delivered directly into the blood via contaminated parenteral solutions (e.g., homemade intravenous fluids). Other microbes and microbial components (e.g., flagellin) or secreted toxins (e.g., staphylococcal exotoxins) can enter the circulation in similar ways, although our understanding of these pathways in horses is less well understood.

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Interaction with Pattern Recognition Receptors

Animals have the ability to recognize many distinctive patterns on molecules that signal potential danger. As a group, these molecules that express danger motifs are aptly termed *damage-associated molecular patterns* (DAMPs). Included among DAMPs are microbial signals like endotoxin, collectively termed *pathogen-associated molecular patterns* (PAMPs), and *alarmins,* endogenously produced molecules that originate from damaged or inflamed tissues[44,45] (Table 32-4). A limited number of germ-encoded receptor types, both soluble and cell-associated, are dispersed throughout the body to detect potential threats (both septic and nonseptic). These are pattern-recognition receptors (PRRs) and are exemplified by Toll-like receptors (TLRs) on (and in) cells and complement receptor proteins and Hageman factor in plasma.[44-46] A partial list of these and other PRRs is given in Table 32-5. The interaction between DAMPs and PRRs is the initial event in the innate immune responses that result in the clinical presentation of endotoxemia or other forms of sepsis.

In 1985 almost nothing was known about the way in which LPS molecules interacted with cells of the immune system. In fact, endotoxin was widely believed to enter cells not via engagement of cell-surface receptors but by hydrophobic insertion into the membrane (Fig. 32-65). Since then, sequential discoveries of a plasma LPS-binding protein (LBP; 1989 for humans,[47] 2005 for horses[48]), CD14 (1990 for humans,[49] 2003 for horses[50]), and TLRs (1998 for humans,[51] 2005 for horses[52]) have elucidated the molecular processes of endotoxin binding and signaling (see Fig. 32-65). LPS first interacts with LBP, a normal plasma acute-phase protein; this interaction facilitates binding to the soluble or cell-associated co-receptor CD14. The LPS/LBP/CD14 complex recruits and activates TLR4 dimer and an accessory component MD-2 in preparation for LPS signaling. On ligation of the receptor, the conserved intracellular domain of TLR4 (Toll-IL-1 receptor [TIR]) initiates multiple downstream pathways that culminate in translocation to the nucleus of inducible transcription factors including nuclear factor κB (NF-κB) and activator protein 1 (AP-1).[53] NF-κB binds to consensus sequences on the promoter or enhancer regions of an array of genes whose products are involved in the inflammatory response.[53] It has been argued that the global activation of TLR4 typical of sepsis also requires the actions of endogenous agonists (e.g., proteases).[54] Endotoxin also may activate NF-κB via TLR4-independent interactions with β_2-integrins, heat-shock proteins, and the intracellular Nod-1 receptor.[55]

Endotoxin engages TLR4 on cells of the innate and adaptive immune systems, especially mononuclear phagocytes (monocytes and macrophages), neutrophils, endothelial cells, and dendritic cells. Pulmonary intravascular macrophages and Kupffer cells likely are the most important mononuclear phagocytes in this regard. Although endotoxin binds predominantly to TLR4, a still-growing family of TLRs (13 in rodents, 10 in humans, unknown in horses) is available

TABLE 32-4

Partial List of Damage-Associated Molecular Patterns (DAMPs)[44,45]

PAMPs	Alarmins
LPS (endotoxin)	HMGB1
Lipoprotein	S-100 proteins*
Peptidoglycan	HSPs
Flagellin	Defensins
Lipoteichoic acid	Cathelicidins
Zymosan	
Viral double-stranded RNA	
N-acetyl glucosamine	

*Proinflammatory proteins released by phagocytic cells during innate immune responses.

HMGB1, High-mobility group box 1 (protein); *HSPs,* heat shock proteins; *LPS,* lipopolysaccharide; *PAMPs,* pathogen-associated molecular patterns.

TABLE 32-5

Partial Listing of Pattern Recognition Receptors (PRRs)[44-46]

Cell-Associated	Soluble
TLR (1-11)	Hageman factor
RAGE	MBL
Nod1/Nod2	C3b, Bb
CD14	Ficolins

MBL, Mannan-binding lectin; *Nod,* nucleotide-binding oligomerization domain; *RAGE,* receptor for advanced glycation end products; *TLR,* Toll-like receptor.

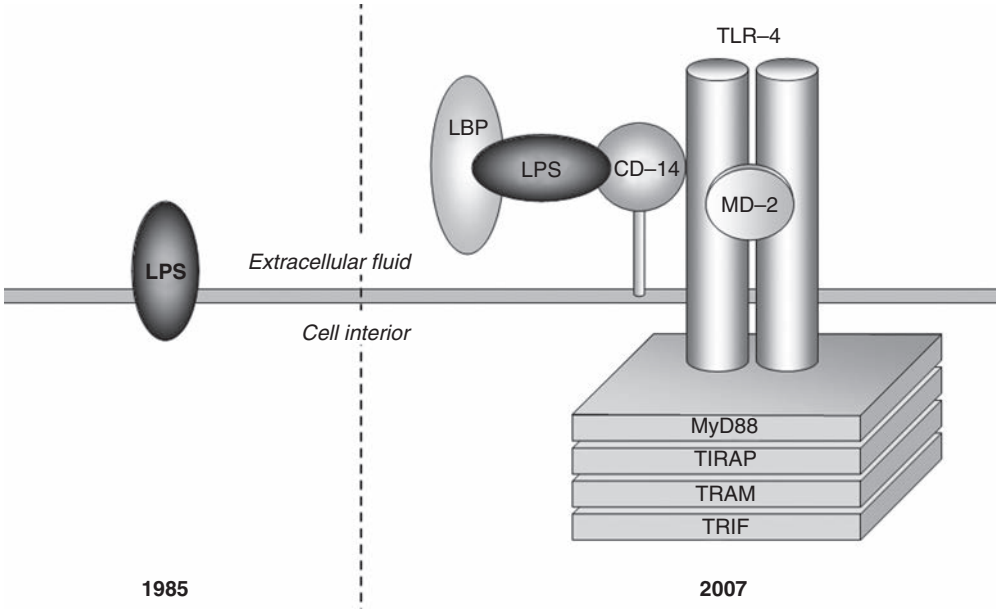


FIG. 32-65 Binding of lipopolysaccharide *(LPS)* to mammalian cell membranes. In 1985 it was widely believed that LPS initiated cellular signaling by hydrophobic interactions with the plasma membrane. By 2007 the components of the signaling complex were more fully understood. In addition to the extracellular receptor components (discussed in the text), the intracellular Toll-IL-1 receptor *(TIR)* domain is shown interacting with four adaptor molecules (MyD88, TIRAP, TRAM, TRIF) to initiate a molecular signaling cascade that ultimately leads to gene activation.

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TABLE 32-6

Ligands for Human Toll-like Receptors[56]

TLR1	Triacyl lipopeptides
TLR2	Lipoprotein
	Peptidoglycan (gram-positive bacteria)
	Lipoteichoic acid (gram-positive bacteria)
	Zymosan (yeast)
	Lipoarabinomannan (mycobacteria)
TLR3	Viral double-stranded RNA
TLR4	LPS
	Respiratory syncytial virus fusion protein
	HSP70
TLR5	Flagellin
TLR6	Diacyl lipopeptides
	Zymosan
TLR7/8	Viral single-stranded RNA
TLR9	Unmyethylated CpG-containing DNA
	Herpesvirus DNA
TLR10	Not determined
TR11	Uropathogenic bacteria

LPS, Lipopolysaccharide; *TLR,* Toll-like receptor.

to bind to other DAMPs (Table 32-6).[56] During sepsis, this diversity of TLRs allows redundant signaling of inflammatory cells. For example, non-LPS components of gram-negative bacteria may bind other TLRs (e.g., flagellin binds to TLR5, lipoprotein and peptidoglycan to TLR2), whereas PAMPs from gram-positive bacteria, viruses, or fungi bind different TLRs in the course of polymicrobial sepsis.[56] Equine TLR signaling has been characterized in many cells and tissues.[57-59] It is interesting to note that whereas LPS is a potent stimulator of equine monocytes via TLR4, flagellin (via TLR5) preferentially stimulates neutrophils and induces little response from monocytes,[60] suggesting differential expression of these TLRs between cell types in the horse that could play a role in clinical sepsis. Thus, while TLR ligand-specificity appears to be well conserved across species, specific TLR expression varies among cells, tissues, and species and can result in varied responses to the same DAMP. Tissues subject to attack by mediators produced after the initial round of TLR binding can also feed back and amplify the inflammatory response by releasing alarmins (e.g., high-mobility group box 1 [HMGB1]),[61] which in turn can bind to TLR or other PRRs.

Simultaneous with cellular activation, endotoxin and other microbial products interact with soluble PRRs normally present in plasma. Of particular importance, endotoxin binds to complement proteins to initiate the lectin-dependent and alternative pathways of complement activation and activates coagulation factor XII (Hageman factor) to set off the "contact" system of coagulation.

Mediators Are Released

Endotoxin-induced NF-κB activation in peripheral blood and tissue leukocytes (and many other cell types) acts via multiple signaling pathways to induce the expression of more than 200 genes, many of which are involved in the pathogenesis of sepsis.[45,53,62] These include genes for proinflammatory cytokines (e.g., TNF, IL-1β, IL-6, IL-8, IL-12, IL-18), chemokines (e.g., IL-8, MIP), type 1 IFNs, procoagulants, adhesion molecules, immunoreceptors (e.g., TNF receptors), enzymes (e.g., elastase), and acute-phase proteins (e.g., fibrinogen). NF-κB activity is further amplified by the paracrine actions of these proinflammatory cytokines and by other DAMPs, cellular hypoxia, cellular necrosis, and chemical stress (including oxidant stress). Two of the cytokines secreted by macrophages, IL-12 and IL-18, stimulate IFN-γ synthesis and secretion from natural killer (NK) and other cells.[63] Because IFN-γ is a potent stimulator of both innate and acquired immune responses, it is considered to be a principal link between the two systems.

Endotoxin activates coagulation factor XII (Hageman factor), leading both to liberation of bradykinin and to initiation of intravascular coagulation. Even more important, complement is activated by alternative, lectin-mediated, and classical pathways to yield numerous active peptide products that are important for opsonization, inflammatory cell trafficking, and microbial cell lysis. Other microbial structural components and products similarly stimulate inflammation, complement activation, and coagulation, although specific pathways and molecular mechanisms are not well characterized for horses.

SIRS in Early Sepsis

The initial, early phase of sepsis is often referred to as the "hot" phase and is characterized by inflammation, coagulation, and necrosis. The principal NF-κB–mediated events during early sepsis are summarized in Fig. 32-66. This phase has been described as a "cytokine storm," during which there is flooding of inflammatory, procoagulant, and vasoactive mediators throughout the body. The net effects of these mediators promote microvascular injury and hypotension. The singular contributions of many mediators to sepsis is demonstrated by experiments using sepsis models in which blocking or deleting a single mediator has had a positive effect on outcome.

In early sepsis, large numbers of neutrophils accumulate on the endothelial surfaces of organs undergoing failure, and insult to one organ can trigger the widespread recruitment and sequestration of neutrophils in others. Such a scenario may contribute to the association of laminitis with severe intestinal disease,[64-67] although altered insulin and glucose dynamics,[68,69] vascular derangements,[65] or contributions of multiple inflammatory mediators[70] may also play a role in the development of laminitis in septic horses.

In response to PAMPs (including LPS), inflammatory cytokines produced by macrophages and other cells, and complement peptides, endothelial cells, and neutrophils express selectins.[45] Selectins on endothelial cells (E and P) and neutrophils (L) reciprocally engage glycoprotein ligands to "tether" the neutrophil to the endothelial surface. A series of these transient interactions between ligands and receptors allows neutrophils to roll along the endothelial surface (Fig. 32-67). Neutrophil capture is most efficient in areas of low shear force, such as the walls of postcapillary venules and in pulmonary capillaries. During rolling, neutrophils are activated or "triggered" by selectins, chemokines, and PAF expressed on endothelial cells. The firm attachment or arrest step of the cascade is mediated by the avid interaction of neutrophil integrins with adhesion molecules of the immunoglobulin superfamily expressed on endothelial cells. During firm attachment the activated neutrophil spreads out and, in the healthy animal, squeezes between the intercellular junctions of adjacent endothelial cells and migrates into tissues up a gradient of chemotactic factors such as microbial chemotaxins, LTB_4, IL-8, or C5a. By contrast, when compared with normal neutrophils, those found in septic animals have defective chemotactic responses but bind with greater avidity to the endothelium and to other neutrophils. When cultured, macrophages and neutrophils from patients with gram-negative sepsis are hyporesponsive to LPS, suggesting a functional switch to LPS tolerance during the early stages of endotoxemia[71] (see Fig. 32-67). Sequestration of neutrophils on activated endothelium and in neutrophil aggregates accounts for the neutropenia found in most horses with endotoxemia. It is interesting to note that the lifespan of these sequestered neutrophils is prolonged during sepsis because normal apoptosis is prevented,[72] which might potentiate the inflammatory response during early sepsis.

Tightly adherent neutrophil-endothelial conjugates formed during sepsis seal off microscopic pockets between the juxtaposed cells into which cellular products can be concentrated. Of particular significance are the reactive oxygen species (ROS) produced as a result of the activation of NAD(P)H-oxidase in neutrophils (respiratory burst) and xanthine oxidase in endothelial cells.[44,62] Digital laminae of horses may be particularly vulnerable to the effects of ROSs because of low content of the endogenous oxidant scavenger superoxide dismutase.[73] In the presence of neutrophil granule myeloperoxidase and H_2O_2, highly toxic hypochlorous acid is formed on the endothelial surface. Superoxide anion generated as part of the

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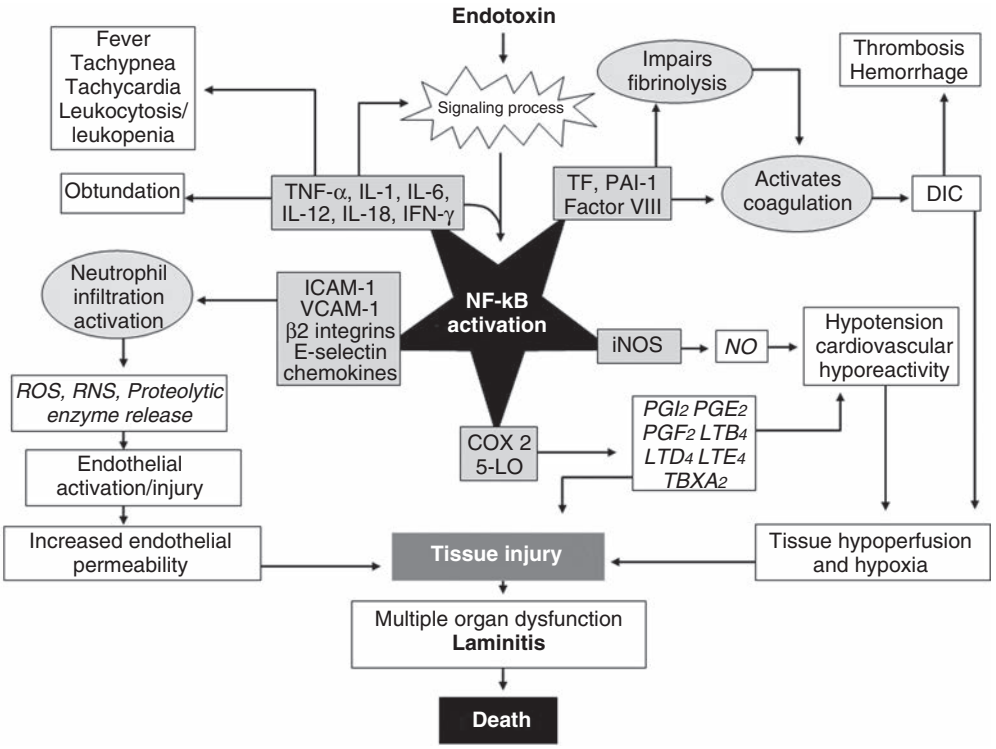


FIG. 32-66 Nuclear factor κB (NF-κB) signaling plays a central role in the pathophysiology of septic shock. *ICAM-1,* Intercellular adhesion molecule 1; *5-LO,* 5 lipoxygenase; *PAI-1,* plasminogen activator inhibitor 1; *TF,* tissue factor; *VCAM-1,* vascular cell adhesion molecule 1. Other abbreviations are explained in the text. *(Modified from Fig. 3 in Braun U. 1993. Ultrasonographic examination of the left kidney, the urinary bladder, and the urethra in cows. Zentralbl Veterinarmed A 40:1.)*

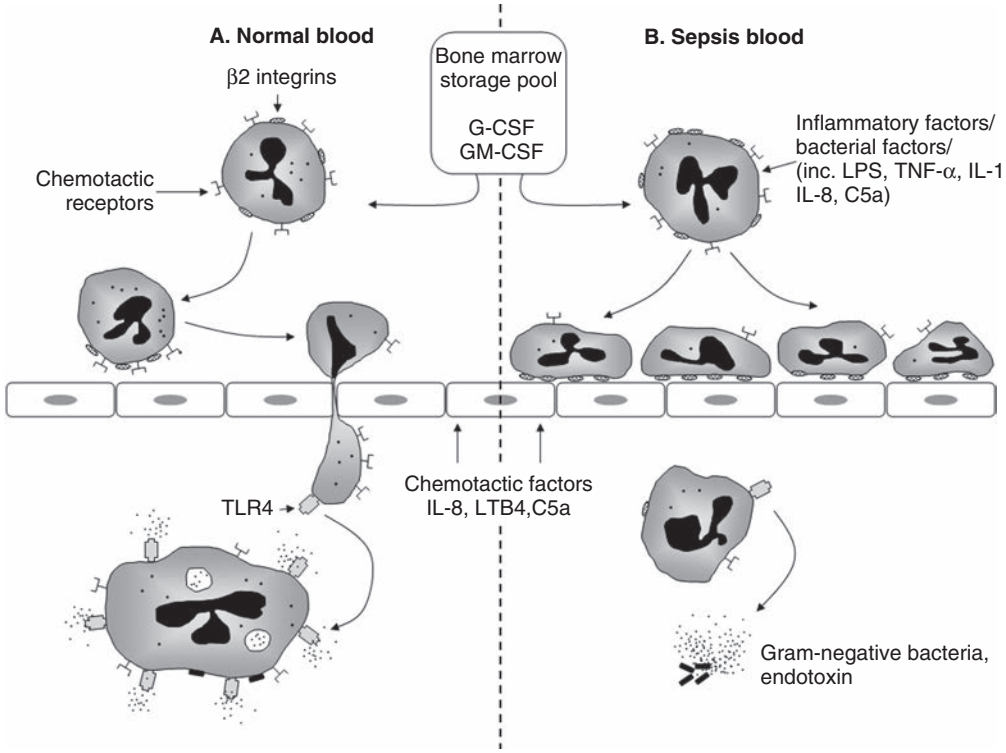


FIG. 32-67 Recruitment and activation of neutrophils to bacterial infection in healthy horses and septic or endotoxemic horses. In response to bacterial infection, cytokines are generated that induce the release of neutrophils from the bone marrow. In the normal state, large numbers of blood neutrophils enter sites of bacterial infection by first adhering to the activated endothelium of local postcapillary venules before migrating up a concentration gradient of chemotactic factors. Endotoxin is bound to Toll-like receptor 4 (TLR4), and bacteria are eliminated by phagocytosis. In patients with endotoxemia or sepsis, high levels of circulating inflammatory factors promote upregulation of surface integrins to promote firm endothelial adhesion to postcapillary venules. However, some of these factors also downregulate the expression of chemotactic receptors. Consequently, neutrophils are strongly bound but less responsive to underlying chemotactic factors. *G-CSF,* Granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor. *(Modified from Fig. 2 in Braun U, Linggi T, Pospischil A. 1999. Ultrasonographic findings in three cows with chronic ragwort (Senecio alpinus) poisoning. Vet Rec 144:122.)*

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neutrophil respiratory burst also reacts with nitric oxide (NO) from endothelial cells to yield reactive peroxynitrite radicals (both reactive nitrogen species, RNS). Other potentially corrosive substances are contributed by neutrophil granules and include elastase, serine proteases, matrix metalloproteinases (MMPs), and defensins. In addition to direct damage caused by membrane lipid peroxidation, ROSs and RNSs indirectly stimulate the expression of multiple inflammatory, procoagulant, and vasoactive mediators via activation of NF-κB in both neutrophils and endothelial cells.[44] Mediators such as bradykinin, PAF, C3a, C5a, and leukotriene B_4 (LTB_4) directly increase vascular permeability by promoting active retraction of endothelial cells via phosphorylation of the light chain of nonmuscle myosin.[44] Vascular leak then facilitates the movement of these potentially harmful substances into tissues.

In healthy animals, the antithrombotic phenotype of endothelial cells is maintained by the presence of low amounts of prostacyclin (prostaglandin I_2 [PGI_2]) and NO, and surface expression of thrombomodulin, protein S, and protein C complex and TPA.[74] During endotoxemia, endothelium supports extrinsic pathway activation because of leukocyte-induced physical damage, expression of the procoagulant tissue factor, downregulation of antithrombin-III and protein C, and inhibition of fibrinolysis through expression of plasminogen activator inhibitor 1 (PAI-1).[75-77] Additional procoagulant effect may be provided by deposition on the endothelial surface of all of the components of the intravascular coagulation system. Microvascular perfusion is further compromised by sepsis-associated increase in "stiffness" of both red blood cells (RBCs) and white blood cells (WBCs),[78] rendering such cells less able to deform and squeeze through narrow capillaries.

The effect of endotoxemia and sepsis on vascular tone depends on the stage and severity of disease and the particular organ (vascular bed) considered. Neuroendocrine responses to sepsis lead to the upregulation of predominantly pressor mediators, including arginine vasopressin, angiotensin II, serotonin, epinephrine, and norepinephrine. Inflammatory mediators are a mix of vasoconstrictors (thromboxane A_2 [TXA_2], endothelin, C3a, C4a, C5a) and vasodilators (PGE_2, PGI_2, adenosine, bradykinin, NO). In animals with serious sepsis, balances of constricting and dilating influences unique to each vascular bed, loss of vasoregulatory tone, and refractoriness of damaged endothelium to vasoactive substances cause maldistribution of blood flow among organs and systemic hypotension.

Because of poor perfusion pressure, direct microvascular injury, thrombosis, and loss of endothelial integrity (capillary leak), ischemia and hypoxia of organs and tissues occur.[27] Indeed, the fundamental event in serious sepsis is the development of global tissue hypoxia, perhaps also complicated by *dysoxia*.[45] Global tissue hypoxia results when systemic oxygen delivery fails to meet the oxygen requirements of tissues, and dysoxia results when tissues are unable to effectively use delivered oxygen. During serious sepsis, widespread microvascular and mitochondrial injury decrease oxygen delivery and consumption at the cell, tissue, and organ levels.[44,79,80] Oxygen delivery to tissues is a product of cardiac output and oxygen content (which itself is a product of hemoglobin oxygen saturation and hemoglobin concentration). The product of systemic oxygen delivery and the percentage of oxygen extracted (normally <25%) by the tissues is the systemic oxygen consumption. The balance between systemic oxygen delivery and consumption is reflected by the mixed venous hemoglobin oxygen saturation (SVO_2). SVO_2 has been shown in other species to be a useful surrogate for cardiac index as a target for goal-directed therapy.[81] Central venous oxygen saturation ($ScVO_2$), obtained through a central venous line, is a reasonable and easily measurable substitute for SVO_2 (which must be measured via a Swan-Ganz catheter).

Various hemodynamic combinations may create a systemic imbalance between tissue oxygen supply and demand[45,82]:

- *Hypovolemia.* Because of decreased preload caused by hypovolemia, concomitant left ventricular dysfunction, and reflex systemic arterial vasoconstriction, early endotoxemia is often characterized by low cardiac output (i.e., hypodynamic circulatory insufficiency).
- *Compensated but maldistributed perfusion.* After fluid-electrolyte resuscitation, compensatory mechanisms and low afterload drive transition to a hyperdynamic state. Even with normal or increased cardiac output, perfusion abnormalities may persist owing to regional hypoperfusion associated with derangements in blood flow distribution and loss of vasoregulatory control to vascular beds. This state is often described as *distributive shock.*
- *Myocardial depression.* Myocardial depression secondary to effects of inflammatory mediators and apoptosis of cardiomyocytes is the predominant cause of death in severe sepsis and septic shock.[83] Myocardial injury, as indicated by increased cardiac troponin concentrations, was recently reported in horses undergoing emergency abdominal surgery,[84] suggesting similar pathology likely develops in horses with sepsis and SIRS.
- *Increased metabolic demands.* SIRS increases metabolic demands, as evidenced by increased splanchnic and total body oxygen consumption.
- *Impaired oxygen use.* The bioenergetics of cellular extraction and use or respiration may be abnormal partially because of mitochondrial dysfunction.[44,79,80]

These derangements may occur independently of measured hemodynamic parameters. The theoretic components of each of these hemodynamic states are shown in Table 32-7.

In sum, current thoughts on early sepsis pathophysiology support development of a self-perpetuating imbalance in the systemic redox state resulting in oxidative stress that is believed to be at the root of SIRS and resultant organ dysfunction in sepsis.[44,79,80] Activation of local and systemic inflammatory responses results in production of ROS and RNS, which can directly and irreversibly damage cells and inhibit normal cellular activity, as described earlier. In healthy animals, ROS and RNS production is tightly regulated by inducible antioxidant enzymes, production of which is regulated by the nuclear transcription factor Nrf2.[44] However, Nrf2 activity is impaired by excessive ROS and RNS production, resulting in less activation of these antioxidant pathways and generating an overall oxidant environment.[44] Mitochondria are a key source of ROS and RNS, but they are also very sensitive to oxidative injury. Mitochondrial dysfunction and oxidative stress can result in tissue dysoxia and organ failure, as well as further stimulate inflammatory responses and NF-κB activation, creating the vicious cycle characteristic of SIRS and MODS.

TABLE 32-7

Effect of Hemodynamic State on Parameters of Cardiovascular Function

Pathologic State	MAP	CVP	$ScVO_2$	Lactate	CO	SVR
Hypovolemia	Variable	↓	↓	↑	↓	↑
Compensated but maldistributed	Normal to ↑	Normal	↑	Normal to ↑	↑	↓
Myocardial depression	Variable	↑	↓	↑	Normal to ↓	Normal to ↑
Increased metabolic demand	Variable	Normal	↓	Normal to ↑	Variable	Variable
Impaired O_2 usage	Variable	Normal	↑	↑	Variable	Variable

Adapted from reference 82.

CO, Cardiac output; *CVP,* central venous pressure; *MAP,* mean arterial pressure; *$ScVO_2$,* central venous oxygen saturation; *SVR,* systemic vascular resistance.

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Immunosuppression in Late Sepsis

It recently has become apparent that many patients with sepsis are profoundly immunosuppressed, as shown by lymphopenia, anergy, and susceptibility to opportunistic infections[44,45,85] (e.g., pulmonary aspergillosis in horses with enteric salmonellosis).[86,87] This immunosuppression has been explained by the reactive production of antiinflammatory mediators in response to the cytokine storm and is termed *compensatory antiinflammatory response syndrome* (CARS).[88] Although many such mediators are produced and can have favorable antiinflammatory effects when used as therapy in models of sepsis, it is now clear that three additional and primary mechanisms involving both innate and adaptive immune responses contribute to sepsis-associated immunosuppression: (1) widespread apoptotic death of lymphocytes (particularly B cells and CD4-positive T-helper cells) secondary to activation of intracellular caspases; (2) dendritic cell loss and dysfunction, leading to inefficient or impaired antigen presentation; and (3) impaired phagocyte chemotaxis and killing responses.[44,85,89] It is interesting to note that macrophages and neutrophils are spared premature apoptotic death; neutrophils are prevented from physiologic apoptosis during sepsis and remain viable in sequestered sites.[72] In people with sepsis, aspects of this immunosuppression are characterized by loss of cutaneous delayed-type hypersensitivity responses,[44] although this has not been investigated in horses to date. The relationship and interplay between SIRS and immunosuppression in sepsis are still unclear, and it cannot necessarily be inferred that hot and cold phases always occur sequentially in the same patient.

Signs of Endotoxemia and Sepsis

Clinical Signs

The clinical signs of horses given intravenous endotoxin experimentally may range from fever without obvious malaise to multiple organ failure and death. Signs of the primary disease resulting in endotoxemia (e.g., severe pain caused by intestinal strangulation or diarrhea in horses with *Salmonella* colitis) may greatly influence the overall clinical presentation of horses with naturally acquired endotoxemia. The clinical signs of polymicrobial or gram-positive sepsis are generally indistinguishable from the signs associated with endotoxemia/gram-negative sepsis (described later).[39,40,90,91]

Typically in an adult horse given a moderate sublethal dose of endotoxin intravenously (e.g., 0.1 to 1 μg of LPS per kilogram of body weight), an early period of mild tachypnea peaks within 30 minutes and resolves within 2 hours. During this period, mucous membranes are pale. Beginning within 90 minutes of LPS injection, depression, restlessness, and inappetence are present and rectal temperature begins to rise. Auscultable intestinal sounds usually cease during this period and remain depressed for several hours. Intermittent signs of colic usually are seen, including recumbency (usually without rolling). Small amounts of loose feces usually are passed. Heart rate peaks during the stage of maximal abdominal discomfort (approximately 2 hours after administration of endotoxin), then temporarily declines. During this time, mucous membranes become congested, the capillary refill time is prolonged, and a dark "toxic" line may become apparent around the gingival margins of the teeth. Beginning at 4 to 6 hours after endotoxin administration, there is a secondary phase of tachycardia and tachypnea that likely is related to development of systemic hypotension and fever. This secondary phase persists for several hours. Horses presented clinically with mild to moderate endotoxemia or sepsis usually resemble experimental animals during the period 2 to 6 hours after intravenous endotoxin administration.

At higher LPS doses (e.g., 100 μg/kg) in experimental animals or in patients with severe endotoxemia or sepsis, signs of circulatory failure and disordered hemostasis dominate the clinical picture. Usually these horses are stuporous and totally anorectic. Signs of dehydration such as reduced skin turgor, dry mucous membranes, and sunken eyes are obvious. As systemic blood flow becomes more compromised, rectal temperature may drop into or below the normal range. Urine output is reduced or nonexistent. There are dark, congested mucous membranes, rapid and weak peripheral pulses, cold extremities, and sweating, and the horse may have muscle tremors or become recumbent.

Vascular damage may be seen as petechial and ecchymotic hemorrhages on mucous membranes. A poor prognostic sign is the development of a hypercoagulation syndrome, during which routine venipuncture or catheter placement initiates thrombosis along the entire visible length of the jugular veins (or other superficial veins). If both jugular veins are thus occluded, there usually is massive swelling of the soft tissues of the head, and associated laryngeal edema may cause signs of upper respiratory tract obstruction. In some horses, thrombosed superficial vessels can easily be palpated through the skin of the legs and abdomen. Infarction of bowel segments or lungs may cause severe clinical signs that are unresponsive to treatment. A rare syndrome of thrombosis of major limb arteries found in young foals is likely a result of sepsis syndrome.[92,93] At the time that hypercoagulation syndrome is recognized clinically, there is often also evidence of a secondary bleeding tendency (a consequence of platelet and clotting factor depletion and uncontrolled activation of fibrinolysis in disseminated intravascular coagulation [DIC]), seen as prolonged hemorrhage from venipuncture sites and widespread mucosal petechiation. In cases with a severe pulmonary component, there may be hemorrhage into the respiratory tract with progressive tachypnea and dyspnea. Alterations in coagulation (both hyper- and hypocoagulable states) were recently shown to be associated with incidence of SIRS and mortality in horses with acute gastrointestinal disease[34,94,95] and with mortality in septic foals.[96]

If moderately to severely affected animals survive for more than 24 hours, there usually is visible edema of the ventral abdomen and limbs. Signs of MODS/L may first become apparent at this stage (see Table 32-3). Laminitis may present or progress in severity as a result of mechanical failure of the lamina even after improvement or resolution of other systemic signs of SIRS and sepsis. It is important to note that experimental endotoxin infusion does not reliably reproduce laminitis in horses, so other DAMPs or cellular responses in the sepsis syndrome likely play a role in laminar failure in equine sepsis.

Clinicopathologic Signs

Early and profound leukopenia is principally caused by neutropenia (usually accompanied by left shift and a toxic appearance of stained cells). Lymphopenia (<1000/μL) is found in the most severe cases and likely reflects sepsis-induced apoptosis and immunosuppression. Adult horses with sepsis often are hyperglycemic, whereas neonates with sepsis are usually hypoglycemic. Other abnormalities are nonspecific and reflect altered tissue perfusion and organ dysfunction (see Table 32-3).

In horses with moderate and severe cases of endotoxemia, there also may be clinicopathologic evidence of disordered hemostasis, including any to all of the following: reduction in the circulating platelet count (<100,000/μL), reduction in plasma fibrinogen concentration; prolongation of the activated partial thromboplastin, prothrombin, or thrombin time; increased activity of PAI-1; and increased concentration of fibrin degradation products. Recent studies have used viscoelastic coagulation testing to provide a more global assessment of coagulation function in horses with SIRS and foals with sepsis, and have provided further documentation of hyper- and hypocoagulable states and the association between coagulation derangements and increased disease severity and mortality in equine sepsis.[34,96] In horses with acute gastrointestinal diseases, there also is increased activity in peritoneal fluid of many of the elements of the fibrinolytic system, including tissue plasminogen activator (TPA). Depletion of key clotting factors can most simply be detected as prolongation of plasma recalcification time.[97]

Although the measured concentration of endotoxin in blood does not correlate well with incidence or severity of clinical signs, demonstration of circulating endotoxin is definitive proof of endotoxemia.

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Among horses with acute gastrointestinal disease, 12% to 29% have detectable plasma endotoxin.[41,42] Experimentally, plasma endotoxin usually is assayed by some variant of the *Limulus* amebocyte lysate bioassay, which requires anticoagulation of samples with LPS-free heparin. A simple horse-side test for endotoxin that was marketed for use in clinical practice is no longer commercially available, although measurement of endotoxin activity in equine blood via neutrophil chemiluminescence has recently been described.[98] Tests for other microbial PAMPs that could play a role in equine sepsis (e.g., staphylococcal toxins, flagellin, etc.) are currently unavailable or limited to research settings.

Assessment of the Stage of Sepsis

Horses with signs of sepsis or endotoxemia should be staged according to the criteria found in Fig. 32-64 and Table 32-3. It is especially important to recognize that horses with serious sepsis need aggressive intervention in order to survive.

Treatment of Sepsis

There is no "silver bullet" for treatment of sepsis or endotoxemia. It has to be admitted that, almost without exception, potentially novel treatments for gram-negative sepsis that have been promising at the experimental level have failed when applied in clinical settings in human beings (and to the limited number of equine studies). A short list of such trials includes anti–TNF-α, IL-1–receptor antagonist, ibuprofen, PAF antagonist, elastase inhibitor, nitric oxide synthase (NOS) inhibitor, antithrombin III (AT-III), and tissue factor pathway inhibitor. It is clear that most experimental sepsis models do not replicate naturally occurring sepsis, at least as it occurs in humans and probably in horses. Several of many likely explanations for the disparity between the results of experimental models and large clinical studies are (1) heterogeneity of presentations among enrollees in clinical studies; (2) diversity in genetic susceptibility to sepsis among outbred populations; (3) differences between experimental and clinical study species; (4) differences in timing of potential treatments relative to the onset of sepsis between the two study populations; (5) preponderance of "cold sepsis" and immunosuppression states in naturally occurring sepsis compared with the "cytokine storm" of early sepsis usually re-created in experimental models.

Even among sepsis models, results for the same candidate treatment are often inconsistent. For example, neutralization and inhibition of inflammatory cytokines such as TNF-α usually have salutary effects in LPS-infusion experiments; however, equivalent studies involving the cecal ligation and puncture model in mice (widely considered to be one of the best sepsis models) usually have shown either neutral or negative effects on mortality.[99] Evidence-based medicine so far acknowledges only one agent, drotrecogin alfa (activated protein C),[100] as able to reduce mortality in some patients with sepsis, although there has been some recent controversy regarding the side effects of the drug and subsequent studies showing less convincing benefit in a clinical setting.[62,101-103] Despite this theoretic potential in some patients with endotoxemia and severe sepsis, drotrecogin alfa is cost-prohibitive in horses.

Fortunately, there is powerful evidence to support the value of early aggressive cardiovascular resuscitation. Use of oxygen, fluids, pressors, inotropes, and packed RBCs during the first 6 hours after admission to achieve a sequence of physiologic goals reduced in-hospital mortality of human patients with serious sepsis from 46.5% in the group that received standard therapy to 30.5% in patients given early goal-directed therapy (EGDT).[104] Similar protocols now are widely used in emergency rooms throughout the United States and in many other countries.[82,105] Many of the underlying principles of EGDT can be applied to resuscitation of septic horses, especially neonates (Fig. 32-68). It is reasonable to conclude that improvements in cardiovascular support of horses with sepsis will continue to be of much more value than any single therapeutic agent available now or in the future. In fact, because clinical sepsis is likely almost always caused by multiple pathogen and host-derived DAMPs stimulating multiple, complementary and redundant inflammatory pathways, successful management of sepsis is much more likely when therapy focuses on combating the clinical sequelae of severe SIRS and subsequent immunosuppression rather than targeting a specific inflammatory mediator or PAMP.

A prioritized strategy for management of horses with sepsis or endotoxemia is as follows: (1) cardiovascular resuscitation; (2) laminitis prevention; (3) removal of the cause(s) of sepsis; (4) neutralization of circulating endotoxin or other PAMPs; and (5) inhibition of PAMP-induced inflammation. These approaches are most applicable to horses with serious endotoxemia or sepsis, as based on the stages outlined in Fig. 32-68.

Cardiovascular Resuscitation

Expansion of blood volume remains the cornerstone of treatment for horses with serious sepsis or endotoxemia. Most cases (e.g., adults with blood lactate of 2 to 4 mmol/L) can be treated successfully with intravenous balanced polyionic solution according to guidelines for estimating water deficits provided in the fluid therapy section of this chapter. Urination should begin during the rapid replacement of estimated losses. Ideally the fine control of fluid replacement should be based on clinical evidence of blood volume and perfusion (e.g., mucous membrane color, heart rate, capillary refill time, pulse quality, jugular refill time, extremity temperature), as well as serial measurements of packed cell volume (PCV) or plasma protein concentration and blood lactate concentration. Some clinicians prefer the early use of compatible plasma (5 L for a 450-kg horse, 1 to 2 L for a neonate) or other colloid solutions such as 6% hydroxyethyl starch solution to replace the extravasated colloid lost as a result of vascular leak. Plasma has the advantage of providing immunoglobulin, acute-phase proteins, and anticoagulants, and can provide anti-endotoxin antibodies (see Hyperimmune Plasma and Serum section).

In horses with the most life-threatening forms of endotoxemia and sepsis (lactate >4 mmol/L [>5 mmol/L in neonates <24 hours old], MODS/L, septic shock), aggressive hemodynamic monitoring and EGDT are indicated. Owners should be informed that such treatment still carries at best a guarded prognosis for survival, financial commitment often in the range or $5000 to $20,000 or more if complications develop, and transfer to a referral center. However, early and aggressive intervention is essential in sepsis therapy; in critical care parlance, terms such as the *golden 6 hours* and the *silver 24 hours* exemplify this concept.[82]

Relatively simple equipment and supplies but time-intensive monitoring and treatment are needed for effective EGDT in septic horses and foals. A central venous catheter (e.g., for ~50-kg neonates, two-lumen indwelling catheter, 7-French × 30 cm; for ~500-kg adults, two-lumen indwelling catheter, 9-French × 90 cm), a blood gas and lactate analyzer, an indirect arterial blood pressure monitor, and a central venous blood pressure monitor (transducer and data display and recorder, or water monometer) are required for the full EGDT bundle; however, much can be achieved with a jugular catheter, water manometer, and lactate analyzer. The details of an intensive approach to EGDT for the first 6 hours after admission are shown in Fig. 32-68. $ScVO_2$ has been shown to correlate well in this context with cardiac index. It is important to remember that jugular blood SO_2 correlates poorly with central measurements in endotoxemic pigs[106] and probably should not be used for that purpose, so a central venous catheter really is critical for equine EGDT. Although labor-intensive, none of these monitoring techniques is technically difficult. One advantage of being able to measure both lactate and $ScVO_2$ is that inferences can be made as to the particular hemodynamic derangement responsible for signs of global tissue hypoxia (see Table 32-5).

When the goals of EGDT have been met, fluid management should continue according to standard protocols (see Fluid Therapy for Horses with Gastrointestinal Diseases section) with adjustments made according to the results of continued monitoring of clinical signs of blood volume status and perfusion as described earlier, blood acid-base status, PaO_2, $ScVO_2$, lactate, CVP, and mean arterial

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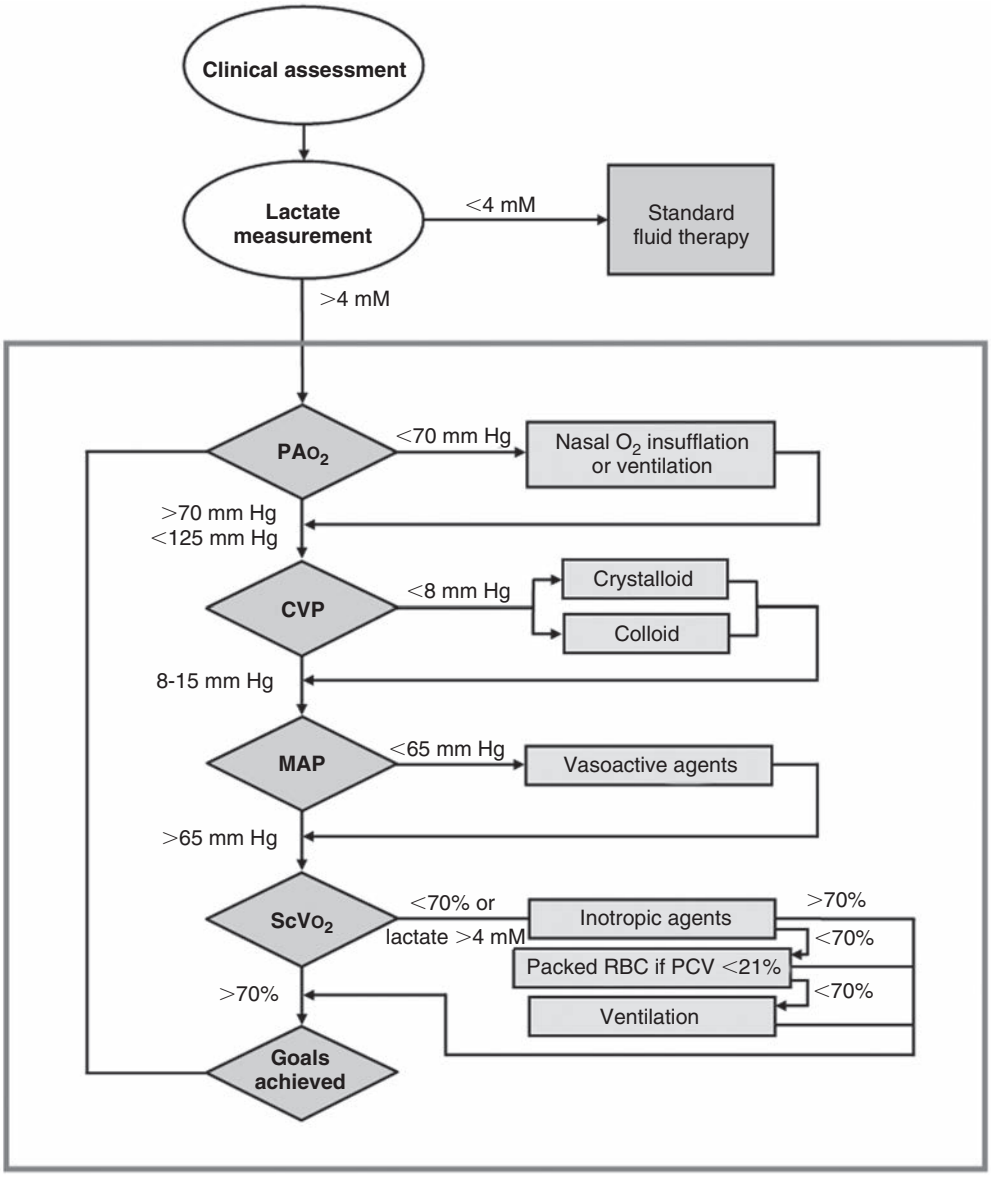


FIG. 32-68 Protocol for early goal-directed therapy. An initial 20-mL/kg bolus of isotonic crystalloid (or equivalent colloid) is given, followed by boluses of 10 mL/kg every 30 minutes until CVP reaches 8 to 15 mm Hg. If the heart-base adjusted MAP is still less than 65 mm Hg, vasopressors are given to effect. Norepinephrine, dopamine, or vasopressin can be used according to the clinician's preference. If the $ScVO_2$ is still less than 70%, dobutamine continuous rate infusion can be increased in increments up to 15 µg/kg/min. If the PCV is less than 21% after the preceding steps and $ScVO_2$ is less than 70%, packed cells should be given to increase oxygen-carrying capacity. *CVP,* Central venous pressure; *MAP,* mean arterial pressure; *PCV,* packed cell volume; *$ScVO_2$,* central venous oxygen saturation.

pressure (MAP). If the blood bicarbonate concentration is lower than 16 mmol/L after EGDT goals have been met (or plasma total CO_2 concentration is lower than 17 mmol/L), sodium bicarbonate should be given intravenously to replace calculated deficits. During correction of acidemia, intravenous fluids should be supplemented with potassium (10 to 20 mmol/L) to prevent correction-induced hypokalemia. A maintenance-rate infusion of glucose should be given to neonates with sepsis (4 mL of 5% dextrose-containing fluids per kilogram per hour) and hypoglycemic adults (2 mL of 5% or 0.2 mL of 50% dextrose per kilogram per hour). Glucose concentration should be regularly monitored, and the use of concurrent insulin therapy should be considered in persistently hyperglycemic animals.

Laminitis Prevention

Adult horses with serious sepsis are at high risk for the development of laminitis. Among the clinical risk factors likely operative in the setting of sepsis are body condition score higher than 5, being a pony, 24 hours or more since onset of signs of endotoxemia or sepsis, rectal temperature above 101.5° F, CRT >2 seconds, or cold extremities. The digital laminae are likely injured early in sepsis, potentially irreversibly, by processes associated with the cytokine storm and resultant global tissue hypoxia. Insulin resistance, hyperglycemia, microvascular injury and thrombosis, and protease activation may also be involved in the pathogenesis of sepsis-associated laminitis. The laminitis prevention bundle provided in Box 32-2 provides a reasonable preventive strategy based on current understanding of laminitis pathophysiology, but it must be implemented very early (preferably before increased digital pulses are detected) and is not universally protective. Global tissue hypoxia is addressed with standard or EGDT fluid resuscitation, and small vessel plugging addressed with flunixin (reduced TXA_2), pentoxifylline (vasodilation with PGI_2, suppression of inflammatory cytokines, increased RBC deformability), cryotherapy (suppression of lamellar inflammation), and plasma and heparin (increased active AT-III). The use of insulin (with or without glucose) infusions in horses with sepsis may also be indicated to combat persistent hyperglycemia associated with sepsis-mediated insulin resistance. However, because insulin infusions at very high rates have been associated with laminitis development in normal horses and

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BOX 32-2

Laminitis Prevention Bundle

Fluid resuscitation
Cryotherapy
Flunixin (0.25 mg/kg q8h)
Pentoxifylline (10 mg/kg PO bid)
Plasma (10 mL/kg)/heparin (4 U/mL plasma)

ponies[107,108] and hyperinsulinemia is associated with endocrinopathic laminitis,[109] glucose and/or insulin infusions could possibly potentiate the development of laminitis in susceptible animals. The use of insulin-sensitizing drugs such as metformin or pioglitazone could have potential in treating sepsis-mediated insulin resistance in horses, but to date these drugs have not been examined in clinical equine sepsis and recent evidence suggests that their effects on insulin sensitivity in horses may be variable at best.[110-112] If laminitis is already present, or if it develops during the course of treatment, it should be treated as described in Chapter 38.

Removal of the Cause(s) of Endotoxemia and Sepsis

Removal of the cause of sepsis usually involves both removal of the source of endotoxin or other microbial PAMPs, as well as correction of the abnormality that allows access of endotoxin or other PAMPs into the blood. In some cases, the source can be mechanically removed; for example, bacteria and associated inflammatory effusion can be drained from pleural or peritoneal cavities or carefully siphoned from the postpartum uterus. Antimicrobial therapy also is essential. In general, broad-spectrum bactericidal drugs should be selected because septic horses may be immunosuppressed. In horses in which endotoxemia or sepsis is associated with diarrhea or other signs of colitis or typhlitis, the use of antimicrobial drugs is controversial because of their causal association with severe colitis. Antimicrobials probably should be given to equids with colitis only in the following situations: (1) the horse is younger than 6 months; (2) there is suspicion of clostridial or antimicrobial-associated enteritis (consider use of metronidazole); (3) there is degenerative left shift or severe leukopenia with total neutrophil or lymphocyte count of less than 1000 μg/mL; (4) there is concurrent peritonitis; or (5) there is clinical evidence of dyshemostasis (e.g., jugular thrombosis or abnormal coagulogram). However, these recommendations and outcomes following treatment of equine colitis with and without antimicrobials have not been critically evaluated to date. It should also be noted that effective antimicrobial therapy could temporarily worsen clinical signs by causing the release of endotoxin from killed bacteria. This possibility should be anticipated and minimized by the timely use of nonsteroidal antiinflammatory drug (NSAID) or other antiendotoxic therapy (see Nonsteroidal Antiinflammatory Drugs section).

When intestinal strangulation is the cause of sepsis, surgical correction is of paramount importance. For the purposes of perioperative management, however, it should be noted that resumption of intestinal blood flow could worsen endotoxemia and sepsis: sequestered endotoxin and other microbial components may be flushed into the circulation through compromised intestinal walls. At least in the case of small intestinal ischemia, the mucosal barrier to endotoxin may be further compromised by ischemia-reperfusion injury when full blood flow is restored by luminal decompression or other manipulation. Again, prophylactic or intraoperative use of NSAIDs, ROS scavengers, polymixin B, and/or hyperimmune plasma or serum (as described in the following subsection) prior to or immediately after correction of a strangulating intestinal lesion may be warranted.

Neutralization of Circulating Endotoxin

HYPERIMMUNE PLASMA AND SERUM. An antiserum (Endoserum [Immvac Inc., Columbia, Mo.]) and several hyperimmune plasmas (e.g., Equiplas-J [Plasvacc, Templeton, Calif.]) produced by immunization of horses against R-mutant endotoxins are used in horses with suspected endotoxemia (in some cases, this is an off-label use). As is the case with studies in human beings and small experimental animals, use of cross-reactive endotoxin antibodies in horses with either experimentally or naturally acquired endotoxemia has yielded conflicting results. In several studies there was impressive reduction of mortality rate or improvement in clinical signs when antiendotoxin serum or plasma was given to horses[113-115]; however, in other studies no improvement was demonstrated.[116,117] Pretreatment of foals with antiserum was associated in one report with significant worsening of clinical response to endotoxin administered intravenously compared with foals that received no pretreatment.[118] These disparate results probably reflect, at least in part, variation in the quality of antisera and experimental conditions; therefore, no blanket recommendation can be made as to the clinical use of such products. As evidence of the potential general value of hyperimmune plasmas, it is worth noting the reduction in mortality achieved when antiendotoxin plasma raised against the *E. coli* mutant J5 was given to bacteremic humans (39% for controls versus 22% for those give antiendotoxin plasma) in a masked, well-controlled study at a single hospital.[119] In contrast, subsequent large multicenter studies of two different antiendotoxin monoclonals failed to show beneficial effects.[120,121] A recent equine study demonstrated no effect of hyperimmune plasma on clinical parameters or peak plasma TNF-α concentrations in horses undergoing an experimental low-dose endotoxin challenge, although peak plasma TNF-α bioactivity was reduced in horses receiving plasma as compared with controls.[122] This suggests that hyperimmune plasma may contain factors such as soluble TNF-α receptor that could limit the activity of endotoxin-induced inflammatory cytokines. Hyperimmune plasmas (raised against any antigen[s]) also contain colloid, anticoagulant, and increased amounts of substances such as acute-phase proteins, which might have a nonspecific beneficial effect in the setting of endotoxemia and sepsis. Therefore the use of 10 to 40 mL of hyperimmune plasma (of any specificity) per kilogram can be justified in treatment of serious endotoxemia or sepsis in horses.

POLYMYXIN B. Polymyxin B is a broad-spectrum cyclic peptide antibiotic with potent endotoxin-binding activity. Potentially lethal side effects of respiratory paralysis and nephrotoxicity have precluded use of this agent as a systemic antimicrobial drug; however, polymyxin B retains endotoxin-neutralizing capacity at nontoxic dosages. Pretreatment of foals with polymyxin B at a dosage rate of 6000 U (1 mg)/kg significantly suppressed clinical and cytokine responses to intravenous endotoxin without causing toxic side effects.[118] Repeated administration to ponies of 15,000 U/kg also produced no sign of toxicity.[123] At a dose of 5000 U/kg, polymyxin B protected horses even when given 30 minutes after the start of LPS infusion.[124] The results of a pharmacokinetic and pharmacodynamic study of polymyxin B in horses suggested that the drug could safely be given at 6000 U/kg every 8 hours to maintain continuous endotoxin neutralization.[125] Lower doses also appear to have anti-TNF-α effects, but for shorter time periods.[124,126] Thus, in horses with moderate or severe endotoxemia, consideration should be given to the cautious use of polymyxin B (Polymyxin B sulfate [Bedford Laboratories, Bedford, Ohio]) given intravenously two or three times daily at a dosage rate of 5000 to 6000 U/kg. Each treatment should be diluted in saline and given over at least 15 minutes. However, it is important to note that although polymyxin B and the nontoxic polymyxin B-dextran 70 conjugate PMX622 safely prevented signs of endotoxemia when given before LPS to otherwise healthy horses,[124,126,127] the drug has not advanced beyond phase 1 trials in human patients because experimental studies showed that it did not protect mice when given after intraperitoneal endotoxin.[128]

Inhibition of Endotoxin-Induced Inflammation and Related Sequelae

NONSTEROIDAL ANTIINFLAMMATORY DRUGS. Through inhibition of cyclooxygenase (COX), NSAIDs reduce the formation of prostanoid metabolites (e.g., thromboxanes and prostaglandins)

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from arachidonic acid and thereby attenuate much of the adverse effect of endotoxin. Flunixin meglumine, phenylbutazone, ketoprofen, carprofen, meloxicam, firocoxib, and aspirin are examples of this class of drugs used in horses. When flunixin is administered at 0.25 mg/kg IV or PO every 6 to 8 hours in horses, endotoxin-induced prostanoid production is prevented, and maximal antiendotoxic effects are produced in experimental situations without obscuring the signs of colic or risking toxic side effects of the drug.[129] It should be noted that flunixin treatment does not affect endotoxin-induced leukopenia. Because there is evidence that aspirin does not prevent endotoxin-induced aggregation of equine platelets,[130] there appears to be no rationale for the practice of adding aspirin to the NSAID regimen. Most NSAIDs inhibit constitutive COX-1 activity (in addition to endotoxin-induced COX-2 activity), so there is some morbidity associated with their use. There may be gastric ulceration, right dorsal colitis, renal papillary necrosis, and possibly impairment of intestinal motility.[131,132] Further, flunixin meglumine has been shown to slow mucosal healing and increase mucosal permeability to LPS in ischemic-injured equine jejunum,[133,134] although similar inhibition of mucosal barrier function does not appear to occur in the equine colon.[135] However, concurrent administration of misoprostol (a PGE-1 analog)[136] or a lidocaine constant rate infusion[137] ameliorated these effects in an equine model, suggesting these drug combinations might be more appropriate than flunixin alone for horses with endotoxemia caused by intestinal ischemia.

In light of this toxic potential of equine NSAID use, it has also been suggested that use of COX-2–selective drugs may minimize side effects while maintaining efficacy. Three NSAIDs with documented analgesic effect in horses—firocoxib, carprofen, and meloxicam—have been shown to be COX-2 selective.[138,139] Etodolac, a COX-2–specific drug in dogs and humans, is not COX-2 selective in horses when used at analgesic doses (23 mg/kg PO once or twice daily).[140] Firocoxib and meloxicam do not appear to retard small intestinal mucosal healing or increase LPS permeability in ischemic-injured equine jejunum as flunixin can,[133,141] suggesting these agents might be better suited for provision of analgesic, antiinflammatory, and antiendotoxic effects in horses after intestinal ischemia. It is important to remember, though, that COX-2 activity may also have potentially beneficial effects in horses with sepsis; for instance, COX-2 products (e.g., PGE_2, PGI_2) mediate epithelial restitution in damaged equine colon[131] and are thought to be important in maintaining the antithrombotic phenotype of normal endothelium. NSAIDs in the coxib class, which are potently COX-2 specific, have also been shown to increase the risk of atherosclerotic cardiovascular disease in humans.[142] Similar risks for coxibs in horses have not been described, but at present firocoxib is the only drug in this class labeled for equine use and it has been in use clinically only for a short period.

Finally, although various NSAIDs have been shown to effectively prevent the clinical and molecular sequelae of equine endotoxemia in experimental models,[76,129,143-150] there is no convincing study that shows NSAIDs save lives in human or equine patients with naturally occurring sepsis. A large multicenter, controlled, masked, prospective study of ibuprofen in humans with sepsis syndrome showed no effect of this drug on the development of shock or acute respiratory distress syndrome, and no improvement in survival.[151] Similar studies have not been conducted in horses to date.

METHYLXANTHINE DERIVATIVES. Inflammatory cytokine production by macrophages is suppressed in dose-dependent fashion by methylxanthine derivatives. This effect appears to be caused by phosphodiesterase inhibition and consequent elevation of intracellular cyclic adenosine monophosphate (cAMP). Pentoxifylline, a drug that is in widespread use in human beings as a hemorheologic agent, has also been shown to increase RBC deformability in horses.[152] Pentoxifylline also inhibits TNF production in horse blood and in cultured equine macrophages while increasing secretion of prostacyclin.[153,154] Studies in other species suggest that pentoxifylline stimulates production of the antiinflammatory cytokine IL-10, suppresses neutrophil activation, and inhibits activation of NF-κB.[155] A pharmacokinetic study in horses has indicated that administration at 10 mg/kg PO two times daily provides serum concentrations equivalent to those used therapeutically in humans.[156] Finally, intravenous pentoxifylline significantly, albeit only partially, reduced adverse signs in horses given LPS.[157] The usefulness of this finding is called into question, though, by the observation that the lethality-sparing effect of pentoxifylline in endotoxemic mice was removed if the drug was given in combination with indomethacin, a potent NSAID.[158,159] In this study, it was concluded that upregulation of prostacyclin production by pentoxifylline, which was prevented by concurrent indomethacin, reduced mortality in subject mice by preventing endotoxin-induced leukopenia. It is interesting to note that pentoxifylline alone increased WBC counts in horses, although this effect is prevented by flunixin.[154,157] Thus, there may be a conceptual and potential beneficial effect of pentoxifylline therapy (10 mg/kg PO bid) in endotoxic horses, although any effect could be partially or wholly neutralized by concurrent NSAID administration (as is commonly done in equine practice).

CORTICOSTEROIDS. The corticosteroid class of drugs theoretically has many useful actions in combating inflammation in endotoxemia and sepsis. These include reduced production of cytokines, inhibition of TNF production by macrophages, stabilization of cell membranes, and prevention of neutrophil activation. It is surprising, however, that neutral or negative effects of moderate or high-dose steroid use were found in large, multicenter studies of humans with gram-negative sepsis,[160] most likely related to immunosuppressive effects at these doses. Corticosteroids also are widely believed to increase susceptibility to laminitis in endotoxemic horses, perhaps by increasing the sensitivity of digital vessels to the constrictive actions of circulating catecholamines or by inducing insulin resistance and hyperglycemia.[161] Use of high-dose corticosteroids is currently contraindicated in the treatment of endotoxemia or sepsis in people and horses.

Some human patients with sepsis appear to respond to low, "physiologic" doses of hydrocortisone.[161-165] Most of these patients have high baseline cortisol concentrations but are thought to be in a state of adrenal insufficiency termed *critical illness-related corticosteroid insufficiency* (CIRCI), a syndrome that also appears to occur in some septic neonatal foals and some horses with systemic illness and SIRS.[35,166-168] Low-dose hydrocortisone is associated with reduced vasopressor use and lower mortality rates in people with septic shock in a number of reports,[162,163,169-171] although other studies have not demonstrated a beneficial effect.[172] At present, low-dose hydrocortisone therapy is recommended for septic patients meeting criteria for CIRCI but not universally for all septic patients.[170] The use of low-dose hydrocortisone therapy has not yet been reported in septic equine patients, but a 3.5-day tapering low-dose hydrocortisone regimen (1.3 mg/kg/day divided q4h IV) administered to healthy neonatal foals was recently shown to ameliorate LPS-induced inflammatory cytokine production from peripheral blood leukocytes without impairment of neutrophil function in an ex vivo model.[173]

HEPARIN. The use of heparin in horses with endotoxemia is somewhat controversial. It prevents microvascular thrombosis principally by promoting the anticoagulant activity of AT-III. Unfortunately, heparin cannot reverse existing thrombosis, and because AT-III is consumed during severe coagulopathy, it may not prevent additional intravascular coagulation in such cases. Fresh and fresh-frozen plasma are good sources of AT-III, but they also provide clotting factors that could potentiate intravascular coagulation. When given at the recommended intravenous or subcutaneous dose of 40 U/kg tid or 150 U/kg bid, respectively, unfractionated heparin causes intravascular agglutination of equine RBCs.[174] Therefore it could be argued that the use of heparin might actually exacerbate intravascular cellular plugging, which is theorized to play a role in some cases of laminitis in equine sepsis. This side effect can be avoided by using *low-molecular-weight* heparin (LMWH), which is nonagglutinating but retains anticoagulant activity, principally via

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inhibition of factor Xa.[175] Two clinical studies have suggested that LMWH may have benefits over unfractionated heparin for the prevention of jugular thrombosis or laminitis in some equine colic patients,[176,177] although this is not universally accepted. The use of heparin should be considered in horses with sepsis that are at high risk for laminitis (e.g., DPJ, colitis, or grain overload) or that have evidence of hypercoagulation syndrome (early evidence of dyshemostasis such as abnormal coagulogram or spontaneous venous thrombosis). In the latter setting, heparin should be given with plasma (10 to 40 mL/kg) at a dose of either 200 to 300 IU/kg/day for unfractionated heparin (either divided bid-tid IV or SC or as a continuous intravenous infusion) or 50 IU/kg for LMWH (SC q24h). Foals at risk for thrombosis may require a higher dose of LMWH, in the range of 100 IU/kg.[178]

SCAVENGERS OF REACTIVE OXYGEN SPECIES. ROSs are thought to cause corrosive tissue damage during endotoxemia and potentiate the production of inflammatory cytokines via activation of NF-κB. Surgical deflation of distended small intestine is thought to lead to ischemia-reperfusion injury, a process that generates ROSs from epithelial xanthine oxidase. The life-saving process of fluid resuscitation in horses with hypovolemic shock may even lead to whole body ischemia-reperfusion and systemic release of ROSs. Despite these key associations between oxidant stress and sepsis, little effort has been made to intervene therapeutically at this level. There is some evidence that allopurinol, a hydroxyl radical scavenger and inhibitor of xanthine oxidase activity, has positive clinical effect during sublethal endotoxin infusion in horses.[179] A recommended dose for allopurinol is 5 mg/kg IV. Because dimethyl sulfoxide (DMSO) has been shown to be a potent scavenger of hydroxyl radicals with efficacy in rodent sepsis models,[180] it has been considered for use in the treatment of equine endotoxemia although effects in experimental models have been variable. DMSO is typically administered via rapid intravenous infusion (or by nasogastric tube) as a 10% to 20% solution in saline at a dose of 0.02 to 1 g/kg every 6 to 12 hours. However, intravenous infusion of DMSO at the low and high ends of this dose range was recently shown to have little to no effect on clinical signs (with the exception of fever at the high dose), clinicopathologic abnormalities, and TNF-α production following endotoxin infusion in horses.[181] DMSO may also reduce intestinal mucosal injury after ischemia-reperfusion, although to date, evidence for efficacy in this setting in horses is also mixed.

Ethyl pyruvate, a stable analog of pyruvate, has been shown to have remarkable protective efficacy in a variety of models of septic and nonseptic shock in rodents and other species, with these beneficial actions ascribed to its antioxidant effects.[182] Because this agent is inexpensive and can be given in intravenous crystalloid fluids, it could have potential for the treatment of endotoxemia and sepsis in horses. Recent reports in equine experimental endotoxemia support this theory, demonstrating beneficial effects on clinical manifestations of endotoxemia (except fever) and suppression of proinflammatory gene expression.[183-185] Use of ethyl pyruvate in clinical cases of equine sepsis or endotoxemia is not described to date, and other antioxidants that have shown benefit in rodent sepsis models (e.g., vitamin C, vitamin E, and *N*-acetylcysteine) have not been evaluated in horses.

Miscellaneous Treatments

A number of other treatments for endotoxemia and sepsis have been described in horses and other species, although on the whole, currently available data are less supportive of their use in clinical cases. Naloxone, a narcotic antagonist, at a dose of 0.2 mg/kg, blunted some of the cardiovascular effects of high-dose endotoxin in one study,[186] but a dose of 1 mg/kg had no effect in another.[187] Of importance, 0.75 mg/kg naloxone caused signs of colic in conscious horses,[188] probably by blocking the actions of endogenous β-endorphins at the high affinity μ-receptor. The detergent tyloxapol was remarkably effective in preventing the effects of endotoxin in anesthetized horses.[189] The mechanism of antiendotoxic action of tyloxapol is unknown, but the detergent has been shown to have wide-ranging effects on cells and proteins, some of which may preclude its use in clinical cases. For example, the detergent has been shown to inhibit cellular phagocytosis, clearly an important event in innate immunity and sepsis. Also, this agent induces marked hyperlipidemia (up to 100-fold higher than controls) in horses because of interference with lipoprotein metabolism. Similarly, a phospholipid emulsion effectively prevented adverse effects of subsequent endotoxemia; however, the treatment induced hemolysis sufficient to preclude its use in clinical cases.[190] A published report[191] on the use of the sulfonyl analog of the alpha-phenyl-*N*-tert-butyl-nitrone spin trap molecule suggests that this agent was effective in reducing clinical signs in horses given endotoxin. However, a cautionary note was the observation that some rodents given the same agent at high doses suffered enhanced endotoxin-induced mortality.

Platelet activating factor inhibitors have been effective antiendotoxic agents in some species but have not yet shown much positive clinical effect in horses or humans.[192] In dogs and other experimental animals, inhibitors of NO production such as N^G-monomethyl arginine reverse endotoxin–induced (or more likely TNF-induced) hypotension[193]; however, NOS inhibitors generally have no protective effect in sepsis models. Furthermore, NO production may not be increased in horses with endotoxemia.[194] The antifibrotic pyridine compound pirfenidone (5 methyl-1-phenyl-2-[1H]-pyridone) had no effect on endotoxin-induced clinical signs, leukopenia, or TNF-α production in horses.[195] Hyperbaric oxygen therapy also did not appear to have any protective effect on clinical or cytokine changes in experimental endotoxemia in horses.[196]

Ketamine administered at a constant rate infusion (CRI) has been theorized to have beneficial effects in equine endotoxemia after it was shown in vitro to suppress the production of inflammatory mediators by LPS-stimulated equine peritoneal macrophages.[197] Ketamine CRI at 1.5 mg/kg/h for 320 minutes achieves blood concentrations compatible with this inflammatory effect and has been shown to be safe and nonsedating in horses. However, pretreatment with ketamine had no effect on clinical signs, leukopenia, or inflammatory cytokines in horses after endotoxin infusion.[198] The putative antiinflammatory actions of ketamine appear to be mediated by the actions of adenosine on the adenosine A2A receptor[199]; as the equine adenosine A2A receptor was recently cloned and characterized pharmacologically, it may prove to be a potential direct target for antiinflammatory drugs in the future.

Future Treatment Considerations

In sum, current research in horses, people, and experimental animals suggests that a single therapeutic agent with universal benefit in endotoxemia and sepsis will be very hard (or impossible) to find. Most antiinflammatory approaches that show promise in experimental endotoxemia, even if they are aimed at the "root and trunk" of the inflammatory cascade (e.g., NF-κB activation), do not work consistently in severe sepsis models (e.g., cecal-ligation puncture) or in phase 3 clinical trials of human patients. It is becoming increasingly clear that a substantial portion of the morbidity and mortality associated with sepsis may result as much from "cold" sepsis, the state characterized by profound immunosuppression, as from the cytokine storm in "hot" sepsis. Immunosuppressed patients could be injured further by antiinflammatory therapy, which might explain some of the discrepancy between specific therapeutic efficacy in experimental versus clinical sepsis. This raises the issue of the need for accurate recognition of the stages of sepsis. Plasma biomarkers such as procalcitonin, C-reactive protein, or HMGB1 levels have been used to diagnose sepsis, define sepsis categories, and provide prognostic information in humans,[200,201] although a universally reliable biomarker or combination of markers has yet to be identified. These or equivalent markers need to be introduced into equine sepsis diagnosis.

On the treatment horizon are some different approaches that have the potential to be both effective and affordable. There is some indication that IFN-γ, a cytokine that is pivotal in both innate and acquired

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immunity, may be beneficial for combating immunosuppression in bacterial sepsis.[202] IL-7 and IL-15 may also prevent or modulate immunosuppression in sepsis by preventing leukocyte apoptosis and supporting both innate and adaptive immune function.[44] There also remains enthusiasm in human critical care for antioxidant strategies aimed at effective means to suppress or scavenge ROSs.[44,79,80] In this regard, the remarkable effects of ethyl pyruvate in multiple models of inflammation, which likely mediates via its antioxidant effects, offer considerable promise. Antioxidant vitamins also may be both beneficial and cost-effective in equine endotoxemia and sepsis. Inhibition of complement activation with anti-C5a antibody shows promise in some sepsis models and is currently in clinical trials in people.[44] Finally, one of the most exciting possibilities in the distant future is the use of gene therapy to transiently transfect host cells in a targeted way with genes supporting immune and bactericidal function.[203]

Medical Disorders of the Small Intestine

Jennifer L. Davis • Nicola Pusterla

Ulcerative Duodenitis

Pathophysiology Ulcerative duodenitis is a rare condition that most often affects foals and, to a lesser degree, yearling horses. One retrospective study cited 32 of 691 (4.6%) nonsurviving foals that had ulceration of the duodenum and of those foals, only 1 of 691 (0.14%) had duodenal involvement alone.[1] Lesions occur primarily in the proximal duodenum and may include erosions, focal ulceration, and diffuse inflammation with or without ulceration. The terms *duodenal ulceration* and *ulcerative duodenitis* may refer to differing clinical manifestations of the same problem, and the terms are used interchangeably in this section.

The pathophysiology of duodenal ulcer disease in foals is less well understood than gastric ulcer disease. The disorder is classically considered to be a peptic disease, one in which damage to the duodenal mucosa results from excessive exposure to hydrochloric acid and pepsin. This concept may require revision. Equine duodenal ulcer disease has been presumed to be similar to the disorder in humans, but most cases of duodenal ulcer disease in people are associated with *H. pylori* infection.[2] *H. pylori* bacteria have not been reported in equine gastrointestinal tissues; however, *H. pylori* colonize only gastric (glandular) mucosa, and infection of the duodenum must be preceded by metaplasia of areas of duodenal mucosa to gastric mucosa. This is thought to occur from chronic peptic injury. In humans the incidence of duodenal ulcer disease increases with age,[3] which contrasts with horses, in which duodenal ulcer occurs primarily in animals less than 1 year old.[4]

Duodenal ulceration and inflammation have been recognized to occur in cases that were clustered geographically (same farm) and temporally. All of these foals had moderate to severe gastric ulceration, and they had extensive inflammation with varying degrees of erosion or ulceration in the proximal duodenum (see Color Plates 32-10 and 32-11). A similar temporal and geographic association was reported in two cases of ulcerative duodenitis in yearlings.[5] These findings seem inconsistent with a purely peptic insult as the cause for the ulcerative duodenitis. In one report of seven foals with ulcerative duodenitis,[6] lesions typically extended into a large area of the proximal duodenum, were characterized by mucosal necrosis, and often had a sharp line of demarcation between affected and more normal-appearing mucosa. In the foals of that report, no common microbial organism other than *E. coli* was identified, and a cause for the ulcerative duodenitis was not determined. In most foals with duodenal disease the lesions were not focal ulcers but rather appeared as more generalized inflammation. An infectious cause seems likely but has not been identified. In the 1980s rotavirus infection was thought to be associated with gastroduodenal ulcer disease in foals, but most foals with duodenal ulcer disease do not have rotavirus infection.

Duodenal ulcer disease in foals may have a component of peptic injury. The duodenal mucosa possesses some intrinsic properties that are protective against peptic injury, although these are not as elaborate as in the gastric glandular mucosa. The most important factor that protects the duodenal mucosa from acidic gastric secretions may be the sodium- and bicarbonate-rich secretions that probably originate from the pancreas and that will neutralize acid entering the duodenum from the stomach.[7]

Clinical Signs The signs of duodenal ulceration or ulcerative duodenitis have been classically described as being the severe forms of gastric ulcer signs,[8] and in many cases duodenal and gastric ulcers occur simultaneously. However, many foals with ulcerative duodenitis will not have signs similar to those of gastric ulceration until severe gastric ulceration has occurred. Thus the primary signs of duodenitis can be nonspecific; they include fever, mild to moderate abdominal discomfort, mild obtundation, and diarrhea. A complete blood count (CBC) will often reveal peripheral blood leukocytosis and hyperfibrinogenemia.

Gastric ulceration frequently occurs along with duodenal ulceration and may be secondary to physiologic or anatomic obstruction to gastric emptying. The gastric ulceration tends to be severe (see Color Plate 32-12), often leading to gastroesophageal reflux and esophagitis. Foals with esophagitis often exhibit ptyalism. In general the sequelae of duodenal ulceration are more severe than those of primary gastric ulceration. Complications of duodenal ulceration include duodenal perforation with peritonitis or adhesions, duodenal stricture with complete or partial obstruction (Figs. 32-69 and Fig. 32-70), ascending cholangitis and hepatitis, and ascending pancreatitis.

Diagnosis Duodenoscopy is the most specific means of diagnosis. It requires an endoscope with at least a 200-cm working length in foals up to 6 months of age, and in older foals a longer endoscope is required to examine the duodenal mucosa. Because of the size of the stomach and the anatomic configuration of the duodenum in foals, it is usually not possible to advance the endoscope past the duodenal ampulla. Occasionally the endoscope can be advanced into the descending duodenum.

A diagnosis is most readily made in cases in which lesions are diffuse or located within the ampulla. Excessive enterogastric reflux of bile through the pylorus is consistent with duodenal dysfunction. Ulceration at the pylorus or pyloric antrum may accompany duodenal ulceration and thus provide an indication of potential duodenal involvement. Severe gastric ulceration in foals should alert the

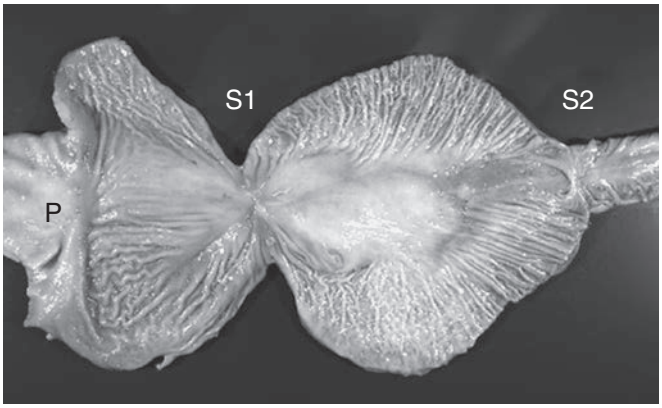


FIG. 32-69 Proximal duodenum of a 10-month-old horse with a history of chronic poor appetite and condition. The pylorus *(P)* is at the left. There are two strictures in the duodenum: S1 is orad from the major duodenal papilla, and S2 is aborad from the duodenal papilla. The segment of the duodenum between the strictures is dilated. *(Courtesy Dr. M.J. Murray.)*

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FIG. 32-70 Duodenal stricture *(S1)* of the horse in Fig. 32-69. The diameter of the duodenal lumen at the stricture is only 3 mm. *(Courtesy Dr. M.J. Murray.)*

endoscopist to the potential for duodenal involvement. In such cases, oral histamine-2 (H_2)–receptor antagonist therapy may be less effective in resolving gastric lesions than in cases of primary gastric ulceration, because of delayed gastric emptying secondary to duodenal ulceration. Therefore, if a foal has received such treatment before endoscopy and if gastric ulceration is severe, suspicion of duodenal ulceration should increase.

Other diagnostic procedures that may be helpful include evaluation of peritoneal fluid; serum liver enzymes, particularly biliary-associated enzymes (γ-glutamyltransferase [GGT], alkaline phosphatase [ALP]); serum bile acids; and radiography. With severe duodenal ulceration, survey radiographs of the cranial abdomen may reveal accumulation of fluid within the stomach and gas ascending the biliary ducts.[9] If barium contrast medium is placed into the stomach, complete emptying is usually delayed (>2 hours) and an irregular mucosal border may be noted in the descending duodenum. It should be recognized that in most cases radiography would not contribute to a diagnosis of duodenal ulcer per se, although duodenal stricture may be noted. If the descending duodenum is to be imaged, the volume of contrast medium placed in the stomach should not exceed 0.5 to 1 L in a foal and 1 to 2 L in a weanling or yearling, or the proximal descending duodenum will be obscured by contrast medium within the stomach.

Treatment The effectiveness of treatment of duodenal ulceration or ulcerative duodenitis depends on the extent and severity of ulceration and the absence of complications, particularly perforation and stricture of the duodenum. Treatment objectives are to decrease duodenal inflammation, treat secondary gastric and esophageal ulceration, promote gastric emptying, and treat related problems such as peritonitis. If duodenal ulceration is confirmed or even suspected on the basis of clinical signs, treatment should be aggressive.

In acute cases of ulcerative duodenitis there usually is a pronounced lymphocytic infiltration of the mucosa. In more chronic cases there is a mixture of neutrophils, macrophages, fibroblasts, and fibrinonecrotic exudate. Definitive antiinflammatory therapy has not been described for these cases, and the use of corticosteroids or nonsteroidal antiinflammatory drugs (NSAIDs) is controversial because they may worsen gastric ulcer disease through inhibition of protective prostaglandin synthesis.

Suppression of gastric acid secretion is still an important objective in the treatment of ulcerative duodenitis in foals, because most affected foals have gastric ulcers. Initially, acid suppression should be accomplished via parenteral administration of H_2 antagonist (cimetidine, 7 mg/kg IV q6h, or ranitidine, 1.5 mg/kg IV q8h) or proton pump inhibitors (pantoprazole 1.5 mg/kg IV q24h). Oral medications are unlikely to be adequately delivered to and absorbed from the small intestine in the first days of treatment. Gastric emptying can be enhanced with bethanechol (0.02 mg/kg SC q6-8h or 0.35 mg/kg PO q8h when the foal can consume orally). In foals that have severe duodenal disease or that have required surgery, bethanechol has been given for up to 3 months. Once the foal can accept oral medication, it should be treated with the proton pump inhibitor omeprazole at a dose of 4 mg/kg once daily for the paste formulation. It should be noted that in the 24 hours after the first dose, acid suppression is incomplete, and maximal suppression of acid secretion is achieved between days 1 and 5.[10] Therefore a common practice is to administer an H_2 antagonist IV for the initial 2 days of treatment with omeprazole in foals with duodenitis.

Misoprostol is a synthetic prostaglandin E_1 analog that has been successfully used in treating duodenal ulcerations in humans. Doses of 2 to 5 μg/kg q8-12h can be used in horses, although side effects may include abdominal pain and diarrhea. Sucralfate promotes duodenal mucosal healing in humans.[11] The dose of sucralfate that is effective in humans with duodenal ulceration ranges from 1 to 2 g two to four times daily. Foals treated for duodenal ulceration that do not have impaired gastric emptying should be administered 2 to 4 g of sucralfate three times daily. *Sucralfate should not be used as the sole therapeutic agent for duodenal ulceration.*

Foals with duodenitis must usually be prevented from nursing or eating for 1 to 3 days. During this time, parenteral feeding should be considered. Depending on the age of the foal, administration of parenteral nutrition should provide 40 to 60 kcal/kg/day.

If medical therapy is ineffective or if sequelae of duodenal ulceration cause complications, surgical intervention may be required. Gastroenterostomy has been reported to be effective in some cases through bypassing the affected portion of duodenum and allowing for an alternative route for gastric emptying.[9] However, short-term survival and long-term quality of life and use are often unsatisfactory. Patients that have a successful surgical outcome require long-term aftercare and usually require long-term maintenance acid suppression and treatment with a prokinetic drug until gastric emptying is normalized. Therefore an owner should be prepared to make a significant time and financial commitment before surgery is considered.

Duodenitis-Proximal Jejunitis

Duodenitis–proximal jejunitis (DPJ), also known as *anterior enteritis* or *proximal enteritis,* describes a clinical syndrome that is characterized by inflammation and edema of the duodenum and proximal jejunum, excessive fluid and electrolyte secretion into the small intestine, and, consequently, large volumes of enterogastric reflux. The syndrome of DPJ was first described in 1982[12] and was more fully characterized in 1987.[13] A subsequent report[14] described clinical and clinicopathologic parameters in horses with DPJ that differed somewhat from cases in the 1982 report, suggesting that either the cases were of similar etiopathogenesis but of different severity, or that the cases were of different etiopathogenesis with the only similarity being the segment of bowel affected. A diagnosis of DPJ is often applied to cases in which there is abdominal discomfort, small intestinal distention, and excessive enterogastric reflux without obstruction, yet it is unclear whether all of these cases lie along a spectrum of severity of DPJ or whether there are several disease entities that affect the proximal small intestine and that share clinical features. The latter seems more likely.

Pathophysiology In horses with DPJ, lesions are consistently found in the duodenum, but the severity and frequency of lesions in the jejunum are variable. Serositis is a consistent finding, characterized by bright red to dark red petechial and ecchymotic hemorrhages

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on the serosal surface.[13] Histologic lesions include hyperemia and edema of the mucosa and submucosa, villous epithelial degeneration, epithelial cell sloughing, neutrophilic pleocytosis, hemorrhages in the muscular layers, and fibrinopurulent exudation on the serosa.

With DPJ there is an increased volume of duodenogastric reflux, typically 50 to 100 mL/min. This reflux has been considered to result from increased intestinal fluid secretion and decreased motility. Mechanisms of intestinal fluid secretion include passive transmucosal exudation, secondary to mucosal and submucosal inflammation and characterized by a protein-rich fluid secretion, and active fluid secretion, caused by increased cyclic nucleotides and characterized by fluid with a high electrolyte and low protein content. The components of fluid in the intestines of horses with DPJ have not been characterized, but they are likely to result from a combination of passive and active secretion. In some horses the hemorrhagic nature of the gastric reflux implies increased capillary permeability of the duodenal mucosa, whereas in other horses the watery nature of the reflux, the presence of serum electrolyte disturbances,[15] and the absence of peripheral hypoproteinemia are most consistent with an active secretory process.

Another potential source of the large volume of fluid secreted into the proximal small intestine and refluxed into the stomach is the pancreas. Normally there is periodic orad movement of duodenal contents into the stomach, which has been observed endoscopically and has been documented by collecting gastric contents with and without pyloric obstruction.[7] The duodenal contents have a large component of water, sodium, and bicarbonate, as well as bile salts from the liver. These secretions are presumed to originate from the pancreas, as well as the liver, and pathology of either of those organs may contribute to the pathophysiology in cases of DPJ.

Suppurative cholangiohepatitis has been reported in cases of small intestinal inflammation secondary to DPJ.[16,17] The pathophysiology behind this observation may be related to an increased luminal pressure in horses with DPJ, increasing the likelihood of intestinal content regurgitation into the bile ducts. It is also possible that horses with DPJ absorb inflammatory mediators or bacterial products from the small intestine via the portal blood flow or systemic circulation.

Although the exact cause of DPJ is not known, several bacteria and toxins have been implicated. *Clostridium difficile* has been frequently implicated in causing the disease. One prospective study cultured toxigenic species of *C. difficile* from the reflux of 10 of 10 horses diagnosed with DPJ, and only 1 of 16 horses diagnosed with other causes of nasogastric reflux. Of the strains cultured from these horses, 8 of 10 produced both A and B toxins, whereas the remaining two produced only toxin B.[18] This is significant in that toxin B has been shown to cause inhibitory electromechanical disturbances to smooth muscle in the small intestine, which may be a possible cause of ileus in these horses.[19] Toxin A has also been shown to promote inflammatory cell infiltration into the smooth muscle layers.[20] Influx of neutrophils and release of inflammatory mediators in the intestinal wall have been shown to activate nitric oxide pathways, which results in inhibition of the enteric nervous system, increases in sympathetic tone, and a subsequent reduction of contractile activity in the gut.[21] *C. difficile* can also be cultured from the proximal intestinal tract in horses without evidence of gastrointestinal disease, however, and these strains can produce both toxin A and B.[22] *Clostridium perfringens* and *Salmonella* spp. have also infrequently been associated with DPJ, but the significance of these pathogens remains unknown.

Feeding practices may be associated with the development of DPJ. In one study, horses with DPJ were fed significantly more concentrate and were significantly more likely to have grazed pasture than horses with other types of colic or horses with lameness.[23] This may indicate that these horses are exposed to some type of toxin or infectious agent through different types of feed. *Fusarium moniliforme* has been cultured from the feed of horses with naturally occurring DPJ. Under experimental conditions, *F. moniliforme* producing fumonisin B1 mycotoxins also caused lesions consistent with DPJ.[24] Neurologic lesions were present in those horses, however, and both of those horses died with lesions consistent with equine leukoencephalomalacia. Cantharidin toxins can also cause reddening of the mucosa in the small intestine, as well as excessive gastric reflux,[25] and may be a cause in some cases. It is possible that this one syndrome has multiple initiating causes and that no one causative agent will ever be definitively identified.

Clinical Signs and Differential Diagnosis

The major differential diagnoses for DPJ include simple or strangulating small intestinal obstructions. Differentiation can be extremely difficult in some cases and may delay surgical intervention in cases of small intestinal obstruction, to the detriment of the patient. The criteria used to discriminate between DPJ and obstructive lesions include degree of pain, presence of fever, and changes in hematologic parameters and abdominal fluid.

Horses with DPJ have a history of an acute onset of moderate to severe abdominal pain that often is followed by varying degrees of depression. Nasogastric intubation yields a large volume of enterogastric reflux, which is frequently orange-brown in color, with a fetid odor. Rectal palpation reveals multiple loops of mild to moderately distended small intestine. The initial volume of reflux may range from as little as 4 to 5 L to up to 32 L. The duration of the reflux may be as short as 24 to 48 hours, but it usually lasts 3 to 7 days. Horses are often febrile (rectal temperature higher than 38° C [101° F]) and dehydrated and have injected mucous membranes, prolonged capillary refill time, diminished intestinal sounds, tachycardia (>60 beats/min), and tachypnea.[12-15,26,27] Horses with DPJ also tend to have a higher incidence of gastric ulceration than horses with abdominal pain secondary to other causes.[28] Although abdominal pain usually abates after gastric decompression, most horses remain depressed, which perhaps is the most consistent and characteristic clinical sign of the disease. If the fluid that accumulates in the proximal intestinal tract is not removed periodically, signs of abdominal pain recur.

Assessments of the degree of small intestinal distention and the thickness of the intestinal wall can be useful indicators. Often, horses with DPJ have generalized distention of small intestine, but when palpated per rectum the intestine does not feel taut. In many cases of small intestinal obstruction the bowel will feel tightly distended, but this is not universally true. Ultrasonography can be used, both transrectal and transabdominal, to determine the diameter of the small intestine, evaluate contractions, and measure the thickness of the wall of the intestine. With acute obstruction one can see several segments of small intestine that are 6 to 10 cm in diameter, have no contraction, and have a wall diameter of 3 to 5 mm. With DPJ, small intestinal diameter may be less, and the thickness of the intestinal wall may exceed 6 mm.

Culture of the reflux for *Clostridium* and *Salmonella* spp. can be attempted. This can be difficult, however, given the special conditions required for anaerobic cultures, as well as the intermittent shedding of *Salmonella* spp. into the gastrointestinal tract of normal horses. Also, the large volume of reflux in these cases may dilute the bacterial population to the point where isolating low numbers of bacteria is difficult.

Clinicopathologic Findings

Clinical laboratory findings include increased packed cell volume (PCV) and total plasma proteins (hemoconcentration). Abdominocentesis often reveals an elevated peritoneal fluid total protein concentration and a mild to moderate increase in the peritoneal white blood cell (WBC) count (>5000 cells/μL).[26] The peritoneal fluid is usually yellow and turbid, but in severe cases diapedesis occurs, resulting in a serosanguineous color. An abdominal fluid total protein concentration above 3.5 g/dL is associated with a poorer prognosis.[26] The WBC count in the peripheral blood may be normal, increased, or decreased.[13,14] In addition, hypocalcemia, hyponatremia, hypochloremia, hypokalemia, and acid-base alterations have been reported in horses with DPJ.[15] An elevated anion gap may be present, secondary to decreased calcium and magnesium or increased lactate or albumin concentrations.[26] Increases in the anion gap to 15 mEq/L or above have also been associated with a poor prognosis. Horses with enteritis

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have been found to have higher plasma D-dimer concentrations and more severe coagulopathies on admission than horses with other types of colic.[29]

Elevations in liver enzymes, particularly GGT, may be seen in horses with DPJ and may be a useful way to help differentiate between DPJ and strangulating lesions of the small intestine.[16,17] A study examining a large series of DPJ cases retrospectively to determine the prevalence of hepatic damage in horses with small intestinal inflammation showed that horses with DPJ had significantly higher hepatic enzyme activities than the control group of horses with small intestinal strangulating obstruction (SISO).[17] Over 50% of horses with proliferative enteropathy (PE) had biochemical evidence of hepatic disease (high GGT, aspartate aminotransferase [AST], or ALP activity). Horses with DPJ had a 12.1-fold higher risk of having a high GGT activity and a 1.8-fold risk of having a high AST activity than horses with SISO. AST activity in horses with PE ranged from 133 to 2994 IU/L (reference range 215.8 to 365 IU/L), GGT ranged from 7 to 117 IU/L (reference range 6.2 to 19.1 IU/L), and ALP ranged from 86 to 1103 IU/L (reference range 69.4 to 293.7 IU/L). Bile acid concentrations were rarely abnormal, indicating that hepatic failure was uncommon. Histopathologic evidence of liver pathology was a common feature in the horses with PE that had either biopsies or necropsies performed. Centrilobular necrosis and inflammation were noted in some cases.

Treatment Because the causative agent(s) of DPJ are unknown, treatment remains empiric and consists of aggressive supportive therapy. The continuous production of enterogastric reflux requires gastric decompression every 1 to 2 hours to relieve pain and to prevent gastric rupture. The stomach should be decompressed frequently, regardless of whether or not the horse is showing signs of abdominal pain, as these signs may be masked by severe depression or the administration of analgesic or antiinflammatory medications. Horses should receive nothing by mouth until small intestinal function has returned, recognized clinically by cessation or reduction of the nasogastric reflux to 1 to 2 L over a 4-hour period and increased frequency of borborygmi. The time necessary for gastric decompression varies with each patient. Repeated rectal examinations after the first day of therapy will inconsistently reveal distended loops of small intestine, depending on the frequency of removal of the reflux and the severity of the initial lesion. Ultrasonography may reveal fluid-filled small intestine when such bowel is not discernible by rectal palpation. Loops of small intestine are most frequently visualized in the ventral flank area, near the udder or prepuce; therefore this area should be examined in all cases of suspected small intestinal distention.

Intravenous administration of a balanced electrolyte solution is necessary to maintain intravascular fluid volume and cardiovascular performance. In some horses even rapid administration of fluid fails to adequately restore and maintain intravascular volume because of enteric fluid losses that can be as great as 8 L per hour. In addition, the very large volume of isotonic crystalloid fluid that must be given intravenously to keep pace with enteric fluid losses in horses with DPJ may accelerate the flux of fluid from the vasculature into the intestinal lumen because of reduced intravascular oncotic pressure, increased capillary perfusion pressure, and increased capillary permeability in the inflamed intestine. Consequently, the balance between adequate hydration and the volume of enterogastric reflux obtained requires careful and frequent monitoring.

Administration of colloid solutions may be of benefit in preserving intravascular volume without promoting enterogastric reflux. The most frequently used colloids in the horse include hyperimmune plasma and hydroxyethyl starch solutions. Plasma products require a large volume of administration to exert a colloidal effect, which is cost prohibitive in many cases. Smaller doses, however, may have a beneficial effect in horses with DPJ, particularly in animals showing signs of sepsis or endotoxemia. Hydroxyethyl starch solutions have been shown to significantly increase plasma oncotic pressure in ponies administered 10 mL/kg[30] and represent a reasonably priced alternative to plasma. These solutions have been associated with changes in the hemostatic profile in normal ponies at higher doses of 20 mL/kg[31] and should be used only with caution in horses already at risk for coagulopathies.

During the initial hours of therapy, even aggressive intravenous fluid administration may result in only moderate clinical improvement. A positive clinical response—as evidenced by improved hydration status, decreased heart rate, decreased enterogastric reflux, improved attitude, and improvement in parameters reflecting kidney function (decreased blood urea nitrogen [BUN] and serum creatinine)—correlates with resolving intestinal inflammation.

NSAIDs should be used judiciously to avoid masking the clinical signs of a potential surgical lesion. Flunixin meglumine can be used at a dose of 0.25 to 0.5 mg/kg PO every 6 hours to reduce the untoward effects of arachidonic acid metabolites.

Antimicrobial agents are typically administered to horses with DPJ, although the necessity for antimicrobial treatment in horses with DPJ is uncertain. Given the association of DPJ with *C. difficile,* administration of intravenous penicillin G sodium or potassium (22,000 to 44,000 IU/kg IV q6h) is warranted. Metronidazole also has excellent activity against *C. difficile;* however, administration is difficult because nothing can be administered per os. Rectal administration of metronidazole has been studied[32] and can be used in these cases. The dose and frequency of administration should be increased because bioavailability after rectal administration is much less than after oral administration (30% vs. 74%, respectively). Broad-spectrum antimicrobial treatment may be indicated in horses with low WBC counts, but care must be taken in selecting an antimicrobial to avoid potential adverse effects, particularly nephrotoxicosis with aminoglycosides in a dehydrated patient with compromised renal function.

Horses with DPJ may have to be kept from eating for several days and are often in a hypermetabolic state; therefore they rapidly develop a negative energy and nitrogen balance. In these horses parenteral nutritional support should be considered. Parenterally administered solutions containing glucose, balanced amino acid solutions, lipid emulsions, balanced electrolyte and trace minerals, and vitamins have been administered to adult horses with a variety of intestinal disorders, including DPJ. Providing for part of the horse's nutritional requirements (8000 to 12,000 kcal/day) is possible with glucose–amino acid solutions that are of moderate cost. The rationale for this treatment is that through provision of nutritional support to an anorectic, severely ill horse, the healing process will be facilitated, complications will be reduced, and the duration of hospitalization may be shortened. Thus the overall cost of providing nutritional supplementation, enteral or parenteral, to horses with DPJ may well be offset by quicker recoveries and diminished requirements for other costly treatments.

Prokinetic agents may also be useful in cases of DPJ. Of the available prokinetics, lidocaine is used most frequently.[33] A loading dose of 1.3 mg/kg slow intravenous bolus followed by a continuous infusion of 0.05 mg/kg/h has been shown to shorten the time of reflux and decrease the hospital stay in horses with DPJ.[34] It may do this by decreasing sympathetic tone, acting as an analgesic agent, or decreasing granulocyte infiltration in the intestinal wall. Its use should be reserved for horses in which a surgical lesion has been ruled out, as it can very effectively mask intestinal pain. Horses should be refluxed frequently during the infusion and checked for other signs of complications, such as laminitis, routinely. Metoclopramide, erythromycin lactobionate, and cisapride are also used in cases of DPJ.[33] The efficacy of prokinetics in this disease is debated, mainly because they require a healthy intestine in order to exert an effect. A more in-depth discussion of prokinetic agents can be found in the section on gastrointestinal ileus in this chapter.

Medical therapy is sufficient in most cases of DPJ; however, surgical exploration is sometimes necessary for definitive diagnosis, or if horses show uncontrolled pain, have prolonged nasogastric reflux (>7 days), excessive fluid losses that cannot be corrected with conventional fluid therapy, or clinical and laboratory findings strongly suggestive of an intestinal obstruction. Retrospective analysis

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comparing medical and surgical therapy of DPJ showed that surgical cases had a significantly decreased survival and a longer duration and larger total volume of nasogastric reflux. They were also more likely to develop complications such as diarrhea, and showed an increased rate of incisional infection compared with other horses operated on for other types of colic.[35]

Complications Complications of DPJ include septic peritonitis, myocardial and renal infarction, aspiration pneumonia, adhesions of the proximal small intestine, and laminitis. Animals with severe cases of DPJ may develop infarction of a segment of the small intestine that requires surgical removal. The prognosis for surviving the initial intestinal insult is good in cases of DPJ. The death and function losses from this disease are more commonly related to the secondary complications such as laminitis and intraabdominal adhesions. In one report, laminitis occurred in 28% of horses with DPJ, and associated factors were high body weight and hemorrhagic gastric reflux.[36] Laminitis prophylaxis is routinely incorporated into the medical therapy and can include cryotherapy, NSAIDs, topical glyceryl trinitrate, and DMSO (200 mg/kg given as a 10% solution in normal saline). In one study horses that received heparin as a prophylactic treatment for laminitis were less likely to develop clinical laminitis than horses that did not receive heparin.[36]

Equine Proliferative Enteropathy

Nicola Pusterla

Equine proliferative enteropathy (EPE) is a disease of foals caused by the obligate intracellular organism *Lawsonia intracellularis*. This disease affects mainly weanling foals and occasionally young adults and is characterized by fever, lethargy, peripheral edema, diarrhea, colic, and weight loss. The diagnosis of EPE may be challenging and relies on the presence of hypoproteinemia due to hypoalbuminemia, thickening of segments of the small intestinal wall observed on abdominal ultrasonography, positive serology, and molecular detection of *Lawsonia intracellularis* in feces. The disease has almost reached a worldwide occurrence and has been reported in the United States, Canada, Europe, South Africa, Australia, Brazil, and Japan.[37-41]

Epidemiology In pig populations, the chronic form of the disease is maintained by subclinically affected pigs or is established environmentally in some sites, allowing transmission of *L. intracellularis* to serial flows of pigs.[42] Mice and rats have been shown to be important reservoirs of *L. intracellularis* on pig farms with prevalences of animals testing positive on polymerase chain reaction (PCR) assays varying substantially between farms (4% to 83%).[43,44] Rodents appear to be suitable reservoir hosts because of their susceptibility to *L. intracellularis,* their close contact to domestic animals, and their high reproductive rate, and they maintain *L. intracellularis* across generations. The source of infection has not been determined for horses. Exposure to pig feces has been speculated as a potential source of infection for horses since the first reported cases of EPE. However, in most cases of EPE, no history or evidence of direct or indirect exposure to pigs or pig feces has been reported. Further, multilocus variable number tandem repeat (VNTR) profiles of pig and equine isolates differ greatly. A recent experimental study has shown host specificity for *L. intracellularis* isolates cultured from pig or horse intestines.[45] The study showed that clinical signs, longer periods of shedding, and stronger serologic immune responses were observed in animals infected with species-specific isolates. Previous studies have shown that a variety of wild and domestic animals (including dogs, cats, rabbits, opossums, skunks, mice, and coyotes) can shed *L. intracellularis* on farms with diagnosed EPE cases.[46,47]

Fecal-oral transmission of *L. intracellularis* has been documented in naive foals housed with clinically infected foals experimentally challenged with an equine isolate of *L. intracellularis*.[48] A recent study has shown that feces from experimentally infected rabbits with an equine isolate of *L. intracellularis* served as infectious material for weanling foals.[49] Although infected rabbits and foals remained asymptomatic, infection was supported by fecal shedding of *L. intracellularis* and detection of specific antibodies to *L. intracellularis*. Although the natural infectious dose for foals has not been determined, pigs receiving as low as 10^5 *L. intracellularis* organisms have been shown to develop infection.[50]

In piglets, large group size, weaning, transportation, diet change, and mixing have been associated with clinical disease. Predisposing factors such as the stress of weaning, overcrowding, decline in *L. intracellularis*–specific colostral antibodies, endoparasitism, and introduction of new animals have been suggested as factors in the development of EPE in foals.[37] In pigs, infection and fecal shedding of *L. intracellularis* may persist for as long as 12 weeks.[50] This is in sharp contrast to experimentally infected foals showing onset and duration of fecal shedding ranging from 10 to 14 days and 17 to 27 days, respectively.[48] Previous work has shown that *L. intracellularis* is likely to survive in environmental conditions for 1 to 2 weeks at 5° C to 15° C.[51]

Pathophysiology The mechanism of enteritis after infection with *L. intracellularis* involves invasion of the proliferating crypt cells in the ileum, causing excessive mitotic division and severe hyperplasia.[52,53] The hyperplastic mucosa becomes grossly thickened and develops a corrugated appearance. As would be expected, this thickening of the mucosa, along with the proliferation of immature crypt cells rather than mature villous cells, leads to a limited brush border development and a decreased absorptive capacity, which results in the weight loss and hypoproteinemia present in these cases. The organism can divide within the infected cells and migrate up to the mucosal layers as the cells proliferate and advance. The main differential diagnosis in these cases is *Rhodococcus equi* enteritis, which can also cause ulceration in the areas of Peyer patches throughout the small intestine, cecum, and colon.

Clinical and Laboratory Findings EPE manifests in characteristic signalment, seasonality, clinical signs, and blood work abnormalities. The disease is generally manifested in foals less than 1 year of age and in North America is often seen between August and February.[38] Although the disease is commonly seen in weanling foals 4 to 7 months of age, cases of EPE have been seen in young adults.[41] Lethargy, anorexia, fever (>38.5° C), peripheral edema (ventrum, sheath, throatlatch, and distal limbs), weight loss colic, and diarrhea are among the most common clinical findings in affected foals. Early clinical signs are generally unspecific and include mild depression, partial anorexia, and fever. Although diarrhea is commonly seen in affected foals and can vary from cow pie to watery, some affected foals may have normal fecal character. Fatal necrotizing enteritis associated with *L. intracellularis* has recently been reported with foals developing acute onset of clinical signs followed by rapid clinical deterioration and death caused by endotoxemia, bacteremia, or disseminated intravascular coagulation.[54]

Foals with EPE may also have concurrent disorders such as respiratory tract infections, gastric ulcerations, and intestinal parasitism. It must be kept in mind that signs of EPE may resemble those of more common gastrointestinal disorders such as parasitism, bacterial infections *(Clostridium* spp., *Salmonella* spp., *Rhodococcus equi*, *Neorickettsia risticii),* rotavirus, coronavirus, ulcerations, sand accumulation, intestinal obstruction, and intoxication with plants, chemicals, and pharmacologic agents such as NSAIDs or antimicrobials. Similar to pigs, the disease can be subclinical in foals and be manifested by a self-limiting and transient decrease of total serum protein concentration coupled with decreased daily weight gain when compared with unaffected foals.[48] It will remain to be determined if growth retardation or unthriftiness are associated with subclinical infection.

The most consistent laboratory finding of clinical EPE is hypoproteinemia due to hypoalbuminemia. Total protein is generally less than 5.0 g/dL and albumin is usually less than 2.0 g/dL. In a

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recent case report, hypoalbuminemia was the only consistent clinicopathologic abnormality of 57 affected foals with albumin concentrations ranging from 0.9 to 3.3 g/dL (normal reference range 2.7 to 4.2 g/dL).[38] The exact mechanisms by which hypoalbuminemia develops in affected foals have not been investigated. It appears that decreased feed intake, coupled with malabsorption and protein-losing enteropathy due to the proliferative nature of the disease, may explain why low albumin occurs.[55] Affected foals may also demonstrate nonspecific blood abnormalities such as anemia or hemoconcentration, leukocytosis or neutropenia, hyperfibrinogenemia, increased activity of muscle enzymes, and electrolyte abnormalities (hypocalcemia, hypochloremia, and hyponatremia). Urine analysis to rule out protein-losing nephropathy and cytologic evaluation of abdominal fluid to rule out protein lost to a third space are generally unremarkable.

Diagnostic Workup A presumptive diagnosis of EPE is generally made based on age of the affected animal, clinical signs, hypoproteinemia/hypoalbuminemia, presence of thickened small intestinal loops on ultrasonographic evaluation, and ruling out other causes of enteropathy and protein losses. Abdominal ultrasonography, although not very sensitive, may show segments of thickened small intestine and excessive abdominal fluid. In these cases, abdominocentesis will yield a noninflammatory transudate. An antemortem diagnosis is generally confirmed via PCR detection of *L. intracellularis* in feces or rectal swab and/or serologic findings.

It is essential to combine both molecular and serologic diagnostic testing, as these modalities have high analytical specificity but variable sensitivity depending on the situation. Negative PCR results can be expected if the fecal samples are collected from foals with prior antimicrobial treatment or during advanced disease stage, when *L. intracellularis* organisms are no longer expected in the feces. Negative serologic results can be expected in the early stage of the disease, when humoral immune responses are not yet strong enough to be detectable by serology. Further, differences in sensitivity among different PCR and serologic assays can lead to divergent results. Among PCR assays, the use of a real-time platform has been shown to yield the best sensitivity and to reduce the likelihood of crossover or carryover contamination (i.e., false-positive results).[56-58] Several serologic assays, including indirect fluorescent antibody test (IFAT), enzyme-linked immunosorbent assay (ELISA) and immunoperoxidase monolayer assay (IPMA), have been validated and established for pigs.[59-61] A comparative study using equine serum samples has shown that various serology assays are accurate; however, the IPMA is the most specific when determining the presence of anti–*L. intracellularis* antibodies in adult horses with EPE.[62]

Pathologic Findings Lesions are most frequently found in the distal jejunum and ileum, although diffuse thickening of the small intestine may occur.[52] Classically there is pronounced mucosal thickening with varying severity of ulceration and transmural edema. The affected bowel appears to be stiff, and the mucosal surface has a corrugated appearance. Mucosal pleocytosis is a common feature, but in different cases the predominating inflammatory cell type will differ. A lymphocytic or plasmacytic cellular infiltration may be present. There is crypt proliferation, accompanied by crypt elongation and epithelial hyperplasia. The villi are blunted and may become fused. Silver staining with Warthin-Starry stain reveals elongated, curved bacilli in the apical zone of the crypt epithelial cells.

Treatment It is important to treat affected animals early, before lesions become advanced and result in marked weight loss and critically low serum protein values. Treatment of EPE in horses involves the use of antimicrobials such as macrolides, alone or in combination with rifampin, chloramphenicol, oxytetracycline, doxycycline, or minocycline, administered for 2 to 3 weeks. The choice of antimicrobial in the treatment of EPE should take into account the risk of inducing disturbance of the gastrointestinal flora and renal toxicity. This is especially a concern when treating older foals with severe hypoalbuminemia. Supportive therapy with crystalloid fluids to correct dehydration, electrolyte imbalances, and azotemia secondary to fluid losses from profuse diarrhea is warranted. Colloidal support with plasma or hydroxyethyl starch solutions can help correct the edema and decreased colloid oncotic pressure. NSAIDs should be used with caution in foals showing signs of dehydration.

Prognosis in these cases is generally good with early and correct diagnosis of the problem. Therapy can be prolonged and should be continued until the diarrhea and hypoproteinemia have resolved and there is no longer evidence of thickened small intestine on ultrasound.

Concurrent medical conditions should also be addressed. Rapid clinical improvement following treatment is to be expected; however, it may take weeks for the hypoproteinemia to resolve. Spontaneous recovery of clinically infected foals has not been documented, and up to 93% of treated foals usually survive the disease.[38] Generally nonsurvivors develop complications associated with gastrointestinal translocation, gastrointestinal perforation, or kidney failure.[54] Frazer reported that clinically affected and successfully treated foals sold for an average of 68% of the average price of unaffected foals by the same stallion.[38] However, their monetary earnings from racing were not significantly different from those of other horses.[63]

Monitoring and Prevention Early recognition of clinical cases and separating them from the rest of the susceptible foals until full recovery or cessation of fecal shedding appears to be a logical biosecurity measure to prevent spread and environmental contamination. The monitoring of a herd with endemic EPE status includes the regular physical evaluation of resident foals and the monthly or bimonthly assessment of total protein concentration and monthly serologic status. Monitoring for exposure to *L. intracellularis* and hypoproteinemia/hypoalbuminemia should begin at least 4 weeks prior to the historical first detection of clinical cases.

The lack of epidemiologic data regarding potential natural reservoir hosts as well as the lack of information pertaining to the biology of *L. intracellularis* precludes the institution of any management changes on endemic farms. Further, maintaining good pest control and preventing non-equine domestic and wild animals from gaining access to feed and feeding areas may potentially minimize the risk of disease spread.

Prevention strategies have been best described in pigs using in-feed antimicrobials and a commercially available *L. intracellularis* vaccine.[64-66] Recent work has shown that detectable humoral and cellular responses can be measured in foals administered an avirulent live *L. intracellularis* vaccine.[67,68] The *L. intracellularis* vaccine has been shown to be safe and the administration well tolerated by the foals. A field efficacy trial performed on EPE endemic farms in central Kentucky in 2008 showed that vaccinated foals maintained higher daily weight gains and higher total protein concentrations when compared with a nonvaccinated, naturally seroconverted group.[69] Under experimental conditions, weanling foals vaccinated intrarectally with an avirulent live vaccine against *L. intracellularis* were protected against clinical and subclinical EPE following challenge exposure with a virulent *L. intracellularis* isolate of equine origin.[70] This was determined by lack of clinical disease, absence of hypoproteinemia and ultrasonographic abnormalities compatible with EPE, and a significant reduction in *L. intracellularis* fecal shedding in vaccinated foals compared with nonvaccinated foals. Further, average daily weight gains from the vaccinated foals over the entire study period were similar to those of the control foals and significantly higher when compared with those of the nonvaccinated foals, highlighting the benefit of the vaccine in the prevention of subclinical disease. The extralabel use of the *L. intracellularis* vaccine should be considered on naive and endemic farms in an attempt to reduce or prevent EPE. Timing of vaccine administration should again be synchronized with historical disease occurrence. Further, routine monitoring for clinical signs and hypoproteinemia/hypoalbuminemia is still recommended even when vaccine prophylaxis is used.

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Rhodococcus equi Enteritis

Rhodococcus equi most frequently causes a severe pyogranulomatous pneumonia in foals 2 to 3 months of age. Extrapulmonary disorders (EPDs) have been associated with *R. equi* infection in foals, and the presence of EPDs is associated with an increase in mortality. Gastrointestinal EPDs may occur in as much as 50% of cases. Diarrhea is reported to occur in up to 33% of *R. equi* cases. Enterocolitis and typhlitis have been reported in 31 of 150 foals from one study. Intraabdominal abscesses (25 of 150) and abdominal lymphadenitis (25 of 150) were also reported in that same study. Septic peritonitis was present in 11 of 150 foals.[71]

Pathophysiology Intestinal infection with *R. equi* can occur through either fecal-oral transmission or swallowing of infected sputum. The organism invades and reproduces within the macrophages, causing a pyogranulomatous disease. In a survey of normal foals on two different farms, *R. equi* was shed in the feces of 16 of 17 and 19 of 26 foals, respectively.[72] Only two foals developed clinical signs of intestinal disease, and the shedding of bacteria in the feces increased threefold to fourfold during those times. Such foals, as well as adults, are likely the source of repeated contamination on endemic farms. Whether or not the organism causes disease is based on the presence of virulence factors, particularly VapA, which has been most commonly associated with disease in pneumonic foals.

Clinical and Laboratory Findings Foals diagnosed with *R. equi* enteritis typically manifest the signs of pneumonia first, although foals in which the enteric form is the major pathology have been reported.[73] With the enteric form of the disease, diarrhea, weight loss, and colic are present. Foals are often febrile, anorectic, and depressed. Typical clinicopathologic findings include leukocytosis with neutrophilia and severe hyperfibrinogenemia. Ultrasound of the abdomen may reveal pyogranulomatous abscesses in the lymph nodes.

A diagnosis of *R. equi* enteritis can be presumed in pneumonic foals showing signs of gastrointestinal disease that culture positive for *R. equi* in transtracheal wash fluid. *R. equi* can also be cultured from the feces, small intestinal luminal contents, or, occasionally, the peritoneal fluid of affected animals. A PCR based on the *vapA* gene has been developed and can be used as an adjunct diagnostic in these cases.[74]

Pathologic Findings The most common small intestinal lesion is multifocal ulcerative enteritis in the area of the Peyer patches of the ileum. Other parts of the small intestine may be affected, with lesions present throughout the entire small intestine.[74] These lesions frequently extend into the cecum and colon as well. A suppurative exudate is also present, along with pyogranulomatous inflammation of the mesenteric lymph nodes. Co-infection with *L. intracellularis* has also been reported to occur.[75]

Treatment Treatment of *R. equi* enteritis is similar to treatment of *R. equi* pneumonia. Erythromycin estolate (25 mg/kg PO q6-8h) or erythromycin phosphate (37.5 mg/kg PO q12h) combined with rifampin (5 to 7.5 mg/kg PO q12h) has been the traditional treatment for these foals, and it is still effective but requires a long duration of treatment and is difficult for owners to administer because of the frequency of the treatments. Alternative treatments include azithromycin (10 mg/kg PO q24h for 5 days, followed by q48h) and clarithromycin (7.5 mg/kg PO q12h). To prevent relapses it is very important to continue treatment until the hematologic abnormalities and radiographic or ultrasonographic examinations have returned to normal.

Complications Complications associated with *R. equi* enteritis include septic peritonitis and the development of intestinal adhesions. These may lead to death of the animal or chronic abdominal problems in those that survive. Therapy is often prolonged in these cases, and owners should be warned that foals with extrapulmonary disorders associated with *R. equi* pneumonia have a more guarded prognosis.[71]

Enteric Pythiosis

Pythium spp. are protistal organisms that belong to a group of phycomycotic organisms that also includes *Conidiobolus* and *Basidiobolus* spp. They are a frequent cause of severely pruritic cutaneous granulomas in horses along the Gulf Coast and southern United States. Much less frequently, the disease can cause granulomatous lesions in the small intestine.

Pathophysiology *Pythium* spp. are presumed to be transmitted via contact with contaminated water. Once ingested, the organisms are thought to penetrate the intestinal mucosa through an existing lesion, because necrotic tissue is considered chemotactic.[76] *Pythium* spp. may be able to penetrate healthy tissue, however, because some cases in dogs have been reported to have mesenteric lymph node involvement without any mucosal lesions.[77]

Clinical and Laboratory Findings Four reports of enteric pythiosis can be found in the literature.[78-81] In all cases, masses occurred in the mid to distal jejunum. One horse died suddenly, one was euthanized during surgery, and two were successfully treated with a jejunal resection. Organic iodide therapy was instituted in one horse postoperatively for 30 days. In three cases clinical signs of intestinal disease had been present for several months before diagnosis. Chronic colic, weight loss, inappetence, and ill thrift have all been reported and could be related to the intestinal lesion. None of the reported animals had skin lesions. Hematologic evaluation was nondiagnostic in the three cases in which it was performed.

Grossly, lesions are caseous with discrete yellow foci ("kunkers"), and the intestinal wall is thickened because of a pyogranulomatous inflammation. Microscopically, a diffuse, mixed inflammatory infiltrate, along with granulation tissue, is found in the submucosa, tunica muscularis, and mesenteric attachments. Culture of the organism is difficult in these lesions; however, an indirect immunoperoxidase technique to stain for *Pythium*-positive hyphae is available in some laboratories.[80]

Treatment Treatment of phycomycetes is often difficult. They are not true fungi; therefore they are resistant to many antifungal drugs. Systemic amphotericin B is only rarely effective in treating the cutaneous disorder. Organic iodides are inexpensive and safe when administered orally, but the mechanism of action as an antimicrobial drug is not understood, and the efficacy of this compound to treat this disease has not been proven. A vaccine can be formulated against the organism, and this has been shown to shrink the lesions in horses with cutaneous disease. Whether or not it would work in enteric disease is unknown at this time. In addition, premortem or presurgical diagnosis of the disease is extremely difficult, making surgical resection and biopsy the most effective treatment.

Inflammatory Bowel Disease

Several intestinal disorders characterized by inflammatory cell infiltration have been placed under the umbrella of inflammatory bowel disease (IBD), including granulomatous enteritis, multisystemic eosinophilic epitheliotropic enterocolitis, eosinophilic enterocolitis, lymphocytic-plasmacytic enteritis, and basophilic enterocolitis.[82-88] IBD in humans is typically characterized by a neutrophilic inflammation, but neutrophils are just the effector cell in a highly complex disease process.[89] The syndromes described for equine inflammatory intestinal disorders therefore appear to differ from those of human IBD; given the different types of cellular infiltrates found in affected horses, these disorders presumably reflect different pathophysiologic mechanisms. Thus use of the term *inflammatory bowel disease* is not intended to imply either a similarity to the condition described in

human beings or similarity among the various syndromes described in horses.

Clinical and Laboratory Findings Horses with IBD typically have progressive weight loss despite a good appetite and have intermittent abdominal discomfort. If the disease predominates in the small intestine, diarrhea may not be a feature. In some cases there will be associated dermatitis.[90] Horses often present with peripheral edema secondary to hypoproteinemia from enteric protein losses. Ultrasonographic examination may reveal thickened small intestine (>5 mm wall diameter).

Clinicopathologic abnormalities may include anemia, hypoalbuminemia, hypoproteinemia, and malabsorption of glucose and D-xylose. Hypoalbuminemia in the absence of proteinuria or severe liver dysfunction is consistent with protein-losing enteropathy. Some horses may have a relative gammopathy. Serum electrolyte concentrations and total CO_2 are usually normal. Subclinical disseminated intravascular coagulation with thrombocytopenia and increased fibrinogen degradation products have been identified in horses with chronic enteritis.[85,91] Serum antibodies to gluten have been detected in horses with IBD, as well as those on a gluten-rich diet.[92] This suggests a potential pathogenic role of gluten in at least some cases of equine IBD, and dietary changes may play an important role in treatment.

In many horses inflammatory cells infiltrate throughout the intestinal tract. Therefore rectal mucosal biopsy may be useful to identify cases of IBD in horses.[93] If the proximal duodenum is involved, endoscopic biopsies can be used for diagnosis (Fig. 32-71). A definitive diagnosis often requires biopsy of the small intestine, large intestine, or both. With appropriate instruments this can be done by laparoscopy, although an exploration via a ventral midline approach permits a more thorough evaluation of the abdomen. In most horses cellular infiltration can be found to varying degrees throughout the intestinal tract.

Histopathologic evaluation of biopsy specimens can be used to differentiate among the various IBDs reported in horses, based on the following criteria.[86] A diagnosis of granulomatous enteritis is made when aggregates of macrophages and epithelioid cells are found in the mucosa, submucosa, or both, along with villous atrophy. In lymphocytic-plasmacytic enterocolitis, lymphocytes and plasmacytes are present in the lamina propria, and villous atrophy usually occurs. For multisystemic eosinophilic epitheliotropic disease, eosinophils, lymphocytes, and macrophages are found in the mucosa and submucosa. In rare cases, basophils have also been reported.

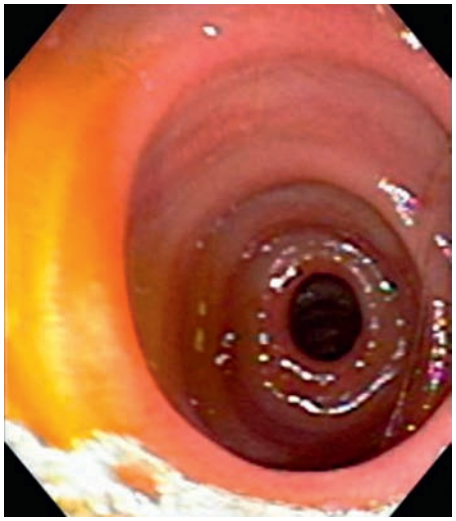


FIG. 32-71 Endoscopic view of the duodenum in a horse with lymphocytic-plasmacytic enteritis. Note the heterogeneous appearance of the duodenal mucosa.

IBD syndrome, termed *idiopathic focal eosinophilic enteritis* (IFEE), involves focal areas of eosinophilic inflammatory infiltrates within the small intestine.[88,94-98] Affected horses typically are examined not because of chronic weight loss or diarrhea, but rather as acute colic cases. Hypoproteinemia and malabsorption are not present. The lesions are intramural masses or circumferential mural bands. Eosinophils with or without lymphocytes are seen infiltrating all layers of the intestine, with varying degrees of fibrosis.[98] Further characterization of the inflammatory lesions indicate that IFEE most likely represents a focally exacerbated inflammatory reaction in horses with diffuse eosinophilic enteritis.[97] No underlying cause of the disease has been found, although food allergy, parasitism, and *Pythium* spp. have all been suggested.[98] The incidence, or at least the diagnosis, of this disease appears to be increasing.

Treatment and Prognosis Because the specific diseases included under the general category of IBD are quite different, a generalized treatment recommendation cannot be made. Most reported cases of IBD in horses have been fatal, even with aggressive treatment with corticosteroids. Classically reported cases of eosinophilic, lymphocytic, and basophilic enteritis have failed to respond to treatment. If treatment is attempted, immunosuppressive doses of dexamethasone, up to 0.2 mg/kg, once daily are recommended. Successful remission of granulomatous enteritis was reported in one patient that was treated with dexamethasone[99]; however, in the vast majority of cases treatment is unsuccessful. Cases of IFEE should be differentiated from other types of IBD with regard to treatment and prognosis. These cases frequently respond to surgical decompression without resection if circumferential mural bands are the only lesion present.[98] In cases of intramural masses, surgical resection of the lesions usually resolves the problem.[96] Other treatments attempted include anthelmintic drugs with larvicidal activity, hydroxyurea, metronidazole, clioquinol (iodochlorhydroxyquin), and sulfasalazine.[100]

Neoplasia

Primary and secondary neoplasia involving the alimentary tract of horses is relatively uncommon, although several cases have been reported.[101] Typical signs associated with, but not diagnostic for, small intestinal neoplasia include colic and weight loss. In most horses with focal intestinal neoplasia the problem becomes apparent when only lumen obstruction develops. Lymphosarcoma can be disseminated throughout a large portion of intestine, eventually resulting in a malabsorption and weight loss syndrome. Lymphosarcoma affects horses of all ages and can be manifested as an enteric disorder, as well as affecting other systems.[102] The diagnosis of enteric lymphosarcoma can occasionally be made on the basis of cytologic examination of fluid obtained by abdominocentesis. In other cases intestinal biopsy is required to diagnose the neoplastic disorder. The prognosis is best if the tumor is discrete and can be removed surgically. A combination chemotherapy protocol of cytarabine (170 mg/m^2 IM), cyclophosphamide (142 mg/m^2 IV), and prednisolone (86 mg/m^2 PO q48h) has been reported to be effective in the treatment of mixed-cell thoracic lymphoma.[103] In other cases, corticosteroid therapy may induce clinical remission for several months, although it is not curative.

Other neoplasms affecting the small intestine are unusual, typically arising from the wall of the bowel, and include adenocarcinoma,[104] leiomyosarcoma,[105] and neurofibroma.[106] These tumors often result in intestinal obstruction and signs of abdominal discomfort. Discrete tumors may be surgically removed.

Paraneoplastic syndromes may be the first sign of neoplastic processes in the horse. Pemphigus, hypoglycemia, hypercalcemia, erythrocytosis, and neuropathies have all been associated with tumors in horses.[107] Paraneoplastic processes may also lead to intestinal tract dysfunction in horses with extraintestinal tumors. Amyloid deposition secondary to multiple myeloma in a horse has been described.[108]

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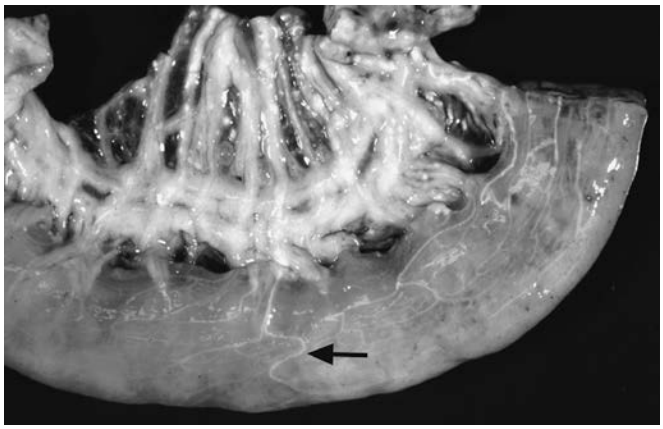


FIG. 32-72 Section of small intestine from a foal with chyloabdomen and a *Rhodococcus equi* abdominal abscess. Mesenteric lymphatics are distended with white chyle, as are serosal lymphatics. *(Courtesy Dr. M.J. Murray.)*

Small Intestinal Fibrosis

Small intestinal fibrosis is a rare syndrome that causes weight loss, chronic colic, and progressive debility in horses and ponies. Clusters of affected animals are reported in Colorado[109,110]; however, newer reports have been published in horses from Missouri.[111] The pathophysiology behind the fibrosis is not known, although ingestion of toxins (*Convolvulus arvensis* or common bindweed), inhibitors of 11β-hydroxysteroid dehydrogenase, or compounds with mineralocorticoid activity has been suggested.

Rectal palpation typically reveals thickening of the small intestinal wall, which may be confirmed by ultrasound.[110] Grossly, the overall length of the intestine may be shortened by as much as 50%.[109,110] The histologic lesions include arteriosclerosis, capillary endothelial hypertrophy, extensive fibrosis of the submucosa, and hypertrophy of the muscularis mucosae and tunica muscularis.[109] The prognosis for the disease is determined by the length of the intestine that is involved. Surgical resection may be attempted.

Lymphangiectasia and Chyloabdomen

There are few reports of lymphangiectasia and chyloabdomen in the literature. Lymphangiectasia is dilation of the lymphatics of the small or large intestine (Fig. 32-72), usually caused by an abscess[112] or neoplasia. There are reports of chyloabdomen resulting from congenital lymphatic defects in a neonatal foal, intraabdominal abscesses in a foal, and abdominal adhesions in a miniature horse.[112-114] Typically, thickening of the intestinal wall and leakage of chyle into the peritoneal cavity results from obstruction or rupture of the lymphatics. Animals can have signs that include abdominal discomfort, diarrhea, and chronic weight loss. Diagnosis is made on the basis of abdominal fluid analysis and ultrasonography. Chylous abdominal fluid appears milky and may contain a high percentage of lymphocytes. Ultrasonograms may reveal segments of thickened small intestine. Diagnosis is confirmed at surgery or postmortem examination, and treatment, if possible, is usually surgical, although in my experience medical resolution of the effusion has been achieved.

Surgical Disorders of the Small Intestine

Anthony T. Blikslager • John F. Marshall

Simple Obstruction

Simple intestinal obstruction is a physical obstruction of the lumen without obstruction of vascular flow. The most common causes are intraluminal masses composed of feed material (e.g., ileal impaction) or accumulation of parasites (e.g., ascarid impactions). There are other instances in which the bowel is obstructed without associated compromise of blood supply, most commonly by extraluminal compression by a mass or band of tissue in horses with intraabdominal adhesions. The large volume of fluid entering the small intestinal lumen on a daily basis[1,2] causes the obstructed intestine to become distended. Therefore, although the blood supply is not directly involved in simple obstructions, progressive and marked distention can result in decreased mural blood flow[3,4] and eventual necrosis of tissues.[5]

Ascarid Impactions

Impactions caused by *Parascaris equorum* typically occur in weanling foals (median age, 5 months; range, 4 to 24 months) that have been on a poor deworming program and that are administered an anthelmintic when they have a heavy parasite burden.[6] Products that cause sudden ascarid paralysis or death, including piperazine, organophosphates, and pyrantel pamoate, have been incriminated.[7] However, it is likely that any effective broad-spectrum anthelmintic, such as the avermectins, will have the same effect. Clinical signs include variable onset of colic after administration of an anthelmintic (usually within 1 to 5 days) and signs compatible with small intestinal obstruction, including nasogastric reflux.[6] The onset of the disease varies according to the degree of obstruction.[7] Diagnosis may be tentatively based on the history in a foal that appears unthrifty, has been recently dewormed, and has signs referable to small intestinal obstruction. The presence of dead ascarids in nasogastric reflux would raise the index of suspicion of this particular form of obstruction.[6] Abdominal radiographs or ultrasound will likely indicate the presence of multiple loops of distended small intestine but neither is needed if clinical signs indicate the need for immediate surgery. Surgical treatment typically involves an enterotomy made over the intraluminal impaction and removal of ascarids.

Although simple intestinal obstruction tends to carry a favorable prognosis for survival, ascarid impaction is a notable exception. The mortality rate in these cases is high (up to 92% in one study) as a result of severe intestinal compromise, peritonitis, and development of adhesions. The severe intestinal compromise is almost entirely attributable to the duration of impaction, which, for unknown reasons, is not as readily recognized in foals as it is in adults. Reasons for this could include failure of the owner or farm manager to recognize colic in foals or failure on the part of the owner or veterinarian to recognize the implications of colic in foals. Although foals readily display signs of colic, other medical causes of colic such as gastric ulcer disease or enteritis might be higher on the list of differential diagnoses than for adults. Second, the size of a foal may make episodes of colic appear more manageable than in adults, in which colic-induced trauma, especially to the head, may force the issue of referral and surgery at an earlier stage. This is speculative, but early intervention in foals with ascarid impaction would likely result in dramatic reductions in the reported mortality rate.[6] However, more recent reports indicate an increasing survival rate. For example, one report indicated that 80% of horses (12 of 15 horses studied) survived to discharge and 60% (6 of 10 for which follow-up data were available) survived for at least 1 year.[8] This improvement was related to changing the surgical technique to manually evacuating ascarids into the cecum rather than performing an enterotomy.[8] However, many cases have multifocal and marked impaction by ascarids that are large and difficult to manipulate. Whether or not an enterotomy is needed may therefore relate to the initial severity of disease.

Ileal Impaction

Ileal impactions occur most commonly in adult horses in the southeastern United States. Although feeding of coastal Bermuda hay has been implicated in the regional distribution of this disease, it has been difficult to separate geographic location from regional hay sources as risk factors.[9] However, a study from the southeastern United States showed that feeding coastal Bermuda hay and failing

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to deworm with an anthelmintic with efficacy against tapeworms are significant risk factors for ileal impaction.[10] Furthermore, in a study performed in the United Kingdom, horses with evidence of tapeworm infection were at risk for developing ileal impaction.[11] Signs are typical for an adult horse with small intestinal obstruction, including onset of moderate to severe colic and palpable loops of distended small intestine per rectum as the condition progresses. As the ileum is the most distal aspect of the small intestinal tract, nasogastric reflux may take a considerable time to develop and is found in only approximately 50% of horses requiring surgical correction of ileal impaction.[12,13] The diagnosis is usually made at surgery, although an impacted ileum may be palpated per rectum.[14] However, multiple loops of distended small intestine frequently make the impaction difficult to palpate. Nonetheless, clinicians working in the southeastern United States who evaluate horses with cases of mild or moderate colic that have a history of eating coastal Bermuda hay, and in which distended loops of small intestine can be detected adjacent to the cecum, should have ileal impaction high on the list of differential diagnoses. Ileal impactions may resolve with medical treatment. In particular, horses with clinical signs compatible with obstruction of the small intestine and normal abdominal fluid should be treated medically unless pain is unmanageable or subsequent abdominal fluid samples indicate intestinal compromise. In those cases in which surgery becomes necessary, fluids (2 to 3 L) can be directly infused into the mass, allowing the surgeon to break down the impaction. However, extensive small intestinal distention and intraoperative manipulation of the ileum frequently leads to postoperative ileus (POI).[15] Therefore some surgeons now elect to perform an enterotomy and to flush the contents from the intestinal lumen with minimal manipulation. Although early studies indicated a guarded prognosis,[13] a more recent study indicates that the prognosis is excellent for both medically and surgically managed ileal impactions.[16]

Ileal Hypertrophy

Ileal hypertrophy is a disorder in which the muscular layers (both circular and longitudinal) of the ileum hypertrophy for unknown reasons. Parasitism has been implicated, particularly for those parasites that tend to localize to the ileum (such as tapeworms),[17] but this has never been proven. In some cases the jejunum may also be hypertrophied, either alone or in combination with the ileum.[18] It is clear from these findings that initial functional obstruction initiates this syndrome, causing the musculature of the intestine to hypertrophy in order to push intestinal contents aborally, but there is no evidence as to the mechanisms of this disease. Clinical signs include chronic intermittent colic as the ileum hypertrophies and gradually occludes the lumen. In one study partial anorexia and chronic weight loss (1 to 6 months) were documented in 45% of the horses.[19] The diagnosis is usually made at surgery, although in some cases the hypertrophied ileum may be palpated per rectum or seen on ultrasonographic evaluation of the abdomen.[19] For treatment, an ileocecal or jejunocecal anastomosis to bypass the hypertrophied ileum is performed. Without surgical bypass, intermittent colic persists, and the thickened ileum may ultimately rupture. According to one recent report of 11 horses with hypertrophy of the ileum, only 1 horse survived, indicating a poor prognosis. The most common reason for euthanasia was spontaneous ileal rupture.[18]

Meckel Diverticulum

A Meckel diverticulum is an embryonic remnant that may become impacted. The diverticulum arises from the vitelloumbilical duct, which fails to completely atrophy, and becomes a blind pouch projecting from the antimesenteric border of the ileum.[20,21] Occasionally an associated mesodiverticular band may extend from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated. Mesodiverticular bands may also originate from the embryonic ventral mesentery and attach to the antimesenteric surface of the bowel, thereby forming a potential space within which intestine may become entrapped (Fig. 32-73).[22] Clinical signs range from chronic colic for an impacted Meckel diverticulum to acute severe colic if a mesodiverticular band strangulates intestine. The diagnosis is made at surgery, and treatment requires resection of the diverticulum and any associated bands.[23]

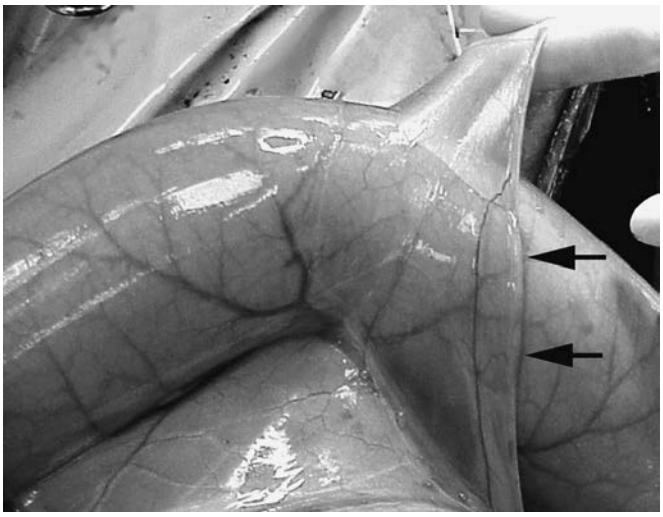


FIG. 32-73 Jejunal mesodiverticular band. This anomaly was discovered in this horse as an incidental finding during exploration of the abdomen. Intestine may become entrapped within the mesenteric pocket formed by the attachment of the ventral to the dorsal mesentery *(arrows)*.

Strangulating Obstruction

Strangulation obstruction of the intestine is characterized by simultaneous occlusion of the intestinal lumen and its blood supply. Although strangulation of the intestinal lumen results in clinical signs similar to those of simple obstruction, occlusion of the blood supply results in a more rapid deterioration of the intestinal mucosa and subsequent onset of endotoxemia. Therefore clinical signs (including pain, heart rate, mucous membrane color, and capillary refill time) are typically more severe, and the prognosis is less favorable.

A great deal of work has been done to characterize mucosal injury that occurs during strangulation[24,25] and reperfusion.[26] In general, the lesion that develops during strangulation is severe, leaving little viable bowel for further injury during reperfusion.[27] The severity of the ischemic lesion is partly attributable to the fact that in most cases initial occlusion of veins and partial occlusion of arterial blood supply during strangulation induces a hemorrhagic lesion. This results in extensive congestion and mucosal degeneration (Fig. 32-74).[24] Bowel peripheral to the strangulating lesion may also become injured as a result of distention.[28] In addition, distended small intestine that remains viable after surgical correction of strangulation may be subject to reperfusion injury through the generation of reactive oxygen metabolites after surgical correction of the lesion.[29] While attempts at reducing mucosal injury in the horse with antioxidants have met with some success,[30] their clinical use is limited.

The prognosis for survival in horses with small intestinal strangulating obstruction (SISO) is generally lower than with most other types of colic. A number of studies have reported short-term survival rates for horses with SISO of between 55% and 84%. A large single-center study that included 147 horses with small intestinal disease found that short-term survival rate was significantly lower for horses with SISO (54.8%) than for those with a simple obstruction (79.6%).[31] In contrast, a review of 74 horses found no significant difference in short-term survival rate between horses with SISO (84%) and those with a simple obstruction (91%).[32] When communicating with owners, it is important to discuss potential postoperative complications and long-term survival rates. Studies following horses after discharge from the hospital have found significantly lower survival

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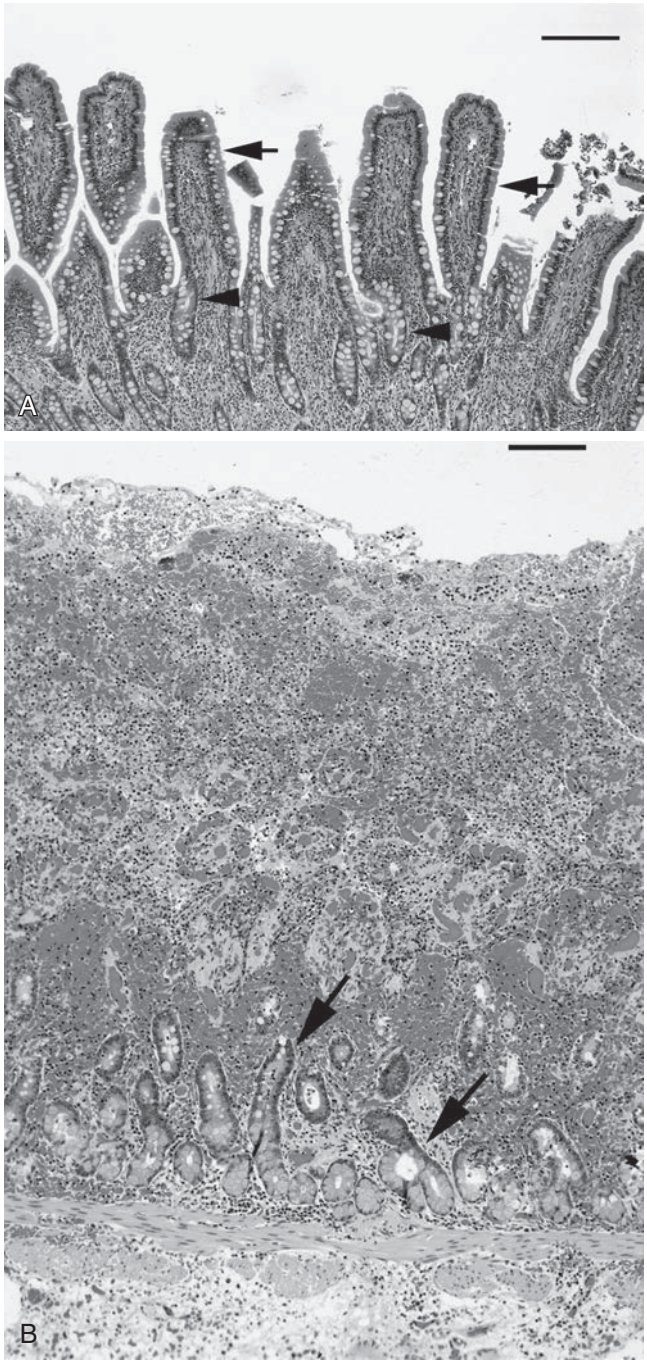


FIG. 32-74 Histologic appearance of normal and strangulated jejunal mucosa. **A,** Normal equine jejunal mucosa, with extensive villi *(arrows)* and mucosal crypts *(arrowheads).* **B,** Hemorrhagic strangulating lesion of the jejunum, with complete loss of villi and extensive hemorrhage. Note the presence of crypts *(arrows),* which remain relatively undamaged. (1 cm = 100 µm.)



FIG. 32-75 Intraabdominal adhesion in a foal. Note the presence of a mature fibrous adhesion between two segments of jejunum *(arrows)* that resulted in kinking and partial obstruction of affected intestine.

rates after 12 months ranging from 47% to 68%.[32-35] Episodes of colic are the most frequently reported complication following discharge[34,36] and are significantly more common in horses with small intestinal obstruction than those with large colon disease.[34] A significant reason for repeated episodes of colic and reduced long-term survival in patients that have had small intestinal surgery is intraabdominal adhesions (Fig. 32-75). For example, in one study 22% of horses undergoing small intestinal surgery required further surgery or were euthanized because of adhesions, and only 25% of horses that had a clinical problem with adhesions survived.[37] A more recent study of 99 horses requiring repeat celiotomy found that intraabdominal adhesions were the most common pathologic finding.[38] However, in this study horses with small intestinal lesions were not more likely to develop adhesions than those with large colon lesions and horses with adhesions were no less likely to survive than those without.[38]

Epiploic Foramen Entrapment

The epiploic foramen is a potential opening (because the walls of the foramen are usually in contact) to the omental bursa located within the right cranial quadrant of the abdomen. It is bounded dorsally by the caudate process of the liver and caudal vena cava and ventrally by the pancreas, the hepatoduodenal ligament, and the portal vein.[39,40] Clinical signs include acute onset of severe colic with examination findings compatible with small intestinal obstruction. Although the condition was reportedly more prevalent in older horses, recent studies have not detected an age predilection.[41] However, studies have detected a seasonal pattern for this disease. Specifically, more horses appear to suffer from epiploic foramen entrapment during the fall and winter months, which may reflect management practices.[42] An additional factor associated with epiploic foramen entrapment is crib-biting. One possible reason for this association is the development of negative intrathoracic pressure during cribbing, which might then result in cranial movement of intestine into the vicinity of the epiploic foramen. The association between crib-biting and epiploic foramen entrapment has been shown in separate studies performed in the United Kingdom and the United States.[43]

The diagnosis is definitively made at surgery, although ultrasonographic findings of distended loops of edematous small intestine adjacent to the right middle body wall are suggestive of epiploic foramen entrapment.[39] Entrapped small intestine may enter the foramen from the visceral surface of the liver toward the right body wall or in the opposite direction. However, in the vast majority of cases the intestine enters the foramen in a left-to-right direction.[39,44] Entrapped small intestine may be limited to a portion of the intestinal wall (parietal hernia).[45] In addition, the large colon may become entrapped within the epiploic foramen.[46] In treating epiploic foramen entrapment, the epiploic foramen must not be enlarged either by blunt force or with a sharp instrument, because rupture of the vena cava or portal vein and fatal hemorrhage may occur. In addition, excessive force used to extract entrapped bowel during surgery may also result in rupture of a mesenteric branch of the cranial mesenteric

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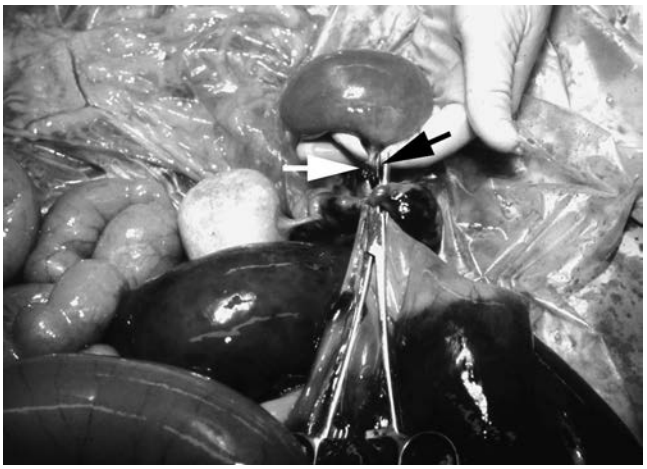


FIG. 32-76 Strangulating lipoma of the ileum. A lipoma, together with its mesenteric stalk *(arrows)*, has become intertwined with a loop of the ileum, resulting in a hemorrhagic strangulating obstruction.

artery. The finding of intraabdominal hemorrhage in some cases of epiploic foramen entrapment before surgery may result from compromise of the mesenteric blood supply rather than the major blood vessels that border the epiploic foramen. Prognosis has substantially improved over the past 25 years, with short-term survival rates (discharge from the hospital) ranging from 74% to 95% in the most recent studies.[39,47,48]

Strangulation by Mesenteric Pedunculated Lipoma

Lipomas form between the leaves of the mesentery as horses age, and mesenteric stalks develop as the weight of the lipoma tugs on the mesentery. The stalk of the lipoma and a loop of small intestine or small colon may become intertwined, causing strangulation (Fig. 32-76). Strangulating lipomas should be suspected in mature horses (>10 years old) with acute colic referable to the small intestinal tract.[49] In addition, geldings and ponies appear to be at risk for developing strangulating lipomas,[50] possibly because of differences in fat metabolism. One study documented a case of strangulating lipoma in a much younger patient, indicating that although the aging process is associated with development of lipomas, this disease cannot be ruled out preoperatively purely on the basis of age.[51,52] The diagnosis is usually made at surgery.

Treatment involves surgical resection of the lipoma and strangulated bowel, although strangulated intestine is, on occasion, viable. Studies indicate that approximately 60% to 78% of horses are discharged from the hospital after surgical treatment.[49,53,54]

Small Intestinal Volvulus

A volvulus occurs when a segment of small intestine is twisted greater than 180 degrees along the axis of the mesentery. Small intestinal volvulus is theoretically initiated by a change in local peristalsis, but the mechanisms of this disease are unclear.[55] It is reportedly one of the most commonly diagnosed causes of small intestinal obstruction in foals.[56] It has been theorized that young foals may be at risk for small intestinal volvulus because of changing feed habits as they adapt to a forage-based adult diet. However, a report of 115 cases of small intestinal volvulus found that 74% of the cases were aged 3 years or older.[57] Onset of acute, severe colic, a distended abdomen, and radiographic or ultrasonographic evidence of multiple loops of distended small intestine in a young foal would be suggestive of small intestinal volvulus. However, volvulus is not possible to differentiate from other causes of small intestinal obstruction preoperatively.

In adult horses, volvulus frequently occurs in association with another disease process, during which small intestinal obstruction results in distention and subsequent rotation of the small intestine around the root of the mesentery (e.g., in horses that have strangulation caused initially by a pedunculated lipoma). Although any segment of the small intestine may be involved, the distal jejunum and ileum are most frequently affected, most likely because the mesentery is longer in the more distal bowel. The diagnosis is made by palpating a twist at the origin of the cranial mesenteric artery during surgical exploration. Treatment includes resection of devitalized bowel, which may not be an option because of the extent of small intestinal involvement. For example, if complete volvulus of the small intestinal tract occurs, the only option would be to untwist the intestine and hope that the bowel was sufficiently viable to survive the disease process. This would in turn depend on the duration of disease and the extent of intestinal ischemia (i.e., how tightly the intestine twisted as the volvulus developed). Prognosis is based on the extent of small intestine involved and its appearance after surgical correction of the lesion.[58] For example, the degree of sepsis may relate to the surface area of devitalized tissue. In addition, the length of the time it takes to complete the surgery can become problematic, particularly in patients with sepsis, in which it is difficult to maintain adequate arterial blood pressure. Nonetheless, survival in patients with extensive small intestinal resection may not relate to the absolute length of intestine resected.[59] The prognosis for short-term survival is good; one study suggested that 80% of horses are discharged following surgery.[31]

Inguinal Hernia

Inguinal hernias are more common in Standardbred and Tennessee Walking horses, which tend to have congenitally large inguinal canals. Inguinal hernias may also occur in neonatal foals, but they differ from hernias in mature horses in that they are typically nonstrangulating. Typical historical findings in mature horses with inguinal hernias include acute onset of colic in a stallion that has recently been used for breeding. A cardinal sign of inguinal herniation is a cool, enlarged testicle on one side of the scrotum.[60,61] This is attributable to occlusion of the testicular blood supply in most cases rather than strangulated intestine within the scrotum itself. Inguinal hernias can also be detected on rectal palpation, and ultrasound of the testicle is very helpful in determining the diagnosis, particularly considering the differential diagnosis of testicular torsion. The nature of the hernia (direct versus indirect) is determined by the integrity of the parietal vaginal tunic. In horses in which the bowel remains within the parietal vaginal tunic, the hernia is said to be indirect, because the bowel remains within the peritoneal cavity. Direct hernias are those in which bowel ruptures through the parietal vaginal tunic and occupies a subcutaneous location, followed by strangulation. Direct hernias most commonly occur in foals and should be suspected when a congenital inguinal hernia is associated with colic, swelling that extends from the inguinal region of the prepuce, and intestine that may be palpated subcutaneously.[62,63] Although most congenital indirect inguinal hernias resolve with repeated manual reduction and/or application of a diaper, surgical intervention is recommended in foals with congenital direct hernias in order to reduce the hernia as well as repair the parietal vaginal tunic.

In stallions with indirect inguinal hernias, herniated bowel can be manipulated through the rectum to reduce the hernia, but this procedure is not generally recommended because of the risk of a rectal tear. In addition, the inability to visually assess the integrity of the bowel may be problematic. However, in many cases taken to surgery the short segment of herniated intestine will markedly improve in appearance once it has been manually or surgically reduced, and in some cases the affected intestine can be left unresected. In these cases, subsequent laparoscopic closure of the internal vaginal ring is recommended to prevent recurrence.[64] In nonreducible hernias, the affected testicle will be congested because of vascular compromise within the spermatic cord, and although it may remain viable, it is recommended that it be resected. Furthermore, the inguinal canal should be partially closed at surgery to prevent recurrence, and the risk that this procedure will reduce spermatic cord vasculature is another problem. The prognosis in adult horses is good, with 76% of horses

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alive 6 months after discharge.[61] Horses that have been unilaterally castrated during surgical treatment of inguinal hernias may be used for breeding. In these horses, the remaining testicle will have increased sperm production, although an increased number of sperm abnormalities will be noticed after surgery because of edema and increased temperature of the scrotum.

Strangulating Umbilical Hernias

Although umbilical hernias are common in foals, strangulation of herniated bowel is rare. In one study, 6 of 147 horses with umbilical hernias (4%) had incarcerated intestine.[65] Clinical signs include a warm, swollen, firm, and painful hernia sac associated with signs of colic. The affected segment of bowel is usually the small intestine, but herniation of the cecum or large colon has also been reported.[66] In rare cases a hernia that involves only part of the intestinal wall may be found and is referred to as *Richter hernia.* In foals that have Richter hernia, an enterocutaneous fistula may develop. In one study, 13 of 13 foals with strangulating umbilical hernias survived to discharge, although at least 3 horses died because of long-term complications.[66]

Diaphragmatic Hernias

Herniation of intestine through a rent in the diaphragm is uncommon in the horse, accounting for 0.3% of all cases of colic in a large multicenter study.[31] Any segment of bowel may be involved, although small intestine is most frequently herniated.[67] Diaphragmatic rents may be congenital or acquired, but acquired hernias are more common. Congenital rents may result from incomplete fusion of any of the embryonic components of the diaphragm: pleuroperitoneal membranes, transverse septum, and esophageal mesentery. In addition, abdominal compression of the foal at parturition may result in a congenital hernia. Acquired hernias are presumed to result from trauma to the chest or a sudden increase in intraabdominal pressure such as might occur during parturition, distention of the abdomen, a sudden fall, or strenuous exercise.[68] In one study, 19 of 40 horses diagnosed with diaphragmatic hernia (48%) had a history of recent trauma.[68] Hernias have been located in several locations, although large congenital hernias are typically present at the most ventral aspect of the diaphragm and most acquired hernias are located at the junction of the muscular and tendinous portions of the diaphragm. In addition, a peritoneal-pericardial hernia has been documented in at least one horse.[69]

The clinical signs are usually associated with intestinal obstruction rather than respiratory embarrassment. However, careful auscultation may reveal an area of decreased lung sounds associated with obstructed intestine and increased fluid within the chest cavity. Such signs may prompt thoracic radiography or ultrasound, both of which can be used to make a diagnosis. In one review, 7 of 40 horses reported in the literature with diaphragmatic hernia (18%) had dyspnea.[68] Auscultation may also reveal thoracic intestinal sounds, but it is typically not possible to differentiate these from sounds referred from the abdomen. In one report, two of three horses diagnosed with small intestinal strangulation by diaphragmatic hernia had respiratory acidemia, attributable to decreased ventilation.[70] Given the difficulties in correcting diaphragmatic hernias and the associated complicating factors such as pneumothorax, these cases are generally considered to have a poorer prognosis than other causes of colic. A recent report of 31 cases found that 46% of cases undergoing surgical treatment survived to discharge while the overall success rate was only 23%.[71]

Intussusceptions

An intussusception involves a segment of bowel (intussusceptum) that invaginates into an adjacent aboral segment of bowel (intussuscipiens). The reason for such invagination is not clear, but it may involve a lesion at the leading edge of the intussusception, including small masses, foreign bodies, or parasites. In particular, tapeworms *(Anoplocephala perfoliata)* have been implicated.[72] Ileocecal intussusceptions are the most common intestinal intussusceptions in the horse and typically affect young animals. For example, in one study evaluating 26 cases of ileocecal intussusception, the median age of the horses was 1 year old.[73] Acute ileocecal intussusceptions are those in which the horse has a duration of colic of less than 24 hours and involve variable lengths of intestine that ranged in one study from 6 cm to 457 cm long. In acute cases the involved segment of ileum typically has a compromised blood supply. Chronic ileocecal intussusceptions typically involve short segments of ileum (up to 10 cm long), and the ileal blood supply is frequently intact. Abdominocentesis results are variable because strangulated bowel is contained within the adjacent bowel. There is often evidence of obstruction of the small intestine, including nasogastric reflux and multiple distended loops of small intestine on rectal palpation. Horses with chronic ileocecal intussusceptions have mild, intermittent colic, often without evidence of small intestinal obstruction. A mass may be palpated in the region of the cecal base in approximately 50% of cases. Transabdominal ultrasound may be helpful in discerning the nature of the mass. The intussusception has a characteristic target appearance on cross-section.[74]

Other segments of the small intestine may also be intussuscepted, including the jejunum. In one study on 11 jejunojejunal intussusceptions, the length of bowel involved ranged from 0.4 to 9.1 m.[75] Attempts at reducing intussusceptions at surgery are usually futile because of intramural swelling of affected bowel. Jejunojejunal intussusceptions should be resected. For acute ileocecal intussusceptions the small intestine should be transected as far distally as possible, and a jejunocecal anastomosis performed. In cases with particularly long intussusceptions (length up to 10 m has been reported), an intracecal resection may be attempted. For horses with chronic ileocecal intussusceptions, a jejunocecal bypass without small intestinal transection should be performed.

In one study that evaluated the survival of horses with ileocecal intussusceptions, 7 of 7 horses with chronic intussusceptions survived long term (>4 months), whereas only 5 of 12 horses with acute intussusceptions (42%) survived long term.[73] In a separate study that evaluated survival in horses with jejunojejunal intussusceptions, 6 of 11 horses (54%) were discharged from the hospital after surgery, and 4 of 11 horses (36%) survived long term (>16 months).[75]

Other Small Intestinal Strangulations

Entrapment of the small intestine may occur through rents in the mesentery, internal ligaments such as the gastrosplenic ligament,[76] the broad ligament, and the proximal aspect of the cecocolic ligament.[77] Entrapments may also occur through trauma-induced body wall hernias. For all of these conditions it is often necessary to enlarge the rent or hernia to allow reduction of entrapped small intestine. In the case of body wall hernias, the defect should be closed with suture or patched using mesh. Entrapment of small intestine within mesenteric rents appears to be particularly problematic because it is difficult to reduce and has an unfavorable prognosis. The latter may be a result of the fact that large lengths of intestine may become strangulated, and because the mesenteric vasculature is frequently compromised to the extent that intraabdominal hemorrhage has been noted in some cases.[78]

Nonstrangulating Infarction

Nonstrangulating infarction occurs secondary to cranial mesenteric arteritis caused by migration of *Strongylus vulgaris*[79] and has become a rare surgical disorder since the advent of broad-spectrum anthelmintics. Although thromboemboli have been implicated in the pathogenesis of this disease, careful dissection of naturally occurring lesions has not revealed the presence of thrombi at the site of intestinal infarctions in most cases. These findings suggest that vasospasm plays an important role in this disease.[79] Clinical signs are highly variable, depending on the extent to which arterial flow is reduced and the segment of intestine affected. Any segment of intestine supplied by the cranial mesenteric artery or one of its major branches may be affected, but the distal small intestine and large colon are

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more commonly involved. There are no clinical variables that can be used to reliably predict or differentiate this disease from strangulating obstruction. In some cases massive infarction results in acute, severe colic. Other cases may have intermittent colic as smaller emboli are released into the colonic blood supply. Occasionally an abnormal mass and fremitus may be detected on palpation of the root of the cranial mesenteric artery per rectum. This disease should be considered a differential diagnosis in horses with a history of inadequate anthelmintic treatment and the presence of intermittent colic that is difficult to localize. Although fecal parasite egg counts should be performed, they are neither indicative of the degree nor specific for the type of parasitic infestation.

In addition to routine treatment of colic, dehydration, and endotoxemia, medical treatment may include aspirin (20 mg/kg q24h) to decrease thrombosis. Definitive diagnosis requires surgical exploration. Surgical treatment depends on the distribution of infarction. Unfortunately, these cases are difficult to treat because of the patchy distribution of the lesions and the possibility of lesions extending beyond the limits of surgical resection. In addition, further infarction may occur after surgery. The prognosis is fair for horses with intermittent mild episodes of colic that may be amenable to medical therapy, but horses that require surgical intervention have a poor prognosis.[79]

Medical Disorders of the Large Intestine

Samuel L. Jones

Acute Diarrhea

Diarrhea in the horse can be defined as the passage of fecal material that has increased water content. It can vary from soft, formed stools with a mild to moderate increase in water content to projectile fecal passages that contain little solid matter. The passage of excessive water in the feces reflects disruption of the normal balance of fluid and electrolyte secretion and absorption in the intestinal tract. In adult horses diarrhea results almost exclusively from disorders of the large intestine, although diarrhea may be a feature of some descending small colon disorders. Diarrhea can result in significant losses of water, electrolytes, and plasma protein and is often accompanied by local and systemic inflammatory responses.

Diarrhea disorders in adult horses can be divided into those characterized by inflammation of the cecum and large intestine (typhlitis, colitis) and those in which there typically is not an inflammatory response. Inflammatory disorders can be those characterized by an acute inflammatory response (salmonellosis, Potomac horse fever [PHF], and clostridiosis, described later), disorders associated with endoparasitism (small and large strongyle larval migration or encystation), disorders arising from toxicity (cantharidin toxicity, described later, and nonsteroidal antiinflammatory toxicity), and disorders included under the umbrella term *inflammatory bowel disease* (IBD). Disorders that can manifest with diarrhea but that typically do not have colonic inflammation include those in which there is increased intestinal hydrostatic pressure (congestive heart failure, cirrhotic liver disease), intraluminal osmolarity, and poorly defined disorders in which fluid secretion may be stimulated by the enteric nervous system.

Colitis is active inflammation within the colon that is usually associated with myriad local and systemic pathophysiologic events. Diarrhea is an important problem in horses with colitis, but impaired cardiopulmonary function, coagulopathies, and other sequelae of activation of inflammatory mediator cascades and septicemia can be most life-threatening. Complications that occur in patients with colitis, regardless of cause, include overwhelming sepsis triggered by endotoxemia, septicemia and hematogenous organ colonization by bacteria, immune suppression and susceptibility to superinfection with bacteria or fungi, cecum or colon infarction, jugular vein thrombosis, and laminitis.

A variety of inflammatory cells and mediators affect the equine colon. With acute colitis the neutrophil is the effector cell, and the cascade of activation of inflammatory mediators associated with acute colitis is designed to bring neutrophils to where chemical signals indicative of bacterial infection have been detected. Signs of sepsis associated with endotoxemia frequently accompany, or even precede, diarrhea in horses. Severe tissue inflammation can result in ulceration of the mucosal epithelium, resulting in chronic malabsorption and protein-losing enteropathy. Malabsorption of volatile fatty acids (VFAs) and metabolic alterations that result from excessive production and release of inflammatory mediators can lead to an energy deficit and catabolism of body tissues.

Specific diseases affecting the equine large colon (e.g., salmonellosis, PHF, clostridial colitis, and cantharidin toxicity) may have different activators of local and systemic inflammatory responses, and they can produce unique toxins that further contribute to tissue injury. Regardless of the cause, the clinical problems of affected horses are often similar, and the clinician must consider treatments that modify inflammatory changes and replace losses of fluid, electrolytes, and plasma protein. In many cases the cause of the diarrhea is not determined. Descriptions of important causes of diarrhea in horses follow.

Salmonellosis

Salmonella bacteria possess an array of virulence factors that confer attributes of mucosal adhesion and invasion, produce enterotoxins that stimulate intestinal fluid secretion, activate local inflammation (including recruitment of inflammatory cells and the release of their mediators), cause local cytotoxic effects, and initiate systemic responses attributable to lipopolysaccharide (LPS).

Epidemiology Numerous *Salmonella* serotypes have been associated with equine colitis, and overall more than 2500 serotypes of *Salmonella* have been described. *Salmonella enterica* serovar Typhimurium is the most frequently isolated serotype in horses, with dozens of other serotypes isolated sporadically. There are many reports describing clusters of cases of equine salmonellosis in which specific *Salmonella* serovars predominate. Nosocomial infections associated with *Salmonella* Krefeld,[1-3] *Salmonella* Typhimurium,[2] *Salmonella* Anatum,[4] *Salmonella* Infantis,[5] and *Salmonella* Newport[6] have been reported. Pertinent features of these bacteria are the ability to withstand a wide range of environmental conditions, the ability to rapidly invade and spread within the host (and thus be shed into the environment through the feces), and the range of severity of illness that results from infection.

Other key elements that influence whether clusters of cases will occur given the presence of a *Salmonella* serovar in the environment are availability and population density of susceptible hosts and the size of the infective dose of the pathogen. It is for these reasons that veterinary hospitals, breeding farms, and other facilities that may have a high density of horses are most vulnerable to the development of *Salmonella* outbreaks. In several studies at veterinary teaching hospitals, horses that were at greatest risk for developing salmonellosis or shedding *Salmonella* in their feces were those treated with antimicrobial drugs or admitted for treatment of colic.[7-9] Such horses are the majority of patients in any equine referral hospital and account for a significant biosecurity concern in equine hospitals and potentially in the home stables of shedding patients after discharge if susceptible animals have contact with discharged horses that are shedding.[10] Breeding farms are susceptible to *Salmonella* outbreaks (or other enteric infections) because of the concentration of large numbers of immunologically immature newborn animals. In either case the particular *Salmonella* organism involved in disease outbreaks may not have to be especially virulent, because the inherent susceptibility of the host provides the microbe the opportunity to colonize and invade the host. Also of importance is the ability of the organism (inherent or acquired) to persist in the environment, lying

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in wait for both susceptible hosts and environmental conditions that favor its propagation and dissemination.

Serovars or strains of *Salmonella* that have newly acquired virulence plasmids can rapidly become established and spread among farms, sales areas, veterinary clinics, and veterinary teaching hospitals. Often the origin of these "new" bacteria is undetermined, but in some cases the organism can be traced to contaminated feed,[11] a specific shedder or index case introduced into the environment,[6] or domestic, feral, or wild animals.

Salmonellae are ubiquitous in the environment, and the prevalence of fecal shedding varies by the group of horses sampled and the method of detection. Prevalence of fecal shedding, based on fecal culture, in asymptomatic horses admitted to teaching hospitals varied from 1% to 5%.[12,13] In a nationwide survey of prevalence of *Salmonella* in fecal samples from horses on farms and ranches, *Salmonella* bacteria were cultured from less than 1% of horses.[14] The incidence of *Salmonella* shedding in feces has been reported to be 17% in horses admitted to a teaching hospital for lameness examination and 35% to 60% or higher in hospitalized horses with gastrointestinal disease.[9,15] In these reports the polymerase chain reaction (PCR) technique was determined to be specific for *Salmonella* DNA, but the test cannot differentiate between shedding of live bacteria and DNA from dead organisms.

Horses are not considered to be carriers per se of *Salmonella,* because no host-adapted *Salmonella* spp. have been identified in horses. *Salmonella abortus equi* has now disappeared in the United States. Horses that shed *Salmonella* spp. in the feces usually do so transiently for several days to weeks; infrequently horses may shed salmonella bacteria for several months.

In acutely affected horses, large numbers of highly infective salmonellae can be shed in the diarrheic feces. Susceptible animals such as young foals, hospitalized horses receiving antimicrobial drugs, and horses under stress can become ill after becoming infected by numbers of salmonellae 100 to 1000 times less than those required to infect immunocompetent normal horses. Thus particular care should be taken in the management of horses and foals with diarrhea in environments in which there are other animals at risk (e.g., hospitals, breeding farms, show stables, racetracks). Asymptomatic shedders generally pass relatively small numbers of salmonella organisms in the feces and do not appear to pose an important threat to healthy horses not being treated with antibiotics,[10] although asymptomatic shedders have been responsible for outbreaks of salmonellosis in hospitals and on breeding farms.

Clinical Findings

Salmonellosis typically is characterized by an acute colitis that results in profuse diarrhea and occasionally abdominal pain. Horses with salmonellosis often have signs of sepsis associated with endotoxemia and suffer from cardiovascular shock, vascular leak syndrome, and coagulopathies. Horses are usually febrile, tachycardic, moderately to severely obtunded, and dehydrated. With other clinical syndromes of *Salmonella* infection, diarrhea is not a feature. These syndromes include fever and leukopenia, colic, and proximal enteritis with gastric reflux.

Diagnosis

Confirmation of salmonellosis requires bacteriologic culture and/or PCR detection of *Salmonella* bacteria. Multiple fecal cultures and/or quantitative PCR for *Salmonella* spp. should be performed on all horses with diarrhea, particularly if they have signs of systemic inflammation (fever, neutropenia or leukopenia, tachycardia, or tachypnea). It is recommended that at least three to five fecal samples collected 12 to 24 hours apart be submitted to increase the sensitivity of culture.[16] Samples with little solid matter often yield negative culture results, even when the horse is infected with *Salmonella.* Formed fecal samples are more likely to result in a positive culture result from infected horses. A 5- to 10-g amount of feces should be submitted for culture in selective media such as tetrathionate broth or selenite broth and brilliant green agar or XLD agar. Culture of a rectal mucosa biopsy may be a useful adjunctive test used to diagnose salmonellosis. PCR is a sensitive screening tool for detection of fecal *Salmonella* DNA and is important for environmental monitoring and biocontrol measures in hospitals. Quantitative PCR is very sensitive and specific when compared with conventional culture and has a high positive predictive value for individual patients with clinical signs consistent with salmonellosis.[17]

Treatment and Prevention

In most cases of salmonellosis, aggressive treatment facilitates resolution of the severe diarrhea and associated metabolic disorders within 7 to 10 days of the onset of illness. Intravenous administration of polyionic fluids is required to replace fluid and electrolyte losses and to augment preload in horses with poor venous return (see the Fluid Therapy for Horses with Gastrointestinal Diseases section in this chapter and Chapter 44 for more comprehensive information about fluid therapy in horses with diarrhea). Plasma may be required to replace lost plasma proteins and increase plasma colloidal pressure. Alternative colloidal fluids, such as hetastarch, may be useful and more cost-effective than plasma in horses with vascular leak syndrome and hypoproteinemia. Flunixin meglumine is often used to treat inflammation in horses with signs of sepsis. Flunixin and other nonsteroidal antiinflammatory drugs (NSAIDs) should be used with caution and at the lowest dose possible to prevent worsening of colonic mucosal damage or inhibition of mucosal repair. Other antiinflammatory strategies may be used to treat sepsis associated with salmonellosis. Total or partial parenteral nutritional support is often indicated to provide adequate calories and amino acids during the most debilitating period of the illness. Antimicrobial administration to horses with suspected or known salmonellosis is not universally practiced. Antimicrobial administration may decrease the spread of *Salmonella* bacteria to other organs and may have some direct effect on *Salmonella* bacteria in the colon. Traditionally, use of antimicrobial drugs such as chloramphenicol, trimethoprim-sulfonamide (TMS), gentamicin, and cephalosporins has not appeared to accelerate resolution of signs of colitis. Fluoroquinolones, such as enrofloxacin, although potentially arthropathic in young horses, may be more effective because of high lipid solubility and bactericidal activity against *Salmonella* bacteria. The prevalence of infection and shedding of multidrug-resistant *Salmonella* strains appears to be increasing in high-risk facilities such as equine veterinary hospitals.[6]

Horses that have severe diarrhea and sepsis for 10 days or longer are unlikely to survive, even with intensive therapy, because they often have extensive ulceration of colonic mucosa and chronic, severe inflammation within the wall of the colon. Ulceration may be exacerbated by administration of NSAIDs. Complications such as catheter-associated thrombophlebitis, colonic infarction (Fig. 32-77), colonization of other organs by salmonellae or other enteric bacteria, and laminitis can occur.



FIG. 32-77 Colonic infarction in a horse with salmonellosis. Tenesmus and rectal prolapse were early clinical signs of colonic infarction. *(Courtesy of Dr. M.J. Murray.)*

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Measures designed to prevent the spread of *Salmonella* in an environment with potentially susceptible hosts need not be excessively laborious or expensive. The goal is to minimize the size of the infective dose of an enteric pathogen to which a susceptible host may be exposed. Thorough cleaning of areas where fecal contamination is likely and prevention of mechanical distribution of contaminated material are the most important measures that should be taken. Extensive use of disinfectants may not be necessary if cleaning measures are adequate. Cleaning must include removal of organic debris, which can be accomplished with several products designed for that task. Areas that require particular attention are stalls, including water buckets or automatic watering systems, drains, and cracks in the floors and wall; stall implements; surgical areas, including drains; and nasogastric tubes and pumps.

If a diarrheic horse is in the environment, it should be isolated to the greatest degree possible, and biosecurity measures should be instituted to prevent transmission and to detect and monitor any potential outbreak.[6] Bedding material should be removed frequently to minimize accumulation of potential enteropathogens. Personnel entering the stall should be restricted to the professional staff, and they should wear gloves, disposable coveralls, and disposable plastic boots. Footbaths with disinfectant are only effective if they are kept clean and fresh because they quickly accumulate organic material that interferes with the disinfectant activity of the footbath. Vacated stalls should be thoroughly cleaned, allowed to dry, and disinfected, and selected sites in the stall (floor, drain, waterer) must be determined to be negative for *Salmonella* by culture and/or PCR. Biosecurity protocol compliance is critical to prevent an outbreak.

Potomac Horse Fever

PHF is an infectious enterocolonic disorder caused by *Neorickettsia risticii* (formerly *Ehrlichia risticii*).[18-20] The organism is an obligate intracellular parasite, infecting peripheral monocytes and macrophages, colonic and small intestinal epithelial cells, and colon mast cells.[21] The pathophysiology of the disease is incompletely understood, although horses infected with *N. risticii* often have clinical signs and complications similar to those in horses with salmonellosis. After experimental inoculation with *N. risticii,* horses had a mild, transient fever 2 to 4 days after infection.[22] By 10 to 14 days after experimental infection, horses became febrile, had a poor appetite, and exhibited mild to severe gastrointestinal signs ranging from mild colic and soft stool to profuse diarrhea.

In clinical cases of PHF, there are signs of sepsis, including fever, leukopenia, congested mucous membranes, and hypercoagulability. The early fever observed in experimental cases is usually not detected by owners, and when clinical signs are seen it is presumed that the horse was infected 10 to 14 days previously. Hypoproteinemia is a frequent finding in horses with clinical cases of PHF, which reflects loss of serum protein through inflamed intestinal mucosa. It is interesting to note, however, that the magnitude of intestinal inflammation is typically much less than with salmonellosis, yet the magnitude of hypoproteinemia (total protein < 3 g/dL) can be as severe.

Laminitis is a frequent sequela and may occur in 30% in horses with PHF. *N. risticii* has also been associated with abortion in mares, although this is an unusual occurrence.[23] In some horses that show significant seroconversion to *N. risticii,* laminitis is the only clinical sign.

Mode of Transmission

Although originally described as a disease of horses living near the Potomac River in Maryland and Virginia, horses with serologic evidence of exposure to *N. risticii* have been reported in most U.S. states. Because early research on PHF demonstrated that infection was readily transmitted through blood,[32] it was presumed that the natural mode of transmission involved an insect or arthropod vector. However, several studies have failed to demonstrate any such vectors.[24,25]

The association between an affected horse and proximity to a river (within 5 miles) remains strong. Investigators have found a possible link between this association and how the disease may be transmitted. *N. risticii* and *Neorickettsia helminthoeca* were found to share a high degree of DNA homology.[26] *N. helminthoeca* is transmitted to mammals via a trematode that parasitizes fish and aquatic snails.[26] This prompted investigators to search for evidence that *N. risticii* might reside in trematodes and their hosts found in riverine inhabitants. *N. risticii* DNA was detected in operculate snails (Pleuroceridae: *Juga* spp.) collected from stream water in a northern California pasture in which PHF is enzootic.[27] Moreover, *N. risticii* was detected in trematode stages found in the secretions of freshwater snails and in aquatic insects.[28,29] The sequences of these genes were virtually identical to those of the genes of an equine *N. risticii* strain isolated from horses located on a property near the snail collection site. Further work demonstrated *N. risticii* DNA in two trematodes, *Acanthatrium* spp. and *Lecithodendrium* spp., found in bats and swallows, suggesting that these animals may serve as a reservoir and that trematodes are a vector for the organism.[30] Oral transmission of *N. risticii* with infected cell cultures has been produced experimentally,[31] supporting a role for ingestion of *N. risticii,* rather than blood transmission, as the route of natural infection. Oral transmission and clinical signs of PHF were demonstrated in horses fed *N. risticii*–infected aquatic insects (caddis flies), suggesting that ingestion of infected aquatic insects may be the natural route of infection.[32,33] Ingestion of water containing infected trematode stages released from aquatic snails may also be a route of infection.

Diagnosis

Accurate confirmation of PHF can be difficult, because clinical signs of disease are nonspecific and available diagnostic tests are not entirely reliable. Conventional recommendation is that paired acute and convalescent blood samples should be submitted for indirect fluorescent antibody (IFA) or ELISA testing for antibodies to *N. risticii.* However, serologic evaluation to confirm the disease is not as straightforward as in many other infectious diseases. A fourfold increase in titer between acute and convalescent sera is considered to confirm infection with *N. risticii,* but failure to seroconvert does not rule out infection. Because the onset of clinical signs can be delayed as long as 14 days after infection, horses may seroconvert by the time an acute sample is obtained.[31] The magnitude of titer does not always correlate with active infection, because many horses in endemic areas have high titers but no disease. Vaccination also can affect the titer. There is significant interlaboratory variability in results of IFA tests, and false-positive results occur frequently.[34] Therefore it has been suggested that IFA testing for antibodies to *N. risticii* not be performed in areas that are not endemic for *N. risticii.*[34]

The current standard for diagnosis of PHF used by most clinicians is quantitative PCR testing of whole blood samples to detect *N. risticii* DNA in leukocytes.[35] PCR testing appears to be sensitive and specific in horses with compatible clinical signs, but a thorough evaluation of the test has not yet been completed.

Treatment and Prevention

Treatment with oxytetracycline (7 to 11 mg/kg IV twice daily for 4 days) effectively eliminates *N. risticii* from the horse in experimental infections. Fever should resolve within 48 hours of beginning treatment with oxytetracycline, and diarrhea typically resolves within 24 to 72 hours of beginning treatment. In one horse we treated, clinical signs persisted until the dose of oxytetracycline was increased to 15 mg/kg twice daily. Orally administered doxycycline (10 mg/kg q12-24h) may be effective, although in horses with severe gastrointestinal signs, absorption of doxycycline may be adversely affected. Doxycycline must not be given intravenously because it will cause the horse to collapse. Some horses have had clinical relapses 2 to 3 weeks after initial resolution of clinical signs that were responsive to tetracycline. Horses do not remain chronic carriers of *N. risticii.*

In most cases of PHF, intravenous administration of polyionic fluids is required to replace fluid and electrolyte losses and to augment preload in horses with poor venous return. Plasma may be required to replace lost plasma proteins. Other colloidal fluids may also be used in patients with hypoproteinemia or sepsis. Because horses

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improve rather quickly once treatment with oxytetracycline has begun, parenteral nutritional support is usually unnecessary.

Vaccination has appeared to diminish the incidence and severity of disease, but PHF may still develop in vaccinated animals. Experimental results with vaccine were mixed, and the duration of immunoprophylaxis was very limited.[36] Disease severity has appeared to be less in vaccinated animals, although in the summer of 1994 many vaccinated horses developed severe cases of PHF. All of these horses were located in the area where PHF was originally described, and a new strain of *N. risticii* was identified.[37] PCR analysis has revealed multiple strains of *N. risticii,* which may account for the unreliable efficacy of the vaccine.[38] Horses in endemic areas should be vaccinated in the early spring and early to mid-summer on an annual basis.

Clostridial Diarrhea

Enteric clostridiosis was reported as a clinical problem in the 1970s, and clostridial bacteria were implicated as the causative agents of colitis X.[39] Difficulty in substantiating clostridial bacteria as the cause of enterocolitis in horses led to a de-emphasis of this potential cause for diarrhea in adult horses. In the 1990s, improved laboratory techniques for identification of clostridial toxins resulted in increased confirmation of clostridial bacteria as common causative agents of colitis in foals and adult horses.

The two most important clostridial species affecting the equine intestinal tract are *Clostridium difficile* and *Clostridium perfringens.* Most reported cases in adult horses have involved *C. difficile,* although in one report the prevalences of *C. difficile* toxin A and *C. perfringens* enterotoxin in fecal samples from horses with diarrhea were similar, and in some horses toxins from both clostridial species were identified.[40] (Also see p. 824 for more on *Clostridium perfringens* types and toxins.)

Pathogenesis

C. difficile is a gram-positive sporulated obligate anaerobe responsible for most cases of antibiotic-associated diarrhea in many species, including horses, and for a substantial proportion of nosocomial infections in humans and horses.[41,42] *C. difficile* produces two important toxins, named toxin A and toxin B. Most isolates of *C. difficile* produce both toxins, but some isolates produce only one of these. Toxin A can elicit both fluid secretion and a pronounced inflammatory response in the bowel. Toxin A has intestinal secretory and cytotoxic effects,[43,44] increases intestinal permeability,[45] and can activate epithelial cells, neutrophils, mast cells, monocytes, and macrophages to release a multitude of proinflammatory cytokines and vasoactive mediators.[46-48] An interesting feature of toxin A is its induction of the neurotransmitter substance P in both the intestine and dorsal root ganglia, and the apparent dependence on substance P for expression of the full pathologic effects of toxin A in the intestine of rodents.[49] Thus, the effects of toxin A appear to be mediated both through direct effects on intestinal cells and via the enteric nervous system.

Toxin B exhibits enterotoxigenic (secretory) activity and has also been shown to have potent cytotoxic effects on human colonic epithelium.[50] Toxin B has little relevance to the pathogenicity of *C. difficile* in animal models, however, and the roles of toxins A and B in the pathogenesis of equine clostridial enterocolitis are not known.

Strains of *C. perfringens* are classified on the basis of the toxins that are produced, with at least a dozen identified to date.[51] *C. perfringens* type A and type C have been recovered from equine specimens,[52] and several *C. perfringens* toxins have been identified in equine specimens.[53,54] *C. perfringens* type A is the most frequently isolated type, and its enterotoxin is released on sporulation of *C. perfringens* within the intestine. Other exotoxins of *C. perfringens* have phospholipase activity (alpha-toxin), necrotizing cytotoxic effects (beta-, epsilon-, and iota-toxins), and hemolytic effects (theta-toxin).

Clinical Features

Clostridial enterocolitis affects foals and adult horses. In some reports, toxigenic *C. perfringens* organisms were isolated from more than 50% of foals with diarrhea.[54,55] The clinical presentation in foals with *C. perfringens* is predominantly hemorrhagic diarrhea with sepsis. *C. perfringens* can cause septicemia and can often be cultured from the blood of foals with hemorrhagic diarrhea. In some foals, classic necrotizing enterocolitis will be manifested by gas- or fluid-distended intestines and thickened intestinal mucosa. These changes can be appreciated radiographically and ultrasonographically, and intramural gas produced by clostridial bacteria may be detected with ultrasonography as hyperechoic areas within the bowel wall. *C. difficile* infection is also a cause of acute enterocolitis in foals.[56]

Adult horses with clostridial enterocolitis frequently have diarrhea but may have abdominal discomfort or fever as the primary presenting problem. There are no clinical features that consistently distinguish clostridiosis from salmonellosis, and a spectrum of clinical signs exists, from moderate illness to severe toxemic colitis. Most horses with clostridial enterocolitis develop diarrhea, but in some cases enteritis manifested by ileus and gas distention of the small intestine may be the primary problem. Although both *C. perfringens* and *C. difficile* and their toxins have been detected in a significant number of adult horses with colitis, *C. difficile* appears to be more common.[57-59] Indeed, *C. difficile* appears to be the most common cause of antibiotic-associated diarrhea and is a very significant cause of nosocomial diarrhea in horses.[42,60] The most common antibiotics associated with *C. difficile* colitis in horses are erythromycin, trimethoprim/sulfonamides, β-lactam antimicrobials, clindamycin, rifampicin, and gentamicin. Strain differences among isolates of *C. difficile* cultured from the diarrheic feces of horses in intensive care units are associated with toxigenicity, severity of disease, and metronidazole resistance.[42,61] *C. perfringens* and *C. difficile* have been implicated in duodenitis–proximal jejunitis, but a cause-and-effect association has not been proven.

Similar to salmonellosis, clostridial enterocolitis can develop into a widespread problem affecting several animals in a hospital or equine facility.[62] Risk factors for developing nosocomial clostridial enterocolitis are similar to those for nosocomial salmonellosis: antimicrobial administration, concurrent gastrointestinal disease, and age susceptibility (foals). In addition, *Clostridium* spp. are well suited to persist in the environment because of the production of spores that are resistant to environmental extremes and many disinfectants.

Diagnosis

Diagnosis of clostridial enterocolitis requires identification of toxigenic clostridia from intestinal contents or tissue. Several direct and indirect methods are used to detect toxigenic clostridia; these methods include culture, identification of toxins, and identification of toxin genes. Culture of *C. difficile* or *C. perfringens* requires anaerobic conditions, and the ability to culture these organisms from ingesta or fecal specimens rapidly diminishes with increased time from collection to arrival at a laboratory. It is recommended to transport samples, chilled (not frozen) on ice, immediately or by overnight delivery for best recovery of clostridial organisms. Tissue specimens submitted for culture, toxin identification, or toxin gene identification should be handled similarly. Because nonpathogenic clostridia are common,[59,63] isolates should be tested for toxin production either by PCR or bioassay before a definitive diagnosis is made in horses with clinical signs consistent with clostridial enterocolitis. Commercially available tests for clostridial toxins include an ELISA for *C. difficile* toxin A/B, a latex-agglutination test for *C. perfringens* enterotoxin, and an ELISA for *C. perfringens* enterotoxin. *C. difficile* A/B toxin tests have the advantages of being rapid, sensitive, and specific. Tests for *C. perfringens* enterotoxin are not as reliable for definitive diagnosis in most species. Also available is quantitative PCR for *C. difficile* toxin A/B genes that can be applied directly to intestinal content or fecal samples without prior culture and isolation of the bacteria.[64]

Treatment

Supportive care may be required, as with other cases of acute diarrhea in horses. Treatment with metronidazole (15

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to 20 mg/kg PO q6-8h) appears to be effective in eliminating enteric clostridial infection in most cases. In one veterinary teaching hospital, isolates of *C. difficile* were resistant to metronidazole,[65] and vancomycin was used with reported success. Large-scale resistance to metronidazole has not been reported elsewhere, and it should be the first choice in the treatment of suspected clostridial enterocolitis. *Saccharomyces boulardii* is a nonpathogenic yeast used in the treatment of *C. difficile* diarrhea and colitis in humans. The yeast releases a protease that specifically degrades *C. difficile* toxins A and B, and this has been shown to be protective in experimental *C. difficile* colitis in rats and to prevent damage to human colonic epithelium by *C. difficile* toxins A and B in vitro.[66] Although *S. boulardii* (25 g PO q12h) has been shown to colonize the intestinal tract in horses,[67] the efficacy for prevention or treatment of enterocolitis in horses is not clear. *S. boulardii* decreases the severity and duration of enterocolitis in one small study[68] but not in a larger study of antibiotic-associated diarrhea in horses.[67] Di-tri-octahedral (DTO) smectite powder (Bio-Sponge [Platinum Performance, Buellton, Calif.]) has been shown to bind clostridial toxins[70] and may be useful for treating clostridiosis in horses. DTO smectite is available as a powder or paste and should be administered according to the manufacturer's instructions for 3 to 5 days.

Cantharidin (Blister Beetle) Toxicity

Pathogenesis Cantharidin is the toxic principal found in beetles of the genus *Epicauta,* commonly known as blister beetles.[71-73] Ingestion of the beetles in contaminated alfalfa hay results in absorption of cantharidin through the gastrointestinal tract. Blister beetles feed on the flowers of alfalfa and are incorporated into baled alfalfa hay if the hay is cut and processed simultaneously.[71-73] Large swarms of beetles may be found in relatively small portions of hay. The lethal dose of cantharidin is less than 1 mg/kg, but the concentration of cantharidin varies from species to species of blister beetles.[71,72] Therefore as many as 100 to as few as 6 to 8 beetles may be lethal. Often more than one horse will be affected. The fatality rate may be 50% or greater.[71,74]

Cantharidin is a potent irritant, causing cell damage and necrosis on contact.[71,73,74] The mucosa of the gastrointestinal tract is most commonly affected in horses because they ingest the toxin. Ulceration throughout the alimentary tract has been observed in natural and experimental cantharidin toxicity. Diarrhea probably results from the severe ulceration and inflammation of the large intestine, causing increased secretion of water, electrolytes, and protein. Large volumes of fluid and protein are lost in the gastrointestinal tract, causing hemoconcentration and profound hypoalbuminemia in some cases.[71,72,74] Cystitis, nephrosis, and myocarditis occur in natural and experimentally produced cases of cantharidin toxicity.[71,73,74] Cystitis and nephrosis occur from the high concentration of cantharidin in the urine. The cause of the myocarditis and myocardial necrosis is unknown, but they may also be direct effects of the toxin on the myocardium. Elevated plasma CK activity is often observed and has been postulated to arise from the damaged myocardium.[71,72] Horses have a characteristically stiff gait, but histopathologic evidence of skeletal muscle injury that explains the elevated plasma CK activity has not been observed.[72] Hypocalcemia and hypomagnesemia are characteristic features of cantharidin toxicity in horses that have not been explained.[71,72,74] Hypocalcemia may occur from hypoalbuminemia, but the ionized calcium concentration is often decreased, along with the total calcium concentration, indicating that hypoalbuminemia is not responsible for the hypocalcemia.[72]

Clinical Features Cantharidin toxicity can cause a range of clinical signs, from mild depression and abdominal discomfort to fulminant signs of toxemia and rapid death, depending on the ingested dose of toxin.[71,72,74] Most commonly, clinical signs include depression, sweating, irritability, abdominal pain, elevated heart and respiratory rates, fever, polyuria, polydipsia, and profuse diarrhea.[71,72,74] Blood is rarely seen in the feces. Affected horses frequently posture to urinate; indeed, stranguria and pollakiuria are characteristic of cantharidin toxicity.[71] Signs of hypocalcemia include synchronous diaphragmatic flutter and tremors. A stiff and stilted gait may be evident. Neurologic signs such as head pressing, swaying, and disorientation may be noted.[74] Signs of systemic inflammation from endotoxemia may be seen in severe cases. Some horses develop severe depression and toxemia and may die within hours after ingestion of cantharidin without developing diarrhea.[71,74] Hematologic abnormalities are similar to those of other causes of acute diarrhea, reflecting dehydration and sepsis. Hypocalcemia (both ionized and total calcium concentrations) and hypomagnesemia are characteristic biochemical features of cantharidin toxicity and may be profound. Azotemia with a urine specific gravity in the hyposthenuric range is common.[71,72,74] Microscopic hematuria and mild proteinuria may be evident.

Diagnosis Tentative diagnosis can be made based on clinical signs and the finding of blister beetles in the hay. Determining the species of the insects may be necessary to estimate the amount of cantharidin ingested. All species of *Epicauta* contain cantharidin, but some have small amounts. Definitive diagnosis requires the measurement of the cantharidin concentration in gastric or intestinal contents and urine.[71,75]

Treatment Fluid therapy and maintenance of electrolyte balance are important, as in all cases of acute diarrhea. Particular attention should be paid to the degree of hypocalcemia and renal function as a fluid therapy plan is developed. Specific therapy is limited. Administration of absorbent powders via nasogastric tube is important early to prevent further systemic absorption of cantharidin and local toxicity. Mineral oil administration may also help reduce absorption of the toxin. Pain control may be needed for colic or urinary pain. Nonsteroidal antiinflammatory therapy should be used judiciously to avoid further injury to the intestinal mucosa and renal toxicity. Alternative analgesics, such as butorphanol or a lidocaine controlled-rate infusion, may be better choices.

ANTIMICROCIAL-ASSOCIATED DIARRHEA. The onset of acute diarrhea in horses has been associated with the use of several antimicrobial drugs. Lincomycin administered orally and tetracycline administered parenterally have been demonstrated to induce severe diarrhea in horses.[76,77] The oral administration of trimethoprim-sulfonamide, kanamycin, erythromycin, metronidazole, and penicillin and parenteral administration of ceftiofur and gentamicin have been implicated with onset of diarrhea, including fatal colitis, in horses. In one report there was no association between trimethoprim-sulfonamide and diarrhea.[78] However, in other reports, prior administration of antimicrobial drugs was positively associated with onset of colitis and negatively associated with prognosis for survival in horses with colitis.[79]

Antimicrobial-associated diarrhea is presumed to be secondary to disruption of normal colonic microflora and the proliferation of an enteropathogen, such as *Salmonella* spp., *C. perfringens,* and *C. difficile.* Of these, *C. difficile* is the most common cause of antimicrobial-associated diarrhea in horses.[42] Of interest, it was reported that mares whose foals were treated with erythromycin for *Rhodococcus equi* infection developed severe, acute colitis, from which *C. difficile* and its toxins were isolated.[80] The mares had erythromycin detected in their feces, and exposure to the erythromycin was presumed to have occurred by the mares licking erythromycin from the foals' faces.

OTHER CAUSES OF ACUTE DIARRHEA. NSAID toxicity has been associated with diarrhea secondary to damage to the colonic mucosa. Grain (carbohydrate) overload may cause acute diarrhea resulting from overproduction of lactate in the colon. A combination of hyperosmolarity of the luminal contents and damage to the colonic mucosa account for the pathophysiology of grain overload. The clinical signs are similar to those of other acute diarrheal diseases in

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horses and depend on the severity of the overload. Hyperlactemia, metabolic acidosis, and sepsis are key features of grain overload, and laminitis is a common sequela. Acute diarrhea in adult horses has also been associated with conditions such as lymphosarcoma enterocolitis and other IBDs, intestinal lymphosarcoma, peritonitis, heavy metal intoxication, anaphylaxis, and stress.

CLINICAL ASSESSMENTS OF PATIENTS WITH ACUTE DIARRHEA. The diagnostic evaluations performed on horses with acute diarrhea are intended to provide the clinician with information to accurately assess the horse's condition and thus direct therapy toward specific requirements. The first part of the evaluation is a thorough physical examination, with particular attention paid to the horse's hydration status (skin turgor, gum moisture, capillary refill time), evidence of sepsis (fever or hypothermia, hyperemic mucous membranes, prolonged capillary refill time), cardiovascular system (heart rate and rhythm, character of peripheral pulse, capillary refill time), and signs of laminitis (lameness, digital pulse, palpable temperature of hoof walls). Horses with colitis are often moderately to severely dehydrated, with either purplish or brick-red mucous membranes. Purple mucous membrane color reflects venous congestion and poor venous return, whereas brick-red membrane color reflects venous congestion and poor venous return plus arteriole and venule shunting and poor tissue oxygen exchange.

Blood pressure should be monitored, and whereas direct measurements via an arterial catheter are the most accurate, indirect pressure measurements obtained using a Doppler transducer placed over the coccygeal artery are satisfactory. Hypotension and hypertension occur in horses with colitis, and the blood pressure status of a patient often is unpredictable. Blood pressure can be monitored as frequently as labor permits and should be done hourly if vasoactive pharmaceutical agents are used.

Laboratory tests that should be performed include complete blood count (CBC) and plasma protein and total solids. Total hemoglobin and packed cell volume (PCV) are used to assess hydration status. Total protein is used to assess hydration status and degree of protein loss through inflamed intestinal mucosa, and in more chronic cases through protein catabolism. Comparison of clinical hydration, PCV, and total protein is useful in determining the extent of protein loss, and daily evaluations can be used to determine the rate of protein loss. Colloid oncotic pressure measurements are useful, particularly if colloidal fluids other than plasma are given.

Total white blood cell (WBC) count, WBC differential, and WBC morphology are used to assess severity of sepsis; plasma fibrinogen is used to assess the severity of inflammation. Typically the total WBC and neutrophil counts decrease initially. This is primarily attributable to bacterial endotoxins and the host's mediators of systemic inflammation and it occurs in most cases of acute colitis, not just in those caused by *Salmonella* spp. The morphology of the WBCs reflects the severity of the inflammatory response. "Toxic" changes such as basophilia, granulation, vacuolation of the cytoplasm, and scalloped borders of the cell membrane or adherence of neutrophils to red blood cells (RBCs) do not reflect injury to the neutrophils by toxins but reflect the cells' responses to stimulation by proinflammatory agents (tumor necrosis factor [TNF], interleukin 1 [IL-1]) and the production of inflammatory mediators by the neutrophils that are toxic to bacteria. The degree of these changes in circulating neutrophils can be used to assess the severity of disease and also to assess the progress the horse is making. Often the initial sign that the horse is improving is a decrease in the "toxic" appearance to the neutrophils and a regenerative neutrophil response. A horse that continues to have severe neutropenia with a degenerating left shift or neutrophils, with cytoplasmic vacuolation, granulation, and basophilia, for more than 10 days has severe colitis that is unlikely to resolve.

Serum chemistry tests that should be performed include electrolytes (sodium, chloride, potassium, and calcium), blood urea nitrogen (BUN) and creatinine, blood lactate concentration, and assessment of acid-base status (blood pH and bicarbonate, or total CO_2). Horses with diarrhea often are hyponatremic, hypochloremic, and hypokalemic. With decreased feed intake, hypocalcemia occurs. A high gap metabolic acidosis with hyperlactemia may be noted, particularly in horses with sepsis. The severity of these electrolyte disturbances should be monitored, often daily, to allow for appropriate therapy. Parameters that assess renal function, BUN and creatinine, are frequently increased in horses with diarrhea for several reasons. Prerenal azotemia resulting from dehydration and decreased filtration across the glomerulus accounts for some of the increase in these parameters. Hyponatremia and hypochloremia can cause a decrease in glomerular filtration and an increase in BUN and creatinine secondary to tubuloglomerular feedback. Horses that are adequately hydrated yet moderately hyponatremic (serum sodium 120 to 128 mEq/L) often remain azotemic until sodium levels increase above 130 mEq/L. In addition, horses with toxemic colitis often have damage to renal parenchyma, presumably the result of the effects of inflammatory mediators and alterations in renal blood flow.

The acid-base status can be evaluated by estimating serum bicarbonate on the basis of the total CO_2 or directly from a venous or arterial blood gas analysis. Evaluation of a venous blood gas sample is useful in assessing perfusion and oxygen extraction. An increased venous oxygen partial pressure (>60 mm Hg) is indicative of poor capillary perfusion and oxygen delivery to the tissues. Affected horses usually have brick-red mucous membranes.

PRINCIPLES OF THERAPY FOR ACUTE DIARRHEA. Because the pathophysiology of equine colitis is complex, treatment is often multifaceted. Many of these treatments provide well-documented benefit, whereas with others the efficacy is based on empiric judgment only. Outcome is determined not only by the severity of the primary disease causing colitis but also by complications that may arise from the disease.

In cases of acute colitis, fluid administration remains the treatment of primary importance. Most patients require intravenous administration in the early stages. The fluids used must replace fluid, sodium, chloride, and potassium losses. Often, large volumes are required for several days. (More specific guidelines for fluid therapy in colitis patients are covered in the Fluid Therapy for Horses with Gastrointestinal Diseases section and in Chapter 44.)

Most horses with colitis become hypoproteinemic secondary to protein leakage through the inflamed colon and catabolism of albumin secondary to negative energy balance. Hypoproteinemia frequently leads to edema formation in several areas of the body, including the intestinal tract, and can compromise the clinician's ability to keep the patient properly hydrated through fluid administration. Intravenous plasma therapy is often beneficial. Plasma, 4 to 10 L, should be given intravenously. Other colloidal fluids may be more cost-effective for increasing colloidal oncotic pressures in hypoproteinemic horses but do not have the additional properties of plasma that may be beneficial.

Plasma contains proteins besides albumin and therefore can be of benefit beyond improvement of plasma oncotic pressure. The immunoglobulin present in plasma is of recognized benefit in the treatment of failure of passive transfer in foals. The role of nonspecific immunoglobulin in the treatment of colitis is not known. Fibronectin is essential to the normal function of the monocyte-macrophage system in the processing of a variety of antigens. Other plasma proteins such as elastase and proteinase inhibitors, complement inhibitors, antithrombin III (AT-III), and other inhibitors of hypercoagulability may be beneficial to patients with colitis.

The nutritional requirements of patients with colitis need to be considered, particularly in a case that may be protracted. Horses with colitis are typically anorectic, and the disruption of normal physiologic processes in the inflamed cecum and colon limits the effectiveness of these organs to digest and absorb nutrients. In addition, several mediators of inflammation and septicemia alter protein and calorie metabolism, resulting in a catabolic state. Therefore, even if the horse eats, it is likely to be in a severe caloric deficit for some time. Normally an average horse requires approximately

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15 Mcal/day. An endotoxemic horse may require 25 Mcal/day. In a catabolic patient, muscle and fat tissue are mobilized and used in lieu of ingested nutrients. The plasma protein pool, including albumin and immunoglobulins, also is catabolized. In many cases of colitis the decrease in plasma protein may be as much a result of catabolism as of leakage through the inflamed colon. A variety of products can be used for enteral feeding (see Chapter 50).

Colitis is an inflammatory disease, and limiting inflammation is desirable when treating patients, particularly those with severe disease. Moreover, horses with acute colitis, regardless of the cause, have signs compatible with systemic inflammation associated with sepsis. Flunixin (0.25 to 0.5 mg/kg IV q6-8h) is the most commonly used antiinflammatory therapy in horses with colitis. However, the use of flunixin should be judicious and must be carefully monitored to avoid unwanted side effects on the gut mucosa and kidneys. Other antiinflammatory therapies, such as lidocaine controlled rate infusions, may also be beneficial.

Sepsis is a common clinical feature in horses with acute colitis. Most of the clinical signs of sepsis are likely attributable to the effects of endotoxin. Therefore specific therapy for endotoxemia may be warranted.

The use of antimicrobial drugs in the treatment of colitis is controversial. In cases of colitis caused by *N. risticii,* the efficacy of tetracycline, 6.6 to 11 mg/kg IV once or twice daily, is documented.[81,82] In other cases of colitis, including *Salmonella* colitis, in which specific antimicrobial sensitivities to the *Salmonella* spp. have been established, the efficacy of antimicrobial administration is less well documented. Many clinicians believe that the use of an antimicrobial for which the *Salmonella* spp. have demonstrated sensitivity, such as chloramphenicol, enrofloxacin, gentamicin, amikacin, or a third-generation cephalosporin, does not significantly alter the course of the disease or hasten the elimination of the organism from the body. However, there is no published evidence either supporting or not supporting the efficacy of antimicrobial treatment for salmonellosis, and the use of antibiotic therapy remains a judgment of the clinician. In patients with sepsis, the use of broad-spectrum antibiotics is justified to prevent bacteremia or organ colonization by *Salmonella* spp. or other enteric organisms. Antibiotics such as chloramphenicol and enrofloxacin that are lipid permeable and/or are concentrated in cells are a benefit because *Salmonella* reside, proliferate, and persist intracellularly in macrophages and other cells.

Medications that minimize or abolish colonic fluid secretion would be of tremendous benefit in the treatment of equine colitis. Medications such as kaolin, bismuth subsalicylate, and activated charcoal are frequently used in cases of colitis in adult horses, but their efficacy as antisecretory agents in this context has not been established. These medications are more effective in foals with diarrhea, probably as a result of an effect on the small intestine rather than the colon. Absorbent powders such as activated charcoal or DTO smectite (Bio-Sponge) may be useful to absorb bacterial toxins, particularly in horses with clostridiosis.

Chronic Diarrhea

Chronic diarrhea is one of the most frustrating disorders encountered by equine practitioners, with regard to both determining the cause and therapeutically managing the diarrhea.[83] Chronic diarrhea may be defined as persistent diarrhea of at least a month's duration. Although there are many causes of chronic diarrhea, these cases can generally be divided into two groups: diarrhea resulting from a chronic inflammatory condition and diarrhea resulting from a disruption in normal physiologic processes. With inflammatory conditions there will be histologic changes in the colon mucosa, including pleocytosis (neutrophils, eosinophils, and lymphocytes), mucosal congestion, and mucosal erosion and ulceration. Submucosal edema, capillary congestion, and lymphatic congestion may be present. With physiologic disorders there are no morphologic changes in the colon, and diarrhea is presumed to result from abnormal VFA synthesis or absorption. A small percentage of horses with chronic diarrhea have a primary disorder of a system other than the intestinal tract, such as congestive heart failure or hepatic disease. A thorough physical examination and evaluation of a minimum database (CBC, serum chemistry profile, urinalysis) should differentiate horses with primarily nonenteric disorders.

Causes

Inflammatory disorders that can cause chronic diarrhea include disorders caused by infectious agents such as chronic salmonellosis; chronic parasitism with *Strongylus vulgaris, Strongylus edentatus,* and larval cyathostomiasis; abdominal abscessation; and, in weanling foals, equine proliferative enteritis caused by *Lawsonia intracellularis,* gastrointestinal *R. equi* infection, and rotavirus infection.

Noninfectious inflammatory causes include cellular infiltrative disorders such as granulomatous enteritis and lymphosarcoma, as well as sand enteropathy. Sand causes diarrhea through continued irritation of the mucosal lining of the colon. In weanling foals, gastric ulceration and gastric emptying disorders have been associated with chronic diarrhea that resolved when H_2 antagonist therapy was started. NSAIDs can cause chronic diarrhea, which is accompanied by varying degrees of pathologic change in the large intestine.

Noninflammatory chronic diarrhea of colonic origin is thought to be a result of abnormal fermentation of cellulose by the resident bacteria in the large intestine. In vitro fermentation of feces from normal horses and horses with chronic diarrhea revealed that feces from the diarrheic horses produced more gas, acetate, and propionate than feces from normal horses.[84] Whether this reflects fermentative activity within the colon is not known, but an abnormal increase in acetate could lead to fluid retention within the colonic lumen, because acetate inhibits colonic absorption of sodium and water.

Diagnosis

The diagnostic approach to cases of chronic diarrhea should be based on an attempt to differentiate inflammatory from physiologic causes. The evaluation can be extensive and expensive, and the owner should be prepared for the cause of the diarrhea to remain undetermined. Horses with chronic diarrhea may be adequately hydrated if water consumption has matched water losses. Often, however, such horses are brought to the veterinarian in a condition of mild to moderate dehydration. Moderate weight loss also has often occurred. On physical examination, signs of toxemia (injected mucous membranes, congested or hyperemic mucous membranes) should be noted.

A CBC should be evaluated for signs of chronic inflammation. Such changes include a decrease in the RBC count and PCV as a result of decreased erythrogenesis secondary to sequestration of iron by bone marrow macrophages (anemia of chronic inflammation). The WBC count may be normal or moderately increased. The fibrinogen levels can be normal or increased. Changes in WBC count and fibrinogen levels are influenced by the degree of inflammation and whether the inflammatory response is localized. Therefore a normal CBC does not rule out an inflammatory cause of the chronic diarrhea.

Peritoneal fluid analysis may reveal an increase in protein or WBCs, which is indicative of an inflammatory process within the peritoneal cavity. Often, however, colon inflammation is not reflected by alterations in the peritoneal fluid.

Serum chemistry values vary in horses with chronic diarrhea. Many affected horses have evidence of hyponatremia, hypokalemia, hypochloremia, azotemia, and metabolic acidemia. Other horses with less severe chronic diarrhea may have no serum chemistry abnormalities.

The total serum protein is usually decreased with a chronic inflammatory disorder of the colon, reflecting protein leakage from the capillaries and disruption of the colonic mucosal integrity. This is usually reflected by hypoalbuminemia. In some cases, hyperglobulinemia occurs and total protein concentration may be normal.

Increases in hepatic-associated enzymes, including sorbitol dehydrogenase, γ-glutamyltransferase (GGT), and aspartate aminotransferase (AST), and serum bile acids indicate that hepatic disease is present. Hepatic changes and dysfunction such as inflammation,

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fibrosis or fatty infiltration, or biliary inflammation can be associated with diarrhea.

Feces should be examined for parasite ova; cultured for *Salmonella* spp., *C. difficile,* and *C. perfringens;* and tested for clostridial toxins. Weanling age foals should be tested for *L. intracellularis* and *R. equi*. In cases of acute diarrhea, it has been recommended that five consecutive fecal samples be cultured for *Salmonella* spp., but in cases of chronic diarrhea, many more are often necessary. As many as 15 fecal cultures may be needed to get a positive *Salmonella* spp. culture. In addition, a rectal mucosal biopsy should be cultured. In weanlings the feces should be examined for rotavirus by transmission electron microscopy or ELISA. Although it is an unusual cause of diarrhea in weanlings, rotavirus should be considered when dealing with a problem of chronic diarrhea in several foals on the same farm.

An oral glucose absorption test can be done to determine if there is small intestinal malabsorption, which would indicate a widespread small and large intestinal disorder if both diarrhea and glucose malabsorption are present.

A rectal mucosal biopsy may provide evidence of a widespread inflammatory disorder, such as one of the IBDs.[85] Biopsies should be evaluated by a pathologist experienced in examining equine tissue specimens, and some caution should be taken to avoid overinterpretation of the presence of few lymphocytes, plasma cells, and eosinophils.

Frequently the results of the previously mentioned diagnostic procedures do not determine the cause of the chronic diarrhea. In such cases an exploratory laparotomy may be warranted. This is particularly true if episodes of abdominal discomfort accompany the chronic diarrhea. In addition to exploration of the abdomen for the presence of masses or abscesses, the colon and cecum should be thoroughly examined. Biopsies from several sites of the colon, cecum, and mesenteric lymph nodes should be submitted for histopathology and culture for *Salmonella* spp.

Treatment Treatment of horses with chronic diarrhea is often empiric, because either a cause has not been determined or the cause is not amenable to treatment. With inflammatory causes such as lymphosarcoma and granulomatous enteritis, the disease is usually untreatable. Some cases of eosinophilic colitis have been treated successfully with corticosteroids.

Chronic parasitism may be resolved with appropriate anthelmintic therapy, although damage to the mucosa may have become too extensive to allow normal absorption to occur. Administration of larvicidal doses of fenbendazole (15 mg/kg PO daily for 5 days) is usually effective. Concurrent administration of prednisolone (1 mg/kg PO once daily for 5 to 7 days) may minimize inflammation secondary to killing migrating larvae within the vasculature and mucosa of the colon.

Chronic salmonellosis does not lend itself to specific treatment, because antimicrobial therapy is generally unrewarding in resolving *Salmonella* infection in horses.

Administration of products containing bismuth subsalicylate is effective in some cases of chronic diarrhea. The action of bismuth subsalicylate is mediated through inhibition of prostaglandin synthesis and possibly by other undefined mechanisms. In full-size horses a large volume, 1 to 4 L/day, must be administered to be effective.

Iodochlorhydroxyquin administered orally is effective in managing some cases of chronic diarrhea caused by maldigestion of cellulose by colonic microorganisms.[86] The actual mechanism of action of iodochlorhydroxyquin in resolving the diarrhea is not known. The drug was originally administered to horses with chronic diarrhea because an increase in fecal trichomonads was observed. However, this observation likely reflected that trichomonads were washed out of the cecum and colon rather than that they were the cause of the diarrhea. Iodochlorhydroxyquin has minimal effect on colonic protozoal populations. It is not uniformly effective, and in many cases its effectiveness is only transient. Stools may initially become formed, but the diarrhea often recurs within several days. An initial dose of 20 mg/kg/day is recommended. If diarrhea recurs, decreasing the dose to 10 mg/kg/day is sometimes effective. If the medication is effective, it must be continued, because if it is discontinued, the diarrhea resumes.

Changes in diet occasionally are helpful in horses with noninflammatory chronic diarrhea. Feeding a complete pelleted feed may positively affect the constituent VFAs produced in the colon and thus facilitate water absorption. Alternatively, trying different types of roughage may result in selecting one that creates a more favorable metabolic environment in the large intestine.

The removal of sand from the colon by nonsurgical means is difficult, and in one report the administration of psyllium to remove experimentally introduced sand was not effective.[87] Other treatments used with anecdotal, but undocumented, success include fecal transfaunations, probiotics, cultured yogurt, and brewer's yeast.

Surgical Disorders of the Large Intestine

John F. Marshall • Anthony T. Blikslager

Simple Obstruction

Simple obstructions of the large intestine tend to have a more gradual onset than those of the small intestine and, in the case of large colon impactions, are frequently amenable to medical therapy.[1] Cecal impactions present much more of a dilemma because of the greater propensity of this organ to rupture[2] and the relative difficulty of surgically manipulating the cecum.[3]

Cecal Impaction

Cecal impaction may develop as a primary condition or may arise as a complication in hospitalized horses, particularly those that have undergone surgery.[4] Reasons for development of cecal impaction in hospitalized horses are unclear, although motility disturbances arising from postoperative pain may play a role. Cecal impactions may occur as one of two types: impaction of the cecum with firm ingesta or gross distention of the cecum with fluid ingesta. The latter has been termed *cecal dysfunction* and may be initiated by abnormalities in cecal motility. Evidence in favor of this supposition includes the fact that the right ventral colon is typically empty in horses with cecal dysfunction, suggesting a lack of aborad movement of digesta through the cecocolic orifice. However, clinical differentiation of cecal impaction and cecal dysfunction may be very difficult.[5] Horses with dry-ingesta–filled cecal impactions tend to be presented with the condition as the primary complaint, and there is often a gradual onset of abdominal pain over a number of days. Such impactions have a propensity to rupture before the development of severe abdominal pain or systemic deterioration and therefore must be closely monitored. In horses with cecal dysfunction, there is frequently an association with surgery, particularly orthopedic surgery. For horses that develop this condition in the postoperative period, it is often very difficult to detect because there is an expectation for horses to show some degree of depression after surgery and because horses are often already on analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) or opiates. The simplest method to detect these cases is to closely monitor fecal output in the postoperative period.[6] A normal horse should produce six to eight piles of manure per day, whereas an abnormal horse may have no evidence of defecation or a marked reduction in fecal production (less than three piles of manure per day). These horses should be carefully evaluated for both pain and intraabdominal evidence of an impaction and treated accordingly.

The diagnosis of primary cecal impaction is based on palpation of a firm, impacted cecum or a grossly distended fluid-filled cecum per rectum. According to one study such findings were detected in 89% of horses with cecal impaction that underwent per rectum

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palpation of the abdomen.[5] In some cases, cecal impactions may be difficult to differentiate from large colon impactions. However, careful palpation will reveal the inability to move the hand completely dorsal to the impacted viscus because of the cecum's attachment to the dorsal body wall.

Treatment for horses with dry-ingesta–filled cecal impactions may include initial medical therapy, including aggressive administration of intravenous fluids, judicious use of analgesics, and administration of oral laxatives (e.g., 2 to 4 L of mineral oil per 500 kg).[7] Other oral laxatives have also been recommended, including magnesium sulfate (1 g/kg in 4 L of water PO up to twice daily for up to 3 days) and psyllium (1 kg q6-8h). However, if the cecum is grossly distended or if medical therapy has had no effect within a reasonable period of time, surgical evacuation of the cecum via a typhlotomy is indicated. In addition, it is advisable to perform an ileocolostomy in order to bypass the cecum, as postoperative cecal motility dysfunction with recurrence of the disease is common.[8] However, this aspect of surgical treatment remains controversial and there are cases of cecal impaction, particularly those secondary to feed impaction, which, if identified early, can be treated via typhlotomy alone.[9]

In horses with cecal dysfunction, immediate surgery is indicated. In addition, cecal bypass is often warranted because it is suspected that motility disturbances initiate the disease, and therefore recurrence in the absence of cecal bypass may occur. However, this decision can be made based on the appearance of the cecum at surgery.

The prognosis depends on the type of cecal impaction encountered. In a report in which dry-ingesta–filled cecal impactions were treated by typhlotomy and ileocolostomy or jejunocolostomy, seven of nine horses (78%) lived long term.[3] The cecum of horses in which cecal dysfunction develops has a great propensity to rupture, which is universally fatal. The prognosis for this condition tends to be less favorable because of postoperative complications. A recent long-term study of horses undergoing typhlotomy alone (3 horses) or typhlotomy and ileocolostomy (17 horses) found that 55% of horses were alive after 1 year.[10]

Large Colon Impaction

Impactions of the large colon with ingesta occur at sites of anatomic reductions in luminal diameter, particularly the pelvic flexure and the right dorsal colon.[11] Although there are a number of reported risk factors, most have not been proven. However, a sudden restriction in exercise associated with musculoskeletal injury appears to be frequently associated with onset of impaction. A further consideration is equine feeding regimens, which usually entail twice-daily feeding of concentrate. Such regimens are associated with secretion of large volumes of fluid into the small intestine, resulting in transient hypovolemia (15% loss of plasma volume).[12] This leads to activation of the renin-angiotensin-aldosterone system, and because aldosterone stimulates absorption of fluid from the large colon, this may dehydrate colonic contents.[12,13] Large concentrate meals may decrease small intestinal transit time, resulting in increased presentation of soluble carbohydrate to the cecum and large colon. Large shifts of fluid into the colon occur as concentrates are readily fermented in the large intestine, which would be expected to activate the renin-angiotensin-aldosterone system. This in turn triggers net fluid absorption from the large colon. The effects of these large fluid fluxes on development of large intestinal disorders remains to be fully characterized, but undoubtedly they play some role in the syndrome of colic. From a practical standpoint, intestinal fluid fluxes may be reduced with frequent small feedings in those horses requiring concentrate to maintain condition.[12]

Clinical signs of large colon impaction include slow onset of mild colic that is typically well controlled with administration of analgesics but becomes increasingly more severe and refractory if the impaction does not resolve. The diagnosis is based on rectal palpation of a firm mass in the large colon. However, the extent of the impaction may be underestimated by rectal palpation alone because much of the colon will be out of reach. Adjacent colon may be distended if the impaction has resulted in complete obstruction. Initial medical treatment should be attempted. Intermittent abdominal pain is controlled with administration of analgesics (flunixin meglumine 0.25 mg/kg IV q6h to 1.1 mg/kg IV q12h; butorphanol 0.05 mg/kg IV as needed [prn]; xylazine 0.3 to 0.5 mg/kg IV prn). Detomidine (4 to 10 mg IV prn) can be administered but with great caution, as this agent readily masks severe pain. In addition to analgesics, an oral laxative should be administered via nasogastric tube. Although mineral oil (2 to 4 L/500 kg PO) is commonly used as a laxative, hydration of the colonic contents can be better achieved by administration of magnesium sulfate (1 g/kg in 4 L of water PO) or sodium sulfate (1 g/kg in 3 L of water PO) by stomach tube.[14] Although sodium sulfate has been shown to result in greater colonic content hydration than magnesium sulfate, it also results in significant thirst and hypocalcemia; thus magnesium sulfate is preferred.[14] Access to feed should not be permitted but water should be freely available. For impactions that persist, aggressive oral and/or intravenous fluid therapy should be instituted. One study demonstrated the increased efficacy of a continuously administered oral rehydration solution in softening feces as compared with intravenous fluids, which are probably best suited to restoring the systemic extracellular fluid compartment.[15] If the impaction remains unresolved, the horse becomes uncontrollably pained, or extensive gas distention of the colon occurs, surgery is indicated. At surgery the contents of the colon are evacuated via a pelvic flexure enterotomy. The prognosis is good for those horses in which impactions resolve medically (95% long-term survival in one study) and fair for horses that require surgical intervention (58% long-term survival in the same study).[1]

Enteroliths

These mineralized masses are typically composed of ammonium magnesium phosphate (struvite).[16] One study has suggested that an increase in magnesium in the diet may predispose to the formation of enteroliths.[17] Enteroliths almost always form around a nucleus such as a silicon dioxide stone, a nail (Fig. 32-78), or piece of rope that has been ingested and are most commonly found in the right dorsal and transverse colons. Although enterolithiasis has a wide geographic distribution, horses in California have a high incidence. In one California-based study, horses with enterolithiasis represented 28% of the surgical colic population. In addition, Arabians, Morgans,

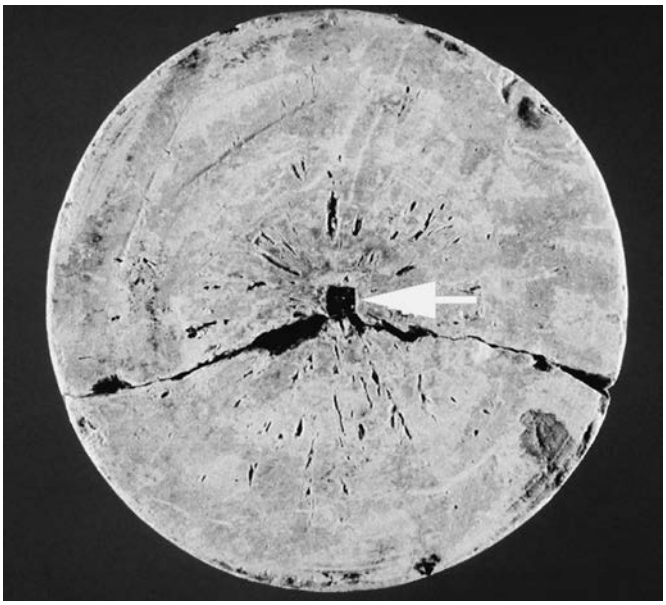


FIG. 32-78 Cut section of an enterolith. Note the presence of a nail head *(arrow)* that served as a nucleus for the formation of a struvite enterolith. *(Courtesy Dr. David G. Bristol.)*

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American Saddlebreds, and donkeys are at risk of this disease.[18] A prospective, unmatched case-control study performed in California indicated that horses fed a diet composed predominantly of alfalfa hay are at risk for development of enterolithiasis, and allowing horses to graze on pasture was protective against this disease.[19]

Initially, clinical signs include intermittent abdominal pain in mature horses (almost always older than 4 years of age),[20] with few abnormalities on rectal examination. As enteroliths become larger, they may occlude the lumen of the colon and cause acute pain and large colon distention that necessitate surgical exploration. In some cases an enterolith is forced into the small colon, where it causes acute small colon obstruction. Enteroliths may be diagnosed by abdominal radiography or at surgery. On rare occasions, an enterolith may be palpated per rectum, particularly if it is present in the distal small colon.

In general, surgery is required for these cases, although there are reports of enteroliths being retrieved per rectum. In fact, in one study 14% of horses presented for treatment of enterolithiasis had a history of passing an enterolith in the feces.[18] However, enteroliths are typically located in the right dorsal colon, transverse colon, or small colon. At surgery the enterolith is gently pushed toward a pelvic flexure enterotomy, but removal frequently requires a separate right dorsal colon enterotomy to prevent rupture of the colon. After removal of an enterolith, further exploration must be conducted to determine if other enteroliths are present. Solitary enteroliths are usually round, whereas multiple enteroliths have flat sides. The prognosis is good (92% 1-year survival of horses recovered from surgery in one study of 900 cases) unless the colon is ruptured during removal of an enterolith[18]; colon rupture occurred in 15% of these cases.[18]

Sand Impactions of the Large Colon

Sand impaction of the large colon is common in horses with access to sandy soils, particularly horses whose feed is placed on the ground. Sand accumulates in the large colon, particularly the right dorsal colon and pelvic flexure, but it may be present in multiple locations.[21,22] In addition, sand may trigger diarrhea, presumably as a result of irritation of the colonic mucosa.[23] In horses with sand impactions, clinical signs are similar to those of horses with large colon impactions. In addition, sand may be found in the feces, and auscultation of the ventral abdomen may reveal sounds of sand moving within the large colon.[24] Radiography of the cranioventral abdomen may be useful for the detection of sand within the large colon and can serve to monitor resolution of sand accumulation.[25] The diagnosis is definitively made at surgery but may be tentatively based on clinical signs compatible with a large colon impaction together with evidence of sand in the feces. To determine the presence of sand, several fecal balls are placed in a rectal palpation sleeve or other container, which is subsequently filled with water. If sand is present, it will accumulate at the bottom of the container.

Initially, medical therapy using a laxative such as mineral oil, magnesium sulfate, or psyllium combined with enteral or intravenous fluid therapy is warranted and is usually successful in the management of uncomplicated sand enteropathy.[25] Administration of psyllium hydrophilic mucilloid in water by stomach tube may facilitate passage of sand, although an experimental study failed to show a benefit of this treatment.[26] If colic becomes intractable, surgical evacuation of the large colon should be performed. Care must be taken to prevent tearing of the colon due to the weight of sand during exteriorization.[27] The prognosis is good.

Nonstrangulating Obstruction of the Colon

Several configurations of displacements, including nephrosplenic entrapment of the colon, obstruct the colonic lumen but do not compromise the colonic blood supply. Therefore technically these are simple obstructions. However, the lumen may not be completely obstructed, and some degree of venous congestion is common.[28] In some cases nonstrangulating obstructions are difficult to differentiate from large colon volvulus, because a volvulus of less than 270 degrees will not result in strangulation of blood supply but can cause considerable abdominal pain and gas distention of the abdomen. In this regard, nonstrangulating obstructions represent early stages of strangulating obstructions. Clinical signs include mild to moderate colic with evidence of large colon distention on palpation of the abdomen per rectum. The diagnosis is confirmed at surgery.[29] If pain is recurrent, particularly if it is of increasing intensity and frequency, or if there is evidence of intestinal compromise (particularly progressive changes in abdominal fluid and cardiovascular parameters indicating systemic deterioration), the horse should be taken immediately to surgery. The prognosis for nonstrangulating obstructions of the large colon is good, with more than 80% of horses surviving to hospital discharge.[30]

Right Dorsal Displacement of the Large Colon

With right dorsal displacement of the colon, the colon displaces to the right of the cecum. Findings on rectal palpation typically include colonic bands coursing horizontally across the abdomen, with evidence of colon lateral to the cecum. In the most common configuration of right dorsal displacement, the large colon wraps around the cecum (pivoting counterclockwise around the cecum, looking from above the horse) with the pelvic flexure lying in the left dorsal quadrant. Alternatively, the colon may wrap around the cecum in the opposite direction, with the pelvic flexure lying in the right dorsal quadrant.[31] A recent study suggested that although the prognosis for recovery following surgical correction of right dorsal displacement is good, this condition is associated with an increased risk of colic episodes in the postoperative period.[32] The reason for this has not been elucidated but may reflect a possible different etiology between right dorsal displacement and other simple obstructions of the large colon.

Nephrosplenic Entrapment (Left Dorsal Displacement) of the Large Colon

On the left side, colon displacements most commonly involve entrapment of the colon over the nephrosplenic ligament, although left dorsal displacements may be detected before the colon is fully entrapped. Clinical signs include gradual onset of mild to moderate colic as the entrapped colon fills with gas. Palpation per rectum will reveal a gas-distended ventral colon and displacement of the spleen toward the center of the abdomen. Careful palpation following colonic bands up to the left dorsal quadrant often reveals the presence of colon between the left kidney and the spleen. Diagnosis may be based on palpation per rectum of the colon traversing the nephrosplenic ligament. Alternatively, a tentative diagnosis can be reached using abdominal ultrasonography.[33] The spleen can be visualized on the left side of the abdomen, but the dorsal spleen and left kidney will be obscured by gas-distended bowel, which may be followed cranially from the paralumbar fossa. As with other examination techniques, ultrasonography is not uniformly reliable and false-positive results and false-negative results may occasionally occur. A definitive diagnosis may require surgery. Treatment has traditionally been surgical intervention, during which the colon is gently rocked free of the nephrosplenic space. However, good success rates for nonsurgical intervention have been reported using either light exercise (trotting) or physical manipulation (rolling) to return the colon to a normal location.[34,35] If such manipulations are to be attempted, the clinician must be certain of a diagnosis. Phenylephrine (3 to 6 µg/kg/min over 15 minutes) may be administered prior to exercise or rolling to decrease the size of the spleen.[36] In cases exhibiting mild pain and normal abdominocentesis findings, light trotting exercise for a period of 30 to 45 minutes might correct the displacement.[34,37] Alternatively, the horse is anesthetized and placed in right lateral recumbency in preparation for rolling. The horse is rotated up to dorsal recumbency, rocked back and forth for 5 to 10 minutes, and then rolled down into left lateral recumbency.[38] Regardless of the nonsurgical technique adopted, the resolution of displacement should be monitored by repeat palpation of the nephrosplenic space per rectum and

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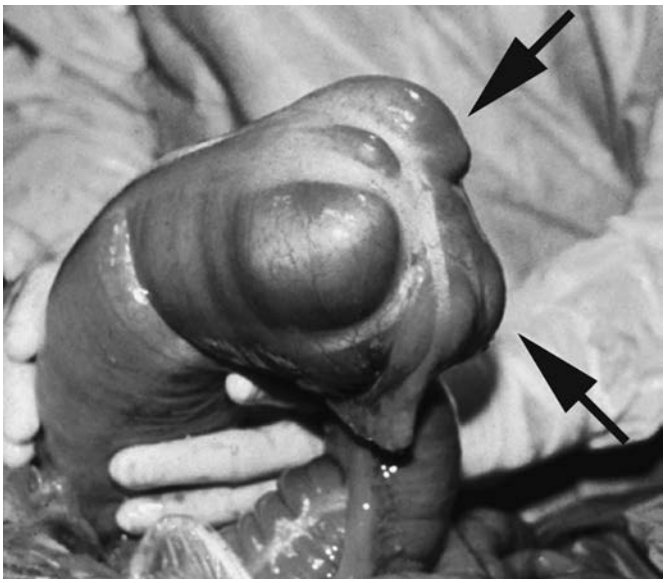


FIG. 32-79 Operative view of a foal with atresia coli. Complete atresia of the pelvic flexure has resulted in a blind-ended ventral colon *(arrows)* resulting in gas distention of the colon. The ventral colon was subsequently anastomosed to the dorsal colon in this foal.

ultrasonography to determine whether or not the entrapment has been relieved. If the entrapment remains or there is any deterioration in clinical signs, the horse should be taken to surgery.

Regardless of technique, the prognosis is good. Several studies have reported survival rates in excess of 90%.[34,39] Recurrence of left dorsal displacement has been described and may affect up to 8.1% of horses.[34] To prevent recurrence, laparoscopic closure of the nephrosplenic space may be performed following correction of the displacement.[40]

Atresia Coli

Atresia of any segment of the colon is a rare congenital abnormality in horses (Fig. 32-79).[41] The heritability and causes of the condition are unknown. One potential mechanism for development of the lesion is intestinal ischemia during fetal life, which secondarily results in necrosis of a segment of intestine. Clinical signs include a failure to pass meconium and colic within the first 12 to 24 hours of life. Secondary abdominal distention results from complete intestinal obstruction, and abdominal radiographs may reveal gas-distended colon. The diagnosis is made at surgery. Any portion of the colon may be absent, but the distal segment of the large colon and/or the proximal small colon is usually most severely affected. If sufficient tissue is present, anastomosis to the proximal blind end of the colon may be attempted. The prognosis depends on which segment of the colon is absent but is usually poor because of an absence of distal colon.

Strangulating Obstruction

Although simple obstruction of the large colon carries a very favorable prognosis, strangulating obstruction of the large colon is associated with high fatality rates. Two forms of strangulating obstruction are recognized: hemorrhagic strangulating obstruction, in which the arterial blood flow remains patent while veins are collapsed, and ischemic strangulating obstruction, in which both the arteries and the veins are collapsed. The differentiating factor between the two is likely how tightly twisted the volvulus is. It has been suggested that ingesta-filled intestine is more likely to develop a hemorrhagic lesion during volvulus because the intestinal contents prevent the intestine from twisting tightly.[42]

Large Colon Volvulus

Clinical signs of large colon volvulus include rapid onset of severe, unrelenting abdominal pain.[43] Although postparturient broodmares appear to be at risk, this association has not been conclusively determined. Once the large colon is strangulated (>270 degrees volvulus), gas distention is marked, leading to gross distention of the abdomen, compromised respiration as the distended bowel presses against the diaphragm, and visceral pooling of blood as the caudal vena cava is compressed. Horses with this condition are frequently refractory to even the most potent of analgesics. These horses may prefer to lie in dorsal recumbency, presumably to take weight off the strangulated colon. An abbreviated physical examination is warranted in these cases, because the time elapsed from the onset of strangulation to surgical correction is critical. Experimentally the colon is irreversibly damaged with 3 to 4 hours of 360-degree volvulus of the entire colon.[44] Despite severe pain and hypovolemia, horses may have a paradoxically low heart rate, possibly related to increased vagal tone. However, in those cases with a high heart rate this can be associated with a poor prognosis.[45] More accurate prognostic information can be obtained from plasma lactate. A plasma lactate concentration of 6 mmol/L is 84% sensitive and 83% specific for predicting nonsurvival.[46] Results of abdominocentesis are often not indicative of the degree of colon compromise,[47] and in many cases abdominocentesis should not be performed because of extreme colonic distention. Palpation per rectum will reveal severe gas distention of the large colon, often restricting access to the abdomen beyond the pelvic brim. The diagnosis may be tentatively based on signalment, severity of pain, and degree of distention.

At surgery the volvulus is typically located at the mesenteric attachment of the colon to the dorsal body wall, and the most common direction of the twist is dorsomedial using the right ventral colon as a reference point. However, the colon may twist in the opposite direction, twist more than 360 degrees (up to 720 degrees has been reported), or twist at the level of the diaphragmatic and sternal flexures. In all cases the colon should be decompressed as much as possible, and in many cases evacuation of colon contents via a pelvic flexure enterotomy will facilitate correction of the volvulus. A determination must be made after correction of the volvulus as to whether the colon has been irreversibly injured. This is frequently based on mucosal color and bleeding (if an enterotomy has been performed), palpation of a pulse in the colonic arteries, serosal color, and appearance of muscular motility. However, determination of viability based on these parameters is unreliable. Currently, one of the most reliable techniques for determining viability is histologic evaluation of frozen sections of colonic mucosa. Biopsies may be obtained at the pelvic flexure because it has been determined that mucosal changes are uniform throughout strangulated colon.[48] A prediction of viability is based on the degree of luminal and crypt epithelial loss and the interstitium-to-crypt (I:C) ratio (based on measurements of the crypt width and the width of interstitial space between crypts). In one study, morphologic changes consisting of an I:C ratio less than 3 and 60% loss of glandular epithelium predicted survival with a sensitivity and specificity of 95% and 92%, respectively, in a population of 52 horses.[49] In addition, it has been suggested that accuracy of viability determination can be increased by combining histologic evaluation with surface oximetry or laser Doppler determination of blood flow.[50] Unfortunately, frozen histologic sections are not available at most referral centers on an emergency basis. A recent retrospective study of formalin-fixed pelvic flexure biopsies from 28 horses found that morphologic scoring could not accurately predict short-term survival.[51] One study assessed intraoperative colonic intraluminal pressure as a more practical potential indicator of outcome in horses with large colon volvulus but found this measurement to be of little benefit in accurately making this determination.[52]

If the colon is judged to be irreversibly damaged, the feasibility of a large colon resection can be considered. Although 95% of the colon can be resected (that part of the colon distal to the level of the

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cecocolic fold), damage from the volvulus usually exceeds what can be resected. In these cases surgeons may elect to resect as much damaged bowel as possible or may advise euthanasia.

Postoperative complications include hypovolemic and endotoxemic shock, extensive loss of circulating protein, disseminated intravascular coagulation, and laminitis. In addition, large colon volvulus has a propensity to recur. Recent reports have described the prognosis for survival to hospital discharge for cases of large colon volvulus as between 58% and 74%.[53-56] Studies that have completed long-term follow-up have found that survival rates decline to between 34% and 66% after 2 years.[52,53] Although one study documented a recurrence rate of less than 5%,[47] some authors believe recurrence may be as high as 50%. Methods to prevent recurrence can be considered in patients considered at risk for recurrence.[57,58]

Intussusception

The most common intussusception of the large intestine is cecocolic intussusception, although when this is compared with all forms of colic, it is a relatively rare condition of the horse, accounting for 11 of 842 horses (1.3%) taken to surgery because of colic at one hospital.[59] The condition tends to occur in young horses (2 to 3 years of age) and may be associated with intestinal parasites, particularly tapeworms[60] and heavy larval cyathostome burden.[61] Clinical signs include acute onset of colic that varies in severity according to the degree of intussusception. Initially, the cecal tip inverts, creating a cecocecal intussusception, which does not obstruct flow of ingesta. As the intussusception progresses, the cecum inverts into the right ventral colon (cecocolic intussusception), which obstructs flow of ingesta and often causes severe colic. In one report on cecocecal and cecocolic intussusception, 26 of 30 horses had acute colic signs.[60] However, the condition may also present as a chronic disease.[60] The cause of abdominal pain is often difficult to differentiate in these cases, although it is sometimes possible to detect a mass on the right side of the abdomen and the concurrent absence of a palpable cecum. Treatment involves manual surgical reduction by retracting the intussusceptum directly or via an enterotomy in the right ventral colon with or without a partial typhlotomy.[60] The prognosis is usually regarded as poor because of severe compromise to the cecum and the risk of cecal rupture or severe contamination during surgery. However, a report of 18 horses without peritonitis and recovered from surgery found that 15 survived long term.[60]

Colocolic intussusceptions are rare but have reportedly affected the pelvic flexure and the left colon.[62-65] Although the condition is reportedly more common in young horses, older horses may be affected. Clinical findings may include a palpable mass on the left side of the abdomen. Ultrasonography may also be useful. Treatment requires manual reduction of the intussusception at surgery, or resection of the affected bowel.

Disorders of the Descending (Small) Colon

Vanessa L. Cook

Colic resulting from a problem with the small colon is comparatively rare—it has been identified in only 4.2% of surgical colics.[1] However, American Miniature Horses (AMHs) seem to be at increased risk for obstruction of the small colon,[2] with small colon lesions comprising 60% of surgical colics in that breed.[3] The Arabian breed may also be overrepresented compared with the hospital population.[1,2] It is interesting to note that horses over 15 years of age also seem to be at an increased risk for small colon conditions,[2] especially strangulating lipoma, injury from foaling, and submucosal hematoma.[1] Mares may also be at increased risk for small colon lesions, possibly because of hormonal fluctuations affecting gastrointestinal motility,[2] because of the small colon's predisposition to injury during foaling, or because of the possibility that the small colon could become entrapped by an ovary.

One of the biggest challenges with small colon lesions is that the associated clinical signs and rate of physiologic deterioration are less severe than with a more oral obstruction, often resulting in later referral.[1,2] A complete examination including rectal examination and abdominocentesis provides useful information in determining the diagnosis and indicating surgical intervention.[1] However, because the small colon lies caudally in the abdomen, transabdominal ultrasonography may be less useful than it is for lesions in other sections of the intestinal tract. Transrectal ultrasonography, performed with care, may be a more sensitive method to detect a compromised small colon and may aid in earlier diagnosis.[4]

Conditions affecting the small colon can be divided into congenital diseases, simple obstructions, vascular lesions, and strangulating lesions.

Congenital Diseases

Atresia Coli and Aganglionosis

Atresia coli is much more rare in foals than it is in calves, with a reported incidence of 0.44%.[5] There are several theories on the pathogenesis of this disease, but an ischemic vascular accident that results in atrophy of the affected segment is the most widely accepted one.[6] There are four types of atresia.[7] Type 3, blind-end atresia, with no connection of the atretic segments, is the most common type found in foals.[5,8] Atresia coli may be confused with overo lethal white syndrome, in which affected foals have myenteric aganglionosis of the distal intestinal tract resulting from a mutation in the endothelin receptor type B gene.[9,10] However, in this condition the intestinal tract is patent but nonfunctional. Loss of neurons in the myenteric plexus of the small colon can also be found in equine dysautonomia (grass sickness), although it is usually less severely affected than the ileum.[11]

Foals with atresia are usually normal at birth but develop progressive abdominal distention and colic within 24 hours of birth. Atresia can be differentiated from other causes of colic in foals by the complete absence of feces with no meconium staining on digital rectal examination or even after an enema.[6] It may be possible to confirm a blind-ending rectum or distal small colon by digital palpation or passage of a soft catheter or endoscope. However, the defect is usually too proximal to visualize this way, and perforation of the friable colonic mucosa can easily occur; therefore this method is not recommended for diagnosis. Plain radiographs do not usually identify the atresia but can help to differentiate it from a meconium impaction. Retrograde contrast radiography, as described later in this section for meconium impaction, may give a more definitive answer.[12] A large volume of barium sulfate, up to 20 mL/kg, may be needed if the atresia is proximal to the transverse colon. If atresia is present, the contrast agent will be seen to end abruptly at the atretic segment.

The only chance for survival in cases of atresia is early exploratory celiotomy to assess the affected segment and determine if surgical correction is possible. In calves with atresia, the prognosis is vastly improved if the diagnosis is made early and the animal is alert and is stabilized medically before surgery.[13,14] However, in foals, despite attempting surgical resection of the atretic segment and anastomosis, the prognosis is grave, with a 100% mortality rate reported in several studies.[5,8]

Simple Obstructions

Simple Impaction

Small colon impaction is the most common abnormal condition of the small colon in adult horses, affecting 1.9% to 2.5% of all horses seen for colic at referral institutes.[15,16] Several studies report a strong association between small colon impaction and diarrhea. The most

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recent study documents that horses with diarrhea are 10 times more likely to develop a small colon impaction than horses without diarrhea.[17] In other studies, diarrhea developed during hospitalization in 70% of all horses with small colon impaction, and 43% of those treated surgically cultured positive for *Salmonella* spp.[15] These studies suggest that impaction of the small colon may be a sequela to colonic inflammation, such as *Salmonella* infection. Therefore some hospitals use isolation protocols for all horses with a small colon impaction. Previous reports have documented a dramatic increase in the incidence of small colon impaction in the fall and winter, possibly because of decreased water intake or close housing that increases the incidence of infectious colitis, but a definitive reason is unknown. It is interesting to note that this seasonal incidence was not significant in the most recent study, possibly because of the milder winters in the southern United States.[17]

Diagnosis of a small colon impaction is most easily made by rectal palpation, with an accuracy of 79% to 87%.[15,17] A solid tube of ingesta with loss of the normal sacculations is found. However, great care should be taken when performing a rectal examination because the rectal mucosa may be edematous, and frequently the horse will strain.[18] It now appears that the best parameter for determining when surgical treatment of these cases is required is the presence of abdominal distention. It has been reported that horses with a small colon impaction and abdominal distention are five times more likely to require surgical correction than horses without abdominal distention.[17] Unlike other types of colic, this single factor has been found to be more significant than heart rate, temperature, or duration of colic when determining the need for surgical intervention.[17] However, transabdominal trocharization in the right paralumbar fossa is an extremely effective and safe method to relieve gas accumulating orad to the impaction. This can be performed to relieve abdominal distention and improve the chance of success with medical therapy rather than proceeding directly to surgery.

Medical therapy should consist of intravenous fluid therapy to correct electrolyte abnormalities, combined with enteral fluid therapy with a balanced electrolyte solution, and analgesics as necessary.[15,16] Typically 4 to 6 L of warm water with 1 oz of sodium chloride alternating with 1 oz of potassium chloride is administered by gravity flow every 2 hours. Administration of *N*-butyl scopolammonium bromide may relax the smooth muscle spasm around the impaction and allow it to pass more easily. The length of time for the impaction to resolve with medical treatment is often longer than for large colon impactions, with a mean time to resolution of over 2 days.[17] Surgical correction of the impaction via exploratory celiotomy is usually performed via a high enema combined with extraluminal massage by the surgeon. The impacted small colon is extremely friable, and great care should be taken by the surgeon when manipulating the bowel in order to avoid serosal tears. Application of sterile carboxymethylcellulose to the serosal surface may help lubricate the intestine and reduce the trauma of manipulation. In severe cases, infusion of the impacted contents with isotonic fluids or an enterotomy in the small colon may be necessary to facilitate evacuation of the impaction.[18] An additional concern is the risk of reimpaction of the small colon as ingesta from the large colon move aborally after surgery. Therefore, if there are ingesta in the large colon at the time of surgery, a pelvic flexure enterotomy is also recommended to empty the large colon and reduce the risk of recurrence.[15] Surgical correction of the impaction can be time-consuming; to reduce anesthesia time it is advisable to assemble the items needed for a high enema, such as a stomach tube with a rounded atraumatic end, stomach pump, and buckets of warm water, in the operating room before induction.

The prognosis for medical and surgical treatment appears to be similar in most studies.[15,17] It is interesting to note, however, that overall prognosis appears to have improved in recent years, increasing from approximately 75% in cases from 1986 to 1996[15] to approximately 95% in cases from 1999 to 2004.[17] Therefore, overall, the prognosis for small colon impaction is excellent, even if surgical intervention is necessary. However, because of the underlying inflammatory cause of this condition, length of hospitalization and associated costs tend to be higher than those incurred with a simple large colon impaction.[17]

Fecaliths, Enteroliths, and Foreign Bodies

Simple obstruction of the small colon also occurs from inspissated feces (fecaliths), enteroliths, foreign bodies, or, less frequently, concretions of plant material (phytobezoars) or masses of matted hair (trichobezoars).

Fecaliths are improperly formed fecal balls that are larger than normal at 4- to 6-cm diameter in miniature horses.[19] They are a common cause of colic in young miniature horses,[19] with an occurrence rate of 63% in a study of surgical colic in miniature horses.[20] Causes of fecaliths are probably similar to those of other impactions and include poor-quality roughage, dental disease causing problems with mastication, and reduced water intake.[19,20] Fecaliths that become lodged in the small colon usually cause complete intestinal obstruction and require surgical removal as described later. When managing colic in miniature horses, regardless of the cause, the patient should have serum triglyceride concentration monitored to allow early detection and treatment of hyperlipemia.[21]

Enteroliths are mainly composed of magnesium ammonium phosphate deposited in concentric layers around a nidus such as a small rock.[22] The incidence is very high in certain regions, such as California, where enterolithiasis constitutes 15.1% of all colic seen at the University of California, Davis,[23] compared with less than 2% of colic cases at Texas A&M University.[24] Several studies report an increased incidence in Arabians, although the reason for this is unknown. Enteroliths can lodge in the large colon, transverse colon, or small colon, but the last is a relatively common site, with over 41% to 45% of enterolithiasis cases involving an obstructive enterolith in the small colon.[23,25] Horses with enteroliths were found to have certain changes in the composition of their colonic contents, compared with other surgical colic cases, which may predispose them to enterolith formation. These differences include a more alkaline pH, more colonic fluid, and higher mineral concentrations.[26] Certain management practices may also predispose to enterolith formation, including a high proportion of alfalfa in feed and less access to pasture.[24,26] Clinical signs of enterolithiasis are similar to those seen with other nonstrangulating obstructions of the large or small colon. However, many horses with enterolithiasis have a history of intermittent colic, and some may even have passed enteroliths in the feces.[23] Horses with an enterolith in the small colon are more likely to be tachycardic and leukopenic than horses with an ascending colon enterolith.[25] Abdominal radiographs may be a useful aid in diagnosis, although the sensitivity is reduced when the enterolith is in the small colon.[27] Medical management aimed at reducing colonic pH has been suggested to try to prevent recurrence after surgery. However, when an enterolith lodges in the small colon, it usually causes complete obstruction and acute colic that require surgical intervention as described later. Rupture of the gastrointestinal tract is particularly common if the enterolith is lodged in the small colon and surgery is delayed.[23] Such cases should therefore be prioritized as requiring emergency surgery, even when there is a history of chronic colic. The vast majority of enteroliths that obstruct the small colon lodge in the proximal third,[25] presumably because of the change in lumen diameter between the transverse colon and descending colon.

Obstruction of the small colon can also occur from ingestion of foreign material such as rope, twine, rubber fencing, cloth, or tires.[28,29] This is usually a problem in younger horses, possibly because they are more inquisitive and will eat nonfood items found in their environment. It is possible for the foreign body to cause signs of small intestinal obstruction first, followed by a period of quiescence while it passes through the large colon before it finally causes complete obstruction of the small colon and acute onset of severe colic[30] and abdominal distention.[28] The fibers become covered in crystalline material during their transit through the intestinal tract, and the resulting irregular sharp projections cause pressure necrosis and mucosal ulceration,[1] which can be seen during exploratory celiotomy

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oral to the site where the foreign body has finally become lodged. These sharp projections make it virtually impossible to manipulate the foreign body orally or aborally within the lumen, making removal more complicated.

The majority of these obstructions requires exploratory laparotomy and an enterotomy to allow the obstruction to be removed.[19,23,28] Regardless of the cause of the obstruction, the overlying intestine is friable and can easily rupture either during induction of anesthesia[28] or during surgical manipulation.[23,29] If possible, the mass should be gently manipulated more proximal or distal to the original site at which it lodged, so that the enterotomy can be performed in uninjured intestine.[1] However, foreign bodies in particular may be difficult to manipulate, and the enterotomy may have to be performed directly over the top of the obstruction. The site selected for the enterotomy should be isolated from the abdomen with sterile towels before the enterotomy incision is made. The incision should be made longitudinally through the antimesenteric taenia in order to preserve luminal diameter, reduce hemorrhage, and maximize speed and ease of the procedure.[31,32] The enterotomy can be closed in one layer using an inverting suture pattern.[32] Small areas of necrosis caused by transmural pressure from the obstruction can be managed by oversewing the affected segment. Problems arise when intraluminal obstructions occur at the proximal portion of the descending colon, where the lumen narrows between the transverse and descending colon. Here, manipulation of the obstruction aborally into a section of small colon that can be exteriorized may be impossible. In such cases an antimesenteric teniotomy, through the seromuscular layer alone, can be performed. This will allow the obstruction to be advanced aborally into a section that can be exteriorized, while the intact mucosa prevents abdominal contamination.[33] The enterotomy and seromuscular incision are then closed as described earlier. An alternative approach is to perform a high enema to repulse the obstruction orally into the ascending colon where it can be removed via a pelvic flexure enterotomy. The overall prognosis for enteroliths of the descending colon is excellent. A recent study reports a 94% short-term survival rate, if horses euthanized at surgery are excluded.[25] Common postoperative complications include fever, anorexia, and diarrhea, which do not seem to worsen the prognosis but may prolong hospitalization.

Meconium Retention

Meconium is composed of substances that are present in the intestinal tract at birth, such as glandular secretions, sloughed cells, and swallowed amniotic fluid, and is therefore sterile. It is thick and tarry and is usually passed within 48 hours of birth. Several studies indicate a higher incidence of meconium retention in colts than fillies, presumably because of the longer, narrower pelvis in males.[34,35] Any factors that reduce intestinal motility (such as failure to ingest colostrum) and dysmaturity can result in difficulty passing meconium, which is described as *meconium retention*. This results in progressive clinical signs of colic such as tail flagging, straining, and reduced suckling. This can progress to more severe signs of colic over time, such as rolling and abdominal distention. These signs are similar to those seen with ruptured bladder, and the two conditions can occur together; therefore a complete examination of the foal is important.

It may be possible to palpate meconium retained at the pelvic inlet by careful digital rectal examination. If the meconium is retained more proximally, it may be identified on a plain lateral radiograph. Confirmation of the obstruction may be provided by retrograde contrast radiography, which provides excellent sensitivity and specificity for evaluation of the transverse and descending colon.[12] After plain radiographs are obtained, a Foley catheter is placed into the rectum and inflated. Up to 20 mL/kg (approximately 1 L) of 30% barium sulfate is carefully allowed to flow in by gravity until it squirts around the catheter or discomfort is observed.[12] Lateral and, more important, ventrodorsal radiographs are then obtained. If a meconium impaction is present, the contrast agent stops before it reaches the transverse colon. A high meconium impaction may be visualized on transabdominal ultrasonography.

Supportive medical management of all foals should be performed first, including correction of fluid and electrolyte imbalances, provision of nutritional support, and correction of failure of passive transfer if indicated.[36] Judicious use of analgesics such as flunixin meglumine or butorphanol and oral fluids may aid resolution of the impaction. However, the most effective treatment is administration of an enema. The enema can be a commercial phosphate enema or simply soap and water administered through a Foley catheter using gravity flow as described previously. In cases that are refractory to simple enemas, an acetylcysteine enema may be effective. Acetylcysteine is a mucolytic, which acts by breaking disulfide bonds to make meconium less viscous. These enemas are available commercially (E-Z Pass Foal Enema Kit [Animal Reproduction Systems, Chino, Calif.]) or can be formulated by adding 20 g of baking soda to 200 mL of water, and then adding 8 g of acetylcysteine powder to make a 4% solution.[34] The solution is infused slowly through a Foley catheter, which is then clamped to allow the solution to be retained for up to 45 minutes to allow maximum activity of the acetylcysteine. Successful resolution of the meconium retention occurred in all acetylcysteine-treated foals in one study, although 5% of foals required three enemas before resolution was obtained.[34]

Previous reports have indicated that approximately one third of foals with meconium retention require exploratory celiotomy for resolution.[35] However, this study was carried out prior to the increased use of acetylcysteine retention enemas, and it is likely that the current rate of surgical intervention is much lower. Considering the high rate of adhesions in neonatal foals undergoing exploratory laparotomy,[35,37] this should result in an improved prognosis for this condition.

Other Causes of Simple Obstruction

Because of the proximity of the descending colon to the urogenital tract, it is possible for the descending colon to be obstructed by intraabdominal structures such as an ovary or retained testicle. Although such conditions occur infrequently, the most common is for the small colon to become entwined around an ovary.[1] The intestine can be freed and is not usually compromised, but the ovary itself is usually nonviable and requires resection.[38] A similar problem has been reported from the spermatic cord of a retained teratoma occluding the small colon.[39]

Vascular Lesions

Intramural Hematoma

Intramural hematoma of the small colon is relatively rare, although some cases may not be diagnosed if they do not cause complete obstruction and if they resolve without intervention.[40] Hemorrhage occurs between the mucosa and muscularis layers, which expand to occlude the lumen and cause complete obstruction. The length affected has been reported to range from 24 to 65 cm. The cause is unknown, although in people, blunt abdominal trauma has been associated with the condition.[41] In one equine case series, iatrogenic rectal trauma was implicated as the cause.[42] There is an increased incidence in older horses, with those affected having an average age of 11 years in one study.[1] Affected cases frequently have blood in the rectum and may show signs of vascular compromise from blood loss.[1,42]

Exploratory celiotomy with complete resection of the affected segment and end-to-end anastomosis (as described later) is necessary. Because of the long length of the affected segment, it may be difficult to exteriorize and resect all damaged intestine. However, if the entire affected segment can be removed, the prognosis is good; one study reported a 75% survival rate.[40]

Mesocolic Tears and Rectal Prolapse

Tears in the mesentery of the small colon can occur as a complication of parturition, especially in multiparous mares,[43,44] and result in segmental ischemic necrosis of the small colon. Trauma and straining during parturition can result in tearing of the mesocolon and

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devitalization of the associated descending colon, which may progress to an intussusception of the small colon, which manifests as a type III or IV rectal prolapse. In a type III rectal prolapse the rectal ampulla prolapses, as with a type II prolapse, but in addition, a portion of the small colon intussuscepts into the rectum. In type IV rectal prolapse part of the small colon and the rectum intussuscepts through the anus.[43,45] Gentle palpation around the prolapse can help determine the type of prolapse. Although a rectal prolapse is readily identifiable, tears of the mesocolon resulting in devitalization of the small colon result in a more insidious onset of clinical signs, including depression and lack of feces.[43,44]

The mesocolic tear is frequently located caudally, resulting in the affected area being inaccessible via a midline celiotomy. Therefore it may be more prudent to first perform standing flank laparoscopy to determine the location and extent of the lesion.[46] This allows assessment of the lesion to determine if resection and anastomosis of the affected segment via celiotomy are feasible, or if a permanent colostomy is required.[47]

Strangulating Obstructions

Strangulating Lipoma

Pedunculated lipomas can cause a strangulating or nonstrangulating obstruction of the small colon, but this occurs much less frequently than in the small intestine. In a large retrospective study, lipomas were found to involve the descending colon in less than 10% of cases.[48] The overall incidence of lipomas affecting any portion of the gastrointestinal tract is increased in older geldings[48,49] and in Saddlebreds and Arabians.[48] It is therefore likely that lipomas specifically affecting the descending colon have a similar distribution. Fig. 32-80 illustrates a pedunculated lipoma that had strangulated a short section of the small colon. Clinical signs typical of a strangulating obstruction are seen, with a significantly elevated heart rate, abnormal abdominocentesis, and distended large colon on rectal examination.[1] In addition, on rectal examination a constriction of the lumen of the small colon caused by the lipoma may be palpated and feels like a blind end or narrowing of the lumen. Surgery is necessary to free the constricting lipoma, followed by resection and anastomosis if the intestine is nonviable (Fig. 32-81). Strangulating lipomas of the small colon are the most common reason for a resection and anastomosis.[50] The prognosis is worse if resection is required, with a 50% survival rate in one study, compared with 100% survival for nonstrangulating lipomas.[1] However, a recent multicenter study has documented a substantially better survival rate after resection and anastomosis of the small colon, the majority of which were horses with a strangulating lipoma.[50] In this study 84% of cases were discharged from the hospital with a median duration of hospitalization of 8.5 days. The end-to-end anastomosis is usually sutured in two layers, with a simple continuous pattern in the mucosa followed by closure of the serosa with an inverting suture pattern interrupted at 180 degrees. It is possible that failure of the anastomosis occurs more commonly in the small colon than the small intestine, but numbers are too low to definitively state this.[50] Many surgeons perform a concurrent pelvic flexure enterotomy to reduce the risk of impaction at the anastomosis after surgery, but this does not appear to improve postoperative survival.[50] Diarrhea, fever, and delayed passage of feces are common postoperative complications, but long-term survival is good with 93% of horses discharged alive at 6 months.[50]

Other Causes of Strangulating Obstruction

Several other causes of strangulating obstruction can occur, but each condition is relatively rare. These include volvulus of the small colon[30] and strangulation through internal hernias such as a vaginal tear[2] or tears in the gastrosplenic ligament.[51]

Prognosis A good survival rate was found in two large studies reviewing small colon disorders, with 71% and 91% of patients being discharged from the hospital.[1,2] The main reason for euthanasia at the time of surgery was an inability to completely exteriorize the affected segment to allow adequate resection and anastomosis.[1] Previous reports have suggested that resection and anastomosis in the small colon may carry a poor prognosis because of a relatively poor blood supply, higher bacterial counts, solid fecal material, and increased collagenase activity compared with the small intestine.[30] However, if the patients euthanized at surgery are excluded, short-term survival after surgery for a small colon lesion is excellent, with a report of 100% survival in one study.[52] In addition, horses that required resection and anastomosis did not have a worse prognosis for survival[2] and are less likely to develop the complications associated with small intestinal resection, such as postoperative ileus (POI).[53]



FIG. 32-80 A short section of small colon that had been strangulated by a pedunculated lipoma.

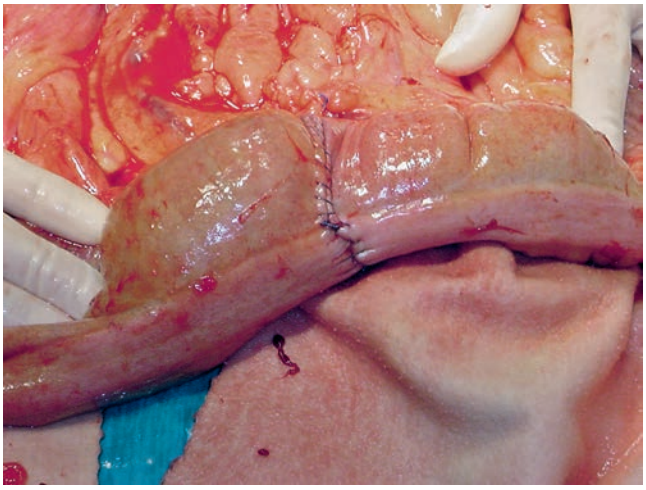


FIG. 32-81 The same case as in the previous figure after resection of the ischemic segment and end-to-end anastomosis.

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Disorders of the Peritoneum in Horses

Tiffany L. Hall

Peritonitis

Anatomy and Physiology The peritoneum consists of a single layer of mesothelial squamous cells covering the peritoneal cavity and abdominal organs. These cells rest on a thin basal lamina attached to a layer of loose connective tissue, allowing a variable degree of motion. The peritoneum is coated with a thin serous film that serves to minimize friction and facilitate free movement between abdominal viscera. In males the peritoneum forms a closed sac, whereas in females it communicates with the external environment via the fallopian tubes.

The peritoneum is divided into the visceral peritoneum and the parietal peritoneum. The visceral peritoneum, which encloses the intraperitoneal organs and forms the omentum and mesenteries, is supplied by the splanchnic vasculature and is innervated by the visceral autonomic nervous system. The parietal peritoneum lines the abdominal walls, pelvis, and diaphragm and receives its blood supply via branches of the lower intercostal, lumbar, and iliac arteries, which drain via veins into the caudal vena cava. Irritation of the parietal peritoneum gives rise to afferent stimuli that are perceived as somatic pain, which is transmitted by the intercostal and phrenic nerves, and may manifest as splinting of the abdomen and a reluctance to move. In contrast, there are no pain receptors in the visceral peritoneum.

Peritoneal fluid is constantly being produced and absorbed through the passive diffusion of fluid and solutes across the semipermeable peritoneum. Transperitoneal fluid movement is increased during peritoneal inflammation and may cause a rapid, massive transudation of fluid into the peritoneal cavity that can lead to hypotension and shock.[1]

The peritoneal lymphatics, particularly the diaphragmatic lymphatics, play a major role in the removal of fluid and solutes from the peritoneal cavity, emptying primarily into the thoracic duct and providing the first line of defense against peritoneal contamination. Cellular defenses are provided by peritoneal macrophages, mast cells, mesothelial cells, and activated peritoneal T cells. Peritoneal macrophages have antimicrobial activity resulting from their complement receptors, phagocytic ability, cellular recruitment, and T cell–mediated immune responses. Peritoneal mesothelial cells are an abundant source of plasminogen activator, which is responsible for normal fibrinolytic activity on peritoneal surfaces.[1]

Pathogenesis Peritonitis is inflammation of the peritoneum resulting from a number of infectious and noninfectious causes. It is classified as primary or secondary, acute or chronic, and localized or diffuse. Common causes of peritonitis in horses are listed in Box 32-3. Primary peritonitis is uncommon in adult horses but may be diagnosed in foals with sepsis or young horses infected with *Streptococcus equi*. More commonly, peritonitis occurs secondary to translocation of bacteria from the gastrointestinal tract, following urogenital trauma, or from other inflammatory conditions. A subset of infectious peritonitis with a unique presentation and associated with *Actinobacillus equuli* has been described and is discussed at the end of this section.

Recent retrospective studies concluded that a cause of peritonitis is often not identified (50 of 65 and 19 of 55 of cases).[2,3] In both groups, cases of confirmed gastrointestinal rupture were excluded from analysis and horses having undergone abdominal surgery were excluded from one study. The conditions most commonly associated with peritonitis in these studies included recent abdominal surgery (18 of 55), postpartum complications (22 of 120), suspected cyathostomiasis (4 of 65), infiltrative bowel diseases (3 of 65), and internal abscesses (3 of 65).[2,3]

The local response of the peritoneum to insult is similar regardless of the cause. Initially, peritoneal mast cells and macrophages release histamine and serotonin, resulting in vasodilation and increased vascular permeability with transudation of fibrinogen-rich plasma into the peritoneal cavity. The release of tumor necrosis factor (TNF) and interleukin 1 (IL-1) stimulates neutrophil chemotaxis and degranulation, and the inflammatory response is promoted by the release of platelet-activating factor (PAF), prostaglandins, and leukotrienes. Damage to mesothelial cells results in release of tissue thromboplastin and decreased levels of plasminogen activator, which favors fibrin formation and deposition.[4] Fibrin functions to confine bacteria and seal the peritoneal defect; however, if the immune system fails to clear the bacteria and foreign debris, the inflammation will continue and fibrin production results in abscess and adhesion formation.

Clinical Features Clinical signs of peritonitis vary and depend on the cause and duration of the peritonitis. Localized infections often have limited systemic symptoms, whereas diffuse peritonitis can elicit generalized signs of endotoxemia and sepsis. Horses with peracute peritonitis caused by intestinal rupture show signs of acute, severe sepsis and cardiovascular collapse with tachycardia, tachypnea, sweating, varying degrees of abdominal discomfort, and death within hours.

BOX 32-3

Causes of Peritonitis in Horses

Gastrointestinal

- Intestinal perforation
- Rectal tear
- Intestinal ischemia
- Proximal enteritis
- Colitis
- Intestinal parasites
- Intestinal neoplasia
- *Actinobacillus equuli*

Iatrogenic

- Celiotomy
- Enterocentesis
- Chemical irritation (lavage solutions)
- Colpotomy/castration

Foals

- Bladder rupture/uroabdomen
- Umbilical/urachal Infection
- Septicemia
- Necrotizing enterocolitis
- *Rhodococcus equi*

Extragastrointestinal

- Neoplasia of abdominal organs
- Hemorrhage of abdominal organs
- Abscessation of abdominal organs
  - *Streptococcus equi*
  - *Streptococcus zooepidemicus*
  - *Corynebacterium pseudotuberculosis*
- Hepatitis
- Nephritis
- Pancreatitis
- Cystitis
- Urolithiasis
- Endometritis
- Uterine/vaginal tears
- Scirrhous cord
- Systemic amyloidosis
- Viral infection
  - Influenza
  - Equine viral arteritis
  - Equine infectious anemia

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Based on two retrospective studies of 65 and 55 horses, the most common presenting clinical signs for peritonitis include colic, depression/lethargy, tachycardia, tachypnea, pyrexia, and altered mucous membrane character.[2,3] Much of the clinical presentation reflects the degree of systemic inflammation and is associated with endotoxemia and hypovolemia. Colic symptoms may be related to inflammation of the parietal peritoneum and are characterized by a "guarded" or splinted abdomen and a reluctance to move or defecate.[5] Sympathetic stimulation, hemoconcentration, and/or serosal surface trauma may decrease gastrointestinal motility, and subsequent ileus can lead to gastric fluid accumulation and small intestinal distention, which intensify the abdominal pain. In addition, gastrointestinal impactions commonly develop as fluid is reabsorbed from the cecum and large colon in an attempt to replace intravascular fluid deficits resulting from extravasation of fluid into the peritoneal cavity.

Rectal examination may identify either roughened peritoneal surfaces or an abnormally empty abdomen in cases of intestinal rupture. Distended bowel associated with the presence of adhesions or ileus may occur. Occasionally, abdominal masses, abscesses, or enlarged mesenteric lymph nodes may be palpable; however, in many cases, no abnormalities are identified on rectal palpation. Animals with a recent history of foaling or castration should have a urogenital examination performed to rule out vaginal, cervical, and uterine tears in mares or infected castration sites in males.

Diagnosis

ULTRASONOGRAPHY. Ancillary diagnostics such as transabdominal and transrectal ultrasonography aid in diagnosis and identification of the source of peritonitis. The clinical utility of ultrasound greatly depends on the quality of equipment and the experience of the practitioner; identification of abnormalities in cases of peritonitis ranges from 50% to 90%.[2,3] The most common finding on transabdominal ultrasound is an increase in volume or altered echogenicity of peritoneal fluid. Other findings can include intraabdominal abscesses, lymphadenopathy, or the presence of dilated small intestine with or without increased intestinal wall thickness. Fibrinous strands or fibrin adhesions may also be identified by ultrasound (Fig. 32-82) and a site for abdominocentesis selected. Perirectal masses may be observed on transrectal ultrasound, particularly in cases associated with vaginal tears.

HEMATOLOGY AND BIOCHEMISTRY. Alterations in laboratory values are widely variable depending on the cause and duration of peritonitis. Hematologic abnormalities seen in acute, severe peritonitis include elevated packed cell volume (PCV) secondary to transudation of fluid into the peritoneal cavity and severe neutropenia associated with endotoxemia and systemic inflammation. Initially an increase in plasma protein levels occurs, reflecting the degree of hypovolemia; however, in chronic cases hypoproteinemia may be present. Peripheral cell counts will vary from leukopenia to leukocytosis and a left shift with greater than 5% immature neutrophils is observed in approximately 40% of patients.[3] Hyperfibrinogenemia is a common finding with levels ranging from 490 to 1120 mg/dL in a review of 65 cases.[2] Peritonitis of longer duration and internal abscesses may present with a normal or increased systemic neutrophil count, monocytosis, and elevated plasma protein and/or fibrinogen levels.[6]

Alterations in serum chemistry and blood gas reflect the patient's cardiovascular status at the time of presentation, associated with the degree of systemic inflammation. Prerenal azotemia, hypokalemia, hyponatremia, and hypochloremia may be seen, as well as acidosis and an increase in unmeasured anions, such as lactate, as the patient's condition declines. Other changes on serum chemistry could indicate an underlying condition in a specific organ system.

ABDOMINOCENTESIS. Peritoneal fluid analysis confirms the diagnosis of peritonitis, although the cause may remain unknown. Expected values for peritoneal fluid in normal horses, as well as in horses having undergone abdominal exploratory and castration and in postpartum mares, are listed in Table 32-8.[7-10] The cytologic appearance of the leukocytes and mesothelial cells should be normal, although activated mesothelial cells are not an unusual observation in normal horses.

Evaluation of fluid character and quantity can aid in developing and prioritizing a differential list. Turbid, cloudy fluid indicates an increased cell count. Serosanguineous fluid indicates an increase in erythrocytes or free hemoglobin that may be caused by intestinal degeneration with transmural erythrocyte leakage, splenic puncture during abdominocentesis, abdominal viscera laceration, or skin contamination. Green fluid results from enterocentesis or intestinal rupture, and brown fluid is associated with late-stage tissue necrosis. The quantity of fluid varies among horses and can be increased in acute, diffuse peritonitis or absent in low-grade and localized peritonitis. The presence of large quantities of dilute, colorless fluid should alert the clinician to the possibility of ascites or uroperitoneum.

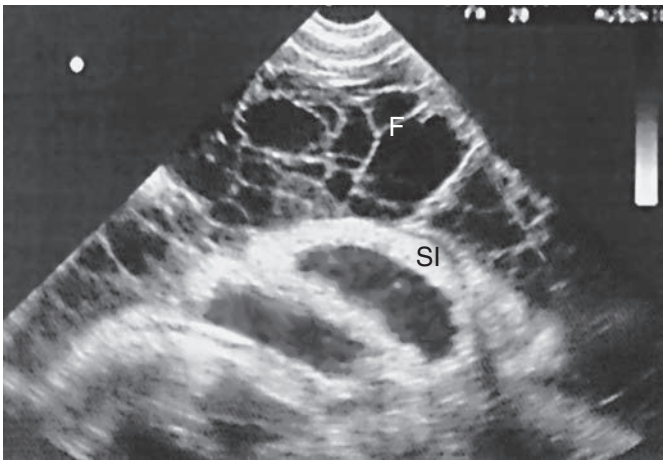


FIG. 32-82 Abdominal ultrasound of adult horse with chronic peritonitis showing web of fibrin *(F)* surrounding anechoic fluid. Small intestinal wall *(SI)* is thickened. *(Courtesy Dr. David Schmitz, Texas A&M University.)*

TABLE 32-8

Peritoneal Fluid Analysis in Normal Horses and Following Conditions That Alter Peritoneal Fluid Values[7-10]

	Normal	Post Celiotomy	Post Castration	Post Foaling	Dystocia
Fluid character	Clear, straw colored	Clear, straw colored	Clear to cloudy	Clear, straw colored	Serosanguineous
Total nucleated cell counts (#/μL)	<5000	200,000 (day 4 post)	30,000 (day 5 post)	<5000	40,500 (day 1 post)
Cell morphology	24%-60% nondegenerate neutrophils	Nondegenerate neutrophils	85% neutrophils	Increased nondegenerate neutrophils	NA
Total protein	<2.0 g/dL	6 g/dL (day 6 post)	NA	<2.0 g/dL	4 g/dL (day 1 post)
Cytology	Mesothelial cells may be activated	NA	NA	NA	NA

NA, Not available.

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Cytologic examination of the peritoneal fluid should include a Wright-Giemsa and a Gram stain. Peritoneal fluid cell morphology is an important diagnostic aid and can be evaluated from the Wright-Giemsa stain. Neutrophils are evaluated for degenerative changes such as nuclear swelling and cytoplasmic vacuolation, indicating activation associated with the presence of bacterial toxins. Identification of exfoliative cells from neoplasms, such as melanoma, is rare but diagnostic and will aid in directing therapy and prognosis.[11] The Gram stain is used to identify bacteria and guide initial antimicrobial therapy until culture and sensitivity results become available.

Peritoneal fluid parameters consistent with peritonitis vary widely, depending on the disease process. Cytologic findings show increases in total nucleated cell counts and protein with the predominance of degenerative neutrophils and intracellular bacteria. Nucleated cell counts ranged from 5800 to 350,000 cells/μL and protein levels up to 8 g/dL in one study,[2] but cell counts as high as 800,000 cells/μL have been reported in horses with peritonitis. Cytologic evidence of extracellular bacteria can result from skin contamination and should be interpreted in light of the clinical signs and remainder of the fluid analysis.

Distinguishing between early, mild septic peritonitis and nonseptic peritoneal inflammation using clinical findings and routine fluid analysis alone may be difficult; however, peritoneal fluid pH and glucose concentrations have been found to be significantly lower in horse with septic peritonitis compared with those with nonseptic peritonitis and with healthy horses. In a prospective study in 46 horses, serum-to-peritoneal fluid glucose concentration differences greater than 50 mg/dL were diagnostic for septic peritonitis. Peritoneal fluid pH less than 7.3, glucose concentration below 30 mg/dL, and fibrinogen concentration above 200 mg/dL were highly indicative of septic peritonitis.[12] A more recent study found that peritoneal concentrations of L- and D-lactate were highest in horses with peritonitis compared with other causes of colic; however, determination of bacterial originating D-lactate is not available in the clinical setting.[13] In addition to these findings, other markers of inflammation and coagulopathy are altered in cases of septic peritonitis, including significant elevations in peritoneal transforming growth factor beta 3 (TGF-β3) compared with other causes of colic and significantly higher peritoneal D-dimer concentrations compared with healthy horses or those with obstructive colic.[14,15]

BACTERIAL CULTURE AND SENSITIVITY. Microbiological culture and sensitivity testing is recommended to help identify bacterial agents and direct antimicrobial therapy. Serial cultures of the peritoneal fluid may be necessary to identify emerging or resistant bacterial strains. Optimal bacteria isolation from peritoneal fluid requires the use of an enriching broth, blood culture medium, and/or antimicrobial removal device.

Bacteria were cultured or identified on cytology in 48 of 67 horses (71.6%) and 28 of 36 cases (77.8%) with peritonitis. *E. coli, Staphylococcus epidermidis,* and *Staphylococcus aureus* were the most common bacteria isolated from peritoneal fluid samples.[3,5] Anaerobes are frequently cultured from peritoneal fluid of equine peritonitis cases, with *Bacteroides fragilis* most commonly identified.[16] Failure to identify or culture bacteria from peritoneal fluid does not rule out septic peritonitis.

Treatment

Horses with peritonitis often require early, aggressive therapy to address hypovolemia and dehydration, correct metabolic and electrolyte abnormalities, and reduce the effects of endotoxemia. The goals of therapy are to (1) stabilize the patient, (2) treat the inciting cause of peritonitis, (3) manage pain and inflammation, and (4) minimize complications.

FLUID THERAPY. Horses with peritonitis present with varying degrees of dehydration; thus fluid resuscitation with balanced, polyionic crystalloids should be the first step in treatment. Hypertonic solutions may be indicated in cases presenting with signs of hypovolemic shock, which may develop secondary to massive fluid shifts into the peritoneal cavity as a result of severe, acute inflammation. Because third spacing of albumin can lead to hypoproteinemia, administration of colloid solutions may be beneficial. Hydroxyethyl starch solutions (6%) are effective in fluid resuscitation and can increase colloid oncotic pressure at doses of 8 to 10 mL/kg.[17] Large volumes of hyperimmune plasma may be used to raise plasma protein levels; however, lower doses of 4.4 mL/kg may help in cases demonstrating signs of endotoxemia.[18]

Acid-base disorders, as well as shifts in calcium, potassium, sodium, and chloride concentrations may be observed in cases of peritonitis. Monitoring of acid-base status and electrolyte concentrations is recommended during the course of therapy with intravenous or oral supplementation as needed. See the Fluid Therapy for Horses with Gastrointestinal Diseases section for a more in-depth discussion of fluid resuscitation and selection.

ANTIMICROBIAL THERAPY. Antimicrobial therapy should be initiated in all cases of peritonitis as soon as fluid has been collected for culture, even when the inciting cause cannot be immediately identified. The site of infection, pathophysiology, likely pathogens involved, and concurrent patient conditions should be taken into consideration when selecting an antimicrobial regimen. Lipophilic antibiotics (fluoroquinolones, potentiated sulfonamides) will reach higher concentrations within the peritoneal cavity and in abscesses compared with hydrophilic antibiotics (aminoglycosides, β-lactams); however, in the acute stages of the disease, inflammation of the peritoneal surfaces often results in therapeutic levels of hydrophilic antibiotics.[18] Further, intravenous administration is recommended as drug concentrations achieved are more reliable compared with oral administration in cases suffering from dehydration or ileus.

Based on the predominance of mixed bacterial infection and concurrent gastrointestinal disease, a broad-spectrum antimicrobial regimen is recommended until culture and sensitivity results are available. Administration of a combination of β-lactam (potassium penicillin G 20,000 IU/kg IV qid or ceftiofur sodium 2.2 mg/kg IV bid) and aminoglycoside (gentamicin 6.6 mg/kg IV q24h) is appropriate. Enrofloxacin (7.5 mg/kg IV q24h) may be substituted for gentamicin based on its increased lipophilicity, activity against *Staphylococcus,* or in cases of renal compromise. Metronidazole (20 mg/kg PO or per rectum q6-8h) is often added to this regimen based on the frequency of *B. fragilis* isolated in horses with peritonitis.

Oral antibiotic administration may be initiated after patients are stabilized and should be based on culture and sensitivity. Commonly administered antibiotics would include trimethoprim-sulfa (20 to 30 mg/kg PO bid), chloramphenicol (50 mg/kg PO qid), or doxycycline (20 mg/kg PO q24h) depending on the underlying condition, client finances, and concurrent conditions. Resistance to trimethoprim-sulfa is not uncommon[18] and thus it should be used cautiously; however, it is a good option for long-term treatment or in combination with rifampin (5 mg/kg PO bid) when intraabdominal abscesses are suspected. Chloramphenicol is bacteriostatic and should not be used as a first line in compromised patients; however, it has a broad spectrum of activity against aerobes and anaerobes with few reports of resistance. Doxycycline should be used only when indicated (based on culture results), but it does have the added benefit of antiinflammatory properties.

Neonatal foals with peritonitis should be maintained on broad-spectrum intravenous antibiotics, as for septicemia, including a combination of β-lactam (ampicillin 20 mg/kg IV qid or ceftiofur sodium 5 mg/kg IV bid) and aminoglycoside. Amikacin (20 to 25 mg/kg IV q24h) is often used in place of gentamicin as it has increased activity against organisms commonly isolated from neonates and decreased potential for nephrotoxicity in these patients. However, therapeutic drug monitoring is recommended.

Older foals and weanlings have a higher incidence of *Rhodococcus equi* and *S. equi* infection; thus antimicrobial regimens in these patients include either penicillin (procaine penicillin G 20,000 IU/kg IM bid) or a macrolide/rifampin combination in the absence of

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other inciting causes. Azithromycin (10 mg/kg PO q24-48h) and clarithromycin (7.5 mg/kg PO bid) have a broader spectrum of activity and fewer side effects compared with erythromycin (37.5 mg/kg PO bid).[19,20]

The duration of antimicrobial therapy is dependent on the inciting cause and the patient's response to treatment. Most peritonitis cases will require a minimum antimicrobial course of 7 to 10 days and cases with intraabdominal abscesses may require a 6- to 8-week course of antimicrobials. Antibiotics should be continued for several days after clinical signs resolve and peritoneal fluid counts return to normal in cases of idiopathic peritonitis. Other methods for monitoring progress and determining termination of therapy include serial ultrasound evaluation, complete blood counts, and fibrinogen levels in cases of internal abscesses.

ANTIINFLAMMATORY THERAPY. All horses with peritonitis will have varying degrees of local and systemic inflammation, and some may present with endotoxemia or endotoxic shock. Administration of medications with antiinflammatory properties, as well as those that bind and inactivate endotoxin, may be beneficial.

Nonsteroidal antiinflammatory drugs (NSAIDs) should be administered in all cases of peritonitis for both analgesia effects and ability to reduce the production of inflammatory mediators via cyclooxygenase (COX) inhibition. Flunixin meglumine is most often used and may be administered at higher doses (1.1 mg/kg IV or PO bid) in horses showing signs of discomfort or at lower doses to minimize side effects while taking advantage of antiinflammatory properties (0.25 mg/kg IV or PO q6-8h). Other NSAIDs such as phenylbutazone (2.2 mg/kg IV or PO bid) or COX-2 selective firocoxib (0.1 mg/kg IV or PO q24h) may be used in place of flunixin meglumine.

Lidocaine has gained considerable use as an antiinflammatory in recent years. Research demonstrated that horses administered lipopolysaccharide (LPS) intraperitoneally and treated with lidocaine (1.3 mg/kg IV bolus followed by CRI 0.05 mg/kg/min) had significantly lower clinical scores of endotoxemia and lower concentrations of plasma and peritoneal TNF-α compared with those receiving saline.[21]

Therapy targeted at binding and inactivating endotoxin includes the administration of hyperimmune plasma, endoserum, and polymyxin B. Polymyxin B (3000 to 6000 IU/kg IV bid) has been demonstrated to effectively bind circulating endotoxin; however, there is a risk of nephrotoxicity and its use is cautioned in cases with azotemia or preexisting renal insufficiency. The pathophysiology and therapy for endotoxemia is discussed in depth elsewhere in this chapter.

ANTHELMINTICS. Peritonitis may develop in association with intestinal cyathostomiasis or verminous arteritis secondary to *Strongylus vulgaris* migration; therefore, anthelmintic administration is recommended in cases with a high suspicion or poor deworming history. Traditionally, fenbendazole (15 mg/kg PO for 5 days) or ivermectin (0.2 mg/kg PO) is recommended following stabilization of the peritonitis patient; however, resistance has been reported. Alternative deworming protocols may include administration of moxidectin (0.4 mg/kg PO) or oxibendazole (10 mg/kg PO for 3 days).

SURGICAL MANAGEMENT. Surgical intervention in peritonitis may be indicated to identify and correct the underlying cause, particularly when leakage or compromise of the intestinal or urogenital tracts is suspected. Occasionally, intraabdominal abscesses may be identified on ultrasound which could be drained via catheter or marsupialization. Peritoneal lavage and drainage should also be considered based on peritoneal fluid analysis and is recommended when total nucleated cell counts exceed 100,000 cells/μL. The benefits of lavage and drainage include (1) reduction of bacterial numbers and concentrations of inflammatory mediators, (2) removal of foreign debris from the peritoneal/serosal surfaces, and (3) dilution of adhesion-promoting substances. Horses treated with peritoneal lavage must be monitored for dehydration, protein loss, and electrolyte imbalances. Complications associated with peritoneal drains include visceral puncture during insertion, ascending infection, subcutaneous leakage and edema, and herniation of intestine or omentum through the drain.[22]

Several techniques for peritoneal lavage and drainage have been described elsewhere, including the placement of ventral midline catheters in the standing horse, the use of active intraabdominal systems, and open peritoneal drainage.[18,23,24] Briefly, standing intraabdominal catheters may be placed aseptically under ultrasound guidance by insertion through the skin, subcutaneous tissues, and external muscle layers at ventral midline, then secured in place using a purse-string and several half-hitches. Foley, mushroom, or thoracic catheters may be used and should have numerous fenestrations, which are maintained within the body wall at all times to minimize leakage of fluid into the surrounding tissues. Catheters are then either allowed passive drainage and connected to a Heimlich valve, or connected to an active-drain system, to prevent ascending contamination.

Balanced, polyionic solutions with a neutral pH are used to lavage the abdomen. Antibiotics, antiseptics (povidone-iodine), and heparin have been suggested as additives to the lavage solution; however, no controlled studies have been performed to demonstrate any benefit. Severe inflammation of the peritoneal surfaces has been reported following the use of 3% or greater povidone-iodine lavage solutions. Peritoneal lavage is performed by allowing 10 to 20 L of solution to enter the abdomen via gravity flow through the ventral catheter. The catheter is then clamped and the patient walked for 10 to 20 minutes to encourage distribution of the lavage fluid after which the clamp is removed and fluid drained. This is repeated 1 or 2 times daily for 3 to 5 days or until fluid analysis normalizes.

A retrospective evaluation of 67 horses receiving active intraabdominal drainage following celiotomy found a high incidence of minor complications (49%), including obstruction of the drainage system, leakage of fluid around the system, and subcutaneous fluid accumulation. Further, the incidence of incisional infection in this group was higher (32%) compared with the control group (23.5%); however, this was attributed to the severity of the primary condition for which the patients had undergone surgery.[24]

Although open peritoneal drainage is preferred in humans and is reported to be successful in management of dogs and cats with peritonitis, this method has not been promoted in horses. In an experimental study, horses with induced peritonitis receiving open drainage therapy using a plastic mesh sutured at the ventral abdominal wall had a significantly increased inflammatory reaction at the linea alba compared with those that were closed routinely. Further, all horses in the open drainage group developed incisional infections following removal of the mesh.[23]

ADHESION PREVENTION. Development of intraabdominal adhesions has a significant impact on long-term outcomes for horses with septic peritonitis. Systemic administration of antimicrobials, dimethyl sulfoxide, and flunixin meglumine has been promoted to reduce adhesion formation by decreasing peritoneal inflammation.[25] In addition, the systemic administration of heparin (20 to 40 IU/kg SC q8h) has been advocated for up to 72 hours in horses at risk of adhesion development or coagulopathy.[25] Heparin acts to decrease fibrin formation through its inhibition of thrombin.

Various intraperitoneal therapies have been evaluated in horses for the prevention of adhesions. Abdominal lavage, both intra- and postoperatively, has demonstrated benefit in reducing the incidence of adhesion formation in horses undergoing exploratory celiotomy and those with peritonitis.[22,24] Introduction of heparin directly into the peritoneum during abdominal lavage may be beneficial, with dosages of 20,000 IU recommended[26]; however, studies evaluating the effects of concurrent systemic and local administration on systemic coagulation have not been reported in the horse. Intraperitoneal administration of recombinant tPA and 0.4% sodium hyaluronate has been shown to decrease adhesion formation; however, these are

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currently cost prohibitive in clinical cases.[25] The use of 1% sodium carboxymethylcellulose (2 L throughout the abdomen and applied to intestinal surfaces intraoperatively) has the most dramatic impact on adhesion formation, significantly decreasing the incidence of adhesions in experimental horses and associated with a decreased risk of death compared with untreated horses.[27,28] In a study of 203 clinical cases, 75% of horses receiving sodium carboxymethylcellulose during surgery survived to 180 days compared with 75% of untreated horses surviving to 8 days postoperatively.[28]

Prognosis Prognosis depends on the cause, severity, duration, and complications associated with peritonitis. Prognosis is poorest for those horses suffering from gastrointestinal perforation or rupture and best for horses with peritonitis associated with *A. equuli*. In two recent retrospectives, short-term survival was 86% (56 of 65) and 78% (43 of 55); however, both of these studies excluded horses diagnosed with gastrointestinal rupture.[2,3] Another retrospective evaluation of 67 cases, including those with gastrointestinal rupture, demonstrated a higher mortality rate (40%).[5] In that study, serum creatinine levels, anion gap, and pH at the time of presentation were significantly different between survivors and nonsurvivors; however, more recent research has not confirmed these findings. Celiotomy was found to have a negative impact on survival, with an odds ratio of 9.87 for nonsurvival in cases undergoing exploratory within 2 weeks of diagnosis or as a part of the treatment for peritonitis.[3]

Complications are not uncommon, occurring in 40% (22 of 55) of cases, and can have a negative impact on long-term survival.[2,3] Reported complications include thrombophlebitis, ileus, diarrhea, drain site complications, intraabdominal adhesions, and laminitis. Monitoring and prophylactic therapy for these conditions may help reduce their impact on outcome. With early diagnosis, correction of the inciting cause, aggressive medical therapy, and peritoneal lavage, a fair-to-good prognosis can be given in acute cases of septic peritonitis in the horse.

Actinobacillus Peritonitis

A subset of peritonitis attributed to *A. equuli* infection has been reported among horses in Australia, New Zealand, and North America. Infection is generally thought to be secondary to translocation of the bacteria from the gastrointestinal tract or associated with *Strongylus* migration; however, the exact origin is unknown.[29-31] Horses present with symptoms of mild to moderate colic (60%), tachycardia (94%), tachypnea (90%), decreased to absent borborygmi (88%), and elevated rectal temperature (77%). A chronic form of the disease with a history of progressive weight loss is also reported. A poor deworming history was noted in 9 of 18 horses tested having elevated numbers of strongyle ova on fecal examination.[29,30]

As with other causes of peritonitis, hemoconcentration, an absolute left shift, and hyperfibrinogenemia are common. In addition, peritoneal fluid cell counts are markedly increased—100,000 cells/μL in 88% of samples (46,000 to 810,000/μL)—and protein is elevated in 98%. In contrast to other cases of peritonitis, cytologic findings are characterized by a predominance of nondegenerate neutrophils, and pleomorphic gram-negative rods are identified in 53% of slides. In that report, a pure growth of *A. equuli* was obtained in 72% of cases.[30] These cases responded rapidly to antibiotic administration (100% short-term survival) and most isolates were sensitive to penicillin; however, it is recommended that therapy include penicillin/gentamicin or oral therapy with trimethoprim-sulfa until sensitivity results are available. Therapy should be continued for 7 days beyond return of peritoneal fluid analysis to normal values.

Presentation of horses with mild to moderate signs of colic, lethargy, elevated heart and respiratory rates, and marked elevations in peritoneal fluid protein and cell counts, which does not progress to endotoxemia or shock, and characterized by a rapid response to antimicrobial therapy sets peritonitis associated with *A. equuli* apart from other causes of peritonitis.

Hemoperitoneum

Hemoperitoneum is defined as the abnormal accumulation of blood within the abdominal cavity. Several recent retrospective case series have evaluated the causes, clinical presentation, and outcomes associated with the diagnosis of hemoperitoneum.[32-34] The various conditions diagnosed in horses presented with hemoperitoneum are summarized in Box 32-4. Clinical signs and prognosis depend on the cause and severity of the hemorrhage; however, most cases present with symptoms referable to abdominal discomfort/colic (78% to 79%) and hemorrhagic shock (60% to 85%), including tachycardia, tachypnea, pale mucous membranes, depression, weakness, and cool extremities.[33,34]

Antemortem diagnosis of hemoperitoneum is made based on the identification of hemorrhagic effusion within the abdominal cavity either by ultrasound or abdominocentesis. Characteristic swirling of echogenic fluid is noted on ultrasound in cases of intracavitary hemorrhage, and a specific origin of hemorrhage may be identified by ultrasound in 25% to 44% of cases.[33,34] Peritoneal fluid analysis confirms hemorrhage based on findings of packed cell volumes greater than 5%, elevated protein levels, and gross appearance. Hematology and biochemistry are often unremarkable; however, alterations in acid-base status, blood gas analysis, and plasma lactate concentrations reflect the severity of hemorrhagic shock.

Therapy for hemoperitoneum includes emergency stabilization of hemorrhagic shock, promotion of clot retention, and addressing the primary cause. Treatment of hemorrhagic shock includes conservative volume resuscitation with intravenous crystalloids, colloids, and blood transfusion (see the Fluid Therapy for Hemorrhagic Shock section in Chapter 44). Additional medications to support perfusion (inotropes, vasopressors) may also be indicated. Antifibrinolytics (aminocaproic acid at 3.5 mg/kg IV, conjugated estrogens at 25 to 50 mg/500 kg) are often administered to prevent breakdown of clots and help suppress continued hemorrhage.[35] Exploratory laparotomy

BOX 32-4

Causes of Hemoperitoneum in Horses

Idiopathic

Trauma
Splenic rupture
Rib fracture
Pelvic fracture (iliac artery)

Neoplasia
Renal carcinoma
Granulosal cell tumor
Metastatic neoplasia

Female Reproductive Tract
Uterine artery
Broad ligament tear
Uterine tear/rupture
Ovarian hematoma
Ovarian dysgerminoma

Vascular
Aortic aneurysm
Mesenteric rents
Disseminated intravascular coagulation (DIC)

Hepatic Rupture
Hepatic lipidosis

Splenic Rupture
Amyloidosis
Hemangiosarcoma

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may have both diagnostic and therapeutic indications as the source of bleeding may be identified and corrected.[34] Abdominal drainage and lavage is often not performed in these cases, unless severe abdominal distention precludes allowing autotransfusion. Antimicrobial administration is indicated if bacterial contamination is likely in order to guard against development of septic peritonitis.

Prognosis for horses presenting with hemoperitoneum is guarded, with overall survival rates ranging from 39% to 74%, and depends greatly on the severity of hemorrhage, ability to control hemorrhage, and underlying cause.[32-34] Nonsurvival is associated with respiratory rates higher than 30 bpm, diagnosis of neoplasia (odds ratio 35.08), mesenteric vessel injury (OR 243.5), and uterine artery rupture (OR 13.72).[33] Idiopathic hemoperitoneum is associated with the best long-term survival outcomes.[34]

Gastrointestinal Ileus

L. Chris Sanchez • Guy D. Lester

A number of factors are responsible for movement of feed through the gastrointestinal tract, and disturbance to any of these can result in ineffective transit and signs of abdominal pain. Gastrointestinal motility involves an extremely complex interaction among the enteric nervous system, intestinal wall, and luminal contents. Other factors potentially influencing the transit of digesta include gravity, the volume and viscosity of intestinal contents, and pressure gradients created by simultaneous contraction and relaxation of adjacent bowel segments. The inhibition of propulsive bowel activity is usually referred to as *ileus*.

Several equine diseases and syndromes that likely involve altered gastrointestinal motility include postoperative ileus (POI), cecal emptying defect, gastroduodenal ulcer disease, simple bowel distention, intra- and extraluminal obstructions, peritonitis, and inflammatory bowel diseases (IBDs). Ineffective intestinal motility can also be a feature of several neonatal diseases, including prematurity, systemic sepsis, and neonatal encephalopathy, and can be found in postparturient mares. Certain parasitic infections, electrolyte derangements, and endotoxemia can modify intestinal transit in horses of all ages. Intestinal motility is also disturbed by general anesthesia and sedation, especially with the α_2 receptor agonists.

Physiology of Intestinal Motility

The control of intestinal motility is complex and involves a combination of central innervation, autonomic innervation, and the enteric nervous system. Intestinal contractions are primarily controlled by the enteric nervous system and do not require extrinsic neural input. The inherent rhythmicity of electrical activity in the intestine is controlled by the interstitial cells of Cajal (ICCs). These are highly specialized cells that are electrically coupled to the smooth muscle syncytium via gap junctions.[1] ICCs are responsible not only for generation of slow waves (cyclical electrical activity) but also for coordination of pacemaker activity and propagation of slow waves along the intestine. ICCs appear to be critically involved in a range of motility disorders in human beings, including gastroparesis, pseudoobstruction, and chronic constipation.[1] In horses a reduction in ICC density has been demonstrated with equine grass sickness and other large intestinal diseases.[2,3] The inherent "excitability" of smooth muscle cells in response to stimuli varies among regions of the gastrointestinal tract and among species. This variability in cell excitability is dependent on the magnitude of the membrane potential, which in turn is regulated by the number and subtype of potassium channels.[4]

The enteric nervous system plays an important role in control and coordination of intestinal contraction. Contractile events are influenced by central and autonomic innervation, but external neural input is not required for contraction. The parasympathetic supply to the gastrointestinal tract is via the vagus and pelvic nerves, and the sympathetic supply is through postganglionic fibers of the cranial and caudal mesenteric plexuses. A complex network of interneurons within each plexus integrates and amplifies neural input, and the intensity and frequency of resultant smooth muscle contractions are proportional to sympathetic and parasympathetic input. Additional binding sites for a number of other endogenous chemicals, including dopamine, motilin, and serotonin, can be found within the enteric nervous system and on smooth muscle cells.[5] It is important to appreciate that mechanisms to slow progressive intestinal motility are also critical in order to retain feed for adequate digestion and absorption of nutrients. The terms *jejunal* and *ileal brake* have been used to describe the slowing of transit caused by mediators such as peptide YY, noradrenergic nerves, and opioid, serotonergic, and chemosensitive afferent neurons.[6]

Acetylcholine (ACh) is the dominant excitatory neurotransmitter in the gastrointestinal tract and exerts its action through muscarinic type 2 (M_2) and M_3 receptors. Sympathetic fibers innervating the gastrointestinal tract are adrenergic, postganglionic fibers with cell bodies located in the prevertebral ganglia. Activation of α_2-adrenergic receptors on cholinergic neurons within enteric ganglia inhibits the release of ACh and therefore reduces intestinal contraction. The β_1, β_2, and β-atypical receptors are directly inhibitory to the intestinal smooth muscle.[7] Inhibitory nonadrenergic, noncholinergic (NANC) neurotransmitters include adenosine triphosphate (ATP), vasoactive intestinal peptide (VIP), and nitric oxide (NO).[8,9] These neurotransmitters are critical for mediating descending inhibition during peristalsis and receptive relaxation. Substance P is a NANC neurotransmitter that may be involved in contraction of the small intestine and large colon.[10-12] The rate and force of intestinal contractions along the small intestine and large colon of the horse are key determinants of intestinal motility. Of even greater importance to the net propulsion of digesta are the cyclical patterns of contractile activity. These patterns are known as the small intestinal and colonic migrating motility complexes (MMC).[13] The colonic complex usually originates in the right ventral colon and variably traverses the ascending and descending colons. Many of these complexes are temporally related to a specialized motility event of the ileum known as the migrating action potential complex.

Mediators of Gastrointestinal Ileus and Major Disease Categories

Inflammation within the intestinal muscularis and inhibitory neural events are important initiators of intestinal ileus.[14,15] Intestinal inflammation is not only important in primary inflammatory intestinal diseases in horses, such as duodenitis–proximal jejunitis (DPJ) and colitis, but also induced after simple intestinal handling during laparotomy. Experimental data from other species suggest that handling of the small or large intestine at the time of surgery induces an intense inflammatory response within the muscularis and a reduction in the intensity of smooth muscle contraction.[15-17] Furthermore, the inflamed intestine fails to contract normally in response to putative prokinetic agents. Additional studies have identified that this inflammatory response was not restricted to segments that were manipulated at the time of surgery but also involved other regions throughout the gastrointestinal tract.[14] Intestinal handling in experimental animals causes local overproduction of NO because of the upregulation of inducible nitric oxide synthase (iNOS) by resident macrophages.[18] NO is a key inhibitory neurotransmitter of the NANC system.[9] Consequently, NOS inhibition could be an important target for prevention of ileus.

The inhibition of motility associated with peritoneal inflammation may also be mediated through neural reflexes. The afferent segment is partly composed of capsaicin-sensitive visceral afferent C-fibers that terminate in the dorsal horn of the spinal cord, where they can activate inhibitory sympathetic fibers or, alternatively, synapse directly on the sympathetic ganglia. Consequently, the efferent limb of the reflex expresses increased sympathetic outflow,

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primarily mediated through stimulation of α_2-adrenoreceptors, with subsequent inhibition of ACh release. This provides the rationale for α_2 blockade in the treatment of ileus. Intraluminal infusion of capsaicin before abdominal surgery ameliorated the severity of POI in experimental rats.[19] This finding highlights the importance of visceral afferent fibers in the development of POI.

Ileus can also occur with intestinal obstruction or displacement. Mild to moderate distention of the bowel, such as that occurring in the early stages of an intraluminal obstruction, evokes an increase in local contractile activity.[20,21] Excessive distention results in inhibition of motility within the distended segment of bowel. Intestinal stasis is not always detrimental and, under certain conditions, may be protective.

Endotoxemia is a feature of many diseases of the equine gastrointestinal tract, and endotoxins can independently exert a negative effect on intestinal motility and transit.[22] Various mediators are likely involved, but activation of α_2-adrenoreceptors and production of prostanoids appear to be important, as the inhibitory effects of experimental endotoxin infusion are ameliorated by pretreatment with yohimbine or NSAIDs (phenylbutazone or flunixin), respectively.[23,24] Endotoxin infusion induced an inflammatory response in the intestine of rats that mimicked that induced by handling during laparotomy.[25]

Cecal Emptying Defect (Cecal Impaction)

An important and specific motility problem involving the cecum occurs sporadically in adult horses and foals.[26-30] The pathophysiology of cecal emptying defect is not known. This syndrome may best mimic POI in humans, which is generally considered a large intestinal disorder. An important difference in horses is that laparotomy is a rare predisposing factor, and most cases occur in horses undergoing routine extraabdominal surgical procedures. General anesthesia is a potent inhibitor of gastrointestinal motility in horses, but the effects are short-lived and reversible within hours of anesthetic withdrawal.[31] The return of normal motility in horses after experimental ileus was most delayed in the cecum, suggesting that this may be a common site of ileus in horses.[32]

Retrospective data regarding cecal impactions suggest that two subtypes exist, and recent retrospective studies highlight those differences. In a United Kingdom report of 20 horses undergoing surgery because of cecal impaction, the condition appeared secondary to previous orthopedic (10 of 20) or colic (5 of 20) surgery in the majority of horses.[33] Short-term survival in that report was 65%, and all but 3 underwent cecal bypass. Alternatively, in a Texas report of 114 horses with cecal impaction, approximately half were treated medically and half surgically.[34] Of the horses allowed to recover from surgery, 95% survived to discharge, and typhlotomy alone was performed in 34 of 37 horses. Eighty-one percent of horses treated medically survived to discharge.[34] These reports appear to describe the two types of cecal impactions nicely, and the secondary (also called type II) impactions appear associated with cecal emptying defect and are therefore often categorized as a form of POI. In postoperative horses, cecal impaction was evident at a mean of 3.6 and 7.5 days following orthopedic and colic surgery, respectively.[33] The earliest detectable signs include lethargy and a reduction in appetite, fecal output, or both. Ineffective emptying results in overfilling of the cecum with moist contents, which is manifest by signs of mild to moderate colic. If the condition is recognized late or untreated, the cecum may rupture, resulting in fatal peritonitis.

Postoperative Ileus

The most frequently reported form of ileus occurs after laparotomy and is termed *simple* or *uncomplicated postoperative ileus.* When intestinal motility is disturbed for longer periods after surgery, typically for more than 72 hours, the term *complicated* or *paralytic ileus* is used.[35] POI in horses is most commonly associated with surgery of the small intestine, particularly after resection and anastomosis. As stated previously, inflammation is likely a key mediator of POI. The true incidence of POI in horses undergoing laparotomy for gastrointestinal disease is difficult to determine because of variation in definition, surgical skill, and anesthetic technique. POI was reported as a complication in only 10% of horses that underwent laparotomy for a small intestinal lesion at one referral practice[36] but 27% in another.[37] In the latter study, horses with DPJ were included, but 30% of horses developed POI after small intestinal resection. In a multicenter study 47 of 251 (19%) horses undergoing laparotomy for acute colic including small and large intestinal disease developed POI.[38] As stated previously, the retrospectively collected POI data are extremely hard to interpret, and many mechanical obstructions and surgical complications can mimic POI[39]; thus, authors are encouraged to adopt uniform definitions of POI and make every attempt possible to distinguish POI from intestinal obstruction.[40]

POI can have a significant negative impact on short-term postoperative survival.[41-43] Motility dysfunction is likely present in all horses after laparotomy, but most cases are subclinical and require minimal intervention. In symptomatic animals, clinical signs are typically observed within 24 hours of recovery; these signs include colic, tachycardia, dehydration, decreased borborygmi and fecal output, and sequestration of fluid within the stomach. Rectal examination and ultrasound may reveal small intestinal distention with rare or absent wall movement. The severity and duration of intestinal stasis is variable, lasting from minutes to days.

The development of small intestinal POI, but not cecal emptying dysfunction, is influenced by the duration of surgery.[27,38] Technique may have a weak influence on small intestinal POI after jejunojejunostomy. The duration of intestinal ileus was shorter in animals that received a side-to-side stapled anastomosis than in those that had a hand-sewn end-to-end procedure.[41] The duration of ileus after stapled end-to-end anastomosis was no different from that after either procedure.

Reported risk factors for the development of POI in horses include age (>10 years), small intestinal resection and anastomosis, breed, heart rate at admission, large volume (>8 L) reflux at admission, and duration of anesthesia and surgery.[37,38,43,44] Jejunocecostomy and side-to-side jejunojejunostomy have been associated with an increased risk of POI.[36,45] Pelvic flexure enterotomy and intraoperative and postoperative lidocaine infusion have been associated with a decreased incidence of POI.[38,43-45]

Miscellaneous Motility Disruptions

Other disruption of normal intestinal motility can occur in the horse. Many, but not all, are associated with analgesic or sedative drug administration. The inhibitory effects of α_2-adrenergic agonists, such as xylazine and detomidine, on intestinal motility in horses are well described.[46-54] The activation of postganglionic cholinergic nerves in the myenteric plexus by this class of drugs results in reduced ACh release from autonomic and enteric nerves. Intravenous xylazine inhibits cecal and large colon motility for 20 to 30 minutes without seriously disrupting small intestinal myoelectric activity, and detomidine can reduce large intestinal myoelectric activity for up to 3 hours. The α_2-antagonist yohimbine has a weak but positive effect on cecal emptying in normal ponies, suggesting that normal motility is under constant α_2-adrenergic tone.[48]

Other analgesic medications can also decrease gastrointestinal motility. Opioids such as morphine have long been associated with decreased motility in humans.[55] Morphine has been shown to delay gastrointestinal transit and decrease gastrointestinal moisture content in the horse.[56,57] Butorphanol administered alone appears to reset the antroduodenal MMC without substantial negative effects on motility, but it will decrease duodenal motility when combined with xylazine above the effects of xylazine alone.[50,58] The role of selective or preferential μ- and κ-receptor agonists can vary in different regions of the equine gastrointestinal tract, in that κ-receptor agonists appear to have a more inhibitory effect in the jejunum whereas μ-receptor

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agonists appear to inhibit the large colon more significantly.[59,60] Ketamine has also been shown to increase total gastrointestinal transit in healthy horses.[61]

Atropine is a postganglionic blocking agent that binds to muscarinic receptors. When administered at 0.04 mg/kg, individual small intestinal, cecal, and colonic contractions are inhibited for about 120 minutes, but small intestinal and colonic migrating complexes are suppressed for up to 8 hours.[62] The negative effect of atropine on gastrointestinal motility in the horse can also be evident with topical ophthalmic administration of atropine.[63] This effect, in combination with pain and other management factors, likely relates to the high reported risk of colic in horses hospitalized for ocular disease.[64]

Gastric and small intestinal ileus, with no identifiable mechanical or physical disruption to motility, has also been identified as a cause of acute colic in postparturient mares.[65] An apparent etiology for this condition has not been identified, but most mares responded well to decompression.

Diagnosis

The diagnosis of ileus is based on history and physical examination findings. Important tests include determination of pulse rate and rhythm, auscultation and percussion of the abdomen, rectal palpation, and passage of a nasogastric tube. A complete blood count (CBC) with fibrinogen estimation and cytologic analysis of peritoneal fluid may improve the accuracy of diagnosis. Affected animals may be colicky because of accumulation of fluid in the upper gastrointestinal tract (classical POI) or cecal contents (cecal emptying defect). Decompression of the stomach is important diagnostically and therapeutically in horses with POI after small intestinal surgery. Failure to relieve pain with gastric decompression could point toward mechanical obstruction, severe inflammation of the intestine, or peritonitis. Most animals with ileus are depressed and have reduced fecal output and intestinal borborygmi. Intestinal sounds should, however, be interpreted with caution, because the presence of borborygmi does not always equate to progressive intestinal motility and may merely reflect local, nonpropagated contractions. Rectal palpation findings in cases of persistent POI or DPJ are usually nonspecific but may reveal dilated, fluid-filled loops of small intestine. Roughened peritoneal surfaces can occasionally be palpated with peritonitis. Cecal distention with either firm or fluidy contents can be palpated in horses with cecal dysfunction.

It is important to distinguish functional ileus from mechanical obstruction. This can be extremely difficult, but horses with mechanical obstruction typically have sustained high volumes of gastric reflux that vary little over time. Distinguishing mechanical obstruction from POI is especially important, as horses with mechanical obstruction in the postoperative period may benefit from early repeat laparotomy.[39]

Treatment

Supportive care

The management of gastrointestinal ileus is dependent on the segment of gastrointestinal tract involved. Therapy for ileus of the proximal gastrointestinal tract typically involves a combination of gastric decompression, fluid and electrolyte therapy, and antiinflammatory drugs. Nasogastric decompression is the mainstay of management to prevent excessive distention of the stomach and small intestine. This often necessitates placement of an indwelling nasogastric tube, a procedure that some have speculated may in itself delay gastric emptying. The placement of an indwelling tube for 18 hours did not adversely affect the emptying of liquids, but in a recent study a delay was noted when the tube was left in place for 72 hours.[66,67] Both studies used apparently healthy animals.

Electrolyte balance is important, particularly with respect to maintaining adequate extracellular concentrations of potassium, calcium, and magnesium. Calculation of appropriate fluid replacement volume should include maintenance requirements (40 to 60 mL/kg/day) plus an estimate of losses, especially those lost through gastric decompression. Overhydration should be avoided. Whereas medical therapy with fluid replacement and antiinflammatory drugs may be helpful for horses with primary cecal impaction, surgical therapy is likely required for horses with secondary cecal emptying defect.[33,34,68] Surgical management may include typhlotomy alone, typhlotomy with a bypass procedure such as ileocolic or jejunocolic anastomosis, or a bypass without typhlotomy.[33,68] If affected horses survive postoperatively to discharge from the hospital, long-term survival appears good.[33]

A significant clinical or economic benefit of parenteral nutrition in adult horses with gastrointestinal disease has also yet to be demonstrated.[69-71] Parenteral nutrition should be considered when feed has been withheld for more than 96 hours, particularly in the horse with a surgical wound, increased metabolic demands, or risk of hyperlipidemia. Limited exercise, in the form of hand-walking, may provide some benefit to these animals, although there is no evidence that exercise has a direct impact on intestinal motility in either horses or humans with POI.[72]

The pivotal role of intestinal inflammation provides a strong rationale for the use of antiinflammatory drugs in affected animals. Flunixin meglumine is widely used in equine practice as an analgesic and antiinflammatory agent, and it also ameliorates many of the adverse systemic effects of endotoxin. A potential negative effect of NSAIDs on large intestinal contractility has been suggested on the basis of in vitro studies[73]; however, a similar response has not been reported in whole animal studies.[46,48,74] Novel antiinflammatory agents may play a role in the future, but they are not yet available for widespread use. For example, carbon monoxide (CO) has prevented POI in experimental animals, a benefit not only when CO was inhaled but also when CO was dissolved in a peritoneal lavage solution, making potential administration considerably easier and safer.[75] CO has potent intestinal antiinflammatory properties and is derived from the degradation of heme by the enzyme heme oxygenase. Expression of a heme oxygenase isoform (HO-1) can be induced by a variety of stimuli. The use of lidocaine will be discussed along with potential prokinetic drugs, but its primary benefits are likely associated with antiinflammatory effects.

Broad-spectrum antimicrobial drugs are indicated when sepsis is suspected or if the immune system is compromised, as in cases with moderate to severe endotoxemia. Theoretic concerns have been raised regarding the use of aminoglycoside antibiotics in animals with ileus. Inhibition of intestinal contractions occurred when sections of intestine were exposed to high concentrations of aminoglycoside antimicrobial drugs, but this inhibitory effect is unlikely to occur at clinically relevant doses.[76] The administration of benzyl penicillin and/or ceftiofur was associated with an increased risk of colic in the week after anesthesia for diagnostic imaging or nonabdominal surgical procedures.[77] Potassium penicillin appears to have a modest, positive effect on large intestinal motility and frequency of defecation in the horse.[78]

Motility Modification

Motility-modifying drugs could play an important role in the prevention and treatment of gastrointestinal ileus. An effective prokinetic agent could shorten the length of hospitalization, thereby reducing the cost of treatment and the number of potential complications such as weight loss, thrombophlebitis, and laminitis. There is also evidence that the development of abdominal adhesions could be minimized with the use of an effective prokinetic drug.[79,80] A potential negative impact of prokinetic use in the postoperative period after anastomosis is increased predisposition to dehiscence.[81]

Most motility-modifying drugs require a healthy intestinal wall in order to enhance intestinal contraction. There are several examples in horses in which the expected contractile response to certain drugs is blunted in the face of disease. It is reasonable to assume that many putative prokinetic drugs would be partially or

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totally ineffective in horses with abdominal disease. This would include intestine that has undergone prolonged or excessive distention or that is in any inflammatory condition, such as after intestinal manipulation or associated with primary inflammatory diseases such as DPJ or *Salmonella* enteritis. Numerous drugs have been investigated in humans with POI, but currently there is no prokinetic agent that has been found to be safe and effective.[82] The financial pressures associated with equine patient management often compel attending veterinarians to experiment with a range of putative prokinetic drugs.

Lidocaine, an aminoamide local anesthetic, appears to be the most commonly used putative prokinetic agent in the management and prevention of POI.[83] Intravenous infusion of lidocaine may suppress primary afferent neurons, thereby limiting reflex efferent inhibition of motility. It is also possible that lidocaine may block the inhibitory effect of NANC neurotransmitters on smooth muscle.[84] Lidocaine also has significant antiinflammatory properties, including amelioration of the cytokine response to endotoxemia, reduced neutrophil free-radical production, impaired leukocyte phagocytic function, and inhibition of leukocyte migration through suppression of chemokines.[85,86] In addition, lidocaine has been shown to decrease, relative to untreated controls, clinical scores following experimental endotoxin administration in healthy horses.[86] Lidocaine administration can also ameliorate the inhibitory effects of flunixin meglumine on jejunal mucosal barrier recovery following ischemia.[87,88] Because systemic administration of lidocaine was shown to increase somatic thermal antinociceptive, but not visceral distention, threshold, the beneficial effect of lidocaine in horses with gastrointestinal disease may not be associated with analgesia.[89]

A combination of intraoperative and postoperative lidocaine infusion is commonly used as a preventive strategy against POI. Postanesthetic treatment typically involves a slow intravenous bolus of 2% lidocaine (1.3 mg/kg) followed by a constant infusion at 0.05 mg/kg/min for 24 hours, with a target serum concentration between 1 and 2 mg/dL. In a prospective study of horses undergoing laparotomy for colic, the authors failed to demonstrate any difference between lidocaine and saline infusion with respect to return of borborygmi, time to first feces, or gastric reflux.[90] The study was limited by a low incidence of small intestinal strangulating lesions and POI. Lidocaine infusion was associated with a reduction in reflux duration, time to fecal passage, and hospital stay for survivors in a study of 32 horses with POI or DPJ.[84] In a larger retrospective study of 126 horses undergoing surgery for small intestinal colic, lidocaine administration was associated with a reduced incidence of POI and increased short-term survival.[43]

The rate of lidocaine infusion requires close monitoring, because infusion can be associated with reversible side effects that include muscle fasciculations, ataxia, and seizure. The drug is highly protein-bound, so hypoproteinemic horses may be more susceptible to signs of toxicity.

Bethanechol is a methyl derivative of carbachol and is an ACh receptor agonist. The drug acts both at the level of the myenteric plexus and directly on intestinal smooth cells through muscarinic receptors. The actions are primarily mediated through activation of M_3 receptors, although M_2 receptors are also involved to a lesser extent.[91] There is evidence in other species that activation of M_2 receptors not only facilitates intestinal contraction but also may lead to antinociception.[92] Bethanechol is not degraded by the enzyme anticholinesterase. As anticipated, the drug has a range of cholinergic side effects, including abdominal discomfort, sweating, and salivation, although these are minimal when the drug is administered subcutaneously at 0.025 to 0.05 mg/kg of body weight. Bethanechol is one of the most useful prokinetic agents in equine practice, as it exerts effects throughout the gastrointestinal tract; however, it does not appear to be commonly used.[83] It is most commonly used in the management of delayed gastric emptying and slowed small intestinal transit. Experimentally the drug has been shown to significantly increase gastric contractility and hasten the emptying of liquid and solid phase markers from the stomach of normal horses.[93] The drug has potent effects in the hindgut as well. Bethanechol increases both the relative strength and duration of wall contractions in the cecum and right ventral colon and consequently speeds up cecal emptying.[48] When given to ponies at a dose of 0.05 mg/kg SC, the drug increased electrical activity in the large colon for approximately 80 minutes.[74] There are wide ranges in reported dose rates of bethanechol, with the most commonly recommended dose range from 0.025 to 0.05 mg/kg SC.

Neostigmine increases receptor levels of ACh by inhibiting cholinesterase. The drug (0.022 to 0.025 mg/kg IV) promotes cecal and colonic contractile activity and enhances cecal emptying in normal ponies.[48] Neostigmine has been used in the management of small intestinal ileus but significantly delayed the emptying of 6-mm beads from the stomach of normal adult horses.[57] A survey of prokinetic use indicated that neostigmine was more commonly used in the management of large intestinal disease.[83]

Metoclopramide is a moderate partial 5-hydroxytryptamine 4 (5HT-4)–receptor agonist, a moderate 5HT-3-receptor antagonist, and an antagonist of both dopamine 1 (DA_1) and 2 (DA_2) receptors. It has been suggested that the 5HT-4 agonist properties are primarily responsible for the prokinetic effects of metoclopramide. Antagonism of prejunctional DA_2 receptors facilitates ACh release and smooth muscle contraction. The effect on dopamine receptor antagonism is absent in newer benzamides. Metoclopramide crosses the blood-brain barrier, where its antagonist properties on central DA_2 receptors can result in extrapyramidal signs, including seizure. These have been observed when the original reported dose of 0.25 mg/kg, given by intravenous infusion over 30 minutes, was used in practice.[94] These signs were responsible for poor acceptance of the drug in equine practice. An experimental bolus of endotoxin caused a delay in gastric emptying, as assessed using the acetaminophen absorption test; this delay was partially ameliorated through pretreatment with metoclopramide (0.125 mg/kg in 1 L infused over 15 minutes), but again the investigators reported adverse side effects.[95] Most investigators have failed to demonstrate significant effects of metoclopramide in experimental animals, but constant intravenous infusion (0.04 mg/kg/h) in a population of postoperative horses significantly decreased the volume and duration of gastric reflux over control and intermittent drug infusion groups.[96] Infusion was well tolerated and was superior to intermittent infusion or no treatment at all.

Cisapride is a second-generation benzamide that is commonly reported to act as a primary 5HT-4 agonist and 5HT-3–receptor antagonist. Furthermore, stimulation of 5HT-4 receptors within the enteric nervous system enhances release of ACh from the myenteric plexus, thereby promoting intestinal contraction. In vitro studies of equine jejunum concluded that the contractile actions of cisapride in the species were primarily mediated through 5HT-2 and not 5HT-4 receptors and that the response was noncholinergic.[97] Several reports suggest efficacy of cisapride in the management of intestinal disease in horses, including the resolution of persistent large colon impaction, treatment of equine grass sickness, and prevention of POI in horses after small intestinal surgery.[98-101] Cisapride has the potential to cause adverse cardiac side effects mediated through blockage of the rapid component of the delayed rectifier potassium current that include lengthening of the QT interval and development of torsades de pointes, a potentially fatal arrhythmia. These adverse effects have resulted in drug withdrawal in the United States and in many other countries.

Another benzamide, mosapride, resulted in increased myoelectric activity of the small intestine and cecum of horses after oral administration. The authors reported that mosapride is a selective 5HT-4 agonist; consequently, the reported effects are surprising given that the actions of 5-HT on the equine jejunum were reported to be primarily mediated through activation of 5HT-2 and 5HT-3 receptors.[97] Further work has demonstrated increased gastric emptying, jejunal and cecal motility following mosapride administration (2 mg/kg PO) to healthy horses.[102] Mosapride (1.5 mg/kg PO) was also shown to increase electrointestinography maximum amplitude within the

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small intestine, relative to untreated controls, following jejunocecostomy in normal horses.[103]

Tegaserod, a selective 5-HT4–receptor agonist, is used in humans for the treatment of irritable bowel syndrome.[104] In horses, tegaserod has been shown to decrease total gastrointestinal transit time[105] and increase pelvic flexure contractile activity in vitro.[106,107] Tegaserod appears safe when administered orally to horses, and therapeutic plasma concentrations, based on in vitro work, were obtained after administration of a single dose orally at 0.27 mg/kg.[106]

Domperidone acts as a competitive antagonist at peripheral DA_2 receptors; these receptors are inhibitory. The drug has been used to manage gastroparesis in humans for many years.[108] The primary use in equine practice is in the management of mares grazing endophyte-infected tall fescue (1.1 mg/kg/day PO), principally because of drug-enhanced prolactin release from the anterior pituitary. The potential prokinetic effects of domperidone have not been extensively studied in horses, but a modest efficacy of domperidone (0.2 mg/kg IV) was demonstrated in a model of experimental ileus in two ponies.[109]

Erythromycin is a direct motilin receptor agonist acting directly on smooth muscle cells as well as within the enteric nervous system to facilitate the release of ACh and motilin. Erythromycin enhances gastric emptying in normal horses but, in contrast to most other species, has a more pronounced effect on the hindgut.[93,110] This is somewhat surprising given that a higher density of motilin receptors was reported in the duodenum than in either the cecum or pelvic flexure of the adult horse.[111] Erythromycin lactobionate (1 mg/kg IV) hastens cecal emptying in normal animals and induces propagating colonic MMC-like activity across the colon. Administration is often associated with defecation and abdominal discomfort. Several problems limit the use of erythromycin as a prokinetic agent in equine practice. The principal use in human medicine has been restricted to management of acute exacerbations of diabetic gastroparesis, facilitation of feeding tube placement, and upper gastrointestinal endoscopy.[112] Although it has been shown to enhance emptying in normal horses, it was not as effective as bethanechol.[93] Given its potent prokinetic effects in the cecum, erythromycin may be helpful at preventing cecal impaction in horses after anesthesia. However, its effectiveness on cecal motility appears to be markedly reduced in the immediate postoperative period.[32] High doses, constant infusion, or prolonged use of erythromycin also induces receptor tachyphylaxis and therefore reduced efficacy. There is also evidence that as little as 2 hours of intraluminal distention leads to a reduction in the total number of motilin receptors and in the amount of motilin receptor mRNA, although erythromycin binding to remaining motilin receptors is not affected.[113] Erythromycin can induce diarrhea in adults; therefore administration over many days should be avoided. The diarrhea induced by erythromycin is most likely mediated by *Clostridium difficile* overgrowth and toxin elaboration.[114]

Given that opiates have an inhibitory effect on normal intestinal motility, it is not unreasonable to assume that antagonists may have the potential for prokinetic activity. Naloxone (0.05 mg/kg IV) has been shown to induce contractile activity in the cecum and left colon.[115] The administration of naloxone was often followed by defecation within 15 to 20 minutes. Naloxone has not been beneficial in preventing POI in human beings.[116] Peripherally acting opioid antagonists, such as *N*-methylnaltrexone (MNTX), can improve gastrointestinal tract function in humans requiring opioids for pain management. An in vitro study reported a direct contractile effect of MNTX on the circular muscle layer of the jejunum and large colon.[117] In healthy horses, MNTX administration increased daily fecal weight and, when administered concurrently with morphine, partially prevented morphine-associated increases in intestinal transit time and decreases in fecal production.[118]

α_2-Adrenoreceptor antagonists, such as yohimbine and tolazoline, counteract increased sympathetic outflow in response to nociceptive stimulation. Yohimbine (75 µg/kg by slow intravenous infusion) hastens cecal motility and emptying in normal ponies and also attenuates the negative effects of endotoxin on motility.[23,48]

Prevention and Early Identification

Close monitoring is essential when horses have multiple risk factors for either POI or other forms of ileus, such as administration of opioid agonists, α_2-adrenergic agonists, and atropine, either alone or in combination. Monitoring fecal output closely can often help owners and practitioners identify horses developing impaction, thus allowing for early medical therapy. Similarly, close postoperative monitoring and gastric decompression is important for early detection of POI.

For horses at risk of cecal impaction or other miscellaneous motility disorders, limiting the number of drugs likely to inhibit motility and altering the diet to include increased water consumption and decreased bulk may be beneficial.

Nonsteroidal Antiinflammatory Drug Toxicity

Samuel L. Jones

Use of nonsteroidal antiinflammatory drugs (NSAIDs) is common in equine practice because of their antipyretic, analgesic, and antiinflammatory properties. These drugs are used to treat horses with colic, endotoxemia, musculoskeletal disorders, and other medical problems. In addition to these therapeutic properties, NSAIDs also exhibit unwanted toxic side effects. NSAIDs have a relatively narrow therapeutic range, and when they are administered at excessive doses, toxicosis can occur within a few days. Although generally safe when administered at recommended doses,[1] some horses may exhibit signs of toxicosis at these doses within days or weeks.[2,3] The risk of toxicity is exacerbated in animals that are dehydrated or septic (e.g., endotoxemic patients). Recommended doses for NSAIDs commonly administered to horses include the following:

- Phenylbutazone, 2.2 to 4.4 mg/kg IV, PO q12h
- Flunixin meglumine, 1.1 mg/kg q12h or 0.25 mg/kg IV, PO q8h
- Ketoprofen, 2.2 mg/kg IV q24h
- Naproxen, 5 to 10 mg/kg IV, PO q12-24h
- Aspirin, 12 to 25 mg/kg PO q12-48h
- Meloxicam, 0.6 mg/kg IV q24h
- Firocoxib, 0.1 mg/kg PO q24h, 0.09 mg/kg IV q24h

Pathophysiology and Predisposing Factors The principal mechanism of the therapeutic and toxic effects of NSAIDs is related to their inhibition of prostaglandin synthesis by inhibition of the cyclooxygenase (COX) enzyme. Two isoforms of the COX enzyme have been identified: COX-1 and COX-2.[4] COX-1 is generally constitutively expressed and is thought to play an important role in maintaining physiologic homeostasis; it is found in such tissues as the gastrointestinal mucosa and kidney and in the endothelium and platelets. In contrast, COX-2 is primarily an inducible enzyme that has a critical role in inflammation and is produced by a variety of cells, including monocytes, neutrophils, epithelial cells, fibroblasts, synoviocytes, and chondrocytes.

It has been postulated that drugs that nonselectively inhibit both COX-1 and COX-2 have greater toxic potential because they inhibit prostaglandins necessary for physiologic homeostasis as well as prostaglandins that mediate inflammation and pain.[4] Both COX-1– and COX-2–dependent prostaglandins play an important role not only in maintaining the epithelial barrier in the gut but also in healing the epithelium when the mucosa is damaged (e.g., because of ischemic injury or infection). Most of the commonly used NSAIDs in horses are considered to be nonselective. Exceptions include meloxicam (3.8 to 10 times more selective for equine COX-2 versus COX-1[5,6]) and firocoxib (268 to 643 times more selective for COX-2 than for COX-1[7]). NSAIDs that are COX-2 selective are less ulcerogenic in other species and may be so in horses. For example, COX-2 selectivity

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decreases the adverse effects of NSAIDs in a model of epithelial repair in horses.[8]

Although the COX-1 versus COX-2 scheme is currently considered valid, evidence exists that it may be overly simplistic. For example, COX-1 may play an important role in inflammation and is at least partly inducible.[9] In contrast, COX-2 can be induced physiologically in various organs and tissues and by stimuli other than inflammation.[4,10] In horses, gastric ulcerogenicity of even the nonselective NSAIDs varies (phenylbutazone > flunixin meglumine > ketoprofen).[11] This difference in toxicity among drugs may relate not only to the COX selectivity but also to other factors such as tissue distribution.

The gastrointestinal tract and the kidneys are the most common targets for NSAID toxicity. NSAID-induced injury can develop anywhere in the gastrointestinal tract (from the mouth to the rectum). Two well-recognized syndromes may be attributed, at least in part, to NSAID toxicity. The first is gastric ulceration. In the stomach, inhibition of COX can increase acid secretion, decrease output of mucus and bicarbonate, impair vasodilation, and diminish epithelial restitution, cell division, and angiogenesis.[12] Inhibition of COX also impairs the healing of existing ulcers. A second syndrome attributed to NSAID toxicity is right dorsal ulcerative colitis (RDUC). Although the right dorsal segment of the large intestine is most commonly affected, other segments may also be involved. Ulcerative lesions in the large intestine can be particularly troublesome because they can cause chronic debilitation, are difficult to diagnose, and can be refractory to treatment. In the kidney, prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) produce vasodilation in the autoregulatory response of renal blood flow to hypoperfusion; consequently, hypovolemia, hemorrhage, or renal disease will increase the risk of renal NSAID toxicosis. Damage is greatest at the renal crest (papilla), and papillary crest necrosis may be associated with subsequent nephrolithiasis or ureterolithiasis and chronic renal failure.[13] In humans the most common side effect of NSAIDs is bleeding, caused in part by reduced function of platelets and in part by gastrointestinal hemorrhage.

Not all of the adverse effects of NSAIDs are attributable to COX inhibition. The NSAIDs also cause injury from a variety of mechanisms, including microvascular damage, increased intracellular concentration of reactive oxygen and other free radicals, direct local injury (particularly with ion trapping in the stomach), inhibition of cell division, and reduced hydrophobicity of the gastric mucous coat.[10,12] Inhibiting COX may shunt arachidonic acid metabolism toward the lipoxygenase pathway, thereby producing other biologically active eicosanoids. The clinical significance of this shunting is unclear, but the potential for deleterious effects exists.

Although the toxicity of NSAIDs is related to the dose and duration of administration, some horses develop toxicosis at recommended doses. Predisposing factors such as dehydration, renal disease, hepatic disease, or sepsis may contribute to the development of NSAID toxicity. Dehydration, renal disease, and hepatic disease predispose to NSAID toxicosis because of reduced tissue perfusion and reduced drug elimination. Sepsis may predispose to NSAID toxicosis because of secondary hypovolemia, decreased tissue perfusion, and direct and indirect effects of various mediators produced in response to sepsis (e.g., platelet aggregating factor). In humans, risk of NSAID-induced ulceration is increased among those with various gastrointestinal disorders (e.g., inflammatory bowel diseases [IBDs]). NSAIDs inhibit the ability of injured equine intestinal mucosa to repair, which may increase the risk of ulceration in horses with ischemic damage or intestinal infections. Body weight may be a predisposing factor in that NSAIDs are often administered to ponies, miniature horses, and small horses at doses higher than those recommended for their body weight. Inadvertent overdosing can occur regardless of body weight or size (e.g., administration of a 12-g tube of phenylbutazone paste when administration of an anthelmintic paste was intended).

Some horses may have an idiosyncratic predisposition, particularly for ulceration of the right dorsal colon. Experimentally, arthritic laboratory animals were more susceptible to NSAID-induced gastropathy than were healthy animals.[14] This finding may have relevance to horses because NSAIDs are often administered to chronically lame horses. Two or more NSAIDs are used concurrently in some situations. It is important to recognize that the effects of combining NSAIDs are additive, such that administering two NSAIDs at each of their recommended doses is similar to giving twice the recommended dose of one NSAID. Combination of two NSAIDs will prolong their pharmacologic effect and increase the risk of toxicity.[15]

Clinical Signs

Clinical signs of NSAID toxicity are usually referable to the alimentary system and vary depending on the segment involved. Oral or lingual ulceration may lead to difficulty in prehension and mastication. Esophageal ulceration may result in excessive salivation and apparent signs of pain (stretching of the neck, groaning) during swallowing. Gastric ulceration may result in slow consumption of feed, inappetence (particularly for grain in some horses), or anorexia. Horses that have gastric outflow obstruction associated with gastroduodenal ulceration may exhibit ptyalism, reflux esophagitis, and, in severe cases, spontaneous nasogastric reflux. Horses with ulceration anywhere in the gastrointestinal tract may exhibit signs of colic, which may be intermittent and may vary in severity. Horses with colonic ulceration may have soft stool or diarrhea and ventral edema secondary to enteric protein loss. Diarrhea can be severe, even fatal. Endotoxemia may result from intestinal mucosal damage caused by NSAIDs. Clinical signs of endotoxemia (e.g., tachycardia, altered appearance of mucous membranes, fever, and dehydration) may be seen in some horses with NSAID enteropathy. In some horses, hematuria may be seen.

Horses may have clinical signs days to weeks after having been administered NSAIDs. Such horses typically are presented because of recurring colic, weight loss, or loose manure. It is particularly important in these horses to determine whether there is any history of NSAID administration, even if it was several weeks previous to the time of presentation.

Diagnosis

Diagnosis is usually made on the basis of history of NSAID use, clinical signs, and clinicopathologic findings. The most consistent clinicopathologic abnormalities in horses with NSAID toxicosis are hypoproteinemia and hypoalbuminemia, presumably from loss of protein through inflamed and/or ulcerated intestinal mucosa. These findings are more commonly observed with damage to the distal intestinal tract and are not reliable for diagnosis of NSAID gastropathy. Some horses have decreased serum concentration of calcium, presumably attributable to intestinal loss of protein-bound calcium. In horses with NSAID-induced diarrhea, hyponatremia, hypochloremia, hypokalemia, acidemia, and hypovolemia may be observed if the diarrhea is severe. In such cases, hypovolemia may make the serum protein concentration appear to be higher than its actual value would be were the horse adequately hydrated.

In chronic cases, horses may be anemic from inflammation, intestinal loss of blood through ulceration, or reduced function of platelets. Occult blood may be found in the feces of horses with lesions in the more distal portions of the intestinal tract. Tests for occult blood often lack sensitivity, and false-positive results may be expected for up to 24 hours after rectal palpation.

The concentration of leukocytes is usually within the reference range, although leukocytosis and hyperfibrinogenemia, associated with inflammation, and leukopenia and neutropenia, presumably caused by endotoxemia, can be seen in some horses with acute NSAID toxicosis affecting the distal intestine. Generally, results of peritoneal fluid analysis are within reference ranges, but increased concentration of nucleated white blood cells (WBCs), total protein, and fibrinogen may be seen when there is advanced intestinal damage or intestinal vascular infarction. When findings of cytologic examination of peritoneal fluid are abnormal, results are more consistent with nonseptic than septic inflammation; however, septic

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inflammation may be observed when severe intestinal ulceration leads to transmural lesions and septic peritonitis.

Several clinicopathologic changes may accompany NSAID-induced renal damage. The most consistent finding is decreased urine specific gravity, from 1.008 to 1.020. Inability to properly dilute urine can be found with acute NSAID toxicosis for years after the original insult. This results from preferential damage to areas of the kidney that contribute most to concentrating urine (medulla, papilla). In chronic cases urine specific gravity typically ranges from 1.013 to 1.020. Some horses with NSAID toxicosis are azotemic. In acute cases azotemia can result from dehydration, NSAID-induced alterations in renal blood flow, and tubuloglomerular feedback mechanisms. Chronic azotemia, with serum creatinine ranging from 2.1 to 3.5 mg/dL, results from tubuloglomerular feedback mechanisms that reduce glomerular filtration to compensate for reduced reclamation of solutes in the medullary collecting ducts. In acute NSAID toxicosis, there may be overt hematuria. In other cases, urinalysis may reveal occult blood, increased renal cells, and increased WBCs. In chronic cases other than decreased urine specific gravity, urinalysis results are typically normal.

Endoscopy can be useful to visualize the location and extent of esophageal and gastric lesions. NSAID-induced gastric lesions are more common in the glandular epithelium, although nonglandular lesions can be observed. Contrast radiography or scintigraphy may be useful to document delayed gastric emptying in some horses. Lesions of the jejunum, ileum, cecum, and colon can be difficult to identify without celiotomy and enterotomy. Isotope-labeled WBC scintigraphic scans may identify colonic ulceration[16]; the sensitivity and availability of the procedure is limited, however. Ultrasonography may reveal thickening of the right dorsal colon or other colonic segments, but the technique appears to lack sensitivity.[17] Horses with renal crest necrosis may have increased ultrasonographic echogenicity of the renal crest and echogenic debris in the renal pelvis.

Management Administration of NSAIDs should be discontinued if NSAID toxicosis is suspected. Gastric lavage and administration of 1 gallon of mineral oil per 450 kg of body weight via nasogastric tube may be of benefit in horses with acute NSAID overdose to reduce the absorption of the administered NSAID. Treatment for gastric ulceration with a proton-pump inhibitor (e.g., omeprazole [GastroGuard, Merial Ltd., Iselin, N.J.]), an H_2-receptor blocker (e.g., ranitidine), and/or sucralfate should be implemented for horses with gastric ulceration. Sucralfate (10 to 20 mg/kg PO q8-12h) may also have a benefit in more distal segments of the equine intestine affected by NSAID toxicity. Sucralfate reduced ulceration in the stomach, small intestine, and colon and reduced protein loss in weanling age horses treated with an overdose of phenylbutazone.[18]

Regardless of the site of NSAID toxicity, administration of PGE analogs or mimics may be of benefit because administration of a synthetic analog of PGE_2 has been demonstrated to prevent phenylbutazone-induced gastrointestinal lesions in horses.[19] Misoprostol, a synthetic analog of prostaglandin E_1, ameliorated the effect of flunixin and promoted repair in vitro of equine intestinal mucosa damaged by ischemia.[20] Misoprostol can be administered orally starting at doses of 5 µg/kg q12h or 2 µg/kg q6h. Some horses will develop signs of abdominal discomfort or diarrhea at these doses; another protocol is starting at 1.5 µg/kg q8h for 2 to 4 days and increasing at increments of 0.5 µg/kg q8h every 2 to 4 days until a maintenance dose of 2.5 to 3 µg/kg q8h is achieved. Because of the paucity of experimental and clinical data for this drug, dosage schedules should be individually tailored for the horse's illness and tolerance to the drug.

For horses with hypovolemia secondary to colitis, administration of crystalloid fluids is indicated. Infusion of plasma may benefit horses with NSAID-induced enteropathies and signs of endotoxemia. The aim of plasma transfusion in a hypoproteinemic horse with colitis need not be to increase the plasma concentration into the reference range, because this may be cost-prohibitive and infused protein may be rapidly lost via the intestinal tract. Smaller volumes of plasma (1 to 3 L in an average-size horse) may exert beneficial effects by increasing colloid oncotic pressure and perhaps by modulating the effects of endotoxemia. Alternative colloidal fluids may be beneficial as well. Hetastarch (5 to 10 mL/kg IV q48-72h) may maintain plasma colloid oncotic pressure in the acute stages of the NSAID toxicity. Administration of broad-spectrum antimicrobial drugs may be indicated when signs of endotoxemia are observed. Parenteral administration of antimicrobial drugs is preferable to oral administration in horses with colitis because of the presumed increased risk of antimicrobial-associated diarrhea with the oral route. Oral administration of metronidazole (10 to 15 mg/kg PO q8-12h) might be an exception to this guideline, because evidence exists that metronidazole may exert an antiinflammatory effect and enhance healing in NSAID-induced intestinal ulceration.[21]

For horses with RDUC, dietary management directed toward providing a low-bulk diet in the form of a pelleted concentrate and restricting or eliminating ingestion of roughage is recommended. The aims of this approach are to decrease the mechanical and physiologic load of the colon. A complete pelleted diet (i.e., a diet that contains both concentrate and adequate but relatively low dietary roughage) will decrease intestinal fill in the colon. A diet lower in fiber should decrease the physiologic load of the colon because the cecum and large colon are the primary sites in horses of fiber digestion and exchange of fluid and electrolytes. Concentrate should be fed in smaller amounts and frequently (four to six feedings per day). Addition of corn oil may provide additional calories and may also aid in healing of the damaged intestinal mucosa by promoting PGE_2 production. Some horses will not eat complete pellets, and some horses that have roughage withheld will eat bedding or wood as a consequence. These horses should be allowed to eat fresh grass in small amounts on a frequent basis (four to six times daily). The importance of, and optimal duration for, restriction of roughage is unknown, but it likely requires months for the colon to heal. Horses should be changed from, and returned to, their usual diet over a period of several days to decrease the risk of inducing other digestive disorders.

Feeding psyllium mucilloid may promote colonic healing in horses with RDUC. In other animal species, psyllium mucilloid has been demonstrated to increase the concentration of short-chain fatty acids of the large bowel, and increased short-chain fatty acids can promote colonic mucosal repair.[22] The amount and duration of psyllium mucilloid administered orally that is required to alter the colonic concentration of short-chain fatty acids and the role of short-chain fatty acids in repair of RDUC in horses is unknown. Continuous feeding according to manufacturer's recommendations for 3 to 6 months is suggested, or feeding 1 to 2 oz of psyllium mucilloid once or twice daily for the same duration may be considered.

Horses with strictures of the pylorus, duodenum, jejunum, or colon may require surgical management. Bypass or resection of affected intestinal segments may be necessary.

Limiting the extent of predisposing factors, such as dehydration, should decrease the risk of NSAID toxicosis. Avoiding use of NSAIDs or limiting the dose and duration of treatment to the minimum that is required to control the primary problem is recommended to decrease the risk of NSAID toxicosis. Other approaches to analgesia, such as regional (epidural or perineural nerve blocks of distal limbs) anesthesia or administration of butorphanol or lidocaine via constant rate infusion should be considered.

Fluid Therapy for Horses with Gastrointestinal Diseases

Tiffany L. Hall

Most horses presenting with acute gastrointestinal disturbances will require fluid therapy to address decreased intake or excessive loss

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of fluids and correct alterations in acid-base and/or electrolyte balance. Conditions such as high-volume diarrhea and gastric reflux necessitate aggressive fluid therapy to correct hypovolemia, whereas other conditions (including intraluminal impactions) may require a more conservative approach to maintain appropriate hydration. Assessment of hydration status and acid-base balance in horses presenting with gastrointestinal disease, as well as an understanding of the primary gastrointestinal condition, is critical to developing a plan for fluid therapy. This section focuses on fluid therapy in horses with gastrointestinal disease. (For a more in-depth discussion of critical care and fluid therapy for horses, including selection of fluid types, monitoring and assessing fluid resuscitation, and complications associated with fluid therapy, please see Chapter 44.)

Identifying Patients Requiring Fluid Therapy

Clinical assessment begins with distinguishing hypovolemia from dehydration (Fig. 32-83). Hypovolemia is an emergency due to an acute decrease in circulating blood volume resulting in decreased tissue perfusion, anaerobic metabolism, organic acidosis, and ultimately shock. Clinical diagnosis of hypovolemia is based on altered perfusion parameters, including increased jugular refill time, prolonged capillary refill, tachycardia, poor peripheral pulse quality, decreased extremity temperature, decreased urine production, and/or altered mentation. Dehydration, on the other hand, is associated with a more insidious decrease in total body water and clinical signs reflect this, including decreased skin turgor, decreased tear film, sunken eyes, and tacky mucous membranes.

Laboratory parameters are beneficial in evaluating hydration status, developing a fluid plan, and monitoring response to therapy. Packed cell volume (PCV) and plasma total solids (TS) are commonly used to assess hypovolemia; however, these are neither sensitive nor specific. Splenic contraction and protein loss are two conditions commonly seen in horses presenting with acute abdomen which affect the clinical utility of PCV/TS alone in assessing hydration. PCV/TS values are most useful when greatly increased or when used serially to monitor the response to fluid therapy.

Increased concentrations of blood lactate serve as an indicator of decreased tissue perfusion. The most common causes of increased lactate in the horse with gastrointestinal disease are hypovolemia, endotoxemia, and intestinal ischemia secondary to strangulation. Lactate can be measured in the field on whole blood using handheld analyzers. Increased blood lactate concentrations were associated with worse outcomes in equine colic[1] and should be suspected in metabolic acidosis (decreased pH, negative base excess) in the absence of hyperchloremia or hyponatremia.[2]

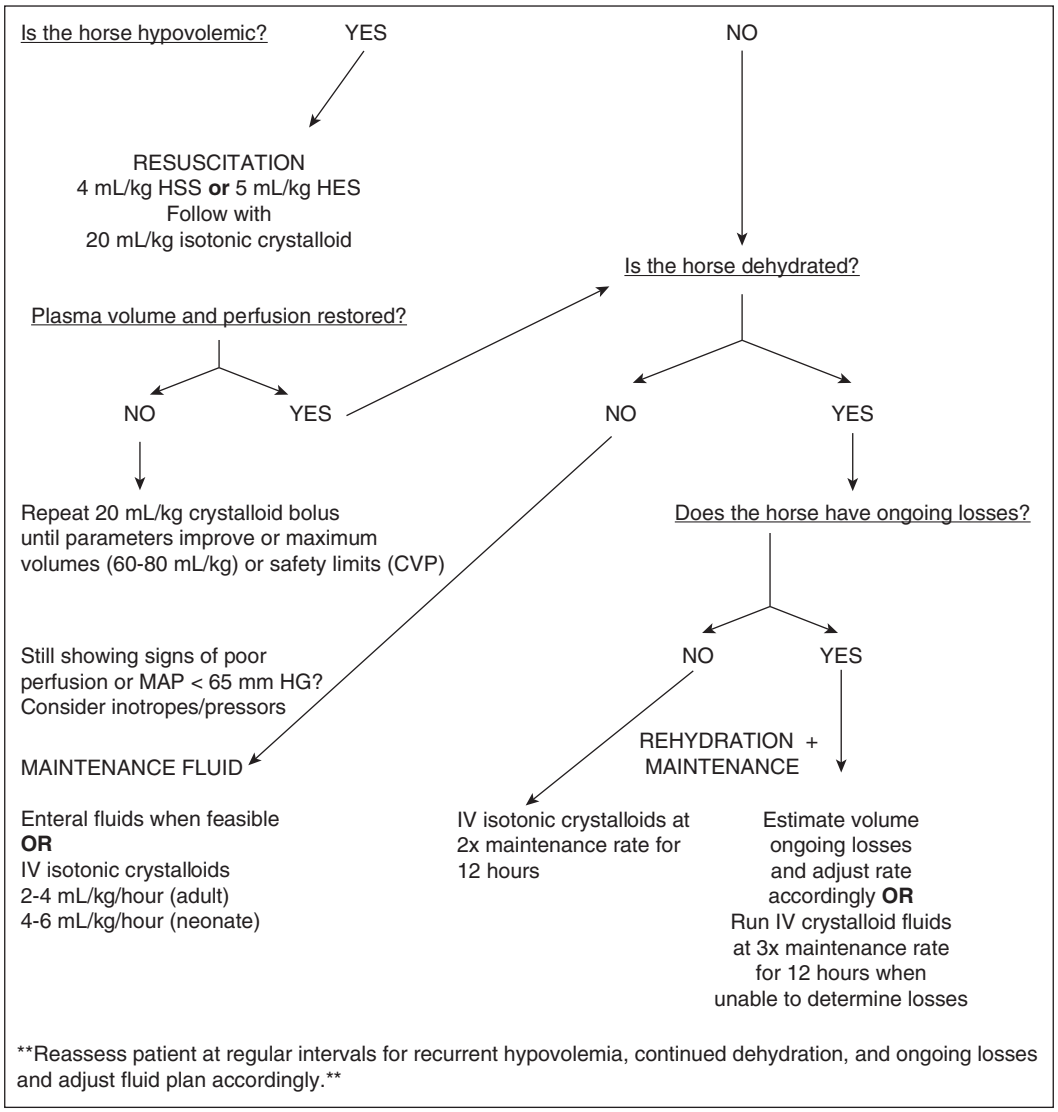


FIG. 32-83 Clinical assessment of perfusion parameters and hydration status.

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Plasma or serum creatinine concentrations are useful to assess hydration status in the absence of renal dysfunction. Creatinine concentrations up to 3.5 mg/dL (310 µmol/L) are common with moderate to severe hypovolemia, and concentrations as high as 5 mg/dL (450 µmol/L) are possible with prolonged or marked hypovolemia. Even in severe hypovolemia, the creatinine concentration will not increase by much more than 2.3 mg/dL (200 µmol/L) per day.[3]

Urine specific gravity provides valuable information regarding renal function and hydration status. High urine specific gravity (>1.040) indicates probable dehydration and normal renal function. Isosthenuria (1.010 to 1.015) indicates possible renal damage or a recent high fluid load. Urine specific gravity is especially useful in monitoring hydration status of neonates, as these patients are normally hyposthenuric (<1.010) when well hydrated, although this can be affected by the types of fluids administered (colloids vs. replacement fluids vs. maintenance), medications, inappropriate antidiuretic hormone (ADH) secretion, and glucosuria.

Central venous pressure (CVP) is an indirect measure of the quantity of blood returning to the heart, or preload, and is often used in the hospital setting to assess restoration of circulating volume, assuming normal cardiac function. The normal CVP of the adult horse is 7 to 12 mm Hg. Assessment of CVP is one of the more accurate, readily available methods of evaluating response to fluid therapy; however, measurement is affected by a number of factors, including catheter placement, head position, and presence of distributive shock.[4]

Measurement of blood pressure, particularly mean arterial pressure (MAP), is also important in determining efficacy of fluid resuscitation for improving tissue perfusion. Blood pressure in the horse may be determined directly or indirectly using oscillometric devices. When CVP is normalized, indicating restoration of blood volume, but MAP is decreased (<60 to 65 mm Hg), inotropes and pressors are often used to improve vascular tone and restore normal tissue perfusion.[4]

Formulating a Fluid Therapy Plan

The goals of fluid therapy are to increase cardiac output, by increasing and then maintaining cardiac preload; improve oxygen delivery; and correct electrolyte and acid-base disturbances. The plan for fluid therapy consists of four overlapping phases: (1) resuscitation, (2) rehydration, (3) maintenance, and (4) ongoing loss provision. Frequent monitoring of the patient and adjustment of the fluid plan are also important to a successful outcome. The fluid plan should be based on the clinical status of the horse, an understanding of the primary disease process, and any laboratory information available.

Resuscitation

Rapid fluid resuscitation is indicated in horses with clinical signs of hypovolemia. Reversal of hypovolemia is associated with improved outcome in human medicine and is shown to improve cardiovascular parameters in horses.[5-7] Balanced polyionic, isotonic crystalloid solutions are frequently used to restore circulating volume in hypovolemic equine patients; however, the use of colloids and/or hypertonic crystalloid solutions may provide more rapid results when available and indicated.

The use of small volume resuscitation with hypertonic crystalloid and/or colloid solutions has been promoted to rapidly restore plasma volume in horses presenting with signs of hypovolemia.[8] The administration of hypertonic saline solution (HSS) was found to restore plasma volume and induce urination more rapidly than administration of an equal volume of isotonic crystalloids.[9] Hetastarch (hydroxyethyl starch solution [HES]) has been shown to increase circulating blood volume and improve tissue perfusion based on decreases in heart rate and urine concentration following administration of 10 mL/kg HES with concurrent 10 mL/kg isotonic saline to horses with colic.[10] Further, in horses undergoing exploratory laparotomy, cardiovascular indices were significantly improved following preoperative administration of 4 mL/kg 10% pentastarch compared with 4 mL/kg 7.2% saline.[11] The administration of HSS is associated with development of an inorganic acidosis and hypokalemia, and the plasma expansion effects of small volume resuscitation are short-lived; thus fluid therapy should include concurrent or immediate follow-up with polyionic, isotonic crystalloid solutions when hypertonic or colloid solutions are used.[8,9]

During resuscitation, isotonic crystalloid solutions are administered at doses of 20 to 40 mL/kg in adults (10 to 20 mL/kg in neonates) as rapid bolus. Following each 20-mL/kg bolus, clinical evaluation of the patient, including evaluation of perfusion parameters, is performed in order to assess the need for repeat boluses. If perfusion parameters and blood pressure have not normalized on obtaining a normal CVP or at the completion of a total maximum "shock dose" of 60 to 80 mL/kg crystalloids, then inotropes and pressors are often incorporated and the fluid rate adjusted to maintenance rates. In horses and foals presenting for gastrointestinal disorders, alterations in vascular permeability and decreases in protein concentrations must be considered in determining the volume of crystalloid to be administered.

Rehydration

In horses that do not present with signs of hypovolemia or whose hypovolemia has been reversed, dehydration is corrected over the first 12 to 24 hours of hospitalization. To rehydrate the patient, isotonic crystalloids are administered at rates in excess of ongoing losses plus maintenance requirements. Clinically, this is accomplished in most patients with gastrointestinal disease by administering isotonic crystalloid fluids at two to three times the maintenance rate. Once dehydration is corrected, based on clinical parameters such as PCV/TS and urine specific gravity, these rates are slowed to that needed to maintain hydration. Horses with urine specific gravities below 1.020, and foals with urine specific gravities below 1.010, are unlikely to be dehydrated.

Maintenance

Depending on the gastrointestinal disease, horses presenting for acute abdomen may have free-choice food and water withheld for a period of time during which fluid requirements must be supplemented to maintain hydration. The mean daily water intake (including the water content of feed) of normal resting adult horses is 57 to 64 mL/kg/day at ambient temperatures of 5°C to 25°C (41°F to 77°F). Mares restricted to 40 mL/kg/day demonstrated significant dehydration.[12] Maintenance fluid rates for adult horses (2 to 4 mL/kg/h) and neonatal foals (4 to 6 mL/kg/h) can be met through enteral administration when appropriate for the diagnosis and when gastrointestinal function is normal. When enteral administration is contraindicated, polyionic, isotonic crystalloids are most frequently used for the parenteral administration of fluids.

Frequent monitoring of electrolyte concentrations, as well as monitoring hydration status, should be part of the maintenance fluid plan. Replacement crystalloid solutions higher in electrolyte concentrations are usually administered over maintenance crystalloid solutions given the size of equine patients, the volume of fluids required, and availability. (See Chapter 44 for a comparison of commercially available fluid solutions.) Some patients, particularly neonates or those losing large volumes of fluid, are at risk of developing a free water deficit and subsequent inorganic acidosis when maintained on isotonic, replacement, crystalloid solutions. Monitoring of electrolytes, particularly sodium and chloride, will help identify these patients. In adults, physical examination and monitoring of body weight, PCV/TS, creatinine concentrations, and urine specific gravity are useful in evaluating the efficacy of a fluid treatment plan. Overhydration in adults with normal renal function may be indicated by frequent urination, urine specific gravity below 1.013, and development of dependent edema. In neonatal foals, body weight, urine production, urine specific gravity, and evaluation of perfusion parameters are used to monitor hydration status, and detection of excessive fluid supplementation can be difficult as nursing, neonatal

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foals normally produce hyposthenuric urine. Development of preputial or stifle edema is an indication of overhydration in neonates. As such, it is important that the volume of all intravenous solutions and enteral feedings be accounted for when calculating fluid rates in neonates to prevent volume overload.

Ongoing Losses

Horses that present with gastrointestinal conditions resulting in excessive fluid losses such as gastric reflux and diarrhea will require supplementation in excess of maintenance fluid rates. Calculating the volume of fluid lost is the most accurate method of determining how much fluid will need to be replaced. Whereas the volume of nasogastric reflux can be tracked, determining the volume of fluid lost in adults and ambulatory foals with diarrhea is not possible; therefore, frequent assessment of the patient by clinical examination and determination of relevant laboratory parameters are useful in evaluating the fluid plan to prevent continued dehydration or recurrence of hypovolemia.

Special Considerations in the Fluid Therapy Plan

The selection of fluids to be administered, rate and route of administration, parameters to be monitored, and frequency of monitoring are based on thorough individual case assessment. In addition to the various phases of fluid therapy, special circumstances encountered in horses with gastrointestinal disease must also be considered in the fluid therapy plan. These include commonly observed electrolyte disturbances, acidemia, hypoproteinemia, and endotoxemia. Table 32-9 lists common fluid choices and additives for conditions observed in horses with gastrointestinal disease.

Enteral Fluid Administration

Enteral fluid therapy may be sufficient to correct and maintain hydration in horses with gastrointestinal disease that have mild dehydration and normal small intestinal function.[13] In horses with gastrointestinal disease but no apparent dehydration, administration of an electrolyte paste and provision of fresh drinking water may be sufficient to supplement water and electrolytes.[14] However, enteral fluid therapy is contraindicated in horses with small intestinal obstruction or ileus and is not sufficient to treat hypovolemia.

Enteral fluids are often included in the treatment of impaction colics. Nasogastric administration of a balanced electrolyte solution (5.27 g NaCl + 0.37 g KCl + 3.78 g $NaHCO_3$ per L water) at 5 L/h is superior to enteral magnesium sulfate, enteral sodium sulfate, or enteral magnesium sulfate with IV crystalloids at promoting hydration of colonic contents and does not alter plasma electrolyte concentrations.[15,16] An isotonic solution for enteral administration can be made without the use of weight scales by measuring salt crystals in the barrel of a syringe (15 mL of Lite salt and 15 mL of table salt added to 4 L of water).[17] In a prospective clinical trial, enteral fluids administered at 8 to 10 L every 2 hours were successful in the treatment of 99% of colonic impactions and 83% of left-sided colon displacements.[18] As enteral fluids are significantly less costly than commercially available intravenous fluids, this is an ideal treatment in some gastrointestinal conditions.

Electrolyte Disturbances

Horses with gastrointestinal disturbances will often have changes in plasma electrolyte concentrations, which may need to be addressed during fluid therapy. Portable blood gas and electrolyte measuring equipment allows the field veterinarian to easily obtain

TABLE 32-9

Fluids and Additives for Electrolyte Disturbances in the Horse

Metabolic Disturbance	Recommended Fluid	Dose
Lactic acidosis	Polyionic crystalloids with or without small volume resuscitation (HSS/HES)	Up to 60 mL/kg/h
Hyponatremia	Isotonic crystalloids	Sodium should be corrected no faster than 1 mEq/L/h
With hypochloremia	Polyionic crystalloids or sodium chloride	
Without hypochloremia	Sodium bicarbonate	
Hypernatremia	5% Dextrose or 2.5% dextrose/0.45% sodium chloride	Sodium should be corrected no faster than 0.5 mEq/L/h
Hypochloremia	Polyionic crystalloids or sodium chloride	0.9% or 7.5%, to effect
Hyperchloremia	Increase free water intake or administration	
With hypernatremia	Polyionic maintenance crystalloid or 5% dextrose	To lower sodium no faster than 0.5 mEq/L/h
Without hypernatremia	Sodium bicarbonate	5%, slowly, to effect
Hypokalemia	Potassium chloride	10-40 mEq/L 0.5 mEq/kg/h Maximum 1 mEq/kg/h
Hyperkalemia		
With clinical signs	Calcium gluconate	1 mL/kg IV over 10 min 250 mL/1 L sodium chloride
Or >7 mEq/L	Sodium bicarbonate	1-2 mEq/L IV over 15 min
Without clinical signs	5% Dextrose in polyionic crystalloids	2 mL/kg IV over 5 min
Hypocalcemia	Calcium gluconate	250-500 mL 23% solution/5 L
Hypercalcemia	Polyionic crystalloids (without calcium)	4-16 mg/kg as an initial dose
	Magnesium sulfate	10 mL/5 L (max 50 mg/kg)
Hypomagnesemia	Magnesium sulfate IV	4-16 mg/kg as an initial dose
Hypermagnesemia	Calcium gluconate	250-500 mL of 23% solution
Hypoalbuminemia	Fresh or fresh frozen equine plasma	To effect, not to exceed 10 mL/kg
	Hetastarch	5-10 mL/kg to increase COP

COP, Colloid oncotic pressure; *HSS/HES,* hypertonic saline solution/hydroxyethyl starch solution (hetastarch); *IV,* intravenous; *PO,* by mouth.

Always take into account all disturbances present before commencing treatment.

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information necessary to guide electrolyte supplementation and selection of appropriate fluids. Without case-specific determination of electrolyte concentrations, maintenance phase fluids in gastrointestinal disease should be limited to administration of isotonic, polyionic crystalloid fluids supplemented with 10 to 20 mEq/L of potassium chloride.

Generalized changes in electrolytes among horses with gastrointestinal disease are related to decreased feed intake, increased loss, and sequestration. Decreased sodium and chloride concentrations may be observed in cases of acute colitis, peritonitis, or intestinal torsion.[19] Hypochloremia without hyponatremia is also observed in proximal enteritis and grass sickness associated with loss of hydrochloric acid in gastric reflux.[20] Hypokalemia is commonly seen in horses following colic surgery because of decreased feed intake, enhanced mineralocorticoid release, and kaliuresis associated with administration of sodium-containing fluids. Hypokalemia is also seen with colitis and metabolic alkalosis. Potassium is primarily an intracellular ion and decreases in whole body potassium may not be detected by plasma measurements; therefore, it is common to supplement potassium in maintenance fluids. Hypocalcemia is commonly observed in horses presenting with gastrointestinal disorders, including those with surgical colic, colitis, functional disorders of the small intestine, organic acidosis, and endotoxemia.[21] Plasma ionized calcium provides a better indicator of physiologic calcium status, as hypoalbuminemia occurs in many gastrointestinal conditions. In one report, 44% of horses with gastrointestinal disease had low plasma magnesium concentrations.[22] Hypomagnesemia may be associated with refractory hypocalcemia and hypokalemia; thus supplementing magnesium may be beneficial in those situations. Hypophosphatemia has been reported in horses with strangulating intestinal lesions or intestinal ileus.

Acidosis

Inorganic and organic metabolic acidoses occur frequently in horses presenting with gastrointestinal disorders. Inorganic acidosis occurs with hyponatremia (colitis, peritonitis, intestinal torsion) and relative or absolute hyperchloremia (colitis, free water deficit). These patients often have a normal anion gap. Organic acidosis in horses with gastrointestinal disease is common, secondary to elevated lactate concentrations and associated with an increased anion gap. Increased blood or plasma lactate concentrations in these cases are usually a result of poor tissue perfusion or inappropriate anaerobic metabolism in endotoxemia.

Metabolic acidosis in horses with gastrointestinal disease will usually resolve with correction of hypovolemia and restoration of tissue perfusion. Occasionally, in the case of inorganic acidosis, electrolyte abnormalities may be severe enough to require selection of a particular commercially available fluid. Administration of sodium bicarbonate to correct acidemia is reserved for cases in which the blood pH falls below 7.2 or where there is a severe hyponatremia with relative hyperchloremia, and only in patients with normal respiratory function.

Other, less frequently observed acid-base disorders in horses with gastrointestinal disorders include inorganic metabolic alkalosis (hypochloremia or hypoalbuminemia), respiratory alkalosis (hyperventilation associated with pain), and respiratory acidosis (hypoventilation caused by extreme abdominal distention or respiratory center depression).[2]

Hypoproteinemia

Hypoalbuminemia is seen in horses with moderate to severe compromise of the colon, parasitism, intestinal malabsorption, or third spacing (peritonitis). Endotoxin exposure and ischemia-reperfusion injury induce capillary damage that allows plasma albumin to leak out into the interstitium. Clinical signs of hypoalbuminemia are peripheral, tissue, and organ edema leading to reduced oxygen uptake by cells and, in severe cases, organ failure. Albumin is a weak acid; thus severe hypoalbuminemia may contribute to metabolic alkalosis or mask concurrent metabolic acidosis.[2] Determination of the colloid oncotic pressure (COP) of the plasma is most useful in guiding colloidal fluid therapy, particularly when synthetic colloids have previously been administered.[23] COP and total protein concentrations were found to decrease over the course of anesthesia in horses undergoing colic surgery.[24]

Hypoalbuminemia and decreased COP should be treated when acute or if there are clinical signs. Options for colloidal support in horses include plasma transfusion and synthetic colloid solutions, such as HES. Approximately 6 to 8 L of fresh-frozen plasma are required to effectively treat significant hypoproteinemia in the adult horse, making plasma cost prohibitive in the treatment of decreased COP.[25] However, plasma has a role in treatment of systemic inflammatory response syndrome (SIRS) by providing antithrombin III (AT-III) and other cofactors. The administration of 6% HES at 8 to 10 mL/kg to conscious hypoproteinemic horses significantly improved COP for 6 hours after infusion and maintained an oncotic effect for 24 hours; however, administration of 2.5 mL/kg 6% HES did not alleviate the decrease in COP observed in healthy horses receiving crystalloid during general anesthesia.[26,27]

Endotoxemia

Horses presenting with gastrointestinal disorders, particularly ischemic lesions and conditions involving inflammation of the bowel, are at risk of exposure to endotoxin as damage to the intestinal mucosa allows intraluminal bacteria to gain systemic access. During endotoxemia, capillary damage leads to increased vascular permeability, altering fluid dynamics and contributing to tissue edema. HSS has been shown to reduce the capillary endothelial swelling that may occur as part of SIRS and improve tissue microcirculation and oxygen delivery.[28]

Studies of the effects of HSS in horses with experimentally induced endotoxemia have yielded mixed results. Whereas one study found that administration of 5 mL/kg HSS following administration of a low dose of endotoxin (1.64 ± 0.22 μg/kg) to conscious horses improved cardiac output and decreased peripheral vascular resistance compared with isotonic saline, a study in horses under general anesthesia did not support these findings.[29] Administration of combined 5 mL/kg HSS and 10 mL/kg HES to horses with hyperdynamic shock induced by administration of 50 μg/kg endotoxin did not improve cardiopulmonary parameters while horses were under general anesthesia.[30] The combination of HSS and HES may protect against hypocalcemia associated with endotoxemia without negatively affecting coagulation beyond that seen in control horses.[31]

Nutritional Support

Horses presenting with gastrointestinal disease will often be inappetant or will be held off feed as part of their treatment for a variable amount of time. An enteral diet based on the horse's normal diet is the first choice for nutritional support; however, in adult horses held off enteral feeding for over 3 days because they have gastric reflux, ileus, esophageal obstruction, or anorexia should be supplemented parenterally.[32] In addition, horses with moderate obesity which are not eating may be at increased risk of developing hyperlipemia and should be supplemented earlier. Parenteral nutrition can range from the administration of 1% dextrose in intravenous fluids to the administration of a combination of dextrose, amino acids, and lipids based on the maintenance energy requirements for the individual patient. (See Chapter 50 for a complete discussion of nutritional support in the horse.)

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Ruminant Alimentary Disease

Bradford P. Smith, *Consulting Editor*

Dental and Periodontal Diseases

Guy St. Jean

Eruption of Teeth

Determining an animal's age by examining the teeth is not an exact science, because the appearance of the teeth can be affected by inherited factors, nutrition, and geographic location.[1,2] At birth or within 2 weeks, four deciduous incisors usually are present. All eight deciduous incisors erupt within the first month.[3] The fourth incisor (corner) is a modified canine tooth. The incisors meet with the dental pad of the upper jaw for the purpose of gripping and cutting herbage. Usually, all three pairs of deciduous premolars have erupted at birth or shortly afterward.[1,2] In cattle, the formula for the deciduous teeth is as follows:

$$2\,(\text{incisors } 0/4, \text{premolars } 3/3) = 20$$

The age at which permanent teeth erupt often is the best criterion for determining the animal's age if a registration certification is not available. However, systemic illnesses and malnutrition can retard dental development and cause retention of the deciduous teeth.[4] The first molars erupt at 8 months of age and are fully developed at 12 months. At 18 months, the second molar is fully developed. The third molar erupts at 24 months and is fully developed at 30 months. The permanent premolar teeth start to replace the deciduous at 24 months and the 3 permanents are usually present at 3 years.[1,2] The first pair (centrals) of permanent incisors erupt at 18 to 24 months of age. The second pair (medials) of incisors appears at 24 to 30 months. At 3 years of age, the third pair (laterals) of incisors erupt. Between 3½ and 4 years of age, the fourth pair (corners) of incisors erupt.[3,4] Consequently, cattle have a complete set of permanent teeth at age 4½ years. Cattle have a shallow depth of the alveolar socket and associated tooth root. This may lead to dental attrition in cattle more readily than in horses. However, this also makes dental extraction easier in cattle compared with horses. The formula for the permanent teeth in cattle is as follows:

$$2\,(\text{incisors } 0/4, \text{premolars } 3/3 \text{ molars } 3/3) = 32$$

The deciduous and permanent dental formulas of the sheep and goat are identical to those of cattle.[3] In sheep and goats, the periods of eruption are as follows: The incisors are present at birth or within the first 4 weeks. The premolars erupt 2 to 6 weeks after birth. The first pair of permanent central incisors (centrals) replaces the deciduous teeth at 12 to 18 months. The third pair (laterals) erupts between 30 and 36 months; and the fourth pair (corners) appears at 3½ to 4 years. The three permanent premolars have erupted between 18 and 24 months of age; the first molar at 3 months, second molar between 9 to 12 months, and the last molar between 18 to 24 months.[3]

Examination of Teeth

Dental disease in ruminants should be considered first on a flock or herd basis.[5,6] Determining dental health is particularly useful when unconventional feeds are incorporated into the herd nutritional program.[7,8] The clinical manifestations of dental diseases include inadequate food intake, inadequate calf development, weight loss, unthriftiness, low body condition score, quidding, low pregnancy rate in replacement heifers, and mandibular or maxillary swellings, or draining tracts.[3,6-9] Dental examination is especially of concern when animals are grazing on short grass. Examination of the herd should then be followed by dental examination of individual animals. For examination of the premolars and molars, the tongue should be withdrawn from the mouth and held at the commissure of the mouth opposite the teeth being examined. Use of a headlight or flashlight is useful to perform a good oral examination. A small dose of xylazine (0.03 to 0.04 mg/kg IV) and the use of a mouth speculum allows for much more thorough dental examination, including manual palpation in cattle. Radiographic examination can also be important in certain cases.

The incisors have a sharp edge in front and are used for gripping and cutting herbage.[3,6] The incisors should be aligned closely with little space between them.[3,6] In sheep, the periodontium of the incisor allows a movement of up to 2 mm anterioposteriorly to accommodate rotating or turning forces during grazing.[9] This makes the sheep incisor very prone to loss following periodontal damage. The length of the premolar and molar teeth and their firm placement in the alveolar bone means that they are lost less often than the incisors.[1,2,6]

Dental Attrition and Erosion

Rapid wearing of teeth is seen most commonly in grazing sheep 5 years of age and older. Sheep and cattle grazing forage-deficient or sandy pastures and arid ranges in Africa, Australia, New Zealand, and the southwestern United States often display accelerated rate of tooth wear.[6,10] In Rhodesia, the incisors of Hereford cattle had an increased rate of wear because of softer enamel, compared with those of indigenous cattle.[11]

Examination of an animal with dental attrition reveals worn incisor and/or molar teeth (or both); often only short stumps are seen. The teeth also may be loose, fractured, or missing. Dental attrition from excessive wear needs to be differentiated from periodontal disease that causes tooth loss.[6,12,13] The pathogenesis of excessive tooth wear relates to tooth hardness and diet quality. Ingestion and mastication of soil and sand with forage abrades and wears the incisor and molar teeth. In New Zealand, dental attrition in sheep was attributed to acids and enzymes in the herbage consumed, acting on the tooth dentine.[10] A calcium deficiency or calcium/phosphorus imbalance, creating softness of the tooth enamel and dentine, may accelerate the rate of wear.

In the United States feeding fermented sweet potato cannery waste to cattle resulted in substantial increases in incisor erosion.[7,8] Cattle producers feeding sweet potato cannery waste noticed poor growth rate, inadequate calf development, low pregnancy rates in heifers, and worn, mottled, discolored incisors.[7,8] Sweet potato cannery waste is highly acidic (pH 3.2) and causes calcium loss and tooth erosion. Deciduous teeth are etched more rapidly, placing young cattle at higher risk for severe tooth wear and dental infection. In addition, the distance between the original enamel surface and the pulp chamber is less in deciduous teeth than in permanent teeth, which is again more significant in younger cattle.[7,8] Mixing 10% broiler litter with sweet potato cannery waste raised the pH to 4, thus providing a palatable high-quality feed and preventing the severe dental problems associated with sweet potato cannery waste alone.[7]

A syndrome involving excessive wear of deciduous incisor teeth, maleruption of permanent incisors, and an increased prevalence of dentigerous cysts in sheep has been reported from New Zealand.[14] Excessive wear of the incisor teeth of cattle also was recorded on the same farms. Ingestion of soil during winter because of the inclement weather, overgrazing of pastures, and the presence of low copper levels in the blood of affected animals were the main causes for the

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syndrome.[14] Dental attrition is prevented by providing supplemental feed to avoid overgrazing of pastures. The addition of 1% ground limestone to the feed in calcium-deficient areas is recommended.[15]

Periodontal Disease

Periodontal disease refers to a disease involving the supporting tissue that surrounds the teeth.[16,17] Periodontal disease of sheep is endemic in parts of New Zealand. A periodontal disease known as *cara inchada,* or "swollen face," has caused losses of cattle in Brazil.[18,19] Periodontal disease is characterized by protruding and loose incisors.[6,12] With time, incisors, premolars, and molars may be missing. Why periodontal disease is prevalent in sheep, but less common in cattle, is unknown. Periodontal disease results in pain on mastication, leading to poor maceration of food and reduction in food digestibility.

Periodontal disease has been associated with bacterial plaque-induced gingivitis.[16,19-21] The acute gingivitis is replaced progressively by a chronic inflammation in the gingival sulcus. The periodontal ligament is destroyed by plaque-forming oral microorganisms and host enzymes. At this stage, periodontal pockets are formed, which lead to loosening of teeth. This process may take months or years. With time, extension of the infection progresses to the apical area. The gum margin begins to recede over the lesion, food accumulates within the pocket, and the entire alveolus becomes infected. At that point, the tooth becomes a sequestrum. The alveolar pyorrhea causes a periostitis of the external surface of the alveolar process, and swelling is observed. Once a tooth is lost from an affected alveolus, granulation tissue fills the alveolus. Deep to granulation tissue, alveolar bone is redeposited.

Bacteria such as *Bacteroides* spp., *Actinomyces* spp., and spirochetes; metabolic or immune disorders in the host; and mechanical or chemical agents have been implicated in the pathogenesis of periodontal diseases in sheep.[6,20,22,23] Bacterial invasion in the gingival pockets has been associated with a defect of host immune competence.[24] Hypomagnesemia has been a common finding in sheep with periodontal disease, but this may be secondary.[23] Gingival trauma may be important in the etiology.[25] Dissolution of the enamel at the attachment of the gingival epithelium by organic acids from microorganisms of the soil may be a predisposing factor.[26] The serum values for calcium, albumin, alkaline phosphatase, and citrate were lower for sheep with periodontal disease compared with sheep not affected by dental disease.[27]

A postmortem examination of Scottish-Hill sheep revealed that 60% of 478 aged sheep had either loose or missing teeth. Gingival pockets were present in 87% of the population and were correlated with tooth looseness.[28] In the United States a 25% mortality caused by dental disease in a herd of 300 ewes has been reported.[29] The clinical signs were depression, anorexia, ataxia, and emaciation.[29] Necropsy revealed dental disease of the mandibular teeth with plaque, plant fibers in periodontal pockets, and osteomyelitis of the mandibular bone. An initial trauma to the gingiva from cheatgrass awns in the hay field was implicated.[29]

A particular type of periodontal disease in cattle has been reported from Brazil.[18,19] This condition involves an inflammatory process of the periodontium of calves and older Zebu cattle that results in alveolar periostitis of the maxilla or, less often, the mandible.[18,19] Examination reveals deep periodontal pockets and loss of or loosened teeth. Affected animals suffer from malnutrition, diarrhea, and loss of condition and often die. *Bacteroides* and *Actinomyces* organisms often are found in the lesion and are suspected of causing the disease.[18] This disorder is seen only in certain areas of Brazil, and the cattle improve if moved to unaffected areas. In one trial the development of periodontal disease in calves was avoided by administration of the antimicrobial drug spiramycin.[19]

The assumption that incisor condition is a good indicator of future productivity is not well founded. Little scientific evidence exists on which to base the practice of culling sheep with periodontal disease. Three farms with a high prevalence of periodontal disease were selected, and the body condition and weight of the sheep were compared with those of sheep with no signs of periodontal disease. On only one farm was a significant association noted between periodontal disease and body condition or weight. It was concluded that periodontal disease in sheep may impair productivity on some farms, but not others.[30,31]

Treating periodontal disease on a flock basis often may prove impractical. Dental treatment, drug therapy, and management change have been tried in sheep. One form of dental treatment, tooth grinding, consists of trimming the incisors to the level of the lower dental pad.[12] Two trials of the productivity effects of tooth grinding have been conducted. Neither has shown any positive benefit from the procedure.[30] An attempt to influence the development of periodontal disease in sheep by long-term treatment with tetracycline and metronidazole has proved ineffective.[21] In commercial sheep, surgical treatments could improve conditions such as periapical and gingival abscesses, but these treatments are not economically feasible.

Sheep can live without incisors provided that they do not have to graze too closely. Supplementary feeding or improved pasture usage for these sheep should provide a net gain to the owner. When premolar and molar teeth are involved, this approach is unlikely to be effective because of the inability to chew and ruminate efficiently.

Dentigerous Cysts

Dentigerous cysts have been described in ruminants, particularly sheep.[14,31] These are odontogenic cysts of unknown cause that manifest as localized, bony swellings. Radiographs demonstrate the cystic nature of the swelling and reveal one or more teeth in the cyst.[14,31] For valuable individuals, treatment is surgical.

Developmental Anomalies and Retention of Deciduous Teeth

Developmental anomalies have been reported in cattle.[5] Occasionally, tooth buds fail to develop. The fourth pair of permanent incisors is the set most often absent. The mandibular premolar on one or both sides also occasionally fails to form. The permanent incisor teeth have been observed to be rotated up to 180 degrees in the alveolus. Rotation of the first permanent mandibular premolar has been seen. The rotation was 90 degrees, and no cause could be detected. Retention of a deciduous premolar is common in 12- to 18-month-old cattle. This results in difficulty in masticating food and excessive salivation. The treatment consists of removing the deciduous premolar with a forceps.

Overgrown or Loose Molar Teeth

Overgrown molar teeth are found most commonly in old ruminants. The opposite tooth is often missing. Food accumulates between the affected tooth and the cheek, causing obvious swelling of the face. Interference with mastication often is noted. The offending tooth should be rasped regularly or removed. A power tool to grind cheek teeth works well. Premolar or molar teeth can become loose in advanced cases of actinomycosis affecting the jaw. It may be difficult to determine whether the loose tooth is a cause or result of the bony abnormalities. One cow with maxillary lymphosarcoma and loose teeth has been reported.[32]

Broken Teeth

Broken incisors are not common because of the loose alveolar attachment of these teeth. Broken premolars and molars are more common because these teeth are more solidly attached in their alveoli; breakage usually results from attempts to masticate hard objects. Most fractures usually involve only a portion of the tooth, do not involve the root, and are asymptomatic. A sagittal tooth fracture that includes the root causes pain and may result in reduced feed intake and loss of condition. (Treatment is described later, in the section Tooth Root Abscess.)

Dental Caries

Dental caries, or decay, creates areas of decalcification of the tooth.[3] Dental caries is rare in ruminants,[3] but it sometimes can be found in

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both temporary and permanent teeth and in both dentin and enamel.[5] Interference with prehension usually is not seen. On oral examination, an orange or black pigment is seen in the defective enamel or exposed dentin; these areas should be probed with a fine dental pick or needle. Caries may be filled or the tooth extracted. In rare cases the caries can reach down the pulp cavity to the root apex, causing periodontal abscesses. (See Tooth Root Abscess, later.)

Osteodystrophia Fibrosis

Osteodystrophia fibrosa is caused by resorption of calcium from bone and its replacement by connective tissue.[33] It is seen most commonly in the goat. Osteodystrophia fibrosa can result from calcium, phosphorus, or vitamin D deficiencies or from hyperparathyroidism. Usually a growing animal is presented with a bilateral, soft, nonpainful, swelling of the maxilla and/or mandible.[33] The diagnosis is based on radiographic evidence of poorly mineralized bone and inward rotation of the premolar and molar teeth. The treatment consists of supplementing the ration with adequate mineral levels while maintaining a ratio of calcium to phosphorus of 2:1.

Tooth Root Abscess

Dental repulsion is done preferably under general anesthesia with the affected tooth uppermost. A straight incision is made directly over the longitudinal axis of the tooth. Only the bone lateral to the tooth is removed. If necessary, a chisel is used to free the tooth of bone at its rostral and caudal surface, taking care not to disturb the neighboring teeth. A dental punch is placed on the tooth root, and dental repulsion is performed. The ventral aspect of the incision can be left open for drainage, or the alveolus can be packed with dental wax, gauze, or dental material, such as Optosil (Heraeus Kulzer GmbH, Hanau, Germany).[7] Abscessed maxillary cheek teeth often result in maxillary sinusitis. The sinus must be curetted at the time of surgery and flushed daily for 1 to 2 weeks following surgery. Antibiotics are administered for 1 week, according to culture antimicrobial sensitivity results. After removal of the affected tooth, the abscess and clinical signs usually will resolve, but chronic sinusitis may require a bone flap and extensive curettage.

Dental Fluorosis

Dental fluorosis is associated with continuous ingestion of small but toxic amounts of fluorine in the diet or drinking water. Most reported occurrences of fluorosis are in cattle. Sheep are less susceptible. Developing teeth are very sensitive to the ingestion of excess fluorides. Fluorides inhibit the action of ameloblasts and odontoblasts during tooth formation, resulting in failure of the tooth to accept minerals. Fluorosis results in striations or patches (yellow, brown, green, or black) in enamel. Some erosion of the permanent tooth can be seen. Cattles are susceptible to dental fluorosis during enamel matrix formation from approximately 6 months to 3 years of age. Severe dental fluorosis results in dental wear, inability to graze properly, and difficult mastication and food intake because of tooth pain. In addition to clinical signs, the diagnosis can be made by analyzing the fluorine concentration in the blood and urine. Normal cattle have blood levels of up to 0.2 mg fluorine per mg/dL of blood and 2 to 6 mg per kg in urine. Cattle with fluorine intakes sufficient to cause intoxication may have bloods levels of 0.6 mg per kg and urine levels of 16 to 68 mg/kg. Treatment is usually to remove the animals from the source of fluorine.

Salivary Gland Diseases

Guy St. Jean

The parotid, mandibular, and sublingual glands are the three largest salivary glands in ruminants.[1] In cattle the mandibular gland is larger than the parotid gland. The adult bovine produces 50 L or more of saliva in 24 hours. Saliva is secreted continuously, but the rate of secretion is increased by feeding, rumination, and the presence of coarse feed in the rumen.[1] The saliva provides a fluid medium for transport of ingesta during deglutition and regurgitation. It also maintains adequate phosphate for bacterial digestion of cellulose in the rumen and contains bicarbonate, which acts as a buffer to maintain ruminal pH above 5.5. Ruminant saliva contains approximately 80 mEq of bicarbonate per liter.

Excessive Salivation

Excessive salivation (ptyalism) is a sign of many pathologic conditions. The volume of saliva may be normal, but if it is not being swallowed, salivation can appear excessive. As a precaution against exposure to rabies, gloves should be worn to examine the mouth of any animal that is salivating excessively. Excessive salivation may be seen with dental disease, stomatitis, foreign objects in the mouth or pharynx, or esophageal obstruction. It also has been seen with ruminal disorders, in cows that have eaten spoiled silage, and with impaction of the abomasum. Ptyalism may be a clinical sign in rabies, pseudorabies, meningoencephalitis, and slaframine toxicity.[1,2] Mercury, iodine, lead, copper, and arsenic also can stimulate secretion by the salivary glands. Treatment depends on the underlying causes.

Sialocele

A sialocele develops when saliva escapes from a duct or salivary gland and enters the surrounding tissue. The saliva contains enzymes that irritate the tissue. The accumulation of saliva is surrounded by inflamed tissue, which gives the lesion a cystic appearance. A soft, fluctuant swelling usually is seen. Signs of pain may be observed during mastication. Trauma or foreign body usually is the cause of a sialocele. The diagnosis is based on the history, palpation, paracentesis ultrasound, and sialography. Needle aspiration may yield yellow mucoid saliva. Two treatments have been described.[3,4] The first involves removal of both the mandibular and sublingual glands and ducts.[3] Surgical extirpation of the mandibular salivary gland in the caudal area of the mandibular spaces has been performed successfully in cows, sheep, goats, and buffaloes.[1] Exposure of the tissue by opening the capsule of the gland facilitates the process of extirpation and prevents trauma of the surrounding nerves and blood vessels.[3] In the second treatment option the sialocele is opened, drained, and chemically débrided using a caustic agent like iodine or copper sulfate.[4]

Parotid Gland Carcinomas

In three cows at slaughter that had parotid gland carcinomas, the neoplastic cells appeared to originate from ductal and acinar epithelium.[5] Ocular squamous cell carcinoma may spread locally to the parotid or mandibular lymph nodes.[6]

Sialoadenitis

Inflammation of the salivary glands usually is caused by nonspecific infections, penetrating wounds, or plant awns. Diffuse swelling of the salivary glands may be observed, and the swelling may be hot and painful on palpation. Abscess formation is a common complication. The pain may interfere with mastication and swallowing. Treatment consists of systemic antibiotics and antiinflammatory and analgesic drugs. Abscesses should be drained when they localize. Salivary fistulas can be sequelae to salivary abscesses.

Actinobacillosis (Woody Tongue, Wooden Tongue)

Bradford P. Smith

Definition and Etiology *Actinobacillus lignieresii,* a gram-negative rod, is a normal inhabitant of the rumen and mouth of many cattle and sheep and probably goats. When the organism enters the soft tissues through a lesion, actinobacillosis results in a granulomatous abscessation. Ruminants of all ages can be affected, and the disease appears to have a worldwide distribution. The classic site of

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infection is the bovine tongue; because the condition causes a very hard, diffuse nodular swelling, it has been given the name "woody tongue" or "wooden tongue." The prevalence of woody tongue in bovines at slaughter is 0.7% to 3.6%.[1] Atypical actinobacillosis lesions of cattle can occur in the lips, nose, or lymph nodes of the head or neck or at other sites. Although the lesions normally occur sporadically, herd outbreaks with up to 73% morbidity have been reported.[1,2] Sheep are most commonly affected by hard swellings of the lips, often with fistulous tracts. Actinobacillosis has also been reported to cause tongue lesions in sheep and horses. These lesions appear to be rare in goats.

Clinical Signs and Differential Diagnosis Actinobacillosis lesions usually involve soft tissues. When the tongue is affected, the major clinical signs are inability to prehend food normally, excessive salivation, and sometimes a visibly enlarged tongue that protrudes from the mouth. The submandibular area often is enlarged and firm. On palpation the tongue is firm to very hard, painful, and nodular (Fig. 32-84). Nodular lesions often are slightly ulcerated. The base of the tongue is most frequently affected, but the shaft may also be involved. An ulceration filled with plant awns or stems often is seen in the sulcus lingualis at the junction of the base and shaft of the tongue. Because cattle use the tongue to prehend food, anorexia results when the tongue is painful and inflexible. Actinobacillosis must be differentiated from dental disease, oral foreign bodies, pharyngeal trauma, and other diseases that cause oral pain.

Atypical lesions in cattle involve sites other than the tongue.[3] Lymph nodes of the head and cranial cervical area are most frequently affected, but where any abrasion is present, granulomas or abscesses may develop, followed by licking or contact with pus draining from a lesion on another animal. Because plant awns and stems create entry sites for the organism in the mouth, most lesions are in the head. Granulomas in the nose and eyelids and needle puncture wounds over the left jugular vein have been reported. These granulomas may be confused with tumors, polyps, or cysts. Granulomas have been reported in the esophagus, pharynx, palate, flank, internal iliac lymph nodes, and testes; multiple subcutaneous lesions with regional lymph node involvement also have been reported. Three cases involving cutaneous lesions of the facial tissues were described as extensive swollen plaques under alopecic areas. Most granulomatous abscesses in a herd outbreak of actinobacillosis involved the tongue, muzzle, and lips and the submandibular, parotid, and cranial cervical areas. Generalized involvement or granuloma formation in internal organs may also occur.

Lesions in sheep typically involve the lips and face or parotid and submaxillary regions. The nasal cavity and internal organs occasionally may be involved. Soft tissues of the head may be infected through fight wounds. Lesions of the lips must be differentiated from those of contagious ecthyma, and granulomatous abscesses in other sites must be differentiated from caseous lymphadenitis lesions. Lesions of the tongue of sheep, essentially identical to those found in cattle, have been reported as a cause of green staining of the lips and "cud-dropping" in sheep.

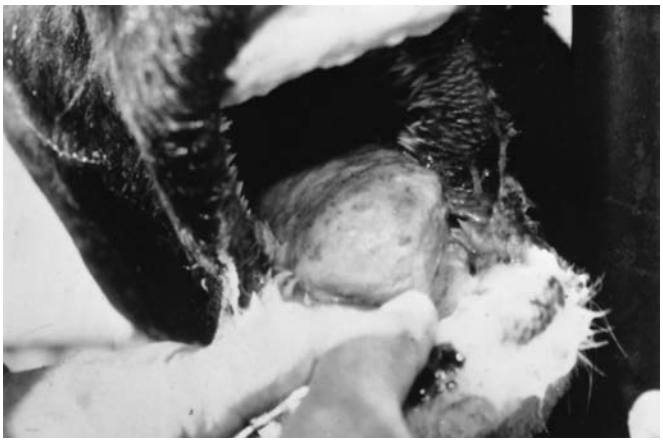


FIG. 32-84 Firm, enlarged bovine tongue typical of woody tongue caused by *Actinobacillus lignieresii*. Partly ulcerated areas of mucosa overlie hard nodules.

Clinical Pathology Diagnosis of actinobacillosis requires biopsy and culture of the lesion. The pus usually is not malodorous. Pus crushed between two glass slides shows "sulfur granules," "club-like rosettes," or "club colonies." Similar colonies may be found in actinomycosis and some staphylococcal infections. *A. lignieresii* are small, gram-negative rods. Definitive diagnosis relies on culture. No reliable serologic test is available for actinobacillosis, and the hematologic and clinical chemical findings may be normal or typical of a response to chronic infection.

Pathophysiology *A. lignieresii* is a normal inhabitant of the mouth of ruminants and can be found in many plant awns. When mucosal lesions occur as a result of plant awns (e.g., foxtails), thistles, or particularly stemmy coarse feed, actinobacillosis may occur. Cattle often have a small ulcer in the sulcus lingualis at the junction of the base and shaft of the tongue. Plant fibers are sometimes found in the granulomatous lesions of actinobacillosis. Once inoculated into tissues, the organism may cause a local lesion, lesions in draining lymph nodes, or both. Lesions elsewhere on the body may be contaminated by saliva or by pus from other draining lesions or directly by plant awns on which *A. lignieresii* resides.

Epidemiology Most cases of actinobacillosis are sporadic. Herd outbreaks may be associated with abrasive feedstuffs and crowded conditions in which the organism is spread rapidly to wounds on other animals by way of saliva. In one herd outbreak, 73% of a group of heifers (4 to 24 months of age) were affected 1 month after feeding of a coarse, stemmy haylage had begun.[2] Atypical lesions often are associated with a previous wound at the site, such as a nose lead wound, multiple needle punctures, or a head butting wound. Outbreaks of actinobacillosis in wounds of the head, neck, body, and limbs have been reported.

Necropsy and Biopsy Findings Actinobacillosis lesions typically are firm, pale, gritty, granulomatous abscesses. Grossly they are similar to exuberant granulation tissue and connective tissue, often appearing to have a yellowish granular (1 to 3 mm) surface. Masses contain multifocal necrotic foci, often filled with nonodorous, thick, yellow-white pus. On histological exam the lesion is a granulomatous abscess. An outer capsular region of connective and granulation tissue surrounds an area of leukocytes and rosettes ("club colonies"). Mononuclear cells, plasma cells, and eosinophils predominate. Many neutrophils are seen at the center of the lesion. Multinucleated giant cells or plant fibers, or both, may be seen.

Treatment and Prognosis Treatment usually is successful, and the condition has an excellent prognosis when only the tongue is involved. The prognosis may be only slightly less optimistic when internal organs and atypical sites are involved. Sodium iodide (70 mg/kg given IV as a 10% to 20% solution) is the treatment of choice. Intravenous treatment is given once and repeated at least one more time at a 7- to 10-day interval. In refractory cases intravenous therapy may be repeated more often (2- to 3-day intervals). In severe cases daily organic iodides can be administered orally at a rate of 60 mg/kg/day[4] in addition to the intravenous iodide. If signs of iodinism develop (excessive tearing, coughing, inappetence, diarrhea, and/or dandruff), iodine administration should be halted; the adverse signs normally disappear shortly thereafter.

The onset of therapeutic benefit of sodium iodide is remarkably rapid. Within 48 hours after treatment, the tongue is flexible enough to allow the animal to eat. Although the mode by which iodides exert their beneficial therapeutic effect in actinobacillosis is not well understood, it seems most likely that they exert some antiinflammatory effect on the granulomatous inflammation. Iodides have little in

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vitro bacteriostatic or bactericidal effect at the concentrations given,[5] yet the onset of action is very rapid. They probably act in some way other than by direct antimicrobial effect. The old belief that iodides cause abortion at the recommended dose has been cast into doubt by the author's clinical experience and by reports of others,[6] who gave one and one-half to two times the recommended intravenous dose without inducing abortion. Nevertheless, there are anecdotal reports of the association, and when products are labeled with a contraindication for use in pregnant cattle, due caution should be exercised. Iodides should be given slowly and with caution to horses because of the possibility of severe generalized adverse reactions to intravenous sodium iodide.

Most strains of *A. lignieresii* are sensitive in vitro to a number of antimicrobial drugs, including ceftiofur, ampicillin, penicillin, florfenicol, sulfas, aminoglycosides, and tetracyclines. Each isolate should be tested for antimicrobial sensitivity. Therapy with an antimicrobial drug to which the isolate is sensitive is recommended in severe, generalized, or refractory cases of actinobacillosis. Therapy should also include iodides.

Surgical debulking of lesions, particularly if they interfere with airflow, is also possible for atypical cases in which a large granulomatous mass is present and the mass has proved refractory to medical therapy. Hemostasis may be a problem after surgical debulking.

Prevention and Control Prevention relies mainly on avoidance of coarse, stemmy, scabrous feeds and pastures full of hard, penetrating plant awns (e.g., foxtails) or thistles. If an outbreak occurs, immediate change to a softer feed is advised, and affected animals should be treated individually. Rapid resolution of the outbreak can be expected once these steps have been taken. If atypical lesions occur, a cause of skin wounds in the area should be sought and resolved.



FIG. 32-85 Hard swelling on the distal mandible of a cow, typical of lumpy jaw caused by *Actinomyces bovis*. Loss of teeth and bone destruction, along with fibrosis and callus formation, are seen in this advanced case. The oral mucosa is secondarily ulcerated by trauma.

Actinomycosis (Lumpy Jaw)

Bradford P. Smith

Definition and Etiology Actinomycosis is caused by *Actinomyces bovis,* a gram-positive, nonencapsulated, branching, filamentous bacterium that is a normal inhabitant of the ruminant mouth. The disease occurs mainly in cattle but on rare occasions may affect sheep or goats, and one report of the disorder in a horse involving *Actinomyces viscosus* and *Actinomyces odontolyticus* was found.[1] It enters the tissues and bone through oral abrasions, openings, and punctures associated with dental or gingival disease, hard plant awns (e.g., foxtails), thorns, stickers, or dry, coarse, stemmy feeds. Lesions may begin as cavities (caries) in the dentin or dental pulp.[2] Lesions are sporadic and occur mainly in the mandible and less commonly in the maxilla. The preponderance of mandibular lesions, with the development of periosteal new bone and fibrosis, gives the disease its common name of "lumpy jaw." Lesions occasionally occur in soft tissues of the head, esophagus, forestomachs, and trachea. Occasionally *A. bovis* may cause granulomatous abscesses in other soft tissues. Most of the early reports of esophageal groove and forestomach involvement incriminate actinobacillosis rather than actinomycosis.

Clinical Signs and Differential Diagnosis Bovine actinomycosis typically causes a hard, immovable, painless, bony mass on the mandible (Fig. 32-85). The lesion is most common on the horizontal ramus. Initially it is nondraining (has no fistulous tracts), but it may develop fistulous tracts and involve tooth roots as the condition progresses. When teeth become involved, evidence of pain when chewing may be seen, and weight loss may result. A careful examination of the mouth is required to detect loose teeth, plant awns, or severe gingivitis and to rule out a pathologic fracture. If a fistula is present, it is useful to flush the tract with organic iodine and perform contrast radiographs to determine if it communicates with the mouth. The differential diagnosis includes tooth root abscess, fracture, tumors, and osteomyelitis caused by other organisms. A mandibular swelling that continues to enlarge despite therapy should be radiographed for evidence of a fracture or sequestrum. Atypical actinomycosis with lesions in soft tissue causes a variety of clinical signs, depending on the location.

Clinical Pathology and Diagnosis Hematologic and clinical chemistry findings may be normal or may reflect a chronic infection. Radiographs of the lesion are helpful in determining if there is dental involvement or a pathologic fracture. The radiographic lesion consists of multiple central radiolucent areas of osteomyelitis surrounded by periosteal new bone and fibrous tissue. If a fistulous tract is present, a contrast study done while flushing into the tract may help determine the extent of the fistula. Before flushing, material from the core of the lesion should be aspirated or biopsied. A Gram stain and culture of pus should be performed. The organism is gram-positive, filamentous, and branching. "Sulfur granules" similar to those described for actinobacillosis may be seen. Many authors report that they were unsuccessful at culturing the organism.

Pathophysiology and Epidemiology *A. bovis* appears to enter the bone through mucous membrane punctures caused by foreign bodies, plant awns, or coarse, stemmy feeds or through a diseased tooth or areas of gingivitis that allow oral bacteria access to the bone. Cases usually are sporadic.

Necropsy and Biopsy Findings Actinomycosis causes a granulomatous abscess. Scattered through the mass of tissue are basophilic clumps of bacteria surrounded by eosinophilic clublike projections. The bacteria are long, filamentous, branching rods. Surrounding them is cellular reaction composed of neutrophils, epithelioid cells, macrophages, and occasional multinucleated giant cells. In the outer fibrous tissue are plasma cells.

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Treatment and Prognosis Treatment of actinomycotic bone lesions usually results in arrest of the lesion, but seldom does the size of the hard mass regress significantly. The prognosis for arrest of the lesion with vigorous treatment is good. If the mass does not have any fistulous tracts and no affected teeth are loose, medical therapy alone may be sufficient. If the mass has fistulous tracts, it should also be vigorously curetted and flushed with povidone-iodine or other organic iodine. The lesion has a rich blood supply, and curettage can result in severe hemorrhage. If the cavity is large, it may be necessary to flush and pack with iodine-soaked gauze daily for several days, then less frequently as healing progresses. One paper reports on the successful treatment of three cases of actinomycosis by using repeat treatments consisting of curettage followed by cryotherapy with liquid nitrogen poured into the lesion. The authors repeated the treatment on day 2, day 9, and day 16.[3] If there is an open fistula into the mouth (as judged by vigorous flushing) or if teeth are involved, the affected tooth or teeth should be carefully removed or repaired endodontically.[2] Care must be taken to prevent mandibular fracture, and the animal must be sedated or anesthetized to allow for proper intraoral manipulation. The empty alveolus should be carefully packed with gauze or a dental acrylic to which a wire or umbilical tape is attached and pulled through the fistula. The wire is tied externally to a small gauze roll to keep the alveolar packing firmly in place. The wire should be untied daily and the tract flushed thoroughly with povidone-iodine until the wound is completely granulated. Once granulation begins, it may not be necessary to check and flush the lesion more than once a week. The alveolus will take several weeks to close, pushing the gauze or acrylic out as it does so.

Medical treatment of actinomycosis involves the use of sodium iodide, isoniazid, and penicillin or another antimicrobial drug to which the organism is sensitive. Sodium iodide is given IV at a dose of 70 mg/kg as a 10% to 20% solution. It can be given every 7 to 10 days or more often until signs of iodinism occur (i.e., lacrimation, cough, inappetence, diarrhea, and dandruff). If repeated intravenous treatments are difficult, oral organic iodides can be given at the rate of 60 mg/kg/day for 3 weeks. As with actinobacillosis, the beneficial therapeutic effects of iodides appear to lie in their ability to reduce granulomatous inflammation rather than in direct antimicrobial effects. Iodides do not appear to cause abortion and can be safely given to pregnant cows,[4] although care should be used because there are anecdotal reports to the contrary, and products are labeled with a contraindication for pregnant cattle.

Isoniazid (10 mg/kg/day given PO for 1 month) is effective at arresting actinomycosis of the mandible in cattle.[5] It is inexpensive and readily consumed in a small amount of grain. A prolonged withdrawal period before slaughter for human consumption is required. The drug appears to be nontoxic at this dosage, but it may cause abortion and should not be used in pregnant cattle.

Penicillin (10,000 U/kg IM twice daily) or another antimicrobial drug such as florfenicol or ampicillin can be added to the treatment regimen in cases involving valuable animals or when twice-daily treatment for 7 to 14 days is possible. Streptomycin was found effective in one study, but because of the prolonged persistence of tissue residues, aminoglycosides generally are considered unacceptable in food animals.

Prevention and Control *A. bovis* is a normal mouth inhabitant of ruminants; therefore the only possible means of prevention is to avoid feeding coarse, stemmy feeds, feeds with hard, penetrating plant awns, or feeds with other sharp materials. The recommendations in this regard are similar to those for actinobacillosis.

Pharyngeal Trauma and Abscess

Bradford P. Smith

Definition and Etiology Pharyngeal trauma occurs relatively frequently in cattle, resulting in cellulitis, abscessation, or hematoma formation. One case resulted in megaesophagus. Pharyngeal trauma is almost always associated with use of a balling gun, long dose syringe, speculum, paste wormer gun, rigid probe of calf esophageal feeder, or rigid stomach tube.[1] Occasionally a foreign body such as a sharp stick or wire can perforate the pharynx. Hematomas may result from unidentified blunt trauma. The puncture or laceration may be very small and usually is located in the area near the origin of the esophagus. The result is that feed and saliva enter the retropharyngeal area, and inflammation develops (also see Chapter 31, Retropharyngeal Lymph Node Abscessation).

Clinical Signs and Differential Diagnosis The clinical signs include anorexia, drooling of saliva, malodorous breath, extended head and neck, localized or diffuse pharyngeal pain, feed coming from the external nares, and forestomach stasis or bloat. Severe cases may involve obvious pharyngeal swelling, fever, easily elicited cough on laryngeal palpation, dyspnea, and aspiration pneumonia. Intraluminal submucosal pharyngeal abscesses with similar clinical signs have been reported. Differential diagnosis in cattle must include retropharyngeal abscesses (also see Chapter 31, Retropharyngeal Lymph Node Abscessation), pharyngeal foreign body, actinobacillosis, and lymphosarcoma or other tumor that involves the pharyngeal lymph nodes.

If megaesophagus occurs, it must be differentiated from diaphragmatic hernia with herniation of the reticulum into the thorax; other outflow obstructions involving the reticulum can result in frequent regurgitation and vomiting, as can a number of other diseases, including esophageal foreign body and esophageal diverticulum. Several toxins also cause vomiting (see Chapter 7). Rabies is easily differentiated, because the only clinical signs common to both are anorexia and salivation. Careful digital palpation of the pharynx often is diagnostic, although restraint is difficult because the area is painful and swollen, causing dyspnea and struggling. A well-lubricated stomach tube should be gently passed to relieve bloat and ascertain that no esophageal obstruction is present. Pharyngeal trauma is rare in sheep and goats, and retropharyngeal abscesses caused by *Corynebacterium pseudotuberculosis* (caseous lymphadenitis) are the most common cause of pharyngeal swelling.

Clinical Pathology and Laboratory Aids Endoscopy and radiography may be of great help in diagnosing the site of the lesion, the extent of cellulitis, and the presence of a foreign body. Endoscopy reveals a swollen, collapsed pharyngeal air space. The wound may be visible, and it may have exudate at its origin. Endoscopy can help rule out intraluminal masses and foreign bodies. Retropharyngeal cellulitis, abscess, or hematoma often can be visualized radiographically, and radiopaque foreign bodies can be seen (Fig. 32-86). Gas in the

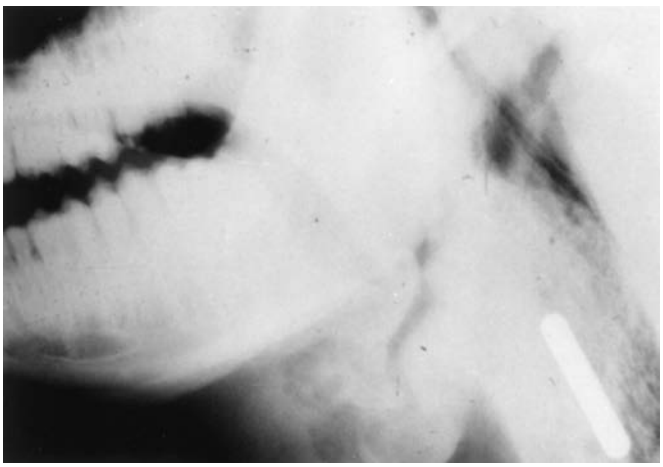


FIG. 32-86 Pharyngeal trauma in a 2-year-old bull caused by a magnet that was given forcefully with a balling gun 24 hours previously. The magnet is visible in the retropharyngeal tissues surrounded by cellulitis, with swelling and gas in the tissues. The area is swollen and painful.

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soft tissues or a discrete mass can be seen with cellulitis and abscess, respectively. Gas often can be seen in the lumen of the esophagus as well. Radiographs of the lung may be helpful if aspiration pneumonia is suspected. The results of hematologic analysis may reflect an infectious inflammatory process.

Pathophysiology Inflammation, swelling, and necrosis in the retropharyngeal tissues interfere with normal swallowing by causing pain when swallowing is attempted, physical interference with passage of a bolus, and neurologic involvement. The resultant dysphagia may predispose the animal to inhalation of feed and saliva.

If the retropharyngeal inflammation affects the pharyngeal branch of the vagus nerve on the dorsolateral surface of the pharynx, the esophageal and pharyngeal phases of swallowing and eructation are disturbed.[1] The resultant pharyngeal paresis may lead to reflux of feed through the nares. Involvement of the adjacent cranial laryngeal nerve makes the laryngeal mucosa less sensitive to foreign material and thus diminishes the cough reflex. Severe inflammation may involve the vagus nerve itself and cause forestomach stasis with bloat and laryngeal motor dysfunction.[1-3] Eructation also involves pharyngeal muscular activity, and the maneuver is likely to be quite painful when cellulitis is present in the area.

Treatment and Prognosis In spite of the fact that affected animals often are completely anorectic and febrile and look very ill, most cases of pharyngeal puncture or laceration resolve successfully if the animal can be vigorously treated with broad-spectrum antimicrobial drugs for 7 to 14 days, if aspiration pneumonia can be controlled by limiting access to feed, and if adequate supportive care can be given. Tetracyclines, sulfas, ampicillin, ceftiofur, trimethoprim-sulfonamide (TMS), and florfenicol or penicillin plus an aminoglycoside have been used successfully. NSAIDs should be given for analgesia and for their ability to reduce inflammation. Oral administration of boluses should be avoided.

The animal should have access to water; if it cannot drink, a soft stomach tube should be used several times daily to gently administer a total of 30 to 50 L (8 to 13 gallons) of water plus electrolytes daily. The most important electrolyte to administer is potassium: 60 to 100 g of potassium chloride should be given daily with the water. Once the animal can drink without coughing or nasal reflux, soft green grass or a soft mash should be offered. If this is well tolerated, it should be continued for 2 weeks, after which green pasture or soft, green, leafy alfalfa hay or other equally palatable feed should be gradually and carefully introduced into the diet.

If a discrete retropharyngeal abscess forms, it is best first to attempt drainage into the pharynx through the original laceration by pushing a finger into the healing wound until pus escapes. If this fails, a surgical approach to the area may be necessary. Surgery is rarely required in cases of pharyngeal trauma or laceration with cellulitis.

Prevention and Control Careful use of balling guns, paste wormer guns, and other equipment that can damage the pharynx is the best prevention. Adequate restraint of the head of any animal that is to be orally treated also helps prevent pharyngeal trauma.

Bluetongue

N. James MacLachlan • Christie E. Mayo

Definition and Etiology Bluetongue is an arthropod-transmitted viral disease of domestic and wild ruminants.[1,2] Clinical disease is largely restricted to sheep and certain wildlife, but other ruminants, including cattle, may show disease in some circumstances. Cattle are considered to be especially important amplifying reservoir hosts of bluetongue virus (BTV).

BTV occurs throughout tropical and temperate regions of the world, where different constellations of BTV serotypes are transmitted by different species of *Culicoides* midge vectors in relatively distinct global "episystems."[3,4] Whereas infection often occurs year-round in tropical climates, it is distinctly seasonal in temperate areas, occurring only in the late summer and fall months, and bluetongue is usually manifest only in the temperate areas at the upper and lower limits of the global range of the virus. The global distribution of BTV has altered recently, perhaps as a consequence of the impact of climate change on the *Culicoides* midges that serve as biological vectors of the virus.[5-7] In particular, since 1998 multiple BTV serotypes spread throughout the Mediterranean Basin and, in 2006, additional virus serotypes invaded and spread throughout extensive portions of northern Europe to precipitate an economically devastating epidemic.[8] Coincident with this invasion of multiple serotypes of BTV into Europe, at least 10 novel BTV serotypes have also appeared in the southeastern United States.[2,9]

Although BTV has now been isolated from ruminants and/or *Culicoides* midge vectors from all continents except Antarctica, the international movement of ruminants is highly regulated, and often severely restricted, for fear of importing BTV into free countries or regions.[10] The continuing occurrence of disease outbreaks globally, the wide host range, the potential for establishment of endemic infection (as has recently occurred in extensive portions of Europe that previously were free of the virus), and the similarity of some signs of bluetongue to those of vesicular diseases have all made BTV infection the subject of intense regulatory interest worldwide. Import regulations promulgated in reaction to the disease have been more of a threat than the disease itself to the livestock industries of some countries.[11]

BTV is the prototype virus in the genus *Orbivirus* within the family Reoviridae.[12] Other closely related viruses in this genus include epizootic hemorrhagic disease of deer and African horse sickness viruses. The genome of BTV includes 10 distinct segments of double-stranded RNA, each of which encodes at least one protein. The serologic classification of BTV into serotypes is based largely on the protein product of just one genomic segment (the *L2* gene that encodes the VP2 outer capsid protein), but virulence and other characteristics of individual virus strains may not be related to this protein. There is marked genetic variation among field strains of BTV, even viruses of the same serotype and from the same region.[13] The genetic diversity and heterogeneity of field strains of BTV arises as a consequence of both genetic shift and drift. Specifically, genetic shift occurs by reassortment of the individual viral gene segments during infections of cells with more than one virus serotype or strain. Individual genes also evolve by genetic drift during alternating replication in the insect and animal hosts of the virus.[14]

The genetic determinants of BTV virulence are uncertain. At least 26 BTV serotypes are recognized worldwide, but virus strains of the same serotype may have markedly different virulence even to highly susceptible ruminants.[1,2,10,15] For example, BTV serotype 8 is present in the Caribbean Basin where it has not been associated with major outbreaks of disease, whereas the strain of BTV serotype 8 that incurred recently into northern Europe was highly pathogenic and caused significant production loss and mortality in a variety of livestock species, including cattle.[3,8,15]

Clinical Signs and Differential Diagnosis Clinical bluetongue disease is manifested in two ways: (1) reproductive syndromes and (2) bluetongue per se, a systemic hemorrhagic viral fever that affects multiple organs but especially the upper gastrointestinal tract, skin, and lungs.[1,2,15] Sheep most commonly are affected, particularly European fine-wool breeds such as the merino and crosses thereof. Bluetongue also occurs in cattle, goats, and South American camelids, but less commonly than in sheep and only after infection with especially virulent virus strains.

In susceptible sheep, the first clinical signs of bluetongue appear after an incubation period of 3 to 7 days or sometimes longer. These signs include a transient fever (up to 41.1°C [106°F] or higher); edema of the face, lips, muzzle, and ears; excessive salivation; and hyperemia of the oral mucosa (Fig. 32-87). Affected sheep usually produce a profuse serous nasal discharge that becomes mucopurulent after a few days, leaving crusts around the nostrils and muzzle. The

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FIG. 32-87 Face of a sheep with severe bluetongue; note submandibular edema and hyperemia and cyanosis of the lips and tongue (bluetongue).

tongue may be cyanotic (hence the name), although this is a relatively infrequent manifestation. The oral lesions progress to petechial hemorrhages, erosions, and ulcers, which are especially prominent on the dental pad and the commissures of the mouth. The oral lesions can be sufficiently painful that animals will not eat, and severely affected sheep will stand over water without drinking. Lameness and stiffness caused by coronitis and myopathy can be severe, and the coronary band characteristically shows petechial hemorrhages and hyperemia. Hemorrhages also may be evident in the subcutis of nonhaired skin such as the inguinal region. Lameness may progress to "knee walking" or recumbency. The hooves may slough, and breaks in the wool are common. Diarrhea, with or without blood, can occur. Many sheep become depressed, are unable to rise, and die, but some severely affected sheep make a full recovery. Pulmonary edema is often marked, especially in fatal cases, and some cases appear to livestock owners to be pneumonia. Indeed, acute secondary bacterial bronchopneumonia is often superimposed on the characteristic pulmonary edema of bluetongue. Cardiac necrosis may result in sudden death at any time, even in an animal that appears to be recovering. Although the lesions and signs of bluetongue are characteristic, as is the seasonal occurrence of disease in temperate regions such as much of the United States, the differential diagnosis for sheep showing some of these signs includes sore mouth (contagious ecthyma), foot-and-mouth disease (FMD), peste des petits ruminants (PPR), and sheeppox.

The reproductive and teratogenic effects of BTV in sheep and cattle vary depending on the virus strain, the host, and other factors. Reproductive effects, including abortions, stillbirths, and weak but live "dummy lamb" births, were profoundly evident when live attenuated vaccine was administered to pregnant ewes in California in the 1950s.[16] In South Africa, where BTV infection has been recognized as endemic since the first descriptions of the disease before 1900, teratogenic effects have not been commonly linked to the virus despite the use of polyvalent live attenuated vaccines and nearly continuous exposure to the virus.[1] However, fetal infections were clearly documented in cattle after these same vaccines were introduced into Europe recently and, furthermore, it was unquestionably established that these vaccine viruses also circulated naturally after they were introduced into Italy.[17] With the notable exception of circulation of live attenuated vaccine viruses, abortion and teratogenic defects are uncommonly associated with natural BTV infection of livestock in endemic areas.[18] However, major outbreaks of abortion have occurred following the introduction of virulent BTV into immunologically naive populations of sheep. Furthermore, the strain of BTV serotype 8 that was responsible for the recent epidemic in northern Europe crossed the placenta in a substantial proportion of pregnant ruminants, including cattle.[8,15] Some have questioned whether this remarkable property of this northern European strain of BTV-8 might imply that it was, at some time in its history, propagated in cell culture, as is done with live attenuated vaccine viruses.

Clinical disease is uncommon among cattle infected with most virus strains, particularly in BTV-endemic areas.[1,2,10] However, as evidenced emphatically by the recent BTV-8 epidemic in northern Europe, disease certainly can occur in BTV-infected cattle. Severely affected cattle exhibit many of the same signs as do affected sheep. Excessive salivation may be the first clinical sign. Hyperemia and necrosis of the muzzle ("burnt muzzle") and a patchy dermatitis may also occur, along with necrosis of the skin of the teats. In cattle, depending on which signs are exhibited, the differential diagnosis should include mucosal disease (BVD), malignant catarrhal fever (MCF), vesicular diseases, rinderpest (RP), photosensitization, bovine papular stomatitis (BPS), and infectious bovine rhinotracheitis (IBR). Clinical disease in cattle can also be difficult to distinguish from FMD and vesicular stomatitis (VS), and appropriate regulatory officials should be notified in such outbreaks. Furthermore, recent outbreaks in the United States, North Africa, and the Middle East confirm that the related epizootic hemorrhagic disease virus can also cause a bluetongue-like disease syndrome in cattle that also mimics FMD.[19]

Ocular lesions occur in some BTV-infected ruminants. The syndrome was well characterized during the BTV-8 epidemic in northern Europe when calves infected transplacentally in late gestation developed transient corneal opacity (blue-eye) following ingestion of colostrum that contained BTV-8–specific antibody.[20] Similarly, non-African ungulates such as European bison at the Berlin zoo developed similar ocular lesions following BTV-8 infection.[21] "White eye calf" syndrome was described in Oregon in the 1970s and associated with BTV and/or epizootic hemorrhagic disease virus infection.[22] It may be that the lesions result from deposition of immune complexes in the eye, analogous to the immune complex–mediated uveitis that follows immunization of dogs with certain canine adenovirus vaccines.

Laboratory Diagnosis and Immunology Serologic diagnosis of BTV infection in livestock is routinely done by competitive ELISA that detects antibodies to the core VP7 protein of BTV. The test is highly sensitive and specific, and detects antibodies to most if not all BTV serotypes. These antibodies persist for long periods following natural infection, although it is not currently possible to distinguish animals that were naturally infected with BTV from those that were immunized with live attenuated vaccine. It is to be stressed that presence of antibody indicates only prior exposure to BTV and implies nothing about disease causality. Serotype-specific antibody is only assessed currently using laborious and expensive virus-serum neutralization assays.

Identification of BTV infection in animals is most readily accomplished using a group-specific quantitative polymerase chain reaction (PCR) assay. Such assays now are routinely available in diagnostic laboratories, and can identify all known serotypes of BTV. Furthermore, the amount of viral nucleic acid in the same can be quantitated, which can be useful in ascribing disease causality; specifically, acutely affected animals generally have large amounts of BTV nucleic acid in their blood and tissues, which is reflected by low cycle threshold (Ct) values on the assay. It is to be stressed that ruminants remain positive for BTV nucleic acid for up to 6 months or longer following infection, meaning that the mere detection of either viral nucleic acid by quantitative PCR or antibody to BTV by competitive ELISA is not proof of disease causality. Serotype-specific PCR assays can be used to serotype the virus present. The availability of these assays has largely obviated the need for virus isolation, which is cumbersome, laborious, expensive, and takes several weeks typically. Virus isolation also requires specialized laboratory facilities as some virus strains require initial propagation in embryonated chicken eggs before they will grow in cell culture systems.

The development of immune tolerance to BTV (in utero infection producing antibody-negative, virus-positive individuals), as happens in BVD infections, now is regarded as unimportant to the natural

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epidemiology of BTV infection although some controversy persists.[15] It is to be stressed that fetuses infected with BTV in late gestation are born viremic and, potentially, before they have had the time necessary to develop an immune response; the fact that these animals are born viremic (virus positive) and antibody negative should not erroneously be interpreted to mean that they are immunologically tolerant.

Pathophysiology Bluetongue is proposed to be a hemorrhagic viral fever analogous to viral hemorrhagic fevers of humans like Ebola.[15,23] Specifically, BTV replicates within the endothelium and mononuclear phagocytic cells of infected animals. Vascular injury, particularly to small vessels, is responsible for the manifestations of clinical bluetongue disease. Release of cytokine and vasoactive mediators from infected cells leads to capillary leakage and, subsequently, the edema and hemorrhage that is characteristic of fulminant cases. Direct virus-induced vascular injury leads to thrombosis and subsequent infarction of tissues, causing ulcers and manifestations such as the characteristic cyanotic (infarcted) tongue in some severely affected sheep. Teratogenic effects result from direct virus-mediated destruction of proliferating progenitor cells within the central nervous system of the developing fetus, following transplacental transmission of the virus in pregnant ruminants. Teratogenic defects occur only when the fetus is infected at critical stages of organogenesis, which is prior to midgestation (approximately 150 days in cattle and 70 days in sheep). Transplacental infection soon after conception can lead to early embryonic death and infertility.

Epidemiology The development of clinical bluetongue disease is the product of a complex interaction among host, virus strain, vector, and environmental influences.[1,2,10] For example, many of the virus strains that circulate in endemic areas such as California are mildly pathogenic for livestock in the region. Epizootics typically occur when a new virus strain or new animals are introduced into a previously stable ecosystem, as occurred, for example, with the introduction of a highly virulent strain of BTV serotype 8 into northern Europe in 2006.[8] In addition to sheep, this virus caused serious disease in cattle, South American camelids, goats, non-African wild ungulates such as yaks and European bison, and even some carnivore species.[21] Environmental alterations that favor the proliferation of midge vectors in a region also potentially can facilitate disease epidemics.

BTV infects wild and domestic animals primarily through the bite of the vector midge of the genus *Culicoides*. There are over 1400 *Culicoides* species globally; however, only a few have been identified as BTV-competent vectors.[1-6,10] In temperate regions of the world, *Culicoides* midges are abundant in midsummer to early fall, and outbreaks of bluetongue in livestock occur during this time when temperatures support both midge activity and BTV replication within the vector. Other routes of virus transmission are possible even during the interseasonal period in temperate regions (winter, spring, and early summer). For example, it has been shown that BTV can be spread to newborn ruminants via the ingestion of infective colostrum.[24,25] Lastly, although BTV can be transmitted sexually in infected semen and transplacentally from dam to offspring, the importance of these potential routes of virus transmission remains conjectural and they are unlikely to have any major role.[15] Specifically, animals infected in early gestation develop teratogenic brain defects and have cleared infectious virus by the time of birth. Those fetuses infected in late gestation can certainly be born viremic and potentially contribute to virus amplification and circulation. Embryo transfer currently is not viewed as a significant risk of BTV transmission provided that the embryo is washed at least 10 times. In summary, dissemination of BTV by vector *Culicoides* midges is by far the most common method of transmission in endemic areas.

In much of North America, the prevalence of bluetongue closely mirrors the distribution and abundance of *Culicoides sonorensis,* with lower rates in northern climates that are less hospitable to the midge and higher prevalence in California and other warmer southern regions.[3,4] However, the vector species in the southeastern United States where 10 additional serotypes of BTV recently appeared are less defined. Similarly, vector species other than *C. sonorensis* are important elsewhere in the Americas as they are in different regions of the world. In the absence of competent vector populations, animal-to-animal transmission appears to be incapable of maintaining endemic BTV infection; thus BTV serotype 8 has quickly disappeared from most of northern Europe.

It remains uncertain as to how BTV is maintained (over-wintered) in temperate areas where infection is highly seasonal.[2,10] Although viremia can be prolonged in both cattle and sheep, BTV infection is not persistent in domestic ruminants and insufficient to sustain the virus through the several months of the over-wintering period (approximately December through June in the northern hemisphere). Infection of vector midges is persistent and life-long; however, the lifespan of midges is relatively short so that it is unlikely that infected individuals could survive the entire over-wintering period. A plausible scenario is that a low-level cycle of infection between the animal and insect hosts of the virus or, alternatively, that vertical transmission of BTV occurs in vector *Culicoides* midges. There is no evidence to date that the latter occurs.

The severity of clinical signs in BTV-infected sheep varies by breed. Early in the history of the bluetongue investigation, it was noted that African breeds showed few if any signs of infection, whereas imported European breeds showed fulminant disease.[1,2] More recently, breed differences in immunologic response and susceptibility to disease expression following vaccination with live attenuated BTV vaccine have been reported.[26]

Necropsy Findings The lesions of bluetongue are characteristic, particularly in sheep.[1,15,27] These include ulcers and hemorrhage throughout the oral cavity, including the dental pad and tongue, which may extend from the esophagus into the forestomachs; coronitis; subcutaneous hemorrhages and edema, along with edema between the fascial planes of the neck and abdominal musculature; pulmonary edema; hemorrhages on the endocardial and epicardial surface of the heart and pulmonary artery; and necrosis of both skeletal and cardiac muscle. Especially characteristic lesions include gelatinous edema around the nuchal ligament (in addition to the other sites previously listed), subintimal hemorrhages in the pulmonary artery, and discrete focal areas of acute myocardial necrosis in the papillary muscle of the left ventricle. Microscopically, there is cuffing of inflammatory cells around small vessels in the affected skin and gastrointestinal mucosa with pronounced hypertrophy of the endothelium lining affected vessels, acute and focally extensive necrosis with the musculature of the heart and some skeletal muscles, and pulmonary edema.

Treatment, Prevention, and Control Treatment of bluetongue in affected ruminants is nonspecific and aimed at supportive and nursing care. Animals with severe oral lesions are reluctant to eat or drink. Valuable animals can be fed gruels of alfalfa pellets by stomach tube and can be encouraged to eat soft feeds or green grass. Muscle and coronary band pain may limit mobility; therefore water and shade must be close at hand. Sulfas or other relatively broad-spectrum antimicrobial drugs can be administered in an attempt to prevent or treat secondary bacterial pneumonia. NSAIDs, including aspirin and flunixin, are commonly used.

Elimination of *C. sonorensis* from the environment usually is not practical, but housing sheep indoors during the peak of activity (dusk, early evening) to minimize exposure to biting midges may be beneficial. Grazing wet areas such as irrigated pasture only during the heat of the day also may help, as most insects are not active in extreme temperatures. Midges that feed on ivermectin-treated cattle are killed, but the exchange of virus may be made before the insect's demise. *C. sonorensis* larvae develop in fine-grained mud with high organic matter content, such as around farm reservoirs, overflowing watering troughs, and shallow septic systems. Elimination of these breeding grounds combined with larvicidal treatments may help in some situations. Especially valuable animals can be housed in

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insect-protected enclosures to prevent any contact with vector midges during outbreaks, or they may be treated with repellants to minimize the likelihood of vector attack.

Both inactivated and live attenuated (modified live) BTV vaccines are available in some parts of the world, and these logically should be based on the local strains and serotypes.[1,2,28,29] Inactivated vaccines are inherently safer than live attenuated ones because the latter have the potential for transmission in nature, reversion to virulence, and the capacity to cross the placenta. There is little cross-protection between BTV serotypes, so animals need to be vaccinated against all serotypes of the virus circulating in a given region. Live attenuated vaccines to BTV serotypes 10, 11, and 17 are available in California from the California Woolgrowers' Association, but not to BTV serotype 13 that also is present in California.[25] These vaccines should be given at least 2 weeks before breeding season to avoid teratogenic effects, and vaccination should be done prior to the seasonal period of virus transmission (late summer and fall) to avoid infection of vectors and so minimize the likelihood of recombination of vaccine and field viruses. Pregnant ewes in late gestation may be vaccinated, but there is some risk of inducing abortion; vaccine should not be administered in early or mid-gestation because of potential teratogenic defects. Vaccinated breeding rams may have some risk of transiently decreased fertility. Vaccinated and naturally infected animals cannot readily be distinguished by current serologic diagnostic tests. New-generation BTV vaccines have been developed, including vectored recombinant vaccines, and in addition to being very safe, these vaccines also have the potential to distinguish vaccinated and infected animals (so-called DIVA).[30]

Contagious Ecthyma (Sore Mouth, Orf, Contagious Pustular Dermatitis, Scabby Mouth)

Bradford P. Smith*

Definition and Etiology Contagious ecthyma (CE) (sore mouth, orf, contagious pustular dermatitis, scabby mouth) is a common disease of sheep and goats that is transmissible to humans and has a worldwide distribution. The disease has a short 2- to 14-day incubation and tends to be more severe in goats, with Boer and Boer cross goats most likely to have severe generalized infections with proliferative dermatitis, chronic pneumonia, arthritis, and lymphadenopathy.[1] A good review of human lesions was published in 2005.[2] The colloquial name *sore mouth* describes the most common presentation of the disease in sheep and goats; the name *orf* (possibly from the old Norse term *hrufa,* meaning a crust or scab) is more commonly used for the disease in all species in England and for human disease in the United States. The agent is a DNA poxvirus of the parapoxvirus subgroup, which includes the closely related viruses pseudocowpox (another cause of orflike "milker's nodules" in humans), the agent of bovine papular stomatitis (BPS), parapoxvirus of red deer in New Zealand, squirrel parapoxvirus, and parapoxvirus of gray seals. Biological and genetic differences exist among strains of CE virus, so that cross protection may be limited and vaccines need to target the field strain. Wild ruminants (reindeer, musk ox, and others) and camels are also affected. A study demonstrated that the sheep orf virus does not cause lesions in camels, and vice versa, so it is likely that no infection is transmitted between camels and sheep or goats. The virus is epitheliotropic, usually creating proliferative lesions in the skin of the lips, nostrils, oral mucosa, teats, and occasionally the vulva.

Clinical Signs and Differential Diagnosis The most common presentation is of a young animal with crusting, proliferative lesions of the mucocutaneous junctions of the mouth and nose

*Paul G.E. Michelsen contributed to writing this chapter in previous editions. His contribution to this section is acknowledged.



FIG. 32-88 Typical scabby lesions of contagious ecthyma (sore mouth, orf) on the lips of a young goat. Lesions tend to be proliferative rather than ulcerative.



FIG. 32-89 Typical proliferative lesions of contagious ecthyma (sore mouth, orf) on the gums of a young sheep.

(Fig. 32-88). Proliferative lesions may be seen on the gums (Fig. 32-89). Older immunologically naive animals may be affected, and lesions may occur at the coronary band, on the tongue, interdigitally, on the conjunctiva of the eye, on the external genitalia, or on the udder or teats, with the last site affected especially in does or ewes nursing affected kids or lambs. The disease progresses through papular, vesicular, and pustular stages, which are rarely seen, before the characteristic presentation of proliferative, coalescing, scabbed lesions appears. One recent report described the characteristic proliferative scabs on the margins of healing burn wounds. Affected animals may be reluctant to nurse, eat, walk, or be nursed, depending on the location of lesions. Secondary bacterial infection or myiasis of affected parts may occur. The disease usually runs its course in 3 to 6 weeks, but chronic cases have been reported. Complete healing without scarring is the norm as scabs fall off. Severe infections may result in stunting of growth, particularly in goats. Overwhelming infection has been noted on rare occasions, with extension of lesions into the deeper respiratory or gastrointestinal tracts. Does and ewes with severe udder infection may develop mastitis from secondary bacterial infection. Sheeppox and goatpox may occasionally produce lesions similar to those of CE, but they are virulent diseases with systemic signs, including conjunctivitis, pyrexia, anorexia, and rhinitis. One report from China describes an outbreak in goats consisting of mixed infections with goatpox, orf, and *Mycoplasma capripneumoniae,* resulting in a 60% mortality rate.[3] Animals with bluetongue may have a crusted mouth and nose and eye lesions in the

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convalescent phase, but bluetongue is a disease with more evidence of oral erosive rather than proliferative lesions and systemic signs, including pyrexia, reluctance to move, lesions on the tongue, and conjunctivitis. Bluetongue has a seasonal incidence (late summer, early fall) that coincides with the activity of its insect vector. CE may be seen at any time but typically occurs in spring in the lamb or kid crop. Ulcerative dermatosis (lip and leg ulcer) is an uncommon disease caused by a virus similar to that of CE, but the lesions are crusted ulcers, to be distinguished from the crusted proliferations of CE. The author has observed a series of cases of what appeared to be mild CE of long duration (several years in one individual) in a family of Nubian goats; this was confirmed by an immunofluorescence assay. Smith and co-workers reported on five sheep, 4 months to 3 years of age, that developed severe refractory distal limb lesions resembling warts. Two also had lesions on the head. The sheep were from three different flocks; one was a Hampshire and four were Suffolk. Lesions were confirmed as orf by electron microscopy and immunohistochemistry.[4] A report from Texas describes severe multifocal persistent orf lesions in 16 Boer or Boer cross-bred goat kids 2 to 5 months of age, from two different farms. Some of the kids had been vaccinated with live-virus vaccine at 1 day of age, others at 2 weeks of age. Lesions were found on lips, nose, ears, body, legs, and feet.[5]

Laboratory Diagnosis The diagnosis usually is made in the field by recognition of the typical lesions in a naive flock or in a naive group (young lambs or kids) in a disease-endemic flock. Definitive diagnosis usually involves identifying the distinctive cross-hatched virus particles in typical early lesions with electron microscopy, PCR, immunohistochemistry, or inoculation into known protected or susceptible animals. Minced biopsy tissues have been used as a source of virus that is identified by fluorescent antibodies after it has been growing in embryonic ovine kidney cell cultures. Complement fixation (CF) tests to detect antibodies (using patient serum) or antigen (using vesicular fluid or a suspension of scabs) have also been used.

Pathophysiology The disease follows a similar time course in animals and human beings—approximately 6 weeks. Six stages have been described,[6] which begin after an incubation period of 3 to 14 days. Each stage lasts approximately 1 week.

1. *Maculopapular stage:* An erythematous spot becomes elevated. Histologically this stage shows vacuolization of cells in the upper one third of the epidermis with intracytoplasmic eosinophilic inclusions in the affected cells.
2. *Target stage:* A red halo of dilated blood vessels and inflammatory cell infiltrates surrounds a white ring of vacuolated epidermal cells with intracytoplasmic and intranuclear inclusions, which surrounds a red center of pyknotic epidermal cells.
3. *Acute stage:* The lesion is a red, weeping nodule. Microscopically there is reticular degeneration of the epidermis with vesicles. The dermis is infiltrated with macrophages and lymphocytes and is denuded of epidermis in places. The hair follicles are distended with pyknotic epidermal cells.
4. *Regenerative stage:* The nodule is now dry with small black dots (the pyknotic follicle cells, now extruded to the surface) in a thin yellow surface.
5. *Papillomatous stage:* The surface of the nodule is roughened with papillomas, which microscopically prove to be fingerlike, downward projections of epidermis through a full thickness of dermis.
6. *Regressive stage:* The lesion decreases in size and elevation above the surface, the papillomas regress, and several crusts may come off. Microscopically the papillomas and infiltrates regress, leaving normal architecture.

Orf virus encodes for a protein that is apparently homologous to mammalian vascular endothelial growth factors. This family of molecules mediates vascular permeability, angiogenesis, and endothelial cell proliferation, which may account for the swollen, proliferative nature of orf lesions.[7] Transient fever and lymphadenopathy are occasionally seen in humans. Lesions in humans that are not biopsied or excised heal without a scar.

Orf virus encodes a range of immunomodulatory genes that interfere with host antivirus immune and inflammatory effector mechanisms, allowing time for virus replication in epidermal cells.

Epidemiology The naturally occurring disease is primarily one of sheep, goats, and human beings, but it has also been reported in a variety of wild ruminants. Experimental transmission has been achieved in cattle, rabbits, horses, and monkeys. No naturally occurring clinical cases in these species have been reported. All ages and classes of sheep and goats are affected, and clinically normal sheep can infect naive individuals.[8] In herds and flocks in which the disease is endemic, it usually is seen in the lamb or kid crop and on the udders and teats of some of the nursing mothers. Animals that have had a bout of disease are solidly immune for 1 to several years, but morbidity is high (often 80%) among naive individuals. Humans are infected through contact with affected animals or fomites that have contacted affected animals (including one report of transmission by a pickup truck that had been used to haul sheep).[6] Effective disinfectants include hypochlorite, alkalis, Virkon, and glutaraldehyde. Human-to-human transmission can occur. Mortality is low among animals except when young individuals are severely affected and quit nursing or have mothers with severe udder lesions. Overwhelming infections are rare except in Boar or Boer cross goats, but some outbreaks are more severe than others.

The virus is quite resistant to many environmental conditions and persists from year to year on infected premises. Dried scabs allow the virus to persist for years, but wet conditions are less hospitable to it. Reports of persistently infected sheep point to another possible source of infection in wet climates.

Treatment, Prevention, and Control The infection usually is self-limiting and of minor consequence. Young individuals may need to be tube-fed if the lesions are severe enough to preclude suckling. Secondary infections, myiasis, or mastitis may be treated with topical disinfectants, antibiotics, or insecticides as appropriate. The hard crusts should not be removed, because doing so may delay healing and promote scarring. Also, humans should limit contact with affected animals and should wear gloves when handling them is necessary. Anecdotal reports, each consisting of one case, have claimed good results for treatment of human orf with intralesional corticosteroids, interferon (IFN), idoxuridine in DMSO, diethyl ether, or cryotherapy. An immunosuppressed human with a huge orf lesion on the finger was successfully treated with topical cidofovir antiviral cream. Similar good results were obtained in a group of 12 severely affected, bottle-fed lambs with painful intraoral lesions. The proliferative tissues were débrided and cauterized with a portable diathermy unit. The exposed submucosa was then frozen twice with liquid nitrogen spray. Healing occurred by second intention, with rapid recovery of affected lambs.

The infection is prevented by maintaining a virus-free herd or flock by not introducing or contacting infected individuals. Lesions often are not apparent on carriers.[8] Once established, the disease is persistent on the premises because of virus in scabs. Vaccination should be undertaken only if the infection is persistent, because the vaccine consists of virulent live virus. Vaccination can also be achieved with dried scabs from the previous year's outbreak because there are distinct antigenic differences among orf viruses[9]; the scab material is rubbed into scarified skin in an inconspicuous location (inner thigh, under the tail, in the axilla). A localized inflammatory reaction at the site 1 week after vaccination indicates a successful inoculation. Infected or vaccinated animals should not contact unexposed animals until the lesions have healed. Lambs born to immunized ewes may not be protected by colostral antibodies even though their levels of antibody postsuckling are high[10]; this points to the importance of cell-mediated immunity in protection from the disease. Lambs should be vaccinated at 6 to 8 weeks of age and are immune 3 weeks later. Yearly vaccination of the new lamb or kid crop

and new additions to the herd using farm-specific strains of orf should prevent devastating outbreaks on infected farms. At a minimum it appears that goat isolates should be used for kids and sheep isolates used for lambs.[9,10,11]

Bovine Papular Stomatitis (Proliferative Stomatitis)

Bradford P. Smith

Bovine papular stomatitis (BPS) is a disease principally of young cattle caused by a parapoxvirus closely related to CE and pseudocowpox. There are many similarities among BPS, CE, and pseudocowpox, and they may indicate a single virus adapted to different species.[1] There are as many antigenic differences among strains of BPS as among BPS, CE, and pseudocowpox.[1] Local strains therefore are recommended for vaccination. Infection usually is asymptomatic, but lesions consisting of raised papules may be noted on the muzzle, nose, oral mucosa (particularly the hard palate), or esophagus, where they are important differential diagnoses for lesions caused by VS, FMD, and BVD. In young feedlot cattle, 2- to 10-mm lesions of BPS are common for the first 4 weeks after arrival.[2] Morbidity may approach 100%. BPS may also occur as a chronic disease in young cattle.[3] It may be the same disease as proliferative stomatitis, muzzle disease, mycotic stomatitis, erosive stomatitis, ulcerative stomatitis, and necrotic stomatitis.

Ulcerative esophagitis caused by BPS virus in a 5-month-old, unthrifty calf was associated with a 20% morbidity rate in a group of 25 calves.[4] Outbreaks of severe disease associated with BPS with a mortality rate over 50% have been reported. Weight loss and diarrhea accompanied by papular lesions are commonly associated with the severe syndrome. Many lesions are erosions or shallow ulcers with elevated borders, whereas others are obvious raised papules. Lesions are found in the mouth, esophagus, and rumen. There are no lesions on the feet. BPS is commonly seen in calves 1 to 12 months of age and is rare in adult cattle, but outbreaks of confirmed BPS in Brazil and Japan involved the teats of dairy cows as well as the hands of milkers.[5,6] A confirmed case of severe esophageal lesions in an adult bull that died after 2 months has also been reported.[7] The disease is spread by animal contact and appears to be worldwide in distribution.

The first evidence of the disease is the appearance of 2- to 4-mm hyperemic foci, most commonly in the ventral margins of the nares. Similar lesions next appear in the mouth. Within 18 hours they become raised papules. Some lesions enlarge to form raised plaques over 1 cm in diameter. Lesions regress in 1 day to 3 weeks, leaving a yellow, red, or brown spot that persists for several weeks more.[8] Secondary lesions come and go, with some calves being visibly infected for 4 months.[8] Most animals have no fever or obvious clinical signs, and they continue to eat normally. Leukopenia was not seen in experimentally infected calves.[8] Secondary lesions appear to be spread through the blood; intravenous inoculation results in similar upper alimentary tract lesions.[9]

Histologic lesions consist of hydropic degeneration of the epithelial cells of the oral mucosa, hyperplasia of the papillae of the lamina propria, and eosinophilic inclusions in the cytoplasm of the degenerating epithelial cells. Lesions reaching the ulcerative stage show secondary necrosis, bacterial invasion, and sloughing of epithelium.

BPS has been associated with the "rat tail" syndrome of feedlot cattle.[10] Thirty-six of 84 Texas feedlots reported the problem, with a morbidity rate of 1% to 10%. The syndrome consists of diarrhea, salivation, poor weight gain, and loss of hair from the end of the tail. Sarcocystosis has also been mentioned in association with "rat tail" syndrome.

BPS is capable of causing painful proliferative lesions in human beings.[11] The lesions resemble those caused by CE or pseudocowpox. Most often the affected individual has a recent history of examining the mouths of cattle, often with cuts or abrasions on the hands. Lesions in humans apparently are limited to the primary site of inoculation on the hands.

Although ovine ecthyma vaccines are commercially available, no vaccine is marketed for protection against BPS. Local strains of parapoxviruses would be most likely to be more protective than commercial vaccine strains.

Diseases Caused by Bovine Virus Diarrhea Virus

Paul H. Walz

Definition and Etiology Infections with bovine virus diarrhea virus (BVDV) are endemic worldwide, and bovine virus diarrhea is recognized as one of the most important infectious diseases of cattle. Although the definition of the virus and its associated disease implies alimentary tract disease in cattle, BVDV is a pathogen capable of infecting other ruminants and pigs, and affecting multiple physiologic systems, including the reproductive, respiratory, circulatory, immunologic, integumentary, musculoskeletal, and central nervous systems.[1] Reproductive losses and respiratory tract disease are the most important economically, and infection of the reproductive system is critical to maintenance and transmission of BVDV within and among cattle populations through the generation of persistently infected (PI) offspring.[2] Infection of pregnant cattle prior to day 125 of gestation can result in the birth of calves that are immunotolerant to and persistently infected with BVDV.[3] PI calves are the most significant reservoir of BVDV and are at risk for the sporadically occurring, usually fatal mucosal disease.

BVDV is the prototypic member of the genus *Pestivirus* within the family Flaviviridae.[4] The pestiviruses are enveloped, single-stranded, positive-sense RNA viruses. Currently, the genus *Pestivirus* contains four recognized species, which include the two genotypes of BVDV (BVDV-1 and BVDV-2), classical swine fever virus and border disease virus.[4] Genetically distinct pestiviruses that have not yet been designated as species are also described and include Giraffe virus, Bungowannah virus, Pronghorn virus, and HoBi-like viruses. The HoBi-like viruses, which are also referred to as BVDV-3 or atypical pestiviruses, have received considerable attention because of their recent emergence and spread across multiple areas of the world purportedly via contaminated fecal calf sera.[5] So far, the HoBi-like viruses only appear to infect ruminant hosts, specifically cattle and water buffalo.[5]

Similar to many RNA viruses, mutations can occur within BVDV genomes leading to genetic, antigenic, and pathogenic variation. BVDV exists as a quasispecies, which are different but closely related mutant viral genomes subjected to continuous competition and selection. Nucleotide sequence differences are the most reliable criteria for differentiation of BVDV species. Subgenotypes of BVDV are described within BVDV-1 and BVDV-2 species, 12 among BVDV-1 viruses (BVDV-1a through BVDV-1l)[6] and 2 among BVDV-2 viruses (BVDV-2a and BVDV-2b).[7] Within the United States cattle population, there are three major subtypes, BVDV-1a, BVDV-1b, and BVDV-2a, with the BVDV-1b subtype predominating from diagnostic laboratory submissions and PI prevalence studies, accounting for 78% of bovine persistent infections in one North American study.[8] Predominance of the BVDV-1b strains in North America is noteworthy because most vaccines licensed and marketed in the United States contain BVDV-1a and BVDV-2 strains.[9] Strains of BVDV can also be further subdivided into cytopathic (CP) or noncytopathic (NCP) biotypes based on their effect on cultured cells, with CP strains causing vacuolation and death of cultured cells. The effect of the virus in cultured cells does not correlate with virulence, as NCP BVDVs are associated with cases of severe clinical disease, and only NCP strains of BVDV have been demonstrated, both naturally and experimentally, to induce persistent infection.[10] The NCP biotype predominates in the cattle population, accounting for approximately 65% to

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90% of BVDV isolates.[11] The NCP biotype is often the source for CP strains, which arise by mutations and recombination in the NCP strain.

Epidemiology

PREVALENCE. BVDV is distributed in cattle populations throughout the world as indicated by serologic surveys that test for the presence of neutralizing antibodies to the virus. Exposure to PI animals or vaccination against BVDV can result in a seropositive animal within a population. Prevalence of seropositive cattle varies among countries, ranging from 13% to 90% of cattle surveyed.[12] Differences in seroprevalence rates among countries largely depend on the management of cattle populations examined. Use of vaccines, open versus closed cattle production units, population densities, indoor versus pasture housing, communal grazing, and presence of PI animals will greatly influence prevalence of seropositive cattle. Surveys in North America have indicated overall seropositive rates of 40% to 90%.[13,14] In contrast, the prevalence of PI cattle is much lower and is generally believed to be between 1% and 2% of all cattle. In randomly selected beef herds in five U.S. states, an individual animal prevalence and a herd prevalence of BVDV persistent infection were 0.17% and 2.7%, respectively.[15] Other PI prevalence studies in beef cow-calf operations within more geographically focused areas within the United States have demonstrated rates between 0.09% and 1.7%[14,16,17]; however, not all studies used randomly selected herds and this factor can impact prevalence rates considerably. Surveys conducted on U.S. dairy operations have demonstrated individual animal prevalence rates of 1.9%[14] and 0.13%.[18] PI cattle can be found in clusters within groups of cattle as a result of BVDV exposure in pregnant cattle at similar gestation, and this can elevate the prevalence within a studied population.[15,18] Although it is generally believed PI calves have poor survivability, PI animals can survive to adulthood, become pregnant, and give birth to PI offspring. Of PI calves identified from randomly selected beef herds, 61% survived to weaning and thus were capable of providing a source of virus throughout the breeding season and early gestation.[15] The prevalence of PI calves arriving at U.S. feedlots has been demonstrated to be between 0.1 and 0.3%,[19,20] and this PI rate in feedyards is similar to the 0.17% reported for U.S. beef cow-calf operations.[15]

HOST RANGE. Cattle are considered the natural host for BVDV; however, BVDV does not possess strict host specificity.[21] Historically, pestiviruses were assigned according to the species from which they were isolated, with BVDV, classical swine fever virus, and border disease virus isolates being recovered from cattle, pigs, and sheep, respectively. Through serologic evidence, BVDV infections have been identified in more than 50 species within 7 of the 10 families of the mammalian order Artiodactyla.[22-24] Species other than cattle that have been reported susceptible to BVDV infection include pigs, sheep, goats, bison, captive and wild cervids, and Old World and New World camelids.[21] Of the heterologous hosts, sheep and goats are considered to have high potential for BVDV infections because they are phylogenetically most closely related to cattle, and sheep and goats can have close contact with cattle under certain management conditions such as subsistence agriculture and hobby farming. Recently, alpacas and white-tailed deer have received attention as heterologous hosts for BVDV infections because of the identification of PI animals. Several cases of PI alpacas have been reported in North America and Great Britain.[25,26] PI alpacas can survive for several months, but low birth weights, failure to thrive, and chronic respiratory and gastrointestinal infections are described in PI alpacas.[27] The BVDV-1b strain is most frequently isolated from PI alpacas[25,28,29] and could be the result of introduction and intraspecific spread and maintenance of BVDV-1b into North American alpaca populations or that unique BVDV-1b subgenotypes are able to establish transplacental infections in alpacas.[26] A prevalence study on BVDV infections in alpacas was conducted in the United States, and 25% of herds tested had seropositive alpacas, with 6% of alpaca herds possessing a PI alpaca.[30] Other seroprevalence studies have been performed for alpacas, with rates less than 20% reported in both North and South America.[31,32]

Infection of wildlife with BVDV has been demonstrated by several serosurveys and, less frequently, virus identification in individual animals. The livestock-wildlife interface is of great concern for a number of infectious diseases, including the related classical swine fever virus in wild boars. Wildlife may become infected with BVDV, but other factors, including shedding of the virus, intrapopulation maintenance, and amount of interspecific contact may influence the establishment of BVDV wildlife reservoirs. Persistent infections of white-tailed deer with BVDV have been demonstrated by both experimental and natural exposure.[33,34] Similar to cattle, the most dramatic effects of BVDV infections in white-tailed deer involve the reproductive system. Shedding of BVDV through nasal or rectal routes has been demonstrated in acutely infected and PI white-tailed deer, and shedding has resulted in transmission to other white-tailed deer.[35,36] Apparent prevalence rates of persistent infections in U.S. cervid populations were between 0.03% and 0.3% in tested populations.[37-39] Whether the source for BVDV infection in these populations was contact with cattle or the result of an endemic cycle is unknown.

Identification of heterologous PI hosts may have important implications for the epidemiology of BVDV, as these nonbovid PI animals may serve as reservoirs for BVDV. As reservoirs, nonbovid PI animals could threaten the health and well-being of other artiodactyls, including cattle, and adversely affect outcomes and the ultimate success of organized BVDV control and eradication efforts.[40]

TRANSMISSION. Methods of BVDV transmission can be classified into vertical and horizontal transmission. With BVDV, horizontal and vertical transmissions are closely related, as horizontal transmission to a pregnant cow can result in vertical transmission to the developing fetus (Fig. 32-90). As stated previously, PI cattle can reach adulthood. Calves delivered from PI dams will themselves be PI; however, most PI offspring are the result of an acute infection, or horizontal transmission, in the dam.[15] Horizontal transmission of BVDV can occur continuously by PI animals and briefly by animals during an acute infection. As with other viral diseases, factors controlling BVDV transmission in a susceptible population are the infectiousness of the virus, the contact rate between infectious and susceptible animals, the duration of infectiousness, and the proportion of the population that is naive and susceptible.[41] Cattle PI with BVDV shed large amounts of virus their entire life and are the major source of BVDV transmission both within and among herds. These PI cattle are capable of shedding virus from nasal secretions, urine, feces, milk and colostrum, uterine fluids, saliva, tears, and semen.[42] Direct contact with these body fluids from PI cattle is the most efficient method of horizontal BVDV transmission, with inhalation and ingestion being the most common routes for transmission. While heterologous PI hosts are capable of shedding equivalent amounts of BVDV in nasal secretions as PI cattle,[34] they are assumed to play a reduced role in BVDV transmission because contact rates are less between infectious heterologous hosts and susceptible cattle. Acutely infected cattle also have a limited role in BVDV transmission because levels and duration of virus shed are considerably lower; however, potential for transmission of BVDV following acute infection can be greatly influenced by the virulence of the acutely infecting strain of BVDV, the proportion of naive animals being exposed, and the immune cross protection acquired either through vaccination or exposure to field strains of virus. Acutely infected calves will shed greater levels of virus and for a longer duration following an infection with a highly virulent strain of BVDV,[43] theoretically providing a source of transmission. However, an experimental study demonstrated no spread of infection from acutely infected to susceptible animals even though they were in close contact, further emphasizing the importance of virus and host characteristics during transmission.[44] Following acute BVDV infection, virus can be found in nasal secretions usually only for a few days between 4 and 10 days after exposure.

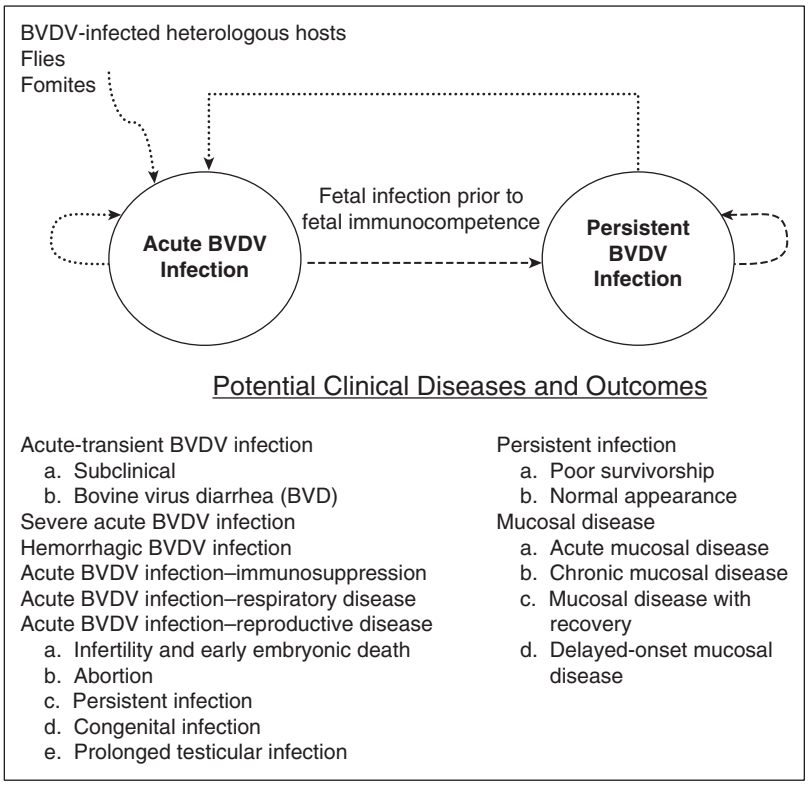


FIG. 32-90 Two forms of bovine virus diarrhea virus (BVDV) infection: acute and persistent. Routes of horizontal transmission are indicated by dotted lines (most important is from persistently infected [PI] cattle to naive cattle); routes of vertical transmission are indicated by dashed lines (most important is acute BVDV infection in pregnant cattle). Potential clinical diseases are not exclusive and multiple clinical forms can be observed in the same population of cattle.

Although contact with PI cattle is the most important source for BVDV transmission, infections with BVDV in the absence of PI cattle have been described in seronegative herds.[45] Spread of BVDV can occur in the absence of PI cattle as a result of direct contact with acutely infected animals, contact with heterologous hosts, or indirect contact. Being that BVDV is an enveloped virus, the virus is unstable at low or high pH and at high temperatures but can survive in a cool, protected environment for several weeks.[42] Temperature has a major influence on BVDV survival in manure slurry with virus infectivity remaining for more than 6 weeks at 5° C (41° F) but less than 2 weeks at 20° C (68° F).[46] On the basis of research with the related classical swine fever virus, BVDV is probably susceptible to common disinfectants such as chlorhexidine, phenols, iodophors, aldehydes, and hypochlorites.[47] Indirect transmission through contaminated needles and equipment and insect vectors has been demonstrated experimentally.[48,49] Insects such as stable flies, horse flies, and face flies can potentially serve as a source of BVDV infection[48,50]; however, the horn fly, which is a common fly species affecting cattle, was not able to transmit BVDV between PI cattle and BVDV-naive cattle.[51]

Bulls acutely and persistently infected with BVDV are capable of shedding virus in semen and have the potential for horizontal and vertical transmission.[52-54] The virus may survive cryopreservation and processing of semen for artificial insemination.[55] Although acutely infected bulls shed lower concentrations of BVDV in semen than do PI bulls, infection of artificially inseminated heifers may result from using semen from acutely infected bulls prior to seroconversion.[53] Prolonged, localized testicular infections have also been described following experimental BVDV infection of postpubertal bulls; however, their prevalence and epidemiologic significance are probably low.[56]

Herd-to herd transmission usually occurs through acquisition of PI cattle or pregnant cattle that are carrying a PI fetus. Cattle operations that have purchased cattle within the past 5 years are at highest risk for having PI animals.[57] Purchase of new cattle incubating an acute infection or exposure to other cattle through fence line contact, communal pastures, and animal exhibitions can also be a source of BVDV introduction into a herd.

Clinical Signs and Differential Diagnoses

BVDV infection in cattle may result in a complex spectrum of clinical manifestations ranging from subclinical to fatal disease. The virus is capable of infecting multiple organ systems, often with several organ systems involved concurrently.[9] Clinical manifestations are dependent on the interplay of host factors, environmental stress levels, and viral factors.[12] Host factors influencing the outcome of viral infection include immune status, pregnancy status, gestational age of the fetus at the time of infection, and whether the host is immunotolerant or immunocompetent. Viral factors include biotypic variation, genotypic variation, and antigenic diversity. When describing the clinical manifestations of BVDV infection in cattle, it is important to note that both BVDV-1 and BVDV-2 strains can be involved in the entire spectrum of clinical disease, including acute and persistent infections. Two states of infection (acute and persistent) are possible with BVDV infections in ruminants, and this will be the basis for discussion of clinical signs and pathogenesis within this text (see Fig. 32-90).

Disease Associated with Acute BVDV Infection

The terms *acute, primary,* and *transient* have all been used to describe BVDV infection in postnatal cattle, which possess the ability to respond immunologically to BVDV. Although postnatal cattle are able to respond immunologically to BVDV, immunosuppression induced by the virus is an important contribution to pathogenesis and clinical disease. For discussion of clinical disease states, acute BVDV infections can be further subdivided into six disease categories: acute-transient BVDV infection, severe acute BVDV infection, hemorrhagic BVDV infection, acute BVDV infection-immunosuppression, acute BVDV infection–respiratory disease, and acute BVDV infection–reproductive disease.[9,40]

ACUTE-TRANSIENT BVDV INFECTION. Acute-transient BVDV infection occurs in postnatal cattle. In most situations, the disease occurs in cattle considered naive to BVDV, but disease could potentially occur in cattle seropositive to BVDV that become infected with a heterologous BVDV strain. Most acute BVDV infections occur

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without clinical manifestations, with up to 90% of BVDV infections estimated to occur without clinical signs[12]; however, if cattle are observed closely, mild fever, leukopenia, and a decrease in milk production can occur. Exposed cattle develop BVDV-specific neutralizing antibodies. Even though BVDV infection may be subclinical, if the infected animal is pregnant, deleterious effects can be manifested in the fetus.

Bovine virus diarrhea (BVD) is the term used to describe the clinical form of BVDV infection in immunocompetent cattle and digestive tract disease manifested by severe diarrhea was part of the original description of BVD in 1946.[58] The incubation period for acute BVDV in naive cattle is 5 to 7 days. Following oronasal uptake, BVDV initially replicates in nasal mucosa and tonsils. Viremia will typically last for several days starting around day 3 after infection, but it can last for up to 15 days. During this period of viremia, spleen, thymus, lymph nodes, gastrointestinal epithelium, and the respiratory tract can become sites of further viral replication. Clinical signs of bovine virus diarrhea include depression, oculonasal discharge, anorexia, fever, oral erosions and ulcerations, diarrhea, and decreased milk production in lactating cows. A rapid respiratory rate may be observed, which may be interpreted incorrectly as pneumonia. Clinical pathologic changes such as leukopenia are observed in calves acutely infected with BVDV.[12] The major decreases in the total leukocyte count have been in the numbers of neutrophils and lymphocytes.

One of the most important determinants for the outcome of acute BVDV infection in susceptible animals is the virulence of the infecting BVDV strain.[59] Experimental infections with BVDV strains of low and high virulence reveal similar initial infection and spread but differing amounts of virus in tissues and speed of dissemination through the body.[60] Virulent strains of BVDV result in widespread distribution of virus in tissues, and BVDV strains that induce high levels of viremia result in more severe clinical signs.[43] Viral replication and antigen distribution can be detected in the thymus, lymph nodes, Peyer patches, tonsils, and spleen with all strains of BVDV. In contrast to low virulent strains of BVDV where antigen is only found outside of lymphoid tissues in the intestinal mucosa, antigen can be found in bone marrow, intestinal mucosa, respiratory tract, endocrine tissues, and nervous system tissues following acute infection with high virulent strains of BVDV.[60] The HoBi-like viruses have received considerable attention because of their recent emergence and detection in South America, Europe, and Southeast Asia, and natural descriptions and experimental reproductions of the infection have revealed very mild disease signs in cattle. Most descriptions of HoBi-like virus infection in natural settings relate the infection to either respiratory disease or reproductive disease, specifically abortion. During experimental reproduction of the disease, clinical signs associated with HoBi-like virus infection can be indistinguishable from low virulent BVDV infection.[5]

Disease associated with acute BVDV infection is often observed in seronegative cattle between the ages of 6 and 24 months. It is generally believed that maternally derived BVDV-specific antibodies have waned and acquired immunity is not yet formed, thus making calves as early as 4 to 6 months of age susceptible. Maternally derived BVDV-specific colostral antibodies are thought to be protective unless sufficient antigenic diversity exists between challenge strain and strain against which the maternal-derived colostral antibodies were developed. Disease as a result of acute infection can be observed in preweaned calves.[61] Acute disease in neonatal or preweaned calves can result in signs of pneumonia or enteritis, often occurring in association with failure of passive transfer. Studies have investigated the duration of maternal colostrum–derived antibodies against BVDV-1 and BVDV-2, and a major finding from these studies is the variability in duration between calves as a result of colostrum quality and consumption. Estimated mean time to reach seronegative status in dairy calves receiving maternal colostrum was 117.7 ± 37.7 days for BVDV-1 and 93.9 ± 61.9 days for BVDV-2.[62] Another study reported that the mean duration for colostrum-derived antibodies in beef calves was 185.6 ± 59.8 days for BVDV-1 and 157.8 ± 56.1 days for BVDV-2.[63]

Diarrheal diseases considered as differential diagnoses for acute BVDV infection in adults include salmonellosis, winter dysentery, paratuberculosis, intestinal parasites, malignant catarrhal fever, arsenic poisoning, and copper deficiency (molybdenosis). The differential diagnoses for acute BVDV infection for the neonatal period includes other causes of diarrhea in young calves such as rotavirus or coronavirus infection, cryptosporidiosis, enterotoxigenic *Escherichia coli* infection, salmonellosis, and coccidiosis. Other causes of calf pneumonia such as bovine respiratory syncytial virus, pasteurellosis, hemophilosis, or mycoplasma infection should also be considered.

SEVERE ACUTE BVDV INFECTION. In the late 1980s and early 1990s, an atypical and significantly more severe form of BVDV infection was recognized in Quebec,[64] Ontario,[65] the United States,[66] and the United Kingdom.[67] The disease had a peracute course, caused high morbidity, and resulted in substantial numbers of deaths in all age groups. In Quebec, mortality due to BVDV in veal operations was estimated at 25% of 143,000 calves for 1993.[64] The outbreak in Ontario involved 150 dairy, 600 beef, and 100 veal herds. The severity of disease varied among herds, with some herds experiencing 10% to 20% mortality rates in all age groups of cattle. Clinical manifestations of severe, acute BVDV infections include diarrhea, pyrexia, decreased milk production, and oral ulcerations frequently observed in older cattle. The presence of severe clinical disease combined with oral ulcerations made mucosal disease a primary differential diagnosis. Other differential diagnoses for diseases that cause oral lesions in cattle include malignant catarrhal fever, vesicular stomatitis, papular stomatitis, foot-and-mouth disease, and bluetongue. Abortions in cattle also were a common occurrence. These outbreaks of severe clinical disease were reported to be associated with recent introduction of cattle to the herd or history of inadequate vaccination programs.[65] Analysis of BVDV isolates from outbreaks in Canada and the United States was performed, and NCP isolates were obtained from affected cattle. Nucleotide sequencing of the RNA genome of these isolates revealed a distinct group of BVDV, which were designated as BVDV-2,[68] which then later became a separate species within the genus *Pestivirus*.

The outbreaks of severe BVDV infections clearly demonstrated that some BVDV strains can cause severe life-threatening disease in postnatal, immunocompetent cattle. Prior to 1993, it was believed that the majority of BVDV infections in immunocompetent adult cattle resulted in subclinical or mild disease. Although BVDV-2 strains were associated with severe acute BVDV infections, not all BVDV-2 strains will cause severe disease. Furthermore, it is likely that some BVDV-1 strains are capable of inducing severe clinical disease under unfortunate conditions involving host, agent, and environment factors.

HEMORRHAGIC BVDV INFECTION. The hemorrhagic syndrome, which is characterized by thrombocytopenia, is an additional form of severe acute BVDV infection in immunocompetent cattle.[69] The first descriptions of hemorrhagic syndrome included both calves and adult cattle naturally infected with BVDV, with severe depressions in platelet counts and high case fatality rates being reported.[70] Clinical manifestations of the hemorrhagic syndrome are primarily related to thrombocytopenia and include bloody diarrhea, epistaxis, petechial hemorrhages, ecchymotic hemorrhages, hyphema, and bleeding from injection sites or insect bites. Fever, diarrhea, rumen stasis and dehydration are also common. In addition to thrombocytopenia, leukopenia characterized by severe neutropenia and lymphopenia are clinical pathologic abnormalities. Thrombocytopenic BVDV infections have been experimentally reproduced, almost exclusively with NCP BVDV-2 strains[43,69]; however, hemorrhagic syndrome has been reported following experimental inoculation of colostrum-deprived calves with a BVDV-1b strain.[71] Platelet dysfunction has also been described with experimental BVDV infection[72];

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thus quantitative and qualitative platelet defects contribute to the hemorrhagic diathesis observed in infected cattle. Bone marrow infection and, specifically, BVDV infection in bone marrow megakaryocytes may be important in the etiology of BVDV-induced thrombocytopenia.[43,73] Diseases that can mimic hemorrhagic syndrome include septicemia with subsequent development of disseminated intravascular coagulation, sweet clover poisoning, and bracken fern poisoning.

ACUTE BVDV INFECTION–IMMUNOSUPPRESSION. Although the majority of BVDV infections in immunocompetent cattle are transient and self-limiting, it is apparent that when infection occurs in the presence of other microorganisms, BVDV can contribute to disease that becomes clinically evident. Numerous studies, under both natural and experimental conditions, have demonstrated the relationships between BVDV and other infectious agents. The virus has been reported to enhance the pathogenicity of bovine herpesvirus-1 (BoHV-1), actinomycosis, papular stomatitis, enteritis caused by *Salmonella* spp., colibacillosis, metritis, and mastitis. The role of BVDV in synergistic or mixed infections with other agents is most likely due to immunosuppression.[9] Mechanisms responsible for BVDV-induced immunosuppression are likely multifactorial; however, critical information on mechanisms of the suppression, the duration and extent of recovery, and the long-term effects are currently speculative.[40] The ability of BVDV to induce quantitative and qualitative defects in leukocytes could provide some contribution to immunosuppression. The defects involve immune system cells of both the innate and adaptive immune responses. A transient leukopenia occurs in most cattle acutely infected with BVDV which may be more severe with BVDV-2 than BVDV-1. Decreases in helper ($CD4^+$), cytotoxic ($CD8^+$), and gamma/delta (g/d) T lymphocytes, as well as B lymphocytes and neutrophils, have been reported and these decreases are often strain dependent.[74] Several possible explanations exist for the mechanism of leukopenia, and these include immune system removal of BVDV-infected immune cells, destruction of immune cells by BVDV, and increased trafficking of immune cells into tissue sites of viral replication. During acute infection, various levels of lymphoid depletion are observed in the thymus, spleen, lymph nodes, and gut-associated lymphoid tissues (Peyer patches).[75] The NCP BVDV strains are lymphotrophic, and lymphocyte apoptosis in lymphoid tissues results in cytolysis and lymphoid depletion.

Decreased functional responses in immune system cells have also been described during acute BVDV infection, and affected cells include lymphocytes, neutrophils, and monocytes and macrophages.[76,77] Dysfunction in both B and T cells has been demonstrated by poor culture response to phytohemagglutinin, pokeweed mitogen, and concanavalin A stimulation and by decreased production of IFN.[26,78] Infection of peripheral monocytes in vitro caused a significant decrease in the chemotactic responses to lymphokine.[79] Immunohistochemical and flow cytometric studies have demonstrated that BVDV infects and replicates in antigen-presenting cells.[80] Infection of monocytes with BVDV has been shown to stimulate the synthesis of cytokines that may be responsible for the reduced ability to stimulate T-cell responses to specific antigens and mitogens. A decrease in the secretion of tumor necrosis factor (TNF)–α from lipopolysaccharide (LPS)- or *Salmonella*-stimulated bone marrow–derived macrophages that had been infected with BVDV has been reported.[81] These abnormalities, combined with environmental and/or management stressors, contribute to immunosuppression and concurrent infection with other pathogens. Increased susceptibility to other secondary infections is a consequence of BVDV-induced immunosuppression.

ACUTE BVDV INFECTION–RESPIRATORY DISEASE. Substantial data exist demonstrating that BVDV infection is important in polymicrobial disease, and the bovine respiratory disease complex in feedlot animals and intensively housed calves is the best example of this type of disease process. In North American feedyards, bovine respiratory disease is the most frequently reported cause of morbidity and mortality. The role of BVDV in the bovine respiratory disease complex is debatable as to whether BVDV-induced immunosuppression or primary infection of the respiratory tract plays the major role, but BVDV can be isolated from pneumonic cattle more frequently than can other viruses.[82] Certain BVDV strains may be pneumotropic, as evidenced by some BVDV strains causing interstitial pneumonia in experimentally inoculated calves.[83] BVDV may play a secondary role in bovine respiratory disease complex through immunosuppression. Although BVDV is frequently isolated from cattle with pneumonia, it is often isolated with the other infectious agents typically associated with bovine respiratory disease complex. Reports from disease outbreaks and experimental studies have supported a synergistic role of BVDV with bovine herpesvirus type 1 (BoHV-1) and bovine respiratory syncytial virus (BRSV).[84,85] Calves experimentally inoculated with BVDV 7 days prior to inoculation with BoHV-1 developed more severe clinical disease, with dissemination of BoHV-1 into nonrespiratory tissues including intestinal and ocular tissues, as compared with calves inoculated with BoHV-1 alone.[84] Initial BVDV infection may impair the ability of calves to clear BoHV-1 from the lungs and to contain BoHV-1 at the local infection site. Synergism between BVDV and bacterial pathogens, specifically *Mannheimia haemolytica* and *Mycoplasma bovis* has also been described.[86,87] Viral-bacterial synergy in bovine respiratory disease complex likely is the result of BVDV compromise of the host defense mechanisms. Viral damage of nasal turbinate and tracheal epithelium alters mucociliary clearance of bacteria with subsequent bacterial attachment and colonization. The innate defenses of the lung are compromised with BVDV infections of macrophages and neutrophils, resulting in depletion, destruction, or impairment in function. Suppression of B- and T-cell–mediated immune responses can also occur as a result of BVDV infection.[9]

ACUTE BVDV INFECTION–REPRODUCTIVE DISEASE. Reproductive tract infections have been described for male and female cattle. The importance of BVDV on the male reproductive tract has not received attention equivalent to the effects on female reproduction for a number of reasons, but from a transmission standpoint, acutely infected bulls and PI bulls are capable of shedding virus in semen.[52] Acceptable or unacceptable semen quality may be observed in bulls acutely infected with BVDV. Although acute BVDV infections generally result in a transient viremia with subsequent clearance of the virus by the host immune system, a localized, prolonged infection of testicular tissue with NCP BVDV has been described under both natural and experimental conditions.[52,54] The original description of prolonged testicular infection with BVDV was identified in the testes of a seropositive, nonviremic bull at an artificial insemination center.[54] Despite absence of viremia, the bull continuously shed infectious BVDV in semen throughout his life, and the semen of this bull resulted in infection and subsequent seroconversion of an inseminated seronegative heifer.[88] Furthermore, this bull displayed a consistently high concentration of circulating serum antibodies that neutralized the specific viral strain that was persistently shed in the semen. Since that original description, prolonged testicular infections with BVDV have been reproduced in postpubertal bulls. Viral RNA has been detected in semen for 2.75 years following BVDV exposure, and infectious virus grown from testicular tissue has been detected up to 12.5 months after BVDV exposure.[52] Protection from a systemic immune response due to a blood-testes barrier is believed to be the mechanism for the localized, prolonged testicular infection. Uncertainty currently exists regarding whether bulls with a prolonged testicular infection may become viremic and infectious to other animals.

It is well established that BVDV infection can cause significant reproductive problems in nonimmune pregnant cattle, including fertilization failure, embryonic death, fetal death and expulsion, persistent infection, and congenital defects (Fig. 32-91). Transplacental infection is a common event in pregnant cattle exposed to BVDV, and in experimental studies, transplacental infection occurs with almost 100% efficiency.[89] As discussed previously, most acute BVDV

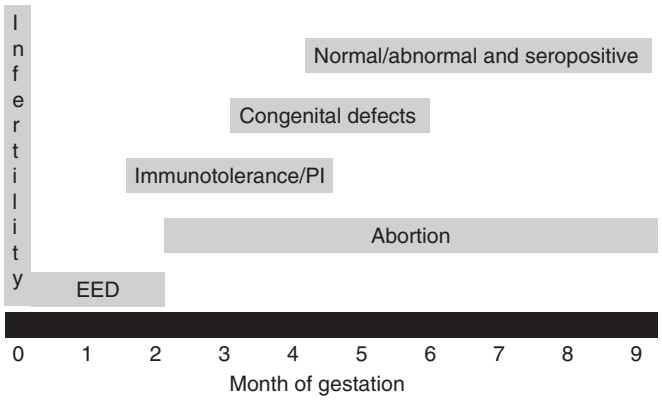


FIG. 32-91 Potential reproductive outcome after infection with BVDV during different stages of gestation. *BVDV,* Bovine virus diarrhea virus; *EED,* early embryonic death; *PI,* persistently infected.

infections are subclinical; yet, infection in pregnant cattle may result in significant disease. The economic damage caused by BVDV in susceptible herds is mainly associated with the outcomes of intrauterine infections. The outcome of fetal infection with BVDV is dependent on three main factors: (1) time of infection (i.e., gestational age of the fetus at the time of infection); (2) organ system involved in the infection; and (3) properties of the virus (i.e., biotype, virulence, and target cell range). It is important to note that BVDV-1 and BVDV-2, as well as CP and NCP strains, can result in reproductive disease, although only NCP strains are capable of inducing PI cattle.

Infertility and Early Embryonic Death. Infection of cattle prior to insemination can result in impaired conception rates.[90] This may be due in part to ovarian infection and dysfunction as a result of BVDV viremia. Viral antigen in macrophage-like cells and ovarian stromal cells and oophoritis have been described in cattle acutely infected with NCP BVDV,[91] and in cattle vaccine with modified live viral vaccines containing CP BVDV.[92] Of particular interest is that pathologic change and BVDV antigen were detected in some cattle up to 60 days after infection.[91] The first 45 days of gestation are the embryonic period, and conception and pregnancy rates are lower if cattle are exposed at the time of insemination and become viremic during the first 3 weeks of gestation. The zona pellucida has been demonstrated to prevent BVDV from infecting the embryonic cells.[93]

Abortion. Abortion may be observed at any time during gestation as a result of BVDV infection. Fetal resorption, mummification, or expulsion can occur following fetal death depending on the gestational age of the fetus at the time of infection.[2] Although fetal death and abortion are most common during the first trimester, mid- and late-term abortions and stillbirths should be examined for BVDV. Diagnostic laboratory surveys indicate that BVDV isolation prevalence from aborted fetuses in the United States is quite variable, with BVDV being isolated from as few as 0.1% to as many as 27.2% of submitted fetuses.[94,95] Following BVDV infection, expulsion of the fetus may occur shortly or may be delayed for several months after infection. As a result of delayed expulsion following fetal death, isolation of BVDV from aborted fetuses may not be successful. This has also been demonstrated experimentally, with abortion being observed 30 to 50 days after experimental infection at around days 100 to 120 of gestation.[96]

Persistent Infection. The fetal gestational ages between day 45 and day 125 are the period of fetal development during which fetal immunocompetence to BVDV occurs. The most outstanding outcome of infection during this period is the development of persistent infection. Immunocompetence to BVDV is not absolute at day 125 of gestation, and the dams of most PI calves were exposed at gestational ages prior to day 100. By definition, cattle that are persistently infected with BVDV are immunotolerant to BVDV. Biotype is important when discussing infection during this period of gestation. Fetal death and expulsion can occur with infection with both CP and NCP strains of BVDV; however, only NCP strains are capable of causing persistent infection.[10] The PI animal cannot recognize the infecting NCP BVDV as foreign. Immunotolerance is specific to the infecting NCP strain of BVDV, and postnatal, PI animals can respond immunologically to heterologous strains of BVDV. For this reason, PI animals may be seropositive to BVDV, and seropositive status cannot be used diagnostically to rule out persistent infection.

Congenital Defects. Congenital malformations are associated with BVDV infection during the gestational period of organogenesis, which occurs approximately between days 100 and 150 of gestation.[89] Congenital malformations that have been reported in association with BVDV infection include cerebellar hypoplasia, hypomyelinogenesis, hydranencephaly, alopecia, cataracts, optic neuritis, brachygnathism, hydrocephalus, microencephaly, thymic aplasia, hypotrichosis, pulmonary hypoplasia, and growth retardation. Congenital malformations may be due to the direct result of viral infection on developing cells or to the host immune response in destroying virally infected cells. During a point-source of exposure of BVDV into a bred population of cattle, congenitally malformed calves will be born just prior to the birth of PI animals, and this information can be useful to determine sampling of calves for BVDV.

BVDV Infection during Later Stages of Pregnancy. Fetal infections in the last trimester can occur, but at this stage of gestation, organogenesis is often complete and fetuses are considered immunocompetent to BVDV. Congenital infection during this period usually results in the birth of a calf that is seropositive on a precolostral blood sample. Detrimental effects of BVDV infection in late gestation seem to be less common; however, weak calves and abortions have been reported.[89] It has generally been accepted that infection in late gestation results in the birth of calves that are clinically normal; however, calves congenitally infected with BVDV may be at greater risk for increased morbidity and mortality postnatally.[97] The congenitally infected calves that are born with neutralizing antibody titers to BVDV have been shown to be twice as likely to experience a severe illness during the first 10 months of life as compared with calves born free of BVDV antibody titers.[97] The prevalence and importance of congenital infections remains to be determined.

Disease Associated with Persistent BVDV Infection

PI cattle are the main reservoir for BVDV. Cattle PI with BVDV are characterized by a wide distribution of BVDV throughout their organs as a result of lacking an immune response to the persisting BVDV strain. In PI animals, the virus is present throughout all organs and tissues; therefore BVDV is shed from multiple sites including nasal discharges, urine, semen, colostrum/milk, and feces. Some PI calves are born weak, stunted, and die shortly after birth[12]; however, many PI calves are born without any observable abnormalities and can survive for at least several months. This is important for beef cattle herds as these animals can survive into the start of the subsequent breeding period and thus become an important source for horizontal transmissions. PI cattle can have decreased survival rates, as evidenced by reports documenting a greater than 50% mortality rate in the first year of life.[98] This mortality may be due in part to the fact that PI cattle may have an impaired immune response, which makes them more susceptible to opportunistic pathogens. Vertical transmission is 100% as PI cows will give birth to PI offspring. PI cattle are at risk of developing mucosal disease.

MUCOSAL DISEASE. Mucosal disease is the most dramatic of BVDV-associated clinical disease due to the severity and characteristics of lesions. Mucosal disease occurs when cattle that are immunotolerant and PI with NCP BVDV become infected with a CP BVDV.[99] Because mucosal disease only occurs in PI cattle and PI cattle comprise less than 1% of the cattle population, it is characterized as a disease of very low morbidity and high mortality. Although the origin of the CP BVDV can be external, such as following the use of modified live virus vaccines, current theory holds that in the majority of cases of mucosal disease, the CP BVDV represents a

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mutation of the NCP BVDV (the persistently infecting biotype).[99] There are multiple clinical forms of mucosal disease, with the variations being due to the antigenic relationship between the persistently infecting NCP strain and the superinfecting CP strain.[99] The multiple clinical forms of mucosal disease can be divided into acute fatal mucosal disease; chronic mucosal disease; chronic mucosal disease with recovery; and delayed onset mucosal disease.[99]

ACUTE MUCOSAL DISEASE. Acute mucosal disease occurs when the superinfecting CP strain shares close antigenic homology to the PI NCP strain. The CP strain may arise de novo by a mutational event from the NCP strain in the PI animal. The mutational event affects the viral biotype but does not affect the viral antigenicity.[100] The clinical findings associated with acute mucosal disease include pyrexia, depression, anorexia, decreased milk production, profuse diarrhea, ptyalism, mucopurulent oculonasal discharge, and oral erosions.[12] Oral erosions are present on the lips, gingival margins, tongue, dental pad, and the hard palate. Experimental reproduction of acute mucosal disease indicates an incubation period of 7 to 14 days.[99] Acute mucosal disease is considered to be 100% fatal.

CHRONIC MUCOSAL DISEASE. Chronic mucosal disease and mucosal disease with recovery are forms of mucosal disease in which the superinfecting CP strain is heterologous to the PI NCP strain. The likely source of the superinfecting CP strain is external, rather than a mutational event in the PI NCP strain. The clinical manifestations of chronic mucosal disease are anorexia, weight loss, diarrhea, chronic bloat, alopecia, erosive lesions on the mouth and skin, and lameness.[12] The lameness may develop as a result of laminitis, interdigital necrosis secondary to erosive lesions, and hoof deformities. Rarely, a PI animal may mount an immune response to the superinfecting heterologous CP strain and clear the superinfection, and this has been referred to as mucosal disease with recovery.[99] It is important to note that the animal remains PI with the NCP strain.

Necropsy Findings Pathologic lesions associated with BVDV infection can be quite diverse in types and degree and, like the clinical manifestations, are dependent on host and viral factors. Age of animal, immune status at the time of infection, and the presence of concurrent infections will greatly influence the pathologies observed. Many lesions observed are not specific to BVDV infection; thus laboratory testing becomes an important component in the diagnostic process. Occasionally, only microscopic lesions are present, and unless histopathology is performed, a lesion can be unnoticed and infection undiagnosed.

ACUTE BVDV INFECTION. Animals that die of acute BVDV infection have less severe lesions. In addition, lesions, when present, can often be nonspecific and subtle. Edematous intestines, occasionally with ecchymotic hemorrhages and mild reaction in mesenteric lymph nodes, can be observed. Occasionally, linear erosions in the alimentary tract and proximal colon are present along with atrophy of gut-associated lymphoid tissues (Peyer patch). Secondary bacterial infections such as enteritis, pneumonia, or mastitis are present and have contributed to death. Animals that die of hemorrhagic syndrome can have evidence of hemorrhage in many organ systems, including the gastrointestinal, cardiovascular, respiratory, and urinary systems. Petechial or ecchymotic hemorrhages are often apparent on mucosal surfaces, and significant hemorrhage in the gastrointestinal submucosa and Peyer patches may also be present. Lesions associated with cases of severe acute BVDV infection can be similar to lesions associated with mucosal disease. Because of this and the severe clinical signs observed, it is usually not possible to differentiate the two forms of disease without supporting laboratory testing.

MUCOSAL DISEASE. Postmortem examination of cattle dying of mucosal disease usually reveals gross abnormalities most prominent in the alimentary system. Animals that die of mucosal disease usually have severe necrotizing erosive or ulcerative lesions involving the mouth, tongue, esophagus, ruminal pillars, omasum, abomasum, intestines, and cecum.[101] Erosive lesions may extend onto the external nares and into the nasal cavity. Ulcers involving the esophagus typically are linearly elongated. The Peyer patches in the small intestine often are necrotic and hemorrhagic. Bowel contents are watery, hemorrhagic, and foul smelling. Pathologic gastrointestinal conditions may be absent or very mild in cattle with chronic mucosal disease, although histopathologic lesions usually are present with atrophy of gut-associated lymphoid tissues present. Skin lesions are often found and include patchy hyperkeratosis around the neck, shoulder, and perineal areas. Erosive lesions involving the perineal area, the prepuce, and the interdigital cleft and coronary band of the hoof may be present. Skin lesions are most apparent in cattle suffering from chronic mucosal disease.

ABORTIONS AND CONGENITAL DEFECTS. Pathologic criteria for the diagnosis of BVDV as a cause of abortion are not established. Fetuses aborted as a result of in utero BVDV infection often are autolytic when expelled. Lesions found in aborted fetuses and the accompanying placentas are nonspecific for BVDV. Under experimental conditions or when aborted fetuses are expelled soon after death, lesions observed include conjunctivitis, peribronchiolar and interalveolar pneumonia, and nonspecific myocarditis. A significant decrease in cerebellar mass may be evident in calves affected by cerebella hypoplasia as a result of in utero infection with BVDV during the second trimester of gestation. Other common congenital defects associated with BVDV infection that may be noted at necropsy include cataracts and thymic hypoplasia.

Diagnosis Numerous methods are available for detecting BVDV infection. The choice of test depends on the clinical problem, the availability of tests by different diagnostic laboratories, and financial considerations (Table 32-10). Because the clinical manifestations of BVDV are diverse, accurate diagnosis of BVDV infection relies on laboratory testing. Sample selection and handling for BVDV testing are critical because the starting test material will largely define success or failure of the diagnostic test.[102]

VIRUS ISOLATION. Virus isolation is a basic, reliable, and widely used method for diagnosis of BVDV infection, and remains the "gold standard" for BVDV diagnostics; however, many diagnostic laboratories use different cell culture systems, and sample handling and processing can have a major impact on results obtained. The BVDV may be cultured and isolated from many samples, including serum, whole blood, semen, nasal swabs, and various types of tissues.[103] Although time-consuming and expensive, mononuclear cells in the buffy coat from whole blood are an ideal sample for individual virus isolation where an acute BVDV infection is suspected, because BVDV is highly cell associated, and the virus isolation is not interfered with by neutralizing antibodies to BVDV in serum.[103] Sample handling is very important for virus isolation using mononuclear cells because they need to be viable when inoculating in the cell culture system.[102] The ideal tissue samples for virus isolation from deceased animals at postmortem exam include lymphoid organ–related tissues such as spleen, the gut-associated lymphoid tissue of the distal small intestine (Peyer patches), mesenteric lymph nodes, and thymus.[103] In addition, pooled tissues from the same animal can be applied to virus isolation. Detection of NCP BVDV strains and confirmation of CP strains as BVDV are performed using immunofluorescence or immunoperoxidase staining techniques or reverse transcription polymerase chain reaction (RT-PCR).

A microtiter virus isolation that has been referred to as the *immunoperoxidase monolayer assay* (IPMA) has been developed, but the test is not ideal for detecting acute infections, nor is it advisable to use this assay for testing calves less than 3 months of age, as these calves likely have colostral antibodies that would interfere with the test.[104]

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TABLE 32-10

Diagnostic Testing for Bovine Virus Diarrhea Virus (BVDV)

Suspected Form of Infection or Purpose for Testing	Diagnostic Test	Specimen	Comments
Acute BVDV infection	Virus isolation PCR	Serum, whole blood, or nasal swabs	Whole blood preferred over serum Viremia may be too transient for successful virus detection Nasal swabs can be useful for establishing role of BVDV in bovine respiratory disease complex
	Serology (virus neutralization tests)	Serum	Pair sera 3 to 4 weeks apart Serology for both BVDV-1 and BVDV-2 should be performed
	Immunohistochemistry Virus isolation PCR Fluorescent antibody testing on fresh tissues	Postmortem tissues	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus (calves), lung (pneumonia)
Reproductive tract disease (infertility and abortion)	Serology (virus neutralization tests)	Serum or fetal fluid	May need to establish serum bank on at-risk animals as seroconversion complete when reproductive problem noticed or compare titers of affected to unaffected cattle Serology for both BVDV-1 and BVDV-2 should be performed Presence of antibodies or BVDV in fetal fluid is suggestive but not definitive for BVDV as cause of abortion Absence of antibodies or BVDV in fetal fluids does not rule out BVDV as cause of abortion
	Virus isolation PCR Immunohistochemistry Fluorescent antibody	Fetal tissues	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus, liver, lung
Persistent infection	Virus isolation (IPMA) Antigen capture ELISA PCR	Serum or whole blood	Should be repeated in 3 to 4 weeks to confirm persistent infection For virus isolation, buffy coats should be used on calves less than 6 months of age because of possible interference of passive immunity
	Antigen capture ELISA Immunohistochemistry Fluorescent antibody PCR	Skin biopsy	Should be retested in 3 to 4 weeks with blood sample to confirm persistent infection Pools of skin or blood may be tested initially by PCR
Mucosal disease	Virus isolation PCR	Serum or whole blood	Isolation of both CP and NCP-BVDV
	Virus isolation PCR Immunohistochemistry Fluorescent antibody	Postmortem tissues	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus, liver, lung
Herd screening	PCR	Bulk tank milk samples Pooled serum, whole blood, or skin biopsies	Bulk milk tank screening only tests lactating cows; limit 300 cows per milk pool Pooling of skin biopsies, whole blood, and serum is controversial; request data on pooling performance from laboratory prior to testing
	Serology (virus neutralization tests)	Serum from sentinel cattle	Unvaccinated cattle 6 to 12 months of age Serology for both BVDV-1 and BVDV-2 should be performed

CP, Cytopathic biotype; *ELISA,* enzyme-linked immunosorbent assay; *IPMA,* immunoperoxidase monolayer assay; *NCP,* noncytopathic biotype; *PCR,* polymerase chain reaction.

BVDV ANTIGEN DETECTION. Direct antigen detection methods have been described for BVDV using blood and a variety of fresh, frozen, or fixed tissues. These methods include immunohistochemistry (IHC), antigen capture ELISA (ACE), and immunofluorescence. Viral antigens can be detected from BVDV-infected tissue, whole blood, serum, milk, or nasal swab samples.[103] These tests are advantageous in that they allow rapid and inexpensive detection as compared with virus isolation. In addition, there is no amplification of antigen so these tests are ideally suited for the detection of animals with considerable amounts of antigen, namely the PI carrier.

Detection of BVDV antigen through IHC or ACE methods on skin samples has become widely used and applied for the detection of cattle PI with BVDV.[105] Skin biopsies may be obtained easily and inexpensively. A major advantage of testing by IHC or ACE on skin samples is that sampling can be performed on young PI calves, which would test negative by virus isolation, microplate virus isolation, and ACE testing on serum because of inhibition by acquired colostral antibodies.[106] Both the IHC and ACE tests are ideally suited for the detection of PI animals, and reports indicate these tests do not detect acutely infected cattle.[107,108] However, a recent report indicates

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positive results may be observed for acutely infected cattle with IHC and ACE tests.[109] With IHC testing, PI animals can be differentiated from acutely infected cattle based on the location of viral antigen in the skin.[110] Cattle vaccinated with modified live viral vaccines do not cause a positive result when tested by IHC or ACE methods.[8,111]

REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION. Since sequences of BVDV isolates became available, molecular techniques have been developed for diagnosis of BVDV, and this method of BVDV diagnosis has gained widespread use as a routine diagnostic method.[105] Development of commercial kits, with rapid and simple viral RNA extraction techniques, has made molecular techniques ideal for detection of viral genomic nucleic acids from many types of samples including serum, whole blood, tissues, and bulk tank milk. The RT-PCR assay is a molecular diagnostic method that is a specific and sensitive technique for diagnosis of BVDV infection. The RT-PCR is more sensitive than virus isolation.[112] The high sensitivity of RT-PCR allowed it to be used for pooled testing, and pooling of whole blood, serum, or milk samples is an economical way to detect BVDV infection in herd screening assays.

SEROLOGY. Detection of antibodies to BVDV is another method to demonstrate virus infection; however, it is often difficult to distinguish antibodies produced in response to a natural infection, following vaccination, or as a result of transfer of maternal antibodies from dam to offspring. Interpretation of serology results is difficult without knowing important information of the herd being tested such as the vaccination history. Serologic testing may be used to assess vaccine efficacy and vaccine protocol compliance as well as determine if BVDV exposure has occurred in the herd.[103]

The BVDV-specific antibodies can be divided into two groups, neutralizing and nonneutralizing antibodies. Although there are several applicable methods, serum use, more appropriately called virus neutralization (VN), and ELISA have been most commonly used for serologic diagnosis of BVDV. Numerous technical and logistical challenges make the VN test less useful than the ELISA.[113]

Treatment and Prognosis

No specific treatment is available for animals showing clinical signs of BVDV infection. Owners should be informed that severely ill animals may have mucosal disease, which normally is fatal. The goals of therapy for cattle suspected of having acute BVDV infection are supportive care and prevention of secondary bacterial infection. Broad-spectrum antimicrobial agents, fluids, electrolytes, and vitamins may be indicated.

Prevention and Control

Control of any infectious disease relies on eliminating the reservoirs of the pathogen and limiting transmission from infected individuals to susceptible animals. The PI animal is the reservoir, and eliminating the potential for the birth of PI calves is key to prevention and control. The goal of BVDV control is to ultimately reduce production losses associated with BVDV infection. Development and implementation of herd health programs that involve vaccination and biosecurity to limit exposure of pregnant cattle to PI cattle are important for success of control. Therefore, when applying prevention and control to BVDV, three major areas should be instituted; these are (1) identification and elimination of PI animals, (2) enhancing immunity through vaccination, and (3) implementing strict biosecurity measures to prevent introduction of PI carrier animals into a population of susceptible cattle. Each of these three principles has been applied to BVDV control[114]; however, BVDV continues to be a major problem to the cattle industry worldwide. Some European countries have successfully eradicated BVDV,[115] and voluntary BVDV control programs have been implemented in the United States. Control and eventual eradication of BVDV can be possible in defined areas, even with large and dense cattle populations.

IDENTIFICATION AND ELIMINATION OF PI CATTLE. The primary source of BVDV is cattle PI with BVDV, because PI animals have a high and persistent viremia and shed BVDV from nearly all secretions throughout their lifetime. Identification and removal of PI animals ideally should occur in breeding herds. In beef cow-calf operations with a controlled breeding season, PI animals should be removed prior to entry of the bull into the breeding herd.[116] In this situation, all calves, replacement heifers, bulls, and nonpregnant dams without calves should be tested for BVDV PI status. Because PI cows always produce PI calves, a negative test result of a calf indicates a negative PI status for the dam.[117] For any calves that test positive, the dam will need to be tested for BVDV PI status. Most PI calves result from an acute infection in the dam, rather than the dam of the calf being PI. For dams that test negative, they may reenter the breeding herd, and they will possess high natural immunity to BVDV. In beef herds with a controlled breeding season, the BVDV status of all animals can be determined if all animals are not pregnant at the time of testing. If cattle are pregnant at the time of testing, those animals will need to be segregated and their calves will need to be tested and found negative prior to return to the breeding herd. In dairy herds and beef herds without a controlled breeding season, young calves should be tested and removed as soon as possible to avoid possible transmission to the breeding herd. Screening young calves for PI status is best accomplished using ACE or IHC methods on skin biopsy samples. The use of skin samples for testing young calves is advantageous over other methods in that it is relatively easy for nonprofessionals to collect the samples, samples may be taken from calves that possess circulating maternal antibodies, and a single positive test usually indicates PI status. Because the occasional acutely infected animal may be IHC or ACE positive, valuable breeding stock should be retested 30 days later using virus isolation or RT-PCR assays on blood samples.[109]

Screening all individuals in a herd for BVDV is very costly, especially considering the low prevalence of PI animals among cattle herds. Instead of whole herd testing, monitoring strategies may be initiated, and these include evaluation of production records, BVDV evaluation of aborted fetuses, use of sentinel animals, pooling strategies using RT-PCR testing, and BVDV testing on sick or deceased individuals within the herd.[116] Monitoring breeding records, calf morbidity and mortality rates, and weaning proportions are considered the minimal level of surveillance, and these involve the least expense, but this level of surveillance is not very sensitive for evaluating the presence of BVDV PI within a herd.[15,116] As an example of the difficulty in using clinical suspicion as a reason to perform herd testing, BVDV was isolated from cattle in 53% of herds where there was no suspicion of the infection,[118] and BVDV PI animals were not identified in 81% of herds where veterinarians suspected BVDV was present.[15] On the other hand, identifying BVDV in sick or dead animals or in aborted fetuses provides the justification for further whole-herd testing for BVDV PI animals.

Because of high sensitivity, RT-PCR assays using pooled samples have been developed and tested to screen populations of animals for BVDV-persistent infection.[112,119] Sample types that have been used in RT-PCR assays of pooled samples include serum, whole blood, bulk tank milk, and skin biopsy samples. With pooling whole blood samples, a single PI animal is detectable in pools of up to 250 negative samples. Recently, an RT-PCR assay has been developed and evaluated for testing pools of skin biopsy samples.[119] Pooled sample testing by RT-PCR is a rapid and cost-effective method for screening populations of cattle for BVDV PI animals. Subsequent testing of individuals within the positive pools may be performed using IHC, ACE, virus isolation, or RT-PCR methods depending on the class of animals being tested. When testing young beef calves, it is important to perform all testing prior to the breeding season to identify and eliminate BVDV PI animals that pose a risk for bred cattle.

ENHANCING IMMUNITY THROUGH VACCINATION. Many vaccines are commercially available for BVDV, and the majority of these USDA-licensed vaccines contains BVDV in combination with other bovine respiratory and reproductive pathogens including bovine herpesvirus-1 (BHV-1), parainfluenza type 3 (PI-3), bovine

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respiratory syncytial virus (BRSV), *Leptospira* spp., *Campylobacter* spp., *Mannheimia haemolytica, Histophilus somni,* and/or *Pasteurella multocida*. Historically, most BVDV vaccines contained only BVDV-1 strains, but because of antigenic diversity among BVDV-1 and BVDV-2, modified live and inactivated vaccines containing both BVDV-1 and BVDV-2 strains have been developed and are now widely available. Advantages and disadvantages of BVDV modified live viral vaccines and inactivated vaccines have been described.[120] One disadvantage of inactivated BVDV vaccines is that two doses are required for the initial immunization. A major problem with programs using inactivated vaccines is the widespread lack of compliance among producers who use inactivated vaccines.[121] Failure to give a booster during the primary series and failure to regularly administer annual boosters with inactivated vaccines are common.[121]

Vaccines are an important component to BVDV prevention and control, and their effectiveness has been to limit disease from BVDV infection. When discussing BVDV vaccination, it is important to discuss reasonable expectations following vaccination and to remember that *disease* and *infection* are not synonymous terms. Experimental and field data indicate vaccination with either inactivated or modified live BVDV vaccines is effective at reducing or obviating clinical disease.[65,122] In addition, modified live viral vaccines containing BVDV-1 strains are effective at limiting or preventing clinical disease when vaccinated animals are subsequently challenged with a virulent BVDV-2 strain.[123,124] Protection from clinical disease is important for stocker/backgrounder and feedlot operations, and immunity to BVDV has been demonstrated to be protective against bovine respiratory disease complex.[125] Preconditioning cattle by vaccinating cattle against BVDV prior to an expected exposure (commingling and shipping) reduces the effects of exposure of cattle to BVDV.

Protection against viremia is the true measure of BVDV vaccine efficacy. To be truly efficacious, vaccination against BVDV should protect against viremia to prevent dissemination of virus throughout the host, including preventing infection of target cells of the reproductive tract that result in fetal infection. In the past decade, the focus for vaccine efficacy has shifted from protection against clinical disease to protection against fetal disease or infection. Published studies indicate the protection against fetal infections following BVDV vaccination varies anywhere from 60% to 100%. This wide degree of variation depends on whether the vaccine is inactivated or modified live, the timing of challenge, and on the degree of homology between the vaccine strains and the challenge strains. Fetal protection studies have been performed evaluating commercial vaccines containing only BVDV-1 strains[126,127] and commercial vaccines containing both BVDV-1 and BVDV-2 strains.[128,129] From published studies, it would appear that protection is superior when animals are challenged with strains from the same genotype.[130,131] An extremely important observation regarding these fetal protection studies is that although protection may not be 100% against all strains of BVDV, the level of protection is far superior to that observed when proper vaccination is not used, as evidenced by very high rates of PI animals in unvaccinated cattle.

BIOSECURITY. Although BVDV prevention and control starts with identification and elimination of PI animals, strict biosecurity is essential to prevent reintroduction of the virus. Strict biosecurity is difficult for most cow-calf and dairy operations to achieve and is even more difficult or impossible for most stocker/backgrounder and feedlot operations to achieve. Biosecurity systems with isolation and testing of all incoming cattle are necessary to ensure that BVDV does not enter the farm. All purchased cattle should be isolated and tested for BVDV persistent infection prior to entry into the herd. In addition, isolation of new additions for 3 weeks prior to entry into the resident breeding herd should prevent transmission of BVDV from acutely infected animals. Most lapses in herd biosecurity involve purchasing cattle that are PI with BVDV or by purchasing pregnant cattle where the BVDV status of the fetus is unknown. If pregnant cattle are purchased, these animals should be isolated and their offspring should be tested to ensure that they are free of BVDV. Semen should be used only from bulls that have been tested for BVDV infection. For purebred herds marketing genetically valuable embryos and livestock, it is important to test embryo transplantation recipients to ensure that they are not PI with BVDV. Exposure of cattle to other cattle or small ruminants at exhibitions should be limited, and animals should be quarantined for 3 weeks prior to reentry into the breeding herd. Most biosecurity principles instituted for BVDV control will have the added benefit for disease control with other pathogens of cattle.

Malignant Catarrhal Fever (Bovine Malignant Catarrh, Malignant Head Catarrh)

Robert J. Callan

Definition and Etiology Malignant catarrhal fever (MCF) is a severe lymphoproliferative disease caused by a group of gamma herpesviruses collectively referred to as malignant catarrhal fever viruses (MCFVs).[1-4] Ten genetically and antigenically related viruses have been identified and make up the group of MCF viruses. Six of these viruses are associated with clinical disease and the remaining four viruses have not yet been associated with disease (Table 32-11). Each virus has a reservoir host where infection is typically asymptomatic. Clinical disease occurs in aberrant hosts and is characterized by acute onset of fever, inappetence, profuse ocular and nasal discharge, ocular signs including corneal opacity and conjunctivitis,

TABLE 32-11

Ten Antigenically and Genetically Related Viruses in the Malignant Catarrhal Fever Virus Group and Their Respective Reservoir and Clinical Hosts[3,4]

Virus	Primary Reservoir Host	Primary Clinical Host
Alcelaphine herpesvirus type 1 (AlHV-1)	Wildebeest (*Connochaetes* spp.)	Cattle and other domestic and wild ruminants
Ovine herpesvirus type 2 (OvHV-2)	Domestic and wild sheep	Cattle, American bison, and other domestic and wild ruminants
Caprine herpesvirus type 2 (CpHV-2)	Goats	White-tailed deer, Sitka deer, roe deer, moose
MCFV of white-tailed deer (MCFV-WTD)[11]	Unknown	White-tailed deer
Ibex-MCFV[49]	Ibex *(Capra nubiana)*	Bongo antelope *(Tragelaphus eurycerus)*
AlHV-2–like virus[50]	Jackson hartebeest *(Alcelaphus buselaphus)*	Barbary red deer *(Cervus elaphus barbarous)*
HiHV-1[51]	Roan antelope *(Hippotragus equinus)*	None identified
Oryx-MCFV[52]	Oryx *(Oryx gazekka)*	None identified
Muskox-MCFV[52]	Muskox *(Ovibox moschatus)*	None identified
Aoudad-MCFV[4]	Aoudad, Barbary sheep *(Ammotragus lervia)*	None identified

MCFV, Malignant catarrhal fever virus.

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alimentary erosions, enteritis, and enlarged lymph nodes. The disease is typically progressive and often fatal.

Clinical MCF is observed in cattle, deer, bison, buffalo, several other domestic and wild ruminants[5] (33 species to date), and pigs. It has worldwide distribution and can be a problem in zoos and game parks. There are two primary etiologic forms of MCF that are designated by the host reservoir of the virus. Wildebeest-associated MCF (WA-MCF) is caused by alcelaphine herpesvirus-1 (AlHV-1). The principal reservoir of AlHV-1 is the blue wildebeest *(Connochaetes taurinus)* and the black wildebeest *(Connochaetes gnou)*.[6] WA-MCF is seen primarily in Africa or in zoologic parks where other ruminants have contact with wildebeest. Sheep-associated MCF (SA-MCF) is caused by ovine herpesvirus type 2 (OvHV-2). Domestic and wild sheep and goats are asymptomatic reservoirs of the virus. SA-MCF is the primary form of MCF that is observed outside of Africa and primarily affects domestic and wild ruminants. MCF caused by OvHV-2 has also been identified in pigs.[7-9] Goats are a reservoir for caprine herpesvirus type 2 (CpHV-2),[10] which has been isolated from cases of MCF in white-tailed deer,[11] Sitka deer,[12] roe deer, and moose.[13] Both AlHV-1 and OvHV-2 can be experimentally transmitted to rabbits and hamsters, in which infection causes an acute, fatal lymphoproliferative disorder similar to natural MCF.[2]

Clinical Signs and Differential Diagnosis Cattle from 4 weeks of age to adulthood can be infected and develop clinical illness. After an incubation period of 2 to 30 weeks, the disease attacks vascular endothelium causing a lymphocytic vasculitis. The incubation period can be prolonged, and in at least one case the incubation period was 200 days. High fever, alimentary erosions, diarrhea, dysentery, corneal opacity, anterior uveitis, conjunctivitis, mucopurulent nasal discharge, thickened cracking skin, encephalitis, lymphadenopathy, and hematuria may be seen (Fig. 32-92). Oral and nasal erosions may be evident but are often too far back in the nasal or oral cavity to be observed externally. Ocular lesions are often present and consist of corneal opacity that originates in the periphery (centripetal) and progresses to the center. Corneal ulceration is generally not present and there is no uptake of fluorescein dye. Generalized weakness and dyspnea occur. Ropy saliva may be dropped from the painful mouth, and scabs may develop on the muzzle. Swelling and hyperemia of the coronary bands may be observed, characteristic of coronitis. The hoof or horns may be shed, and lameness may be pronounced. Hematuria often is present and caused by a hemorrhagic cystitis. Nonsuppurative arthritis can also be observed. Neurologic signs including ataxia or altered mentation may occur and are caused by a nonsuppurative encephalitis. Cutaneous lesions may be observed and consist of multifocal coalescing alopecia with dermatitis and necrosis. When particular signs predominate, the condition may be labeled the alimentary form, the encephalitic form, the head and eye form, or the skin form. One strain of virus can cause all forms, and animals with most of these signs can be seen in a given outbreak. Clinical signs in any single animal may progress rapidly or over a course of weeks. Disease in Sitka deer (and perhaps other species) may consist primarily of dermatitis and alopecia.[14]



FIG. 32-92 A yearling steer with malignant catarrhal fever. Note the corneal opacity, lacrimation, and mucopurulent nasal discharge.

The course of the acute disease is usually 3 to 7 days; some animals survive longer. Disease is generally more severe and progresses more rapidly in bison compared with cattle. The mortality rate is very high. Peracute deaths without any visible symptoms can also occur. A mild form, with transient fever and mild oral and nasal mucosal erosions followed by recovery, has been seen in experimentally infected cattle. Some animals survive clinical disease and in a few cases, may return to normal productivity. Case mortality is generally high and may exceed 90%. However, chronic and recovered cases are described, and in one report, recovery was seen in 50% of cases.[15]

MCF must be differentiated from bovine viral diarrhea mucosal disease (BVD-MD), rinderpest, bluetongue, vesicular stomatitis (VS), and foot-and-mouth disease (FMD). The last two diseases are not usually associated with diarrhea, and VS and FMD tend to have high morbidity and low mortality rates. Clinical bluetongue is rare in cattle and not usually associated with dysentery. Arsenic toxicity and chlorinated naphthalene toxicity have some clinical similarities to the intestinal forms of MCF. Ocular signs, including corneal opacity, conjunctivitis, and discharges, must be differentiated from bovine keratoconjunctivitis (pinkeye), in which the lesion starts at the center of the cornea and corneal ulceration is present. In contrast, the corneal opacity of MCF starts at the limbus and is caused by edema secondary to the loss of the internal endothelial layer of the cornea.[16,17]

Clinical Pathology and Serology Some affected animals show leukopenia caused by lymphopenia and neutropenia if sampled early in the course of disease, but this is an inconsistent finding in natural outbreaks.[18] Joint fluid is cloudy and may contain increased protein and mononuclear cell numbers. Cerebrospinal fluid may have elevated protein concentrations and elevated WBC counts with mononuclear pleocytosis in animals displaying neurologic signs. Serologic tests include ELISA, indirect immunofluorescence, complement fixation, and virus neutralization.[3] Virus isolation can be attempted for cases of MCF caused by AlHV-1. Serologic tests identify antibodies directed to a conserved MCFV glycoprotein and do not discriminate between the different MCF viruses. Serologic tests are best used to screen the infection status of reservoir animals or to identify asymptomatic infection in clinically susceptible hosts. Diagnostic PCR tests have been developed for AlHV-1 and OvHV-2.[3] PCR tests are best used to distinguish between AlHV-1 and OvHV-2 in animals with clinical MCF. PCR tests for the identification of other MCF viruses are available from specific research labs, including a multiplex PCR assay.[3]

A presumptive diagnosis is based on a history of exposure, clinical signs, and evidence of infection supported by serology or PCR. A definitive diagnosis can only be made by the presence of characteristic histopathologic lesions including lymphocytic vasculitis.[3]

Pathophysiology Natural infection occurs through inhalation of aerosolized virus or through direct or indirect contact with ocular or nasal secretions from reservoir hosts. The exposure dose plays a role in the likelihood of developing clinical MCF and the duration of the incubation period.[3,19-23] Experimental transmission studies in sheep and bison show initial replication of the virus in respiratory epithelium.[3,19,20,22,23] OvHV-2 DNA can be identified in the respiratory tract in 9 to 12 days post infection in bison experimentally infected by intranasal inoculation.[24] OvHV-2 infection of lymphocytes is observed by 14 to 21 days post infection. The incubation period for clinical MCF is highly variable and ranges from 14 to over 200 days. MCF virus infection causes infiltration of lymphocytes, particularly T cells, into tissues.[2] This T-cell proliferation is predominated by $CD8^+$ gammadelta T cells and to a lesser extent $CD4^+$ T cells.[25] There is also an increase in large granular lymphocyte

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(LGL) cells that appear to have cytopathic activity. It is believed that the fundamental pathology is caused by an autoimmune-like process involving dysregulation of cytotoxic T cells.[2,25,26]

Epidemiology WA-MCF remains an important disease in cattle and other ruminants that come in contact with wildebeest.[5] AlHV-1, unlike OvHV-1, can be isolated in cell culture and this has aided the ability to study the disease epidemiology and transmission. Wildebeest calves are generally infected with AlHV-1 in utero or soon after birth and shed the virus in ocular and nasal secretions to the age of 4 to 6 months.[6,27,28] As adults, the wildebeest become latently infected and transmit the virus to their offspring. Recrudescence and shedding of AlHV-1 in wildebeest can occur following treatment with corticosteroids. Cattle are infected with AlHV-1 when exposed to young, actively shedding wildebeest calves. The incubation period of WA-MCF under natural exposure conditions in cattle can range from 2 weeks to 6 months and perhaps longer. In general, the incubation period of WA-MCF is shorter than SA-MCF. Some cattle that become infected with AlHV-1 do not develop clinical MCF. Diseased cattle do not shed free infectious virus and thus are not a risk to contact animals.[5]

SA-MCF is the predominant form of MCF seen outside of Africa. The prevalence of OvHV-2 infection determined by PCR or competitive inhibition (CI)-ELISA in healthy adult North American domestic sheep is reported to be 99% and 94%, respectively.[29] Sheep serve as the primary reservoir of OvHV-2, although sheep do not show clinical signs of infection. Less than 5% of lambs are infected at birth.[30] The majority of lambs remain uninfected up to 2.5 months of age. After 3.5 months of age, the lambs develop infections through close contact with adult sheep approaching 100% prevalence by 5.5 months. Shedding and transmission of OvHV-2 is through nasal and ocular secretions.[31,32] Seroconversion and detection of OvHV-2 DNA in nasal secretions lags the detection of viral DNA in blood by several months.[30] Separation of lambs from adults at 2 months of age reliably produces OvHV-2–free sheep.[33] These findings indicate that newborn lambs are not a major source of virus infection for cattle. Peak nasal viral shedding occurs around 6 to 9 months of age and it is these infected adolescent lambs that pose the greatest transmission risk to other animals.[32]

Adult sheep continue to shed low numbers of virus throughout their life.[32] OvHV-2 shedding from adult sheep may be higher during the periparturient period or while on feed in feedlots, resulting in a higher risk to commingled cattle. OvHV-2 is readily transmitted between in-contact sheep; however, transmission by inoculation of whole blood or PBMCs is inconsistent.[34] This suggests that infectious virus is primarily produced and shed by nasal or ocular secretions and that infection of blood cells may be largely nonproductive.

Positive CI-ELISA tests have been identified in bison (2% to 23%), domestic goats (74%), elk (9%), mule deer (2%), white-tailed deer (3%), pronghorn antelope (25%), bighorn sheep (37%), muskox (40%), and mouflon sheep (62%). Black-tailed deer, llama, and mountain goats have been tested and were not found to be seropositive for MCF.[35,36] However, it is not clear if these species play any role as reservoir species.

The sheep-associated form of MCF can be acute or chronic, and animals may recover. Cattle and American bison *(Bison bison)* are the two primary species affected by SA-MCF. The disease usually occurs sporadically, with only one or a few animals affected, but many large outbreaks have been reported.[37-41] Transmission most likely occurs through direct contact, indirect contact, and aerosol of nasal secretions from sheep. In one report, exposure of bison to sheep for less than a day at an auction resulted in high mortality.[41] There is evidence of transmission from sheep to cattle or bison extending over distances of 70 m up to 5.1 km.[39,42,43] In one example of natural infection of bison, the incidence of disease and mortality was inversely related to the distance of exposure.[39] The incubation period following experimental or natural exposure ranges from 14 to 220 days.[21,24,37,40,41] Cattle and bison are considered dead-end hosts and do not spread the infection to other animals.[2,5,41]

Bison are more susceptible to developing clinical MCF than are cattle by both experimental inoculation studies and natural exposure.[19,21,40] In bison, OvHV-2 infection and clinical MCF is observed with intranasal nebulization at doses as low as 10^3 DNA copies of OvHV-2.[19,20] Cattle become infected with doses as low as 10^6 OvHV-2 copies but require at least 10^8 copies to become infected with clinical MCF.[21] In contrast, the minimum infectious dose for sheep is between 10^2 and 10^3 DNA copies but sheep require a dose of 3×10^9 copies to develop nonfatal clinical signs of MCF.[22,23] Several studies have shown that both cattle and bison can be infected with OvHV-2 and not develop clinical MCF.[35,36,38,42,44] These studies show that infection, morbidity, and mortality are related to species susceptibility, inoculation dose, and likely other factors not yet determined. Both asymptomatic and clinically affected cattle and bison do not shed infectious virus and are considered dead-end hosts.

Necropsy Findings The nasal mucosa is hyperemic may have hemorrhagic superficial erosions. The oral mucosa has necrotic papillae and large areas of necrosis and ulceration. Multiple focal ulcerations are seen in the esophagus. Parts of the forestomachs and intestines are thickened, edematous, and occasionally ulcerated and hemorrhagic. The lymph nodes, tonsils, and Peyer patches are enlarged, moist, and friable. Splenic lymphoid follicles are prominent, and the liver is swollen. The adrenal glands are hemorrhagic. The mucosal surface of the bladder has focal areas of hemorrhage. The eyes are hyperemic and show severe corneal edema. The brain may have intersulcal cloudiness and meningeal petechiation consistent with encephalitis. Joints may have swollen and reddened synovia with an increased quantity of cloudy fluid.[45]

Histologically, there is a marked lymphoid accumulation around blood vessels, as well as necrosis of the tunica media and intima in multiple tissues. There is generalized lymphoid hyperplasia and lymphoid infiltrates in subepithelial and intraepithelial locations, associated with epithelial necrosis and sloughing. Similar changes occur in all epithelial tissues.[45] Chronic cases develop chronic obliterative arteriopathy.[15]

Treatment and Prognosis There is no specific treatment for MCF beyond supportive care. Fluid therapy and nursing care may allow some animals to survive and recover from disease. Antimicrobial treatment to help prevent secondary bacterial pneumonia or septicemia may provide some benefit. Treatment with nonsteroidal antiinflammatory drugs may provide comfort but could increase the degree of alimentary erosions or decrease their healing. Gastrointestinal protectants such as Kaopectate or bismuth subsalicylate may provide support to the gastrointestinal tract and help maintain appetite. Maintenance of appetite seems to be one of the key prognostic indicators in clinical cases of MCF. Although some animals that exhibit mild disease may survive, close to 100% of those with severe clinical signs die.

In a recent report, the severity and progression of ocular lesions associated with MCF in cattle were evaluated relative to disease outcome.[16] The degree of corneal edema at presentation did not show prognostic value in predicting disease outcome (death vs. survival). However, improvement of corneal edema over the course of the disease was associated with a better outcome. In addition, animals where anterior uveitis worsened were more likely to die or be euthanized.

Prevention and Control At this time, the primary method of control is to reduce the exposure of susceptible hosts to reservoir hosts. Transmission is related to the distance between reservoir hosts and susceptible hosts so these groups of animals should be physically separated. This can be particularly difficult since transmission from sheep to bison over distances as far as 5 km have been reported.[39] Adult wildebeest and sheep pose a lesser risk of transmission than do neonatal wildebeest and adolescent sheep that shed higher amounts of virus from nasal secretions than the adults. Attempts to keep these younger groups of reservoir animals at a greater distance

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from susceptible hosts should be encouraged. Feedlot sheep from 6 to 9 months of age pose a significant risk. Natural transmission of OvHV-2 between feedlot sheep and dairy cattle or bison is reported and is likely related to the younger age of the feedlot sheep compared with adult breeding animals.[39,40,42]

Currently, there are no commercial vaccines available for prevention of WA-MCF or SA-MCF. Recently, an attenuated AlHV-1 vaccine showed protection against virulent AlHV-1 challenge in cattle for up to 6 months in a portion of the vaccinated animals.[46] Respiratory tract mucosal immunity appears to be critical in preventing initial infection and development of clinical MCF.[2,46-48] Further research identifying critical antigens and methods to induce strong, long-lasting mucosal immunity for both AlHV-1 and OvHV-2 will be necessary to develop effective vaccines for bison and cattle.

Vesicular Stomatitis

Bradford P. Smith

Definition and Etiology Vesicular stomatitis (VS) is a rhabdoviral disease of the genus *Vesiculovirus* that causes sporadic (cyclic) outbreaks in cattle, horses, donkeys, mules, and pigs and typically has a high morbidity but a low mortality rate. Cattle under 1 year of age rarely show clinical signs. Sheep and goats also rarely have clinical signs, and South American camelids are intermediate in susceptibility. VS is seen in the United States, Mexico, and Central and South America. Human beings have sometimes been infected with an influenza-like disease. Four distinct viruses are now recognized: VS Indiana (formerly called Indiana 1), VS New Jersey, Alagoas virus (formerly called Indiana 3), and Cocal virus (formerly called Indiana 2), with Indiana and New Jersey occurring in the United States.[1] Strains within each virus vary in virulence. Vesicles occur in the mouth, on the teats, and in interdigital areas, so the major differential is to eliminate foot-and-mouth disease (FMD) as a diagnosis. Lesions may occur only on the teats or only in the mouth. The vesicles rapidly turn to painful ulcerations that cause dysphagia and reluctance to eat, frothing at the mouth, drooling, agalactia, weight loss, mastitis, and lameness. Death is rare.

Epizootic waves of VS have tended to occur at about 10-year intervals, usually in the summer or fall, but since the major epizootic in 1982 and 1983 in the western United States, the NJ serotype has been identified in the United States each year. An outbreak occurred in 1995 in the western United States, in New Mexico, and Colorado.[2] More cases occurred in 1997 and 1998. From 2004 through 2006, 751 VS outbreaks caused by vesicular stomatitis virus serotype New Jersey (VSNJV) were reported in nine states of the southwestern United States, and overwintering of the virus was demonstrated.[3] Both migratory western grasshoppers and the plants they eat can be infected with VS virus,[4] providing another means of livestock exposure. It is hypothesized that VS virus may be a plant virus that strays into animals, where it causes disease.

Although the NJ serotype has at least 14 distinct genotypes, only a few of these have been found in recent outbreaks in the United States. The NJ serotype should be considered a collection of serologically related but genetically variant viruses. State and federal regulatory veterinarians should be contacted immediately when VS is suspected so that quarantine and disease identification measures can be used quickly to contain an outbreak.

Numerous outbreaks occur yearly from southern Mexico to northern South America. Outbreaks were seen in many parts of Mexico in 2008.[5]

Clinical Signs and Differential Diagnosis After a mean incubation period of 9 days (the range is 3 to 21 days), there is onset of fever and oral lesions that cause excess salivation and reluctance to eat.[6,7] From 5% to 60% of cattle on a farm may show clinical signs. Vesicles are only occasionally visible, because the epithelium rapidly necroses and many lesions quickly turn to ulcers. Lesions on the gums and tongue may coalesce to form large eroded areas (Figs. 32-93 and 32-94). Milk yield falls quickly. Teat lesions are common in dairy cattle, and small ulcers in the interdigital area and on the coronary band are occasionally seen. Recovery varies from 2 to 21 days, depending on the severity of the lesions and management factors such as the type of feed and milking sanitation.[6] Actual healing of the lesions may take 34 to 59 days.[7]



FIG. 32-93 Severe ulceration of the tongue of a dairy cow caused by vesicular stomatitis. A plaque of dying mucosa covered by fibrin is visible at the tip of the tongue, and excessive salivation is obvious. *(Courtesy Dr. Mark Thurmond.)*



FIG. 32-94 Tongue of horse with vesicular stomatitis (VS) demonstrating severe lingual erosions. *(Courtesy Dr. Skip Aaroe.)*

The major differential diagnostic consideration is FMD, which causes almost identical clinical signs. Other diseases of cattle that result in oral lesions (BVD, BPS, bluetongue) do not usually appear as epidemics but rather in one or a few animals (although BPS may have a high morbidity). Other causes of oral lesions such as bristle grass irritation and toxins should be ruled out.

Clinical Pathology and Laboratory Diagnosis The VS virus is difficult to isolate from blood, urine, feces, and oral swabs but has been isolated from tongue epithelium.[7] ELISA, PCR, CF, and a fluorescent antibody test are available for virus identification. Serum neutralizing (SN) titer rises rapidly after exposure and then gradually falls over the first year. SN titers that follow natural exposure may persist for years. Vaccination with inactivated virus results in a rapid rise in titer followed by a gradual decline for a year.[8] The presence of an SN antibody titer does not prevent reinfection or development of clinical signs. Hematologic and clinical chemistry findings generally reflect an acute to chronic inflammatory disease and are nonspecific in helping to make a diagnosis.

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Pathophysiology After a short incubation period of 24 hours, fever and viral invasion of the germinative layer of oral epithelial cells occur. Oral abrasions or trauma may increase susceptibility.[6] Contact of virus with teats or feet can result in lesions in these areas, especially if the teats are chapped or cracked or the feet are traumatized. The lesions progress rapidly from blanched macules to vesicles and soon rupture, leaving sloughed epithelium and ulcerated areas. Healing occurs quite rapidly if feed is soft and nontraumatic.

Epidemiology Older, higher producing dairy cows that have been in milk longer are more susceptible than herdmates to clinical disease caused by VS.[6] Because the virus cannot penetrate intact mucosa, cattle fed coarse feeds or hard pellets that traumatize the oral mucosa are at higher risk. Cows with chapped or cracked teats and those on farms with poor milking hygiene are more likely to get teat lesions.[6] Cow-to-cow contact is a major mode of transmission in outbreaks, and increased interpen movement of cattle, as well as shared feed and water troughs, unless cleaned frequently, increase the risk of development of VS. The virus is transmitted by milking machines and human hands during outbreaks. Insect vectors also contribute to the mechanical spread.

Outbreaks are often associated with the movement of animals from another area, but disease epidemics not associated with new animals do occur. The infection tends to be seasonal (occurring in the summer and fall in temperate areas and at the end of the rainy season in the tropics) and behaves like an arthropod-borne virus. The midge *C. sonorensis* was found in 2005 to be an efficient vector of VS virus. Other biological vectors include sand flies (*Lutzomyia* spp.) and black flies (*Simulium* spp.).[1] Other insects act as mechanical vectors. Antibodies have been found in a number of wild species of animals (deer, raccoon, bobcat, monkey), which may provide a virus reservoir. Active cases of VS occur in Mexico between U.S. epidemics, giving rise to the possibility that cattle from Mexico arriving in the United Sates may also act as sources of VS virus. Sheep and goats in contact often seroconvert, although clinical signs in these species are rare. The virus survives several weeks in cool soils but is inactivated by sunlight and is very resistant to pH changes. Cattle generally show a high morbidity rate and a low mortality rate (1% to 5%). Although many in-contact cattle do not show obvious clinical signs of disease, many more have oral lesions if closely examined, and most animals in the herd seroconvert.

The economic losses associated with an outbreak of VS can be severe, especially in dairy cattle. In the 1982 epizootic in California, losses on two dairies (principally decreased milk production and culling for mastitis) totaled $225,000 during 2 months.[9]

Necropsy Findings Deaths are rare and usually are attributed to secondary bacterial diseases, including environmental mastitis and pneumonia. Cattle become gaunt and weak as a result of dysphagia and resultant reduced food intake. Erosive and ulcerative lesions are usually confined to the mouth. The teats frequently are involved in lactating cows, and lesions on the coronary band and interdigital area occasionally may be seen.

Histologically, intracellular and extracellular edema, ballooning and degeneration of epithelial cells, and vesicle formation accompanied by neutrophilic infiltration are present. There are no inclusion bodies. The characteristic bullet-shaped structure of the VS virus sometimes can be seen with electron microscope examination of fresh lesions or vesicular fluid.

Treatment and Prognosis Mortality can be almost completely prevented if ill cattle are offered shade, fresh water, clean bedding, and soft feed. Offering soft feed hastens recovery and reduces the anorectic period. Debilitated cattle should be given broad-spectrum antibiotics in an effort to control secondary bacterial pneumonia. Cattle with teat lesions are at high risk for developing mastitis and should be carefully milked last and monitored closely for mastitis. The prognosis for survival is very good, but agalactia and mastitis may result in the culling of a large number of animals.

Prevention and Control The reader should use websites such as the World Organisation for Animal Health (OIE) and the U.S. Department of Agriculture (USDA) for the latest information on contagious illnesses. During an outbreak of VS, quarantine of the premises and isolation of sick animals are required. Regulatory officials will help organize and maintain a quarantine. Feed should be soft and fine, because coarse or hard-pelleted feeds increase the spread of the virus and prolong the recovery time. Leftover feed should be removed from feed bunks twice daily, and the bunks disinfected. Water troughs should be cleaned and disinfected daily. VSV is susceptible to numerous disinfectants including 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde, 2% sodium carbonate, 4% sodium hydroxide, iodophor disinfectants, 1% formaldehyde and chlorine dioxide.[1] It is also inactivated by UV light, lipid solvents, or heat. Two hours of exposure to lye (2% NaOH) will *not* deactivate the virus.

Vaccination using killed[10] or live virus vaccines is rarely practiced preventively because the disease occurs as rare epidemics in small areas and because vaccination interferes with serologic testing and monitoring. Vaccination with a killed virus vaccine may be used by regulatory veterinarians in at-risk animals during an epidemic, as it has been shown to be an effective vaccine.[10] Owners and managers must consult state and federal veterinarians before considering VS vaccination.

Foot-and-Mouth Disease (Aftosa, Aphthous Fever)

Bradford P. Smith

Definition and Etiology Foot-and-mouth disease (FMD) is an acute, highly contagious viral disease of cloven-hoofed livestock characterized by vesicular lesions, erosions, and ulcers in the mouth and interdigital areas and on the muzzle, teats, and coronary band. Natural hosts include cattle, sheep, goats, swine, water buffalo, bison, deer, elk, antelope (all wild ruminants), bears, llamas, camels, giraffes, elephants, rats, yaks, capybaras, and hedgehogs.[1] Of these, cattle and swine are the most susceptible, and camelids have low susceptibility. Mature sheep and goats usually have mild signs, and horses are resistant to infection. Livestock of all ages are susceptible, but the mortality rate is higher in young animals because cardiac lesions occur. In rare cases, humans have contracted the disease. It is endemic in Asia, Africa, parts of Europe and the Middle East, and most of South America, where losses involve not only those caused by the disease itself but also the monetary losses that result because fewer animal products are available for export as a result of loss of foreign markets. Great Britain experienced a major epidemic in 2001, and China had one in 2009.[2]

The FMD virus is a picornavirus of the genus *Aphthovirus.* At least seven immunologically distinct types of FMD virus have been identified: A; O; C; SAT 1, 2, and 3; and Asia 1. Within the seven types, at least 60 subtypes have been recognized. African buffalo are the major maintenance host of SAT serotypes, and may harbor the virus for at least 5 years.[3] Vaccination against one subtype may not protect against another. This fact, together with the fact that immunity is generally short term, means that effective vaccination programs are difficult. The virus is rapidly inactivated by high or low pH, sunlight, and very high temperatures but is very resistant to normal environmental conditions and drying. Sodium hydroxide, sodium carbonate, chlorine dioxide, and acetic acid are effective disinfectants,[1] but many common disinfectants are ineffective, and the virus is resistant to iodophors, quaternary ammonium, hypochlorite, and phenol.

Clinical Signs and Differential Diagnosis FMD is clinically indistinguishable from vesicular stomatitis (VS) except that VS also affects horses. Clinical signs of FMD include fever, depression,

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anorexia, listlessness, occasional shivering, excess salivation, lip smacking, nasal discharge, and lameness. Agalactia may occur. In addition to VS, the differential diagnosis includes bovine papular stomatitis, bovine virus diarrhea, bluetongue, rinderpest, malignant catarrhal fever, and severe cases of infectious bovine rhinotracheitis. Teat lesions can be confused with those caused by bovine herpes mammillitis or parapoxviruses.

Vesicular lesions (blisters) 0.5 to 10 cm in diameter rupture within 48 hours, followed by a mucosal slough and large erosion. These lesions appear to be very painful, and affected animals are reluctant to eat or move. The morbidity rate is high, but the mortality rate is low. The disease is economically devastating because it spreads rapidly and causes weight loss, mastitis, loss of milk production, and frequent abortion. An outbreak of FMD in a country previously free of the disease can cost billions of dollars in trade losses over ensuing years. Deaths may occur in young calves, mainly from myocardial necrosis, and secondary bacterial pneumonia and foot infections are common.

Laboratory Diagnosis Because FMD is clinically indistinguishable from VS and other viral mucosal diseases, laboratory confirmation of the diagnosis is obtained through complement fixation (CF), virus neutralization, agar gel precipitation, enzyme-linked immunosorbent assay (ELISA), reverse transcription polymerase chain reaction (RT-PCR),[1] or fluorescent antibody tests. ELISA appears to be more sensitive and type specific than CF[4] and virus neutralization. When VS or FMD is suspected, state and federal authorities should be contacted immediately. In FMD-free countries, quarantine is practical to control spread. Slaughtered animals are burned and/or buried. All animals within 3 km may be destroyed during efforts to halt the disease.

Pathophysiology The usual incubation period is 2 to 14 days. The usual primary sites of infection and replication by the FMD virus are the pharyngeal and digestive mucosa and alveolar epithelium of the udder. The virus replicates in the cells of the stratum spinosum. It spreads locally and also enters the circulation and is carried to other susceptible tissues. Within 2 to 21 days a fever begins, and some vesicles appear. Vesicles develop in the mouth and on the ruminal pillars, and myocardial and skeletal muscle degeneration characterized by Zenker necrosis may occur in young cattle. The mucosal cell disruption results in separation of superficial epithelium from basal epithelium, which fills with tissue fluids. When these epithelial layers slough, erosions are left behind that take days to weeks to heal, depending on their size.

Epidemiology Transmission occurs primarily by means of aerosols, animal contact, and fomites such as shoes, tires, and equipment. The virus may be spread to farms 50 miles distant. Human beings can carry (and subsequently transmit) the virus on their shoes or clothing or in respiratory tract tissues for longer than 24 hours. Recovered cattle usually stop shedding the virus by 2 weeks, but some harbor it for 6 to 24 months and may act as sources of the virus at the start of an epidemic. The virus has been isolated from semen, and the possibility exists of sexual transmission from the African buffalo to cattle. African cape buffaloes can be lifelong carriers.

The virus exists in milk, and it may survive pasteurization. Uncooked or partly cooked meat products or garbage scraps, hides, or other tissues contaminated with the FMD virus from an endemic area of the world may transmit the disease long distances. The virus can persist in frozen meat for years. Besides actively infected animals, sources of infection include bedding, feed, milk, shoes and hands of humans, and equipment.

Necropsy Findings In addition to oral erosions and ulcerations, ulcers may be seen on the ruminal pillars. In young cattle myocardial and skeletal muscle degeneration and necrosis may be noted. Histologically the vesicles are characterized by ballooning, cellular degeneration, intracellular and extracellular edema, and separation of the basal epithelium. There are no inclusion bodies. Muscle lesions (skeletal and cardiac) are characterized by necrosis (Zenker degeneration).

Treatment and Prognosis Where FMD is endemic, quarantine, local eradication, virus typing, and revaccination of contact and at-risk cattle with the appropriate virus subtype should be considered. Good nursing care and administration of systemic antimicrobial drugs to limit secondary bacterial pneumonia and mastitis are recommended. Soft feeds such as chopped green grass (or soaked hay) are much more palatable than dry hay to sore-mouthed animals. The prognosis is good for survival, although many animals abort, lose weight, stop lactating, or have severe bacterial mastitis secondary to viral teat lesions and must be culled. The virus destroys mammary alveolar epithelium permanently.

Prevention and Control The reader should also consult the OIE and USDA websites for current status of this disease. In endemic areas, vaccination and quarantine are the basis for prevention and control. In FMD-free areas (Great Britain, the United States, Canada, Japan, New Zealand, and Australia), the method of choice is rapid identification of an outbreak, quarantine, and slaughter of all affected and exposed herds. Global strategies are also being studied.[5]

Vaccines must be type specific. Most European and South American countries use trivalent inactivated vaccines against types A, O, and C from cell culture virus. Vaccine-induced and naturally occurring immunity is short-lived, and vaccination usually must be repeated two or three times a year.[1] Newer, oil-adjuvanted vaccines may protect for up to 1 year. Because the protection is partial, infection usually results in subclinical or mild disease. Calves nursing immune dams are likewise partly protected by passive antibody for up to 5 months. Recent research examining subunit vaccines is promising.[2] In an outbreak the most effective vaccine is autogenous.

Rinderpest (Cattle Plague) and Peste des Petits Ruminants

Bradford P. Smith

Definition and Etiology Rinderpest and peste des petits ruminants are acute, highly contagious, and usually fatal diseases of ruminants. Rinderpest was officially declared by the World Organisation for Animal Health (OIE) to be globally eradicated in 2011, the second disease after smallpox to be eliminated.[1] Cattle and water buffaloes are most frequently affected, but the disease also occurs in yaks, gaur, sheep, goats, pigs, and other cloven-hoofed animals, in which it is usually less severe. It is rarer in camelids. Many wild animals in Africa are susceptible, including buffalo, lesser kudu, eland, giraffe, warthog, and wildebeest. Rinderpest virus (RPV) and peste des petits ruminants (PPR) are in the Paramyxoviridae family, genus *Morbillivirus.* There is only one known strain of RPV, and it is closely related serologically to the virus that causes PPR. The virus can remain viable for at least 1 year in frozen tissue, but it is killed by direct sunlight in 2 hours. Other morbilliviruses pathogenic for animals include canine distemper and the 1995 Australian morbillivirus, which occurred in horses and humans.

PPR is a closely related highly fatal virus of goats and sheep. It occurs in sub-Saharan Africa, the Middle East, and Asia. Morbidity can reach 100% and mortality can be between 50% and 100%. Cattle and pigs develop inapparent infections. The disease also occurs in wild species, including several gazelles, gemsbok, ibex, and wild sheep. Clinical signs of PPR in goats and sheep are similar to those of rinderpest in cattle. Bronchopneumonia is also common. The reader is referred to the OIE website[2] for current information.

Clinical Signs and Differential Diagnosis The incubation period in cattle is 3 to 15 days, which is followed by sudden onset

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of fever, depression, and anorexia. The nose is dry, and mucous membranes are congested. Within days oral erosions appear where necrotic foci have sloughed. Purulent lacrimation occurs. Diarrhea is severe and may be bloody. Dehydration and emaciation often lead to death. The disease in sheep and goats usually is mild or subclinical, but the PPR virus can cause outbreaks with high morbidity and mortality in small ruminants.

In endemic areas rinderpest is suspected when the signs described earlier occur in groups of animals. In nonendemic areas diseases that appear similar clinically are bovine virus diarrhea (BVD), malignant catarrhal fever (MCF), arsenic poisoning, severe coccidiosis, and severe fulminating infectious bovine rhinotracheitis, as well as FMD and VS. Other causes of severe gastroenteritis and diarrhea (e.g., salmonellosis) must also be considered. In small ruminants with PPR, bluetongue and Nairobi sheep disease must be ruled out.

Laboratory Diagnosis A rapid strip test for PPR can be applied in the field.[3] Laboratory confirmation of rinderpest and PPR can be accomplished by virus isolation, PCR, ELISA, detection of viral antigen by fluorescent antibody testing, virus neutralization, CF, or AGID; detection of rising antibody titer by ELISA or virus neutralization; and histopathologic evaluation, including immunohistopathology. Virus isolation is most successful in the first days of infection (often before the onset of diarrhea). Blood should be taken in heparin. The lymph nodes and spleen are reliable sources of virus, and tears and ocular discharges are also reliable sources. Lymph node biopsy after day 3 of infection is the most reliable means of diagnosis in a living goat. Tissues should be shipped frozen on ice to the laboratory for virus isolation or detection of antigen. Detection of a rising antibody titer can help diagnose the disease retrospectively. Leukopenia may be noted in the acute early states of rinderpest.

Pathophysiology The virus usually enters through the respiratory mucosa. Lymphoid tissue is the primary target of RPV. Lymphocytes are destroyed in the germinal centers of the lymph nodes, Peyer patches, tonsils, splenic corpuscles, and cecal lymphoid tissue. Immunosuppression occurs as lymphoid tissue is destroyed. The virus also attacks the alimentary tract mucosa; Peyer patches are the most severely affected. As alimentary mucosa is lost, diarrhea and emaciation become severe.

Epidemiology Rinderpest and PPR are highly contagious, spread mainly through airborne droplets, direct contact, feces, and contaminated fomites such as human beings. All secretions and feces of infected animals are contagious throughout the course of the disease. The virus is susceptible to most disinfectants. Wild ruminants frequently are a source of infection for livestock. The morbidity rate often approaches 100%, with a 25% to 90% mortality rate, making treatment unrewarding and the prognosis poor. Innate or specific resistance may protect individuals or herds from clinical signs after infection. Recovered animals do not appear to act as carriers for more than a few months. Valuable individuals may be helped by supportive therapy and hydration.

Necropsy Findings Lesions are found mainly in the alimentary tract and lymphoid tissues. Subendocardial hemorrhages may also be seen in animals that die of acute illness. Oral erosions, edema, and congestion of the abomasum are typically seen, and ulcers and hemorrhagic to necrotic Peyer patches occasionally are seen. The cecal and colonic mucosae are hemorrhagic, ulcerated, or necrotic. The lymph nodes are enlarged and have necrotic germinal centers.

Prevention and Control Because there is only one known strain of RPV and protection after infection usually is lifelong, vaccination of cattle at 6 months of age and older in endemic areas with a live cell culture attenuated virus is an effective means of controlling rinderpest.[4] Although there is some debate as to whether this vaccine causes immunosuppression, it has been used safely and effectively in millions of cattle in Africa and Asia. The vaccine does not produce adverse reactions, has a long shelf life, and produces solid immunity. Its major disadvantages are that the lyophilized virus has to be kept cold, and once a vial has been reconstituted, it must be used quickly before the virus dies. There is also a specific PPR vaccine available for goats and sheep.

Control of epidemics in areas where the disease is not endemic involves quarantine and slaughter of infected and contact animals, as well as other contact ruminants and swine. Disinfection of premises while under government quarantine is essential to controlling the disease. The virus is susceptible to most disinfectants and survives in the environment only for 2 to 3 days.

Choke and Esophageal Disorders

Bradford P. Smith • Charles L. Guard

Definition and Etiology *Choke* is the term used for esophageal obstruction. In ruminants it is most common in cattle because of their eating habits, but it has even been reported in a goat that ate thread with a needle attached.[1] If the obstruction is complete, the condition is rapidly fatal (except in neonates) because of the inability to eliminate the gases of fermentation produced in the ruminoreticulum. Partial obstruction produces dysphagia or anorexia. Obstruction may be caused by the ingestion of foreign objects or large chunks of solid feedstuffs such as apples, potatoes, beet tops, corn cobs, or even a mango.[2] It also may be the result of space-occupying lesions in or near the esophagus. Choke must be differentiated from diseases that cause dysphagia by means of pharyngeal lesions and resultant neuromuscular dysfunction. Congenital or acquired lesions of the esophagus, such as aortic arch anomalies and diverticula, may cause signs similar to those of esophageal obstruction.

Clinical Signs and Differential Diagnosis The earliest signs of complete esophageal obstruction from intraluminal objects are anxiety and ptyalorrhea (i.e., saliva dripping from the mouth because of an inability to swallow). The animal may violently swing the head from side to side and make repeated attempts to swallow. Staggering (which must be differentiated from ataxia caused by neurologic diseases) may be observed. Bloat develops soon after at a rate that depends on the nature of the ruminoreticular contents. Objects such as potatoes, apples, or beets may be swallowed whole or in chunks too large to pass the entire esophagus, especially in cattle. Dry grain, particularly in pellet form, may be consumed so rapidly that sufficient saliva is not produced to lubricate the passage of the feed boluses. This is more common in sheep than in other ruminants; spontaneous resolution usually occurs within minutes to hours.

Obstruction from intraluminal objects commonly occurs in the cranial part of the cervical esophagus, at the thoracic inlet, or at the base of the heart. In a 2-week-old calf with a cloth foreign body obstructing the distal esophagus at the cardia, regurgitation after drinking milk was observed.[3] External palpation may localize the site of obstruction in the cervical esophagus. With more slowly developing and incomplete obstruction, anorexia and dysphagia may be observed. Bloat may occur repeatedly and resolve spontaneously or after passage of a stomach tube. The underlying cause may result in signs severe enough to mask the esophageal problem. Cellulitis along the cervical esophagus may result in a reluctance to lower the head or bend the neck laterally. Possible causes of cervical cellulitis include perivascular injection of irritating substances, abscesses, and reaction to *Hypoderma lineatum* larvae.

Esophageal stricture may follow a previous episode of esophageal obstruction or inflammation in adjacent tissues. If no site of obstruction is externally evident, careful attempts to pass a stomach tube usually reveal the site of the problem. Radiography with barium contrast material may help identify the site of strictures, perforations, and diverticula. Endoscopy of the esophagus may also aid in identifying the specific nature of functional or structural abnormalities.

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Megaesophagus has been observed after pharyngeal trauma, as a congenital disorder, and with hiatal hernia. An animal with an esophageal stricture or a diverticulum may reflux boluses of feed mixed with saliva or regurgitate liquid ruminal contents. Failure to gain weight or progressive weight loss accompanies the failure to swallow feed successfully. Signs may be seen only when forage is consumed, whereas water and grain are swallowed normally.

Systemic diseases may lead to esophageal dysfunction. Rabies must always be considered when dysphagia is present, and appropriate precautions must be taken. Botulism also leads to esophageal transport failure, although dysphagia and a weak tongue are more prominent in the failure of affected animals to eat. Tetanus may be similar in appearance to esophageal obstruction because of the presence of bloat, dysphagia, and drooling. Several poisonous plants, including sneezeweed, larkspur, and milkweed, may cause excessive salivation, drooling, and bloat. Consumption of red clover infected with the fungus *Rhizoctonia leguminicola,* which produces the toxin slaframine, results in copious salivation. Pharyngeal trauma and subsequent cellulitis lead to dysphagia and drooling; severe bloat does not occur unless the swelling is sufficient to occlude the esophagus. However, mild bloat frequently accompanies pharyngeal trauma caused by associated vagal nerve inflammation and dysfunction.

Clinical Pathology Common features of long-standing choke are dehydration and metabolic acidosis resulting from continued loss of sodium bicarbonate and sodium phosphate in saliva. As sodium depletion develops, the composition of saliva shifts to include more potassium under the influence of aldosterone. Inflammatory diseases lead to predictable changes in the hemogram.

Necropsy Findings Animals that die of acute esophageal obstruction are bloated and may have saliva and feedstuffs in the upper airway. Postmortem examination of animals with protracted esophageal dysfunction may reveal focal dilations or stenoses of the esophagus. Esophageal perforation may have occurred because of pressure around an intraluminal foreign body or necrosis caused by extension of an adjacent septic process.

Treatment and Prognosis In cases of complete esophageal obstruction, relieving bloat is the first concern. Passage of a stomach tube may be attempted if the animal is not in respiratory distress. Trocharization of the rumen or installation of a temporary fistula may be required. Until the esophagus has been cleared, it is important to keep the muzzle level or pointed down to reduce the risk of aspiration of saliva. Sedative drugs such as acepromazine or xylazine may be useful to calm the animal and permit careful examination. Suitable precautions should be taken if rabies is remotely possible. The history and an examination of the environment should enable the clinician to anticipate the nature of the obstructing object. Palpation of the neck along the left jugular furrow may reveal the site of obstruction in lean or thin-necked individuals. A manual oral examination should precede probing attempts with a stomach tube. Gentle pressure on the stomach tube as it passes down the esophagus should allow localization of the obstruction. A small hand can reach into the cranial part of the esophagus and may retrieve some solid objects. If the object is solid (e.g., a potato), it may be possible to massage it into the pharynx by pressing in the jugular furrow on both sides of the neck. Specialized equipment, such as a probang, is available with a corkscrew-like or pincer-like end that can be used to grasp or engage a foreign body and expedite its retrieval. If a mass of grain is obstructing the esophagus, external massage, probing with the stomach tube, or pumping fluid against the mass through the tube may break it up.

If the choke is intrathoracic and probing with a stomach tube does not relieve the problem, several courses of action are possible. A small ruminal fistula can be inserted to prevent bloat, and the animal can simply be placed in a pen without bedding, feed, or water. Many masses consisting of grain or hay spontaneously pass within 24 hours, whereas solid objects rarely pass spontaneously. If the obstruction does not resolve in 24 hours, the animal can be heavily sedated, a cuffed endotracheal tube can be passed to prevent aspiration, and vigorous lavage with water through a stomach tube can be attempted. The head should be held lower than the body to minimize the risk of aspiration. If the obstruction still cannot be relieved or it is believed that the obstruction is a solid object, a rumenotomy can be performed. Access to the esophagus through the cardia should allow snaring of the object with a loop of stiff wire or breakup of a mass of grain.

The long-term prognosis after choke is good unless esophageal mucosal damage has occurred. Stricture formation may follow cellulitis or pressure necrosis at the site of the obstruction. Aftercare for the choked animal consists of a soft diet and antiinflammatory drugs to minimize tissue swelling. Well-soaked alfalfa cubes made into a mush may pass partly obstructed areas. Hay and grain should be moistened before feeding, and grain should be offered only in small amounts at each feeding. Broad-spectrum antibiotics should be given if mucosal damage is suspected. Maintenance of an indwelling nasogastric tube for feeding for up to 10 days after severe esophageal trauma may be helpful in preventing strictures during healing. Thick gruels made from soaked alfalfa cubes or pellets can be pumped into the rumen by a bilge pump designed for boats, or the animal can be fed and watered through a ruminal fistula. Surgical exploration may be required to determine the cause of esophageal obstruction from space-occupying lesions or strictures. Abscesses may be drained, and granulomatous lesions resected. Esophageal diverticula, aortic arch anomalies, and intrathoracic surgical problems may not be easily treated.

Esophageal Dilation (Megaesophagus) and Hiatal Hernia

Bradford P. Smith

Megaesophagus rarely occurs in ruminants. It has been reported in association with pharyngeal trauma and resultant inflammatory involvement of the vagus[1] and with hiatal hernia (diaphragmatic hernia with herniation of the reticulum into the thorax) in which there was a large megaesophagus (10 cm in diameter × 20 cm in length).[2] Vagotomy and hiatal hernia are recognized as causes of diminished esophageal pressure. A 4-month-old calf with megaesophagus lacked esophageal muscle cells and ganglion cells, and many fat cells were present.[3] The esophagus of a 12-month-old ram with megaesophagus was found to be heavily infected with *Sarcocystis arieticanis,* and eosinophilic inflammation and degeneration of muscle fibers were noted.[4] However, *Sarcocystis* spp. have been found in the esophagus of many sheep without megaesophagus, making the diagnosis difficult. An 18-month-old heifer with megaesophagus also had eosinophilic submucosal infiltration, but no sarcocysts were seen.[5] Megaesophagus in a goat due to unknown causes was also reported.[6]

The principal clinical signs of megaesophagus are regurgitation or vomiting, usually shortly after eating. Mild, recurrent bloat and discomfort when a stomach tube is passed are also observed. In other cattle with a hiatal (diaphragmatic) hernia or an esophageal diverticulum, regurgitation or vomiting and bloat have also been reported. Contortion of the neck while eating, apparently caused by pain, was seen in one cow and is reported in human beings with hiatal hernia. In some cases of herniation of the reticulum into the thorax, bloat and regurgitation are not seen; in others, diaphragmatic hernia resulted in chronic bloat.[7] Diaphragmatic hernias may be either congenital or acquired. It appears that acquired diaphragmatic hernias are most common.

A stomach tube should be passed to the rumen to rule out choke or an intraluminal mass obstructing the esophagus as a cause. If a tube can be passed freely to the rumen, plain and contrast radiographs of the esophagus should be taken. If this is not possible, surgical exploration of the abdomen for a diaphragmatic hernia and digital

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palpation of the cardia and terminal esophagus by means of rumenotomy should be considered.

Megaesophagus associated with pharyngeal trauma has a good prognosis,[1] whereas megaesophagus associated with hiatal hernia has a more guarded prognosis.[2] Supportive treatments and stomach tubing with fluids may be required for 1 to 2 weeks until the animal is able to drink unaided. Longer-term support can be given to a valuable animal by surgically creating a ruminal fistula fitted with a rubber cannula through which feed and water can be given until normal deglutition returns.

Ruminant Abdominal Ultrasonography

Betsy Vaughan

The key to diagnosing ruminant abdominal disorders is to conduct a thorough physical examination (see Chapter 1). A noninvasive and useful adjunct is the use of ultrasound.

Abdominal ultrasound provides a readily available, real-time, noninvasive method of imaging the abdomen in ruminants suspected of abdominal disease. Radiographic examination of the adult bovine abdomen offers limited information because of the large size of the patient and the need for expensive equipment with high milliampere-seconds (mAs) and kilovolt peak (kVp). Although radiographic examination of the small ruminant abdomen offers clinically useful information, it should be used in conjunction with abdominal ultrasonography to evaluate the abdominal organs and to further characterize radiographic abnormalities. Exploratory laparotomy is still commonly performed in cattle with unexplained illness referable to the abdominal cavity. Ultrasonographic evaluation of the ruminant abdomen has become an important part of the diagnostic workup in ruminants suspected of abdominal disease in combination with complete blood count (CBC), serum chemistry, peritoneal fluid analysis, urinalysis, and ruminal fluid analysis and can often provide valuable information that may preclude the need for exploratory laparotomy.[1,2] Abdominal ultrasound is indicated in patients with signs of abdominal pain, stasis, decreased motility, increased motility, lethargy, anorexia, bloat, regurgitation, fever of unknown origin, and suspected renal or liver disease. Ultrasound is also useful for diagnosing thoracic disorders.

Bovine patients should be restrained in a head gate and standing stocks. Squeeze chutes are not ideal because access to the complete abdomen is seldom possible. Small ruminants can usually be restrained with halters or collars. Bovine and small ruminant patients seldom need sedation for restraint during the examination. Patients should be prepared for complete abdominal ultrasound examination by surgical clipping of the left and right sides of the abdomen ventral to a diagonal line extending from the transverse processes of the lumbar vertebrae to the level of the elbow joint approximately at the level of the ventral lung margin. The entire ventral abdomen should be clipped from the xyphoid to the inguinal region (Fig. 32-95). If only one organ is to be examined, then the specific anatomic region should be clipped with wide margins. The clipped area should be washed thoroughly with water, degreased with soap or alcohol if necessary, and ultrasound coupling gel applied to the region. If clipping is not possible, alcohol saturation of the skin and hair may be adequate in patients with a short hair coat. The examination is performed with a low-frequency, curvilinear transducer (2.5 to 5 MHz) in large patients such as adult cattle, which provides penetration to a depth of 24 to 30 cm. A medium frequency (4 to 8 MHz) "microconvex" curvilinear transducer is ideal for evaluating calves and small ruminants. In large patients, superficial structures near the skin surface should also be evaluated using the medium-frequency transducer when image quality permits. This transducer is also useful for performing transrectal ultrasonography of the left kidney, urinary bladder, ureters, and urethra in cattle.

The examination should begin with detailed evaluation of the right paralumbar fossa region followed by evaluation of each intercostal space beginning at the ventral lung margin and scanning ventrally beyond the costochondral junctions. The ventral abdomen is then evaluated from the xyphoid to the inguinal region. The examination is repeated on the left side. The abdomen is evaluated for abnormalities of the kidneys, liver, gallbladder, spleen, rumen, reticulum, omasum, abomasum, duodenum, small intestine, cecum, and colon and for the presence and character of peritoneal fluid.



FIG. 32-95 Patient preparation for abdominal ultrasound examination. The region to be clipped for complete abdominal evaluation is shown, including the paralumbar fossa region, the intercostal spaces from the ventral lung margin to the costochondral junctions, and the entire ventrum from the xiphoid to the inguinal region.

Kidneys

NORMAL APPEARANCE (Fig. 32-96)**.** The right kidney is imaged from the right paralumbar fossa region and right eleventh to twelfth intercostal space at a scanning depth of 10 to 20 cm in cattle and 6 to 14 cm in small ruminants. The anatomic detail of the right kidney is greater than that of the left because of its more superficial location within the abdomen. In small ruminants the left kidney is routinely imaged in the right paralumbar fossa caudal to the right kidney at scanning depths of 8 to 14 cm. The left kidney in cattle can often be seen in this region as well though at greater depth. The left kidney cannot usually be visualized from the left side of the abdomen because it is obscured by the gas-filled rumen. Transrectal imaging of the left kidney should be performed in adult cattle suspected of having renal disease even when it is visualized transcutaneously, because it offers superior anatomic detail.

In cattle the normal right kidney has been reported to range from 8.1 to 11 cm in length and 4 to 7 cm in width.[3] Transrectally the left kidney has been reported to range in width from 4.5 to 7.5 cm in normal cattle. Transrectal length measurements of the left kidney were not reported, as it cannot be imaged in its entirety.[4] However, in the author's experience, normal bovine kidneys routinely measure up to 16 to 18 cm in length when measured transcutaneously. Normal bovine kidneys demonstrate a lobulated appearance with a relatively indistinct corticomedullary junction. Renal parenchyma should be less echogenic than hepatic parenchyma. The renal sinus demonstrates a hyperechoic appearance because of the presence of the renal calyces, adipose tissue, and connective tissue.[3,4]

In small ruminants, renal size can vary greatly depending on the size of the animal. In sheep the right kidney ranges from 7.1 to 8.9 cm in length and 3.4 to 5.5 cm in width, and the left kidney from 7.2 to 9.2 cm in length and 3.5 to 5.4 cm in width.[5,6] Small ruminants demonstrate smoothly marginated, oval kidneys. The renal capsule may be visible as a thin hyperechoic line. As in cattle, the renal parenchyma should be less echogenic than hepatic parenchyma. In contrast to cattle, the corticomedullary junction is clearly distinguishable. The renal pelvis demonstrates a hyperechoic appearance because of the presence of renal calyces, adipose tissue, and connective tissue.[5,6]

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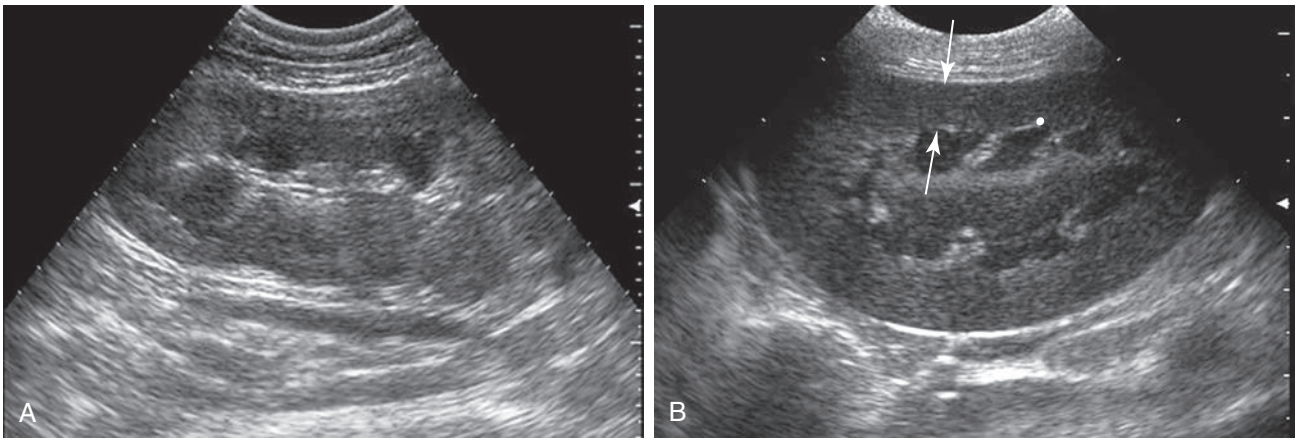


FIG. 32-96 **A,** Normal right kidney viewed from the right paralumbar fossa region in a 5-year-old Holstein dairy cow. Note the lobulated shape and indistinct corticomedullary junction. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 20 cm. **B,** Normal right kidney viewed from the right paralumbar fossa region in a 4-year-old castrated male Nigerian Dwarf goat. Note the smooth renal capsule, ovoid shape, and distinct corticomedullary junction *(arrows).* Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm.

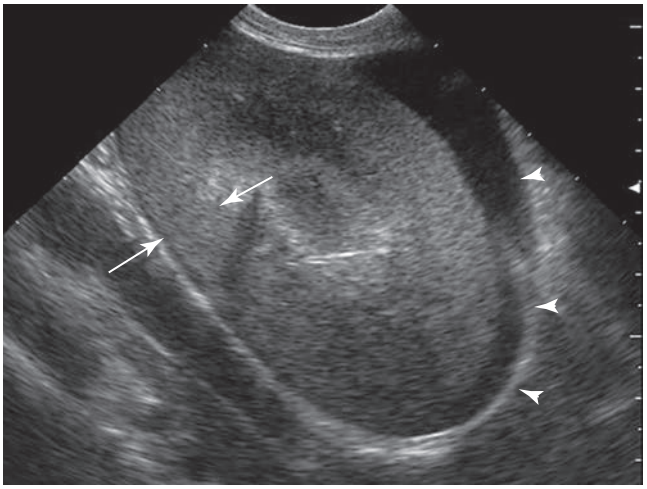


FIG. 32-97 Right kidney viewed from the right paralumbar fossa region in a 12-year-old Pygmy goat buck with acute renal failure. Note the increased cortical echogenicity and thickness *(arrows).* Perirenal edema *(arrowheads)* is seen surrounding the kidney. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm.

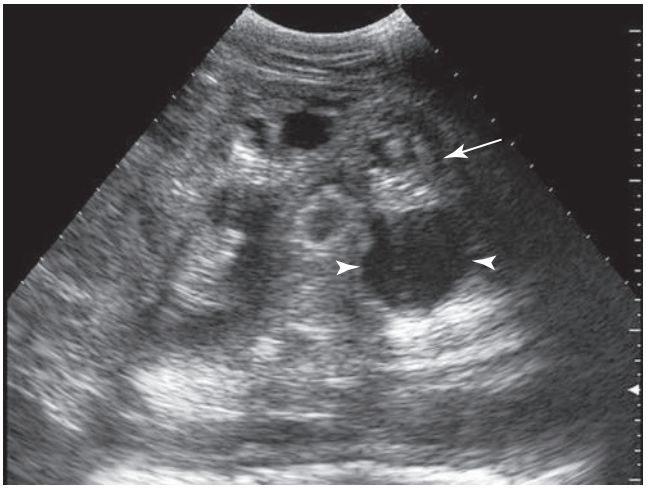


FIG. 32-98 Right kidney viewed from the right paralumbar fossa region in a 2-year-old Angus heifer with severe necrotizing pyelonephritis. Note the abnormal renal architecture with echogenic debris *(arrow)* within the distended renal calyces *(arrowheads).* Image was obtained with a 2.5-MHz transducer at a depth of 20 cm.

ABNORMAL FINDINGS. Changes in size, shape, architecture, and echogenicity are nonspecific ultrasonographic abnormalities that can be seen in ruminants with acute or chronic renal failure, amyloidosis, nephritis, and pyelonephritis. Abnormalities seen in patients with acute renal failure include renal enlargement, thickening of the renal cortex, and perirenal edema (Fig. 32-97). In cases of chronic renal failure, the kidneys are often smaller than normal and may be misshapen. Pyelonephritis is a common cause of fever, colic, and pyuria in cows, often occurring as an ascending infection after abortion or dystocia. Ultrasonographic findings include renomegaly, pyelectasia with echogenic to hyperechoic debris within the renal sinus, and ureteral dilation (Fig. 32-98).[7-10] Ultrasound-guided percutaneous biopsy can be performed safely and is commonly required to distinguish the specific cause of disease in patients with acute or chronic renal disease.[11]

Specific renal abnormalities include nephrolithiasis, hydronephrosis, renal neoplasia, and renal abscessation. Nephroliths are round or irregularly shaped hyperechoic structures within the renal sinus that cast strong acoustic shadows (Fig. 32-99). Associated dilation of the renal sinus or calyces may be seen with obstructive nephrolithiasis. Hydronephrosis is characterized by dilation of renal calyces with anechoic urine and may be seen with a postrenal obstruction (Fig. 32-100). Hydronephrosis is commonly seen in small ruminants with obstructive urolithiasis but can also be caused by extramural obstruction secondary to caudal abdominal masses. Transrectal evaluation of the ureters and urinary bladder is indicated in bovine patients with hydronephrosis or obstructive nephrolithiasis to evaluate for the presence of uroliths within the ureters or urinary bladder.

Congenital renal cysts are relatively common in cattle, sheep, and goats and should be readily recognizable via ultrasound.[10,12-15] Mass lesions within or obliterating the normal renal parenchyma can be seen with neoplasia or abscessation. Both renal abscessation and renal neoplasia are rare in ruminants.[13,14] Renal abscesses may be distinguished from neoplasia based on their ultrasonographic appearance. Renal abscesses are usually encapsulated and contain anechoic to echogenic fluid. Ultrasound-guided percutaneous aspiration can be used to obtain a sample for cytology and culture and to facilitate drainage in affected animals. Ultrasound-guided biopsy is necessary to identify specific neoplastic processes.[11]

Urinary Bladder and Ureters

NORMAL APPEARANCE. The urinary bladder is normally imaged from the right or left caudoventral abdomen in small ruminants at a scanning depth of 5 to 14 cm and appears as an oval or spherical structure with a thin wall containing anechoic urine

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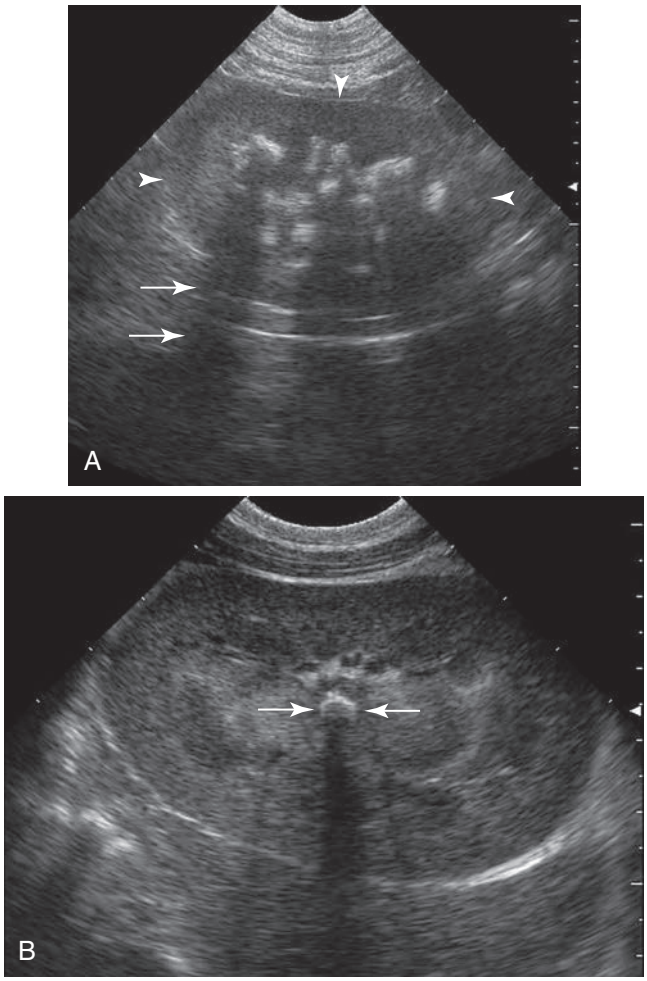


FIG. 32-99 **A,** Severe nephrolithiasis of the right kidney *(arrowheads)* in a 8-year-old Nubian doe. Note the strong shadows cast by the hyperechoic nephroliths *(arrows)*. Image was obtained with a 5.5-MHz transducer at a depth of 12 cm. **B,** Single right nephrolith in the right kidney of a 3-year-old Nigerian Dwarf doe *(arrows)*. No dilation of the renal pelvis is seen. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm.

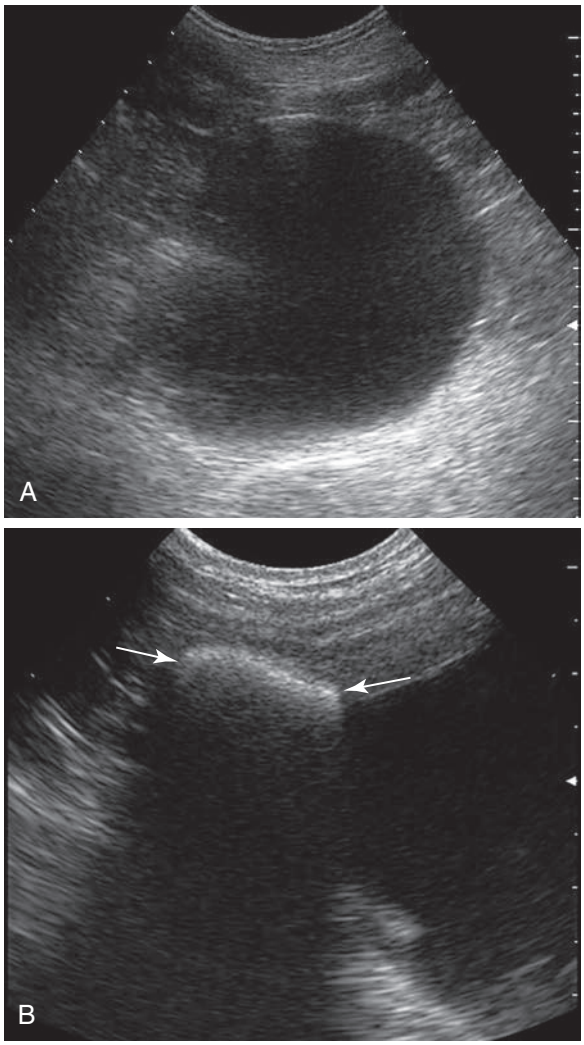


FIG. 32-101 **A,** Normal urinary bladder viewed from the left inguinal region in a 10-year-old Romeldale ewe. Image was obtained with a 3.5-MHz curvilinear transducer at a depth of 15 cm. **B,** Cystic calculi *(arrows)* in an 11-year-old Pygmy doe with urolithiasis. Image was obtained in the left inguinal region with a 7.5-MHz curvilinear transducer at a depth of 5 cm.

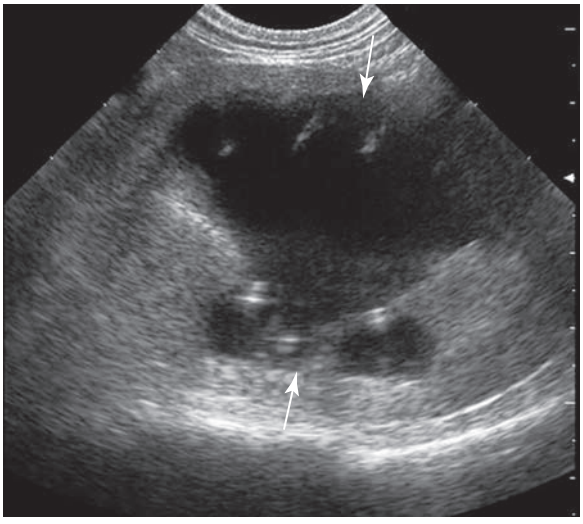


FIG. 32-100 Severe hydronephrosis of the left kidney viewed from the right paralumbar fossa region in a 10-year-old Pygmy doe. This doe had a uterine mass that was compressing the left ureter. Note the severe dilation of the renal pelvis *(arrows)*. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm.

(Fig. 32-101, *A*). The size and shape of the urinary bladder are dependent on its distention at the time of examination. The urinary bladder is often not visible transcutaneously in cows but can be evaluated transrectally along with the urethra and the distal portion of the right and left ureters.[4] The normal urethra is not visualized except at the onset of urination and appears as a thin anechoic line when distended with urine.[4] An attempt should be made to locate the ureters to the right and left of the urinary bladder at the trigone region. The ureters should then be followed cranially as far as they can be visualized.

ABNORMAL FINDINGS. Abnormalities of the urinary bladder include distention secondary to obstruction, thickening of the bladder (cystitis), cystic calculi, mass lesions, and rupture. Severe distention of the urinary bladder can be indicative of mechanical or functional obstruction. For this reason, transabdominal ultrasound examination is commonly used as a screening procedure for obstructive uropathy in small ruminants.[5,14,15] In affected animals the bladder will be markedly distended and may demonstrate multiple pinpoint echogenic or hyperechoic particles within the urine as well as cystic calculi.[5] Cystic calculi are seen within the bladder and can be hyperechoic or hypoechoic with a round or irregular shape. They may or may not cast strong shadows (see Fig. 32-101, *B*). Mass lesions associated with the urinary bladder wall include neoplasia and hematoma that may be difficult to differentiate ultrasonographically.

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Urinary bladder rupture may occur secondary to obstructive urolithiasis or trauma. Ultrasound examination reveals an increased amount of free anechoic fluid within the abdomen. Definitive diagnosis can be made by comparing the concentration of creatinine in abdominal fluid to the serum concentration.[10]

Ureteroliths may be seen on transrectal ultrasound examination in bovine patients and demonstrate the appearance of hyperechoic structures within the ureter that cast strong shadows. Marked ureteral dilation that appears as a tubular structure dilated with anechoic fluid is seen cranial to the ureterolith.[16] Thickening of the ureteral wall may occur secondary to inflammation. Ureteral rupture can occur secondary to obstruction and results in accumulation of anechoic fluid within the retroperitoneal space.[1,16]

Liver

NORMAL APPEARANCE (Fig. 32-102)**.** The right liver lobe is imaged from the right sixth to twelfth intercostal spaces at a scanning depth of 6 to 14 cm in small ruminants and 20 to 30 cm in cattle and demonstrates a homogeneous, echogenic appearance. The branching vasculature of the portal and hepatic veins can be seen in addition to fine vascular markings scattered throughout the hepatic parenchyma.

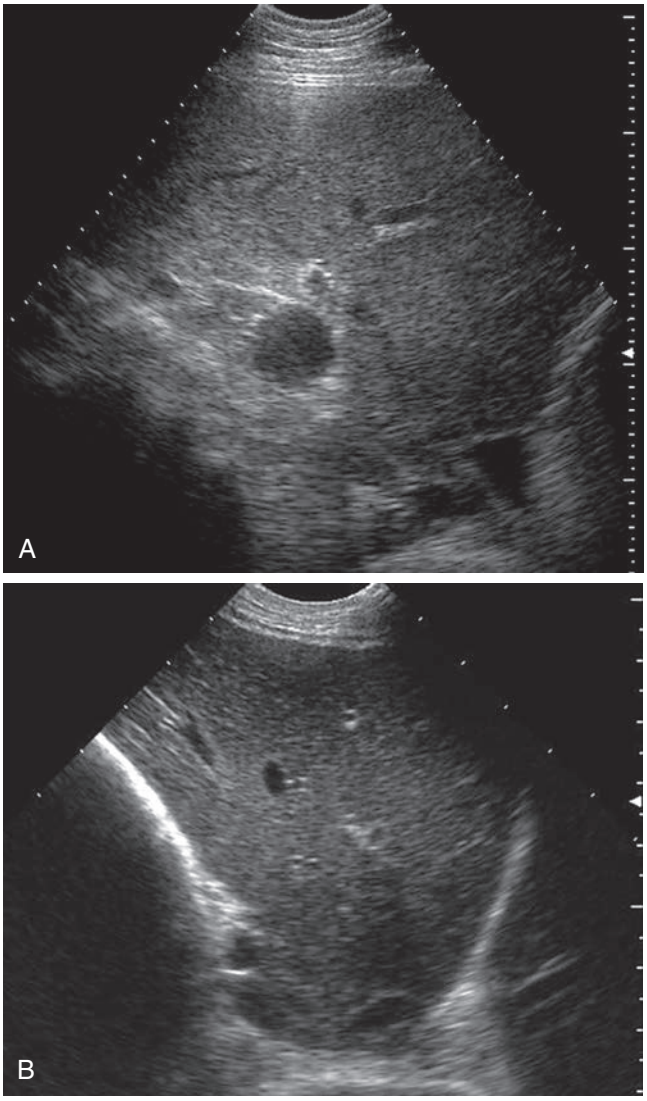


FIG. 32-102 **A,** Normal right liver lobe viewed from the right tenth intercostal space in a 5-year-old Holstein dairy cow. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 27 cm. **B,** Normal right liver lobe viewed from the right tenth intercostal space in a 12-year-old Pygmy buck. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 10 cm. Dorsal is to the right and ventral is to the left.

The liver parenchyma is normally more echogenic than renal parenchyma and less echogenic than splenic parenchyma. In contrast to horses, an anatomic window for direct comparison of the liver and spleen does not exist in ruminants. Subjective comparison between the spleen on the left side and the liver on the right side should be undertaken with caution because changes in image quality and machine settings may lead to a false assessment of echogenicity. Bile ducts are not normally visible ultrasonographically.[17,18] The ventral borders of the liver are usually sharp or mildly rounded and extend near or beyond the costochondral junctions. One proposed method of assessing hepatic size in cattle is to measure the thickness of the liver overlying the portal vein (normally 5.1 to 14.1 cm) and the caudal vena cava (normally 8.2 to 15.4 cm).[19] Cows with high body condition scores and milk production will have larger livers than thin cows with decreased milk production, making assessment of liver size somewhat subjective in cattle.[20] The portal vein and caudal vena cava should also be assessed during the hepatic ultrasound examination. The portal vein is round and is commonly seen deep to the liver in the right eighth to twelfth intercostal spaces, ventral and lateral to the caudal vena cava. The caudal vena cava is usually seen only in the right eleventh and twelfth intercostal spaces, dorsal and deep to the portal vein.[17-19,21,22]

ABNORMAL FINDINGS. Nonspecific ultrasonographic abnormalities of the liver, including hepatomegaly, changes in echogenicity, and a decreased number of fine vascular markings, can be seen with hepatopathies of numerous causes including pyrrolizidine alkaloid toxicosis,[23] hepatic lipidosis, and diffuse infiltrative disease.[17,24] Hepatic lipidosis, in particular, has been reported to result in an overall increase in hepatic echogenicity with decreased fine vascular markings (Fig. 32-103).[17,24]

Variable changes in echogenicity can also be seen during the parenchymal stage of fascioliasis.[25,26] Ultrasound-guided liver biopsies can be used to obtain a definitive diagnosis.

Hypoechoic or hyperechoic mass lesions within the hepatic parenchyma may represent abscessation or neoplasia. Hepatic abscessation is common in cattle and can occur with numerous disease processes, including cholangitis, traumatic reticuloperitonitis (TRP), or bacteremia secondary to rumenitis or omphalophlebitis. Hepatic abscesses demonstrate a variable appearance with a homogeneous or mixed echogenicity, hyperechoic or hypoechoic contents, and a variable degree of encapsulation (Fig. 32-104, *A*).[17,22,27,28] The appearance of the abscess can change throughout the course of disease. Early abscesses may demonstrate a hypoechoic appearance without visible encapsulation. More chronic abscesses are usually well encapsulated with more echogenic contents. Gas echoes within the abscess are

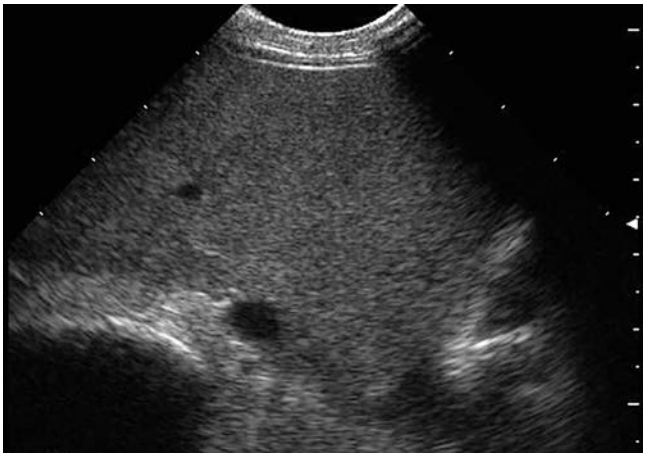


FIG. 32-103 Increased echogenicity and decreased fine vascular markings viewed from the right ninth intercostal space in the right liver lobe of a 4-year-old castrated male Nigerian Dwarf goat with hepatic lipidosis. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 8 cm. Dorsal is to the right and ventral is to the left.

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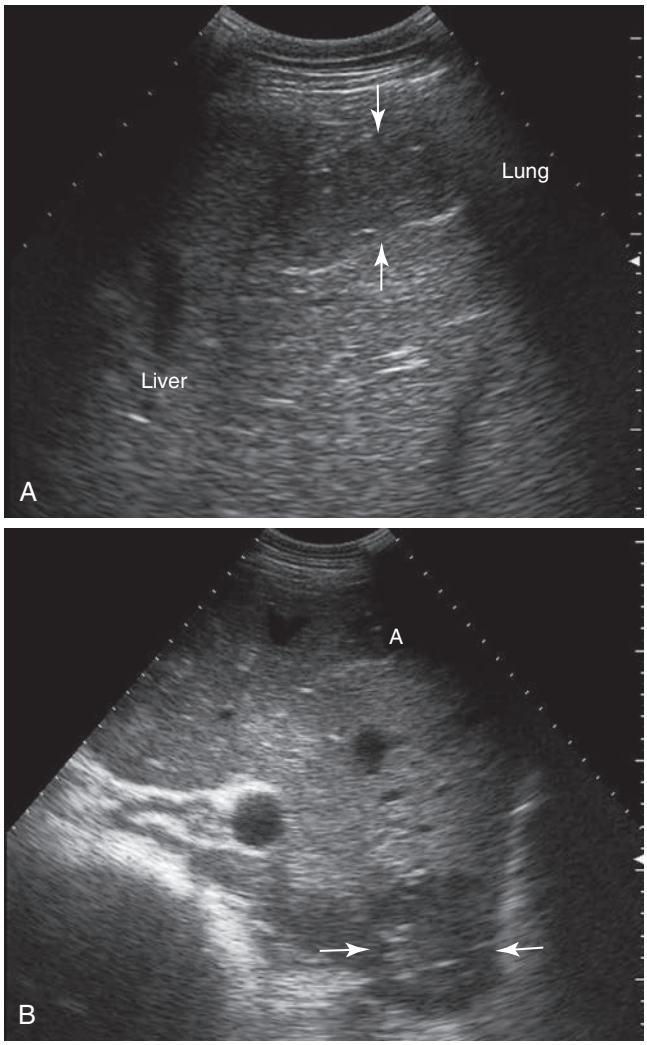


FIG. 32-104 **A,** Hepatic abscess measuring 5.6 cm × 3.1 cm *(arrows)* in a 2-year-old Holstein dairy cow that presented for fever, anorexia, and weight loss. View is from the right tenth intercostal space. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 15 cm. **B,** Thrombus of the caudal vena cava *(arrows)* in the same cow. Image was obtained in the right ninth intercostal space using a 3.5-MHz transducer at a depth of 27 cm. The *A* in the upper right indicates an abscess.

indicative of anaerobic infection. Ultrasound-guided percutaneous aspiration commonly yields fluid for culture and sensitivity.[17,27-29] Thrombosis of the caudal vena cava can occur secondary to hepatic abscessation. Affected cows show dilation of the caudal vena cava characterized by a change in shape from triangular to oval or round. Dilation of the hepatic veins may also be seen. Thrombi are uncommonly visualized ultrasonographically because they are typically located deep within the abdomen or in the thorax.[30-32] If seen, thrombi demonstrate a heterogeneous appearance (see Fig. 32-104, *B*).

Hepatic neoplasia is uncommonly reported in ruminants.[17,33] The ultrasonographic appearance of the liver is variable in these cases. The hepatic parenchyma may be diffusely affected, or discrete single or multiple masses may be seen. Metastatic lesions can be seen within the hepatic parenchyma or may distort the hepatic capsule along the serosal surface.[17,33] Ultrasound guidance is recommended when obtaining percutaneous biopsies to avoid sampling unaffected parenchyma.

Ultrasound can be helpful to diagnose obstructive cholestasis.[17,34,35] Ruminants with obstructive cholestasis will show changes consistent with extrahepatic or intrahepatic obstruction. Extrahepatic obstruction usually occurs at the level of the duodenal papilla. Ultrasonographic findings include dilation of the gallbladder with bile and echogenic sludge, dilation of the common bile duct, and

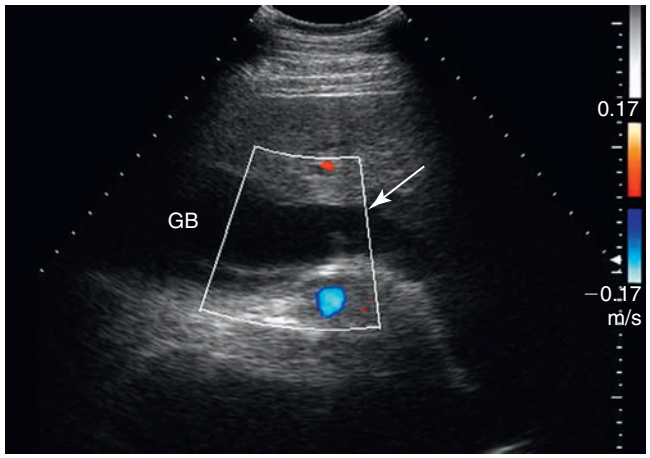


FIG. 32-105 Dilated cystic duct *(arrow)* viewed from the right ventral abdomen in a 3-year-old Holstein dairy cow with extrahepatic cholestasis. Color Doppler confirms the absence of blood flow in the cystic duct. Image was obtained from the right ventral abdomen using a 4.0-MHz curvilinear transducer at 21.5 cm. Dorsal is to the right and ventral is to the left. *GB,* Gallbladder.

dilation of the intrahepatic ducts (Fig. 32-105). Dilation of the intrahepatic ducts results in a "parallel channel sign" because intrahepatic ducts lie parallel to portal veins. The presence of gas echoes within the bile ducts is consistent with anaerobic suppurative cholangitis. The ductal phase of fascioliasis results in distention and tortuosity of the bile ducts.[25,26] Occasionally, moving echogenic forms can be seen within these bile ducts in infected sheep.[25] Mineralization of individual bile ducts can be seen in cases of chronic fascioliasis.[22,35] In contrast, ruminants with hepatocellular cholestasis may show ultrasonographic changes consistent with infiltrative disease or hepatic congestion or may have a normal hepatic ultrasound examination.

Gallbladder

NORMAL APPEARANCE (Fig. 32-106, *A*)**.** The gallbladder is visualized deep to the liver in the right ninth to eleventh intercostal spaces and is a thin-walled, round, or oval structure filled with anechoic fluid that is usually visualized in only one or two intercostal spaces. However, ruminants with anorexia have no reflex stimulus for emptying the gallbladder. This creates a distended appearance without obstruction (see Fig. 32-106, *B*).[18,19,21] The gallbladder is usually seen at a scanning depth of 6 to 10 cm in small ruminants and 12 to 18 cm in cattle.

ABNORMAL FINDINGS. Abnormalities of the gallbladder include biliary distention, wall thickening, sediment accumulation, or cholelithiasis. As mentioned earlier, it is important to differentiate gallbladder distention secondary to anorexia or fasting from distention secondary to cholestasis. Cholestatic obstruction is a serious condition that can lead to rupture if the obstruction is not resolved.[36] Wall thickening may be secondary to edema or inflammation. Choleliths appear as discrete hyperechoic structures that cast strong shadows. Sediment, on the other hand, demonstrates an amorphous echogenic to hyperechoic appearance and will have a dependent location (ventral in standing animals) within the gallbladder (see Fig. 32-106, *C*). Ultrasound-guided cholecystocentesis has been reported to be a valuable diagnostic technique in cases suspect for liver fluke infection *(Fasciola hepatica, Dicrocoelium dendriticum).*[17,37] Both transhepatic cholecystocentesis and transcutaneous aspiration can be performed safely.[17] Bile examination for detection of fluke eggs is superior to fecal examination because liver fluke eggs are stored in the gallbladder for weeks.[17,37]

Spleen

NORMAL APPEARANCE (Fig. 32-107)**.** The spleen is visualized in the left seventh to twelfth intercostal spaces between the rumen and body wall at the cranial extent of the rumen at a scanning depth

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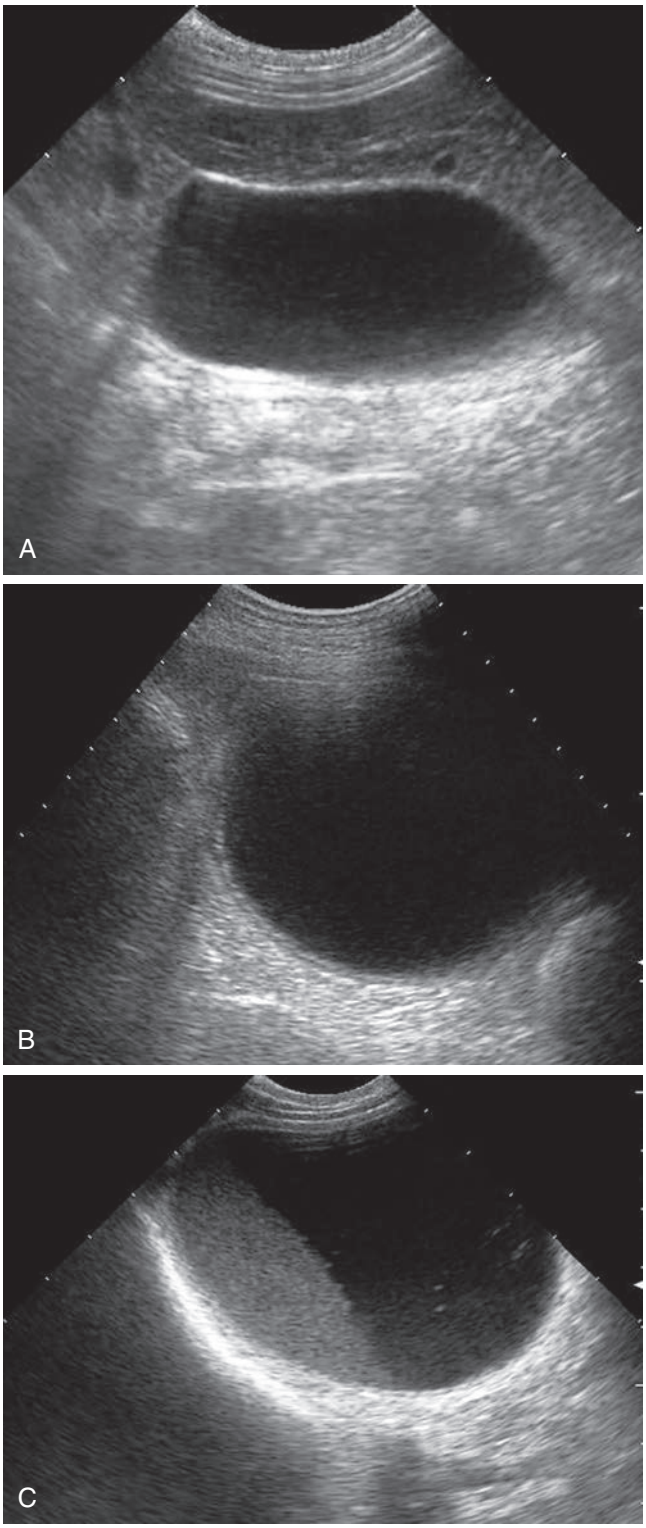


FIG. 32-106 **A,** Normal gallbladder in a 6-year-old Pygmy doe. Image was obtained with a 8.5-MHz curvilinear transducer at a depth of 8 cm. **B,** Distended gallbladder viewed from the right tenth intercostal space in a 3-year-old Holstein dairy cow that presented for anorexia. Image was obtained with a 3.5-MHz curvilinear transducer at a depth of 16 cm. **C,** Distended gallbladder with bile sediment viewed from the right twelfth intercostal space in a 12-year-old Pygmy buck. Image was obtained with a 7.5-MHz transducer at a depth of 10 cm. Dorsal is to the right and ventral is to the left.

of 6 to 14 cm in small ruminants and 16 to 28 cm in cattle. Splenic size is variable, and the spleen occasionally extends to the ventral midline in normal cows.[38] The spleen demonstrates a homogeneous appearance and appears more echogenic and less vascular than the liver. The splenic capsule appears as a thin hyperechoic line.[38,39]

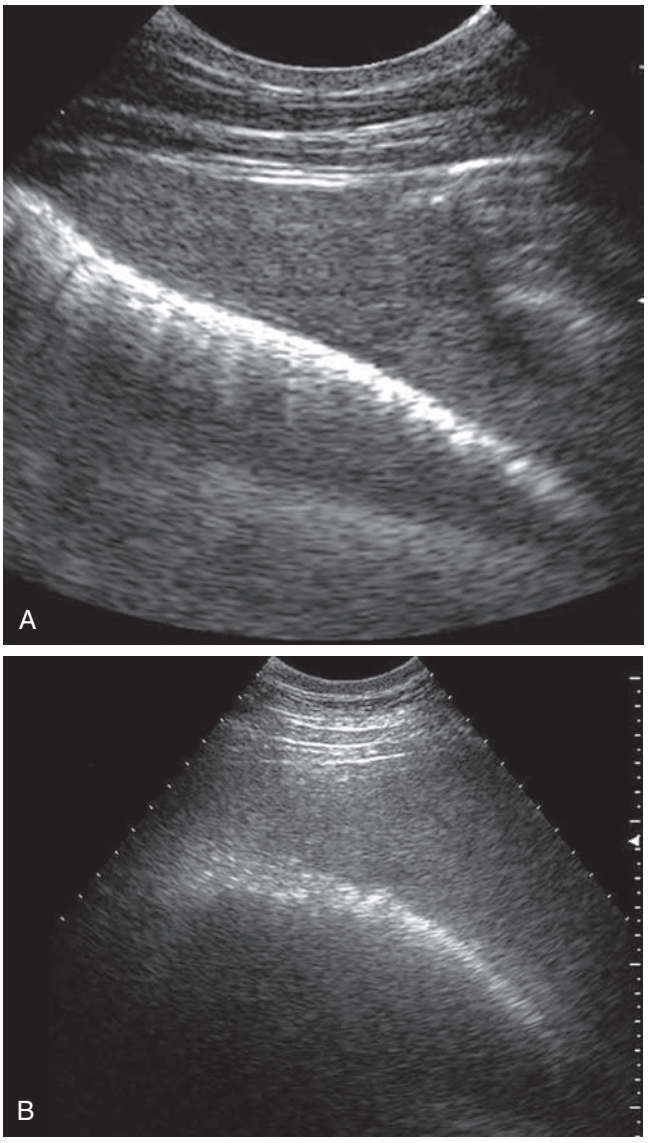


FIG. 32-107 **A,** Normal spleen viewed from the left ninth intercostal space in a 12-year-old Pygmy buck. Note that the spleen appears less vascular relative to the normal liver. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 4 cm. **B,** Normal spleen viewed from the left tenth intercostal space in a 4-year-old Holstein dairy cow. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 16 cm. Dorsal is to the right and ventral is to the left.

ABNORMAL FINDINGS. Splenic abnormalities may include changes in echogenicity indicative of diffuse parenchymal disease or discrete masslike lesions consistent with neoplasia or abscessation. Suppurative splenitis or abscessation can occur secondary to septicemia or TRP.[40] Splenic neoplasia has also been reported in ruminants.[38] Ultrasound-guided percutaneous aspiration or biopsy may provide definitive cytology, culture, or histopathologic diagnosis but should be undertaken with caution in compromised patients because of the risk of hemorrhage.

Reticulum

NORMAL APPEARANCE (Fig. 32-108, *A*)**.** The reticulum is seen in the cranioventral abdomen and both the left and right sixth and seventh intercostal spaces ventral to the spleen and cranial to the rumen at a scanning depth of 4 to 8 cm in small ruminants and 10 to 14 cm in cattle. The reticulum should be evaluated during the examination for normal biphasic contractions, which should occur approximately once per minute. Monophasic, triphasic and quadriphasic contractions have been reported in normal goats.[41] The reticulum contracts approximately 5 to 10 cm away from the abdominal

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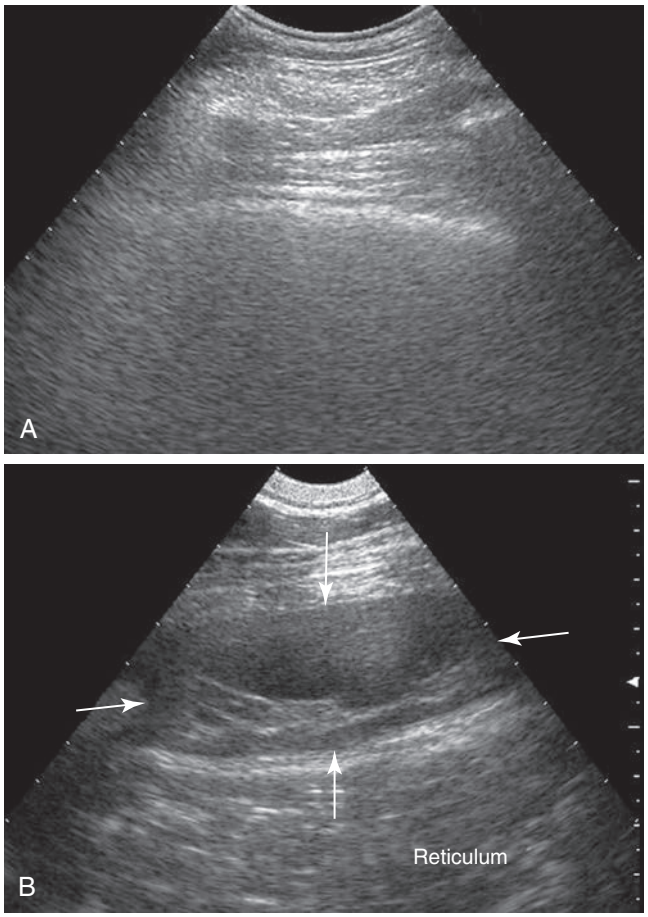


FIG. 32-108 **A,** Normal reticulum viewed from the left cranioventral abdomen in a 5-year-old Holstein dairy cow. Image was obtained with a 3.5-MHz curvilinear transducer at a depth of 14 cm. **B,** Small reticular abscess *(arrows)* viewed from the left seventh intercostal space in an 8-year-old Charolais beef cow suspected of traumatic reticuloperitonitis. A small wire was seen within the reticulum on abdominal radiographs. Image was obtained with a 5.5-MHz curvilinear transducer at a depth of 12 cm. Dorsal is to the right and ventral is to the left.

wall during the first phase of contraction and more than 17 cm away during the second phase of contraction in cattle.[42] When in a relaxed state the reticulum appears as a semicircular structure immediately adjacent to the ventral abdominal wall. Reticular contents cannot normally be visualized because of their gaseous composition. The honeycomb appearance of the reticular mucosa is not commonly distinguishable ultrasonographically.

ABNORMAL FINDINGS. Reticular abnormalities are primarily associated with TRP. Reticular abscesses caused by TRP can be seen between the reticulum and body wall, spleen, diaphragm, or liver.[2,43] These abscesses are usually well encapsulated with an echogenic capsule and may contain anechoic to echogenic contents (see Fig. 32-108, *B*). Abscesses adjacent to the body wall can be incised and drained transcutaneously with ultrasound guidance.[43] Other abnormalities associated with TRP include changes in the contour of the reticulum, echogenic fibrinous deposits on the reticular serosa, nonencapsulated fibrinous exudate between the reticulum and body wall, and adhesions between the reticulum and the peritoneum or adjacent organs.[2,40,43,44] Reticular contractions are often absent, reduced, or indistinct in affected animals and can be an indication of adhesions between the reticulum and body wall.[2,44] The causative foreign bodies are rarely identified ultrasonographically because of the gaseous composition of reticular contents and are better assessed via radiography.[2,44] Reticular hypermotility has been described in cows with reticuloomasal obstruction or stenosis.[45,46]

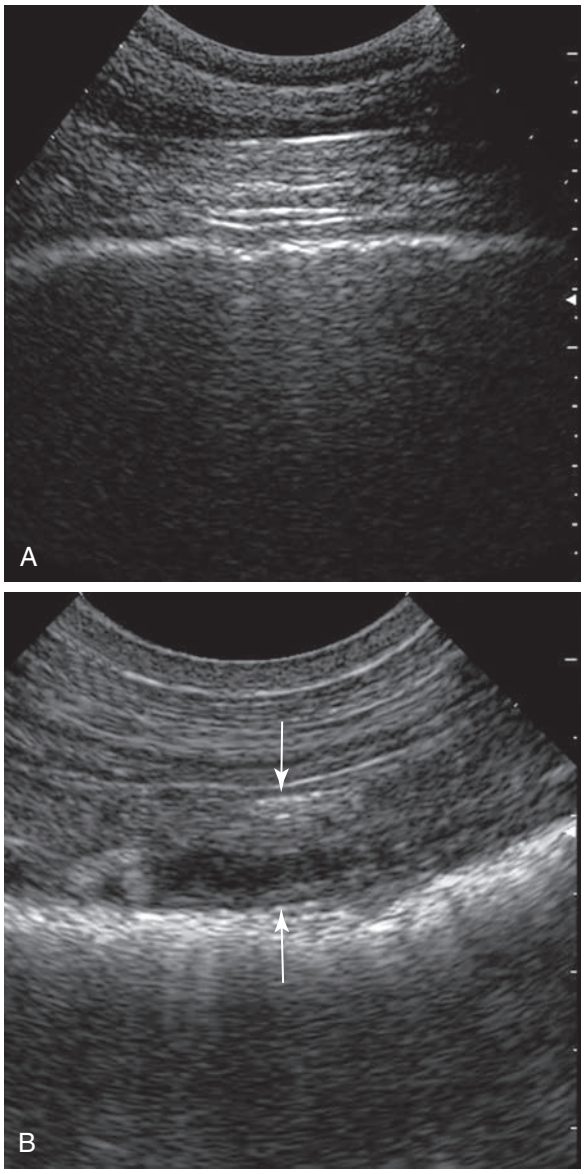


FIG. 32-109 **A,** Normal rumen viewed from the left paralumbar fossa region in a 5-year-old Holstein dairy cow. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 9 cm. **B,** Severely thickened ruminal wall measuring 14.9 mm *(arrows)* viewed from the left paralumbar fossa region in a 12-year-old pygmy buck that recently underwent rumenotomy. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 4 cm.

Rumen

NORMAL APPEARANCE (Fig. 32-109, *A*)**.** The rumen normally occupies the entire left paralumbar fossa region, the left eighth to twelfth intercostal spaces, and the left caudoventral abdomen and is seen directly adjacent to the body wall. The ruminal wall is seen as a smooth, thin hypoechoic line. Hyperechoic gas within the rumen creates a hyperechoic line immediately adjacent to the wall. Ruminal contents are not commonly visualized because of their gaseous composition; however, echogenic ingesta and hypoechoic fluid can be seen dependently in normal cattle. The wall of the craniodorsal blind sac, the ventral sac of the rumen, and the ruminoreticular groove are seen immediately caudal to the reticulum in the cranioventral left intercostal spaces.[2] Contraction of the craniodorsal blind sac of the rumen is commonly seen after the second reticular contraction.

ABNORMAL FINDINGS. Thickening of the ruminal wall may be seen in cases of ruminitis or secondary to ruminotomy or ruminal

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trocarization (see Fig. 32-109, *B*). Abscesses between the rumen and the left body wall may also develop secondary to surgical procedures performed in the left flank region.[47] Such abscesses are usually well encapsulated and contain anechoic to echogenic contents. Echogenic strands of fibrin or fibrinous deposits may be found in association with the abscess. Localized or generalized peritonitis may also occur secondary to abscessation. Abscesses adjacent to the body wall can be aspirated via ultrasound guidance for cytology and culture.

Omasum

NORMAL APPEARANCE. The omasum can be seen in the right sixth to tenth intercostal spaces dorsal to the abomasum and/or the reticulum. Although similar to the reticulum in appearance, the omasum can be differentiated by an increased wall thickness and the absence of visible contractions in cattle.[2,40,48] Active omasal contractions can be seen in goats and occur approximately 1 per minute.[49] Omasal contents and omasal laminae are seldom visualized because of intraluminal gas. Laminae are sometimes seen in ill ruminants with increased omasal fluid contents.[2,50]

ABNORMAL FINDINGS. Ultrasonographic abnormalities of the omasum are limited to changes in position associated with displaced abomasum, traumatic reticuloperitonitis and reticuloomasal stenosis. Increased fluid contents are usually secondary to abomasal reflux. Rarely, omasal motility is visible in cases of reticuloomasal stenosis.[2,50] Omasal impaction cannot be diagnosed reliably via ultrasound examination.[51]

Abomasum

NORMAL APPEARANCE (Fig. 32-110, *A*)**.** The abomasum is normally visualized in the cranioventral abdomen along the ventral midline and in both the right and left paramedian regions caudal to the xiphoid process. In general, the abomasum is situated more to the right of the ventral midline. The abomasum can be distinctly identified because of its visible fluid contents, which demonstrate a heterogeneous anechoic to echogenic appearance. The abomasal wall appears as a thin hyperechoic line. Abomasal folds are sometimes visible. Passive movement of the abomasum is seen during reticular contractions; however, abomasal contractions are usually not seen. The pylorus is rarely identified.[52]

ABNORMAL FINDINGS. Reported ultrasonographic abnormalities of the abomasum in cattle include left and right abomasal displacement, abomasal volvulus, and functional or mechanical pyloric stenosis.[1,2,40,52] In cattle with left abomasal displacement, the rumen is seen adjacent to the body wall ventrally; however, the abomasum is imaged between the rumen and the left body wall dorsally. The rumen is displaced medially at this level, deep to the abomasum. Fluid and ingesta are visible ventrally within the abomasum, and a gas cap is visible dorsally.[1,2,53] With right abomasal displacement and abomasal volvulus, the abomasum is imaged adjacent to the right body wall in the right intercostal spaces. In this case the liver is displaced medially, deep to the abomasum, and cannot be seen. Similar to left dorsal displacement, fluid and ingesta contents are visible in the ventral aspect of the abomasum, and a gas cap is visible dorsally.[1,2,40,54] In cases of pyloric stenosis, the abomasum is dilated but not displaced (see Fig. 32-110, *B*).[2] No gas accumulation is seen, and the abomasal contents demonstrate an anechoic or hypoechoic, fluid appearance. If the abomasal distention is a result of delayed abomasal emptying secondary to ileus, distended, amotile loops of small intestine will be visible in the right ventral abdomen.[40] Transmural thickening of the abomasal wall has been reported in cases of abomasal lymphoma.[55,56] Abomasitis and abomasal ulceration cannot be visualized with ultrasound.[2]

Small Intestine

NORMAL APPEARANCE (Fig. 32-111, *A*)**.** The descending duodenum is visualized from the right tenth intercostal space caudally to the right paralumbar fossa region. The ascending duodenum cannot be visualized because of its location deep within the abdomen. The cranial duodenum may be seen deep or ventral to the gallbladder in the right tenth or eleventh intercostal space. The descending duodenum is then visible deep to the liver in the right eleventh and twelfth intercostal spaces and becomes progressively superficial as it courses caudodorsally such that it is seen adjacent to the body wall in the right paralumbar fossa region. Duodenal contents are often visible and consist of a fluid, feed, and/or mucous mixture with mixed echogenicity. Occasionally, gaseous contents are seen within the duodenum. The descending duodenum can be differentiated from jejunum and ileum by its anatomic location within the abdomen.

The jejunum and ileum cannot be differentiated from one another in adult cattle and are usually seen in the right caudal intercostal spaces, right paralumbar fossa region, and right caudoventral abdomen. Loops of jejunum and ileum demonstrate a similar appearance to the duodenum, with anechoic to echogenic fluid and feed contents. Gaseous contents may also occasionally be seen in the jejunum and ileum. Loops may be seen both longitudinally and transversely and demonstrate consistent, active motility. The wall thickness of normal small intestine is 2 to 3 mm, and the normal diameter ranges from 2 to 4 cm in adult cattle.[2,57]

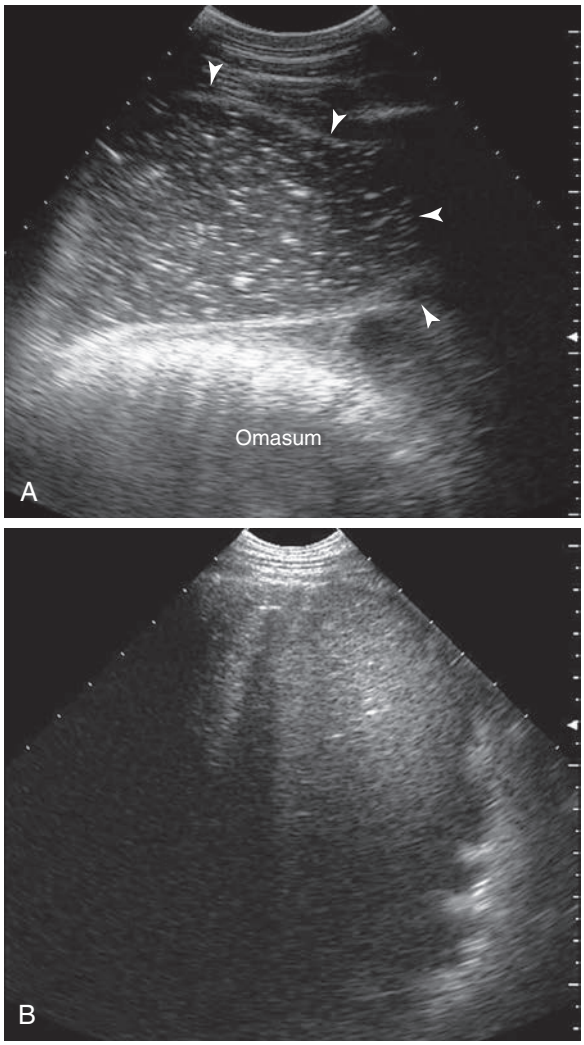


FIG. 32-110 **A,** Normal abomasum viewed from the right cranioventral abdomen in a 5-year-old Holstein dairy cow. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 9 cm. Note that abomasal contents and the walls of the abomasum are visible *(arrowheads)*. **B,** Severe abomasal distention viewed from the right ventral paralumbar fossa region in an 8-year-old Pygmy doe with severe bloat. Postmortem examination revealed marked pyloric stenosis. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 9 cm. Dorsal is to the right and ventral is to the left.

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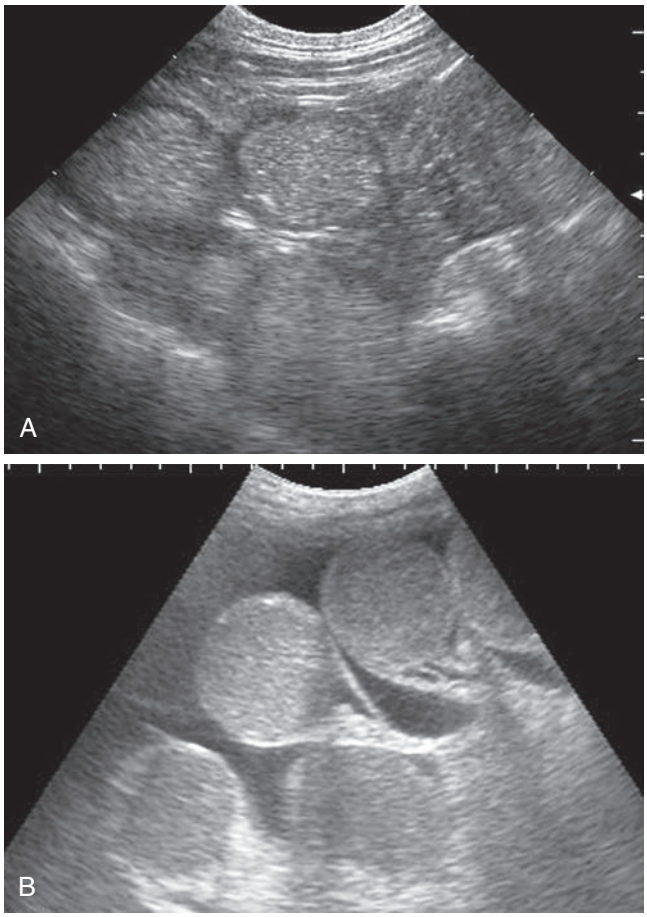


FIG. 32-111 **A,** Normal small intestine viewed from the right paralumbar fossa region in a 5-year-old Nubian buck. This small intestine demonstrated normal consistent motility. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 7 cm. **B,** Severe small intestinal distention with moderate peritoneal effusion viewed from the left ventral abdomen in a yearling Angus heifer with severe ileus secondary to peritonitis. Image was obtained with a 3.5-MHz curvilinear transducer at a depth of 25 cm.

ABNORMAL FINDINGS. Motility, distention, and wall thickness are the most important variables for evaluating small intestinal abnormalities via ultrasound. Ultrasonographic evidence of ileus, characterized by distended, hypomotile to amotile loops of small intestine, can be seen in patients with functional ileus, obstruction, strangulation or incarceration, volvulus, intussusception, and impaction of the small intestine. Small intestinal obstruction may be intraluminal, caused by foreign body, bezoar, impaction, or intraluminal mass or clot formation (hemorrhagic bowel syndrome [HBS]).[1,57-59,60-62] The ventral abdomen should be carefully evaluated in patients suspected of having small intestinal obstruction because affected small intestine is heavier than normal intestine and falls to the most dependent portion of the abdomen. Distended small intestine demonstrates the appearance of a static tubular structure filled with anechoic to echogenic fluid (see Fig. 32-111, *B*). Small intestinal intussusceptions demonstrate a characteristic appearance often described as a "target sign" or "bull's eye" created by a loop of bowel imaged within a second loop.[2,58,63] Extraluminal causes of small intestinal obstruction include compression from adjacent structures such as intraabdominal abscesses or masses or entrapment, which can occur secondary to adhesion formation, rents in the mesentery, extramural masses, or malposition of other abdominal organs.[64] Regardless of cause, small intestinal distention will be seen oral to the obstruction. Small intestinal thickening may also be seen oral to the obstruction owing to secondary hypertrophy. Fluid and feed contents may be seen flowing back and forth with little to no progressive motility. This movement should not be confused with normal peristalsis. Small intestine aboral to the obstruction may appear collapsed and hypomotile. Despite thorough evaluation of the ventral abdomen, the specific cause of ileus may be obscured by the presence of gas-filled bowel or may be too deep within the abdomen to be imaged.[2,58]

Cecum and Colon

NORMAL APPEARANCE. The cecum is normally imaged in the mid to dorsal portion of the right paralumbar fossa region adjacent to the body wall and demonstrates a smooth, curved appearance. Estimates of the diameter of the cecum vary depending on the amount of gas distention present at the time of examination and have been reported to range from 5.2 to 18 cm in normal cattle.[65] The proximal loop of the colon and spiral colon can be visualized dorsal to the cecum in the right paralumbar fossa region and the right twelfth intercostal space. The spiral colon has been described as demonstrating a "garland" appearance with segmental arched lines adjacent to one another.[2,65] Estimation of the diameter of the proximal loop of the colon also varies dependent on gas distention and has been reported to range from 3.1 to 15 cm. The diameter of the spiral colon is smaller, ranging from 2 to 4 cm. The proximal loop of the colon and spiral colon may be difficult to distinguish from gas-filled small intestine; however, the proximal loop and spiral colon seldom demonstrate visible motility or contractions.[65]

ABNORMAL FINDINGS. The diagnosis of cecal dilation is commonly made via rectal palpation but may be more challenging in cases in which dilation of the cecum is not palpable because of retroflexion.[66,67] In cows with cecal dilation, the cecum demonstrates a large radius of curvature and is seen to extend to the ventral portion of the right paralumbar fossa region and sometimes cranially into the right tenth to twelfth intercostal spaces. The proximal loop of the colon will also be dilated in and can be difficult to differentiate from the cecum. The liver may be displaced cranially in cows with severe cecal dilation. Torsion and retroflexion cannot be differentiated by ultrasonographic examination alone but may be diagnosed with a combination of rectal examination and ultrasonographic findings.[66]

Nongravid or Postpartum Uterus

Abnormalities of the uterus may be encountered during transabdominal ultrasound examination in ruminants and will be briefly addressed in the following sections. Evaluation of the gravid uterus and pregnancy diagnosis and monitoring are beyond the scope of this section.

NORMAL APPEARANCE. The normal nongravid uterus is seldom visualized during transabdominal ultrasound examination in ruminants. However, the involuting uterus may be encountered in females that have recently given birth.[68] Transrectal ultrasound is the method of choice to evaluate the bovine uterus.[69] However, abnormalities of the bovine and small ruminant uterus can be identified during transabdominal examination.

ABNORMAL FINDINGS. Abnormalities of the nongravid or postpartum uterus include metritis, pyometra, hydrometra, and uterine neoplasia. In ruminants with metritis or pyometra, the uterus is variably distended with fluid. This fluid may be relatively anechoic, echogenic, or hyperechoic depending on the nature of the debris and inflammatory material within the uterus[68-71] (Fig. 32-112, *A*). Hyperechoic gas echoes can be seen within the uterine fluid in cases of anaerobic or mixed infection. The uterine wall may also be thickened. Hydrometra, or pseudopregnancy, is most commonly reported in goats and is readily diagnosed via ultrasound.[68,72,73] The uterus appears distended with anechoic fluid in the absence of fetuses or placentomes. The dilated uterine horns may be curved or tortuous such that several cross-sections of the horn may be seen in any given scanning plane (see Fig. 32-112, *B*).[68] It should be mentioned that small pockets of fluid may be seen in the normal involuting bovine uterus for up to 4 weeks postpartum.[69,74]

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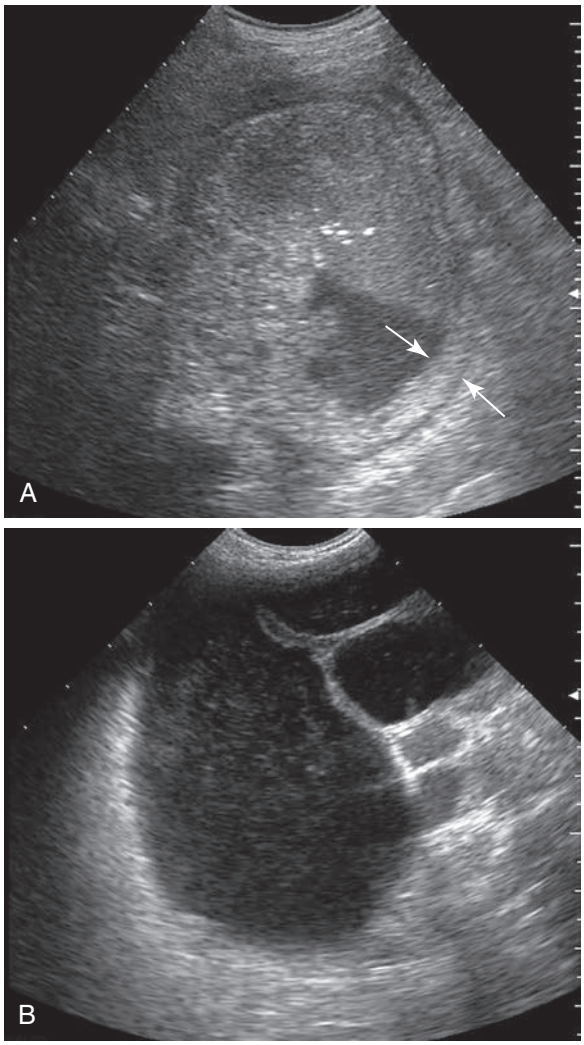


FIG. 32-112 **A,** Enlarged right uterine horn distended with echogenic fluid in a 5-year-old Holstein dairy cow with metritis. This cow had a history of aborting twins 4 days before presentation. Note the associated thickening of the uterine wall *(arrows)*. Image was obtained transabdominally in the right inguinal region with a 3.5-MHz curvilinear transducer at a depth of 18 cm. **B,** Enlarged uterine horn distended with relatively anechoic fluid in a 6-year-old Shetland ewe with hydrometra (pseudopregnancy). This ewe was reported to be 3 months pregnant. Image was obtained in the left flank region with a 7.5-MHz transducer at a depth of 9 cm.

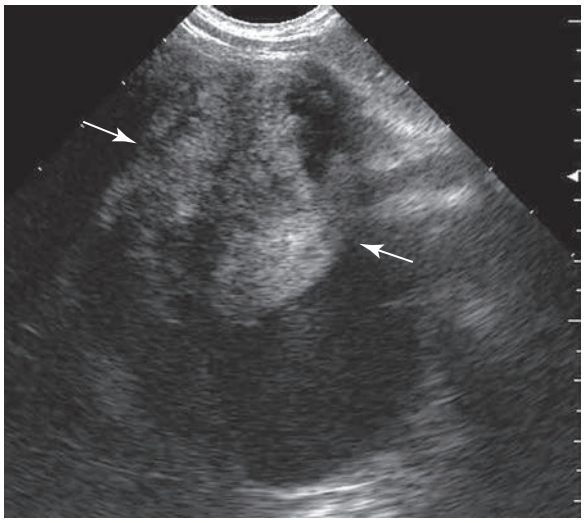


FIG. 32-113 Large uterine mass *(arrows)* viewed from the right ventral abdomen in an 11-year-old Pygmy doe diagnosed with uterine adenocarcinoma postmortem. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 10 cm.

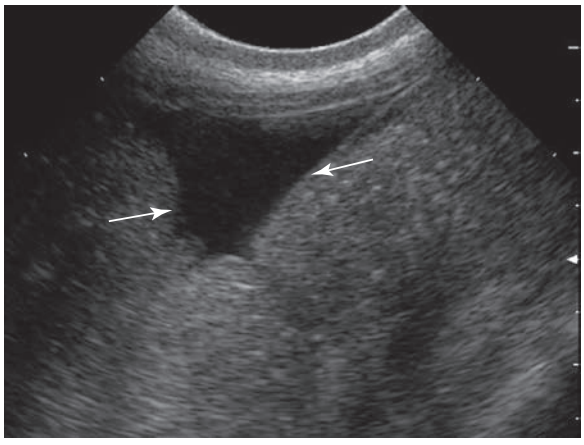


FIG. 32-114 Mild peritoneal effusion *(arrows)* seen between several loops of normal small intestine and the ventral body wall viewed from the right ventral abdomen in a 2-year-old Hampton cross ram. Image was obtained with an 8.5-MHz curvilinear transducer at a depth of 7 cm.

Uterine neoplasia is uncommonly reported in ruminants, but leiomyosarcomas, leiomyomas, carcinomas, chorionepitheliomas, fibrosarcomas, rhabdomyosarcomas, adenosarcomas, and multicentric lymphoma have been found.[75,76] Mass lesions visualized within the uterine wall or lumen are consistent with neoplasia. Masses may be single or multiple with variable echogenicity (Fig. 32-113). Diffuse infiltration of the uterine wall has been reported in cases of lymphoma.[75,76]

Peritoneal Cavity

NORMAL APPEARANCE. The peritoneal lining can be seen as a very thin, smooth hyperechoic line adjacent to the body wall. Minimal free abdominal fluid is seen within the peritoneal cavity. Retroperitoneal adipose tissue appears as a hypoechoic layer of varying thickness between the body wall and abdominal viscera and should not be misinterpreted as cellular peritoneal effusion. Adipose tissue may also be seen within the omentum and mesentery, demonstrating a similar appearance between or among the gastrointestinal viscera. This omental and mesenteric adipose tissue can often demonstrate an organized appearance with visible fine vasculature that can be mistaken for liver, especially in small ruminants.

ABNORMAL FINDINGS. Peritoneal fluid is readily identified on ultrasound as anechoic to echogenic fluid between the body wall and abdominal organs (Fig. 32-114). In cases of severe effusion, the abdominal organs and viscera appear to float within the free fluid. Fibrin deposits are commonly seen in ruminants with inflammatory peritoneal effusion and appear as linear strands extending between organs or between peritoneal surfaces and serosal surfaces of abdominal organs (Fig. 32-115).[1,47] Fibrin can also demonstrate a "shag carpet" appearance along the peritoneal and/or serosal surface. Localized peritonitis may also be seen and has been reported in cows secondary to left flank laparotomy.[47] Hemoabdomen appears as hypoechoic cellular-appearing fluid that swirls with ballottement, peristalsis, or respiration (Fig. 32-116).

Other abnormalities of the peritoneal cavity include mesenteric abscessation, mesenteric lymphadenopathy, fat necrosis, and neoplasia. Intraabdominal abscessation may be identified within the mesentery or associated with abdominal incisions. Abscesses are generally well encapsulated with anechoic to echogenic contents. Enlarged mesenteric lymph nodes can be seen within the small intestinal mesentery and are a nonspecific finding that has been seen by the author in cases of abdominal disease from numerous causes (Fig. 32-117).

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FIG. 32-115 Severe fibrinous peritonitis thought to be secondary to an intestinal rent viewed from the right paralumbar fossa region in a 3-year-old Holstein dairy cow. Note the hyperechoic fibrin strands creating a weblike appearance within the peritoneal cavity. Image was obtained with a 5.0-MHz curvilinear transducer at a depth of 27 cm.



FIG. 32-117 Enlarged mesenteric lymph node viewed from the left ventral abdomen in an 8-month-old Angora kid with disseminated *Rhodococcus equi* infection. Image was obtained with a 7.5-MHz curvilinear transducer at a depth of 5 cm.

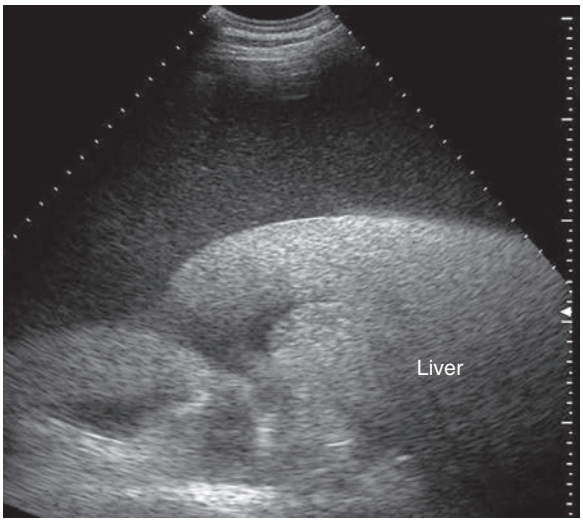


FIG. 32-116 Severe hemoabdomen viewed from the right cranioventral abdomen in a 2-year-old Shorthorn heifer with metastatic granulosa cell tumor. Note the very cellular appearance to the fluid within the peritoneal cavity. The liver is displaced from the body wall and appears to float in the effusion. Image was obtained with a 2.5-MHz curvilinear transducer at a depth of 27 cm.

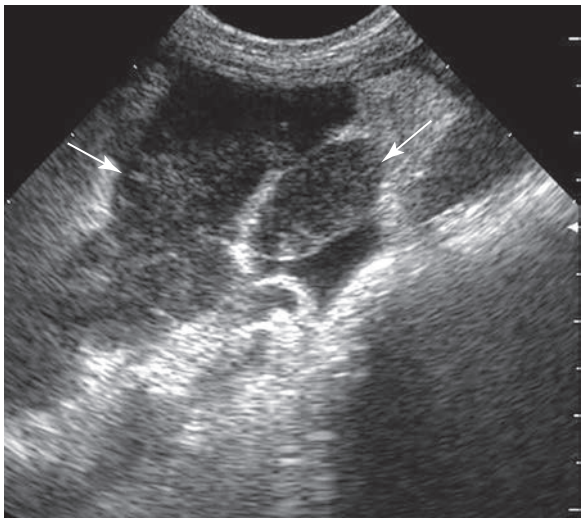


FIG. 32-118 Multiple peritoneal masses *(arrows)* between the rumen and body wall viewed from the left paralumbar fossa region in a 10-year-old Pygmy doe with mesothelioma. Image was obtained with an 8.5-MHz curvilinear transducer at a depth of 6 cm. Dorsal is to the right and ventral is to the left.

Hyperechoic masses surrounding the kidneys and small intestine or in the pancreatic and omental regions have been reported in cattle with abdominal fat necrosis.[77] Ruminants with neoplasia may demonstrate severe peritoneal effusion, most notably in cases of mesothelioma.[78,79] In cases of mesothelioma, multiple echogenic nodules are seen overlying the serosal surfaces of the peritoneum and abdominal organs (Fig. 32-118). Nodules can also be seen in the omentum.[78,79]

Indigestion in Ruminants

Franklyn Garry • Craig McConnel

Definition and Etiology

Indigestion is a general term for a group of diseases characterized by dysfunction of the reticulorumen. Some texts have limited the use of the term to a single, poorly defined entity that includes inappetence, decreased reticuloruminal motility, and abnormal feces, with a nonspecific cause that involves intake of abnormal feed.

The more generalized term applied here incorporates a pathophysiologic classification scheme of forestomach disturbances that has been devised by workers in Germany.[1] An absolute division of the pathologic processes is impossible because the various forestomach functions are interdependent; that is, abnormal motor function affects microbial fermentation by altered mixing or passage of ruminal fluid out of the forestomach chambers, whereas abnormal fermentation products secondarily alter motor function. Nevertheless, this classification provides a clinically useful diagnostic framework by emphasizing the underlying pathophysiologic mechanisms of different forestomach disturbances.

The primary indigestions include those diseases in which the reticulorumen is directly affected and responsible for the major

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BOX 32-5

Classification of Ruminant Indigestion

Primary Indigestions

Reticuloruminal Motor Disorders or Diseases of the Rumen Wall

Traumatic reticuloperitonitis (pp. 781, 805)
Frothy bloat (p. 810)
Free gas bloat (p. 780)
Reticulitis/rumenitis (p. 781)
Ruminal parakeratosis (p. 781)
Vagal indigestion (failure of omasal transport, failure of pyloric outflow, and free gas bloat) (p. 781)
Obstruction of the cardia (p. 784)
Obstruction of the reticuloomasal orifice (p. 784)
Diaphragmatic hernia (p. 784)

Reticuloruminal Fermentative (Microbial and Biochemical) Disorders

Inactivity of rumen microbial flora (caused by poor-quality roughage—rumen impaction) (p. 785)
Simple indigestion (p. 786)
Acute ruminal lactic acidosis (p. 786)
Subacute ruminal acidosis (p. 787)
Ruminal alkalosis (p. 788)
Putrefaction of ruminal ingesta (p. 788)

Secondary Indigestions (Secondary to Systemic Illness)

Secondary reticuloruminal motor inactivity (p. 779)
Secondary reticuloruminal microflora inactivity (p. 784)

disease signs (Box 32-5). These problems can be divided into two categories:

1. Abnormal motor function of the reticulorumen, including disease of the reticuloruminal wall, its innervation, or impedance to the passage of ingesta
2. Abnormal contents of the reticulorumen, with dysfunction of microbial and biochemical fermentation

Secondary indigestions are the sequelae of systemic problems or disease in other organ systems. For example, problems such as endotoxemia, fever, or depression can produce anorexia, secondary ruminal hypomotility, and decreased microbial fermentative function. Primary abomasal disease can depress ruminal function, inhibit ruminal outflow, and reflux abomasal contents back into the rumen.

With the exception of penetrating foreign bodies and sporadic infections of the forestomach wall (e.g., actinomycosis, mucormycosis), indigestions are physiologic abnormalities. In the adult ruminant one or more of the homeostatic processes of the fermentative environment are disturbed (e.g., an excessive carbohydrate intake generates an excessive amount of acid product; abnormal neural regulation of the ruminal motility pattern disturbs the mixing or aboral passage of ingesta). In the young ruminant the forestomachs are actively developing, and indigestions can result from disturbances of the developmental mechanisms. The forestomach diseases of young ruminants generally have received little attention, but they can be recognized and appropriately treated within a classification scheme similar to that for adult ruminants.[2]

Pathophysiology Digestion of feedstuffs in the reticulorumen is accomplished by microbial fermentation. The mucosal epithelium absorbs and exchanges products of fermentation but performs essentially no secretory function. Appropriate forestomach fermentation depends on the coordination of processes that provide a fairly constant reticuloruminal environment. The requirements include addition of appropriate amounts and types of feed substrate and water by ingestion; buffering of substances from the saliva to counteract the acid nature of fermentation products; eructation of the gaseous products of fermentation; coordination of reticuloruminal motility to provide mixing; rumination and remastication; aborad passage of ingesta; temperature maintenance; and exchanges of electrolytes and volatile fatty acids (VFAs) across the ruminal wall. Because these functions are intimately interrelated, abnormalities of any one of them can lead to digestive disturbances.

Disorders of Reticuloruminal Motor Function

Normal Motor Activity

The two reticuloruminal contraction sequences function independently. The primary cycle of contraction occurs approximately once a minute but more often during feeding and rumination. It consists of a biphasic contraction of the reticulum followed by a contraction that runs caudally across first the dorsal and then the ventral ruminal sacs. At the height of the second reticular contraction the omasal orifice relaxes and fluid, mostly composed of reticular ingesta, passes into the omasum. This reticuloruminal motility pattern directly influences ruminal fermentation by mechanically mixing the ingesta to provide contact with the microbes and to macerate the particulate matter. The mixing function prevents local accumulations of substrate or end products of fermentation, distributes the buffering saliva for neutralization of acids, and provides increased contact of the fluid with the ruminal wall to promote VFA absorption. The coordinated sequence of contraction of various parts of the ruminal wall maintains a stratification of fluid and particulate matter that selectively sorts the ingesta by particle size. The sorting function serves to retain large particles for further digestive breakdown while promoting passage of small particles (smaller than 6 mm) into the omasum and lower gastrointestinal tract.[3-5]

The secondary contraction cycle does not involve the reticulum. It begins in the caudal blind sacs, and a wave of contraction runs cranially across the dorsal rumen, pushing the gas cap into the cardia region. Eructation ensues, eliminating the gases generated by fermentation. Typically one secondary cycle contraction follows two primary cycles, so that three contractions occur every 2 minutes.[6] Two additional special contractions have been identified in sheep: primary-secondary contractions and prosecondary contractions.[7] These contractions appear when intraruminal pressure becomes elevated and function as secondary contractions by expelling ruminal gas. The primary-secondary and prosecondary contractions appear to help minimize free gas bloat when gas production is high.

Maintenance of the motility patterns requires well-coordinated neural control. The pathophysiologic mechanism of the first group of primary indigestions (i.e., diseases of the reticuloruminal motor function) involves disturbance of the mechanisms of normal ruminal motility, which secondarily affects ruminal fermentation.

The ruminal contraction sequences described rely almost completely on motor nerve activation arising from the medulla oblongata, in contrast to the intrinsic segmental and peristaltic movements of the intestine. Gastric centers in the medulla integrate sensory input and generate motor impulses, both of which are carried in the vagus nerves. The gastric centers have neither spontaneous activity nor an inherent rhythm. Generation of motor impulses relies on a greater excitatory than inhibitory input from the sensory nerves to determine the rate, magnitude, and duration of primary cycle contractions. During the quiescent period between the primary contractions, while the medulla collects the sensory information, there are no tonic vagal motor impulses.[8,9]

The splanchnic nerves also affect reticuloruminal motility by direct innervation and by neurohumoral effects of adrenal secretion. These nerves are not required for generation of normal contractions. The effect of splanchnic stimulation is inhibition of reticuloruminal motility. Splanchnic sensory nerves innervate sensory receptors in other areas of the gastrointestinal system, and some abnormalities such as intestinal distention or surgical manipulation produce reticuloruminal inhibition by means of reflex from splanchnic afferent activity.[9]

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Primary Cycle Activity

A decrease or absence of normal primary cycle activity (i.e., ruminal hypomotility or stasis) implies either a decrease of vagal motor discharges originating from the gastric centers or an ineffective motor response after motor impulse, as in cases of hypocalcemia. Causes of decreased motor discharges can include the following:

1. Decreased excitatory input to the gastric centers
2. Increased inhibitory input to the gastric centers
3. Depression of the gastric centers
4. Defective vagal transmission of motor impulses
5. Other factors

DECREASED EXCITATORY INPUT. The three most important excitatory inputs to the gastric centers are from (1) low-threshold tension receptors in the reticulum, (2) buccal receptors in the mouth, and (3) acid receptors in the abomasum (Table 32-12). The tension receptors are located in the musculature of the medial wall of the reticulum. They are stimulated by mild distention during the resting phase and thereby influence contraction frequency. They are further stimulated by the tension generated during contraction and thus increase amplitude and duration of the primary cycle contraction. This mechanism is probably responsible for the increased motility seen after feeding or during incipient bloat. Any cause of anorexia leading to decreased ruminal fill decreases this excitatory input, leading to ruminal hypomotility. Feeding mechanically stimulates buccal sensory receptors, providing a potent stimulus to both primary and secondary contraction cycles. This reflex can double the rate of primary contractions but is short-lived and declines as soon as chewing activity ceases. Thus anorexia effectively eliminates this potent excitatory input. Abomasal acidity increases as the abomasum empties and this too provides excitatory input to the gastric centers. The resultant increased reticuloruminal motility leads to increased flow of ingesta to the abomasum, diluting the abomasal acid and maintaining normal filling of the abomasum. Certain types of abomasal disease diminish this stimulus to forestomach motility.[8-10]

Less well-defined stimuli of reticuloruminal motility include the physical and chemical characteristics of the ruminal ingesta. Fiber and water content, as well as the normal chemical products of fermentation, are important for normal ruminal contraction. The exact mechanisms through which these factors enhance ruminal motility have not yet been clearly defined,[11] but low levels of any of these ingesta characteristics impair normal function, causing decreases of both rumination and primary cycle activity. That these excitatory stimuli are decreased or absent under some feeding regimens and with some of the diseases attributable to abnormal fermentation may account for the impression of hypomotility observed clinically.[12]

INCREASED INHIBITORY INPUT. Inhibitory inputs to the gastric center arise from (1) high-threshold tension receptors in the reticulum and cranial ruminal sac, (2) tension receptors in the abomasum, (3) epithelial receptors that detect high concentrations of nondissociated VFAs in the rumen, and (4) pain elicited at any site in the body (see Table 32-12). The high-threshold tension receptors are sensory nerve endings below the epithelial basement membrane of the reticulum and cranial ruminal sac. They respond to extreme distention of the wall and serve to modify the end stage of reticuloruminal contraction. With severe bloat or gross ruminal distention from other causes such as overfilling with indigestible fibrous roughage, they can be continuously activated producing ruminal stasis. Abomasal distention can inhibit primary ruminal contraction cycles presumably through tension receptors in the abomasal wall.[13] In normal circumstances this activity would serve to decrease the flow of ingesta to the abomasum when it is full. With abomasal displacement or impaction, this reflex may partly account for the observed ruminal hypomotility. Epithelial receptors in the reticulum and cranial ruminal sac are sensitive to increased concentrations of nondissociated VFAs. Inhibition of forestomach contractions occurs when conditions of excessive fermentation or acidosis increase the concentrations of these substances. Pain can reduce forestomach motility by increasing sympathetic nervous and adrenal secretory activity and by inhibiting the gastric centers. Although painful stimuli in the abdominal viscera are particularly potent, pain from anywhere in the body can inhibit or abolish reticuloruminal motility.[8-10]

DEPRESSION OF THE GASTRIC CENTERS. Depression of the gastric centers reduces vagal motor activation of forestomach motility and can be induced by central nervous system depressant drugs and anesthetics. Endotoxemia, fever, and possibly blood pH and electrolyte abnormalities can induce ruminal hypomotility or stasis through central effects on the gastric centers. These factors may also inhibit ruminal motility by increasing sympathetic nervous activity. In addition, some toxins or other abnormal fermentation products reduce ruminal motility. These substances may act locally at the ruminal epithelial receptors to generate inhibitory impulses, as do increased VFA concentrations, or they may act centrally after absorption into the blood. For the most part the nature of the substances capable of chemically suppressing ruminal function is unknown,

TABLE 32-12

Factors Influencing Vagal Motor Discharge from the Gastric Centers of the Medulla*

Input	Location	Stimulus
Excitation of the Gastric Centers (Causes Increased Rumen Motility)		
Low-threshold tension receptors	Reticulum, medial wall	Mild distention; tension generated during contractions
Buccal receptors	Mouth	Feeding (only during chewing)
Acid receptors	Abomasum	Increased acidity as abomasum empties
Tension receptors†	Medial wall of cranial rumen sac	Increased rumen gas pressure
Inhibition of the Gastric Centers (Causes Decreased Rumen Motility)		
High-threshold tension receptors	Reticulum and cranial rumen sac	Bloat or other severe ruminal distention
Tension receptors	Abomasum	Abomasal distention
Chemical receptors	Reticulum, rumen	Increased concentration of undissociated volatile fatty acid with rumen acidosis; also locally activated by some toxins
Pain receptors in body increase sympathetic tone and adrenal secretory activity	Anywhere in body; can act directly and through medullary gastric centers	Pain, especially abdominal
Gastric centers	Medulla	Anesthesia, depressant drugs, toxins, endotoxins, fever, acidosis
Hypocalcemia	Reticuloruminal smooth muscle	Hypocalcemia

*There is no inherent reticuloruminal motility such as that found in the intestines.

†Secondary cycle activity; independent of primary cycle activity.

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TABLE 32-13

Causes of Rumen Tympany (Bloat)

Mechanism	Cause	Disease Examples
Obstruction of eructations	Esophageal obstruction	Choke, tetanus, thoracic inflammation or neoplasia with swollen mediastinal lymph nodes
	Cardia obstruction	Papilloma, fibroma, actinobacillosis
	Failure to clear cardia of fluid or ingesta	Lateral recumbency, reticulorumen overfilled with ingesta (as in vagal indigestion, ruminal microbial inactivity with poorly digestible roughage, obstruction of the reticuloomasal orifice)
Ruminal motor dysfunction	Gas trapped in stable foam	Frothy bloat
	Failure of smooth muscle contraction	Hypocalcemia
	Weakened muscle contraction	Chronic ruminal distention with indigestible roughage, outflow obstruction, or vagal indigestion; hypokalemia
	Abomasal distention	Displaced abomasum (especially in calves)
Chemical inhibition	Vagus nerve damage	Thoracic inflammation (especially in calves, neoplasia)
	Ruminal stasis	Rumen acidosis, rumen alkalosis, abnormal fermentation products with simple indigestion

but abnormal fermentation end products are the likely cause of ruminal stasis in indigestion associated with abnormal ruminal contents.[3,8,12,14]

DEFECTIVE VAGAL INNERVATION. Failure of vagal nerve transmission of motor impulses has been implicated as the cause of a reticuloruminal contraction abnormality that leads to failure of aborad flow of ingesta (hence the name vagal indigestion). The left and right vagi in the thorax divide into dorsal and ventral branches that unite to form dorsal and ventral vagi as the nerves enter the abdomen. The ventral vagus innervates the cranial and medial parts of the reticulum, the omasum, and the abomasum. The dorsal vagus innervates the rumen and parts of the other segments of the ruminant stomach. Sectioning of more than 50% of the vagal nerve trunks leads to impaired motility function, but most cases of vagal indigestion show much less nerve involvement. The importance of vagal nerve lesions in the pathogenesis of forestomach disease has been a subject of considerable debate and is discussed more fully later in this chapter.[8]

OTHER FACTORS THAT AFFECT THE PRIMARY CYCLES. Other influences on forestomach motility have been identified. Hypocalcemia inhibits motility by preventing contraction of the musculature after motor nerve discharge. This may explain the reduced ruminal motility seen in early cases of milk fever.[15] Low environmental temperatures[16,17] and milking[18] have been shown to increase ruminal motility mildly, whereas some drugs,[19-21] hyperglycemia,[22] and gastric hormones[23] are effective in decreasing reticuloruminal primary cycle contractions. These factors are not discussed further in this text.

Secondary Cycle Activity

The secondary cycle activity responsible for eructation is elicited independently of the primary cycles. An increase in ruminal gas pressure excites tension receptors in the medial wall of the cranial ruminal sac. This triggers relaxation of the cardia and eructation of the gas accumulated in the cardia region by the secondary contraction cycle. Receptors that apparently distinguish gas from fluid or solid matter inhibit opening of the cardia if it is covered by material other than gas. This reflex inhibition of cardia opening is responsible for bloat in cases in which abnormal ingesta cover the area, such as in recumbent animals, in frothy bloat, and when abnormal motility or overfilling of the rumen precludes clearing of the cardia. Under such circumstances and when ruminal distention is not yet extreme, both primary and secondary cycle contractions may increase in frequency. In other forms of bloat, hypomotility is a prominent feature, and the gas accumulates as a result of the poor motility function. This is the most probable cause of bloat in some of the disturbances of fermentative function.

Gross overdistention of the ruminal wall may inhibit motility by stretching the musculature beyond its ability to contract forcefully. If the process leading to the distention develops slowly, the high-tension receptor inhibition of motility appears to adapt, and complete inhibition of motor impulses does not seem to occur. Rather, in these cases motility is present but weak and relatively ineffective. This motility disturbance is likely when poorly digestible roughage accumulates in the forestomach. Patients with this condition often have mild to moderate chronic free gas bloat, which may result from poor ability of the weakened rumen to clear the cardia and dispel the gas.[1]

Free Gas Bloat

Accumulation of free gas in the dorsal rumen should not be considered a primary disease entity but rather a sign of disease (Table 32-13). However, because free gas bloat often is the most prominent sign and because it accompanies several different forms of indigestion, its pathogenesis is reviewed briefly here.

Ruminal microbial fermentation and neutralization of salivary bicarbonate continually produce gas as an end product (primarily methane and carbon dioxide) in proportion to the rate of fermentation. Normally the ruminant can eructate volumes of gas that exceed the amount produced even at maximum rates of fermentation.[24] Thus an excessive production of gas is not the cause of bloat. Bloat develops either because the evacuation of gas is hindered by a physical obstruction or because the mechanisms that expel the gas are inhibited.[25]

As in choke, physical obstruction of the esophagus by a foreign body can produce dramatic and peracute bloat. Other forms of esophageal occlusion (which may additionally involve inflammation of nerves or ruminal muscle malfunction) include muscular spasm (e.g., tetanus), swollen mediastinal lymph nodes (e.g., chronic pneumonia, thymic lymphosarcoma), and tumorous or inflammatory swellings of the cardia region (e.g., papilloma, actinomycosis). These problems tend to show bloat of a slowly progressive or chronic nature, although the degree of bloat may be marked.

Bloat is a common feature of indigestions caused by microbial fermentative disorders. When ruminal hypomotility occurs, the fermentative rate may decline, but weak ruminal contractions may be inadequate to move the gas layer and to clear the cardia preparatory to eructation. Thus dietary, microbial, or metabolic factors that affect the excitability of the gastric centers or the reticulorumen can result in bloat. Ruminal stasis can result in bloat because eructation occurs only with ruminal contraction. Bloat also accompanies indigestions that produce gross distention of the reticulorumen with fluid or solid ingesta (i.e., vagal indigestion, ruminal acidosis, and microfloral inactivity caused by indigestible roughage). The cause of bloat in these cases may be a combination of ruminal stasis, weakening of

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the ruminal wall caused by the gross distention, and failure to clear the cardia.

As is the case in adult cattle, it appears that free gas bloat in calves has numerous causes, including fermentative indigestions, ruminal wall disturbances, and esophageal involvement in an intrathoracic inflammatory process.[26,27] Chronic bloat in calves has also been attributed to a form of vagal nerve damage resulting from mediastinal inflammation. Distinguishing between vagal nerve impairment and esophageal compression or inflammation as the cause of free gas bloat requires a thorough assessment of ruminal motor function, as described under the section on clinical signs.

Reticulitis and Rumenitis

The most important inflammatory problem is reticuloperitonitis caused by sharp foreign body punctures (traumatic reticuloperitonitis [TRP], hardware disease); this disease is discussed elsewhere in Chapter 32. The localized infection established by reticuloruminal perforation causes inflammation of the forestomach wall and adjacent peritoneal cavity and pain in the anterior abdomen, inhibiting forestomach motility, appetite, and aborad flow of ingesta. Other causes of ruminal wall inflammation can cause acute or chronic forestomach dysfunction.

Most infections of the ruminal wall follow primary mechanical or chemical damage to the mucosa. The secondary invaders colonize the damaged areas and may gain access to the circulation and invade other tissues as well. The ruminal wall may be the niche for some of these microorganisms, and isolates from the ruminal wall have been matched with those isolated from liver abscesses.[28] Probably the most common cause of the initial mucosal injury is acute ruminal acidosis produced by grain engorgement. Chemical damage resulting in ruminal ulcers also occurs in oak or acorn toxicosis and with ingestion of caustic chemicals. Common secondary ulcer invaders include *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Fusobacterium necrophorum,* and several mycotic species.[28,29] Mycotic rumenitis can follow ruminal acidosis and septic diseases, especially after the use of oral antibiotics. It also can occur after feeding spoiled and moldy feeds and without apparent predisposing causes.[30,31] Diseases that cause anorexia plus abomasal reflux of gastric acids may predispose an animal to mycotic rumenitis and omasitis. Mycotic rumenitis can be severe, with vascular thrombosis and infarction and mural necrosis and gangrene sufficient to cause death. Less frequently occurring specific infections of the ruminal wall include actinobacillosis, actinomycosis, and tuberculosis. These infectious inflammatory diseases of the ruminal wall may be distributed widely throughout the forestomach, depending on the initial site of mucosal injury, but they tend to localize in the ventral regions of the reticulorumen. The granulomatous inflammatory lesions of actinobacillosis and actinomycosis are most commonly found in the cranial forestomach in the area of the esophageal groove.

Neoplastic growths in the rumen have also been identified. These uncommon lesions include papillomas, myxomas, fibromas, carcinomas, and lymphosarcomas.[32] These lesions are most commonly localized in the reticulum and cranial rumen near the cardia and esophageal groove.

The importance of these inflammatory reticuloruminal lesions depends on their extent and location. Acute and extensive lesions have been associated with signs similar to those of reticuloperitonitis caused by foreign body puncture, including pain, inappetence, impaired forestomach function, and in some cases death. The more chronic cases may cause forestomach motility disturbances and signs of vagal indigestion. Pedunculated masses especially, but not exclusively, may obstruct the cardia or reticuloomasal orifice and lead to bloat or reticuloruminal outflow disturbance.

Reticuloruminal inflammation can also result from certain generalized infections. These include bovine virus diarrhea, foot-and-mouth disease, malignant catarrhal fever, and rinderpest. In these cases the forestomach problems are unlikely to be the most important clinical manifestation.

Ruminal Parakeratosis

In parakeratosis the papillae are darkly colored, enlarged, thickened, and clumped together. Histologic changes of the epithelial cells include a thickened, cornified layer with abnormal retention of nuclei in the cornified cells. These morphologic changes appear to represent a reaction to persistently high concentrations of volatile fatty acids. The changes occur predominantly in animals on pelleted or very finely ground rations, especially when the ration contains a high amount of energy. These rations tend to increase the proportions of propionate and butyrate, reduce the proportion of acetate generated by microbial fermentation, and produce a lowered ruminal fluid pH. The growth of the ruminal papillae is promoted by contact with the VFAs, especially butyrate, and secondarily propionate.[3] It appears that a disproportion of the concentrations of these VFAs may be the cause of an excessive change in the epithelium of the papillae.[33-35] Initial changes in the epithelium under these conditions appear to increase the absorption of the volatile fatty acids, but in severe cases the absorption decreases. This disease of the ruminal wall is not usually diagnosed as a primary problem. Although it may lead to impaired performance of the animal, the disease signs that lead to its discovery are usually those of chronic acidosis, a disease with which it often coexists. Parakeratosis can predispose to other injuries of the ruminal wall, however, because the abnormal papillae are more easily traumatized, leading to chronic inflammatory disease of the wall as discussed previously. In calves the problem is also associated with the development of hairballs (trichobezoars) because of the propensity of calves on the rations associated with parakeratosis to lick their hair coat.[35]

Vagal Indigestion

Vagal indigestion syndrome (vagus indigestion, Hoflund syndrome) comprises a group of motor disturbances that hinder passage of ingesta from the reticulorumen or abomasum or both. The pathogenesis of the disease has been debated for years and has yet to be completely clarified because many investigations have yielded conflicting information.[36-43]

The name *vagus indigestion* was introduced by Hoflund, who experimentally produced motor defects and disease signs similar to those seen in clinical cases by transecting various branches of the abdominal vagal nerve.[37] On the basis of his experimental results, he defined four types of functional disturbance, with obstruction of ingesta flow at two sites:

1. *Omasal transport failure* (anterior or proximal functional stenosis, reticuloomasal stenosis) impairs flow of ingesta through the reticuloomasal orifice and occurs with (a) atony of the reticulorumen (often associated with chronic recurrent bloat) or (b) normal to increased ruminal motility.
2. *Pyloric outflow failure* (posterior or distal functional stenosis, pyloric stenosis) impairs flow through the pylorus and occurs (a) continuously or (b) in an intermittent, recurrent pattern (incompletely).

Hoflund's description of the syndrome is convenient for explaining the observed functional defects, but its presumed pathogenesis is not supported by the findings of later investigators.[36] The use of the term *stenosis* has also led to some confusion, although it was appropriate in its original context. The term *functional stenosis* suggested that the defect was a functional one that mimicked a stenosis at the site of outflow. However, vagal denervation does not produce a true stenosis, but rather a paralysis and relaxation of either the reticuloomasal orifice or the pylorus. The paralysis can be appreciated in both experimental and clinical cases.

FAILURE OF OMASAL TRANSPORT. Failure of omasal transport with hypermotility of the rumen is the most common naturally occurring form of the disease. Accumulation of ingesta in the reticulorumen leads to gradually progressive distention of the forestomachs, whereas the omasum and abomasum remain relatively empty. The animal's appetite diminishes as the rumen becomes overfilled,

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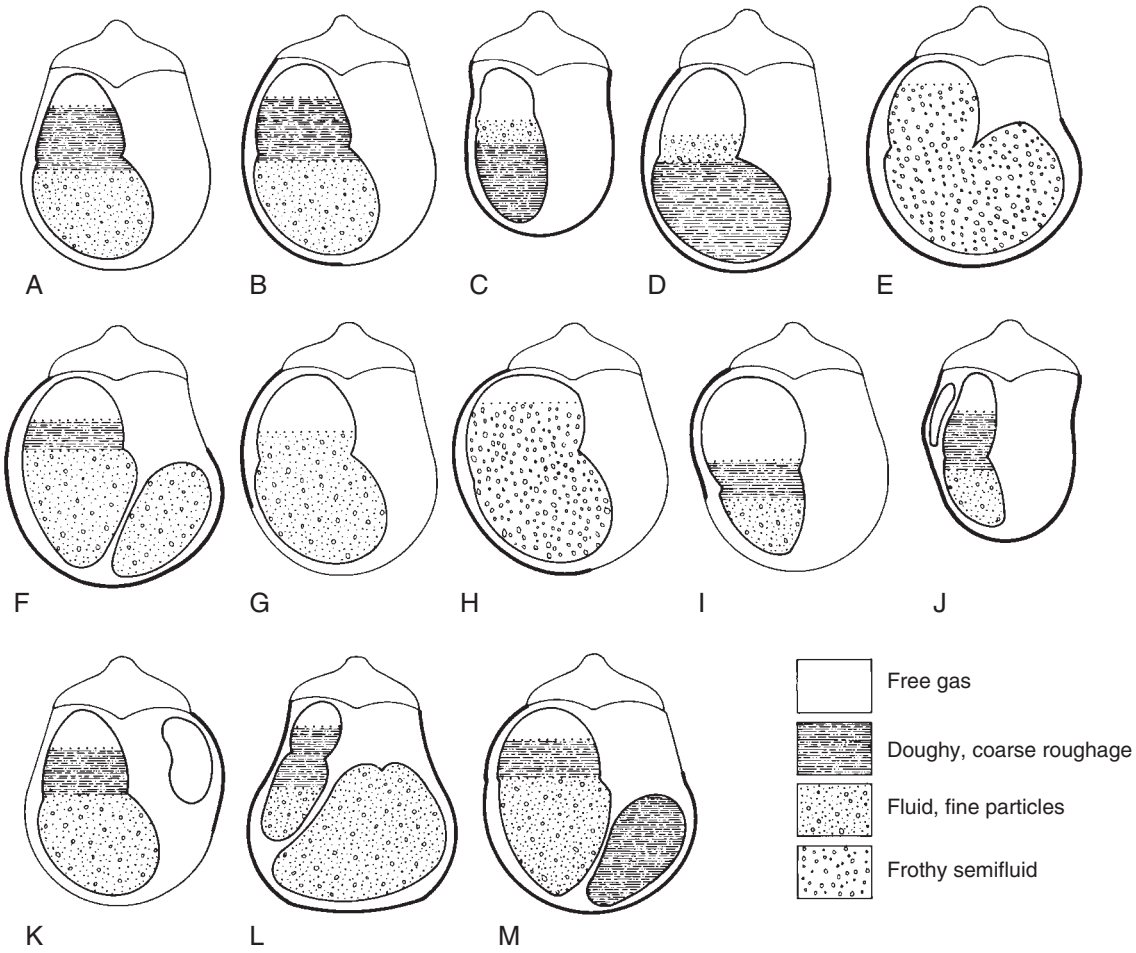


FIG. 32-119 Abdominal contours (viewed from the rear) and abdominal palpation findings characteristic of cattle with various types of indigestion and other abdominal diseases. A thin line for the abdominal contour indicates the normal configuration. Bold lines indicate areas of the abdominal contour that typically deviate from normal in affected animals. **A,** Normal. **B,** Acute onset of rumen stasis with simple indigestion, traumatic reticuloperitonitis (findings: mild ruminal distention with normal layering of rumen content). **C,** Prolonged rumen stasis, anorexia. The most common result of subacute or chronic disorders such as microbial or fermentative indigestions, traumatic reticuloperitonitis, and secondary indigestions (findings: reduced rumen fill, "tucked-up abdomen," firm, doughy contents that gravitate ventrally). **D,** Rumen inactivity with indigestible roughage (findings: rumen distended with firm, doughy contents that accumulate ventrally; recurrent free gas bloat often present). **E,** Omasal transport failure (findings: L-shaped rumen with gross accumulation of frothy ingesta; rumen hypermotility often present; free gas accumulation varies). **F,** Pyloric outflow failure (findings: fluid accumulation in abomasum; abomasal reflux to rumen common; doughy rumen content that usually accumulates dorsally until rumen stasis or anorexia is prolonged; abdominal contour similar to that for omasal transport failure). **G,** Acute rumen acidosis (findings: rumen distended with fluid; some free gas bloat common). **H,** Frothy bloat. **I,** Free gas bloat or chronic free gas bloat (findings: accumulation of gas in dorsal sac; layering or rumen contents usually normal; with chronicity, rumen fill often decreased; associated with some microbial or fermentative disorders and with esophageal and cardiac disorders). **J,** Left displaced abomasum (findings: gas-filled abomasum that often causes slight bulge of paralumbar fossa; rumen fill usually reduced). **K,** Right displaced abomasum, abomasal volvulus, cecal torsion (findings: distention of right flank with gas-filled viscus; rumen fill and consistency usually normal). **L,** Hydrops (findings: ventral abdomen distended with fluid-filled uterus: rumen fill usually decreased). **M,** Abomasal impaction (findings: abdominal contour similar to **E** and **F;** abomasum filled with firm ingesta).

producing one of the most characteristic signs of the disease: inappetence with gross distention of the rumen in the left flank. Continued dilation of the rumen eventually leads to a marked and almost pathognomonic overfilling of the ventral ruminal sac. The rumen assumes an L shape because the ventral sac occupies both the right and left ventral quadrants of the abdomen. The resultant characteristic abdominal contour often is called a "papple" shape (Fig. 32-119, E) because the left side of the abdomen is distended and assumes the appearance of an apple, whereas the right side assumes the contour of a pear. The diminished passage of ingesta passage results in reduced fecal volume. The normal ruminal process of selective retention of fibrous material is disturbed, leading to large particle passage and feces with increased fiber length and a greasy or pasty consistency. Some cases show firm feces with large particle size.[38,39] Affected animals often continue to drink water, but absorption from the rumen is poor, and the water accumulates in the forestomach while the animal becomes mildly dehydrated. Vigorous contractions of the rumen can be palpated in the left paralumbar fossa in most affected animals, although some display almost complete atony. The contraction pattern does not produce the typical stratification of material in the forestomach, but rather it churns the ruminal contents into a uniform frothy fluid.[39,41]

The signs just described, with abnormal flow of ingesta and normal or increased forestomach contractions, can be experimentally reproduced by sectioning the ventral vagal trunk at the cardia and the dorsal trunk just distal to the branching of the ruminal nerves.[37] The forestomach distention, empty omasum and abomasum, and stasis of the forestomach with resultant free gas bloat can be reproduced by sectioning both abdominal vagal trunks along the esophagus. The paralysis produced by vagal denervation can explain the failure of ingesta flow into the omasum by two mechanisms. First, the lower end of the esophageal groove is formed by two muscular lips. These overlap in a manner that allows a passive valve effect that blocks flow into the omasum when they are relaxed or paralyzed. Second, it appears that the flow into the omasum is accomplished by an active pumping motion of the omasum that reduces pressure and draws fluid through the reticuloomasal orifice. Paralysis of the omasal musculature after denervation would eliminate this effect.

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Decreased reticular motility caused by adhesion or paralysis may contribute to the changes in ruminal content and the alteration in particle passage.[39,41]

The most common predisposing cause of naturally occurring omasal transport failure (anterior or proximal functional stenosis) is TRP. Other causes of anterior functional stenosis include abscesses, adhesions, and peritonitis at the reticulum (especially the right side of the reticulum) or reticuloomasal area without identification of an offending foreign body; hepatic abscesses; diffuse peritonitis; neoplasia of the ruminoreticular fold and esophageal groove; inflammatory disease of the reticular and ruminal walls; papilloma or other mass at the reticuloomasal orifice; or herniation of the reticulum through a diaphragmatic defect. Foreign bodies that obstruct the reticuloomasal orifice cause a syndrome indistinguishable from vagal indigestion except by exploratory rumenotomy.[32] To reconcile the experimental findings with those from clinical cases, the development of omasal transport failure has been explained as involvement of the vagal trunks in the inflammatory process at the reticulum. Several findings make this an unlikely explanation in most clinical cases[8,36]:

1. Although sectioning the vagus nerves as described reproduces the syndrome, disturbing only one of the two trunks still allows normal cyclic contractions in most cases. For a clinical lesion to produce disease development, massive involvement of the vagal nerves would be required. By contrast, less than a third of examined cases reported show actual lesions in the nerve branches.
2. The ratio of sensory to motor nerve fibers in the abdominal vagi is approximately 9:1, suggesting the important sensory role of the nerve.
3. Inflammatory lesions of the reticuloruminal wall reported in cases of vagal indigestion are predominantly in the same areas as the important tension receptors that send afferent excitatory impulses to the gastric centers. Induration of the right (medial) wall of the reticulum and in the esophageal groove region may affect intramural nerves and ganglia and reduce the tension receptor activity and therefore the drive for primary cycle activity.

These considerations allow an explanation of some of the inconsistencies found in various cases. Anterior functional stenosis may occur with insufficient vagal sensory excitation, which in turn reduces excitatory input to the gastric centers, diminishes primary cycle motor drive, and results in paralysis of the omasum and reticuloomasal orifice. Alternatively, substantial reticular adhesions that develop after TRP could prevent normal delivery of small particle ingest, with fluid consistency, to the reticuloomasal orifice.[41] Because this reduces or abolishes flow into the omasum, both the omasum and abomasum would remain relatively empty, a common finding in these cases. The hypermotility observed in these cases may be the result of secondary rather than primary cycle contractions.[43] Distention of the cranial ruminal sac would still be able to induce the secondary contractions if this region is not involved in the induration. Without normal primary cycle activity, the typical stratification of the ingesta would be disturbed, as is usually observed. The existence of hypermotile secondary contractions with absence or severe reduction of primary contractions can be detected clinically. Damage to the thoracic or abdominal vagi by inflammatory or neoplastic lesions may lead to the occasional cases that show both anterior functional stenosis and atony of the forestomachs, with resultant free gas bloat. This would be similar to the experimental sectioning of both vagal trunks.

Pyloric Outflow Failure. Failure of pyloric outflow (posterior or distal functional stenosis) causes accumulation of ingesta in the abomasum and omasum. Advanced stages of this form of the syndrome also display gross distention of the reticulorumen. Generally the motility of the forestomach is not markedly affected in the early stages, and normal stratification of ingesta is maintained. Overfilling of the forestomach as a result of reflux of ingesta from the abomasum (internal vomiting) may occur, causing the chloride content of the ruminal fluid to increase (normal is less than 30 mEq/L). In contrast, the ruminal fluid of animals with anterior functional stenosis has a normal chloride content.[38,41] With severe distention forestomach motility is reduced, and the ruminal contents become more fluid.[43] Failure of ingesta to flow into the intestinal tract, combined with sequestration of chloride-rich fluid in the stomach chambers, can cause both marked dehydration and hypochloremic metabolic alkalosis. However, in cases with a gradual, prolonged development such as in anterior stenosis, any dehydration tends to be mild and body fluid electrolyte concentrations do not show remarkable abnormalities. Fecal production in these cases tends to be even less than with the anterior stenosis form of the syndrome.[41]

Failure of pyloric outflow can be experimentally reproduced by sectioning the ventral vagus trunk at the cardia and the continuation of the dorsal trunk as it crosses the omasum.[37] This mimics the usual clinical form of the disease, which is characterized by complete inhibition of flow from the abomasum. Combinations of more distal resections of the nerves produce the syndrome of recurrent atony of the abomasum as it occurs in natural clinical cases. Again, the term stenosis is a misnomer, because a true stenosis or spasm of the pylorus is not identified. Rather, the experimental vagal nerve resection and the naturally occurring cases show a flaccid paralysis, and ingesta accumulates as a result of failure of propulsive activity. The dilation of the abomasum is in the fundus and body and not in the pyloric part.[37]

A common predisposing cause of pyloric outflow failure syndrome is volvulus of the abomasum. Other abomasal disturbances, including right and left displacements of the abomasum and abomasal ulceration, can cause the disease as well. After surgical correction of a volvulus, the abomasum remains atonic, and the disease may develop within several days. Clinical signs compatible with vagal indigestion may arise from gross distention and twisting of the abomasum and lesser omentum resulting in potentially coexisting but distinct injury to the vagal nerves or structural damage to the gastric wall, with or without peritonitis. Although focally extensive vagal nerve lesions have been associated with concomitant vascular damage, indicating that even with nerve regeneration there may not be a return to normal function, the damage appears reparable in some cases as a return to normal function has been observed.[40]

Inflammation and adhesions involving the abomasal fundus and reticulum have been associated with posterior functional stenosis in some studies.[41] Inflammation of the reticular wall may account for the reticular atony reported in some cases. This form of vagal indigestion may be more frequently associated with true vagal nerve impairment than appears to be the case in anterior functional stenosis. Alternatively, reticular adhesions may prevent normal motility, alter the flow of ingesta to the omasum and abomasum, and lead to abnormal filling of the abomasum because of decreased fluidity of abomasal contents.[41]

Another predisposing cause of pyloric outflow failure is advanced pregnancy with a large fetus. An exact pathogenesis has not been clearly defined. Presumably the large, gravid uterus distorts the positioning of the abomasum or physically compresses and obstructs the anterior small bowel, preventing outflow of ingesta from the abomasum. In these patients the gravid horn typically occupies most of the space in the omental sling. In support of these conclusions, the problem can be resolved by inducing delivery of the calf or performing a cesarean section. Supportive care may be required for severely affected cows, but the gastrointestinal system returns to normal function, suggesting that it was secondarily affected by the pregnancy. This problem is referred to as a form of vagal indigestion because it appears as a pyloric outflow failure. Some patients have such severe obstruction of ingesta passage that they may be diagnosed as having an anterior bowel obstruction. This disease has been called *indigestion of late pregnancy*.

Animals affected with any form of vagal indigestion for a prolonged time lose body condition because the failure to pass ingesta into the intestinal tract produces a state of starvation. The weight loss may be overlooked because of the impression of full body size produced by the abdominal distention.

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CHRONIC RECURRENT BLOAT. Chronic recurrent bloat is commonly identified with vagal indigestion in any of its forms. It is mild to moderate in severity, commonly waxes and wanes, and adds to the visual impression of gross abdominal distention. The pathogenesis of this ruminal tympany varies from case to case. Experimental resection of both abdominal vagal trunks stops eructation by causing complete forestomach stasis. In naturally occurring cases in which lesions of the vagal nerve truly inhibit motor impulse transmission, bloat may arise from this mechanism. When vagal nerve damage does not appear to be involved, other mechanisms may explain the bloat (see Table 32-13). Overfilling of the reticulorumen with frothy ingesta, a common finding, can inhibit the cardia dilation reflex that is a prerequisite of eructation. Gross distention of the forestomach can also weaken the contractile ability of the rumen, so that the contractions are not strong enough to clear the cardia before eructation.

Bradycardia is often identified in association with vagal indigestion but can also occur with other forestomach diseases. The finding that atropine administration can abolish the bradycardia of vagal indigestion suggests increased cardiac vagal tone as the direct cause. However, the origin of the vagotonia is unclear. When vagal nerve lesions exist distal to the cardiac innervation, reflex excitatory discharges may effect bradycardia. Experimental resection of the vagal nerves causes bradycardia as a striking feature in most cases, although advanced cases show increased heart rates. By contrast, naturally occurring vagal indigestion shows bradycardia as a feature in only a third or fewer of the cases.[38] These variations may exist because the experimental and natural cases have different causes or because the disease varies in duration. Once the forestomach has become severely distended, the heart rate tends to be elevated, probably as a result of deterioration of hydration and cardiovascular parameters.

Obstruction of the Cardia or Reticuloomasal Orifice

True mechanical obstruction of the forestomach is an uncommon occurrence. The obstruction can be either full or partial and occur at either the cardia or the reticuloomasal orifice. The inflammatory and neoplastic conditions described previously can appear to be obstructive disease when the tissues are sufficiently distorted and lesions involve one of these orifices. Papillomas are most prone to causing an obstruction when they become pedunculated. A variety of foreign bodies create obstruction. In calves, trichobezoars are most commonly the cause, occurring predominantly in animals on a low-roughage diet that consequently lick their hair coats vigorously. In adult cows, ingestion of the placenta occasionally results in an obstruction. Curious ruminants, especially goats, sometimes consume plastic bags or discarded rectal palpation sleeves. These and other nondegradable materials can lead to obstruction even after considerable time has passed.

Cardia obstruction leads to the signs typical of esophageal obstruction, with free gas bloat as a prominent, perhaps life-threatening development. Obstruction of the reticuloomasal orifice produces the same consequences as some forms of vagal indigestion. Failure of ingesta flow beyond the rumen results in accumulation of fluid material in the forestomach and diminished or no passage of ingesta through the intestines. The degree and duration of obstruction determine the severity of associated problems such as dehydration, depression, elevated heart rate, forestomach stasis, colic, and muscular weakness. Only rumenotomy can effectively differentiate these obstructive diseases from other problems with similar signs.

Diaphragmatic Hernia

Defects in the diaphragms of cattle are uncommon. Most cases involve a tear through which the reticulum can herniate. Other abdominal organs may also be involved if the rent is large. The diaphragmatic defect may be congenital or an acquired lesion caused by a local inflammatory process (TRP), sudden external trauma (fighting, hanging up on a fence), or internal pressure (parturition, acute tympany).[44] Entrapment of the reticulum may lead to acute changes in intrathoracic pressure and cause sudden dyspnea, tachycardia, and poor venous return to the heart. Generally, however, this reticular problem causes signs identical to those of vagal indigestion with anterior functional stenosis.[1] Failure of flow through the reticuloomasal orifice may result from vagal nerve damage, or the anatomic distortion alone may explain the motility defect. Entrapment of the reticulum hinders normal reticular movements and distorts the esophageal groove and reticuloomasal orifice. Reticular ingesta can be heard moving inside the thorax; therefore complete reticular paralysis is unlikely. Motility disturbance is reflected by hypermotility of the rumen, generation of frothy ingesta, persistent or recurrent moderate tympany, and overfilling of the rumen. Signs of pain may also be present, as in cases of TRP. Rumination usually is impaired, and large volumes of ingesta may be vomited, especially after eating.

Disorders of Reticuloruminal Fermentative Function (see Box 32-5)

Forestomach Microbial Population

The continuous culture system of the rumen involves an ongoing selection of microorganisms best adapted to grow in a variety of ecologic niches that are in a dynamic state. Numerous control mechanisms govern the environment and the resultant microbial population. Some of these mechanisms are related to the animal itself, such as salivation, mixing and rumination, removal of substances by absorption or diffusion, outflow through the reticuloomasal orifice, and eructation. Others are related to the diet, including nutrient quality of the substrate (feed), balance of required elements, solubility, particle size, presence of inhibitory substances, nutrient quantity, and rate of delivery to the rumen. Control of fermentation also results from microbial interactions such as competition and symbiosis: cross-feeding between species, removal of inhibitory end products, and maintenance of the oxidation-reduction potential. The complexity of the system tends to promote an overall stability. Changes in the controlling factors create selective pressures that lead to population changes in the rumen.[3,45]

The rumen contains large numbers of bacteria, ciliated protozoa, anaerobic ruminal fungi, and bacteriophages.[45] Ruminal bacteria are predominantly anaerobes, with some coexisting facultative anaerobes. Although the facultative organisms are not important in normal ruminal function, they may be in some forms of ruminal dysfunction. Some microbes ferment the primary nutrients in the feed such as cellulose, hemicellulose, pectin, starch, and simple sugars. Other species ferment the products of the primary group such as pentoses, glucose, lactate, succinate, and formate. Many species are very specialized and have numerous growth requirements that may be supplied by the general fermentation. The last group is important for its role in removing end products and cycling essential factors back to the other organisms.[3,46,47]

Effects of Feed Characteristics

The concentrations and proportions of the microbial species vary with the composition of the diet (Table 32-14). An abundant supply of a certain substrate tends to favor a microbial population with a predilection or high capacity for using that material. The most important factors in the rate of digestion are the properties of the carbohydrates and protein in the feed. High-protein diets favor proteolytic organisms, whereas high-starch, low-fiber diets favor starch users. Cellulolytic bacteria are prominent in a high-fiber diet, but their numbers also depend on the fiber size as this factor determines the rate of passage or retention in the forestomach; thus, cellulolytic species can be abundant with a high-concentrate diet if some long-stemmed roughage is included because the retention time of the fiber is prolonged. Diets with readily fermentable carbohydrates and low fiber favor species capable of rapid metabolism and tolerant of low pH. Acid production is rapid and high, and populations of microbes less tolerant of such changes decline.[46,48,49]

The microbial population is also influenced by the limits of supply of certain feed substrates.[50] High rates of fermentation and microbial

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TABLE 32-14

Effects of Feed Characteristics on Ruminal Digestion and Health

Feed	Rumen Content	Effect on Health
Primary forage of high quality, long fiber length, crude fiber > 18% of dry matter; with concentrate supplement at 20% to 50% of total intake, moderate protein level	pH 5.5-7, VFA 60-120 mmol/L, acetic > propionic > butyric acid	Normal, healthy, productive
Excessive forage of low nutrient value (late cut) with little concentrate or protein supplementation	pH 6.5-7, VFA decreased, microbial activity decreased	Poor production or growth, microfloral inactivity and rumen impaction, malnutrition caused by protein, energy, mineral, and vitamin deficiency
High level of concentrate feeding (>60%) with decreased forage and/or fiber length	pH 5-6.5, VFA increased, microbial activity increased	High production, rapid growth; possible chronic rumen acidosis, milk fat depression, chronic laminitis, ketosis, ruminal parakeratosis, excessively fat condition
Extremely high level of concentrates (especially with sudden exposure to ration), low intake of forage	pH 4-5.5, VFA increased, lactic acid increased	Acute ruminal acidosis
Normal levels of forage intake, concentrate with very high protein or NPN supplementation	pH 6.5-7.5, VFA decreased, ammonia increased	Ruminal alkalosis, possible urea toxicity

NPN, Nonprotein nitrogen; *VFA,* volatile fatty acid.

growth on the abundant substrates depend on sufficient amounts of the more limited nutrients. Optimum carbohydrate use requires adequate sources of nitrogen, sulfur, and essential mineral nutrients.[51] When any essential nutrient is deficient, the rate of digestion and thus the digestibility of the feedstuff decrease. Whether the affected animal shows signs of nutrient deficiency or forestomach dysfunction with microbial and forestomach inactivity depends on the limiting nutrient and relative requirement of the host and bacteria for the nutrient. Substances and conditions that inhibit fermentation further reduce digestibility.

The feed material also affects ruminal fermentation by influencing the rate of passage from the reticulorumen. Fine grinding and pelleting of feed increase the rate of passage of the particulate matter from the rumen. Very finely ground rations also reduce the stratification of fibrous material in the rumen. This affects the ability to sort material in the rumen selectively by particle size and density, so that larger particles less thoroughly fermented pass more readily into the lower bowel. Microbes associated with the feed particles are passed out of the rumen with the feed. Thus a faster rate of passage influences the bacterial population because it competes with the generation time of the organisms. Populations of slower growing microbes tend to be most influenced by changes in the retention or passage times. Slow-growing cellulolytic bacteria decline in numbers as the passage rate increases (transit time decreases). High passage rates usually produce faster digestion rates. Although these factors are primarily important to the feed efficiency of the animal, they also affect ruminal function and the adaptation of microbes to feeding changes.[3]

Adaptation of the microbial flora to dietary changes requires a week or longer. The abruptness of a dietary change determines the degree of alteration of the ruminal microbial population and fermentation pattern and the potential for digestive disturbances. With abrupt and dramatic shifts to higher carbohydrate diets, the facultative species may overwhelm the more normal flora by producing excessive acid and lowering the pH. The importance of microbial adaptation to a particular diet is evidenced by the reduction in forestomach disturbances seen when the rumen is inoculated, before a feeding change, with fluid from animals already adapted to the new ration.[52,53]

The end products of microbial fermentation influence not only the microbial population but also ruminal function. High concentrations of nondissociated volatile fatty acids (VFAs) excite sensory epithelial receptors that reflexly inhibit ruminal motility. If a sudden increase in concentrate feeding induces lactic acid fermentation, the ruminal pH suddenly declines and a greater proportion of the VFAs shift to the nondissociated state, inducing ruminal stasis.[54] A consistently high level of concentrate feeding produces rapid fermentation, a high concentration of VFAs, and low pH, and the nondissociated VFA level may reach the threshold for stimulation of the inhibitory epithelial receptors. The ruminal stasis reduces the fermentation rate. Mild cases of ruminal acidosis may show spontaneous recovery of ruminal functions as the absorption of VFAs reduces the concentrations to a noninhibitory level. With more severe ruminal acidosis the generation of acid continues despite the ruminal stasis, giving rise to more severe complications of the disease.

In some instances the effects of ruminal microbial metabolism and microbial end products extend beyond impacts on nutritional status and digestive system function. Several ruminant diseases represent rumen-generated toxicities. These have extremely variable manifestations and include toxicoses from ammonia, nitrate and nitrite, 3-methylindole, dimethylsulfide (*Brassica* spp., onion toxicity), and sulfur-associated polioencephalomalacia.[55-58]

In summary, excesses, deficiencies, or rapid changes of feed substrate can cause imbalance in the microbial population and the fluid milieu. The result can be bacterial overgrowth and overproduction of microbial end products or insufficient microbial growth and fermentation. The effects of these abnormalities on the animal range from ruminal motility dysfunction, to poor growth and performance, to outright toxicity and organic damage.

Inactivity of Ruminal Microbial Flora (Caused by Poor-Quality Roughage, Haybelly, or Ruminal Impaction)

In ruminal microbial flora inactivity, the microbial populations and their metabolic and fermentative processes are diminished as a result of deficiencies of one or more nutrients. This occurs most commonly with poor-quality roughage deficient in protein and readily digestible carbohydrates (late cut, highly lignified hay or straw). Microfloral inactivity can also occur when specific mineral nutrients are deficient or it can be due to inhibitory substances such as antibiotics or some plant products.[3] Microfloral inactivity also occurs with prolonged anorexia, which abolishes the intake of all nutrients and is the primary pathogenesis of many cases of secondary indigestion.

When microbial digestive processes decline, the breakdown of ingested feedstuffs is prolonged. Failure to reduce the particle size of the ingesta leads to a prolonged retention in the forestomach and gradual accumulation of the undigested feedstuff. Gradual distention of the reticulorumen is commonly observed (haybelly). In extreme cases this can mimic the signs of vagal indigestion. Forestomach distention can result in weak contractions and moderate recurrent tympany. Ruminal hypomotility alters the normal stratification of the ruminal contents, and the fibrous components are found mixed in the fluid or compacted ventrally on the ruminal floor. Abnormal passage of ingesta from the forestomach results in decreased fecal

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passage, and the feces usually are dried and contain undigested plant fibers. Other effects on the animal are those of generalized or specific nutrient deficiencies (e.g., decreased growth or production, ketosis, emaciation, and a poor hair coat). When anorexia is the cause of the microbial inactivity, the ruminal fill decreases and the lack of normal distention also induces ruminal stasis.[1]

Simple Indigestion

Simple indigestion is the most common sequela of an abrupt change in the ration. Such feed changes present the ruminal microflora with nutrient substrates (1) to which they are not metabolically adapted, (2) to which they are adapted but in lesser quantities, or (3) that contain inhibitory substances or produce inhibitory substances on fermentation. The result is an imbalance in the microflora and its fermentation products. The difference between this problem and some of the other fermentation disorders is mostly a matter of degree. Generally the disease is relatively mild and self-limiting. Most affected animals show anorexia for 1 to 2 days, break with diarrhea in about 24 hours, and return to feed without treatment when the ruminal fermentation has stabilized and inhibitory substances have been eliminated. Ruminal motility is reduced but usually not absent, the filling of the rumen is not remarkably altered, and if bloat occurs, it is mild. In some cases the ruminal fluid pH may change, but usually not dramatically. Mild acidosis or alkalosis of the ruminal fluid may develop, depending on the nature of the causative feedstuff and its resultant fermentative degradation. Signs of ruminal microfloral inactivity are common. Simple indigestion is an acute problem, in contrast to the microfloral inactivity discussed in the previous paragraphs, in which deficiencies produce microfloral inactivity over time.

Feeds commonly implicated as causes of simple indigestion include moldy or overheated feeds, frosted forages, and partly fermented, spoiled, or sour silages. This form of indigestion also occurs in animals fed high-quality feed, usually after an increase in the rate of feeding or after a change of one of the feed constituents. Thus these mild forms of indigestion can range from a mild acidosis, to an excess of VFAs, to the generation of some bacterial inhibitory products. Because the rumen and its fermentative bacteria are very adaptable, the ways, if any, in which animals given a certain feed experience the problem vary considerably. Often only one or several animals from a group on the ration may have signs.

Acute Ruminal Lactic Acidosis (Grain Overload, Toxic Indigestion)

Acute ruminal acidosis is the most dramatic of the forms of ruminal microbial fermentative disorders and in some cases is lethal in less than 24 hours. It has also received the most research attention; therefore the events in its pathogenesis are more clearly defined than those of the other forestomach disorders. The condition has been named *lactic acidosis, acute ruminal impaction, ruminal overload, acid indigestion, toxic indigestion, grain engorgement, grain overload*, and *D-lactic acidosis*.

This problem is the result of excessive consumption of readily fermentable carbohydrates, which causes a rapid fermentation with production of lactic acid and a decrease in ruminal pH to physiologically inappropriate levels. This occurs when animals consume an excess of concentrate feeds (e.g., if animals are suddenly exposed to the feeds without prior adaptation; if animals already on such feeds suddenly consume an excessive quantity because of accidental access; or if animals that have been off feed return to feed and are offered unrestricted access to concentrates). The problem is more common when animals are grouped than when they are separate, probably because the psychology of competition induces them to overconsume. In general the feeds involved include the cereal grains commonly used in high-production rations and fruit and root crops (e.g., feed beets, sugar beets, potatoes) where they are available. Starch and soluble sugars promote an overgrowth of bacteria that produce glucose and organic acids. The acid end products increase ruminal acidity and osmolality, inhibit or destroy other ruminal microbes, and cause forestomach dysfunction and metabolic disturbances.[54,59-61]

Specific characteristics of the feedstuffs contribute to acidification of the ruminal fluid. Cereal grains inherently possess less buffering capacity than the fibrous forages. Low structured fiber content and decreased forage particle size induce less salivation at the time of ingestion and less rumination subsequently; therefore salivary buffering declines when concentrate feeds are consumed. Some silages contain both high carbohydrate and lactic acid and thus introduce more acid at both ingestion and fermentation.[33,60,62]

Feeding regimens that include significant fibrous roughage limit carbohydrate availability and rates of microbial fermentation and growth. Carbohydrate fermentation efficiency relative to the amount of adenosine triphosphate (ATP) derived from each sugar provides competitive survival value. Slower growing cellulolytic bacteria use substrate most efficiently. When starch or sugar is available in excess, the faster growing species such as *Streptococcus bovis* metabolize carbohydrate faster and produce more ATP per unit time, even though they are less efficient in ATP production per carbohydrate molecule. Under these conditions they can overgrow, producing lactic acid as their end product.[60]

The severity of ruminal acidosis and disease signs vary considerably, depending on the amount and type of carbohydrate-rich feed consumed and the degree of prior ruminal microbial adaptation to the carbohydrate substrate. The disease can range from a mild form of indigestion to an overwhelming toxemia that may be difficult to distinguish from other acute toxicities or various diseases with endotoxemia.

If consumption of fermentable carbohydrate is only mildly excessive, *S. bovis* proliferation decreases when the carbohydrate has been fermented, pH rises toward normal, and the efficient fermenters reestablish dominance. If the carbohydrate source is abundant and its supply is not exhausted, the acidosis becomes more severe. Continued production of lactate by *S. bovis* reduces the fluid pH to the range of 5 to 5.5, and the ruminal fluid osmolality rises concurrently. Both these factors inhibit or kill the ruminal protozoa, which normally use starch and small sugars and help to limit increasing lactic acid levels. There are also numerous species of lactate-using bacteria, of which *Megasphaera elsdenii* and *Selenomonas ruminantium* are the primary examples. These bacteria, which increase in numbers when animals slowly adapt to a high-concentrate diet, are eliminated by abrupt changes and generation of excessive acid; therefore lactate use decreases when the acid is generated too quickly.[52,60]

The lactobacilli are the major group of lactic acid producers in the rumen. The increasing acidity of the fluid enhances the growth of these organisms. Because the lactate-using bacteria are killed off before the lactobacilli overgrow, their diverse end products are unavailable as substrate for other bacteria. The lactobacilli are left as the predominant organisms to use the available carbohydrates. Even the *S. bovis* organisms that began the lactic acid production are inhibited below pH 4.5, leaving the lactobacilli, as the most acid-resistant species, to generate more lactic acid.[54,63]

The acidification of the fluid milieu enhances the lactic acid production by altering microbial metabolism.[60] The loss of the fluid bicarbonate buffer and the increase in available hydrogen ions block the conversion of lactate to propionate even before the lactate users die off. Also, when the pH is above 5 but declining, ruminal fluid amylase activity increases and liberates more free glucose from starch. However, glucose use is reduced, and ruminal glucose accumulates. Apparently the lactate-using bacteria such as *S. ruminantium* degrade less lactate to acetate in the presence of increased glucose concentrations. Thus not only does the microbial population change, but the characteristics of the fluid accelerate the lactic acid production when the available carbohydrate is excessive.

The effects on the animal from the ruminal fluid changes are numerous and detrimental. In the early stages of the acidic fermentation, the VFAs are produced in abundance. Although VFA production decreases as the microbes are increasingly inhibited, VFA concentrations remain elevated in advanced acidosis. The VFAs are

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much weaker acids than lactic acid; thus, as pH drops they accept hydrogen from lactic acid and serve as buffers in the fluid, so that a greater proportion of the VFAs exist in the nondissociated state. This form is more readily absorbable than free ions through the ruminal wall. During absorption some VFAs undergo metabolism by the ruminal wall epithelium, resulting in the release of lactate and ketone bodies into the circulation. Excessive absorption of the volatile fatty acids leads to systemic acidosis, and circulating lactate and VFAs may also directly damage the liver. In addition, the high concentration of nondissociated VFAs at the ruminal epithelium provides a strong inhibitory effect on reticuloruminal motility and leads to ruminal stasis. This effect tends to protect the animal, because it reduces the absorption of detrimental fermentation products from the rumen.[55-58,60,61]

The osmotic pressure of the ruminal fluid increases as lactic acidosis develops.[33,60,61] In a normal animal, ruminal osmolality remains relatively constant at approximately 280 mOsm/L, but osmolality may double in some cases of acute acidosis. Lactic acid accounts for a major fraction of the increase, but some of the components of this change remain unidentified. The increased osmolality inhibits and kills some of the microflora and draws fluid into the rumen, mostly from the extracellular compartment. This accounts for the increased ruminal fluid volume, ruminal distention, and severe dehydration observed clinically. The loss of circulating fluid volume leads to circulatory impairment, decreased renal blood flow and glomerular filtration, and in some cases eventual anuria. Poor peripheral circulation results in hypoxic metabolism and contributes to systemic acidosis.

Although it has been assumed that the systemic acidosis that develops with this disease is attributable to ruminal lactic acid absorption, such absorption does not appear to occur readily.[60] Lactate is absorbed from the rumen at a much slower rate than are the volatile fatty acids because it is highly ionized at a pH near physiologic normal, which tends to inhibit absorption. At lower pH the rumen becomes static, thereby also inhibiting absorption. The hypertonicity of the ruminal fluid further limits absorption of lactate and other substances.[59] It appears that the peak entry of lactate into the circulation occurs in the early phases of the disease. Some lactate may be absorbed from the intestinal tract from fluid passed before the onset of complete stasis. Many experimental trials do not show the development of severe systemic acidosis in the early phase of the disease. It may be that a large component of the later severe systemic acidosis is attributable to circulatory insufficiency rather than to absorption of lactic acid.

Some absorption of the lactic acid does occur, however, as evidenced by the appearance of D-lactic acid in the circulation. Microbes produce both the L- and D-form of lactic acid, whereas animal tissues produce only L-lactic acid.[54] The animals' pathways for metabolism of D-lactic acid are not as efficient as those for L-lactic acid; therefore absorption of both forms leads to an accumulation of predominantly D-lactate in the animal's system. The lactate is eliminated by oxidation, gluconeogenesis, and renal excretion. The animal's hydration status, liver and muscle metabolism, and renal function determine how readily it can eliminate excess lactate. Animals that survive ruminal acidosis often have metabolic alkalosis after the acidotic phase, as a result of lactate metabolism and production of bicarbonate.

Lactic acid is a strong corrosive agent that can destroy the ruminal epithelium, giving rise to the name *toxic rumenitis*. The increased ruminal fluid osmolality also damages the epithelium as extracellular water influx across the epithelium occurs in response to osmotic pressure imbalance and disturbed Na transport.[59] The effects of epithelial destruction can be far-reaching, because the damage persists after resolution of the acute acidosis.[33,64] Some yeast and fungi that are resistant to the high acidity readily colonize the damaged sites, invade the vasculature, and cause thrombosis or spread to the liver and other organs.[30] Ruminal acidosis is considered one of the primary causes of mycotic rumenitis (discussed earlier under Reticulitis and Rumenitis) and mycotic omasitis, although other predisposing causes have been identified.[30,31] Bacterial rumenitis can also result from the chemical damage and may lead to abscess formation, diffuse cellulitis, or perforation and peritonitis. If the animal survives the acute acidosis, it may succumb to secondary ruminal damage.[30] Alternatively, the rumen may heal uneventfully, leaving scars in the ruminal wall, but bacterial access to the circulation through these chemical lesions can result in hepatic abscessation, a common problem of animals fed high-concentrate rations.[65,66]

In addition to lactic acid, several toxic factors have been implicated in acute ruminal acidosis.[54,60] The altered metabolism of the ruminal microflora has been shown to generate increased quantities of histamine, ethanol, methanol, tyramine, and tryptamine. These may play a role in the pathogenesis of the disease, but conclusive evidence is lacking. Histamine has been implicated as an agent in the development of laminitis that sometimes accompanies ruminal acidosis. However, histamine is poorly absorbed from the rumen, especially at diminished pH levels. The destruction of ruminal gram-negative bacteria has been suggested to release large quantities of endotoxin for absorption through damaged mucosal surfaces. Endotoxin would contribute to most of the signs of the disease such as ruminal stasis, poor tissue perfusion with cardiovascular deterioration, weakness, and depression. Increased ruminal and blood concentrations of endotoxin and increased blood arachidonic acid metabolites have been found in cattle with experimentally induced ruminal acidosis, but their importance in naturally occurring disease is not clear.[67-70] With liver impairment or ruminal wall damage, toxin absorption and clearance are likely to be altered. Premature delivery and retained placenta may occur in pregnant animals after acute ruminal acidosis, possibly resulting from the effects of these circulatory toxins and metabolites.[71]

Subacute Ruminal Acidosis

Like acute ruminal acidosis, subacute ruminal acidosis (SARA) is caused by feeding of excessive quantities of concentrate with low levels of well-structured fibrous roughage; however, SARA results from continued ingestion of these feeds over a prolonged period rather than sudden exposure without adequate adaptation. Beef feedlot cattle may be chronically exposed to a ruminal pH between 5.0 and 5.5 from the start of the feeding period until slaughter. Dairy cattle are more likely limited to short periods of low ruminal pH typically between calving and approximately 5 months postpartum.[72,73] In early lactation dairy cattle may be exposed to energy-dense rations too rapidly, whereas the high feed intake of cows in mid-lactation makes them particularly susceptible to sudden ration changes or faults in feed delivery or composition.[74] The ruminal microbial population adapts to a high grain ration, and large numbers of lactate-using and lactate-producing organisms are found. The proportion of cellulolytic bacteria decreases, whereas the starch- and glucose-fermenting species proliferate. The overall effect of the adaptation is development of a microbial population that rapidly ferments the ingested feedstuffs. Lactic acid does not accumulate because it is further metabolized by the bacteria. The increased rate of fermentation instead produces high concentrations of VFAs and results in moderately acidic ruminal fluid with pH values usually ranging from 5 to 5.5,[75] although pH values between 5.5 and 5.8 may suggest cows at risk of SARA.[74] Ruminal buffering of the increased acid load is impaired because the fine particle size of the high-energy rations induces less chewing and less saliva production. As the name implies, the effects on the animal are chronic and insidious.

Along with the high concentration of volatile fatty acids and the low pH, a shift occurs in the proportions of the VFAs in the ruminal fluid. The proportions of butyric and propionic acids increase, and acetate decreases. Butyric and propionic acids stimulate proliferation of the ruminal papillae epithelium. When this process is exaggerated, it can progress to parakeratosis. The ruminal papillae develop an excessively keratinized epithelium and clump together. The parakeratotic changes are associated with decreased absorption of the volatile fatty acids and increased susceptibility to trauma and inflammation.[64] Epithelial damage and the acidic nature of the ingesta appear to be

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responsible for inflammation of the deeper tissues of the ruminal wall in some cases. The ruminal wall lesions allow penetration by bacteria with dissemination to the liver. This commonly results in liver abscessation in affected animals. Liver abscesses usually have no pathognomonic signs. Affected animals tend to show reduced productivity and may have signs of a chronic inflammatory response.[33,57,65,72,74,76]

The diagnosis of SARA is made on a herd level rather than on an individual cow basis. Cattle afflicted with SARA may demonstrate numerous clinical signs including reduced appetite and ruminal hypomotility.[73] High ruminal VFA concentrations can inhibit ruminal motility by stimulating the inhibitory receptors in the epithelium. The finely ground ingesta also induces less active ruminal motility because it lacks the physical bulk of high-roughage diets that stimulate strong and sustained contractions. Although the bacterial population is metabolically very active, the number of species of bacteria is reduced.[77] Likewise the protozoal population is inhibited when the pH remains in the lower end of this range. The microfloral environment is less stable when fewer species are present and is thus more susceptible to sudden changes in the diet.

A continual high acid load may also reduce metabolic efficiency and overall animal performance. High-concentrate diets have been associated with poor use of dietary protein.[46] Other pathologic conditions have been attributed to SARA, including chronic laminitis[78] and cerebrocortical necrosis. These conditions may be induced by some of the toxic by-products of acidic ruminal fermentation, such as endotoxins and hydrogen sulfide.[57,58,67-70,76]

Ruminal Alkalosis

An alkaline ruminal fluid pH occurs most commonly when microbial fermentation is reduced while the animal continues to ingest saliva. A ruminal fluid pH between 7 and 7.5 is found with prolonged anorexia, microfloral inactivity caused by poorly digestible roughage, and some cases of simple indigestion. The low rate of fermentation does not generate enough acid to neutralize the alkaline pH of the saliva. In addition, the absorption of VFAs through the ruminal epithelium proceeds with the generation of bicarbonate in the ruminal fluid. Acetate absorption is associated with greater generation of bicarbonate than is absorption of the other VFAs, and acetate is the predominant VFA produced during fermentation of roughage. Although the fermentation rate is low, the VFA absorption contributes to the ruminal alkalinity. Ruminal alkalosis occurring with these diseases is not the primary problem; therefore, these entities are discussed separately.

Ruminal alkalosis can occur with the generation of excessive ammonia. Ammonia concentrations rise when high-protein diets are fermented. The pH usually does not increase above neutral because these diets also contain sufficient readily fermentable carbohydrate to maintain a slightly acidic pH.

More dramatic elevations in the ammonia concentration, with a ruminal fluid pH above 7.5, occur with overfeeding of nonprotein nitrogen sources such as urea, biuret, and ammonium phosphate (see Chapter 54). Accidental ingestion of some common fertilizers that contain ammonium salts can produce the same results. For the purpose of this discussion, it is important to realize that some of the signs of urea poisoning involve ruminal dysfunction. Severe cases of urea poisoning result in generalized signs such as muscle tremors, incoordination, weakness, tachypnea, and central nervous system excitation, and affected animals die quickly. Signs of forestomach dysfunction such as ruminal hypomotility, bloat, vomiting, and abdominal pain are also present. In milder cases, diminished appetite, ruminal hypomotility, recurrent tympany, and diarrhea may be the most prominent signs, along with muscular weakness and incoordination. Thus the disease may appear as a form of forestomach disease. The ruminal fluid shows an alkaline pH between 7.5 and 8.5 and has a strong odor of ammonia.[55]

Putrefaction of Ruminal Ingesta

Putrefaction of ruminal ingesta infrequently results from overgrowth of a microflora that decomposes feed material in a putrefactive manner. The existence of a high ruminal fluid pH, such as occurs with high-protein feeds, and repeated inoculation with abnormal bacteria allow the development of the putrefactive decomposition. Fermented feeds undergoing spoilage, feed and water contaminated with feces, and spoiling, contaminated concentrates supply the offending microflora, which includes the coliform group and *Proteus* spp.[1] This type of abnormal decomposition is normally inhibited by the existence of an active physiologic microflora. Thus most cattle are remarkably resistant to aberrant digestive patterns even when spoiled feeds are ingested. Cattle affected with this form of indigestion typically follow a chronic course of disease. Ruminal motility declines, appetite is poor, and recurrent tympany develops, sometimes with the generation of frothy ruminal contents. The ruminal fluid characteristically has a blackish green color, a foul, putrefactive odor, poor protozoal and bacterial activity, and a pH in the neutral to alkaline range of 7 to 8.5. The cause of the forestomach hypomotility may be inhibitory products generated by the abnormal fermentation. In cases of prolonged duration, animals lose weight and display a poor hair coat, probably as a result of dietary deficiencies in the abnormal fermentation products.

Forestomach Diseases of Calves

Normal forestomach development and diseases of the forestomachs of calves have been reviewed.[3,79] The newborn ruminant has the same anatomic division of the stomach into four compartments as the adult ruminant. The abomasum is functional as a secretory digestive organ, like the stomach of monogastrics, and has a capacity approximately twice that of the other compartments. The remaining stomach compartments are small and do not perform digestive functions in the first days of neonatal life. The reticulorumen may not develop an adult-type function until 4 months of age or older and does not completely develop proportional dimensions similar to those of the adult until 9 to 12 months of age.[1-3,79,80]

The preruminant calf has been viewed as a functionally monogastric animal, and little importance has been assessed to diseases of the forestomachs. Under most management conditions, however, the forestomachs have begun to develop their digestive function within the first week or two after birth. During the development process the calf's forestomach is susceptible to problems different from those of the adult. After the rumen has developed a functional status similar to that of the adult, it is susceptible to the diseases discussed previously. Typically the feeding management of maturing young stock includes pasture or a mainly forage diet and does not predispose to digestive disturbance.

Esophageal (Reticular) Groove Function

Liquid feed bypasses the reticulorumen in the young ruminant, flowing directly into the abomasum through the esophageal groove. The groove consists of two lips that extend from the cardia to the reticuloomasal orifice. These lips close together, forming a tube to shunt liquid material to the abomasum when the soluble proteins and salts of milk stimulate a reflex through the glossopharyngeal nerve. Other salt solutions and even water can stimulate the reflex in very young animals, but the reflex weakens with age, especially after weaning. The response to stimuli varies among individuals, but generally milk produces the strongest response and plain water the weakest. Both nipple and bucket feeding stimulate closure in very young calves, but beyond 12 weeks of age closure is weak unless stimulated by nipple feeding. In older, weaned animals the reflex can be stimulated weakly for short durations by orally administered strong solutions such as copper sulfate or sodium salts. Intravenous vasopressin can induce more profound closure of the groove and has been advocated to aid ruminal bypass of orally administered treatment.

Milk replacers that contain nonmilk protein appear to stimulate a weaker closure of the esophageal groove than do whole milk or milk replacers containing real milk protein. Likewise unpalatable fluids and spoiled milk do not seem to induce normal closure of the groove.

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Even in healthy calves that consume unspoiled whole milk, some overflow into the forestomach may occur. Failure of esophageal groove closure allows these fluids to pass into the rumen rather than bypassing it. Milk or other fluid administered through a stomach tube or esophageal feeder does not contact the pharynx; therefore, the reflex closure is not stimulated and the fluid deposits in the forestomachs. Under normal conditions fluid in the forestomach of neonatal calves less than 2 weeks old overflows into the abomasum when more than 400 mL has accumulated.

Reticuloruminal Milk Accumulation (Ruminal Drinking)

Milk can gain access to the reticulorumen by several means. Failure of esophageal groove closure, just discussed, is one possibility. In addition, if calves are maintained as preruminants for longer than 3 to 4 months, groove closure weakens and may allow greater escape of fluid to the reticulorumen. Fluid can also accumulate in the forestomach from abomasal reflux (Fig. 32-120). Overfeeding fluids beyond the capacity of the abomasum (about 2 L in the newborn, 35-kg calf) promotes backflow into the reticulorumen. Certain fluids affect abomasal motility and emptying times, prolonging their retention in the organ. These include acidic and hypertonic fluids and severely heat-treated skim milk powder. Nonmilk protein does not curd in the abomasum, as does casein, when it contacts the abomasal enzyme renin. Prolonged fluid retention and failure of curd formation in the abomasum may promote backflow into the rumen, especially when more fluid feed is consumed. Abomasal inflammation or ulceration may also inhibit normal emptying and promote abomasal reflux.

Some amount of milk reflux from the abomasum appears to be a physiologically normal occurrence. In fact, this route supplies some of the inoculum for ruminal microfloral development and strongly influences the species distribution of the microbial population. But prolonged, repeated, or excessive retention of milk in the forestomach can lead to the development of abnormal fermentation patterns. Although amounts of fluid greater than 400 mL do not normally accumulate in the forestomach of the neonate, more fluid can accumulate when the abomasum is already filled and when ruminal size has increased during the development process. In some cases milk flow into the rumen accumulates significantly over prolonged periods.

The predominant organisms comprising the forestomach microflora of the 1- to 4-week-old ruminant are the coliforms and lactobacilli. These lactose-fermenting, facultative anaerobes tend to maintain the ruminal pH in the acidic range before the adult-type, anaerobic, cellulolytic flora becomes established. The high fat and protein content of milk in the rumen can predispose to a flora that decomposes these constituents and produces spoiled and rancid ruminal ingesta. Problems associated with ruminal milk accumulation are compounded when the milk or other fluid ingested is already contaminated or spoiled. The abnormal microflora established under these circumstances does not supply the young animal with the necessary digestive end products, and signs of dietary insufficiency develop. Affected animals fail to grow normally, show a poor hair coat potentially with widespread alopecia, and may have a depraved appetite. The stimuli for normal forestomach development are also deficient; affected animals have a potbellied appearance, and the rumen is distended with fluid and clots of milk. Ruminal motility is poor, and recurrent bloat is a common sequela. The ruminal fluid pH may be alkaline as a result of the proteolytic formation of ammonia, but in most cases the ruminal pH is acidic (below 6) due to an accumulation of volatile fatty acids and lactic acid from bacterial fermentation, and the fluid has a putrid, foul odor.[81] An enteric imbalance also seems to occur, and the feces are commonly pasty or fluid in consistency. Ruminal "drinking" appears to compound problems in calves with infectious enteritis and diarrhea, and affected calves frequently develop systemic acid-base and fluid balance disturbances.[82,83]

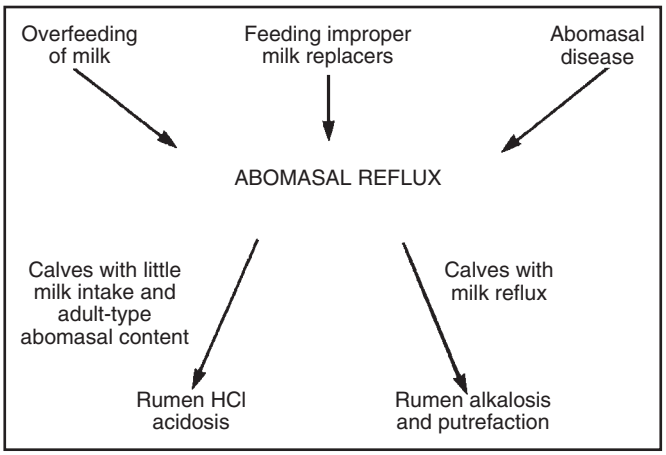


FIG. 32-120 Abomasal reflux in calves.

Problems in Ruminal Development

The age at which the calf has reticuloruminal digestion depends largely on its diet. A plentiful supply of milk delays the time until the calf consumes significant quantities of dry feed. Veal calves maintained without access to solid feed do not have forestomach development. The nervous reflexes that drive ruminal motility, eructation, and regurgitation are already functional before birth, awaiting only the drive of normal stimuli to begin operating. Dry feeds pass into the rumen, and bacterial inoculation from the environment or from abomasal reflux stimulates fermentation to begin. This process can be initiated as early as 1 week of age when calves are encouraged to consume dry feeds.[84]

The increase in the size of the forestomach results from the bulk effect of ingestion of bulky, fibrous feeds.[85,86] Mild distention stimulates ruminal motility and the development of the muscular wall. Mucosal development is stimulated by the presence of volatile fatty acids in the ruminal fluid, resulting from microbial fermentation. Butyrate and propionate are most effective in this regard, whereas acetate is less stimulatory. The thickness of the mucosa increases with proliferation of the ruminal epithelium and elongation of the papillae.[34] These changes serve to increase the ability of the mucosa to absorb the VFAs. Dietary excesses or deficiencies affect the developing rumen by altering the balance of these stimuli.

Calves fed concentrate diets to the exclusion of forages or mixed diets with the hay pelleted or finely ground may experience ruminal parakeratosis as a result of a lack of feed abrasion[87,88] and the excessive production of the stimulatory VFAs: butyrate and propionate.[34] These calves can have a form of chronic ruminal acidosis that results in a reduced growth rate and poor body condition. Ruminal contents are typically fluid with an acidic pH, ruminal hypomotility occurs, and recurrent free gas bloat is common. Affected calves often display a craving for fibrous materials. Hair coat licking is common in these individuals, and hairball formation in the reticulorumen is a common sequela. The hairballs may not be deleterious, but occasionally they cause obstructive disease or abrade the parakeratotic papillae or the abomasal mucosa, predisposing to ulcers and inflammatory lesions. Acute ruminal acidosis is not typically recognized in the young, developing ruminant, probably because feed consumption is limited and because the predisposing adult-type ruminal microflora has not yet developed.

An opposite extreme can occur when the young calf is fed dry forage to the exclusion of more readily digestible carbohydrates. Concentrates and grass contain soluble carbohydrates and are well digested by the developing ruminant. Hays contain much less soluble carbohydrate and an abundance of the structured, slowly digestible forms. These substances are not as well digested by calves because the appropriate cellulolytic microflora is not fully developed. With moderate hay intake and the supply of other sources of nutrition, problems are rarely encountered. When dry roughage is the only available

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feed, especially when the hay is of poor quality, adequate breakdown of the fiber is prolonged. The low availability of nutrient substrate that results from delayed digestion of the structured carbohydrates decreases microbial proliferation and fermentation. Inadequate fermentation of the feedstuff deprives the animal of required nutrients as well and results in poor performance and growth. When the only available feed source is the hay ration, the calf continues to consume while the long undigested fiber accumulates in the rumen. The rumen continues to expand as a result of the increased filling, eventually becoming grossly distended. Recurrent bloat is common in these animals because of the overfilling and poor ruminal contractility. This phenomenon is a frequent occurrence under some management conditions and has commonly been called "haybelly." Affected animals display a typical abdominal contour, with gross distention of the abdominal wall that is more prominent on the left side. The ruminal contents are very firm, the fluid has a pH around neutral and shows little microbial activity or odor, ruminal motility is poor, and despite the full abdomen, the animal is thin. This form of microfloral inactivity is more common in calves than in adults because the young ruminant is less able to ferment fibrous roughage.[1,2]

Recurrent Bloat (Ruminal Tympany)

Moderate gas distention of the rumen is a common sign of disease in calves, usually as a result of free gas accumulation, whereas frothy fermentation is very uncommon in the young ruminant. The pathogenesis of free gas bloat has been discussed, and the same principles hold for the young ruminant. The differences between free gas bloat in the adult and in the young calf are more a matter of chronicity and frequency of occurrence than cause. Digestive disturbances of the adult rumen tend to develop more rapidly and are more readily identified than those of the calf. Because of the involvement of ruminal developmental processes in the pathogenesis of calf indigestion, in young ruminants the diseases are often more chronic than acute in nature. In most cases the calf continues to consume feed, and the abnormal ruminal function and development may be easily overlooked.

Ruminal tympany seems to accompany indigestion in calves more often than in adult cattle and also assumes a more prominent appearance in calves than adults. These factors may be reflections of the juvenile anatomy and the incomplete development of adult function. It is worth noting, for instance, that although left-sided abomasal displacement is an uncommon occurrence in young calves, it almost invariably is accompanied by marked ruminal tympany. In contrast, the disease is common in adult cattle, but ruminal tympany is an infrequent sign of the disease.

Purulent lung infections appear to be a common cause of bloat in calves, probably as a result of intrathoracic compression or irritation of the esophagus or possibly the vagal nerves. However, other causes of bloat that are associated with abnormal ruminal function are also common in calves with indigestion. They include overdistention of the rumen, insufficient clearing of the cardia, and inhibition of motility by abnormal fermentation products. Thus a thorough examination is required to determine the underlying cause of the individual case.

Abomasal dilation and tympany in calves (acute bloat syndrome) is often associated with forestomach distention as well. Although the exact pathogenesis is unknown and appears multifactorial, large amounts of fermentable carbohydrate in the abomasum along with fermentative enzymes likely lead to gas production and bloat.[89-91] This syndrome is discussed in detail elsewhere (see Chapter 20). One presumed cause of bloat in calves that is not a cause of adult bloat is sudden filling of the abomasum by milk feeding during weaning. Calves not yet completely converted to a diet of solid feed still consume milk eagerly. In some cases acute free gas bloat occurs immediately after the milk feeding. Because the esophageal groove directs the milk into the abomasum but the abomasum is already partly filled by ingesta from the developing rumen, acute overdistention of the organ can occur and reflexly inhibit forestomach motility. Feeding smaller milk meals or discontinuing the milk feeding resolves the problem in these cases, lending support to the presumed cause.

Clinical Signs and Differential Diagnosis of Indigestion (Table 32-15)

GENERAL SIGNS. A general physical examination allows the practitioner to recognize signs of reticuloruminal problems and to assess whether a disease that could induce reticuloruminal dysfunction as a secondary phenomenon is present. General signs common to all forms of indigestion include a reduction or absence of appetite, dullness or depression, and decreased animal productivity. The most common signs of ruminal dysfunction are a decrease, absence, or abnormality of ruminal contraction sounds in the left paralumbar

TABLE 32-15

Clinical Signs Typically Associated with Primary Indigestions

Signs	Associated Problems
Fever	Traumatic reticuloperitonitis, reticuloruminitis
Decreased ruminal filling	Fermentative indigestions and secondary indigestions (especially with chronic anorexia) in which passage of material from the rumen is not impeded
Abdominal distention	See Fig. 32-119
Excessive fluid (or froth) in the rumen with loss of normal ingesta stratification	Acute ruminal acidosis, vagal indigestion, frothy bloat, anterior intestinal obstruction
Excessive firm, fibrous material in rumen	Ruminal inactivity caused by poor-quality roughage
Firm, doughy ingesta in ventral rumen with decreased ruminal filling	Prolonged ruminal stasis caused by chronic disease with anorexia
Ruminal hypermotility	Early cases of frothy bloat, some cases of vagal indigestion
Abdominal pain present or can be elicited	Traumatic reticuloperitonitis, abomasal ulceration, reticuloruminitis
Abnormal feces	Traumatic reticuloperitonitis, omasal transport failure, ruminal inactivity with poor-quality roughage, also dental disease and some abomasal disease
Decreased quantity, firm, dry, with increased fiber length	Acute or chronic ruminal acidosis
Feces with abnormal amounts of whole cereal grains	Pyloric outflow failure, abomasal displacement
Greasy consistency with very fine particle size	Acute ruminal acidosis
Foamy, fluid, yellowish color, acidic odor	Fermentative indigestions, enteritis
Pasty to fluid consistency with foul odor	Anorexia (various causes), acute indigestions before later developing abnormalities
Decreased quantity, dry, otherwise unremarkable	Ruminal overdistention with vagal indigestion, inflammation of reticulorumen, reticuloomasal orifice obstruction, diaphragmatic hernia, some intoxications (differentiate from esophageal disease)
Vomiting (rare)	

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TABLE 32-16

Differentiation of Types of Bloat through Nasogastric Intubation

Results of Intubation	Probable Causes of Bloat
Tube does not pass	Esophageal obstruction
Tube passes with resistance and releases ruminal gas	Esophageal compression caused by thoracic inflammatory or neoplastic disease
Tube passes easily and releases ruminal gas	Distortion of the cardia caused by inflammation, neoplasia, or abnormal anatomy such as abomasal displacement
	Ruminal stasis caused by reticuloruminal fermentative disorder, hypocalcemia
	Obstruction of cardia with ingesta (overfilling of rumen) or pedunculated mass
	Rumenitis (reticulitis)
	Weakened ruminal contraction caused by chronic overdistention with ingesta (vagal indigestion, indigestion with poorly digestible forage)
Tube passes easily but does not release gas or releases small amount of foamy ingesta	Frothy bloat
	Frothy ruminal contents caused by abnormal motility in some forms of vagal indigestion

fossa or an abnormal left-sided abdominal contour. The left abdominal wall may show gauntness and decreased filling or display gross distention. It is often the failure to detect signs of another primary disease as the cause of ruminal dysfunction that directs attention to the forestomach as the possible primary site of disease. Indigestion in calves effectively produces a state of malnutrition, and additional signs in these growing animals include poor growth rate and long, rough hair coat. The acuteness of onset and the severity of these signs depend on the inciting cause of the indigestion. Specific abnormalities in the ruminal motility pattern are discussed in more detail, but most indigestions are marked by decreased or absent ruminations (regurgitation and cud chewing) and depressed ruminal contractions. Only early cases of frothy bloat and some cases of vagal indigestion display increased ruminal motility.

Body temperature usually is within normal limits because the causes of indigestion are mainly physiologic abnormalities. Exceptions include TRP and occasional cases of rumenitis with significant inflammation. Disturbances of heart rate, respiratory rate, and body fluid vary tremendously among different forms of indigestion and different cases of any one form of indigestion. For example, an acute onset of severe ruminal bloat can produce severe embarrassment of the cardiovascular and respiratory systems, whereas mild or chronic bloat may produce no remarkable change in these systems. Rapid accumulation of fluid in the forestomach chamber in severe ruminal acidosis with grain overload can induce severe dehydration, systemic acidosis, and increased heart and respiratory rates, whereas slow fluid sequestration in some cases of vagal indigestion may not induce marked changes in these parameters.

The anamnesis is important, especially with regard to the animal's feeding. Characteristics of the feed determine the type of fermentation pattern to be expected. Knowledge of the nutrient content thus allows an assessment of the biochemistry of microbial digestion. Consumption of a high-concentrate, low-fiber ration or legume pasture may lead to frothy bloat. A ration of poor-quality hay or straw may result in low microbial fermentative activity and accumulation of impacted indigestible roughage. Overeating of carbohydrates or sudden access to concentrate feeds without adequate adaptation time can induce chronic or acute ruminal acidosis. The feeding history should agree with the findings from inspection of the ruminal contents, or the history should be suspected to be inaccurate. The amount and consistency of the feces should also provide supportive evidence of the type and amount of feed intake.

ABDOMINAL CONTOURS AND ANIMAL STANCE (see Fig. 32-119)**.** Visual inspection of the abdominal contours allows assessment of the degree of abdomen filling. Indigestions can be characterized by decreased, normal, or excessive filling of the reticulorumen. Most primary and secondary indigestions are associated with ruminal hypomotility and anorexia. Thus the rumen usually shows no obvious distention and may have less filling than normal, especially when the duration of the disease is prolonged. Forms of indigestion in which abnormal ingesta or abnormal ruminal motility prevents effective forward flow of ingesta (overfeeding of poor-quality roughage, vagal indigestion) or in which fluid is actively sequestered in the reticulorumen (acute ruminal acidosis) typically cause some degree of forestomach distention (see Fig. 32-119).

A left-sided or bilateral ventral abdominal wall distention indicates ventral ruminal dilation, although advanced pregnancy and hydrops conditions must be considered. Distention of the dorsal left flank results from ruminal tympany with or without distention of the ventral rumen. Abomasal displacement to the left can produce mild distention of the dorsal left flank under the caudal ribs and extending into the paralumbar fossa, but the abdomen usually is gaunt and empty when viewed from the side or the rear. Occasional cases of left displaced abomasum appear to inhibit eructation and produce gross ruminal tympany as the primary sign. Release of free ruminal gas through a stomach tube and reexamination for abdominal pings reveals this cause of secondary ruminal dysfunction. Frothy bloat in ruminants is discussed further elsewhere in this chapter. Free gas accumulation often occurs secondary to the causes of ruminal motility inhibition and is important as a sign of indigestion (Table 32-16). Right-sided abdominal distention suggests the various conditions of dilation, displacement, and obstruction or ileus of the intestines and abomasum. The diseases that cause obstruction and reflux of abomasal ingesta into the rumen may result in reticuloruminal distention. Both prolonged cases of gastrointestinal obstruction at any site and generalized peritonitis can produce gross bilateral dorsal and ventral distention of the abdomen.

The animal should be studied for signs of pain. A pain-filled expression, reluctance to move, an abnormal, stilted gait, an arched back with a tucked up abdomen, and an extended neck are typical signs of anterior abdominal pain. These signs may indicate TRP, abomasal ulceration, or another source of pain. A similar stilted gait and reluctance to move are typical of laminitis, a common sequela of acute ruminal acidosis.

PALPABLE FINDINGS (see Fig. 32-118)**.** Deep palpation of the left side of the abdomen is used to determine the consistency of the ruminal contents and thus the nature and volume of the ingesta. In normal animals the organized contraction sequence produces a layering effect.[3] Ventrally a fluid consistency can be palpated, whereas dorsally the consistency is firm and doughy. The doughy layer consists of the fibrous portion of the feed. Generally an animal fed a high-roughage diet has a more prominent layer of doughy ingesta. The ruminal contents of an animal fed concentrate feed are softer. In sheep and goats the normal dorsal rumen is softer than that of cattle no matter what the feed. In the normal condition a small layer of free gas is present in the most dorsal region. Distention with gas or foamy feed produces a taut, elastic tension. With free gas bloat the doughy layer can still be appreciated ventral to the gas accumulation, but in cases of frothy bloat the doughy layer is much less prominent. Most cases of vagal indigestion and some cases of high intestinal

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obstruction cause a grossly dilated rumen filled with fluid or foamy contents that may fluctuate on ballottement.

Overfeeding of indigestible poor hay or straw with resultant inactivity of ruminal microbial fermentation leads to accumulation of more fibrous material than normal that barely yields to deep palpation. With prolonged or severe ruminal stasis, as may occur in TRP, the lack of ruminal motility leads to failure to maintain the normal layering of the contents. In these instances the ventral portion of the forestomach is firmer than the area above. During severe ruminal acidosis, fluid accumulates in the forestomach. This can lead to some degree of abdominal distention, and on palpation the ruminal contents are fluid and may even splash with ballottement.

The rumen should also be palpated per rectum; a comparison of these findings with those obtained externally may be revealing. Moderate degrees of free gas accumulation are often more easily detectable per rectum. Palpation per rectum is also useful in distinguishing the presence of an L-shaped rumen, in which the ventral sac of the rumen is grossly distended in cases of vagal indigestion. It is important to differentiate an L-shaped rumen from either abomasal distention or impaction, which can display a similar external abdominal contour. It is also important to palpate for the size of the lymph nodes in the longitudinal groove of the rumen. These can enlarge to prominent size when rumenitis is present. The organs in the right half of the abdomen should be assessed as sources of abdominal problems.

Rectal examination is impossible in small ruminants and calves. External palpation using both hands can be valuable in these animals. In calves and goats it is the best method for detecting bezoars or clotted clumps of milk in the rumen and for palpating intussusception, umbilical abscesses, or grossly abnormal kidneys.

Palpation of the left paralumbar fossa reveals the presence of ruminal contractions. In a normal animal, three contractions should occur over a 2-minute period. One of these contractions should be associated with an eructation of gas, which can be appreciated both visually and audibly. The rate of eructation increases or decreases in proportion to the fermentative production of gas. Most indigestions produce decreased ruminal motility or ruminal stasis. Early cases of frothy bloat and some forms of vagal indigestion can result in prominent hypermotility. The motility pattern is characterized by changes in both frequency and strength, and weak contractions can also be detected by palpation. Some cases of secondary indigestion, in which the decreased ruminal function is a result of inappetence rather than an inhibition of ruminal motility, show a normal contraction frequency but decreased contraction strength. The duration and strength of ruminal contractions are primarily determined by the nature of the forestomach contents, whereas the frequency relies on medullary gastric center control. Decreased ruminal fill, decreased fiber content of the ingesta, or overdistention of the ruminal wall musculature results in reduced strength and duration of the contraction sequence. These distinctions can be important in determining the cause of decreased ruminal motility.

AUSCULTABLE FINDINGS. Auscultation of abdominal sounds is performed over several sites in the left flank and rib areas. Initial auscultation assesses the nature, frequency, and strength of ruminal sounds. This information can be compared with the assessment of ruminal motility gathered on palpation. The sounds represent the friction of fibrous ingesta rubbing against the ruminal wall as the ruminal sacs contract and mix their contents. In healthy cattle on a roughage diet, the normal rustling sound is prominent and prolonged with each contraction cycle. The ruminal contents of animals fed a high-concentrate diet produce less sound because very low fiber rations induce weaker contractions and less fibrous material is in contact with the ruminal wall.

As with palpation, both the frequency and the nature of the sounds yield information about reticuloruminal motility. The ruminal motility pattern is disrupted in vagal indigestion. Although contractions are present and may be more frequent than normal, their lack of normal coordination can lead to a churning of the ingesta without the usual progression of transport. This disrupts the normal stratification of the contents and produces abnormal sounds that are heard as a rumbling, bubbling, or splashing. When stratification is disrupted because of a hypoactive rumen and more fluid is present in the dorsal area of the rumen, contractions produce splashing sounds. The accumulation of gas under these circumstances may produce ringing tones as the fluid moves, similar to the pings found with a displaced abomasum.

Some circumstances require a distinction between primary and secondary contraction cycles, and they can be differentiated by ausculting for reticular contractions. Holding the stethoscope at the seventh intercostal space at the level of the costochondral junction, the examiner can detect a tinkling fluid sound as the reticulum contracts. A hand held in the paralumbar fossa can detect the tensed bulging of the dorsal sac as it contracts, allowing the examiner to determine if the ruminal contraction is associated with a reticular contraction. Reticular contraction and motility can also be assessed by transabdominal ultrasound.[5,92] Hyperactivity of primary cycles associated with feeding or the immediate postprandial period is normal. Mechanical stimulation of buccal sensory receptors can lead to an approximate doubling of the primary cycle rate. Hypermotility that results from excessive secondary contractions, without the normal mixing and propulsion of primary contractions, is abnormal and represents ruminal dysfunction.

Combining the auscultation with percussion or ballottement allows assessment of gas or fluid accumulations. The sounds heard in the left flank should be compared with those in the left rib area and right side of the abdomen. High-pitched pings and fluid tinkling sounds suggest a viscus filled with gas and fluid. In the left flank this may represent a displaced abomasum, gas-forming abscess, pneumoperitoneum, or static rumen. Careful comparison of the sounds heard at different sites, combined with the results of rectal palpation, should allow localization of the source. Generally the rumen can be ruled out as the source of pings if palpation reveals normal doughy ruminal contents, no ruminal tympany is felt per rectum, and sounds of normal ruminal contractions are heard in the paralumbar fossa. Prolonged anorexia associated with infectious or inflammatory diseases such as pneumonia or mastitis can result in a static, underfilled rumen, and occasionally a prominent ping can be ausculted in the left flank, where a filled rumen normally would be found. This condition has been called "ruminal collapse," and careful evaluation is required to distinguish it from left displaced abomasum. Ballottement of the rumen may reveal splashing fluid sounds without a high pitch in cases in which the rumen has accumulated significant fluid. This occurs frequently in cases of severe ruminal acidosis. It may also occur in cases of marked inactivity of the ruminal flora with loss of the normal stratification of ruminal contents.

PAIN ELICITATION. Tests of pain sensitivity in the anterior abdomen (percussion, deep palpation, withers pinch, xiphoid pressure) are performed to examine for localized peritonitis caused by TRP or abomasal ulceration. The same procedures, especially percussion or application of pressure to a localized area in the ventral abdomen, can be used to localize pain associated with rumenitis or ruminal abscessation or perforating abomasal ulceration.[93]

FECAL ABNORMALITIES. The rectal examination presents an opportunity to assess the volume and nature of the feces. The feces are abnormal in most cases of forestomach dysfunction. In adult cattle, passage of ingesta through the digestive tract requires 1½ to 4 days. Changes in the feces caused by acute diseases thus are often delayed by a day or longer beyond the first appearance of other clinical signs. Mature cattle typically pass a total of 30 to 50 kg of feces per day divided into 10 to 24 defecations. The color and consistency of feces are influenced by the feed and should be assessed in light of the feeding history.

Diseases that reduce the flow of ingesta from the rumen to the lower gastrointestinal tract typically result in feces of reduced volume that are firm and dry. These findings are also present with reduced feed or water intake. Assuming that normal intestinal function is

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present, a decreased flow of ingesta from the forestomach allows longer retention in the bowel with greater resorption of water. In severe instances the feces form into firm disks or balls with a dark, shiny mucous covering. These findings are typical of vagal indigestion and forestomach diseases that produce ruminal stasis without a grossly abnormal fermentative pattern. Indigestions with abnormal fermentation may produce decreased quantities of dry feces initially but usually result in other fecal abnormalities as the abnormal ingesta passes into the lower tract. Intestinal obstructions also decrease fecal passage to the point of absence, but usually the material passed also presents other gross abnormalities such as blood, melena, or discolored mucus.

The particle size of fecal material depends on the frequency and duration of rumination, the activity of the ruminal flora, and the function of the rumen in appropriately sorting out material for passage through the reticuloomasal orifice. Abnormalities of these digestive functions lead to passage of ingesta of inappropriate particle size. Plant fibers in normal bovine feces measure up to 0.5 cm. Particles with inadequate breakdown may measure 1 to 2 cm or longer. This long particle size may be seen in the feces of cattle with TRP, some cases of vagal indigestion, and poor-quality roughage with insufficient microfloral activity.[38,39] Similar findings occur with tooth disease and some cases of abomasitis or cellulitis at the cardia or esophageal groove, in which rumination or activity of the reticuloomasal orifice is inhibited. Whole cereal grains (especially whole corn) may pass in the feces of normal cattle, but excessive amounts of grain should raise suspicion of excessive intake and acute ruminal acidosis. Feces with an abnormally fine particle size and greasy-pasty texture are associated with delayed passage from the forestomach. These are common findings in most cases of vagal indigestion and abomasal displacement.

The odor of bovine feces is relatively inoffensive in healthy individuals. Foul odors are the result of abnormal fermentation or decomposition. Thus abnormal odor typically occurs when the ruminal fermentation pattern is altered, as in simple indigestion caused by abnormal feed, ruminal acidosis, ruminal alkalosis, or ruminal content putrefaction. A repugnant odor is also typical of enteritis when blood products, inflammatory products, or tissues decompose in the intestinal tract (e.g., *Salmonella* enteritis). Foamy, fluid feces with a yellow-brown color and acidic smell are typical of ruminal lactic acidosis in adult cattle. Abnormal ruminal fermentation not only produces feces with abnormal odor but also typically leads to a pasty or fluid consistency. Exceptions occur in acute cases, when ruminal stasis or the delay in the passage of ingesta from the forestomach can result in normal or firm feces during initial stages of the disease.

ACUTENESS OF SIGNS. The various forms of indigestion may be manifested as acute, subacute, or chronic illness. In general they do not appear as critical emergencies with fulminating systemic signs and life-threatening conditions. The exceptions to this are frothy bloat and acute ruminal lactic acidosis or grain engorgement.

Cattle examined a few hours after engorgement of grain may yet be alert but anorectic with a mildly distended rumen, weak ruminal contractions, and mild signs of colic. If the acidosis is mild, affected cattle show the signs of indigestion discussed in previous paragraphs and with or without treatment may show return of appetite within a few days. The severe form of indigestion leads to severe systemic involvement, with depression, severe dehydration, weakness, recumbency, profuse diarrhea, and eventually death. The temperature usually is normal to subnormal. The heart rate elevates with the progression of dehydration and systemic acidosis, with rates above 100 beats/min usually associated with a poor prognosis. Respiration generally is increased (60 to 90 breaths/min) and shallow. The rumen accumulates fluid. Animals capable of rising may show a staggering gait and appear blind. The pupillary light reflex may be slower than normal. Recumbent animals usually lie quietly and may be stuporous. As the cardiovascular system becomes more severely affected with increasing dehydration and acidosis, the extremities become cool, and mucous membranes dry. Anuria may follow poor renal perfusion. Rapid progression of signs leading to recumbency bespeaks a poor prognosis, and animals may die within 24 to 72 hours. Therefore if the progression of signs is rapid, emergency therapeutic measures are mandatory.

In cattle with intermediate degrees of ruminal acidosis, other signs may develop secondarily. Acute or chronic laminitis is a common complication.[94] The damage to the ruminal mucosa can lead to mycotic rumenitis or ruminal wall abscessation or can disseminate infection through the bloodstream to other organs, most notably the liver, resulting in the formation of hepatic abscesses.[65]

HEART RATE. Bradycardia of 40 to 60 beats/min is frequently associated with certain types of indigestion. This sign suggests reflex vagotonia to the heart and has been considered indicative of vagal indigestion. The bradycardia can be alleviated by subcutaneous administration of 30 mg of atropine, differentiating increased vagal nerve tone from a primary cardiac conduction disturbance. The atropine test is not especially useful because only a minority of vagal indigestion cases show bradycardia.[38] Advanced cases with severe abdominal distention or fluid imbalances (or both) frequently show elevated heart rates (over 80 beats/min). In most cases the other physical signs are more reliable for establishing the diagnosis. Further, bradycardia may accompany other forms of indigestion when ruminal hypomotility is prominent and no significant abnormalities of fluid or electrolyte balance are present. Even in normal cattle, postfasting heart rates may drop below 50 beats/min.[95] Therefore recognition of bradycardia in association with other signs of ruminal dysfunction is probably most useful as evidence that stimuli for an increased heart rate, such as inflammatory, infectious, or fluid balance disturbances, are not prominent factors in the individual disease occurrence.

VOMITING. Vomiting is uncommon in ruminants, but when it does occur, it generally reflects forestomach disease. Regurgitation from the abomasum frequently occurs with abomasal or intestinal disease. Abomasal reflux is not manifested externally and is discussed elsewhere because it relates to forestomach disease. Small-volume regurgitation and remastication are routine and normal ruminant functions that do not result in expulsion of material from the mouth. Explosive vomiting of fluid ingesta in large quantity occurs when the reticulorumen is irritated and occasionally when it is overdistended. Vomiting may accompany diaphragmatic herniation of the reticulum, inflammation of the reticulorumen caused by actinobacillosis, vagal indigestion, or obstruction of the reticuloomasal orifice. Animals are more prone than normal to vomiting around an orally passed stomach tube when they have almost any indigestive disturbance. Vomiting also occurs with certain intoxications, most notably azalea, rhododendron, and sneezeweed toxicity and some organophosphate toxicities.

Clinical Pathology

RUMINAL FLUID ANALYSIS. Evaluation of ruminal fluid characteristics is an essential procedure in establishing the cause of the indigestions of abnormal fermentation.[60,96] Several important determinations can be made at cowside in an ambulatory practice. Acquiring an appropriate sample is simplified by using proper equipment. The advantages of various collection techniques and devices have been discussed.[97,98] Needle puncture of the ventral ruminal sac (ruminocentesis) may yield a satisfactory fluid sample, and studies demonstrate that ruminocentesis samples provide the most reliable evaluation of ruminal fluid pH for field evaluation of subacute ruminal acidosis.[97-99] Oral or nasal passage of a collection tube produces more fluid volume with no risk of peritoneal contamination but with an increased risk of saliva contamination. An adequate tube for aspiration of a ruminal fluid sample should be at least 2.3 m long to reach the ventral ruminal sac and should have an internal diameter of 1 cm or larger to reduce the incidence of plugging with ingesta. A plastic stomach tube passed orally or nasally can be adapted for use

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by cutting multiple holes into the ruminal end of the tube. A digital examination glove can be placed over the end during passage to limit saliva contamination of the sample and then is forcefully blown off before sampling. The sample can then be withdrawn by a dose syringe. This technique is successful when ruminal fluid is accessible in the dorsal rumen, but the flexibility of the tube is disadvantageous when a prominent layer of fibrous feed is present. Several instruments with a flexible steel outer tube are commercially available and have the advantage of enough stiffness and weight to penetrate the overlying firm layer of ingesta.

Ruminal fluid samples collected in an expeditious manner yield the most useful results. When the animal strongly resists sampling and a prolonged time is required from introduction of the tube until the fluid is obtained, saliva contamination of the sample increases. This contamination alters the pH and consistency of the sample. The specially designed ruminal fluid collection tubes reduce this problem. If the sample must be collected with a standard nasogastric tube, passing the tube nasally avoids the presence of a device in the mouth. This reduces the amount of struggling (once the tube has passed the pharynx) and thus reduces excessive salivation.

The sample should be evaluated as soon as possible after collection to minimize the effects of cooling and air exposure on protozoal activity and pH. The more elaborate chemical tests such as chloride, acid, and ammonia concentrations can be delayed up to 9 hours on a room temperature sample and up to 24 hours on a refrigerated sample and still yield reliable results. Ruminal fluid collected for therapeutic transfaunation also retains its beneficial activity for a similar duration.[100] The ruminal fluid parameters important in a clinical examination are listed in Table 32-17.

Color, Consistency, and Odor. The color, consistency, and odor of aspirated fluid are assessed immediately after collection. Normal color varies, depending on the nature of the feed. Animals fed a hay ration have olive to brownish green ruminal fluid, those on grass show a deeper green color, and cattle fed grain or silage a yellowish-brown color. Fluid from cattle with acidosis tends toward a milky gray. Ruminal fluid from animals with prolonged stasis or decomposition of the ruminal ingesta (or both) is a darker greenish black, and fluid from calves with milk sequestered in the rumen as a result of abomasal reflux or esophageal groove failure is gray and may contain clots of milk.

Normal ruminal fluid has a slightly viscous consistency. The fluid becomes more watery when the microflora is inactive. Saliva contamination causes greater viscosity; therefore, the results from a highly viscous sample should be evaluated with care, and it may be best to discard such samples. Ruminal fluid has a typical odor that has been called "aromatic." The odor is less prominent when the microflora is inactive. Abnormal odors include the acidic smell of lactic acidosis, the putrid, foul odor of protein decomposition or spoiled milk with putrefaction of ruminal ingesta, or the ammonia smell of urea poisoning.

TABLE 32-17

Diagnostic Ruminal Fluid Analysis

Parameter	Normal
Color	Olive, brownish-green
Consistency	Slightly viscous
Odor	Aromatic, strong
pH	6-7 on roughage 5.5-6.5 on grain diet
Sedimentation/flotation	4-8 min
Redox potential (methylene blue reduction time)	3-6 min
Protozoal activity	Multiple forms, active motion
Gram stain	Predominant gram-negative bacterial population
Chloride concentration	<30 mEq/L

Ruminal Fluid Ph. The pH of ruminal fluid fluctuates within a broad range of normal values, varying considerably during the course of a day with shifts of 0.5-1.0 pH unit common during a 24-hour period.[72,101] The pH measured in a given fluid sample depends on the type of feed and fermentation pattern and the interval since the last feeding. Physiologic ruminal fluid pH typically ranges between 6 and 7 in animals on a mostly forage diet but is lower, at 5.5 to 6.5, in animals fed mostly grain.[61,72,98] The lower pH develops with the faster rate of amylolytic versus cellulolytic fermentation. Immediately after feeding the pH tends toward the high end of normal with the addition of feedstuff and saliva, the production of which is determined by the duration spent eating, ruminating, and resting.[102] Over a 2- to 4-hour period the pH decreases to the lower range as the feed undergoes fermentation. With no further feed consumption, fermentation declines and the pH rises with salivary buffering and acid end product absorption. In animals held off feed the ruminal pH rises above 7 within 12 hours after a hay meal and within 24 hours after a high-grain meal. Thus consideration of the most recent feed consumption is important to the interpretation of the ruminal fluid pH measurement.

Saliva contamination of the sample falsely elevates the measured pH value. Because it is impossible to exclude saliva completely from samples collected by tube, a minor false elevation of the pH likely occurs in all such examinations.[98] This can be minimized by expedient collection of a large fluid volume (more than 100 to 200 mL). If the collected volume is small and the sample viscosity is high, the pH measurement will be inaccurate. Modest contamination (5% to 10%) raises the measured pH by approximately 0.1 to 0.2 pH units, whereas excessive contamination with approximately 50% saliva may increase pH by 1 pH unit. Ruminocentesis of the ventral ruminal sac below the left paralumbar fossa is preferred by some clinicians for preventing saliva contamination. This is particularly advantageous for samples collected to monitor ruminal pH for balancing rations and minimizing chronic ruminal acidosis. A sampling strategy that incorporates ruminocentesis and ruminal fluid pH measurement in groups of cows in a herd has been developed to optimally identify cow groups with feeding problems that lead to subacute ruminal acidosis.[97,98]

Ruminal pH values of 7 to 7.5 are common in animals with anorexia and in those that have ingested feed that is not suitable for fermentation (e.g., simple indigestion and inactivity of microflora caused by indigestible roughage). Even higher pH values may be measured with ruminal alkalosis caused by urea ingestion or putrefaction of ruminal ingesta. Low pH values result from engorgement with readily digestible carbohydrates and generation of ruminal lactic acidosis. In extreme cases values occasionally decline to 4 to 4.5. It is important to remember that prolonged anorexia and continued saliva ingestion result in rising pH values in these cases as well and that the ruminal pH of a cow with ruminal acidosis can be normal if a sufficient period of anorexia precedes the ruminal fluid analysis. Conversely, a ruminal pH of 5.5 to 6 is abnormal for a cow fed a roughage diet and may be indicative of unobserved access to grain and resultant lactic acidosis. Subacute or chronic ruminal acidosis usually is accompanied by a ruminal pH in the range of 5 to 5.5.[60,61,72,98] Abomasal reflux into the reticulorumen caused by abomasal disease, vagal indigestion, or intestinal obstruction can cause mild decreases in ruminal pH because of the acidic nature of abomasal contents. However, ruminal pH measurement is a poor means of detecting abomasal reflux because the pH will remain within the wide range of normal values. Abomasal reflux is better assessed by measurement of the ruminal chloride concentration.

Sedimentation. The sedimentation activity time, or sedimentation/flotation test, provides a quick evaluation of microfloral activity. It must be conducted promptly after collection of the sample. The aspirated fluid is allowed to sit in a tube, and the time for completion of sedimentation and flotation of the solid particles is measured. Normally the finer particles settle to the bottom and the coarser particles float, buoyed by the gas bubbles of fermentation. Some of the finer particles sink and then rise again when the fermentation is

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very active. The normal time for completion of this activity is 4 to 8 min. Grossly inactive fluid shows very rapid sedimentation, and none of the material may float. This occurs with ruminal acidosis, prolonged anorexia, and inactive microflora caused by indigestible roughage. When the ingesta is particularly frothy, as in cases of frothy bloat or some cases of vagal indigestion, there may be no appreciable sedimentation or flotation. This test provides a crude evaluation of microfloral activity but does not differentiate well among the different forms of indigestion.

Redox Potential. The redox (reduction-oxidation) potential of ruminal fluid is a biochemical characteristic that reflects the anaerobic fermentative metabolism of the bacterial population.[3] An indirect determination of the redox potential can be achieved by measuring the time required by ruminal fluid to decolorize methylene blue dye. A mixture of 1 mL of 0.03% methylene blue with 20 mL of ruminal fluid at normal body temperature is observed in a tube and compared for color with another unaltered tube of the fluid. With a highly active microflora from an animal fed a hay and grain diet, the initial dark blue color of the mixture decolorizes within 3 minutes, leaving a narrow ring of blue color at the top of the decolorized sample. Fluid from a diet of hay alone requires 3 to 6 minutes and from a mostly grain ration requires as little as 1 min for methylene blue reduction. Reduction times up to 15 min and longer occur with diets of indigestible roughage, in anorexia of several days' duration, and after ruminal acidosis.[96] Thus the methylene blue reduction time provides an assessment of the degree of bacterial fermentative activity.

Microscopic Examination. Evaluation of the number and activity of protozoa in the ruminal fluid provides a sensitive indicator of the normalcy of the sample.[3] This is easily accomplished by examining a drop of fresh, warm fluid under a microscope. The examination requires only low magnification (×40 to ×100) and no special stains. In very active fluid samples the largest protozoa can be seen with the naked eye. They are detectable in a tube as small gray specks of material in active motion in the fluid, and they tend to localize above the sedimented particulate matter. Microscopically both ciliate and flagellate forms of varying sizes and shapes can be observed, with ciliates usually outnumbering the flagellates. The protozoa are normal inhabitants of a healthy ruminant's ruminal fluid, although their specific function is not completely clear and their presence does not appear to be a prerequisite of normal digestive activity. The importance of the protozoa from a clinical viewpoint is their sensitivity to abnormalities in the fluid milieu. The normal animal should show a wide variety of sizes of protozoa, in large numbers that are easy to see, and with active motility. Reduced numbers occur in inactive fluid samples. The larger species are more susceptible to abnormalities; thus a predominance of only small protozoa would suggest a mild indigestive disturbance. All protozoa are killed off when the ruminal pH drops below 5. Thus a recent bout of acidosis results in lack of protozoal activity, even if the pH has subsequently risen back into the normal range. Fluid from such an animal should also show other abnormalities of color and consistency. Very recent disturbances of the fluid may result in the observation of a large number of dead protozoa.

Although elaborate isolation methods for evaluating ruminal bacterial growth are not clinically applicable, examination of an air-dried, Gram-stained smear of ruminal fluid can be useful in diagnosing ruminal acidosis. Normal ruminal fluid should contain a variety of morphologically distinguishable bacterial forms, with a predominance of gram-negative organisms. After the overconsumption of readily digestible carbohydrate (grain engorgement), a population of streptococci and lactobacilli proliferates as ruminal lactic acidosis develops. This shift in the bacterial population can be distinguished microscopically, and a predominance of gram-positive cocci and rods are seen. The findings are best confirmed by comparing a smear from a herdmate.

Ruminal Fluid Chloride. The chloride concentration in ruminal fluid can be determined from the supernate from a centrifuged sample using standard chloride titration devices. A delay in measurement does not appreciably affect the value. Saliva contains concentrations of chloride similar to those of normal ruminal fluid, so that saliva contamination has minimal effect on the results. The normal ruminal fluid chloride concentration is less than 30 mEq/L, with elevated values demonstrating reflux of abomasal ingesta into the rumen or administration of chloride in the feed or as therapy. Accurate assessment of measured values requires information about possible previous administration of electrolytes via the rumen. In the clinical evaluation of forestomach dysfunction, elevated ruminal chloride suggests secondary indigestion caused by abomasal disease or obstruction of intestinal flow. This test can be very helpful in differentiating abomasal reflux from ruminal lactic acidosis as the cause of low ruminal pH and abnormal fluid accumulation in the reticulorumen. With vagal indigestion a high ruminal chloride suggests that the failure of aborad flow is posterior at the pylorus rather than anterior at the reticuloomasal orifice.[41] Generally cattle with elevated ruminal chloride also have hypochloremia and metabolic alkalosis as a result of the chloride sequestration in the forestomach, although very slow development of the sequestration may allow the animal to maintain normal plasma levels by altering other excretion rates.

Numerous other tests of the ruminal fluid have been described for the evaluation of digestive activity of the ruminal microflora. These include cellulose digestion, glucose fermentation, nitrite reduction, and measurements of titratable acidity, volatile fatty acids, lactic acid, and ammonia concentration. These procedures can more clearly define the nature of the ruminal fluid but are not generally used in a clinical setting.

HEMATOLOGY. Hematologic abnormalities are not generally a significant feature of the indigestive disorders. The primary exceptions are TRP or rumenitis, in which neutrophilia and hyperfibrinogenemia are routine findings. This feature of the disease can aid in its differentiation from other forestomach diseases. An inflammatory leukogram can also be observed in some cases of vagal indigestion when inflammatory disease is responsible for dysfunction of vagal innervation and forestomach motility. Chronic bronchopneumonia in calves and TRP in adult cattle are commonly implicated as causes of vagal dysfunction. A hematologic reflection of an inflammatory response may also be seen after ruminal acidosis if the ruminal wall and other organs suffer secondary pathogen invasion, and likewise in the occasional cases of primary rumenitis or reticulitis.

The more common hematologic abnormalities associated with indigestion are reflections of fluid disturbance or stress response. Hemoconcentration is routine and may be severe in ruminal acidosis. Mild dehydration may also accompany the other forms of indigestion, especially when the disease shows a protracted course. A stress leukogram would be anticipated in cases of indigestion that are acute or distressing, such as acute bloat. The hematologic response in secondary indigestions depends on the primary disease.

When indigestion is chronic, especially in calves, in which the indigestive disturbance may go unrecognized or undiagnosed for a long time, a state of malnutrition may develop. In these instances a mild to moderate anemia may develop that may be attributable to micronutrient or macronutrient deficiencies.

BIOCHEMICAL ABNORMALITIES. Most of the primary forestomach diseases do not induce remarkable changes in the biochemical profile. In lactating or heavily pregnant animals, anorexia may induce a secondary form of acetonemia, which is detected by the presence of urine ketones. The animal must be carefully examined to differentiate ketosis with secondary anorexia and decreased ruminal activity from primary indigestion with secondary ketosis. Mild to moderate hypocalcemia and hypokalemia are commonly identified abnormalities in many cases of indigestion, especially when anorexia has been prolonged.

Dramatic alterations of the blood biochemical characteristics may accompany severe ruminal acidosis. Usually the laboratory findings correlate with the degree of severity assessed on physical examination. Affected animals have metabolic acidosis with decreased blood pH and plasma bicarbonate. Blood lactate levels rise with the

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acidosis. The urine pH falls into the acidic range as the kidneys excrete some of the excess acid, but eventually severe dehydration results in renal failure and anuria, eliminating this route of acid excretion. Decreased renal function is reflected by elevated serum creatinine and urea nitrogen concentrations. Other findings commonly include increased serum phosphate concentration, possibly caused by massive cellular destruction, and mildly decreased serum calcium concentration, presumably the result of decreased gut absorption. Other serum electrolyte abnormalities, such as changes in the sodium and chloride concentrations, may reflect fluid balance changes in response to ruminal fluid hyperosmolality.[59] Concentrations of serum enzymes of muscle and liver origin rise when acidosis and dehydration produce cardiovascular impairment with poor tissue perfusion, increased recumbency, and cellular destruction. Portal bacteria and toxins from the damaged ruminal mucosa contribute significantly to the increased serum liver enzymes: aspartate aminotransferase, sorbitol dehydrogenase, orthinine carbamoyltransferase, and γ-glutamyltransferase.

Vagal indigestion may cause no significant blood biochemical abnormalities or can result in severe disturbances of fluid and electrolyte homeostasis. Measurement of the serum electrolyte concentrations provides important clues about the site of obstruction of ingesta flow and is useful in adjusting fluid therapy. When the primary problem is failure of flow through the reticuloomasal orifice, the rumen fills and grossly distends with fluid, but significant abomasal reflux does not occur. These patients generally show mild or no serum electrolyte abnormalities. When ingesta fails to pass from the abomasum, reflux of the high-chloride abomasal contents into the rumen results in elevated ruminal chloride concentrations and associated hypochloremic, hypokalemic metabolic alkalosis. In some instances these abnormalities can be dramatic. Prolonged or severe hypochloremia and hypokalemia may also result in the paradoxic aciduria associated with avid renal sodium resorption in the face of low concentrations of chloride and potassium. Some slowly developing cases may accumulate significant fluid in the reticulorumen but have minimal blood electrolyte changes.

Treatment and Prognosis

Ruminal Wall and Motor Function Disorders

Signs such as ruminal tympany, ruminal hypomotility or stasis, and forestomach distention can all result from a number of causes. Eliminating the underlying causative problem more effectively resolves the disease than treatment directed at the disease signs. Ruminal hypomotility, for example, is commonly a physiologic response to problems such as abnormal ruminal contents, a ruminal wall lesion, pain, or overdistention. In many cases the ruminal motility disturbance serves as a protective role for the animal. Former treatments that were directed at stimulating ruminal motility without addressing the causative disturbance included rumenatorics (i.e., nux vomica, ginger, tartar emetic) or parasympathomimetics (i.e., neostigmine, carbamylcholine). Such agents are not indicated under these circumstances. Likewise the treatment of indigestions with alkalinizing agents such as magnesium hydroxide is indicated only when the pH of ruminal contents is low.

FREE GAS BLOAT. When ruminal tympany is a prominent sign, it requires very critical assessment. Frothy bloat and free gas bloat can be differentiated by a thorough physical examination and knowledge of the feeding history. Passage of a stomach tube to help in this differentiation is very important and may alleviate the acute problem if free gas is present (see Table 32-16). Evidence of respiratory or cardiovascular distress indicates that the bloat is an acute, life-threatening problem that requires emergency treatment. With the exception of cardia or esophageal obstruction, the free gas bloat associated with indigestive disturbances is mild to moderate in severity and chronic or recurrent in nature. It does not represent a major threat to the animal and can be handled by treating the primary forestomach disturbance. Chronic free gas bloat does not respond to the antifermentatives or surfactants commonly used for frothy bloat. Only the restoration of physiologically normal reticuloruminal function corrects this type of bloat. Inhibition of eructation caused by lesions of the cardia region can usually be confirmed only by exploratory rumenotomy. This approach also determines whether the lesion is surgically correctable. Inflammatory lesions may respond to long-term administration of broad-spectrum antibiotics. This is also the treatment of choice when purulent lung infections appear to be the cause of the bloat. Failure to respond within about 3 weeks suggests that the treatment is not effective, and slaughter should be recommended after an appropriate withdrawal time. Detection of abnormal forestomach ingesta should direct treatment to the primary fermentative or feeding disorder.

The various causes of chronic or recurrent bloat usually require chronic treatment for correction. It follows that the bloat will also not completely resolve until the underlying disturbance is corrected. Repeated relief of the bloat may be accomplished by passage of a stomach tube during the treatment regimen. In many cases this proves too tedious or too traumatic for the animal, and the most viable alternative often is the establishment of a temporary ruminal fistula. Several devices are manufactured for this purpose, or the fistula can be created by suturing the rumen to the skin. Release of the fermentative gas in this manner is important for the reestablishment of normal forestomach motility, which is inhibited if distention is extreme. When free gas bloat is the result of an obstruction of eructation or another gastrointestinal tract disease such as abomasal displacement, surgical treatment of the primary problem may be necessary. The tympany responds rapidly in these cases, and ruminal fistulation is not required.

LESIONS OF THE RUMINAL WALL. Diseases of the ruminal wall may be suspected on the basis of the physical examination findings and results of a complete blood count, abdominocentesis, and ruminal fluid analysis. In most cases exploratory laparotomy is required to confirm the diagnosis. Rumenitis or reticulitis may respond to antibiotic therapy, but the prognosis in these cases is guarded. Not only is the forestomach inflammation difficult to resolve, but the hematogenous spread of infection to other organs often causes intractable multiple organ system disease. Parakeratosis is best treated by correcting the causal feeding error (reducing the amount of concentrate and increasing the feeding of long-stemmed forage). The ruminal papillae can grow or regress in a period as short as 3 weeks when the feed is changed from low- to high-concentrate content or vice versa. Exactly how long it takes for parakeratotic papillae to return to normal is not certain, but it probably depends on the degree of change of the diet. The prognosis of this problem is good if inflammation of the ruminal wall is not also involved.

RUMINAL DISTENTION. Vagal indigestion is a chronic and insidious problem that generally warrants a guarded to poor prognosis. The syndrome of abdominal distention with an L-shaped rumen and possibly ruminal tympany has several different causes. Exploratory laparotomy and rumenotomy are essential for establishing an accurate assessment (see Fig. 32-119). Diaphragmatic herniation and masses that obstruct the reticuloomasal orifice cause signs indistinguishable from those of vagal indigestion that result from inflammatory lesions of the reticulum. Surgical correction of a diaphragmatic hernia involving the reticulum can be attempted but has usually proved unrewarding, especially if the lesion is chronic, involves a large defect, or is accompanied by inflammatory reaction. Removal of pedunculated masses or foreign bodies at the reticuloomasal orifice can promptly correct such problems.

The two most common causes of vagal indigestion syndrome are inflammatory lesions of the reticuloomasal region and abomasal diseases that involve gross distention, twisting, or vascular impairment of the organ. Vagal indigestion caused by abomasal disease carries a poor prognosis, whereas the prognosis for cases with reticular involvement is more variable. Animals in either category may respond favorably with appropriate therapy[40,41] (Box 32-6). Surgical

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BOX 32-6

Principles of Treatment of Vagal Indigestion

1. Determine likely cause, often by means of exploratory laparotomy.
2. Administer specific therapy (e.g., antibiotics, antiinflammatory agents, removal of foreign body or relief of obstruction, drainage of abscesses) for causative lesion.
3. Relieve forestomach distention; often this must be repetitively performed.
4. Limit feed and water intake; feed palatable, high-fiber ration.
5. Transfaunate.
6. Fistulate rumen if chronic bloat is a problem.

BOX 32-7

Principles of Treatment of Fermentative Indigestions

1. Determine and resolve initiating cause; adjust feed regimen.
2. Correct ruminal pH.
3. Correct systemic acid-base and electrolyte abnormalities through parenteral fluid therapy (especially Ca^{++} and K^{+}).
4. Remove grossly abnormal ruminal ingesta.
5. Correct ruminal fill (overdistention or emptiness).
6. Transfaunate repeatedly.
7. Resolve inspissation or impaction of ruminal contents when present.
8. Provide oral and parenteral mineral and vitamin supplementation when indigestion or anorexia is chronic.

exploration not only allows an assessment of the cause of the problem but may also allow repair. When abscesses are identified at the reticulum or liver, surgical drainage may help resolve the forestomach motor disturbance.[41] Identification of adhesions and active inflammation indicates that broad-spectrum antibiotic therapy may be beneficial, it being essential that aggressive antimicrobial therapy be administered prior to and following the surgical correction of a right-sided abomasal displacement or volvulus.[40] Gross abomasal distention, indicating pyloric outflow failure, usually warrants a poorer prognosis, as does the presence of granulomatous or neoplastic processes or generalized peritonitis and adhesion formation.[41] When the presence of a large gravid uterus appears to be the inciting cause of outflow failure, induction of parturition or cesarean section usually resolves the problem completely.

The evaluation of animals with vagal indigestion with a large fluid-filled rumen should include assessment of the fluid and electrolyte status. Abnormalities such as dehydration, hypocalcemia, hypochloremia, and hypokalemia should be addressed with supportive fluid therapy. Treatment should be administered parenterally, because oral treatments are ineffective or deleterious. The forestomach should be emptied of the excessive ingesta accumulation either at surgery or with a large-bore stomach tube. This procedure may have to be repeated if the recovery period is prolonged. Relief of persistent forestomach distention is *critical* to the reestablishment of normal motility. Limited feed and water should be offered to prevent repeated accumulations in the reticulorumen, and intravenous fluid therapy should be continued until reticuloruminal motility is reestablished and oral fluid intake can be allowed at normal levels. Once the ruminal distention has been alleviated, several liters of ruminal fluid transfaunate from a healthy donor should be administered.[103] The limited diet must be palatable and should consist primarily of long-stemmed hay or green feed for maximum stimulation of the normal forestomach motility pattern. A temporary ruminal fistula may be indicated if tympany is a prominent sign.

Response to treatment of vagal indigestion usually is a slow process and may require several weeks. Favorable signs include a return of the normal primary and secondary contraction patterns, improvement in appetite, maintenance of normal forestomach dimensions, weight gain, and increased fecal production. Repeated development of forestomach distention, continued scant fecal output, poor ruminal motility, and recurrent bloat are indications that the animal is not responding to treatment and the prognosis is grave.

Fermentative Disorders

With the exception of severe acute ruminal acidosis, the disturbances of reticuloruminal fermentation generally are not fatal unless the disease is undiagnosed for a prolonged period, leading to extreme debility. Treatment of fermentation disorders centers around restoring a normal ruminal fluid environment that allows normal microbial metabolism. Identification of ruminal fluid parameters (see Table 32-17) and the nature of the forestomach ingesta direct the appropriate treatment (Box 32-7).

FEEDING. The first and most important step in treatment of nutritionally related indigestions is correction of the specific causal feeding error. Because the imbalance may have gone on for weeks, especially in cases of calf indigestion, correction of the problem may also take some time. The evolutionary development of the ruminant has adapted it to be a grassland grazer. Economic pressures in the animal industry have caused managers to institute feeding practices that diverge widely from a pasture setting. Fresh green grass, however, remains one of the best means of stimulating normal forestomach digestion and motility. The second best type of diet includes a balance of palatable and digestible sources of energy, protein, fiber, and mineral nutrients. Fiber requirements should be determined by considering both the physical effectiveness of fiber and the production of fermentation acids.[104] The content of structured roughage should not fall below 10% of the ration dry matter, and a crude fiber component above 17% is desirable for any ration.

ALTERATION OF RUMINAL CONTENTS. When the viability or activity of the ruminal microflora is in question, as in the primary fermentative disorders and most cases of secondary indigestion, ruminal transfaunation is indicated.[103] This should be obtained from a healthy individual that preferably is adapted to a ration similar to the one the patient is expected to consume. The fluid can be obtained from an animal with the rumen fistulated, by removal with a stomach tube, or from a local abattoir. After the large particulate matter has been strained from the fluid (cheesecloth or large stockinette can be used), it can be administered through a stomach tube. The transfer from donor to recipient is best accomplished immediately, but fluid that contains active and healthy microflora remains viable for up to 9 hours at room temperature or 24 hours under refrigeration.[100] In calves inoculation with 1 L is appropriate, whereas 3 L is minimal in an adult cow, and 8 to 16 L is more desirable.

Many animals with indigestion exhibit decreased ruminal fill. As discussed, one of the primary stimuli for active ruminal contraction is mild forestomach distention. In addition to the administration of ruminal transfaunate, it usually is beneficial in these cases to administer enough oral fluid to produce mild ruminal distention. This can be accomplished with water warmed to body temperature, and 20 to 30 L of fluid administered through a tube may be required to achieve the desired effect. The addition of salt (sodium and potassium chloride) in amounts sufficient to produce an isotonic solution (about 2 teaspoons per liter) supplements deficiencies and promotes rapid turnover of the fluid from the rumen to the lower tract. Cathartic agents such as magnesium sulfate have been used and may be beneficial but do not serve to supplement the common electrolyte deficiencies.

Correction of pH abnormalities to the normal range of 6 to 7 is important when ruminal acidosis or alkalosis is detected. Alkalinizing agents such as magnesium hydroxide and sodium bicarbonate are indicated for treatment of acidosis at an initial dose of 1 g/kg. Magnesium hydroxide is commonly used by some as a routine treatment for any animals in which ruminal hypomotility has been identified.

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This practice is not justifiable in most cases of ruminal hypomotility because the fluid pH is commonly at or near neutral. The use of magnesium hydroxide in such settings may induce a mild systemic alkalosis, and the agent is better reserved for true cases of acidosis. Ruminal alkalosis can be corrected with the infusion of acetic acid (vinegar, initial dose of 2 mL/kg, up to 12 L). All of these agents are best administered in several liters of warm water to ensure good distribution through the ruminal fluid.

Overdistention of the ruminal wall may be a primary inhibitor of forestomach motility in some cases of indigestion caused by abnormal fermentation. Treatment of free gas bloat has been discussed. When the distention is caused by accumulation of abnormal ingesta, normal contractions do not return and the ruminal tympany is not resolved until the distention is relieved. This situation is best exemplified by cases of microfloral inactivity caused by poor-quality roughage and is the underlying problem in calves with haybelly. One approach to this problem is to restrict the animal to small quantities of readily digestible feed given several times a day. Between meals the animal can be kept in an unbedded stall or muzzled. This process is continued until the accumulated ingesta has passed out of the forestomach. Repeated transfaunations during this time help reestablish a more normal microflora. This approach relies on motility and microbial activity sufficient to break down the ingesta and pass it to the lower tract. An alternative approach is to remove the accumulated ingesta by means of rumenotomy, after which the animal is transfaunated and allowed access to moderate amounts of feed until normal motility is restored. Emptying the rumen surgically is the treatment of choice when spoiled milk, putrefactive ruminal ingesta, or severe ruminal acidosis is detected. Prolonged cases of microbial inactivity or anorexia (or both) with ruminal hypomotility can result in loss of the normal stratification of forestomach ingesta. The fibrous, floating layer sinks to the ventral ruminal sac in these cases, forming a dense, firm mass. Return of normal forestomach motility will be delayed unless this accumulation of material can be eliminated. This can be accomplished during the process of microfloral reestablishment by massaging the mass through the lateral and ventral body wall. Dissolution and passage of the material can be enhanced by the administration of mineral oil (4 L), or dioctyl sodium sulfosuccinate (DSS) (4 to 6 ounces in 2 to 3 L of water). Because DSS kills ruminal protozoa when given in amounts greater than required to saturate the fibrous matter, at least one ruminal transfaunate should be given 1 to 2 days after the last application of this agent.

Animals with prolonged anorexia caused by a depressant or febrile disease that produced secondary indigestion may not return to feed or have normal ruminal motility even after normalcy of the ruminal contents has been restored. Chewing activity is one of the strongest stimulants for ruminal motility, and these individuals sometimes benefit if palatable hay or grass is placed forcefully into their mouth by hand. An alternative is to give such individuals access to pasture. Both the ruminant and its ruminal microflora have trace mineral requirements that are often not met by the types of diets that may induce microfloral inactivity. The ruminal microflora is also responsible for supplying the animal with its vitamin B requirements. The stunted, poor body condition of calves affected by chronic indigestions may reflect these deficiencies, as well as protein energy malnutrition (see Chapter 9). Oral supplementation of minerals and parenteral supplementation of the B vitamins may be helpful until normal ruminal digestive function is established. Adult cattle, especially lactating animals with high metabolic demands, may also benefit from B vitamin supplementation when ruminal function is impaired.

Intraruminal administration of antibiotics has been used to kill undesirable populations of ruminal microflora. A 2- to 3-day course of treatment with a broad-spectrum antibiotic that is not readily absorbed is only useful when an overgrowth of undesirable bacterial species is present and should be followed by transfaunation. Drugs used for this effect have included neomycin or tetracycline for ruminal alkalosis or urea toxicosis, and chlortetracycline or erythromycin for ruminal acidosis. Feeding changes and ruminal transfaunation are also effective in inhibiting the undesirable population and inoculating the desirable population. When spoiled milk, putrefactive ingesta, or extremely acidic ruminal contents are found on ruminal fluid analysis, rumenotomy, removal of the contents, and flushing of the rumen seem the more desirable treatment.

ACUTE RUMINAL ACIDOSIS. Therapy for cases of mild to moderate or chronic ruminal acidosis can follow the guidelines outlined previously. The prognosis in these cases is usually good, although ruminal inflammation and hematogenous dissemination of infection to other organs can produce chronic problems with a poorer prognosis.

Severe grain overload requires prompt and aggressive treatment. Animals showing severe depression, an unresponsive condition, apparent blindness, and gross ruminal distention warrant a grave prognosis. Immediate slaughter should be considered for animals with similar signs but still able to stand.

Emergency rumenotomy and removal of the acidic ruminal contents may be lifesaving if the procedure can be performed before significant amounts of ingesta have passed into the lower gastrointestinal tract. An alternative treatment in less severe cases is repeated flushing of the rumen with warm water through a large-bore stomach tube. Administration of magnesium hydroxide into the rumen and sodium bicarbonate solution (5%) intravenously is necessary to counter the acidosis. Intravenous fluid therapy should be continued until the animal has recovered to provide support against hypovolemic shock. Other treatments that may be considered include nonsteroidal antiinflammatory drugs and intraruminal antibiotics. The other therapeutic measures discussed such as transfaunation and dietary adjustment should be continued during the recovery phase.

SUPPORTIVE TREATMENTS. Indigestion often is accompanied by varying degrees of dehydration and electrolyte imbalance. When these abnormalities are only mild or moderate, the animal's fluid homeostasis may correct as the normal digestive processes are restored. More rapid recovery is achieved if these problems are addressed during the initial treatment, and animals must be treated if the imbalance is severe. Restoration of normal fluid balance improves attitude and appetite and normal gastrointestinal motility.

When laboratory facilities are available and the specific electrolyte imbalances can be assessed, fluid therapy can be tailored to the individual case. Empiric treatment with a balanced electrolyte solution administered intravenously is sufficient in most cases, because gross disturbances of the body fluid electrolytes are uncommon in most indigestions. The greatest exceptions to this are cases of severe ruminal acidosis or vagal indigestion with pyloric outflow failure and sequestration of abomasal chloride. These problems should be identified during the examination.

Hypocalcemia and hypokalemia are routinely present in many cases of indigestion. Low serum concentrations of these elements can produce muscular weakness and impair gastrointestinal motility. Both calcium and potassium should be included in the administered fluids. As an alternative, calcium salts should be administered subcutaneously if intravenous fluid administration is not elected. When anorexia has been prolonged, an additional oral dosage of potassium chloride (120 g/day) may be required even after adequate hydration has been achieved and fluid therapy has been discontinued.

Prevention

Some of the sporadically occurring diseases of the forestomach wall such as granulomatous infections, neoplastic invasions, and diaphragmatic herniation cannot be foreseen or prevented. The most common cause of vagal indigestion syndrome is inflammation of the reticular area caused by TRP. Prevention of this disease by keeping metallic foreign bodies out of the feed or by prophylactic administration of a ruminal magnet is the best prevention of vagal indigestion as well.

The microbial-fermentative forestomach disorders are best prevented by proper feeding management. A well-balanced diet of palatable feeds with an adequate amount of well-structured roughage (not

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finely ground or pelleted) prevents most problems. Dietary changes should be introduced slowly (over 2 to 3 weeks) to allow adaptation of the microbial flora to the new substrate. Calves undergoing ruminal development and cattle fed high-production diets or changing between production groups are at risk of oversights in proper feeding management. Some feed additives have proved effective in preventing the overgrowth of the high acid-producing ruminal microflora. Feed-grade buffers are widely used in both dairy and beef cattle production, in which high-concentrate diets are fed to maximize production. These buffers stabilize the ruminal pH and alter the mechanics of ruminal fluid outflow, thus decreasing the chances of overgrowth of the lactate-producing organisms. Commonly used "buffers" include sodium bicarbonate, sodium sesquicarbonate, sodium bentonite, magnesium oxide, and calcium-magnesium carbonate, of which only the sodium carbonates are truly buffering agents in the chemical sense. The other agents do tend to stabilize ruminal pH, however, and all of these have shown some benefit in reducing the disease problems associated with heavy grain feeding and diets that are low or marginal in effective fiber. The ionophore antibiotics (e.g., lasalocid, monensin) and some other antibiotics (e.g., the sulfur-containing peptide antibiotic thiopeptin) have also proved effective in reducing lactate production in animals fed high-grain diets. The effect of these agents is to suppress the lactate-producing organisms while not appreciably affecting the lactate users. The ionophores are in common use in feedlot cattle and dairy heifer rations because the selective effects of these antibiotics on the ruminal microbes alter the ruminal metabolism in a manner that promotes increased animal weight gain. In 2004 the FDA approved the use of the ionophore, monensin, for lactating cattle in the United States. Although approval was based on increases in milk production efficiency, ionophore use may also reduce the risk of ruminal acidosis and ketosis.[105]

Acute Abdomen in Ruminants

David Francoz • Gilles Fecteau • André Desrochers

Abdominal emergencies in ruminants are both a therapeutic and a diagnostic challenge for the veterinary practitioner. Some of them will require immediate surgical treatment, and others can be treated medically (Fig. 32-121). They are associated with numerous conditions that affect the abdominal cavity and can also be mimicked by diseases of extraabdominal origin (Fig. 32-122).

Four important questions should be addressed while dealing with an acute abdomen in ruminants: (1) Where does the pain originate? (2) Is it a medical or surgical problem? (3) Is medical treatment indicated before surgery? (4) What is the likelihood for survival and productivity? To answer these questions, the clinician should use a systematic approach based on adequate signalment and history, complete physical examination, and judicious choice of ancillary tests. Prognosis should be based on past experiences of others as well as one's own experience.

Even though a precise diagnosis facilitates the institution of appropriate treatment and helps to better predict outcome, emphasis should not be placed solely on the diagnosis. Precise information is not yet available for accurately making a prognosis on the outcome of an acute abdomen in ruminants.

A Concise but Precise Evaluation of the Animal

An animal with acute abdomen may need immediate medical assistance. Therefore the clinician should identify life-threatening problems and take appropriate action rapidly. Acute abdominal emergencies are often associated with either hypovolemic or septic shock.[1] Hypovolemic shock is characterized by increased heart rate, pale mucous membranes, slow capillary refill time, and dehydration.[1] Increased heart rate and dehydration are also observed in case of septic shock, but mucous membranes are hyperemic or bluish in color, and scleral vessels are engorged and dark.[1] Intensive fluid therapy is the treatment of choice for both hypovolemic and septic shock.[1] Consequently, an intravenous catheter should be placed and fluid therapy instituted immediately. However, a complete history and meticulous physical examination should be performed before emergency medical therapy if the condition of the patient is stable.

History

SIGNALMENT. Signalment may identify an animal at higher risk of particular diseases. Age, sex, breed, and production stage are important parameters to take into consideration when elaborating the differential diagnosis. For example, abomasal volvulus develops more frequently in dairy cows than in beef cattle.[2,3] Similarly, uterine torsions are essentially observed at the time of parturition or in the last trimester. Colic in a wether or a buck goat should be considered a result of urolithiasis until proven otherwise.

MANAGEMENT-FEEDING PROGRAM. Feeding management system (feeding cows with silage or a total mixed ration [TMR]), herd size (dairy farms with more than 100 cows), and high-intensity milk production are risk factors associated with the development of hemorrhagic bowel syndrome (HBS).[4] Use of wire on hay bales is associated with higher incidence of TRP. Struvite urolithiasis in cattle occurs more frequently in bulls or steers fed with high-grain diets.

HISTORY AND CLINICAL SIGNS. Previous history of surgery can be associated with the development of adhesions and colic. Recent calving and obstetric manipulations may cause a full-thickness uterine tear and subsequent peritonitis. Paralytic ileus associated with hypocalcemia is reported to occur during estrus.[5] Pleuritis, pleuropneumonia, or rib fractures may mimic abdominal pain. Previous treatments, especially those that can modify clinical signs or the interpretation of laboratory results, should also be noted. Administration of analgesics such as NSAIDs may partially control abdominal pain, attenuate signs of colic, and decrease the heart rate.

Description of the clinical signs observed by the owner and the chronologic sequence of events are of particular interest. Intussusception in cattle is characterized by an acute onset of anorexia, decreased fecal output (often with dark feces containing blood) and milk production, as well as colic. However, even though the abdominal pain eventually becomes less severe, the depression progresses.[6,7] Torsion of the mesenteric root has an acute onset with severe colic and rapid deterioration.[6,8,9] Fecal output, consistency, and appearance are relevant information. Stranguria manifested by unsuccessful micturition efforts is associated with urolithiasis.

Complete Physical Examination

A thorough and complete physical examination is the most important step when approaching an acute abdomen.

VISUAL EXAMINATION. The animal's abdominal profile or silhouette should be observed from the rear and both sides to detect and characterize abdominal distention. Bilateral ventral distention is associated with small intestine disorders, whereas distention in the right paralumbar fossa is associated with cecal and/or colon disorders. In cases of abomasal volvulus, the distended abomasum can be observed caudal to the last rib in the right paralumbar fossa. Gas in the rumen causes a distended upper left abdomen, whereas some forms of vagal indigestion have a "papple" shape (pear on the right and apple on left). Lateral views of the abdomen help to determine whether the distention arises primarily from the paralumbar fossa or extends cranially under the ribs. An arched back may be observed in cases of cranial abdominal pain, sole abscesses, or laminitis (sore feet).

Abdominal pain is an important criterion in deciding if surgery is necessary. Severe colics are classically associated with some surgical intestinal conditions,[6,10] although some animals with severe jejunal distention secondary to acute enteritis may have a similar clinical

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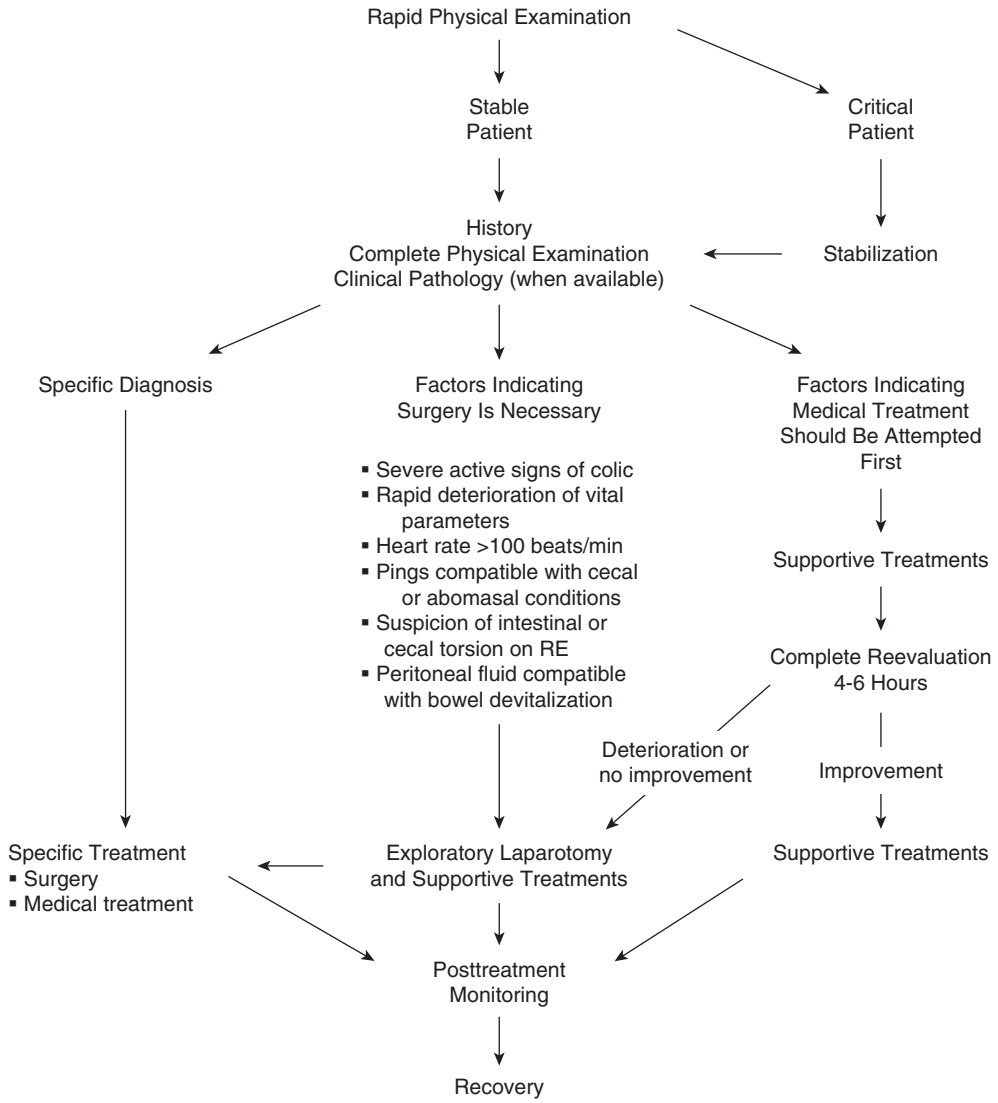


FIG. 32-121 Suggested decision tree for cattle with an acute abdomen. *RE,* Rectal examination.

presentation. Abdominal pain may be a consequence of excess distention of a hollow viscus (excessive intestinal distention), spasms of intestinal smooth muscles, stretching of the mesenteric supporting structure, intestinal ischemia, or chemical irritation of the visceral or parietal peritoneum.[11] Abdominal pain is classified into 2 main categories: visceral pain (hollow viscera and solid organs) and parietal pain (parietal peritoneum, abdominal muscles, rib cage).[11] Although the task is often difficult in animals such as cattle that have unpredictable behavior in response to pain, differentiation between visceral and parietal pain should be attempted in order to identify the cause of abdominal pain.

Pain sensation from the parietal peritoneum travels through the peripheral spinal nerves and usually localizes over the affected area.[11] Because parietal pain is exacerbated by pressure and tension modification, the patient is reluctant to move and has a tonic reflex contraction of the abdominal muscles.[12] No active clinical signs of colic are present. This is typically observed in cases of peritonitis. While reluctant the move, the animal has a splinted abdomen and is responsive to external palpation,[6] such as a positive xiphoid grunt test or not dipping the back when pinched over the withers.

Some pain fiber endings are located in the submucosa and muscle layers of hollow viscera (intestines, bladder) and in the capsule of solid organs (kidney, liver). Consequently, distention, forceful contraction, or traction will produce pain in a hollow viscus. Capsule stretching will create pain in solid organs. Visceral pain is typically recognized by active manifestations of colic: kicking at the abdomen; treading with the rear feet; lying down, standing, and stretching out and grinding the teeth. Goats may also vocalize. The animal is anxious and has an apprehensive attitude. Contrary to parietal pain, visceral pain is transmitted via sensory fibers in the autonomic nerves.[11] Visceral pain is often diffuse and difficult to localize.[11]

EVALUATION OF VITAL PARAMETERS. Assessment of cardiovascular status is essential in the evaluation of an animal with an acute abdomen. Hypovolemic and septic shocks are associated with increased heart rate, pale or hyperemic mucous membranes, slow capillary refill time, and dehydration. Normal to moderately elevated heart rate and adequate hydration status are considered good prognostic indicators regarding the outcome of abomasal volvulus.[13] Circulatory insufficiency, secondary to hypovolemia and caudal vena cava compression, is a complication of abomasal volvulus. Dehydration and acid-base abnormalities are principally caused by fluid accumulation in the abomasum and are associated with a high mortality rate.[13] Heart rate is increased secondary to hypovolemia, compression of the caudal vena cava, and sympathetic nervous system stimulation in response to distention and twisting of the abomasum.[13] Determination of rectal temperature, pulse or heart rate, and respiratory rate (TPR) should always be performed first, as manipulations performed during the physical examination of an abdominal emergency can elicit pain, modifying the heart rate.

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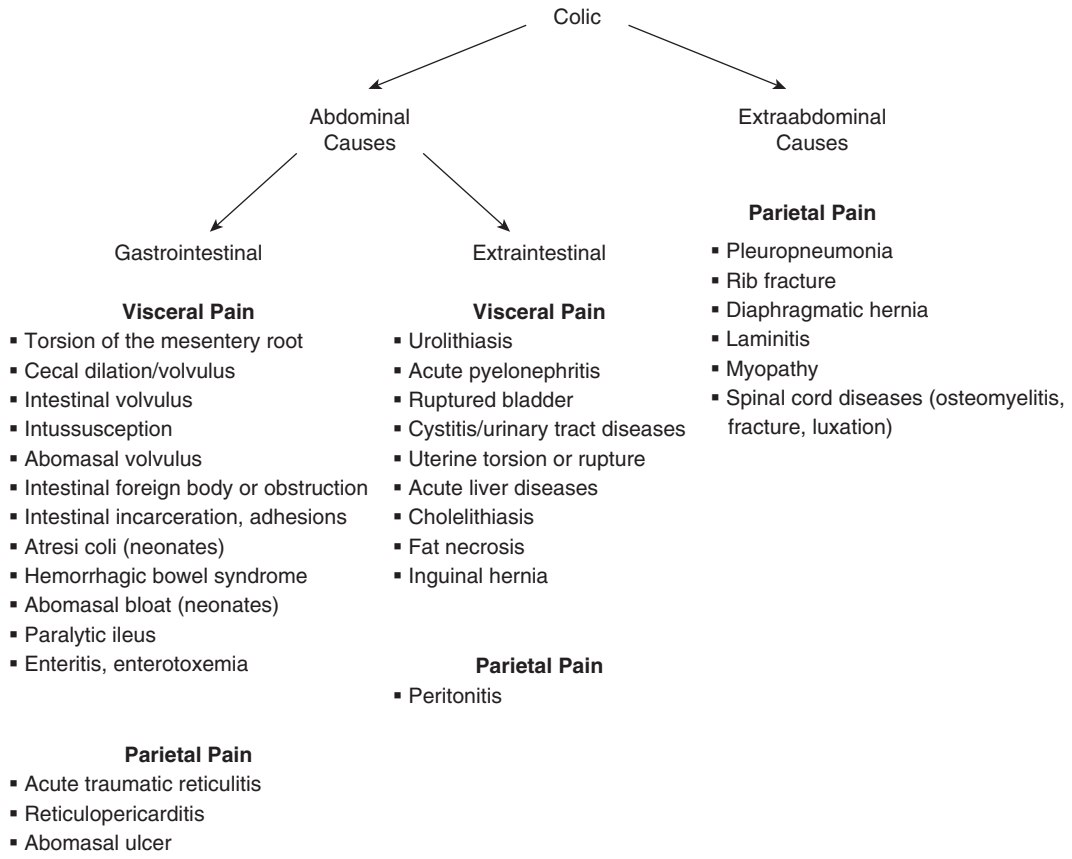


FIG. 32-122 Causes of colic (abdominal pain) in ruminants.

The TPR and amount of pain exhibited may also be used to monitor the evolution of the condition and the response to the initiated treatment.

EXTRAABDOMINAL EXAMINATION. Once vital parameters have been evaluated and the animal appears hemodynamically stable, a thorough complete physical examination of all body systems is performed. Examination of the thorax (pleuropneumonia, rib fractures) and the musculoskeletal system (laminitis, myopathy) are important in eliminating diseases that mimic abdominal pain.

ABDOMINAL EXAMINATION. Abdominal examination is performed by auscultation, percussion, ballottement, and succussion of the abdomen. Pings are tympanic resonance caused by a gas-fluid interface in a distended organ and can be detected by simultaneous auscultation and percussion. Because rectal palpation may create an area of increased resonance on the right dorsal part of the abdomen, detection of pings should be performed before rectal palpation. On the right side of the abdomen, many organs may be responsible for pings. Location, pitch characteristics and variability of the ping are essential to establish a differential and precise diagnosis. Pings localized from the thirteenth rib cranially to the ninth rib are typical of abomasal volvulus or a right-displaced abomasum.[6] Cecal dilation or volvulus creates a ping in the right paralumbar fossa and caudal quadrant,[6] often extending to the hip. Abomasal volvulus will be more likely to have a high-pitched ping, whereas animals affected with peritonitis may have a bilateral low-pitched ping in the upper paralumbar fossa. In normal animals, a monotone pinging area of 15 to 20 cm centered just under the last rib corresponds to gas in the spiral colon (see Chapter 1, Fig. 1-3). Moving or constantly contracting viscera will have changing pitch of their pings, like gas in the descending duodenum, or proximal colon. For this particular reason, it is important to auscultate and percuss for a certain period of time to notice ping variation.

On the left side, pings are principally associated with left abomasal displacement, ruminal collapse, and pneumoperitoneum. Left abomasal displacement typically creates pings dorsally from the eighth to the thirteenth ribs. Pings associated with gas in the rumen, ruminal collapse, and pneumoperitoneum are localized dorsally in the left paralumbar fossa and extend cranially to the eleventh rib. Illustrations and details are presented in Chapter 1 of this textbook. Simultaneous auscultation and ballottement (succussion) of the abdomen may permit detection of fluid-filled viscus with an interface of gas like rumen or abomasum. The location of the fluid splashing sounds on auscultation-succussion may help to confirm and differentiate among auscultation-percussion findings. Tense abdominal muscles, secondary to parietal peritoneum inflammation (parietal pain), may also be detected during succussion.

Cattle with cranial abdominal pain are reluctant to move; they stand with elbows abducted and back arched.[6] During examination, bruxism (grinding of the teeth) may be present.[6] Pain can be elicited by pinching over the withers or applying forceful movement with the knee or upward pressure with a bar or pole over the xyphoid area or anterior abdomen. In response, the animal in pain may grunt or kick and be reluctant to dip the back when the withers is pinched.[6] Sensitivity of this test may be increased by simultaneous auscultation of the trachea. Cranial peritonitis, secondary to TRP or abomasal ulcers, is an important cause of cranial abdominal pain. A complete cardiorespiratory examination may help to differentiate this from thoracic pain.

RECTAL PALPATION. Per rectum abdominal palpation of cattle is an essential part of the acute abdomen physical examination. However, the size of the abdomen limits the systems or organs that can be palpated.

Cecal disorders are clearly diagnosed per rectal palpation. Moreover, cecal dilation or retroflexion can often be differentiated by location of the apex. Based on these findings, medical treatment can be

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started if the caecum is only dilated and the apex is mobile. A firm mass palpated in multiple, dilated, turgid small intestine loops is a typical finding of intussusception[7] or HBS.[4] Adhesions between the kidneys and the rumen, the intestinal convolutions, and decreased rectal mobility in the posterior abdomen are characteristics of a chronic peritonitis. Uterine wall integrity may be evaluated during rectal palpation, although examination per vagina may be necessary to confirm a full-thickness laceration in the early postpartum cow. Feedlot steers with urolithiasis will have a pulsatile pelvic urethra and a distended bladder at rectal palpation. In cases of pyelonephritis, enlargement of one or both ureters may be palpated. Normally, only the left kidney can be palpated per rectum: If infected, it will be painful to the touch, larger, and lobulation less obvious. Pathologic right kidneys are exceptionally reached per rectum especially if hydronephrotic. In small ruminants, urolithiasis is manifested by pulsations in the pelvic urethra that may be felt by digital rectal examination. Distended bladder or enlarged kidney can be detected by deep abdominal palpation and vocalization will be elicited on palpation of the distended bladder.

Presence and macroscopic appearance of feces can be evaluated during rectal examination. Decreased, or absence of, feces is principally associated with intestinal stasis or obstruction, which may occur secondary to a direct mechanical obstruction (requiring surgical treatment) or to gastrointestinal ileus (requiring only medical treatment). However, feces may be present in the first few days following an intestinal obstruction.

Ancillary Tests

PACKED CELL VOLUME AND TOTAL SOLIDS. Shock, sepsis, and toxemia cause hemoconcentration and dehydration and are associated with an increase of PCV and total solids. On the other hand, increased PCV and decreased total solids are observed during the formation of a third compartment filled with a protein-rich fluid such as in generalized peritonitis.[14] In one study, the serum total protein concentration was significantly lower in cows with septic peritonitis when compared with cows suffering from nonseptic peritonitis.[15]

BLOOD GAS ANALYSIS AND ELECTROLYTES. Blood gas analysis as well as determination of electrolyte imbalance may be useful before initiation of treatment. Most adult ruminants with acute abdominal diseases suffer from metabolic alkalosis.[16] Metabolic alkalosis is often associated with abomasal volvulus, intussusception, cecal disorders, abomasal ulcers, peritonitis, renal diseases, and reticuloperitonitis.[16] Hypochloremia and hypokalemia are frequently combined with metabolic alkalosis.[17] Metabolic acidosis may be observed if urinary tract disease, small intestinal strangulation or obstruction, or enteritis with severe diarrhea is present.[16]

Serum chloride concentration, anion gap, and base excess have been proposed as preoperative prognostic indicators in dairy cattle suffering from abomasal volvulus. Poor short-term prognosis was associated with serum chloride concentrations less than 79 mEq/L,[18] base excess values of −0.1 or less,[19] and anion gap values of more than 30 mEq/L.[20] However, a prospective study on the outcome of abomasal volvulus reported that serum base excess and anion gap values did not differ between productive and nonproductive animals.[13] In this study, serum chloride concentration was significantly lower in nonproductive animals, but this prognostic test had numerous false-negative results.[13]

Blood gas analysis and electrolyte measurement results are helpful in the institution and monitoring of fluid therapy.

BLOOD LACTATE CONCENTRATION. Blood lactate concentration is frequently used to assess a compromised cardiovascular or respiratory system, to monitor the response to treatment, and to establish a prognosis for survival. Portable analyzers are now available, making this diagnostic test easily available. In cattle, blood lactate concentrations have been reported to be higher in animals with abomasal volvulus in comparison with animals with left abomasal displacement.[21] Elevated blood lactate was associated with a poor outcome for right abomasal displacement/volvulus in one study,[22] whereas Constable and co-workers did not find any association in their study.[23] In humans,[24,25] and horses[26] blood lactate concentrations are an important indicator of adequate response to treatment and reperfusion of ischemic tissues.

COMPLETE BIOCHEMICAL PROFILE. Evaluation of specific enzyme activity (e.g., hepatic enzymes, BUN, and creatinine) combined with physical examination and other ancillary tests may be useful in establishing a diagnosis and assessing progress.

WHITE BLOOD CELL COUNT AND DIFFERENTIAL. Hematologic findings are rarely specific to a condition and reflect the underlying inflammatory process. In most cases a minimal to moderate inflammatory process characterized by a neutrophilic leukocytosis is observed. Hematologic findings may also provide information about the acuteness of the disease and the severity of the sepsis and toxemia associated. Severe sepsis is associated with neutropenia, degenerative left shift, toxic changes of neutrophil morphology, and lymphopenia. Hematology is also an important ancillary test to monitor the response to treatment.

FIBRINOGEN. In ruminants, increased fibrinogen concentration is an early indicator of inflammation. Studies in cattle report that fibrinogen concentration may increase within 1 to 2 days after induction of inflammatory conditions.[27] Consequently, increased fibrinogen concentration may be observed in some cases of acute abdomen. Normal fibrinogen concentration despite severe visceral involvement should be observed only in peracute cases (within a few hours) (e.g., torsion of the root of the mesentery). Moderate to marked increased fibrinogen concentration is also the signature of chronic active localized inflammatory condition such as reticuloperitonitis, liver abscesses, or pyelonephritis.

URINALYSIS. Urinalysis is helpful in differentiating between colic of urogenital origin versus gastrointestinal disorders. Urinalysis can be rapidly performed using a urinary dipstick (Chemstrip 9, Roche Diagnostics Corporation, Indianapolis, IN) and gross morphologic examination. Renal diseases are associated with proteinuria (>1+), glucosuria, and positive blood reaction. In case of acute urethral obstruction, hematuria and proteinuria are consistently observed. Determination of urinary specific gravity before fluid may help to characterize azotemia.

ABDOMINOCENTESIS. Abdominocentesis is considered an essential ancillary test in the approach to acute abdomen in many species[1,28] including cattle.[6] Because of the ability of cattle to wall off and localize infections in the abdomen, a four-quadrant method of abdominocentesis is suggested by some authors.[6] Ultrasonography can be used to find abnormal fluid location or quantity, improving the precision of the abdominocentesis site. Fluid can be evaluated macroscopically for color, volume, odor, and turbidity. Normal values are reported in the section of this chapter on peritonitis. Peritoneal fluid changes to cloudy yellow, then blood-tinged with fibrin, and finally to black in color as bowel necrosis and hemolysis of extravasated RBCs occur. In case of generalized peritonitis, fluid is abundant, cloudy, and sometimes foul-smelling. Occasionally, digestive fibers can be observed macroscopically if rupture has occurred.

Different parameters may be evaluated in peritoneal fluid. D-dimer, lactate, glucose, alkaline phosphatase and pH of the peritoneal fluid concentrations have been reported to be indicators of intestinal ischemia and peritonitis in horses.[29,30] In one cattle study, decrease in peritoneal fluid glucose concentration was a sensitive and specific marker of septic peritonitis.[15] D-dimer is also elevated in cases of ischemic and inflammatory abdominal conditions.[15,21] L-lactate measurement could also be a useful diagnostic tool for the evaluation of various abdominal ischemic conditions in cattle.[21]

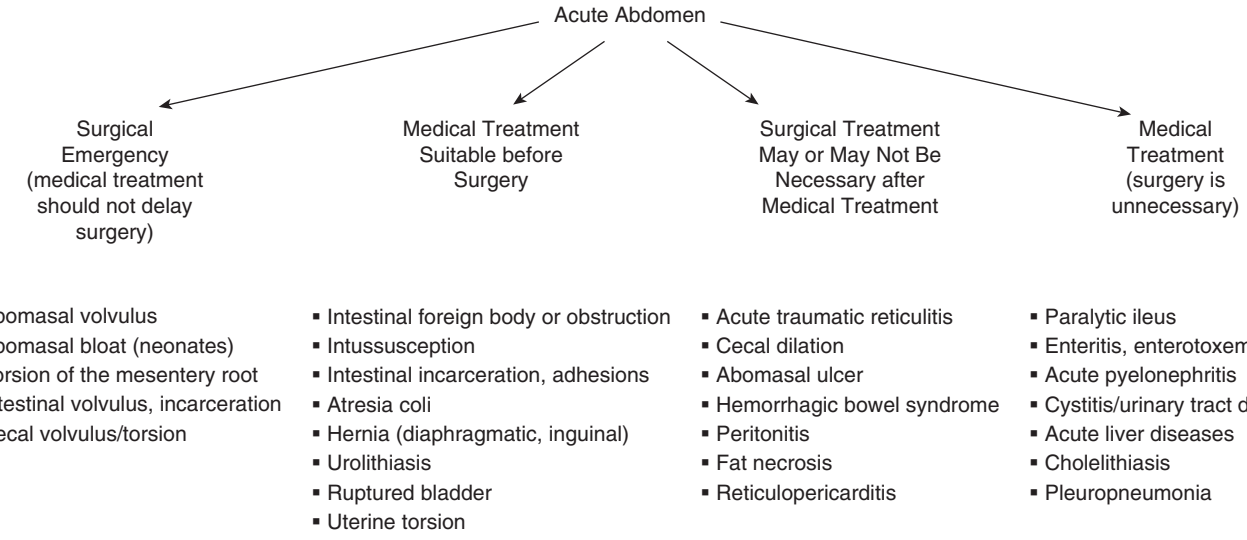


FIG. 32-123 Classification of abdominal causes of acute abdomen based on the need for surgical exploration or medical treatment.

Diagnostic Imaging

ULTRASONOGRAPHY. With the advance of multifrequency abdominal transducers, ultrasonography is used more frequently in ruminant medicine. Information on ultrasound of the ruminant abdomen is available in this chapter.

RADIOGRAPHS. Radiographic images in adult cattle are obtained with powerful machines only available in referral centers. They are one of the most helpful ancillary examinations for the diagnosis of reticuloperitonitis.[31,32] Abdominal radiographs were used for the diagnosis of intestinal atresia and intussusception in calves.[6]

A lateral view of the abdomen of small ruminants may help for the diagnosis of urolithiasis since stones in the urethra or in the bladder may be detected.

Medical or Surgical Decision

A differential diagnosis list and a decision for surgical or medical treatment should be established based on clinical signs and ancillary tests results (Fig. 32-123). If a precise diagnosis is made, adequate treatment can be instituted. When a precise diagnosis cannot be established, attempts should be made to differentiate surgical and medical cases (see Fig. 32-119). Any animals with elevated heart rate, distended organ on rectal palpation, and lacking feces are surgical candidates even if a definitive diagnosis cannot be established. Among surgical cases, intestinal obstructions are those requiring immediate surgery. A mechanical obstruction may be suspected when there is a suspicion of intestinal or cecal torsion on rectal examination, pings indicating a right abomasal displacement or volvulus, peritoneal fluid indicating bowel devitalization, or severe signs of active colic or rapid deterioration.[10] If an intestinal mechanical obstruction is not suspected during the first examination, exploratory surgery may be delayed for up to 36 hours.[33] However, frequent monitoring should be performed and appropriate medical treatment provided to the animal.

SURGERY. Most abdominal surgeries in adult cattle are performed with the animal standing under sedation and local or regional anesthesia. Cattle can tolerate intestinal resection and anastomosis standing if adequate local anesthesia and systemic analgesia are provided. However, some animals will be reluctant to stand because of the primary condition or secondary to electrolyte imbalance. Any traction on the mesentery is painful enough to make an animal go down during the procedure. Surgery should be performed with the animal in recumbency if it is extremely painful or weak and likely to lie down. Because a right paralumbar fossa celiotomy provides the best exposure to the intestinal tract, left lateral or sternal recumbency should be favored. Other than the general status of the animal, the suspected affected organ, presence of aggressive behavior, surgeon preferences, and facilities should be considered in the choice of doing the surgery with the animal standing or in recumbency. If the animal is dehydrated and/or manifests signs of shock, preoperative fluid therapy and analgesics are recommended. For the prevention of surgical infection, appropriate preoperative antibiotic administration is also recommended.

MEDICAL AND SUPPORTIVE TREATMENT. The goal of therapy in an animal with acute abdomen is to initially correct the hemodynamic and metabolic imbalances associated with hypovolemic or septic shock, to control pain, and to correct or treat the primary cause of the disease, when identified. Consequently, medical treatment is based on fluid therapy, NSAIDs, and antimicrobial drugs.

Fluid Therapy. Crystalloid solutions (0.9% NaCl, Ringer's solution) are indicated initially to replenish fluid loss and improve the circulating blood volume. To resuscitate critically ill neonatal patients, recommended intravenous fluid administration rates of isoosmotic crystalloid solution are 80 to 90 mL/kg of body weight per hour.[34] However, such rates are difficult to achieve through a catheter in adult ruminants. Studies demonstrated that perfusion rates of 40 and 80 mL of an isoosmotic crystalloid solution per kilogram of body weight per hour can be used safely in adult ruminants and dehydrated calves, respectively.[35-37] If the animal is not critically ill, fluid and electrolyte deficits should be corrected over 2 to 8 hours. The maximal flow rate usually achieved through a catheter in an adult is 15 to 20 mL/kg/h.

Hypertonic solutions (7.2% or 7.5% NaCl) are also an alternative. Intravenous administration of hypertonic saline provides rapid resuscitation in dehydrated or endotoxemic ruminants.[38] A rate of 4 to 5 mL of hypertonic solution per kilogram should be administered IV through the jugular vein over 8 to 10 minutes. Animals should be provided with a supply of fresh water immediately after the treatment, or an intravenous infusion of an isotonic crystalloid solution should be instituted. Cattle not observed to drink within 5 minutes should have 20 L of water pumped into the rumen.[38] An administration rate for a hypertonic solution of over 1 mL/kg/min should be avoided because it induces a potentially fatal hypotension coupled with a decrease in cardiac contractility.[38]

Correction of Acid-Base and Electrolyte Imbalances. Correction of electrolyte imbalances should be based on laboratory results when available. Previous treatments should be considered (e.g., intravenous calcium, orally administered magnesium hydroxide) to initiate the most appropriate fluid therapy if no laboratory

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results are available.[17] Most animals with acute abdominal diseases suffer from metabolic alkalosis, hypochloremia, and hypokalemia.

Calcium homeostasis is in a precarious balance in postpartum dairy cattle. Hypocalcemia is common in ruminants with gastrointestinal disorders or simply anorexia, particularly in lactating cows.[16,34] Moreover, metabolic alkalosis, frequently observed in cases of acute abdomen, is strongly associated with subclinical hypocalcemia.[5,39] Calcium ions are of particular importance in gastrointestinal motility. First, in the gastrointestinal smooth muscles, the channels responsible for generating action potentials are calcium-sodium channels.[40] Second, gastrointestinal smooth muscle contraction occurs in response to the entry of calcium into the muscle fiber.[40]

Based on these considerations, the intravenous solutions used for the medical treatment of acute abdomen, secondary to a suspected digestive disorder, should contain Na, Cl, K, and Ca.

The Ringer's solution containing 8.6 g of NaCl per liter, 0.3 g of KCl per liter, and 0.3 g of $CaCl_2$ per liter, yielding 147 mEq/L Na, 155 mEq/L Cl, 4 mEq/L K, and 4 mEq/L Ca, is the commercially available solution of choice. In our clinics in Quebec, we use a beneficial homemade solution composed of 7.5 g of NaCl per liter, 1.5 g of KCl per liter, and 5.75 g of Ca^{2+} per liter (25 mL of 23% calcium borogluconate per liter), yielding 128 mEq/L Na, 148 mEq/L Cl, 20 mEq/L K, and 26 mEq/L Ca, for adult cattle. We usually begin our fluid therapy with rapid administration of a 0.9% NaCl solution (15 to 20 mL/kg/h, which is the highest rate possible through a catheter) for rapid correction of dehydration and then administer this homemade solution with an infusion rate of approximately 4 to 5 mL/kg/h.

Control of Pain and Inflammation. Pain and inflammation are important causes of gastrointestinal hypomotility (see Fig. 32-122). Gastrointestinal pain increases sympathetic tone, causing general inhibition of the gastrointestinal tract.[40-42] Numerous inflammatory mediators are released during disease of the gastrointestinal tract, leading to alteration of intestinal motility.[41,43] Peritoneal inflammation or irritation and associated pain are well-recognized initiating factors of ileus in multiple species.[41,43] Release of proteinases, vasoactive substances, free oxygen radicals, and endorphins secondary to ischemia and reperfusion injury, or to endotoxemia, impairs cardiovascular function and decreases gastrointestinal motility.[43] Inflammatory mediators lead to a pain response and modulate the intensity of noxious stimuli.[41,42] Consequently, analgesic and antiinflammatory drugs appear essential in the management of acute abdomen. These drugs must be used with caution. NSAIDs may induce abomasal ulcers, particularly in an anorectic patient. Analgesics may mask clinical signs (pain, fever) and compromise adequate case management by delaying surgery.

NSAIDs are the most commonly used drugs for gastrointestinal pain management in cattle. There is no information comparing the efficacy of the different NSAIDs available in food animal medicine related to their use in the management of acute abdomen. Some authors report that, based on clinical observations, flunixin provides an excellent visceral analgesia.[44] Preoperative administration of flunixin was demonstrated to have a positive impact on animal recovery after left abomasal displacement surgery.[45] Ketoprofen and flunixin appear to have similar activities in endotoxic calves.[46] Consequently, no single NSAID can be recommended based on scientific evidence for the management of abdominal emergencies in cattle. The choice of NSAID becomes a matter of previous experience, comparative medicine, legislation, and cost. In our experience, flunixin and ketoprofen are both adequate for the management of acute abdomen in cattle. In equine gastrointestinal pain, a poor or short duration response to NSAIDs indicates a need for surgery.[42] This principle can be applied to cattle with caution because of their different behavior in response to pain.

α_2-Agonists that function as sedatives and analgesics, such as xylazine, detomidine, and medetomidine, could also be used to relieve pain in cases of acute abdomen. All are considered to be strong analgesics that can alleviate most visceral pain, at least temporarily, in equine medicine.[42] There are few data on the use of α_2-agonists for the management of acute abdomen in cattle. In a cow with a large intestinal obstruction, signs of abdominal discomfort disappear immediately after the administration of a single dose of xylazine (0.05 mg/kg IV) for at least 1 hour.[47] Different side effects must be considered before the administration of α_2-agonists. Xylazine is reported to have significant effects on the gastrointestinal tract in cattle, decreasing reticuloruminal and intestinal motility.[48] Because of the hemodynamic changes associated with the administration of α_2-agonists, these drugs must be used with caution in hypotensive patients and/or those suffering from shock.[49] α_2-agonists can mask surgical pain and delay the decision for surgery. This is particularly critical with the use of detomidine.[42] Finally, dose and administration of α_2-agonists should be used with care if standing surgery is planned, as they may encourage the animal to lie down.

Opioids, morphine or butorphanol can also be used alone or in combination for the control of abdominal pain. Information on their use in this way in cattle is lacking. To our knowledge, opioid usage was studied in cattle in castration, dehorning, and preoperative analgesia but never for abdominal pain control. In our clinic, following the diagnosis of a nonsurgical process or correction of a surgical process, we use morphine (0.1 mg/kg, IM or SC), or butorphanol (0.05 to 0.1 mg/kg, IV, IM, or SC) or a continuous rate infusion of a combination of ketamine (0.2 mg/kg/h) and butorphanol (0.02 mg/kg/h).

Finally, lidocaine may be used for their analgesic effect as well as their potential motility modifier effects. As described in horses, a continuous IV administration of lidocaine at a rate of (3 mg/kg/h) after an initial dose of 1 mg/kg (IV, over 15 min) can be administered. However, no data are actually available of its effect on the control of pain and on the gastrointestinal motility in cattle.

Antimicrobial Drugs. Bacterial translocation from the intestines can occur in cases of mechanical or functional ileus secondary to bacterial overgrowth, inflammation, and impairment of barrier function of the intestinal wall.[43,50] A systemic broad-spectrum antibiotic treatment should be instituted when a septic process is suspected, until bacterial culture results become available. This initial antibiotic therapy should be effective against gram-negative, gram-positive, aerobic, and anaerobic pathogens. The choice of antibiotic should also take into consideration legal aspects and the cost of the treatment. β-Lactams, tetracyclines, and trimethoprim-sulfadoxine appear to be good choices. In cattle there is no accepted recommendation for the duration of treatment. In human medicine, prolonged broad-spectrum antibiotic therapy in cases of surgical acute abdomen does not appear beneficial.[51] Prevention of infective complications was not affected by prolonging the course of antibiotic treatment.[51] In human medicine the current recommended dose is a single prophylactic antibiotic administration when there is no or minimal evidence of contamination, and 5 to 7 days when pus or contamination, either localized or diffuse is present.[51]

Other Treatments. The use of purgatives (magnesium hydroxide, mineral oil, liquid paraffin) in cases of suspected gastrointestinal obstruction or ileus in cattle has no therapeutic basis. Moreover, these treatments may exacerbate the condition. Because the intestines are already filled with gas and fluid, purgatives only impose additional distention. In human medicine, laxatives are frequently used for the treatment of postoperative ileus (POI); however, no study could demonstrate their actual benefit.[52] Braun and colleagues reported that the use of purgatives for the treatment of cecal disorders delayed the time to first defecation.[53] Moreover, magnesium hydroxide may be responsible for detrimental effects such as decreased potassium absorption, metabolic alkalosis,[54] sedation caused by hypermagnesemia,[54] increased ruminal pH,[55] and decreased ruminal microbial activity.[55]

Motility-modifying agents may be used in the management of gastrointestinal disorders. In most cases intestinal motility is restored when pain is relieved and electrolytic imbalances are corrected. Steiner[48] and Constable and colleagues[56] reviewed the different prokinetics that can be used in ruminant medicine and their

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clinical implications. In cattle, based on their reviews, erythromycin (10 mg/kg, IM, bid for 2 days, Erythro-200[48] or 8.8 to 10 mg/kg IM[56]) is the most effective drug for the treatment of abomasal hypomotility and can be used for the postoperative treatment of abomasal displacement or torsion. Bethanechol (0.07 mg/kg, SC, tid for 2 days, not approved for food animal use in the United States) alone or in combination with metoclopramide (0.1 mg/kg, SC or IM, tid for 2 days, not approved for food animal use in the United States), increased the contractility of abomasal smooth muscles, but no data on in vivo efficacy are available.[48,56] Metoclopramide alone is ineffective in cattle and sheep for the treatment of abomasal hypomotility.[48,56] Bethanechol (0.07 mg/kg SC tid for 2 days; not approved for food animal use in the United States) can be used for conservative or postoperative treatment of cecal disorders and treatment of paralytic ileus.[48] Contrary to cattle and sheep, in goats metoclopramide (0.5 mg/kg IM or IV; not approved in the United States) has been reported to significantly increase myoelectric activity of the duodenum.[48] Continuous infusion of neostigmine (87.5 mg in 10 L of sodium chloride-glucose infusion at 2 drops/sec per cow) was successfully used for the conservative and postoperative treatment of cecal disorders.[53] In this clinical report, this protocol was preferred to those previously reported (neostigmine SC every hour over 2 to 3 days in doses that gradually decreased from 12.5 mg to 2.5 mg.[53] Drug administration was easier and involved fewer disturbances for the animal.[53] However, no control group was included in this study. Also, neostigmine has been reported to have a pronounced effect on intestinal contractility, causing uncoordinated spikes to become more frequent, thereby compromising the potential beneficial effect.[57]

No prokinetic drug is reported to directly increase ruminal motility. In cases of prolonged anorexia or acute indigestion, ruminal flora can be disturbed and reduced. Transfaunation may help to rapidly reconstitute the ruminal flora and hasten return to normal function of the rumen and the digestive tract. The technique for and beneficial effects of transfaunation (reduction of ketonuria, increased feed intake, and higher milk yield) have been reported in the postsurgical treatment of left abomasal displacement.[58]

Follow-Up

When a definitive diagnosis cannot be made, close monitoring of the animal may be indicated. Follow-up must also be performed secondary to surgery to ensure adequate response to surgical treatment and to allow possible adjustment of treatment. In a referral hospital the animal should be reevaluated every 4 to 6 hours. In field practice, vital parameters, rectal examination, presence and consistency of feces, and pain may be reevaluated every 6 to 12 hours. A significant reduction of heart rate was observed 4 and 6 hours after the initiation of treatment in cases of cecal dilation.[53] Feces are usually passed within 4 to 6 hours after surgery in cases of intestinal volvulus or cecal disorders. Failure to defecate for 24 hours or more is abnormal in cattle and therefore indicates persistence of intestinal obstruction and may adversely affect the prognosis. Deterioration or persistence of clinical signs despite the initiation of supportive treatment is also an indication for surgery. Surgical exploration is indicated if the following clinical signs are observed: persistence of colic, development of abdominal distention, heart rate over 100 beats/min, scant feces, typical abomasal or cecal pings, or paracentesis indicating bowel devitalization.

The decision for surgery or medical treatment remains challenging in cases of acute abdomen in ruminants. Optimal management of acute abdomen prevents any unnecessary delay in cases requiring surgery and avoids unnecessary surgery. Knowledge of diseases associated with signs of acute abdominal pain is important, but no clinical signs are specific for a particular problem, and a specific diagnosis cannot be established postoperatively in many cases. Based on a systematic approach to clinical examination and a judicious use of ancillary tests, the clinician may be able to identify cases that require immediate or delayed surgery, avoid unnecessary surgery, and establish a cost-effective management plan.

Traumatic Reticuloperitonitis (Hardware Disease, Traumatic Reticulitis)

David Francoz • Charles L. Guard

Definition and Etiology Traumatic reticuloperitonitis (TRP), also called hardware disease, is a common disease of cattle but is rarely seen in small ruminants. It is the most common cause of anterior abdominal pain in cattle. The ingestive behavior of cattle predisposes them to the accidental swallowing of metal foreign objects that settle in the reticulum. Ingestion of a foreign body may also be associated with diseases that cause pica, such as phosphorus deficiency. Subsequently, the foreign object may enter the reticulum and (1) attach to a magnet and prevent any clinical disease; (2) penetrate the reticulum wall only with intramural inflammation; (3) perforate the reticulum wall, penetrate into the peritoneal cavity, and create a localized peritonitis; or (4) migrate into the peritoneal and thoracic cavities.[1] The diaphragm, pericardium, and heart muscle are located just cranial to the reticulum, with the liver positioned medially and dorsally and the spleen laterally and dorsally. These organs may sometimes be penetrated by foreign bodies and become involved in the inflammatory process.

Clinical Signs and Differential Diagnosis TRP in the most severe, acute form is characterized by fever, anorexia, decreased or absent ruminal contractions, and evidence of cranial abdominal pain. Pinching of the withers or upward pressure on the xiphoid region may elicit a grunt on expiration. Affected cattle may stand with an arched back and resist ventral flexion of the back when pinched over the withers (normal cattle flex ventrally). Some cattle grunt spontaneously when forced to move or when defecating or urinating. Lactating cows show a sudden decrease in milk production. Some cows regurgitate ruminal fluid, especially if the oropharynx is mechanically stimulated. Tachycardia, reluctance to move or lie down, mild bloat, constipation, or abducted elbows may also be seen. These typical signs often abate within the first day or two, making diagnosis more difficult. Sudden death has occurred as a result of the laceration of a coronary blood vessel or puncture of the heart by the foreign body.

Less severe or more long-standing cases may have signs that are more subtle and confusing. Cows in early lactation may have ketosis; however, a distinguishing feature of hardware disease is the abrupt onset of anorexia and hypogalactia. Fever may be absent. Weight loss, rough hair coat, diarrhea, or generalized lameness, along with cranial abdominal pain that is difficult to localize, may be the only signs.

If the pericardial sac has been seeded with bacteria, pericarditis usually develops. Clinical signs of pericarditis are presented in detail in Chapter 30. In addition to the clinical signs previously described for TRP (decreased appetite, fever, tachycardia, signs of pain), muffled heart sounds, jugular vein distention, and edema of the submandibular region, brisket, and ventral abdomen are typically observed.[2]

The foreign body may penetrate the liver or spleen, leading to abscess formation. These abscesses as well as reticular adhesions may be responsible for ruminoreticular outflow problems and may lead to vagal indigestion.[3]

TRP must be differentiated from other causes of cranial abdominal pain. They mainly include abomasal ulcers, hepatic abscesses from other causes, and pleuritis. More information about the differential diagnosis of abdominal pain is presented in the section on acute abdomen in cattle. When thoracic structures are involved, TRP must be differentiated from primary pneumonia or pleuritis, diaphragmatic hernia, and heart diseases such as endocarditis, lymphosarcoma of the heart, and cor pulmonale. Finally, TRP must be differentiated from others causes of ruminal distention and vagal indigestion (although TRP is a leading cause of vagal indigestion).

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Clinical Pathology The white blood cell (WBC) count and differential, as well as the determination of plasma proteins and fibrinogen, may indicate an acute or chronic inflammatory process depending on the stage of the TRP. Neutrophilia and a left shift, as well as hyperfibrinogenemia, are expected in acute cases. However, in more chronic cases, changes are less pronounced, and WBC count as well as differential may be normal,[1] but modification associated with chronic inflammatory diseases such as erythrocytopenia, thrombocytopenia, and hypohemoglobinemia may also be noted.[4,5] Gokce and colleagues[4] also reported longer activated partial thromboplastin time, prothrombin time, and thrombin time in cattle affected by TRP in comparison with a control group of healthy cattle.

High total plasma proteins, primarily reflecting high globulin levels, are expected in chronic cases of TRP.[4,6] Higher concentration of total plasma proteins has been observed in cases of TRP compared with other abdominal disorders.[7,8] Plasma protein concentration cutoff points of 87 to 100 g/L have been proposed in these studies. High fibrinogen concentration may be observed in acute (2 to 3 days after the beginning of the disease) and chronic cases. Studies in referral centers have demonstrated highest plasma fibrinogen concentration compared with other abdominal disorders.[7-9] Cutoff points have also been reported in these studies for the differentiation between TRP and other abdominal disorders. Jafarzadeh and colleagues[8] proposed a value of 6.91 g/L (with a sensitivity and specificity of 81% and 72%, respectively) whereas Nazifi and colleagues[9] suggested a value of 5.7 g/L (with a sensitivity and specificity of 32% and 100%, respectively). However, other inflammatory disorders can induce the same modifications, and absence of these abnormalities does not rule out TRP. Consequently, other diagnostic tests (diagnostic imaging) must be performed to confirm the diagnosis. Serum amyloid A (SAA) and haptoglobin concentrations have also been reported to be increased in case of TRP.[7,9,10] Cutoff points for the differentiation between TRP and other gastrointestinal disorders of 0.67 and 0.74 g/L for haptoglobin and 68 µg/mL for SAA have been reported. [7,9] These two parameters seem to be more accurate than plasma fibrinogen or protein concentrations for the differentiation between TRP and other gastrointestinal disorders.[7,9]

Biochemical profile and blood gas analysis are usually within normal range but may reflect anomalies associated with ileus and vagal indigestion such as hypochloremic metabolic alkalosis, hypokalemia, and hypocalcemia.[5,6] Other abnormalities reported include increases in specific and nonspecific indicators of liver damage (such as AST, ALP, LDH, and bilirubin),[1,4,5] and increases in specific and nonspecific indicators of skeletal or cardiac muscles (such as CK [CK-MB], LDH, AST, and cardiac troponin).[4-6]

Radiography and ultrasonography of the reticulum are very useful for the diagnosis of TRP. Radiographs of the reticulum are limited to referral to a location where powerful equipment is available. They are performed on standing animals and allow the detection of a metallic foreign body and the determination of its location in or outside the reticulum. Different parameters may be observed on radiographs for the diagnosis of TPR; they include presence or absence of a foreign body, position of the foreign body, presence of focal gas shadows or gas-fluid interface near the reticulum, and the shape, size, and location of the reticulum.[11-13] Of these parameters, location of the foreign body is the most reliable indicator for the diagnosis of TPR.[11,13] Ultrasonography of the reticulum is presented elsewhere in this chapter. Ultrasonography and radiography are complementary methods that provide different and useful information for the diagnosis and management of TPR.[14] Ultrasonography is also the most useful complementary examination for the diagnosis of pericardial effusion.[2]

Abdominocentesis and pericardiocentesis may be performed blind or with ultrasound guidance. Abdominal fluid analysis and its limitations in cattle are discussed in the section on peritonitis. Pericardiocentesis may be performed at the level of the point of the elbow in the fifth left intercostal space. Aseptic preparation of the skin and local anesthesia of the region to be punctured are required; pulling the left forelimb forward may be helpful. A 5- to 10-cm spinal needle or intravenous catheter can be used; the length required depends on the size of the animal and the amount of subcutaneous fat. Previous ultrasonographic examination is helpful for the choice of the needle. Caution is advised when advancing the needle to prevent laceration of the myocardium. Ultrasound-guided centesis prevents trauma to the myocardium. Visual inspection of the fluid obtained is usually adequate to confirm the diagnosis of pericarditis; it is cloudy and foul smelling. The fluid may be examined bacteriologically and cytologically.

If ileus occurs or vagal indigestion develops, analysis of the ruminal fluid may reveal elevated chloride ion concentration as a result of reflux from the abomasum and omasum (internal vomiting).

Pathophysiology The indiscriminant eating habits of cattle lead to accidental consumption of foreign bodies. Those that are of high specific gravity initially settle to the bottom of the ventral sac of the rumen. Subsequent contraction cycles of the forestomach move those objects from the rumen into the reticulum. If the object is large enough and sharp enough, it can be pushed, most often through the cranial wall of the reticulum, by the forceful, normal reticular contractions. Normal forestomach bacteria leak through the hole thus created and may establish infection locally along the foreign body. Infection also may spread as in the pericardium or locally during abscess formation. The pain and inflammation associated with the trauma and infection lead to decreased appetite and ruminal hypomotility or stasis. Agalactia is abrupt because of the acute anorexia and subsequent failure to absorb precursors for milk synthesis.

Rehage and colleagues[3] demonstrated that the disturbances of digesta through the forestomachs and the abomasum in cows affected with TRP develop in three phases. The first one, characterized by poorly comminuted feces, occurs secondary to virtual immobilization of the reticulum caused by pain and inflammatory adhesions. With extension of the adhesions, additional impairment of reticulum motility develops. At this time, stratification of the food particles in the reticulorumen is lost, volume of these two forestomachs is increased, and ruminal outflow is inhibited. Finally, the consistency of ruminal contents is changed to a pasty mass with high viscosity. Increase in viscosity of ruminal outflow leads to inhibition of the transpyloric outflow. At this time, abomasal volume increases and internal vomiting occurs.

Epidemiology There are few data available on the frequency of TRP in cattle. In one study in Denmark, TRP was diagnosed by veterinarian in 1621 cows of 222,490 in the year prior to slaughter and identified in 1521 of these cows at slaughter. It is interesting that only 48 of these cows had been diagnosed to have a TRP by a veterinarian premortem, and agreement between premortem and postmortem diagnosis of TRP was low.[15] Gröhn and Bruss[16] reported a similar prevalence (0.6%) of TRP diagnosis in dairy cattle in 1990. Data from England and Wales indicated that 141 of 2709 adult cattle carcasses submitted to the Veterinary Laboratories Agency from January 2004 to May 2008 had a diagnosis of TRP.[17] In western Canada, TRP was the most frequent of postmortem findings (8%) in beef cows and replacement heifers where tissues were submitted for histopathologic examination.[18] Most cases are sporadic, but outbreaks have occurred when such things as multistranded cable have been chopped up by a forage harvester and ensiled or when cattle have chewed nails containing charcoal from burned buildings.

The ingestive techniques of cattle allow sharp nonfood items to be prehended and swallowed. Ingestion of such items by sheep or goats is extremely rare. The disease affects confined cattle where mechanical processing of forages or construction activities increases the chances that wire or nails will be included in the feed.

Necropsy Findings Cattle that die peracutely may have a lacerated myocardium with resulting hemorrhage or cardiac

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tamponade. Diffuse peritonitis characterized by copious, foul-smelling peritoneal fluid with an obvious reticular defect may be seen in acute cases. More chronically affected animals may have extensive pericardial effusion with a thick epicardial layer of fibrin if the pericardium was penetrated. If only localized peritonitis with adhesions occurs, then the animal is unlikely to die from this. The penetrating foreign body generally is still present in the wall of the reticulum or pericardium.

Treatment and Prognosis Conservative treatment generally is attempted first and includes the administration of a forestomach magnet, parenteral antibiotic therapy, and confinement. Often the animal is confined to a stanchion or box stall. Many cattle recover after such a course of therapy with resumption of forestomach motility and appetite within 1 to 3 days. Different drugs have been used to enhance the chance of the magnet to enter the reticulum cavity. The effects of premedication with atropine, scopolamine, or xylazine and of standing the cow with its forelimbs 30 cm lower than its hindlimbs on successful administration of a magnet (i.e., adequately located in the reticulum cavity) have been evaluated in healthy cows.[19] Adequate location of the magnet was controlled radiographically 1½ hours after the administration of the magnet. None of the procedures increased the chance of the magnet being successfully placed in the reticulum. Moreover, in all groups (treatment groups and control groups) only 57% of the magnets were adequately located in the reticulum.[19] Braun and co-workers[20] demonstrated that foreign bodies that have penetrated the reticulum wall or that have clearly perforated the reticulum had about a 54% and 32% chance, respectively, to become attached to the magnet. Animals that have not significantly improved by the third day may require a rumenotomy to remove the foreign object. Ideally, radiography combined with ultrasonography is recommended at this time to verify the diagnosis and objectively assess the response to treatment,[20] but ultrasonography alone is most feasible in most practices.

During rumenotomy, abscesses that are tightly adhered to the reticulum may be drained into the lumen of the reticulum. In some instances reticular abscesses may also be drained through an ultrasound-guided transcutaneous incision,[21] ultrasound-guided insertion of a chest trocar, or insertion of a trocar during ventral laparotomy.[1] Treatment of peritonitis requires systemic antibiotic therapy and possibly drainage of the affected area; surgical correction of the inciting cause is discussed in the section on peritonitis.

Prognosis The prognosis of TRP depends mainly on the location of the foreign body and the other organs affected. The prognosis is fair to good when TRP is associated with localized peritonitis and when only the spleen or the liver is also affected. In most cases, as inflammation diminishes, the reticular function can return to normal.[22] The prognosis is poor to guarded in TRP associated with pericarditis, pleuritis, or diffuse inflammatory adhesions in the abdomen.[1,2,22]

Prevention and Control Eliminating sources of sharp foreign objects in the feed supply prevents TRP. Installation of large magnets on feed handling equipment and prophylactic administration of forestomach magnets to all animals at 6 to 8 months of age prevent almost all cases caused by magnetizable objects.

Peritonitis in the Ruminant

Gilles Fecteau

Despite the frequency with which peritonitis is suspected, it remains a frustrating disease for all food animal clinicians. A presumptive diagnosis is often based on clinical signs and history and rarely confirmed by ancillary tests. If response to therapy is satisfactory, the clinician may never confirm the diagnosis or the precise cause.

Review of the Peritoneal Cavity

Histology

The peritoneal cavity is lined by a serous membrane composed of two layers called the *peritoneum*. The deeper layer (subserosa) is composed of loose connective tissue containing collagen, fat cells, reticular cells, and macrophages. Covering that layer is a single-surface layer of mesothelial squamous cells (serosa). On the surface of the diaphragm, special lymphatic collecting vessels are located under the mesothelial basement membrane. Small stomata are found between mesothelial cells. They act as channels for lymphatic drainage from the peritoneal cavity to the thoracic duct.

Normal Peritoneal Fluid

The peritoneum acts as a bidirectional semipermeable barrier to the diffusion of water and low-molecular-weight solutes between the blood and the peritoneal fluid. Peritoneal dialysis uses this principle to treat renal failure. Normal peritoneal fluid provides lubrication for the movement of abdominal organs and apposed peritoneal surfaces. It is formed and resorbed constantly. Normal fluid movement is achieved by movement of the viscera and contraction of the diaphragm during respiration. A normal animal has no more than 1 mL of peritoneal fluid per kilogram of body weight.[1] In acute severe peritonitis, the inflammatory process may induce a net flow of liters of proteinaceous fluid (80 mL/kg/day in humans), leading to hypoproteinemia, hypovolemic shock, or both.[2]

Several authors have described normal peritoneal fluid values.[3-10] Without a systematic review with a meta-analysis, it appears hazardous to present the wide range of reported normal values. Each study should be appraised for its strengths and weaknesses and conclusions drawn accordingly. Later, in the diagnostic section, the author will share his personal experience with interpretation of peritoneal fluid in cattle.

Pathophysiologic Mechanism of Diseases in the Peritoneal Cavity in Response to Injury

Healing

Peritoneal regeneration and healing can occur by reperitonealization or creation of an adhesion with an adjacent nearby mesothelial surface. This adherent type of healing occurs more frequently if the inflammation is severe, with presence of bacteria and/or foreign material.

Host Defenses against Peritoneal Infection

The first mechanism of defense is physical removal of the bacteria. The second mechanism of defense relates to the response to noxious stimuli. This intense acute inflammatory response includes degranulation of peritoneal mast cells with release of vasoactive substances. This creates a net influx of fluid rich in complement and serum opsonins that can bind to the bacteria. Third, the omentum contributes to the defense mechanism by adhering to an infected and/or damaged area to wall off the problem site. Finally, the rapid movement of neutrophils, and later, macrophages, is also an important mechanism of control of infection.

Adhesions

Adhesions are defined as fibrinous or fibrous bands that create an abnormal attachment of two or more surfaces that should be moving freely against each other. Formation of adhesions is part of the healing process and should be interpreted as an effort to control an injury. The omentum is often involved in adhesions and acts as a natural sealing device to control the acute phase of inflammation. Whole blood potentiates adhesion formation by providing more fibrinogen. Adhesion may or may not be reversible, depending on the amount of organization that takes place in the process. Adhesions that are cut or broken usually rapidly reform. As the fibrin deposition process is replaced by capillaries and fibroblasts, the adhesion

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becomes solid fibrous tissue. The three major elements responsible for dissolution of the fibrinous adhesions are (1) adequate oxygen and nutrient supply for the mesothelium, (2) liberation of plasminogen-activating substance by mesothelial and submesothelial cells, and (3) control of the inflammatory process.[2] Mechanical obstruction to the normal flow of ingesta and subsequent development of bowel obstruction are major undesirable side effects of formation of adhesions.

Peritonitis

Definition and Etiology Peritonitis is an inflammatory process involving the peritoneal cavity and its serosal surface, the peritoneum. Peritonitis is not a true synonym of intraabdominal infection because the latter is defined as an inflammatory response of the peritoneum to microorganisms and their toxins that results in purulent exudates in the abdominal cavity. Peritonitis should be considered as the localized equivalent of the systemic inflammatory response syndrome (SIRS), whereas intraabdominal infection is the localized equivalent of sepsis. Intraabdominal abscess is an intraabdominal infection confined within the abdominal cavity. Because most often in farm animals peritonitis is caused by bacteria, the two terms are often used as synonyms. The peritoneal inflammation may result from trauma, surgery, or vascular damage associated with an intestinal obstruction and/or accident or from gastrointestinal ulceration (Box 32-8). Peritonitis is a serious and complex process that is often accompanied by various degrees of abdominal pain, changes in gastrointestinal motility, progressive signs of hypovolemia and septicemia, and/or endotoxemia.

BOX 32-8

Causes and Examples of Peritonitis in Approximate Order of Frequency

Traumatic Perforation

Traumatic reticuloperitonitis
Septic abdominal surgery
Vaginal perforation in heifer during coitus
Penetrating wound

Visceral Rupture

Perforated abomasal ulcer
Perforated ulcer in other part of gastrointestinal tract (oak toxicity of other cause)
Abomasal rupture after torsion
Small intestinal rupture after volvulus, strangulated hernia, intussusception
Ruptured bladder secondary to urolithiasis
Spontaneous uterine rupture during gestation or dystocia

Abscess Formation and Possible Intraabdominal Rupture

Reticuloperitonitis, localized
Liver
Umbilicus
Perimetritis
Pyelonephritis

Iatrogenic

Intraperitoneal injection of irritant solution or contaminated solution
Uterine rupture during dystocia
Perforation of the uterine wall with a pipette
Rectal tear secondary to palpation

Miscellaneous

Hematogenous with systemic infection: tuberculosis, septicemia
Fat necrosis

Classification Peritonitis may be classified according to the clinical presentation and/or the cause. Clinically relevant classifications include acute versus chronic, septic versus chemical, localized versus generalized, and primary versus secondary. Although it is useful to classify types of peritonitis, it is imperative to recognize that it is a dynamic process. An apparently localized nonseptic peritonitis can evolve toward a more diffuse septic process if the primary cause is not resolved.

Pathophysiology After peritoneal injury or contamination, mesothelial cells initiate an inflammatory response, modifying the permeability of the peritoneum and its vascular supply. Several blood constituents are then able to move into the peritoneal cavity. Macrophages and polymorphonuclear cells, humoral opsonins, natural antibodies, serum complement, and a protein-rich fluid are the most important. The inflamed peritoneum also becomes more permeable to toxins, allowing them to be absorbed into the bloodstream. Although this initial response is beneficial to the organism, it induces several systemic abnormalities that the clinician must recognize and treat adequately.

Hypovolemia, hypoproteinemia, bacteremia or septicemia, and toxemia are commonly observed in acute diffuse septic peritonitis. The major adverse effects of peritoneal contamination are (1) rapid clearance of bacteria, producing endotoxemia and/or bacteremia; (2) rapid influx of fluid rich in protein, leading to hypovolemia and hypoproteinemia; (3) deposition of fibrin, occluding lymphatic drainage, contributing to abdominal distention, and enhancing the chance of abscess formation; (4) ileus; and (5) adhesion formation, which may lead to obstruction.

Clinical Signs and Diagnosis Clinical signs are often nonspecific but suggestive of gastrointestinal dysfunction. Severity of clinical signs ranges from mild recurrent discomfort caused by a localized abscess to an acute severe onset of toxemia and hypovolemia leading rapidly to death after the sudden rupture of a viscus. Cattle suffering from acute peritonitis tend to show more characteristic signs. As the condition becomes less acute, the ability of the bovine to seal the infection will attenuate the clinical signs. Chronic but active peritonitis remains to this day a very difficult diagnosis to make without ancillary tests. Abdominal rigidity and tenderness, abdominal distention, scleral injection, fever, anorexia, and sudden reduction in milk production are classic but not pathognomonic findings of acute peritonitis. In the acute stage, abdominal pain and the release of catecholamines often lead to a complete gastrointestinal stasis and ileus. The rumen is then completely atonic. Feces are abnormal in quantity and quality. In the acute stage, feces are present in small amounts and often dry. In more chronic cases, feces are present with a tendency to be diarrheic. Pain, decreased plasma volume, and endotoxemia often result in persistent tachycardia. Anterior abdominal pain, evaluated by the withers pinch test, may be difficult to interpret. This procedure is based on the normal reflex of the bovine to drop its back when the withers and back are pinched (ventroflexion). Cattle with anterior abdominal pain may be reluctant to ventroflex on withers pinch. The sensitivity of this test can be increased by simultaneous auscultation of the trachea during the manipulation. Production of an expiratory grunt is considered a sign of pain during ventroflexion. Cranial ventral pressure with the fist, knee, or some other external force (transverse pole under the abdomen) just behind the xiphoid can help identify the presence of pain (expiratory grunt) and even localize it in some cases. It is my impression that one of the most reliable clinical signs of abdominal discomfort in cattle is reluctance to move. Scleral injection, fever, tachycardia, gastrointestinal stasis, and distention are the clinical signs that should be monitored to evaluate peritonitis.

Ancillary Tests Hematologic findings associated with peritonitis range from a completely normal hemogram to severe leukopenia with degenerative left shift and presence of toxic neutrophils, depending on the severity of the peritoneal contamination. In severe

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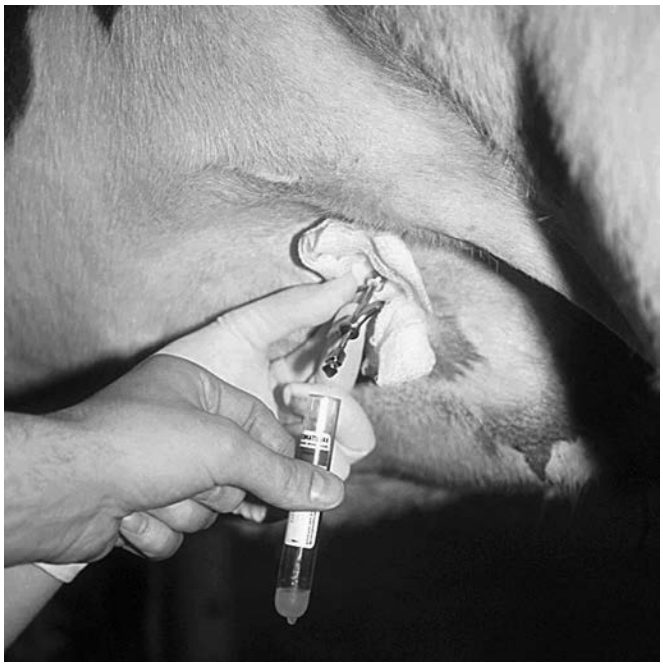


FIG. 32-124 Site of caudal abdominocentesis.

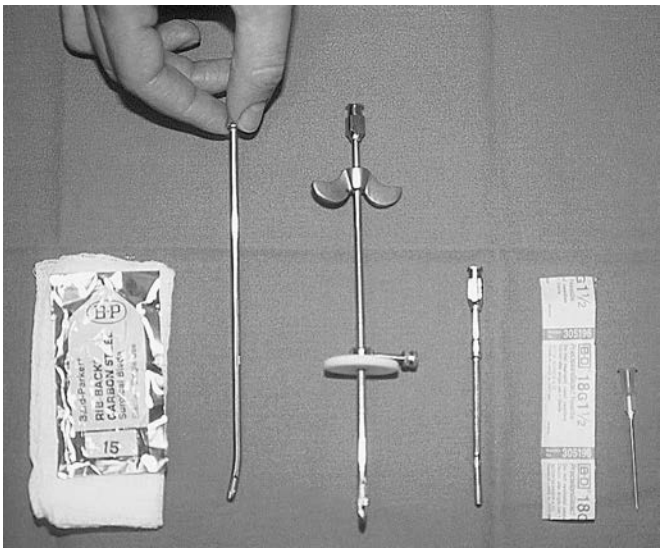


FIG. 32-125 Material used to perform abdominocentesis of the bovine.

cases variations observed reflect the degree of sepsis and toxemia. Packed cell volume (PCV) tends to increase as proteins decrease. In less severe cases, a neutrophilic leukocytosis and hyperfibrinogenemia are often present. Hematologic analysis has been a useful tool to monitor response to therapy after a diagnosis has been made by other ancillary tests. Plasma fibrinogen concentration is also used to monitor the progress of a particular case.

The blood chemistry profile is rarely altered by peritonitis in a way that is diagnostically useful. Chronic inflammation causes a marked increase in serum proteins, particularly the globulin portion. In acute severe cases, secondary findings may include increased serum urea nitrogen and creatinine, mildly increased liver enzymes, reduction in total CO_2, and strong ion difference and reduction in serum albumin. Ileus and upper gastrointestinal stasis may result in marked hypochloremia and alkalosis.

In our experience, abdominocentesis followed by cytologic examination of the peritoneal fluid is a useful aid in making a definitive diagnosis of peritonitis. The technique is simple and without complications. The right side just cranial to the udder is the preferred site (to avoid stomach and omentum) (Fig. 32-124). A needle, a blunt teat canula, or a bitch catheter and scalpel blade may be used with success (Fig. 32-125). The heavy fascia of bulls makes a needle preferable. It is imperative to remember that failure to secure fluid is common and should be interpreted with caution (because fibrinous peritonitis with fluid loculation is common). More than one site should be attempted if no fluid is secured on the first attempt. Interpretation of values and what is considered normal appears difficult when the entire literature is searched.[3-5,11] Recent publications have tried to establish better reference values for cattle.[10] Unfortunately, the range seems extremely wide even in the normal cattle population. Here are some of the criteria we have been using over the years based on some older literature and personal experience. Normal fluid is clear and often in small quantity. Easily collecting a large amount of fluid should arouse suspicion. A sanguineous fluid leads to suspicion of a compromised bowel problem (e.g., intussusception). A cloudy fluid leads one to lean toward peritonitis. Any foul smell is enough to conclude that septic peritonitis is occurring. Cytologically, the total number of cells is not as important as the differential. More than 50% neutrophils is suggestive of a septic process. The protein concentration should be less than 30 g/L (recent publications move the cutoff value higher than this number). No bacteria should be visualized. After exploratory celiotomy and omentopexy on normal cattle, peritoneal fluid has increased specific gravity, total protein, and white blood cells (WBCs) for at least 6 days, even without any peritonitis.[12] One should remember that because of the bovine's ability to deposit fibrin and seal areas of the peritoneal cavity, the interpretation of peritoneal fluid analysis applies only to the immediate area that was sampled. The clinician can be misled to conclude that a nonseptic process is occurring on the basis of a caudal tap, when in fact a septic process has already been sealed by the fibrin deposition in the cranial abdomen.

Abdominal radiographs using a high-power unit are extremely useful in cases in which traumatic reticuloperitonitis (TRP) is suspected. They have limited value in other causes of peritonitis. Ultrasound examination is useful for assessing the size and anatomic relationships of lesions, particularly when considering drainage, aspiration, or surgical exploration of a mass surrounding vital structures (see the section on ultrasound in this chapter). Knowledge of the underlying anatomy is important to prevent misinterpretation. Recognition of free abdominal fluid is easily accomplished by ultrasound examination, and it is also useful to guide a peritoneal tap. Areas that should be scanned include the caudal lower flank area (right and left), right perirenal area, liver, abomasum and pylorus, and right paramedian area. During exploratory surgery, ultrasound can be used to image an internal mass or a viscera appearing abnormal. Intraoperative ultrasound is performed by placing the probe in a sterile sleeve filled with ultrasound gel.

Surgical exploration is often used to confirm or rule out an intraabdominal problem. Information obtained from physical examination and laboratory data is often indicative of a diagnosis but does not provide a specific cause. Cattle are particularly amenable to exploratory surgery, as the procedure is performed when they are standing and is not often associated with complications. Recent advances in minimally invasive surgical technique in cattle are promising. Laparoscopy can be used to diagnose acute and chronic peritonitis, which is otherwise difficult to identify with ultrasound or abdominocentesis. It is easier to evaluate the extent of the lesions with the organs in situ.

Treatment

The basic elements of therapy are support, antibiotics, and surgery.

SUPPORTIVE THERAPY. Depending on the severity of the process, the patient may be in shock. Large volumes of isotonic intravenous fluids and correction of any acid-base deficit are indicated. Electrolyte abnormalities (hypokalemia and hypocalcemia) should

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be identified and corrected. If the animal is hypoproteinemic, plasma or whole blood transfusions may be beneficial. Nonsteroidal and/or steroidal antiinflammatory drugs may be of importance to prevent the synthesis of more inflammatory mediators. Pain control is also important. Transfaunation with normal rumen fluid may be beneficial in cases of prolonged anorexia.

ANTIBIOTIC THERAPY. Systemic antibiotic therapy should be instituted as soon as a decision to treat is made. Until results of culture and antimicrobial susceptibility become available, a broad-spectrum antibiotic should be used. The choice should take into consideration the following: cost of treatment, permitted use in and withdrawal period in food animals, spectrum of activity, and treatment regimen (frequency and route). Tetracycline or a β-lactam antibiotic (third-generation cephalosporin or a synthetic penicillin) appears to be a good choice. Diffusion into the peritoneal cavity is not a major limiting factor, because the permeability of the peritoneum is always increased in peritonitis. However, when fibrin becomes organized and forms multiple small pockets of infected peritoneal fluid, diffusion becomes more problematic. Duration of therapy is empirical in the bovine. In our clinics, we normally recommend at least one week of intravenous therapy followed by another week of intramuscular therapy. Some clients elect to have the 2 weeks of therapy in our hospital and we then maintain them on intravenous antimicrobials.

SURGICAL THERAPY. Surgical control of peritonitis includes peritoneal débridement, irrigation, and drainage. Using ultrasound guidance, it is possible to safely establish drainage from the abdominal cavity. A thoracic chest trocar can be used temporarily until all fluid has been removed.

The concept of abdominal lavage during surgery was adopted by human surgeons around the turn of the century and has been accepted as a part of the treatment of peritonitis since then with fluctuating support.[13] Although the principle of removal of any gross contamination is not in question, the level of aggression with which clinicians should institute abdominal lavage during surgery is still open to debate in human and veterinary literature. There is evidence of a negative effect of lavage on the mesothelial cells, the peritoneal defense mechanisms, and the risk of spreading the infection.[13] The solution used to irrigate is also under debate. There is no significant advantage to adding antibiotics to the lavage solution, and controversy exists regarding the possible advantages of adding an antiseptic.[13] In the bovine, large amounts of fibrin may be deposited in a short period of time; in combination with the omentum, this makes drains plug and become rapidly ineffective.

Prognosis The ultimate outcome of a bacterial peritonitis episode is determined by many factors, some of which are controlled by the clinician. The early decision on treatment (medical and surgical), correct choice of antimicrobials, and adequate supportive therapy contribute to the success or failure of a therapy. The owner's delay in seeking therapy, the primary cause of peritonitis, and the patient's age are important factors beyond the clinician's control. When aggressive therapy is economically possible, survival rates will be good, but long-term sequelae may compromise a complete recovery.

Miscellaneous Conditions

Ascites

Ascites is a collection of serous fluid in the peritoneal cavity. It must be considered as a secondary sign rather than a primary diagnosis. In that regard the primary cause must be identified in order to treat the patient adequately. Common causes of ascites in ruminants include severe liver disease and congestive right-sided heart failure. Young cattle with mesothelioma have remarkable ascites. Ascites remains an uncommon condition that needs to be differentiated from septic causes of peritonitis and from urine accumulation with ruptured bladder.

Pneumoperitoneum

Pneumoperitoneum is commonly observed postsurgically in the bovine. Presence of air in the abdomen can be recognized by simultaneous percussion and auscultation. A low-pitch resonance can be auscultated in the upper flank on both sides of the abdomen. Presence of pneumoperitoneum normally resolves in the week after surgery. No clinical signs seem associated with the presence of pneumoperitoneum, although some clinicians describe abdominal pain associated with no other cause than the presence of air in the peritoneal cavity. Pneumoperitoneum not associated with surgery is indicative of bacterial peritonitis and the presence of gas-producing bacteria (see Box 32-8).

Retroperitoneal Abscess

Retroperitoneal abscess is a particular condition occurring in cattle after a flank laparotomy. Animals are often presented several days after surgery. They are mildly febrile, not performing adequately, and showing clinical signs compatible with peritonitis. The skin wound is often unremarkable, but some pain may be elicited while the flank area is palpated. A substantial mass may be palpated per rectum, localized in the upper quadrant of the side of the previous surgical approach. The mass will be firm, smooth, unmovable, and close to the previous flank incision, and may have adhesions attached to it. Transabdominal or rectal ultrasound examination reveals a large amount of fluid located between the peritoneum and the rectus abdominis or the internal oblique of the abdomen. More superficial abscesses can also occur. A needle aspiration allows visual inspection of a thick, opaque, foul-smelling fluid. Treatment is aimed at establishing drainage and systemic antimicrobial therapy. A large volume of purulent and fibrinous material (up to 40 L) can be removed from the abscess. Rapid decompression may provoke hypovolemic shock, and intravenous fluids should be administered before a large abscess is drained. Prognosis is good, but the recovery phase is extremely long because of the large cavity left after drainage. Early closure of the drain is often observed, necessitating reopening. Some clinicians effectively use Penrose drains as they close a contaminated flank wound, to prevent serum accumulation in the wound and stave off the development of an abscess.

Frothy Bloat

Gilles Fecteau • Charles L. Guard

Definition and Etiology Frothy bloat results from the formation of stable foam in the rumen. Ruminal tympany is synonymous with bloat. The condition may be fatal if the distention is extreme enough to compromise ventilation by compressing the thoracic viscera. Cattle are more susceptible than sheep, but the disease does occur in small ruminants.

Clinical Signs and Differential Diagnosis The degree of forestomach enlargement varies from that producing an even filling of the left paralumbar fossa to that causing a uniform, extreme abdominal enlargement when the animal is viewed from the rear. With intermediate degrees of distention, the left paralumbar fossa bulges beyond the contours of the last rib and the tuber coxae. Clinical signs of colic may be seen, including kicking at the abdomen, treading, frequent lying down and rising, and vocalizations. Some animals adopt a stretched stance with the rear feet placed far back. Sheep with heavy fleece may be significantly bloated without the changes in abdominal contour being obvious. As the forestomach enlarges and compresses the diaphragm, breathing becomes more labored. Open-mouth breathing, cyanosis of mucous membranes, and collapse leading to death may occur within a few minutes if the animal becomes frantic from the abdominal pain and respiratory

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distress. Other conditions to consider in the diagnosis of frothy bloat in ruminants include other causes of ruminal enlargement: free gas bloat and vagal indigestion. Many systemic conditions influence the motility of the forestomach and thus may produce mild bloat coincidentally.

Clinical Pathology Clinical pathologic measurements are not necessary for the diagnosis and management of most cases of frothy bloat in ruminants. Evaluation of a sample of ruminal contents may provide useful information for prescribing treatment and prevention. The presence or absence of froth and the pH are critical features relating to the cause that influence the choice of therapy. The normal pH of the rumen varies with time after feeding but should be between 5.4 and 6.8.

Pathophysiology Regardless of the cause of forestomach distention, the process may become self-perpetuating because of reflex inhibition of motility. Low-threshold stretch receptors in the ruminal wall augment cyclic forestomach contractions when stimulated. However, stimulation of high-threshold stretch receptors leads to inhibition of motility. Thus, beyond a certain degree of stretching of the ruminal wall, further contractions that may relieve the distention through eructation are prevented.[1]

Frothy bloat is caused by the retention of gases of fermentation within the mass of ingesta that fail to rise and coalesce into a dorsal gaseous layer. This condition can arise from diets of lush legumes or winter wheat pasture or may be seen with high-concentrate finishing rations in the feedlot. In the case of legume-induced disease, bloat has occurred after grazing or feeding of fresh-cut forages or the feeding of alfalfa hay. The structure of stable froth in the affected ruminal contents is not true foam. The ingesta in the septa between adjacent bubbles form a complex structure that prevents coalescence. The viscosity of the fluid may prevent gravitational flow through the septa that would lead to the bubbles' rising and coalescing. Frothy ruminal fluid is higher in chloroplast membrane fragments, soluble protein, and very fine particles than is nonfrothy ruminal fluid.[2] The presence of the resulting frothy ingesta at neural receptors believed to be near the cardia prevents the reflex relaxation of the cardia during the secondary contractions of the forestomach that ordinarily lead to eructation.[3] In addition, the viscosity of the frothy ingesta is such that the cardia may become plugged during attempts to eructate.

Risk factors associated with the occurrence of frothy bloat can be categorized as animal risk factors, plant characteristics (species and maturity), and weather conditions.[2] Individual cattle have been classified as having either high or low susceptibility to legume bloat. Highly susceptible cattle have been shown to have larger ruminal volumes and specific salivary proteins in consistently different proportions compared with bloat-resistant cattle. There is a relationship between plant factors associated with bloat and the rapidity with which leaf structure is disrupted after ingestion.[2] Bloat-inducing plants are more readily macerated, thus providing quicker bacterial access to the inner leaf cells. Less bloat-predisposing cultivars of the main bloat-causing species, such as alfalfa *(Medicago sativa),* red clover *(Trifolium pratense),* and white clover *(Trifolium repens),* have a thicker leaf cuticle, smaller stomata, and a more fibrous leaf structure. Ionophore antibiotics such as monensin inhibit ruminal protozoa that normally ingest chloroplasts, leading to a reduction in the bloat potential of some forages.[4,5]

Grain bloat occurs in a manner similar to that caused by legumes; a stable froth is produced from high-concentrate rations. Particle size and the rate of fermentation are thought to be the determining factors in the froth production. A mucoprotein slime composed of bacterial by-products stabilizes the froth.[4,6] This material tends to be stable at a lower pH than is found in non–grain-fed ruminants, so grain feeding promotes slime accumulation by lowering ruminal pH. Animals (such as dairy cattle) that are fed grain and then legumes may be particularly susceptible to frothy bloat because all the factors leading to froth production and accumulation are present. Both legume bloat and grain bloat may resolve spontaneously if the animal stops consuming the bloat-producing feed and microbial digestion eliminates the froth-stabilizing factors.

Acute distress, often appearing as abdominal discomfort, is caused by overdistention of the forestomach that stimulates pain receptors in the ruminal wall. As the abdominal distention increases, the ability to achieve normal respiratory movements of the diaphragm and rib cage is impaired. This exacerbates the anxiety and distress. Death from asphyxia ultimately results as the lungs are compressed by the cranially expanding diaphragm, and venous return via the posterior or caudal vena cava is compromised.

Epidemiology Frothy bloat often occurs as an epidemic. Pasture bloat may occur wherever alfalfa, red clover, or white clover is grazed. Environmental conditions that produce rapid, early growth lead to a higher incidence of bloat. Frothy bloat also occurs when stocker cattle are grazed on winter wheat pastures in the southern Great Plains of the United States. Death losses at pasture range from 0.5% to 2.5% of cattle at risk on an annual basis. The incidence of feedlot bloat has been estimated at about 1%, with death losses of about 0.1%.[2]

Necropsy Findings The finding of tenacious froth in the rumen, along with other evidence of bloat, is grounds for a presumptive diagnosis of frothy bloat. The challenge for the diagnostician is to determine if the bloat occurred before death; this may not be possible if the animal was not observed before death. The increase in intraabdominal pressure prevents venous return from the hindquarters and may lead to obvious edema in the intermuscular areas. Unfortunately this is not a consistent finding; other evidence of impaired circulation or a differential degree of edema between fore and hind parts must be used to make a diagnosis.

Treatment and Prognosis Passage of a stomach tube is indicated to determine the cause of the ruminal distention and possibly initiate treatment. A sample of the ruminal contents for pH measurement should be obtained at this time. Care must be taken to exclude saliva from the tube by blowing into the rumen, flushing water through the tube, or using a ruminal sampling device that carries the tip of the stomach tube down into the liquid ingesta. If no gas can be released with a stomach tube, the tube should be withdrawn after suction has been applied and examined for the presence of froth. If the animal is not in respiratory distress or extremely colicky, surface-active agents should be administered by means of a stomach tube. Poloxalene or mineral oil can be used.

Some cattle are in violent pain with bloat but not in respiratory distress. Sedation with xylazine may be necessary for further examination and treatment. Animals with extreme distention of the forestomach and in respiratory distress require immediate surgical intervention. A trocar introduced through the left paralumbar fossa after local anesthesia relieves bloat caused by free gas accumulation but may not be adequate for frothy bloat. An emergency rumenotomy may be necessary to evacuate frothy contents.

Prevention and Control Prevention of frothy pasture bloat relies on the general principle of decreasing the rate of rumen fermentation. To significantly modify the rate of rumen fermentation, grazing management strategies and controlling pasture yields and quality remain the most common methods applied to a population. Cattle could be fed other feeds before being turned out and could be allowed limited access to the problem forages. Accurately predicting when forages are safe has not been reliable. Strip grazing is another option allowing cattle a reduced amount of new forage every few days. The choice of forages and the stage of growth are also to be considered. Agronomists are selecting cultivars of the bloat-producing forages for slower rates of initial fermentation. These are likely to become more widely used in the regions in which bloat is a regular occurrence. When grazing strategies and pasture management are not enough, then as an alternative, cattle at risk have been treated

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with supplemental surface-active agents such as poloxalene or oil. In Australia and New Zealand, oils and tallows have been drenched daily, sprayed on fields, and smeared on the flanks to be later licked off, to prevent pasture bloat. Although poloxalene has proved effective, it is more expensive than oils. It can be fed in molasses blocks or individually administered. Ionophore antibiotics such as Rumensin (monensin; 1 mg/kg daily) greatly reduced the incidence of legume bloat. Beginning treatment before exposure to the bloat-inducing feed was more effective than waiting until bloat occurred.

Providing adequate fiber in feedlot rations and slowly introducing higher proportions of concentrates, particularly corn, barley, and soybean meal, permit ruminal adaptation that helps prevent bloat.

Abomasal Displacement and Volvulus

Gilles Fecteau • Charles L. Guard

Etiology Although the precise cause of displacement of the abomasum remains unknown, general agreement exists in veterinary literature that it is a multifactorial syndrome and that abomasal hypomotility is an absolute prerequisite. Abomasal motility can be decreased in many ways. Numerous common disorders of postpartum dairy cattle have been incriminated as possible triggering events to abomasal dilation and displacement. Among the most important, ketosis, low serum calcium, hyperinsulinemia, and reduced insulin sensitivity have been studied and reported in recent publications.[1-6]

Prevalence and Incidence Abomasal displacement occurs either to the right or to the left side of the abdomen when gas accumulates within this viscus. Left-displaced abomasum (LDA) is the more common, accounting for most of the cases. By far the highest incidence is in adult dairy cattle in the early postpartum period, but cases have been seen in all other classes of cattle. LDA is probably a worldwide problem. The prevalence among dairy herds is variable depending on multiple factors such as geographic location, climate, management practices (confinement vs. pasture), and feeding practices.

Pathophysiology After abomasal atony, distention with gas produced by microbial fermentation occurs and most likely precipitates the displacement. It has been hypothesized that the displacement will be oriented (left or right) according to the size of the rumen. If the rumen is small and empty (as in the early postpartum period), the abomasum can move to the left and LDA can occur (Fig. 32-126). A large and filled rumen will make the left displacement less likely, and the abomasum will dilate and in some cases twist to the right (Figs. 32-127 and 32-128).

Surgical Therapy Numerous surgical techniques exist with advantages and disadvantages.[7] All techniques have a common objective to create a permanent attachment usually by suturing either the abomasum or the greater omentum to the abdominal wall. This prevents reoccurrence. The techniques may be classified into three different broad categories: blind technique, surgical (open) technique, and laparoscopic technique. Another way to look at the different options is to classify the techniques as performed on a standing animal or in recumbency. Multiple factors influence the technique used or recommended for a particular case. Cost and preference of the surgeon are very important. Recently, laparoscopic technique has been described and studied.[8-11]

All techniques have been successful when performed adequately. Recently, the less invasive techniques have been studied to evaluate the possible advantages over the more invasive open techniques. The advantages are time to perform the surgery, less frequent use of antimicrobials, a shorter interval from calving to first service, and a faster abomasal emptying.[12-15] Understanding the limitations of each technique will allow the clinician to best serve the patient and client

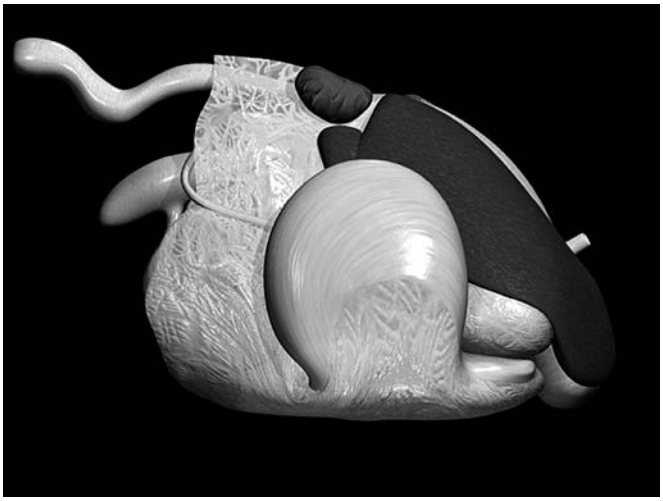


FIG. 32-127 Schematic view of a right-dilated abomasum. *(Courtesy André Desrochers, from Surgery of the abomasum in cattle, Version 2.0, Université de Montréal.)*

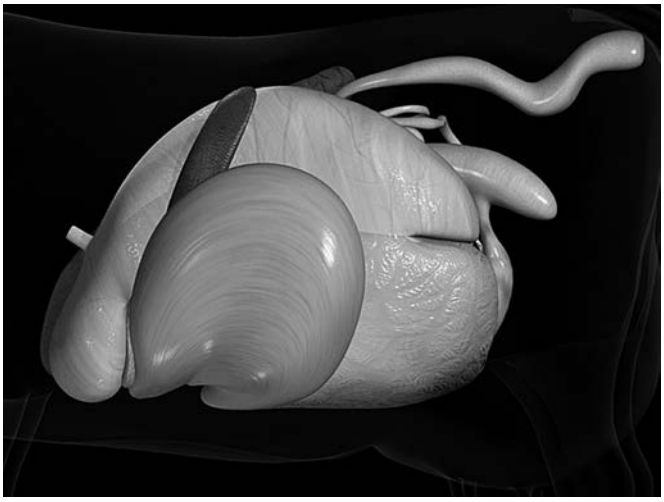


FIG. 32-126 Schematic view of a left-displaced abomasum. *(Courtesy André Desrochers, from Surgery of the abomasum in cattle, Version 2.0, Université de Montréal.)*

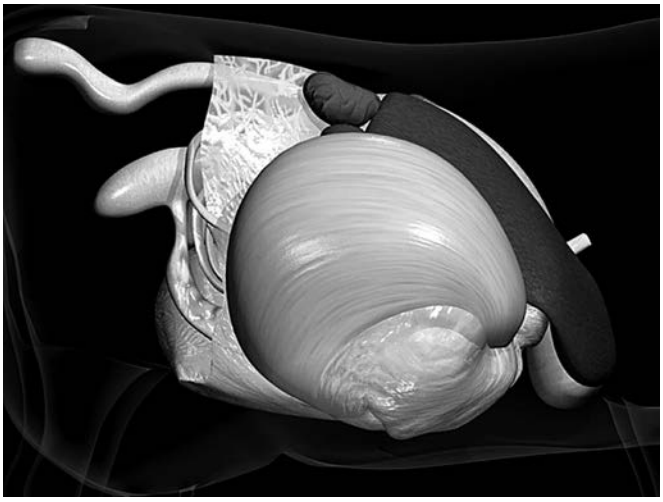


FIG. 32-128 Schematic view of an abomasal volvulus *(AV)*. *(Courtesy André Desrochers, from Surgery of the abomasum in cattle, Version 2.0, Université de Montréal.)*

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in all situations. Success rates and possible economic advantages of having the procedure performed by herd personnel have been discussed in the literature.[16,17]

Left Displacement of the Abomasum

Clinical Signs and Differential Diagnosis Cattle with simple LDA have a reduced appetite (complete anorexia, reduced consumption of concentrates, or alternating periods of normal appetite and anorexia). Milk production is reduced. Ketosis is usually present, either as a predisposing factor or as a consequence. Feces are often normal to softer than normal but reduced in volume. Rectal temperature is normal, unless a concurrent infectious problem is present (metritis, mastitis). Pulse and respiration rates are normal or slightly above normal, unless a concurrent or secondary problem is present. Ruminal contractions are decreased to absent and difficult to hear because the abomasum interferes with transmission of the sound. It is not unusual to observe the animal ruminating despite the displaced abomasum. The last one or two ribs on the left are sprung, but the abdomen is sunken in the paralumbar fossa. Gurgling or tinkling rather than normal scratching sounds may be heard on auscultation in the left paralumbar fossa. Simultaneous auscultation and percussion reveal a ping over the gas-filled portion of the abomasum. With LDA the area of ping may be anywhere from the lower third of the abdomen in the eighth intercostal space to the paralumbar fossa (see Chapter 1, Physical Examination). Attention should also be given to the cranial and lower aspect of the flank because in some cases the ping will be audible only in this area. On rare occasions, during rectal examination the clinician may be able to palpate the abomasum to the left of the caudodorsal blind sac of the rumen or at least perceive that the rumen is displaced medially.

Ruminal tympany, pneumoperitoneum, and collapsed rumen may all produce pings on the left side of the cow. Physometra (air in the uterus) and dilation and displacement of the cecum to the left of the rumen (which is rare) may also produce left-sided pings. Having an assistant blow on the stomach tube passed into the rumen while auscultating over the left side differentiates the rumen from other structures. Percutaneous needle aspiration of fluid or gas from the suspected abomasum aids in correct identification. A pH of less than 4.5 as determined with wide-range pH paper or the odor of abomasal gas (slightly acrid or burned almonds) confirms the presence of LDA. Ultrasound examination could also be helpful in determining the position of the pylorus and to compare the position with the actual normal variation.[18]

Clinical Pathology The most important abnormalities detected by clinical chemical evaluation usually are the serum electrolyte, acid-base levels, and liver metabolism and integrity. Sequestration of the hydrochloric acid secreted into the abomasum or by means of reflux in the ruminoreticulum may occur and lead to metabolic alkalosis. The blood pH and bicarbonate concentration are slightly elevated, with a concomitant small decrease in the blood chloride concentration. Ketosis is frequent and liver enzymes are often elevated, reflecting a degree of hepatic lipidosis.[6,19,20] The serum calcium level may be below normal as a result of decreased intake and absorption. Hypokalemia may develop as a consequence of both the metabolic alkalosis and reduced intake and absorption. Cattle with LDA tend to be hypophosphatemic.[21]

The complete blood count (CBC) analysis may reveal a mild dehydration and a stress leukogram. If LDA is combined with bleeding abomasal ulcers, it may produce severe anemia. The presence of a concurrent disease may lead to specific changes (e.g., left shift with acute coliform mastitis). The peritoneal fluid of cows with abomasal displacement reveals changes compatible with ischemia and inflammation.[22]

Epidemiology Cows in early lactation (particularly the first month) are at greatest risk of developing LDA. The overall incidence is highly variable among herds and related to nutrition program and related problems. Retained placenta, metritis, and increased serum concentration of β-hydroxybutyrate (BHBA) were associated with a greater risk for LDA.[3] Cows identified with subclinical ketosis early in lactation (3 to 5 DIM) were 6.1 times more likely to develop an abomasal displacement compared with cows identified later in lactation.[1] Serum BHBA above 1200 μmol/L in the first week following calving were associated with an increased risks of subsequent abomasal displacement (OR = 2.6).[2] On a herd basis, in one study in Sweden, large herd size, high maximum daily milk yield, keeping dry cows in one group, and not cleaning the feeding platform daily appear to be important risk factors for a high incidence of abomasal displacement or clinical ketosis.[23] The same research group also identified that high-incidence herds have a lower metabolic index and a higher incidence of ketosis than low-incidence herds.[5] The metabolic index used was the revised Quantitative Insulin Sensitivity Check Index (RQUICKI). Genetic factors may also play a role in the predisposition to LDA. Fox suggested that body depth had increased in dairy cattle since 1945 and that this may provide more room for the relatively empty abdominal viscera to move about at parturition.[24] More recently, cows selected for large body size had significantly greater health cost, related mostly to the greater incidence of LDA.[25] Also, the depth of the abdomen and the vertical distance between the ventral abdomen and the descending duodenum were greater in cows with a previous history of LDA ($n = 44$) than in the controls.[26] Some evidence exists to support a genetic basis for predisposition to LDA, and perhaps this is mediated through body size or conformation.

Treatment and Prognosis Treatment for LDA involves returning the abomasum to its normal anatomic location and preventing reoccurrence ("pexy"); treating the electrolyte, acid-base abnormalities, and energy metabolism problems (ketosis and hepatic lipidosis); and providing therapy for concurrent disease conditions. Prognosis for LDA is good but is influenced by the severity of the concurrent disease. Cattle with severe hepatic lipidosis and LDA should be given a guarded prognosis, as their recovery is often slow and incomplete. Also, some cattle will develop LDA as a consequence of gastrointestinal malfunction. As an example, LDA could be diagnosed in an animal suffering chronic indigestion. The prognosis of this group of cattle is poor because the primary disease is often more serious than the LDA per se.

Prevention and Control The incidence of LDA has been reduced in problem herds by dietary manipulation that reduces the likelihood of forestomach and abomasal atony caused by high-concentrate rations. This includes slow introduction of concentrates after calving, prepartum introduction of ensiled and concentrate feeds, and increase in the particle size of the forage. Maintaining serum calcium concentration around parturition and reducing subclinical ketosis early in lactation are of particular importance. Dietary cation-anion difference (DCAD) is a reliable method of controlling hypocalcemia in dairy cows (see Chapter 41).

Right Displacement of the Abomasum

Simple right displacement of the abomasum (RDA) occurs at approximately 10% to 15% the frequency of LDA.

Clinical Signs and Differential Diagnosis The general systemic state of the cow with a simple RDA is the same as that of the cow with LDA. On the other hand, as the simple RDA evolves toward the volvulus, the systemic changes observed in cattle with abomasal volvulus progressively appear. An area of tympanitic resonance is heard on the right side with simultaneous auscultation and percussion. The ping usually is confined to an area under the last five ribs in the upper half of the abdomen. The condition must be differentiated from other causes of right-sided pings, such as cecal distention (with or without volvulus), gas in the spiral colon,

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pneumorectum after rectal examination, pneumoperitoneum, physometra (gas in the uterus), and abomasal volvulus. Cecal and rectal pings usually are detectable in a linear pattern just below the transverse processes of the lumbar vertebrae extending to the tuber coxae (see Chapter 1, Physical Examination). Rectal examination identifies the gas-filled structure. Pings heard with gas in the spiral colon typically have a variable pitch, depending on the location over the cranial paralumbar fossa and last three or four ribs. Generally the spiral colon may be palpated per rectum as a laterally flattened, mildly distended viscus adjacent to the right body wall. Gas in the uterus can be detected per rectum. Pneumoperitoneum creates a ping that is distributed all along the dorsal portion of the abdominal cavity and is usually heard on both sides.

Abomasal volvulus is the most difficult to differentiate from RDA. Determination of the difference by physical diagnosis in an early case of abomasal volvulus is probably impossible. With time the cow becomes progressively more dehydrated and more severely ill with volvulus than is usual with RDA. Heart rate (above 100 beats/min), ruminal motility (totally absent), and fecal output (almost none) are clinical signs in favor of a diagnosis of abomasal volvulus. Advanced cases of volvulus also have a ping that has an arched dorsal border and a horizontal ventral border caused by the fluid level in the abomasum. This fluid is auscultable on succussion of the abomasum. Even using ultrasound to determine position of the liver, omasum, small and large intestine, the two conditions could not be distinguished from one another.[27]

Treatment and Prognosis Surgical treatment is required to correct RDA. Because of the difficulty of differentiating RDA from early volvulus, intervention should be as prompt as possible. The prognosis for a successful recovery after surgery is comparable to that for LDA if no other concurrent disease is present.

Abomasal Volvulus

Abomasal volvulus, or right torsion of the abomasum, leads to complete obstruction of the flow of ingesta into the duodenum and therefore is a surgical emergency. The condition occurs in all classes of cattle. Although RDA is thought to precede its development, unknown factors lead to abomasal volvulus.

Clinical Signs and Differential Diagnosis The systemic effects of the gastrointestinal obstruction that results from abomasal volvulus progress to a much more severe degree than in LDA or RDA. Sunken eyes and loss of skin turgor accompany the dehydration that develops. The heart rate increases above 100 beats/min, and the pulse is weak and thready. Abdominal distention is marked bilaterally. Complete ruminal stasis develops, leading to bloat, and the abomasum greatly enlarges on the right. Despite the severe degree of gastric distention, colic rarely develops in cattle with abomasal volvulus; it is much more likely with cecal distention. The skin is cool to the touch. Feces are absent or watery but scant. A large area of tympanitic resonance with uniform pitch throughout is detectable on the right, extending from the eighth rib to the middle of the paralumbar fossa. The ventral border of the ping is a horizontal line reflecting the fluid level in the greatly distended abomasum. Borborygmi are absent. Splashing fluid sounds can be heard when the abomasum is ballotted (succussed) behind the last rib.

Other causes of proximal intestinal obstruction and torsion of the intestinal mass around the root of the mesentery must be differentiated from abomasal volvulus. On rectal examination the abomasum can usually be palpated with abomasal volvulus. With intestinal obstruction or intestinal volvulus, distended loops of small intestine can be palpated. Pings caused by gas in the intestines have a variable pitch over the area involved. Cecal distention with rotation can produce a similar degree of abdominal distention high on the right, but the abdomen usually is less filled cranioventrally on the right. A ping extends to the tuber coxae, and the cecum can be palpated per rectum. Diffuse peritonitis leads to complete atony of the gastrointestinal tract, and the abdomen may become distended with gas in all parts of the tract; there is no discrete ping extending over a large area of the right side. As abomasal volvulus progresses, cattle become recumbent and depressed. Death occurs within hours of this stage, which occurs 1 to 3 days after the development of the volvulus.

Clinical Pathology The serum biochemistry profile will show much more dramatic changes with abomasal volvulus than with RDA or LDA. Clinicopathologic consequences include hypovolemia, dehydration, hemoconcentration, metabolic alkalosis, hypochloremia, hypokalemia, and paradoxic aciduria. Hyperglycemia, hypocalcemia, and hyponatremia may also be observed. Later in the condition a superimposed metabolic acidosis is also present. Anion gap gradually increases with the severity of the disease. Systemic shock eventually causes fatality. Reduced fluid intake and sequestration of large quantities of chloride-rich fluid in the stomachs (third space problem) leads to dehydration and hypovolemia. Hyperphosphatemia was also observed, possibly as a consequence of decreased renal blood flow.[21]

Under the influence of carbonic anhydrase, hydrogen ions are normally pumped into the abomasal lumen. A chloride ion follows into the lumen, whereas bicarbonate and sodium remain in the blood. Under normal circumstances the HCl leaves the pylorus, where the hydrogen ions are neutralized by pancreatic and intestinal secretions and the chloride is resorbed. When abomasal volvulus occurs, the HCl is sequestered in the abomasum and regurgitated into the omasum and rumen (internal vomiting). Ruminal chlorides increase. The animal becomes alkalotic and hypochloremic. Because of shifts between intracellular and extracellular compartments, potassium moves intracellularly as hydrogen ions move extracellularly in response to the metabolic alkalosis. This, plus the total anorexia, leads to severe hypokalemia. The hallmarks of abomasal volvulus are metabolic alkalosis, hypochloremia, and hypokalemia.

Paradoxic aciduria occurs in the face of metabolic alkalosis, when the cow should be retaining hydrogen ions. The overwhelming renal physiologic drive appears to be sodium retention. Dehydration and reduced cardiac output result in falling blood pressure. The animal must respond by volume expansion; thus sodium is resorbed in the renal tubules. Chloride is also resorbed. Because there is hypochloremia, the electrical gradient that must be corrected is high; if 140 mEq/L of sodium is resorbed and only 60 mEq/L of chloride is available, there is a net of 80 mEq/L (140 − 60) of cations that must be secreted back into the tubules. This is normally accomplished by secretion of potassium. Because hypokalemia is severe, hydrogen ions are paradoxically secreted to retain electrical neutrality so that blood pressure can be maintained by means of maximum sodium resorption.

Peritoneal fluid (PF) of cattle with abomasal volvulus was studied recently (n = 15).[22] Cows suffering from abomasal volvulus when compared with cows with a diagnosis of LDA had significant PF parameters. Total protein, albumin, L-lactate, CPK, ALP, LDH, and D-dimer were increased while fibrinogen was decreased. Also, a higher percentage of apoptotic and necrotic neutrophils was detected despite the fact that total leukocyte count was not significantly different. At least in one study, evidence of abnormal coagulation profile reflecting possible disseminated intravascular coagulation (DIC) was present in a small proportion of cattle studied (3 of 10). Hemostatic dysfunction could be present in advanced stages of the disease.[28]

Pathophysiology At least some of the factors predisposing to LDA or RDA probably contribute to the development of abomasal volvulus. Whether true RDA precedes abomasal volvulus is not known. Dissection of naturally occurring cases of abomasal volvulus demonstrated that the structures involved in rotation can vary from the reticulum to the omasum at the orad end. The rotation probably occurs most frequently at the reticuloomasal junction. The duodenum is looped around the omasum, regardless of the degree of volvulus. The ensuing displacement leads to a counterclockwise rotation of the abomasum and omasum as viewed from the right side and the

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rear. The duodenum is pulled medial to the body of the omasum and wraps around the neck of the omasum in the final configuration. The continued hydrochloric acid secretion of the abomasum and the gas produced in the omasum and abomasum further stretch and occlude the duodenum. The abomasal blood vessels and the ventral vagal trunk are compromised near the site at which the duodenum wraps around the omasum in long-standing cases. Thrombosis of vessels may occur.

The acid-base and electrolyte abnormalities of early abomasal volvulus are the same as those of LDA. In cases of severe distention of the abomasum and omasum with vascular compromise, systemic cardiovascular insufficiency develops. Reduced perfusion of peripheral tissues may lead to metabolic acidosis terminally. Hemoconcentration develops, although bleeding into the abomasum may occur from devitalized mucosa, leading to a low hematocrit. These changes are compounded by the developing necrosis of the abomasum. The abomasum may physically leak contents through a weakened, overstretched wall. Endogenous inflammatory mediators and bacterial toxins may diffuse from the abomasum to viable surrounding tissues, where absorption occurs. In either case, the viability of the abomasum is lost, and death follows shortly. At least in a sheep model of abomasal volvulus, ischemia and reperfusion injury occur.[29]

Treatment Immediate surgical intervention usually is necessary to save the animal's life. At the same time, fluid, electrolyte, and acid-base abnormalities need correction. For early cases of hypokalemic, hypochloremic alkalosis and dehydration, intravenous fluids consisting of 20 to 80 L of 0.9% sodium chloride with 25 to 100 mEq/L potassium chloride added are administered. Intravenous potassium should not be given at a rate greater than 1 mEq/kg/h to prevent cardiotoxicity. If the serum potassium level is unknown, it is best to stay with an IV rate under 0.5 mEq/kg/h. For advanced cases with metabolic acidosis, balanced electrolyte solutions such as Ringer's solution are indicated. Broad-spectrum antibiotics are appropriate if the integrity of the abomasal mucosa is questionable. NSAIDs are indicated to control pain, inflammation, and shock. Both standing right-sided and recumbent right paramedian approaches have been successful for correcting abomasal volvulus. There may be less cardiopulmonary compromise if the animal remains standing, especially if reperfusion injury is suspected to occur.

Prognosis Establishing an accurate prognosis before surgery would be optimal because at that time salvage remains a possibility and little expense has been incurred. It is not a simple task. A second critical time is shortly after surgery in cows suspected to not fully recover. The decision will be whether to continue to treat (cost) or salvage, if that still is an option.

Preoperative assessment is difficult. In our experience, assessment cannot be based on a single clinical observation or serum biochemistry value. The best published studies looked at two different classifications of outcome: death versus survival and productivity versus nonproductivity. A logistic regression model, looking at heart rate, base excess, and serum chloride level, was developed as a preoperative predictor of death or survival.[30] The study by Constable and colleagues found that four presurgical variables (hydration, heart rate, duration of inappetence, and PAL level) could be used to best predict cattle as productive or nonproductive after surgery.[31]

Assessment of outcome following surgery has been investigated. The overall success rate of surgery varies between 61.5% and 86.3%.[32-35] The number of forestomachs involved in the twist has been found to adversely affect survival and productivity. Wallace found only 20% success in cattle with reticuloomasal-abomasal volvulus.[35] Another study reported success in 55% of cattle with omasal-abomasal volvulus and 87% success in cattle with only an abomasal volvulus.[31] Edema of the abomasum carries a guarded to poor prognosis.[35-37] Edema around the proximal duodenum was associated with a poor outcome in Pearson's study, but Fubini and co-workers found no association with outcome.[36,38] Purple discoloration of the abomasal serosa tends to bode poorly for long-term outcome, as does total distention of this organ, abomasal necrosis, and thrombosis of the gastric veins.[30,35] The measurement of intraluminal pressures of greater than 16 cm Hg also carries a poor prognosis because of mucosal damage.[31] A logistic regression model using some of the surgical findings did not predict outcome any better than with the preoperative model.[30]

After surgical correction, cattle with abomasal volvulus often have diarrhea for 24 hours. Feces then firm up to normal consistency. Postoperative clinical signs associated with a poor prognosis include melena, anorexia, persistent tachycardia, and dehydration.[33,37,39] In our experience, even if appetite and general attitude are initially good (24 to 48 hours after surgery), persistence of a loose low-volume stool 72 hours after surgery may indicate complications.[40] Once clinical signs compatible with chronic indigestion develop, the survival rate is only 11.5% to 20%.[35,41] Prolonged treatment seems irrelevant. Prokinetics and their possible benefit in postoperative care was recently studied and reviewed.[42,43] Erythromycin (10 mg/kg) given preoperatively ameliorates abomasal motility in cattle suffering from abomasal volvulus.

Necropsy Findings Cattle that die of abomasal volvulus are grossly dehydrated, and the abomasum is greatly distended or ruptured. The omasum often is also greatly distended when torsion occurs at the reticuloomasal junction. Cattle that die or are euthanized after developing postoperative complications have one or more of the following postmortem lesions: gastric compartment dilation, peritonitis, abomasal wall necrosis or ulcer, vascular thrombosis, or vagal nerve lesions.[40]

Prevention and Control Because factors predisposing to atony of the forestomach and abomasum probably are important in the genesis of abomasal volvulus, prevention should be similar to that outlined for LDA.

Abomasal Ulcers

David Francoz • Charles L. Guard

Definition and Etiology Abomasal ulcers occur in cattle of all ages and rarely in sheep and goats. Signs of loss of gastric epithelium may range from no clinical signs, to hemorrhage and subsequent melena, to peritonitis if the erosive processes penetrate all layers of the abomasum. The exact cause of abomasal ulcers is still obscure and may be multifactorial. In calves, development of abomasal ulcers has been proposed to be associated with mineral deficiencies (mainly copper),[1,2] stress,[3] proliferation of microorganisms (*Clostridium perfringens* type A or D, *Escherichia coli,* Sarcina-like spp., fungi, or others),[3,4-8] and/or abrasion of the abomasal mucosa by roughage, geosediments, or trichobezoars.[9] However, all of these hypotheses have failed to demonstrate alone their involvement in the development of abomasal ulcers.[3,6,10] In adult cattle, the disease is associated with stress such as recent parturition, peak milk production or presence of concurrent diseases (mainly those of the peripartum period), and with diets high in starch.[11,12] Lymphosarcoma of the abomasum may also lead to clinical signs of ulcer disease. Finally, abomasal ulcers are an adverse effect of antiinflammatory drugs.

Clinical Signs and Differential Diagnosis Smith and colleagues[13] have classified abomasal ulcers into four types: (1) nonperforating, (2) nonperforating with severe blood loss, (3) perforating with local peritonitis, and (4) perforating with diffuse peritonitis (Table 32-18). These classifications are useful for describing the various clinical pictures that may be observed when examining an animal with abomasal ulceration.

The mildest form (type 1) is caused by nonperforating ulcers that do not result in extensive hemorrhage. Affected animals may have mild or no clinical signs. The signs are mild abdominal pain, shown by partial anorexia, decreased ruminal motility, and mild ruminal

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TABLE 32-18

Abomasal Ulcers

Type	Lesions	Clinical Signs
Nonperforating	Mucosal and some submucosal tissue loss; focal mural thickening; local serositis	Partial anorexia; decreased ruminal motility; positive fecal occult blood
Nonperforating with severe blood loss (bleeding)	Penetration of mucosa and submucosal blood vessel; hemorrhage into abomasums	Partial anorexia; decreased ruminal motility; anemia; pale mucous membranes; melena; tachycardia; cool extremities
Perforating with local peritonitis	Penetration from mucosa to serosa; leakage of abomasal contents; localized peritoneal reaction with adhesion formation	Total anorexia; low-grade fever; decreased to absent ruminal motility; localized abdominal pain; very similar to traumatic reticuloperitonitis
Perforating with diffuse peritonitis	Penetration from mucosa to serosa; widespread contamination of the peritoneal cavity with abomasal contents; significant exudate in peritoneal cavity; fibrin deposition of all serosal surfaces	Total anorexia; fever early, then hypothermia; ileus of entire gastrointestinal tract; tachycardia; shock; terminally recumbent with grunt on respiration

tympany. There is usually no febrile response. Manure may be normal or reduced in amount and stale because of prolonged transit. In some cases abdominal pain may be evident on manual pressure on the right ventral abdomen. Traumatic reticuloperitonitis (TRP) or indigestion may be suspected. In one study, about two thirds of such cows had a positive test finding for fecal occult blood.[14]

In cattle with ulcers that erode into major gastric blood vessels (type 2), blood loss can be sufficient to cause signs of anemia and hemorrhagic shock. These animals have dark blood clots in their manure or tarry, black feces with the characteristic smell of partly digested blood. The mucous membranes may be pale, tachycardia and a pounding heart may be pronounced, and the respiratory rate may be elevated. There are other possible sources of proximal gastrointestinal hemorrhage in cattle, but abomasal ulcers are by far the most common cause. Among them, bleeding abomasal ulcers must be differentiated from melena sometimes seen with intussusception or hemorrhagic bowel syndrome (HBS; see Diseases Caused by *Clostridium perfringens* Toxins, in this chapter). The packed cell volume (PCV) usually is increased with intussusception,[15] normal or increased in HBS,[16-18] and decreased with a bleeding ulcer.[19] Total anorexia and rumen stasis usually are present. The rumen may have a fluid consistency, and if the animal is able to stand, abdominal pain sometimes is evident.

Abomasal ulcers that perforate the serosal surface may lead to localized peritonitis (type 3) from contamination with abomasal contents. If the lesion is small or the local inflammatory reaction sufficiently swift, localized peritonitis results. This condition is most like TRP in presenting signs. The animal may be moderately febrile and partly or totally anorectic, and milk production may decrease acutely. There is evidence of abdominal pain, usually localized to the right ventral quadrant (positive withers pinch test). Ruminal motility may be absent, and mild bloat may be present. As with hardware disease, the signs usually abate over the course of a few days if the infection is successfully contained. In some cases the infection is confined to the omental bursa, where extensive fluid and pus may accumulate. The course of omental bursitis is much more prolonged than that of simple localized peritonitis and usually results in a guarded prognosis.

Major leakage from a perforating ulcer leads to acute diffuse peritonitis (type 4). The course of the disease usually is rapid, with signs of septic shock developing within 24 hours of the onset. Total anorexia and ruminal stasis are accompanied by tachycardia with a weak, thready pulse and a heart rate over 100 beats/min. Pain may be evidenced by grinding of the teeth or groaning. The extremities are cool, and the animal usually becomes recumbent. Abdominal enlargement may be evident as a result of both ruminal tympany and the accumulation of peritoneal fluid. Dehydration is detectable by skin pinch or by observation of the position of the eye in the orbit. Septic shock from other causes may be difficult to distinguish from that caused by perforated abomasal ulcers in the terminal stages of the disease. Diffuse peritonitis from uterine, cecal, or intestinal ruptures have the same final course. Abomasal volvulus of more than a day's duration has similar characteristics but can be differentiated by the right-sided ping and fluid in the abomasum.

Clinical Pathology Antemortem diagnosis of abomasal ulcers may be challenging, particularly in cases of nonperforating and non-severely bleeding ulcers. Fecal occult blood test may be helpful. The test is inexpensive and can be performed during the physical examination. Testing multiple samples may increase its sensitivity.[20]

Serum pepsinogen concentration has been reported to be increased in one study in cases of severe abomasal ulceration.[21] Since serum pepsinogen concentration can also be elevated in other abomasal diseases such as nematode infection, this test is not specific.[21,22] Serum gastrin concentration has also been reported to be increased in cases of type 2 ulcers in comparison with healthy cows.[12] However, the sensitivity and specificity of this test are not known.

Abdominocentesis confirms diffuse peritonitis (a large quantity of abdominal fluid is obtainable); centesis fluid may contain leukocytes with phagocytosed or free bacteria and even feed particles. In localized peritonitis the results of abdominocentesis may be normal.

Abdominal ultrasonography is also useful for the diagnosis and the evaluation of peritonitis (see section on abdominal ultrasound). Braun and colleagues reported that percutaneous ultrasound-guided abomasocentesis can be safely performed for the evaluation of abomasal fluid.[23] According to the authors, the presence of blood or hemoglobin is principally associated with abomasal ulcers.

If peritonitis is present, leukocytosis usually is present, with neutrophilia predominating in many cases. The plasma fibrinogen is increased (over 700 mg/dL) in most cattle with peritonitis. This may be evaluated in the field with a glutaraldehyde coagulation test on whole blood. The hematocrit is normal or elevated with peritonitis, but plasma protein levels may be decreased as a result of protein accumulation in the peritoneal cavity or increased if dehydration is severe. If blood loss is severe, the PCV is decreased. Cattle over 5 years of age with a bleeding abomasal ulcer should be tested for bovine leukosis virus. Results of a complete biochemistry profile or blood gas analysis are nonspecific. In most cases, they reflect a digestive stasis (hypochloremic metabolic alkalosis), but in animals in shock a metabolic acidosis may be observed. Blood urea nitrogen (BUN) may be increased. This can be a result of blood degradation in the intestine or hypovolemia and prerenal azotemia. The utility of BUN in the diagnosis of abomasal ulcers by identifying digestive hemorrhage remains to be determined.

Pathophysiology The specific events leading to erosion and ulceration of the abomasal mucosal epithelium are unknown but probably are similar to those in other species. Cytoprotective mechanisms include a mucous barrier, cloudy mucus containing bicarbonate ions to neutralize back-diffusing hydrogen ions, and high

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submucosal rates of blood flow to remove back-diffusing hydrogen ions. When these mechanisms are disturbed, gastric (abomasal) ulcers can occur. Stress, concurrent diseases, corticosteroids, and NSAIDs are among factors known to contribute.

Epidemiology Abomasal ulceration occurs in cattle of all ages. At slaughter many healthy veal calves are found to have clinically inapparent abomasal erosions and ulcers, with prevalence reported ranging from 32% to 76%.[24-27] Abomasal ulcers were observed on gross postmortem examination and histologic examination in 3.9% and 18.9% of beef calves that died between the fourth day after birth and weaning.[28] In clinically affected calves, perforation with peritonitis (rather than hemorrhage) usually develops. In clinically normal slaughter cows, 20.5% had type 1 ulcers.[29] In adult cattle with abomasal ulcers causing illness, approximately one third of clinical cases in a referral population had significant hemorrhage.[30] Of these, half had lymphosarcoma and, for the most part, were older than 6 years of age. The age of the cattle with nontumor-associated bleeding ulcers was generally younger (7 of 12 were less than 5 years old). In the remaining two thirds of the cattle, ulcers had perforated, with about half having diffused and half having localized peritonitis.[31] Most adult cattle with abomasal ulcer disease are in the first month after calving and have a concurrent disease. Many cows have been discovered to have an abomasal ulcer at surgery for displaced abomasum. Metritis, mastitis, and ketosis are the other diseases commonly seen with abomasal ulcers.

Necropsy Cattle with bleeding abomasal ulcers resulting in death are very pale and may have blood or bloody fluid throughout the distal gastrointestinal tract. The lesion in the abomasum is typically small and involves an abomasal blood vessel in the submucosa. Most bleeding and perforating ulcers were found in the fundic portion of the abomasum in the region of the proper gastric glands. The most ventral portion of the abomasum in its normal position is frequently affected.[19] Most animals have a single bleeding ulcer, but approximately 60% have one or more additional ulcers or erosions.[19] Cattle with diffuse peritonitis have many liters of foul-smelling fluid in the peritoneal cavity. Fibrin usually covers the serosal surface of all abdominal organs. The defect in the serosal surface of the abomasum is usually nearly round and 3 to 6 cm in diameter. Abomasal fluid freely enters the peritoneal cavity. Omasal bursitis may be present, with the omental recess filled with purulent to fibrinous fluid. In these cases the remainder of the abdomen may not be grossly affected. Asymptomatic abomasal ulcers (often 50 to 200) may be found coincidentally in cattle that die of septic metritis or mastitis. These ulcers generally show no signs of hemorrhage and go undetected until necropsy.

Treatment and Prognosis Treatment is aimed at correcting dietary problems, reducing stress, ameliorating concurrent disease problems, and initiating specific therapy for the clinical problems caused by the ulcer. Removal of high-energy feedstuffs and replacement with good-quality hay plus confinement to a stall are beneficial.[32] The buffer effect of food is very important for the control of abomasal pH. Consequently, the return to a normal appetite is the main goal of the treatment of abomasal ulcers.[33]

Blood transfusions may be necessary for cattle that have lost enough blood to lower the hematocrit to 14% or below. Usually 4 to 6 L given once is adequate, but repeated transfusions occasionally may be necessary. Crossmatching usually is not necessary for cattle unless repeat transfusions are performed over a period of more than 3 days. Broad-spectrum antibiotics are administered to cattle with signs of peritonitis. Principles and details on the treatment of peritonitis are described in the section on peritonitis in ruminants. Intravenous or oral fluids may be necessary to treat dehydration and metabolic or acid-base disturbances that occur concurrently. Animals with diffuse peritonitis must be given intravenous fluids with caution because of the risk of pulmonary edema associated with the low colloid oncotic pressure (COP) of their plasma.

Numerous studies have been performed to evaluate the effect of different therapeutic agents on abomasal pH of healthy calves. Results of these studies have been summarized by Constable and colleagues.[33] The therapeutic agents studied in normal calves included oral administration of an antacid agent containing aluminum hydroxide and magnesium hydroxide (25 mL and 50 mL, tid), oral administration of specific H_2-antagonists (cimetidine, 100 mg/kg and 50 mg/kg, tid; and ranitidine, 10 mg/kg and 50 mg/kg, tid), and oral administration of the proton pump inhibitor omeprazole (4 mg/kg q24h). All these extralabel treatment regimens induce an increase in mean 24-hour abomasal luminal pH. Oral administrations of the antacid agent induced a dose-dependent increase in luminal pH and were more efficacious when administered postprandially. Because some deleterious effects were observed when this antacid was administered at the dose of 50 mL tid, this should be considered the maximal dosage rate in calves.[33] Cimetidine (100 mg/kg tid) was the most effective. However, ranitidine (50 mg/kg tid) was the most cost-effective in these studies. Interestingly, the effect of omeprazole on abomasal pH decreased over the time (decreased effect observed on day 5 of daily treatment).[34] Results of these studies need now to be confirmed in ill calves. In adults, oral administration of these therapeutic agents is of doubtful benefit because of dilution in the rumen and slow release into the abomasum. Oral medications administered after stimuli that induce reflex esophageal groove closure would be more likely to have the desired effect. Traditional stimuli have included copper sulfate solutions and 10% sodium bicarbonate solution. Vasopressin (0.25 IU/kg IV) was shown to induce reliable abomasal deposition of materials given by drench to adult goats.[35] Intravenous administration of H_2-antagonists at lower doses may be efficacious, but their use by this route is cost-prohibitive ($100 to $200 USD per day) or reserved for very high-value animals. In our clinic in Quebec, we use ranitidine 1 to 1.5 mg/kg IV tid for high-value animals; our clinical impression is that this is effective.

The prognosis is good for ulcers that are neither bleeding nor perforated. For those animals that stop bleeding and those with localized peritonitis, survival and eventual return to normal function can be expected. Many dairy cattle stop lactating during the acute course of the illness and do not return to milk until the next lactation. Because abomasal ulcers generally occur within the first month after calving, most of these animals are salvaged for slaughter. Most cattle with diffuse peritonitis die despite aggressive specific therapy. Early recognition and immediate surgery followed by antibiotic and fluid therapy may save some valuable individuals. Cattle with ulcers that occur secondary to lymphosarcoma should be euthanized or slaughtered.

Prevention and Control Because the exact cause of development of abomasal ulcers is unknown, prevention is difficult. Dietary management that reduces other abomasal diseases likewise reduces the incidence of abomasal ulcers. Avoiding abrupt changes in rations and including adequate fiber sources of sufficient particle size to facilitate normal ruminal function also promote normal abomasal function. Minimizing stress caused by overcrowding, excessive competition, adverse environmental conditions, and minimizing mastitis and metritis should also reduce problems with abomasal ulcers. Elimination of animals infected with the bovine leukosis virus from the herd eliminates lymphosarcoma as a cause of abomasal ulcers. Judicious use of corticosteroids and NSAIDs is also important.

Abomasal Dilation and Emptying Defect of Suffolk Sheep

David Francoz • Charles L. Guard

Definition and Etiology A syndrome of abomasal dilation and mechanical transport failure has been described in adult Suffolk sheep.[1] The condition resembles but is uniquely different from

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abomasal impaction of cattle wintering on very poor-quality roughage. It has been mainly reported in Suffolk sheep but a similar syndrome has been described in two Hampshire,[2] one Dorset,[3] and one Texel sheep.[4] No hereditary pattern of disease has yet been found.[1,5] An abomasal emptying defect syndrome has also been reported in Toggenburg goats, which could suggest that this syndrome may therefore occur in goats.[6]

Clinical Signs and Differential Diagnosis The disease is manifested primarily by anorexia and weight loss. Most patients eventually die. Animals described in reports from several teaching hospitals were adults of both sexes.[1,5] Not all animals had all of these signs, but the following have been reported: watery green diarrhea or normal feces; ruminal tympany; pear-shaped abdominal distention; increased, normal, decreased, or absent ruminal contractions; a palpable (by ballottement) firm mass in the right lower abdomen; mild abdominal pain; tachycardia; duration of observed signs from days to months; partial to total anorexia; dullness and depression; marked to undetectable weight loss; ketonuria.

Wasting diseases of sheep include malnutrition, parasitism, dental problems, Johne's disease, caseous lymphadenitis, other chronic infections, and neoplasia. Abomasal emptying defect is distinguishable by the palpable abomasum in advanced cases and the exclusion of other possible problems. Other causes of abomasal enlargement or impaction resembling those reported in cattle must also be considered. However, when a mature Suffolk from a well-nourished flock shows weight loss and a palpable abomasum, this syndrome must be considered highly likely. Confirmation should involve response to therapy but may require necropsy or exploratory surgery.

Clinical Pathology Reports on cases seen in North America have found hematologic and blood chemical determinations of little benefit in the diagnosis. The hypochloremic metabolic alkalosis common in cattle with abomasal problems has not been consistently observed in affected sheep. Elevated ruminal chloride ion values have been the most consistent laboratory findings in published reports.[5] The normal ruminal chloride level in sheep is 8 to 15 mEq/L; affected sheep have had values ranging from 34 to 130 mEq/L due to internal vomiting. Mild hypocalcemia was observed in all cases in one report.[5]

Pathophysiology The mechanisms underlying the dilation of the abomasum and the failure to transport ingesta to the intestines are unknown. None of the problems commonly associated with abomasal impaction and dilation in cattle have been identified in affected Suffolk sheep. It has been advanced that abomasal emptying defect of Suffolk sheep may be an acquired form of dysautonomia.[1]

Epidemiology The disease has been reported mainly in sheep of the Suffolk breed and has been seen mostly in winter months in association with lambing and feeding of concentrates. Both rams and ewes have been affected. Most cases are sporadic, but at least two outbreaks have been reported.[1,5] The incidence in one report was 13 of 92 mature ewes affected in the flock during one winter.[5] In the other, 5 ewes of the same flock (200 ewes) were submitted for necropsy the same day.[1] In both studies, pedigree analysis of affected sheep in these flocks showed no hereditary pattern. One report from a diagnostic laboratory in England described abomasal impaction in a Texel ewe and in a Suffolk ram that were simultaneously diagnosed as having scrapie.[4] It remains to be seen if any causative connection exists between the two diseases. Because no antemortem tests exist for the diagnosis of scrapie, this relationship will be difficult to establish. In one study, six sheep were immunohistochemically tested for scrapie; five were negative, and one was positive and presented equivocal microscopic lesions.[1]

Necropsy Findings The abomasum is greatly distended in sheep that die of this condition. The contents are either dry or liquid but most often have resembled normal ventral ruminal sac contents. The pylorus has always been patent. Normal ingesta have been observed throughout the remainder of the intestinal tract. Incidental findings have included aspiration of ruminal contents and subsequent pneumonia, abomasal ulcer with local peritonitis, passive congestion of the liver, megaesophagus, and esophageal ulcers. Reports of histopathologic findings include no lesions other than thinning of the abomasal muscle layers (presumably as a result of stretching),[5] mononuclear cell infiltration of the main muscle layers of the abomasum,[7] and one case of myxomatous changes in the abomasal branches of the vagus nerve.[8] Chromatolytic and necrotic neurons without signs of inflammation within the celiacomesenteric ganglia were found in six of six sheep examined.[1]

Treatment and Prognosis Medical therapy alone with cathartics and laxatives has been of limited benefit. Mineral oil, dioctyl sodium sulfosuccinate, and magnesium sulfate have all been used. Neostigmine and calcium gluconate were not useful.[7] Abomasotomy has led to death from complications in many affected sheep, but those that have survived more than 2 days and have been treated with metoclopramide (dosage not reported) have shown varying degrees of recovery. Metoclopramide is a dopamine antagonist that has been used in ruminants to facilitate abomasal emptying. However, experimental studies in cattle and sheep have failed to demonstrate any beneficial effect of metoclopramide on abomasal emptying.[9,10] On the other hand, erythromycin, a motilin agonist, has been shown to increase abomasal emptying rate in cattle.[9,10] Its utility in sheep remains to be determined. Despite these successes, most affected sheep die of cachexia. Because of the expense, poor response, and risks associated with abomasotomy, this treatment is reserved for valuable breeding stock.

Prevention and Control Until more is known about the pathogenesis of this specific defect in abomasal function in Suffolk sheep, no useful recommendations for prevention can be made.

Abomasal Impaction

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Definition and Etiology Abomasal impaction is the accumulation of firm ingesta in the abomasum with failure of aboral transport. Depending on the cause, abomasal impaction can be classified as primary or secondary. In primary abomasal impaction, no underlying cause can be identified and the impaction is considered idiopathic. On the other hand, secondary abomasal impaction can be the result of feeding poor-quality, coarse roughage as the sole feed. Several animals in a herd may be affected over a short period. Calves may also have impaction of the abomasum caused by eating bedding or indigestible objects when fed low-quality milk replacers. The distended abomasum is filled with a firm mass of fibrous ingesta. Animals on low-fiber diets may consume wood or baling twine. Hairballs occasionally accumulate in the abomasum of calves. Indigestible material creates a mechanical outflow obstruction. Abomasal distention may occur with normal diets after correction of abomasal volvulus, secondary to reticuloperitonitis, or secondary to the development of adhesions between the abomasum and the rumen and/or the abdomen. Lymphoma involving the abomasum or other space-occupying lesions adjacent to the pylorus may lead to abomasal distention. These conditions are referred to as *vagal indigestion*. Abomasal emptying defects of Suffolk sheep were addressed in the previous section.

Clinical Signs and Differential Diagnosis Beef cows with abomasal impaction develop abomasal and ruminal enlargement over a period of days to weeks. Closely monitored animals have reduced feed intake and a reduced volume of firmer than normal feces. The animal may have bilateral ventral abdominal enlargement and bulging of the left paralumbar region. Ruminal contractions are

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of normal or increased frequency but are often reduced in amplitude. In the later stages of the disease, ruminal motility often is absent. Cattle with advanced abomasal impaction may be recumbent and groan with each respiration. The consistency of the ruminal ingesta, as judged by ballottement, may be more fluid than expected on the basis of the coarse diet. Other animals have a uniformly firm and distended rumen. The pulse and respiration are usually normal until the animal is near death, at which time tachycardia develops. The abomasum may be palpable as a firm mass following the right coastal arch. Rectal examination reveals a distended rumen; often the ventral sac extends to the right body wall (L-shaped rumen). The pyloric part of the distended abomasum may be palpable in the right ventral quadrant. Wintering beef cows usually are pregnant, and therefore the uterus prevents palpation of the abomasum. Feces are absent or very scant and dry. Mucus may be all that clings to the clinician's sleeve after rectal examination. Adult dairy cows have a consistently decreased appetite, but other signs are inconsistent.[1] In calves the abomasum may fill most of the abdomen and be doughy or firm on external palpation. The body condition of affected animals is invariably poor because negative energy balance precedes and is amplified by the impaction. If the abomasum ruptures, signs of generalized peritonitis occur. Death usually follows within hours of rupture.

In dairy cows, abomasal impaction should be considered in the differential diagnosis of nonspecific clinical signs of decreased milk production and appetite.[1] Conditions that cause dehydration and bilateral abdominal distention with absence of feces must be considered in the diagnosis. In many of these cases exploratory celiotomy is necessary to arrive at a definitive diagnosis.

Clinical Pathology

The hypochloremic, metabolic alkalosis typical of upper gastrointestinal obstruction in ruminants does not always develop in abomasal impaction.[1] Initially some fluid ingesta may pass through the abomasum, preventing chloride sequestration. However, some cattle have metabolic alkalosis with chloride accumulating in the rumen to a level greater than 30 mEq/L (internal vomiting). Terminally a metabolic acidosis from starvation may mask the metabolic alkalosis. Anemia and leukopenia can accompany the cachexia of chronic abomasal impaction in poorly fed animals. If abomasal rupture has occurred, profound hemoconcentration and leukopenia are present. Abdominocentesis generally is not useful in diagnosing abomasal impaction, because peritoneal fluid is abnormal only after abomasal rupture.

Pathophysiology

Animals fed roughage that is poorly digestible and incapable of meeting their energy requirements consume as much as the rumen will physically permit. The flow of ingesta from the forestomachs to the abomasum normally contains only small, finely digested particles of forage material. With chronic engorgement of highly lignified, poorly digestible forage, larger particles escape the forestomach and accumulate in the abomasum. Once a mass of fiber forms in the abomasum, further accumulation of particulate material is enhanced. With time, the mass fills the abomasum. Additional ingesta distend the abomasum to several times normal size. Also, abomasal secretion may be inhibited by the cachexia and chronic distention of the organ.

Abomasal transport failure after correction of abomasal volvulus is typical of vagal indigestion syndrome. Abomasal wall and vagal nerve damage, as well as peritonitis occurring secondary to the volvulus, prevent the return of normal abomasal muscular activity.[2] Vagal tone sometimes increases, and bradycardia is observed. Hypochloremic, metabolic alkalosis does develop frequently, with chloride accumulating in the ruminoreticular contents (>30 mEq/L). The abomasum distends moderately, presumably as a result of atony.

Pyloric obstruction caused by foreign bodies or occlusion caused by lymphoma leads to mechanical outflow obstruction and must be considered. Chloride escapes back into the rumen, and metabolic alkalosis develops. The abomasum retains motility, but it is ineffective in moving ingesta into the duodenum.

Necropsy Findings

Emaciation and a firm, grossly enlarged abomasum are consistent with primary abomasal impaction. In Holstein cows, a syndrome has also been described in which the impaction affected only the pyloric part of the abomasum.[1] The abomasal contents resemble normal, dry ruminal contents. The rumen is also enlarged but either filled with homogeneous, watery ingesta that lack normal stratification or impacted with dry ingesta, similar to the abomasum. The abomasum is dilated, flaccid, and filled with fluidy ingesta if secondary to an abomasal volvulus. Intraluminal foreign body or tumor involvement of the abomasal wall is self-evident.

Prognosis

Because most cases of abomasal impaction are quite advanced when brought to the attention of the veterinarian, treatment usually is unrewarding. In dairy cows the short-term prognosis was reported to be good (93%) for impaction that affects only the pyloric antrum and guarded (50%) for impaction involving the entire abomasum.[1] The clinician must weigh the severity of the metabolic disturbances and the likelihood of recovery. Salvage by slaughter is often the most economic recommendation. If therapeutic measures do not resolve the impaction, death usually occurs within a few days of the onset of severe signs.

Treatments

Medical management includes correction of fluid and electrolyte abnormalities. Early cases may be resolved with easily digestible feeds, aggressive fluid therapy, and oral administration of laxatives such as mineral oil (4 L daily). The use of prokinetic drugs may be indicated in order to increase abomasal emptying rate and the passage of ingesta through the pylorus. However, no data are available on the efficacy of the administration of prokinetic drugs in the specific treatment of abomasal impaction. Constable and colleagues[3] published a comprehensive review on the data available for the recommendation of the use of prokinetic drugs in abomasal disorders. They conclude that, to date, (1) erythromycin (8.8 to 10 mg/kg IM bid), is the most effective drug to increase abomasal emptying rate; (2) based on in vitro studies, bethanechol (0.07 mg/kg SC tid) is potentially effective but there are actually no controlled clinical trials demonstrating its effectiveness; and (3) finally, metoclopramide is an ineffective prokinetic drug in cattle to promote abomasal emptying rate and cannot be recommended. Pregnancy may be terminated by induction of parturition with corticosteroids and/or prostaglandin, leading to improved comfort.

Different approaches have been proposed for a surgical treatment of abomasal impaction. Rumenotomy, followed by installation of a nasogastric tube inserted into the abomasum through the omasum, can be performed. Through the indwelling tube, laxatives and emulsifiers may be given during the postoperative days to aid in softening and removing the abomasal contents. Mineral oil (8 mL/kg/day), dioctyl sodium sulfosuccinate (50 mg/kg/day), magnesium hydroxide (1 g/kg/day), and magnesium sulfate (2.5 g/kg/day) have each been recommended. Right paralumbar fossa, right paracostal, or right paramedial approaches can also be used to gain direct access to the abomasum. In our clinic, we prefer the right paracostal approach, with the animal in left lateral recumbency, for abomasotomy and removal of abomasum contents. However, even with this approach, complete exteriorization of the abomasum and exploration of the oral portion of the abomasum and omasum is not possible, particularly in large animals. Even if the prognosis for restoring the abomasal function is poor to guarded, we have some positive results depending on the cause of impaction and the extent of abomasal lesions. External massage may help break up the contents of the abomasum. Intraluminal administration of 5% dioctyl sulfosuccinate solution or saline can also be performed.[1]

Prevention and Control

Prevention of primary abomasal impaction requires proper dietary management of cattle in cold weather. Because animals outside without shelter have substantially increased maintenance energy requirements in cold, windy weather, straw or corn stover (stalks) is not adequate as the sole feed. Concentrates and better-quality forage prevent abomasal impaction.

Monitoring body condition during winter weather alerts the good manager that supplemental feed is needed before abomasal impaction occurs.

Obstructive Intestinal Diseases

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Definition and Etiology Several conditions may lead to obstruction of the flow of ingesta through the intestinal tract. These conditions can be divided into functional and mechanical obstructions. Functional obstructions (pseudoobstruction or ileus) are the consequence of neuromuscular perturbations of the gastrointestinal tract. Mechanical obstructions are the consequence of physical obstruction of the intestinal tract secondary to digestive tract lesions (intussusception, volvulus, or congenital lesions) or extradigestive lesions (mesenteric fat necrosis, fibrous adhesions, or hernia). Each of the specific diseases is discussed in the following paragraphs and summarized in Table 32-19.

Clinical Signs and Differential Diagnosis Acute manifestations of obstructive diseases include a reduced amount of feces or failure to pass feces, progressive abdominal enlargement with areas of tympanic resonance on the right side of the abdomen, and sometimes colic. If pain is severe, forestomach atony may occur. Mechanical obstructions may lead to circulatory shock and collapse. Electrolyte abnormalities depend on the site of the obstruction; those in the jejunum or near the duodenum or pylorus lead to sequestration of abomasal secretions and result in hypochloremic, hypokalemic metabolic alkalosis. Obstructions of the cecum, colon, or rectum may lead to dehydration without alkalosis. If bowel necrosis or rupture occurs, acidosis may result from the circulatory collapse that accompanies peritonitis and the absorption of toxins.

Volvulus of the Duodenal Sigmoid Flexure

A new syndrome affecting the duodenal sigmoid flexure has been reported in Holstein cattle by Vogel and colleagues.[1] The etiology and pathophysiology of this condition are not known, but the authors advanced a potential role of duodenal ulcers and/or previous omentopexy (years to months before development of volvulus of the duodenal flexure). Animals have clinical presentation resembling abomasal volvulus with anorexia, decreased milk production, scant feces, tachycardia, moderate dehydration, tympanic resonance in the tenth to twelfth right intercostal spaces, and succussion of fluid in this area.[1] Clinical chemistry revealed a severe hypokalemic and hypochloremic metabolic alkalosis as well as hyperbilirubinemia. Interestingly, those modifications were more pronounced than those observed in cases of abomasal volvulus. Confirmation of the diagnosis is made by palpation of a counterclockwise duodenal sigmoid flexure volvulus during right flank exploratory laparotomy. Treatment consists in manual reduction of the volvulus, massage of the duodenum, and fluid therapy to correct electrolytic disorders. Prognosis of the condition is reported to be fair with 22 of 29 animals that were treated successfully.

Intestinal Atresia or Stenosis

Intestinal atresia or stenosis is a congenital anomaly reported in calves and lambs. Clinical signs usually become evident within a few days after birth. Animals with anal or distal rectal atresia usually have the slowest onset of signs, whereas proximal obstructions lead to more rapid onset of signs. Malformations of the anus and rectum are believed to be hereditary,[2] and breeding of surgically corrected survivors should be discouraged. Jejunal atresia in the Jersey cow has been reported to be inherited as an autosomal recessive trait. The etiopathogenesis of atresia coli in calves is not well understood, but autosomal recessive inheritance has been reported[3] and Holstein calves seem to be predisposed.[4] Rectal palpation of the amniotic vesicle for early pregnancy diagnosis (<42 days of gestation) is also suggested to be a cofactor for the development of atresia coli.[4,5] If the anus or distal rectum is atretic, animals strain or pump their tails in an attempt to defecate. A fistulous connection may exist between the rectum and the urogenital tract (e.g., either the vagina or the pelvic urethra). Visual and digital exploration of the perineum reveals the absence of feces and may permit definition of the specific defect. Stenosis or atresia of the intestinal tract may occur to any degree and can be differentiated in four types according to classification in humans: narrowing, a membranous diaphragm with a perforation, or an imperforate membrane (type 1); a cordlike remnant of the intestine (type 2); a unique blind-ended dilation with complete separation of the intestine (type 3, the most frequent); and multiple sites of atresia (type 4).[6] All have been described in cattle. Affected neonates show depression and mild colic and progress to cardiovascular collapse after the intestine proximal to the obstruction becomes distended with fluid and gas. Tympany may be easily detected by percussion. If the anus and rectum are normal, a digital examination usually reveals only mucus or blood (or both). Because the rectal and descending colon walls are thin in cases of atresia coli, retrograde

TABLE 32-19

Causes of Intestinal Obstruction in Ruminants

Disease	Animals Most Commonly Affected	Signs
Intestinal atresia or stenosis	Neonates	No feces; abdominal distention
Intestinal volvulus around mesenteric root	All ruminants; neonates more common	Colic; rapid abdominal distention; collapse; shock
Intussusception	All ruminants; LI or SI of neonates; SI of adults	Colic early, then chronic low-grade pain; dehydration; mucus plus blood in dark red feces; slow abdominal distention; decreased fecal output; mass palpated per rectum; distended loops of intestine per rectum
Cecal dilation and volvulus	Adult dairy cattle in early lactation	Mild to severe colic; distended abdomen, especially upper right; ping in right paralumbar fossa; distended cecum palpated per rectum
Intestinal tumors	Sheep, rare in cattle	Progressive weight loss; cattle—may palpate mass per rectum; sheep—identify by celiotomy or necropsy
Mesenteric fat necrosis	Cattle, especially Channel Island breeds	May discover masses on routine examination; progressive weight loss; scant or no feces; dilated loops of bowel per rectum
Intestinal incarceration	All ruminants	See Intussusception
Pseudoobstruction or ileus	All ruminants	Scant or no feces; right-sided ping; succussable fluid on right; often associated with peritonitis

LI, Large intestine; *SI,* small intestine.

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tubes or catheters should be used with extreme caution to prevent rupture of the bowel or should be avoided completely.[6] Complete intestinal volvulus must be considered in the differential diagnosis, but histories are often different.

Surgical repair is indicated if the animal is of high value. However, the prognosis for normal and productive life is guarded. Many affected neonates develop severe complications in the immediate postoperative period. Pneumonia, sepsis, and peritonitis are among the most frequent complications, and the development of bowel stasis or ileus is common. When registered animals are involved, a letter should be sent to the appropriate breed registry stating that the defect has been corrected.

Volvulus of the Large and Small Intestine around the Mesenteric Root

Volvulus of the large and small intestine around the mesenteric root leads to severe colic and relatively rapid abdominal enlargement. Circulatory shock develops rapidly. Ruminants of any age are susceptible, but most cases are seen in preruminant neonates. Severe colic is seen, including kicking and vocalization. Affected animals rapidly become recumbent, and hypovolemic shock develops. The heart and respiratory rates increase greatly as shock develops. Variable-pitched resonant sounds may be heard bilaterally over the abdomen using simultaneous percussion and auscultation. In adult cattle, the tympany is restricted to the right side. Succussion reveals splashing sounds, particularly on the right side. Rectal examination reveals distended loops of gut. Surgical correction is the only successful treatment option.[7] The prognosis depends on the degree of devitalization of bowel. Animals surgically corrected during the early stages respond better.

Volvulus of smaller portions of the intestinal tract leads to signs similar to those of complete intestinal volvulus around the root of the mesentery, but often this is slower in onset. Colic with accompanying tachycardia, ruminal stasis, and anorexia is present to varying degrees. The abdomen is moderately distended on the right when the animal is viewed from the rear. Simultaneous auscultation and percussion on the right side reveal multiple-pitched, resonant pings from the gas accumulated proximal to the obstruction. Rectal examination may reveal scant feces, mucus, or blood. The affected bowel usually is palpable as grossly distended with gas and some fluid. Because of their relatively long mesentery, the spiral colon (or part of it), the distal jejunum, and the proximal ileum may develop an obstructive volvulus. Therapy requires correction of acid-base and electrolyte abnormalities and rapid surgical manipulation by means of celiotomy.

Intussusception

In the development of an intussusception, the oral portion of gut (intussusceptum) usually is engulfed and propelled distally by peristaltic action of the enveloping portion (intussuscipiens). Constable and colleagues reported an increased prevalence in calves less than 2 months of age compared with adults, and in Brown Swiss compared with Holstein cows.[8] The condition has also been reported in goats[9] and in sheep.[10,11] Intussusception may occur in either the large or the small intestine of calves but is much more frequent in the jejunum.[8] Clinical signs include colic caused by the tension on the mesentery on the invaginating portion of the intestine. With time, ischemia of this portion leads to pain and eventually loss of sensation. Distention of the intestine with fluid and gas proximal to the obstruction leads to abdominal pain. Therefore a cow may show violent behavior or kicking at the abdomen in the first few hours that is eventually succeeded by treading and repeated lying and standing. Over the course of several days the intussusceptum may become totally devitalized and slough. This is accompanied by severe peritonitis, and in the event of bowel rupture, toxic shock will develop. The exact cause of intussusception remains unknown. Intramural or luminal mass or lesions, viral enteritis, intestinal parasitism, abrupt dietary changes, administration of intestinal motility modifier drugs, and foreign body or prior surgery have all been reported to be potential causes, but in most cases, intussusception is idiopathic.[8]

Dehydration develops as gastrointestinal secretions accumulate in the gut lumen. In adults, hypochloremic, hypokalemic metabolic alkalosis develops gradually. The rumen becomes distended with fluid as its contents become more finely digested and abomasal reflux accumulates. The right side of the abdomen (or both sides) also enlarges as a result of the distention of the small intestine. Simultaneous auscultation and percussion of the right side of the abdomen reveals areas of variable-pitched resonance. Rectal examination reveals distended loops of small intestine. The intussusception may be palpable as a firm mass, and the cow may demonstrate pain when the mass is palpated. Feces are absent within hours of the onset of signs. The examiner may find mucus and blood in the descending colon. In long-standing cases the scant feces are very dark red and must be distinguished from the black feces (melena) associated with abomasal bleeding. Fluid obtained by abdominocentesis shows an increase in erythrocytes and leukocytes and an elevated protein level. Fever is often present because of peritonitis. If the condition is long-standing and bowel rupture has occurred, bacteria may be present. The complete blood count (CBC) may reveal neutrophilia and an elevated plasma fibrinogen level.

In neonates with enteritis, fecal output decreases as appetite is lost after intussusception. A fever may develop as peritonitis occurs. Calves and other neonates may not exhibit obvious signs of colic. Percutaneous abdominal palpation using both hands in an attempt to detect a mass is often successful in delineating an intussusception in a neonate. When neutrophilia, hyperfibrinogenemia, and loss of appetite develop after enteritis, intussusception should be suspected.

Treatment requires both surgical correction of the obstruction and parenteral restoration of fluid and electrolyte balance. Because of the losses of chloride and potassium and the development of alkalosis, 0.9% sodium chloride solution with 30 mEq/L or more of added potassium chloride is recommended. Intravenous potassium should not be given more rapidly than 1 mEq/kg/h (conservative rate is 0.5 mEq/kg/h). Once intestinal patency has been restored, oral fluid and electrolyte supplementation usually allows the patient to achieve normal status.

The prognosis is usually good if surgery is performed early in the course of disease. Complications such as peritonitis can occur and need to be controlled to maintain the chance of success. A retrospective study of 336 cases of intussusception reports a postoperative survival rate of 43% and an overall survival rate of 35%.[8]

Intestinal Incarceration

Intestinal obstruction may occur in ruminants as a result of accidental entrapment of loops, usually of jejunum, around remnants of embryonic structures or through acquired defects in mesentery or the abdominal wall. Remnants of the urachus, the omphalomesenteric duct, the left umbilical vein, and the ductus deferens have been described as responsible for incarceration of the jejunum. The authors of one report indicated that 26% of cows examined had a persistent round ligament of the liver and falciform ligament.[12] Thus tears in the falciform ligament leading to intestinal entrapment may be among the most common causes of the relatively rare problem of intestinal incarceration in cattle. Duodenal obstruction caused by malposition of the gallbladder was also reported in a heifer.[13] Intestinal adhesions caused by intraperitoneal injections of irritating substances may also lead to intestinal obstruction. Initial signs of colic followed by depression, anorexia, progressive abdominal distention, and absence of feces usually develop. Distended loops of small intestine usually are palpable per rectum. Treatment of intestinal incarceration requires surgical intervention.

Cecal Dilation and Volvulus

Cecum distention may be classified as (1) cecal dilation: The cecum is only distended by gas and the apex of the cecum is displaced

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toward the rectum and may be palpated by transrectal palpation; (2) cecal retroflexion (that can cause vascular damage and ischemia, i.e., volvulus): The cecum is distended, displaced, and folded dorsally or ventrally, the apex of the cecum is consequently oriented cranially and is usually not palpable per rectum; (3) cecal torsion: The cecum is distended and rotated along its long axis, the apex of the cecum is displaced toward the rectum and can be palpated transrectally.[14] In a large study of 461 cases of cecal dilation, preoperative clinical diagnosis based on rectal palpation was cecal dilation alone in 291 animals (63.2%), cecal dilation and retroflexion in 94 animals (20.4%), cecal dilation and torsion in 20 animals (4.3%), and in the remaining 56 animals, no diagnosis of cecal dilation could be made preoperatively.[15] In adult cattle, cecal dilation generally is believed to precede retroflexion or torsion.

The etiology and pathophysiology of cecal dilation and retroflexion or torsion remain unknown. Different feeding or management practices may predispose to cecal disease.[15] Increased luminal concentration of volatile fatty acids (VFAs) was classically believed to play a major role in the etiopathogenesis of cecal disorders. However, results of studies on the impact of VFAs on cecal motility have been contradictory. In one study, increased concentration of VFA had only minimal effect on large intestine motility and was unlikely to play an important role in the development of cecal disorders.[16] Factors that affect motility, as described for displaced abomasum, are likely similar.

Cattle with cecal dilation have a more gradual onset of illness than that noted with cecal retroflexion or torsion. The time required for dilation to develop into retroflexion or torsion is unknown. With simple dilation, feed intake and milk production decrease. Mild abdominal pain may be observed. Feces are usually still present, but the consistency may be loose and the amount reduced. Rumen motility is decreased. Distention of the right paralumbar fossa without the ribs being sprung is frequently observed in our clinic and has been mentioned in different reports. However, Braun and colleagues[15] reported that only 42 animals of the 461 cattle affected with cecal dilation, retroflexion, or torsion had distention of the right flank. The most important clinical findings for the diagnosis of cecal dilation are (1) the presence of a large area of resonance (ping), auscultable from the tuber coxae to a variable distance cranially (see Chapter 1, Fig. 1-3), associated or not with a positive succussion of the right flank[15]; and (2) the transrectal palpation in the pelvic canal or nearby of the apex of the gas-filled cecum. Cattle with cecal retroflexion or torsion have more severe clinical signs. They show an abrupt onset of anorexia, agalactia, and severe abdominal pain. Tachycardia and forestomach stasis are also present. Feces are scant or absent. The abdominal distention usually exceeds that caused by simple cecal dilation. The area of resonance in the right paralumbar fossa is larger, and fluid usually can be detected in the cecum and proximal colon by succussion. In cases of retroflexion, the apex of the cecum is not usually palpable per rectum; rather, the distended body of the cecum or proximal colon impinges on the pelvic canal because the apex is directed cranially. In cases of cecal torsion, the apex of the cecum can be palpated per rectum as well as a tense ileocecocolic ligament that spirals around the cecum.[14] Distended small intestine may be palpated with either dilation or retroflexion or torsion.

Although some cows with simple dilation have no acid-base abnormalities, most with cecal retroflexion have some degree of metabolic alkalosis with hypochloremia and hypokalemia. Hypocalcemia is reported to be observed in about 85% of cases of cecal dilation, retroflexion, or torsion.[15]

Medical management of cecal dilation is usually successful with use of fluid therapy to restore normal hydration status and correction of electrolyte abnormalities including hypocalcemia, as well as administration of nonsteroidal antiinflammatory drugs (NSAIDs) to control abdominal pain. Laxatives have also been recommended for the medical treatment of cecal dilation. However, Braun and co-workers[17] reported that the use of laxatives (liquid paraffin) for the treatment of cecal disorders delayed the time to first defecation. Moreover, magnesium hydroxide may be responsible for detrimental effects such as metabolic alkalosis,[18] increased ruminal pH,[19] and decreased ruminal microbial activity.[19] Prokinetic drugs that can be used in the management of cecal disorders are presented in the section on the acute abdomen in cattle. Finally, animals should be fed a high-fiber diet.

Braun and colleagues[15] reported that 122 of 461 animals with cecal dilation, retroflexion, or torsion were first managed medically. Forty-two of these 122 animals finally required surgery. Considerations for conservative versus surgical treatments are presented in the section on acute abdomen. Cattle with cecal retroflexion or torsion require immediate surgical intervention, fluid management to correct the hypochloremic, hypokalemic metabolic alkalosis, hypocalcemia, and administration of NSAIDs to control pain. The prognosis for surgical patients depends on the degree of ischemic injury to the cecum and other structures involved in the obstruction. The recurrence rates after surgery range from 10% to 13.8% within a year of the first incident.[15] In cattle with recurrence of cecal dilation or with devitalized portion of the cecum wall, amputation of the cecum is recommended.

Intestinal Tumors

Intestinal tumors are rare in cattle. The most commonly reported intestinal tumors in cattle are adenocarcinomas. However, lymphosarcoma, adenoma, adenomatous polyps, carcinoid, leiomyoma, leiomyosarcoma, and fibrosarcoma have also been described.[20] The incidence of adenocarcinoma in sheep is relatively high in some areas of the world, such as New Zealand.[21] The predisposing factors for adenocarcinomas are not known, but different environmental carcinogens have been suspected.[21,22] In sheep, no association with infectious agents (herpesviruses, *Helicobacter* spp., or *Mycobacterium avium* subsp. *paratuberculosis*) was found.[21] Genetic predisposition is suspected,[22] but no significant genetic defects were found in one study.[21]

Affected cattle or sheep may have a protracted course of weight loss with no other observable signs until near death. Alternatively there are reports of acute gastrointestinal disturbances manifested by colic, abdominal distention, and auscultable right-sided pings.[23] Although these cases are rare, they must be differentiated from other causes of acute obstruction in cattle such as cecal volvulus, intussusception, or abomasal volvulus. In cattle in which rectal examination is possible, the lesion may be detected on routine examination as an intramural mass or annular constriction of the jejunum or ileum. In sheep, the diagnosis is usually made at necropsy. Clinical signs in affected animals might include diarrhea, abdominal distention caused by the accumulation of gas and ingesta proximal to the obstruction, or ascites. The well-characterized lesions in sheep involve local spread of the tumor through the lymphatics and intraperitoneally. Ultimately, cellular deposits occur on all visceral and parietal peritoneal surfaces, severely impairing lymphatic drainage from the abdomen.

Mesenteric Fat Necrosis

Mesenteric fat necrosis affects cattle of all breeds, but more commonly Aberdeen Angus and Jersey cattle.[24] It has also been reported in a pigmy goat.[25] The cause remains unknown but dietary factors have been implicated, such as consumption of feed containing long-chain, saturated fatty acids; trace element deficiency; trauma; hormonal disturbance; and ingestion of endophyte-infected fescue.[24,25] The lesions develop as an inflammatory response around degenerating adipose cells. The triglycerides in these cells are thought to undergo hydrolysis to glycerol and fatty acids. The longer the carbon skeleton is and the greater the degree of saturation is, the more resistant are the fatty acids to removal by normal cellular mechanisms. Remaining clumps or crystals of fatty acids serve as inflammatory foci for the subsequent necrotic masses.[24] Affected cattle have subnormal serum free cholesterol and elevated serum free fatty acids.[26] Cattle with fat necrosis may eventually develop an intestinal obstruction. The clinical signs resemble those of progressive intestinal

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obstruction from other causes. Weight loss, anorexia, diarrhea, bloody stool, abdominal enlargement, and right-sided ping are all possible signs. Fever, tachycardia, and signs of discomfort such as tenesmus, treading, and teeth grinding may be seen as the obstruction becomes more severe. Many affected cattle have no clinical signs, and the condition is discovered during rectal examination for other reasons. Rectal examination may be impossible because of stricture of the rectum, or dystocia may occur as a result of the necrotic fat masses in the pelvic canal. Fat necrosis usually affects mature cattle,[24] but there is a report of a 6-month course of illness attributed to fat necrosis in a 13-month-old Black Angus heifer.[27] Ultrasonographic appearance of abdominal fat necrosis has been described and appears to be a useful diagnostic tool, associated or not with ultrasound-guided biopsy.[28]

Animals with fat necrosis that becomes clinical usually are not treated. Different treatments have been attempted over the years, but none was considered effective. Experimental therapy of subclinical fat necrosis using a compound that alters lipid metabolism in fungi was successful in one study.[26] The fungicide isoprothiolane was given at a dosage of 20 g/day PO for 8 weeks. Approximately half of the treated cows had a 50% reduction in necrotic masses by 12 weeks; at follow-up evaluation in 1 year, the masses were not detectable in half the surviving cows. Cows given such unapproved drugs should not be used for food.

Hemorrhagic Bowel Syndrome (Jejunal Hemorrhage Syndrome)

Hemorrhagic bowel syndrome (HBS), also called *jejunal hemorrhage syndrome* (JHS), is an acute enteric disease of cattle characterized by segmental intraluminal hemorrhage with subsequent obstruction of the small intestine (also see Diseases Caused by *Clostridium perfringens* Toxins, in this chapter). The disease seems to have been described for the first time in 1991[29] and is now reported in different countries. HBS mainly affects dairy cows, but it is also reported in beef cows and bulls.[30,31] It is principally a sporadic disease, but outbreaks in dairy herds have been reported.[32,33]

The pathogenesis of HBS is still unknown and may be multifactorial. Different pathogens have been implicated. They include *Aspergillus fumigatus,*[34] *Clostridium perfringens* type A and *Clostridium perfringens* type A with β2 toxin,[32,33,35,36] and recently mycotoxic fungi in association with Shiga toxin–producing *Escherichia coli* (STECs).[37,38] *C. perfringens* type A was the first pathogen recognized as potentially implicated in the disease and is evoked as the most likely cause by many authors.[32,33,35,36] However, it is very difficult to clearly define the precise role of *C. perfringens* in the pathogenesis of HBS because *C. perfringens* type A is present in the intestine of healthy cows and is known to proliferate rapidly after death. Ewoldt and Anderson were unable to reproduce the disease by direct inoculation in the abomasum or jejunum of *C. perfringens* type A with β2 toxin.[39] Additionally, different cases of HBS have been reported without any detection of *C. perfringens* type A.[37,38,40] *A. fumigatus* was also not found in different studies on HBS.[37,38] Inversely, recent studies in dairy and beef cattle have demonstrated that mycotoxigenic fungi in the feed (other than *A. fumigatus*) and STECs may play a role in the pathogenesis of HBS.[37,38] Authors of these studies suggested that mycotoxins could contribute to pathogen colonization, but further studies are still required to evaluate more specifically the possible interaction between mycotoxins and STECs and their involvement in HBS. Different risk factors have been described in the development of HBS. They include lactation stage (being in the first 100 days of milk and in the second or higher lactation), feeding regimen (being fed with a total mixed ration [TMR] or a high-energy diet with low fiber), and herd size (herds with more than 100 cows).[32,33,36] Berghaus and colleagues, in their study on risk factors associated with HBS, conclude that all management practices associated with high-producing cows may promote the occurrence of HBS.[41] In one study, Brown Swiss cattle were more frequently affected by HBS in comparison with other dairy cattle.[42]

Affected animals may be found dead, but they typically demonstrate an acute decrease in milk production, anorexia, mild increase in heart rate, normal temperature and respiratory rate, and slight to moderate dehydration. These clinical signs worsen rapidly as the condition evolves. Mucous membranes are frequently pale or congested, which reflects the cardiovascular and hypovolemic shock. Animals usually have slight to moderate right abdominal distention. Clinical signs of abdominal pain may be present. Ruminal contractions are decreased or absent depending on the stage of the disease. The rumen may also be distended. In most cases, transrectal examination demonstrates intestinal distention and scant to absent feces. An intestinal mass is rarely palpable per rectum. When present, feces contain digested and/or clotted blood. HBS must be differentiated from other causes of intestinal obstruction (intussusception, intestinal incarceration, volvulus of the intestine around the mesenteric root), dysentery (salmonellosis, coccidiosis, winter dysentery, coagulopathies), and melena from abomasal ulcers.

Signs of intestinal obstruction are observed during the transabdominal ultrasonography (distended intestinal loops, decreased or absent peristalsis).[43] In some cases hyperechoic structures (blood clots) are observed in the lumen of the intestine.[31,36,43] Hematologic findings are consistent with a slight to moderate inflammatory process. Hematocrit is usually normal as a result of combined hemorrhage and hypovolemic shock. A hypochloremic, hypokalemic metabolic alkalosis is frequently observed on blood gas analysis, consistent with a proximal intestinal obstruction. Postmortem lesions consist of segmental necrohemorrhagic enteritis of the small intestine. The jejunum is the portion of the intestine most frequently involved.[30,31,36] An intraluminal blood clot associated with intramural hematoma and ulceration is observed. Histologic examination of the intestinal wall frequently reveals submucosal hemorrhage, edema, and neutrophilic infiltration, as well as necrosis and ulceration of the mucosa.[30,31,36]

The medical treatment of HBS consists mainly of fluid therapy to restore electrolyte imbalance and to correct dehydration and antimicrobial drugs and NSAIDs to control pain and inflammation. In our clinics we also found a beneficial effect of transfusion of 5 to 6 L of blood.[31] Surgical treatment consists of right flank laparotomy associated with enterectomy of the affected intestines. If the intestines do not look devitalized, the clot can be dislodged by manual massage or enterotomy.

The prognosis for animals with HBS is guarded. Mortality rates of 100%[30] and 77%[36] have been described. However, prognosis of 55% (20 of 36)[31] and 58% (18 of 31)[42] have been reported from two referral centers. In the first study, two animals out of five that were treated medically and 18 animals out of 30 treated surgically survived.[31] In the other study, all dairy cows underwent surgery; among the 18 animals that survived, 6 had a recurrence within the following 12 months and 13 were still alive after 12 months. In this study, short-term prognosis was reported to be significantly improved when the blood clot could be dislodged by massage.[42]

Because the etiopathogenesis of HBS is not well understood, it is difficult to provide recommendations for the prevention of HBS. Prevention may focus on management practices, and particularly feeding practices, to provide adequate fiber length and quantity in the diet. Because the role of *C. perfringens* type A in the pathogenesis of HBS is not proven, the recommendation of a specific vaccination against this bacterium may be questionable. However, a vaccine, *C. perfringens* type A toxoid, is available in the United States. Vaccination with the commercially available seven-way clostridial vaccines does not appear to protect against development of HBS.[41] In one study, a combination of a prebiotic and a probiotic in the feed was associated with a reduction of the disease in dairy cattle.[38]

Ileus (Pseudoobstruction)

Failure to pass feces usually is a sign of intestinal obstruction. However, in adult lactating dairy cattle, a condition of ileus of the intestinal tract that mimics complete intestinal obstruction is

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commonly observed. The condition often resolves spontaneously or with medical treatment (fluids, calcium, and pain management); in rare instances surgical decompression of the affected bowel is required. Cows are most often in early lactation, and treatment is sought for partial anorexia. Colic sometimes is the presenting sign. Clinical examination reveals a normal temperature, a normal to elevated heart rate, and normal respiratory rate. Ruminal motility is decreased. Slight right-sided abdominal enlargement may be seen early and may progress to extreme distention of the abdomen on the right. No borborygmi are heard on the right side, but fluid tinkling sounds may occur. Simultaneous auscultation and percussion reveal areas of variable-pitched resonance. Succussion produces sloshing sounds. On rectal examination a distended spiral colon, cecum, or small intestine may be palpated. Early in the course of the disease the distention is not extreme, and compression easily flattens the affected bowel. If abdominal distention is severe, introducing the arm into the abdominal cavity may be difficult because of the pressure of distended bowel at the pelvic inlet. No feces are passed, but the examiner's arm may be coated with sticky mucus and feces with a stale odor. Serum electrolytes and acid-base status are usually normal. Serum calcium may be decreased. Differential diagnoses to consider include intussusception, intestinal incarceration, intestinal volvulus, and cecal dilation. There is no blood in the feces, and no masses are palpable per rectum with pseudoobstruction.

Because most obstructive lesions of the intestine in cattle are not immediately life-threatening, symptomatic therapy or simply close observation may be elected for 24 hours. If surgery is elected in the absence of an obstructive lesion, the bowel may be decompressed and drained. This is a laborious procedure that requires multiple punctures unless the distention is restricted to the cecum and spiral colon. Despite the lack of correction of a specific underlying defect, many cows begin passing feces soon after an exploratory celiotomy. Manipulation of the intestinal tract alone seems to have beneficial effects. This response is difficult to differentiate from the spontaneous recovery that may occur without surgery in cows. Relief of distention of portions of the intestinal tract may remove reflex inhibition of motility that can occur in response to extreme stretching of mural tension and pain receptors. The cause of pseudoobstruction of the intestine is unknown, and little pathophysiologic information has been elucidated. Medical management is described in detail in the acute abdomen section. It mainly includes administration of fluids, calcium, and NSAIDs. Numerous practitioners also administer oral laxatives, but as mentioned earlier, the practice of using magnesium salts may be questionable and could have deleterious effects.

Diseases Caused by *Clostridium perfringens* Toxins (Enterotoxemia, Yellow Lamb Disease, Lamb Dysentery, Necrotic Enteritis)

Paul G.E. Michelsen • Bradford P. Smith

Definition and Etiology

Clostridium perfringens is a toxin-producing, anaerobic, spore-forming rod. It is a variable species that causes a variety of diseases in human beings and animals. Some biotypes are normal inhabitants of soil, and some are commensal intestinal organisms of animals. A sometimes confusing nomenclature has evolved to organize the complexity of *C. perfringens* biology. Clinical isolates are assigned to one of the types (A through E) on the basis of possession of the major toxins (alpha, beta, epsilon, iota) (Table 32-20). In addition to these four major toxins, strains of *C. perfringens* may produce any of at least eight other recognized soluble antigens, some of which have pathogenic importance and could be called toxins. Beta 2–toxin may be an important toxin as well. Most of these antigens are named with Greek letters. The soluble *C. perfringens* toxin responsible for one type of food poisoning in humans has not received a Greek-letter name but is commonly known as enterotoxin (or CPE, which stands for *C. perfringens* enterotoxin). Enterotoxin is also the general name for toxins that affect the intestines, and many of the *C. perfringens* antigens with Greek-letter names are also enterotoxins. In this discussion the toxin that causes food poisoning in human beings is denoted CPE to distinguish it from enterotoxin as a class of toxins. CPE is not recognized as the major component of classic *C. perfringens* disease in animals, but it may be important in some cases.[1,2]

The different biotypes of *C. perfringens* cause different diseases because they have different toxins, but a clear-cut assignment to one of the groups is not always possible, and overlap is considerable in

TABLE 32-20

Types of *Clostridium perfringens* by Toxin Type and Diseases That Have Been Attributed to the Type*

Group Typing Toxins					
Type	Alpha	Beta	Epsilon	Iota	Diseases Attributed
A	XX	—	—	—	Gas gangrene (along with other organisms) Avian necrotic enteritis Hemorrhagic enteritis in cattle Yellow lamb disease Enterotoxemia of mink Type A enterotoxemia of horses Abomasal tympany and ulcers of calves Sudden infant death syndrome (crib death) Food poisoning in humans
B	X	XX	X	—	**Lamb dysentery** Enterotoxemia of sheep and goats (Iran) Enterotoxemia of foals (Britain)
C	X	XX	—	—	**Necrotic enteritis** (neonatal hemorrhagic enterotoxemia of calves, lambs, kids, foals, piglets) Necrotic enteritis of fowl, struck (enterotoxemia) of sheep (Britain) Necrotic enteritis of humans (pigbel, Darmbrand)
D	X	—	XX	—	**Enterotoxemia** ("overeating disease," "pulpy kidney disease") of sheep, goats, and cattle
E	X	—	—	X	Enteritis in rabbits Occasionally isolated from sheep and cattle Abomasal tympany and ulceration of calves

*Diseases of major veterinary importance are in boldface.

X, Toxin of minor importance; *XX,* toxin of major importance; —, not present.

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the clinical signs caused by the various toxins. Many different diseases in many different animals have been ascribed to *C. perfringens,* but the ubiquitous nature of the organism and the fact that it rapidly overgrows into tissues after death makes the significance of its isolation questionable at times unless the toxin is also demonstrated.

One additional potentially confusing bit of nomenclature concerns the term *enterotoxemia.* Although this term is widely applied to various diseases caused by *C. perfringens,* it is strictly appropriate only for diseases in which the major signs are caused by systemic spread of the toxin in the blood.

One group of diseases caused by *C. perfringens* type C is commonly called "hemorrhagic enterotoxemia," even though the disease is not always hemorrhagic and, although the toxin may incidentally reach the circulation, it is produced in the intestine and exerts its major effects locally. A better descriptive name for this disease has been proposed to be *necrotic enteritis.* It is important to realize that many of the effects of other biotypes of *C. perfringens* are systemic and that enteric clinical signs may be entirely lacking with disease caused by *C. perfringens* types A and D. Each type is discussed in the following paragraphs. Type E is only occasionally isolated from livestock and is not discussed.

Diagnosis of Disease Caused by Clostridium perfringens Meaningful diagnosis of *C. perfringens* as the cause of death or disease in an animal requires an integrative, open-minded approach. Type A is routinely isolated from soil and clinically normal animals. Types C and D are only rarely isolated from soil but can be isolated from asymptomatic individuals, especially those with neutralizing antibody to toxin. The bacterium proliferates after death, often crowding out other enteric organisms and invading tissues beyond the gut. The isolation of *C. perfringens* from a necropsied animal is not by itself sufficient basis for the diagnosis; however, if toxin is also demonstrated in gut contents and the history and lesions are compatible, a diagnosis of death from *C. perfringens* intoxication can be made.

Until recently, an isolate of *C. perfringens* was assigned to one of the five biotypes by demonstrating toxin production with mouse-protection assays or enzyme-linked immunosorbent assay (ELISA) techniques. This has been replaced by a multiplex polymerase chain reaction (PCR) technique that detects the genes for toxin production in a clinical isolate.[3] CPE, which causes food poisoning in human beings, can be detected with commercially available assays and is also detected by the multiplex PCR technique. Meaningful samples for bacterial isolation come from freshly dead animals. Samples of gut contents should be collected into sterile containers and cooled or frozen. In addition to typing bacterial isolates, demonstration of toxin or toxin genes via PCR in gut contents may aid in diagnosis. False-negative results may occur in type C disease if proteases inactivate the beta-toxin.

In the absence of definitive microbiological evidence, a presumptive diagnosis of type C or D disease must be based on the history, clinical signs, pathologic findings, and differential diagnoses. Administration of toxoid vaccines (and antitoxin to stop an outbreak) is effective and may be recommended without conclusive evidence for causation. This "whole herd" protection test may be as close as one gets to definitive diagnosis in field situations. Examination of gut-content smears from various levels of the gastrointestinal tract to demonstrate large numbers of bacteria resembling *C. perfringens* may be a helpful piece of information, but the significance of such a finding by itself is questionable. Glucosuria in urine obtained from the bladder at necropsy is often seen in sheep (but not other species) with type D disease.

Type D disease should be distinguished from other causes of acute death (see Chapter 14). A history of sudden death in a rapidly growing, apparently healthy individual is characteristic. A single lamb is much more likely to have overeating disease than is a twin. Other causes of acute disease in well-fed individuals include systemic pasteurellosis (lambs), acute bloat, grain overload, polioencephalomalacia, and thromboembolic meningoencephalitis (cattle). These generally have a longer disease course than type D enterotoxemia.

Clostridium perfringens Type A (Jejunal Hemorrhage Syndrome, Yellow Lamb Disease, and Others)

C. perfringens type A can be found in many soils and is a normal inhabitant of the gut in many species. Although all five types of *C. perfringens* produce alpha-toxin, type A strains usually produce more than other types. The toxin is a phospholipase and causes lysis of red cells, platelets, and leukocytes (equine and caprine red cells are resistant to the hemolyzing effects of toxin). The toxin also causes vascular permeability through endothelial damage and can cause necrosis at the villous tips in the intestines. There is also a report of type A having the gene to produce a beta 2–toxin.[4] The beta 2–toxin may act synergistically with alpha-toxin to cause necrotic and hemorrhagic intestinal lesions.

Hemorrhagic Bowel Syndrome

Hemorrhagic bowel syndrome (HBS; also called jejunal hemorrhage syndrome [JHS] or hemorrhagic enteritis) is an acute, often fatal condition of cattle characterized by segmental intraluminal hemorrhage in the small intestine.[5] The jejunum is the most commonly affected portion of the small intestine. The disease is considered to be an emerging disease of lactating dairy cattle in the United States, with 9.1% of herds in a 2002 National Animal Health Monitoring System (NAHMS) study reporting at least one case of HBS during the previous 5 years. It appears that high milk production is related to the condition, probably through feeding practices and management factors.[6]

Affected animals usually are anorectic, have a moderately elevated heart rate, and have a normal to subnormal temperature. Other signs consistent with small intestinal obstruction also develop, but abdominal pain is not usually observed. Feces may contain partially digested or clotted blood, and distended loops of intestine may be palpable per rectum. Transabdominal ultrasound may show an increased intestinal diameter proximal to the lesion, hyperglycemia, hyponatremia, hypochloremia, hypokalemia, and hypermagnesemia.[7]

Both medical and surgical approaches to treatment have had limited success. On postmortem examination *Clostridium* spp. may be seen in affected tissues. The odds of isolating *C. perfringens* type A from intestines of cows affected with HBS were 8.5 times greater than for cows with left-displaced abomasum (LDA).[5] Another theory is that *A. fumigatus* is the causative agent of HBS.[5]

Increasing the percentage of long-stem fiber in the diet is associated with a decrease in number of cases of HBS. [6] The value of vaccination in preventing HBS has yet to be documented.[5] An attempt to reproduce the condition by inoculating either abomasa or jejuna of cows with *C. perfringens* type A failed to produce illness or lesions.[8]

Yellow lamb disease (so named because of the icteric nature of necropsied lambs) is an uncommon disease attributed to *C. perfringens* type A. Widespread hemolysis leads to anemia, weakness, hemoglobinuria, and icterus. The animals have a high temperature and usually die within 6 to 12 hours of onset. Differential diagnoses for yellow lamb disease include other causes of hemolytic disease, such as leptospirosis and copper toxicosis. As with other type A infections, the diagnosis is always questionable because of the commensal nature of the organism and its rapid invasion after death. The finding of predominantly large gram-positive rods in impression smears from intestinal mucosa lends support to the diagnosis. One report implicates type A in neonatal calves with ruminal and abomasal tympany, abomasitis, and abomasal ulceration. The calves were 2 to 21 days old and died acutely or had signs of colic and depression of short duration. Type A is a relatively common cause of food poisoning in human beings. Speculation links this type to human sudden infant death syndrome ("crib death") as well.

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A type A vaccine is produced that claims to protect against HBS in cattle and against abomasal ulcers, abomasal hemorrhage, and abdominal tympany in calves.

Clostridium perfringens Type B (Lamb Dysentery)

Lamb dysentery is a disease of young lambs in Britain and South Africa. Type B has not been reported in North America. Its clinical course and presentation are similar to those of necrotic enteritis caused by *C. perfringens* type C. Lambs less than 1 week of age become depressed and die. A yellowish diarrhea becomes brown from blood as the disease progresses. Morbidity may be high, and mortality approaches 100%. Necropsy findings include ulcers (rarely perforating) in the small intestines and dehydration of the carcass and tissues. Sanitation and the use of type B vaccine aid in prevention and control. Types B and C toxoids cross-protect because of the overlap in toxin types (beta is the major toxin of both).

Clostridium perfringens Type C (Necrotic Enteritis, Neonatal Hemorrhagic Enterotoxemia, Pigbel, Struck)

Definition and Etiology *C. perfringens* type C elaborates the alpha (hemolytic)-toxin common to all types, in minor amounts, and the beta-toxin in major amounts. The amount of beta-toxin produced may determine the pathogenicity of a type C strain. In addition, type C strains produce the cytotoxic and hemolytic alpha-toxin, which is used to assign strains to group C if they have lost the ability to produce beta-toxin in culture. Beta-toxin appears capable of producing all the signs of necrotic enteritis; the role of alpha-toxin or CPE in disease is unclear.

Necrotic enteritis is primarily a disease of neonates and occurs in calves, lambs, foals, and piglets. A similar disease in adult sheep, known as *struck,* has a very limited geographic range in Great Britain.

Clinical Signs and Differential Diagnosis Affected animals may die acutely without diarrhea, but this is rare. The diarrhea may be yellow or, in more hemorrhagic cases, brownish. Gray-red streaks of necrotic mucosa may be present in the stools. Foals with type C disease at first show acute abdominal pain, then explosive yellow diarrhea that becomes brown and hemorrhagic. Animals become dehydrated, anemic, weak, and moribund, despite intensive therapy. Morbidity and mortality are high, but the disease is quite sporadic in occurrence. Salmonellosis and coccidiosis should be considered in the differential diagnosis, but necrotic enteritis is the more common disease in very young animals.

Pathophysiology The causative beta-toxin is readily destroyed by proteolytic enzymes such as trypsin. The neonate is especially predisposed to beta-toxin attack by the presence of trypsin inhibitors in colostrum, the function of which is to prevent proteolytic degradation of immunoglobulins. Necrotic enteritis in humans is believed to be caused by decreased proteolytic activity arising from low-protein diets or the consumption of sweet potatoes, which contain heat-stable inhibitors of trypsin. The scattered cases of necrotic enteritis in adult animals may be the result of similar dietary factors. Type C disease has been reproduced experimentally in maturing lambs by administering type C cultures and soybean flour, which contains potent protease inhibitors.

Ingestion of a protein-rich diet into a protease-deficient intestinal tract allows rapid growth of *C. perfringens* organisms. The bacteria attach to the villi, and elaboration of the cytotoxic beta-toxin results in necrosis and invasion of deeper intestinal layers. Death may result from the direct effects of the severe diarrhea or may be caused by secondary bacteremia or toxemia from the compromised gut barrier.

Epidemiology Neonates that ingest type C organisms during the first few days of colostrum feeding are at risk. They pick up the organism from an environment contaminated by an asymptomatic shedder or from contaminated feed. Type C may be isolated from asymptomatic individuals on occasion, but it is not considered a normal commensal as is type A. Once established on a premise, the disease may become endemic. In foals the disease is significantly associated with housing in a stall or drylot during the first 3 days of life, previous presence of livestock on the farm, low amounts of grass hay fed postpartum, being born on dirt, and having stock horse parentage (e.g., Quarter Horse, Paint). Feeding smaller amounts of grain prepartum is associated with decreased incidence of the disease.[9]

Necropsy Findings Necrosis of the mucosa of the small intestine, especially the jejunum, is the consistent finding in all species. The large intestine may be similarly affected in the horse, whereas in other species it may be normal except for intraluminal blood. The peritoneal cavity often contains excessive fluid, which clots when exposed to air. The mesenteric lymph nodes may be hemorrhagic. Microscopically, affected gut shows necrosis and hemorrhage throughout the mucosa and submucosa, as well as mucosal and submucosal thrombosis.[10] The tips of the necrotic villi are covered with numerous large gram-positive rods. Positive diagnosis is based on demonstrating the beta-toxin in intestinal contents.[10]

Treatment, Prevention, and Control Once a case becomes clinically apparent, treatment generally is unsuccessful because of the fulminant nature of the disease. Foals can be treated with supportive intravenous broad-spectrum antibiotics (to cover gram-negative bacteremia caused by loss of gut integrity), fluids, plasma (intravenous and oral), withdrawal of milk for 24 hours, oral metronidazole, and intravenous *C. perfringens* types C and D antitoxin. Metronidazole (10 mg/kg PO or IV given twice daily) can be given to at-risk foals in the face of an outbreak, beginning at 8 to 12 hours of age and continuing for 5 days. Toxoid has been administered to horses to control the disease on an apparently endemic property, with good results. Antitoxin consisting of *C. perfringens* types C and D antitoxin may be given to animals at risk in an outbreak, and *C. perfringens* types C and D are common components of multivalent vaccines. The primary vaccination series consists of two injections 1 month apart, with the final dose given 2 weeks before parturition, and a yearly booster thereafter. Neonates should be vaccinated at 8, 12, and 16 weeks of age on problem farms.

Clostridium perfringens Type D (Enterotoxemia, Overeating Disease, Pulpy Kidney Disease)

Definition and Etiology Enterotoxemia caused by *C. perfringens* type D is a disease of major importance in sheep and of lesser importance in cattle and goats. It is caused by strains of the bacterium that produces the epsilon-toxin. This type is not a common soil organism, as is type A, but it may be isolated from the feces of apparently normal sheep and, less often, cattle. Most clinical disease occurs in animals fed a highly nutritious diet, especially grain-fed livestock. The disease has been seen in lambs as young as 1 to 5 days of age.[11]

Clinical Signs and Epidemiology The sudden death of a well-fed, rapidly growing animal is the most common presentation of enterotoxemia. The disease may run its course in 30 to 90 minutes, with affected lambs showing ataxia, trembling, stiff limbs, opisthotonos, convulsions, coma, and death. At the onset of clinical signs, the animal is hyperglycemic. At death it is glucosuric. The differential diagnoses should include other causes of neurologic signs and acute death: anthrax, botulism, black disease, leptospirosis, listeriosis, enterotoxigenic *E. coli* infection, septicemia, polioencephalomalacia,

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toxic indigestion (grain overload), systemic pasteurellosis, and tetanus.

Sublethal doses may result in brain damage and focal symmetric encephalomalacia (see Diseases of the Nervous System, Chapter 35). Affected lambs are dull and unresponsive to normal environmental stimulation. The major differential diagnosis is polioencephalomalacia. Experimental intravenous injection of type D epsilon-toxin into calves produced neurologic signs and severe acute pulmonary interlobular edema. The histologic lesions in the brain consisted of perivascular proteinaceous edema in the interna capsule, thalamus, and cerebellar white matter, whereas in the lung intraalveolar and interstitial edema was found. These are similar to some of the lesions found in sheep and goats with type D enterotoxemia.

The disease in goats is usually confined to the intestinal tract and seldom involves system signs seen in sheep.

Pathophysiology In some feedlot situations the animal ingests *C. perfringens* type D on a regular basis, but the acid environment of the abomasum and continuous peristalsis, as well as low amounts of fermentable substrate, conspire to keep bacterial numbers low and moving out of the animal. The intestinal environment also influences the amount of toxin produced.

Some factor of overnutrition, often heavy grain feeding or very rich pasture, provides substrate for rapid proliferation of the type D organism, leading to elaboration of the prototoxin. Cleavage of the prototoxin by proteases yields the active toxin. Epsilon-toxin increases intestinal permeability, causing edema in a variety of organs, notably the lungs, kidney (hence the name "pulpy kidney disease"), and brain (focal symmetric encephalomalacia). The epsilon-toxin has been shown to attach to the distal and collecting tubules where it causes severe damage.[12] Excess pericardial, peritoneal, and pleural fluid (with or without fibrin) and subcapsular petechiation in the kidneys may be seen.[13] These lesions cause rapid deterioration and death. Hyperglycemia and glucosuria are the result of massive hepatic glycogen release caused by the epsilon-toxin.

Necropsy Findings Postmortem lesions are inconsistent. The pulpy kidney lesion may not be seen in freshly examined specimens. The epicardium, serosa, thymus, and diaphragm may have small areas of hemorrhage. The pericardial sac often contains excess fluid. The lungs may be edematous. Glucosuria is considered a hallmark of type D enterotoxemia but is sometimes not present. Ten calves with experimentally induced type D showed acute pulmonary edema, excessive protein-rich pericardial fluid, watery contents in the small intestine, and multifocal petechial hemorrhages on the jejunal mucosa.[14] The brain of one calf that survived for 8 days showed multifocal, bilateral, and symmetric encephalomalacia in the corpus striatum. The most striking histologic changes consisted of perivascular high protein edema in the brain, and alveolar and interstitial proteinaceous pulmonary edema. The animal that survived for 8 days and that had gross lesions in the corpus striatum showed histologically severe, focal necrosis of this area, as well as in the cerebellar peduncles and thalamus.[14] Histologic lesions in sheep include pleural and interlobular and perivascular edema in the lung, as well as perivascular edema in the brain of some affected animals.[13]

Treatment, Prevention, and Control If initiated at the first suspicion of overeating disease, type D antitoxin and oral antibiotics (sulfa) may have dramatic results. The diet should be adjusted downward (more grass hay, less grain and legumes) in outbreaks to try to minimize the substrate, especially starch, that reaches the bacteria. Lambs on rich pasture should be moved to poorer pasture or corralled and fed hay until they have been vaccinated twice. Lambs and calves brought into a feedlot should be vaccinated twice before arrival and should have the concentrate ration increased slowly to minimize microfloral disruptions.

Antitoxin can be given in an outbreak, but previous vaccination is more effective. Vaccination with type D bacterin-toxoid is effective in preventing disease. Two doses are given 14 to 56 days apart, before heavy grain feeding or exposure to rich pasture begins. The aluminum hydroxide adjuvanted vaccines may cause raised subcutaneous lumps (most noticeable on goats) that may go on to abscess. Dairy goats fed continuous high-grain rations may need to be vaccinated more often for continuous protection. One study of three commercial vaccines found that one of the vaccines provoked no antibody response in goats 14 days after vaccination and that at 28 days after vaccination, even the goats that had responded to the other two vaccines had titers no higher than unvaccinated controls. The vaccine is not licensed in the United States for use in goats but is routinely used. Bummer lambs may be protected by feeding bovine colostrum from cows vaccinated several times with the sheep vaccine to provide high titers in colostrum. Colostral titers from the dam are protective to 12 weeks of age, after which vaccination should be used to provide active immunity against the disease.

Beta 2-Toxigenic *Clostridium perfringens* Typhlocolitis in Horses and Ruminants

Beta 2–toxin is a newly described *C. perfringens* toxin that may play a role in intestinal diseases of ruminants and adult horses, particularly typhlocolitis. Affected animals may have a history of recent stress or antibiotic administration and show hemorrhagic, profuse, watery diarrhea; low body temperature; severe leukopenia; and hypoproteinemia.[15] The diagnosis depends on demonstration of the beta-2 gene by PCR.[16]

Oak (Acorn) Toxicosis

Bradford P. Smith

Definition and Etiology Toxic signs can appear in ruminants,[1,2] and occasionally in horses,[3] that ingest large quantities of oak buds, oak leaves (green or dried), or acorns. Most species of oak (*Quercus* spp.) cause similar signs when ingested, although there are marked differences in the amount of toxin among the 75 oak species.[4] The metabolites of oak tannins and volatile phenols present in the buds, leaves, twigs, and acorns are responsible for causing toxicosis. The mouth, esophagus, gastrointestinal tract, and kidneys (renal tubular nephrosis) are the organs most affected. Because they are less selective in what they ingest, cattle seem to be the most frequently affected species. Signs begin shortly after ingestion of 50% or more of the diet as oak, and young cattle (under 300 kg) often appear to be more severely affected than adult cattle. One paper found that adult sheep weighing about 40 kg could be fed up to 2.2 kg per day of acorn powder without detriment.[5] Acorns tend to be relatively low in crude protein (2% to 7%) but high in starch, with variable levels of tannins.

Factors leading to toxicosis include the presence of large acorn crops when forage is scarce, wind or hail that causes large numbers of acorns to drop suddenly, or the sudden presentation of oak buds and young leaves to hungry cattle, as in spring windstorms or snowstorms that cover the grass and break branches. In the southwestern United States, range cattle regularly consume some oak species, which are apparently highly palatable and nutritious.[6] The condition has been described wherever oak grows, including most of the United States, France, Great Britain, Germany, Sweden, Australia, China, and South Africa.

Acorn calf syndrome is completely different from the oak toxicosis described in this section. Acorn calves are congenitally malformed calves born to dams that ingest large numbers of acorns under poor forage conditions during the second trimester of pregnancy. The cause appears to be a combination of poor nutrition and exposure to acorns. The calves have very short leg bones and may have abnormal hoof development and a short or long narrow head. In badly affected herds, as many as 15% of calves are affected. The disease has been reproduced experimentally. Supplementation of the herd with adequate protein and energy eliminates the disease.

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FIG. 32-129 Perirectal and vulvar edema in a 3-month-old calf with acute oak bud toxicity. Acute acorn or oak poisoning causes similar lesions.

Clinical Signs and Differential Diagnosis The course of oak toxicosis usually is 1 to 12 days, but some cattle have a protracted, debilitating disease.[1,2] An outbreak in England is described in which the first death from renal failure occurred 21 days after the animals had been removed from exposure and housed.[7] In the peracute stages, cattle are recumbent, weak, anorectic, and listless.[1] The rectal temperature is normal or below normal, and the heart and respiratory rates are elevated. Marked edema is present in the perineum and vulva (Fig. 32-129), and edema is obvious in the submandibular area, brisket, and ventral abdomen. Hydration appears adequate, but anuria is present. Firm, dark, mucus-covered feces usually are present. Evidence of hydrothorax, hydropericardium, and ascites may be noted on physical examination. Some cattle may simply be found dead.

A day or two after ingestion the animals appear anorectic and listless and have decreased ruminal motility. Many calves have hemorrhagic diarrhea or dark diarrhea that tests positive for fecal occult blood. The feces may have a smell of phenol. Dehydration occurs rapidly, but vital signs may be remarkably normal until hypovolemia develops. As uremia progresses, scleral vessels become dark and engorged, and the breath may take on the smell of ammonia. The major differential diagnoses are other causes of renal failure and other toxins and clostridial diseases; viral diseases that cause ulceration of the alimentary tract should also be considered. Protracted cases most often result from renal failure and uremia, although some animals have chronic oral, esophageal, or gastrointestinal ulceration or perforation with abscessation.

In horses signs usually are peracute or acute; they include sudden death or colic, tenesmus, and hemorrhagic diarrhea.[3] Acorn husks and shells may be noted in the feces. As with most colics, tachycardia, hyperpnea, and injected oral mucous membranes are seen. Increased abdominal borborygmi often are present, and hemoglobinuria may occur. Determination of serum or urinary phenolic (hydrolyzed tannin) content, based on a gallic acid standard, may be used in acute cases.[3]

Clinical Pathology In cattle with peracute and acute signs, the serum urea nitrogen and creatinine are elevated, whereas other laboratory values may show considerable variation.[2,3] Initially hyponatremia, hyperkalemia, hypochloremia, hyperphosphatemia, and a marked hypocalcemia (5.1 to 6.8 mg/dL) accompany a mild metabolic acidosis with a very high anion gap (29 to 32).[1] Neutrophilia with mild hyperfibrinogenemia may be present. Although sorbitol dehydrogenase and γ-glutamyltransferase (GGT) may be elevated, biopsy does not indicate that significant hepatic disease occurs with oak toxicosis. Animals may be anuric. If urine is being produced, often isosthenuria, proteinuria, and glucosuria occur. The urinary fractional excretion of sodium was elevated in one steer.[6]

In protracted cases the major findings are elevated serum urea nitrogen, creatinine, and anion gap, with variable hyponatremia, hypokalemia (vs. hyperkalemia in acute stages), hypochloremia, and hyperphosphatemia. A mild metabolic alkalosis may be present. Hyperfibrinogenemia and an increase in total plasma proteins also are variable. An elevated white blood cell (WBC) count most often reflects chronic ulceration or abscessation (neutrophilia or monocytosis or both). Liver enzymes usually are normal in protracted cases. Urinalysis results are similar to those in acute cases; in addition, hematuria often is present. By 6 weeks after exposure, a normocytic, normochromic anemia may develop as a result of chronic inflammation and uremia, and hypoalbuminemia may result from chronic renal and gastrointestinal losses. By 8 weeks after exposure, surviving cattle have largely returned to normal renal function as determined by normal serum urea nitrogen and creatinine concentrations and by the ability to concentrate urine after a 24-hour water deprivation test.[1]

Laboratory findings in horses are similar to those in ruminants, except that during the acute stages rapid hemoconcentration and marked increases in packed cell volume (PCV) occur.[3] Although protein, occult blood, and hemoglobin casts have been reported to be present in the urine, the urine specific gravity was 1.052.

Pathophysiology The toxicity of oak is attributed to its high concentration of tannins, which are hydrolyzed in the rumen to gallic acid, pyrogallol, and other compounds. The tannins themselves may contribute to oral, esophageal, and gastrointestinal damage by binding to proteins, including those in epithelial cells. This results in oral, esophageal, and ruminal ulcers or perforations. Protein-bound tannins are liberated in the acidic abomasum, making them available once again to damage intestinal epithelium. Some hydrolyzed tannins are absorbed and bound to plasma proteins and endothelial proteins, resulting in hemorrhage and fluid loss from the vascular compartment into body cavities and tissues; this results in edema. The gallic acid and pyrogallols are extremely toxic to renal tubules, causing acute tubular necrosis, anuria, electrolyte abnormalities, and uremia. Ruminants are more susceptible than horses because of the hydrolysis of the gallotannins in the rumen.

Epidemiology Young cattle in the 100- to 300-kg range seem to be particularly susceptible. In the southwestern United States oak toxicosis accounts for considerable economic loss in cattle.[6] The disease is seen sporadically in other ruminants and in horses. The morbidity rate in cattle varies considerably, with several to many calves in a pasture usually affected, and case fatality rates frequently exceed 80%.[2]

The disease is most often associated with ingestion of acorns in the fall and buds or young leaves in the spring. Cattle turned onto a pasture with oak trees under which acorns have accumulated may have toxicosis even when adequate forage is available.[2] In other cases windstorms have dropped numerous acorns or branches in a pasture to which cattle were already accustomed. In the early spring a heavy, unseasonable snowstorm may occur, covering the grass and bending young trees and breaking branches so that oak buds and young leaves are accessible.[1] Young leaves and acorns are more palatable than older leaves and also contain more tannins (up to 10% dry matter in acorns). The seedlings, buds, and acorns of small scrub oak may be important forages for cattle in parts of the United States.[6]

Necropsy Findings In peracute and acute cases prominent edema is often the most striking lesion. Ascites, hydrothorax, hydropericardium, perirenal edema, and subcutaneous edema are found. The kidneys are normal in size with multiple diffuse hemorrhages on the surface and extending into the cortex. The liver is slightly swollen and pale or mottled. Digestive tract lesions vary from congestion to hemorrhage and deep ulceration or perforation with necrotizing inflammation. Mucosal ulceration is found in the pharynx,

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esophagus, rumen, abomasum, small intestine, cecum, and colon. Free blood or melena may frequently be observed.

Diffuse renal tubular damage is present. The changes include coagulation necrosis of cortical tubular epithelium and dilated tubules devoid of epithelium but with intact basement membranes. Many medullary tubules contain hyaline, granular, or cellular casts. The principal renal lesion is necrosis of the proximal convoluted tubules, but glomerular degeneration and fluid in Bowman capsules are also seen.

By 3 to 6 weeks after exposure, the lesions include gastrointestinal ulceration, often with secondary infection; some healed ulcers; secondary bacterial bronchopneumonia; and slightly swollen, pale brown kidneys. Histologically, atrophy of the cortical tubular epithelium with a marked interstitial fibrosis and mononuclear infiltrate is seen. Evidence of tubular epithelial regeneration may be present. The liver appears normal.

Treatment and Prognosis In acute stages intravenous fluid therapy aimed at promoting diuresis and correcting acid-base and electrolyte abnormalities may be lifesaving. Calcium, sodium, and chloride deficits should be replaced, and sodium bicarbonate should be given if needed to correct metabolic acidosis. In anuric animals furosemide (1 mg/kg given IV) can be administered every 12 hours, along with adequate fluid therapy. Corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) are not likely to have a measurable effect on the course of the disease because they are unlikely to alter the direct toxic effects of the toxic metabolites. The prognosis is guarded and must be considered poor in animals that remain anuric despite therapy. The case fatality rate undoubtedly depends more on the amount of toxic material ingested than on therapy. Antibiotics, given to prevent secondary pneumonia and abscessation, ruminal transfaunation, and readily accessible grass hay and water are recommended components of nursing care.

If the animal survives the acute stage and begins to eat voluntarily, the prognosis for recovery is good unless secondary pneumonia or gastrointestinal abscessation after perforation occurs. Renal function can return to normal by 5 to 10 weeks, and weight gains as high as 1.76 kg/day may be recorded in recovered cattle.[1]

Colicky horses can be treated as one would usually treat colic (intravenous fluids, analgesics, oral laxatives). Particular attention should be paid to diuresis, acid-base balance, and maintenance of serum calcium levels.

Prevention and Control No specific antidote exists for oak toxicosis, but supplementation with calcium hydroxide (hydrated lime) immediately before anticipated exposure to oak has been effective under experimental conditions.[8] Feed containing 10% or less calcium hydroxide is palatable. Consumption of 0.9 kg/head/day of cubed or pelleted supplement containing 10% hydrated lime is effective in preventing toxic manifestations.

Supplementation of cattle suddenly exposed to oak with any feed reduces death losses, apparently by allowing hungry cattle to consume the supplemental forage preferentially.[1,8] In an outbreak in California caused by spring snows in which 2700 cattle died of oak toxicosis, ranches where hay was immediately supplemented had minimum losses compared with ranches where feed supplementation was not offered.

Winter Dysentery in Cattle (Bovine Coronavirus)

Gilles Fecteau • Charles L. Guard

Definition and Etiology Winter dysentery is an acute, contagious diarrheal disease of cattle (especially dairy) that occurs in epizootic fashion in a herd, usually during the colder months of the year (November to April). It is usually recognized by the clinical syndrome that occurs in herds and by exclusion of other causes of contagious diarrhea.[1] In the United States the disease is more common in the northern states; however, it has been reported in Australia, Sweden, the United Kingdom, Israel, France, Belgium, Japan, and Canada. The period of illness in an individual is brief (a few days to a week), and within a herd the outbreak usually lasts less than 2 weeks. Recovery is spontaneous in most individuals, but in some cases supportive therapy is necessary. The morbidity rate is usually high (from 30% after a few days to almost 100% after 1 week to 10 days). Mortality is usually rare.

The etiology of winter dysentery is a bovine coronavirus that may be related (antigenic differences are reported) to the coronavirus that causes diarrhea in neonatal calves.[2-7] By immune electron microscopy, antigenic cross-reaction has been demonstrated between the original Nebraska calf coronavirus diarrhea agent and coronavirus isolated from field outbreaks of winter dysentery.[4,6]

Clinical Signs and Differential Diagnosis Winter dysentery is an explosive diarrheal disease accompanied by some degree of anorexia and depression. In lactating cows, milk production is severely reduced. If the diarrhea is severe or persists longer than one or 2 days, dehydration may develop. Loss of body condition is apparent. Rumen motility usually is reduced, but intestinal borborygmi may be increased. Thirst often is increased, and polydipsia follows the diarrhea. Rectal examination may reveal dilated intestinal loops. The feces vary from light tan to dark brown; bubbles commonly form in the puddles that are deposited several feet behind the cow. Blood may be present in the feces of several animals in a group, typically in the first lactation heifers. The amount of blood may range from just visible to large clots, or it may be uniformly mixed into the feces. Some animals may have thick mucus in the feces. The odor in a barn during an outbreak of winter dysentery has been described as musty, fetid, and sweet and nasty.[8]

Fever usually is not present during the diarrheal phase of the disease but has been reported to precede it[1] or have no consistent relationship.[9] Mild respiratory signs consisting of serous nasolacrimal discharge and a soft cough have been inconsistently observed before diarrhea. Diarrhea caused by bovine virus diarrhea virus (BVDV), coccidiosis, and salmonellosis must be considered in the differential diagnosis of winter dysentery. With winter dysentery no mucosal lesions are visible on physical examination. The absence of coccidial oocysts or parasite ova in the feces helps exclude these agents as responsible for the diarrhea. The rapid occurrence of multiple cases within a herd, and often within herds in a locality, suggests winter dysentery. Fecal culture for *Salmonella* yields negative results in uncomplicated cases of winter dysentery.

Clinical Pathology No consistent hematologic changes that would be of diagnostic benefit have been observed. If significant dysentery persists for longer than a day, signs of anemia may develop.

Pathophysiology Epithelial cells of colonic crypts are destroyed by viral action, leading to necrosis and hemorrhage. Even though histologic changes have been observed only in the colonic mucosa, blood was observed from the distal duodenum aborally in cattle that died of winter dysentery.[7] Loss of intestinal mucosal epithelium from colonic crypts leads to transudation of extracellular fluid and blood.

Epidemiology The incubation period is thought to be 2 to 8 days. The most susceptible animals are first and most severely affected. In a small, housed herd, the typical incidence of diarrhea during an outbreak begins with the explosive appearance of signs in 10% to 15% of animals on the first day. The second day another 20% to 40% are affected. On subsequent days similar proportions become ill. By the end of a week the first affected animals are completely recovered, and only a few new cases occur. Typically within 2 weeks of the onset of diarrhea, all animals have recovered. This period is marked by significant reduction in milk production. In large herds

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the outbreak may be prolonged for 6 to 8 weeks. This scenario is typical of a herd that had not experienced an epizootic of winter dysentery during the preceding few years. In some herds milder outbreaks occur annually, with fewer animals showing diarrhea and with less severe clinical signs.

Treatment and Prognosis Most animals with winter dysentery recover spontaneously in a few days without specific treatment. Many palliative treatments have been recommended and used over the years. On the basis of 30 years of observations, Roberts[10] considered none of these treatments to alter the course of the disease. Provision of adequate fresh water, palatable feed, and free-choice salt is the most useful nonspecific therapy. The occasional animal with prolonged or severe dysentery may need a transfusion of 4 to 8 L of whole blood.

Salmonellosis in Ruminants

Bradford P. Smith

Definition and Etiology Salmonellosis is one of the few diseases that appear to be increasing in prevalence, especially in dairy cattle. Large dairy farms are more likely to be infected than small dairy farms.[1] Milk yield decreased significantly in affected herds and the reduction was detectable several months after the increase in bulk tank milk *Salmonella* antibodies. It took more than 1 year for milk yield to return to preinfection levels.[2] According to one study, 75% of dairies sampled in California had evidence of *Salmonella* infection.[3] A multistate study found that 56% of dairies sampled contained cows shedding *Salmonella* in feces.[4] *Salmonella* of concern for livestock fall mainly into one species, *Salmonella enteric* subsp. *enterica,* with numerous serovars or serotypes, such as *S. enteric* subsp. *enterica* serovar Typhimurium, with the words *serotypes* and *serovars* used interchangeably.[5] We shorten it to *Salmonella* Typhimurium by convention. More than 2500 *Salmonella* serotypes (serovars) have been identified, and many are potential animal and human pathogens. Multidrug-resistant *Salmonella* Typhimurium DT104 (serogroup B) and *Salmonella* Newport (C2) are particularly virulent to animals and human beings. The presence of identical strains of *Salmonella* Newport among bovine and human isolates indicates that zoonotic transmission is likely.[6] Fortunately 10 serotypes of *Salmonella* in serogroups B, C, D, E, and K are responsible for most disease in cattle; therefore control programs can be aimed at these. Table 32-21 lists the serotypes most commonly isolated from ill cattle in 2010 in the United States.[7] Note that group K, not long ago considered an exotic serogroup, has appeared in the number 2 position. *Salmonella* organisms are gram-negative enteric bacteria that are facultative intracellular parasites. Most serotypes are non–host-specific, but a few are host-adapted. *Salmonella* Dublin is host-adapted to cattle, *Salmonella abortus ovis* and *Salmonella* Arizonae to sheep, and *Salmonella abortus equi* to horses. Host-adapted serotypes are found most often in their host species, where true long-term carriers exist.[8] In contrast, non–host-adapted serotypes rarely achieve carrier status and usually infect an animal for a period of 3 to 16 weeks before infection is cleared,[8] although one cow with multidrug-resistant *Salmonella* Newport excreted the organisms for 190 days.[6] Infection with either host-adapted or non–host-adapted serotypes can be symptomatic or asymptomatic, depending on the dose, the virulence of the serotype, and the host's immune status. There appears to be an association between an increased incidence of *Salmonella* infections and intensive management practices such as large farms, crowded conditions, and high-protein diets. In the absence of carriers, chain infections and persistence of *Salmonella* in the environment are responsible for long-term persistence of a given strain on a given dairy.[6]

Salmonella are grouped into serogroups (A to Z and 51 to 65), depending on their cell wall antigens (somatic antigens that comprise specific oligosaccharides, often called *O antigens, LPSs,* or *endotoxin*). Thus, for example, local and regional laboratories often report that an isolate is a group D *Salmonella.* The most common group D isolate of cattle is *Salmonella* Dublin, although nonmotile isolates that do not express flagella at that time also can be found. We found that these would express motility and be typed as *Salmonella* Dublin if we inoculated the isolate into semisolid media where it had to move to get nutrition (Smith BP, personal observation). Final confirmation that the *Salmonella* isolated is indeed *Salmonella* Dublin comes from the National Veterinary Services Laboratory in Ames, Iowa, or from some other laboratory in which antisera and facilities exist for identification of all 2500 serotypes on the basis of flagellar (H) antigens and somatic (O) antigens. Some serotypes also express capsular (Vi) antigens composed of mucopolysaccharide under some conditions. Identification of the serotype is important in planning control strategies. In addition to the serotypes listed, lambs may be infected with *Salmonella* Arizonae, which comes from several different serogroups. *Salmonella* organisms are relatively easy to culture from the feces or tissues of infected animals, using common enteric agar such as XLT4 or brilliant green (BG) agar, with tetrathionate and selenite as selective enrichment media.

TABLE 32-21

Most Frequently Identified *Salmonella* Serotypes (and the Serogroup) from Ill Cattle in the United States in 2010*

Serotype (Serogroup)	Percentage of 1396 Isolates
Dublin (D)	19%
Cerro (K)	15%
Montevideo (C1)	7.5%
Typhimurium (B)	7%
Newport (C2)	6.4%
1,4,5,12:i: (B)	6.4%
Kentucky (C3)	6.1%
Typhimurium var. 5 (B)	4.2%
Anatum (E1)	3.3%
Agona (B)	2.8%
All others	24%

Data taken from 2011 USAHA Proceedings.

*Reported as percentage of 1396 isolates submitted to National Veterinary Services Laboratory (NVSL) for serotyping.

Clinical Signs and Differential Diagnosis *Salmonella* infection can cause a variety of clinical signs. The most common signs are fever and diarrhea[9] after an incubation period of 1 to 4 days after exposure or a recrudescence from the carrier state. Animals of all ages may be affected, but serious illness is observed most frequently in very young animals and parturient dairy cattle.

The character of the diarrheic feces varies from watery to mucoid with fibrin and blood. Sheets of fibrin may appear to be sloughing mucosa. The feces often have a putrid, foul odor because of the presence of plasma proteins associated with severe inflammatory bowel disease. Salmonellosis causes an acute protein-losing enteropathy. The systemic effects of endotoxins (and other toxic material) absorbed through the damaged bowel mucosa may be severe (fever, anorexia, depressed attitude, shock).

Bacteremia may occur rapidly, especially in neonates infected with *Salmonella* Dublin, *Salmonella* Typhimurium, or *Salmonella* Newport. Peracute to acute septicemia in calves may produce lesions in many organ systems. Affected calves usually are under 2 months of age (the range is 1 day to 6 months). Dyspnea, respiratory symptoms, sudden death, and occasionally diarrhea are the principal signs of *Salmonella* Dublin infection, the incidence of which usually peaks in 6-week-old calves. Blood culture results frequently are positive. Pure cultures of *Salmonella* Dublin often can be grown from specimens from the lungs of 4- to 8-week-old calves with

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pneumonic (septicemic) salmonellosis. Calves infected with *Salmonella* Typhimurium are only 14 days of age on average (the range is 1 to 35 days) and have mainly enteric lesions, including enlarged mesenteric lymph nodes, abomasitis, fibrinonecrotic plaques in the ileum, and hemorrhage of Peyer patches.[10]

Dry gangrene of the extremities may occur in calves after *Salmonella* infection, particularly with *Salmonella* Dublin. Legs, ears, and tails are most commonly affected, and cold agglutinins are suspected to be involved.[11]

In adult cattle, diarrhea or abortion may occur.[8] Abortion may occur by two mechanisms, because both culture-positive and culture-negative fetuses and placentae may be found in an outbreak. In the former, bacteremia in the dam results in infection of the placenta or fetus, with resulting fetal death and expulsion. Bacteremia and endotoxemia associated with diarrhea and damaged gut mucosa in cattle may result in release of $PGF_{2\alpha}$ and subsequent lysis of the corpus luteum. Abortion follows in 2 to 3 days, and the fetus and placenta will have culture-negative findings. When the fetus has a culture-negative finding, many other causes of abortion must be considered. Many infectious agents that infect only the dam can act similarly to cause luteolysis and abortion.

Differential diagnoses for the enteric form of salmonellosis in neonates include all the common enteropathogens of neonates: *Escherichia coli,* rotaviruses and coronaviruses, clostridia, cryptosporidia, and other forms of coccidia. Concurrent infection with these agents is common. In older animals outbreaks should be differentiated from those caused by bovine virus diarrhea (BVD), winter dysentery, and feed-induced indigestion. Pneumonic and bacteremic salmonellosis in 4- to 8-week-old calves must be differentiated by culture from pneumonic pasteurellosis; in goats, from mycoplasmal infection; and in lambs, from septicemic pasteurellosis.

Clinical Pathology

Salmonella enteritis often results in changes in the hemogram,[12] as effects of endotoxin manifest.[13] Plasma fibrinogen frequently is elevated because of the inflammatory nature of the disease, and either neutrophilia or neutropenia may be seen. In severe cases a left shift may be present. Initial dehydration may result in an elevated packed cell volume (PCV) and plasma protein level. The plasma protein level often drops over a period of days as protein is lost into the bowel lumen. Many other nonspecific abnormalities in clinical chemistry values are often seen, including elevated liver enzymes, decreased plasma calcium, and indications of prerenal azotemia if dehydration occurs.

Definitive diagnosis of salmonellosis requires culture of the organism from feces, blood, or tissues. PCR is also available. A 2007 study found that culture was most sensitive and specific when compared with enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR).[14]

Pathophysiology

Salmonellae are invasive organisms that may penetrate ocular, nasal, oral, or intestinal mucous membranes. *Salmonella* infection is most often transmitted by fecal-oral contamination from livestock or rodents, or by feeding of contaminated protein source animal by-products (e.g., fish meal, meat meal, bone meal, or feather meal, many of which are contaminated) or contaminated forages or plant proteins such as soybean or cottonseed. Of cattle feed tested for *Salmonella* in 2010, some 6.1% was positive, according to U.S. Food and Drug Administration (FDA) surveillance data. Even if small numbers of organisms are initially present, they multiply rapidly in moist warm conditions.

Once eaten, salmonellae attach to mucosal cells, probably by means of a nonfimbrial adhesion.[15] Attachment is increased if gastrointestinal stasis is present or the normal competitive flora has been disturbed or is not yet established, as in neonates. Salmonellae cause degeneration of nearby cells and penetrate both through microvilli and through tight junctions between cells.[16] The bacteria pass through the enterocytes to the lamina propria, where they stimulate an inflammatory response and are engulfed by macrophages and neutrophils.[17] Intracellular bacteria reach regional mesenteric lymph nodes or beyond. The organism has a predilection for lymphoid tissues and is found in highest numbers in Peyer patches and mesenteric lymph nodes.[18] Thrombi form in vessels, and tissue damage can be severe. Virulent salmonellae are capable of surviving in host tissues and multiplying, often as facultative intracellular parasites in macrophages and reticuloendothelial cells.[19] In the case of carrier animals, salmonellae survive in cells in the presence of high titers of specific extracellular serum immunoglobulins. Intracellular salmonellae can also avoid many antimicrobial drugs and complement. Stress may cause a latent infection to recrudesce, resulting in fecal or mammary gland shedding or clinical disease.

The cell wall of all gram-negative bacteria contains lipopolysaccharide (LPS) as a component. LPSs are also called *endotoxins,* and they are extremely biologically active, setting off an immunologic cascade of events that can lead to leukopenia, fever, anorexia, and eventually shock and death.[13]

Epidemiology and Control

Salmonella Dublin is an endemic herd problem and is shed by lower numbers of animals compared with *Salmonella* Typhimurium, which tends to be epidemic and shed in higher numbers by many more animals at a time.[20] In the northeast United States, in 11% of 831 herds with suspected clinical cases of salmonellosis, the leading isolates were *Salmonella* Newport and *Salmonella* Typhimurium.[21] A study of calves in California found that 18% of 1-day-old calves shed some serotype of *Salmonella,* but this percentage declined rapidly over the first 11 weeks of life. Farms that received calves from other sources were 35 times more likely to have calves that were shedding *Salmonella* in feces than were closed herds.[22] Infection with host-adapted *Salmonella* serotypes may occur as a cyclic endemic disease, especially in calves when *Salmonella* Dublin is involved. *Salmonella* infections on a farm are maintained by carrier animals shedding *Salmonella* Dublin in the feces[8] or milk,[23] chain infections in infected calves and cows, rodents, and environmental contamination. *Salmonella* carriers infected with a host-adapted serotype such as *Salmonella* Dublin may shed constantly or intermittently. Cattle with the highest risk of becoming *Salmonella* Dublin carriers are heifers infected between 1 year of age and first calving and cows infected in the parturient period,[24] but calves surviving *Salmonella* Dublin infection and illness may also become carriers. Infected carriers that are not shedding are called *latent carriers;* stress may cause shedding in feces or milk to recrudesce. A single infected, asymptomatic fecal shedder may produce one billion *Salmonella* Dublin organisms per day to contaminate the environment (one million organisms per gram of feces). Unlike other serotypes, *Salmonella* Dublin may be carried as a chronic gut and mesenteric lymph node infection and passed in feces or carried as an intramammary infection and passed in contaminated milk.

Calving areas must be constantly cleaned and disinfected between calvings. Raw milk feeding to calves may be a source of *Salmonella* (100 to 100,000 organisms per milliliter of milk).[23] Infected calves constantly amplify the number of organisms in the environment, causing exposure of other calves. Calves with clinical signs may shed billions of *Salmonella* into the environment daily.

Environmental contamination can be difficult to eliminate, because salmonellae survive for months in moist areas out of direct sunlight and in lagoons and drainage areas. *Salmonella* Dublin was recovered from feces dried for 41 months.[25] Freezing feces at −20° C (−4° F) kills 85% of salmonellae in 2 days and over 95% by 1 month.[26] Direct sunlight and drying in hot weather are effective at eliminating salmonellae.

Research has documented contaminated irrigation water as an important source of *Salmonella* organisms. In some cases municipal sewage treatment plant effluents had contaminated water.[27] On one dairy farm, river water used to sprinkler irrigate green chop contaminated the green chop, which was fed to cows. On another farm, *Salmonella*-contaminated river water was used to irrigate cotton. When the cottonseed from that gin was used as feed, cattle became infected. On a third dairy, contaminated irrigation water resulted in haylage containing *Salmonella* organisms.[28]

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Feedlot cattle colonized by *Salmonella* organisms could pose a public health risk when meat is contaminated at slaughter. In a study by National Animal Health Monitoring System (NAHMS), 7.5% of cattle on feed the longest shed salmonellae, whereas 3.5% of cattle that had recently entered the feedlot were shedding salmonellae in the feces.[29] Contamination of the animals before entry can cause the entering cattle to have a higher rate of shedding than was found in cattle that had been in the feedlot for several months.[30] Standing water contaminated with feces is frequently highly contaminated with *Salmonella;* culture of temporary shallow lakes (called *playas* in the southwestern United States) yielded numerous *Salmonella* serotypes.[31] An unusual outbreak of *Salmonella* Newport in cows and calves on a beef farm resulted in a cow mortality rate of 7.9% (32 of 407) and a calf mortality rate of 14.4% (52 of 361). BVD virus was also diagnosed in the group, and it was suspected of playing an immunosuppressive role.[32]

Control of *Salmonella* infection requires an integrated herd approach.[33,34] Sick pens were found to be 7.4 times more likely to yield *Salmonella* as were pens of preweaned calves.[35] Management interventions that were found effective in helping control *Salmonella* on dairy farms include separation of sick and parturient cattle into hospital and maternity pens, respectively (considered the most important and effective intervention), switching from a phenolic disinfectant to a peroxygen biocide such as Virkon S (DuPont, Sudbury, UK) for equipment disinfection, use of separate footwear or footbaths for personnel in the hospital and maternity pen sections, strict protocols for disinfection of hands and equipment between handling each sick or periparturient cow, strict separation of feeds used in the hospital and maternity pens, and use of clean bedding in the hospital and maternity pens.[6] Having one person manage the calves, good colostrum management, and not purchasing cattle from an infected premise had beneficial effects in reducing infection.[36]

To detect herds infected with *Salmonella* Typhimurium or *Salmonella* Dublin, a herd serologic profile based on ELISA can be used.[37] The commercial test available in the United States is the PrioCHECK Salmonella Ab bovine ELISA (Prionics, Switzerland). One lab that runs such tests on milk or serum is the Animal Health Diagnostic Center at the College of Veterinary Medicine, Cornell University (http://ahdc.vet.cornell.edu/). Rectal swab sampling and culture of cull dairy cows was found not to be a satisfactory method of detecting *Salmonella*-infected herds.[38] To control *Salmonella* Dublin, carrier cows and calves over 6 months of age are identified by serologic testing (ELISA) for anti-*Salmonella* antibody.[23,39-41] Suspect animals are culled or tested further by serologic means or by multiple fecal cultures and milk cultures (five samples at weekly intervals). Animals with positive test results are culled. In infected herds, *Salmonella* Dublin carriers (fecal or mammary) usually make up 0.4% to 3% of a dairy herd. Animals that remain seropositive over a 2-month period should be considered carriers, even if a culture result is negative on five samples.[23] A Danish study [42] found that only 14 of 31 persistently seropositive animals were culture positive for *Salmonella* Dublin at postmortem examination, and one seronegative animal was culture positive. One study found that ELISA serology had a good negative predictive value for cattle 100 to 300 days of age, whereas fecal culture had a poor predictive value.[43]

To control all non–host-adapted and host-adapted serotypes of *Salmonella,* calves and cows are promptly treated when signs of illness occur, and strict procedures to prevent the spread of infection are instituted. A study of 14 farms infected with *Salmonella* Typhimurium DT104 showed that clinical disease ceased by 4 months, but widespread infection and contamination continued. Over time the number of infected farms gradually declined, and vaccination correlated positively with a herd remaining free of clinical illness from DT104.[44] Control measures include the use of separate feeding utensils for each calf, washing of boots and hands by calf raisers between calves, isolation of ill calves to noncontact pens, and thorough disinfection of pens between calves. Decontamination of pens is most effectively accomplished if an all-in, all-out system is used. Pens are divided into four groups, with each group of pens used for calves born during a given week. When 3- to 4-week-old calves leave their pens as a group, these pens are cleaned and disinfected with a chlorine product such as bleach, a peroxygen product such as Virkon S, or a phenylphenolic disinfectant. This helps prevent continuous recycling of bacteria to each group of new calves. Environmental monitoring by frequent swab cultures of pens is the best way to check the effectiveness of the sanitation and disinfection program. Infection with *Salmonella* Typhimurium and other non–host-adapted serotypes most often occurs as an epidemic after the organisms enter the farm by means of purchased cattle, rodents,[45] rendering trucks, or feedstuffs. Even *Salmonella* Dublin may be maintained on a farm by mice.[45] A case control study of farms infected with *Salmonella* Typhimurium DT104 found that the most effective interventions included purchasing cattle directly rather than through a sales yard, quarantining purchased cattle for 4 weeks, housing sick cattle in dedicated isolation areas, and preventing wild bird access to feed storage areas.[46] Feeds may be contaminated by irrigation water,[28] in manufacturing when by-product ingredients contain *Salmonella* organisms, on the farm, or in shipment by birds or rodents or contaminated trucks. When an epidemic involving an exotic serotype occurs, feedstuffs should be examined as a likely source. Exotic serotypes are *Salmonella* from serogroups other than B, C, D1, E1, and K; that is, all those groups not listed in Table 32-21. Feedstuff contamination with the serotypes not considered exotic may also occur. High-protein supplements, rumen bypass protein, or calcium-phosphorus supplements of animal origin are sources of epidemics of various *Salmonella* serotypes in livestock. Many animal by-product feedstuffs in the United States are contaminated with *Salmonella* organisms. Once a *Salmonella* serotype enters a herd, the bacteria are rapidly spread among livestock and into the environment, where they may cause a prolonged course of herd illness and can be difficult to eliminate. Such appeared to be the case with *Salmonella* Newport and *Salmonella* Montevideo in dairy cattle in California in the past (Table 32-22). These and other group C *Salmonella* spp. tend to become endemic and persist for years on a dairy farm once it has become infected. Note that by 2010 Montevideo was the third and Newport the fifth most prevalent serotype from ill cattle in the United States (National Veterinary Services Laboratory [NVSL] data). Culture of feeds before use on a farm currently is the only means of preventing the introduction of exotic *Salmonella* serotypes, because national and international feed quality controls currently appear to be inadequate.

Vaccination Control by vaccination of dams using killed bacterins may be somewhat beneficial in protecting neonates under 3 weeks of age through colostral and milk immunoglobulin. Because most dairy calves are taken from their dam and fed milk replacer

TABLE 32-22

Changing Incidence of *Salmonella* Serotypes on California Dairy Farms as Illustrated by the Percentage of Farms from Which Each Serotype Was Isolated in 1985 to 1986 Compared with 1987 to 1988

Serotype	1985-1986 Percentage of Farms (No.)	1987-1988 Percentage of Farms (No.)
Dublin	78 (29)	53 (49)
Newport	19 (7)	36 (33)
Typhimurium	3 (1)	7.6 (7)
Montevideo	0	6.5 (6)
Infantis	0	2.2 (2)
Anatum	0	1.1 (1)
Arkansas	0	1.1 (1)

Blanchard P, Anderson M. Unpublished data based on calves brought for necropsy from Tulare area farms, 1988.

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after day 1 to day 3 of age, the potential benefit of intraluminal milk antibody from the dam is lost. This may account in part for the fact that vaccination of cows by itself often is insufficient to protect calves from salmonellosis. In neonates over 3 weeks of age, colostral immunity appears to play only a small role in protecting against salmonellosis. Because both humoral and cell-mediated immunity are important in protecting against salmonellosis,[47-49] active immunity is superior to passive. Modified live, genetically altered vaccines that stimulate humoral and cell-mediated immunity offer better protection for calves than do killed whole cell vaccines.[49,50]

The role of increased nonspecific immunity to gram-negative core antigens (through immunization with rough mutants of *E. coli* and salmonellae lacking complete cell walls) is being investigated. Some studies have been able to demonstrate an increased survival rate for salmonellosis after vaccination with a mutant strain of *E. coli* (J5),[51] designed to produce antibodies to the common core antigens of gram-negative bacteria. Two such products available in 2012 are Enviracor J-5 (Zoetis, Florham Park, N.J.) and J-Vac (Merial, Duluth, Ga.). Endovac Dairy (Re mutant *Salmonella* produced by Immvac Inc., Columbia, Mo.) is marketed with the same goal.

Available commercial *Salmonella* vaccines are killed whole cell bacterins for use in cattle and a genetically altered modified live *Salmonella* Dublin vaccine for calves (EnterVene-D [Fort Dodge Animal Health, Fort Dodge, Ia.], two doses 2 weeks apart). Some practitioners report that they have used the live vaccine orally and found it to be effective but with fewer adverse reactions than when used parenterally. The only products that are solely *Salmonella* vaccines contain *Salmonella* Typhimurium or *Salmonella* Typhimurium and *Salmonella* Dublin or live *Salmonella* Dublin organisms, or siderophore receptor protein (SRP) *Salmonella* Newport subunits (also see Chapter 48). Autogenous bacterins can be made for serotypes not commercially available when they are isolated from animals on a farm and believed to be the causative agent of disease. A subunit vaccine with SRP (SRP vaccine) is being marketed by Zoetis under conditional U.S. Department of Agriculture (USDA) license for vaccination against *Salmonella* and other gram-negative bacteria. Siderophores are iron chelating proteins produced by all *Salmonella,* so producing antibodies against SRPs from *Salmonella* Newport should theoretically be effective for all serotypes of *Salmonella,* and because they are a subunit, they should be less toxic. The initial vaccination requires 2 doses at 2- to 4-week intervals, followed by a yearly booster.

A major problem associated with *Salmonella* bacterins and modified live *Salmonella* vaccines is adverse reactions. Adverse reactions vary from fever, depression, and anorexia to collapse and death after vaccination. Animals may have severe reactions after the first, second, or third dose. The apparent cause of these severe reactions is a high degree of sensitivity to the presence of gram-negative endotoxin, which results in a rapid immune cascade leading to shock.[13] This sensitivity is genetically controlled, possibly accounting for the high frequency of adverse reactions in one herd and their absence in a neighboring herd. High ambient temperatures also increase sensitivity to the adverse effects of endotoxin. Adverse reactions usually can be averted or reversed by using epinephrine (1 mL of 1 : 1000 [1 mg/mL] for every 50 kg of body weight given IM or IV) as soon as evidence of polypnea, dyspnea, or weakness appears.

Lack of efficacy of killed *Salmonella* bacterins in calves is evident in experimental studies. Commercial bacterin vaccines in aluminum hydroxide administered directly to calves at 2 and 4 weeks of age failed to protect the calves when they were orally challenged at 6 weeks of age.[51] Other research has demonstrated protection in older vaccinated calves that were challenged intravenously.[52] Calves under 12 weeks of age do not serologically respond with anti-LPS antibodies after vaccination with two or three doses of killed bacterins in aluminum hydroxide.[53] On the other hand, calves over 12 weeks of age and cows do respond serologically to two doses of the same vaccine.[54] The ELISA titer in cows is short-lived (2 to 4 weeks); therefore the timing of vaccination before parturition is critical if the aim is to increase the anti-*Salmonella* colostral immunoglobulin G titer.[54] Under experimental conditions, calves fed colostrum from vaccinated dams were not protected against oral challenge at 3 weeks of age.[12] One report suggests that vaccination with killed *Salmonella* Typhimurium vaccine prevented reinfection and recrudescence of clinical signs after an outbreak of DT104 and helped in eliminating the organism from the farm.[46] As mentioned previously, these differences may in part be explained by whether or not a calf continues to receive milk from its dam and thus has or does not have intraluminal antibodies. Other live vaccines have been found effective in calves and capable of cross-protection against other serotypes, including a DNA adenine methylase–deficient *Salmonella* Typhimurium[55] and an avirulent live *Salmonella* Choleraesuis strain 54,[56] but neither was licensed for cattle in the United States as of 2012.

Necropsy Findings

ENTERIC FORM. Calves often are emaciated and have serous atrophy of fat. Especially with *Salmonella* Typhimurium, the ileal, cecal, or colonic mucosae may be thickened and hemorrhagic with adherent fibrinonecrotic plaques. Fibrin may be found in sheets, especially pronounced in the areas of Peyer patches. The abomasum, duodenum, and jejunum are often involved but less severely. The abomasum usually contains brown, fetid liquid. Bowel contents often are watery and may contain fibrin, blood, or both.[10] The mesenteric lymph nodes frequently are enlarged and dark. Chronically affected cows or calves may have discrete areas of necrosis in the cecum or colon that may involve the entire thickness of the wall.[10]

SEPTICEMIC FORM. Gross lesions of bacteremic *Salmonella* infection are acute and usually subtle. Serosal and subcutaneous petechiae are widespread. The spleen usually is enlarged. The lungs are edematous and fail to collapse and have random foci of hemorrhage or congestion.[10] The wall of the gallbladder is thickened and may contain hemorrhages. The bile frequently is inspissated into a firm coagulum.[10] Less common lesions include jaundice, cystitis, meningitis, osteomyelitis, arthritis, and dry gangrene of ears, tail, or feet. Gastrointestinal lesions may or may not be present.

Treatment

The keys to successful treatment of bacteremia caused by gram-negative bacteria are (1) antimicrobial drugs, (2) fluids and electrolytes, and (3) NSAIDs. *Salmonella* Typhimurium antiserum is available commercially. Adverse reactions by cattle to horse serum are common; care should be taken.

Early in the course of disease in calves, appropriate antimicrobial therapy often increases the survival rate markedly, because bacteremia frequently occurs. Appropriate antimicrobial therapy depends on culture and antimicrobial sensitivity patterns. Many of the most virulent *Salmonella* types are now multidrug-resistant, but isolates of relatively nonpathogenic *Salmonella* on dairies and feedlots found on surveys are usually sensitive to most antimicrobials.[22,57] In general, most *Salmonella* organisms are sensitive to florphenicol, ceftiofur (and other third-generation cephalosporins), trimethoprim-sulfonamide (TMS), gentamicin, amikacin, and fluoroquinolones such as enrofloxacin.[19,22] Higher than label doses of ceftiofur used in calves with experimentally induced *Salmonella* Typhimurium infections did not alter mortality but did reduce fecal shedding and promote more rapid clearance.[58] Sulfas and fluoroquinolones may not be used extralabel in food animals in the United States. Aminoglycosides such as neomycin, gentamicin, and amikacin produce long-term tissue residues and should be avoided in animals intended for use as food. Susceptibility to ampicillin, amoxicillin, sulfas, and tetracycline varies considerably, whereas resistance to penicillin, streptomycin, erythromycin, and tylosin is anticipated. TMS combinations are relatively inexpensive, especially when given orally, but oral TMS should be used only in calves younger than 3 weeks of age. In calves over 3 weeks of age, trimethoprim should be given intravenously because it is destroyed in the rumen and not absorbed. Antimicrobial drugs such as fluoroquinolones, florfenicol, or TMS that achieve good intracellular levels and have a large volume of distribution appear to be more effective than those that do not achieve good intracellular levels (e.g., gentamicin and amikacin). Florfenicol or

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cephalosporins such as ceftiofur are good choices for therapy against many *Salmonella* isolates depending on susceptibility testing results. Antimicrobial drugs may not be effective at altering the clinical course of strictly enteric infections without bacteremia, but because bacteremia frequently accompanies salmonellosis, systemic antimicrobial therapy often is chosen.

The effects of endotoxins can be partially dampened or controlled by the judicious use of nonsteroidal antiinflammatory drugs (NSAIDs). The cascade of events caused by bacterial endotoxin (LPS from the cell wall) must be brought under control early and rapidly, by the use of drugs such as flunixin (Banamine) at a dose of 1.1 to 2.2 mg/kg IV every 12 hours. Once the animal is stabilized, NSAIDs should be discontinued, as continued administration can lead to adverse side effects such as abomasal ulceration.

Intravenous fluid therapy to maintain blood volume and pressure and correct acid-base or electrolyte abnormalities is important in any animal that is dehydrated or in shock (see Chapter 20, Neonatal Diarrhea; Chapter 32, Equine Fluid Therapy, for adult equine; and Chapter 44, on critical care). Measurement of blood gases and electrolyte values is useful to assist in fluid therapy formulations. Fluids containing sodium, with supplementation of glucose, should be administered intravenously as needed. Metabolic acidosis with mixed water and electrolyte losses is most often seen. Oral fluids and electrolytes may also be effective supplements. The prognosis is good if animals are treated aggressively and early in the course of illness.

Control of Infectious Disease in a Veterinary Hospital Veterinarians must also be aware of preventing the spread of *Salmonella* and other nosocomial diseases within an animal hospital and should have an effective written infectious disease control program in place.[59] In one study 1.4% of cattle, mostly from dairies, shed salmonellae when in a veterinary clinic,[60] whereas the author has found an average of 7% of cattle (mainly dairy cows) in our large animal clinic are shedding *Salmonella.*

Clusters of cases occurred mainly in August and September in one northeast U.S. veterinary hospital, with 15 different serotypes involved; the most common were Typhimurium (33%), Newport (23%), and Agona (12%).[61]

See Chapter 46, Biosecurity and Infection Control for Large Animal Practices.

Paratuberculosis (Johne's Disease)

Raymond W. Sweeney

Paratuberculosis is a chronic enteric disease of ruminants caused by infection with *Mycobacterium avium* subsp. *paratuberculosis* (MAP). Cattle, goats, sheep, deer, and camelids are most commonly affected, but the disease is also reported in wild ruminants and other species. In the United States, at least 68% of dairy herds have MAP-infected animals, with a much lower prevalence among beef herds (7.9% in one study).[1,2]

The causative organism, MAP, is a hearty organism that survives for prolonged periods in the environment including soil and water. However, it has fastidious growth requirements in vitro, and culture on solid media may require 8 to 16 weeks. Recent studies indicate that MAP is also able to assume a spore-like bioform that is resistant to heat treatment in vitro, which may account for the organism's ability to survive pasteurization.[3] In vivo, the organism is an intracellular pathogen with the ability to survive within macrophages by preventing the maturation and acidification of the phagocytic vacuole. The term *Johne's disease* is often used to refer to the clinical syndrome of diarrhea and weight loss that results from MAP infection.

Transmission and Susceptibility Paratuberculosis is most commonly transmitted by the fecal-oral route. The organism is shed in the feces of infected animals (usually adults) and ingested by susceptible (usually young) animals. Critical points for potential exposure include maternity pen surfaces, cows' udders, contaminated feed or feeding implements, and calf housing areas. Small amounts of manure from heavy-shedding animals can result in vast contamination and exposure of susceptible young stock. Recent studies have also shown that MAP may be aerosolized and spread with dust barns with infected animals, raising the possibility of exposure through inhalation, or oral ingestion of organisms where contaminated dust has settled on feeding utensils, etc.[4] The organism can also be shed directly into colostrum and milk of infected cows, or these products can be contaminated by organisms on the skin, at the time of collection if insufficient sanitation is practiced. Transplacental transmission has been demonstrated and becomes more likely (40% of fetuses from cows with clinical signs) as the infection progresses to advanced stages.[5,6]

Resistance to infection with MAP in calves increases with the age of the animal, with neonates considered particularly susceptible. Most studies indicate that by the age of 1 year, susceptibility is equivalent to that of an adult animal.[7] While adult animals are more resistant to infection than juveniles, natural resistance in adult animals can be overcome by exposure to high doses of MAP organism. Furthermore, if infection with MAP occurs in an adult animal, the prolonged incubation period that ensues may result in the animal being culled for other reasons before clinical manifestations of paratuberculosis are recognized. In addition to age, the exposure dose will influence not only whether an animal becomes infected, but also the rate of progression of the disease. Exposure to higher doses of MAP is thought to lead to more rapid progression of the infection and manifestation of clinical disease at a younger age. Finally, there is growing evidence that genetic factors may play a role in susceptibility. Evidence gleaned from studies of breed differences, sire line differences, and DNA markers or candidate genes have indicated a clear genetic influence on susceptibility to MAP.[8] In the near future it may be possible to identify sires and dams with decreased susceptibility to MAP for breeding purposes.

Pathogenesis and Stages of Infection Although tonsillar invasion by MAP following oral ingestion in calves has been demonstrated experimentally, most evidence suggests that the intestinal epithelium, particularly the ileum, is the usual portal of entry. The Peyer patches are populated by specialized intestinal epithelial cells (M cells) that deliver the MAP organisms to macrophages in the submucosa of the intestine.[9] The progression of infection from this point is determined by a balance of the host's innate and adaptive immune response vs. the ability of the MAP organisms to evade destruction. In the early phases of infection, macrophages activated by T-helper type 1 (Th1) cytokines, such as interferon-gamma (IFN-γ), are able to limit proliferation of MAP and expansion of the infection.[10,11] Some animals might even eliminate the infection at this stage. In those animals that do not clear the infection, the MAP infection is kept in check by the immune system, with limited slow progression initially. However, this comes at a cost to the host, and the persistent presence of MAP antigen in the intestinal and gut-associated lymphoid tissue incites a chronic inflammatory response. Inflammatory cells are recruited to the area, resulting in granuloma formation with MAP-laden macrophages, epithelioid cells, lymphocytes, and multinucleate giant cells.[12] This period of insidious, slow proliferation is associated with a clinically silent "eclipse" phase, during which there is neither detectable fecal shedding of MAP nor detectable serum antibody production. Tests of specific cell-mediated immunity, such as detection of IFN-γ production in vitro following peripheral blood lymphocyte proliferation, might yield positive results during this eclipse phase, but are not available on a practical basis at this time.

Eventually, the host cell-mediated immune response is no longer able to contain the infection. The previously effective Th1-type response is replaced by development of a T-helper type 2 (Th2)–type response with elaboration of cytokines such as IL-4 and IL-10, which are associated with antibody production and waning of cell-mediated

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immunity.[13] Although there are no outward signs of clinical disease, and production is not yet affected, detectable fecal shedding (at a low level) begins at this stage, followed by development of detectable antibodies.[14,15] The asymptomatic fecal shedder has the potential to spread the disease within herds or between herds without arousing suspicion, as it appears clinically healthy.

As the infection progresses, MAP organisms begin to spread to extraintestinal sites, either via blood or through the lymph. This can result in transplacental infection, and direct shedding in milk and colostrum, as noted earlier. Fecal shedding of MAP also increases, so that high levels of fecal shedding may be detected before clinical signs are observed. In this subclinical phase of infection, effects on production parameters in dairy cattle are variably affected. A 16% reduction in milk production during the final lactation before culling has been reported, with little (4%) or no reduction in the penultimate lactation.[16,17] Studies on the effect of MAP infection on parameters of reproduction efficiency (days open) and udder health (somatic cell count) have had mixed results.[17,18] Thus, producers are often reluctant to cull asymptomatic infected cows, as the animals remain apparently productive members of the herd.

Ultimately, the MAP infection, and accompanying inflammatory response, progressively leads to severe granulomatous infiltration of the bowel, causing thickening of the intestinal lining, with clubbing of villi and marked lymphangiectasia. The resulting maldigestion and protein-losing enteropathy result in the clinical syndrome recognized as Johne's disease.

Clinical Johne's Disease The hallmark clinical sign of Johne's disease in cattle is watery (pipe-stream or projectile) dark green diarrhea. The diarrhea is not associated with tenesmus, there is not typically blood or mucus present, and the animal does not exhibit signs of fever, dehydration, or inappetance, but rather maintains a good appetite and possibly increased water consumption. Rapid weight loss usually accompanies the diarrhea, and edema due to hypoproteinemia develops in the submandibular and brisket areas (Figs. 32-130 and 32-131). Clinical laboratory tests will reveal hypoproteinemia, hypoalbuminemia, and possibly anemia of chronic disease. In this stage of the infection, MAP organisms are shed in the feces in massive quantities and these animals can serve as a huge source of environmental contamination. Differential diagnosis might include severe parasitism, renal amyloidosis, vena cava thrombosis, lymphosarcoma, or copper deficiency. If the animal is not culled at this point, progression to end-stage Johne's disease, with inappetance, cachexia, and death will ensue. Postmortem examination reveals grossly visible thickening and increased corrugation of the lining of the epithelium, and potentially enlargement of the mesenteric lymph nodes in the ileocecal region. Histopathologic examination reveals the aforementioned granulomatous inflammation in gut and associated lymphoid tissue, with macrophages laden with acid-fast staining bacilli.

In sheep, goats, and camelids, diarrhea may not be a prominent feature of clinical Johne's disease as it is in cattle. Although watery feces may sometimes be found, more often, feces may be normal or lose their pelleted form and take the form of dog stool. Weight loss is prominent, and the hypoproteinemia with submandibular edema is a frequent finding. Goats, in particular, may become quite anemic, more than might typically be expected with anemia of chronic disease. Of course anemia, hypoproteinemia, and weight loss may be exacerbated by concurrent intestinal parasitism, which may initially obscure the diagnosis of Johne's disease. Johne's disease in farmed deer may differ in that there may be a shorter incubation period with rapid progression to clinical disease with diarrhea and emaciation. Also, postmortem examination of deer with Johne's disease may reveal caseation and/or calcification of mesenteric lymph nodes.

DIAGNOSIS. The available diagnostic tests are divided into two broad categories: (1) immune-based diagnostic tests that detect the host's antibody or cell-mediated immune response to MAP infection, and (2) organism detection tests that detect MAP organisms or MAP bacterial DNA in fecal or tissue samples.

Immune-Based Tests. Tests of cell-mediated immunity include the intradermal Johnin test, which is similar to a tuberculin test, and in vitro lymphocyte stimulation with MAP antigens with detection of IFN-γ production. The intradermal Johnin test is generally regarded as unreliable because of both false-positive and false-negative reactions. Stimulation in vitro of peripheral blood lymphocytes with antigens of MAP, followed by detection of IFN-γ in cell culture supernatant, has shown the ability in a research setting to detect animals early in the course of MAP infection, in the eclipse phase before antibody production and fecal shedding are detectable. However, the tests are not available in a practical commercially available setting.

The most commonly applied immune tests are those that detect antibodies in serum or milk. These include the complement fixation (CF) test, the agar gel immunodiffusion (AGID) test, and enzyme-linked immunosorbent assay (ELISA). The ELISAs have superior performance to the CF or AGID tests when applied to serum from cattle, but some nations still list CF or AGID testing as an import requirement. The ELISA is the most specific and sensitive of the commercially available antibody tests. It may be applied to serum or milk, and studies have shown comparable results when ELISA is applied to both matrices. The ELISAs are attractive because of their



FIG. 32-130 A Guernsey cow exhibiting clinical signs of Johne's disease, including thin body condition and fecal staining on hind end. *(Courtesy of Dr. Robert H. Whitlock, Kennett Square, Pa.)*



FIG. 32-131 Holstein cow exhibiting submandibular edema associated with clinical Johne's disease, hypoproteinemia, and protein-losing enteropathy. *(Courtesy of Dr. Robert H. Whitlock, Kennett Square, Pa.)*

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relatively low cost and amenability to automation, which makes testing of large numbers of samples practical and cost-effective. Many Dairy Herd Improvement Association (DHIA) services now offer the option to include Johne's ELISA testing on milk samples, adding to the convenience of testing. Preservatives added to DHIA milk samples do not interfere with milk ELISA testing.

Antibody detection tests are hindered only by the natural biology of the disease, in that infected cattle do not normally produce detectable antibodies until after fecal shedding has begun. Thus, the sensitivity to detect asymptomatic cattle that are "low fecal shedders" may be as low as 15%, whereas 90% of clinically affected, "heavy shedding" cattle will be positive. The ELISAs generally enjoy a high specificity (98% to 100%).[19,20]

Organism Detection Tests. Organism detection tests on fecal samples include both culture and polymerase chain reaction (PCR) detection methods. They have the advantage over antibody-based tests in that they (1) generally allow detection earlier in the course of infection, since fecal shedding usually precedes antibody detection; (2) allow quantification of the degree of fecal shedding to assess the biosecurity impact of individual animals; and (3) definitively identify MAP in a herd at the time of first diagnosis. They have the disadvantage of being more expensive than ELISA, and in the case of culture, requiring a long incubation period to obtain results. Cultures performed on solid Herrold's Egg Yolk Medium may require up to 16 weeks for incubation. Many laboratories now employ a liquid culture system that can shorten the culture time to 1 to 2 months. Commercially available real-time PCR tests for fecal samples also permit quantification of MAP shedding and have sensitivity comparable to or better than culture. The specificity of culture and PCR methods is generally regarded as 100%, but it should be remembered that when MAP-contaminated feed is consumed by uninfected cattle, the MAP organisms may pass through the gastrointestinal tract and cause a transient positive result on fecal PCR or culture. A list of USDA-approved or accredited laboratories for Johne's disease testing is available at the U.S. Department of Agriculture, Animal and Plant Inspection Service (USDA-APHIS) website (http://www.aphis.usda.gov/animal_health/lab_info_services/approved_labs.shtml).

Testing Scenarios. Diagnostic tests should be selected on a case-by-case basis, depending on the clinical scenario, the objectives of the producer, and the inherent advantages and disadvantages of each test. For example, to confirm the diagnosis of Johne's disease in an adult cow with weight loss and diarrhea, a clinician will not have the luxury of waiting for fecal culture results before making a culling or treatment decision. Thus, a test with rapid turnaround time is indicated, and both ELISA and fecal PCR would provide rapid results with a high predictive value positive (or negative). If the case in question is the index case in a herd, then organism detection would be more appropriate than ELISA, to provide a definitive confirmation that MAP is the etiologic agent since the implications of a diagnosis for the herd may be great. Postmortem demonstration of typical lesions and identification of MAP by culture of mesenteric lymph node or ileum can also be used to confirm a diagnosis.

An alternative objective might be to identify asymptomatic cattle in a herd that is known to be infected with MAP, for purposes of culling in an eradication program, or segregation for calving pen or colostrum management. In higher prevalence herds, serum or milk ELISA can be used if the magnitude of the ELISA result is used to interpret the results (i.e., as opposed to just "positive" or "negative"). Animals with a negative ELISA result, even if infected, are unlikely shedding MAP in feces, milk, or colostrum at a significant level. Animals with "low positive results" are more likely shedding MAP in feces and might remain in the herd if production is good, but their status should be kept in mind when managing calving pens and colostrum. Cows with "high positive" ELISA results suggest heavy fecal shedding and a potential significant source of farm contamination; these cows should be culled as soon as possible. Although more expensive, fecal culture or PCR can similarly be used to identify asymptomatic infected cattle with greater sensitivity than ELISA. Where management/control is the objective, a low positive result will warrant appropriate calving pen and colostrum management but not necessarily culling, whereas a high positive result may warrant sooner culling. In an aggressive eradication program, any fecal culture positive result might result in a decision to cull, either immediately or at the end of the lactation. Testing can be performed on an annual, whole-herd basis, or in some systems, cows can be tested at the time of drying off. Using this method, if ELISA, fecal culture using liquid medium, or fecal PCR is employed, the results will be available prior to calving to guide management decisions.

A third scenario is to determine if a herd has MAP infection, or documenting test-negative or low-prevalence status for certification programs. One of the more cost-effective methods for this purpose, on dairy farms, is to perform fecal culture or PCR on environmental fecal samples collected from areas with high cow traffic and from the manure pit or storage lagoon. Culturing from 5 to 6 such sites has been shown to detect at least 70% of herds with infected animals.[21]

The USDA-APHIS Uniform Program Standards for Voluntary Johne's Disease Control Programs (VJDCP) provide testing guidelines for establishing herd infection status. Although individual states' programs may vary, the current standard establishes six classification levels. Levels 1 to 3 identify herds with low test-positive prevalence, or herds with 1 year of all-negative test results, while levels 4 to 6 identify herds with 2 or more years of test-negative results, with level 6 having the highest certainty of infection-free status. Herds establish classification status by whole herd (or statistically determined subset for large herds) ELISA or organism detection testing (individual samples or pooled). The reader is referred to the VJDCP Program Standards for more information on more detailed testing requirements (http://www.aphis.usda.gov/animal_health/animal_diseases/johnes/index.shtml).

Finally, testing may be desired to screen animals purchased as herd replacements or for use as embryo transfer recipients. Unfortunately, currently available tests are not useful for detecting infection in these animals, which are often of a young age (<3 years) and in the "eclipse" phase of infection. Greater assurance of likelihood of infection-free status in young stock can be obtained through testing of adult animals in the herd of origin. Purchasing animals from herds that have achieved VJDCP Classification level 4 or above will give the greatest assurance that the animals are not infected. If the seller does not participate in a VJDCP, results of comparable testing on adult cattle older than 3 years of age in the herd should be requested. If such results are not available, screening of potential replacements by ELISA and fecal PCR should be performed, recognizing that if the animal is in the eclipse phase, false-negative results are possible, and continued monitoring on an annual basis after addition to the herd is warranted.

Nonbovids. In goats, serum ELISA and fecal culture and PCR have similar accuracy to that found in cattle. However, serum testing for antibodies in sheep is less reliable, and organism detection tests on feces are recommended. The sheep strain of MAP is more difficult to grow in vitro than the cattle strain that affects dairy cattle, beef cattle, goats, and camelids in the United States. Development of specialized liquid media for culture of MAP from sheep feces has improved sensitivity, but best results will probably be achieved by employing fecal PCR testing. In camelids, PCR and culture in liquid media have similar sensitivity to detect MAP in feces.

TREATMENT. In most production situations, treatment for MAP infection is not attempted. However, in some cases treatment may be desirable to allow for preservation of genetics (e.g., through embryo transfer or in vitro fertilization), or for sentimental reasons, especially those animals viewed as pets. Before undertaking treatment, the owner must be made aware that treatment may result in remission of clinical signs and reduction of fecal shedding, but the infection is rarely eliminated, and daily treatment will most likely be required for the life of the animal, with relapse likely when treatment is discontinued. Treatment of a clinically affected pregnant cow to salvage her fetus is not recommended because of the high likelihood of transplacental infection of the fetus. Additionally, any chemotherapeutic

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program will involve extralabel use of antimicrobials, which in the United States must be performed in accordance with the regulations set forth in the Animal Medicinal Drug Use Clarification Act (AMDUCA). As reliable withdrawal times are not established for many of the antimicrobials employed in treatment of Johne's disease, owners should be informed that once treatment begins, the animal or its products should never enter the human food supply chain.

The therapeutic agents most often employed include those used to treat mycobacterial infections in humans (isoniazid, rifampin, clofazimine), monensin, and aminoglycosides, and combination therapy is often recommended, at least to induce remission. Clofazimine, an antileprosy drug, has been used successfully by the author at a dose of 2 mg/kg q24h, alone or in combination with other agents. Improvement in fecal consistency and plasma total protein occurred within 7 to 14 days of starting treatment. However, recently this drug has not been available in the United States, prompting use of other combinations. Thus, a typical currently employed treatment protocol, if clofazimine is not available, for cattle, goats, sheep, and camelids includes rifampin (10 mg/kg PO q24h) and isoniazid (10 to 20 mg/kg PO q24h). Gentamicin (6.6 to 8.0 mg/kg IV q24h) for the first 5 to 10 days of treatment may hasten onset of remission, provided renal function is normal and can be monitored for signs of nephrotoxicosis. For cattle, monensin should also be recommended. Approved for its effect as a coccidiostat and for its effect on rumen microflora and digestion efficiency, it has also been shown to inhibit MAP growth in vitro and ameliorate the disease in experimentally and naturally infected cattle.[22,23] Use of monensin as a feed additive also has the potential to play a chemoprophylactic role in prevention of MAP infections in susceptible cattle.

PREVENTION AND CONTROL. For herds not currently infected with MAP, prevention relies primarily on establishing a closed herd. If herd replacements must be purchased, the herd of origin should be screened as indicated earlier, and ideally have achieved level 4 or higher status in the VJDCP.

For herds that are infected, clear objectives should be established. For large production herds with high turnover, no steps may be economically warranted. For other herds, management to reduce transmission and ameliorate the economic impact of the disease may be desirable, and in other herds eradication may be the goal. Regardless of the goal, a test-and-cull strategy employed without other management changes to reduce transmission will not be successful.

Whether the goal is eradication or managing the disease to minimize losses, a risk assessment should be performed to identify potential areas of MAP transmission, especially to susceptible young stock, and a management plan developed. A plan must be individually tailored to a specific facility, but in general key control points are calving pens, calf feeding (colostrum and milk) management, and calf housing, especially as they pertain to potential exposure of calves to feces of adult infected cows, or to fecal-contaminated surfaces. Handbooks for veterinarians to assist them in performing risk assessments and management plans for both dairy and beef cattle, designed by the Johne's Disease Committee of the U.S. Animal Health Association, are available at http://www.johnesdisease.org/. On most dairy farms, control strategies will focus on calving pen hygiene, early removal of calves from the calving pen after birth, providing an uncontaminated source of colostrum and milk or colostrum replacer and milk replacer, and calf housing free of contamination by feces from adult cattle. Testing in some form to identify and remove or segregate highly infectious adult cattle is usually warranted. In beef cow-calf operations, preventing transmission to calves again must focus on manure contamination of calving areas, manure contamination of cows that are nursing calves, and other possible sources of calf exposure to feces from potentially infected adult cattle. Recommendations can be adapted as appropriate for use with small ruminants and camelids, again to focus on prevention of transmission to susceptible young stock.

Vaccination has been employed with mixed results in cattle and small ruminants. In the United States, vaccination of cattle is permitted in some states, on approval by the State Veterinarian. The only licensed vaccine (Mycopar [Boehringer Ingelheim Vetmedica, St. Joseph, Mo.]) is a killed oil suspension of *M. avium*. The vaccine is generally regarded to reduce the incidence of clinical disease, and in some instances also reduce the level of fecal shedding, yet in other studies prevalence of fecal shedding was not affected. Vaccination should be considered as a useful adjunct, particularly in herds of high prevalence and losses due to clinical Johne's disease. Vaccination alone, without implementation of management changes to reduce exposure of calves to MAP, is often unsuccessful as any resistance achieved by vaccination may be overcome by heavy MAP exposure.

ZOONOTIC POTENTIAL. Traditionally, MAP was not regarded as a pathogen of humans. However, because of some similarities between Crohn's disease in people and Johne's disease in ruminants, the possible connection between MAP and Crohn's disease has undergone further scrutiny. These studies, especially those that employ PCR methods to identify MAP in tissue samples from people with Crohn's disease, have definitively shown an association between presence of MAP in intestinal tissue and Crohn's disease.[24] However, what is more difficult to determine is whether this association is causal or secondary. Crohn's disease is thought to involve an overly florid immune response to antigens in the gastrointestinal tract. Proponents of the hypothesis that MAP causes Crohn's disease believe that MAP antigens are responsible for that response, whereas skeptics believe that MAP may be present secondarily to damaged mucosa with diminished resistance to MAP colonization. Undoubtedly, Crohn's disease is a multifactorial disease influenced by a complex interaction of genetics, environment, cigarette smoking, and potentially infectious agents. Human exposure to MAP occurs potentially via survival of MAP in pasteurized milk or drinking water contaminated by fecal runoff from infected farms. Increasingly, regulatory agencies around the world are treating paratuberculosis as a food safety issue. Although it may be difficult to scientifically establish an etiologic connection between MAP and Crohn's disease, in the author's opinion, even the potential for a role of MAP in Crohn's disease or other human conditions should motivate producers and veterinarians to control the disease in food-producing animals.

Copper Deficiency in Ruminants

John Maas • Bradford P. Smith

Definition and Etiology

Copper deficiency occurs when the diet contains an abnormally low amount of copper (primary copper deficiency) or when copper absorption or metabolism is adversely affected (secondary copper deficiency). If inadequate amounts of copper are available to tissues in the form of essential metalloenzymes, the signs of copper deficiency (hypocuprosis) may occur. Clinical signs in ruminants include diarrhea, decreased weight gain, unthrifty appearance, anemia, changes in coat color (achromotrichia) or wool quality, anemia, spontaneous fractures, lameness (epiphysitis), and demyelinization (enzootic ataxia of sheep and goats, or swayback). One of these syndromes usually predominates in a given herd.

The minimum recommended dietary copper concentration (dry matter basis) is 4 to 10 ppm (mg/kg) for cattle,[1,2] 5 ppm for sheep,[3] and 7 ppm for merino sheep.[3] Young animals and fetuses are more susceptible to copper deficiency than are mature animals, and cattle are more susceptible than are sheep. Secondary copper deficiency is associated with high dietary levels of molybdenum, sulfates, zinc, iron, or other compounds. Secondary copper deficiency often presents with clinical signs of diarrhea and weight loss or unthriftiness. It has been called *teart, peat scours, renguerra, pine,* and *salt lick disease.*[4] Salt sickness in Florida appears to be the result of combined copper and cobalt deficiencies. The cause of copper deficiency in clinical cases is often multifactorial and can be difficult to quantify. In addition, unknown factors cause clinical expression of copper deficiency in ruminants to be manifested as a variety of syndromes.

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Clinical Syndromes and Differential Diagnosis Profuse watery diarrhea with poor weight gains and/or weight loss is a common syndrome seen in ruminants with copper deficiency.[4] When it occurs on boggy pastures that contain high concentrations of molybdenum, it has been referred to as *teart*.[4] Decreased weight gains or weight loss as a herd problem can have many other causes, including parasitism, trace mineral deficiencies (selenium, cobalt), protein calorie malnutrition, and Johne's disease. A syndrome characterized by epiphyseal enlargement, stiffness, and unthriftiness is seen in young ruminants and is the result of copper deficiency[5] and is sometimes called *pine*.[4] Copper deficiency can cause spontaneous fractures in ruminants. Enzootic neonatal ataxia (swayback) of lambs and kids is characterized by progressive incoordination and recumbency that begins with the hindlimbs and progresses to the forelimbs. It has also been reported in deer and pigs. Inadequate keratinization of wool and achromotrichia is the result of imperfect oxidation of free thiol groups during hair growth and keratinization. Subsequently, the wool fibers do not crimp normally, and they appear to be "stringy" or "kinky." A copper-containing enzyme, tyrosinase (polyphenol oxidase), is needed to convert L-tyrosine to melanin. With copper deficiency, this conversion is slow and hair is lighter in color than normal (achromotrichia). Loss of wool crimp and pigmentation changes in sheep or cattle, respectively, occur late in the course of copper deficiency. In addition to the previously listed clinical syndromes that may occur alone or jointly, copper deficiency may be associated with anemia[6] (altered iron metabolism) or infertility.[7] Infertility is probably multifactorial and may not respond to an increase in copper intake alone. Copper deficiency also seems to result in decreased immune function in ruminants.[8,9]

Pathogenesis A frank dietary deficiency of copper results in hypocuprosis and eventual clinical signs. Also, a variety of conditions can decrease copper absorption from the gastrointestinal tract (large intestine in sheep and small intestine in cattle). The interactions between dietary copper, molybdenum, and sulfates (or sulfur) are important (Fig. 32-132). Excess dietary molybdenum can lead to the formation of sparingly soluble cupric molybdates in the rumen that are not absorbed from the intestine. The addition of excess sulfur or sulfates in the diet and/or water can result in the formation of insoluble copper thiomolybdates in the rumen. The interactions among these three elements are complex.[10] The infertility seen with secondary copper deficiency may be caused by excess circulating oxythiomolybdates, which interfere with the release of luteinizing hormone.[11]

It is important to note that at low sulfur concentrations in the diet, excess molybdenum has a minimum effect on decreasing copper absorption. Even when no dietary molybdenum or sulfates are present, only about 5% of ingested copper is normally absorbed. Excessive calcium in the diet, particularly in the form of limestone, decreases copper absorption. Excessive iron, 30 mg/kg of body weight or 1200 ppm in the diet of calves, reduces copper absorption.[12] Overgrazing, with the subsequent ingestion of excess soil, also decreases copper absorption. In addition, excess cadmium (3 to 7 ppm) or excess zinc (100 to 400 ppm) reduces hepatic copper concentration, probably through the combined effects of decreased absorption and competition with copper for hepatic metallothionein.[13,14] It had been suggested that excess dietary selenium might interfere with copper absorption and/or utilization, but this has been shown not to occur.[15] Copper is an essential component of a number of mammalian enzymes. Some of the medically important copper-containing enzymes are (1) the cytosol form of superoxide dismutase (copper and zinc), (2) cytochrome oxidase (c and aa_3), (3) lysyl oxidase, (4) ascorbic acid oxidase, and (5) ceruloplasmin.[16] In addition, normal copper nutrition appears essential for iron absorption and transportation of iron to the liver and reticuloendothelial system and is thus necessary for normal hemoglobin formation. The precise pathophysiology of most of the copper deficiency syndromes is not known. However, the central role of copper in preventing cellular oxidative damage and its role in iron and sulfur metabolism are probably important.

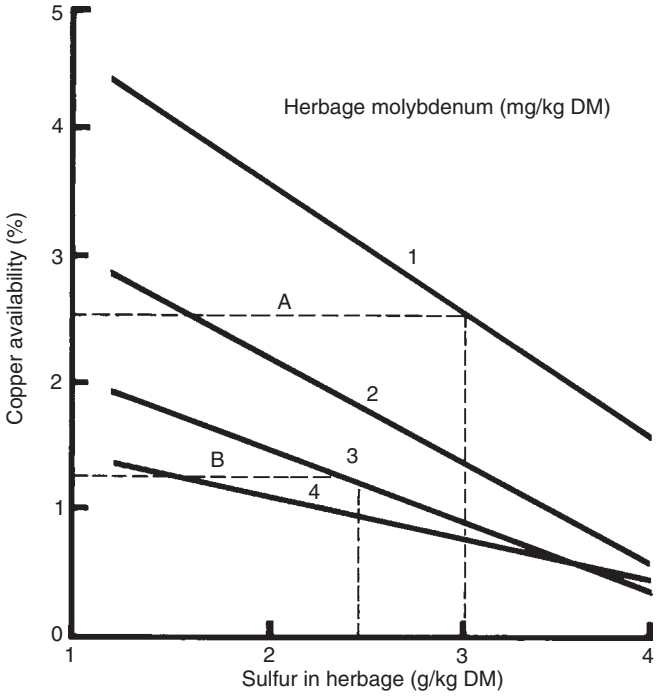


Fig. 32-132 Estimating the availability of copper in herbage from its molybdenum and sulfur concentrations: the difference of 3 mg of molybdenum and 0.5 g of sulfur per kilogram of dry matter (DM) between pastures A and B is sufficient to reduce availability from 2.6% to 1.3%, doubling the grazing animal's requirement of copper from the pasture. *(From Suttle NF. 1986. Copper deficiency in ruminants: recent developments. Vet Rec 119:519.)*

Epidemiology Copper deficiency can occur when diets are inadequate in copper or contain excess amounts of interfering substances, particularly sulfates and molybdenum. This occurs in many parts of North America. Forages and water can be sources of molybdenum, sulfur, and sulfate. To avoid primary copper deficiency, pasture (dry matter) should contain over 5 ppm of copper, with 3 to 5 ppm considered marginal and less than 3 ppm deficient. Soil copper concentrations are generally slightly lower than those of the harvested forage. Molybdenum adversely affects plant uptake of copper. Forage molybdenum concentrations greater than the copper concentrations often lead to secondary copper deficiency, even when forage copper is adequate. Because copper content in grasses and legumes can be different, forage samples must be randomly selected to reflect dietary intake. Forage copper concentrations as high as 12 to 27 ppm have been associated with copper deficiency when molybdenum levels are high.[4] The critical ratio of copper to molybdenum in feeds is 2:1, with 5:1 recommended for sheep and 5:1 to 10:1 for grazing cattle.

Clinical Pathology and Diagnosis The primary site of copper reserves is the liver and the copper concentration in the hepatic tissue is the best indicator of copper status (Fig. 32-133). The reference range for hepatic copper concentrations in cattle is approximately 90 to 200 µg/g (ppm) and in sheep 90 to 250 µg/g on a dry weight basis (dry matter basis [DMB]).[4,17,18] Hepatic copper concentrations as high as 250 µg/g DMB are not unusual in supplemented ruminants (even over 350 µg/g DMB in sheep). Blood (serum or plasma) copper concentrations can be maintained near normal until hepatic copper concentration falls to 35 ppm DMB or less, at which time the serum copper concentration invariably begins to decrease.[19] When using blood samples for copper determination, serum or plasma are normally preferred. Plasma copper concentration is usually about 5% greater than an identical serum copper concentration.[20] Normal serum copper is 0.7 to 1.2 ppm (µg/mL).[4,16] Serum or plasma copper concentrations of 0.4 ppm or less are considered as

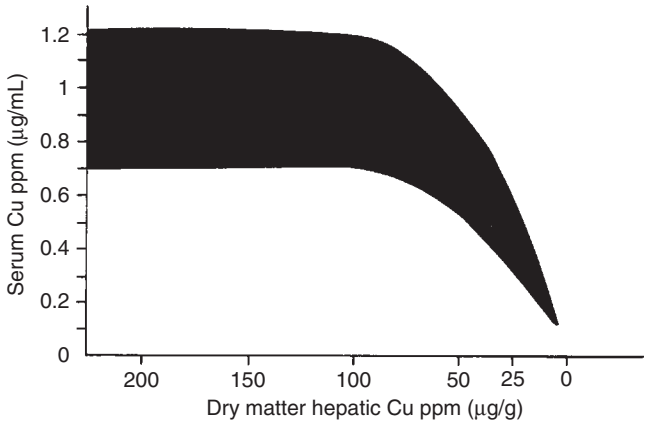


FIG. 32-133 Relationship between serum and hepatic copper concentration in ruminants.

evidence of frank deficiency. Values of 0.4 to 0.7 ppm are marginal and it is difficult to estimate the actual liver copper concentration based on these serum copper ranges. Approximately 50% to 90% of the copper in serum or plasma is present in ceruloplasmin. The remainder is bound to albumin or amino acids. The correlation between serum copper and serum ceruloplasmin was found to be weak (0.50)[20]; thus, ceruloplasmin is not commonly used to aid in diagnosing copper deficiency. Additionally, serum ceruloplasmin increases with inflammatory conditions and can result in false-normal values. Hepatic copper concentration is the preferred diagnostic sample and is easily secured at necropsy. Hepatic copper values less than 35 ppm DMB are considered deficient.[4,17-19] However, surgical biopsy is necessary for live patients, and, because laboratories generally require 100 mg or more of tissue, a biopsy instrument with an internal diameter of 3 to 5 mm is necessary.[21] The biopsy procedure in cattle is performed by locating the tenth intercostal space on the right side of the animal along a line from the tuber coxae (point of the hip) to the point of the shoulder.[21] This site is surgically prepared and blocked with lidocaine (12 mL of 2% lidocaine) and a stab incision is made. The biopsy instrument is directed slightly ventrad and craniad and advanced through the intercostal space and the diaphragm to enter the liver where the biopsy sample is obtained.[21] The liver biopsy can place the patient at increased risk for black disease or bacillary hemoglobinuria in some areas of the United States. This risk should be decreased by prior vaccination and a single dose of procaine penicillin G (4 million IU SC) administered at the time of biopsy. This technique has been shown to be safe and effective.[21] The tissues of young animals (neonates) contain variable amounts of copper compared with adults of the same species. In sheep, serum and liver copper concentrations are the same for lambs (1 week of age) and adults.[22] The plasma copper levels in lambs are low at birth but rise to adult values by 1 to 7 days of age. Plasma copper levels in the bovine neonate are lower than in mature cattle.[23] In the bovine neonate hepatic copper concentration changes little from birth to maturity; however, copper distribution in the liver is quite variable in the neonate.[18,23] Because of these differences, interpretation of neonatal serum copper concentrations is difficult. Milk is a poor source of copper, containing only 0.2 to 0.6 ppm in normal ewes and 0.01 to 0.02 ppm in severely copper-deficient ewes or cows. Milk copper in cattle is 0.05 to 0.2 ppm. To make matters worse, molybdenum is concentrated in milk.[24] Recently, research has allowed for the estimation of true wet weight (fresh) and/or dry weight of hepatic samples by concurrently measuring potassium in the specimen.[25] This allows for much more accurate estimation of hepatic copper concentration in samples that have become dehydrated prior to reaching the diagnostic laboratory. This technique allows the laboratory to accurately estimate the original wet weight or to calculate the dry weight with time-consuming drying of the specimen.[25]

Treatment and Control Treatment of copper-deficient animals is usually possible, and the prognosis is guarded to good, depending on the severity of the deficiency and the associated syndrome(s). When excess molybdenum, sulfate, and other factors leading to secondary deficiency are present, they can be overcome to some extent by increasing dietary copper or by injecting copper glycinate. Copper glycinate must be prescribed by the attending veterinarian and dispensed by a compounding pharmacy as no commercial over-the-counter products are currently available. Injectable copper glycinate (30% copper by weight) is given to adult cattle at the rate of 400 mg (120 mg copper) subcutaneously. Calves are given 100 to 200 mg of copper glycinate (30 to 60 mg of copper), depending on their age. One injection may be effective as a treatment/supplement for up to 4 to 6 months in cases of primary copper deficiency. However, in cases of excess molybdenum, sulfates, and/or sulfur, repeat injections may be necessary. Injections of copper glycinate frequently result in large swellings, granulomas, or abscesses and may be cosmetic considerations for some cattle. The reactions can be minimized by using sterile technique and using the subcutaneous tissue of the brisket as the injection site. Acute deaths can occur in calves following the use of copper glycinate injections. In some countries copper EDTA (copper disodium edetate) solutions are used as injectable copper supplements. The dosage of copper is usually the same as that recommended for copper glycinate solutions. However, acute deaths can also occur following its use in cattle.[26] Copper can be supplemented to cattle in salt-mineral mixes in situations in which adequate consumption (1 to 2 ounces [28 to 56 g]/cow/day) of the salt-mineral mix occurs. These mixes are usually 0.2 to 0.6% copper. Feed grade copper sulfate ($CuSO_4$-5 H_2O) is 25% copper on an as-fed basis (40% copper on dry matter basis). Feed-grade copper oxide is usually 50% copper as fed (80% copper on a 100% dry matter basis). To make a 0.4% copper salt mixture, add 7.2 g of $CuSO_4$ or 3.6 g of CuO to each 454 g (1 pound) of salt. For large batches add 32 pounds of $CuSO_4$ or 16 pounds of CuO per ton of salt. Salt mixtures for copper-deficient sheep should usually contain only 0.0625% to 0.13% copper (0.25% to 0.5% copper sulfate). Copper supplements can be added to a total mixed ration easily in the form of trace mineral–vitamin premixes or premix-containing pellets. Copper sulfate can be added to molasses or other sweet feed at 0.363 g/head/day for mature cattle and correspondingly less for calves. This would supply approximately 91 mg of copper to a 450-kg (1000-pound) cow per day or 10 ppm of the total diet (20 pounds [9.1 kg] of dry matter). The copper in $CuSO_4$ is more available than that in CuO. Another method of copper supplementation involves the oral administration of copper oxide needles (fine rods, 1 to 10 mm long) placed in gelatin capsules that dissolve in the reticulorumen and liberate the CuO wires. These wires reside in the reticulum and abomasum and slowly release copper for absorption. These boluses are currently available in the United States (Copasure [Animax, Bury St. Edmunds, Suffolk, UK) and contain either 25 g or 12.5 g per bolus. The usual recommended dosage is 25 g per animal 500 pounds or greater. One 12.5-g bolus is recommended for calves and the usual dose is 2 to 4 g for ewes and does,[4,27,28] which is an extralabel recommendation for sheep and goats. The copper oxide needles are thought to provide copper supplementation for 4 to 12 months. Sheep are particularly susceptible to copper toxicity, and appropriate care is necessary when supplementing them. Sheep can easily be intoxicated when consuming cattle supplements or feeds. Continued monitoring of hepatic copper concentration from slaughtered animals or via liver biopsy is an important tool in evaluating copper supplementation methods in cattle and sheep. Lambs can be given 35 mg of copper sulfate per head twice weekly to prevent swayback in endemic areas. The usual recommendation by the National Research Council (NRC) is 10 ppm (10 mg/kg) of the total diet on a dry matter basis for cattle. However, diets of 20 ppm are commonly fed to lactating dairy cattle. The most recent NRC recommendations for dairy cattle state that 40 mg/kg (ppm) of the diet on a dry matter basis is the maximum tolerable level. This is due to a number of copper toxicity episodes in the United States when the total diet contained 40 to 50 mg/kg copper

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or more in the total ration. Copper has the smallest margin of safety of all the trace minerals in ruminants. The most important goal of copper supplementation is to provide adequate dietary amounts without oversupplementing or risking toxicity.

Cobalt Deficiency in Ruminants

Robert Sager • John Maas

Definition and Etiology A number of syndromes occur in ruminants as a result of a primary cobalt (Co) deficiency in their diet. These include ill thrift or enzootic marasmus and anemia. These conditions are characterized by decreased growth, weight loss, diarrhea, decreased feed efficiency, unthrifty appearance, anorexia, and anemia. A Co deficiency syndrome referred to as *ovine white liver disease* has been described in sheep.[1-3] This syndrome is also characterized by ill thrift, weight loss, serous ocular discharge, and occasionally photosensitization.[1-3] Histopathologic lesions of this syndrome included accumulation of lipid droplets and lipofuchsin particles, dissociation and necrosis of hepatocytes, and sparse infiltration by neutrophils, macrophages, and lymphocytes.[4] Cobalt-deficient animals are more prone to parasitic infestation, particularly *Ostertagia ostertagi* in cattle.[1] Also, Co fed at levels above National Research Council (NRC) minimal recommendations has resulted in increased antibody production to a single antigen in weaned beef calves.[5]

Clinical Signs and Differential Diagnosis Cobalt deficiency in ruminants is associated with the nonspecific signs of decreased growth, weight loss, diarrhea, ill thrift, pica, emaciation, pale mucous membranes (anemia), and lacrimation. Clinical disease is more common in young, growing animals. Sheep are apparently more susceptible to Co deficiency than cattle. Primary differential diagnoses include helminthic parasitism; protein-calorie malnutrition; coccidiosis; Johne's disease; nutritional deficiencies of selenium, copper, or vitamin D; and other chronic diseases that may be associated with weight loss. Cobalt-deficient ruminants are commonly anorexic and fail to thrive on lush pasture or high-quality feeds. Anemia with Co deficiency is characterized as normocytic normochromic and must be differentiated from other causes of anemia. Cobalt-deficient cattle are more susceptible to infestation with *Ostertagia ostertagi* and to the effects of parasitism.[4] The primary differential diagnosis when considering Co deficiency is invariably internal parasitism.

Clinical Pathology and Diagnosis Because the role of Co in ruminant nutrition is tied to the formation, absorption, and use of vitamin B_{12}, the most significant biochemical role of Co is correlated with tissue vitamin B_{12} concentrations. However, the effects of starvation tend to increase vitamin B_{12} concentrations in the liver and kidneys.[6] If Co deficiency occurs with other conditions that cause anorexia, the tissue vitamin B_{12} concentrations may appear falsely elevated (normal). The appropriate analytic methods for serum B_{12} vary from humans to ruminants, so extrapolation of ruminant serum B_{12} concentrations analyzed in a human laboratory may not be possible. Serum or plasma vitamin B_{12} levels exhibit a marked diurnal variation.[7] Additionally, serum vitamin B_{12} concentration more closely reflects short-term Co intake and can be decreased when adequate liver reserves of vitamin B_{12} remain. In normal, Co-sufficient ruminants' serum vitamin B_{12} values are usually 0.1 to 0.3 ng/mL (parts per billion [ppb]). When serum vitamin B_{12} values decrease, clinical signs of Co deficiency can become evident.[8,9] Because serum B_{12} values can give spurious results, the concentration of Co in hepatic tissue is probably the best current standard for determining Co status and making clinical decisions. The liver concentration of B_{12} for cattle and sheep considered to be adequate is 0.30 to 2.24 µg/mL (ppm) on a wet weight basis.[10,11] Table 32-23 contains reference ranges for cattle and sheep.

TABLE 32-23

Reference Values for Cobalt and Vitamin B_{12}

Analyte	Cattle	Sheep
Serum Cobalt	0.1-0.3 ng/mL (ppb)[11,12]	0.1-0.3 ng/mL (ppb)[11,12]
Serum B_{12}	1-3 ng/mL (ppb)[10,11]	1-3.5 ng/mL (ppb)[11]
Liver Cobalt	80-160 ng/g (ppb) wet weight[10-12]	80-160 ng/g (ppb) wet weight[10-12]
Liver B_{12}	0.3-2.24 µg/g (ppm) wet weight[10,11]	0.3-2.24 µg/g (ppm) wet weight[10,11]

Adult bovine liver is 27% dry weight (approximately 30% dry weight).[30] Therefore, the wet weight to dry weight conversion can be easily made. Also, the measurement of liver potassium can be used to estimate either the true wet weight or true dry weight on samples that are not fresh or have become dehydrated or for laboratories that only measure dry weight or wet weight (as received).[30]

Pathophysiology Cobalt deficiency in ruminants induces a deficiency of vitamin B_{12} (cyanocobalamin). It is the lack of vitamin B_{12} that is thought to cause the majority of clinical signs and clinicopathologic abnormalities observed. Monogastric species need to ingest vitamin B_{12} preformed, whereas ruminants can manufacture adequate vitamin B_{12} if the rumen microorganisms are supplied with adequate Co in the diet. The rumen microorganisms incorporate Co into vitamin B_{12} and a number of physiologically inactive vitamin B_{12}–like compounds. The production of vitamin B_{12} from dietary Co was estimated to be about 15% in Co-deficient sheep and only about 3% in Co-sufficient sheep.[13] About 50% of the vitamin B_{12} produced is absorbed in normal animals, but only 3% to 5% of vitamin B_{12} is estimated to be absorbed by Co-deficient sheep.[14] Although the absorption of vitamin B_{12} formed in the rumen is not particularly efficient, with normal dietary Co there are usually no clinical problems, and interference by other dietary components does not appear to be clinically important.

Ruminants use the volatile fatty acids acetate, propionate, and butyrate as their primary energy sources. Propionate produced in the rumen is the precursor of glucose for ruminant metabolism. The general metabolic steps for conversion of propionate to glucose are shown[15] in Fig. 32-134.

A primary defect in Co-deficient ruminants is the inefficient metabolism of propionate at the point in the pathway at which methylmalonyl-CoA mutase, a vitamin B_{12}–requiring enzyme, catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA.[16] As Co deficiency becomes severe, the rate of propionate clearance from the blood decreases, and the intermediate metabolite methylmalonyl-CoA accumulates. [17] With severe Co deficiency, the amount of methylmalonic acid excreted in the urine increases. As the half-time for propionate clearance increases, the voluntary feed intake of Co-deficient sheep decreases.[17] These changes correlate with the degree of anorexia and weight loss observed in severely Co-deficient sheep.

The decreased growth, weight loss, unthrifty appearance, and anorexia are closely correlated to the observed abnormalities of carbohydrate metabolism. The diarrhea commonly observed with Co deficiency is not well explained; however, an increase in susceptibility to parasitism[4] might explain a portion of this clinical observation.

The anemia that is associated with Co deficiency occurs late in the development of the syndrome and is characterized as normocytic normochromic.[18] Cobalt deficiency results in the depression of the vitamin B_{12}–containing enzyme 5-methyltetrahydrofolate homocysteine methyltransferase.[19] This interference with the recycling of methionine has a marked influence on folate metabolism. In addition to potentially resulting in anemia through inefficient folate metabolism, the decreased activity of this methyltransferase could lead to a deficiency of methionine; this is a possible reason for nitrogen retention and the decreased body growth and wool growth observed.

Epidemiology and Cobalt Requirements Co deficiency in ruminants occurs in selected regions throughout the world and in

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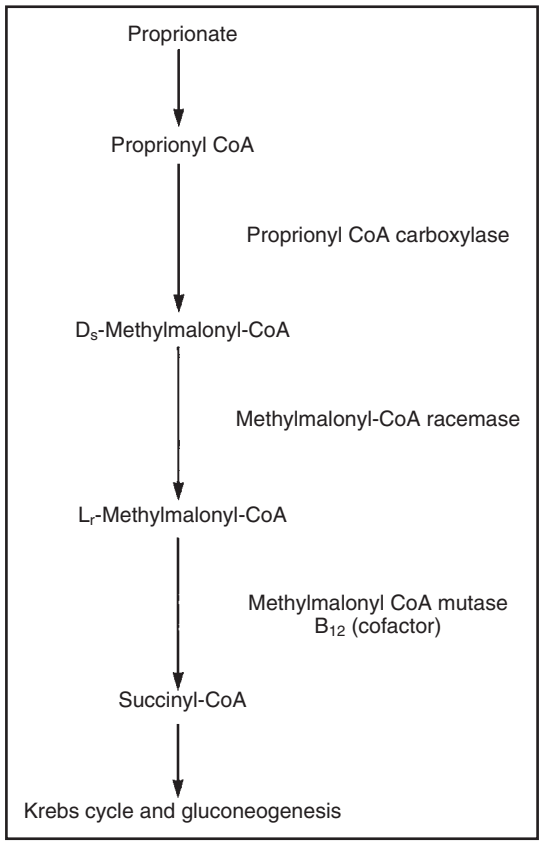


FIG. 32-134 Pathway for conversion of proprionyl CoA (from proprionate) to succinyl CoA.

association with a variety of soil types. Clinically recognizable Co deficiency is reported in New Zealand, Australia, Brazil, United Kingdom, Ireland, Scandinavia, and North America. In the United States, Co deficiency is most commonly seen in Florida, in the Northeast, along the eastern seaboard, in the upper Midwest, and around the Great Lakes.[20] Although various soil types are associated with Co deficiency, heavy fertilization with limestone reduces the Co available to plants and animals.[21] The dietary requirement of Co by ruminants is generally recommended to be 0.1 mg/kg of dry matter (DM) of the complete ration.[22-24] The Co requirement of young, rapidly growing lambs is thought to be 0.2 mg/kg (ppm) of DM of the diet.[25] When pasture Co concentrations are less than 0.07 mg/kg of DM or 0.04 mg/kg of DM for sheep and cattle, respectively, signs of deficiency can be expected to develop. On a practical basis, diets with 0.1 mg/kg of DM are considered to be adequate. Legumes have relatively high Co concentrations. Rapidly growing grasses have much lower Co concentrations, and cereal grains are poor sources of Co.[22] Oilseed meals are generally good sources of Co. Cobalt supplemented at levels above NRC recommendations (0.2 mg/kg versus 0.1 mg/kg) has been associated with increases in the immune response to one antigen in cattle.[5]

Treatment and Control Treatment is best accomplished in the short term with vitamin B_{12} injections. Ruminants poorly absorb oral vitamin B_{12}; thus injections are the most efficient. Lambs receiving 100 µg of vitamin B_{12} per week or 150 µg B_{12} every other week show remission of clinical signs.[26] Sheep receiving injections of 300 µg of vitamin B_{12} weekly or cattle receiving 2000 to 3000 µg of vitamin B_{12} weekly would also be expected to regain normal status.

Rations with 0.1 to 0.2 mg/kg (ppm) of DM Co would be expected to prevent Co deficiency in ruminants. Salt-mineral mixes containing 0.1% Co also provide adequate supplementation. 0.1% Co in salt can be made by mixing cobalt carbonate (which is 46% cobalt) at the rate of 4.35 pounds/ton of salt, or 1 g of cobalt carbonate per pound of salt. A pound equals 453.59 grams.

Cobalt sulfate as a top dressing for pastures (1.5 kg/hectare every 3 to 4 years or 0.3 kg/hectare every 1 to 2 years) has been used to increase Co concentration of pasture forage. Heavily limed pastures[21] and soils high in manganese oxide[27] decrease Co availability, and Co top dressing of the pastures or Co (B_{12}) supplementation to the animals should be considered.

A variety of rumen pellets containing Co are used to supplement grazing ruminants. These pellets have been successful in maintaining normal Co status in animals.[25-29] The pellets are not commercially available in the United States at this time.

The perennial grass, *Phalaris tuberosa,* can cause a syndrome in ruminants that is referred to as "phalaris staggers." Co supplementation can aid in prevention of this syndrome, because it inactivates or decreases absorption of the neurotoxin contained in *P. tuberosa, Phalaris minor* (canary grass), or *Phalaris* hybrids (ronpha).[29] The increased level of Co in the rumen is the important factor in preventing this condition; administration of oral or parenteral vitamin B_{12} is not effective.[26] Treatment of clinical phalaris staggers with Co is not effective, however.

Because Co is poorly absorbed, toxicity is an uncommon problem, and diets in excess of 30 mg/kg of DM are necessary for toxicosis to occur in most cases.[22-24]

Rectal Prolapse in Ruminants and Horses

Spring K. Halland

Definition and Etiology Rectal prolapse is the protrusion of the rectal mucous membranes through the anus. This evagination may be extensive and may include part of the small colon. Rectal prolapse occurs in all domestic animals, with the highest incidence in cattle, sheep, and swine. The age at which prolapse most commonly occurs is 6 to 12 months in sheep, 6 months to 2 years in cattle, and 6 to 12 weeks in swine.[1] Rectal prolapse is much less common in horses and occurs more often in mares than in males.[2]

Rectal prolapse generally is the result of an increase in the pressure gradient between the abdominal or pelvic cavity and the anus. Factors that cause the increased pressure gradient can be divided into four categories: (1) factors that result in increased abdominal fill (e.g., excess fat, bloat, and large or multiple fetuses); (2) factors that cause tenesmus (e.g., enteritis, colitis, intestinal parasitism [coccidiosis], liver disease, constipation, proctitis, urinary obstruction, dystocia, aftermath of rectal examination, and false copulation); (3) conditions that result in chronic or excessive coughing (e.g., pneumonia, parasitism, and adverse environmental conditions); and (4) miscellaneous conditions (e.g., use of growth implants, space-occupying lesions, congenital or acquired sphincter tone problems, and short tail docking [especially noted in sheep]). One study strongly revealed that sheep with short docked tails (as close to the body as possible) had a 7.8% higher incidence of rectal prolapse when finished on a high-concentrate diet.[3] Certain toxicities such as from lead, fluoride, estrogen, and zinc have been implicated as playing a role in rectal prolapse.[4] Any combination of factors may precipitate a rectal prolapse. Identification of predisposing factors becomes important in management of the case.

Clinical Signs Four categories have been used to described rectal prolapse: type I, mucosal prolapse; type II, complete prolapse; type III, complete prolapse with invagination of the colon; and type IV, intussusception of the peritoneal rectum or colon through the anus (Fig. 32-135).[2] Types I and II are much more common and more amenable to correction. On physical examination, types I, II, and III are continuous with the mucocutaneous junction of the anus, whereas with type IV a protrusion with a palpable trench inside the rectum

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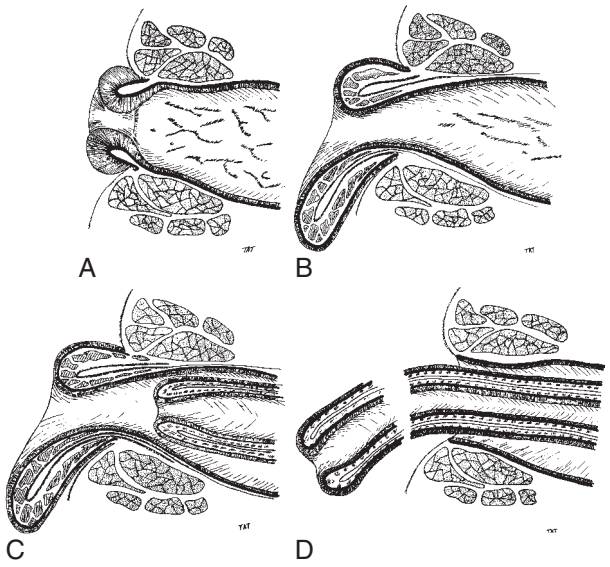


FIG. 32-135 **A,** Type I rectal prolapse. Mucosal prolapse, involving only mucosa and submucosa of the rectum. **B,** Type II rectal prolapse. Complete prolapse, involving full wall thickness of the rectum. **C,** Type III rectal prolapse. Complete prolapse plus intussusception of peritoneal rectum or small colon. **D,** Type IV rectal prolapse. Intussusception of the peritoneal rectum or small colon or both. *(From Robinson NE [ed]. 1987. Current therapy in equine medicine, ed 2. Saunders, Philadelphia, Pa.)*

is seen.[5] Chronic cases can be seen and usually are type I or II. Types III and IV often cause loss of vascular integrity to the rectum or small colon and require more immediate intervention. Types III and IV may accompany dystocias in mares.[6]

Treatment and Prognosis The first aim of therapy is identification and alleviation of the cause if possible. Early identification and correction of the prolapse is essential to saving tissues and the animal. The animal's value and intended use and the affected tissue's viability need to be considered when deciding on conservative or surgical options. The color of the membranes is a good parameter for determining if the tissue is salvageable. In general, the rectum is a forgiving structure, and attempts should be made to salvage the prolapsed tissue unless it is obviously cyanotic, necrosed, and devitalized. To prevent further damage, animals should remain standing and restrained in a small area until the prolapse can be corrected.

Types I and II usually are treated conservatively. A caudal epidural is used to reduce straining and facilitate correction of the prolapse. A range of 4 to 6 mL of 2% lidocaine is usually adequate for juvenile to adult cattle. The addition of a small amount of xylazine to the lidocaine epidural will extend the duration of the anesthetic. Sedation may also be necessary, depending on the individual animal. Effective conservative therapy includes thorough cleansing of the prolapse with warm water and mild soap to remove all debris. This allows evaluation for trauma, tears, necrosis, or sloughing. Edema can be removed by gentle kneading combined with topical application of glycerin or sugar. Generous lubrication and massage allow for reduction of the mass into the rectum. To ensure that the rectum is maintained in place, purse-string sutures using umbilical tape or other nonabsorbable suture are placed circumferentially around the anal sphincter, with care taken not to enter the rectum. The purse-string should not be so tight as to prohibit the passage of feces. If necessary, it should be loosened daily to expedite removal of accumulated fecal material. The purse-string should be removed in 3 to 4 days. Broad-spectrum antimicrobial drugs should be administered if tissue compromise is a factor. When indicated, stool softeners and enemas may be used to ease the passage of feces through the rectum.

Surgical intervention often is necessary if type I or type II prolapse cannot be reduced, if tissue necrosis is extensive, or if prolapse recurs after conservative therapy.[5] Submucosal resection, amputation, or the use of a prolapse ring are all accepted surgical options. Prolapses of types III and IV that cannot be manually reduced often require a celiotomy for surgical reduction of the intussusception or resection or both. An important fact to remember is that even with manual reduction of a type IV prolapse, significant vascular compromise may have occurred, resulting in bowel leakage and peritonitis. Vascular damage encountered by the colon may necessitate a colostomy.[6] Broad-spectrum antimicrobial drugs should be administered in these cases.

Unique problems are encountered when conservatively managing equine rectal prolapse versus ruminant prolapse. Equine patients may experience more hindlimb ataxia with caudal epidurals, which can be prevented by using different combinations of xylazine, lidocaine, detomidine, morphine, and/or mepivacaine in the epidural. Placement of an epidural catheter can facilitate long-term therapy if needed. Another problem encountered is that horse feces often are too large and dry to readily pass through the purse-string in the anus. The use of enemas and stool softeners offers some assistance. The sutures tend to cause greater anal irritation than is seen in ruminants, causing the horse to strain against them.

The common complications after rectal prolapse include prolapse recurrence, rectal strictures, obstipation, formation of a pararectal abscess, and peritonitis. The prognosis for all types of rectal prolapse depends on early identification and reduction of the prolapse. Prolapses of types I and II that can be managed conservatively have a favorable outcome. Surgical correction of types I and II also carries a good prognosis but with a higher incidence of postsurgical complications. Because of the cost of surgical repair, market animals often are slaughtered if conservative management fails. Rectal prolapses of types III and IV carry a fair to guarded prognosis, which depends on the extent of tissue involvement and viability, the surgeon's skill, and postsurgical complications.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Fluid Therapy for Horses with Gastrointestinal Diseases

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• CHAPTER 33

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Diseases of the Hepatobiliary System

GEOF W. SMITH and JENNIFER L. DAVIS, *Consulting Editors*

Diagnosis of Liver Disease*

Geof W. Smith

In making a diagnosis, the veterinarian should first attempt to determine that the animal *has* liver disease and then move toward trying to identify a specific cause. Therefore, this chapter first discusses the diagnosis of liver disease, then the individual conditions causing disease in horses and ruminants. The signs of liver disease are due to failure of some of the liver's many functions, but these signs are often not apparent early in the course of disease. Special tests may be necessary to detect early damage or minor impairment of function that has not yet produced clinical signs.

Liver Diseases versus Liver Failure

As with many other organs like the heart and kidney, the liver can be diseased or damaged long before it fails to function. Early liver diseases are often inapparent to the owner or veterinarian through physical findings alone. Such cases are usually detected by finding elevated levels of liver enzymes in the serum. Pathologic changes in the liver may include biliary hyperplasia, death of hepatocytes, and fibrosis—all potentially occurring long before any signs of failure develop. Some functions may fail before others, and onset of liver failure varies with the species and disease process involved.

Liver Reserve and Regeneration

The liver has a large reserve capacity, and close to 80% of it can be removed before regeneration and recovery are no longer possible. Regeneration can occur in areas receiving portal blood, but most cell division takes place in Rappaport zone 1 (the portal area), with cells being pushed to the central lobular area. The liver undergoes constant repair, and in humans it is estimated that hepatocytes are renewed every 50 to 75 days.[1]

Normal regeneration does not occur in some cases. Antimitotic agents such as pyrrolizidine alkaloid metabolites or antineoplastic drugs can prevent cell division. Regeneration may be restricted by connective tissue. Once fibrosis has bridged the various lobules, additional regeneration is impaired because the fibrosis itself perpetuates the condition. Loss of a stroma to build on or lack of portal blood supply also reduces regeneration.

*Contributions to previous editions by Erwin G. Pearson acknowledged.

Signs of Liver Disease and Pathophysiology

Many signs can be present with liver disease, but no sign is pathognomonic or present in every case. Table 33-1 lists some of the signs that may be present and other possible causes of the same signs.

The clinical history is useful in some cases but not consistently. For example, liver flukes in cattle are generally restricted to certain geographic areas and occur more commonly when animals are grazing land infested with snails. Another example would be acute serum hepatitis in horses, which is known to occur most commonly in Equidae 4 to 8 weeks after administration of horse serum. In other cases the lack of specific history information may not rule in or rule out specific causes of liver disease. For example, there may not be a history of animals consuming plants containing pyrrolizidine alkaloids because of the delay between consumption and the onset of clinical signs.

With the exception of change in liver size and pain over the liver elicited with pressure, most signs are related to failure of some function. Liver flukes may cause anemia and hypoproteinemia because of the effect of the parasite and its metabolites. Liver abscesses and other infections may produce signs like fever and anorexia owing to release of pyrogens and other inflammatory mediators (caused by the organism and not necessarily related to the liver itself).

Icterus is typically seen in acute liver disease in horses but is not seen in many cases of chronic liver disease, and it is seen less often in ruminants unless biliary blockage occurs. Icterus is due to failure of uptake, conjugation, or excretion of bilirubin. Excess production caused by hemolysis must also be considered when icterus is present. This is likely the most common cause of icterus in ruminants and occurs with several hemolytic diseases such as anaplasmosis and copper toxicity. Horses are frequently icteric (up to 6 mg/dL unconjugated bilirubin) from anorexia or fasting even when the liver is normal.

Weight loss is a common but nonspecific finding in some cases of chronic liver disease. It may be caused by anorexia or failure of metabolic functions of the liver and is probably not related to impaired fat absorption. Diarrhea is also seen, especially in cattle with chronic liver disease. It is thought to be related to portal hypertension and increased hydrostatic pressure, although the exact mechanisms are not completely understood. Diarrhea probably is not caused by fat malabsorption or steatorrhea, because the normal herbivore diet contains less than 3% fat.

Ascites can also occur in animals with liver failure. The ascites results from portal hypertension caused by venous blockage producing increased hydrostatic pressure and by protein leakage into the

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TABLE 33-1

Signs of Liver Disease or Failure

Sign	Pathogenesis	Other Causes
Icterus (E)	Failure of uptake, conjugation, or excretion of bilirubin	Massive hemolysis Bile blockage Fasting in the horse
Weight loss (E, B)	Energy demand greater than absorbed or metabolized	Poor nutrition, chronic inflammation, parasites, neoplasia, maldigestion, malabsorption
Ascites (B)	Portal hypertension and lymph leakage caused by cirrhosis or veno-occlusion	Cardiac failure Hypoproteinemia Cushing syndrome
Change in liver size	Nodular hyperplasia, tumor, cirrhosis Fatty degeneration	Right-sided heart failure Work hypertrophy Anemia
Diarrhea (B)	Bile deficit malabsorption Intestinal edema, portal hypertension	Gastrointestinal (GI) or systemic disease
Pruritus	Retention of bile salts	Dermatologic or central nervous system (CNS) disorders
Dermatitis Unpigmented areas	Hepatogenic photosensitization	Primary phototoxic photosensitization
CNS signs Behavioral change, ataxia, dysmetria, circling, stupor, coma, tremors, bellowing	Hepatic encephalopathy (see text)	Brain diseases Metabolic diseases Toxic diseases
Tenesmus (B)	Hepatic encephalopathy	Rectal or colonic disease CNS disease Urogenital disease
Rectal prolapse (B)	Tenesmus	Rectal or colonic disease
Change in feces color	Bile pigment deficit Undigested fat	Diet GI disease
Hemorrhage	Failure to synthesize clotting factors II, V, VII, IX, X	Other clotting factor or platelet deficit, trauma, disseminated intravascular coagulation
Pain over liver, inflammation, swelling	Abscesses	Traumatic reticulitis
Inspiratory stertor (E) Dyspnea	Hepatic encephalopathy	Upper airway obstruction

B, Frequent sign in cattle; *E,* frequent sign in horses.

peritoneal cavity. Production of hepatic lymph high in protein (>3 g/dL) is increased. Because the liver sinusoids are permeable to plasma proteins, the protein-containing lymph leaks into the interstitial space and then into the peritoneal cavity.[2,3] Fluid moves into the abdominal cavity secondary to both osmotic and hydrostatic forces, according to Starling law. The abdominal fluid present with liver disease is a modified transudate, but the protein content may be relatively high (3 to 3.5 g/dL) owing to leakage of protein from the liver. Hypoalbuminemia can aggravate the ascites, but if it occurs alone, it usually will result in submandibular and brisket edema.

Hepatic photosensitization may lead to dermatitis of the white areas, wherein the skin of these areas first becomes erythematous, then thickened with keratin crusts, and finally necrotic. This is caused by the photodynamic agent phylloerythrin, which is formed in the gastrointestinal (GI) tract of large animals by bacterial degradation of chlorophyll. After absorption into the portal circulation, phylloerythrin should be conjugated by the liver and excreted into the bile. With cholestasis, phylloerythrin may be carried to the skin, where it acts as a photodynamic agent.[4] After bile duct ligation, the level of phylloerythrin steadily increases.[5] Although a small amount is removed by the kidneys, the rate is not fast enough to prevent accumulation in the plasma and skin. Phylloerythrin in the skin reacts to sunlight and emits energy that causes lesions of the white areas.[4]

Pruritus is seen in a few cases of liver disease in horses. In humans, pruritus is assumed to be due to bile acid accumulation in the skin when it is not excreted by the liver. This same process may occur in horses, but pruritus is not usually seen in large animals with liver disease.

A change in fecal color is not usually noted in either adult cattle or horses with liver disease, because other pigments like chlorophyll contribute to the color. In young animals with simple digestive tracts, much of the fecal color is from stercobilin, a metabolite of bilirubin, so with cholestasis, feces may be somewhat lighter in color.

A few signs may be seen terminally in liver disease. Hemorrhage may occur when clotting factors are not synthesized in adequate amounts. Factors I, II, V, VII, IX, and X are all produced by the liver,[1,3] but the disease is usually advanced before a deficit develops.

Tenesmus, often followed by rectal prolapse, is seen in some cattle with liver disease. This may be associated with diarrhea, be part of hepatic encephalopathy, or be aggravated by edema of the bowel secondary to portal hypertension.

Pharyngeal or laryngeal collapse with loud stertorous inspiratory noises and dyspnea has developed in some cases of hepatic failure, especially in ponies. The exact mechanism for this is not known, but it may also be part of hepatic encephalopathy.[6] Horses sometimes develop a terminal hemolytic crisis caused by increased red blood cell (RBC) fragility. This has not been observed in ruminants.

Hepatic Encephalopathy

Hepatic encephalopathy is a neuropsychiatric syndrome caused by hepatic dysfunction or portosystemic shunting of the intestinal blood.[7] It is considered a potentially reversible metabolic or neurotransmitter disorder, but it is associated with characteristic (although nonspecific) lesions in the central nervous system (CNS), such as altered astrocytes.

Signs of hepatic encephalopathy are often subtle and nonspecific. Behavioral changes may be detected by the owner, who is more familiar with the patient's normal activity. Some docile animals become excitable and difficult to control, whereas other normally unruly animals may become passive. Depression and incoordination are frequent manifestations, and some animals may walk aimlessly or even head press (Fig. 33-1).[8] Apparent blindness is seen in some horses, and foot stomping was reported in 7 of 25 cases.[9] These animals eventually develop a stupor and may end up in hepatic coma. Yawning may be seen in horses, and ponies may have a stertorous

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respiratory noise. Ruminants show signs of tenesmus and sometimes vocalize excessively. In humans, hepatic encephalopathy is diagnosed by neuropsychological tests, which are not possible in animals.[10]

The pathophysiology of hepatic encephalopathy remains undefined and is controversial.[8] It occurs when portal blood bypasses the liver, as with congenital shunts in dogs, or with shunts secondary to portal hypertension induced by alcoholic cirrhosis in humans, or when the blood goes through an inadequately functioning liver. How neurologic function is altered has not been determined, but speculation abounds.

It seems possible to incriminate synergistic neurotoxins that bypass the liver. Most will agree that ammonia levels play a central role in pathogenesis. Blood ammonia is elevated in most cases of hepatic encephalopathy because the liver is not metabolizing ammonia to urea. Encephalopathy can be precipitated in cirrhotic patients by adding ammonia-generating substances, and there is an increase in cerebrospinal glutamine, the product to which ammonia is detoxified. Astrocytes contain the enzyme glutamine synthetase, which adds a molecule of glutamate to ammonia to form glutamine. The amount of glutamine formed in the brain correlates with the severity of hepatic encephalopathy.[11] However, much higher concentrations of ammonia are needed to induce coma in normal animals, and there is poor correlation between ammonia levels and degree of encephalopathy.[9] Cases of hyperammonemia and encephalopathy without liver disease have been reported in horses.[12]

Magnetic resonance imaging (MRI) of human cirrhotic patients reveals increased image intensities from the globus pallidus region, probably caused by manganese deposits.[10] Serum manganese is increased in these patients, which correlates with the increased MRI intensities and negatively with neuropsychological tests. This would indicate that manganese is another potential toxin that can enter the brain if not effectively removed from the blood by the liver.

There may be an imbalance of true inhibitory and excitatory neurotransmission. γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter. The increase in GABAergic tone was originally thought to result from an increase in GABA or its receptor sites. More recently, it has been proposed that neurosteroids with GABA-agonist properties could be involved.[13] Ammonia is believed to play a role in the metabolism of GABA in the brain and thus could act synergistically.[14] Also, receptor sites for benzodiazepine are increased in the brain of animals with hepatic encephalopathy.[15] Benzodiazepine augments the activity of GABA in stimulating the inhibitory neuron and causing sedation.

False neurotransmitters have been proposed to cause the abnormal nerve function. Increased amounts of tryptophan, phenylalanine, and tyrosine in the brain could cause more serotonin to accumulate in the brain. Plasma amino acid ratios are altered in horses with pyrrolizidine alkaloid–induced liver disease.[15] Concentrations of branched-chain amino acids (valine, isoleucine, leucine) are decreased, and concentrations of aromatic amino acids (tyrosine, phenylalanine, free tryptophan) are increased, partially because the liver is not adequately metabolizing aromatic amino acids. Amino acids are transported across the blood-brain barrier by a common transport system, so they compete for entry into the CNS. It has been suggested that higher levels of aromatic amino acids in the CNS would lead to formation of increased amounts of inhibitory neurotransmitters or to alteration of catecholamine or monoamine neurotransmitters like GABA or L-glutamate.



FIG. 33-1 Severe depression and headpressing in a horse with hepatoencephalopathy. Edema of the head developed secondary to the horse hanging its head.

Laboratory Tests and Liver-Derived Serum Enzymes

A number of enzymes are compartmentalized in the hepatocyte or in bile duct epithelium. This compartmentalization is useful in holding insoluble molecules close to the enzymes for chemical reactions. Hepatocyte damage may result in release of the enzymes into the circulation, and cholestasis may cause increased release from bile epithelium. Serum levels of these enzymes may therefore be an indication of hepatocyte integrity or bile excretion. Table 33-2 lists frequently tested enzymes and their characteristics. Serum concentrations for some of these enzymes vary with the age of the animal and sometimes even with type or use. Table 33-3 lists some approximate upper limits of normal for animals of various ages. Normal values, especially for the enzymes, should be established by each laboratory.

The cytosol of the hepatocyte contains high activities of the enzymes aspartate aminotransferase (AST, formerly serum

TABLE 33-2

Liver-Derived Enzymes

Enzyme	Specificity	Problems
GGT	Liver	High in young animals from colostrum
	Kidney*	
	Pancreas	
ALP	Liver	Not specific
	Bone	
	Intestine	
	Macrophages	
	Placenta	
IDH (SDH)	Liver	Not elevated in chronic disease; short life; not stable
GDH	Liver	Not elevated in chronic disease
AST (SGOT)	Liver	Not specific
	Muscle	
	Heart	
ALT (SGPT)	Liver	Low concentration in cattle and horses; not a good indicator in large herbivores
LDH	None unless isoenzymes	Not elevated in chronic disease; short life; not specific
OCT	Liver	Analysis not routinely available

*Elevated in urine, not blood.

ALP, Alkaline phosphatase; *ALT,* alanine aminotransferase (formerly SGPT, serum glutamic-pyruvic transaminase); *AST,* aspartate aminotransferase (formerly SGOT, serum glutamic-oxaloacetic transaminase); *GGT,* γ-glutamyltransferase; *GDH,* glutamate dehydrogenase; *IDH,* L-iditol dehydrogenase (formerly SDH, sorbitol dehydrogenase); *LDH,* lactate dehydrogenase; *OCT,* ornithine carbamoyltransferase.

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TABLE 33-3

Upper Limits of Normal for Some Liver Function Tests (from Various Sources)

Test	Horses				Cattle				Sheep	Goats
Age	<1 wk	1-4 wk	1-12 mo	Adult	<1 wk	1-4 wk	1-6 mo	Adult	Adult	Adult
Total bilirubin (mg/dL)	4.5	3.0	2.0	2.0	2.4	0.9	0.4	0.3	0.4	0.5
Direct bilirubin (mg/dL)	0.8	0.7	0.7	0.4	0.6	0.3	0.2	0.1	0.1	0.1
Total bile acids (μmol/L)	NA	NA	NA	14	45	35	60	120	25?	NA
BSP (half-life, $T_{1/2}$ min)	NA	NA	3.7	3.7	15	8	5	3	4.0	2.1
AST (IU/L)	600	540	700	270	60	60	60	60	110	80
GGT (IU/L)	170	170	40	30	4200	1300	NA	24	55	50
ALT (IU/L)	2800	1200	840	194	1150	1000	NA	81	188	386
IDH (IU/L)	8	8	NA	5.8	NA	NA	NA	15.3	28	23
GDH (IU/L)	NA	NA	NA	11	24	22	19	19	NA	NA
LDH (IU/L)	NA	NA	NA	412	1380	1280	NA	1445	440	392

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *BSP,* bromsulphalein (sodium sulfobromophthalein); *GGT,* γ-glutamyltransferase; *GDH,* glutamate dehydrogenase; *IDH,* L-iditol dehydrogenase (formerly SDH, sorbitol dehydrogenase); *LDH,* lactate dehydrogenase; *NA,* not available.

glutamic-oxaloacetic transaminase [SGOT]), L-iditol dehydrogenase (IDH, formerly sorbitol dehydrogenase [SDH]), ornithine carbamoyltransferase (OCT), glutamate dehydrogenase (GDH), and lactate dehydrogenase (LDH). These are generally referred to as *leakage enzymes,* since with acute or chronic hepatocellular injury or necrosis the activity of these enzymes increases because they essentially "leak" out of hepatocytes into the serum.[16] Cholestasis increases production of other enzymes such as γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP). Activity of these enzymes generally increases secondary to biliary obstruction caused by conditions like liver fluke infection or cholelithiasis. The cholestatic enzymes are more likely to have high serum concentrations in chronic hepatic disease than the leakage enzymes because of bile duct constriction or obstruction secondary to fibrosis.[16] GGT also is present in pancreas, mammary gland, lung, kidney tubules, and other duct epithelium, but serum levels usually are not elevated with renal disease, because the enzyme is lost in the urine. Serum concentrations are normally higher in neonatal calves (sometimes >4000 IU/L after suckling)[17] because the enzyme is concentrated in colostrum.[18,19] GGT levels are also higher in foals than in adult horses, but the higher concentrations may partly be the result of increased production.[20] GGT is elevated in many horses with right dorsal displacement of the large colon, possibly caused by transient extrahepatic bile duct obstruction.[21] Elevated GGT is the most sensitive indicator of liver disease in the horse, and levels will remain elevated for several weeks.[9,22]

ALP is often elevated in chronic liver disease of the horse but is variable in ruminants. ALP can come from other sources like bone, intestines, placenta, and macrophages, so it is not specific. Both ALP and GGT are elevated with cholestasis.[23] The dehydrogenases (i.e., IDH [SDH], LDH, GDH) are found in hepatocytes and are elevated with acute hepatocyte damage, but serum concentrations may return to normal or below normal in chronic liver disease.

IDH is liver specific and extremely useful in detecting active hepatocellular necrosis, but it is not as stable as some of the enzymes (levels drop significantly after 24 hours of refrigeration). Increased IDH activity can be seen in ruminants with infectious, inflammatory, toxic, or metabolic insults to the liver. In cases of chronic disease, however, the IDH concentration may be normal because either too few hepatocytes are damaged or the hepatocellular mass is substantially reduced.[24] AST and LDH are found in many tissues other than liver (especially muscle), so they are nonspecific unless isoenzymes are determined. Muscle injury or necrosis, especially in recumbent animals, will often result in marked increases in both AST and LDH. The clinician must evaluate AST and LDH concentrations in conjunction with muscle-specific enzymes like creatine kinase (CK). Elevations in these enzymes together with increased CK activity generally suggests muscle injury. However, AST elevations occurring with CK values that fall within the reference range gives a strong suggestion of hepatic disease. AST and LDH concentrations are also found in erythrocytes, so if the serum is severely hemolyzed or allowed to remain on the clot for an extended period, falsely elevated values from leakage from red blood cells will result.

Ammonia is produced in the GI tract from the digestion of proteins and amino acids, absorbed by the intestine into blood, and carried to the liver in the portal circulation. Ammonia is converted to urea in the liver by the hepatic urea cycle. Ammonia is a useful test for assessing liver function, but it is generally not included in most serum biochemistry panels because it is highly volatile and requires special sample handling. Serum urea nitrogen (SUN) may also have some value as an indicator of hepatic disease in ruminants, since urea is produced in the liver. In severe cases of liver failure, SUN is usually low and ammonia often high. However, since rumen bacteria synthesize protein from urea, ruminants that have been off feed have low SUN concentrations because all the urea is being used by rumen bacteria for protein production. Thus low SUN levels are not always specific for hepatic disease.

No single liver enzyme value can consistently confirm or rule out the presence of liver disease. A combination of tests, including serum enzymes, total bile acids, ultrasound, and liver biopsy, may be needed. Some blood constituents may be altered because of failure of certain metabolic functions of the liver, but none of these changes is specific for liver disease. Blood glucose is sometimes slightly lower in severe liver disease, especially in young animals, possibly because of decreased gluconeogenesis, but none of 28 adult cases in one study had low blood glucose concentrations, and in fact, 14 cases had hyperglycemia.[9] In some toxic liver diseases, blood ammonia levels can increase fourfold or more because the urease necessary to convert ammonia to urea is found only in the liver. For the same reason, SUN may decrease, especially in the terminal phases. In the later stages, blood-clotting factors may be diminished, with delayed partial thromboplastin time (PTT) and other clotting times.

Terminally, serum albumin concentration may decrease. Considerable protein synthesis takes place in the liver, which produces all the plasma proteins except γ-globulins. The amount of these proteins in the blood, however, depends not only on the rate of synthesis but also on the rate of removal. The albumin half-life in cattle is about 16.5 days; in the horse, 19.4 days; and in sheep, 14 days.[25] Therefore, serum albumin is reduced mainly in chronic liver disease. With liver damage, the synthesis of α-globulins and β-globulins is increased, so total plasma protein concentration is invariably normal or elevated, but the albumin/globulin (A/G) ratio may be decreased. The healthy liver has a large reserve for protein synthesis, and lost protein can be replenished. In one study, 18% of the horses with chronic liver disease and 6% of those with acute liver disease had albumin concentrations below the reference value.[26] In a British study, only 6 of 37 liver disease cases were hypoalbuminemic, and none of these was hypoproteinemic.[9] Therefore, it is assumed that hypoalbuminemia is not a common feature in horses with liver disease, and that

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hypoproteinemia is rare. Amino acid ratios are altered in liver disease; short branched-chain amino acids are decreased, whereas aromatic amino acids are increased.[27]

Excretion Tests for Liver Function

Because the liver excretes a number of endogenous compounds and foreign substances injected into the animal, the rate of excretion or clearance of these substances can be used to test the excretory function of the liver. Bilirubin itself can be used and, if elevated above normal, would indicate liver failure, bile blockage, or excess production from hemolysis. In the horse, bilirubin is also increased during fasting in animals without liver disease.[28] With liver damage in the horse or ruminant, most of the retained bilirubin is unconjugated (indirect reacting), and the direct-to-total ratio is usually less than 0.3. With bile blockage or intrahepatic cholestasis, the direct-to-total ratio may be greater than 0.3 in the horse or 0.5 in cattle.

Bilirubin is the main bile pigment and is produced from heme, 75% of which comes from RBCs. When the erythrocytes are broken down, heme is converted first to biliverdin and then to bilirubin in the macrophage system. This unconjugated bilirubin is insoluble and must be bound to albumin for transfer; the kidneys do not remove this bound bilirubin. Unconjugated bilirubin is taken up by the hepatocytes with cytosolic binding proteins within the hepatocyte. In the hepatocyte, some bilirubin is conjugated to diglucuronide, but in the horse, more than half the bilirubin in bile is conjugated with glucose. Conjugated (direct-reacting) bilirubin is water soluble, and some will enter the general circulation; if concentration is sufficiently high, the kidneys will filter it into the urine. Conjugated bilirubin is secreted into the bile canaliculi by an energy-dependent transport process. In most species, this is the rate-limiting step, but this may not be true in large herbivores. Conjugated bilirubin passes into the intestine through the bile ducts, and if they are blocked, both conjugated and unconjugated bilirubin will increase in the plasma. In the intestinal tract, bilirubin is converted to urobilinogen by anaerobic bacteria. Some urobilinogen is absorbed and reexcreted by the liver, but a small fraction will pass the normal liver and be excreted in the urine. With complete biliary blockage, there will be no urobilinogen in the urine, and with hemolysis, there may be increased urobilinogen in the urine. Urobilinogen is not very stable in the urine, so analysis must be done within 1 or 2 hours or the amount detected will be erroneously low.

Fasting decreases the efficiency of plasma bilirubin removal in all species, but the horse shows a greater rise in plasma bilirubin, often reaching a plateau two to three times the normal state. This increase is due to a decrease in removal of bilirubin by the hepatic transport and not by an increase in its production.[28,29] In normal ruminants, total bilirubin concentrations are low compared to other species, and the magnitude of increase is generally small and inconsistent even with severe liver damage.[2] Ruminants with cholestatic disease may have moderate increases in serum bilirubin, but this is not a consistent finding. Increases in direct bilirubin are usually the result of hemolysis.

Serum total bile acid concentration is a good test of liver function in horses. The concentration of bile acids in the serum will be increased if there is hepatocyte damage, blockage of bile flow, or shunting of portal blood to the systemic circulation, bypassing the liver. The liver synthesizes bile acids from cholesterol. Cholic and chenodeoxycholic acids are the primary bile acids that are conjugated with amino acids before excretion into the bile. Only conjugated bile acids are present in the intestine; they are soluble and form micelles with fat because of their detergent properties. Most bile acids excreted in bile are resorbed by an active transport system in the ileum and carried by the portal circulation back to the liver for reexcretion. In most species, more than 95% of the bile acids are resorbed and recirculated through the enterohepatic circulation.[30]

Many simple-stomached animals have a postprandial increase in serum bile acid because bile is released from the gallbladder during eating and subsequently resorbed by the ileum. This does not seem to be important in the horse, which has no gallbladder, or in cattle, in which no relationship to feeding could be found.[31] Table 33-3 lists the upper limits of normal for liver function tests in large animals of various ages. In cattle there is an hour-to-hour fluctuation that could be as much as 60 μM/L, along with considerable variation between individual cattle.[31,32] In dairy cattle a significant decrease in serum bile acid concentrations occurs throughout the course of lactation.[33] In the horse, serum concentration above 14 μM/L would indicate liver damage, bile blockage, or shunting.[33] Serum total bile acid concentration is likely a more sensitive indicator of liver disease in the horse than serum bilirubin; only 8 of 34 horses with liver disease had elevated bilirubin, but 31 of 37 had elevated bile acids.[9] In adult cattle, because of the hour-to-hour variations, bile acid concentration on a single sample would have to be above 126 μM/L in beef cattle and 88 μM/L in dairy cattle to be an indication of liver disease.[34,35] Although ruminants have a large normal range for bile acid concentrations, significant increases have been shown to be a specific indicator of hepatic disease.[35]

A number of dyes are excreted primarily by the liver; sulfobromophthalein (bromsulphalein [BSP]) is used most often. In large animals, BSP clearance (half-time) is used much more than the retention test. In the test, 500 to 1000 mg (≈2 mg/kg) of BSP is injected intravenously. Blood samples are taken before the injection and two to four times 5 to 12 minutes after the injection (i.e., at 5, 7, 9, and 11 minutes). These samples are analyzed for color produced by BSP, and a half-life is determined by plotting the points on semilog paper. Normal horses have a BSP half-life of less than 3.5 minutes, and for ruminants it is less than 5 minutes. This may be increased in very young animals (see Table 33-3) and in pregnant females. Other dyes, such as indocyanine green, have some advantage (less renal excretion than BSP) but at present are too costly for use in large animals.

Liver Biopsy

Liver biopsy can be very useful, not only in confirming the presence of liver disease but also in determining or ruling out some etiologies. It is a relatively safe and simple procedure but should be avoided when liver abscesses are suspected. A number of biopsy instruments are available, including aspiration punches, but the Tru-Cut biopsy needle or similar notch-cutting needles seem to work quite well. In all species the skin over the biopsy site should be clipped and prepared for aseptic insertion of the needle. A local infiltration of 2% lidocaine helps reduce the animal's reaction, but it may still flinch when the pleura and peritoneum are penetrated. A small stab wound through the skin at the site of insertion is made with a scalpel blade.

The site of skin puncture for liver biopsy in the horse is the right fourteenth intercostal space at the intersection of a line drawn from the tuber coxae to the point of the shoulder.[36] Some operators recommend more cranial insertion (twelfth or thirteenth space), but more lung is penetrated at points farther cranial. If a more cranial position is selected, it should also be more ventral. If the needle is directed slightly cranial and ventral, it is more likely to remain in the liver parenchyma and not penetrate larger vessels on the visceral surface or pass on through into the right kidney, pancreas, or colon. Ultrasound guidance will increase the chances of obtaining liver specimens without penetrating other organs.

Cattle need to be suitably confined for liver biopsy. A biopsy can often be performed on quiet dairy cows in a stanchion while the tail is elevated ("tailed"). Although identification of the liver with ultrasound is preferable to a blind stick, the puncture site in cattle can be located by extending a horizontal line cranial from the middle of the paralumbar fossa. The needle is inserted where this line crosses the eleventh intercostal space on the right side. The lungs do not extend as far caudal as in the horse, so the liver is more exposed. The needle is directed slightly cranial and ventral, as in the horse.[2]

Liver biopsy in sheep and goats is slightly more difficult; additional sedation is usually required. A site at the ninth or tenth intercostal space at the level of the ventral end of the last rib has been

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recommended. The biopsy needle is advanced in a craniomedial direction until the liver is penetrated.

Diffuse or zonal lesions, as seen in most toxic, infectious, and metabolic liver diseases, can usually be diagnosed by liver biopsy. Focal lesions (e.g., abscesses, granulomas, neoplasias, as well as liver flukes) are easily missed by liver biopsy. If a liver abscess is suspected, biopsy is contraindicated because of the potential danger of rupturing an abscess. A scoring system has been developed for the prognostic evaluation of equine liver biopsies.[37] Examining liver biopsy tissue can confirm the presence of liver disease, help establish the type of disease, and aid prognosis.

Ultrasound Examination

Ultrasonographic examination of the liver is an extremely useful tool in diagnosing liver diseases (see ultrasound images in Chapter 32). Using ultrasound the clinician can determine the size of the liver, where it is located, and the diameter of the primary hepatic vessels. Hepatic abscesses, cholelithiasis, neoplasia, and fibrosis can be diagnosed by ultrasound in the horse.[38] In cattle, diseases such as fascioliasis, liver abscesses, neoplasia, thrombosis of the caudal vena cava, and even hepatic lipidosis can often be detected using ultrasound.[39-43] Ultrasound of the liver can also facilitate collection of a biopsy sample, aspiration of an abscess, or even cholecystocentesis (aspiration of a bile sample for diagnosis of liver flukes). Parenchymal pattern of the liver is changed with diffuse fibrosis. The bovine liver is situated immediately underneath the right body wall, with the cranial portion hidden by the lung. Hepatic ultrasonography is performed on the right side of the standing animal. The examination is usually done from caudal to cranial, beginning at the last rib and moving forward past the tenth intercostal space using a 3.5- to 5-MHz linear probe.[39] On sheep the examination is done on the right side in the seventh through twelfth intercostal spaces.[44] In horses the ultrasonic examination is performed below and caudal to the lung in the sixth to fourteenth intercostal spaces.[44] The liver can also be visualized on the left side of the horse in the lower intercostal spaces.

Prognosis

The severity of clinical signs may be the most useful noninvasive prognostic test in horses with liver disease.[45] Indicators of a poor prognosis in liver disease include an albumin concentration less than 2.5 g/dL in horses or an increased globulin level, a prothrombin time (PT) greater than 30% of normal, and greatly elevated GGT and ALP, especially if IDH (SDH) or LDH are normal or decreased. Marked fibrosis that bridges the liver lobules on histopathologic examination suggests a poor prognosis. Severe pyrrolizidine alkaloid toxicosis carries a particularly grave prognosis because remaining hepatocytes are inhibited from regeneration by mitotic arrest. Terminal clinical signs include development of hemolytic crisis in the horse and marked hepatoencephalopathy in the patient with a fibrotic liver.

Infectious, Toxic, and Parasitic Liver Disease

Acute Hepatitis in Horses

Jennifer L. Davis

Etiology *Theiler disease,* also known as *idiopathic acute hepatic disease* (IAHD), *serum hepatitis, postvaccinal hepatitis,* and *acute liver atrophy,* is the most common cause of acute hepatitis and hepatic failure in horses.[1-5] The disease was first recognized by Sir Arnold Theiler in large numbers of horses in South Africa. Horses developed the disease following immunization against African horse sickness with simultaneous administration of live virus and hyperimmune equine serum.[6] Since then, IAHD has been documented as a potential complication of any equine serum or plasma product used in horses. It is primarily a disease of adult horses[7] and has been most often associated with use of either tetanus antitoxin (TAT) or commercial equine plasma.[3,5,8-11] A recent outbreak was also associated with equine antiserum to botulinum toxin.[12]

Mares appear to be affected with IAHD more frequently than males, with recently parturient lactating mares at greatest risk.[7,10] The susceptibility of postparturient mares to IAHD is unexplained. One theory is that the common practice of administering TAT at the time of foaling makes postparturient mares the most likely adult horses to receive TAT, thus increasing their risk. There has been a seasonal nature reported for some epidemics of IAHD[7,13] with most cases occurring in the summer months. During some outbreaks, it has also been observed that some affected horses have not been treated with TAT or plasma[1,7,13] which has suggested an infectious agent may be involved.

Little has been known about the etiology of IAHD until recently. An investigation into an outbreak of IAHD in a group of horses receiving prophylactic botulinum antiserum has resulted in strong evidence that a viral etiology is present.[12] This virus, designated as *Theiler disease–associated virus* (TDAV), was isolated from horses that had received a similar batch of the antiserum. TDAV was also isolated from the antiserum itself, and no other detectable viruses were present in both the antiserum and clinical cases. Not all horses that tested TDAV positive developed clinical or biochemical evidence of hepatitis, however, which may suggest that other host factors, immune-mediated hypersensitivity reactions, or co-infection with other etiologic agents may be necessary for disease.[12,14] Horses may become chronically infected with virus, as evidenced by the fact that 25% of TDAV virus–positive horses were still positive 1 year after the outbreak.

Clinical Signs The clinical effects of IAHD are associated with signs of acute hepatic failure and typically occur 2 or 3 months following administration of blood products.[12] These signs include depression, jaundice, inappetence, pica, yawning, photoactive dermatitis, and hepatic encephalopathy.[†] Fever has been described as absent or rare in horses affected with IAHD.[4] Reported atypical signs include progressive weight loss, ventral subcutaneous edema, jugular pulses, ileus, and acute respiratory distress.[10,11,16] Intravascular hemolysis has been reported to lead to hemoglobinuria in some terminal cases of IAHD.[2] Evidence exists for a subclinical or chronic component in some cases.[10,17] However, some horses that received TAT have clinicopathologic evidence of liver dysfunction without developing clinical signs, indicating that disease severity may vary.[5,10,17]

Diagnosis Diagnosis of IAHD is based on the anamnesis, clinical signs, and findings from serum biochemical analysis, hepatic biopsy, and necropsy. High serum levels of unconjugated and total bilirubin and serum bile acids, coupled with high serum activity of GGT, IDH (SDH), AST, LDH, and ALP are indicative of hepatic necrosis in horses.[18] Additional findings with severe disease may include decreased BUN, hyperammonemia,[18] prolonged clotting times (PT and activated partial thromboplastin time [APTT]), and decreased albumin. IAHD may be confirmed by hepatic biopsy or postmortem examination of hepatic tissue. The liver is often small and has a characteristic "dishrag" appearance (Fig. 33-2). Typical histopathologic changes seen in biopsy specimens or obtained at postmortem examination include widespread necrosis of hepatocytes that is most severe in the centrilobular and midzonal areas, with the few living cells confined to the periportal areas.[9] The normal architecture of the centrilobular and midzonal areas is replaced by a pale, eosinophilic granular mass in which ghost outlines of necrotic hepatocytes are present.[9] A mild inflammatory cell infiltrate is seen in the portal areas, as well as a number of spindle-shaped fibroblastic cells.[9]

[†]References 2, 3, 7, 9, 14, and 15.

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FIG. 33-2 Characteristic small, "dishrag" liver from a horse with Theiler disease. *(Photo courtesy Sam Jennings, North Carolina State University.)*

The histopathologic lesion is frequently more advanced than the clinical course of the disease would suggest.[9]

Treatment There is no specific treatment for IAHD.[19] Treatment should be aimed at supporting liver function and controlling abnormal behavior. Dietary adjustments are important and should consist of reducing the quantity of protein in the diet while increasing carbohydrate intake.[2] Sorghum, milo, or beet pulp, which contains high levels of branched-chain amino acids, can be mixed with molasses to improve palatability and caloric content.[2] Diets high in branched-chain amino acids tend to lessen the degree of abnormal behavior associated with hepatic encephalopathy.[19] Oral (PO) neomycin, lactulose, and mineral oil may be administered to decrease ammonia production and absorption from the GI tract. Xylazine or detomidine may become necessary to sedate horses that display severe signs of hepatic encephalopathy.[19] Benzodiazepines (diazepam or midazolam) should be avoided. Continuous intravenous (IV) administration of dextrose and balanced electrolyte solutions to reduce hepatic workload and maintain plasma volume is recommended.[17] If spontaneous bleeding occurs at injection sites or at sites of self-inflicted injury, plasma transfusions may be necessary to replace the deficient clotting factors.[2] The use of glucocorticoids for treating IAHD is controversial but may be indicated based on some histopathologic evidence of an immune-mediated etiology.[14,18]

Currently, no preventive measures are available. However, since administration of TAT to recently parturient lactating mares is associated with substantial risk for development of fatal IAHD,[7,10,17] this practice should be strongly discouraged and its use restricted to clinical situations necessitating tetanus prophylaxis in which a history of active tetanus (toxoid) immunoprophylaxis is absent or unknown. The risk of postvaccinal IAHD should be addressed with the owner before administration of TAT. Although the prevalence of serum hepatitis associated with administration of commercial plasma appears to be low in the horse, it should be considered an uncommon risk that can have a fatal outcome.[11]

IAHD may be observed sporadically or affect a group of horses. Recognition of IAHD in one horse should necessitate careful observation of horses on the same premises for either clinical or serum biochemical signs of IAHD.[12,17] Based on recent case reports, it appears not all cases of IAHD are clinically apparent, and screening for its presence with routine serum biochemical analysis is useful in detecting subclinical cases.[10-12,17]

Black Disease

Geof W. Smith

Etiology Infectious necrotic hepatitis (black disease) is a peracute, highly fatal disease occurring worldwide. The disease most commonly affects sheep, particularly adults in good body condition, but cattle, horses, goats, and occasionally pigs may also be affected.[1,2] There has even been recent speculation that black disease is the cause of epidemic catarrh of sheep, a significant cause of mortality in Australian sheep dating back to the mid 1800s.[3] Black disease is caused by toxins produced by the bacterium *Clostridium novyi* type B; *C. novyi* is commonly found in the soil and can also be present in the digestive tracts and livers of animals grazing affected pastures. Clostridial organisms require an anaerobic environment for growth, so black disease only occurs when there has been enough damage to the liver to provide the anaerobic environment required for growth of the organism and subsequent toxin production. In practice, the liver insult is almost always caused by larval migration of the common liver fluke, *Fasciola hepatica.* Therefore, this is a seasonal disease related to the liver fluke cycle and occurring in animals typically infested by *F. hepatica.* Other liver parasites, such as *Fascioloides magna* or *Dicrocoelium dendriticum* (especially in France), are occasionally implicated, as is damage to the liver by biopsy or trauma severe enough to result in anaerobic conditions in the liver. Such a scenario should be considered when sudden deaths occur at times flukes are not usually migrating or in families like Equidae that are not normal hosts for *F. hepatica.* Black disease occurs worldwide wherever liver flukes are present.

Pathophysiology The *C. novyi* strains that cause black disease produce at least two potent exotoxins: alpha toxin and beta toxin. The alpha toxin enters cells by receptor-mediated endocytosis and inhibits ras and rho guanosine triphosphatases by glycosylation.[4] The beta toxin is a necrotizing and hemolytic phospholipase C (lecithinase). Other toxins may contribute to the pathophysiology as well.

Type B *C. novyi* is widely distributed in soils, and its spores are continuously ingested and shed in feces of grazing animals. Some of these organisms cross the intestinal mucosa and become disseminated throughout the animal's macrophage system, including the Kupffer cells of the liver. When localized anaerobic conditions occur in the liver, as with migration of liver fluke larvae, these resident spores may germinate and enter a vegetative state. As they proliferate, they release their toxins and create enlarging zones of coagulative necrosis in the liver. The exotoxins produced will enter the circulation, where they cause damage to neurons, vascular endothelium, and other tissues, eventually causing sudden death of the animal.

Clinical Signs Peracute death is the most common clinical presentation associated with black disease. When affected animals are recognized prior to death, clinical signs are relatively nonspecific. The animal will often be off by itself and will appear depressed, anorexic, and possibly in respiratory distress. Temperature is elevated initially (40° to 41°C [104° to 106°F]) but declines before death. Sheep become sternally recumbent and generally die after a clinical course of only a few hours. Venous congestion darkens the skin, giving the disease its common name, *black disease.*[2] Unlike closely related bacillary hemoglobinuria, or "redwater" (see later discussion), affected animals do not show red urine or bleeding from the nose or rectum. Clinical signs in cattle are similar, but the clinical course of disease occurs over 1 to 2 days.

Diagnosis Necropsy is often difficult because autolysis of the tissues after death is usually rapid. Fluid is often found in the pericardial sac and pleural and peritoneal cavities. Endocardial and

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epicardial hemorrhage is also a consistent finding. Urine is grossly normal. Tissues, especially solid organs like liver and kidney, appear to be in a much more advanced state of autolysis than time of death would suggest. The liver will usually be swollen and congested with small pale areas of coagulative necrosis, particularly along its diaphragmatic surface. The primary lesions of black disease are single or multiple areas (2 to 3 cm in diameter) of hepatic necrosis that appear yellow to white in color and are surrounded by a broad zone of hyperemia.[4]

Diagnosis of black disease is generally made by a combination of history, clinical presentation, necropsy findings, and isolation of *C. novyi* type B from the liver. A history of sudden death, particularly in endemic fluke areas, is highly suggestive of black disease, especially during warmer weather when fluke transmission is active. Flock or herd vaccination will be either overdue or absent. Time of death should be ascertained as closely as possible. The animal is usually presented in lateral recumbency without signs of struggle. It will be severely bloated even if death has occurred quite recently, giving the impression of a carcass in a more advanced state of decomposition than timing would suggest. Acute liver fluke infection in sheep can have a high mortality by itself, and postmortem findings may be similar to black disease. Other causes of sudden death (e.g., enterotoxemia, blackleg, anthrax) should also be ruled out.[2]

If necropsy does not confirm a diagnosis of black disease, or if additional documentation is necessary, a simple Gram stain of an impression smear taken from the margin of the liver lesion will typically reveal numerous gram-positive rods. Because clostridial organisms proliferate rapidly after death, such findings must always be interpreted carefully, with consideration of time elapsed between death and necropsy. Further diagnostic measures include anaerobic culture and isolation of *C. novyi* type B, identification of the specific toxins, and fluorescent antibody identification of the organism. Characteristic histopathologic changes may also be seen in fixed sections of liver associated with necrotic lesions. Impression smears obtained from the liver lesions are ideal for fluorescent antibody identification of *C. novyi* type B.

Treatment and Control Treatment of black disease is rarely undertaken because of its peracute presentation; animals are usually found dead. Although *C. novyi* is highly sensitive to penicillin and the tetracyclines, toxin production is usually too far advanced for antibiotics to be of value. If used, they should be administered at high doses, intravenously if possible, for most rapid onset (20,000 to 40,000 IU/kg penicillin or 10 mg/kg oxytetracycline q12h), followed by intramuscular (IM) or IV doses at appropriate intervals. Supportive fluid therapy should be initiated to correct dehydration. Even with aggressive therapy the prognosis is poor and the chances for survival slim. In the event of an outbreak, vaccination should be initiated immediately, along with possible metaphylactic administration of penicillin or oxytetracycline.

A good prevention program involves both proper fluke control and the use of clostridial bacterins. Efforts to clear soils of the offending organism are unrewarding. However, it is recommended that carcasses of animals dying from black disease be burned, buried deeply, or removed from the premises. Commercial bacterin/toxoids against *C. novyi* are available in combination with other clostridial organisms. These products are generally safe and highly effective. Duration of protection is short, however, and should not be relied on for more than 5 to 6 months. Animals vaccinated when younger than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on meat marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may be sufficient. In more moderate climates with longer periods of fluke exposure, two vaccinations per year may be required.

Control of liver fluke infestation is also closely linked to prevention of black disease. Control measures include pasture or range management, control of water sources, strategic treatment of animals with appropriate anthelmintics, and limiting access to streams, canals, ponds, and marshes. This is a complex subject, and the reader should refer to the section on liver flukes for more detail.

Bacillary Hemoglobinuria ("Redwater")

Geof W. Smith

Etiology Bacillary hemoglobinuria (redwater, icterohemoglobinuria) is a disease causing sudden death in cattle, small ruminants, and occasionally horses. The disease was first reported in California in 1916 and is caused by the toxins of *C. novyi* type D *(Clostridium haemolyticum)*. Bacillary hemoglobinuria is quite similar to black disease, where clostridial infections of the liver occur under anaerobic conditions, primarily liver fluke migration (see earlier discussion). The major toxin in *C. novyi* type D *(C. haemolyticum)* infection is the beta toxin, which is a phospholipase C that causes hepatocyte necrosis, hemolysis, and damage to capillary endothelium.[1] This results in hemoglobinuria and loss of fluids into tissues and cavities. The primary action of beta toxin is to induce localized hepatic necrosis and intravascular hemolysis. Like *C. novyi* type B, type D is also found in the soil. Spores are routinely present in the liver and can be passed in feces and urine of healthy animals grazing affected pastures. Disease occurs only when there is sufficient insult to the liver to provide the anaerobic conditions required for bacterial growth and toxin production. In almost all cases the liver insult is caused by migration of *F. hepatica* (common liver fluke) larvae.[2-4] As in black disease, *F. magna, D. dendriticum* (the lancet liver fluke), and *Cysticercus cellulosae* have also been occasionally implicated in the disease, as has liver biopsy or trauma severe enough to result in liver bruising.[5] Bacillary hemoglobinuria is, for the most part, a seasonal disease occurring at the time of larval fluke migration. In the United States, most cases are seen during summer and early fall.

Bacillary hemoglobinuria is a regionalized disease. It has been reported that *C. novyi* type D is limited to alkaline soils, but the disease is also endemic in regions with acid soils. Outbreaks often follow flooding, which can bring spores into previously uninfected areas. The factors affecting distribution of the disease are not well understood. Even in areas where it is common, distribution is erratic, with some farms severely affected while others nearby are disease free.

Pathophysiology Spores of *C. novyi* type D are ingested by susceptible animals, cross the intestinal mucosa, and are transported to the liver and other organs, probably within the phagosomes of cells of the mononuclear macrophage series. The spores can persist in the liver within Kupffer cells for long periods. Any localized anaerobic area of the liver will allow these spores to germinate. Release of toxins from the bacteria further exacerbates the anaerobic environment, favoring accelerated bacterial proliferation, toxin production, and hepatic necrosis. Absorption of toxins into the circulatory system rapidly leads to intravascular hemolysis, icterus, hemoglobinuria, and death.

Clinical Signs Bacillary hemoglobinuria is most common in animals older than 1 year of age. Like black disease, sudden death without obvious clinical signs is common in animals that have peracute disease. In those rare cases where disease is recognized antemortem, signs include depression, anorexia, and fever of 40° to 41°C (104° to 106°F), declining as death approaches. Breathing may be rapid and shallow, and blood or blood-tinged froth may be present in the nostrils. Rectal bleeding or bloody feces may also be observed. Severe hemoglobinuria or passage of dark-red, port wine–colored urine is often reported. Blood is thin and watery and coagulates slowly. Mucous membranes are pale and icteric. Severity of signs

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increases as the disease progresses. Postmortem, the animal is usually in lateral recumbency, severely bloated, and without signs of struggle. Blood is often present in the nostrils, mouth, rectum, or vagina. The carcass appears to be in an advanced state of decomposition even when it is actually quite fresh. A tentative diagnosis can be made on the basis of history and observation of the carcass.

At necropsy the mucous membranes and tissues can appear icteric. Skinning the animal reveals numerous subcutaneous petechial and ecchymotic hemorrhages, edema, and sometimes emphysema. There will be significant amounts of red-tinged abdominal and thoracic fluid. Hemorrhages are present on all serosal surfaces. Dark-red urine is present in the bladder. Lymph nodes are congested and usually hemorrhagic. There may be hemorrhage into the bowel lumen. The spleen is enlarged. The lungs are usually filled with blood-tinged froth or foam. Pericardial fluid is blood tinged, and hemorrhages are present on both the epicardium and endocardium. Organs such as liver and kidney appear to be in advanced stages of autolysis, even in fresh carcasses. The pathognomonic lesion is the so-called ischemic hepatic infarct, which has a zone of hyperemia at its interface with viable liver tissue. This area of coagulative necrosis, sometimes partially liquefied at its center, can reach up to a 30-cm diameter and have a very irregular outline.[3] Unlike a classic infarct, the lesion in bacillary hemoglobinuria results from progressive enlargement of the focus of coagulative necrosis caused by the bacterial toxins. Any thrombosis seen in the lesion is secondary, with the vasculature being included in the necrotic process, along with other hepatic tissue.[5]

Diagnosis Antemortem animals with bacillary hemoglobinuria will be anemic and have elevated hepatic enzymes such as AST and GGT.[6,7] Total bilirubin concentrations are also dramatically elevated.[6] If a urine sample can be collected, hemoglobinuria will be obvious. Postmortem, a Gram-stained impression smear from the liver will reveal numerous typical clostridial organisms. Smears may also be made from spleen, blood, or abdominal fluid, with the same outcome. Postmortem presence of clostridial organisms must be interpreted with caution because they are always present and proliferate rapidly after death. It is important to have an accurate estimate of time of death to determine the significance of these findings. Laboratory confirmation depends on identification of both the causative bacteria and the toxin. Fresh (refrigerated) and formalin-fixed liver lesions should be submitted. Fluorescent antibody tests on impression smears taken from a liver "infarct" will be positive for *C. novyi* type D antigens. Extensive biochemical and toxin identification tests are confirmatory but seldom used if lesions and fluorescent antibody tests are compatible. A polymerase chain reaction (PCR) assay that can detect *C. novyi* type D in the blood of affected cattle has also been reported.[6]

Treatment and Prevention Although successful treatment of cattle with bacillary hemoglobinuria has been described,[6,8] it is seldom undertaken because of the acute nature of the disease. If there is opportunity for treatment, penicillin at high dosages (at least 20,000 to 40,000 IU/kg IV or IM twice daily) is the antibiotic of choice, although tetracyclines (10 mg/kg IV twice daily) are acceptable. Fluids are given intravenously or intraruminally to correct dehydration. Because of severe hemolytic anemia, blood transfusion is recommended and should be repeated as necessary. In animals that recover, there will be a noticeable reduction on a daily basis in the severity of hemoglobinuria.[6]

An effective prevention program requires consideration of both the pathophysiology and immunology of the disease and the natural history of the liver fluke *(F. hepatica)* that is so intimately involved in expression of bacillary hemoglobinuria. Efforts to clear soils of the offending organism are unrewarding, but carcasses of animals dying from bacillary hemoglobinuria should be burned, buried deeply, or removed from the premises.

Commercial bacterin/toxoids against *C. novyi* type D are available in both monovalent form and in combination with other clostridial vaccines. These products are generally safe and highly efficacious. Duration of protection is short, however, and should not be relied on for more than 5 to 6 months. Animals vaccinated when less than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on beef marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may be sufficient. In more moderate climates with longer periods of fluke exposure, two vaccinations per year may be required.

Control measures include pasture or range management, control of water sources, strategic treatment of animals with products effective against flukes, and limiting access to streams, canals, ponds, and marshes. This is a complex subject, and the reader should refer to the section on liver flukes for more detail.

Liver Disease in Foals

Jennifer L. Davis

Liver disease in foals may be primary or secondary and can be due to infectious, parasitic, congenital, metabolic, or toxic causes. When diagnosing hepatic dysfunction in foals, it is important to use age-specific reference ranges to interpret biochemical indicators of hepatic disease. Several hepatic enzymes can have increased activity even in healthy neonates.[1-3] Total bilirubin may be elevated as fetal hemoglobin converts to adult hemoglobin. Elevations may also be due to a deficiency in liver binding and conjugating enzymes.[1] ALP remains elevated for an extended time in young horses as a result of increased osteoblastic activity, with normal values as high as 3752 U/L reported.[4] Increased GGT activity may be present in foals for 2 to 4 weeks after birth, whereas only slight increases of IDH (SDH) are expected during the same period.[1,3] Increased variability in ALP and GGT in healthy foals can make interpretation of hepatic function difficult. Serum bile acids (SBAs) are significantly greater in foals than adult horses for the first 6 weeks of life. According to one study, this is potentially due to upregulation of hepatic production, reduced excretion, differences in bile acid composition of the neonate, or enhanced intestinal/portal uptake.[3] An additional finding of that study was that SBAs were not significantly different between healthy and sick foals, whereas another study noted that elevated liver enzymes were common in sick foals, and those foals with high liver enzymes were more likely to have sepsis than other diseases.[3,4]

Tyzzer Disease

Tyzzer disease is an acute hepatitis affecting foals 7 to 42 days of age, with no known breed or sex predeliction.[5-12] It has also been reported in calves, lambs, and other species.[13-15] The causative organism is *Clostridium piliforme* (formerly *Bacillus piliformis*), a spore-forming intracellular obligate anaerobe.[23] Multiple strains can infect Equidae, and they are susceptible to at least two distinct strains (isolate E and R1), with no evidence of cross-reactivity of antibodies between isolates.[16,17]

Although the exact pathogenesis is unknown, bacterial spores can be shed in the manure of carrier horses, suggesting a fecal-oral route of transmission with subsequent GI and hepatic colonization.[18] Several risk factors have been associated with development of disease, including time of year, age, and resident status of the mare.[19] Foals born between March 13 and April 13 were found to be more likely to develop disease in one study, and this was thought to be due to the increased number of animals present on the farm during that time. Foals from younger mares (<6 years of age) and those not from endemic farms were more likely to develop disease, possibly owing to lack of antibiotics in the mare's colostrum or antibodies present to

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different strains of *C. piliforme*. Immunocompromised foals may be at greater risk.[11,12]

Disease may occur sporadically or as an outbreak.[12,18,19] Clinical signs are nonspecific and include severe depression, fever, icterus, and diarrhea progressing to seizures, coma, or sudden death.[5-12] Bloodwork abnormalities indicate overwhelming sepsis characterized by leukopenia, hyperfibrinogenemia, profound hypoglycemia, and severe acidosis, with concurrent elevations in IDH (SDH), GGT, AST, ALP, and LDH-5.[9,11,27] Diagnosis is usually made postmortem and is based on the presence of acute multifocal hepatitis and enteritis, with intrahepatocellular filamentous bacteria present at the periphery of the lesion.[21] Silver stains (e.g., Warthin-Starry) may help facilitate diagnosis. The fastidious nature of the organism makes culture difficult. PCR techniques have been used for detection of *C. piliforme* in multiple species, including foals.[20] This test may aid in early diagnosis and treatment.

Treatment of Tyzzer disease can be attempted, but the disease is highly fatal, with most foals dying within 2 to 48 hours (median survival 30 hours). There are reports of successful treatment of three suspected cases[19,22] and one confirmed[20] case in foals. When attempted, treatment should be early and aggressive and consist of antibiotics (including potassium penicillin or ampicillin), parenteral nutrition, correction of acidosis, and other supportive care.[20] Currently, there are no preventive measures available for Tyzzer disease in the foal.

Drug-Induced Hepatotoxicity

Rarely, foals treated with macrolides, trimethoprim-sulfas, or histamine-2 (H_2) blockers for pneumonia or diarrhea develop an increase in serum hepatic enzymes despite clinical improvement. With changes in drug treatment, serum enzymes return to normal, suggesting these cases may have drug-induced hepatopathy.[23] Steroid-induced hepatic lipidosis has been observed in foals receiving both prolonged and high doses of corticosteroids.

Equine Herpesvirus 1

Equine herpesvirus 1 (EHV-1) infection of a near-term fetus may result in the birth of a nonviable foal with hepatic, respiratory, and/or GI disease.[24] Affected foals may have severe neutropenia and lymphopenia, and icterus is a common clinical sign. Surprisingly, significant elevations in serum hepatic enzyme activities are not present even though a severe multifocal necrotizing hepatitis with inclusion bodies is present at necropsy.[25] Generally the clinical condition rapidly declines within 5 days after birth despite aggressive and early treatment. Treatment with oral acyclovir (8 to 16 mg/kg q8h) may improve survival rates.[26]

Other Bacterial Causes

Leptospirosis was reported to cause jaundice and death in a 10-day-old foal.[27] Although *Leptospira interrogans* serovar *Pomona* is known to cause abortion and liver disease (giant cell hepatopathy) in the equine fetus, it is also apparently a rare cause of neonatal liver disease. *Actinobacillus equuli* typically causes bacteremic embolic nephritis and acute death in very young (3-day-old) foals. It may also cause widespread multifocal hepatitis in foals. *Streptococcus zooepidemicus* bacteremia may also cause multifocal hepatic abscesses. Other bacteria and bacterial toxins may initiate an exaggerated response to sepsis (systemic inflammatory response syndrome [SIRS]), which may result in multiple organ dysfunction, including hepatic failure. Many vasoactive mediators are involved in this process; the hemodynamic system becomes ineffective, and certain organs (e.g., liver) may fail because of hypoxia. Diffuse hepatic necrosis and hepatocellular apoptosis are the characteristic lesions. The clinical signs may be identical to Tyzzer disease, except the syndrome may affect a much wider age range. Prompt and aggressive treatment is often successful. Appropriate treatments include broad-spectrum antibiotics, fluids, oxygen, and antioxidants such as dimethyl sulfoxide (DMSO) and acetylcysteine. Bacterial sepsis rarely may cause acute portal vein thrombosis. Variable degrees of hepatic hypoxemia and inflammation accompany the thrombosis. Hepatoencephalopathy does not generally occur in foals, unlike in adult horses, with portal vein thrombosis. The thrombus can be seen on ultrasound examination. Diarrhea from portal hypertension may occur in foals. Complete recovery may follow long-term antimicrobial therapy.

Neonatal Isoerythrolysis

Foals with severe and prolonged neonatal isoerythrolysis (NI) may develop liver failure,[28] which may result from a combination of chronic hypoxia and multiple blood transfusions. Foals receiving a total volume of blood products of 4 L or more were 19.5 times more likely to develop liver failure than foals receiving a lower volume.[29] Multiple blood transfusions are thought to result in iron overload and subsequent iron toxicity. One study showed that deferoxamine, an iron chelator used to prevent iron toxicity in humans receiving multiple transfusions, enhanced urinary iron elimination and decreased hepatic iron accumulation after blood transfusion in healthy foals.[30] The results of this study suggest that giving foals with NI subcutaneous (SC) injections of 1 g of deferoxamine q12h starting prior to blood administration may help prevent liver failure in those receiving multiple transfusions.

Kernicterus, or bilirubin encephalopathy, is another potential complication of NI in foals. Neurologic signs, including seizures, develop secondary to the neurotoxic effects of unconjugated bilirubin on the central nervous system.[29,31] Kernicterus is more likely to develop in foals with total bilirubin of 27 mg/dL or greater and is associated with a poor outcome.[29]

Iron Toxicity

Iron toxicity is the best documented of the toxic causes and can occur following administration of nutritional supplements or iron formulations containing ferrous fumarate.[32,33] Toxicity manifests in newborn foals given iron prior to receiving colostrum; colostral-acquired glutathione or other substances may be protective against hepatotoxicity.[33] When iron is given at birth and before colostrum, clinical signs typically develop 2 to 5 days later, although in rare cases, signs may develop in older foals. The initial clinical signs are associated with hepatoencephalopathy and include seizures, marked depression, ataxia, aimless wandering, head pressing, and abnormal behavior. Icterus is noted in most foals at the time neurologic signs are exhibited, although some foals may die so peracutely that icterus is not noticed. Abnormally high ammonia, total bilirubin, GGT and ALP activity, and packed cell volumes were present, as was an abnormally high ratio of aromatic to branched-chain amino acids. PTT and PT were prolonged, and some foals had high IDH (SDH) activity.[32] Affected foals had small livers with prominent bile duct proliferation, hepatic cell necrosis, mild periportal fibrosis, and histopathologic changes in the brain consistent with hepatoencephalopathy.[32-34]

Congenital/Inherited Diseases

Congenital portosystemic shunts (CPSS) occur infrequently in the equine and bovine patient.[35] Clinical signs may not be noted until foals are 2 to 3 months old and begin ingesting large amounts of grain or grass. Waxing and waning signs of encephalopathy are the most common signs in foals. Encephalopathic signs and tenesmus are characteristic of the disease in calves. Elevated plasma bile acids and ammonia levels in foals together with encephalopathic signs and normal concentration of hepatic-derived serum enzymes should arouse suspicion of a portosystemic shunt. Shunts may be single or multiple and may be intra- or extrahepatic. Diagnosis of CPSS can be made by computed tomography (CT) scan, positive-contrast portography, transrectal portoscintigraphy (in foals) or transabdominal ultrasound examination. Further corroborative evidence can be gained by ultrasound-guided percutaneous transsplenic injection of agitated saline with simultaneous echocardiography to look for contrast in the right atrium and ventricle.[36] Successful medical management followed by shunt ligation has been described in a foal and calf.[35-37]

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Hepatic failure has been seen in Morgan foals.[38,39] The onset of clinical signs (depression and weight loss) occurred soon after weaning. Liver enzymes and ammonia are elevated, and variable degrees of portal and bridging fibrosis with bile duct hyperplasia, karyomegaly, and cytomegaly are often seen on microscopic examination. The disease is fatal and may end with a terminal hemolytic crisis. The cause of the disease is unknown but is thought to be an inherited defect in mitochondrial transporter proteins, such as ornithine, that are required for complete urea synthesis.[39]

Glycogen branching enzyme deficiency is a fatal autosomal-recessive disease of Quarter Horses and Paint Horses caused by a mutation of the glycogen branching enzyme 1 (GBE1) gene that drastically decreases the amount of GBE protein in homozygotes.[40] Diseased foals cannot store and mobilize glycogen to maintain normal glucose homeostasis. Those that survive to parturition are often born weak and hypoglycemic/hypothermic but improve with bottle feeding. Other clinical presentations include progressive muscle weakness, inability to rise, collapse, seizures, flexural limb deformities, respiratory failure, and sudden death. Common laboratory findings include leukopenia, intermittent hypoglycemia, and moderate elevations of serum CK, AST, and GGT activities. Genetic testing is available, but diagnosis can also be made based on liver and muscle biopsies from affected foals. There is no treatment, and all cases to date have been fatal.

Chronic Active Hepatitis

Jennifer L. Davis

Chronic active hepatitis (CAH) is an idiopathic progressive hepatopathy with insidious onset. The etiology and pathogenesis are unknown but may be similar to human autoimmune or hypersensitivity conditions. Toxic and infectious etiologies have also been proposed, or it may be a manifestation of chronic cholangitis/cholangiohepatitis. In one retrospective report of 88 cases of liver disease in adult horses, CAH accounted for 9.9% of all cases reported.[1] Seven out of 9 cases in that report were in ponies, although a true breed predisposition has not been reported.

Clinical signs are those of progressive liver failure and include weight loss, depression, anorexia, colic, icterus, and fever.[2] These signs may be intermittent. Signs of concurrent intraabdominal diseases or other autoimmune diseases may also be present. In rare cases, a moist exfoliative coronary dermatitis may occur, which is thought to be an immune-mediated issue.[3] Concurrent elevations in hepatic enzymes will be present, particularly GGT and ALP, with lesser elevations in IDH (SDH) and AST, as well as bile acids and direct bilirubin. The degree of elevation in liver enzymes cannot be used as an indicator of disease severity, since the liver may have significant fibrosis at the time of diagnosis. Other supportive clinicopathologic findings include an inflammatory leukogram, bilirubinuria, prolonged BSP clearance, and a polyclonal gammopathy. Ultrasonography may reveal a small liver with increased echogenicity indicative of hepatic fibrosis. Differential diagnosis includes pyrrolizidine alkaloid toxicity, bile stones, abdominal abscesses, and other chronic wasting diseases.

The final diagnosis of chronic active hepatitis is made histologically via biopsy of the liver or at necropsy. The principal features are localized primarily along the portal/periportal areas and include infiltration of inflammatory cells, biliary hyperplasia, and fibrosis or cirrhosis.[1] A mononuclear cell infiltrate (lymphocytes/plasmacytes) often predominates, but a neutrophilic component may be present with a primary or secondary infectious process. Bacteria, particularly gram-negative enteric bacteria, may be present in some lesions, and biliary hyperplasia may be marked if there is cholangiohepatitis. Grossly, the liver appears firm and is often pale brown to green in color, and the cut surface may have prominent irregular markings. An antinuclear antibody (ANA) titer and immunofluorescent staining of skin lesions (if present) may reveal evidence of an autoimmune reaction.

Treatment of CAH involves supportive care. Specific treatments can be determined based on biopsy results. If the predominant cell types are lymphocytes or plasma cells, corticosteroids may be beneficial. Dexamethasone (0.05-0.1 mg/kg/day IV, IM, or PO decreased over 2 to 3 weeks) or prednisolone (1 mg/kg/day PO for several weeks) is recommended. Antibiotics are indicated when a bacterial cholangiohepatitis is suspected on the basis of the histologic features of the liver, culture of the liver biopsy, and presence of a persistent intermittent fever. Other recommended therapies are aimed at resolving inflammation and preventing the progression of fibrosis. Flunixin (0.5-1 mg/kg PO q24h) or low-dose phenylbutazone (0.5 g/day PO) can be used. Vitamin E (10,000 U PO q24h) is recommended to protect membrane phospholipids from oxidative damage and suppress activation of inflammatory cells. Pentoxifylline (8 mg/kg PO q8h) has been used as a weak inhibitor of the inflammatory cytokines tumor necrosis factor (TNF)α and interleukin (IL)-6, although results are variable, possibly owing to the low oral bioavailability in horses. Colchicine (0.03 mg/kg PO q24h) can be used to inhibit production of collagen and macrophage/cytokine-induced inflammation.

The prognosis for CAH is variable and depends on the underlying cause and duration of disease prior to diagnosis. A retrospective study reported that five of nine horses with chronic active hepatitis survived, but they were 7.4 times more likely to die than those where a diagnosis of unclassified hepatopathy was made.[1] Liver biopsy and response to therapy are the best guides in formulating a prognosis. The prognosis for improvement and long-term survival is extremely poor in horses that have functional hepatic failure with widespread fibrosis and disruption of normal hepatic parenchyma. The prognosis is fair to good in patients with early (less severe) lesions, particularly those with a lymphocytic/plasmacytic cellular infiltrate that responds well to corticosteroids. The presence of cirrhosis in the biopsy sample warrants a grave prognosis.

Pyrrolizidine Alkaloid Toxicity

Geof W. Smith

Etiology Pyrrolizidine alkaloid (PA) toxicity is a chronic, progressive, often-delayed intoxication that results when animals consume plants containing PAs. Plants containing these alkaloids are found all over the world, and poisoning of horses, cattle, poultry, and even humans has occurred in many different countries. PA toxicity primarily manifests as liver failure.[1] More than 350 types of PAs have been identified in over 6000 plant species.[2,3] The primary plants of importance in the United States come from the *Senecio* and *Crotalaria* genuses, but others exist. Table 33-4 lists the most common plants causing PA poisoning around the world.

PA toxicity is seen wherever plants containing the alkaloids are found. The plants are not very palatable and in most cases are not readily eaten, but animals may eat them when the growth of the toxic plant is so thick that the animal cannot separate it from normal forage, or when other forage is sparse. The plants are toxic in hay, including pelleted and cubed hay. PAs also survive ensilage; oat silage contaminated with *Amsinckia* or other PA-containing plants has been responsible for disease in dairy cattle. Seeds of *Heliotropium* plants have also poisoned feedlot cattle.[4]

The approximate toxic dose of dried *Senecio* as a percentage of body weight for each species is horses, 5%; cattle, 2% to 5%; goats, 125% to 400%; and sheep, over 150%. Most tansy ragwort contains less than 0.2% PA by weight, but there are reports of much higher levels in some of the other plants. Horses were consistently poisoned by greater than 250 mg of total PA per kg body weight.[5] The PA in hound's tongue is extremely toxic to horses.[6] This dose does not have to be eaten all at once, since the effects are cumulative. Because signs often are delayed, some animals may not become ill until a year or more after removal from feed sources containing the toxins.[7,8] Signs do not occur until hepatocyte loss and replacement by fibrous tissue have caused failure of liver function.

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TABLE 33-4

Common Plants Containing Pyrrolizidine Alkaloids (PAs)

Botanical Name (Genus/Species)	Common Name
Senecio jacobaea	Tansy ragwort
Senecio vulgaris	Common groundsel
Senecio douglasii var. *longilobus*	Threadleaf groundsel
Senecio riddellii	Riddell groundsel
Senecio triangularis	Tarweed
Senecio alpinus	Alpenkreuzkraut (Europe)
Amsinckia intermedia	Fiddleneck
Crotalaria spp.	Rattlebox
Echium plantagineum, *E. lycopsis*	Patterson's curse, Salvation Jane or Viper's bugloss
Heliotropium europaeum	Common heliotrope
Symphytum officinale	Comfrey
Cynoglossum officinale	Hound's tongue (houndstongue)
Eupatorium maculatum	Bruner's trumpet
Baccharis pteronioides	Yerba de pasmo
Borago officinalis	Borage
Erechtites spp.	
Trichodesma spp.	

Pathophysiology There are a number of PAs, and many of the poisonous plants contain four to six different alkaloids. About 50% of the alkaloids are toxic, and some are more toxic than others. The alkaloid concentrations vary slightly among plants from different areas, but there is greater variation in concentrations from different parts of the same plant.[9] PAs are not directly toxic; they must be bioactivated to toxic alkaloids (pyrroles) in the liver. After absorption the portal circulation carries the alkaloids to the liver, where they are metabolized by microsomal enzymes of the hepatocyte to more toxic pyrroles.[3,10] The pyrroles may cross-link double-strand DNA in a dose-dependent manner.[11] The degree of DNA cross-linkage depends on the concentration of the pyrrole, but not on the base sequence of the oligonucleotide target.[12] The cross-linking of DNA produces an antimitotic effect.[13] The hepatocytes cannot divide and often become megalocytes as cytoplasm expands without nuclear division. As cells die, they are replaced by connective tissue rather than new hepatocytes. This antimitotic effect may explain why megalocytosis (large hepatocytes and large nuclei) is commonly seen with PA poisoning.

With progressive death of hepatocytes and subsequent fibrosis, liver function begins to fail. Blood supply through the hepatic lobule is disrupted by fibrosis, making regeneration impossible. This becomes a veno-occlusive disease, resulting in marked portal hypertension. The increased portal hydrostatic pressure leads to diarrhea and ascites in ruminants. It is unclear why diarrhea and ascites are seen infrequently in horses with PA toxicity.

Clinical Signs The clinical signs of PA poisoning are basically those of liver failure. The most common signs of PA toxicity in the horse are weight loss, slight to moderate icterus, and abnormal behavior (e.g., wandering, ataxia). Signs seen less frequently in horses include photosensitization of the white areas and, in rare cases, diarrhea. A few cases in ponies have shown loud, stertorous inspiratory noises, possibly caused by pharyngeal-laryngeal paralysis.[13,14] Abortion may occur from ingestion of sublethal doses.[15] Subtle signs such as poor performance (inability to race up to previous standards) may be seen in horses with pyrrolizidine-induced liver damage before the onset of liver failure. Secondary gastric impaction has been reported in ponies.[16] Cattle more frequently show diarrhea, weight loss, tenesmus, prolapsed rectum, and ascites. Calves are much more susceptible to PA toxicity than mature cattle. Behavioral changes or subtle neurologic signs may also be seen in cattle, but icterus is uncommon. Differential diagnosis includes other diseases causing liver failure (e.g., aflatoxicosis or liver flukes) and some chronic debilitating diseases such as GI parasites and Johne's disease.

Sheep and goats are more resistant to PA toxicosis but can be affected by certain alkaloids at doses 30 times or more than the dose that affects cattle and horses. A consortium of ruminal microbes from sheep degrades PAs found in *Senecio jacobaea* to less toxic metabolites.[17] Liver microsomal enzymes in sheep may also play a role in detoxifying PAs, but this alone does not seem to account for the differences in susceptibility.[18]

Diagnosis Hepatic enzyme activities are generally elevated during periods of active hepatocyte destruction caused by PA poisoning. Although the dehydrogenases (e.g., IDH, GDH, LDH) are elevated initially, they may have returned to normal by the time the animal first shows clinical signs of functional failure. Because lesions are largely in the portal region, GGT and ALP tend to be consistently elevated.[7,19] In a study of sublethally poisoned horses, AST and the ratio of branched-chain to aromatic amino acids were persistently elevated.[15] Bile acid concentrations are increased and levels above 50 μM/L would be a poor prognostic indicator in the horse.[5] Serum protein concentration is usually normal, and only terminally does albumin decrease or blood clotting become altered. Bilirubin, both direct and indirect, tends to be increased in the horse at the later stages of the disease process.

Although liver biopsy can be very useful in the diagnosis of PA toxicity, other causes of chronic hepatitis (e.g., aflatoxins) may produce a similar histologic appearance. The triad of fibrosis, bile duct proliferation, and megalocytosis is characteristic of PA poisoning. Modest changes in hepatocytes and biliary hyperplasia are reversible. Fibrosis bridging portal areas indicates an eventually fatal condition, as does the extensive fibrosis of an end-stage liver.

Cattle dying of PA poisoning have ascites and prolapsed rectums and are thin and emaciated. Horses are usually thin and may be icteric. In all species the liver tends to be small, pale brown to yellow, and firm and may appear to be scarred. Hepatic megalocytosis is considered the hallmark of PA poisoning, but it has also been seen in aflatoxicosis and is not always apparent in the earliest stages of PA toxicity. Biliary hyperplasia may occur early in the disease. Nonspecific nuclear changes, such as invaginations of cytoplasm into the nucleus, have been seen.[7,9] Isolated hepatocyte necrosis is seen later, and finally, portal or massive generalized fibrosis develops. Once bridging of connective tissue between the portal areas occurs, the disease is fatal.

Treatment Liver failure may occur with either acute or chronic liver disease. The two must be differentiated for prognosis because end-stage fibrosis caused by PAs has virtually no chance for regeneration and recovery. No satisfactory treatment for PA poisoning exists. Once obvious clinical signs of liver failure develop, the animal usually dies within 5 to 10 days. Horses with mild clinical signs and reversible histologic lesions survived if they retained an appetite and were not exposed to any more PA-contaminated feed.[15] An accurate prognosis concerning mildly affected cases may best be obtained from a combination of consecutive liver biopsies and liver-derived serum enzyme activity, as well as from SBA concentrations.[5,15] Preventing further exposure to the toxic plants is indicated and may delay or stop the progression of the liver lesions, particularly if an uncontaminated feed source is provided before clinical signs develop.

Therapy of liver failure is inappropriate if severe fibrosis has occurred, because regeneration is impossible. If the animal still has a reasonable appetite and only modest degrees of fibrosis histologically, treatment may be attempted by providing a low-protein, high-energy diet.

Prevention and Control PA poisoning is prevented by keeping susceptible animals from pasture, hay, cubed hay, or seeds that contain PA plants. Because most poisonings are attributed to contamination of forages or feed, careful inspection of feed is recommended. *Senecio vulgaris* tends to contaminate mainly first-cutting

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TABLE 33-5

Hepatotoxic Plants

Common Name (Botanical Name)	Approximate LD50 (% BW)*	Geographic Distribution	Liver Lesion
For pyrrolizidine alkaloid–containing plants, see Table 33-4.			
Lantana *(Lantana camara)*	1	Northern North America	Necrosis, canalicular collapse
Rabbitbrush *(Tetradymia glabrata)*	0.5	Dry desert	Necrosis
Horsebrush (*Tetradymia* spp.)		Western U.S.	Necrosis
Sacahuista *(Nolina texana)*	1.1	Southwestern U.S.	Fatty and centrilobular necrosis
Lechuguilla *(Agave lecheguilla)*	4-15	Southern U.S., Mexico	Necrosis, photosensitivity
Puncture vine *(Tribulus terrestris)*	?	Warmer regions	Biliary fibrosis, necrosis (big head)
Whitebrush (*Lippia/Aloysia* spp.)	?	Southern U.S., Mexico	Fatty degeneration
Panic grasses (*Panicum* spp.)	?	Texas-California, South America	Biliary fibrosis, necrosis
Kleingrass *(Panicum coloratum)*	?	Southern U.S.	Necrosis, obstructed bile ducts
Bermudagrass *(Cynodon dactylon)*	?	North America	?
Cocklebur *(Xanthium orientale)*	0.75-3	North America	Hemorrhagic centrilobular necrosis
Lupine (*Lupinus* spp.)	Varies	Western North America	Necrosis
Mycotoxin from *Phornopsis inferior*			
Cottonseed (*Gossypium* spp.)	Varies; gossypol content	Southern U.S.	Necrosis
Gossypol pigment			Cardiac lesions
Poisonous mushrooms *(Amanita phalloides, Galerina venenata)*	Few mushrooms	North America	Necrosis, central nervous system signs
Blue-green algae *(Microcystis aeruginosa, Nodularia spumigena)*	? 0.001	Ponds, worldwide	Necrosis, dissociation
Alsike clover *(Trifolium hybridum)*	Varies	Cultivated	Portal fibrosis, biliary hyperplasia
Mexican fireweed *(Kochia scoparia)*	?	Southwest U.S.	?
Coffee senna *(Cassia occidentalis)*	0.05% BW (horse); 0.5%-2% (cattle)	North and South America, Africa, Asia, and Australia	Pericentrolobular vacuolar degeneration and necrosis
Cycad palm (*Cycas/Zamia* spp.)	?	South America, Australia	?
Yellow-wood *(Terminalia oblongata)*	?	Australia, Africa	Centrilobular necrosis
Sneezeweed (*Helenium* spp.)	0.25	Northern U.S., Canada	?
Moldy alfalfa *(Medicago sativa)*	?	Wet areas	Biliary hyperplasia, necrosis
Bitterweed (*Hymenoxys* spp.)	1	Southwestern U.S.	?

*Lethal dose (as percentage of body weight).

?, Unknown; *BW*, body weight.

alfalfa, whereas *Amsinckia intermedia* is often found in planted fields of oat hay. *Senecio* can be controlled by cultivation, because it is a biennial, or by herbicide spraying in the early rosette stage. Species-specific herbicide regimens have been developed for most plants containing alkaloids and are widely available through state weed and extension services. Sheep are sometimes used to graze *Senecio*-infested pastures to control the weed, because they are less susceptible to PA poisoning.

Other Hepatotoxins

The liver is particularly vulnerable to toxic insults because it is the first organ to receive toxins absorbed from the GI tract. Enzymes in the hepatocyte may either activate a toxin or, in some cases, metabolize it before it can cause damage. Most hepatotoxic agents are described in more detail in Chapter 54. Some of the more common liver toxins are listed in Tables 33-5, 33-6, and 33-7, but these are not complete lists because many other plants and chemicals can damage the liver under the right conditions. Once a toxic liver disease has been diagnosed, possible sources of the toxin might be identified from these tables. A more detailed description of toxins affecting the liver can be found in Chapter 54.

Liver Flukes in Ruminants

John B. Malone

Etiology The common liver fluke *Fasciola hepatica* causes a disease of production in ruminants that mimics the production effects and clinical appearance of the GI nematode-parasite complex. The disease often has its maximum economic effect in late fall and winter when animals are most likely to be under seasonal nutritional stress. *F. hepatica* is unique among the common helminths of ruminants in that it has an asexual multiplication phase of the life cycle in snail intermediate hosts that is highly sensitive to environmental conditions. *F. hepatica* is well known for its exponential propagation of infective stages under favorable conditions, sometimes leading to explosive seasonal outbreaks of severe parasitism, especially in sheep. In addition, liver parenchyma migration forms leave necrotic tracts in their wake that are a primary predisposing factor in some areas for acute fatalities caused by *C. novyi* types B (black disease) and D (bacillary hemoglobinuria), discussed earlier in the chapter.[1]

The geographic distribution of *F. hepatica* in the United States is limited mainly to areas in the south-central states and Florida and to the Pacific Northwest, where neutral well-buffered soils are found and local hydrologic conditions provide suitable habitats for lymnaeid snail intermediate hosts. The important vector species in temperate climates, recently renamed based on molecular evidence as *Galba* sp. or *Lymnaea* sp.,[2] are semiaquatic "mud" snails found in disturbed mud banks and hoofprints in shallow depressions in fields, drainage channels, and temporary water bodies in alluvial river basins, bottomlands, and coastal regions of the southeastern United States. Springs, small streams, seeps, and sloughs serve as habitats in areas of greater terrain relief in the western states. Most infections occur by grazing in and around water in fluctuating habitats that stay wet for more than half the year.

The life cycle development of both the snail host and the parasite in the snail occurs only when temperatures are above 10°C (50°F) and while snail habitats are wet. This leads to a distinct seasonal transmission in the mild, wet winter and spring of the south-central states and Florida and a late spring to fall transmission in the cooler climates of the western states (Figs. 33-3 and 33-4). It takes a

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TABLE 33-6

Hepatotoxic Chemicals

Chemical	Source	Approximate Lethal Dose*	Liver Lesion
Carbon tetrachloride (CC14)	Tremacide Fumigant Solvent	10-40 mg/kg	Fatty degeneration, centrilobular necrosis, cirrhosis
C1-Hydrocarbons PCBP Solvents	Insecticides	Varies with species, chemical, and route	Necrosis
Pentachlorophenols	Wood preservative, herbicide, fungicide, molluscacide	100-200 mg/kg	Centrilobular fatty degeneration
Polybrominated biphenyl (PBB)	Fire retardant	100 mg/kg	Hemorrhagic necrosis, fatty degeneration
Carbon disulfide (CS2)	Boticide Solvent Fumigant	100 mg/kg	Necrosis
Coal tar pitch	Clay pigeons Pipe sealer Tar paper	Swine 15 g/pig	Hemorrhagic necrosis
Phenol	Wood preservative	30 mg/kg	Hemorrhagic centrilobular necrosis
Iron	Iron supplements Injectable iron	>150 mg/kg young animals	Portal necrosis
Copper	Species inappropriate supplements Fungicides, algicides Molluscacide Foot baths	Depends on species and molybdenum intake	Portal vacuolation and necrosis (hemolytic crisis)
Phosphorus	Fertilizer Matches Rodenticide	1-4 mg/kg	Portal necrosis and fatty degeneration
Tannic acid	Oak Skin astringent	20 mg/kg	Centrilobular necrosis (also renal damage)
Paraquat/diquat	Herbicide	4-10 mg/kg	Centrilobular necrosis (also lung damage)
Mycotoxins, aflatoxin B	Moldy feed	3 mg/kg	Centrilobular necrosis, biliary hyperplasia, megalocytosis
Rubratoxin B	Moldy feed	?	Necrosis
Sporidesmin	Moldy feed	?	Bile duct occlusion (big head)
Ochratoxin A	Moldy feed	?	Necrosis (also renal damage)
Phomopsin A	Lupine	?	Necrosis

*Lethal dose varies with individual, species, route of entry, rate or chronicity, enzyme induction, and many other factors.

?, Unknown.

minimum of 42 days at 25° C (77° F) or the accumulation of approximately 600 growing-degree days to complete intramolluscan development, with release of cercariae that encyst as infective metacercariae on pasture vegetation (600 growing-degree days = 25° C minus the base temperature of 10° C = 15 growing-degree days × 42 days; an equivalent value for the life cycle is 15° C or 5 growing-degree days × 120 days). Using soil water budget analysis to indicate the length of time habitats are wet and the accumulated sum of growing-degree days over 600, a climate forecast index can be calculated for use in describing the pattern of seasonal transmission at a given site and to provide an indicator of the risk of economic losses in a given climate year. Two weeks of sustained summer heat and drought ends the transmission season by killing pasture metacercariae and forcing snail populations to estivate in soil or perish. In the cooler climates of the western United States, the season ends with drying of springs, seeps, sloughs, and other habitats or with the onset of sustained cold winter weather. Variation in the annual climate alone may lead to a 100-fold variation in fluke burdens in different climate years.[3]

The amount of snail habitat present on individual farms related to pasture wetness conditions, such as premises with low-lying heavy clay soils with a high water table, is also an important consideration in evaluating the need for fluke control. This factor has also been shown to lead to a 100-fold variation in the risk of fluke losses in the same year on different premises in otherwise ecologically similar areas.[4] The snail habitat area on most enzootic livestock operations typically is only 1% to 5% of the total land area; operations with over 5% habitat may be associated with a high risk of liver fluke losses.

Clinical Signs Subclinical production effects of *F. hepatica* include reduced rate of gain and feed efficiency in growing stock. Economic effects have been experimentally demonstrated in calves on a marginal nutritional plane in the first 5 to 6 months after infection, resulting in an 8% loss in the rate of gain with a mean of 40 flukes and a 28% loss with 140 flukes. In cattle it is estimated that herd economic losses are "negligible" with a burden of less than 10 flukes per animal, "possible" at 10 to 40 flukes, and "probable" with over 40 flukes. Clinical disease is seen with a burden of more than 200 flukes. In cow-calf operations, flukes often act in concert with periods of nutritional stress and concurrent heavy GI nematode infections, causing further reduction of body condition, poor milking ability, and slower return to estrus. This translates to reduced reproductive efficiency, prolonged calving interval, and lightweight calves at weaning.[5]

In cattle, flukes may lead to chronic disease or, in rare cases, subacute disease. When clinical signs occur, the typical population "overdispersion" (individual variation in parasite burdens) is manifested first in the 10% to 20% minority of the herd that harbor most of the parasite numbers. Signs may consist of weight loss, emaciation, depression, anorexia, rough hair coat, anemia, hypoproteinemia, submandibular edema, and, in rare cases, mild icterus. The anemia

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TABLE 33-7

Drugs Used in Large Animals That Could Damage the Liver

Drug	Lesion*
Carbon tetrachloride	Centrilobular necrosis or fatty degeneration
Hexachloroethane	Centrilobular or massive necrosis
Carbon disulfide	Necrosis
Alcohol	Necrosis/cirrhosis
Tetracycline	Fatty degeneration (also renal damage)
Clindamycin	Cholestasis, icterus
Erythromycin	Cholestasis, icterus
Isoniazid	Active hepatitis → cirrhosis/massive necrosis
Rifampin	Cholestasis, icterus
Nitrofurantoin	Active hepatitis → cirrhosis
Anabolic steroids	Cholestasis, icterus
Phenothiazine	Cholestasis, icterus tranquilizers
Halothane	Active hepatitis → cirrhosis/massive necrosis
Fluothane	Active hepatitis/massive necrosis
Isoflurane	Active hepatitis/massive necrosis
Some diuretics	Cholestasis, icterus
Diazepam	Cholestasis, icterus
Phenobarbital	Necrosis/cholestasis icterus
Aspirin	Active hepatitis → cirrhosis
Oil of pennyroyal	Centrilobular necrosis
Tannic acid	Centrilobular necrosis, fatty degeneration (renal damage)
Dantrolene	Active hepatitis → cirrhosis
Copper disodiumedetate	Massive centrilobular necrosis
Iron (injectable)	Necrosis, portal, cirrhosis, hemosiderosis
Glucocorticoids	Hepatocellular vacuolization
Ionophores (salinomycin)	Hepatic lipidosis, necrosis

*May vary with dose and time.

associated with *F. hepatica* infections is more than can be accounted for by fluke blood feeding. Evidence indicates that depression, anemia, and biliary hyperplasia result from high levels of proline, a product of fluke metabolism.[6] Cattle are able to mount a protective immune response, with partial acquired resistance to *F. hepatica* beginning at 5 to 6 months after initial exposure.[7] This and the short lifespan of flukes in cattle typically lead to a linear reduction of fluke numbers, with few surviving by the end of 1 year. Sheep and goats are more susceptible, and fatal acute disease with ascites, abdominal hemorrhage, pallor, and icterus can occur in association with massive entry to the bile ducts at 6 to 10 weeks after infection by 1000 to 5000 or more migrating immature forms from the liver parenchyma. Subacute disease has been associated with a burden of more than 800 flukes acquired over time. Chronic clinical disease in sheep with submandibular edema, ascites, and emaciation has been associated with fluke burdens above 200.[8]

Necropsy findings attributable to migrating young flukes are caused by tortuous tunnels of coagulative necrosis that organize and fibrose, ultimately leading to a diffusely fibrotic liver parenchyma, especially in the ventral lobe, which in severe cases undergoes marked atrophy. Fibrous tags may result from fibrinohemorrhagic deposits left by large numbers of flukes at liver penetration 3 to 4 days after infection. Inflammatory events associated with penetration of the bile ducts at 6 to 8 weeks after infection are especially pathogenic. Once in the bile ducts, flukes grow rapidly from 1 mm to 2.5 cm or more and induce a proliferative cholangiohepatitis. The spines and suckers of flukes erode and denude the bile duct epithelium, leading to a fibrosed, thickened duct wall that is irregularly dilated and stenotic and begins to calcify in cattle (but not sheep) at about 20 weeks after infection. The bile becomes darkly discolored and laden with regurgitated fluke ingesta, plasma proteins, and inflammatory cells. The extent of pathologic change is generally proportional to the fluke burdens of current or recurring previous infections.[8]

Diagnosis Fecal sedimentation methods are the standard means of diagnosing liver flukes, although classical methods are cumbersome. A reusable commercial "nematode counting chamber" (1-mL volume of sediment fluid) is available (Chalex, Wallowa, Ore.) that can be examined on a standard microscope stage. It reduces sample processing time by half and is suitable for use by practitioners for quantitative examination of individual animals or 10- to 15-animal herd composite samples. For herd or lot evaluations in cattle, egg counts of less than one egg per 2 g (EP2g) and 25% prevalence 2 to 4 months after the transmission season ends have a "low probability" of economic losses; 1 to 3 EP2g indicates "possible" economic loss; and 10 EP2g or more indicates "high probability" of heavy infections and economic loss. It is important to differentiate *F. hepatica* eggs from the eggs of *Paramphistomum* species, a nonpathogenic "rumen fluke" often found in the same herds in both the southern and the western enzootic areas. Flukecides used against *F. hepatica* are ineffective against rumen flukes, and egg counts thus persist after treatment. *Paramphistomum* eggs are gray (rather than amber), slightly smaller, and more pointed at the operculum end than *F. hepatica*. *Paramphistomum* egg counts can be used as a general indicator of the probable risk of *F. hepatica* in the absence of control in the southern states, because *Paramphistomum* flukes are known to be transmitted by the same snail vector in that region.[5]

Diagnostic enzyme-linked immunosorbent assays (ELISAs) have been developed to detect serum antibodies or coproantigen in the feces of infected animals or in bulk milk samples.[9,10] These tests have not yet found wide use outside of research laboratories in the United States but are marketed in Europe.[10] Blood and serum clinicopathologic results reflect the anemia, hypoproteinemia, and mild eosinophilia caused by *F. hepatica*. Pathologic changes in the liver bile ducts and parenchyma are reflected by an elevation in serum liver enzymes (e.g., GGT, GDH).

Treatment and Prevention Prevention is the key to control in foundation herds and flocks, because even low numbers of eggs shed can multiply asexually in snails and lead to significant infection rates during the following transmission season. A single routine fall or late fall-winter treatment after the end of the transmission season with a highly effective drug is recommended to remove adult flukes before winter stress and to prevent egg shedding and snail infection in the next season (see Figs. 33-3 and 33-4). Most of the pathogenic and economic effects of flukes in cattle are reported to occur within the first 5 to 6 months after the major exposure period and may be related to metabolic products associated with the rapid growth and heavy egg production phases of the life cycle. This, coupled with linear loss of heavy fluke burdens in cattle and the onset of effective immunity at 20 weeks after exposure, suggests the value of early flukecide treatment within 2 to 3 months after the transmission season ends. In some herds an optional curative treatment in spring may be needed in very high-risk years or on high-risk premises, or as a second treatment to remove flukes acquired during late, extended transmission on irrigation pastures or wet coastal areas in the west.

Flukecidal drugs available in the United States are effective against mature flukes in bile ducts (albendazole, 10 mg/kg; clorsulon, 2 mg/kg). Clorsulon at 7 mg/kg has added efficacy against juvenile flukes over 6 weeks old in the bile ducts. The optimum time to treat should be based on the estimated susceptibility of mature fluke populations (>12 weeks old after end of transmission season) but early enough to remove flukes while they are most pathogenic (<6 months old). Triclabendazole, which is widely used in other countries, is reported to be more than 90% effective against migrating flukes over 2 weeks old and 99% effective against mature flukes and thus can be effectively given just after transmission ends. However, significant triclabendazole drug resistance issues have emerged.[10,11] Worldwide,

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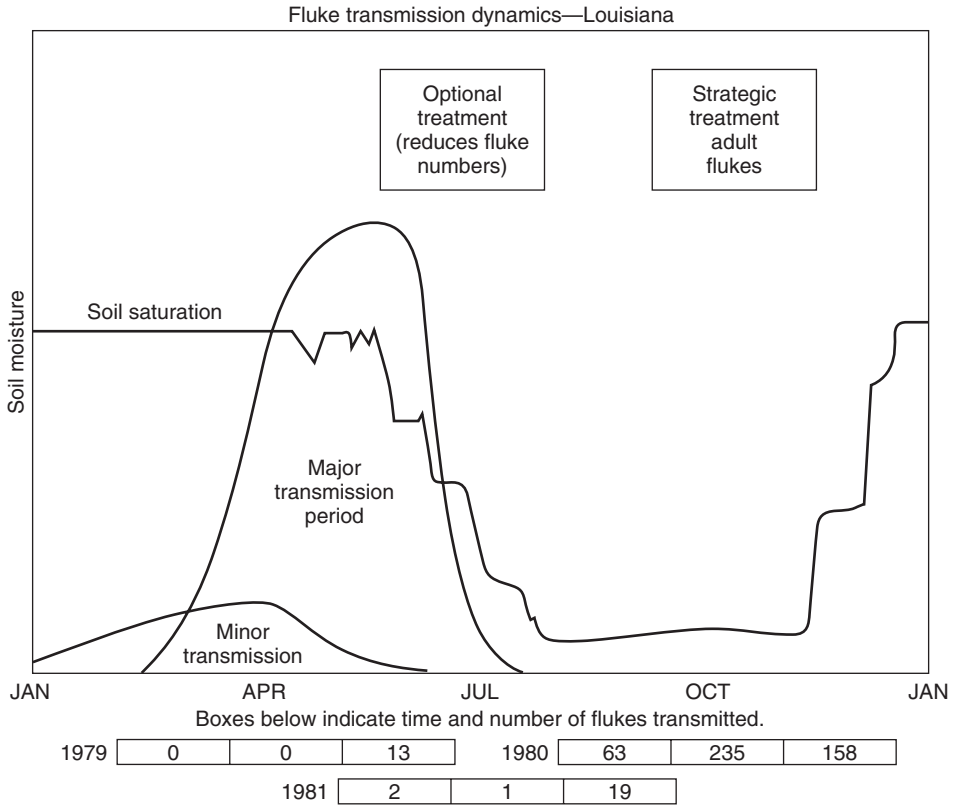


FIG. 33-3 Pattern of *Fasciola hepatica* transmission typical of the southern United States (based on 10 years of experimental data from Alexandria, Louisiana) and strategic treatment recommendations with adulticidal drugs. *(From Malone JB, Loyacano AR, Hugh-Jones ME, et al. 1984. A three-year study on seasonal transmission and control of Fasciola hepatica in cattle in Louisiana. Prev Vet Med 3:131.)*

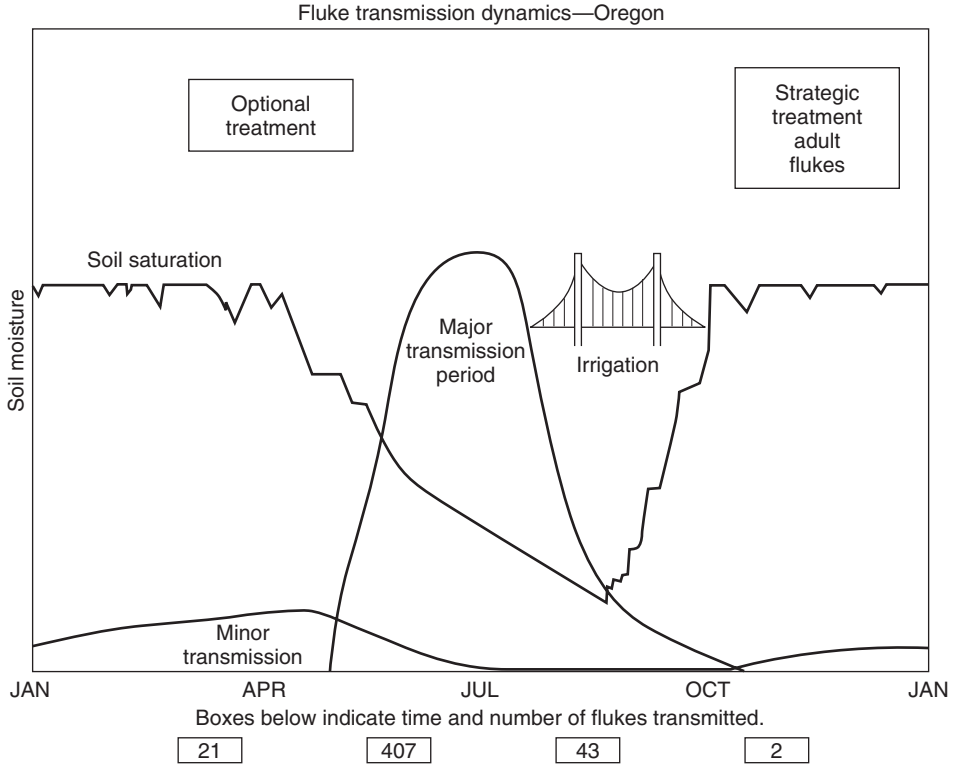


FIG. 33-4 Pattern of *Fasciola hepatica* transmission typical of the U.S. Pacific Northwest in natural rainfall and irrigated zones (based on experimental data from Langolis, Oregon) and strategic treatment recommendations with adulticidal drugs. *(From Rickard LG, Zimmerman GL, Hoberg EP, et al. 1992. Influence of ivermectin and clorsulon treatment on productivity of cow-calf herd on the Southern Oregon coast. Vet Parasitol 41:45.)*

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a number of other drugs are available, including oxyclozanide, niclofolan, bithionol, and hexochlorophene (80% to 99% of adult flukes), nitroxanil, closantel (>90% adult and 50% to 90% juvenile bile duct flukes), rafoxanide (>50% late migratory flukes, >90% juvenile and adult bile duct flukes), and diamphenathide (>90% migratory flukes, 50% to 80% bile duct flukes).

The economic benefit of routine flukecide treatment of feedlot calves from enzootic areas in the United States has not been consistently demonstrated industry-wide because of the high variability of fluke burdens in animals from enzootic areas, or because lots are often of mixed origin. Fluke-related losses would be expected to be mainly absorbed by stocker operations, where lightweight calves are typically placed on small grain pastures for extended periods before feedlot, a common practice in the south-central states. The economic return of treatment at feedlot should be evaluated on a case-by-case basis, because significant losses may occur if the lot originates from the same premises and the history suggests a high risk of recent heavy infection rates, such as in favorable climate years or use of irrigated pastures in fluke areas. Fecal egg counts on 10 to 15 randomly selected animals may aid in herd evaluation. An example case of the explosiveness of the life cycle is the greatly reduced feedlot performance and 100% liver condemnations of a lot from a stocker operation in the Pacific Northwest. The animals originated from irrigated pastures where some habitats stayed wet year-round, and untreated calves from fluke areas were allowed to contaminate pastures with eggs, which translated to infection later in the grazing season and to the next stocker group rotated onto the premises.

Other Flukes

Fascioloides magna, the large American liver fluke, may infect cattle and sheep that graze common areas with deer, the natural host. The life cycle is similar to that of *F. hepatica,* but with a wider variety of lymnaeid snail hosts and a broader geographic distribution in the Gulf States, the Great Lakes area, and the Northwest. Cattle are abnormal dead-end hosts that react with an intense encapsulation response, forming a closed cyst that does not allow escape of eggs and obviates diagnosis by fecal examination. The liver parenchyma and regional lymph nodes have a characteristic diffuse black pigmentation. The major economic effect of *F. magna* in cattle is condemnation of livers and other organs, such as lungs, in which aberrant migration sometimes occurs. In sheep and goats, however, *F. magna* does not encyst and migrates uninterrupted. One or two *F. magna* flukes kill sheep before the flukes have time to mature, and this parasite limits sheep production in some areas. Albendazole given at high dosage is moderately effective against *F. magna.*

In tropical regions, *F. hepatica* is replaced by *Fasciola gigantica,* a similar species that is somewhat larger, has a longer prepatent period (10 to 12 weeks), and is of somewhat greater pathogenicity. *Dicrocoelium dendriticum* occurs worldwide but in North America is an unimportant species, mainly limited to areas of central New York, with smaller foci in Pennsylvania, New England, Quebec, and British Columbia. Albendazole (20 mg/kg) and high doses of thiabendazole (150 to 300 mg/kg) are effective treatments.[1]

Hepatic Abscesses

T.G. Nagaraja

Etiology Hepatic abscesses occur sporadically in most animals but are most common in ruminants, particularly cattle fed high-grain diets. Hepatic abscesses occur at all ages and in all types of cattle, including dairy cows, but have the greatest economic impact in feedlot cattle, in which the prevalence ranges from 1% to 2% to as high as 90% to 95%, but averages 20% to 30% in most feedlots.[1] Because hepatic abscesses are generally a direct result of feeding practices, diet is an important factor influencing the prevalence. Hepatic abscesses do occur in dairy cows, and anecdotal observations have suggested as high as 40% to 60 % of prevalence in packing plants that routinely slaughter culled dairy cows.[2]

Hepatic abscesses are generally polymicrobial infections, and in most cases the organisms are anaerobes. In the bovine, *Fusobacterium necrophorum* (formerly *Sphaerophorus necrophorus*), a gram-negative, pleomorphically rod-shaped anaerobe, is the primary etiologic agent.[3] The organism also is implicated as the primary pathogen in necrotic laryngitis (calf diphtheria), foot rot, and foot abscesses in cattle.[4,5] *F. necrophorum* is a normal inhabitant of the rumen, and its role in ruminal fermentation is mainly to utilize lactic acid to produce volatile fatty acids and also digest ruminal epithelial and feed protein.[6] The organism is in higher concentration in grain-fed than forage-fed cattle, possibly because of the increased availability of lactic acid from fermentation of starch in the grain. Several virulence factors have been implicated in the pathogenesis of *F. necrophorum* infections.[5,6] These include leukotoxin, endotoxic lipopolysaccharide (LPS), hemolysin, hemagglutinin, capsule adhesins or pili, platelet aggregation factor, dermonecrotic toxin, and extracellular enzymes (e.g., proteases, deoxyribonucleases).[6] Leukotoxin is believed to be the major virulence factor. The leukotoxin is cytotoxic to polymorphonuclear neutrophil leukocytes (PMNs), macrophages, hepatocytes, and ruminal epithelial cells. Because of leukotoxin, the organism is able to survive, proliferate, and establish to set up infection of the ruminal wall and liver. There are two subspecies of *F. necrophorum,* subsp. *necrophorum* (formerly biotype A) and subsp. *funduliforme* (formerly biotype B). These two subspecies differ in cell morphology, colony characteristics, growth patterns in broth, and most importantly, in virulence factors. Subspecies *necrophorum* is more virulent (produces more leukotoxin) and thus more frequently encountered in liver abscesses than subsp. *funduliforme,* which tends to occur more often in mixed infections.[7,8]

In most situations, *Arcanobacterium pyogenes* (formerly *Actinomyces, Corynebacterium,* and now included in a new genus called *Trueperella*), a gram-positive rod-shaped organism, is the second most frequent pathogen isolated from liver abscesses. The ruminal wall appears to be the niche for *A. pyogenes,* a facultative bacterium, because the wall provides an aerobic microenvironment in an otherwise anaerobic environment of the rumen.[9] The organism may also act in synergy with *F. necrophorum* to cause liver abscesses.[10] A variety of other anaerobic and facultative bacteria, such as *Bacteroides* spp., *Clostridium* spp., coliforms, *Mobiluncus* spp., *Mitsuokella* spp., *Pasteurella* spp., *Peptostreptococcus* spp., *Porphyromonas* spp., *Prevotella* spp., *Propionibacterium* spp., *Staphylococcus* spp., *Streptococcus* spp., and many unidentified gram-positive and gram-negative bacteria, are often isolated from liver abscesses of cattle.[5,7,10]

Pathophysiology Abscesses in the liver result from entry and establishment of *F. necrophorum* either alone or with other bacteria. The routes by which the bacteria can gain access to the liver include the portal vein, hepatic artery, umbilical vein (in newborn with omphalophlebitis), bile duct system, and direct extension. Entry through the hepatic artery (after an episode of septicemia) or the bile ducts (usually from obstruction, infection ascending from duodenum, or migration of flukes) is a rare occurrence. Direct extension of infection from adjacent tissues and organs, usually of traumatic origin (e.g., direct puncture of the liver by a foreign body lodged in the reticulum), is more likely to occur in dairy cows. Traumatic reticuloperitonitis caused by metallic objects lodged in the reticulum and perforating through the reticular wall, rarely involving the ruminal wall, is often a predisposing factor for liver abscesses in dairy cows. However, in both dairy cows and feedlot cattle, the most common route of entry of bacteria into the liver is the portal vein.

Liver abscesses are secondary to the primary foci of infection in the ruminal wall. Evidence to support this is the high correlation between ruminal wall lesions (rumenitis) and liver abscesses, thus the term *rumenitis–liver abscess complex* (Fig. 33-5). More direct evidence for the pathogenesis of liver abscesses was obtained by restriction fragment length polymorphism analysis of rRNA genes (ribotyping) of *F. necrophorum* and *A. pyogenes* isolates from the rumen and liver abscesses of the same animal. The genetic similarity between the isolates from liver abscesses and ruminal walls

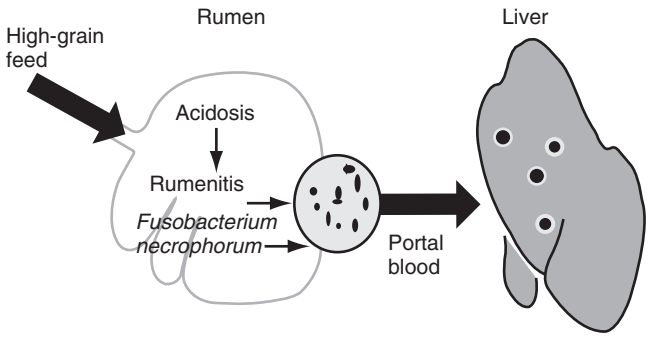


FIG. 33-5 Pathogenesis of liver abscesses in cattle fed high-grain diets. *(Modified from Nagaraja TG, Chengappa MM. 1998. Liver abscesses in feedlot cattle: a review. J Anim Sci 76:287.)*

supported the hypothesis that *F. necrophorum* and *A. pyogenes* isolates of liver abscesses originated from the rumen.[9,11] It is well accepted that ruminal lesions resulting from acidosis are the predisposing factors for hepatic abscesses. Acid-induced rumenitis and damage of the protective surface usually are associated with a sudden change to high-energy diets and other dietary indiscretions, such as a change in feeding patterns, letting cattle become overly hungry, feeding unpalatable diets, and feeding very little roughage. The ruminal damage often is aggravated by foreign objects in the feed, sharp feed particles, or hair.[10] The ruminal wall that is damaged from acidity or penetration of foreign objects becomes susceptible to invasion and colonization by *F. necrophorum.* Once colonization has occurred, *F. necrophorum* can gain entry into the blood or cause ruminal wall abscesses and subsequently shed bacterial emboli to the portal circulation. Bacteria from the portal circulation are filtered by the liver, leading to infection and abscess formation.

The virulence factors of *F. necrophorum* play a critical role in the penetration and colonization of the ruminal epithelium and entry and establishment of infection in the liver.[6] The protease activity, dermonecrotic activity, and cytotoxic effect of leukotoxin on ruminal cells may aid in penetration and colonization of the ruminal wall. *F. necrophorum*, being an anaerobe, must overcome both high oxygen concentrations and phagocytic mechanisms to survive, proliferate, and initiate abscess formation. The leukotoxin may protect it from phagocytosis. Also, the release of cytolytic products such as lysosomal enzymes and oxygen metabolites, resulting from destruction of phagocytes, has a detrimental effect on the liver parenchyma. Synergism with facultative bacteria, intravascular coagulation induced by endotoxic LPS and platelet aggregation factor, formation of fibrin-encapsulated abscesses, and impairment of oxygen transport by damaged erythrocytes (action of hemolysin) all may contribute to the establishment of an anaerobic microenvironment conducive to the growth of anaerobic bacteria within the ruminal wall and liver.

Pathology Abscesses found in the liver at slaughter or necropsy often are well encapsulated, possessing thick, fibrotic walls (Fig. 33-6). The earliest lesion is a microabscess induced by an embolus of *F. necrophorum* in the sinusoid, and the lesion then progresses to coagulative necrosis by involving adjacent hepatocytes. Subsequently, the lesion gradually changes into a pus-filled, encapsulated, true abscess. Histologically, a typical abscess is pyogranulomatous with a necrotic center, encapsulated, and often surrounded by an inflammatory zone.[8] Hepatic abscesses are pus filled, have capsules that vary in thickness, and range in size from a minute pinpoint to over 15 cm (6 inches) in diameter. The number of abscesses in the liver can vary from one to hundreds, and sizes range from less than 1 cm (0.4 inch) to greater than 15 cm in diameter, often encircled by a hyperemic zone. The larger abscesses may be the result of small abscesses coalescing early in development. The distribution of abscesses in the liver shows no consistent pattern, with superficial and deep abscesses distributed almost evenly. Often, small abscesses are scattered



FIG. 33-6 Liver from a feedlot steer demonstrating a large liver abscess

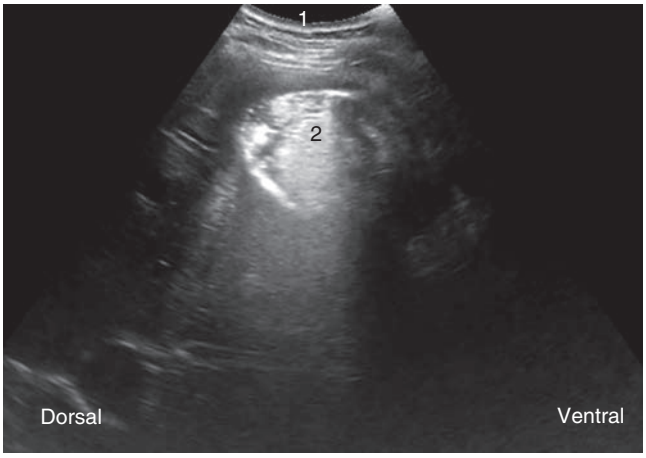


FIG. 33-7 Ultrasound image from the 11th intercostal space of a cow. Abdominal wall *(1),* liver abscess *(2).*

throughout the organ, whereas large abscesses are located close to the portal entry. Abscesses eventually become sterile and are replaced by fibrous scars, with eventual resorption.

Clinical Signs and Diagnosis Liver abscesses are detected only at the time of slaughter. Cattle, even those that carry hundreds of small abscesses or several large abscesses, seldom show any clinical signs. Occasionally the rupture of a superficial abscess or erosion and perforation of the caudal vena cava could lead to extensive spread and massive infection of other organs and eventual death. Generally, hematology and liver function tests have not proved to be good indicators of liver abscesses.[12] In animals in which abscesses were induced by experimental inoculation of *F. necrophorum,* hepatic dysfunction was documented by elevated serum protein, bilirubin, and enzymes such as GGT and IDH (SDH) concentrations.[13] In a group of Holstein dairy cattle where the presence of liver abscesses was diagnosed via ultrasound or exploratory laparotomy, the most common clinical sign was anorexia.[14]

Ultrasonography is a useful technique in the diagnosis of various hepatic diseases in cattle because of the location and tissue consistency of the liver (Fig. 33-7).[15] The technique has been shown to be useful for monitoring the onset and progression of experimentally induced abscesses where the site of injection is known.[13] The development of abscesses in feedlot calves has been recorded by ultrasonographic examination at regular intervals from weaning to slaughter.[12] However, its application to the diagnosis in feedlot cattle is limited

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because the ultrasonographic scanning cannot visualize the whole liver, particularly the left side facing the internal organs, and parts of lobes are covered by other organs (e.g., lungs, kidneys).

Treatment and Prevention Both *F. necrophorum* and *A. pyogenes* are susceptible to penicillins and macrolides.[1] Although successful treatment of cattle with liver abscesses has been described,[14] antibiotic treatment is seldom practical in cattle because complete recovery is difficult to attain. Cattle with sequelae (e.g., caudal vena cava thrombosis syndrome), for economic reasons, are generally culled for slaughter.

According to the U.S. Feed Additive Compendium, five antibiotics (bacitracin methylene disalicylate, chlortetracycline, oxytetracycline, tylosin, and virginiamycin) are approved for prevention of liver abscesses in feedlot cattle.[16] These antibiotics vary in their inhibitory effect on *F. necrophorum* and *A. pyogenes* and their effectiveness in preventing liver abscesses. Tylosin, a macrolide, is the most effective antibiotic and the most commonly used feed additive (6 to 8 g/ton, or 60 to 90 mg/head/day) in the feedlot. Studies show that tylosin feeding reduces abscess incidence about 40% to 70%. A bacterin vaccine (Fusogard, Novartis Animal Health), injected subcutaneously in 2-mL doses 21 days apart, has been shown to be effective in reducing the incidence and severity of liver abscesses in feedlot cattle. A vaccine combination of *F. necrophorum* leukotoxoid and *A. pyogenes* bacterin (Centurion) given to feedlot cattle has been shown to reduce the prevalence and severity of liver abscesses.[17] However, this vaccine is no longer available commercially. In addition to inclusion of antimicrobial compounds in the feed or vaccination, prudent bunk management to minimize ruminal acidosis is well accepted as a key factor for effective control of liver abscesses. Some of the management recommendations include gradual adaptation to high-grain diets, avoiding either under- or overfeeding, increasing feeding frequency to spread the intake, increasing roughage content of the feed, imposing quality control in mixing feeds, and providing adequate bunk space and fresh clean water.[18]

Sequelae Septic cardiac and pulmonary emboli are also associated with liver abscesses in feedlot and dairy cattle. Occasionally, sudden death has been reported in cattle secondary to rupture of liver abscesses, with septic embolization in the right side of the heart. Generally the condition starts as phlebitis caused by the extension of liver abscesses involving caudal vena cava. The phlebitis leads to thrombus formation anywhere between the liver and right atrium, but most often at the point of entry of caudal vena cava into the diaphragm. The clinical syndrome and the extent of lesions observed depend on the degree of thrombosis and type of organisms involved. The syndrome can range from death caused by rupture of caudal vena cava to various degrees of pulmonary embolism, pneumonia, infarction, endocarditis, hemoptysis, and epistaxis. Collectively, these lesions are categorized under caudal vena cava thrombosis (CVCT) syndrome.[19,20]

Economic Importance Liver abscesses are a major economic liability to the producer, the packer, and ultimately the consumer of beef. Abscesses are the leading cause of liver condemnation in the United States. National Beef Quality Audits (NBQA; 1995-2011) indicate that liver condemnation consistently ranks among the top 10 concerns of the packers.[21] The greatest economic impact of hepatic abscesses is not from the condemnation of liver but from the reduced animal performance. Cattle with abscessed livers have reduced feed intake, reduced weight gain, decreased feed efficiency, and decreased carcass dressing percentage. These effects are evident only in cattle with the most severe abscesses (one or more large abscesses or multiple small abscesses).

Hepatic Abscesses in Horses

Hepatic abscesses occur sporadically in horses and are generally part of the intraabdominal abscess complex. In studies that have evaluated horses with intraabdominal abscesses, 12% (3/25)[22] and 53% (8/15)[23] of horses had abscesses in the liver. Hepatic abscesses in horses are usually associated with septic portal vein thrombosis but may also develop as an extension of the inflammatory process involving the intestinal tract or as sequelae to abdominal surgery.[24] A variety of bacterial species, particularly anaerobes, have been cultured from the pus. The most frequently isolated bacteria include *Streptococcus equi, Escherichia coli, Bacteroides fragilis, Corynebacterium pseudotuberculosis, Fusobacterium necrophorum,* and *Peptostreptococcus* species.[23-25]

Clinically, horses with hepatic abscesses cannot be differentiated from other intraabdominal abscesses. Generally, horses have a history of fever, loss of appetite, signs of colic, depression, and weight loss. Clinicopathologic changes are typical of chronic bacterial infection and include leukocytosis, thrombocytosis, hypoalbuminemia, and decreased A/G ratio.[23-25] The prognosis is generally poor because of failure to respond to antimicrobial treatment. Percutaneous or surgical drainage has been shown to be effective, with high survival rate in humans with hepatic abscesses.

Hepatic Lipidosis‡

Geof W. Smith

Fat Cow Syndrome, Lipid Mobilization Syndrome

Hepatic lipidosis (fat cow syndrome) is a multifactorial condition occurring in dairy cows after parturition. The syndrome is characterized by progressive depression and failure to respond to treatment of other predisposing diseases. It is associated with excessive mobilization of fat to the liver in well-conditioned or overconditioned cows. This mobilization of fat is induced by the negative energy balance and hormonal changes that occur around the time of calving. This negative energy balance in most cases is aggravated by concurrent periparturient diseases that reduce feed intake and increase energy needs.[1-3]

Fat cow syndrome occurs sporadically in dairy cows but more frequently in cows that become overconditioned during late lactation and during the dry period.[2] The overconditioning may be caused by a poor breeding program associated with cows spending prolonged time in the low lactation strings and having excessive weight gain. Mortality can exceed 25%, with even higher rates occurring without intensive treatment and correction of concurrent diseases. Clinical disease in obese cows that enter the dry period can be minimized by carefully controlling their diets to meet National Research Council (NRC) requirements and preventing milk fever.

Clinical Signs The clinical condition occurs in the postparturient period. Most affected cows are either obese or very well conditioned, with a large amount of omental and subcutaneous fat. Presenting signs usually include depression, anorexia, weight loss, and weakness that can lead to recumbency. Most will have nonspecific signs like decreased rumen motility and decreased milk production. Other signs vary and are related to concurrent diseases. The concurrent diseases most frequently seen are metritis, retained fetal membranes, mastitis, parturient paresis, and displaced abomasum.[1] It is important to look for these other diseases; even if mild, they could be significant in these cases and must be treated.

Diagnosis Most laboratory tests are poor indicators of hepatic lipidosis and are of little value in determining disease severity.[4] Liver-derived enzymes are usually elevated above the level in the dry cow but are often within normal ranges. Liver enzymes most consistently

‡Contributions to previous editions by John Maas and Erwin G. Pearson are acknowledged.

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elevated in cases of hepatic lipidosis are ornithine carbamoyl transferase (OCT), total bilirubin, and AST.[5] Bile acid concentrations have not been shown to be significantly increased in most cows with fatty liver.[5] Many cows with hepatic lipidosis have a leukopenia and a degenerative left shift, but this is not specific. As expected, nonesterified fatty acid (NEFA) levels will be increased, and triglycerides and cholesterol will be decreased. Most of the total cholesterol is in lipoproteins. The sulfobromophthalein dye excretion test may be useful prognostically because those with a half-life longer than 9 minutes have a more guarded prognosis.[6]

Several recent studies have examined ultrasound as a tool to detect hepatic lipidosis in cattle. With increasing fat accumulation in the liver, an increased gray level is seen in the ultrasound image, and the liver appears brighter. However this is subjective and is also dependent on the settings of the machine. One study found that the liver increases in size and becomes rounded with increasing severity of lipidosis; however, measuring the thickness of the liver and angle of the ventral margin had limited diagnostic value.[7] Another study used digital analysis of hepatic ultrasound images via a computer-aided ultrasound system and found that imaging findings correlated well with liver triacylglycerol concentrations.[8] Digital analysis of B-mode liver images used a computer program to correct for abdominal wall effects and removal of artifacts. Although not commonly available at this point, the use of ultrasound and computer-aided correction has the potential to help determine the severity of hepatic lipidosis.

Although clinical chemistry and ultrasound may be helpful in diagnosing hepatic lipidosis, a liver biopsy is the gold standard. Liver biopsy may confirm the fatty infiltration of the hepatocytes, but a moderate to high amount of fat is present in the liver of all postparturient, high-producing dairy cows, even those that remain healthy.[9] Fat is usually quantified by histologic methods by determining percentage of hepatocytes containing lipid vacuoles, measuring total hepatic fat on a wet weight basis, or by floating in copper sulfate solutions of various specific gravity (to estimate total fat on a wet-weight basis).[10] Classification schemes characterizing severity of hepatic lipidosis based on percentage of hepatocytes containing fat vacuoles have been presented (e.g., <50%, 50% to 75%, and >75% being equal to mild, moderate, and severe lipidosis, respectively).[4] More recent studies have advocated the use of triacylglycerol analysis on a wet-weight basis to differentiate degrees of hepatic lipidosis.[3] These studies categorized hepatic lipidosis as normal, mild, moderate, and severe by triacylglycerol concentrations of less than 1% (<30 mg/g), 1% to 5% (30 to 50 mg/g), 5% to 10% (50 to 100 mg/g), and greater than 10% (>100 mg/g), respectively.[3] At present, triacylglycerol analysis of hepatic tissue is not a routine procedure in veterinary diagnostic laboratories, so total hepatic fat concentrations remain the gold standard for laboratory diagnosis. Clinically, little correlation exists between the amount of hepatic fat and signs of disease until the fat is more than 34% wet weight, at which point the liver tissue will float in distilled water with a specific gravity of 1.000.

Generalized obesity is noted at necropsy unless the animal has been sick for more than 1 to 2 weeks. Changes in the liver are most striking; it is enlarged, with swollen and rounded edges, is pale yellow in color, and may float in water. Histologically, there is fatty infiltration of the hepatocytes, especially in the centrilobular and intermediate areas. However, these liver tissues are sometimes not much different from those of healthy, high-producing dairy cows in early lactation.

Pathophysiology Storage of excess energy as fat and the periodic mobilization of fat for use as energy by the body is crucial.[2,3] The liver plays a major role in lipid metabolism and must process the absorbed chylomicrons, the volatile fatty acids, and many of the fatty acids and much of the glycerol obtained by mobilization of fat from adipose tissue (Fig. 33-8). The liver of large herbivores has unique functions because much of the dietary energy is absorbed as volatile fatty acids and not glucose. Glucose is still needed (in high amounts in lactating animals) and must be produced by gluconeogenesis, 85% of which takes place in the liver.[11]

Negative energy balance is induced by lactation, fetal growth, exercise, decreased feed consumption, environmental chilling, and diseases (Fig. 33-9). During these periods of negative energy balance and before lactation, blood glucose may drop slightly, the insulin/glucagon ratio drops, and these and other hormones (e.g., catecholamines, growth hormone) activate hormone-sensitive lipases that convert tissue fat to free fatty acids (FFAs) or nonesterified fatty acids (NEFAs) and glycerol (Fig. 33-10). Following a 4-day period of fasting in cattle, plasma insulin concentrations decreased and insulin-stimulated blood glucose reduction was decreased as compared to cows that were not fasted.[12] In this study insulin response was negatively correlated with plasma NEFA and liver triglyceride concentrations suggesting that decreased insulin response may be an important complication of negative energy balance. In the liver the glycerol may be used to produce glucose or may be recombined with FFAs to make triglycerides (TGs). In addition to being recombined with glycerol to make TGs, the fatty acids may be degraded through β-oxidation, and the two carbon fatty acids converted to acetyl coenzyme A (CoA). The acetyl CoA combines with oxaloacetate to enter the tricarboxylic acid (Krebs) cycle for the production of energy. This pathway is in competition with the use of oxaloacetate for gluconeogenesis.[2] If there is not enough oxaloacetate available, the acetyl CoA is converted to ketone bodies, which in high concentrations can reduce feed consumption and perpetuate the negative energy balance.

When the liver is overwhelmed with mobilized NEFAs, greater amounts of TGs are deposited within the hepatocytes. These TGs eventually leave the liver as very low-density lipoproteins (VLDLs), which are plasma-soluble complexes of phospholipid, cholesterol, TG, and apolipoprotein A. Hepatic lipidosis results when the rate of hepatic triglyceride formation exceeds oxidation of fatty acids and the formation and release of VLDLs into the peripheral circulation. A number of factors have been incriminated for the inability of the liver to secrete adequate VLDLs to keep up with the deposition of TGs brought about by FFA mobilization from fat. Ruminants have a poor ability to export excess lipid from the liver as VLDLs. This is particularly true in bovine hepatic lipidosis[13,14] and is theorized to result from a shortage of apolipoprotein A. Hepatic lipidosis can be induced in cows by inhibiting the production of apolipoprotein,[15] and the lowest concentrations of lipoproteins occur in the serum of cows with the most severe hepatic lipidosis.[14] Cows on low-protein diets in the dry period are more likely to develop hepatic lipidosis than those on higher protein diets, regardless of the energy content.[13] Depression in dry-matter intake in the final week before calving will increase the liver TG content after calving in dairy cows.[16] Hepatic lipidosis can be consistently reproduced experimentally in cattle by limit feeding or fasting overconditioned cows immediately after calving.[2] In the past, a lack of phospholipid or its precursor choline has been incriminated but never substantiated. However, in the face of an energy shortage, it seems redundant and a waste of energy to repackage fat and send it back to the tissues, even if the liver is being overwhelmed with fatty acids. Some of the same endocrine hormones that activate hormone-sensitive lipase and inhibit lipogenesis and glycogen synthesis may also inhibit production of VLDLs.

It has also been suggested that subclinical liver damage may inhibit the production of VLDLs, but experimental studies have indicated no significant elevation in liver-specific enzymes before lipid accumulation.[9] Function may eventually be impaired by the accumulation of fat, because fasted cows have a decrease in the surface area of rough endoplasmic reticulum and the number of mitochondria per unit volume.[17] Changes in the liver seem to be functional and not degenerative.[18] Hepatic lipidosis appears to be a reversible condition if the cause is removed and energy balance becomes positive (less negative). In cows fasted and then returned to full feed, all major liver functions returned to normal within 18 days of refeeding, and all lactating dairy cows with postparturient hepatic lipidosis had normal liver fat (<15%) content at 6 months after calving.[17]

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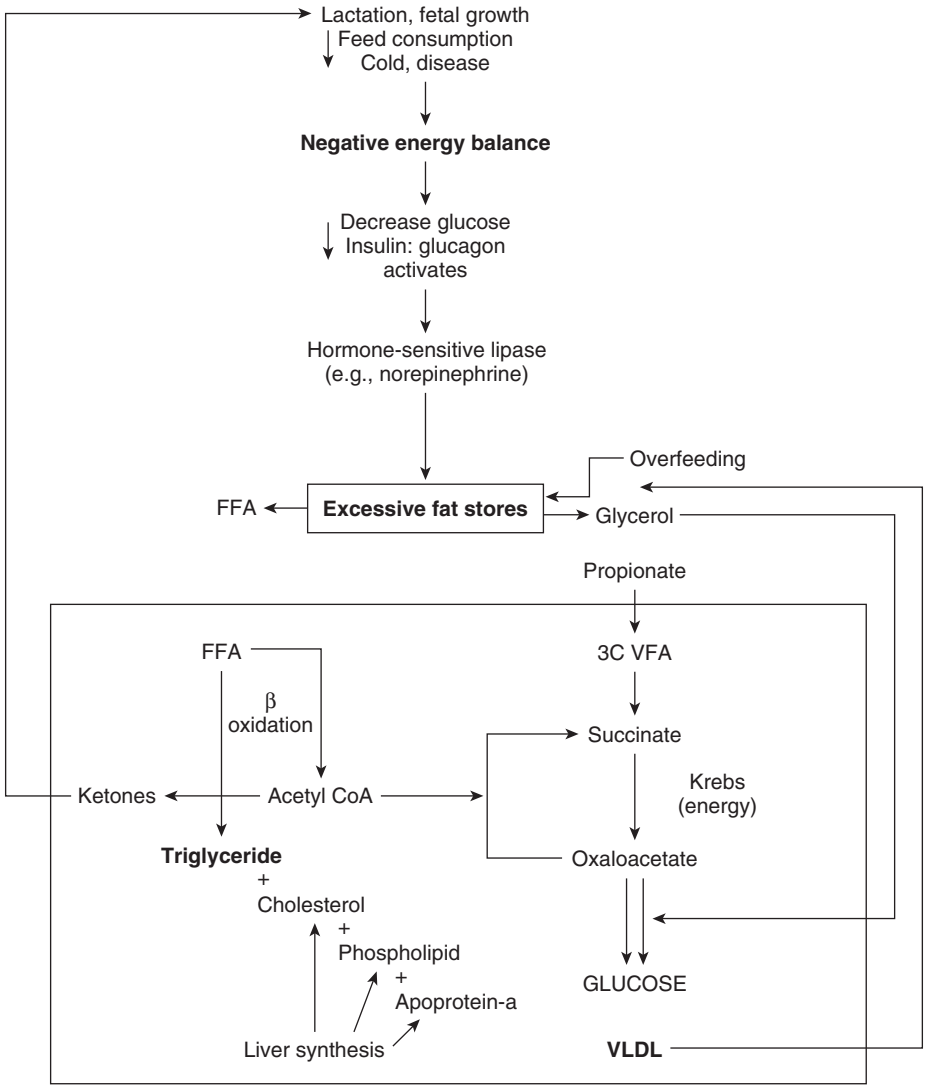


FIG. 33-8 Metabolism of fat in animals with hepatic lipidosis.

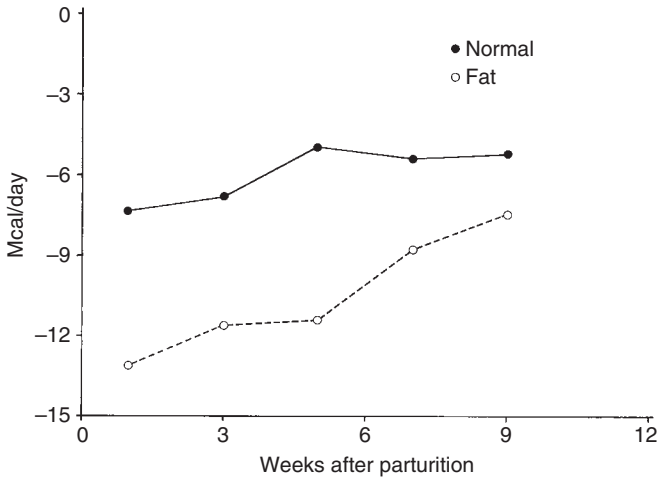


FIG. 33-9 Energy balance (megacalories per day) in normal-condition and obese dairy cows after parturition. *(From Perkins B. 1983. PhD thesis. Cornell University, Ithaca, NY.)*

All high-producing dairy cows have increased amounts of fat (15% to 32% by weight) in the liver before calving and during the first few weeks after parturition.[9,18] These fat accumulations in the liver begin before calving as the animal prepares for lactation, and the blood glucose concentration is actually lower before calving.[19] The amount of fat in the liver depends on the amount available and the extent of negative energy balance. Fatter cows tend to lose weight more rapidly and have more fat accumulation in the liver.[9]

Treatment Treatment of mild to moderate fatty liver closely parallels that of traditional ketosis. With severe hepatic lipidosis, the most important principle of therapy is elimination of negative energy balance and the factors or diseases causing it. Continual IV glucose at a rate of approximately 100 to 200 mg/kg/h may provide continuing energy and induce an insulin/glucagon ratio that will decrease hormone-sensitive lipase mobilization of fatty acids and stimulate production of VLDLs. Insulin itself may be given to alter this ratio directly. In cattle, 200 U of protamine zinc (NPH or Lente) insulin has been given every 12 hours per 1000 pounds of body weight, along with glucose. In cattle not on a continuous drip of glucose, the clinician must use insulin with caution because even low doses can result in profound hypoglycemia. Administration of glucagon at

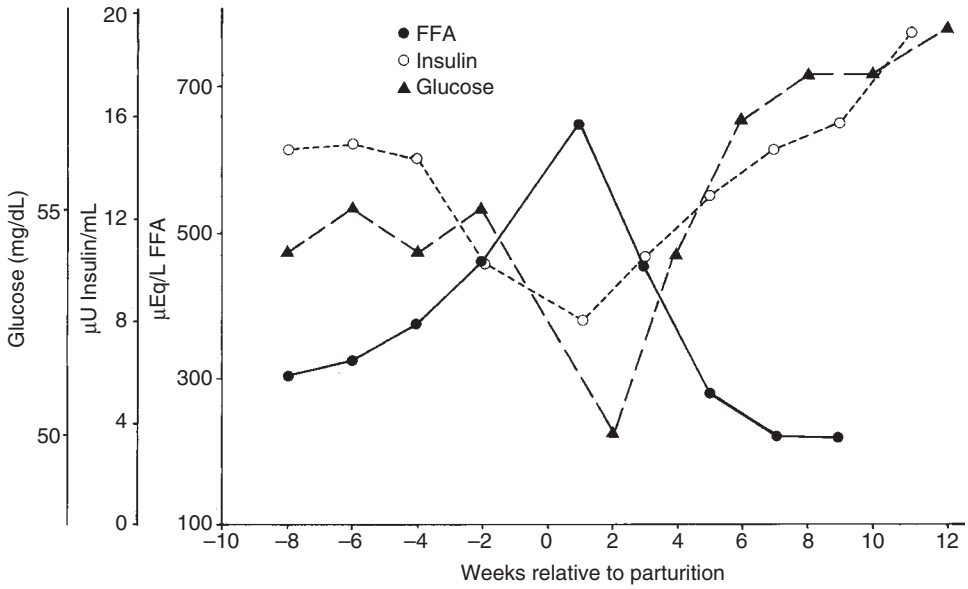


FIG. 33-10 Plasma levels of glucose, insulin, and free fatty acids *(FFA)* in dairy cows before and after parturition. *(From Perkins B. 1983. PhD thesis. Cornell University, Ithaca, NY.)*

doses of 7.5 to 15 mg/day has been shown to increase glucose and insulin concentrations and decrease plasma NEFA and liver triacylglycerol concentrations,[20] but clinical use of glucagon is prohibitively expensive. Cows with severe ketosis are generally treated with glucocorticoid injections (10 to 30 mg of dexamethasone, 2 to 5 mg of flumethasone, or 100 to 200 mg of prednisolone), with glucose precursors such as propylene glycol, glycerol, or other compounds that can be administered orally or parenterally.[3]

Precursors of lipoproteins such as choline, which is a component of phospholipid, have been advocated to increase the rate at which TGs leave the liver as phospholipids (VLDLs), but no controlled studies have proved their efficacy. Choline is degraded in the rumen,[21] but theoretically, choline chloride (25 g in 250 mL of sterile saline) given subcutaneously could have limited efficacy. Choline should *not* be given intravenously because it acts as a neuromuscular blocking agent. Addition of inositol both before and after birth did not reduce the incidence or severity of hepatic lipidosis.[22] Methionine at 40 to 50 g/day has also been used for the same purpose. Nicotinic acid (niacin) fed at 6 to 12 g/head/day may help reduce lipolysis at the tissue level and thus reduce the amount of fat presented to the liver.[23] Treatment of hepatic lipidosis with nicotinic acid is often associated with a rebound of clinical signs, and its use as a preventive measure is recommended.

Despite the treatments listed above, it is imperative to get cows suspected of having fatty liver eating again. Everything possible should be done to encourage dry-matter intake. Appetite can sometimes be enhanced by transfaunating with rumen fluid from a normal cow. This may increase the absorption of volatile fatty acids used for energy and for glucose precursors. Prognosis must be guarded unless the concurrent diseases can be treated successfully and the liver fat mobilized. It is most important to treat the primary disease. Reducing the negative energy balance and treating the hepatic lipidosis must be attacked vigorously.

Prevention Prevention is based on preventing overconditioning during the late lactation period and dry period and treating periparturient diseases in a timely manner. Hepatic lipidosis and associated conditions are most common in dairy cattle. Preventing obesity in cows during late lactation is an important factor in controlling this disease. This process involves a successful breeding program (maintaining a 12- to 13-month calving interval) and closely matching energy in the ration to the level of milk production during late lactation. Once the cow reaches 7 months of pregnancy and the dry period, any dietary restriction below requirements for maintenance and pregnancy are certain to be counterproductive.

Prevention of hepatic lipidosis involves minimizing or eliminating the primary risk factors associated with disease both pre- and postpartum. The primary prepartum risk factors for fatty liver include obesity (body condition score ≥ 4.0), severe feed restriction, feeding excess energy, and long calving interval. Postpartum risk factors include other concurrent diseases, anorexia or fasting, feed restriction, and sudden feed changes.[3] Adequate protein in the dry period is essential.[11,15] It has been shown that cows fed higher-protein diets during the dry period will perform better in the lactation that follows. Feeding good-quality to excellent-quality roughages (hay, silages) to meet most of these requirements is preferred. Additional grain 2 to 4 weeks before parturition is important to acclimate the ruminant to anticipated changes in the rations fed after calving. It must be stressed that high-quality dry cow rations be fed *but not overfed.* Dry-matter consumption should be limited to approximately 2% of body weight per day while meeting requirements. Other factors in the dry cow ration also must be considered to prevent periparturient diseases such as milk fever, displaced abomasum, mastitis, metritis, ketosis, ruminal lactic acidosis, and retained placenta. Rations should be adequately supplemented with cobalt, the precursor of vitamin B_{12} that is a cofactor in the rate-limiting step in conversion of propionate (the primary glucose precursor) to succinyl CoA. Nicotinic acid has been included in the dry cow ration at 6 g/head/day and in the early-lactating cow ration at 12 g/head/day to aid in the prevention of ketosis, which is a major risk factor for the development of hepatic lipidosis. The use of monensin in the dry cow ration and the early-lactation ration shows promise to aid in preventing ketosis and thus may be of some benefit in preventing hepatic lipidosis.[24,25] Other approaches such as sodium borate or administration of glucose precursors in the dry period have also been attempted.[3]

Immediately and aggressively treating cows (particularly obese cows) for other diseases that occur after calving is important in preventing fatty liver. This includes both infectious diseases (e.g., mastitis, metritis) and metabolic diseases like hypocalcemia. It is important to limit stress on fresh cows and provide adequate bunk space, good ventilation, and high-quality feed. Anything possible to encourage dry-matter intake is important. Several different therapies have been promoted to improve the metabolic state of cows during late gestation by supplying an extra source of glucose and decreasing the mobilization of NEFAs from fat. For example, subcutaneous injections of glucagon beginning 2 weeks prior to calving increased

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glucose and insulin concentrations and decreased plasma NEFA levels in a model of hepatic lipidosis.[26] Slow-release doses of insulin (0.14 IU/kg) have also shown some efficacy in preventing triacylglycerol accumulation in the liver, but higher doses (0.29 IU/kg) can result in profound hypoglycemia.[27] Growth hormone had no beneficial effect.[28]

Protein-Energy Malnutrition/Pregnancy Toxemia of Beef Cows

Protein-energy malnutrition (PEM) and pregnancy toxemia of beef cows are conditions of pregnant beef cattle on marginal diets, usually occurring in the winter and characterized by weight loss, weakness, depression, and sometimes inability to rise. The condition is the result of the negative energy balance caused by decreased quality and quantity of feed when caloric requirements are increased by fetal development and cold weather. Growing, pregnant heifers are especially susceptible because energy requirements for growth are superimposed on the other caloric requirements. A number of other factors, such as unpalatable feed, snow cover, and diseases, may reduce caloric intake. Fatty infiltration of hepatocytes occurs transiently in early PEM, and at necropsy the liver is smaller than normal.

Animals are usually thin and have a long hair coat. In some cases they are down and unable to rise but are still alert. The body temperature may be normal or subnormal. Occasionally the cows also develop diarrhea. Most animals die 7 to 14 days after becoming recumbent.[29] Differential diagnosis includes Johne's disease, lymphosarcoma, parasitism, chronic pulmonary disease, other deficiencies, and debilitating diseases.

Diagnosis Diagnosis is usually based on demonstrating decreased caloric intake and ruling out other chronic diseases that could cause debility. Laboratory tests support but do not rule out the disease. Total serum calcium may be decreased. Packed cell volume also may be decreased, and serum insulin levels may be reduced. Ketonuria is not typical in PEM. At necropsy, muscle mass usually is decreased. Serous (brown) atrophy of fat is often present, especially in the coronary groove, bone marrow, and perirenal areas. Lesions of concurrent disease also may be found if PEM is acute, and a fatty yellow liver may be noted.

Treatment Treatment is often unrewarding. Efforts to reverse an advanced catabolic state may fail. A 454-kg cow requires 13 Mcal of metabolizable energy daily, or approximately 6.5 L of 50% glucose solution by continuous drip. Alfalfa pellet gruels are helpful if force-fed, and approximately 11 kg/day of alfalfa is recommended. Propylene glycol (150 to 200 mL) orally twice daily can be helpful as a glucose precursor. Treatments include IV fluids, improving the energy balance, and treating any concurrent disease.

Prevention Nutrient requirements increase greatly for beef cattle during the third trimester of pregnancy. As forage quality (digestibility) decreases, the time feed material stays in the rumen increases (increased rumen turnover time). Therefore, as quality decreases, the maximum dry-matter intake (DMI) decreases, which greatly decreases the maximum nutrient (energy) intake. This compounding effect of poor-quality forage on maximum intake is particularly important for preventing hepatic lipidosis and the accompanying protein-calorie malnutrition (PCM) of pregnant beef cattle in the winter. The approximate maximum DMI of forage of poor quality (oat straw, corn stover), medium quality (meadow grass hay), and excellent quality (alfalfa hay [25% crude fiber], corn silage) is 1% to 1.5%, 2%, and 2.5%, respectively. Environmental temperature can increase energy needs for beef cattle on pasture or range; as the temperature falls from 20° C (68° F) to 10° C (50° F), roughly 10% more energy is necessary for maintenance, and at freezing temperatures, 0° C (32° F), 20% additional energy is required. The key to preventing PEM in pregnant beef cattle is adequate body condition (scores 5 to 7) entering the third trimester and availability of good-quality to excellent-quality forage in adequate amounts.

Pregnancy Toxemia in Ewes and Does

Pregnancy toxemia, also known as *ketosis* or *twin-lamb disease,* is a condition occurring in ewes and does during the last 2 to 4 weeks of gestation. It is characterized by anorexia, weakness, and depression. Nearly 80% of the fetal growth occurs in the last 6 weeks of gestation, which can result in a negative energy balance occurring from the increased energy demands of rapid fetal growth in late gestation and insufficient feed intake. The incidence of pregnancy toxemia is greater in ewes with more than one fetus, during the last 2 to 4 weeks of gestation, and in does with three or more fetuses.[30] Poor-quality feed, cold weather, lack of exercise, and stress of movement also may increase the incidence. Many ewes are overly fat initially. Does seem to be more resistant to pregnancy toxemia than ewes, in that three or more fetuses are usually required to produce the condition.

Animals with pregnancy toxemia are usually separated from the rest of the flock or herd. They have a poor appetite, and many appear blind. They eventually become more depressed and recumbent. Neurologic signs such as tremors, star-gazing, incoordination, circling, and grinding the teeth may precede terminal depression. Differential diagnosis includes other periparturient diseases, such as mastitis and hypocalcemia, as well as polioencephalomalacia, enterotoxemia type D, and toxicoses.

Diagnosis Ketonuria is usually present and detected before ketonemia. Hypoglycemia is not a consistent finding but is sometimes present. The ewes and does often are generally acidotic and may have lowered serum calcium and potassium levels.[31] Blood urea nitrogen (BUN) and creatine levels are elevated terminally in some cases. Fatty acid concentrations in the plasma are usually elevated above 500 μEq/L. Serum β-hydroxybutyrate concentrations are elevated (>1 mmol/L).[32] A nonspecific but marked neutrophilia may be found in some affected animals and is particularly dramatic in does, sometimes reaching 35,000 neutrophils/μL.

Treatment Treatment of pregnancy toxemia is based on two principles: (1) administering exogenous energy sources (i.e., glucose) and (2) removing the factors increasing the energy demand on the animal (i.e., fetuses). Mortality is high unless treatment is started early and the fetuses are removed—the most important step—either by inducing parturition or by cesarean section. Parturition can be induced in ewes with 15 to 20 mg of dexamethasone; in does the dose is either 10 mg of dexamethasone or 10 μg of prostaglandin $F_{2\alpha}$.[30,33] A cesarean section may be performed if the animal's value warrants it and there does not seem to be enough time to induce parturition. Besides removing the fetuses, the ketotic condition should be treated with IV glucose (250 to 500 mL of 10% to 20% glucose as an IV bolus followed by a slow IV drip of 5% to 10% glucose). Acidosis and hypocalcemia must be corrected if present. Administration of oral propylene glycol as a glucose precursor has also been advocated. Although recommended doses vary, an initial treatment of 2 doses (150 to 200 mL) given at a 12-hour interval followed by 60 mL per dose thereafter for 3 to 6 additional days appears to work well.[33] Giving recombinant bovine somatotropin at a dose of 0.15 mg/kg of body weight also has shown some benefit.[34] The energy intake must be increased. If the ewe is down and unable to stand, removal of the fetuses should be performed by cesarian section as soon as possible. In such cases the prognosis is often poor, so euthanasia of the ewe or doe must be considered. Immediately after parturition or cesarian section, the animal should be started on broad-spectrum antibiotics along with flunixin to prevent metritis.[33]

Prevention Preventing pregnancy toxemia and the associated severe hepatic lipidosis in ewes and does requires measures similar

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to those outlined for PCM in beef cattle. Both overconditioned and thin ewes and does in the third trimester of pregnancy are at increased risk. Because of the common occurrence of twins and triplets, nutrient requirements for pregnant ewes greatly accelerate during this period. Good-quality to excellent-quality forage for feeding sheep is very important. An additional tool for diagnosing underfeeding in ewes is measurement of plasma β-hydroxybutyrate (BHB). This test greatly facilitates assessment of nutritional inadequacy in pregnant ewes. Plasma BHB concentrations of 0.8 mmol/L or higher are diagnostic of the need for increased energy consumption by pregnant ewes. Does have been shown to have a significant decrease in blood pH, bicarbonate concentration, and base excess values well in advance of the clinical signs associated with pregnancy toxemia.[31] Therefore these parameters could also be early indicators of disease in pregnant sheep or goats.

Hyperlipemia/Hypertriglyceridemia in Ponies

Hyperlipemia is a life-threatening condition that occurs in horses, ponies, and occasionally in donkeys.[35-37] It is characterized by a fatty liver and serum that is cloudy with accumulation of lipids. TGs are usually much higher than 500 mg/dL.[35] The condition is caused by decreased caloric intake, which causes fat mobilization and fat accumulation in the liver and accumulation in the plasma. The decreased food intake may be secondary to other diseases. Suggested predisposing factors include hypophagia, pregnancy, or lactation, often in obese ponies, American Miniature horses, or donkeys.[36-38] The incidence of hyperlipemia is greater in ponies than in horses. It is seen more often in the winter, especially from February to May in animals receiving poor feed. Pregnant animals and those that are lactating are affected more frequently.

Equine hyperlipemia is characterized by production of an abnormal very low-density lipoprotein (VLDL) fraction ($VLDL_1$) that has a reduced content of apolipoprotein B-100 and an increased content of apolipoprotein B-48.[39] The substitution of B-48 for B-100 is thought to allow greater TG content because B-48 is the apolipoprotein of importance in chylomicrons. The activities of lipoprotein lipase and hepatic lipase, the enzymes responsible for VLDL catabolism, were increased in hyperlipemic ponies.[39] It was concluded that overproduction of VLDL is the cause of hyperlipemia, possibly complicated by defective catabolism.

Hyperlipidemia is a mild condition of ponies and horses characterized by mildly elevated TG concentrations (>500 mg/dL), clear plasma, and no evidence of hepatic dysfunction.[35] An increase in caloric intake is usually sufficient to reverse the condition. The more severe condition, hyperlipemia, is discussed further.

Clinical Signs The clinical signs of hyperlipemia are nonspecific. Ponies usually are anorexic, depressed, weak, and uncoordinated. Diarrhea, colitis, and abdominal pain are frequently seen in presenting cases.[40]

Diagnosis Diagnosis is based on examination of the blood and plasma to detect the white to yellow opacity caused by the presence of lipids. Bilirubin usually is elevated, as in most horses that are fasted. TGs are increased to above 500 mg/dL in hyperlipemia, and fatty acids are also increased. Bromosulfophthalein clearances are delayed, and terminally a large base deficit may be caused by metabolic acidosis.[35]

Postmortem examination reveals fatty infiltration of the liver and kidneys, which are pale and swollen and have a greasy texture. In ponies the liver is sometimes ruptured, resulting in intraabdominal hemorrhage and death. Renal lesions may be seen histologically. There may be a primary disease that produces anorexia and secondarily has resulted in hyperlipemia.

Treatment It is most important to treat any primary disease to alleviate the cause of anorexia and correct the negative energy balance. Nutritional support is critical, either in the form of dextrose-supplemented fluids or partial parenteral nutrition. Heparin is also recommended in some cases and has been shown to decrease triglyceride concentrations in affected horses.[40] Regular insulin (0.2 IU/kg) every 3 to 6 hours can be used initially for severely lipemic animals; however, this is usually discontinued within 24 hours and a longer-acting product used for maintenance. Protamine zinc insulin (PZI) has been used at an intramuscular (IM) dose of 30 IU twice daily with 100 g of PO glucose for a 200-kg pony. This is continued on odd days; on even days, IM injections of 15 IU of PZI are given twice daily.[35] Ultralente insulin can be given at a dose of 0.4 IU/kg SC q24h.[40] A slow IV drip of glucose for several days or until lipemia clears may be indicated. Heparin (100 to 250 IU/kg twice daily) has been used to alter the lipoprotein lipase activity and inhibit hormone-sensitive lipase of adipose tissue, but it may alter coagulation enough to cause hemorrhage.

The presence of hyperlipidemia is readily detected and easily solved by increasing caloric intake. Although therapy of hyperlipemic ponies and horses is often unrewarding, the diagnosis is relatively straightforward, and prevention depends on providing adequate feed of good quality.

Congenital Hyperbilirubinemia

Geof W. Smith

Gilbert Syndrome

Gilbert syndrome is an unconjugated hyperbilirubinemia in the presence of normal erythrocyte lifespan. It occurs occasionally in humans and has been described in Southdown sheep.[1] Gilbert syndrome involves a failure of unconjugated bilirubin to cross the liver cell membrane and be conjugated. This is most likely caused by a defect in carrier proteins or the conjugating enzyme.[2] Hepatic bilirubin clearance is about 30% of normal when tested with a loading dose of radiolabeled bilirubin.[3]

Affected Southdown sheep may show icterus or at least elevated plasma bilirubin levels, both conjugated and unconjugated. Affected sheep also cannot excrete bromsulphalein (BSP) into the bile. No histopathologic lesions are present, other than some pigment in the hepatocytes. The condition is inherited as an autosomal dominant trait in humans.[2] The bile acid levels are normal in humans, but one sheep exhibited defects in hepatic bile acid clearance.[4]

Dubin-Johnson Syndrome

Dubin-Johnson syndrome is a failure of conjugated bilirubin to enter the bile canaliculi. This has been diagnosed sporadically in humans and in Corriedale sheep.[5] There may be an impairment not only in bilirubin but also in excretion of other conjugated organic anions. Sheep affected by this syndrome may be jaundiced or have hyperbilirubinemia. Both conjugated and unconjugated bilirubin are increased, and BSP clearance is delayed. Bile acids are reported to be normal in humans, but delayed clearance was reported in three Corriedale sheep.[4] Histologically, the hepatocytes contain a black, melanin-like pigment.[5]

Persistent Hyperbilirubinemia in Thoroughbreds

A persistent hyperbilirubinemia has been reported in a Thoroughbred racehorse that had no evidence of liver damage, cholestasis, or hemolysis and was not fasting.[6] The horse was persistently icteric and had serum total bilirubin concentrations of 8.7 to 9.4 mg/dL; 90% or more of the plasma bilirubin was the unconjugated form. Serum bile acid concentration, along with the liver enzymes GGT, AST, and IDH (SDH), were within normal limits. The horse acted clinically normal, and the plasma fatty acid concentration was also within normal

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limits. The condition was similar to Crigler-Najjar type II syndrome in humans, which involves a deficiency in bilirubin-uridine diphosphate glucuronyltransferase needed to conjugate bilirubin, but this was not verified.

Miscellaneous Liver Diseases

Geof W. Smith

Rift Valley Fever

Rift Valley fever, also known as *enzootic hepatitis,* is an acute febrile arthropod-borne disease of sheep, goats, cattle, and humans present in most countries of sub-Saharan Africa. With the current threat of bioterrorism, it could appear in other parts of the world.[1,2] Rift Valley fever is caused by a virus of the genus *Phlebovirus.* More than 20 species of mosquitoes have been implicated as possible vectors for the virus, including some North American mosquitoes that are competent laboratory vectors.[2] The disease causes abortion in pregnant females and a febrile condition with rapid death in lambs, kids, and calves. The mortality rate in young animals approaches 100% but it is much less (20% to 30%) in older animals.[2] Clinical signs may include fever, anorexia, weakness, salivation, diarrhea, and sometimes abdominal pain, and almost all pregnant animals will abort. The primary gross lesion is hepatomegaly and hemorrhage. Histologically, a focal hepatic necrosis is identified, and eosinophilic intranuclear inclusion bodies are present. Confirmation of the diagnosis is made in the laboratory by virus isolation or immune tests. If the disease is suspected, state and federal regulatory veterinarians should be contacted.

Telangiectasia

Hepatic telangiectasia, commonly known as *sawdust livers* in packing houses, is a focal degeneration in liver lobular circulation characterized by red-brown foci 1 to 5 mm in diameter. These lesions account for more than 10% of the bovine liver condemnations but do not result in any clinical signs.[3] Microscopically, hepatocytes are distorted and sinusoids congested.[4] Hypotheses proposed to explain the pathogenesis of the lesions include necrotizing hepatitis, ischemia induced by emboli or other vascular pathologies,[5] dilation of Disse spaces, reduced density of the reticulin framework, vitamin E–selenium deficiency, alteration of the sinusoidal barrier, and immune-mediated disease.[3] Some human pathogens have been isolated from these livers as well as normal livers, but livers are condemned on the basis of aesthetics according to current U.S. Department of Agriculture (USDA) regulations.[3]

Ischemia, Hypoxia, and Congestion

Ischemia and hypoxia can lead to death of hepatocytes, but less severe insults cause fatty infiltration because lipoprotein synthesis depends on oxidative metabolism. This damage is more apparent in the centrilobular areas, which are the last to receive blood and oxygen. Chronic passive congestion causes the grossly visible "nutmeg liver," caused by distention of the sinusoids and central veins with blood. The liver may be enlarged in these cases, but other signs related to the liver are not usually present. More significant findings will be detected in the cardiovascular system.

Fetal Liver Damage

The liver of the fetus may be damaged by infectious and toxic agents, but the result is usually abortion or birth of a weak neonate with signs related to other systems. The lesions in the liver may be diagnostic of the disease. Equine herpesvirus infection of the fetus causes hepatocyte necrosis, with acidophilic intranuclear inclusion bodies in more than 50% of the hepatocytes. Aborted fetuses of cattle with infectious bovine rhinotracheitis may have some focal necrosis of the liver, but this is not enough to be diagnostic.

Failure of Drug Metabolism and Excretion

Jennifer L. Davis

Hepatic disease can affect drug metabolism in several ways. Ascites, if present, can alter drug disposition, and drug dosages should be adjusted based on lean body weight, taking into account the amount of fluid present.[1] Also, since the liver is the primary organ involved in the metabolism of exogenously administered substances and represents an important method for excretion of drugs via the bile, liver disease can affect drug metabolism and clearance.

Factors influencing hepatic drug metabolism and clearance include hepatic blood flow, hepatic metabolism, and protein binding. Drugs are often classified as having high hepatic extraction ratios (flow-limited drugs) or low hepatic extraction ratios (capacity-limited drugs). Flow-limited drugs are quickly and efficiently extracted by the liver, and their rate of elimination is limited only by hepatic blood flow. Chronic liver disease with decreased parenchymal blood flow or hepatic shunts can decrease blood flow in the liver and greatly compromise clearance of flow-limited drugs like morphine, verapamil, and lidocaine.[1] These drugs undergo a high first-pass metabolism following oral administration and, as such, are usually given at high oral doses. The dosage of these drugs may need to be decreased by up to 50% in patients with liver disease, because bioavailability will be greatly increased and elimination decreased, possibly resulting in toxic levels of the drug.[1,2] The opposite may be true for drugs that require hepatic activation, and thus subtherapeutic levels may be present.[3]

Capacity-limited drugs are slowly extracted by the liver, and their elimination is independent of blood flow but highly dependent on hepatocellular uptake and metabolism. The effect of liver disease on drug metabolism in these cases is more variable, and drug clearance can be increased, as with atenolol, or decreased, as with diazepam and chloramphenicol.[1,2] The majority of phase I (oxidation-reduction) reactions and phase II (glucuronidation) reactions take place in the hepatocytes, and diseases that result in hepatocellular destruction can reduce the ability of the liver to metabolize drugs. The purpose of these reactions is to make compounds more water-soluble and prepare them for excretion via the kidney. Clearance of drugs eliminated by phase I reactions can be significantly decreased with hepatic disease, whereas phase II reactions are often not affected unless severe disease is present or certain types of glucuronidation are needed.[4,5] For example, ester glucuronidation will be decreased in patients with cirrhosis of the liver and have a lower clearance rate compared to drugs metabolized by ether glucuronidation.[4]

Humans with intrahepatic cholestasis showed a decreased activity of phase I cytochrome P450 enzymes and impaired microsomal drug metabolism in vitro, and this was well correlated with serum concentrations of total bilirubin and bile acids.[6] Making direct correlations between human drug metabolism and veterinary species is difficult, however. Recent work shows a large interspecies variation in the types and activity of hepatic metabolizing enzyme among humans, horses, and cattle.[7,8] Further classification of the equine and bovine P450 enzymes and their roles in drug metabolism are needed.

Cholestatic diseases have been shown to decrease biliary excretion of a number of drugs in both animal models of disease and human patients with naturally occurring biliary obstruction. Increased plasma levels, prolonged mean residence times, increased area under the concentration-time curve, and decreased total body clearance have all been demonstrated.[9-11] In horses administered enrofloxacin intravenously, those animals with GGT activity greater than 200 U/L had a lower clearance and higher area under the curve than horses with GGT activity less than 200 U/L.[12] Renal clearance of some drugs may be increased as a compensatory response for the impaired biliary excretion, as is the case with cefpiramide in cholestatic human patients.[13] This decreased biliary clearance can be

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used to an advantage in certain instances when treating biliary tract infections in order to attain higher concentrations of the drug in the bile ducts, as long as the drug has a large therapeutic index.[13]

A deficiency in hepatic drug metabolism capacity may impair drug metabolism and elimination in young animals. This has been demonstrated in foals administered chloramphenicol, which is extensively metabolized in the liver via glucuronic acid conjugation and primarily excreted through the biliary system into the feces. Clearance was decreased and half-life prolonged in animals less than 1 week of age.[14] Nonsteroidal antiinflammatory drugs (NSAIDs) also show impaired metabolism in neonatal foals. Phenylbutazone, ketoprofen, and flunixin meglumine all have prolonged terminal half-lives over the first few weeks of life.[15-17] Neonatal foals also have a low capacity to metabolize enrofloxacin to ciprofloxacin, whereas in adult horses ciprofloxacin concentrations are about 17% of the enrofloxacin concentrations.[18] Drug metabolism also differs in neonatal calves and sheep, which may result in prolonged withdrawal times necessary for veal calves and lambs. Studies have shown that hepatic metabolic enzymes are similar to adult levels in sheep and calves by 7 days of age.[19,20] At this point, no quantitative research has been performed that specifically examines the development of metabolic pathways in the neonatal foal. It is likely these are decreased in the early stages but rapidly develop and are within a range similar to adult horses within the first 1 to 4 weeks of life, as is seen in other veterinary species.

Neoplasia of the Liver

Geof W. Smith

Primary neoplasia of the liver is uncommon in large domestic species. Only 0.011% of slaughterhouse animals seen in one study had liver tumors.[1] Metastatic tumors such as lymphoma are more common (Fig. 33-11), but the clinical signs of these are more likely to reflect changes at the primary site. Metastasis of lymphosarcoma in cattle is most common, but signs produced by growth in other organs (e.g., lymph nodes, abomasum, heart, uterus, spinal cord) are more predominant. In the horse, lymphosarcomas and carcinomas have metastasized from the digestive tract.[2]

Horses

Although uncommon, a number of different primary hepatic neoplasias have been reported in horses.[3,4] The nomenclature seems inconsistent throughout the years of reporting, and the signs are usually more consistent with neoplasia in general than with hepatic failure. Weight loss, weakness, anorexia, lethargy, and occasionally colic may be seen in these animals. Serum concentrations of liver-derived enzymes are elevated in many cases. The tumor can often be located by ultrasonography, but the definitive diagnosis of the type of tumor is based on histopathologic examination of biopsy tissue.

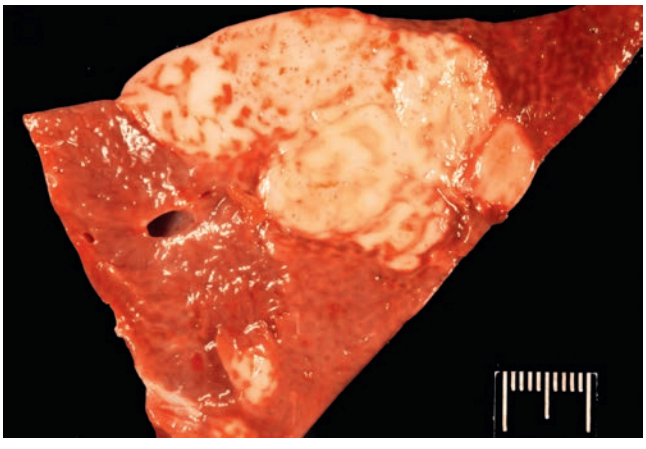


FIG. 33-11 Lymphoma in the liver of a horse. *(Photo courtesy Luke Borst, North Carolina State University.)*

Hepatoblastoma has been reported in foals, young horses, and an equine fetus.[4,5] Young horses present with weight loss or failure to grow, lethargy, anorexia, and possibly icterus. Serum concentrations of several hepatic enzymes are increased. Ultrasonography reveals hepatomegaly and a heterogeneous appearance of the hepatic parenchyma. Erythrocytosis is seen in some cases because of a paraneoplastic syndrome and increased production of erythropoietin.

Hepatocellular carcinoma is seen in both old and young horses. These horses lose weight and are listless. Serum concentrations of LDH, GGT, and AST are often elevated. Erythrocytosis with a normal concentration of serum protein is seen in most cases as a result of paraneoplastic syndrome with elevated erythropoietin.[3,4,6]

Cholangiocarcinoma or cholangiocellular carcinoma arises from the intrahepatic bile duct epithelium and appears to be a disease of older horses.[4,7] Lethargy, fever, abdominal pain, anorexia, and ventral edema have been reported with this tumor. Some of these animals have anemia rather than the erythrocytosis reported with hepatocellular tumors. GGT and ALP concentrations may be elevated, but IDH (SDH) comes from hepatocytes and is usually within normal range.

Cattle

In addition to the lymphosarcomas, primary hepatocellular carcinomas have been described in cattle.[8] The most common presenting clinical signs are anorexia and weight loss of weeks to months in duration.[9] Liver-derived enzymes are generally elevated, and polycythemia (erythrocytosis) is a common laboratory finding in these cases.[9,10] Ultrasound of the liver may be helpful in diagnosing hepatic tumors in cattle.[9]

Hemochromatosis

Hemochromatosis is a disorder caused by deposition of hemosiderin in the parenchymal cells, resulting in tissue damage and dysfunction of the liver and other tissue. It is most frequently seen in humans and mynah birds, but hemochromatosis has been described as a new disease of Salers cattle[11] and has been reported in three horses.[12] In humans the types include idiopathic hemochromatosis, an autosomal recessive familial condition associated with increased iron stores, cirrhosis, and saturation of the iron transport capacity.[13] Both horses and cattle show increased iron deposits in the liver; histopathology of liver biopsy specimens reveals brown pigment that stains for iron in the hepatocytes as well as Kupffer cells. An increased concentration of iron can be measured in the liver, and there is fibrosis and elevated liver-derived enzymes.

In Salers cattle the condition appears to be a homozygous recessive condition more like the human familial type. There is an inappropriate absorption of iron by the GI tract, with subsequent hepatic storage (iron overload) and eventual loss of hepatic function. It has been reproduced by experimental breeding in Salers cattle.[14] The primary clinical signs in cattle are decreased weight gains, poor body condition, dull hair coat, loss of incisor teeth, and sometimes diarrhea. Serum concentrations of liver enzymes are elevated, and there is marked hepatic fibrosis, in addition to the hemosiderin deposits in the liver. Total serum iron, total iron-binding capacity (TIBC), and saturation of transferrin (>60%) are increased, similar to the familial disease in humans. Liver iron concentration will be greater than 5000 μg/g (ppm) on a wet basis (normal herdmates of affected cattle, 84 to 100 ppm).

Horses with hemochromatosis present with evidence of liver disease. Serum concentrations of the liver enzymes ALP, GGT, and AST are elevated, and serum total bile acids are greater than 40 μM/L. In the cases reported, total serum iron was not elevated, and unlike the idiopathic human condition or the cattle cases, there was no saturation of the iron-binding capacity. Total liver iron has been as high as 6700 ppm (normal, 100 to 300 ppm).[12]

Hemochromatosis should be suspected in animals with emaciation or elevated liver enzymes and in Salers cattle with greater than

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60% saturation of transferrin. It can be confirmed by histopathologic examination of the liver, with excessive iron accumulation in hepatocytes. Clinicians should differentiate hemochromatosis from hemosiderosis, in which iron accumulates in the reticuloendothelial system and not hepatocytes, and which can be caused by hemolysis and other conditions.

In humans, hemochromatosis is treated by reducing the iron stores through phlebotomies and blood removal. The one horse on which this was tried had advanced disease with severe cirrhosis, and it succumbed a few days after the blood removal. Removal of 160 L of blood over 12 months failed to reduce liver iron concentration in one heifer[11] but produced some improvement in other calves.[14] Deferoxamine is given to some human patients to induce a negative iron balance and reduce the rate at which iron accumulates.

Gallbladder and Biliary Tract Disease

Jennifer L. Davis

Biliary tract disease in large animal medicine is rare and results from both intrahepatic and extrahepatic causes. Intrahepatic causes of cholestasis include cholangitis, cholecystitis, choledocholithiasis, and presence of a foreign body. Extrahepatic causes include abscess formation, obstructive or inflammatory intestinal disease, and neoplasia.

Choledocholithiasis, Cholelithiasis, and Hepatolithiasis[§]

By definition, *cholelithiasis* describes the presence of biliary calculi in either the bile ducts or gallbladder, whereas *choledocholithiasis* describes stones found in the common bile duct. *Hepatolithiasis* indicates the presence of calculi in the intrahepatic bile ducts above the right and left hepatic ducts and is a variation of cholelithiasis. These conditions have been described in horses, cattle, sheep, and pigs, but they do not seem to be recognized as a clinical problem in sheep, and rarely in cattle.[1-15] Choledocholithiasis is the most common cause of biliary obstruction in large animals and occurs more frequently in horses.[1-9]

Biliary stone formation begins with precipitation or aggregation of normally soluble components of bile. Other mechanisms involved in the pathogenesis include ascariasis, ascending biliary infection or inflammation, biliary stasis, changes in bile composition, and presence of a foreign body.[14] Several pathogenic bacteria *(Salmonella* spp., *E. coli, Aeromonas* spp., *Citrobacter* spp., group D *Streptococcus* spp., *Clostridium perfringens)* have been cultured from the bile ducts of horses and cows with cholelithiasis.[2,6,9,16] Whether these bacteria were the cause or the result of the stone formation remains unclear. In most reports the chemical analysis has shown that choleliths have a mixed composition, containing bilirubin, bile pigments, cholesterol esters, esters of cholic and carboxylic acid, calcium phosphate, and sodium taurodeoxycholate.[6,8,9] In one study, 80% of the choleliths contained less than 10% cholesterol.[9]

Cholelithiasis should be suspected in horses when a triad of clinical signs exists: recurrent abdominal pain, intermittent pyrexia, and icterus. Hyperammonemic hepatic encephalopathy, photosensitization, and weight loss are other, less common features of cholelithiasis.[3,5,6,14,16] A subclinical presentation due to partial obstruction of the biliary tree may be recognized only on postmortem examination.[11] A large cholelith was the cause of duodenal obstruction in a horse presented for colic.[12]

Elevations in the serum activity of ALP, AST, GGT, IDH (SDH), and total bilirubin are associated with cholelithiasis.[3,6,9,14,16] The rise in total bilirubin is due to an elevation in both direct and indirect bilirubin. In the horse, cholestasis should be suspected if more than 25% to 30% of the total bilirubin is the direct type.[1] Serum bile acid concentrations also increase when bile flow is obstructed. Other laboratory abnormalities that may be seen include hyperammonemia, increased urine bilirubin, and prolonged partial thromboplastin and thrombin times.[5,6,9] The most common alterations in the leukogram include a neutrophilic leukocytosis. Elevations in globulin and fibrinogen may also occur.[5]

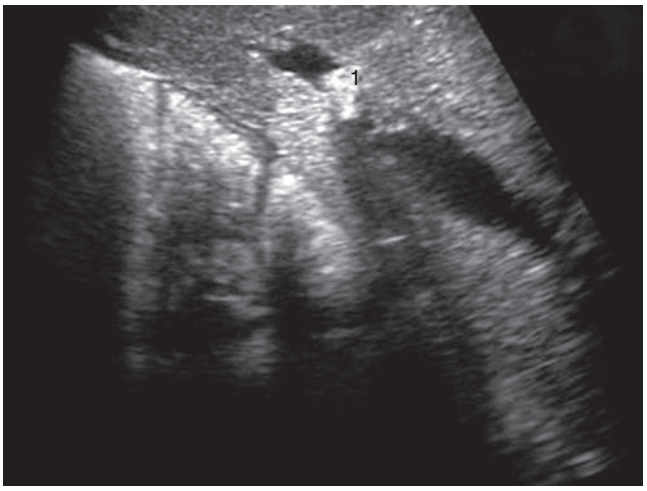


FIG. 33-12 Ultrasound image of a cholelith taken from the right side of a horse. Note the hyperechoic stone *(1)* visible inside of a distended bile duct. Hyperechoic parenchyma is also noted beneath the stone, which may represent hepatic fibrosis.

Ultrasound examination of the liver is a safe, noninvasive tool for diagnosing cholelithiasis. Hepatomegaly and bile duct dilation are seen in horses with biliary calculi. The echogenicity of the hepatic parenchyma is increased compared with that of normal horses and may approach that of the spleen. The bile ducts are thick and distended. The *parallel channel sign* (dilation of interhepatic biliary radicals adjacent to the portal vein) may also be seen. Several choleliths are generally seen, but a single stone may be present (Fig. 33-12). Choleliths may be hyperechoic, casting acoustic shadows, or they may be sonolucent. Choleliths are most likely to be visualized in the cranioventral part of the right hepatic lobe, especially in the sixth to eighth intercostal spaces. Cholelithiasis can accurately be diagnosed by ultrasound in at least 75% of horses if an adequate scanning image of the liver is obtained and bile duct dilation and choleliths are visualized.[8]

The differential diagnosis for a horse with the clinical signs associated with cholelithiasis include other causes of liver disease and mild recurrent abdominal discomfort, including verminous arteritis, mesenteric abscesses, sand enteropathy, enterolithiasis, abdominal neoplasia, and urolithiasis.[3]

Hepatomegaly is usually noted at necropsy, although a shrunken liver may be observed. The liver is firmer than normal, has a consistent texture, and varies in color from red to green-brown. The hepatic ducts and common bile duct are generally dilated and may contain the calculi (Fig. 33-13). Histologically, periportal fibrosis is a common finding. Bile duct stasis and hyperplasia are usually noted; suppurative cholangitis is less common.[9,14,16]

Treatment of cholelithiasis initially includes broad-spectrum IV antibiotics (penicillin plus gentamicin or enrofloxacin) and oral metronidazole. This is followed by long-term oral antibiotics, based on culture and sensitivity if available. If culture and sensitivity results are not available, treatment should be aimed at suspected gram-negative enteric bacteria or anaerobes. Potentiated sulfonamides or enrofloxacin plus metronidazole are good choices. Chloramphenicol has a good spectrum against most cultured bacteria, but since it is highly metabolized by the liver, it should not be used if hepatic function is severely compromised. Antibiotic treatment should continue for

[§]Contributions to previous editions by Terry C. Gerros are acknowledged.

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FIG. 33-13 Multiple choleliths present with the bile ducts of a horse.

6 weeks past the time when GGT values return to normal. DMSO (0.5 to 1 g/kg IV as <10% solution for 3 to 5 days) has also been recommended as a treatment to help dissolve intrabiliary sludge or small calcium bilirubinate stones. DMSO may cause hemolysis at higher concentrations, and horses with liver disease may already have fragile RBCs, so care should be taken with treatment. Fluid therapy may also help to thin secretions and promote bile flow. Anti-inflammatory drugs are also recommended. Choledocholithotomy and choledocholithotripsy, described in horses, have had limited success.[5-7] The prognosis is related to the degree of hepatic fibrosis, severity of clinical signs, and the number and location of the stones. Recent reports show a 75% to 80% survival rate with medical or medical plus surgical therapy.

Cholangitis and Cholangiohepatitis

Clinical disease of the bovine gallbladder is rare. Obstructive gallbladder disease has been associated with abdominal fat necrosis, choleliths, fascioliasis, foreign bodies, hepatic abscesses, neoplasia, and suppurative cholecystitis.[17,18] Adenomas and adenocarcinomas (most common tumors found in gallbladder), papillomas, and lymphosarcoma (rare) can cause obstruction.[17,19] Rupture of the gallbladder was found on necropsy of a cow in which icterus, anorexia, decreased milk production, and diarrhea had been present.[20]

Cholangitis and cholangiohepatitis may be primary or secondary and can result from cholelithiasis, duodenal inflammation, intestinal obstruction, neoplasia, parasitism, and certain toxins.[21] Sporidesmin, a fungal toxin from *Pithomyces chartarum,* causes cholangiohepatitis in cattle and sheep. Cholestasis and ascending infection resulting in cholangiohepatitis have been noted in horses with primary intestinal diseases such as proximal enteritis, right dorsal displacement of the large colon, and less frequently, left dorsal displacement of the large colon.[22-24] Duodenal strictures secondary to severe gastroduodenal ulceration have also been reported as a cause. Clinical signs associated with cholangitis and cholangiohepatitis in the horse may include anorexia, pyrexia, subtle behavioral changes, chronic weight loss, colic, and icterus. Septic peritonitis may occur as an extension of bacterial infection into the intraperitoneal space.[25] Alterations in hepatic enzyme activity may indicate hepatocellular damage, cholestasis, or both. Histopathologic examination and bacterial culture are indicated to further identify the causative agent. In cases of suspected bacterial etiology, long-term antibiotic therapy is indicated.[25] Antibiotic choice should be based on bacterial sensitivity, but in cases where no bacterial organism is identified, an antibiotic that is secreted or cleared in the bile is warranted.

Therapy of Liver Failure

Jennifer L. Davis

Antibiotic Therapy

Antibiotic therapy is indicated in cases of cholelithiasis, cholangitis, and cholangiohepatitis, as well as liver dysfunction secondary to systemic diseases causing sepsis in horses. Initial treatment should include broad-spectrum IV antibiotics, such as potassium penicillin plus either gentamicin or enrofloxacin, and oral metronidazole to cover *Bacteroides fragilis*. This is followed by long-term oral antibiotics based on culture and sensitivity (if available).[1] If no culture is available, the clinician should suspect gram-negative enteric bacteria with or without concurrent anaerobic infection. Trimethoprim sulfonamide combinations or enrofloxacin plus metronidazole are good choices. Chloramphenicol has a good spectrum against most cultured bacteria, but since it is highly metabolized by the liver, it should not be used if hepatic function is severely compromised.

Cattle with single or multiple liver abscesses often respond to penicillin therapy, but long-term therapy is required, and there is a significant rate of recurrence of clinical signs after therapy is withdrawn. Echolucent abscesses of small to medium size have the best prognosis. Abscesses with an echodense appearance are difficult to treat. Single large abscesses are best treated by surgical drainage, especially those interfering with vagal nerve function. High levels of IV penicillin and an aminoglycoside should be administered to foals with suspected Tyzzer disease.[2]

Treatment of Hepatoencephalopathy

Treatment of hepatoencephalopathy (HE) involves treatment of the underlying hepatic disease combined with supportive and palliative care. This includes IV fluids, broad-spectrum antibiotics, and gastroprotectants. Padding and wraps should be provided to help prevent self-trauma. Sedation may be necessary to control behavior or aid in treatments, but many of these drugs are metabolized in the liver, so care should be taken during dosing. Small doses of α_2-agonists like xylazine or detomidine are recommended. However, these drugs can cause respiratory depression at higher doses, and hypoventilation may aggravate signs of HE. Diazepam and other benzodiazepines should *not* be used; they may enhance the effects of GABA on inhibitory neurons, worsening HE.[3] Based on this, use of the benzodiazepine receptor antagonists has been recommended to lessen HE signs in humans.[4] The overall success of flumazenil in treating HE in humans and dogs has been low, and it has rarely been used in the horse. Sarmazenil, which has a different mechanism of action, appears to be more promising for reversing signs of HE in dogs[5] and has been used for treating moxidectin intoxication in a foal.[6]

Dietary management of HE is very important. Liver failure results in increased serum glucagon, and muscle catabolism releases amino acids. At the same time, hepatic metabolism of aromatic amino acids (AAA) is reduced and accumulation occurs, whereas muscle and adipose tissue can metabolize branched-chain amino acids (BCAA), resulting in less accumulation. AAA can act as false neurotransmitters, aggravating signs of HE, so a low-protein diet with a high BCAA/AAA ratio is recommended.[7,8] Low-protein/high-starch feeds include grass or oat hays, beet pulp, cracked corn, milo, sorghum, barley, and oats. If affected horses are anorexic, forced enteral or partial parenteral nutrition may be used. Lipids should not be added if there is any possibility that lipidosis is present, and special formulations of amino acids that consist mainly of BCAA should be used.

Other treatments for HE are designed to reduce intestinal ammonia absorption. Neomycin (10 to 30 mg/kg PO q6-12h) is an

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aminoglycoside antibiotic that suppresses enteric ammonia production. Because it is more nephrotoxic than gentamicin and can be irritating to intestinal mucosa (causing diarrhea), less than 2 days of use is recommended. Lactulose (0.2 to 0.5 mL/kg PO q6-8h) is poorly absorbed by the small intestine and acidifies the intestinal contents, causing a gradient to occur and ammonia to migrate from the blood into the colon, where it is trapped as ammonium and expelled. Acetic acid (vinegar, 0.5 mL/kg PO q12h), mineral oil, and metronidazole (10 to 15 mg/kg twice daily) have also been used to decrease ammonia absorption. Metronidazole should be used with caution because it is metabolized by the liver, and signs of toxicity may mimic HE.

Treatments aimed at reducing cerebral edema may also be necessary. Drugs frequently used include furosemide (1 mg/kg IV/IM q8-12h), mannitol (0.25 to 2 g/kg as a 20% solution IV over 20 to 30 minutes q12-24h), and hypertonic saline (4 to 6 mL/kg IV). It is also important to ensure the horse does not become too sedate with administration of α_2-agonists; it must be prevented from hanging its head and worsening edema. The prognosis for HE is poor unless the underlying disease can be quickly treated.

Fluid and Colloid Therapy

Dehydration should be corrected with a balanced electrolyte solution, preferably without lactate. Lactate is normally metabolized to bicarbonate in the liver and has an alkalizing effect. However, in horses with severe hepatic dysfunction, lactate may build up in the system and cause a worsening of acidosis. Sodium chloride (0.9%) with added calcium, dextrose (2.5% to 5%), and supplemental potassium (20 to 40 mEq/L) can be used. Additional potassium can also be given orally (5 to 20 g twice daily) to prevent or treat hypokalemia, since low potassium increases production and absorption of ammonia from the kidney.[9] Acidosis may be severe in many horses with hepatic failure, but attempts at correction must be made slowly.[10] Too rapid an increase in pH may exacerbate HE. Bicarbonate therapy should be instituted when the venous pH is less than 7.1. The prognosis is poor in horses that maintain persistent acidosis.

Glucose decreases ammonia concentration, reduces the reliance on catabolic gluconeogenesis, decreases protein catabolism, and spares hepatic energy consumed in hepatic gluconeogenesis, so it should be supplemented in cases of hepatic disease. The goal is to maintain blood glucose concentrations in the range of 90 to 120 mg/dL. In the case of hypertriglyceridemia with concurrent insulin resistance, supplemental insulin can be administered, as described in the section on hepatic lipidosis.

Polycythemia may be relatively unresponsive in some cases of hepatic failure and should not be used as the primary guide for judging adequate fluid therapy. Fresh or fresh-frozen plasma can be used to increase colloidal oncotic pressure, clotting-factor transport proteins, and antiproteases. Stored whole blood should not be used because ammonia levels may be high. Hetastarch should also not be used in hepatic failure, owing to its potential effects on coagulation.

Treatment of Inflammation and Fibrosis

Corticosteroids may be beneficial in treating lymphocytic/plasmacytic variants of chronic active hepatitis. Dexamethasone (0.05 to 0.1 mg/kg/day IV, IM, or PO decreased over 2 to 3 weeks) or prednisolone (1 mg/kg/day PO for several weeks) are recommended. Other recommended therapies for resolving inflammation and preventing progression of fibrosis can also be used. Flunixin meglumine (0.5 to 1 mg/kg PO) or low-dose phenylbutazone (0.5 g/day PO q24h) can be used for antiinflammatory effects. Vitamin E (10,000 U PO q24h) is recommended as an antioxidant and antiinflammatory agent. Pentoxifylline (8 to 10 mg/kg PO q12h) is a methylxanthine derivative and works as a nonselective phosphodiesterase inhibitor, resulting in weak inhibition of the inflammatory cytokines TNFα and IL-6. It also acts to increase RBC deformability, perhaps preventing microthrombosis. In horses, results with pentoxifylline are variable, possibly because of the variable bioavailability with extended dosing.[11] Colchicine (0.03 mg/kg PO q24h) can be used to inhibit production of collagen and macrophage/cytokine induced inflammation, potentially resulting in decreased fibrosis. Numerous side effects are reported in humans, including nervous system, renal, and dermatologic problems.

Miscellaneous Treatments

Supplemental *S*-adenosylmethionine (SAMe) (20 mg/kg PO q24h) is used for treatment of liver diseases; endogenous production is reduced secondary to reductions in methionine adenosyltransferase.[12] Presumed beneficial effects of SAMe in liver disease include augmentation of glutathione synthase levels in the hepatocyte, stabilization of membrane function, modification of cytokine expression, and inhibition of apoptosis in normal cells. *N*-acetylcysteine (NAC) (70 mg/kg IV q6h × 8 treatments) is a cysteine donor thought to be cytoprotective. It may improve hepatic microcirculation and oxygen delivery, enhance hepatic metabolic functions by restoring glutathione levels, block TNFα release, and act as a free radical scavenger.[12] DMSO (0.5 to 1 g/kg IV as <10% solution for 3 to 5 days) may act as an antioxidant as well as aid in dissolving intrabiliary sludge or small calcium bilirubinate stones. However, it may also precipitate a hemolytic crisis in animals with fragile RBCs. Ursodeoxycholic acid and silymarin are often used for hepatic disease in small animals, and there are anecdotal reports of use in horses, but safety and efficacy have not been proven. Ursodeoxycholic acid, a synthetic bile acid, is converted to toxic bile acids in the rabbit GI tract, which is similar to the horse's, so until a proven benefit is determined, this drug should not be used.[13]

Treatment of other concurrent disease should also be considered. If the hyperlipemia is thought to be associated with a pituitary adenoma, treatment with pergolide (1 to 5 mg/day PO) is warranted. Hyperlipidemia associated with diarrhea and azotemia may also occur in horses in late pregnancy, and abortion may be advisable.[14,15] Hepatic failure in cattle associated with septic metritis or mastitis, as well as biliary obstruction from hepatic abscesses, can often be successfully treated by force-feeding (e.g., alfalfa gruel, electrolytes) and systemic antibiotics.[16] Treatment of hepatic fascioliasis should be instituted as previously discussed.

Pancreatic Disease

Jennifer L. Davis

Pancreatic disease is rare in both cattle and horses. In the horse, acute and chronic disease has been reported, whereas only chronic disease has been reported in cattle.

Recognized causes of pancreatitis include migrating parasites, bacterial and viral infections, immune-mediated damage, biliary or pancreatic duct inflammatory disease, vitamin D toxicity, and deficiencies of vitamin A or E, selenium, and methionine.[1-4] Drugs known to induce pancreatitis in humans that are used frequently in horses include furosemide, tetracycline, estrogen, and certain corticosteroids and sulfonamides.[1,3] One case report in a pony suggests an association with Cushing syndrome.[5] The cause of acute pancreatitis in the horse is unknown, but it has been associated with grain overload and severe abdominal pain.[6] Three reports of acute pancreatitis in the foal suggest a possible relationship with sepsis, GI disease, vasculitis, and pancreatic lymphatic obstruction.[7,8] Pancreatitis was also diagnosed postmortem secondary to severe gastroduodenal ulceration in a foal.[9] The final common pathway may result from autodigestion by activated enzymes, but the exact mechanism remains speculative.

Clinical signs associated with acute pancreatitis are nonspecific and mimic those associated with an acute GI crisis. Characteristic clinical features are moderate to severe abdominal pain, gastric reflux, hypovolemic shock, and cardiovascular compromise.[1,4,10,11]

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Gastric distention accounts for the pain and gastric reflux associated with acute pancreatitis. Hypovolemic shock, occurring secondary to fluid losses into the peritoneal cavity and bowel lumen, results from release of vasoactive substances from the pancreas. Tachycardia, tachypnea, prolonged capillary refill, and congested mucous membranes result from hypovolemia and cardiovascular compromise. In foals, neurologic signs including dilated pupils, blindness, obtundation, and seizures have also been reported.[7] Hypoglycemia or pancreatic encephalopathy due to cerebral microthrombosis and infarction, as seen in humans, may be implicated.

Laboratory confirmation of pancreatic disease is difficult and not routinely attempted. The diagnosis is usually confirmed on histologic evaluation of the pancreas after necropsy. Laboratory tests that may be of value in the diagnosis of pancreatitis in the horse include measuring serum amylase and lipase activity, peritoneal fluid (PF) amylase concentrations, fractional excretion of amylase, and plasma trypsin levels.[4] Serum amylase values from normal horses range from 14 to 35 IU/L (mean, 21 ± 6), whereas PF values range from 0 to 14 IU/L (mean, 5 ± 4).[12] Serum lipase values from normal horses range from 23 to 87 IU/L (mean, 58 ± 19), whereas PF values range from 0 to 36 IU/L (mean, 14 ± 12).[12] Elevations of pancreatic enzyme activity are difficult to interpret because the enzymes may be elevated in horses with proximal enteritis, colic, primary renal failure, and damage to intestinal mucosal cells, as well as in pancreatitis.[4,12,13] Amylase also originates from the salivary glands, and lipase can be released from the liver. Clinical cases documented at necropsy had serum amylase activity greater than 700 IU/L; this magnitude of elevation may be helpful in differentiating acute pancreatitis from other causes. In acute pancreatitis, PF amylase levels are higher than serum levels.[13] Plasma trypsin levels increase in horses with suspected pancreatic damage and may be a better indicator of pancreatic disease.[14] Trypsin is specific to the pancreas and activates its own zymogen and those of all the other pancreatic enzymes. In one study of horses with acute abdominal disease in which pancreatic damage was suspected, trypsin activity was significantly higher than in healthy horses (196 ± 128.2 ng/mL vs. 28.5 ± 19.2 ng/mL).[14] In cattle with experimentally induced pancreatitis, serum amylase and lipase concentrations increased rapidly but returned to normal within a few days, suggesting this may not be a useful test for cases of chronic pancreatitis.[15] GGT does not appear to be a sensitive indicator of pancreatic disease in horses. In foals, an inflammatory peritoneal effusion with increased peritoneal protein and triglyceride concentrations, along with hypertriglyceridemia, has been documented.[7] Pancreatitis has not been successfully imaged with ultrasonography in the horse.[16] A technique for ultrasound examination of the right lobe of the pancreas in healthy cattle has been described.[17] Using this technique, experimentally induced acute pancreatitis was monitored ultrasonographically in cattle. Twenty-four hours after induction of pancreatitis, an increased echogenicity was noted, but within 3 days, hypoechogenicity was noted secondary to necrosis, hemorrhage, and inflammatory exudates, as confirmed at necropsy.[15]

Medical management of acute pancreatitis is symptomatic. Prevention of gastric rupture by continuous gastric decompression and control of abdominal pain are crucial in the treatment of pancreatitis.[3] Large volumes of balanced polyionic electrolyte solutions are necessary to maintain the circulating volume and prevent shock. Because hypocalcemia may be a problem, serum calcium concentration should be monitored. Broad-spectrum antibiotics are warranted because of the potential for secondary bacterial infection. NSAIDs and analgesics are used to control inflammation and pain.

Chronic interstitial pancreatitis (CIP) in horses and cattle seldom has clinical significance. In horses, *Strongylus equinus* and *Strongylus edentatus* are most often identified as the etiologic agent of CIP; however, *Parascaris equorum* has been identified in one case report.[3,18,19] In cattle, CIP has been primarily associated with the trematodes *Eurytrema pancreaticum* and *Eurytrema coelomaticum;* these parasites have not been isolated in the United States.[13]

Reports of pancreatic disease in adult cattle have been limited to endocrine dysfunction.[20-22] The most frequently reported disorder is type I diabetes mellitus, but the etiology in most cases is not determined.[20-22] Histopathologic examination generally reveals an absence of beta cells in the islet tissue. Foot-and-mouth disease virus has been associated with diabetes mellitus in cattle following convalescence.[13] Hypoplasia of the acinar pancreatic tissue has been described in calves.[13] Clinical signs include steatorrhea and diarrhea. Insulin-dependent diabetes mellitus with pancreatic beta cell dysfunction has been documented rarely in horses.[23,24] Transient type 1 diabetes has also been diagnosed in the foal,[25] and recent work shows that method of delivery (spontaneous vs. induced foaling) may have a significant effect on their pancreatic function.[26] Induced parturition was associated with two- to threefold higher cortisol levels and with differences in the absolute and age-related changes in basal concentrations of glucose, α-amino nitrogen, and insulin.[26] Adenocarcinoma of the exocrine pancreas is reported in rare equine cases and should be considered in horses exhibiting the clinical signs of pyrexia, depression, weight loss, and icterus.[2,27,28]

Pancreatic calculi found in older cattle (>5 years) during necropsy are considered incidental findings.[13] The calculi are composed primarily of calcium carbonate and calcium phosphate. Their presence may be associated with grazing on silica-rich soil, vitamin A deficiency, or chronic inflammation of the pancreatic ducts.[13]

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Diseases of the Renal System

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Acute Renal Failure

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Acute renal failure (ARF) in the horse is usually due to exposure to nephrotoxins or vasomotor nephropathy (e.g., hypoperfusion or ischemia). The most common pathologic lesion with ARF is acute tubular necrosis (ATN).

Toxic Nephropathies

Aminoglycosides

Administration of aminoglycoside antibiotics is one of the most common causes of ATN in the horse. These antibiotics exert their toxic effect by accumulating within proximal tubular epithelial cells. Their entrance into the tubular epithelial cell is thought to be via urine after filtration through the glomerulus.[1] Once toxic amounts are sequestered within the cell, cellular metabolism is disrupted and tubular cell swelling, death, and sloughing into the tubular lumen occur. Release of lysosomal enzymes and intracellular accumulation of calcium are likely involved in cell death.

Most cases of aminoglycoside nephrotoxicity are not due to drug overdosing or administering the drug to an azotemic patient.[2] The healthy kidney can usually tolerate a single major overdose (i.e., 10 times the normal amount) without detrimental effects, so toxicity is almost always the cumulative effect of *repeated* administration of aminoglycosides. Because the drugs are water soluble and thus highly distributed in extracellular fluid (ECF), their clinical pharmacokinetics are strongly influenced by variations in patient ECF volume owing to disease state or age, so different doses and dose intervals may be required to attain desired peak and trough levels depending on patient specifics.[3,4] Because renal cellular uptake of gentamicin is saturable, nephrotoxicity is associated with insufficiently low trough levels rather than excessively high peaks.[5] The maximal trough concentration to minimize the risk of nephrotoxicity is unknown in horses. In humans, trough gentamicin concentrations over 2 µg/mL have been associated with nephrotoxicity.[6,7] However, optimal trough concentration for minimizing nephrotoxicity after administration of gentamicin to humans is controversial, with recommendations ranging from maintaining a trough less than 2 µg/mL to maintaining a period of less than 0.5 µg/mL for at least 4 hours.[8-10] Nephrotoxicity typically develops after several days of aminoglycoside administration to horses with diarrhea or septicemia that are not adequately hydrated,[11] or because of other factors that may exacerbate a decrease in renal perfusion (e.g., concurrent treatment with nonsteroidal antiinflammatory drugs [NSAIDs]). The shift to once-daily aminoglycoside dosing in horses, compared with previous dosing of aminoglycosides two or three times daily, has become a standard practice that likely reduces the potential for nephrotoxicity (by ensuring a longer period of the day with appropriate serum trough concentrations) but still provides a similar therapeutic response.[12-15]

Prolonged administration (>10 days) of aminoglycoside antibiotics without monitoring of aminoglycoside trough concentrations or serum creatinine concentration is a common history with aminoglycoside nephrotoxicity in the horse. Typically, gentamicin or amikacin may be safely administered for longer than 10 days if the patient is adequately hydrated and appropriate trough concentrations and creatinine concentration are maintained. With regard to the latter, experimental induction of gentamicin nephrotoxicity in ponies was reflected by a rather small increase (0.3 mg/dL) in creatinine.[16] Although it has not been proven, the neonatal equine kidney is likely more susceptible to aminoglycoside toxicity than the adult kidney. This is probably reflective of the prolonged elimination half-life seen in foals.[4,17] Sick foals appear to be at greater risk for aminoglycoside nephrotoxicity,[18] although this may simply reflect an increased incidence of septicemia in sick neonates and longer courses of treatment with aminoglycosides.

When aminoglycosides are administered to high-risk patients (concurrent dehydration or neonates), volume deficits must be replaced and serum trough concentrations or creatinine monitored frequently.[19] Aminoglycoside nephrotoxicity rarely develops in horses receiving appropriate fluid therapy. Increased urinary sodium excretion and fluid diuresis appear to have a protective effect on the kidney. In contrast, hypokalemia (or total body potassium depletion) and low calcium intake may predispose horses to aminoglycoside nephrotoxicity by decreasing urine output.[20] Supplementation with oral electrolytes (e.g., 1 to 2 oz of NaCl and KCl daily) may be of benefit to horses being treated with aminoglycoside antibiotics by increasing water intake and urine output and replacing potassium deficits in anorectic horses. In contrast, furosemide should not be administered prophylactically in an attempt to prevent aminoglycoside nephrotoxicity.[21] In patients with prerenal azotemia that receive aminoglycoside antibiotics, it is important to monitor creatinine closely and consider prolonging the interval between drug administration until volume deficits are corrected. However, because nephrotoxicity is a cumulative effect of repeated dosing, delay of administration of the initial dose of an aminoglycoside pending

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rehydration of a critical patient (e.g., septic neonate, extremely dehydrated horse) is unwarranted.

Aminoglycoside nephrotoxicity should be considered in horses that become inexplicably depressed and inappetent while being treated with aminoglycosides or within a few days after aminoglycoside therapy is discontinued. Renal failure can develop even after the drug is withdrawn, so monitoring renal function 2 to 4 days after discontinuing aminoglycoside therapy may be advised in high-risk patients. Polyuria may be observed before the onset of depression and anorexia or, if the patient becomes oliguric, mild stranguria and repeated posturing to urinate may be observed. A tentative diagnosis of nephrotoxicity is based on history of aminoglycoside use and supportive laboratory data. Abnormal laboratory findings associated with tubular damage that may be detected before onset of azotemia include enzymuria and cylindruria.[16,22] Although these parameters can be monitored for early detection of tubular injury, their finding does not necessarily indicate if or when aminoglycosides should be discontinued or to what degree the interval of administration should be prolonged.[23]

When ARF from aminoglycoside use develops, it usually manifests as nonoliguric to polyuric renal failure; outcome is generally favorable so long as the duration of ARF is not prolonged and other underlying disease processes can be corrected. Peritoneal or pleural dialysis, plasmapheresis, or hemodialysis might be considered as methods to lower serum concentrations of nephrotoxic agents and uremic toxins. However, the amounts removed by a single use of some of these therapies are small and generally not worthy of pursuit in horses with nephrotoxic renal failure.[24]

Pigment Nephropathy

Acute tubular necrosis and development of ARF subsequent to rhabdomyolysis (myoglobin pigment) can occur if the episode of tying up is severe and/or the associated dehydration is prolonged.[25,26] Pigment nephropathy can also occur secondary to any other causes of muscle necrosis. Observation of grossly discolored urine is not a prerequisite for development of renal failure. Hemolysis, which may be secondary to a variety of toxins and primary conditions, appears to be a less common cause of pigment nephropathy than myopathy, although ARF can occur sporadically. Horses with severe hemolysis or those with hemolysis accompanied by disseminated intravascular coagulation (DIC) are at greater risk of developing pigment nephropathy.[27] In one study, 40% of 32 horses with red maple toxicosis and hemolysis had evidence of renal insufficiency, but it was not found to be an important risk factor for mortality.[28] Renal failure due to pigment nephropathy should be suspected in horses that become anorectic and more depressed during the week after an episode of tying up or during a hemolytic crisis. Measuring serum activities of creatine kinase (CK) and aspartate aminotransferase (AST) may help confirm that ARF has developed in association with rhabdomyolysis. There is little preformed creatinine in muscle, so rhabdomyolysis alone does not produce an increase in it.[29]

VITAMIN K_3. Vitamin K_3 (menadione) was a common cause of ATN and ARF in certain parts of the United States before its withdrawal from the market. Nephrotoxicity can occur rapidly after a single parenteral dose of the menadione sodium bisulfite form of vitamin K_3.[30,31] Development of ARF was thought to be idiosyncratic and likely involves direct tubular damage via oxidative stress and pigment nephropathy subsequent to hemoglobinuria.[30,31] Although horses are very sensitive to its nephrotoxic effects, oral supplementation of menadione with a view to enhancing bone strength was recently investigated in horses in Japan, and no nephrotoxicity was reported.[32,33]

Nonsteroidal Antiinflammatory Drugs

Most horses do not experience appreciable adverse effects from NSAIDs as long as they are administered at the proper dose and animals are not dehydrated. However, NSAID use may produce ARF in an occasional horse when excessive doses are administered or when dehydration is not corrected promptly.[22,23] The lesion produced by NSAID toxicity in horses is medullary crest necrosis, which can be manifested by gross hematuria.[34-38] Unless severe, this lesion rarely causes overt clinical signs, and creatinine may actually decrease with fluid therapy. An occasional horse may also develop chronic interstitial nephritis and nephrolithiasis after prolonged use (months to years) of NSAIDs at recommended doses.[39] The *renal medullary rim sign,* an ultrasonographic abnormality consisting of a hyperechoic band parallel to the corticomedullary junction, has been demonstrated in NSAID toxicity in adult horses and foals.[40,41] Presence of concurrent gastrointestinal (GI) disease (ulceration) and protein-losing enteropathy would further support NSAID toxicity in both acutely and chronically affected horses. Interestingly, acute interstitial nephritis was the predominant renal histopathologic lesion recorded in clinically normal Miniature donkeys administered NSAIDs (ketoprofen (2.2 mg/kg IV), flunixin (1 mg/kg IV or PO), or phenylbutazone (2.2-4.4 mg/kg IV or PO) twice daily for 2 weeks.[42] Also, in contrast to horses who may not show increases in serum creatinine while on fluid therapy or until severe renal compromise occurs, donkeys may show more acute increases in serum creatinine with NSAID toxicity.[42]

When renal blood flow decreases because of dehydration or redistribution of cardiac output, counteracting vasodilatory mediators are produced and released within the kidney to attenuate the decrease in renal blood flow. The best studied of these vasodilatory mediators include renal prostaglandins (PGI_2 and PGE_2) and dopamine. Although the role of renal prostaglandins in controlling basal renal blood flow is likely insignificant, they are important mediators of vasodilation during periods of renal hypoperfusion.[43] Renal prostaglandin production is several-fold greater in medullary tissue, such that action of these mediators leads to a greater increase in inner cortical and medullary blood flow. It should not be surprising that the lesion associated with NSAID toxicity is renal medullary crest necrosis (due to ischemia).[44] Similarly, it is important to remember that NSAID use in dehydrated or hypovolemic patients increases the risk of acute nephrosis.[45]

Vitamin D

Vitamin D intoxication may result from ingestion of feed additives or plants (e.g., *Cestrum diurnum*) containing high amounts of vitamin D metabolites or from parenteral administration of vitamin D.[46-48] Cholecalciferol (D_3) is thought to be more toxic than ergocalciferol (D_2) in the horse.[47] In general, horses do not need dietary supplementation with vitamin D if they are exposed to adequate sunlight and have access to green forages. The effect of vitamin D supplementation is cumulative, so signs of toxicity may not develop until several weeks after supplementation was started.

Clinical signs of vitamin D intoxication may be referable to the musculoskeletal, cardiovascular, or urinary systems.[48] Calcification of tendons and ligaments results in lameness, and calcification of cardiac muscle and great vessels can lead to cardiovascular problems. Mineralization of tendons and ligaments may be detected directly by palpation or indirectly through ultrasonographic imaging. Heart murmurs may accompany calcification of the great vessels, and ultrasonographic imaging of the heart and kidney may also reveal evidence of mineralization. Further clinical signs of renal toxicity include polyuria and weight loss.

Abnormal laboratory findings with vitamin D intoxication include azotemia, isosthenuria, hypochloremia, and elevations in both serum calcium and phosphorus concentrations. The latter combination of hypercalcemia and hyperphosphatemia is unusual for any other disease in the horse, although it may be seen with neoplasia on rare occasions. A definitive diagnosis of vitamin D toxicosis can be made by measuring serum concentrations of 25-OHD_3, 25-OHD_2, and 1,25-$(OH)_2D$. Treatment of vitamin D intoxication includes removal of the inciting cause (feed or medication), fluid diuresis, and corticosteroid administration. Provision of feeds low in both calcium and phosphorus may be of benefit in less severely affected horses, but treatment is usually unrewarding once clinical signs due to tissue mineralization have developed.

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Heavy Metals

Accidental ingestion of heavy metals may result in ATN and ARF in horses. Mercury, cadmium, zinc, arsenic, and lead are all nephrotoxic but are rare causes of renal failure in the horse. Mercury has been used experimentally to study renal failure in horses,[49,50] and there are reports of ARF in horses that have had legs "blistered" or "sweated" with products containing inorganic mercury.[51,52] Because inorganic mercury also causes severe damage to intestinal mucosa, signs of GI irritation (e.g., increased salivation, oral erosions, colic, hemorrhagic diarrhea) predominate with mercury intoxication. Further evaluation may reveal oliguria. Exposure to excessive amounts of zinc and cadmium can result in nephrocalcinosis and renal failure, but gait deficits (resulting from osseous effects, particularly in foals) and ill-thrift are more likely presenting complaints than oliguria.[53]

Laboratory findings with heavy metal intoxication are characteristic for ATN: azotemia, hyposthenuria to isosthenuria or anuria (depending in part on concurrent hydration status), hyponatremia, and hypochloremia. In horses with ARF concurrent with GI disease, as with mercury toxicity, severe hypocalcemia may be present. A tentative diagnosis of mercury intoxication may be made from history of exposure, clinical signs of erosive GI disease, and oliguric renal failure. The diagnosis can be confirmed by measuring increased blood and tissue (kidney and liver) concentrations of the metal. In addition to judicious fluid therapy, treatment of ARF induced by exposure to heavy metals should include parenteral dimercaprol, 5 mg/kg intramuscularly (IM) initially, followed by 3 mg/kg IM q6h for the remainder of the first day, then 1 mg/kg IM q6h for two or more additional days, as needed, and 1 lb of charcoal orally. Visceral analgesics (flunixin meglumine) and sedatives (xylazine or detomidine) are often necessary to control abdominal pain.

Acorn Poisoning

Acorn poisoning is less common in equids than cattle but has been reported in horses.[54] Death in horses is usually due to erosive GI disease, changes in vascular permeability, and resulting shock rather than a consequence of uremia. Immature leaves and green acorns are considered more toxic than mature acorns because the former have a higher tannin content. Clinical signs may include diarrhea, edema, and body cavity effusion, and laboratory evaluation usually reveals azotemia, isosthenuria to hyposthenuria, hyponatremia, and hypochloremia. Detection of increased urinary excretion of phenols may be useful to confirm the diagnosis.

Miscellaneous Drugs and Agents

Several other drugs and agents (oxytetracycline, polymyxin B, amphotericin B, imidocarb dipropionate, ochratoxins, pyrrolizidine, cantharidin toxicosis [blister beetle poisoning], and the nematode *Halicephalobus*) have been suspected of causing nephrotoxic ARF in horses. When high doses of oxytetracycline (up to 70 mg/kg) are administered to neonatal foals for correction of limb contracture, ARF is a potential complication, especially if the foals are dehydrated or have concurrent sepsis or hypoxic-ischemic encephalopathy.[55] With renewed interest in polymyxin B as an adjunct treatment for endotoxemia, it is prudent to remember that this drug also has nephrotoxic potential. However, experimental studies have demonstrated that the risk of polymyxin B nephrotoxicity is low, especially when it is conjugated with dextran 70.[56] Amphotericin B also has considerable nephrotoxic potential, but it is rarely administered systemically to horses. Imidocarb dipropionate, used in treating *Babesia equi* infections, has been shown to cause reduced renal function after multiple dosing.[57] Ochratoxins have the potential to produce ATN, but ARF caused by ochratoxins has not been documented in horses. Similarly, pyrrolizidine alkaloid poisoning may cause renal disease in horses, but failure is unlikely. Blister beetle poisoning (cantharidin toxicosis) may cause abdominal pain, shock, hematuria, diaphragmatic flutter, dysuria, and renal dysfunction in horses fed alfalfa hay grown in regions where the beetles are prevalent.[58] One report of renal failure, as well as brain involvement, was associated with granulomas caused by the nematode *Halicephalobus*.[59] Anecdotal reports exist of horses developing renal disease after administration of bisphosphonates for treatment of orthopedic disease. Prudence should be used as renal disease is a reported complication in other species after bisphosphonate administration.[60]

Vasomotor Nephropathy

Any condition that causes sustained marked hypotension or release of endogenous pressor agents can initiate hemodynamically mediated (vasomotor) ARF. Although poorly documented, vasomotor ARF may be more common than nephrotoxic ARF in the horse. However, renal compromise due to a combination of vasomotor and nephrotoxic mechanisms probably occurs more frequently than clinically identified in sick horses receiving drugs with nephrotoxic potential. Hemorrhagic shock, severe intravascular volume deficit (e.g., as with enterocolitis), septic shock, and coagulopathy are important risk factors for vasomotor ARF in horses.[61] Another cause may be adverse drug reactions, including those accompanying intravenous (IV) administration of vitamin and mineral products or immunomodulators. The predominant lesion in vasomotor nephropathy is ATN, although diffuse renal cortical or renal medullary necrosis may also occur in some cases.

Clinical signs of vasomotor ARF are nonspecific and more often referable to the primary disease (e.g., hemorrhage or diarrhea). Additional subtle signs (e.g., more marked depression and anorexia than would be expected with the primary disease), with or without signs of mild colic, may increase suspicion of ARF. If sedation for colic signs is deemed necessary, xylazine or detomidine can be administered if intravascular volume and blood pressure are not overly compromised. Occasionally, horses with severe ARF may also be ataxic or manifest neurologic signs similar to hepatoencephalopathy.

Oliguria, often seen as a lack of expected urination in response to fluid therapy, is an important early indicator of vasomotor ARF, and production of dilute urine (specific gravity <1.020) that may be discolored (hematuria or hemoglobinuria) may be observed when urine is eventually voided. If urine produced is grossly clear, microscopic hematuria is usually present and will produce a positive result on reagent strip analysis of urine. Glucosuria due to severe proximal tubular damage may also be detected in an occasional horse with vasomotor ARF. Although the pathophysiologic relationship to ARF is not well defined, diarrhea and severe laminitis may develop in more serious cases of vasomotor ARF.

Acute Glomerulopathy

Although subclinical glomerular damage likely accompanies some diseases affecting horses, especially immune-mediated disorders (e.g., purpura hemorrhagica), acute glomerulonephritis (GN) is a rare clinical problem.[62] A syndrome of arteriolar microangiopathy and intravascular hemolysis that causes distention of glomerular capillary loops with fibrin thrombi and accumulation of large amounts of proteinaceous debris in the Bowman capsule has also been described in a few horses.[63] Affected horses presented with oliguric ARF accompanied by hematuria, proteinuria, and intravascular hemolysis; response to treatment was poor. The cause of the syndrome in horses is not definitively known. Renal lesions resemble those found with hemolytic-uremic syndrome (HUS) in humans, which is caused by toxins of *Escherichia coli*. In a recent case report of HUS with glomerular thrombotic microangiopathy in a postpartum mare, *E. coli* O103:H2 was isolated from the uterus and gastrointestinal tract.[64] Glomerulopathy with ARF caused by *Streptococcus mitis* has also been documented as a component of toxic shock in a horse.[65] Bacterial toxins, a consumptive coagulopathy, immune complex deposition, vasoactive amines, and hemodynamic alterations may all be contributors to this rare syndrome in horses. Acute glomerulopathy should also be considered in horses with severe ARF that do not have a predisposing primary disease leading to vasomotor ARF and that have not been exposed to nephrotoxins. Gross hematuria, proteinuria, and oliguria would support an acute glomerulopathy, and renal biopsy can be pursued to confirm the lesion.

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Acute Interstitial Nephritis

Acute interstitial nephritis is a rare syndrome of ARF accompanied by rapid elevations in creatinine and clinical signs of uremia. Renal lesions include interstitial edema with a mild inflammatory infiltrate. Although adverse drug reactions (idiosyncratic) may be a cause, the etiopathogenesis of this disease in horses is unknown. In humans, eosinophilic infiltrates in renal biopsy tissue are supportive of adverse drug reaction. Although there are no published reports of the syndrome in horses, the author (TJD) has examined three horses with apparent acute interstitial nephritis. However, experimentally, in Miniature donkeys, interstitial nephritis (rather than medullary crest necrosis) was the predominant renal histopathologic lesion recorded following IV administration of NSAIDs twice daily for 2 weeks.[42] Because of the pronounced interstitial edema that may accompany this disease, treatment with corticosteroids may be of benefit in suspect cases.

Leptospirosis

Krista Elise Estell

ARF due to infection with *Leptospira interrogans* should be considered when an underlying renal disease is not apparent and there has been no exposure to nephrotoxins. *L. interrogans* serovar *pomona* has been documented as a cause of interstitial nephritis in horses, though the most common pathologic isolates are *L. interrogans* serovar *kennewicki* in the United States and *L. interrogans* serovar *icterohaemorrhagiae* and *Leptospira kirchneri* serovar *grippotyphosa* in the United Kingdom.[66-70] The most frequent clinical sign in both experimental and natural infection is fever, but anorexia and depression may also be present, and hematuria was observed in one foal.[71] Clinical pathologic abnormalities include azotemia and isosthenuria without bacteriuria. Leptospiruria is not a consistent finding, making diagnosis difficult. Diagnosis of *Leptospira* spp. can be achieved by urine polymerase chain reaction (PCR); administering furosemide and testing the second voided sample may increase sensitivity of this test. Serum titers performed by microscopic agglutination rise quickly after experimental infection.[72] Demonstration of a rising titer or baseline titer above 1:6400 indicates active infection.[73] Treatment includes fluid therapy and penicillin.

Diagnosis

ARF should be suspected in patients showing more marked depression and anorexia than would be expected with the primary disease process and in those that fail to produce urine within 6 to 12 hours of initiating fluid therapy. Rectal palpation in horses with ARF may reveal enlarged, painful kidneys in some cases. Enlargement can be confirmed by renal ultrasonography, which may also reveal perirenal edema, loss of detail of the corticomedullary junction, or dilation of renal pelves.[74-76] However, subtle changes in renal architecture can be difficult to detect via ultrasound, and sensitivity of this diagnostic modality largely depends upon operator experience and image quality.

The diagnosis of ARF is confirmed on the basis of history, potential exposure to nephrotoxins, clinical signs, and laboratory findings. Relative to baselines, the increase in serum or plasma creatinine concentration is often several-fold greater (e.g., up to 5 to 15 mg/dL) than that of blood urea nitrogen (BUN) concentration (e.g., up to 50 to 100 mg/dL), resulting in a BUN/creatinine ratio that is often less than 10:1. Hyponatremia, hypochloremia, and hypocalcemia are usually present, and in more severe cases, hyperkalemia, hyperphosphatemia, and metabolic acidosis may also be detected.

In addition to assessment of the magnitude of azotemia and alterations in serum or plasma electrolyte concentrations and acid-base balance, urinalysis should be performed on all horses in which ARF is suspected. As mentioned, a low urine specific gravity (<1.020) in the face of dehydration and gross or microscopic hematuria are common findings with ARF. Evidence of more substantial proximal tubular damage, including increased urinary enzyme activity and glucosuria, may be detected in some horses. Significant proteinuria (urine protein/creatinine ratio > 2:1 [see Chronic Renal Failure]) would support the presence of glomerular disease. Examination of urine sediment may reveal casts and increased numbers of erythrocytes and leukocytes, and the amount of urine crystals may be decreased. Increased fractional clearances of sodium and phosphorus are also common findings with ARF. It is important to remember that administering IV fluids to healthy horses will also result in increased fractional clearances of sodium, chloride, and phosphorus.[77] Electrolyte clearances are ideally determined using the initial urine sample voided after admission or a sample collected by catheterization (i.e., before urine is substantially altered by fluid therapy).

The most accurate assessment of renal function involves glomerular filtration rate (GFR), which can be measured by performing timed urine collections (inulin and endogenous or exogenous creatinine clearances) or assessing plasma disappearance of several compounds (sodium sulfanilate, phenolsulfonphthalein, or radiolabeled substances).[78] Recently GFR has been determined in a foal using computed tomography (CT) with single-slice dynamic acquisition and Patlak plot analysis.[79] In a clinical setting, measurement of GFR in cases of ARF is rarely pursued because multiple measurements are required to assess changes in GFR, and prognosis for recovery is more likely related to the duration of decreased GFR rather than to the magnitude of the decrease. Because of the inverse relationship between GFR and creatinine, changes in GFR can be more practically assessed by daily serum creatinine measurement.

Glomerular injury and tubular necrosis can be further confirmed by performing a renal biopsy, but biopsy is often not indicated because the diagnosis of ARF is usually evident. In a recent retrospective study of 151 renal biopsies in horses carried out at 14 different equine hospitals, biopsy specimens yielded sufficient tissue for a histopathologic diagnosis in 94% of cases, but diagnoses had only fair (72%) agreement with postmortem findings.[80] Immunofluorescent (IF) testing and electron microscopic (EM) examination are routinely performed on human renal biopsy samples to assess mechanisms of renal injury and extent of damage to glomerular and tubular basement membranes. If such detailed evaluation of renal biopsy tissue were routinely performed in horses with ARF, better information regarding etiopathogenesis and prognosis would likely be provided by the pathologist.

At present, renal biopsy is most often indicated to evaluate horses with ARF when exposure to nephrotoxins or another underlying primary disease process is unapparent. Life-threatening hemorrhage is a potential complication of renal biopsy. The above-mentioned study found a complication rate of 11.3%, generally associated with hemorrhage or signs of colic. Treatment for complications was required in only 3% of cases, and there was only one fatality.[80] Risk factors for complications included biopsy of the left kidney, a diagnosis of neoplasia, and low urine specific gravity.[80] Biopsy of the right kidney with ultrasonographic guidance, usually through the seventeenth intercostal space, is the preferred procedure.[81] Proper instrumentation (automatic or spring-loaded biopsy instruments) and adequate restraint (stocks and sedation) are important considerations. Renal tissue collected should be placed in formalin for histopathologic examination, as well as frozen (or placed into additional media specified by the testing laboratory) for IF testing and EM examination. Although biopsy of the right kidney alone usually is adequate for assessment of the disease process affecting both kidneys, samples of the left kidney can also be collected by guiding the biopsy instrument through the spleen. Again, ultrasonographic guidance is especially vital when collecting a biopsy from the left kidney or when biopsy of a specific area of either kidney is desired.

General Principles of Treatment

The general principles of ARF treatment in the horse are similar to those recommended for humans.[82,83] Initial therapy should always focus on judicious IV fluid administration to replace volume deficits

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and correct electrolyte and acid-base abnormalities. The magnitude of azotemia and serum concentrations of sodium, chloride, potassium, and bicarbonate should be monitored daily. Horses with polyuric ARF often require sodium and chloride replacement. This can be accomplished by using 0.9% NaCl as the fluid administered or through supplementation of these electrolytes in grain feedings or as oral pastes. Serum potassium concentration in horses with nonoliguric ARF is often normal, and except for postrenal problems (e.g., obstruction or rupture), therapy intended to lower serum potassium is usually unnecessary. Similarly, it is usually unnecessary to correct the mild hypocalcemia that can accompany ARF in horses.

After correcting volume deficits and electrolyte and acid-base abnormalities, an attempt should be made to determine whether the animal is oliguric or nonoliguric (polyuric); the prognosis for recovery appears to be more favorable with nonoliguric ARF. This often becomes apparent by simple observation: oliguric horses fail to produce expected amounts of urine in the initial 12 to 24 hours of IV fluid therapy and the bedding remains dry. Nonoliguric horses repeatedly void moderate volumes of dilute urine during the initial 6 to 12 hours of treatment. Edema can develop rapidly in horses with oliguric or anuric ARF and is often initially noticed in the conjunctiva (Fig. 34-1). Other manifestations include generalized subcutaneous swelling of dependent areas, progressing to tachypnea and altered mental status if pulmonary and/or cerebral edema develop. In horses with prerenal azotemia (as opposed to intrinsic ARF), serum creatinine concentration should decrease by at least 30% to 50% within the initial 24 hours of fluid therapy. In contrast, creatinine concentration may remain unchanged or even increase in ARF.

During therapy for ARF, regular assessments of attitude, vital parameters, packed cell volume, and total plasma protein concentration are important. Monitoring should also include measurement of body weight once or twice daily (patients should not gain weight with continued fluid therapy after initial rehydration) and comparison of fluid input with fluid (urine) output. Although there is no convenient method of collecting all urine voided by ambulatory foals or mares, urine output can be rather easily quantified in male horses by placing a urine collection device around the abdomen.[84] When desired, monitoring urine output in critically ill foals and mares can be accomplished by use of an indwelling Foley catheter and urine collection bag (closed system), but ascending infection is a risk.

In severely ill patients, especially those with vasomotor nephropathy, systemic blood pressure (BP) can be monitored to confirm that fluid therapy has been adequate to restore BP. Some horses may remain hypotensive (systolic BP < 80 mm Hg) despite administration of large volumes of IV fluids, owing to extravascular accumulation as edema or a third-space fluid. If systemic BP remains low, hypertonic saline, dobutamine, or other pressor agents may be required to restore BP and glomerular filtration. Fluid and sodium replacement in horses with oliguric renal failure and normal systemic BP must be monitored closely; overzealous fluid administration to horses with oliguric or anuric ARF will result in edema formation. Central venous pressure (CVP) can also be monitored as a more precise measurement of fluid balance in critical patients. CVP is measured with a manometer with the baseline at the level of the right atrium, attached to an IV catheter placed into the anterior vena cava via the jugular vein (normal CVP in horses, <8 cm H_2O).



FIG. 34-1 Severe conjunctival edema from intravenous (IV) fluid therapy in a 3-year-old Arabian with oliguric acute renal failure (ARF). The ARF and a multifocal granulomatous pneumonia occurred after IV administration of an approved immunomodulator.

In horses that remain oliguric after 12 to 24 hours of appropriate fluid and electrolyte replacement and restoration of systemic BP, furosemide at 1 mg/kg IV q2h should be administered. Unfortunately, furosemide treatment is often ineffective in increasing renal blood flow, GFR, and tubular flow in horses with ARF.[83,85] Continuous infusion of furosemide at 0.12 mg/kg/h, preceded by a loading dose of 0.12 mg/kg IV, was considered superior to intermittent use in one study.[86] If urine is not voided after the second dose, administration of mannitol (1 g/kg IV as a 10% to 20% solution) and/or a dopamine infusion (3 to 7 µg/kg/min IV) can be instituted. Dopamine administration should only be performed in a hospital setting where heart rate and BP can be monitored frequently and development of tachycardia and hypertension avoided. Dopamine use for selective renal vasodilatory and natriuretic actions has been called into question because most studies in humans have not demonstrated prevention of ARF in high-risk patients or improved outcome in those with established ARF[87]; in one study, dopamine actually worsened renal perfusion in human patients with ARF.[88] Further, the drug may precipitate serious cardiovascular and metabolic complications in critically ill patients. If these treatments are successful in converting oliguria to polyuria (may require 24 to 72 hours), they can be discontinued, but maintenance of urine production must be monitored closely over the next few days. Fortunately, the majority of horses with ARF resulting from ATN are nonoliguric rather than oliguric, and furosemide, mannitol, or dopamine are unnecessary.

When this treatment approach to oliguria remains unsuccessful for more than 72 hours, the prognosis becomes grave. One study of horses with colic or colitis found that horses with persistent azotemia after 72 hours of fluid therapy were three times as likely to die or be euthanized as the horses without persistent azotemia.[89] However, dialysis therapy may be a further treatment option in selected patients. Hemodialysis has been successfully used to treat two adult horses with myoglobinuric ARF[90,91] and a neonatal foal with oxytetracycline-induced ARF.[55] Peritoneal dialysis has been attempted in a few horses with nephrotoxic-induced ARF, but omental plugging of the catheter has limited its success, and special dialysis catheters are required for effective fluid exchange. Pleural dialysis is another option for which fluid exchange is less problematic. Hemodialysis or dialysis would likely be most effective in horses with nephrotoxic ARF, whereas vasomotor nephropathy is best treated by addressing the predisposing condition and instituting appropriate fluid therapy.

After volume deficits have been restored and polyuria achieved, patients usually need only continued fluid therapy (0.9% NaCl or another balanced electrolyte solution, 40 to 80 mL/kg/day) to promote a continued decrease in creatinine. Fluid therapy may have to be continued (20 to 40 mL/kg/day) for several days until creatinine returns to the normal range or a steady-state value and the horse is eating and drinking adequate amounts. Supplementation with oral electrolytes (1 to 2 oz NaCl twice daily) will also promote greater fluid intake and diuresis. Potassium supplementation (1 oz KCl twice daily) may also be required because diuresis results in kaliuresis. When horses remain anorectic during treatment, the addition of 50 to 100 g dextrose/L fluids can provide needed calories, and if anorexia

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persists for several days, caloric intake may have to be provided by nasogastric tube feeding or total parenteral nutrition.

Within the week after fluid therapy is discontinued, creatinine should be measured again to ensure it has not increased. Occasionally, creatinine may not decrease to below 2 to 3 mg/dL despite continued fluid therapy. As long as the horse is eating and drinking well, IV fluids can be discontinued. In some horses, further recovery will be seen as a return of creatinine to normal range within the next couple of months, whereas in other patients a persisting elevation in creatinine indicates permanent loss of renal function.

Serum Creatinine Elevations in Newborn Foals

During the first 1 to 3 days of life, the creatinine concentration in newborn foals is often 30% to 40% higher than in their dams.[92] The cause is unclear but likely related to an inability of creatinine to equilibrate rapidly across placental membranes. As supportive evidence, creatinine concentration of normal amniotic fluid (which contains fetal urine) at term is approximately 10 mg/dL (and may exceed 30 mg/dL in some mares).[93] This transient increase in creatinine, which may occasionally exceed 20 mg/dL in premature foals, has been called a "spurious" elevation—a misleading characterization because creatinine truly is increased. Further, in a recent retrospective study, 20 of 28 foals with hypercreatinemia had clinical signs of mental abnormalities and/or seizures.[94] When elevated creatinine is detected in an otherwise healthy foal (that has also been observed to urinate normally), there may be no cause for alarm, but if levels do not decline rapidly after birth (or remain >2.5 mg/dL on day 3 of life), peritoneal or retroperitoneal accumulation of urine, renal hypoplasia, or other causes of renal failure should be considered. Unlike creatinine, BUN values in foals are typically low (<10 mg/dL) after day 2 and remain low for the first several months of life. This finding can be attributed to the anabolic state of the growing foal.

Urinalysis results in normal neonatal foals are also different from those in adult horses. Specifically, for 1 to 2 days after birth, normal foals may have marked proteinuria resulting from filtration of small-molecular-weight proteins absorbed with colostrum. Fluid intake on a predominantly milk diet is high in foals (250 mL/kg/day, compared to 50 mL/kg/day of water intake by adults), so after day 2 of life, foal urine is hyposthenuric (specific gravity 1.002 to 1.006) and remains that way for several months. Finally, urinary enzyme activity and sodium and chloride clearances may be greater than adult values, and urine pH is neutral to acidic in foals.[95]

Acute Renal Failure in Foals

ATN is the most common pathologic lesion causing ARF in neonatal foals. Many cases develop during or after episodes of diarrhea, likely caused by poor perfusion (vasomotor nephropathy) subsequent to varying degrees of dehydration. Surprisingly, the diarrheal disease in some affected foals does not appear to be serious, but they may develop ARF. Similar to adult horses with ARF, the prominent clinical signs are depression and development of edema. Abnormal laboratory findings include azotemia, hyponatremia, hypochloremia, and hypocalcemia. Foals are more likely to develop significant hyperkalemia and hyperphosphatemia than adult horses with ARF. A urine specific gravity less than 1.018 and microscopic hematuria are usually also found in foals with ARF. Urine output of sick neonates should be monitored closely because they may become oliguric to anuric 12 to 24 hours before significant depression or azotemia is recognized. In addition, fluid retention during incipient ARF is another cause of inappropriate weight gain (e.g., >2 kg in 24 hours), which can often be detected before obvious edema develops.

Nephrotoxicity, most often due to aminoglycoside or tetracycline administration, is another important cause of ARF (usually nonoliguric) in neonatal foals. As in adult horses, the recent change to once-daily aminoglycoside dosing appears to have decreased the incidence of hospital-acquired ARF in foals. Seriously ill and/or premature foals appear to be at even greater risk of nephrotoxicity than term foals, owing to reduced renal clearance.[96] Although there is a general impression that amikacin may be less nephrotoxic than gentamicin in foals, no data exist to support this notion. Regardless of which aminoglycoside antibiotic is selected, monitoring trough concentrations (<2 mg/mL for gentamicin, <4 mg/mL for amikacin) is warranted to decrease the risk of aminoglycoside toxicity in high-risk neonates. It should be noted that the actual optimal trough concentrations are unknown in horses and are based on those used in human medicine. Dosage adjustment may be necessary in seriously ill neonates or premature foals, because renal clearance may be decreased, necessitating an increased dosing interval to achieve low enough trough concentrations. Judicious fluid therapy to correct dehydration and maintain BP is an important precaution. To complicate matters, foals also have a larger volume of distribution than adult horses and require an increased dose of aminoglycosides to attain therapeutic peak concentrations.[4,97] Volume of distribution may be increased even further in premature foals and with certain disease processes that increase extracellular fluid volume.

Treatment principles for ARF in neonates are essentially the same as for adult horses (see earlier discussion). However, greater attention must be paid to monitoring responses to fluid therapy, including twice-daily measurement of body weight. Although foals that have a bout of ARF in the neonatal period would seem at greater risk of developing chronic renal failure later in life, no long-term follow-up study has corroborated this speculation.

Septic Renal Disease in Foals

Multifocal renal abscesses or infarcts may be a complication of neonatal septicemia and can lead to ARF. *Actinobacillus equili* is the most common pathogen causing renal abscesses, but affected foals often die or are euthanatized because of overwhelming sepsis before clinical signs of ARF develop. Foals 2 to 4 days of age appear to be at greatest risk of developing acute *Actinobacillus* septicemia; when this problem is suspected, IV therapy with penicillin and gentamicin (at prolonged dosage) is recommended (see Chapters 18 and 20). Subsequent fibrin deposits in the kidney have also been identified in some foals with septicemia and ARF.[98]

Chronic Renal Failure

Thomas J. Divers • Theresa Lynn Ollivett

Chronic renal failure (CRF) in the horse may be divided by clinical and pathologic findings into two broad categories: primary glomerular disease and primary tubulointerstitial disease.[1,2] However, pathology in one portion of the nephron usually leads to altered function and eventual pathology in the entire nephron, so CRF is an irreversible disease process characterized by a progressive decline in GFR. The rate of decline in GFR is variable among affected horses, making the short-term (e.g., months to 2 years) prognosis guarded to favorable while the long-term prognosis remains poor.

Primary *glomerular* diseases that can lead to CRF in horses include GN, nonspecific glomerulopathy, renal glomerular hypoplasia, and amyloidosis. Primary *tubulointerstitial* diseases causing CRF include incomplete recovery from ATN, pyelonephritis, nephrolithiasis, hydronephrosis, renal dysplasia, and (rarely) papillary necrosis. Collectively, the latter disorders produce pathology categorized as *chronic interstitial nephritis.* Unfortunately, because renal disease is often advanced when horses are first presented for clinical evaluation, the inciting cause leading to CRF may be difficult to ascertain, and end-stage kidney disease (ESKD) may be the pathologic diagnosis. The inciting cause may more likely be discerned from the history (long term) rather than clinical findings at presentation, especially for primary tubulointerstitial diseases. Adjunctive diagnostic evaluation, including laboratory assessment, renal ultrasonography, and renal biopsy, may provide further evidence to document the inciting cause.

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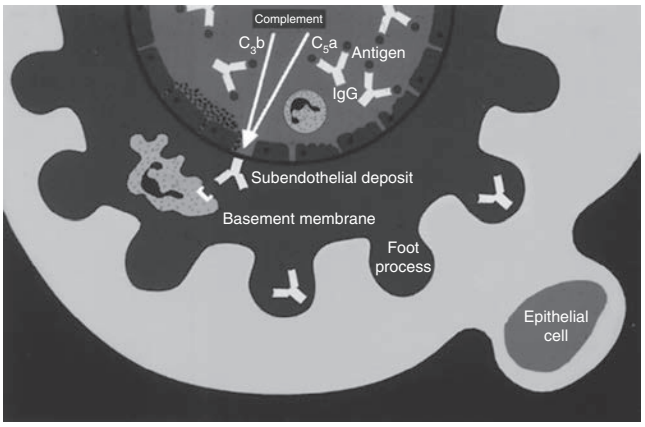


FIG. 34-2 Depiction of a subendothelial immunologic reaction suspected to occur in horses with streptococcal antigen-antibody–associated glomerulonephritis.



FIG. 34-3 Yearling Thoroughbred with chronic renal failure caused by renal dysplasia. Failure to grow normally and lethargy were the primary complaints.

Causes

Proliferative Glomerulonephritis

Proliferative GN, indicating increased cellularity of the glomerular tufts consequent to influx of inflammatory cells and proliferation of mesangium, is the most common glomerular disease causing CRF in horses. It is thought to result from deposition of circulating immune complexes along the glomerular capillaries or in situ formation along the glomerular basement membrane (GBM) (Fig. 34-2). Deposition of immune complexes causes activation of complement and vasculitis (type III hypersensitivity response). In one study, deposits of immunoglobulin (Ig)G and complement along the GBM were found through IF staining in a large percentage (22 of 53) of horses at necropsy.[3] However, only 1 of these 53 horses developed CRF. Thus, although immune (antigen-antibody) complex deposition and subclinical GN may be common in horses, progression to CRF appears to be an infrequent occurrence. In this necropsy survey the predominant IF staining pattern was granular (patchy deposits of immune complexes and complement along GBM), but linear deposits were found in two horses. The latter finding was supportive of true autoimmune disease with more diffuse deposition of anti-GBM antibodies (type II hypersensitivity response) along the basement membrane antibody.

Streptococcal antigens have been suggested to be an important trigger for development of proliferative GN,[4] and in one horse with CRF, streptococcal antigens were confirmed to be present in diseased glomeruli.[5] Although equine infectious anemia virus is the only other antigen that has been detected in glomeruli of horses with proliferative GN,[6] subclinical GN likely accompanies other chronic infections in horses. It has also been suggested that equine GN may also be associated with either mixed or monoclonal cryoglobulins forming antibody-antibody glomerular deposits.[7] In one horse with no evidence of viral or bacterial infection, deposits consisting solely of IgM were identified within the GBM.[8] Fortunately, GN in most patients is rarely of clinical significance.

Chronic Interstitial Nephritis

Chronic interstitial nephritis (CIN) and fibrosis may be the most common cause of CRF in horses. Interstitial nephritis (tubulointerstitial disease) usually develops as a sequela to ATN consequent to exposure to nephrotoxins or vasomotor nephropathy. Other causes include drug-induced interstitial nephritis, urinary obstruction, pyelonephritis, renal hypoplasia/dysplasia, and papillary necrosis. Although the majority of horses that develop ARF attributable to these causes recover with apparently normal renal function (they remain nonazotemic), a few may survive with significant loss of renal functional mass and subsequently (often years later) develop signs of CRF due to CIN.[9] In horses younger than 5 years of age that develop CRF unattributable to other causes, anomalies of development (e.g., renal hypoplasia, dysplasia, polycystic kidney disease) should be strongly suspected[2,10-13] (Fig. 34-3).

Pyelonephritis

Bilateral septic pyelonephritis is a rare cause of CRF in horses.[14-16] Pyelonephritis is usually due to an ascending infection and often accompanied by nephrolithiasis or ureterolithiasis. Multiparous mares (especially those with a history of dystocia) and horses with bladder paralysis are at greater risk for bacterial colonization of the lower urinary tract and subsequent development of ascending infection. Chronic distention with bladder paralysis compromises the integrity of the ureteral orifices, leading to vesicoureteral reflux and pyelonephritis. With long-standing bladder paralysis, the ureteral orifices may appear wide open during cystoscopic examination, and in an occasional affected horse, the endoscope can be advanced into the ureter with little resistance. With unilateral pyelonephritis, adequate renal function is usually maintained by the contralateral kidney, but passage of small uroliths into the bladder can lead to recurrent urethral obstruction. Gram-negative organisms appear to be the most common causative agents, although *Staphylococcus, Streptococcus,* or *Corynebacterium* spp. may be isolated in some cases, and mixed bacterial infections are not uncommon.

Miscellaneous Causes

Other reported causes of CRF in horses include amyloidosis,[17] neoplasia,[18] focal glomerulosclerosis-like disease,[19] and chronic oxalate nephrosis.[20] One study described CRF secondary to polycystic kidney disease in an aged pony with hematuria; the pony also had hepatic cysts.[21] Renal amyloidosis has been reported only in horses used for production of antiserum.[17] So-called oxalate nephropathy in horses is likely a misnomer; the presence of oxalate crystals in renal tissue of horses with CRF is typically a consequence rather than the cause of CRF.[20]

Clinical Signs and Laboratory Findings The most common clinical sign observed in horses with CRF is weight loss.[2] A small plaque of ventral edema, usually between the forelimbs, is another frequent finding.[2,22] Moderate polyuria and polydipsia (PU/PD) are usually present at some stage of the disease process, but PU/PD may not be noticed except by the astute owner or trainer.[2] Dysuria is generally not reported unless CRF is due to pyelonephritis, which may be associated with bladder paralysis, lithiasis, and lower urinary

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FIG. 34-4 Dental tartar caused by chronic azotemia in a 5-year-old Standardbred with chronic renal failure.

tract infection (UTI). Normal equine urine is rich in crystals and mucus, making a prediction of urine abnormalities on gross observation difficult. However, hematuria or pyuria (gross or microscopic) may be reported in some (but not all) horses with pyelonephritis, urinary calculi, or neoplasia. Often, urine produced by horses with CRF is light yellow and transparent because it is relatively devoid of crystals and mucus. Accumulation of dental tartar (especially on the incisors and canine teeth [Fig. 34-4]), melena, and oral ulcers are other findings that may be detected in horses with CRF. Growth may be stunted in horses with renal hypoplasia, dysplasia, or polycystic kidney disease. Although abdominal pain would be expected in horses with obstructive nephroliths or ureteroliths, colic signs are not often reported in horses with lithiasis producing obstruction of the upper urinary tract.[9,23] Rarely, signs of uremic encephalopathy such as obtundation, anxiety, head pressing, and seizure may be present.[24,25]

Clinicopathologic findings in horses with CRF vary depending on appetite, diet, and the cause and severity of renal damage. Most horses with clinical signs of CRF have moderate to severe azotemia (creatinine usually ≥5 mg/dL). The BUN/creatinine ratio may vary depending on protein intake, muscle mass, hydration, and degree of azotemia, but is usually 10:1 or greater. Mild hyperkalemia, hyponatremia, and hypochloremia are typically found in horses with CRF. Hypercalcemia, with serum concentrations sometimes exceeding 20 mg/dL, appears to be a laboratory finding with CRF that is unique to the equid. One study of horses evaluated at referral hospitals for renal failure reported 56% of 39 horses with CRF to be hypercalcemic,[26] and a larger study of 99 horses with CRF found 67% to be hypercalcemic.[2] Hypercalcemia in horses with CRF is not due to hyperparathyroidism[27]; its presence or absence appears to be more closely related to dietary intake than to the magnitude of azotemia. For example, four of four nephrectomized ponies fed alfalfa hay developed marked hypercalcemia,[28] whereas serum calcium concentration remained within the normal range in four of four nephrectomized ponies fed grass hay (although filterable calcium did increase).[29] Similarly, hypercalcemia in horses with spontaneously occurring CRF can resolve within a few days of changing diet from alfalfa to grass hay.[13] Serum phosphorus concentration in horses with CRF is usually normal to decreased, and hypophosphatemia is more often detected with concurrent hypercalcemia. Hypermagnesemia may also be detected in some horses with CRF. Acid-base balance usually remains normal until CRF becomes advanced, but metabolic acidosis is a common finding in horses with end-stage disease.

Many horses with CRF are moderately anemic (packed cell volume, 20% to 30%) secondary to decreased erythropoietin production by the diseased kidneys. Those with CRF resulting from GN frequently have hypoalbuminemia and hypoproteinemia, and horses with advanced CRF of any cause may also have mild hypoproteinemia associated with intestinal ulceration. Hyperglobulinemia may be detected in horses with immune-mediated diseases or chronic pyelonephritis. Horses with CRF can also develop hypercholesterolemia and hypertriglyceridemia (hyperlipidemia), and horses with advanced CRF may occasionally have grossly lipemic plasma.[30]

Urinalysis findings may also vary depending on the cause of CRF. As mentioned, urine collected from horses with CRF is relatively devoid of normal mucus and crystals, making samples transparent. Urine specific gravity is typically in the isosthenuric range (1.008 to 1.014), although heavy proteinuria in an occasional horse with GN may produce values up to 1.020. Quantification of urine protein concentration (as for cerebrospinal fluid) is required to accurately assess proteinuria. Urine protein concentration in normal horses is usually less than 100 mg/dL, and the urine protein/creatinine ratio should be less than 1:1.[31,32] With significant proteinuria, urine protein/creatinine ratio is usually greater than 2:1.[5] In the earlier stages of GN, excessive urine protein is primarily albumin, but with progression of glomerular pathology, an increasing amount of globulin is also lost in the urine. Horses with CIN usually do not have significant proteinuria. Hematuria (gross or microscopic) may be present with pyelonephritis, urinary calculi, or neoplasia and can produce trace proteinuria, but urine protein/creatinine ratio usually remains less than 2:1. Horses with septic pyelonephritis would be expected to have pyuria (>5 leukocytes/high-power field) and significant bacteriuria on sediment examination, but these findings are not consistently detected; a urine sample should be submitted for quantitative bacterial culture in all horses with CRF. More than 10,000 colony-forming units (CFU)/mL of urine are typically found with infection, although lower numbers do not always rule out septic pyelonephritis.

Diagnosis A diagnosis of CRF is most often made in horses with azotemia and isosthenuria that present with a complaint of weight loss or decreased performance. As discussed earlier, determining the inciting cause of CRF can be difficult because the disease has often advanced to ESKD when horses are initially presented for evaluation. Urinalysis does not often reveal the cause of CRF except in some horses with pyelonephritis. In theory, assessment of urine protein concentration and urine protein/creatinine ratio should be helpful in separating glomerular disease from tubulointerstitial disease, but in practice, these laboratory measures have not consistently been elevated in horses with histopathologic evidence of GN. However, detection of moderate to heavy proteinuria (urine protein/creatinine ratio > 2:1) without hematuria provides support for glomerular disease.

Rectal examination may be helpful in determining the cause of CRF. Horses with pyelonephritis, as well as those with ureteral calculi, often have enlarged ureters that can be palpated dorsolaterally as they course through the retroperitoneal space. Although kidneys of horses with CRF are often small with an irregular surface, these changes are not always apparent on palpation of the caudal pole of the left kidney. The right kidney cannot usually be palpated in the horse unless it is greatly enlarged or displaced caudally by the liver or a mass. Ultrasonographic imaging is useful for evaluating kidney size and echogenicity and may reveal fluid distention (hydronephrosis, pyelonephritis, polycystic disease) or presence of nephroliths.[33-35] Horses with significant renal parenchymal damage and fibrosis often have loss of detail of the corticomedullary junction, and echogenicity of renal tissue may be similar or even greater than that of the spleen. In contrast, intravenous pyelography (IVP) provides little information in adult horses, and its use is generally limited to foals less than 50 kg. When hematuria or dysuria accompanies CRF, cystoscopic examination can be helpful in determining the side (right vs. left) from which renal hematuria is originating and further allows assessment of the ureteral orifices and urine flow from each kidney.

As described under Acute Renal Failure, measurement of GFR provides the most accurate assessment of renal function, and repeated measurements at monthly or longer intervals can be useful to monitor rate of progression of CRF. It is also a useful measure to document a reduction in renal function in horses that are thought to have

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early CRF, before significant azotemia has developed. GFR can be measured by several methods, including urinary clearance of endogenous or exogenous creatinine, inulin, or technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) (all require timed urine collections) or plasma disappearance of sodium sulfanilate, phenolsulfonphthalein, or radiolabeled compounds (e.g., ^{99m}Tc-DTPA).[13,36-39] Assessment of renal function by nuclear scintigraphic imaging of the kidneys has also been described, but in horses this technique appears to be better for documenting decreased individual kidney function (i.e., with unilateral or asymmetric disease) than for quantitative assessment of GFR.[40,41] In most clinical settings, performing a 24-hour endogenous creatinine clearance is the most practical and economical method for measuring GFR. The major challenge is application of a urine collection device for collection of all urine produced. Once urine has been collected, a well-mixed sample is submitted to the laboratory, along with a sample of serum obtained during the collection period, and GFR is estimated by the following standard clearance formula:

$$\text{GFR}\,(\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = \{([\text{Cr}_{\text{urine}}]/[\text{Cr}_{\text{serum}}])\}\times \text{UF/bwt}$$

where *UF* is urine flow (mL min^{-1}) and *bwt* is body weight in kilograms.[37] GFR in horses with normal renal function ranges from 1.5 to 3.0 mL · kg^{-1} · min^{-1}, and values less than 1.0 mL · kg^{-1} · min^{-1} are indicative of a decrease in GFR. Although repeated measurement of endogenous creatinine clearance provides useful information about the rate of decline in GFR in horses with CRF, simply measuring creatinine and assessing body condition at monthly or longer intervals are the most common methods used to evaluate the progression of CRF in affected horses.

The inciting cause of CRF can be confirmed in some horses by renal biopsy. As discussed under Acute Renal Failure, renal biopsy should be approached cautiously and pursued only if findings are likely to change treatment or prognosis. Treatment for CRF consists of supportive care, and because the long-term prognosis is poor, renal biopsy is rarely indicated in horses with CRF. Further, most horses have rather advanced CRF at the time the disease is initially detected, and biopsy results in these patients may not provide useful information regarding the inciting cause.

Treatment Treatment of horses with CRF is most likely to produce improved renal function if there is an acute reversible component exacerbating CRF (i.e., acute-on-chronic syndrome). Similar to ARF, sudden exacerbation can be caused by exposure to nephrotoxins or vasomotor nephropathy secondary to diseases producing hypovolemia (e.g., diarrhea or sepsis causing volume depletion). Ascending UTI or obstruction can also exacerbate CRF. If an acute component is detected, it should be corrected rapidly (as described for ARF) with the goal of minimizing further loss of functional nephrons. In addition, surgical removal or fragmentation of stones may be indicated in horses with calculi thought to be disrupting urine flow.

In horses with relatively stable CRF, management changes should be kept to a minimum and, when necessary, made gradually. Treatment of horses with stable CRF consists of supportive care: providing sufficient fluids, electrolytes, and nutritional support.[42] Water should be available at all times, and salt can be provided freely so long as edema or hypertension is absent. If edema develops, salt should be restricted, even in the face of hyponatremia. In addition to creatinine, serum electrolyte concentrations and acid-base balance should be measured regularly (e.g., monthly or longer intervals). If serum sodium and chloride concentrations are decreased, 60 to 120 g (≈2 to 4 oz) of salt may be added to the feed, provided edema is not present. If metabolic acidosis is detected (e.g., blood pH < 7.35 or serum bicarbonate concentration < 20 mEq/L) and the patient is not edematous, sodium bicarbonate ($NaHCO_3$) powder (100 to 200 g/day) or a mix of $NaHCO_3$ and salt should be added to the diet. The goal of supplementation with salt and $NaHCO_3$ is to maintain serum electrolyte concentrations and acid-base balance within reference ranges. However, the effect of electrolyte supplementation on progression of CRF is unclear because high-salt diets may actually hasten the decline in GFR and exacerbate proteinuria in human patients with CRF.[43]

Although no adverse effects of hypercalcemia in horses with CRF have been documented, decreasing calcium intake (e.g., replacing alfalfa or other legume hays with grass hay) may result in a return of serum calcium concentration to the normal range. The hypophosphatemia that usually accompanies hypercalcemia in horses with CRF may prevent mineralization of soft tissues. There appears to be no need for vitamin D supplementation in horses with CRF, but regular administration of vitamin B complex and anabolic steroids may be helpful to stimulate appetite. If appetite remains good, anabolic steroids may further limit muscle wasting and may increase packed cell volume (PCV). Attenuation of anemia in human and canine patients with CRF by administration of recombinant erythropoietin has been one of the most significant advances in management of CRF, because it has eliminated the need for blood transfusions, improved exercise capacity, and decreased morbidity associated with the uremic syndrome.[44] In an occasional horse with advanced CRF, marked hyperlipemia may develop, and administration of heparin (40 to 100 units/kg subcutaneously [SC] twice daily) may stimulate lipoprotein lipase and decrease plasma triglyceride concentration.[45] This treatment is not without risk, however; it may cause a further decline in PCV and potentiate bleeding tendencies in a uremic patient. NSAIDs and corticosteroids are best avoided in horses with CRF due to primary tubulointerstitial disease. If these drugs are essential for treatment of a complicating problem, they should be used judiciously.

Treatment of CRF due to GN appears to be even less rewarding than treatment of CRF caused by tubulointerstitial disease (CIN). Immunosuppressive therapy has been of limited benefit in slowing the progression of the disease and may even hasten weight loss, although short-term improvement with dexamethasone therapy has been documented in one horse.[8] For patients with significant edema, treatment with diuretics may result in transient improvement, and plasma transfusions may be of temporary benefit to horses with edema and hypoalbuminemia.

As CRF progresses, partial anorexia and lethargy lead to more rapid loss of body condition, so nutritional management aimed at maintaining body condition is probably the most important aspect of supportive care for these horses. Increasing carbohydrate (grain) intake and adding fat to the diet are recommendations to increase caloric intake. Fat can be added by feeding corn oil (up to 16 oz/day) or a commercial fat supplement. Increased intake of omega-3 fatty acids (e.g., available in linseed oil or flaxseed oil) has been demonstrated to slow the progression of renal failure in experimental models, but potential benefits in spontaneously occurring CRF are less clear.[46,47] Restricting dietary protein intake by human and veterinary patients with CRF was once thought to have beneficial effects,[48] but the current recommendation is to provide adequate amounts of dietary protein and energy to meet or slightly exceed predicted requirements while maintaining a neutral nitrogen balance.[49] In horses with CRF, adequacy of dietary protein intake can be assessed by the BUN/creatinine ratio; values greater than 15:1 suggest excessive protein intake, and values less than 10:1 may indicate protein-calorie malnutrition. Finally, an important but often overlooked aspect of nutritional management of horses with CRF is provision of a highly palatable diet. Feeding smaller meals more frequently and varying the diet (e.g., offering various types of concentrated feeds, as appetite may vary from day to day) are helpful methods to increase food intake.

Additional treatments for CRF in human patients include antihypertensive agents, including diuretics, β-adrenergic blockers, and angiotensin-converting enzyme (ACE) inhibitors.[50] ACE inhibitors may have an additional benefit of limiting proteinuria.[51] Little is known about the roles of systemic or intrarenal hypertension in progression of renal disease in horses, and there are no reports of potential benefits of use of antihypertensive medications in horses

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with CRF. Efforts are under way to examine the roles of mediators of inflammation in development of renal fibrosis, with the hope that future specific interventions may be developed to limit the progressive interstitial fibrosis that occurs in all patients with CRF.[52]

Horses with end-stage CRF often develop oliguria and uncontrollable metabolic acidosis. At this stage, CRF can only be managed by hemodialysis or peritoneal/pleural dialysis. However, pursuit of either hemodialysis or peritoneal dialysis in horses with CRF is impractical because, even when successful, dialysis prolongs the life of the patient for only a short time.

Prognosis The progressive loss of nephron function characteristic of CRF precludes successful long-term treatment in horses, but many horses with early CRF may be able to continue in performance or live as a pet for months to a few years. In general, as long as creatinine remains less than 5.0 mg/dL and the BUN/creatinine ratio is less than 15:1, affected horses seem to maintain a reasonably good attitude, appetite, and body condition. Once creatinine exceeds 5.0 mg/dL, the rate of progression of CRF appears to accelerate, and signs of uremia (e.g., anorexia, poor hair coat, loss of body condition) become more apparent over a few weeks to months. Although this threshold value for creatinine is a useful figure for offering an initial prognosis for most horses with CRF, it is important to remember that progression of CRF is highly variable among affected animals. Thus, each case must be handled on an individual basis, with the emphasis on maintenance of body condition until humane euthanasia may become necessary.

Urinary Tract Infections

Thomas J. Divers • Dominic R. Dawson Soto

UTIs can be anatomically divided into two categories: those affecting the upper urinary tract (kidneys and ureters) and those involving the lower urinary tract (bladder and urethra). Lower UTI in horses usually results from anatomic or functional causes of abnormal urine flow, especially bladder paralysis (see Urinary Incontinence). Although recognized less frequently, upper UTI is often a more serious, potentially life-threatening problem. In horses, UTI is also frequently accompanied by urolithiasis and partial obstruction. With the exception of single large cystoliths (that predispose affected horses to lower UTI), it is often difficult to determine whether development of nephroliths, ureteroliths, multiple small cystoliths, and urethroliths was a predisposing cause or a consequence of UTI. The pathophysiology, diagnosis, and management of equine UTI has recently been extensively reviewed.[1]

Risk Factors and Causes

The most common risk factors for development of UTI in horses are bladder paralysis, concurrent urolithiasis, and urethral damage (e.g., foaling trauma in mares, neoplasia or habronemiasis in stallions and geldings). The shorter urethra and its location near the anus also increase the risk of lower UTI in healthy females. For example, in humans, silent lower UTIs and pyelonephritis resulting from infection with bacteria shed from the GI tract can develop in prepubertal girls and during pregnancy or after menopause in adult women.[2] This increased risk at certain times has been further attributed to a lack of estrogen, a hormone that appears to be important for production of glycosaminoglycans that cover uroepithelial surfaces and inhibit attachment of bacteria.[3] Whether fillies or pregnant mares are at increased risk for UTI has not been studied. However, horses with bladder paralysis (detrusor dysfunction) or decreased urethral sphincter tone (from trauma or neurologic disease) are clearly at greater risk of UTI than horses with normal detrusor and urethral sphincter function. Finally, because bladder catheterization cannot be performed in a sterile manner because of normal bacterial flora in the vestibule and distal urethra, contamination of the lower urinary tract is an accepted risk of this procedure. Nevertheless, development of lower UTI is an unlikely complication of bladder catheterization in otherwise healthy animals, because host defense mechanisms, including urine flow, are highly effective in eliminating contaminating bacteria. When urethral or bladder mucosa has been damaged or urine stasis (bladder paralysis) is present, bladder catheterization has a greater risk of producing UTI.

In a group of horses with neurologic bladder dysfunction complicated by UTI, *E. coli, Staphylococcus* spp., *Corynebacterium* spp., and *Pseudomonas aeruginosa* were the microbes isolated most frequently.[4] In the author's experience (TJD), *E. coli, Proteus mirabilis, Klebsiella* spp., and *Enterobacter* spp. are the most common pathogens isolated from individual horses with UTI. *P. aeruginosa* can cause lower UTI in some horses, but it can also be isolated from the urethra of many clinically normal horses. Gram-positive organisms are less frequent causes of UTI in horses, although *Streptococcus, Staphylococcus,* and *Corynebacterium* spp. are occasionally identified pathogens.[5,6] In horses with abnormal urine flow (e.g., with uroliths) or instrumentation of the urinary tract (e.g., indwelling bladder catheters, ureteral stents), UTI with *Enterococcus* spp. (formerly *Streptococcus faecalis*) may also develop. Similarly, lower UTI with *Candida* spp. develops in recumbent neonatal foals receiving broad-spectrum antibacterial therapy. Additional organisms such as *Actinobacillus equuli, Rhodococcus equi,* and *Salmonella* spp. have been identified in septic foals.[7] In horses without an obvious predisposing factor, primary immune dysfunction, such as pituitary pars intermedia dysfunction, should be considered.

Clinical Findings Clinical signs of UTI usually reflect the location, severity, and duration of the infection. Lower UTI is typically characterized by recognizable disturbances in urine flow but seldom causes signs characteristic of a systemic infection (e.g., fever, weight loss). Dysuria, stranguria, pollakiuria, and incontinence are consistent with lower UTI. Urine scalding of the perineum may develop with chronic UTI in mares (but should not be confused with estrus), and the sheath opening and dorsal aspects of the hindlimbs may be coated with urine crystals or blood in affected stallions and geldings. Gross hematuria may be observed if urinary calculi are present or if bladder or urethral mucosa has been eroded. Hematuria of bladder origin typically produces hematuria throughout urination, but gross discoloration of urine is most obvious at the end of urination. Hematuria caused by renal hemorrhage was a major component of pyelonephritis reported in seven horses.[8] In an occasional horse, gross pyuria may also be observed as passage of mucopurulent debris in otherwise clear urine. Horses with upper UTI are more likely to have signs characteristic of a systemic infection (e.g., fever, weight loss), but because UTI is typically accompanied by concurrent lower UTI, dysuria may also be present. As an example, recurrent urethral obstruction with small uroliths may be the presenting complaint for chronic upper UTI.

Rectal examination may help confirm a predisposing cause of lower UTI (e.g., enlarged and atonic bladder, cystic calculi, accumulation of sabulous urine sediment, bladder mass). Chronic cystitis also usually leads to bladder wall thickening, but this change is not easily detected by rectal palpation. Although ureters are not usually found during rectal examination of the normal horse, careful palpation of the dorsolateral aspects of the caudal abdomen (retroperitoneal space) usually reveals enlarged ureters in horses with upper UTI. With pyelonephritis, palpation may further reveal an enlarged, painful, or shrunken and misshapen kidney.

Diagnosis A diagnosis of UTI is based on clinical signs and laboratory analysis of blood and urine samples. With lower UTI, results of a complete blood cell count (CBC) and serum biochemical profile are usually within reference ranges, whereas CBC results with upper UTI often support a systemic inflammatory response. With chronic upper UTI, increased total protein and globulin concentrations are often detected, and azotemia may also be present. Detection of greater than 20 organisms and more than 10 white blood cells

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(WBCs) per high-power field on sediment examination of a urine sample collected during midstream voiding or via bladder catheterization is highly supportive of UTI, and growth of 10^4 or more organisms per milliliter of urine confirms the diagnosis.[9,10] When evaluating a horse for possible UTI, urine samples collected should be examined and processed for bacterial culture within 30 minutes after collection, or they should be refrigerated because bacteria can continue to proliferate when urine is stored at room temperature.[9]

Detection of azotemia, low urine specific gravity, and WBC casts in urine sediment are indicative of upper UTI, especially when accompanied by signs of systemic illness. Ultrasonographic examination of the kidneys is useful for detecting abnormal renal size, shape, or consistency in horses with upper UTI.[8,11-13] Transrectal ultrasound can further characterize the bladder, particularly thickening of the bladder wall, ureters, and left kidney. The right kidney is rarely to never visualized. Endoscopic examination of the lower urinary tract is useful for evaluating the integrity of urethral and bladder mucosa, detecting small uroliths, and assessing urine flow from each ureteral orifice.[14,15] With long-standing cystitis, especially when bladder paralysis is the underlying cause, ureteral orifices may become dilated (and appear wide open), allowing for vesiculoureteral reflux and development of ascending pyelonephritis. When unilateral pyelonephritis is suspected on the basis of ultrasonographic findings, catheterization and collection of urine samples individually from each ureter can be helpful to document unilateral disease. Ureters may be catheterized by passing sterile polyethylene tubing through the biopsy channel of the endoscope during cystoscopy or can be accomplished in mares by directing blunt-ended catheters (e.g., 8-Fr polypropylene) through the urethra into each ureteral orifice.[16]

Treatment

Treatment of UTI consists of proper antimicrobial therapy and correction, if possible, of predisposing anatomic or functional causes. Selection of the appropriate antimicrobial agent is best determined by prior knowledge of:

- Susceptibility patterns of the causative agent(s)
- Concentration of the antibiotic in renal tissue and urine
- Activity of the antibiotic at different pH values
- Ease of administration
- Toxicity
- Expense
- Compatibility with other antimicrobial drugs

Recommended antimicrobial agents for UTI treatment in horses are discussed next. It should be emphasized that in vitro resistance to a particular antibiotic may not preclude successful treatment with the drug, so long as high concentrations are achieved in urine. Similarly, in vitro susceptibility does not always guarantee a successful response to treatment. For example, *Enterococcus* spp. are routinely found to be susceptible to trimethoprim-sulfa combinations; however, this pathogen is inherently resistant to these combinations in vivo.[17]

TRIMETHOPRIM/SULFONAMIDE COMBINATIONS. Trimethoprim-sulfonamide combinations have been highly successful in treating lower UTIs in some species.[18-20] Although sulfonamides alone can be effective in treating many lower UTIs,[21] addition of trimethoprim improves the antibacterial spectrum without a prohibitive increase in expense or toxicity.[22] When selecting a trimethoprim-sulfonamide combination for treatment of horse with a UTI, metabolism of the sulfonamide should be considered; sulfamethoxazole is largely metabolized to inactive products before urinary excretion, whereas sulfadiazine is excreted largely unchanged in urine.[23] Although less of a risk with newer preparations, horses with acidic urine, dehydration, or poor renal perfusion may develop hematuria and crystalluria with sulfonamides.[24]

PENICILLIN AND AMPICILLIN. Parenterally administered penicillin is effective for treating upper or lower UTIs caused by susceptible *Corynebacterium, Streptococcus,* and some *Staphylococcus* spp.[25] Ampicillin has also been used successfully for treatment of both upper and lower UTIs in animals and human patients.[18,26] Although many isolates of the Enterobacteriaceae family demonstrate resistance to ampicillin in vitro, this drug is highly concentrated in urine, and many organisms that are resistant in vitro may be killed in the urine of treated animals.

GENTAMICIN AND AMIKACIN. Gentamicin and amikacin, which can be nephrotoxic, should be reserved for treating lower UTIs caused by highly resistant organisms or acute, life-threatening upper UTIs caused by gram-negative organisms. Pharmacokinetic studies in adults and foals are available.[27,28] Potentiated penicillins (ticarcillin or ticarcillin/clavulanic acid) may be considered as an alternative to aminoglycosides in horses with severely compromised renal function (e.g., creatinine > 3.0 mg/dL).

CEPHALOSPORINS, TETRACYCLINES, AND CHLORAMPHENICOL. Cephalosporins, tetracyclines, and chloramphenicol are frequently and effectively used to treat UTIs in other species.[26] Cephalosporins are concentrated in urine. Ceftiofur has broad-spectrum antimicrobial activity and could be selected when urinary pathogens demonstrate resistance to trimethoprim-sulfonamide combinations or penicillin. Tetracycline and chloramphenicol are predominantly metabolized in the liver, with variable excretion in bile. However, when acceptable serum concentrations are achieved, excretion of active drug into urine may be high enough that either drug may be effective for treatment of UTIs caused by susceptible organisms.[29,30]

OTHER ANTIMICROBIAL AGENTS. Nitrofurantoin has an impressive in vitro spectrum, demonstrating activity against most common gram-negative organisms including *Salmonella.*[13] The drug is inexpensive, is easily administered as an oral suspension, and achieves high concentrations in urine. Although this antimicrobial agent has not been well studied in horses, adverse effects and acquired resistance appear to be uncommon. However, nitrofurantoin does not attain high concentrations within renal parenchyma, so its efficacy in treating upper UTI would be questionable. Further limitations of nitrofurantoin usage include decreased antimicrobial activity at an alkaline pH, and increased risk of toxicity has been described in other species as GFR falls (e.g., with CRF). Because urine concentration and antimicrobial activity of nitrofurantoin after oral (PO) administration have not been well substantiated in horses, use of this antibiotic should be reserved for selected cases where specific susceptibility of a gram-negative organism has been demonstrated, or when expense precludes selection of another antibiotic for long-term therapy.

It is not unusual to find highly resistant organisms in urine of horses with chronic UTIs, especially those with bladder paralysis that have been repeatedly catheterized and have received a variety of antibiotic agents. In some cases the organisms may be highly resistant to all drugs approved for use in the equine. One of the authors (TJD) has successfully treated a few adult horses and a yearling with UTI with PO enrofloxacin (7.5 mg/kg q24h), without apparent adverse effects. Potential cartilage damage in younger horses should be considered and discussed with the owner before treatment with enrofloxacin is pursued. Ciprofloxacin has also been associated with emergence of resistant *E. coli* in humans, so care should be taken to use the drug under the guidance of appropriate culture and sensitivity profiles.[31]

When treating UTIs in horses, antimicrobial therapy should be continued for at least 1 week for lower UTIs and 2 to 6 weeks for upper UTIs. Ideally, a midstream voided urine sample should be submitted for bacterial culture 2 to 4 days after initiation of therapy and again 1 to 2 weeks after treatment has been discontinued. If the UTI recurs and the same organism is isolated, a focus of upper UTI should be suspected. Ultrasonographic or nuclear scintigraphic examination of the kidneys should be considered in such cases to rule out a nephrolith or other parenchymal disease. Cystoscopy and ureteral catheterization can also be pursued to evaluate for unilateral or bilateral infection of the upper tract. In contrast, recurrence of UTI

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with a different pathogen suggests an anatomic or functional cause of abnormal urine flow as a predisposing cause of recurrent lower or upper UTI.

Although unstudied in horses, the use of lactobacillus suppositories in human females predisposed to UTI has decreased the incidence and may be useful in mares.[32] Preliminary research on vaccines against bacterial virulence factors to reduce the incidence of UTIs in predisposed populations of humans and mice appears promising, but research on the benefits of vaccination in horses is lacking.[33,34]

Urinary Incontinence

Elizabeth Ann Carr • Dominic R. Dawson Soto

Urinary incontinence in the horse can result from urolithiasis, congenital anomalies or defects of the lower urinary tract, trauma, neoplasia, neurologic diseases accompanied by bladder dysfunction, and decreased urethral tone. Bladder and urethral calculi frequently result in transient incontinence secondary to cystitis or partial obstruction. Ectopic ureter and other congenital malformations of the urinary tract generally produce incontinence from birth, although development of incontinence in adult horses has been described.[1-4] Traumatically induced incontinence may develop after breeding injury or dystocia in mares or in both genders after sacral or spinal injury.[5] Incontinence has also been speculated to develop with long-standing lumbosacral or lower back problems that make it difficult for horses to posture to urinate. Over time, incomplete bladder emptying allows crystals normally present in equine urine to accumulate in the ventral aspect of the bladder. This crystalloid sediment becomes heavy and in some cases quite firm and further prevents complete bladder emptying. This condition, which has been termed *sabulous urolithiasis,*[6] can accompany bladder paralysis of any cause but may also be able to produce myogenic bladder dysfunction in the absence of an underlying neurologic problem. Horses with neoplasia of the lower urinary tract can also present with incontinence, but other complaints (e.g., stranguria or hematuria) are usually reported as well.

Neurologic disorders that often result in bladder paralysis and incontinence include equine herpesvirus (EHV) myelitis, equine protozoal myeloencephalitis, aberrant larval migrans, cauda equina neuritis, and sorghum toxicosis. These diseases, along with other problems affecting gray matter of the sacral segments, result in loss of lower motor neuron (LMN) function, whereas lesions of the lumbar or higher portions of the spinal cord result in loss of upper motor neuron (UMN) function. LMN damage leads to loss of detrusor muscle function and overflow incontinence. A large, easily expressed bladder is found on rectal palpation. Initially, UMN disease is characterized by increased urethral resistance, leading to increased intravesicular pressure before voiding can occur. Voiding may occur as short bursts of urine passage with incomplete bladder emptying, and rectal examination may reveal a turgid bladder that is small to increased in size. Although UMN signs are initially different from those of LMN disease, incontinence is not usually recognized until overflow incontinence develops as a result of sabulous urolithiasis and progressive loss of detrusor function. The latter progression can explain why bladder paralysis and incontinence may occasionally be found in horses with other neurologic diseases like cervical stenotic myelopathy, equine degenerative myelopathy, and even viral encephalomyelitis. Presence of other signs associated with LMN dysfunction (e.g., loss of anal or tail tone) or UMN dysfunction (e.g., ataxia) may aid in differentiating the inciting cause of bladder paralysis. Despite many possible causes, the prognosis for recovery from incontinence resulting from bladder paralysis is generally poor because sabulous concretions and UTI quickly complicate the problem.

A final syndrome of incontinence caused by decreased urethral sphincter tone has been reported in a few mares.[7,8] This condition has been attributed to hypoestrogenism, because incontinence improved after treatment with exogenous estrogen.

Diagnosis

In addition to taking a complete history and performing physical and neurologic examinations, it is helpful to observe the incontinence or any attempts to urinate. Rectal palpation, transrectal ultrasonography of the bladder and upper urinary tract, transabdominal ultrasound of the kidneys and endoscopy of the lower urinary tract are useful to rule out uroliths, neoplasia, and congenital anomalies as causes of incontinence. If trauma or sacral bony abnormalities leading to incontinence are suspected, radiographs or pelvic ultrasound should be performed. Although most affected horses remain nonazotemic (unless significant obstruction or bilateral pyelonephritis has developed), laboratory analyses of blood and urine, including a quantitative urine culture, should be performed in all horses with incontinence, because UTI is a common sequela. Urethral and bladder pressure profiles can be used to assess urinary sphincter and detrusor muscle function. Normal values for both mares and geldings have been reported.[9-10] When an underlying neurologic problem is suspected, cerebrospinal fluid (CSF) collection and analysis may also be of value.

A review of 21 horses presented to Michigan State University's Veterinary Teaching Hospital between 1995 and 2000 with a primary complaint of incontinence revealed that 15 horses had bladder paralysis, three had urolithiasis, and one foal had bilateral ureteral ectopia. Another horse had incontinence of undetermined cause that appeared to respond to treatment with phenylbutazone. The remaining horse had a urachal diverticulum, hydroureters, cystitis, pyelonephritis, an atonic bladder, and urethral sphincter dysfunction that was supported by an abnormal urethral pressure profile.[11] Of the 15 horses with bladder paralysis, four developed the problem after foaling, two of which had dystocia. Fat necrosis around the urethra and bladder neck was found postmortem in one of the latter mares. Bladder paralysis was attributed to equine protozoal myelitis (EPM) in two horses and to EHV myelitis, cauda equina neuritis, and cervical stenotic myelopathy in one horse each. One horse had segmental neuronal degeneration in the lumbosacral and caudal spinal cord, and another horse had histopathologic evidence of denervation atrophy of the detrusor that was attributed to prior spinal cord trauma. An underlying neurologic disease causing bladder paralysis could not be determined in the remaining four horses. Although originally presented for evaluation of acute-onset severe spinal ataxia and weakness, another mare developed signs of UMN bladder dysfunction (squirts of urine and a turgid bladder on rectal palpation) during hospitalization. Bladder function returned to normal as the neurologic disease improved over 2 weeks.

Treatment

Treatment for incontinence varies with the underlying cause. Removal of calculi and appropriate antimicrobial therapy are effective treatments for urolithiasis. Surgical correction is generally required for treatment of congenital anomalies, but owners should be discouraged from using affected animals for breeding. EHV myelitis and EPM carry the most favorable prognoses for recovery, although bladder paresis may persist for several weeks to months (personal observation with EHV-1, DR Dawson). To prevent continued distention and further damage to the detrusor, removal of sabulous crystalloid material (by bladder lavage through a catheter or by cystotomy) and temporary placement of an indwelling bladder catheter are indicated in cases of recent onset of bladder paresis. Debate exists in the human literature regarding the preference of intermittent versus continuous urinary catheterization. In horses, both methods carry potential risks—infection and/or trauma from repeated catheterization—and each case should be evaluated individually to choose the most appropriate method.[12,13] Antimicrobial treatment, ideally based on urine culture results, is also indicated in all horses with bacterial cystitis secondary to bladder paralysis.

Bethanechol (0.03-0.04 mg/kg SC q6-8h or 0.22-0.45 mg/kg PO q6-8h), a parasympathomimetic agent that appears to have a somewhat selective effect on smooth muscle of the GI tract and bladder, has been recommended for improving detrusor tone and strength of contraction in horses with bladder paralysis. However, response to treatment has usually been disappointing, perhaps because of

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long-standing paralysis before incontinence is recognized. Use of phenoxybenzamine (0.7 mg/kg PO q6h), an α-adrenergic blocker that decreases urethral sphincter tone, has also been recommended in combination with bethanechol in cases with UMN bladder dysfunction. In horses with evidence of urethral sphincter hypotonia, the sympathomimetic agent phenylpropanolamine (1-2.5 mg/kg PO q8-12h) has also been used, but a successful response has not been reported. Dosing regimens for these autonomic drugs have been extrapolated from other species, because no pharmacokinetic data are available for the equine species.

In general, treatment with these autonomic drugs has largely been ineffective in controlling incontinence due to bladder paralysis, and the long-term prognosis for recovery is usually poor. On a more positive note, treatment of a few mares with urethral sphincter hypotonia with estradiol cypionate or benzoate (5 to 12 µg/kg IM every day for 3 days, then every other day) has been effective at resolving incontinence as long as detrusor function was normal. Estrogen may modulate the effect of norepinephrine on α-receptor activity in the urethral sphincter, thereby improving urethral sphincter tone. Of further interest, incontinence in two mares with partial detrusor dysfunction was also reported to improve after treatment with estrogen,[8] although the mechanism by which estrogen would improve detrusor function is unclear.



FIG. 34-5 Urine scalding in an 8-month-old Thoroughbred filly with a left ectopic ureter. The filly recovered after a nephrectomy.

Ectopic Ureter

Thomas J. Divers • Stephanie A. Brault

Although rare, ectopic ureter is the most frequently reported developmental anomaly of the equine urinary tract. This abnormality is the result of an error in embryologic development causing one or both ureters to empty into the urethra, uterus, or vagina instead of attaching normally to the dorsal wall of the urinary bladder. Of the cases reported, almost 90% have been fillies, and the primary complaint is urinary incontinence and perineal dermatitis (urine scalding).[1-4] However, this gender distribution may reflect easier recognition of urinary incontinence in females rather than a true gender predilection. In the male, intermittent urine dripping from the end of the penis is less easily recognized; further, urine entering the pelvic urethra may pass retrograde into the bladder.

Diagnosis Ectopic ureter should be suspected in young horses with incontinence observed shortly after birth. Renal function is usually normal, but the affected ureter may be extremely dilated. In young foals (e.g., <50 to 75 kg) an excretory urogram (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis via ultrasonographic guidance) may aid in diagnosis of ectopic ureter.[4,5] Unfortunately, most patients are not presented until they are too large for this procedure to be performed (Fig. 34-5). Ultrasonographic examination may reveal mild dilation of the renal pelvis on the affected side. Vaginoscopic and cystoscopic examinations should also be pursued in older foals to determine whether the problem is unilateral or bilateral, and when unilateral, to determine which ureter is ectopic. In the latter case, cystoscopic examination should reveal urine entering the bladder from only one normal ureteral opening, located at either 2 or 10 o'clock in the bladder neck. Urine can be seen squirting from normal ureteral openings every 20 to 30 seconds. Observation of normal bouts of voiding, in addition to incontinence, further supports a unilateral problem. To determine the location of the opening of the ectopic ureter, visual examination of the vestibule and vagina (using a blade speculum) should be performed initially to look for intermittent urine flow from the area of the urethral papilla. Ectopic ureteral openings are usually not apparent unless urine flow is seen. IV administration of dyes including sodium fluorescein (11 mg/kg IV; yellow-green color), indigotindisulfonate (indigo carmine, 0.25 mg/kg IV; blue-purple color), azosulfamide (1.9 mg/kg IV; red color), or phenolsulfonphthalein (0.01 mg/kg IV; red color) to discolor the urine may help locate ectopic ureteral openings.[1,2] Nuclear scintigraphy has also been employed to assess renal function and anatomy of involved urinary tract structures prior to correction.[6]

Treatment If the ectopic ureter is unilateral, ultrasonographic examination of the opposite kidney appears normal, and azotemia is not present, the preferred treatment may be surgical removal of the kidney on the affected side and ligation of the ureter. Nephrectomy may produce an increase in creatinine (0.5 to 1 mg/dL) for a few days, but creatinine returns to the prenephrectomy value within a week. If both ureters are ectopic, which is not unusual, implantation of the distal ureters into the bladder neck should be attempted. Several surgical techniques have been described. Complications can include ascending infection, resulting from dilated ureters, and development of adhesions, but successful repairs have also been reported.[1-6]

Neoplasia

Thomas J. Divers • Stephanie A. Brault

Neoplasia of the urinary tract is rare in horses. Primary kidney neoplasms include renal cell carcinoma and nephroblastoma, with the former being the most common tumor of the kidney.[1] Renal cell carcinoma (or adenocarcinoma) occurs more frequently in older horses, but nephroblastomas may be detected in young horses. Squamous cell carcinoma is the most common bladder tumor, but horses may also develop transitional cell carcinoma.[2,3] Fibromatous polyps may also occur in younger horses, but bladder tumors usually develop in middle-aged to older horses. Adenoma, lymphosarcoma, hemangiosarcoma, and melanoma may also involve the kidneys and, on rare occasions, the bladder.[4,5]

Clinical Signs and Diagnosis Clinical signs in horses with renal neoplasia include hematuria, weight loss, and recurrent colic. Sudden death may occur if the neoplasm hemorrhages into the abdomen or thorax. Renal tumors may result in marked enlargement of the kidneys such that both left and right kidneys may be found on rectal palpation. In other cases, tumors may be small, circumscribed lesions within a kidney (Fig. 34-6) that cannot be felt during rectal palpation. Small tumors may also be difficult to visualize on

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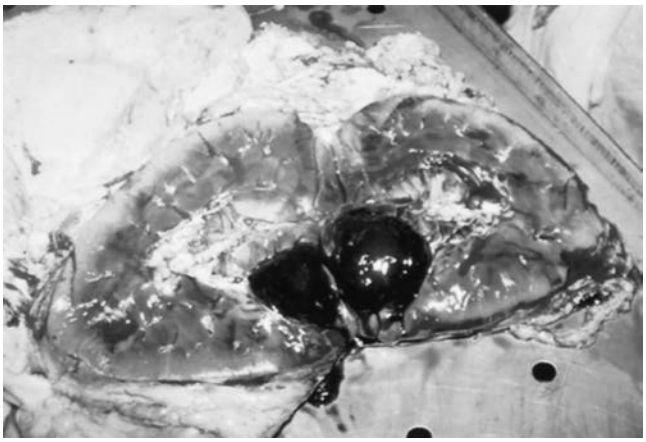


FIG. 34-6 Cut section of the left kidney from a 25-year-old horse with chronic weight loss, hematuria, and severe anemia. The kidney appeared normal except for a small 4 × 5 cm carcinoma with surrounding hemorrhage.

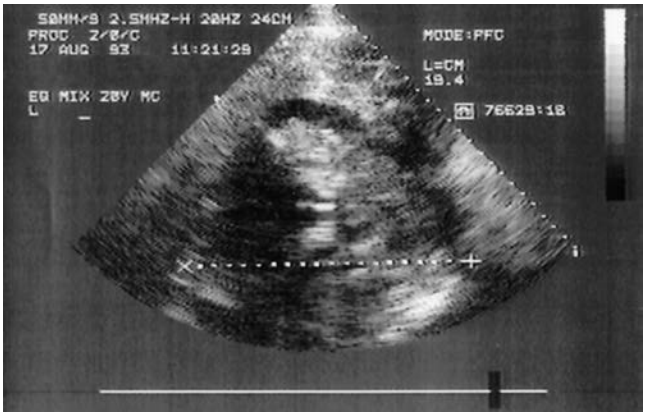


FIG. 34-7 Sonogram of the left kidney area of a 19-year-old horse with chronic hematuria. A 26 × 20 × 19 cm echocavitated mass (renal carcinoma) originates from the left kidney.

ultrasonographic examination. The diagnosis is based on history, clinical signs, and ultrasonographic findings (Fig. 34-7). Affected horses usually are not azotemic, but mild anemia may be detected when gross hematuria is observed. Although neoplastic cells are unlikely to be found in urine, cytologic examination of urine sediment is warranted. Renal biopsy has been found to be associated with a low rate of serious complications and provided a histopathologic diagnosis in most cases, although horses with neoplasia had greater odds of complications than those with any other histopathologic diagnosis.[6] Nephroblastoma usually remains limited to the kidney; renal cell carcinomas typically metastasize. The liver and lungs are the most common sites of metastasis,[7,8] but tumors can also spread to unusual sites, leading to signs as varied as lameness[9] or an ulcerated mass on the premaxilla.[10] Multiple myeloma involving the kidney resulted in hypercalcemia and a high serum parathyroid hormone–related protein concentration.[11] Hypoglycemia was the chief clinical sign in a 6-year-old horse with renal cell carcinoma producing insulin-like growth factors.[12]

In addition to hematuria and weight loss, horses with bladder tumors may also present with pollakiuria and stranguria. With bladder tumors, a mass can usually be palpated on rectal examination, but it should not be confused with a cystolith or accumulation of sabulous concretions in the ventral aspect of the bladder. Horses with gross hematuria may be mildly anemic but usually are not azotemic. Other than hematuria and associated proteinuria, urinalysis results are often unremarkable, but with bladder tumors, cytologic

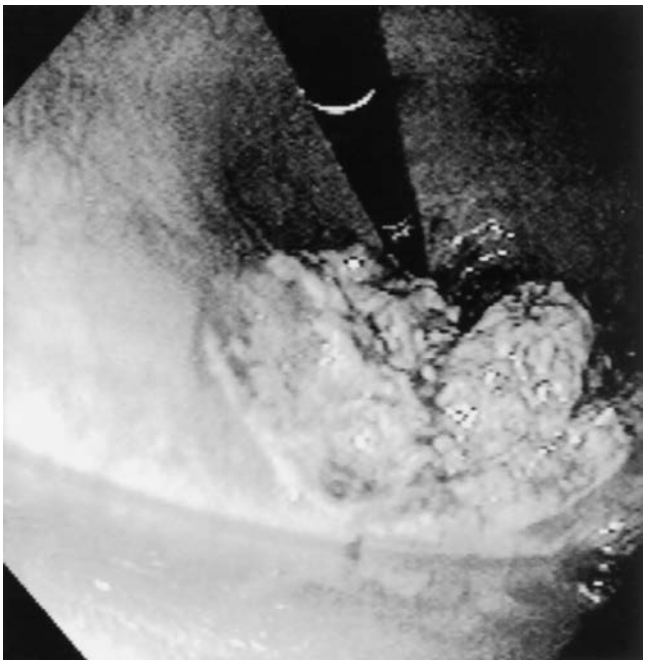


FIG. 34-8 Cystoscopic image of a squamous cell carcinoma of the bladder causing intermittent hematuria in a 14-year-old warmblood mare. The endoscope has been passed beyond the tumor and retroflexed to provide a view directed caudally; a pool of urine is in the foreground, and the tumor can be seen in the ventral aspect of the bladder neck.

examination of urine sediment is more likely to reveal neoplastic cells than with renal tumors.[2,13] A diagnosis of bladder neoplasia may be confirmed by cystoscopic examination and biopsy (Fig. 34-8).

Treatment The treatment of choice for unilateral renal neoplasia is nephrectomy. Unfortunately, most cases of renal cell carcinoma have metastasized by the time the diagnosis is made, and surgical intervention is of little benefit to horses with disseminated disease. Thus, careful evaluation for metastatic disease should be pursued before contemplating a nephrectomy.[14] Treatment of bladder tumors includes surgical excision and/or topical chemotherapy using either 5-fluorouracil or triethylenethiophosphoramide.[2]

Urolithiasis and Obstructive Disease

Thomas J. Divers • Theresa Lynn Ollivett

Renal and Ureteral Calculi

Renal and ureteral calculi can produce partial or complete obstruction of one or both sides of the upper urinary tract. Nephroliths usually develop within or adjacent to the renal pelvis, and obstruction can lead to hydronephrosis. Most ureteroliths likely originate as nephroliths that pass into the ureter, where they become lodged and enlarge over time. Ureteral stones have a propensity to lodge in the distal ureter and can sometimes be palpated rectally dorsal and lateral to the bladder neck. Occasionally, small nephroliths may pass all the way down the ureter into the bladder; unlike their human counterparts, affected equine patients are rarely recognized to manifest renal colic.[1,2] Renal and ureteral calculi are most often composed of calcium carbonate crystals; calcium phosphate stones may occasionally develop. Although usually not recognized clinically, a nidus of damaged tissue (e.g., interstitial inflammation, infection, or fibrosis; area of medullary crest necrosis adjacent to renal pelvis) is likely necessary for initiation of stone formation. Anomalies of development (e.g., renal hypoplasia, dysplasia, polycystic disease) or prior

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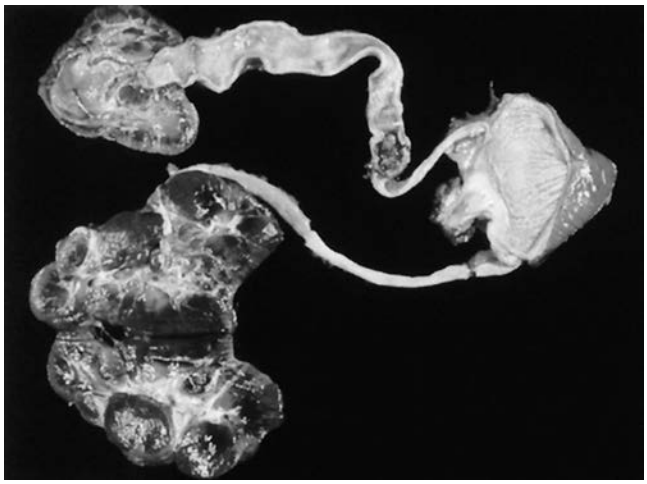


FIG. 34-9 Urinary tract removed from a 5-year-old Standardbred with chronic renal failure caused by intermittent or persistent obstruction by renal and ureteral stones. Note the location of the ureteral obstruction near the bladder. This is the most common site for the obstruction to occur.

exposure to nephrotoxins could also provide a nidus for stone formation.

Bilateral nephrolithiasis and ureterolithiasis have been best described in a series of young adult racehorses, and development of subclinical medullary crest necrosis as a result of NSAID use was a suggested risk factor[3]; this was also seen in a 2-year-old gelding.[4] When both sides of the upper tract are affected, the condition typically progresses to CRF before horses are presented for evaluation (Fig. 34-9). As described for CRF, the most common presenting complaint is weight loss, but polyuria and poor performance may be earlier complaints in competitive horses. Establishing a diagnosis of urolithiasis causing unilateral upper tract obstruction is more challenging because clinical signs are mild (recurrent colic) or nonexistent and azotemia is usually absent. In fact, unilateral upper tract stones may be detected as incidental necropsy findings in horses of all ages. In horses with clinical signs, careful rectal palpation may reveal a turgid ureter and presence of a ureterolith. When passed from the upper tract into the bladder, small uroliths may be voided without problem or may cause urethral obstruction in males. Horses with repeated bouts of urethral obstruction should be thoroughly evaluated for presence of upper tract disease.

In horses with bilateral disease leading to CRF, azotemia and isosthenuria are present. As already mentioned, azotemia is usually absent with unilateral obstruction. With either scenario, gross hematuria is uncommon unless stones have been passed into the bladder or urethra, but urinalysis usually reveals pigmenturia, and microscopic hematuria is confirmed by examination of urine sediment. Although UTI is not usually present with upper tract obstruction due to lithiasis at the initial evaluation, it may develop with catheterization or other instrumentation used for relief of the obstruction. Thus a quantitative urine culture should be considered part of the minimum database, especially if pyuria or bacteriuria is detected on sediment examination. Transabdominal ultrasonography is a valuable tool for detection of nephroliths, dilation of the renal pelvis (or complete hydronephrosis), and fibrosis (increased echogenicity) within the kidney.[5-7] However, small nephroliths (<1 cm in diameter) can occasionally be missed despite a complete ultrasonographic examination. Transrectal ultrasonography is also useful for detecting ureteral dilation and lithiasis.

If upper urinary tract obstruction is diagnosed before development of more severe azotemia (creatinine > 5.0 mg/dL), surgical removal is recommended. A nephrotomy and/or ureterotomy may be required.[1,3] When equipment is available, electrohydraulic lithotripsy is the preferred technique for removal of ureteral stones.[8] This procedure involves passing an endoscope into the ureter until the stone can be seen, then advancing a lithotriptor through the biopsy channel of the endoscope until the end touches the ureterolith (Fig. 34-10, *A*). An irrigating solution is pumped through the endoscope to distend the distal ureter, and an electrical impulse delivered by the lithotriptor causes a shock wave at the surface of the stone. Because the majority of calcium carbonate stones are inherently fragile,[9] fragmentation by lithotripsy is usually rapid (see Fig. 34-10, *B*), and remaining fragments are flushed distally by further infusion of irrigating solution (see Fig. 34-10, *C*). Before surgical intervention is pursued, both kidneys should be thoroughly evaluated for evidence of other stones, because upper tract lithiasis is often bilateral.

In addition to intermittent signs of mild colic, unilateral nephroliths may occasionally cause intermittent or persistent gross hematuria. In the absence of azotemia and evidence of disease of the contralateral kidney, unilateral nephrectomy is the treatment of choice for obstructing nephroliths and remains a reasonable alternative to lithotripsy for treatment of unilateral ureteroliths[10] (Figs. 34-11 and 34-12).

Cystic Calculi

Although occurrence is rare compared with other species, cystolithiasis is the most common form of urolithiasis in horses, and intact males appear to be at greater risk.[2,11] Calculi that develop in the bladder are usually single, large, spiculated stones composed of calcium carbonate crystals.[9,11,12] Less often, stones are a mix of calcium carbonate and calcium phosphate crystals; these stones often have a smooth surface and are more resistant to fragmentation.[13] Risk factors for development of bladder stones in horses are not well understood, but anatomic defects (e.g., diverticuli) or suture material persisting or migrating from prior urogenital surgery may predispose horses to cystic calculi.[14] Although bacteria can often be detected by culture of the center of equine calculi, their role in stone formation is unclear.[2] Considering that normal equine urine is rich in calcium carbonate crystals, it is surprising cystoliths are not more common in horses than in ruminants or small animals. Their low occurrence can likely be attributed to the large amount of mucus that is also present in horse urine. Mucus, produced by glands in the renal pelvis and proximal ureter, appears to act as a lubricant to prevent adherence of crystals to uroepithelium.

The most common clinical sign exhibited by horses with cystic calculi is hematuria after exercise. Pollakiuria, stranguria, or incontinence may also be observed. Less frequently, dysuria may be caused by accumulation of urine sediment in the ventral aspect of the bladder. This condition, sabulous urolithiasis, usually develops secondary to bladder paralysis.[15] Urinary incontinence is common in horses with sabulous urolithiasis, and prognosis is guarded to poor because of underlying detrusor dysfunction; however, return to athletic function is possible.[16]

Presence of a cystolith can be confirmed by rectal examination. It is important to remember that most bladder stones can be palpated with only the hand and wrist in the rectum. As a result of frequent urination, the bladder is usually small, and cystic calculi can be missed if the examiner passes quickly beyond the calculus during the rectal examination. Careful palpation may also allow discrimination between soft-tissue masses of the bladder (neoplasia) and sabulous urolithiasis. With the latter, firm sediment is usually palpated well over the pelvic brim in the ventral aspect of a distended bladder. Manipulation of the bladder is accompanied by incontinence, and sabulous uroliths may be indentable when palpated after the bladder has been emptied via catheterization. Although rarely needed to confirm the diagnosis, ultrasonographic examination of the entire urinary tract should be considered because calculi may be present in multiple locations. Because UTI can sometimes accompany cystolithiasis, urinalysis and a quantitative urine culture are warranted during the initial evaluation of all horses with bladder stones.

Treatment of cystic calculi usually consists of surgical removal accompanied by a 7- to 10-day course of postoperative antibiotic treatment. Cystotomy can be performed via celiotomy with or

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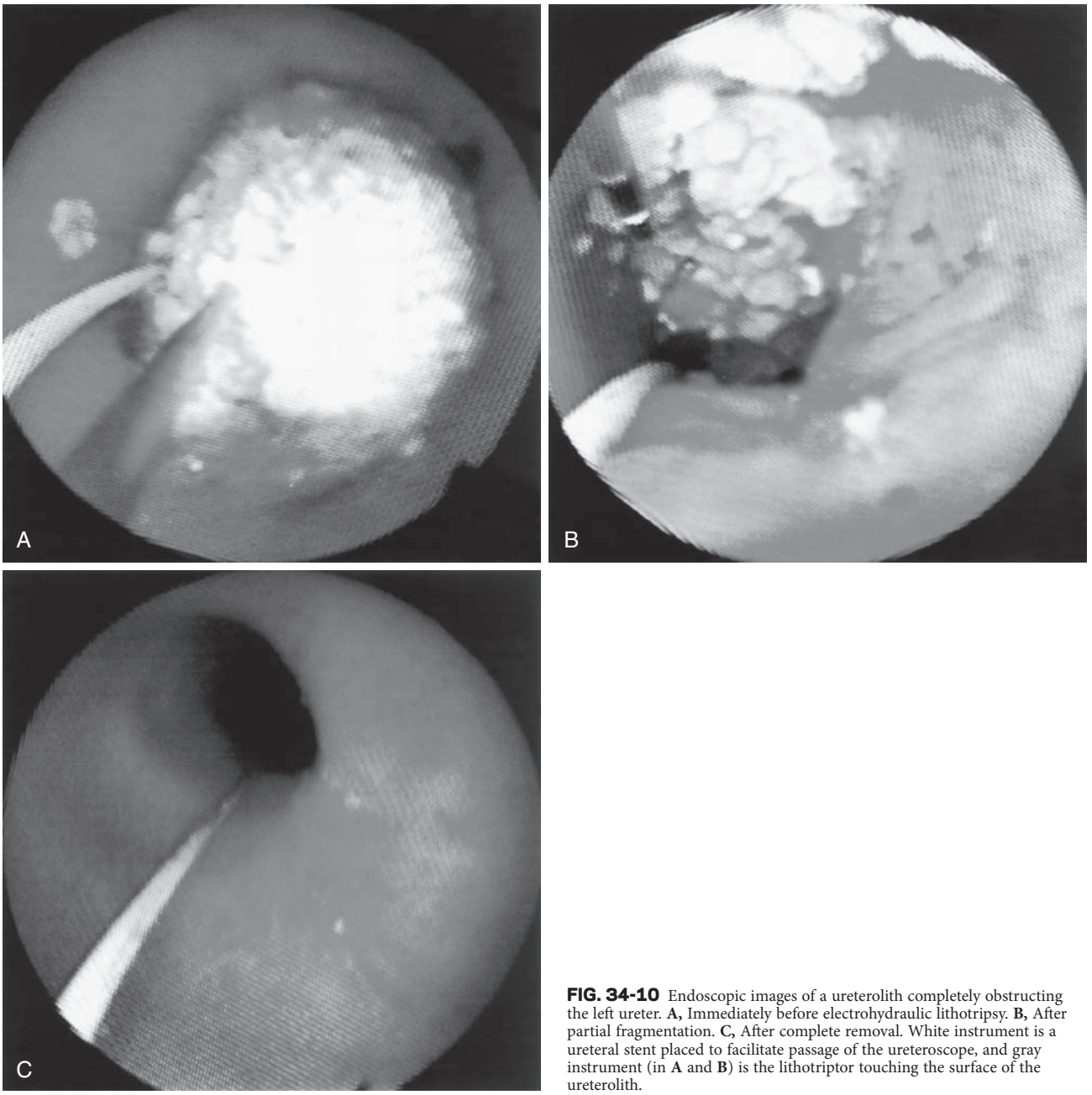


FIG. 34-10 Endoscopic images of a ureterolith completely obstructing the left ureter. **A,** Immediately before electrohydraulic lithotripsy. **B,** After partial fragmentation. **C,** After complete removal. White instrument is a ureteral stent placed to facilitate passage of the ureteroscope, and gray instrument (in **A** and **B**) is the lithotriptor touching the surface of the ureterolith.



FIG. 34-11 Left kidney of a 12-year-old Thoroughbred that presented with a complaint of intermittent hematuria. Right kidney appeared normal on ultrasound examination, and renal function was normal.



FIG. 34-12 Left kidney shown in Fig. 34-11 was removed with the horse anesthetized but strapped to the surgery table in an upright position. This is the preferred surgical position for nephrectomy or nephrotomy in adult horses.

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without laparoscopic assistance or a pararectal approach (Gäkel operation), or the stone can be removed after fragmentation with a lithotriptor passed via a perineal urethrotomy.[13,17-20] In mares, urethral sphincterotomy after epidural anesthesia with xylazine has been advocated as a practical method for stone removal. However, with sedation and epidural anesthesia, manual distention of the urethra often allows several fingers or a small hand to be passed into a mare's bladder, and depending on size, the stone can be retrieved intact or after fragmentation. Placing the cystolith into a sterile rectal sleeve or surrounding it with a similar smooth plastic material allows easier removal of spiculated stones and fragments. If available, electrohydraulic pulsed-dye or holmium:YAG laser lithotripsy may be the least traumatic method of fragmentation and removal of bladder stones in both genders, but success may be limited by the ability to lavage all stone fragments from the bladder.[21-26]

Historically, risk of recurrence after surgery has been considered low, but in a series of 68 cases of urolithiasis (at all levels of the urinary tract), 12/29 horses (41%) with follow-up had recurrence 1 to 32 months after surgery. Recurrence was more common with perineal urethrotomy than cystotomy and was attributed to the former's inability to completely remove all fragments by lavage.[2] This relatively high recurrence rate indicates that postoperative management changes are warranted to decrease risk of future stone formation. Changing from legume to grass hay is the most practical recommendation to decrease urinary calcium excretion. Urinary acidification with ammonium chloride (50 to 200 mg/kg/day PO) or ammonium sulfate (200 mg/kg/day PO) has also been recommended to decrease the amount of urine crystals in equine urine.[25,27] Unfortunately, these ammonium salts are rather unpalatable and should be administered as two or three doses daily for effective urinary acidification. Ascorbic acid administered through a nasogastric tube effectively acidified urine in one study, but when relying on voluntary consumption, results were variable.[28] IV administration of ascorbic acid was reported to effectively acidify urine, but side effects such as anxiety, sweating, tachycardia, tachypnea, mydriasis, and an intense diuresis were noted.[29] The actual benefit of urinary acidification in horses has never been established, and recurrence of urolithiasis may be more likely related to inadequate mucous secretion or persistence of damaged uroepithelium in the upper or lower tract. A more practical recommendation may be to administer 2 to 4 oz of salt in the feed daily to increase water consumption and urine flow. The increase in urine flow is accompanied by a decrease in urine pH to near-neutral values.

Urethral Obstruction

Calculi, neoplasms, congenital anomalies, and preputial edema and inflammation may all produce partial or complete obstruction of the urethra. Urethral calculi are most often calcium carbonate stones that lodge in the pelvic urethra in stallions or geldings,[30] and the most common neoplasm causing urethral obstruction is squamous cell carcinoma of the penis.[31] Preputial edema and inflammation may develop as a consequence of trauma or parasitism (habronemiasis). In addition, overweight horses may develop recurrent preputial inflammation and infection associated with fat deposition in the sheath. Horses with the latter condition may fail to drop the penis during urination, and urine scalding within the sheath is likely a contributing factor to recurrent inflammation.

Complete urethral obstruction usually causes moderate to severe signs of colic, and an enlarged, turgid bladder is detected on rectal palpation. Careful palpation of the urethra below the anus may reveal the location of an obstructing urolith or frequent contraction of the urethralis muscle. Rarely, postrenal ARF may develop, or the bladder may rupture. Partial urethral obstruction is usually accompanied by dysuria, incontinence, and urine scalding of the hindlimbs. A diagnosis of urethral obstruction is based on clinical signs, rectal examination findings, external examination of the penis and prepuce, and passage of a catheter or endoscope through the urethra to the bladder.

Treatment of urethral obstruction usually involves surgery. Urethral calculi can be removed either by a subischial urethrotomy over the site of obstruction or by hydropulsion through the urethrotomy incision. Excessive tissue trauma should be avoided because it may increase the risk of urethral stricture and recurrent urolithiasis. If available, holmium:YAG laser lithotripsy and radial extracorporeal shockwave therapy have been successful in fragmenting urethral calculi.[32,33] Laboratory assessment of fluid and electrolyte status is important for correction of dehydration, azotemia, and electrolyte alterations that may develop with sweating (caused by pain), bladder rupture, or anuria. With squamous cell carcinoma, aggressive surgical resection of involved tissues is warranted with larger lesions, whereas smaller lesions may be amenable to treatment with 5-fluorouracil ointment. However, because recurrence rate of squamous cell carcinoma of the penis and prepuce is 20% or greater,[31] surgical removal should be initially considered in all affected horses. Detrusor function may be decreased if bladder distention had been ongoing for several days, and an indwelling bladder catheter (closed system) or treatment with bethanechol (0.03-0.04 mg/kg SC q6-8h or 0.22-0.45 mg/kg PO q6-8h) may help with recovery of detrusor function.

Idiopathic Renal Hematuria

Harold C. Schott, II

Idiopathic renal hematuria (IRH) is a syndrome characterized by sudden onset of gross, often life-threatening hematuria.[1] Hemorrhage arises from one or both kidneys and is manifested by passage of large blood clots in urine. Endoscopic examination of the urethra and bladder usually reveals no abnormalities of these structures, but blood clots may be seen exiting one or both ureteral orifices. Although a definitive cause of renal hemorrhage may be established in some horses (e.g., renal adenocarcinoma, arteriovenous or arterioureteral fistula),[2,3] the disorder is termed *idiopathic* when a primary disease process cannot be found. Both genders, a wide age range, and several breeds of horses (including a mammoth donkey and a mule) have been affected. However, more than 50% of animals with IRH have been Arabians.

Use of the term *idiopathic renal hematuria* to describe this syndrome of horses was adopted from its use in human patients and dogs with severe renal hemorrhage.[4-8] *Benign essential hematuria* and *benign primary hematuria* are other terms that have been used to describe less severe hematuria that is not associated with trauma or other obvious causes of hematuria. In humans and dogs, hematuria is more often a unilateral than a bilateral problem, similar to what has been observed in the few affected horses. The pathophysiology remains poorly understood, but macroscopic hematuria has been associated with immune-mediated glomerular damage (e.g., acute postinfectious GN, membranoproliferative GN, IgA nephropathy, or Berger disease), thin basement membrane nephropathy, and the loin pain–hematuria syndrome in human patients.

Although hematuria and pigmenturia can accompany several systemic diseases in horses,[9-12] patients affected with IRH appear to have spontaneous severe hematuria in the absence of other signs of disease. Although one report suggested that severe renal hemorrhage was caused by pyelonephritis,[13] supportive data were lacking. In cases managed by one of the authors (HCS), neither UTI nor lithiasis was detected, and the magnitude of hematuria often resulted in the need for repeated blood transfusions. As with hemorrhage associated with guttural pouch mycosis, the syndrome may produce episodic hemorrhage. Initially, hemorrhage is noted by finding a large amount of clotted blood in stall bedding or in the pasture. However, other client complaints (e.g., depression, anorexia, weight loss) are typically absent. Examination may reveal dried blood at the end of the penis or in the sheath of males or on the vulvar lips and between the hindlimbs of mares. In both genders, neoplasia of the external genitalia or urinary tract is an important differential diagnosis, and in

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mares, varicosities in the area of the vestibulovaginal sphincter also must be considered, especially in multiparous mares. When blood is not detected in the sheath or vulvar areas, further evaluation may be unrewarding because the renal bleeding may cease spontaneously. In the absence of positive urine culture results, bleeding has anecdotally been attributed to cystitis and pyelonephritis, because hemorrhage stops during a course of antimicrobial therapy. More likely, spontaneous resolution has occurred. The magnitude of hematuria is considerably greater with IRH than with most UTIs, pyuria is absent, and urine culture results are negative. In our experience, one or two initial episodes of hemorrhage are followed by a more severe hemorrhagic crisis within months to 2 years after observation of the initial bleeding episode. Of interest, renal colic has been notably absent in the history of affected horses.

Diagnosis A diagnosis of IRH is made by exclusion of systemic disease, other causes of hematuria, and alterations in hemostasis. Physical examination may reveal tachycardia, tachypnea, and pale membranes, consistent with acute blood loss. Rectal palpation may reveal an enlarged, irregular bladder resulting from the presence of blood clots. Azotemia is uncommon. Endoscopic examination is important to document that hematuria is originating from the upper urinary tract and to determine whether hemorrhage is unilateral or bilateral (Fig. 34-13). Repeated examinations may be required to answer the latter question. Ultrasonographic imaging is necessary to rule out nephrolithiasis or ureterolithiasis and may occasionally reveal a distended vascular space or renal vascular anomaly as the cause of hematuria. Renal scintigraphy can be a useful technique in affected horses, providing semiquantitative information about renal function when a nephrectomy is being considered. Renal biopsy and IF staining may assist in documenting immune-mediated glomerular injury, but the significance of such results is not well understood at this time.

Treatment Treatment for IRH consists of supportive care for acute blood loss, including blood transfusions. Medications intended to promote hemostasis (e.g., α-aminocaproic acid, formalin) have also been administered, but their efficacy has not been validated. Because the condition may be self-limiting in some patients, supportive care is warranted. With severe and recurrent hematuria of unilateral renal origin, a nephrectomy may be indicated, but owners should be warned of the risk of hematuria developing in the contralateral kidney. In our experience, risk of contralateral renal bleeding appears to be greater in the Arabian breed.

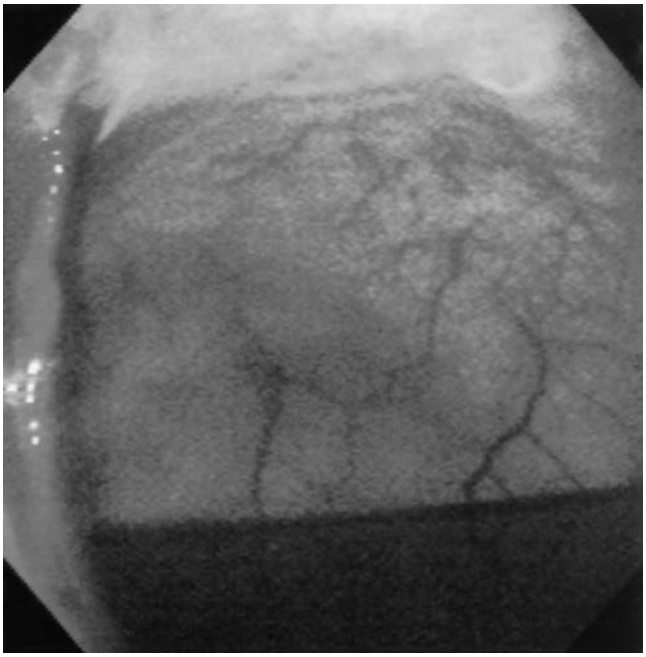


FIG. 34-13 Cystoscopic image of a 19-year-old Arabian mare with idiopathic renal hematuria. A large blood clot can be seen exiting the left ureter, whereas the right ureteral opening appears normal.

Urethral Hemorrhage

Harold C. Schott, II

Although a recognized cause of hemospermia in stallions, defects or tears of the proximal urethra at the level of the ischial arch are a more recently described cause of hematuria in geldings.[1-3] Urethral defects typically result in hematuria at the end of urination, in association with urethral contraction. Affected horses generally void a normal volume of urine that is not discolored. At the end of urination, a series of urethral contractions results in squirts of bright red blood. Occasionally, a smaller amount of darker blood may be passed at the start of urination. In most cases, the condition does not appear painful or result in pollakiuria. Interestingly, the majority of affected stallions with hemospermia and geldings with hematuria have been Quarter Horses or Quarter Horse cross-breeds that have been free of other complaints.[4,5] Treatment with antibiotics for a suspected cystitis or urethritis has routinely been unsuccessful, although hematuria appears to resolve spontaneously in about 50% of affected horses. Because the defects are difficult to detect without use of high-resolution videoendoscopic equipment, previous reports of urethral bleeding have been attributed to urethritis or hemorrhage from "varicosities" of the urethral vasculature. However, vasculature underlying the urethral mucosa becomes quite prominent when the urethra is distended with air during endoscopic examination, especially in the proximal urethra (to the point that blood can be seen flowing in the submucosal vasculature). Thus it would be logical to suspect that hemorrhage could arise from an apparent urethritis or urethral varicosity, although these problems are poorly documented in horses.

Examination of affected horses is often unremarkable, and laboratory analysis of blood reveals normal renal function, although mild anemia can be an occasional finding. Urine samples collected midstream or by bladder catheterization appear grossly normal. Urinalysis may have normal results, or an increased number of red blood cells (RBCs) may be found on sediment examination, a finding that would also result in a positive reagent strip result for blood. Bacterial culture of urine yields negative results. The diagnosis is made with endoscopic examination of the urethra, during which a lesion is typically seen along the dorsocaudal aspect of the urethra at the level of the ischial arch. External palpation of the urethra in this area is usually unremarkable but can assist in localizing the lesion, because external digital palpation can be seen through the endoscope. With hematuria of several weeks' duration, there is little evidence of inflammation; rather, the lesion appears as a fistula communicating with the vasculature of the corpus spongiosum penis (Fig. 34-14).

Although the pathophysiology of this condition remains unclear, it has been speculated that the defect is the result of a "blowout" of the corpus spongiosum penis (cavernous vascular tissue surrounding the urethra) into the urethral lumen.[3] Contraction of the bulbospongiosus muscle during ejaculation causes a dramatic increase in pressure in the corpus spongiosum penis, which is essentially a closed vascular space during ejaculation. The bulbospongiosus muscle also undergoes a series of contractions to empty the urethra of urine at the end of urination, so the defect into the urethra may develop by a similar mechanism in geldings. Once the lesion has been created, it is maintained by bleeding at the end of each urination, and the surrounding mucosa heals by formation of a fistula into the vascular tissue. An explanation for the consistent location along the dorsocaudal aspect of the urethra at the level of the ischial arch has not been documented but may be related to the anatomy of the musculature supporting the base of the penis and an enlargement of the corpus spongiosum penis in this area. Narrowing of the lumen at the distal

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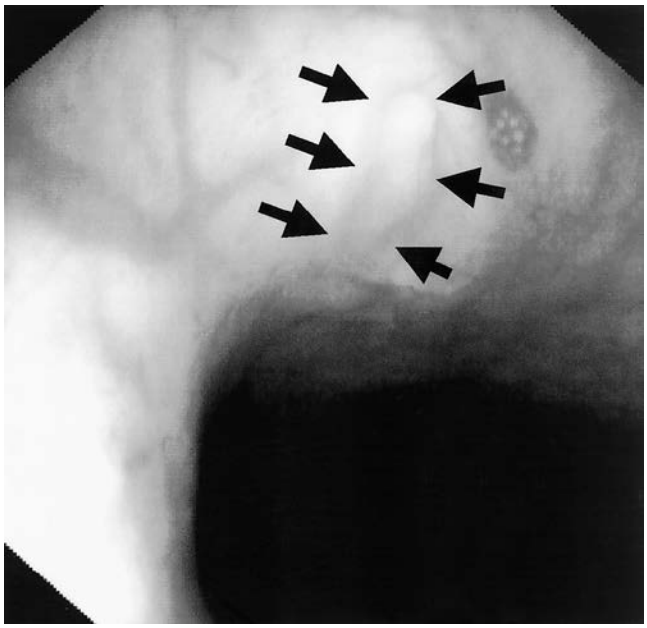


FIG. 34-14 Endoscopic image of the proximal urethra of a gelding with hematuria at the end of urination. A urethral defect can be seen between the arrows along the caudal aspect of the urethra as it passes dorsocranially over the pelvic brim.

extent of the ampullar portion of the urethra may also contribute to the location of the defects. An anatomic predisposition in Quarter Horses has not been documented but could be speculated based on an apparent increased risk in this breed.

Because hematuria may resolve spontaneously, no treatment may be initially required. If hematuria persists for more than a month or if significant anemia develops, a temporary subischial "incomplete" urethrotomy has been successful in some affected geldings. After sedation and epidural or local anesthesia, a catheter is placed in the urethra, and a vertical incision is made into the corpus spongiosum penis but not into the urethral lumen. The surgical wound requires several weeks to heal, and moderate hemorrhage from the corpus spongiosum penis is apparent for the first few days after surgery. Hematuria should resolve within a week after this procedure. Additional treatment consists of local wound care and prophylactic antibiotic treatment (typically a trimethoprim-sulfonamide combination) for 7 to 10 days.

Polyuria and Polydipsia

Harold C. Schott, II • Theresa Lynn Ollivett

Polyuria and *polydipsia* (PU/PD) are defined as urine output in excess of 50 mL/kg/day and fluid intake of more than 100 mL/kg/day.[1,2] These values equate to production of 25 L of urine and consumption of 50 L of water for a 500-kg horse. It is important to remember that urine production and water consumption vary with age, diet, workload, environmental temperature, and GI water absorption.[3,4] For example, urine production increases by 50% to 100% when the diet is changed from a grass to a legume hay.[5] Similarly, horses in heavy exercise, stabled in hot climates, or with chronic diarrhea may have a water intake in excess of 100 L/day yet produce normal volumes of urine. The major causes of PU/PD in horses include renal failure (discussed previously), pituitary adenoma (Cushing disease), and primary or "psychogenic" polydipsia. Less common causes include excessive salt consumption, central and nephrogenic diabetes insipidus (DI), diabetes mellitus, sepsis/endotoxemia, and iatrogenic causes (e.g., sedation with α_2-agonists, corticosteroid therapy, diuretic use).[2]

Polyuria/Polydipsia with Cushing Disease

Pituitary adenoma and the resulting syndrome of hyperadrenocorticism (Cushing disease) is common in older horses.[6] Although the most consistent clinical sign in horses is hirsutism, PU/PD may be reported; in one review of 17 horses with Cushing disease, PU/PD was found in 13 (76%).[7] However, in another series of 21 cases, PU/PD was not in the history of any of the affected horses.[8] This discrepancy can be explained by the fact that PU/PD associated with Cushing disease is generally of lesser volume than that observed with psychogenic PD or DI.

Cushing disease may lead to PU/PD by several mechanisms. First, polyuria may be the result of an osmotic diuresis. The renal threshold for glucose in horses (≈150 to 175 mg/dL) appears to be lower than in small animals.[9] When plasma glucose concentration exceeds the renal threshold, the resultant glucosuria can lead to an osmotic diuresis. Although often implicated as the cause of PU/PD in horses with Cushing disease, glucosuria was found in only one of five affected horses in one report.[8] Further, horses with hyperglycemia and glucosuria may still be able to concentrate their urine in response to water deprivation.[10] A second mechanism implicated in the development of PU is antagonism of the action of antidiuretic hormone (ADH) on the collecting ducts by cortisol. Although frequently cited as the mechanism of PU in canine hyperadrenocorticism, experimental evidence to support this mechanism is lacking in both dogs and horses. There is considerable species heterogeneity in the effects of corticoids on ADH activity, and in some species a primary dipsogenic effect may be more important. Growth of the adenoma may lead to impingement on the posterior pituitary and hypothalamic nuclei (located immediately dorsal to the pituitary gland), the sites of ADH storage and production, respectively. Decreased ADH production and release would result in central DI as a third mechanism for PU.[6] Therefore, PU/PD seen in some but not all horses with pituitary adenomas is likely the combined result of several mechanisms.

Psychogenic Polydipsia

Although rare, primary or "psychogenic" PD is probably the most common cause of PU/PD in adult horses for which clients will have a primary complaint of excessive urination.[4,11] Horses with this problem are generally in good body condition and not azotemic. The magnitude of their PU/PD is typically dramatic, with owners reporting that horses drink two to three times more water than their stablemates, and stalls can be flooded with urine. In some horses, primary PD appears to be a stable vice that reflects boredom, whereas in other cases it may develop after a change in environmental conditions, stabling, diet, or medication administration. Anecdotally, it has been reported to be more common in southern states during periods of high temperature and humidity.

The diagnosis of primary PD is made by exclusion of renal failure and hyperadrenocorticism. Other factors (e.g., salt supplementation, medication administration) must also be excluded. DI is excluded by demonstrating urinary concentrating ability after water deprivation.[12,13] Urine specific gravity should exceed 1.025 after water deprivation of sufficient duration (12 to 24 hours) to produce a 5% loss of body weight. In horses with long-standing PU, the osmotic gradient between the lumen of the collecting tubule and the medullary interstitium may be diminished (medullary washout). In these horses, ADH activity may not lead to an increase in urine specific gravity to values greater than 1.020. Consequently, in horses with primary PD of several weeks' duration that fail to concentrate their urine after 24 hours of water deprivation, a modified water deprivation test may be tried. This is performed by restricting water intake to about 40 mL/kg/day for 3 to 4 days. By the end of this period, urine specific gravity should exceed 1.025 in a horse that has had medullary washout. If urine specific gravity remains in the isosthenuric range (1.008 to 1.014), the polyuric horse should be further evaluated for early CRF, in which urine concentrating ability may be compromised before the

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onset of significant azotemia. In theory, this could occur when two thirds to three fourths of functional nephrons have been lost. Subtle signs of decreased performance and mild weight loss would also support early renal failure.

Management of horses with primary PD is empirical. Because this is a diagnosis of exclusion, once it has been established that the horse does not have significant renal disease, it is safe to consider restricting water intake to meet maintenance, work, and environmental requirements of the horse. In addition, steps should be taken to improve the attitude of the horse by reducing boredom. Increasing the amount of exercise and turning the horse out to pasture are possible options, along with providing a companion or diversions in the stall. Increasing the frequency of feedings or amount of roughage in the diet may increase time spent eating and thereby reduce the habitual drinking.

In an occasional case of primary PD, PU/PD may be attributed to excessive salt consumption and is manifested by an increased fractional sodium clearance.[3] Such "psychogenic salt eaters" appear to be less common than "psychogenic water drinkers" because the former would have to consume a substantial amount of salt to develop PU. In fact, salt intake may have to exceed 5% to 10% of dry matter intake before PU/PD becomes apparent.[14,15] Successful management consists of limiting water intake and preventing access to excess salt.

Diabetes Insipidus

DI may be due to inadequate secretion of ADH (neurogenic DI) or decreased sensitivity of the epithelial cells of the collecting ducts to circulating ADH (nephrogenic DI).[1,2,16] With both forms of DI, dramatic PU/PD may be reported, and affected animals fail to concentrate urine in the face of water deprivation.

In human patients, neurogenic DI is the more common form of DI, with both hereditary and acquired forms described.[16] Two well-documented equine cases of neurogenic DI have been described.[17,18] Neither animal could concentrate urine in response to water deprivation, but administration of exogenous ADH resulted in an increase in urine specific gravity and decrease in urine volume. In a Welsh pony in which the condition was considered idiopathic, the absence of an increase in plasma ADH concentration after water deprivation further supported a diagnosis of neurogenic DI.[17] Acquired neurogenic DI secondary to encephalitis was confirmed histologically in the other horse.[18]

Nephrogenic DI is most often a familial disorder in humans, with an X-linked semirecessive mode of inheritance.[16] Therefore the disorder is carried by females and expressed in male offspring. Nephrogenic DI has been described in sibling Thoroughbred colts, suggesting that an inherited form may also occur in horses.[19] These two colts could not increase urine specific gravity in response to water deprivation, although they did show appropriate increases in plasma ADH concentration. DI has also been reported in a 15-year-old gelding.[20] In all three cases, a lack of response to exogenous ADH administration confirmed resistance of the collecting ducts to ADH. Nephrogenic DI can also develop in association with drug therapy or a variety of metabolic, infectious, or mechanical (postobstruction) disorders. Anomalous or neoplastic disorders resulting in structural deformation of the kidneys are other potential causes of nephrogenic DI.[16]

After determining that an equine patient with PU/PD is not azotemic, the initial diagnostic test to differentiate DI from primary PD is a water deprivation test.[17,18] However, horses with suspected DI should be monitored closely during water deprivation, because affected horses will continue to excrete excess water in the face of water deprivation. As a result, they may become substantially dehydrated (10% to 15%) within the first 12 hours of water deprivation. When a patient fails to concentrate urine during water deprivation, neurogenic DI can be differentiated from nephrogenic DI by measuring plasma ADH concentration or by administration of synthetic ADH (as illustrated by the cases previously described). Currently, equine ADH cannot be measured at commercial laboratories, but synthetic ADH (60 IU q6h IM or SC) can be administered in combination with monitoring urine specific gravity.

Treatment of DI is directed at managing PU/PD. With neurogenic DI, hormone replacement therapy with desmopressin (dDAVP, a potent ADH analog administered as eyedrops) has been a successful treatment in small animal patients.[21] However, this treatment has not been described in horses and may be cost prohibitive. With nephrogenic DI, hormone replacement therapy is ineffective, and the only practical form of treatment for many years has been to restrict sodium and water intake and administer thiazide diuretics. The latter treatment may reduce PU by 50% in human and canine patients.[16,22] Thiazide diuretics inhibit sodium reabsorption in the distal tubule (diluting segment of nephron) and increase solute delivery to the collecting duct, but the mechanism by which such therapy benefits patients with nephrogenic DI is not well understood. Administration of prostaglandin inhibitors or amiloride may also decrease PU in patients with nephrogenic DI. The former agents probably work by decreasing renal blood flow and GFR, whereas amiloride, a sodium channel blocker, is thought to act similar to the thiazide diuretics.[5] No reports have documented the use of these treatments in horses.

Diabetes Mellitus

Diabetes mellitus (DM) is a state of chronic hyperglycemia usually accompanied by glucosuria. The resultant osmotic diuresis is an occasional cause of PU/PD in horses and was described to result in a water intake in excess of 80 L/day in one report.[23] Type 1 (insulin-dependent) DM is due to lack of insulin, which in human patients is usually attributable to viral or autoimmune disease. Individuals with type 2 (non–insulin-dependent) DM have normal to high insulin concentrations, but their tissues are insulin insensitive. The most common cause of equine type 2 DM is Cushing disease, in which elevated plasma cortisol concentration appears to antagonize the effects of insulin. Although uncommon, there are a few reports of both type 1 and type 2 DM that were not caused by a pituitary adenoma and resulted in PU/PD as one of the presenting complaints.[23-25]

Sepsis/Endotoxemia

PU/PD has been described in horses with sepsis or endotoxemia, although other clinical signs (e.g., fever, abdominal pain, weight loss) predominate.[26] The mechanism of PU/PD is unclear but may result from endotoxin-induced prostaglandin production. Prostaglandin E_2 (PGE_2) is a potent renal vasodilating agent that can antagonize the effects of ADH on the collecting ducts.[27] Some horses with chronic gram-negative bacterial infections (e.g., peritonitis, pleuritis) may have low-grade or intermittent endotoxemia as a mechanism for PU/PD, similar to the PU observed with canine pyometra.[28]

Iatrogenic Polyuria

A final cause of PU/PD may be iatrogenic secondary to several treatments. The most obvious iatrogenic cause is fluid therapy, for which PU is a desired response. PU has also been observed with exogenous corticosteroid administration, although the mechanism remains unclear. Humans and dogs appear to experience a potent thirst response to exogenous corticosteroids, so PD may be an important cause of the PU observed. In horses receiving chronic dexamethasone treatment for immune-mediated disorders, profound glucosuria (2 to 3 g/dL) may be observed and could lead to an osmotic diuresis. Finally, a transient diuresis or polyuria accompanies sedation with the α_2-agonists xylazine and detomidine.[29] Although these agents also cause transient hyperglycemia and occasional glucosuria, a more likely mechanism for PU is existence of α_2-adrenoreceptors on collecting duct epithelial cells. Activation of these receptors is another mechanism by which the action of ADH can be antagonized.[30]

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Renal Tubular Acidosis

Monica Aleman • Krista Elise Estell

Renal tubular acidosis (RTA) is a syndrome characterized by abnormal renal tubular function that results in a hyperchloremic metabolic acidosis with a normal anion gap.[1-4] Hyperchloremia develops as a result of enhanced renal conservation of chloride consequent to bicarbonate loss. RTA can be categorized as *primary* (genetic or idiopathic) or *secondary* when attributed to an underlying disease process or drug administration. Drug-induced RTA has been documented in human patients after administration of amphotericin B, trimethoprim-sulfamethoxazole, outdated tetracyclines, gentamicin, cephalosporins, carbonic anhydrase inhibitors, lithium carbonate, and other organic compounds.

Three types of RTA have been described: I (distal), II (proximal), and IV (hyperkalemic distal).[2-4] Types I and II have been reported in dogs, cats, and horses. Type I develops when distal tubular excretion of hydrogen ions (H^+) becomes compromised, and affected patients are unable to produce acidic urine. Type II results from decreased proximal tubular bicarbonate resorption and subsequent loss of bicarbonate in the urine. Because H^+ ions are normally excreted as bicarbonate is reabsorbed in proximal tubules, acidosis with both type I and type II RTA results from decreased H^+ excretion. Type I RTA results in more severe acidosis and electrolyte abnormalities, since the distal tubule is responsible for maximal acidification of the urine. In the absence of H^+ excretion, K^+ is excreted to maintain electroneutrality and can result in severe hypokalemia. Type II RTA often is a self-limiting problem but may be accompanied by more widespread proximal tubular dysfunction, leading to defective resorption of glucose, amino acids, phosphate, potassium, sodium, calcium, magnesium, uric acid, and other organic acids. The latter disorder is known as *Fanconi syndrome;* as with RTA, it may be a primary (inherited) problem or can develop secondary to kidney, metabolic, and autoimmune diseases or drug administration.[2-4] Although there are no well-documented reports, Fanconi syndrome likely develops in an occasional horse as a sequela to proximal tubule damage. Mixed type I and II RTA has been documented and is notably refractory to treatment, likely because of widespread tubule dysfunction.[5] To date, type IV RTA has only been described in human patients.[4]

RTA is a sporadically occurring metabolic disorder in horses.[6-9] There is no obvious breed or gender predilection, and to date, no evidence indicates that RTA is an inherited condition in horses. Typically, affected horses present with profound depression and anorexia and may have a history of poor performance, weight loss, and signs of abdominal pain. Vital parameters are generally within normal ranges, and horses do not appear clinically dehydrated. Hematologic and clinical chemistry findings are usually within reference ranges, with the exception of electrolyte concentrations and acid-base balance. A profound metabolic acidosis (plasma bicarbonate concentration < 13 mEq/L and venous blood pH < 7.25) and hyperchloremia (serum chloride concentration = 105 to 120 mEq/L) are characteristic for horses with RTA. A compensatory decrease in carbon dioxide partial pressure (P_{CO_2}) is also observed in most horses with RTA. Hypokalemia (and total body potassium depletion) due to the combined effects of anorexia and ongoing loss of potassium in urine may occur in horses with RTA, particularly in patients with type I.

Mild to moderate azotemia may be detected in horses with RTA, especially when they are dehydrated at presentation. Affected horses may also have evidence of renal tubular damage detected on urinalysis (e.g., pigmenturia, glucosuria), and urine specific gravity may be low. Despite profound metabolic acidosis, urine pH is generally neutral to alkaline. If pursued, renal biopsy results generally support tubulointerstitial disease (TIN).

Differentiation of type I from type II RTA in human and canine patients is most easily accomplished by assessing urine pH; it remains neutral to alkaline with type I and should be neutral to acidic with type II.[2-4,9] Most horses with RTA have had neutral to alkaline urine, but because herbivores normally have alkaline urine, this distinction may be less useful. A few reports have described horses with acidic urine, supporting type II RTA, but urine pH values near neutral are difficult to interpret.[9-11] Assessment of all laboratory abnormalities (Table 34-1), along with additional testing (e.g., ammonium chloride challenge, urinary ammonium concentration, administration of thiazide diuretics) may allow further discrimination between type I and type II RTA.[5,10,12] However, this distinction may not be entirely necessary, because the approach to treatment and the prognosis are similar for both types of RTA in horses.

TABLE 34-1

Classification of Type I and Type II Renal Tubular Acidosis

	Distal or Type I	Proximal or Type II
Acidosis	Severe	Self-limiting
Hypokalemia	Severe	Mild to moderate
Serum phosphate	Normal	Low
Urine pH	Neutral to alkaline	Neutral to acidic

Treatment of RTA consists primarily of IV and oral administration of sodium bicarbonate. For initial correction of acidosis, IV $NaHCO_3$ must be administered aggressively, and large amounts (3000 to 9000 mEq) are often required to return plasma bicarbonate concentration to values above 20 mEq/L. Half the estimated bicarbonate deficit is generally replaced with IV $NaHCO_3$ over 6 to 12 hours, and the remaining deficit is replaced with a combination of IV and oral $NaHCO_3$ (initial oral dose: 100 to 150 g twice daily; 1 g contains 12 mEq $NaHCO_3$). Close monitoring of serum electrolyte concentrations and acid-base balance is required to adjust the rate of IV $NaHCO_3$ replacement. Marked improvement in attitude and appetite usually accompanies correction of the acidosis, but unfortunately, relapse after discontinuation of IV therapy can occur. Continued oral administration of $NaHCO_3$ for months to years may be required for maintenance of a normal acid-base status.

Because potassium excretion is proportional to the bicarbonate delivery to the distal tubule, initial correction of acidosis with $NaHCO_3$ promotes kaliuresis and may exacerbate potassium depletion. Therefore, concurrent supplementation with IV or oral potassium chloride is advisable during initial correction of the acidosis. Complications associated with rapid correction of acidosis have not been described, but transient diarrhea may develop if large quantities of $NaHCO_3$ (>200 g) are given by nasogastric tube to horses that are completely anorectic.

Recurrence of metabolic acidosis also can occur when oral $NaHCO_3$ is discontinued, especially in horses that have evidence of renal damage. Relapses can be immediate or delayed for weeks to months. Reinstitution of $NaHCO_3$ supplementation usually corrects the metabolic abnormalities and accompanying depression and anorexia. The short-term prognosis for horses with RTA is good, and although the long-term prognosis has not been well documented, several horses have been reported to recover completely.[6,7,9]

Bladder Rupture in Adult Horses

Thomas J. Divers • Dominic R. Dawson Soto

On rare occasions, bladder rupture may occur in adult horses. The problem can develop in association with urolithiasis, foaling, prolonged recumbency, or trauma.[1] As azotemia develops, affected horses become depressed and inappetent. Uroabdomen may produce signs of abdominal discomfort and tachycardia.[2] Clinical signs may not be apparent for several days. Stranguria may be observed depending on the cause of the rupture. Abdominal distention may not be as apparent in adult horses as in foals.

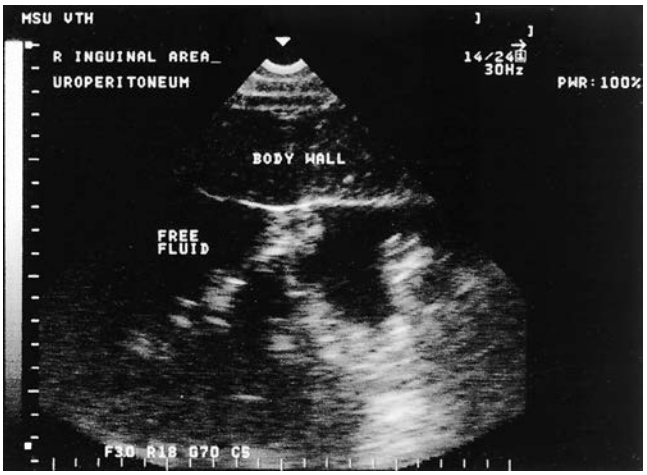


FIG. 34-15 Transabdominal ultrasonographic image of the right inguinal area of an adult horse with a ruptured bladder. A large amount of free hypoechoic fluid is apparent.



FIG. 34-16 A 2-day-old foal exhibiting stranguria caused by a ruptured bladder. Note the caudal position of the hindlegs, suggesting that the foal is straining to urinate rather than defecate. Differentiating between stranguria and tenesmus (meconium impaction) is not always easy.

The diagnosis is based on history, rectal examination findings, laboratory results, and findings on urinary ultrasonographic or cystoscopic examination. Postrenal azotemia develops within 24 hours after rupture and is accompanied by hyponatremia and hypochloremia. Unlike uroperitoneum in neonates, hyperkalemia is not a consistent finding. Transabdominal ultrasonographic examination of the abdomen reveals a large amount of peritoneal fluid (Fig. 34-15); abdominal fluid is easily recovered on abdominocentesis, and peritoneal fluid creatinine is twofold or greater than that of serum. Detection of calcium carbonate crystals on cytologic examination of peritoneal fluid is also diagnostic for uroperitoneum. Endoscopic examination of the bladder should allow determination of the location and extent of the bladder tear. Rarely, uroperitoneum may also develop in some horses without full-thickness disruption of the bladder wall, and it is difficult to establish definitively the cause of uroperitoneum in these cases.

Surgical repair is indicated in horses with large tears in the ventral half of the bladder. In mares, standing surgical repair may be feasible.[3] In patients with small dorsal tears or incomplete tears, use of an indwelling bladder catheter (closed system) to keep the bladder small may allow the tear to heal without surgery.[4] Before surgery, IV fluids should be administered to correct dehydration, along with broad-spectrum antibiotics as prophylaxis against sepsis. If the abdomen is distended, urine accumulated in the abdomen should be removed (e.g., by placement of chest tube or other large catheter through the ventral abdominal wall) before anesthesia is induced to avoid further compromising respiration.

Urinary System Disorders in the Foal

Thomas J. Divers • Dominic R. Dawson Soto

Umbilical disorders of the neonatal foal, including patent urachus, urachal infections, and omphalitis, are discussed in Chapter 17.

Uroperitoneum

Bladder Rupture

The most common bladder disorder in otherwise healthy newborn foals is bladder rupture.[1-3] In septic foals, bladder necrosis leading to leakage of urine can be experienced, possibly secondary to hematogenous spread of bacteria.[4] There may be an increased incidence in colts, but some reports fail to support this.[5] Clinical signs include stranguria and repeated posturing to urinate during the first few days of life. Urine accumulates in the abdomen, typically leading to depression and abdominal distention between days 2 and 4 of life. Repeated posturing and stranguria can easily be misinterpreted as tenesmus associated with meconium impaction (Fig. 34-16). Further, affected foals may continue to void small volumes of urine, so establishing a diagnosis of ruptured bladder can initially be challenging until more obvious signs of uroperitoneum (e.g., decreased nursing, abdominal distention) develop.

Laboratory findings in foals with uroperitoneum include hyponatremia, hypochloremia, hyperkalemia, and azotemia.[1-3,6] Foals receiving continuous fluid therapy prior to the diagnosis may not exhibit typical electrolyte changes, and instead suspicion of uroperitoneum should be raised with other signs such as decreased urinary output, abdominal distention, weakness, or other changes in clinical condition. An occasional foal may also develop intermittent fine muscle tremors or a cardiac arrhythmia resulting from these electrolyte alterations, especially hyperkalemia. Transabdominal ultrasonographic examination usually reveals a large quantity of free fluid in the abdominal cavity, but occasionally the bladder can still appear fluid filled, depending on the size of the leak. A peritoneal fluid creatinine/serum creatinine ratio greater than 2:1 or the presence of calcium carbonate crystals in the abdominal fluid confirms uroperitoneum.[1-3,6]

Treatment of bladder rupture includes surgical closure of the defect, supportive care, and broad-spectrum prophylactic antibiotics for 3 to 7 days postoperatively.[1,2,6,7] An emergency surgical procedure is usually not required, and in most cases, postponement of the surgery for several hours until electrolyte abnormalities are partially corrected (most notably correction of hyperkalemia to a serum concentration < 6.0 mEq/L) is recommended. This can usually be accomplished by IV administration of 1 to 3 L of a 0.9% NaCl/5% glucose solution. Treatment with insulin should be avoided unless hyperkalemia is causing significant electrocardiographic (ECG) abnormalities and response to initial fluid therapy is poor. With marked hyperkalemia or abdominal distention causing respiratory embarrassment, slow drainage of urine from the abdomen (e.g., by chest tube or similar catheter) may be necessary before induction of anesthesia; IV fluid support should be provided during drainage. Despite significant azotemia in some affected foals, use of aminoglycoside antibiotics is generally safe because the azotemia is postrenal rather than reflecting intrinsic renal disease. In most cases, placement of a urinary catheter to maintain an empty bladder for the initial 2 postoperative days is unnecessary, but careful monitoring of urine output along with serial abdominal ultrasound is recommended if a catheter is not placed. Postoperative bladder atony requiring bethanechol and an indwelling urinary catheter has been reported.[8] Uroperitoneum may recur after surgery in an occasional foal as a result of ongoing leakage from the bladder tear. When this complication occurs, it can

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usually be managed conservatively by placement of an indwelling bladder catheter (closed system) for 3 to 5 days. Rarely, a second celiotomy may be required.

Urachal Urine Leakage

Uroperitoneum may also develop in foals with urachal infection or ischemia. Affected foals are often septicemic or hospitalized for treatment of prematurity, hypoxic-ischemic encephalopathy, or botulism, and uroperitoneum is recognized later (e.g., after 5 to 10 days of treatment).[7,9] Prolonged recumbency and bladder distention are likely risk factors. The urachus of many affected neonates appears normal during the first 2 days of life, but in some cases, particularly with septicemia, may subsequently become patent. Urine leakage through the umbilicus may or may not be accompanied by leakage into the abdominal cavity or subcutaneous tissues of the abdominal wall. In other affected foals the umbilicus remains normal, and all urine leakage accumulates into the abdominal cavity. When monitored, inappropriate weight gain (e.g., >2 kg in 24 hours) is another common finding in hospitalized neonates that develop uroperitoneum, along with decreased urinary output.

Laboratory abnormalities typical for uroperitoneum may be found in affected foals but are not consistently abnormal, because these patients are often being treated with IV fluids. Correction of the problem includes surgical removal of the diseased urachus, closure of the bladder apex, and continued supportive care for the primary disease. The prognosis for a successful outcome for these foals is not as favorable as for simple bladder rupture, because they often have a degree of peritonitis (increasing risk for adhesions), and uroperitoneum is often only one of several complications of the underlying disease.[7,9]

In an occasional foal, the urachus may also rupture more distally than usual and lead to subcutaneous accumulation of urine, ventral abdominal swelling, stranguria, signs of colic, and distress.[10] The swelling may be differentiated clinically from a hematoma or septic omphalitis because it may enlarge quickly and often becomes cold. Ultrasonographic examination and/or local aspiration of fluid and measurement of creatinine (twofold or greater than in serum) confirm the diagnosis. Prompt surgical removal of the leaking urachus is indicated.

Ureteral Defects

Ureteral defect(s) or disruption may also lead to development of uroperitoneum in both male and female foals.[11-14] Stranguria is usually absent, and urine initially accumulates in the retroperitoneal space, but with time the retroperitoneal tissue ruptures, causing uroperitoneum. Affected foals may not be presented until 5 to 10 days of age because urine accumulation is slower than with a ruptured bladder. Clinical signs include decreased nursing, depression, and mild colic, and in fillies an external bulging of the vagina may be observed. Laboratory findings are typical for uroperitoneum, and with significant hyperkalemia, intermittent muscle fasciculations may be also noted.

If urine accumulation remains localized to the retroperitoneal space, ultrasonographic examination of the lower abdomen may be normal, but a large amount of retroperitoneal fluid will be detected around the kidney and upper flank (within retroperitoneal space) on the affected side(s). In addition, the renal pelvis may be mildly dilated.[15] If the peritoneal membrane is ruptured, physical and ultrasonographic examination findings are similar to those seen with a ruptured bladder, but careful ultrasonographic examination may also reveal a full bladder or concurrent retroperitoneal fluid accumulation. As with a ruptured bladder, the ratio of retroperitoneal or peritoneal fluid creatinine/serum creatinine is greater than 2:1. In small foals (e.g., <50 to 75 kg), excretory urography (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis with ultrasonographic guidance) may be useful for localizing the ureteral defect(s).

One or both ureters may be involved, and during surgical exploration, one or more defects can usually be found in the proximal half of the ureter, often near the renal pelvis. During surgery the defects can be localized by placing a catheter into the ureter through a cystotomy and injecting dye (e.g., Evans blue, methylene blue). Successful correction of unilateral and bilateral defects can be accomplished by placing a stent in the affected ureter(s) for 7 to 10 days.[11,12]

A report describing bilateral ureteral defects adjacent to the renal pelves provided histopathologic evidence that the lesions were traumatic in origin rather than developmental anomalies.[14] The foal in that report had previously been kicked by its dam. One of the authors (TJD) has seen three foals with similar ureteral defects, all of which also had multiple rib fractures. Ureteropelvic junction injuries and proximal ureteral tears are a recognized complication after blunt abdominal trauma in human patients.[16] Taken together, these observations suggest that many ureteral defects in foals may more likely be traumatically induced at foaling rather than being developmental anomalies.

Cystitis

Cystitis in foals can develop in septic, recumbent, premature, or neonatal foals being treated with broad-spectrum antibiotics. Evidence indicates that bacterial infection of the urinary tract, whether primary or due to hematogenous spread, may contribute to the development of uroperitoneum.[4,5] When cystitis is suspected, the bladder should be catheterized and a urine sample submitted for urinalysis and quantitative culture. UTIs with *Candida* spp. are fairly common in recumbent neonates. Specific antimicrobial therapy is not usually necessary for *Candida* cystitis as long as systemic antibiotics can be discontinued. If antibiotic therapy continues, dissemination of the yeast infection can spread to other sites (e.g., joints).

Ruminant Renal System

David C. Van Metre, *Consulting Editor*

Ulcerative Posthitis and Vulvitis

Stacey R. Byers

Ulcerative posthitis and vulvitis (enzootic balanoposthitis, pizzle rot, sheath rot) is an ulcerative bacterial infection of the mucous membrane and surrounding skin of the prepuce and vulva of small ruminants.

Clinical Signs and Differential Diagnoses In male small ruminants, the infection begins as a moist ulcer, usually at or near the mucocutaneous junction of the prepuce. A thin, loose, brown to red, malodorous scab (Fig. 34-17) covers the ulcer. If the scabs are removed, little or no hemorrhage occurs. Focal swelling is often noticeable at the cranial aspect of the prepuce, and the area is painful on palpation.

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FIG. 34-17 Ulcerative posthitis in a Suffolk ram.

If untreated, the infection spreads along the mucosal surface inside the prepuce, creating the more serious internal form of ulcerative posthitis. In such cases the entire prepuce may be swollen and elongated. Affected animals often show dysuria, and goats may vocalize during voiding. As the local inflammation progresses, ulceration may result in fibrous adhesions between the penis and prepuce. Severe inflammation of the glans penis can cause stricture of the urethral process (pizzle) and restrict urine egress, resulting in signs similar to those of obstructive urolithiasis. Impairment of breeding soundness may result from admixing of blood or exudate into the ejaculate, penile adhesions, scarring of the preputial orifice, or suppurative urethritis. Pain may limit libido as well. Weight loss may occur in chronic cases.

Ulcerative lesions of similar appearance can develop on the vulva and perineum of affected ewes and does. Gross vulvar enlargement may be noticed from a distance. Dysuria may result from involvement of the urethral orifice. The fibrosis and contracture that develop in chronic severe cases may distort normal vulvar conformation to the point of impairing copulation or parturition.

Ulcerative dermatosis (lip and leg ulcer) in sheep is dermatitis caused by poxvirus-related contagious ecthyma. Infection with this agent may manifest as balanoposthitis and vulvitis, and the crusted ulcers that develop closely resemble those induced by infection with *Corynebacterium renale*. Ulcerative dermatosis can be differentiated from ulcerative posthitis, since lesions are also present on the face and legs. The lesions readily bleed and often contain a nonodorous purulent discharge.

Contagious ecthyma (orf) occasionally affects the genitalia and perineum, although lesions are much more frequently found on the lips, face, and udder. These lesions are raised, appear proliferative, and are covered with a thick, durable scab.

Urolithiasis must be strongly considered in the differential diagnosis of any dysuric male small ruminant. Although rare in small ruminants, preputial trauma, particularly if resulting from entrapped grass awns, can cause preputial swelling, pain, and exudation within the preputial cavity. External ulcerative lesions would not be expected in such cases.

Caprine herpesvirus 1 (CHV-1) infection has been documented to cause posthitis in a buck goat on a California farm wherein this agent had caused abortions.[1] The affected buck had shallow, red, irregularly shaped ulcers in its prepuce that tested positive for CHV-1 by PCR. Biopsy of the ulcers revealed intranuclear inclusion bodies within the stratum spinosum of the preputial epithelium. Acute pustular vulvovaginitis, characterized by marked vulvar swelling, erythema, and focal pustules of the vaginal mucosa, has been described in does infected with CHV-1; notably, there were no abortions in the affected herd nor lesions detected in comingled bucks.[2] The bucks of that herd were seropositive to CHV-1 and were considered a potential source of the virus.

Corynebacterium pilosum, Corynebacterium cystitidis, Mycoplasma mycoides subsp. *mycoides* Large Colony, *Actinobacillus seminis, Ureaplasma* spp., *Mycoplasma ovine-caprine* serogroup 11, and *Mycoplasma capricolum* subsp. *capricolum* have also been implicated in posthitis in sheep.[3,4]

Pathophysiology

C. renale is the bacterium most commonly implicated in ulcerative posthitis. These are aerobic, gram-positive, pleomorphic, club-shaped bacteria that are normal inhabitants of the skin and external genitalia of small ruminants. The bacteria contain the enzyme urease. A high-protein diet results in increased ammonia production in the rumen, which is converted to urea in the liver. The urea is eliminated through the renal system. *C. renale* proliferates, and the urease hydrolyzes the urea back to ammonia, causing chemical irritation and ulceration of the prepuce and surrounding skin.

Epidemiology

The condition appears to be more common in males than in females. Risk factors are associated with increased or excessive dietary protein concentration (usually >16%) such as alfalfa hay or lush legume or legume-grass pastures. However, diets with protein levels as low as 12% have been implicated.[4] Rams, pet wethers, club or show lambs or kids, wool and fiber production animals, and feedlot lambs are most predisposed to the disease. Increasing the plane of nutrition in intact males prior to breeding predisposes to development of this disease, and multiple animals can be affected simultaneously.[5] Breeds with dense wool or hair, such as Merino sheep and Angora goats, are also at risk owing to urine soaking the coat near the preputial orifice.

Disease can occur in individual or multiple animals, since the organism can persist in wool, hair, and scabs for as long as 6 months. The organism can also survive freezing in scabs and exudative material. Venereal transmission of the disease has been documented; several months may pass between exposure of ewes to infected rams and development of vulvitis in the ewes. Production losses result from debilitation caused by pain, incapacitation of breeding animals, loss of breeding soundness, and deformation of external genitalia.

Treatment and Prognosis

Reduction of protein and nonprotein nitrogen intake is crucial for successful treatment of affected animals and for prevention of additional cases. Dietary changes alone may result in satisfactory cure if the lesions are early in development. Incorporation of grass hay feeding into a program of legume pasture grazing may help limit protein intake.

Affected animals should be isolated to limit venereal or contact transmission. Wool or hair should be removed from the skin surrounding the prepuce or vulva, and a topical antibiotic may be applied. Caustic antiseptic solutions should not be used. Treatment with systemic antibiotics is indicated for advanced cases or for outbreaks, in which handling of several animals for topical therapy is not feasible. *C. renale* is sensitive to penicillin, ampicillin, cephalosporins, and oxytetracyline. Treatment should continue until the lesions have dried and acute inflammation has subsided. Topical therapy of the preputial mucosa includes application of mastitis treatment tubes, triple antibiotic ointment, or "petercillin." Petercillin is prepared by mixing 240 g anhydrous lanolin, 20 mL of procaine penicillin G (300,000 U/mL), and 200 mg aqueous prednisolone. A small amount can be warmed up and injected into the prepuce using an AI infusion pipet or small feeding catheter. Oral or injectable NSAIDs can be used to decrease the inflammation and pain associated with the infection.

Surgical treatment of advanced cases is recommended for severe strictures. The ventral preputial tissue can be resected to allow for normal urine flow or be incised along part of its length.

Response to treatment is optimal early in the infection, before deformation of the prepuce or vulva as a result of fibrosis. The chances for full recovery without recrudescence are poor if dietary protein intake is not reduced. Complete recovery of breeding soundness is unlikely in animals with internal ulcerative posthitis. In breeding males, the presence of ulcerative posthitis does not directly

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influence semen motility or morphology, but since the pain involved is likely to suppress libido, proper treatment and documentation of lesion resolution is recommended in affected males prior to the breeding season.[6]

Prevention Prevention primarily involves limiting both protein and nonprotein nitrogen intake. Breeding males should be body-condition scored early enough before the breeding season so that any necessary weight gains can be made slowly rather than a sudden onset immediately prior to breeding season. Separation of affected males will help decrease spread through contact with exudative materials. Shearing, especially at the time of highest protein intake, may be efficacious in reducing disease incidence.

Urolithiasis

Stacey R. Byers

Definition and Etiology Urolithiasis is a common metabolic disease in all livestock species, but castrated small ruminants appear to be particularly at risk. Uroliths cause disease through trauma to the urinary tract and obstruction of urinary outflow. Urolithiasis can occur in outbreaks or as an endemic problem in group-housed animals or as an individual disorder in animals kept as pets. A definitive diagnosis of urolithiasis in a single animal suggests that all males in the population are at risk for the disease because of the importance of dietary and environmental factors in its pathogenesis.[1]

The clinical signs of urolithiasis vary and are based on duration, extent (complete vs. partial), and location of the obstruction. The early clinical signs can be remarkably subtle and may include anorexia, depression, and mild bloat. A history of colic and straining to urinate or defecate may be provided, and novice owners often mistake stranguria for constipation or tenesmus. If investigating a sick, castrated small ruminant, urolithiasis should be high on the differential list regardless of the clinical signs.

Four common disorders can result from urolithiasis: acute urethral obstruction, chronic urethral obstruction, urethral rupture, and urinary bladder rupture. Less commonly seen are ureterolithiasis and hydronephritis.

Clinical Signs and Differential Diagnoses

Acute Urethral Obstruction

Impacted calculi lead to urethral trauma and progressive bladder distention, resulting in stranguria and abdominal pain. Affected animals may be restless, tread, swish their tails, and grind their teeth. Goats and camelids may vocalize. Tachycardia, tachypnea, and mild bloat secondary to ruminal stasis are common findings. Stranguria is manifested as repetitive bouts of stretching and contraction of the abdominal muscles. Straining may induce secondary rectal prolapse, so urethral obstruction should be investigated as the primary disease in cases of rectal prolapse. Rarely, affected calves develop a visible dilation of the urethra at the midline of the perineum proximal to the obstruction.[2] Anuria occurs if urethral obstruction is complete, whereas urine may dribble in cases of partial obstruction. Crystals or blood may be found on the hairs of the preputial tuft; in cases of anuria the hairs are dry. If a urine sample can be collected for dipstick analysis, proteinuria and occult hematuria are frequently detected.

Rectal examination (digital rectal examination in small ruminants) often reveals pulsation of the pelvic urethra. In cattle, bladder distention is palpable per rectum, although if bladder or urethral rupture has occurred, the bladder is typically not palpably enlarged.

Abdominal palpation may be useful in affected small ruminants, small camelids, and pot-bellied pigs. The examiner should place the fingertips of each hand into the ventral flank on each side of the abdomen. While slowly pressing the fingertips toward midline in the caudal abdomen, the examiner may encounter an orange- to grapefruit-sized, firm, spherical structure, which is the distended bladder (Fig. 34-18). Severe bladder distention will not be palpated in cases of incomplete urethral obstruction or bladder rupture.



FIG. 34-18 Palpation of the bladder of a Barbados wether.

The lumen of the bovine urethra narrows at the distal aspect of the sigmoid flexure, near the insertion of the retractor penis muscles.[3] Calculi most frequently become lodged at this site in cattle, and pain or focal swelling over this area may be appreciated.[3] The urethral process is the most common site of calculous obstruction in sheep and goats and should always be examined in suspected cases of urolithiasis.[4]

Owing to the frequent lack of specific clinical signs, acute urethral obstruction can resemble a variety of diseases. Tachycardia, colic, bloat, and anorexia are characteristic of GI obstruction, but auscultation and percussion of the abdomen, abdominal succussion, rectal examination, and transabdominal or transrectal ultrasonographic examination should differentiate this condition from acute urethral obstruction. Encephalopathies, salmonellosis, coccidiosis, and proctitis from rectal prolapse or trauma frequently cause tenesmus. Additional signs of primary neurologic or GI dysfunction should be evident with these diseases.

Although rare in male ruminants, primary UTI may result in dysuria and pollakiuria. Bladder distention is uncommon with UTI, and large numbers of WBCs and bacteria are present in the urine sediment.

Occasionally an animal with urolithiasis successfully voids the obstructing urolith(s). The resultant traumatic urethritis might cause dysuria, but the rate and ease of urination typically improve over time and with antiinflammatory treatment.

Juvenile male camelids have been observed straining or posturing to urinate. On cystotomy, no uroliths have been discovered. Etiology has not been conclusively determined, but transrectal ultrasound has identified prostatitis in some individuals. It is suspected that hormonal influences or ascending UTIs may be contributing to prostatic or urethral inflammation.

In younger animals, it is important to consider congenital abnormalities (e.g., ectopic ureter(s), pelvic displacement of the urinary bladder, urethral duplication). Congenital abnormalities may be manifest at birth or not until later, depending on the level of observation and whether the defect results in obstruction, partial obstruction, or constant urine dribbling.

Chronic Urethral Obstruction

Uncommonly, partial urethral obstruction causes chronic dysuria and stranguria if calculi impair but do not completely obstruct urine outflow.[5] If a chronic partial obstruction is present, the affected animal has a characteristic slow or intermittent urine flow during voiding. Lethargy, reduced appetite, and thin body condition are

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evident if renal failure has developed. On rectal examination the bladder may be small, and thickening of the bladder wall may be palpable.[5]

Urine dribbling may also occur in animals with neurologic disease, previous urethral trauma (stricture formation), congenital anomalies of the urogenital tract, infection, or neoplasia. Contrast urethrography may be used to identify the presence of strictures or anomalous structures. Small ruminants with the internal form of ulcerative posthitis may dribble urine. In such cases, characteristic preputial lesions are present. Tumors of the urinary tract, although rare compared to urolithiasis, may cause gradual obstruction in cattle, small ruminants, and camelids.

If there is a complete urethral obstruction for approximately 36 hours or more, the animal is at risk of developing bilateral hydroureter and hydronephrosis, and imaging studies of the kidneys and ureters are warranted.

Urethral Rupture

Urethral rupture is a common complication of urethral obstruction in ruminants and camelids. The wall of the obstructed urethra undergoes pressure necrosis, causing leakage of urine into the subcutaneous tissue of the perineum and ventral abdomen. Sequelae include cellulitis, penile adhesions (possibly creating phimosis), urethral fistula formation, and urethral stricture. Erection failure secondary to vascular obstruction of the corpus cavernosum of the penis has been reported as a sequela to urethral obstruction and rupture in a goat.[6]

Affected animals are frequently depressed and inappetent and have bilaterally symmetric, pitting edema in the ventral perineum, inguinal region, prepuce, and ventral abdomen (Fig. 34-19). Swelling of the abdominal wall may extend as far forward as the axillae. The affected areas are initially warm and painful on palpation. As necrosis progresses, the tissues become cool, dark, nonpainful, and potentially gangrenous. A fistula may develop to allow urine to escape. Fever may occur if tissue necrosis and sloughing are extensive. Transrectal palpation or ultrasound reveals a small bladder.

Ventral abdominal swelling is also found with umbilical or scrotal hernias and omphalophlebitis. These conditions can be differentiated from urethral rupture by careful palpation of affected tissues, aspiration of any fluid pockets for cytologic examination, and ultrasonography. In bulls, penile hematomas may cause localized swelling of the prepuce in the prescrotal region and caudal sheath, but the swelling does not involve the ventral abdominal wall. Aspiration of a suspected penile hematoma is not recommended because of the risk of iatrogenic infection.

Urinary Bladder Rupture

In all ruminants and camelids, prolonged bladder distention secondary to urethral obstruction may result in pinpoint perforations, tears, or necrosis of large areas of the bladder wall. In cows, bladder rupture may also occur as a rare complication of dystocia.[7] Rupture of an urachal remnant may also result in uroperitoneum.[8] The dorsum of the bladder fundus is the most common site for rupture, but rupture in other bladder regions occurs.

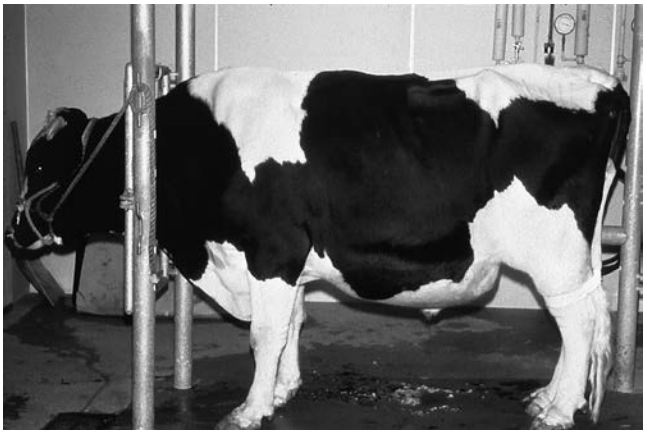


FIG. 34-19 Urethral rupture in a Holstein steer. Tissue swelling from urine accumulation may extend to the sternum and axillae.

Relief of bladder distention causes cessation of stranguria. Bilateral distention of the ventral abdomen develops within 1 to 2 days after rupture and is accompanied by worsening clinical signs of depression, anorexia, weakness, dehydration, and shock. Ballottement of the abdomen may elicit a fluid wave. Rectal temperature may be normal, but shock may result in hypothermia. The animal's breath may smell like ammonia. On transrectal or transabdominal palpation, the bladder is small or not palpable. Transabdominal ultrasonography reveals a large volume of free fluid and a collapsed or partially filled bladder. Abdominocentesis yields a large volume of blood-tinged fluid; the fluid may smell like urine when heated, although this is quite subjective. On occasion, urine will translocate into the thoracic cavity or into the scrotum through the inguinal canals. Uremia and dehydration result in debilitation and eventual death if medical and surgical treatments are not provided.

Seepage of urine across the bladder wall and into the abdominal cavity may occur in cases of severe bladder distention; in such cases, rupture is often imminent. Differential diagnoses for bladder rupture include diffuse peritonitis, ileus, enteritis, vagal indigestion, ascites secondary to liver fibrosis, caudal vena caval thrombosis, and hypoproteinemia. Marked peritoneal cavity effusion may be found in cases of mesothelioma or lymphoma. These conditions are differentiated from bladder rupture through transrectal examination, ultrasonography, cytologic and chemical analysis of peritoneal fluid, evaluation of serum chemistry, and abdominal exploratory surgery.

Ureterolithiasis and Nephrolithiasis

Animals with acute ureteral obstruction may show severe colic with stretching, kyphosis, treading, collapse, and vocalization. Signs of distress may be less severe or even absent if obstruction is intermittent or incomplete.[9] Enlargement of the blocked ureter may be palpated transrectally, and if the left ureter is obstructed, enlargement of the left kidney may be appreciated. Transabdominal or transrectal ultrasound may aid in the diagnosis. Rarely, pyelonephritis is the inciting cause of ureteral obstruction, because necrotic debris and calculi may be released into the ureter from the infected renal pelvis. Pyelonephritis can also be a consequence of ureteral or renal calculosis.[9,10] With ureteral or renal rupture, uroperitoneum or retroperitoneal accumulation of urine may occur.

Similar signs of abdominal pain or colic can result from GI or urinary tract obstruction in ruminants and camelids. Auscultation and percussion of the abdomen, rectal examination findings, ultrasonography, or radiography may allow for differentiation of GI obstruction from ureteral or renal obstruction. Cases of ureteral or renal calculosis without colic may show nonspecific signs of illness, and serum chemistry, urinalysis, and ultrasound examination are needed for definitive diagnosis.

Ancillary Diagnostic Tests

EXAMINATION OF URETHRAL PROCESS IN SMALL RUMINANTS. Sedation or general anesthesia facilitates extrusion of the penis for examination. Because of its diuretic effect, xylazine may exacerbate bladder distention and is not recommended. Diazepam (0.1 mg/kg IV slowly) and acepromazine (0.05 to 0.1 mg/kg IV or IM) have been used successfully, either as sole agents or in combination with butorphanol (0.05 to 0.1 mg/kg IV). Alternatively, the use of isoflurane by mask can be used.

An adjunct or alternative to sedation is administration of epidural anesthesia, which provides greater patient comfort and eliminates muscular resistance to penile extrusion. One milliliter of 2% lidocaine per 15 kg (33 lb) of body weight is injected into the epidural space at the lumbosacral junction. Lower dosages may provide sufficient anesthesia. The total dose should not exceed 15 mL of 2% lidocaine in any small ruminant, regardless of size. If CSF is obtained,

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half of the epidural lidocaine dosage can be administered as a true spinal block. Hindlimb motor blockade is expected with either epidural or true spinal anesthesia at this site; the effects typically last 1 to 2 hours.

To exteriorize the penis, the sheep or goat is propped up on its rump, and the hind legs are pulled up alongside the trunk. For larger sheep or goats, this can be aided by a person sitting in a chair, with the animal propped up between his or her legs. It is critical that the animal be positioned such that its spine is perpendicular to the floor. Addition of lidocaine jelly or several milliliters of 2% lidocaine added to a water-based lubricant and squirted into the prepuce may decrease discomfort for exteriorizing the penis. The examiner can then exteriorize the penis by pushing the sigmoid flexure cranially from the base of the scrotum while pulling the sheath caudally. In some cases, preputial mucosa must be carefully grasped with small forceps or Allis tissue forceps to aid in extruding. The penis can then be grasped with a piece of gauze to keep it exteriorized. The urethral process can then be inspected and palpated for the presence of discrete uroliths or sand-like grit within the lumen. If the urethral process is obstructed, it can be amputated with a scalpel blade (see Surgical Treatment).

ULTRASONOGRAPHY AND RADIOGRAPHY. A presumptive diagnosis of urolithiasis can usually be made through historical and physical examination findings. Ultrasonographic and radiographic evaluation of the urinary tract may allow for confirmation of a diagnosis and prognosis.[11-15] In cases of prolonged urethral obstruction (≥48 hours) or urethral obstruction with severe azotemia, it is prudent to perform ultrasonographic examination of the kidneys before considering surgical treatment (see ultrasound images of the bladder in the ruminant section of Chapter 32). Detection of severe hydronephrosis warrants a poor prognosis for recovery.

Ultrasonographic evaluation of the bladder of pot-bellied pigs, small ruminants, and camelids is most easily accomplished through transabdominal scanning directed caudodorsally from the inguinal area. Both kidneys of small ruminants and camelids and the bovine right kidney can be examined from the right paralumbar fossa. In cattle, transrectal examination of the pelvic urethra, bladder, ureters, and left kidney can be performed. Marked distention of the bladder, thickening of the bladder wall, and echogenic material within the bladder lumen may be seen with acute urethral obstruction. A large volume of free fluid in the abdomen is characteristic of uroperitoneum and is suggestive of existing or impending rupture.

Radiographic examination of the urinary tract is limited to pot-bellied pigs, camelids, small ruminants, and young cattle. Lateral views of the abdomen can be used to detect radiodense calculi in the bladder and urethra. This is accomplished most easily with the animal in lateral recumbency with the hindlimbs pulled caudally. It is also recommended to image the entire urethra to determine the presence and location of stones. Positive-contrast urethrography allows for detection of radiolucent urethral calculi, urethral stricture, or urethral rupture. After catheter placement about 5 cm into the penile urethra, injection of a volume of 10 to 30 mL of water-soluble contrast media has been used with success in adult bucks and rams. To avoid accidental introduction of bubbles into the catheter, it should be completely filled with contrast material before insertion. Injection should be performed slowly with minimal pressure to avoid iatrogenic urethral rupture. Following tube cystostomy, contrast urethrethrography can be performed by injecting the contrast material into the bladder through the catheter. The catheter can then be clamped shut temporarily to evaluate for the continued presence of stones, strictures, or urethral rupture.

CLINICAL PATHOLOGY

Acute and Chronic Urethral Obstruction. Hematologic and serum chemistry findings may be unremarkable in ruminants with acute urethral obstruction uncomplicated by urethral or bladder rupture. Hyperglycemia and a stress leukogram may be present. With time, hemoconcentration and azotemia develop secondary to reduced water intake. Hematuria and proteinuria are consistent abnormalities, whereas crystalluria is a variable finding. With chronic urethral obstruction, hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and severe azotemia with isosthenuria suggest extensive nephron damage caused by hydronephrosis. Pyuria is present with traumatic urethritis, cystitis, or secondary bacterial infection.

Bladder Rupture. Bladder rupture and accumulation of urine in the abdomen result in hematologic and serum biochemical parameter alterations that worsen as time progresses. Urine osmolality is normally two to three times that of extracellular fluid (ECF), and urine contains higher concentrations of urea, creatinine, and potassium but lower concentrations of sodium and chloride than ECF. Therefore, movement of water, urea, and electrolytes occurs along diffusion gradients, resulting in hyponatremia, hypochloremia, hyperphosphatemia, uremia, and hemoconcentration.

Serum potassium concentration in ruminants with bladder rupture is more variable, depending on appetite and time before diagnosis. Although animals with uroperitoneum are at risk of hyperkalemia, serum potassium concentration tends to be normal or low in ruminants with bladder rupture, even if uroperitoneum exists for several days. Anorexia may contribute to hypokalemia or normokalemia in these cases, and aldosterone release secondary to volume depletion results in dramatic increases in salivary potassium excretion, providing an alternative route of potassium excretion in affected animals. Once in the GI tract, potassium absorption may be diminished by ileus and preferential absorption of sodium over potassium. Alkalosis, which occurs secondary to hypochloremia, may also serve to reduce ECF potassium concentration by encouraging movement of potassium intracellularly.

Although only a small fraction (<10%) of phosphorus excretion in the ruminant is via urine, hyperphosphatemia may occur secondary to uroabdomen. Potential mechanisms for hyperphosphatemia include phosphorus diffusion from the urine into the ECF, reduced glomerular filtration, and tissue hypoxia causing breakdown of organic phosphate compounds in cells. In addition, reduced salivary flow from anorexia may limit phosphorus excretion in the saliva, contributing to phosphorus retention. Anorexia, ileus, and a competitive effect of hyperphosphatemia may contribute to reduction in serum calcium concentration in cases of uroabdomen.

Measurement of creatinine in the peritoneal fluid can be used to confirm a diagnosis of uroperitoneum. Creatinine is a relatively large polar molecule that does not readily diffuse from the abdominal cavity into the ECF space. Therefore, peritoneal fluid creatinine can be compared to serum creatinine concentration, with a peritoneal fluid/serum creatinine ratio of 2:1 or higher indicating uroperitoneum.

Uroperitoneum may induce a mild chemical peritonitis. However, experimentally induced bladder rupture did not cause peritonitis in steers, even after several days of uroperitoneum.[16] Nonetheless, WBC count and blood fibrinogen levels may increase in cases of ruptured bladder, possibly reflecting more extensive tissue necrosis and inflammation in natural cases. With uremia, impairment of blood coagulation may become an important clinical consideration. Reduced platelet aggregation and alteration of coagulation factor function occur in uremic patients of other species.[17] Bleeding diathesis and elevation of partial thromboplastin time (PTT) have been reported in azotemic cattle.[18] Bleeding complications should be considered prior to surgical treatment.

Urethral Rupture. Leakage of urine into the subcutaneous space following urethral ruptures produces hematologic and serum biochemical alterations that are similar but less severe than those seen with bladder rupture. The muscles and subcutis holding the urine do not possess as large a surface area as the peritoneal cavity. Therefore, less rapid and less extensive movement of water, ions, and waste products occurs, and the resulting changes in serum electrolytes and creatinine are less marked than in bladder rupture. Tissue necrosis and secondary infection may result in neutrophilia, leukocytosis, and hyperfibrinogenemia.

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Ureterolithiasis and Nephrolithiasis

Azotemia and secondary hydronephrosis are most severe if the obstruction is bilateral. With chronic ureteral obstruction, hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and severe azotemia with isosthenuria suggest extensive nephron damage caused by hydronephrosis. Pyuria is present with traumatic urethritis, cystitis, or secondary bacterial infection.

Pathophysiology Multiple factors influence the development of urinary calculi, but of primary importance is the development of high urinary concentrations of soluble ionized minerals (crystalloids) that aggregate to form insoluble crystals. Supersaturation of urine with a calculus-forming crystalloid is a prerequisite for urolith development,[19] but supersaturation alone is not solely responsible for urolith initiation, because normal urine is typically supersaturated with a variety of calculogenic ions. Urine contains variable concentrations of mucopolysaccharides, ions, and organic acids that act as intrinsic inhibitors of crystallization. Through physical and electrochemical interactions, these compounds maintain calculogenic minerals in a colloidal suspension. Calculus formation is initiated if supersaturation of urine with appropriate crystalloids exceeds the protective capabilities of the crystallization inhibitors. The crystalloids are rendered insoluble and precipitate out of the aqueous phase of urine. Calculi enlarge as further mineral precipitation takes place on the crystal surfaces. Dietary, environmental, and management influences interact to determine the degree of supersaturation of urine with calculogenic minerals. Dehydration, with resultant concentration of urinary minerals, would appear to be a potential contributing factor in the development of all types of uroliths.

The solubility of some calculogenic crystalloids is influenced by urinary pH. Struvite (magnesium ammonium phosphate), calcium phosphate, and calcium carbonate uroliths are less soluble in alkaline urine, whereas calcium oxalate solubility is not affected by changes in urine pH within the physiologic range. The effect of urinary pH on silica calculi is debatable, but recent findings show a trend toward reduction in formation under conditions of mild aciduria.[20]

Primary UTIs are considered an uncommon cause of ruminant urolithiasis. Purulent debris within the urinary tract may serve as a nidus for crystal development, and bacterial ureases may increase urinary pH, thereby reducing the solubility of certain crystalloids. Pyelonephritis, with presumed secondary urolithiasis, has been reported in cattle.[10] Urolithiasis may be considered as both a rare cause and a rare consequence of a UTI.[9,10]

Vitamin A deficiency has been incriminated as a contributory factor for urolith development by leading to metaplasia of urinary tract epithelium.[19] This may create nidi for calculogenesis through desquamation of cells or altered cell surface characteristics.

Feeding patterns may influence the formation of urinary calculi. In ruminants, providing a ration in one or two feedings per day induces ADH release soon after feeding which resulted in a marked but transient decline in urine output and an increase in urine concentration.[21] These changes in urine composition can be limited through ad libitum feeding. The influence of water hardness (dissolved mineral content), in particular in magnesium concentrations, has been implicated in the pathogenesis of this disease in ruminants.[22]

PHOSPHATIC CALCULI. Ruminants consuming rations high in phosphorus (grain-based rations) typically develop struvite (magnesium ammonium phosphate hexahydrate) calculi or apatite (calcium phosphate) calculi.[1,19,23-25] Rations where the calcium/phosphorus ratio is less than 2:1 are particularly prone to cause outbreaks of urolithiasis.[19] However, the role of phosphorus in urolith formation is not clearly defined, and struvite urolith formation appears to be primarily affected by the magnesium and to a lesser extent, other minerals in the diet.[19,26-28] Magnesium absorbed from the gut is excreted through the kidneys. Experimental increases in dietary magnesium levels to 0.6% of dietary dry matter induced calcium phosphate and struvite urolithiasis in calves.[28] High potassium in the diet alters the dietary cation-anion difference (DCAD) and increases the risk of urolith formation (see more about DCAD in Prevention).[29]

Pelleting of rations has been associated with an increased incidence of phosphatic urolithiasis.[1] Ruminant saliva is rich in phosphorus, and the GI tract is the primary route of phosphorus excretion in ruminants. In theory, ruminants consuming pelleted rations produce less saliva, which would reduce GI phosphate losses and increase urinary phosphate excretion.[1]

Struvite uroliths are typically white or gray, usually smooth, radiopaque, and easily broken.[19] They can be found as a single stone or sand-like debris, which is more commonly seen in ruminants.

SILICA CALCULI. Silica urolithiasis is primarily a problem of ruminants grazing native rangeland grasses of western North America. For example, in western North America, silica calculi can be found in the urinary tracts of 50% to 80% of range cattle, with urinary tract obstruction occurring in a variable percentage of these animals.[21] The silica fraction of these grasses tends to increase with maturity and may continue to increase even after growth ends. In some areas, 4% to 8% of total grass dry matter may be silicon compounds.[20] A fraction of dietary silica, as unpolymerized silicic acid, is dissolved in the ruminal fluid of the grazing animal, absorbed, and excreted in the urine.[19] In sheep and cattle on range, water intake is usually intermittent. During periods of water deprivation, avid water and sodium resorption by the kidneys results in the formation of highly concentrated urine. Silicic acid may be concentrated to such an extent that it polymerizes to the less soluble form, polysilicic acid. Polysilicic acid in turn forms large micelles in solution that quickly become insoluble when bound to urinary mucoproteins.[30]

Dietary deficiencies of copper and zinc have been identified as contributory factors in silica urolith formation in rats.[31] The incidence of silica urolithiasis can be increased by feeding sheep rations that have a high calcium/phosphorus ratio (≥2.8:1) and induce more alkaline urine.[20,32] It is important to note that a high calcium/phosphorus ratio in the diet can help to prevent one type of urolith (struvite) but may be a contributory factor for another (silica). This underscores the importance of both ration and urolith mineral analyses in the formulation of preventive measures for this disease.

Silica uroliths in ruminants are hard, smooth, white to brown, radiopaque, and often layered.[19] The uroliths are usually composed of about 20% mucoprotein, 75% silicon dioxide, and variable amounts of calcium oxalate and calcium carbonate.[19,21]

CALCIUM-BASED CALCULI. The two main types of calcium-based uroliths are calcium carbonate and calcium oxalate. Calcium carbonate uroliths (Fig. 34-20) are common in small ruminants grazing lush, rapidly growing clover pastures or being fed alfalfa hay.[33,34] Forages like these are rich in calcium and low in phosphorus and magnesium and have high oxalate content. In the gut, oxalate avidly binds calcium and makes it unavailable for absorption. With gradual introduction of oxalate-rich diets, ruminal bacteria efficiently metabolize oxalate to bicarbonate, so metabolism of oxalate

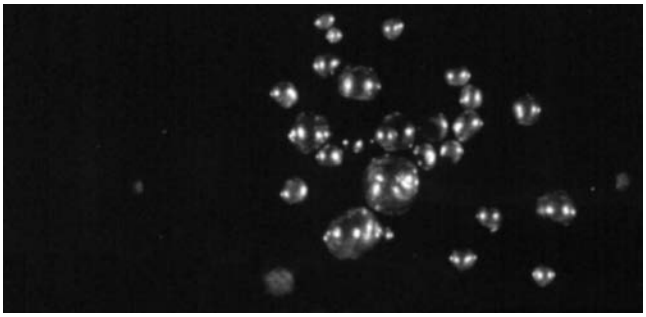


FIG. 34-20 Calcium carbonate calculi.

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in the rumen may increase the availability of dietary calcium.[35,36] These factors may combine to increase urinary calcium excretion and alkalinize urine, thereby promoting calcium carbonate calculogenesis.

Although humans at risk for calcium oxalate stones should limit foods high in oxalates, similar dietary and metabolic factors that influence formation of calcium oxalate uroliths have not been elucidated in ruminants.[19,37] Reports indicate that oxalates in the diet, as well as low calcium and decreased water intake, may increase the risk of forming calcium oxalate stones.[38,39] Given its very low solubility, calcium oxalate crystals are often present in normal urine and may be incorporated into other uroliths as a trace component.

Calcium carbonate uroliths have a characteristic round, smooth shape and golden color and are often present as multiple uroliths scattered throughout the lower urinary tract. Calcium oxalate uroliths are typically dense, hard, white to yellow, and either smooth or jagged.[19]

Epidemiology

GENDER. Obstructive urolithiasis in ruminants and camelids is almost exclusively a disease of males and castrated males. Urinary calculi appear to develop to a similar degree in female ruminants, but most calculi can pass through the relatively short, distensible urethra of the female, making urethral obstruction uncommon. The urethra of the male is long and surrounded by the less distensible corpus spongiosum and tunica albuginea.

Research indicates calculi form to a similar extent in the urinary tracts of bulls and steers. Because of the trophic effect of testosterone, the urethral diameter of yearling bulls is roughly 25% greater than that of yearling steers. Urethral obstruction therefore is more common in steers.[21] A similar predisposition for urethral obstruction may exist for wethers relative to buck goats.[40] However, because many wethers are kept as pets, factors such as diet, environment, and age are likely to differ compared with bucks. Specific gender risks in camelids and pot-bellied pigs is not well described; in commercial pigs, urolithiasis is generally associated with husbandry problems such as improper calcium/phosphorus ratio in the ration and inadequate water availability.[23]

SEASON. The incidence of urolithiasis increases in the late fall and winter in North America.[21] Limited water availability, increases in the silica content of range grasses, and a larger population of susceptible animals (young, growing males) during this time of year may be responsible for this trend. In warmer climates, urolithiasis is more frequently a problem in the arid months of the year, underscoring the role of water intake in the pathogenesis of the disease.[21]

AGE. Cattle of various ages may develop obstructive urolithiasis. The tendency for this disease to be seen in younger ruminants may be the result of dietary influences, because younger animals are more often fed concentrates for weight gain and eventual slaughter than are mature males kept for breeding. Because relatively fewer mature males are kept for breeding, the apparently increased prevalence of urolithiasis in younger animals may simply reflect the greater numbers of younger males and castrated males at risk.

OTHER. Inherent differences in an individual animal's mineral metabolism or urinary tract health may also play a role; some animals can ingest a calculogenic diet and remain unaffected, others develop uroliths rapidly. Animals prone to develop uroliths may have ineffective protective capabilities within the urinary tract, such as a lack of crystallization inhibitors. UTI is not a major risk factor for urolithiasis in ruminants, swine, and camelids.

Certain breeds of ruminants appear to be predisposed to urolithiasis; for example, African pygmy goats appear to be prone to developing this disease. Again, because these goats are often kept as pets, it is possible these animals may be fed or managed in ways that increase their disease risk.

BOX 34-1

Urolith Analysis Laboratories

Urinary Stone Analysis Laboratory
Department of Medicine and Epidemiology
School of Veterinary Medicine
University of California at Davis
Davis, CA 95616
1-530-752-3228

Dr. Carl Osborne
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
University of Minnesota
1352 Boyd Avenue
St. Paul, MN 55108
1-612-625-7744

Urolithiasis Laboratory
PO Box 25375
Houston, TX 77265-5375
1-800-235-4846

Necropsy Findings

When the urethra is opened along the sagittal plane, hemorrhage and necrosis of the urethral mucosa are evident at the site of obstruction. Particular attention should be paid to examination of the distal urethra in camelids, the urethral process in sheep and goats, and the sigmoid flexure in cattle. Calculi may be relatively large, discrete mineral aggregates or very fine and sand-like. Calculus material should be collected for analysis of mineral composition (Box 34-1). Occasionally, no calculi can be found in the urinary tract, but mucosal trauma and necrosis of the bladder or urethra persist.

Urethral rupture is characterized by the subcutaneous accumulation of urine in the inguinal area, prepuce, and ventral abdomen and hemorrhage at the site of the urethral defect.

In cases of bladder rupture, the abdominal cavity is filled with a large volume of blood-tinged fluid. Defects in the bladder wall vary in size and location, and necrosis of large areas of bladder wall may be present. In rare cases the bladder wall is intact but obvious uroabdomen exists, suggesting transmural seepage of urine.

Hydronephrosis, hydroureter, and bladder wall hypertrophy may be present in animals with chronic urethral obstruction.[5]

Treatment and Prognosis

SALVAGE. Steers and feeder lambs may be sent for immediate slaughter if urethral obstruction is diagnosed before development of azotemia or urinary tract rupture.

MEDICAL TREATMENT. Medical treatment of urolithiasis is aimed at relief of the obstruction and correction of any fluid and electrolyte abnormalities. The antispasmodic effect of certain tranquilizers may facilitate passage of a urethral obstruction.[1] These drugs may also aid in relaxation of the retractor penis muscle, which results in straightening of the sigmoid flexure to facilitate passage of calculi. In small ruminants, however, medical treatment with IV fluids, NSAIDs, or tranquilizers alone has not met with much success, and surgical intervention is usually necessary.[4,41]

While stabilizing a patient before surgery or as an adjunct to medical treatment, the bladder can be drained with a percutaneous catheter inserted in the lower flank or ventral abdomen.[42] Long IV catheters or a suprapubic catheter can be inserted, using ultrasonography as a guide, and temporarily left in place. Percutaneous infusion using Walpole solution has been used following cystocentesis in goats.[42] Urine was removed and the solution infused into the bladder 1 to 3 times to decrease the urine pH to 4 to 5. This process was thought to promote chemical dissolution of uroliths in the bladder and urethra.

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Ruminants and camelids with urinary tract obstruction, particularly those with uroperitoneum, often require preoperative stabilization of hypovolemia and correction of electrolyte abnormalities, especially if surgery is to be performed under general anesthesia or with the animal restrained in recumbency. Fluid therapy should be guided by analysis of serum electrolyte concentrations. An initial bolus of hypertonic (7%) saline followed by physiologic (0.9%) saline solution can be used to correct intravascular volume deficits, hyponatremia, and hypochloremia. Calcium salts can be added to the fluids if indicated.

Empirical supplementation of IV fluids with potassium should be avoided because the potential for hyperkalemia always exists. Hyperkalemia can induce bradycardia and fatal cardiac dysrhythmias, and this effect is augmented by concurrent hyponatremia. Administration of dextrose, sodium bicarbonate, and/or insulin (regular insulin at 0.25 to 0.4 U/kg SC or IM) reduces serum potassium concentration by promoting movement of potassium from the extracellular to the intracellular space. Blood glucose should be closely monitored when insulin is administered. Uremic animals undergoing IV fluid therapy may develop pulmonary edema, so attention must be paid to respiratory rate, auscultatory findings, and respiratory effort during fluid therapy.

Slow drainage of urine from the abdominal cavity reduces pressure on the diaphragm and slows progression of metabolic derangements caused by uroperitoneum. In long-standing cases of uroabdomen, urine may also be present in the thorax, further warranting close observation of respiratory function during anesthesia. Thoracocentesis to remove thoracic urine is indicated if respiratory function is compromised; otherwise, abdominal drainage usually induces resolution of thoracic urine accumulation.

Although bacterial infection is not considered to be a common primary cause of urolithiasis, secondary UTIs may develop after surgical intervention. Loss of the flushing effect of urination, urinary mucosal damage, impaired host cellular defenses secondary to uremia, and indwelling urinary catheter placement may contribute to the development of ascending UTI. Perioperative antibiotic therapy is therefore prudent, with due consideration of withholding times in animals intended for slaughter.

SURGICAL TREATMENT. Surgical treatment of urolithiasis is dictated by economic considerations, intended use of the animal, available facilities and equipment, and status of the patient. Removal or bypass of the obstruction and restoration of urine output are the goals of surgical treatment. The prognosis for both short- and long-term survival will vary according to the patient's status and the surgical procedure chosen. ARF is an occasional sequela to urinary tract obstruction and should be considered in the prognosis.

Urethral catheterization and retrograde flushing have been used to dislodge urethral calculi and restore urine flow, but successful clearance of the urethra is rarely achieved, and retrograde flushing under pressure may result in urethral rupture.[4] Retrograde passage of a catheter may also allow for localization of the urethral obstruction, potentially guiding further surgical treatment. Passage of a catheter into the bladder of ruminants and camelids is difficult because of the presence of a urethral recess located near the ischial arch. Catheters passed retrograde almost invariably become lodged in this recess.

Surgical options include amputation of the obstructed urethral process, penectomy, perineal urethrostomy, prepubic urethrostomy, urethrotomy, cystotomy, tube cystostomy, and bladder marsupialization. In sheep and goats, *amputation of an obstructed urethral process* is a simple procedure that may at least temporarily restore urethral patency. The urethral process can be removed without detrimental effects on breeding soundness. Success rates for initial restoration of urine flow after urethral process amputation range from 37.5% to 66%.[4,43] However, recurrence of urethral obstruction is extremely common, and urethral patency is often maintained for only hours to days before reobstruction occurs.[4,43] Therefore, urethral process amputation is palliative and may provide enough time to allow feeder lambs to survive until slaughter. For pet wethers, rams, and bucks, recurrence of urinary tract obstruction is common if this is the only procedure performed.

Penectomy is an option for animals intended for slaughter. *Perineal urethrostomy* is a surgical option for ruminants not intended to be used for breeding. In small ruminants, postoperative stricture of the stoma or recurrent obstruction with additional calculi is a long-term risk.[4] *Ischial urethrostomy* with placement of a Foley catheter into the bladder has been used as a treatment for urolithiasis in heavy feedlot steers and bulls.[3,44] If urethral damage is not severe, this procedure allows the breeding ability of bulls to be maintained.[3]

Prepubic urethrostomy has been reported in a sheep and a goat.[45] In this procedure a midperineal penectomy is performed. The perineal segment of the penis and pelvic portion of the urethra are dissected free from the surrounding soft tissue using perineal and ventral celiotomy incisions, respectively. Bilateral ileal and ischiadic osteotomies may be required to free the pelvic urethra. The urethral mucosa is then sutured to the skin of the caudoventral abdomen to create a long-lasting stoma.

Urethrotomy (removal of obstructing calculi and primary closure of urethra) is another option.[3] Urethral stricture, adhesions resulting in phimosis in breeding males, and reobstruction with additional calculi are long-term complications.

Cystotomy allows for maintenance of breeding soundness and removal of additional calculi from the bladder. In small ruminants and camelids, bidirectional (normograde and retrograde) flushing is used to restore urethral patency.[4,43] Even if the urethra is successfully cleared of calculi, traumatic urethritis may cause significant postoperative dysuria in these animals. Therefore, some surgeons prefer also to perform a tube cystostomy to allow for rest and healing of the irritated urethra.

Tube cystostomy (surgical or percutaneous placement) allows urine to exit the bladder through a temporary Foley or other type of suprapubic catheter, which is anchored in the bladder lumen and exits the ventral abdomen.[41,46,47] Urethral patency is apparently restored when calculi are spontaneously expelled from the urethra, dissolved, or refluxed into the bladder, at which time the catheter can be removed. Spontaneous resolution of urethral obstruction with tube cystostomy may take several weeks or longer; a mean time of about 11 days in small ruminants has been reported.[41,46,47] To judge when removal of the catheter is appropriate, the catheter can be clamped shut and the animal observed for urination through the urethra. Fewer complications of tube cystostomy have been reported with surgically placed tube cystostomies versus percutaneously placed cystic catheters.[40,41,46] The primary complication is a dislodged catheter followed by tears of the bladder, leakage of urine into the abdomen, adhesions of the bladder to intestine or body wall, and obstruction of the catheter.

In cases of urethral rupture where patency of the entire urethra is the preferred outcome, tube cystostomy is often the sole feasible option. Primary repair of the urethral defect is rarely successful because of swelling and maceration of the damaged mucosa and risk of stricture formation. Contrast medium can be introduced into the bladder through the catheter to monitor urethral patency, locate urethral obstruction, or identify urethral rupture.[12] The catheter can also be used to lavage the bladder to facilitate dissolution of calculi using Walpole solution or a commercially available urinary lavage product (Renacidin, Guardian Laboratories, Hauppauge, N.Y.).[42,47]

In cases of bladder rupture, the urine should be drained from the abdominal cavity, and a surgical procedure should be performed to divert urine to the exterior. If primary repair of the bladder defect is desired, a laparotomy and cystotomy or tube cystostomy can be performed with the animal under local or general anesthesia. Primary repair of the bladder defect is not always necessary, however, because spontaneous sealing of the bladder with fibrin or omentum can occur. Depending on the size and location of the bladder defect, daily or continuous abdominal drainage may have to be performed until spontaneous sealing occurs. Tears are more likely to seal spontaneously if they are located on the dorsal aspect of the bladder.

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In *bladder marsupialization* the apex of the bladder is exteriorized using a small paramedian incision, and the seromuscular layer of the bladder is circumferentially secured to the abdominal wall. A cystotomy is performed, and the bladder mucosa is secured to the skin, creating a permanent opening for urine drainage from the bladder to the exterior.[48] Advantages of bladder marsupialization include decreased hospitalization time and expense for the owner. However, complications include chronic urine scalding, stricture formation, reobstruction, and bladder prolapse. Failure of bladder marsupialization was reported to be 33% in one study.[40]

Ureteral calculi may be removed by *ureterotomy.*[49] *Nephrectomy* may be performed in unilateral cases of obstructive nephrolithiasis.[50] If unilateral nephrectomy is under consideration, measurement of BUN, serum creatinine, and urine specific gravity should be performed. Renal biopsy and ultrasonography may be useful to evaluate the remaining kidney.

POSTOPERATIVE CONSIDERATIONS. Continued assessment of hydration, urine output, and serum urea nitrogen, creatinine, and electrolyte concentrations is indicated after surgery. Postobstruction diuresis may result from tubular damage, accumulation of urea or natriuretic factors, or preoperative fluid therapy. Induction of modest diuresis through fluid therapy after surgery may help to reduce azotemia and accumulation of blood clots and bacteria in the urethra.

Antimicrobial therapy with an antibiotic that achieves high urine concentrations (e.g., penicillin, ampicillin, sulfonamides) is warranted. Duration of therapy depends on the surgical procedure chosen, residue withholding considerations, and whether UTI exists at surgery. For tube cystostomy, antimicrobial therapy is recommended by some while the tube is in place and for at least 1 week after the tube is removed. Antimicrobial therapy should be maintained for at least 3 weeks after surgery in animals with active UTI.

Prevention

A preventive approach to a urolithiasis problem begins with a search for risk factors associated with the diet, management, and the environment. Whenever possible, ration analysis and mineral analysis of the urolith(s) should be performed to accurately identify causative dietary factors. Consult Box 34-1 for analysis laboratories. If uroliths are not obtained, ration analysis and a thorough dietary history may provide a strong suggestion of the urolith type. In light of the central role of urinary supersaturation in calculogenesis, the ultimate aim of preventive measures should be reduction of urinary concentration of calculogenic mineral ions. In addition, the urine should be diluted to such an extent that the calculogenic ions are less prone to precipitate. Dilution of urine is achieved through increased salt and water intake.

DIETARY MANAGEMENT. Prevention of urinary calculi can be difficult because of the conflicting dietary effects of minerals, pH, individual animal susceptibility, feed availability, and so forth. General guidelines for prevention of phosphatic calculi require adjustment of the dietary calcium/phosphorus ratio to a level of 2:1 or greater, which can be performed by reducing the amount of grain or other high-phosphorus dietary components and/or increasing calcium in the diet with forages like alfalfa or other legumes. Use of a 0-mEq/kg DCAD diet using ammonium chloride has been shown to help reduce urinary pH to between 6.0 and 6.5 without significantly decreasing blood pH.[29] Increasing the quantity of long-stem forage in the ration may increase salivary flow and fecal phosphate excretion.

Because restriction of dietary silica intake in ruminants grazing native grasses is not feasible, dietary management is limited to salt (sodium chloride or ammonium chloride) supplementation to increase water consumption and thereby produce a diuretic effect to reduce urinary calculogenic compounds. Loose salt or lick salt is unlikely to be ingested in sufficient quantities to affect water intake. Gradually increasing quantities of sodium chloride supplementation of palatable creep feeds up to a level of 15% of dry matter has been effective for range calves.[51] The feeders should be located near a reliable source of palatable water. Ammonium chloride supplementation (1% of dry matter) has also significantly reduced silica urolith development in lambs.[20,32] In the same study, reduction of the dietary calcium/phosphorus ratio from 2:1 to almost 1:1 resulted in a trend toward reduced silica calculi formation. The role of copper and zinc deficiencies in ruminant silica urolithiasis remains to be determined.

Prevention of calcium carbonate uroliths in pet small ruminants can be reduced by feeding or supplementing with grass hay rather than feeding alfalfa alone. Salting the grass hay with increasing concentrations of salt may increase water consumption to help maintain a dilute urine. Use of ammonium chloride can aid in urine acidification and increase water consumption.

Ammonium chloride supplementation fed at a level of 0.5% to 1.5% of ration dry matter was found to reduce urine pH to 6 to 6.5 in a group of goats.[29] A urine pH in this range should increase the solubility of struvite and apatite crystals. However, the pH of the urine is also influenced by the relative concentrations of strong cations (sodium and potassium) and strong anions (chloride and sulfate) of the entire ration, so the efficacy of ammonium chloride in reducing urinary pH may vary among different livestock operations, because the concentration of these cations and anions will vary among rations.[29,52] Long-term supplementation with ammonium chloride has been reported to result in chronic metabolic acidosis with a corresponding decrease in bone density.[53] Feeding a too-high concentration, resulting in a DCAD diet of −150 to −75 mEq/kg, caused excessively low urine and blood pH.[29] Ammonium chloride is not palatable, so mixing the salt with a more palatable low-potassium product (e.g., sucrose) is typically necessary. Reports indicate that some species appear to have a renal physiologic adaptation resulting in gradually increasing urine pH with long-term feeding of ammonium chloride, but this effect has been variable in ruminants.[29,54,55] Owners can monitor for changing urine pH with urine pH strips used on a weekly basis.[29] Pulsed feeding of ammonium chloride (e.g., 2 weeks on, 2 weeks off) can be attempted if the urine pH begins to increase.

WATER MANAGEMENT. Maximizing water intake is an important aspect of urolithiasis prevention, regardless of the urolith type involved. Cleaning water containers should be a regular practice. Water palatability may also be improved by providing shade for water containers during the summer. White water containers allow owners to see contamination of the water with dirt and feed; this may prompt more frequent cleaning. Heaters should be used to warm water during the winter. Automatic waterers should be checked regularly for proper function. Shallow containers capable of rapid refilling provide higher rates of water turnover, resulting in less stagnation.

In operations involving multiple animals or large pastures, placement of multiple watering sites might allow for more frequent intake. This is especially true for sheep, whose banding instinct usually prevents individuals from traveling alone to distant watering sites.

Urachal Disorders

Stacey R. Byers

Definition and Etiology

Abnormalities of the umbilicus and umbilical remnants, including the urachus, are frequently encountered disease conditions of neonatal calves. Infections of the urachus are often associated with omphalophlebitis, which commonly arises from environmental contamination of the umbilicus at birth. Cloned calves appear to be predisposed to having a patent urachus.[1] The association of umbilical abnormalities with calfhood morbidity and mortality has been established.[2] Occasionally, more insidious and chronic conditions of the urachal remnant are observed in older calves and mature cattle, with internal abscessation, adhesions, sepsis, peritonitis, uroperitoneum, cystitis, and intestinal strangulation

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reported.[3-8] Urachal fistulas or acquired patent urachus is infrequently observed in ruminants.

Chapter 20, Manifestations and Management of Disease in Neonatal Ruminants, provides more information on these disorders.

Clinical Signs and Differential Diagnoses Calves with internal urachal abscesses, adhesions, and other sequelae are usually older than 4 weeks of age. A history of umbilical infection during the neonatal period may or may not exist, and external umbilical abnormalities may not be present. Clinical signs may be nonspecific and include fever, lethargy, poor body condition, rough hair coat, and poor growth or productivity. Dysuria, pollakiuria, stranguria, and colic may be evident on examination or may be included in the medical history. When an infection extends into the bladder lumen, hematuria and pyuria are present.[4,8] Transabdominal palpation of the umbilicus and abdomen in smaller calves may reveal painful and enlarged umbilical remnants. Transabdominal ultrasound of the umbilicus and ventral abdomen is useful to identify abnormal structures, but adhesions may not be visualized.[9] Complications from associated septicemia (e.g., lameness and joint distention, pneumonia, hypopyon, meningitis) can occur.

If the urachus fails to regress completely, a persistent communication between the bladder apex and the pouch-like urachal remnant occurs. The volume of urine retained in the urachal remnant is variable. Animals with this problem may dribble urine from the urachus during micturition or remain asymptomatic. Urine retention can predispose the animal to UTIs.

Spontaneous rupture of the infected urachal stalk may result in the acute onset of peritonitis. If the urachal remnant communicates with the bladder lumen, rupture of the urachus results in uroabdomen. Rupture may occur spontaneously or after abdominal trauma or parturition in older animals.

A detailed ultrasonographic examination of the interior of the umbilical remnant and caudoventral abdomen is warranted in suspected urachal or umbilical abnormalities.[9] The bladder and other viscera may assume abnormal shape or position as a result of urachal adhesions. The luminal contents of the urachal remnant and bladder may appear flocculent in cases complicated by concurrent cystitis. Uroabdomen is characterized by accumulation of echolucent fluid in the abdominal cavity, with variable amounts of fibrin deposition evident.

Because of the variable nature of urachal problems, the differential diagnosis will vary according to the organ(s) involved. Urachal adhesions to the intestine or uterus may result in colic, signs of intestinal obstruction, and postpartum peritonitis or uroabdomen. Concurrent signs involving the lower urinary system might indicate the potential for primary ascending infections, such as cystitis or pyelonephritis. In cases of uroabdomen in males, obstructive urolithiasis is an important differential. Urolithiasis, urethritis, or neurologic disease may be included in differential diagnoses of dysuric animals. Nephritis of hematogenous origin is worthy of consideration in animals showing ill-thrift, colic, kyphosis, or abnormal urine.

Clinical Pathology Laboratory findings may be variable, but an inflammatory leukogram, hyperfibrinogenemia, and hyperglobulinemia are expected. Urinalysis may be normal or indicative of cystitis if the urinary bladder is involved. Abdominocentesis findings are variable and depend on the presence and extent of peritonitis associated with the urachal lesion. Voluminous blood-tinged abdominal fluid suggests uroperitoneum, and analysis of the fluid and serum creatinine concentration is indicated (see Urolithiasis section).

Pathogenesis Following bacterial infection of the urachus, the inflammatory response within the abdomen precipitates development of fibrinous adhesions between the urachus and surrounding viscera, including the rumen, intestine, uterus, bladder, or ovaries. Abscesses may form in single or multiple locations in the urachal stalk; although uncommon, abscesses involving the apex of the urinary bladder result in concurrent cystitis.[4,8] Urachal fibrosis and adhesions may serve as a means of mechanical interference of bladder emptying, resulting in secondary cystitis from chronic urine retention.[8] Infrequently, the urachal abscess perforates, with subsequent peritonitis, sepsis, or uroperitoneum.[3,4] Most urachal infections involve *Trueperella pyogenes* or *E. coli,* but other organisms may be present as well.[5,9,10]

Treatment and Prognosis Ventral midline celiotomy, paramedian celiotomy, or laparoscopy under general anesthesia is recommended to enable complete evaluation of the abdominal cavity.[11,12] Resection of the urachal remnants, with careful dissection of adhesions, is often required for complete resolution. Resection of the apex of the urinary bladder is necessary if the urachus incorporates or communicates with the bladder. Perioperative and postoperative antibiotic therapy is essential, and appropriate antibiotic selection should be based on culture and sensitivity of the abscess(es) or urine.

Outcomes of the surgical management are often satisfactory, but recurrence of adhesions should always be considered as a potential outcome. A guarded to poor prognosis is warranted for severe peritonitis or extensive adhesions. Without surgery, medical management with long-term antibacterial therapy would be expected to provide limited success, because the structural problems created by adhesions and abscesses are not directly addressed.

Urinary Bladder Eversion and Prolapse

Stacey R. Byers

Definition and Etiology Urinary bladder eversion or prolapse are uncommon events that occur during or shortly after parturition in cows.[1-5] With eversion, forceful straining moves the bladder fundus caudally, eventually turning the bladder inside out. The bladder is then forced out of the urethral orifice. Prolapse of the bladder is more frequently associated with dystocia.[1,2] In this condition a full-thickness tear of the vaginal wall occurs during delivery, allowing the bladder (and possibly other viscera) to be displaced from the abdominal cavity into the vagina.

Clinical Signs and Differential Diagnosis Cows with either eversion or prolapse of the bladder have a smooth, spherical mass within the vagina, usually protruding from the vulva. An affected cow may be alert and ambulatory, but if concurrent hypocalcemia, exhaustion, or peritonitis exists, the cow may be recumbent and depressed. Careful vaginal examination is required to differentiate these two conditions from each other and from vaginal prolapse, vaginal polyps, fat protrusion from a vaginal tear, vaginal neoplasia, fetal membranes, and uterine prolapse. Prevention of straining through epidural anesthesia is essential because expulsive efforts can cause herniation of viscera through the urethra (bladder eversion) or through the vaginal tear (bladder prolapse).[1] Epidural anesthesia also facilitates cleaning of the area, because straining may result in continual fecal contamination of the perineum and vestibule.

With a urinary bladder eversion, the mucosal surface of the bladder is exposed. The ureteral openings may be visible on its dorsal aspect, although these may be occluded and difficult to see if the wall of the bladder is edematous.[4] Vaginal palpation reveals that the protruding tissue originates from the urethral orifice. With time, constriction of the everted bladder by the narrow urethra may cause venous congestion, edema, thrombosis, and eventual necrosis.[1] Palpation and ultrasonographic examination are required for detection of herniation of other viscera through the urethral orifice and into the interior of the everted bladder. Strangulation of incarcerated bowel may occur.[2,3] Careful fine-needle aspiration of the interior of the eversion has been used to differentiate eversion from prolapse of the bladder. With bladder eversion, aspiration may yield peritoneal fluid, but laceration of herniated bowel is a concern.[1]

The serosal surface of the bladder is exposed with a urinary bladder prolapse. Careful palpation of the vagina reveals that the

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bladder protrudes from a full-thickness tear in the floor or lateral wall of the vagina. Other viscera may be present in the vagina as well. Fine-needle aspiration yields urine from the bladder lumen.

Treatment and Prognosis Manual reduction of an everted bladder may not be possible if it is edematous or if other viscera have herniated into its interior. The dorsal aspect of the urethra may be incised to widen the route through which the bladder is to be replaced.[1,2] Laparotomy is required for assessment of the viability of herniated bowel, and subtotal cystectomy may be performed if extensive bladder trauma or necrosis has occurred.[2] The viability of the involved structures is of primary concern for prognosis. Bladder paralysis and rupture are potential sequelae to ischemic damage that develops during eversion.[1] Cystitis and pyelonephritis may develop as well, and antibiotic therapy is warranted if repair is attempted. Animals with chronic conditions may develop hydroureter, hydronephrosis, and renal failure.[5]

A bladder prolapse can be resolved by first passing a flexible catheter into the urethra to remove urine from the bladder. This also confirms the diagnosis and facilitates bladder replacement. After catheterization and removal of urine, the bladder can be replaced into the abdominal cavity, and the vaginal tear can be sutured. Severe contamination of the peritoneal cavity may render attempts at treatment unjustified. Antibiotic therapy is indicated for surgical candidates.

Pelvic Entrapment of the Bladder

Stacey R. Byers

Definition and Etiology In pelvic entrapment of the bladder, the apex and fundus of the bladder are displaced caudodorsally into the pelvic cavity, resulting in impaired urine outflow. Occurrence has been associated with postpartum straining, perineal hernia, and vaginal prolapse.[1-3]

Clinical Signs and Differential Diagnoses Bladder emptying is impaired, and the presence of the bladder in the pelvic inlet induces straining. An affected cow or sheep may show tenesmus, pollakiuria, and stranguria. On rectal examination a soft, fluctuant mass may be detected beside the vagina.[1] In calves, radiography has been used to demonstrate the pelvic position of the bladder.[3] Ultrasonographic examination can also be a useful diagnostic tool.[2]

Differential diagnoses include proctitis, vaginitis, retained placenta, bladder paralysis, cystitis, and perivaginal abscess. Needle aspiration of the bladder per vaginum has been used to make a definitive diagnosis, although the danger of uterine puncture should be considered.

Treatment and Prognosis Draining the bladder through catheterization or needle aspiration facilitates replacement of the bladder by manipulation per vaginum. However, fibrinous adhesions between the bladder and vagina may make laparotomy necessary to replace the bladder.

Enzootic Hematuria

Stacey R. Byers

Definition and Etiology Enzootic hematuria is a disease of chronic or intermittent hematuria in cattle and small ruminants and is associated with chronic ingestion of bracken fern (*Pteridium aquilinum;* Fig. 34-21).[1] A different fern species, *Cheilanthes sieberi,* may induce this disease in Australian cattle.[2] Hemorrhagic cystitis is the initial consequence of exposure to the toxic compound(s) in the plant. With continued ingestion of bracken fern, cattle develop bladder neoplasms of epithelial, mesenchymal, or mixed origin. Bladder infection with bovine papillomavirus type 2 is involved in carcinogenesis.[1]

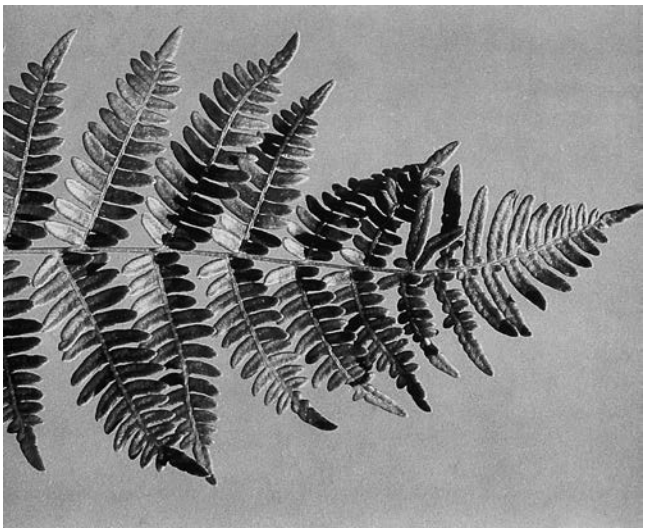


FIG. 34-21 Bracken fern *(Pteridium aquilinum).*

The syndrome of enzootic hematuria is quite different from acute bracken poisoning. Enzootic hematuria occurs after ingestion of large quantities of bracken fern (approximating the animal's body weight), usually over 1 to 3 months. Acute bracken poisoning manifests as an acute coagulopathy or fulminant septicemic crisis associated with severe bone marrow suppression. Acute bracken poisoning is further described in Chapter 54.

Clinical Signs and Differential Diagnoses Affected animals are typically in a group that is grazing a particular pasture or being fed a particular type or cutting of hay. Protracted, possibly intermittent, hematuria is the first clinical sign detected in most animals. Blood clots may be voided on occasion. Chronic blood loss eventually results in tachycardia, tachypnea, exercise intolerance, pale mucous membranes, and a decline in productivity and body condition. Bladder wall thickening and bladder tumors may be palpated per rectum. Proliferative changes or overt neoplasia of the bladder may cause dysuria, pollakiuria, and rarely, obstruction of the bladder trigone. Occasionally, blood clots may cause urethral obstruction. Depending on the magnitude and duration of bracken fern ingestion, hematuria may last for months to years before severe debilitation or death occurs. Ultrasonographic examination of the urinary bladder of affected animals may reveal bladder thickening and an irregularly shaped bladder wall. In an Indian study, affected cattle showed a bladder wall thickness of 4 to 5 mm (normal, 1 to 2 mm).[3]

Examination of serum for evidence of hemolysis and analysis of sediment from a freshly voided urine sample for intact RBCs allow for differentiation of hematuria from the hemoglobinuria found in hemolytic diseases. Icterus, also characteristic of ruminant hemolytic disorders, is not found in cases of enzootic hematuria. Hematuria may be evident in a UTI, but pyuria and bacteriuria are marked, and anemia, if present, is usually mild. Simultaneous involvement of several animals is uncommon with UTI but common in enzootic hematuria. Hematuria may also be evident in cattle affected by malignant catarrhal fever. Protracted, severe hematuria is rare in cases of urolithiasis, and anemia is also not expected. Without necropsy, a diagnosis of enzootic hematuria requires documentation of access to bracken fern in animals with characteristic clinical signs and laboratory data.

Clinical Pathology Severe anemia is often seen on hematologic examination of cattle and sheep with enzootic hematuria. Evidence of a regenerative response may not be present if bone marrow suppression is severe. The platelet, segmented neutrophil,

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and lymphocyte counts may be reduced. Urinalysis reveals hematuria, proteinuria, and variable pyuria.

Pathophysiology All parts of the plant are toxic to sheep and cattle. Several compounds in bracken fern possess irritant, mutagenic, immunosuppressive, or carcinogenic activities. These include ptaquiloside (aquilide A), quercetin, and α-ecdysone.[4-7] The carcinogenic principles are present in the milk of cows grazing bracken fern.[8] Bracken fern compounds may cause recrudescence of latent bovine papillomavirus 2 (BPV-2) infections through immunosuppression. Mutagenic compounds in bracken fern interact with BPV-2 in bladder infections to induce local neoplasia.[1,2] Growth of the resultant neoplastic tissue may be enhanced by further exposure to mutagenic bracken fern compounds.

In multiple species, cyclooxygenase-2 (COX-2) is overexpressed in epithelial neoplasms, including those of the urinary bladder origin. Certain types of tumors of urinary epithelium may co-express COX-1 and COX-2. Bladder carcinomas from cows with enzootic hematuria have been shown to express both COX-1 and COX-2 at a high level relative to normal controls when evaluated by immunohistochemical methods.[9] The efficacy of COX-2 inhibitor drugs on cancer prevention or treatment in cattle at risk for bladder tumors remains to be investigated.

Epidemiology Enzootic hematuria has a wide geographic distribution, with cases reported in North and South America, the United Kingdom, Australia, and several European countries. Bracken fern is found in all areas of the United States except the Great Plains, with most livestock poisonings occurring in the Pacific Northwest and upper Midwest. The plant grows best in well-drained, fertile soils and is often localized in open areas of forests. Sheep and cattle are poisoned by grazing the plant or consuming contaminated hay.

Enzootic hematuria is primarily seen in adult sheep and cattle. Cattle grazing infested pastures may develop hematuria by 2 to 3 years of age. Papillomas of the bladder have occurred as early as 1 year after bracken feeding begins, with invasive carcinomas arising 2 to 6 years later. Within endemic areas, up to 90% of adult cattle may be affected.[10]

Necropsy Findings Tissue pallor from anemia is often appreciated. The bladder wall is thickened and the mucosa hemorrhagic and ulcerated. Microscopic examination of the bladder wall reveals capillary engorgement, intramural hemorrhage, and metaplasia of the bladder epithelium. Several types of bladder tumors and mixed-origin neoplasms may be present. Metastasis of epithelial neoplasms to the regional lymph nodes or other organs can occur.[10]

Treatment and Prevention Treatment of enzootic hematuria is limited to reduction or elimination of bracken fern in the diet. Wooded areas that support growth of bracken fern can be fenced off, and forage improvement may help limit incorporation of the plant into hay. If such measures are not feasible, a program of early culling may help prevent low productivity from anemia and neoplasia. Hematuria will cease if bracken feeding is discontinued before the onset of tumor formation.

Urinary Tract Infection

Brandon J. Dominguez

UTIs in ruminants typically present as cystitis, ureteritis, and pyelonephritis from ascending infection with *C. renale* or *E. coli*.[1] Other coliform species[2] and other close relatives of *C. renale* may be involved with lesser frequency.[3] Less commonly, *Salmonella* spp., *T. pyogenes, P. aeruginosa, Streptococcus* spp., and *Staphylococcus* spp., among others, have been implicated in renal infections of hematogenous origin (suppurative embolic nephritis).[4,5] In small ruminants, *Corynebacterium pseudotuberculosis* has been cultured from renal infections.[6]

Clinical Signs Cystitis is suggested clinically by dysuria and pollakiuria; hematuria and pyuria may not be grossly apparent. Affected cattle may dribble urine, tread their feet, swish their tail, or retain an arched stance after voiding. Occasionally, blood, purulent debris, or urinary crystals may be found on the ventral commissure of the vulva.[1] The bladder may be thickened and painful on rectal palpation, and on cystoscopy, catarrhal, hemorrhagic, fibrinous-purulent, and fibrinous-hemorrhagic lesions may be observed.[7] Generalized signs of malaise are not seen if infection is limited to the bladder.[1]

Acute cases of pyelonephritis are often presented with a history of sudden reductions in feed intake and milk production. Fever, increased heart rate, increased respiratory rate, decreased skin turgor, enophthalmos, ruminal stasis, scleral injection, and occasional episodes of mild colic may be noticed in addition to signs of cystitis.[1] When the left kidney is involved, renal enlargement, pain, and loss of the normal lobulation may be noted on rectal palpation. Affected calves may dribble urine, resulting in phosphate calculi present on the vulvar hairs. This may be accompanied by wet hair on the perineum and hind legs, progressing to excoriations due to urine scald.

Evaluation of the right kidney can be accomplished via ultrasound (see ultrasound images of urinary tract in ruminant section of Chapter 32) with a 5.0-MHz or lower frequency transducer in the 12th intercostal space and right paralumbar fossa.[8,9,10] In small or thin cattle, the left kidney may be visible in the left paralumbar fossa on transcutaneous ultrasound. Alternatively, the left kidney can be assessed with a 5.0-MHz or higher transducer via the rectum. Renal enlargement, abnormal kidney shape, dilated renal calyces, and flocculent echogenic material in the renal pelvis and ureter are suggestive of pyelonephritis.[8,9,10] The ureters may be palpated per vaginum, with the examiner using his or her fingers to detect one or both enlarged painful ureters adjacent to the ventral vaginal wall.[1]

Chronic pyelonephritis presents with vague signs.[1] Weight loss, muscle wasting, poor growth, anorexia, diarrhea, and reduced milk production may be evident from history. No abnormal behavior or posturing during urination may be noted. Pale mucous membranes (due to anemia) may be noted during physical exam. A loss of lobulation on the left kidney may be evident on rectal palpation; pain and enlargement may not be noted.[1] Cystic lesions may be noted ultrasonographically in chronic renal disease.[10]

Differential Diagnosis Mild colic may be a symptom of numerous GI or intraabdominal disorders, and urinalysis findings will be normal. Dysuria may be the result of vaginitis, perivaginal abscess, pelvic entrapment of the bladder, vulvar trauma, or postparturient swelling of the vagina and vulva. Urolithiasis can cause dysuria and hematuria, but males are typically affected, whereas females are predisposed to UTI. On palpation, bladder distention will be evident in cases of urolithiasis, a finding not expected with UTI. A careful neurologic exam will help determine whether there is underlying bladder paresis or incomplete voiding from neurologic diseases. Hematuria may be due to bleeding from parturition, papillomas in the urinary tract, postparturient hemoglobinuria, or enzootic hematuria. In cases of enzootic hematuria, multiple animals are typically affected, and presence of bracken fern can be demonstrated. Additionally, a profound anemia is expected with enzootic hematuria, and if pyuria or bacteriuria is present, it will be mild. Papilloma of the bladder may be ruled out with cystoscopy.

Clinical Pathology A neutrophilic leukocytosis with hyperfibrinemia is expected in cases of pyelonephritis. If the duration of the infection has been several days, a hyperglobinemia will develop. Continued severe proteinuria, resulting in hypoalbuminemia, can lead to diarrhea because of decreased plasma oncotic pressure. As the chronicity of the disease lengthens, anemia may develop. This may be due in part to the decreased production of erythropoietin in the affected renal tissue and from blood loss through urination.[1] Measurement of serum BUN and creatinine is critical for prognosis in cases of

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pyelonephritis.[7,11] When azotemia and isosthenuria are combined in cases of pyelonephritis, bilateral kidney involvement is indicated, and the prognosis for successful treatment is poor.[1] Prerenal causes should be considered when evaluating the severity of azotemia.

Urinalysis is necessary for definitive diagnosis of UTI. A midstream or endstream caught sample should provide the most accurate results as contaminants in the distal urogenital tract are purged. Concomitant metritis, vaginitis, or prostatitis may contaminate urine with blood, bacteria, and inflammatory cells. Hematuria, proteinuria, and bacteria should be present in the urine of a UTI-afflicted cow. Specific gravity may be in the range of 1.005 to 1.020.[10] A Gram stain of the urine may yield preliminary identification of the causative organism.

Pathophysiology Initiation of an ascending infection is dependent on the amount and virulence of bacteria introduced into the urinary tract. Urogenital trauma during calving or obstetric manipulation, abnormal vulvar confirmation, conditions leading to urine retention, and bladder catheterization may provide routes of introduction for pathogens. Impaired bladder emptying due to bladder adhesions, urachal remnant infection, or diseases of the spinal cord may create an environment for the establishment of cystitis and ascending infection. Urethral trauma from catheterization, urolithiasis, breeding, or urogenital papilloma may be adequate to initiate infection.[12] Vesiculoureteral reflux due to decreased bladder contractility or ectopic ureters may occur, aiding in the expansion of infection up the urinary tract. Ureteral and renal obstruction due to inflammatory debris, hemorrhage, and fibrin deposition may lead to episodic signs of colic. After pyelonephritis is established, necrosis of papillary and tubular epithelium leads to an accumulation of necrotic debris in the renal pelvis, loss of functional nephrons, abscessation, fibrosis, and distortion of the renal shape. Struvite uroliths and other renal calculi may develop when necrotic debris serve as foci of crystal deposition in the alkaline microenvironment created by bacterial urease activity.[4]

C. renale is a large, pleomorphic, non-motile, gram-positive bacillus.[3] It is grouped with and closely related to two other *Corynebacterium* that may cause pyelonephritis, *C. cystitidis* and *C. pilosum*.[5] *C. renale* pyelonephritis has been documented in a sheep[12] and induced experimentally in goats.[13] Evidence suggests that *C. renale* may be maintained in the environment for several weeks.[3] The bacterium may be transmitted by direct vulvar contact between cows or by splashing of urine from infected cows. Iatrogenic transmission may occur via contaminated obstetrical instruments or urinary catheters. Bulls may spread *C. cystitidis* and *C. renale* through sexual contact.[14] *C. renale* adhere to the urinary tract epithelium via pH-mediated pili.[15] Adherence is enhanced in alkaline conditions and reduced in acidic conditions.[16] This pH influence may explain the improvement in clinical signs realized after the feeding of urine-acidifying salts. The organism uses ureolysis and ammonium production to maintain urine alkalinity and promote colonization of the epithelium. A serum antibody response will develop after renal infection. This humoral response is rarely curative, nor does it provide resistance to reinfection.[1]

E. coli, among other coliforms, is frequently implicated in ruminant UTI.[1] The serotype(s) and virulence factors of *E. coli* specifically involved in bovine pyelonephritis are unknown at this time. Because of the ubiquitous nature of this gram-negative coliform, it is thought that infection originates from fecal contamination or a loss of natural defenses in the urogenital tract.

Epidemiology On-farm prevalence of pyelonephritis varied from 0.3% to 2.7% in an Israeli study.[11] Female animals have a greater potential for infection owing to a shorter urethra in addition to potential contamination and trauma during parturition and breeding. A majority of pyelonephritis cases develop within 90 days post calving, which suggests that the postpartum period is a significant risk period in the development of infection.[4] Reproductive tract abnormalities such as pneumovagina, metritis, and poor perineal conformation were identified in 7 out of 15 cows diagnosed with pyelonephritis.[1]

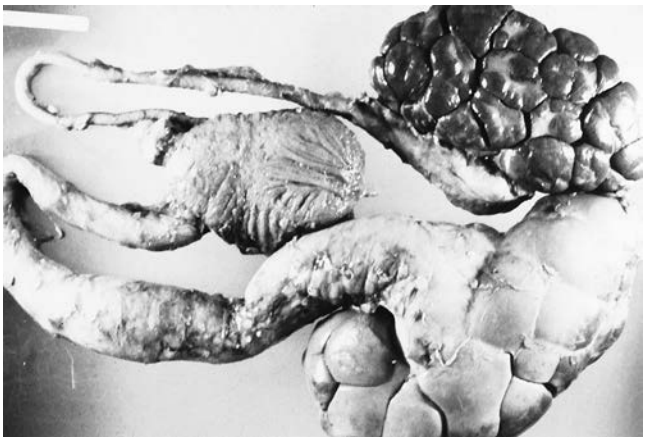


FIG. 34-22 Postmortem specimen of unilateral pyelonephritis and ureteritis in a cow. The affected kidney and ureter are greatly enlarged.

C. renale has typically been regarded as the most common pathogen in bovine pyelonephritis.[2,10] In some studies, *E. coli* has been found as the more prevalent bacteria in pyelonephritis cases.[4,5,17] *C. renale* and *C. pilosum* have been found in healthy cows, whereas *C. cystitidis* is considered the most virulent pathogen in the *C. renale* group.[5] Once established, *C. renale* can be difficult to eradicate on a herd level.

Necropsy Findings The bladder will have evidence of hemorrhage, ulceration, and fibrin deposition on the epithelial surface, which may extend through the urethra. Polypoid growths may develop with chronic infection. As these resemble tumors, histopathologic examination is necessary for definitive diagnosis.[2] Ureters may be noticeably enlarged on one or both sides and full of purulent debris. Acute to subacute pyelonephritis cases may show gross enlargement of the affected kidney(s). A viscous gray, odorless exudate may be found in the renal pelvis and extend into the medulla and cortex, especially on sagittal section. A Gram stain of the exudate is helpful for differentiation of the cause. Chronic cases of pyelonephritis may have gross distortion of renal size and shape due to abscesses (Fig. 34-22).

Treatment and Prognosis Aggressive and long-term antibiotics are required for successful treatment of UTI. Prolonged antibiotic therapy is often required. Diuresis with oral or parenteral fluid therapy is beneficial in facilitating the removal of necrotic debris and bacteria from the urinary tract.[1] Nephrectomy in cases of unilateral pyelonephritis that are unresponsive to medical therapy is an option.[10] Studies have indicated that there is no apparent limitation on growth and production following unilateral nephrectomy if the remaining kidney is normal and healthy.[18]

Penicillin is typically the first choice treatment of *C. renale* and *E. coli* infection. Twice daily IM administration of procaine penicillin G (22,000 to 44,000 IU/kg) or ampicillin trihydrate (11 mg/kg) is effective.[1] Higher serum and urinary concentrations may be attained with IV administration of sodium or potassium penicillin (22,000 to 44,000 IU/kg q6h) or sodium ampicillin (10 to 50 mg/kg q8h). Cows with coliform UTI should be continually monitored for appetite, attitude, pyrexia, and reagent-strip urinalysis. If there is no improvement within 96 hours of treatment, therapy should be modified.[1] Gentamicin (2.2 mg/kg IM bid),[1] trimethoprim-sulfadiazine (15 mg/kg IV once daily),[2] or ceftiofur (3 mg/kg IV bid)[19] have been used to treat refractory coliform UTI. The nephrotoxicity of gentamicin is an important consideration.[1] Current U.S. regulations limit the use of ceftiofur in food-producing animals to label dosage, routes, and frequencies.[20] Meat and milk withdrawal times must be extended appropriately after prolonged and extralabel dosages of any antibiotic.

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Urinalysis and urine culture should be assessed 1 week after therapy is discontinued to confirm resolution.

Treatment is more likely to be successful the earlier it is initiated in the course of disease. Case fatality and nonvoluntary cull rates due to pyelonephritis in dairy cattle have been reported between 18%[1] and 47%[4] for treated cases. Recrudescence rates have been reported at 9.4%.[11] Cystitis alone yields a better prognosis than concurrent ureteritis or pyelonephritis, especially if bilateral disease is evident. Cows with marked azotemia noted by a BUN above 100 mg/dL and/or a creatinine above 1.5 mg/dL and pyelonephritis were at much greater risk of culling than nonazotemic cows with pyelonephritis.[11]

Prevention and Control Isolation of diseased animals, particularly with *C. renale,* is recommended to limit the spread of the organism. Cleaning and disinfection of contaminated areas is advisable. Aseptic technique during urogenital and obstetric procedures can limit iatrogenic transmission. Venereal transmission is difficult to control in herds with natural service and subclinically infected bulls. Artificial insemination or mass treatment programs could be introduced in herds with increased problems due to UTI.

Amyloidosis

David C. Van Metre

Amyloidosis is caused by deposition of insoluble fibrillar protein in various organs.[1] Amyloid may generate from a variety of normal or abnormal precursor proteins. Amyloid develops when these precursor proteins become abnormally folded. Misfolded proteins are normally degraded intracellularly by proteasomes or by macrophages in the extracellular space; this regulatory mechanism fails to occur in amyloidosis. Amyloid molecules tend to aggregate together into β-pleated sheets that are highly resistant to degradation. As a result, amyloid gradually collects in tissues, eventually resulting in dysfunction of the parent organ. In animals, the kidney, spleen, and liver are most commonly affected.[1]

Renal amyloidosis in cattle is an uncommon chronic wasting disease marked by chronic diarrhea and sustained heavy proteinuria.[2-6] It occurs secondary to long-standing inflammatory diseases such as traumatic reticuloperitonitis and metritis. Amyloid deposition in the kidney disrupts the normal glomerular structure, resulting in a protein-losing nephropathy. In a study sample population of 82 cattle with chronic bacterial infections, renal amyloidosis was identified in 5 animals (6%).[4]

Clinical Signs The most common clinical signs of bovine renal amyloidosis include chronic diarrhea, weight loss, generalized edema, and poor productivity in mature animals.[2-6] Reduction in appetite, lethargy, and other signs may reflect the underlying inflammatory disease. Enlargement of the left kidney may be palpated during rectal examination. The enlarged kidney is not painful and maintains its normal lobulation. Because of its abnormally high protein content, urine may form a stable foam after hitting the ground or being shaken in a container.

Clinical Pathology Cattle with renal amyloidosis consistently develop marked proteinuria and hypoalbuminemia.[2-6] Hyperfibrinogenemia and/or hyperglobulinemia may be present, and other inflammatory changes may be apparent on the hemogram. Serum creatinine and BUN levels may be elevated if renal damage is advanced. Amyloidosis would be supported by finding persistent heavy proteinuria in the absence of RBCs, WBCs, or bacteria in the urine sediment. Importantly, one would expect a positive reaction for protein on urine dipstick when the urine is alkaline (as it often is in ruminants), so more specific tests for protein (e.g., sulfosalicylic acid precipitation test) should be used to confirm the presence of true proteinuria. Polarized light microscopy and electron microscopy have been used to examine urine sediment for the presence of amyloid protein in urine.[5]

Differential Diagnosis Amyloidosis must be differentiated from other diseases causing chronic diarrhea, hypoproteinemia, weight loss, and poor productivity. Diseases to consider include Johne's disease, copper deficiency, salmonellosis, bovine viral diarrhea, GI parasitism, liver fluke infestation, bovine leukosis virus infection, and GN. GN is the only other differential diagnosis wherein persistent proteinuria is an expected feature. Renal biopsy can be performed to differentiate GN from amyloidosis in the live animal.

Pathophysiology Light-chain (AL) amyloidosis is associated with immune cell dyscrasias (e.g., plasmacytoma, multiple myeloma) and is quite rare in domestic animals.[1] Amyloidosis of cattle is classified as the reactive (AA) type,[2-6] which is frequently associated with chronic inflammatory disease in domestic animals and humans.[1,7,8] Concurrent inflammatory disease—traumatic reticuloperitonitis, pneumonia, mastitis, and metritis—have been found in some but not all cattle with amyloidosis.[2-6] Serum amyloid A protein (SAA) is an acute-phase protein that is synthesized in the liver and is a precursor of amyloid A (AA) fibril in tissues[1,7,8]; SAA concentrations increase in cattle with inflammatory disease.[4] Amyloid deposition in this population may be due to abnormal catabolism of SAA or an inherent structural abnormality in SAA that renders it prone to misfolding and deposition as amyloid in organs.[1,7,8] AA fibrils are resistant to proteolysis, allowing for their accumulation in tissues over time. Accumulation of amyloid in the glomerulus alters glomerular filtration and enables sustained albuminuria and a gradual loss of plasma oncotic pressure. Diarrhea develops as a result of gut wall edema or amyloid deposition in the GI tract.[3] The resulting clinical picture resembles the nephrotic syndrome of humans: massive proteinuria, hypoalbuminemia, and generalized edema.[7] Renal or pulmonary thrombosis may develop secondary to loss of low-molecular-weight anticoagulant proteins through the compromised kidney.[9]

Necropsy Findings Renal enlargement with yellow-tan to white discoloration is frequently present. A waxy quality of the renal parenchyma may be appreciated on the cut surface of the kidney.[2] Generalized edema resulting from hypoalbuminemia may be present. Some animals will have renal or pulmonary thrombosis.[3] Primary inflammatory disease is expected to be found in other sites.

Histologic examination of the kidney may reveal amyloid deposition in the glomerulus, interstitium, and tubule lumen. Congo red staining is typically used to demonstrate amyloid; under normal light, stained amyloid appears pink, whereas under polarized light, stained amyloid displays a bright green birefringence.[1,7,8]

Prognosis The prognosis for affected cattle is poor. The resilient nature of the amyloid protein generally results in its persistence in tissues, even if the underlying cause of inflammatory disease is successfully treated.[7] Specific treatment for amyloidosis has not been reported in cattle.

Glomerulonephritis

David C. Van Metre

GN is a rare clinical disorder of ruminants that may result from deposition of antigen-antibody complexes in the glomerulus or binding of antibody to intrinsic or foreign antigens localized to the glomerulus. Immune system targeting of glomerular tissues leads to glomerular injury. Nonimmune mechanisms may be involved in certain forms of the disease.

Clinical Signs Cattle with GN may have a history of weight loss, poor productivity, and chronic diarrhea.[1,2] Lethargy and generalized edema may be detected on physical examination. Rectal palpation may reveal a mildly enlarged but nonpainful left kidney.[2] GN

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may be clinically occult in cattle acutely[3] or persistently infected with bovine viral diarrhea (BVD) virus[4] and in cattle with fascioliasis.[5] GN has been associated with pregnancy toxemia in ewes[6]; affected animals tend to show clinical signs typical of pregnancy toxemia (see Chapter 33).

Mesangiocapillary GN has been described in Finnish Landrace lambs of specific lineage in Scotland and Canada.[7] The disease is heritable, but the exact mode of inheritance remains unknown. Clinical signs of this disease begin within hours after birth to 3 months of age. Affected lambs may be dull, ataxic, and appear blind. Fine muscle tremors, colic, and convulsions may also be seen.

Differential Diagnosis The differential diagnosis for cattle with GN is similar to that for amyloidosis (see preceding section).

Clinical Pathology Heavy proteinuria, mild anemia, and hypoalbuminemia have been reported in cattle with GN.[1,2] Granular casts, RBCs, and leukocytes were found in the urine sediment of one affected cow.[1] Azotemia, proteinuria, and ketonuria are found in ewes with GN associated with pregnancy toxemia.[6] Mesangiocapillary GN in Finnish Landrace lambs is characterized by uremia, hypoalbuminemia, proteinuria, hypocalcemia, and hyperphosphatemia.[7]

Pathophysiology In humans, GN may result from a variety of infectious, toxic, or autoimmune disorders, all of which induce eventual immunologic injury to the glomerulus.[8] Antibodies may be directed against host or foreign antigens located in the vascular endothelium, mesangial cells, or basement membrane. In addition, circulating immune complexes may deposit in the glomerulus. The ultimate consequences are activation of complement and chemotaxis of leukocytes, both of which result in glomerular injury and increased glomerular permeability.[8]

Passage of plasma albumin through the damaged glomerulus results in chronic albuminuria, eventually leading to reduced plasma oncotic pressure and generalized edema. Urine losses of the anticoagulant protein antithrombin III may result in a hypercoagulable state.[9]

Immunohistochemical data suggest involvement of immune-mediated mechanisms for spontaneous GN in cattle[1,2] and sheep,[7] GN associated with persistent BVD infection[4] and fascioliasis in cattle,[5] and mesangiocapillary GN of Finnish Landrace lambs.[7] Galav and colleagues demonstrated glomerulonephritis in calves experimentally infected with an Indian BVD 1b isolate; viral antigen was detected in affected glomeruli, but immune complexes were not, indicating that certain strains of this virus may incite direct glomerular injury.[3] Notably, glomerulonephritis may also be an incidental histologic finding in animals with acute septic disease.[7]

The clinical and histopathologic characteristics of GN of pregnancy toxemia in ewes resemble those of the preeclampsia syndrome of women.[6] Enlarged glomeruli with reduced blood content in glomerular capillaries are found throughout the renal cortex of affected ewes. The renal lesion in preeclamptic women may result from endothelial injury during DIC or an excessive glomerular vasomotor response to angiotensin.[10] The lesion can be reversible in women, but the consequences of this condition in ewes have not been described.

Treatment and Prognosis Treatment of GN in ruminants has not been described. Because most cases of GN are advanced at diagnosis, the prognosis is poor. Mesangiocapillary GN in Finnish Landrace sheep is not invariably lethal, and some affected lambs may survive into adulthood.[6]

Congenital Defects

David C. Van Metre

Most severe urinary tract congenital defects of ruminants manifest at an early age, but they occasionally remain clinically occult until adulthood[1] and should be considered in the differential diagnosis for a young animal with renal disease or abnormal urination. However, tubular necrosis caused by severe volume depletion, nephrotoxins, and infectious diseases is much more common. If a congenital defect of the urinary tract is identified, careful examination of other body systems should be performed; 73% of lambs with urogenital defects were found to have one or more defects in other organ systems.[2]

Renal Defects

Renal cysts are considered a common bovine renal defect[3] and have been described in sheep[2] and a goat.[4] These fluid-filled cavities in the renal parenchyma are usually of no clinical significance unless they are large or numerous (polycystic kidneys).[1,3] *Renal agenesis* was found to be the most common renal defect in lambs, with hydronephrosis and renal dysgenesis occurring less frequently.[2] A retroperitoneal perirenal *pseudocyst* (a fluid sac lacking an epithelial layer) has been reported in a ram with acute abdominal pain.[5] Pseudocysts typically develop as outpocketings of the renal capsule and can develop as a result of renal trauma, urinary tract obstruction, or vascular or lymphatic anomalies.

Renal oxalosis is a metabolic disease that is suspected to have an inherited basis; it has been reported in Beefmaster calves.[6] The calves show weakness, lethargy, and anorexia within days to several weeks of age. Dehydration, diarrhea, and alopecia over the head, neck, and extremities may also be seen. Evidence of renal failure is found on serum chemistry analysis. An inherited abnormality of glycine or glyoxylate metabolism may generate high levels of endogenous oxalate, which readily complexes with calcium. As a result, calcium oxalate crystals accumulate in the renal tubules, obstructing outflow of the tubular filtrate. Exposure to oxalate-containing plants and ethylene glycol must be ruled out in all cases of renal oxalosis.

Ectopic Ureter

Ectopic ureter is a rare congenital defect in which one or both ureters terminate in an abnormal location. An ectopic ureter may terminate in the urethra, vagina, or cervix or caudal to the bladder trigone in females. In males the ectopic ureter usually terminates in the urethra, vas deferens, or seminal vesicles. Urinary incontinence is the most common presenting complaint for affected animals.[7] Urine dribbling results in scalding of the perineum and medial surfaces of the hindlimb in heifers, and scalding in males is usually located on the prepuce and ventral abdomen. Occasional episodes of normal micturition may be seen. UTI, polycystic kidney(s), and hydronephrosis may exist concurrent to ectopic ureter(s).

Definitive diagnosis requires IV contrast urography or endoscopic examination of the urinary tract. Options for surgical correction include transposition of the ectopic ureter(s) or, in the case of unilateral involvement, ipsilateral nephrectomy. The latter option is valid only if the contralateral kidney is functional, as determined by blood chemistry, and structurally normal or near normal, as determined by ultrasonography or IV pyelography. Breeding affected animals should be discouraged.

Neoplasia

David C. Van Metre

Other than those associated with ingestion of bracken fern, primary neoplasms of the urinary tract of ruminants are rare. In a North American abattoir survey, primary tumors of the bladder were detected in 0.05% of more than 21,000 cattle examined, with cases of papillomas, adenomas, and transitional cell carcinomas identified in the sample population.[1] Tumors of the genitalia, typically fibropapillomas and squamous cell carcinomas,[2] may impinge upon urine egress from the urethra. In does, ectopic mammary tissue located in the subcutaneous tissue of the vulva can cause vulvar swelling during lactation; this may be misinterpreted as neoplasia.[2]

Renal carcinoma has been described in cattle,[3-5] and nephroblastoma has been documented in a ewe and an aborted lamb.[5] Urinary

tract involvement may be seen in occasional cases of lymphosarcoma in ruminants.[2,6]

Hemolytic Uremic Syndrome

David G. Renter

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TM) disorder characterized clinically by microangiopathic hemolytic anemia, thrombocytopenia, and in many cases renal failure. HUS is characterized morphologically by thrombotic lesions in capillaries and arterioles in tissues, including those of the kidney.[1] The presence of schistocytes (fragmented red cells) in peripheral blood is considered an important diagnostic indicator of TM,[1] but an apparent lack of schistocytes in peripheral blood has been reported in both human[2] and equine[3] cases of HUS. Unlike DIC, TM disorders are generally associated with normal coagulation times and normal to slightly elevated fibrin split products.[1] TM disorders can be classified as typical HUS, atypical HUS, and thrombotic thrombocytopenic purpura.[1] Reports of HUS are rare in the large animal veterinary literature and more common in human medicine.

The typical form of HUS in humans is associated with consumption of food or water contaminated with Shiga toxin–producing bacteria, whereas atypical HUS is associated with inherited mutations of complement-regulatory proteins and diverse causes of endothelial injury, including antiphospholipid antibodies, complications of pregnancy and contraceptives, vascular renal diseases like systemic sclerosis and malignant hypertension, use of chemotherapeutic and immunosuppressive drugs, and radiation.[1] Typical HUS is a major cause of ARF in young children and infants, and the majority of the cases occur after intestinal infection with Shiga toxin–producing enterohemorrhagic *E. coli* (EHEC).[1,4] *E. coli* O157:H7 is the predominant causative serotype of EHEC in human cases of HUS, but many other EHEC serotypes have also caused the syndrome.[4] Although literature on HUS in large animals is limited, case reports on four horses[3,5,6] and two cows[7,8] have demonstrated clinical syndromes and pathologic lesions consistent with HUS in humans.

Clinical Findings Horses with clinical signs indicative of HUS have exhibited fever, lethargy, diarrhea, hematuria, hemoglobinuria, azotemia, oliguria, and ventral edema.[3,5,6] Hematologic findings in three cases included leukocytosis, anemia, and evidence of hemolysis.[5,6] The blood smear of one of the four equine cases of apparent HUS revealed the presence of poikilocytes and schistocytes.[3,5,6] All four horses with evidence suggestive of HUS were euthanized following unsuccessful treatment with fluid therapy and diuretics.[3,5,6]

In a postparturient mare ultimately diagnosed with HUS, there was initial clinical and laboratory evidence of endotoxemia and endometritis.[3] However, after clinical signs of endotoxemia subsided, stanguria, hematuria, hemoglobinuria, tubular casts, thrombocytopenia, hyperfibrinogenemia, azotemia, and a left shift in the leukogram were noted.[3] Her foal was apparently healthy at birth but subsequently developed progressive CNS signs culminating in refractory seizures.[3] Although a direct causal relationship was not established, *E. coli* O103:H2 was recovered from the GI contents of both the mare and foal, as well as from the mare's uterus. In humans, serotype O103:H2 is one of the more common non-O157 EHECs.[4]

A reported fatal postparturient HUS case in a heifer was demonstrated by severe progressive anuric renal failure, acute hemolytic anemia, and consumptive thrombocytopenia.[8] A 6-year-old cow that had evidence of metritis 1 month after parturition was a suspected HUS case, based on clinical and laboratory findings including anemia, hemolysis, thrombocytopenia, azotemia, and a tendency to bleed.[7]

In humans, HUS can present suddenly as generalized hemorrhagic diathesis (especially hematemesis and melena), pallor, severe oligoanuria, hematuria, edema, microangiopathic hemolytic anemia, and on occasion seizures or other prominent neurologic changes.[1,9] In prodromal human cases, HUS develops an average of 1 week after the onset of diarrhea.[9] The classic clinical presentation of typical HUS in people includes the triad of ARF, thrombocytopenia, and hemolytic anemia.[1] Treatment in this acute phase of HUS primarily involves supportive care; there is limited evidence for more specific therapies, and some treatments may be detrimental.[9,10,11] At this writing, conflicting data exist in the published literature regarding the efficacy or potential for harm imparted by certain antimicrobials used to treat HUS. For example, in vitro research indicates that fluoroquinolone administration may result in increased Shiga toxin production by certain strains of causative bacteria,[11] so avoiding use of this drug in cases of suspected HUS is likely prudent. New therapeutic strategies, including those aimed at binding or neutralizing Shiga toxins, have shown promising results in animal models for human disease.[11] Supportive therapy that includes fluid and electrolyte replacement, plasma therapy, and dialysis can be critically important at the acute stage of HUS. Approximately one third of those surviving the acute phase are at risk for chronic sequelae.[10] Although diabetes, intestinal strictures, myocardial infarction, and motor, sensory, or intellectual deficits and other sequelae can occur, chronic renal lesions leading to end-stage renal disease is more common.[10]

Pathophysiology and Necropsy Findings Two processes appear to dominate the pathogenesis of TM and ultimately cause vascular obstruction and vasoconstriction resulting in organ ischemia: (1) endothelial injury and activation, leading to intravascular thrombosis, and (2) platelet aggregation.[1] In humans, endothelial injury appears to be the primary cause of HUS, and HUS is the most common life-threatening complication of hemorrhagic colitis from EHEC infection.[1,4] EHEC produces exotoxins Shiga toxin 1 and Shiga toxin 2, also referred to as *verotoxin 1* and *verotoxin 2*. Shiga toxins are considered a necessary but insufficient cause of typical HUS, because other bacterial and host factors are important for disease progression.[4,12] Many serotypes of *E. coli* (as well as *Shigella* and other Enterobacteriaceae) can carry Shiga toxin genes and are capable of causing disease, yet certain EHEC serotypes (e.g., O157:H7) are more common human pathogens.[4] EHECs are considered noninvasive but attach to the intestinal mucosa and produce characteristic attaching and effacing lesions seen histologically.[1,4,12] Microvascular endothelium is the major target of Shiga toxins, which are released from the bacteria in the intestine and absorbed across the gut epithelium, where they access the systemic circulation and are transported to small vessel endothelial cells.[4,12] The toxins bind to specific glycolipid receptors on the surface of vascular endothelial cells, are internalized by endocytosis, and may injure the cell through inhibition of protein synthesis, stimulation of prothrombotic messages, or induction of apoptosis.[4,12] Exposure of subendothelial collagen followed by activation of the coagulation cascade may result in thrombosis of small vessels in the kidney and other organs. Acute oliguric or anuric renal failure can result from fibrin/platelet thrombi in renal vessels and glomeruli, fibrinoid necrosis of vessel walls, congestion of glomeruli, and tubular ischemia.[1,12]

Cattle feces are considered to be a major source of EHEC, but these bacteria have been isolated from the feces of many other asymptomatic species, including other livestock and humans.[12,13] Although EHECs do not generally cause illness in cattle, they do colonize their large intestine.[13] It is generally believed that the lack of specific glycolipid receptors for Shiga toxins is the reason cattle typically do not develop severe colitis or HUS, despite the common presence of EHEC in their gastrointestinal tracts.[13] Humans are generally infected with EHEC via consumption of food and water contaminated by feces. However, the small infectious dose makes direct contact with EHEC-positive animals (e.g., at petting zoos) and person-to-person transmission also a concern.[12,13]

In four of the large animal cases reported with HUS, the inciting cause was uncertain and isolation of EHEC or other Shiga toxin–producing organisms was not attempted.[5,6,8] One heifer had a necrotizing endometritis, but during postmortem examination of three horses, no focus of infection was identified.[5,6,8] Renomegaly, renal

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infarcts, and scattered petechial and ecchymotic hemorrhages within the renal parenchyma were apparent on gross necropsy. Acute tubular necrosis and fibrin thrombi within the glomerular capillaries were evident on histologic examination.[5,6,8]

In another equine case report, an EHEC serotype O103:H2 carrying a Shiga toxin gene was recovered from both the mare and foal, but direct Shiga toxin assays were not performed.[4] While the causal significance of this finding is unclear, the unusual and concurrent disease progression in both animals may suggest a common etiology. Except for lack of evidence of microangiopathic hemolysis on a blood smear, the mare had clinical and postmortem signs consistent with HUS.[4] Significant renal pathology included evidence for plasma protein and hemoglobin in both cortical and medullary tubules, with occasional epithelial necrosis. In addition, renal capillary lumina were apparently obscured by fibrin, and only remnants of glomerular capillary endothelial cell cytoplasm were evident. Evidence of numerous platelets within the glomerular capillaries and their adherence to exposed basement membranes were apparent, as were other pathologic changes.[4] The foal's brain had evidence of widened perivascular spaces, with apparent perivascular plasma protein accumulations in the corpus striatum and thalamus.[4]

Although the etiology is often undetermined in large animal cases of apparent HUS, the clinical signs and pathologic lesions reported are compatible with a diagnosis of HUS. It may be notable that three of six reported cases occurred postpartum. Based on the HUS reports in large animals, it appears there may be features comparable to the disease syndrome in humans.

Tubular Necrosis

Meredyth L. Jones

Tubular necrosis is a term referring to intrinsic ARF caused by hemodynamic, nephrotoxic, glomerular, or interstitial disorders. Tubular damage may be a primary clinical entity or a secondary effect of another systemic illness. The kidneys receive a large proportion of circulating blood volume, resulting in high rates of toxin exposure, as well as increased vulnerability to ischemia and reperfusion injury in disease states that reduce the delivery or oxygen content of blood. ARF—characterized by a sudden decrease in GFR, nitrogenous waste accumulation, and loss of the ability to manage sodium, electrolytes, protein, acid-base, and water balance—develops over hours or days. Depending on the nature and duration of the primary insult, widespread dysfunction or necrosis of tubular epithelial cells may produce reversible renal injury, ARF, or CRF. Classification and causes of TN are included in Table 34-2.

Clinical Signs

The clinical signs of ARF in ruminants are nonspecific and usually not indicative of overt urinary tract dysfunction. Depending on the inciting cause, anuria, oliguria, or polyuria may exist. Cattle with ARF are frequently presented for evaluation of poor appetite, diarrhea, or epistaxis.[1] Depression, nasal discharge, ileus, melena, and mild free-gas bloat may also be present. If a concurrent septic condition exists, fever, tachycardia, and scleral injection may be present. The saliva may have a strong ammonia smell. Muscular weakness, even recumbency, may result from the acid-base and electrolyte imbalances and intravascular volume depletion that occur with severe acute TN. Rectal palpation findings are usually unremarkable, although renal enlargement and perirenal edema may be found in occasional cases. If untreated, CRF may ensue, usually producing weight loss in addition to the signs listed. In such cases a reduction in size of the left kidney may be appreciated on rectal palpation. Table 34-2 lists additional clinical criteria that may facilitate diagnosis of TN caused by nephrotoxins.

Renal (uremic) encephalopathy is a syndrome of brain dysfunction associated with renal disease. It is characterized by signs of intracranial disease (altered behavior or sensorium, weakness, motor dysfunction, convulsions) that may resolve on restoration of normal renal function or improvement of clinical parameters of renal disease. The pathogenesis of renal encephalopathy is complex and incompletely understood, but neurologic function appears to be impaired by alterations in the extracellular fluid content of acids, phosphorus, amino acids, or certain hormones. Alteration in neurotransmitter balance or release within the CNS may also be involved. Renal encephalopathy appears to be a rare complication of renal failure in ruminants, as reported in two cows and a goat, where the lesions included myelin vacuolation.[2-4]

Differential Diagnosis

Formulation of a differential diagnosis list for a ruminant with TN may be difficult because of the nonspecific nature of the clinical signs and the variety of primary disease conditions that may predispose cattle to TN. Generic systemic illness differentials are similar to those of renal origin. Diseases causing signs of acute severe illness in ruminants include pneumonia, pleuritis, mastitis, metritis, peritonitis, endocarditis, and metabolic derangements.

Pathologic Studies

The CBC and serum biochemistry can provide important evidence for the presence of renal disease and clues to its etiology. Inflammatory diseases are common in ruminants, and the leukogram may reflect those primarily affecting the upper urinary tract. Acute inflammation affecting renal tubules may result in neutropenia or a left shift to immature (band) neutrophils.

TABLE 34-2

Clinical Characteristics of Acute Toxic Nephrosis Caused by Common Nephrotoxins

Nephrotoxin	Clinical Findings*
Aminoglycosides	Usually nonoliguric, ototoxicosis possible; hematuria, glucosuria, proteinuria, increased serum trough concentration of drug
Tetracycline	Hematuria, glucosuria, proteinuria; possible hepatocellular enzyme elevation
Ionophores	Diarrhea, dark urine, dyspnea, cardiac dysrhythmias; elevated CK, AST, and indirect bilirubin
Ethylene glycol	Anuria or oliguria, tachypnea, ataxia, weakness; hemolysis, increased anion gap, increased serum osmolality, increased osmolar gap, acidosis, calcium oxalate crystalluria
Oxalate-containing plants, vitamin C	Hindlimb ataxia or paresis, apprehension, salivation; hypocalcemia, calcium oxalate crystalluria, aciduria, increased renal cortical echogenicity on ultrasonogram
Oak, acorns	Hemorrhagic diarrhea, ascites, hydrothorax, subcutaneous and perirenal edema; hyperfibrinogenemia, increased hepatic enzymes
Myoglobin	Muscle stiffness and weakness, dark urine; elevated serum CK and AST, positive reactions for blood and protein on urine chemistry strip, hemolyzed serum not present
Hemoglobin/ methemoglobin	Icteric to pale mucous membranes, tachycardia, tachypnea, red or brown urine; positive blood and protein reactions on urine chemistry strip, anemia, elevated serum total protein, hemolyzed serum (hemoglobin only)
Arsenic	Colic, hemorrhagic diarrhea, ataxia; elevated blood and liver arsenic levels

*Many general clinical characteristics of acute tubular necrosis are also present. See Clinical Signs and Clinical Pathology.

AST, Aspartate aminotransferase; *CK,* creatine kinase.

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Renal waste products and electrolytes evaluated in the serum biochemistry are useful indicators of renal function. Blood or serum urea nitrogen (BUN) is interpreted as a measure of GFR, reflecting function and perfusion of the kidneys. BUN is influenced by the protein level in the diet and the ability of the rumen to recycle urea. Creatinine is produced and eliminated in constant amounts in the body and is not influenced by rumen physiology, making it superior for evaluation of renal perfusion and function in ruminants, although it may be present in the serum in concentrations above reference ranges in healthy, heavily muscled bulls with adequate renal function. Azotemia may result from prerenal, renal, or postrenal causes, with renal causes indicated by the persistent isosthenuria or hyposthenuria in the absence of iatrogenic causes.

Fractional excretion (FE) of electrolytes can further delineate the nature of renal azotemia. Fractional clearance of sodium has been used to help document renal failure in cattle, with values of 0% to 4% described in normal cattle.[5] Age, ration, and metabolic status may affect FE values.[5] When applying this test, it is prudent to compare the patient's FE value for sodium to that of an age-matched herdmate in a similar physiologic state and on a similar ration. The normal values for several urinary diagnostic indices in healthy calves have been reported.[6]

Hyponatremia, hypochloremia, and metabolic alkalosis may also be present with ARF, with variable potassium levels.[1,7] Because the kidney is the primary organ controlling magnesium excretion in ruminants, hypermagnesemia may occur in TN, particularly under conditions of high magnesium intake.[1,8] Hyperphosphatemia results from reduced phosphorus excretion in saliva during anorexia, reduced urinary phosphorus excretion, and tissue hypoxia.[9,10] Hypocalcemia is also common in TN in ruminants because of reduced calcium intake, GI stasis, urinary losses, and the competitive effect of hyperphosphatemia.[1] Metabolic acidosis may develop in juvenile ruminants with TN and concurrent diarrhea.[5,10]

A urinalysis should be performed on all animals with suspected renal disease. Proteinuria, hematuria, and granular casts may be found in cases of TN.

Pathophysiology The mechanisms of TN include hemodynamic changes within the kidney as well as ischemic and toxic damage to tubular cells. Reduced blood flow to the kidneys most often occurs during generalized loss of vascular volume, as seen with marked blood loss, septicemia, endotoxemia, or severe dehydration. In ruminants, the most common primary conditions resulting in these changes include mastitis, metritis, enteritis, rumen acidosis, and intestinal accidents. These conditions may also cause infarction of the renal cortex and renal vein thrombosis.[1] Acute severe renal TN has recently been reported in lambs as heat stress–related injury, similar to ischemic heat-induced injury in humans.[11] Prolonged severe ischemia may destroy the tubular basement membrane, thereby preventing tubular epithelial cell regeneration.[12] Rumen acidosis or other conditions resulting in severe rumen distention may additionally result in mechanical obstruction of renal vasculature, impairing renal perfusion.[1]

Bilateral bacterial infection of the kidneys may result in ARF or CRF as a result of destruction of nephrons by bacterial toxins and host inflammatory response. Renal infection may be established by ascending UTI or via hematogenous infection of the kidneys.

Pigment nephrosis is an endogenous toxicity that is due to presentation of large amounts of hemoglobin or myoglobin to the kidneys as a result of hemolytic disease or myopathies. These pigments result in renal vasoconstriction and tubular obstruction from protein coagulation.

A variety of toxins (Box 34-2) may result in significant damage to the kidneys by a variety of mechanisms that result in ARF. The high metabolic demands of renal tubular epithelial cells render them susceptible to toxins that disrupt cellular enzymes. The injury caused by most nephrotoxins is compounded by dehydration, which concentrates the toxin in the tubular filtrate, slows toxin clearance, and if severe, reduces renal perfusion. Because some nephrotoxins are therapeutic agents, it is vital that the veterinarian monitor appetite, body weight, water intake, urine output, routine urine chemistry, serum drug concentration, and serum creatinine concentration during administration of these agents. Young or elderly patients, patients with preexisting renal insufficiency or sepsis, those receiving other potentially nephrotoxic drugs, and patients on prolonged or high-dose therapy with these agents warrant the closest attention.[13] NSAIDs block the effects of prostaglandins, which are important for maintaining renal blood flow. NSAIDs can cause medullary crest necrosis when used in pediatric, geriatric, and inadequately hydrated patients or for a prolonged dosing regimen.[14] Some sulfonamide antimicrobials have been associated with deposition of insoluble precipitates in the renal tubules and blocking excretion of creatinine.[15] Aminoglycoside antimicrobials, particularly gentamicin, have cumulative effects on the renal tubules and may cause cell death through mitochondrial injury and other mechanisms.[13,16]

Ethylene glycol, the primary ingredient in many antifreeze products, is converted by the liver into nephrotoxic metabolites, mainly

BOX 34-2

Nephrotoxic Agents

Metals

Arsenic
Mercury
Cadmium
Chromium
Lead
Zinc
Copper (secondary to hemolysis)

Antimicrobials

Aminoglycosides
Tetracyclines
Sulfonamides (rare)
Ionophores
Amphotericin B
Polymyxin B

Analgesics

Nonsteroidal antiinflammatory drugs (NSAIDs)

Plants

Amaranthus retroflexus (pigweed)
Lilium spp. (Easter lily)
Quercus spp. (oaks)
Philodendron spp. (philodendron)
Pinus ponderosa (Ponderosa pine; nephrosis occurs in conjunction with hepatocellular damage and abortion)
Xanthium spp. (cocklebur)
Cestrum diurnum (day-blooming jessamine)
Oxalate-containing plants: *Rumex* (curly dock), *Beta* (beets) *Rheum rhaponticum* (rhubarb), *Halogeton glomeratus* (halogeton), *Sarcobatus vermiculatus* (greasewood), *Oxalis* spp. (soursob), *Chenopodium album* (lamb's quarters), *Salsola pestifer* (Russian thistle)

Endogenous

Hemoglobin
Myoglobin
Calcium oxalate

Miscellaneous

Ethylene glycol
Vitamin C (parenteral form) overdose
Pentachlorophenol
Mycotoxins: ochratoxin, citrinin, fumonisin (high doses)
Cholecalciferol-based rodenticides
Parenteral vitamin D overdose

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glycolic acid. Calcium oxalate crystals form and are deposited into the renal tubules, causing further compromise.[17] Lethal doses for ethylene glycol are 5 to 10 mL/kg in mature cattle and 2 mL/kg in preruminating calves.[18,19] Insoluble oxalate crystal deposition in the renal tubules is also a common pathologic mechanism for some nephrotoxic plant poisonings (e.g., halogeton, greaseweed, pigweed, sorrel, dock, Russian thistle). Several nephrotoxic plants also exhibit effects on other body systems, including the respiratory, GI, cardiac and hepatic systems, with additional symptoms observed. Many of the nephrotoxic plants, particularly those causing oxalate toxicity, are also nitrate accumulators.

Treatment and Prognosis Treatment of ARF should include binding and removing any offending toxin or source, promoting diuresis through IV fluid administration and diuretic medications, correcting acid-base and electrolyte derangements, and close monitoring of positive or adverse responses to treatment. Rumenotomy, with removal of toxic material, is most beneficial if performed soon (within 24 hours) after the animal has ingested a nephrotoxin. Activated charcoal (2 to 4 g/kg PO) may bind the agent in the gut lumen. Magnesium sulfate or other magnesium-containing laxatives should be avoided in such cases because severe hypermagnesemia may result in animals with concurrent compromise of renal function.[8] Drugs that directly target known nephrotoxins, such as heavy metal chelators, may be initiated. Prophylactic diuresis should be instituted as soon as an animal has suspected exposure to a potentially harmful quantity of a nephrotoxin. Delay until the appearance of azotemia results in a significant (>75%) loss of nephron function prior to medical intervention.

The cornerstone of treatment of TN is restoration of adequate renal perfusion and urine production. This is most effectively achieved through IV administration of isotonic sodium-containing fluids, with calcium and potassium supplementation as indicated. Normal (0.9%) saline or 0.45% saline + 2.5% dextrose serve as reasonable base fluids. Additional IV potassium can be substituted if indicated after initial therapy, being cautious to remain below the generally recommended toxicity rate of 0.5 mEq/kg/h. Diuresis should continue until the patient is producing sufficient volumes of urine. If cost or facilities make IV fluid therapy impractical, repeated administration of water and electrolytes by stomach tube is an option. A small-bore stomach tube can be passed through the nasal cavity into the rumen and secured to the animal's halter to allow one person to administer fluids repeatedly without the need for repeated tube passage. Placing a small rumenostomy or securing a nasogastric tube in place allows one person to administer fluids repeatedly with relative ease. Administration of IV or oral fluids at 1.5 to 2 times the adult maintenance level of 60 mL/kg/day may be adequate to induce diuresis. The patient should be monitored for chemosis or labored or rapid respiration, which may be indicative of overhydration. Fluid therapy should be continued until azotemia resolves, at which time the patient's voluntary fluid intake can be assessed. Oral supplementation of potassium and calcium salts may be necessary in some cases because it is often not possible to add adequate yet safe levels of these salts to IV fluids in cases of refractory hypokalemia and hypocalcemia, respectively.

Restoration of urine production is necessary in anuric or oliguric animals. If fluid therapy does not promote diuresis, furosemide (1 mg/kg IV or IM) may be administered. Repeated administration (q1-2h) may be necessary to induce urine production. With repeated use of furosemide, the patient's serum sodium and potassium concentrations must be monitored. Mannitol (0.25 to 1 g/kg IV bolus) can be used to provide osmotic diuresis.

Vasopressors and inotropes may assist, but must be administered using fluid pumps as constant rate infusions (CRI). These have wide and controversial ranges of therapeutic efficacy. Drugs and dosages used anecdotally in ruminants include IV dopamine (2 to 5 µg/kg/min), dobutamine (5 to 10 µg/kg/min), and combination norepinephrine (0.4 µg/kg/min) + dobutamine (5 µg/kg/min), based on available information.[20] It should be noted that use of dopamine alone in cases of ARF may not be as beneficial as once thought, and potential adverse effects have been discovered.[21,22]

Additional supportive therapy may include secure broad-spectrum antimicrobials against susceptible infectious agents, plasma transfusion to treat hypoproteinemia, and nutritional support through parenteral nutrition or rumen transfaunation. Antiinflammatory agents may prove useful but should be used cautiously where renal damage exists and should only be used where the kidneys are being therapeutically well perfused. Urinalysis and fractional excretion of electrolytes can be measured in conjunction with serum monitoring parameters during intensively managed cases.

Lesions that occlude tubular blood flow (renal vein thrombosis, DIC) warrant a poor prognosis, whereas renal failure resulting from toxic causes carries a more favorable prognosis with early diagnosis and aggressive therapy. Return of appetite and progressive reduction in BUN and serum creatinine levels are positive prognostic indicators.[23] Prolonged supportive treatment (2 to 3 weeks) may be necessary to allow for regeneration of tubular epithelium in cases of acute TN.

Leptospirosis

Robert J. Callan

Leptospirosis is a complex disease of both animals and humans caused by pathogenic species of *Leptospira*.[1-8] Pathogenic *Leptospira* species persist as chronic infections of the renal tubules of the maintenance host species, often causing little or no disease. Transmission to incidental hosts results from direct contact with urine from an infected maintenance host or through environmental and feed contamination with infected urine. Infection in the incidental host can cause acute disease in multiple organ systems (e.g., kidney, liver, CNS) and result in abortion or reproductive failure. This discussion focuses on *Leptospira* infection and disease of the urogenital system of ruminants.

Leptospira is a diverse genus of motile, gram-negative, obligate aerobic, tightly coiled spirochetes approximately 0.1 to 0.3 µm in diameter and 6 to 20 µm in length.[1,2,5,8] The bacteria can survive in the environment for up to 6 months.[2,5,9] *Leptospira* spp. prefer a warm, moist environment with a pH of 7.2 to 8.0. Survival is short under dry conditions or at temperatures below 10° C.[2] *Leptospira* does not survive freezing in the environment.[10]

Before 1989, *Leptospira* was divided into the pathogenic species *L. interrogans* and the nonpathogenic saprophytic species *Leptospira biflexa*. The current taxonomy and classification of *Leptospira* use a complex system of both genetic and serologic characteristics.[1,5,11] The *Leptospira* species is determined by DNA sequence similarity.[1,5] Twenty genomospecies are identified based on DNA sequence heterogeneity (e.g., *Leptospira borgpetersenii*).[11] Further classification by serovar is based on antigenic grouping of the lipopolysaccharide (LPS) and other outer surface antigens using the cross-agglutinin adsorption test (CAAT).[11] More than 250 serovars are characterized for pathogenic strains of *Leptospira* (e.g., *L. borgpetersenii* serovar *hardjo*). Serovars may be further divided into serotypes (e.g., *L. borgpetersenii* serovar *hardjo* type hardjobovis). Serogroups represent antigenically related serovars and are determined by the microagglutination test (MAT). There are currently 24 serogroups described for pathogenic strains of *Leptospira*.[11] Since serovars of a given serogroup can be distributed across multiple *Leptospira* species, the serogroup classification does not represent taxonomic relatedness.

Epidemiology Leptospirosis is predominantly observed under conditions where livestock come in direct or indirect contact with urine from an infected maintenance host (Table 34-3).[1,2,5,9] The prevalence of infection within a maintenance host population tends to be high (30% to 50%); in such populations, infection is often spread between animals by direct contact.[2] Transmission to incidental hosts is generally by contact with the environment, feed, or water that is contaminated with urine from an infected maintenance host.

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TABLE 34-3

Current Nomenclature, Maintenance Host, and Incidental Hosts for Common *Leptospira* Isolates in Ruminants

Genomospecies	Serovar	Maintenance Host	Incidental Hosts
Leptospira interrogans	*canicola*	Dogs	Cattle
L. interrogans	*pomona*	Swine, opossums, skunks, raccoons	Horses, cattle, sheep, goats, dogs
L. interrogans	*icterohaemorrhagiae*	Rats	Dogs, cattle, swine
L. interrogans	*bratislava*	Pigs, mice, horses	Dogs, cattle, horses
L. interrogans	*hardjo* type hardjoprajitno	Cattle	Sheep, goats
Leptospira borgpetersenii	*hardjo* type hardjobovis	Cattle	Sheep, goats
L. borgpetersenii	*ballum*	Mice	—
Leptospira kirschneri	*grippotyphosa*	Raccoons, muskrats, squirrels	Cattle, sheep, horses, dogs

Transmission can also occur from contact with an infected fetus or uterine discharge. Survival of the bacteria in the environment and the incidence of infection in animals are increased in regions with warm, humid climatic conditions. The seasonal incidence is higher during the summer or fall in temperate regions and during the rainy season in warm-climate regions.[5] Environmental conditions that contribute to moist surroundings and foot abrasions may contribute to *Leptospira* transmission, particularly in housed dairy cattle.

Cattle are the primary maintenance host reservoir of *L. interrogans* serovar *hardjo* type hardjopragitno and *L. borgpetersenii* serovar *hardjo* type hardjobovis. *L. interrogans* serovar *hardjo* type hardjopragitno is isolated primarily from cattle in the United Kingdom, and *L. borgpetersenii* serovar *hardjo* type hardjobovis is observed worldwide. Cattle can also serve as maintenance or incidental hosts for *L. interrogans* serovar *pomona* and *L. interrogans* serovar *grippotyphosa*.

Serovars *hardjo, pomona,* and *grippotyphosa* are most often implicated in renal infection of cattle.[12] Although data are scarce, renal disease caused by leptospirosis in small ruminants appears to be uncommon.[10,13] Detection of *Leptospira* spp. from vaginal fluid and semen of sheep and goats has been reported and suggests the possibility of venereal transmission in those species.[14] Sheep may serve as subclinical carriers of serovars *hardjo, hardjobovis,* and *pomona.*[3,15,16] Some serovars of *Leptospira* have zoonotic potential, and humans are always considered an incidental host.[1,2,4,5]

An abattoir study of more than 5000 cattle in the United States identified approximately 2% renal carriers of *L. interrogans*.[12] Serovar *hardjo* was the most common renal isolate, followed by serovar *pomona* and serovar *grippotyphosa*. A study of Texas slaughterhouse cattle detected *Leptospira* spp. in 36% of urine samples by PCR. The seroprevalence for serovars *pomona* and *hardjo* was 22% and 15%, respectively.[17] A national survey showed 49% seroprevalence for *L. interrogans* serovars in cattle, with the highest seroprevalence found in cattle from southeastern, south-central, and Pacific Coast states.[18] Because contact with urine from infected animals is a means of transmission within cattle populations, high stocking density or confinement may increase the rate of infection in a herd.

In general, infection of cattle with the host-adapted serovar *hardjo* rarely results in acute severe disease. If present, signs of disease are usually mild in acutely infected cattle and may simply present as cases of undifferentiated fever. Persistent latent urogenital infection usually follows acute infection of host-adapted serovars in cattle, with most overt losses attributable to adverse effects on reproduction.[4,19-21]

Acute severe renal disease is more characteristic of incidental (also termed *accidental*) infection of cattle, particularly calves, with a non–host-adapted serovar of *Leptospira*. However, exceptions to this generalization do occur because host immunity and virulence of the organism are variable.[3,4]

Clinical Findings

Serovar *hardjo* is host-adapted to cattle, and many infections are asymptomatic or result in nonspecific reproductive failure or abortion. *Leptospira* serovar *hardjo* infection of cattle may produce chronic interstitial nephritis of variable severity, but overt renal dysfunction is rarely observed.[22] Chronic infection of the genital tract of cows and bulls is common.[7,23] Protracted shedding of the organism in the urine often occurs, possibly lasting for the life of the animal.[22,23] Infertility, stillbirth, abortion, and birth of weak calves are typical clinical manifestations of infection with serovar *hardjo* in cows.[7,20,24,25] The fetus can be infected in utero, and if it survives the acute infection, it may be born persistently infected.[2] Fever, agalactia, and mastitis may occasionally occur, and the resulting syndrome has been termed the *milk-drop syndrome*[3] or *flabby udder*[4] in lactating cows. The udder is uniformly soft, and the milk may be yellow- or red-tinged and thick.

In contrast, infection with the non–host-adapted serovars can result in severe systemic disease, hemolytic anemia, hepatitis, interstitial nephritis, and tubular nephrosis in calves and less often in adult cattle.[7,22] Meningitis is a rare manifestation.[13] Agalactia and mastitis often occur in lactating cows, and pregnant cows may abort. Urine shedding of non–host-adapted serovars by infected cattle can persist for weeks to months.[4,7,25] Renal lesions result from direct damage to the vascular endothelium during leptospiremia, hypoxia from endothelial damage and hemolysis, tubular epithelial damage from hemoglobin, and interstitial nephritis.[2,5,22] Some *Leptospira* serovars, particularly *pomona,* produce hemolysins that can cause acute intravascular hemolysis and anemia in cattle.

Clinical signs associated with acute infection may include fever, anorexia, lethargy, decreased milk production, petechiation, hemolytic anemia, and hemoglobinuria. Oliguria may be seen with interstitial nephritis or hemoglobinuric nephrosis. Elevated creatinine concentration caused by prerenal or renal causes may be observed on serum chemistry analysis. Examination of the urine may show proteinuria, pyuria, and cellular or granular casts in cases of nephritis. Hemoglobinemia and hemoglobinuria may be observed in patients with leptospire-induced hemolysis and can occasionally result in hemoglobinuric nephrosis (pigment nephropathy).

Pathophysiology

Contaminated feed and surface water, wildlife, rodents, and domestic animals are potential sources of pathogenic serovars for cattle.[2-5] Leptospires penetrate external mucosal surfaces and scarified or macerated skin. The bacteria multiply locally during an incubation period that can last 2 to 20 days.[2,5] After the incubation phase, the organism enters the bloodstream through the lymphatics or by direct penetration into the blood vessel. Leptospiremia results in dissemination throughout the body and infection of multiple organs. This bacteremic phase lasts 4 to 7 days. Fever and other systemic signs are often present in clinically affected animals. Humoral antibodies can be detected at the end of the bacteremic phase. Opsonizing antibodies are generated and aid in clearing infection from most tissues in the host.

During the convalescent phase, leptospires may become localized in the mammary gland, kidney, or genital tract, where they appear to be protected from the immune response.[2,26] Depending on the virulence of the serovar involved, chronic renal infection may create few histologic changes, mild interstitial nephritis, or diffuse, severe, lymphocytic interstitial nephritis with fibrosis.[13] Nephritis may persist long after the host immune response has cleared the organism. Chronic infection of the kidney or reproductive tract allows for

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transmission of the organism in urine, uterine and vaginal secretions, placenta, fetal tissues, and semen.[3,7,23,27] Shedding in the urine may last for weeks to months with non–host-adapted infections. Renal shedding of host-adapted serovars can persist for months to years. The bacteria reside in the lumen of the renal proximal tubules, where they are protected from phagocytes and humoral antibodies. The bacteria do not stimulate a systemic immune response while localized in the proximal tubule lumen, so serum antibody titers can decline and become negative even though the kidney is infected and urinary shedding of bacteria continues.

Multiple potential virulence factors may contribute to leptospirosis.[1,5,8,28] Virulence mechanisms include the toxin effect of lipopolysaccharide, adhesion to cells and extracellular matrix, bacterial motility, hemolysins, and iron sequestration. Leptospiral LPS and outer membrane proteins are believed to contribute to the development of interstitial nephritis. Motility is an important pathogenic mechanism and contributes to invasion and dissemination of the bacteria. As many as 50 genes are related to leptospiral motility.[1] Adherence to cells is in part conferred by fibronectin-binding protein present on the surface of pathogenic strains but not on nonpathogenic strains. Leptospiral immunoglobulin-like protein A, B, and C (LigA, LigB, LigC) may also be involved in attachment and invasion. Additional proteins that may contribute to virulence include hemolysins, sphingomyelinase C, sphingomyelinase H, and hemolysis-associated protein 1 (HAP-1).[1,5,8,28] There appears to be significant redundancy in proteins associated with virulence mechanisms, making it difficult to isolate individual virulence factors using single gene knockout mutations.

Diagnosis

The microscopic agglutination test (MAT) is the most widely used serologic test for the diagnosis of leptospirosis in cattle. The MAT detects antibodies to specific serovars, but cross-reactivity occurs between related serovars, particularly within the same serogroup. Thus, an infection with one strain may result in increased MAT titer to multiple serovars. Serum antibody enzyme-linked immunosorbent assay (ELISA) tests have been developed for research but have not yet been adopted in the routine clinical diagnostic setting for animals.[29-32]

An elevated serum antibody titer is observed after the bacteremic phase and is suggestive of *Leptospira* infection when associated with concurrent clinical signs, but interpretation of a single titer is problematic in vaccinated animals or when endemic exposure is suspected.[7,8,26] A fourfold increase in MAT titer between acute and convalescent serum samples, or conversion from a negative titer to a titer of 100 or greater, supports a diagnosis for both host-adapted and non–host-adapted serovars. However, vaccinated animals may have a diminished serologic response after challenge and renal colonization with *L. borgpetersenii* serovar *hardjo*.[33] Serologic detection of persistent infection with serovar *hardjo* can be difficult because paired serum titers may be increasing, static, decreasing, or undetectable at the time of clinical examination (e.g., at abortion).[7,26] Serology is unsuitable for screening individual animals for carrier status, because many animals that are chronically infected and shedding may have negative serologic status.[34] Considering the serovar with the highest titer as being the infecting strain is generally recommended. However, recent studies demonstrate that serologic antibody titers may not accurately predict the infecting strain in humans because of cross-reaction between different serovars within the same serogroup.[35] Consultation with a clinical immunologist affiliated with the laboratory performing the MAT is recommended for accurate interpretation of results.

Leptospira shedding in urine and semen can be detected by multiple tests, including urine culture, phase-contrast microscopy, darkfield microscopy, fluorescent antibody (FA), PCR, nucleic acid hybridization, and immunoblot.[8,12,26,27,36-38] Urine cultures are often unrewarding because of the fastidious nature of the organism, and conclusive results may not be obtained for up to 6 months.[8,27] Darkfield microscopy, FA, and PCR assays are typically used by veterinary diagnostic laboratories to identify *Leptospira* species from urine samples. None of these tests will determine the infecting serovar. The sensitivity of detecting *Leptospira* shedding can be improved by performing two tests on a single sample.[27,38] Evaluation of serovar-specific antibody titers from positive animals may aid in identification of the infecting serovar.

Second-voiding urine samples collected after administration of IV furosemide are recommended for urine testing.[10,39] Furosemide is administered at 0.5 to 1.0 mg/kg IV or IM, and the first-voided urine is discarded. A second urine sample is then collected after cleaning the vulva of gross debris. Approximately 10 mL of urine should be collected and stored on ice (not frozen) for transport to the diagnostic laboratory. Urine from 10 to 15 adult animals should be tested when evaluating a herd for endemic *Leptospira* serovar *hardjo* infection.

Biopsy or necropsy samples of renal tissue may be treated with Warthin-Starry or Levaditi silver stains for microscopic examination.[13] Immunoperoxidase staining was shown to be more sensitive for identifying *Leptospira* species in kidney and liver of naturally infected cattle than Levaditi silver stain.[40]

Treatment and Prognosis

Treatment of acute leptospirosis caused by non–host-adapted serovars should focus on eliminating the bacteria, systemic support, and diuresis if renal involvement is observed. In vitro susceptibility has been demonstrated for several antibiotics that could be used in food-producing ruminants, including ampicillin, amoxicillin, penicillin G, erythromycin, tetracycline, tylosin, and tilmicosin.[25,41-43] Daily oxytetracycline (100 mg/mL, 10 mg/kg IV or IM once daily for 5-7 days) or long-acting oxytetracycline (20 mg/kg IM or SC every other day for 2 to 4 treatments) are considered clinically effective, but controlled clinical studies reporting efficacy in acute leptospirosis have not been reported. Penicillin G procaine (25,000 IU/kg IM twice daily) and sodium ampicillin (20 mg/kg IM twice daily) have been suggested for treatment, but the efficacy of these regimens in cattle remains unproven.[10] In humans, doxycycline (100 mg q12h for 7 days) has been shown to reduce the duration and severity of illness.[5] Consideration of other antibiotics for treating acute leptospirosis should be based on their efficacy in clearing renal infections with host-adapted *L. borgpetersenii* serovar *hardjo* (see below).

IV or oral fluids may be indicated for systemic support. In animals with severe hemolysis, blood transfusion may be considered. Diuresis should be established in animals with hemoglobinuria or evidence of ARF from hemoglobinuric nephrosis or interstitial nephritis. The prognosis for renal disease caused by leptospirosis is influenced by the virulence of the serovar involved, host immunity, and extent of renal lesions. Cases with renal azotemia warrant a guarded prognosis because more than 75% of nephrons are affected in such cases, and chronic interstitial nephritis and fibrosis may occur after treatment of the acute disease.

Several antibiotics have been shown effective in clearing *Leptospira* spp. renal colonization and shedding in cattle. Long-acting oxytetracycline (20 mg/kg IM or SC, two doses 10 days apart) has been recommended to treat chronic leptospiral infections or reduce the risk of introduction of infected animals into a herd.[3] Oxytetracycline (20 mg/kg IM once), ceftiofur sodium (2.2 mg/kg IM q24h for five treatments), ceftiofur crystalline free acid (6.6 mg/kg SC at the base of the ear once), tilmicosin (10 mg/kg SC once), and tulathromycin (2.5 mg/kg SC once) have been shown effective in clearing renal shedding of *L. borgpetersenii* serovar *hardjo* type hardjobovis from experimentally infected cattle.[44,45] The efficacy of these antibiotic treatments has not been demonstrated in acute infections with other species and serovars of *Leptospira,* but their use could be considered relative to the lack of clinical data showing specific antimicrobial efficacy for treating acute leptospirosis in ruminants and swine.

Prevention

Draining or fencing off standing water may reduce transmission. Maintaining a dry, clean environment may also help reduce exposure and infection. Limiting rodent and wildlife contact

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with cattle and their feed and water is often difficult to accomplish, but it reduces the potential for transmission of non–host-adapted leptospires.[7] For host-adapted *Leptospira* serovar *hardjo,* preventing or eliminating the renal carrier state in infected cattle is necessary to reduce transmission.

Vaccination is regarded as an effective means of preventing losses from leptospirosis. Conventional pentavalent *(L. canicola, grippotyphosa, hardjo, icterohaemorrhagiae,* and *pomona),* whole-cell, inactivated leptospiral vaccines are recommended in calves and adult cattle as an aid to prevent clinical disease caused by *Leptospira* spp. However, these conventional pentavalent vaccines may not consistently prevent renal colonization and shedding after challenge with host-adapted *L. borgpetersenii* serovar *hardjo* type hardjobovis.[46,47]

A monovalent *L. borgpetersenii* serovar *hardjo* type hardjobovis vaccine (Spirovac, Pfizer Animal Health, New York) is licensed for preventing *Leptospira* serovar *hardjo* infection, including reproductive and renal tract colonization and urinary shedding for up to 12 months. This vaccine stimulates an immune response characterized by IgG1 and IgG2 agglutinating antibodies, as well as antigen-specific T-cell production of interferon (IFN)-γ.[33,48-50] The strong IFN-γ response is consistent with induction of a type 1 immune response and may be responsible for antibody class switching to IgG2, which is a more potent opsonin than IgG1.[48] Combination pentavalent *Leptospira* vaccines have been developed that promote high *Leptospira* serovar *hardjo* antibody titers in addition to the other serovars contained in the vaccine. Because *Leptospira* species are largely extracellular pathogens, the relevant protective immune response appears to be antibody-mediated neutralization and opsonization during leptospiremia.[1,5] There is no indication that cytotoxic immunity is a relevant immune response for protection or resolution of *Leptospira* infection. However, the exact immunologic mechanism responsible for protection from colonization and shedding of *L. borgpetersenii* serovar *hardjo* type hardjobovis in cattle is not fully understood. Vaccine efficacy and the methods used to evaluate vaccine efficacy for *L. borgpetersenii* serovar *hardjo* type hardjobovis infections in cattle remain controversial.

Although vaccines help prevent colonization and shedding of *Leptospira* serovar *hardjo* from the kidney, they are not effective in resolving current renal infection and elimination of the carrier state. Thus, vaccination at an early age followed by annual boosters is recommended to prevent initial renal colonization. Renal shedding in previously infected animals can be resolved by antibiotic treatment, and vaccination can be used to prevent future colonization.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 35

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Diseases of the Nervous System

ROBERT J. MACKAY and DAVID C. VAN METRE, *Consulting Editors*

Cerebrospinal Fluid

Mary O. Smith • Lisle W. George • David C. Van Metre

Cerebrospinal fluid (CSF) is partly derived from and in equilibrium with the extracellular fluid that bathes the brain and spinal cord parenchyma.[1-3] The composition is an indicator of the state of the intrathecal contents. CSF is produced by a combination of ultrafiltration of plasma and active secretion.[5] The sites of CSF production are the choroid plexuses of the lateral, third, and fourth ventricles; the ependymal lining of the ventricular system; the pia arachnoid; and the meningeal blood vessels. The CSF in the ventricular system flows caudally and diffuses out of the lateral apertures in the fourth ventricle. It then circulates around the brain and spinal cord. Circulation of CSF is achieved through regional pressure changes caused by spinal motion and pulsations of blood vessels. Resorption of CSF occurs from both the cranial cavity (75%) and the spinal canal (25%).[6] Some resorption of brain CSF occurs at the arachnoid villi associated with large veins and sinuses, but most resorption occurs at the cribriform plate, into nasal lymphatics.[7,8] Resorption of spinal CSF occurs into the lymphatics associated with spinal nerves.

The predominant direction of CSF flow in the spinal canal is cranial to caudal. CSF can be collected from the cisterna magna when the site of interest is the brain, whereas it should be collected from the lumbar subarachnoid space when the lesion is in the spinal cord. In large animals, however, the risks associated with the general anesthesia required for cisterna magna tap are considerable, so lumbar puncture is usually the most suitable technique for CSF collection in these species, regardless of the site of the lesion.[9,10]

Collection of Cerebrospinal Fluid

Lumbosacral Spinal Tap

For collection of CSF by lumbosacral puncture, the animal is lightly sedated and the skin of the dorsal midline over the junction of the sixth lumbar (L6) and first sacral (S1) vertebrae is surgically prepared (Fig. 35-1). A variety of standard sedative protocols are suitable, although xylazine has been shown to reduce CSF pressure.[11] Correct placement of the spinal needle is more easily achieved with the animal standing. The proper anatomic site for insertion of the spinal needle is between the dorsal spinous process of L6 cranially and S1 caudally and the two tuber sacrales laterally. The overlying skin forms a depression that can be recognized by palpation, although this may be difficult in well-muscled horses. The correct site for needle placement can also be located by determining (1) the dorsal midline at the highest point of the quarters or (2) the point where a line drawn between the caudal aspects of the two tuber coxae intersects the midline.

The skin is anesthetized with 2% lidocaine, and a 1-cm incision is made with a No. 15 scalpel blade. A 6- to 9-inch, 18- to 20-gauge spinal needle is inserted perpendicularly through the incision and advanced until the tip punctures the lumbosacral cistern (a 3½-inch needle can be used in small ruminants, foals, and small cattle). A "snapping" sensation is sometimes felt as the needle passes through the interarcuate ligament. The patient may reflexly contract the tail, anus, and gluteal muscles. Some patients, particularly horses, may respond with violent motor activity. Therefore a lumbosacral spinal tap performed on a conscious horse should be done only when the animal is restrained in stocks. The average depth of insertion is 17.64 cm (7 inches) in horses, 8.26 cm (3⅓ inches) in ponies,[10] and about 7.5-10 cm (3-4 inches) in adult cattle.

The spinal needle is advanced gently to the floor of the spinal canal. Passage of the needle through the terminal spinal cord or the cauda equina does not cause subsequent neurologic abnormalities. When the needle is seated in the spinal canal, gentle negative pressure can be applied by withdrawing spinal fluid into a series of 3-mL syringes. If frank blood is obtained, the tip of the needle is probably in one of the ventral vertebral sinuses. The needle should be withdrawn a few millimeters, and a clean syringe should be attached to the hub. Compression of the jugular vein causes engorgement of the ventral vertebral plexus, which increases CSF pressure in the lumbosacral cistern.

Cisterna Magna Tap

General anesthesia is required for a cisterna magna tap. After the patient has been anesthetized, the dorsal area of the neck overlying the atlantooccipital joint is surgically prepared. The patient's head is held flexed at a right angle to the neck, with the sagittal plane of the head parallel to the floor or table on which the patient is lying. The head must not be allowed to move while the needle is inserted. The needle is inserted at 1 to 2 cm caudal to a point corresponding to the intersection of the dorsal midline, and a line is drawn between the cranial aspects of the wings of the atlas. This point is usually 6 to 9 cm (2½ to 3½ inches) from the poll (Fig. 35-2). A 3½-inch, 18-gauge spinal needle is inserted perpendicular to the skin and aimed toward the nose. The needle is advanced slowly with the stylet seated. After the needle has been advanced a few millimeters, the stylet is removed and the hub of the needle is examined for CSF flow. The stylet is replaced if it is dry and CSF is not spontaneously dripping from the hub, and the needle is advanced another few millimeters and checked again for CSF flow. Entry of the tip of the needle into the cisterna magna may be accompanied by the sensation of "popping" through a tissue plane or by a sudden decrease in resistance to the advancement of the needle. In other cases, however, no such sensation is perceived—thus the precaution of checking for CSF flow every time the needle is advanced a few millimeters.

In most large animals the needle is seated at approximately 5 to 8.75 cm (2 to 3½ inches). While advancing the needle, the heel of the hand should be held firmly against the animal's neck to minimize the possibility of spinal cord injury. The mean depth of insertion is 6.16 cm (2½ inches) in horses[10] and 5.08 cm (2¼ inches) in cattle. In a cisterna magna tap, the needle entry site is close to the cervical spinal cord and the brainstem. To minimize the danger of central

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nervous system (CNS) damage during a cisterna magna tap, the animal should be adequately anesthetized and ventilated, because an increased partial pressure of carbon dioxide (P_{CO_2}) results in elevated intracranial pressure.[12] Removal of fluid from the cisterna magna is contraindicated in a patient with increased intracranial pressure because a possibly fatal herniation of the brain through the foramen magnum may occur. Signs of increased CNS pressure include a moderate to marked decrease in mentation, mydriatic pupils, opisthotonos, extensor rigidity, ventrolateral strabismus, and papilledema.

Ultrasonography can be used as an aid to needle placement for collection of CSF from both the atlantooccipital cistern and the lumbosacral subarachnoid space.[13,14]

Myelography

Contrast material for myelography is injected into the cisterna magna in large animal patients. Withdrawal of CSF before injecting the contrast medium is unnecessary, as is reinjection of CSF after it has been withdrawn. The turnover of CSF is rapid and under strict homeostatic control; therefore withdrawal of CSF through a spinal tap does not have deleterious effects that require its replacement.[15-17]

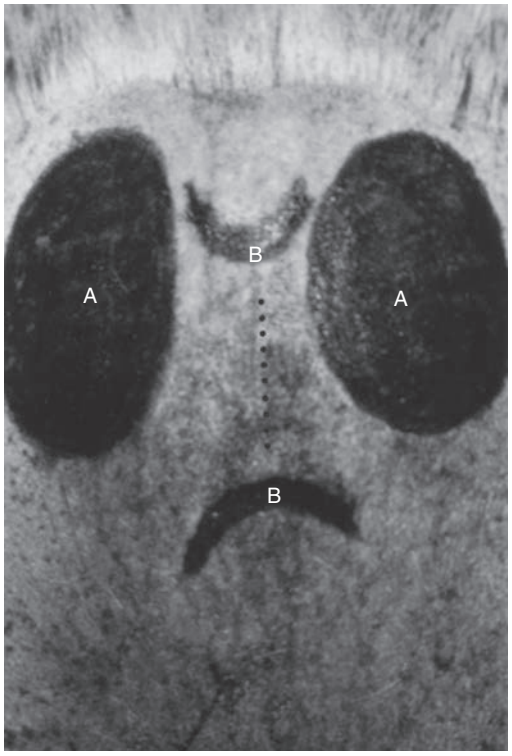


FIG. 35-1 Close-up view of landmarks for a lumbar cistern puncture in a horse. The large dark ovals *(A)* represent the position of the two tubers sacrale. The smaller curved lines *(B)* represent the respective caudal and cranial aspects of the L6 and S1 dorsal spinal processes. The dotted line represents the optimum area for placement of a skin stab.

Analysis of Cerebrospinal Fluid

The color of the CSF should be noted as it flows from the hub of the spinal needle. Blood can originate from the tapping procedure (iatrogenic hemorrhage) or from a traumatic CNS lesion. Iatrogenic hemorrhage is unevenly mixed in the CSF and disappears as the fluid drips from the needle. Fluid collected immediately after placement of the spinal needle tends to be mildly contaminated with blood even when this is not apparent grossly. Successive aliquots are usually less contaminated, so the later aliquots are most suitable for cellular and protein analysis.[18] Blood resulting from CNS hemorrhage is evenly mixed with CSF even after a large amount has been removed. Hemorrhage that has occurred days earlier may have a brownish rather than red discoloration. Prior hemorrhage also results in *xanthochromia,* a yellow discoloration of the CSF. Xanthochromia can be observed in the CSF for at least 10 days after the introduction of blood. Xanthochromic samples do not contain bilirubin.

The normal values for CSF are presented in Table 35-1. Cell counts should be determined in a noncentrifuged specimen as soon as the sample is collected, using a hemacytometer. Automated methods for counting cells are not suitable for CSF because the low numbers of cells in CSF compared with blood result in erroneous counts. Morphologic examination of cells from CSF is most suitably done on cytospin preparations in an appropriately equipped



FIG. 35-2 View of the ideal area for a cisterna magna cerebrospinal fluid tap in a cow. The two lines *(a)* represent the wings of the atlas. The large spot in the center *(b)* is the optimum area for needle insertion. It is essential to prevent head movement by use of anesthesia and restraint.

TABLE 35-1

Normal Range of Values in Cerebrospinal Fluid for Large Animals[1,4,5]

Component	Unit	Equine	Bovine	Ovine	Caprine
Specific gravity	1.004-1.008	1.004-1.008	NA	NA	NA
Refractive index	1.3343-1.3349	1.3343-1.3349	NA	NA	NA
Protein	mg/dL	5-100	20-40	8-70	24-40
White blood cells (WBCs)	WBCs/dL	0-6	0-3	0-5	0-7
Glucose	mg/dL	30-70	35-70	48-109	45-87
Sodium	mEq/L	140-150*	132-144*	145-157*	NA
Potassium	mEq/L	2.5-3.5	2.7-3.2	3-3.3	3
Creatine kinase	IU/L	0-8	2-48	NA	NA
Magnesium	mEq/L	NA	1.7-2.7	NA	NA

*Cerebrospinal fluid (CSF) sodium is the same as serum or plasma sodium when measured with ion-specific electrodes. When other measurements are used, the CSF sodium is usually higher than plasma sodium.

NA, Result not available.

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laboratory. Normal CSF from large animals contains fewer than six white blood cells (WBCs) per deciliter. Some reports have documented occasional WBC counts greater than 40 cells/dL in the CSF of normal horses.[19] Although suggested to correct for the effects of iatrogenic blood contamination, various "correction factors" are inaccurate and should not be used.[18,20]

The refractive index of normal CSF is less than 1.335. The protein concentration of CSF in normal adult ruminants is less than 50 mg/dL, and in normal horses it is less than 100 mg/dL, although reference values vary with the techniques used for protein measurement. Reference values should be established for each laboratory.[21]

Studies of the specific and relative quantities of albumin and immunoglobulins, particularly IgG and IgM, have been stimulated by the increasing importance of immunologic testing of CSF for diseases such as equine protozoal encephalomyelitis. Reference values for a number of parameters have been established.[22] The most important of these parameters are *albumin quotient,* a measure of blood-brain barrier (BBB) permeability,[23] and *IgG index,* a measure of intrathecal production of IgG.[24] The formulae for these parameters are as follows:

$$\text{Albumin quotient} = (\text{CSF albumin}/\text{Serum albumin}) \times 100$$

$$\text{IgG index} = (\text{CSF IgG}/\text{Serum IgG}) \times (\text{Serum albumin}/\text{CSF albumin})$$

Reference values must be established for each species. An elevated albumin quotient indicates BBB leakage or contamination of CSF with blood, with possible introduction of immunoglobulins from serum. An elevated IgG index indicates intrathecal production of IgG and may support a diagnosis of infectious disease of the CNS. The usefulness of these parameters is influenced by a number of other variables, including the immunoreactivity of blood.[24] Therefore clinical interpretations must be made with great caution. The composition of protein from the CSF of horses and cattle has been established.[3-5,10]

The concentrations of glucose and protein in the CSF of newborn foals are almost twice those found in the CSF of adults, but they approximate adult normal values by 2 weeks of age.[25] In contrast, calves between 1 and 2 months have lower protein concentration and higher leukocyte numbers in CSF than adult cattle.[26]

Neural tissue contains the BB isoenzyme of creatine kinase (CK), which increases after damage to the nerve cells.[27,28,30] The molecule does not cross the BBB, so CK in the CSF originates from neural tissue. Contamination of CSF with dura or fat, however, falsely elevates the CK concentration. Some have suggested that CK is an accurate marker and a prognostic indicator for CNS disease, but other studies have not supported this conclusion, and measurement of CK, although interesting, has limited clinical utility.[27,29,30]

The normal CSF concentration of glucose is approximately 80% of that in blood. A decline in the ratio of CSF to serum glucose occurs in animals with bacterial meningitis because of increased use of glucose by inflammatory cells.

Measurement of the sodium concentration of the CSF may be helpful for diagnosing salt poisoning in cattle. In animals that do not have salt poisoning, this value is less than 160 mmol/L; in animals with salt poisoning, the concentration is usually greater than 160 mmol/L.

Diseases Presenting Principally with Forebrain Dysfunction or Multiple-Level Brain Dysfunction

Alphaviruses

Robert J. MacKay

The causative agents of eastern, western, and Venezuelan equine encephalomyelitis (EEE, WEE, and VEE) are New World arboviruses belonging to the genus *Alphavirus* of the family Togaviridae.[1] Ross River virus is an Old World alphavirus in Australia that has been shown to cause fever in some experimentally infected horses and is suspected of causing a syndrome of lethargy, muscle soreness, and ataxia in horses in Victoria and South Australia.[2]

EEE, WEE, and VEE affect all common domestic equid species including horses, mules, and donkeys. Each of the viruses was first isolated during epizootics in the 1930s.[3-5] Alphaviruses are unsegmented, single-stranded, positive-sense ribonucleic acid (RNA) viruses; viral genomes are 11 to 12 kB, and infectious virions are spherical enveloped particles 60 to 70 nm in diameter.[6] Each of the 3 equine alphaviral encephalitides is among the 13 equine infectious diseases that are notifiable to the World Organization for Animal Health (Office International des Epizooties [OIE]). Data on the occurrence of these diseases in the United States are collected by veterinarians, diagnostic laboratories, and state animal health officials and reported to the National Animal Health Reporting System.

At least three subtypes of WEE have been identified. Two of these are found in both North and South America, suggesting that circulation of viruses between the New World continents is common.[6,7] There is a distinct North American variety and three South American antigenic varieties of EEE.[6] In contrast to the situation with WEE, there is no evidence for movement of EEE viruses between North and South America.

The VEE antigenic complex contains 8 viral species, 7 subtypes, and at least 14 varieties,[6,8] most of which are maintained continuously in enzootic life cycles in northern South America. Until the 1990s, when an IE variant caused two outbreaks in Mexico, all equine epizootics had been caused by subtypes IAB and IC.[9]

History and Distribution

WESTERN EQUINE ENCEPHALOMYELITIS. What was almost certainly the first recorded outbreak of WEE in horses occurred in Kansas, Nebraska, Colorado, and Oklahoma during the late summer and early fall of 1912 when at least 35,000 horses died of the disease.[4,10] Epizootics in California and other western states in 1930 to 1932 resulted in the deaths of an estimated 9200 horses and mules (≈50% of those affected).[4,11] In 1938 WEE was recognized in every state west of the Mississippi River and affected more than 184,000 horses in that year alone.[12] By the 1970s, WEE had been recorded as far east as Tennessee. WEE virus was also implicated in outbreaks of fatal equine disease in the early 20th century in Canada and Argentina, and epizootics have since been reported in Saskatchewan, Alberta, and Manitoba in western Canada; Mexico; Central America; and South America.[13] Between 1972 and 1981 there was an annual average of 267 cases of WEE in horses reported by the National Veterinary Services Laboratory in Ames, Iowa[12]; in 1993 there were 15 cases in 10 states, and since 2005 no case has been reported in the United States. There have been isolated cases of encephalomyelitis in Florida horses associated with the Highlands J virus, an eastern member of the WEE virus complex with epidemiologic characteristics similar to those of EEE virus.[14]

EASTERN EQUINE ENCEPHALOMYELITIS. An outbreak of what was probably EEE was recorded in 1831 in Massachusetts.[15] Approximately 100 horses were affected and 75 died. Over the subsequent century, there were at least five other outbreaks consistent with EEE—in Long Island, New York (1845); North Carolina (1902); New Jersey (1905); Florida (1908); and Maryland, New Jersey, and Virginia (1912).[16] In 1933 there was an epizootic involving a least a thousand horses in the coastal regions of Delaware, Virginia, and Maryland.[3] Epizootics of EEE in North America have since occurred periodically in the coastal areas of the Atlantic, the southeastern United States, and Texas. The largest recorded outbreak was in 1947 in southern Louisiana and Texas when 14,344 cases of EEE were recorded, resulting in 11,722 deaths (mortality rate of 81%).[17] Focal outbreaks and sporadic cases have also occurred more or less regularly in Michigan and are occasionally reported from other locations in the eastern half of the United States and Canada. A single case of

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EEE in a stallion in California was reported in 2002.[18] Although the origin of the infection in this horse was not determined with certainty, incompletely activated EEE vaccine was suspected. Despite the availability of effective vaccines since the late 1930s, cases of EEE still occur every year in Florida and other southeastern states. The annual incidence of EEE in horses in the United States over the past 10 years has ranged from 71 (2011) to 732 (2003).

Epizootics of what was probably EEE have been reported in Argentina since 1908. Since then, reports of EEE in Central and South America have been widespread, extending from Panama south to Argentina.[16] The disease has also caused serious losses in the Caribbean with epizootics documented in the Dominican Republic, Haiti, Jamaica, and Trinidad.[15]

VENEZUELAN EQUINE ENCEPHALITIS. The disease in equids was first recognized and described in Venezuela and Colombia in 1938.[5] At intervals of approximately 10 years, there were large subtype IAB or IC epizootics in northern South America that usually involved tens of thousands of horses. Some of these outbreaks may have been caused by incompletely inactivated vaccine. One epizootic in central Colombia during 1962-1964 was estimated to have killed 100,000 horses.[19] An outbreak of VEE caused by subtype IAB began in Peru in the winter of 1969, jumped to Central America in June 1969, and then entered Mexico in 1970. The outbreak spread north to the U.S. border in the spring of 1971, and the first case of VEE in a U.S. horse was confirmed on June 30.[20] By the time of the last case on November 7, 1971, more than 1500 horses had died in the southern counties of Texas. There was no further epizootic activity reported until 1992, when a series of epizootics of subtype IC VEE began. Subtype IE was associated for the first time with fatal VEE in small epizootics in Mexico in 1993 and 1996.[21]

Natural History

EASTERN EQUINE ENCEPHALOMYELITIS AND WESTERN EQUINE ENCEPHALOMYELITIS. In North America, the WEE and EEE viruses are maintained between epizootics by low-level cycling between New World passerine birds (i.e., songbirds) and ornithophilic mosquitoes in freshwater, forested swamp habitats.[1] Snakes may also be an overwintering host for North American EEE virus.[22] Infected mosquitoes can be found throughout the year in Florida and other southeastern states. Under favorable environmental conditions, the viruses periodically spread outward from focal reservoirs to infect the general wild bird population, where they are spread and amplified by rapid bird-mosquito-bird transmission. The mosquito vectors involved in maintenance and amplification of WEE and EEE viruses are usually *Culex tarsalis* and *Culiseta melanura,* respectively. Many avian species including migratory passerine birds (e.g., starlings and northern cardinals) and wading birds become infected and develop high-order viremia and high serum titers to EEE or WEE but usually do not become ill. Some introduced species, including pigeons, house sparrows, Chukar partridges, and Chinese pheasants, may suffer high morbidity and mortality when infected with EEE virus.

Cases of encephalitis usually begin in susceptible horses 2 to 3 weeks after the virus spreads into birds. Human cases may occur several weeks later. *Culex tarsalis* transfers WEE virus from bird to horse (and human). Although *C. melanura* may also function in some locations as a bridge vector for EEE, mosquitoes of a variety of other species usually transfer the virus from bird to horse.[6,16] Although mosquito-mediated transmission of EEE virus between horses has been confirmed in an experimental setting,[23] viremia is low titer, so further infection of feeding mosquitoes with either EEE or WEE virus is unlikely and horses are considered "dead-end" hosts. Both EEE and WEE viruses have been associated with naturally occurring and experimentally induced neurologic disease in calves, and EEE has been associated with fatal infections in New World camelids, deer, ratite birds, cats, dogs, mice, foxes, sheep, and pigs.[6,24-26]

Epizootics of EEE and WEE usually last 1 to 3 months and occur in summer and early fall when warmth and humidity favor breeding, longevity, and mobility of mosquito populations.[27] Outbreaks in Massachusetts and Michigan were most likely during the second consecutive year in which rainfall exceeded the annual mean by more than 20 cm; however, unusually high temperatures did not appear to be a risk factor.[27,28] The month of peak incidence of disease onset varies from June in Florida to August or September in northern and western states.[4,24,29,30] In Florida and some other southeastern states, isolated cases of EEE can be seen at any time of year.[29] Standing surface water for mosquito larval development, bush cover for wild hosts, and the immune status of the various hosts also affect the timing and magnitude of equine epizootics. Many of these physical factors are significantly affected by the cultivation, clearing and irrigation of land, and by drainage of swamps. The proximity and size of plantations of trees were risk factors for EEE for horses in Florida.[31] The equine epizootic usually declines with the onset of cool or dry weather unsuitable for mosquito and/or bird activity, as well as the depletion of susceptible equine hosts by death or development of immunity among survivors.

The epidemiology of EEE and WEE viruses in South America is poorly understood. Small mammals play a greater role in sylvatic cycles of viral transmission than is the case in North America. *Culex (Melanoconion)* subspecies and *Ochlerotatus albifasciatus* appear to be involved in transmission of EEE and WEE, respectively.[7,32]

VENEZUELAN EQUINE ENCEPHALOMYELITIS. Enzootic VEE viruses are maintained by cycling between mosquitoes and small rodents. The Everglades virus, a subtype II found in the Everglades region of Florida, is of this type, cycling between *Culex (Melanoconion)* subspecies mosquitoes and wild rodents.[8] The epizootic varieties IAB and IC have probably arisen on at least four separate occasions by mutation of a single enzootic subtype 1D strain and changes in host range.[9] Because of the high-order viremia that develops in infected animals, the defining characteristic of epizootic VEE varieties is the use of equids as amplification hosts. Domestic rabbits, goats, dogs, and sheep also suffer fatal disease during VEE outbreaks.[8] There does not appear to be any single "epizootic" vector mosquito species; during outbreaks, virus may be isolated from mosquitoes of many different species.[8] Epizootics terminate when susceptible horses are no longer available. The leapfrog spread characteristic of VEE is usually attributed to transport of horses incubating the virus. Movement of infected bats may also contribute to discontinuous spread of virus. By contrast to the situation with the WEE and EEE viruses, birds do not have an important role in amplification and spread of epizootic VEE virus. It is not yet clear whether neurovirulent subtype IE virus is amplified in horses. Evidence from experimental infections suggests that viral titers in blood of infected horses may be insufficient to infect feeding mosquitoes.[33] The interepizootic reservoir of epizootic varieties, if any, is not known.

Clinical Findings

Clinical signs following infection with each of the viruses are similar, although signs of EEE are typically more severe and rapidly progressive than those of VEE and WEE.* Infected horses respond in any to all of the following ways after experimental infections[36]: (1) Inapparent infection with a very-low-grade viremia and fever about 2 days after inoculation. This presentation corresponds to the initial viremia following viral proliferation in regional lymph nodes and probably occurs commonly during outbreaks without progression to subsequent stages. (2) Generalized febrile illness (up to 41.7° C), with anorexia, depression, tachycardia, and diarrhea. This stage is associated with viral proliferation in various body organs after spread from regional lymph nodes. (3) Clinical encephalomyelitis, which is the classic form of the disease. Young horses (especially yearlings) are most susceptible: Approximately 90% of 95 horses with EEE admitted to the University of Florida (UF) were younger than 5 years of age. The onset of neurologic signs, associated with the second febrile crisis, typically occurs about 5 days after infection (range 2 days to 2 weeks), and most deaths occur 2 to

*References 3, 4, 17, 18, 27, 34, 35.

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FIG. 35-3 Eastern equine encephalomyelitis in an 18-month-old Paint filly. At presentation, the filly was febrile (103.8° F), stuporous, cortically blind, and had a marked head tilt and body lean to the left, indicative of asymmetric central vestibular dysfunction. Vaccination history was unknown. With nursing care, this filly completely recovered over several weeks.

3 days later.[35,36] Almost all horses with EEE are febrile at the onset of neurologic signs (mean of 40.3° F in horses admitted to UF), although the temperature declines thereafter. The onset of severe neurologic signs is peracute to acute, and progression is rapid. Horses may be found recumbent and comatose or dead. If observed, initial CNS signs are quite variable and referable to diffuse or multifocal cerebral disease; evidence of brainstem and spinal cord involvement quickly becomes obvious as the illness progresses (Fig. 35-3). Obtundation is the most common initial clinical sign, although owners also report suspected colic as part of the initial presentation. Affected horses often stand apart from pasturemates, have no interest in food, or fail to respond to an owner's call. Further signs of dementia may follow including head pressing, teeth-grinding, hyperesthesia, irritability, aggression (rarely), leaning against a wall or fence, or compulsive walking, often in a circle (especially around the inside of a stall or small paddock). Several observers have noted a "peculiar looseness of the lips" as a characteristic early sign.[4,37] Blindness and lack of a menace response may be noted at this stage. Signs of cranial nerve disease including abnormal pupillary light reflexes, head tilt, nystagmus, tight circling, facial and tongue paralysis, and inability to swallow often occur as the disease advances. Abnormal signs usually present asymmetrically, at least initially. Ataxia and paresis of the trunk and limbs result in a progressively more unsteady gait. Tremors are seen in the antigravity muscles of the limbs. Once recumbent, affected horses seldom regain their footing and are often noted to make galloping or swimming movements in lateral recumbency.[4] Seizures occur in about a third of horses with EEE and may happen at any stage. Mucopurulent nasal and ocular discharges and abrasions/lacerations of the face and limbs are the most common non-neurologic findings; the latter occurs secondary to trauma from falling, seizures, or running into objects.

Mortality rates are 75% to 95% for EEE, 19% to 50% for WEE, and 19% to 83% for VEE.[4,6,17,32,38] Vaccination within the preceding year was associated with lower risk of death in horses with EEE.[27,29] Death is usually preceded by a period of recumbency during which the horse may be semicomatose and convulsing. Surviving horses gradually recover over a period of weeks. Many horses with WEE apparently recover completely, but it is estimated that two thirds of horses that survive EEE have residual signs of CNS damage such as central blindness, dullness, and diminished learning capacity or signs of cranial nerve dysfunction such as facial paralysis and head tilt.[16] Such horses are often referred to as "dummies."

Laboratory Findings Abnormalities seen in hemograms and plasma chemistry panels of horses with alphaviral encephalomyelitis are minor and nonspecific. Horses with EEE may have abnormal WBC counts and high fibrinogen concentration. In 73 horses with EEE admitted to the University of Florida, the following hematologic abnormalities were noted: leukocytosis (56%), neutrophilia (60%), hyperfibrinogenemia (57%), monocytosis (36%), lymphopenia (13%), leukopenia (7%), neutropenia (4%), and lymphocytosis (3%). Slight leukopenia was noted during experimental infections of horses with WEE and VEE viruses. Mild elevations in plasma enzyme activities of affected horses reflect organ damage secondary to anorexia, fever, stress, recumbency, and seizures. Hyponatremia is found in some horses with EEE; in humans with EEE, hyponatremia predicts mortality but its significance is unknown in horses.

The results of CSF analysis for horses with EEE are quite distinctive. More than 95% of horses with EEE admitted to the University of Florida had abnormal CSF cytology. Among UF patients, 88% of samples had high protein concentrations (mean of all samples: 139 mg/dL, range 38 to 526 mg/dL). Nucleated cell counts were high in 87% of samples (mean 248 μL, range 0 to 3100/μL; normal range 0 to 6/μL); pleocytosis is characterized by high neutrophil concentrations (mean 46%, range 0 to 97%). Neutrophils are typically nondegenerate. Protein concentration and nucleated cell counts are typically higher in samples obtained from the atlantooccipital (AO) site than they are in samples from lumbosacral taps. In the WEE outbreaks of 1930 to 1932, CSF nucleated cell counts were typically 12 to 30/μL and most cells were lymphocytes.[11]

Diagnosis A presumptive diagnosis is usually made clinically, especially in areas where these diseases are prevalent during the mosquito season. The finding in a CSF sample of moderate neutrophilic or lymphocytic pleocytosis further supports a diagnosis of alphaviral encephalomyelitis. Hemagglutination-inhibition (HI), complement fixation, fluorescent antibody, and virus neutralization tests have traditionally been used for serologic diagnosis.[16] The immunoglobulin M antibody capture (MAC) enzyme-linked immunosorbent assay (ELISA) is the method of choice for use in horses with viral encephalomyelitis because at titers of greater than 1 : 400 it can distinguish between vaccinal (IgG only) and viral infection–induced (IgM and IgG) titers.[33,39] These assays are available at many state diagnostic laboratories and also at the National Veterinary Services Laboratories (NVSL) in Ames, Iowa. In surviving horses, demonstration of a fourfold or greater rise in HI or plaque-reduction neutralizing titer between acute and convalescent samples provides additional diagnostic support. It should be noted that positive results in these tests could simply reflect *subclinical* infection with either virus. Virus can be isolated from fresh or frozen brain in tissue culture or mice and can be detected in histologic sections by immunohistochemistry or polymerase chain reaction (PCR) techniques.[40]

Differential diagnoses include hepatoencephalopathy; gastrointestinal hyperammonemia; heavy metal or other toxicosis; rabies; other viral encephalomyelitis (West Nile, Borna disease, equine herpesvirus myeloencephalopathy [EHM], Aujeszky disease, louping ill); equine protozoal myeloencephalitis (EPM); trypanosomal (South America), verminous, or bacterial meningoencephalomyelitis; space-occupying lesion within the calvarium (e.g., cholesterol granuloma, neoplasia, brain abscess); brain infarct; brain trauma; and leukoencephalomalacia.

Treatment Treatment is largely supportive and, in the case of EEE, usually ineffective. Any adult horse with EEE that is unable to stand should be euthanized. Such horses should not be subjected to slinging. Hyperthermia is known to exacerbate brain injury and must be treated vigorously with cold water or alcohol baths until rectal temperature is less than 102° F. Convulsions can be

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controlled with diazepam, xylazine, or barbiturates (pentobarbital or phenobarbital).

In addition to excellent general nursing care, all horses should be treated for brain edema and inflammation, although only horses whose signs are mainly cerebral are likely to respond. Drugs used for this purpose include dimethyl sulfoxide (DMSO), 1 g/kg as a 10% solution intravenously (IV) or intragastric, flunixin meglumine (or equivalent nonsteroidal antiinflammatory drug [NSAID]) intramuscularly (IM), IV, or orally (PO) at 1.1 mg/kg q12h for 3 days, dexamethasone (or equivalent corticosteroid) IM or IV at 0.05 to 0.1 mg/kg daily for several days for 3 days then tapered, and mannitol (IV at 0.25 to 1 g/kg as a 20% solution) or hypertonic saline (e.g., 7.2% saline IV at 2 mL/kg 4 to 6 times during the first day). A lengthy course of dexamethasone is believed anecdotally to be an important determinant of neurologic recovery in surviving cases. Treatment should be titrated to minimize neurologic signs but generally must be tapered over several weeks. Complete recovery, if it occurs, may take several months.

Treatment with serum from horses hyperimmunized against WEE virus was thought to reduce mortality modestly during the 1930 to 1932 outbreak; however, these claims were not tested scientifically.[4] Furthermore, administration of large quantities of hyperimmune serum to experimentally infected horses by investigators at Lederle Laboratories was reported to have no beneficial effect.[41]

Adjuvant antiviral therapy with interferon (IFN) α or β has salutary effects in some experimental models of alphaviral encephalitis[42] and could be tried in valuable horses. A reasonable protocol is described in the West Nile encephalitis section. The nucleoside analogue ribavirin boosts the antiviral activity of IFN in vitro against encephalitic alphaviruses[43] and holds some potential as future therapy for EEE in humans and perhaps horses.

Public Health Significance All three viruses infect humans causing subclinical, febrile, or neurologic disease.[6] Since 1964, there have been 640 cases of human WEE reported in the United States, with an average of 27 cases/year in the period up to 1987. Since 1988, there have only been five cases of WEE reported. By contrast, the 268 cases of EEE in humans reported in the United States since 1964 have occurred at a fairly steady rate of 6 cases/year. Epidemics of VEE are closely associated with equine epizootics; thus during the 1962 to 1964 epizootic in central Colombia, which killed about 100,000 horses, 200,000 humans were infected, of whom 0.5% died. Although nonpathogenic for horses, the enzootic Everglades subtype II strain has caused human encephalitis in Florida. No cases of human disease were recorded during the VEE subtype IE equine epizootics in Mexico in 1993 and 1996, and South American strains of EEE are not known to cause encephalitis in humans. Short-term mortality rates of EEE, WEE, and VEE in humans are 74%, 4%, and less than 1%, respectively. Most survivors of EEE suffer long-term neurologic impairment.

Postmortem Findings There is congestion of most organs and a slate-gray discoloration, often with petechial hemorrhage, of the brain and spinal cord, especially obvious on section of formalin-fixed tissue.[40,44,45] Often there is brain swelling and evidence of occipital subtentorial herniation, with brainstem compression. Histologically, there is evidence of acute to subacute and multifocal to diffuse meningoencephalomyelitis. There is predominant involvement of gray matter, with diffuse neuronal degeneration, gliosis, perivascular and neuroparenchymal infiltrates, and meningitis. Neutrophils are prominent in acute EEE, whereas lymphocytes predominate in older lesions. On occasion, eosinophils may predominate in EEE. Lymphocytes are usually the primary inflammatory cell in WEE lesions.[44] Previous therapy with potent antiinflammatory agents, particularly corticosteroids, may suppress the inflammatory-cell infiltrates, which then appear mild.

Bronchopneumonia is found in about 20% of fatal cases of EEE, probably secondary to pharyngeal paresis and aspiration of particulate material. Up to 10% of horses with EEE have histologic evidence of myocardial necrosis, likely a sign of brain-heart syndrome.[45]

Because high infection rates in humans have been documented following exposure to aerosols from infected laboratory animals or from laboratory accidents (or, potentially, equine carcasses), necropsies of horses with suspected VEE should only be performed by personnel who possess demonstrable immunity in the form of neutralizing antibody.[46] All laboratory manipulations must be carried out within certified biological safety cabinets following containment level 3 procedures.

Control Active immunization through use of formalinized vaccines began in 1934 and is still the only commercial method of immunization of horses against EEE and WEE. These inactivated vaccines are also used routinely to protect ratites from EEE and WEE and South American camelids from EEE.[47] The attenuated, tissue-culture-origin vaccine, TC-83, derived from a Trinidad VEE virus isolate, which was originally developed to protect military personnel, provides durable immunity against VEE and was effective in minimizing the incursion of VEE into the United States in 1971[20] and in limiting the 1993 and 1996 outbreaks in Mexico. Although TC-83 is no longer licensed for use in horses in the United States, a formalin-inactivated vaccine containing the TC-83 vaccine strain is available and is often included with EEE and WEE in trivalent products.[48] For any of the formalin-inactivated alphavirus vaccines, adult horses should be given an initial two inoculations 4 to 6 weeks apart at least a month before the anticipated risk period or before the onset of vector mosquito activity and then revaccinated at intervals reflecting the likely risk. Vaccination should begin in January or February in Florida to May or June in parts of Canada and the northern United States. Clinical evidence suggests less than 6 months of protection following vaccination against EEE or WEE, so revaccination at least once during the mosquito season is necessary in areas with warm climates and long mosquito seasons. Vaccinated mares should receive a booster dose 4 to 6 weeks before foaling to provide colostral antibody for newborn foals.

Foals should be given an initial inoculation at 4 to 6 months (vaccinated mare) or 3 to 4 months (unvaccinated mare), then a second inoculation 4 to 6 weeks later and a booster at 10 to 12 months of age. AAEP guidelines for 2012 recommend that foals of vaccinated dams in high-risk areas should be given a primary series of four doses beginning at 2 to 3 months of age. Two additional inoculations are then given at approximately 4-week intervals and a booster at 10 to 12 months of age, before the onset of mosquito season. It will be important to validate this method of vaccination because of concerns that early frequent vaccinations may suppress immune responses to EEE.[49] Until this issue has been resolved, the author will continue to recommend that the initial inoculation be given to foals in high-risk areas no earlier than 4 months of age (as for foals in moderate-risk areas).

Routine surveillance of the virus pool by serum antibody testing of sentinel chickens and virus detection in trapped mosquitoes by health authorities often provides early warning of an impending outbreak and allows time for vaccination of susceptible horses. General mosquito control (removal of standing water, spraying by local authorities) will reduce risk of EEE and VEE in horses.[27] Because of the role of horses in amplification and transmission of VEE virus, quarantine of infected and exposed horses with area-wide and international restrictions on horse movement is an integral part of the management of VEE epizootics.[50]

Miscellaneous and Foreign Emerging Viruses Causing Neurologic Signs

Robert J. MacKay

Since the encroachment of West Nile virus (WNV) in 1999 into North America, the potential for emerging foreign disease with widespread impact has been realized. Given the opportunity, many other

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viral infections could become established in new countries as a result of the globalization of the horse industries and effects of global warming.

Getah/Ross River Viruses

The Semliki Forest complex of the Togaviridae are widespread throughout their geographic range, either in the Orient (Getah) or South Pacific (Ross River).[1,2] Although closely related, there is little geographic overlap among these viruses. As with the North American alphaviruses, these viruses are transmitted by mosquitoes (*Aedes, Anopheles,* and *Culex* spp.).[3-6] The reservoir for Getah virus (GV) is not known, although swine appear important in its transmission to mosquitoes.[6,7] Other feral species are not firmly established. For Ross River virus (RRV), marsupials are important reservoirs.[8] With GV, horses might develop sufficiently high viremia to transmit virus, but this is unlikely with RRV. Many animals have been found to be seropositive to GV, including ruminants, and seroprevalence in horses varies from less than 10% to more than 90%.[6,9-11] RRV is endemic in horses and widespread, with seroprevalence ranging from 50% to 80% in Australian horses.[1,12-14] With the recent increase in Kunjin/West Nile encephalitis in Australia, RRV has become an important differential diagnosis for horses with neurologic disease and is usually included in serologic and PCR testing of diagnostic samples.

Getah virus is likely more pathogenic in horses than RRV.[9,11,15] Clinical signs include pyrexia, edema of the limbs, and stiff gait. Horses may also develop urticaria and submandibular lymphadenopathy. The course of GV disease is 7 to 10 days. With RRV, horses also develop fever, lameness, swollen joints, inappetence, generalized stiffness, and even colic.[1,12,14] High rates of mortality are not a feature of either virus.

Serologic detection of IgM is the mainstay of diagnosis of these viruses, although a vaccine against GV complicates diagnosis.[16,17] RRV can be detected by PCR and isolated from the blood of horses during the disease course.[18] Pathologic changes associated with these viruses are seldom described because of the low mortality of associated diseases. Horses primarily develop perivascular inflammation in the brain.

Treatment is supportive; no antiviral is specific for alphaviruses. A vaccine for GV is available in Japan. An inactivated vaccine against RRV for humans is being tested in Australia, but no equine vaccine is available.[19]

Borna Disease

Classical Borna disease (cBD) is a viral encephalitis principally of horses and sheep that was first recognized in southwestern Germany in the 18th century but is associated with the village of Borna in the Kingdom of Saxony, where the disease emerged in the late 19th century. It is estimated that approximately 16,000 horses died annually in Saxony from 1896 to 1940.[20] These numbers declined rapidly in the 1960s in parallel with declining horse numbers, and only 1216 horses died of cBD in Saxony from 1958 to 1991.[20] Outbreaks of cBD have been restricted to central Europe in the upper Rhine valley around Switzerland, Austria, and Liechtenstein. Borna disease virus (BDV)-associated encephalitis has also been reported in cattle, an alpaca, deer, zoo herbivores, cats, rabbits, and dogs.[21] During recent decades, evidence of BDV infection including antibodies, antigen, RNA, or the virus itself has been reported in many countries and in numerous mammalian species including humans. There is serologic evidence of BDV infection in horses in the United States.[22,23] Some of these reports are questionable because of problems with contamination of samples by laboratory BDV strains and poorly validated immunoassays; however, there are enough well documented infections to confirm widespread distribution of BDV or BDV-like virus.[21] The possibility of involvement of BDV in several human neuropsychiatric diseases has raised interest in BDV but remains controversial.

The etiologic agent of Borna disease is a nonsegmented, negative-sense, single-stranded RNA virus of the order Mononegavirales, family Bornaviridae. Although regional genetic variation occurs, the BDV genome is considered remarkably stable for an RNA virus. Related viruses, termed *avian Borna viruses* (ABVs), have been discovered in birds, and endogenized BDV sequences are common in the genomes of mammals. The significance of this last intriguing finding is unknown.

Most outbreaks in horses and sheep occur during the spring and early summer. Although horse-to-horse transmission is theoretically possible, it is unimportant in the evolution of an outbreak.[21] The virus is likely maintained in small mammals with geographic ranges approximating the endemic Borna disease area. Bank voles, bicolored white-toothed shrews, and bats have been suggested as possible reservoir hosts.[24] BDV is shed through nasal and lacrimal secretions and in the urine of infected animals.[21,25] BDV is resistant to drying and other adverse environmental conditions. It is assumed that BDV enters the horse though intranasal infection and migrates to the brain transaxonally.[26] Direct replication occurs in neurons and glial cells, with centrifugal spread to peripheral nerves and retina. BDV infection of the retina may contribute to the blindness that characterizes acute Borna disease in horses.[27] Subclinical BDV infection is common with seroprevalence of horses in endemic areas of 10% and 20%, and as high as 50% among stablemates of horses with Borna disease. The neurologic signs of Borna disease are associated with the florid cell-mediated initial immune response to the virus. In subclinically infected horses and horses that recover from Borna disease, the virus becomes quiescent and largely undetected by the immune system.

The clinical signs of Borna disease in large animals are similar to those of the other equine encephalitides. The incubation period is thought to be about 2 months in naturally occurring cases. There is a predominance of forebrain signs initially, followed by signs of brainstem and spinal cord involvement. In moderate to severe cases, horse die 1 to 4 weeks after onset of disease. In mild cases, recovery can occur, but persistent abnormalities and exacerbations are common. There is a prodrome characterized by fever, inappetence, colic, and vague behavioral changes. The onset of neurologic signs is marked by changes in mentation with alternating hyperresponsiveness and stupor; compulsive walking, often in circles; teeth-grinding; and aggression. Other signs of brain disease include trismus, pupil constriction, nystagmus, head tilt, and blindness. With progression, there is ataxia and weakness of the limbs and trunk and areas of cutaneous desensitization or hyperesthesia. Collapse into recumbency and seizures are the final stages. The mortality rate is about 80% in horses and 50% in sheep.

For antemortem diagnosis, antibodies to the agent may be found in the serum and CSF of most infected animals by ELISA, indirect fluorescent antibody (IFA), and Western blot.[24] CSF analysis often reveals mononuclear pleocytosis and high protein concentration. Reverse transcriptase nested PCR techniques have demonstrated virus in the CSF and peripheral mononuclear cells.[28] The criteria for diagnosis include a horse with neurologic abnormalities testing antibody positive for BDV in serum or CSF or a horse with neurologic signs and appropriate histopathologic changes.

Pathologic abnormalities resemble those of a viral encephalomyelitis, and confirmatory diagnosis is by immunohistochemistry, virus isolation, and detection of viral nucleic acids.[21,24,29-33] The characteristic microscopic lesion of Borna disease is the Joest-Degen inclusion body in the neuronal nucleus, but this is not always observed. Virus is detectable easily with monoclonal or polyclonal antibodies. Histopathologic changes are those of a typical polioencephalomyelitis, with a particular loss of neurons in the hippocampus. There is involvement of the gray matter of the olfactory bulb, basal cortex, caudate nucleus, thalamus, hippocampus, and medulla oblongata.

No antiviral agents are available for BDV, and use of the amantadine sulfate (developed for treatment of influenza infection) is controversial but commonly used.[34,35] Likewise, vaccination as a protective strategy is controversial. It is widely assumed that a modified live vaccine would offer more protection; however, the live vaccine available until the early 1990s in East Germany was removed from the market because of questionable efficacy.

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Henipavirus

Hendra virus (HeV) infection of horses was first recognized in 1994 during simultaneous outbreaks of severe respiratory disease in Queensland, Australia: one in the Hendra suburb of Brisbane and the other near the town of Mackay. Mortality was high among the 22 affected horses and each outbreak was associated with transmission to humans, 2 out of 3 of whom died.[36-38] Since 1994, there have been at least 33 outbreaks of HeV infection in horses, all in Queensland or northern New South Wales. Cases have occurred every year since 2006, and there were 11 outbreaks involving 23 horses in 2011. Five outbreaks also involved seven human cases, of which four were fatal. Signs of neurologic disease were seen in some horses during the initial outbreaks, and neurologic signs dominated the clinical presentation in five horses in an unusual outbreak at an equine referral practice in the Redlands suburb of Brisbane in 2008. The signs were those of fulminant febrile encephalitis with severe obtundation, dementia, vestibular signs, and progressive ataxia. Nipah virus (NiV) emerged as the cause of porcine respiratory and encephalitis syndrome in Malaya in 1998.[38-40] Signs were predominantly respiratory, and most affected pigs recovered. NiV also caused severe febrile encephalitic illness among workers in contact with infected pigs; 105/265 affected people died. NiV has also been recovered from the brain of a horse with encephalitis.

HeV replicates initially in the respiratory epithelium before spreading hematogenously to multiple organs, including the CNS, to cause widespread vasculitis, endothelia syncytia, vascular thrombosis and hemorrhage, and cellular necrosis.

HeV and NiV are closely related viruses that occupy a new genus, *Henipavirus,* of the family Paramyxoviridae. They are enveloped, single-stranded, negative-sense RNA viruses. The henipaviruses are highly pathogenic for a wide range of mammals including horses, pigs, and humans. The natural reservoirs throughout the geographic range in Northern Australia, Malaysia, and Bangladesh are fruit bats from the genus *Pteropus* (also known as flying foxes).[41] Transmission from bats in each spillover event is likely via contact of the horse with urine or reproductive fluids from infected bats. Horses incubating HeV are infectious to other horses for at least 48 hours before the onset of clinical signs, and at least two outbreaks in stables were caused by introduction of preclinical horses incubating the virus.

Diagnosis is made both by detection of serum neutralizing antibodies by immunoassay and detection of RNA by quantitative reverse transcriptase PCR in blood, other body fluids, or from tissues taken at necropsy.[40,42,43] Virus is secreted in all body fluids and feces of infected horses, and appropriate precautions must be taken to prevent transfer to other horses and humans. Guidelines for biosecurity have been developed by the Australian Veterinary Association (available at http://www.ava.com.au) and by Biosecurity Queensland (http://www.biosecurity.qld.gov.au).

Infected horses are euthanized as a matter of public health. Ribavirin is used with partial success to treat NiV and HeV infections of humans, and a monoclonal antibody (mAb m102.4) has been shown to be protective in experimental animals if given before clinical signs and has been used in several exposed humans.[44] An HeV subunit vaccine (HeV-sG) has been tested successfully in multiple species including horses against both HeV and NiV challenge and was launched commercially in Australia in 2013 for vaccination of horses in endemic areas (EquiVac HeV, Pfizer Animal Health).[44]

California Serogroup Viruses

The Bunyaviridae are mostly arboviruses and are found worldwide. These viruses are usually maintained in mosquito-vertebrate host-mosquito cycles with midges acting as the arthropod hosts for a few viruses.[45] Twelve serotypes, known collectively as the *California serogroup,* have been isolated in North America, South America, Africa, Europe, and Asia. In rare cases, these viruses can cause acute encephalitis in horses. Snowshoe hare virus and Main Drain virus have been associated with encephalitis in horses,[46,47] and serologic evidence of subclinical infections of horses with Jamestown Canyon virus and Cache Valley virus was found in horses in southern California and Michigan, respectively.[48,49] Clinical signs in a horse from which Main Drain virus was isolated included ataxia, weakness, stiff neck, head pressing, dysphagia, tachycardia, and fever.[47]

Equine Encephalosis

Equine encephalosis is an arthropod-borne viral infection, affecting all species of equids, usually characterized by mild or subclinical infection but occasionally causing severe clinical disease.[50] The causal agent, equine encephalosis virus (EEV), is transmitted through the bites of certain *Culicoides* spp. biting midges. EEV is an orbivirus, as are African Horse Sickness virus (AHSV) and bluetongue virus (BTV). All equids (horses, donkeys, zebras) are susceptible to EEV, although donkeys and zebras are thought to be resistant to the clinical disease. The infection is endemic in southern Africa where seven EEV serotypes have been identified.[51] An outbreak of febrile disease due to EEV in Israel in 2008-2009 involved 60 horses, and serologic evidence of the infection has since been found in several other areas outside southern Africa.[52,53]

The virus was originally named for isolation from a horse with typical signs of encephalitis including mild to severe ataxia, reluctance to walk and stiffness, dementia, and seizures.[50] In its current forms, infections are either subclinical or associated with an influenza-like syndrome of fever, edema, tachycardia, tachypnea, and congested mucosae. An AHSV-like syndrome of respiratory distress and cardiac failure has been described, and pregnant horses may abort. A competitive ELISA for detection of group-specific antibody to EEV has been described for use in diagnosis.[54] There is no recognized treatment or method of prevention for EE.

West Nile and Other Flavivirus Encephalitis

Robert J. MacKay

The causative agent of West Nile encephalitis (WNE) is a small, positive-sense, single-stranded, enveloped RNA virus.[1] West Nile virus (WNV) is a member of the Japanese B encephalitis (JE) antigenic complex of neuroinvasive arboviruses within the genus *Flavivirus,* family Togaviridae.[1] In addition to WNE virus, Kunjin, JE, and Murray Valley encephalitis (MVE) viruses are members of the JE antigenic complex that have caused encephalomyelitis in horses outside the United States. There are two main genetic lineages of West Nile encephalitis virus: Outbreaks of neuroinvasive disease in horses and humans have traditionally been associated with lineage-1 isolates that circulate among Mediterranean basin, West African, and northern European countries. A virus of this lineage is responsible for the North American epizootic. Lineage-2 isolates are widespread in sub-Saharan Africa and commonly have infected horses without apparent clinical effect. In the past few years there have been several cases and even outbreaks of neurovirulent equine and human disease caused by Lineage-2 WNV in Africa and Europe.[2,3] The Kunjin virus is a lineage-1 WNE virus that traditionally has caused mostly subclinical or febrile non-neurologic disease in horses and humans in northwestern Australia and Papua New Guinea. A neurovirulent strain of Kunjin virus emerged in 2011 in New South Wales in Australia in the late summer and fall and caused encephalitis in at least 1000 horses in southeastern states with a mortality rate of 10% to 15%.[4-6] This unprecedented epizootic of Kunjin encephalitis (and also of encephalitis due to the arboviruses Ross River virus and Murray Valley encephalitis virus) followed unusually high spring rainfalls in southeastern Australia.[6] Compared with prototypic Kunjin virus (WNV_{KUN}), the neurovirulent strain ($WNV_{NSW2011}$) has acquired at least two of the known virulence markers of the North American strain. There was also a sharp increase in Murray Valley encephalitis cases in horses as part of the 2011 arboviral encephalitis epizootic.[6] Since the last MVE epizootic in 1974, cases had been reported only sporadically.[7] Japanese B encephalitis virus is endemic in east Asia and southeast Asia and has made incursions into the northern tip of

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Australia.[8] It is maintained in cycles among porcine and avian reservoirs using mosquito vector hosts. Humans and horses are dead-end hosts. Cases of encephalitis in horses are seen sporadically throughout the virus's range, and effective vaccines are available.[1] Although there is minimal overlap between the ranges of WNV and JEV, diagnostic serology may yield confusing results in areas where both diseases (and vaccinations) do occur. Louping ill virus and Powassan virus are tick-borne flaviviruses that have the potential to cause encephalitis in horses.[4]

History and Distribution WNV was originally isolated from the blood of a febrile adult woman in the West Nile region of Uganda in 1937. Cases of encephalitis in humans were first recorded in Israel in the 1950s and in horses between 1960 and 1965 in Egypt and France.[9,10] Since 1996 there have been small localized outbreaks of equine WNE in numerous countries in the Mediterranean basin and northern Europe with repeated seasonal epizootics in the Camargue marshlands of France and in the Tuscany region of Italy.[11,12] Although the virus usually did not persist in these locations after equine or human disease waned, there is recent evidence for overwintering of WNV in the Tuscany region of Italy.[12]

In August 1999, the first case of WNE in humans was reported in Queens, New York.[13] Characterization of the virus from this outbreak showed it was highly homologous with Israel 1998 (Is98), a strain of WNV that had originally been isolated from a goose.[14] Eventually, 62 cases occurred in humans in1999 and 7 died. From August to October 1999, 25 horses on Long Island were diagnosed with WNE.[15] Nine of these horses died. Deaths occurred in numerous native bird species, particularly in corvids (crows, ravens, jays) and in exotic species housed at the Bronx zoo. In 2001 the disease became a national epizootic with cases seen for the first time in Florida, Kentucky, Louisiana, Georgia, Alabama, Illinois, Indiana, Mississippi, New Hampshire, North Carolina, Tennessee, and Virginia.[16] There were 738 cases reported nationally, of which 33.2% died or were euthanized. Despite the availability of an effective vaccine from August 2001 onward, there was a dramatic westward spread of WNE in 2002, with 15,257 horses affected in 40 states.[16] The national incidence of the disease in horses declined in 2003 to 5181 cases in 44 states. By 2006 equine cases had been reported from all 48 contiguous states. Total annual cases dropped below 1000 in 2007, and only 79 were reported in 2011. In 2012 there was an upswing in WNE in all parts of the country with 618 total cases, of which 116 were in Texas.[16] The human epidemic dramatically expanded in 2012 with a provisional total of 2734 cases of neuroinvasive disease, second only to the 2866 cases recorded in 2003. This alarming upswing in cases may be explained, at least partially, by the unusually mild winter, early spring, severe drought, and high mean temperatures of 2012.

Natural History

WNV cycles between mosquito vectors and avian reservoir hosts. In temperate climates, the virus overwinters by vertical (transovarial) transmission in vector mosquitoes and possibly by latent infection of avian hosts.[1] *Culex*-species mosquitoes are the most important vectors for the North American epizootic in birds. Different species transmit the virus in different parts of the country. Major vector species include *Culex pipiens* in the northeast and central United States, *Culex tarsalis* from the far west to the panhandle of Texas, and *Culex quinquefasciatus* in the southeastern United States from Texas to Florida. Although birds of more than 300 species have been reported WNV positive, passeriform (true perching bird) and charadriiform (shorebird) species are considered the most competent reservoir hosts for WNV in the United States. Corvid species such as crows and blue jays are efficient hosts but have suffered high mortality during the North American epizootic. The house sparrow (an Old World passerine species) also develops high-titer viremia after WNV infection but is relatively resistant to the adverse effects of the virus. A variety of domestic mammals including sheep, alpacas, and dogs have suffered fatal WNE during the North American epizootic. Horses, humans, and other mammals are "dead-end" hosts and do not amplify the virus in quantities sufficient to infect mosquitoes. In contrast, alligators experience high-titer viremia and may be important reservoirs for infection in the southeastern states.

"Bridge vector" species of mosquito transmit the virus from birds to mammals, including horses. The mosquito species important for bird-horse transmission are not known with certainty but may include members of *C. pipiens* complex, *C. tarsalis,* and *Culex salinarus*.

The occurrence of WNE reflects vector mosquito activity, which is seasonal in temperate zones and year-round in tropical and subtropical regions. Significant viral activity begins in July, with peak incidence in September and October. The epizootic usually declines rapidly after the first frost.

Clinical Signs Experimental infections of horses result in viremia 3 to 5 days after viral inoculation into the CSF and clinical signs beginning at 7 to 10 days.[1] Experience during clinical outbreaks indicates a similar 1- to 2-week incubation period before signs of WNE are seen.

Clinical signs have been extremely varied; however, surveys of cases published across the United States and from Europe have revealed some consistent combinations of signs.[9,12,15,17-20] Roughly a quarter of affected horses have had mild to moderate fever at the time of initial examination, although it is likely that most were febrile before examination. Consensus neurologic signs seen have included limb ataxia (71% of 726 cases from the northeastern United States, Florida, Indiana, Nebraska, and Colorado[9,12,15,17-20]), limb weakness (58%), muzzle twitching (45%), obtundation (43%), recumbency (31%), lip droop (22%), hyperresponsiveness/hyperesthesia (18%), teeth-grinding (12%), dog-sitting (10%), thoracic limb collapse (7%), compulsive walking (7%), muscle atrophy (6%), seizure (4%), blindness (4%), circling (4%), and head pressing (3%). Clinical signs reflect the reported predominance of lesions in the gray matter of the hindbrain and spinal cord of horses with WNE with lesser involvement of the rostral brainstem and forebrain.[21]

The observation of coarse twitching of the muzzle (and to a lesser extent the eyelids) is a particularly distinctive finding in acute cases of WNE. Less frequently, there are fine fasciculations of the cutaneous muscles of the torso and neck. Horses acutely affected may be frantic, fearful, and hyperresponsive to stimuli. This stage is transient (usually <1 day in duration) and typically is the only behavioral change seen. Mild obtundation is common at initial presentation and progresses to stupor with narcoleptic episodes in horses with severe midbrain or hindbrain involvement. In addition, such cases often have facial and/or tongue paralysis or vestibular signs of head tilt and body lean. Ataxia and weakness of the trunk and limbs occur with or without signs of brain disease and may present asymmetrically. Such presentations are clinically indistinguishable from those of horses with equine protozoal myeloencephalitis. Because of the predilection of WNV for involvement of gray matter in thoracic spinal cord segments, horses may present with the unusual combination of acute-onset bilateral thoracic limb weakness/collapse and normal pelvic limb strength (Fig. 35-4). Severely affected horses are often unable to roll from lateral to sternal recumbency and tend to lie quietly without much voluntary activity. Comparable presentations in human patients with paralytic forms of WNE are described as "polio-like."[22] With time, muscles of the thoracic girdle can become severely atrophied and such horses are rendered permanently unable to move from lateral to sternal recumbency even though they may be able to walk once assisted to stand. The convalescent stage of WNE is described later in the Treatment section.

Published mortality rates during the U.S. epizootic have ranged from 22% to 44%. For 2326 reported cases from across the United States, including national statistics for the years 1999 to 2001, the overall mortality rate was 31%. Surprisingly, death rates have been relatively high (43%) for the 1050 cases reported from California during 2004 to 2006. A history of no or incomplete vaccination, persistent recumbency or difficulty standing, paresis of pelvic limbs, and facial or tongue paralysis was associated with poor outcome, and

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FIG. 35-4 West Nile encephalomyelitis in a 3-year-old Thoroughbred gelding with involvement of the gray matter of the spinal cord supplying the thoracic limbs. During the first 5 days after onset, the gelding frequently buckled in its thoracic limbs and collapsed into this position for several minutes before regaining his feet. Pelvic limb strength was normal.

mortality rose with increasing age greater than 5 years.[17,18,20] In one study, females were 2.9 times more likely to die than were males.[18]

Laboratory Findings Abnormalities found in hemograms and serum/plasma chemistry results are usually mild and nonspecific. Of 46 horses admitted to the University of Florida (UF) with acute WNE, the most common abnormalities were lymphopenia (23%), hyperbilirubinemia (72%), and high plasma creatinine concentration (8%).[17] Hypokalemia, hyponatremia, and hypochloremia were also commonly seen, as were high muscle enzyme activities secondary to trauma and prolonged recumbency.

Most affected horses have CSF pleocytosis. Of 30 samples collected in the University of Florida series, 22 (73%) were abnormal on the basis of high nucleated cell count and/or protein concentration.[23] Mild xanthochromia was also commonly seen. Mononuclear pleocytosis was found in 16 (53%), and high protein concentrations with normal nucleated cell counts were found in the other 6. Nucleated cell counts in abnormal samples ranged from 0 to 882 cells/μL (median 14 cells/μL), and protein concentrations ranged from 64 to 316 mg/dL (median 100 mg/dL). Cells were predominantly lymphocytes or macrophages with occasional neutrophils. Of 14 samples with pleocytosis (nucleated cell count >6 cells/μL) without significant red blood cell (RBC) contamination, neutrophil percentage ranged from 0 to 8% (median 2.5%) (Wamsley HL, personal communication, 2007). Interestingly, nucleated cell counts and protein concentrations were significantly higher in lumbosacral samples than in atlantooccipital samples.[23] The CSF analysis has not correlated well with the severity of the clinical presentation.

Diagnosis A presumptive diagnosis is often made clinically, especially in areas where the disease or virus is currently active. Diagnostic confidence is increased by the observation of muzzle twitching. The finding in a CSF sample of mild to moderate mononuclear pleocytosis with low numbers of neutrophils further supports a diagnosis of WNE. In a horse with signs of encephalomyelitis, presumptive diagnosis requires a positive serum MAC (IgM antibody capture)-ELISA test. Single-point assays of anti-WNV IgG such as the plaque-reduction neutralization test are not particularly useful because titers can be affected by prior vaccination; however, demonstration of a fourfold or greater rise in titer between acute and convalescent samples is supportive of the diagnosis in unvaccinated horses. It must be emphasized that serum antibody tests are diagnostic only of WNV infection, not WNE. For every case of WNE, approximately nine horses undergo non-neurologic or subclinical WNV infections.[1] The finding of WNV-specific IgM in CSF increases the specificity for WNE of a positive result.

At necropsy, polymerase chain reaction, immunohistochemical, and viral isolation methods are used to demonstrate presence of viral components in the CNS,[1] although immunohistochemistry for WNV is much less sensitive than it is for EEE.

Differential diagnoses for WNE in horses include alphaviral encephalomyelitis (eastern equine encephalitis, western equine encephalitis), rabies, verminous or bacterial meningoencephalomyelitis, equine protozoal myeloencephalitis, brain or spinal cord trauma, cervical stenotic vertebral myelopathy, hepatic encephalopathy, or compressive mass in the calvarium or vertebral canal.

Treatment There is no readily available antiviral treatment for horses with WNE. Ribavirin, a drug used to treat hepatitis C in humans, is effective against WNV in tissue culture, but its use has not yet been extensively evaluated in human patients with WNE. Type I interferons (i.e., interferon α or β) or interferon inducers stimulate nonselective cellular resistance to viral infection and are used for prevention or treatment of viral diseases. The limited data so far reported for the use of interferon in humans with WNE do not suggest any positive effect on outcome, although there is some anecdotal evidence to support this approach in horses. A reasonable dosage is 3 to 15×10^6 international units (IU) interferon β_{1a} IM or IV (Avonex 30 μg; Biogen IDEC, Cambridge, Mass.) given three times weekly. The concept of therapy with WNV-specific globulin is supported by findings in a guinea pig model of WNE, although no controlled studies of its use have been reported for horses. In a limited series of cases, there was a trend for less recumbency in horses given a hyperimmune globulin product but there was no significant effect on severity of clinical signs or mortality.[1] Several commercial products of this type are available for horses in the United States. These products are given slowly intravenously according to label instructions.

Supportive care is of paramount importance. Secure footing, deep dry bedding, protective covering of distal limbs and bony prominences, climate control, and provision of ample food and water are important in all cases. In recumbent horses, regular repositioning of the horse from one side to the other and attention to decubital injuries are essential. Early and systematic use of slinging is helpful in some otherwise recumbent horses. The Davis-Anderson sling, which transfers some of the horse's weight onto the upper limbs, is likely more effective in WNE horses than slings that rely entirely on torso support. In one series of 12 horses with prolonged recumbency that were treated by slinging, 2 were able to stand unassisted after slinging and 2 were able to stand after slinging was discontinued.[18] In horses that have long-term difficulty in rising to the standing position, semipermanent mobile slinging systems have been devised and marketed. These slings are stocklike frames that have wheels on each corner and webbing that rides under and supports the horse's torso.

Nonsteroidal and other antiinflammatory drugs are typically used empirically in horses with WNE to control local pain, inflammation, and fever. Flunixin, 1.1 mg/kg IV or PO (bid in U.S., sid in Europe); DMSO, 0.25 to 1 g/kg in a 10% solution IV or intragastrically bid; vitamin E, 20 IU/kg PO q24h; and pentoxifylline, 10 mg/kg PO bid are drugs commonly used for this purpose. The use of corticosteroids is controversial. Because there is at least a theoretical concern about recrudescence of WNV infection and clinical relapse in recovering immunosuppressed horses, corticosteroids should only be used in horses that are recumbent or in imminent danger of becoming so. A typical dosage regimen is dexamethasone 0.05 to 0.1 mg/kg IV or 0.1 to 0.2 mg/kg PO once or twice daily for 1 to 3 days. Affected horses are often treated for presumptive EPM with antiprotozoal drugs (e.g., ponazuril, 5 mg/kg PO q24h) until MAC-ELISA results become available.

Recovery, when it occurs, takes from 1 day to several months (mean of 22.3 days for 271 horses recovered from WNE in Nebraska and Colorado[18] and 10.7 days for 569 horses in North Dakota[20]) and is not always complete. Of 125 predominantly pleasure horses in Minnesota that survived WNE, 22 (17.6%) were classified by their owners as incompletely recovered 6 months after diagnosis.[24] Gait abnormalities, behavioral changes, muscle atrophy, and lethargy were among the residual abnormalities reported by the horses' owners. An

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additional 29 horses (23.2%) were considered fully recovered with residual deficits. A surprisingly high 9% of horses suffered some form of relapse of clinical signs 2 weeks to 5 months after diagnosis.

Necropsy Findings Gross abnormalities of the CNS in horses with WNE are limited to meningeal congestion and hemorrhagic foci in the brain and spinal cord. Histologically, there is mild to severe multifocal lymphocytic polioencephalomyelitis with predilection for the ventral and lateral horns of the thoracolumbar spinal cord.[25] In the brain there is lymphocytic perivascular cuffing and microgliosis in the medulla oblongata and pons and, to a lesser extent, in the basal nuclei, thalamus, and mesencephalon. In severe cases, there is evidence of neuronal degeneration characterized by central chromatolysis, cytoplasmic swelling, or cell shrinkage. The cerebral and cerebellar cortices usually are relatively free of lesions.

Control General mosquito control is important at the individual operation level. Local authorities may undertake area-wide mosquito abatement when sentinel chicken serology or viral isolations from wild birds suggest high local WNV activity.

A killed virus vaccine has been available since August 1, 2001, and has had full U.S. Food and Drug Administration approval since 2003. This vaccine is effective beginning about 2 weeks after the second dose of the initial series, but antibody levels drop substantially by 4 months after vaccination. Since then, two additional vaccine types have become available: a recombinant modified-live vaccine in a pigeon pox virus vector and a live chimera virus vaccine based on an attenuated yellow fever virus backbone. Two inactivated vaccines are now available in combinations with alphaviral encephalitis and tetanus vaccines. The live chimera vaccine was withdrawn in 2010 for safety reasons and an inactivated version is now offered. For all products the primary series or booster vaccination is completed at least 1 month before anticipated WNV activity, and boosters are given once or more annually, depending on the length of the vector season. Various challenge models have been used for each of these vaccines (except the killed version of the chimera vaccine) to demonstrate early protection against encephalitis and continuing protection against infection 12 months after a primary vaccination series. Foals of vaccinated mares should begin vaccination at 4 to 6 months of age and should have been given three inoculations by 12 months of age. Boosters should be given at least annually and more often in high-risk areas. Vaccine failures are more common in old horses. A deoxyribonucleic acid (DNA) vaccine against WNV was approved by the U.S. Department of Agriculture in July 2005, but thus far no product has been marketed.

Trauma to the Brain and Cranial Nerves

Robert J. MacKay

Because of their flighty temperaments, fast gaits, and relatively thin calvaria, horses suffer head trauma more often than do other livestock and have a higher rate of neurologic sequelae to such trauma. Head injuries to horses occur from blows to the frontal-parietal area from running into stationary objects or being kicked by other horses, as well as from impact to the occipital protuberance (poll) or temporal areas after flipping over backward during handling or restraint accidents.[1] Specific cranial nerves may also be injured on the outside of the skull by focal trauma. In the special case of temporohyoid osteoarthropathy, fractures of the petrosal bone can occur suddenly without any external trauma. Temporohyoid osteoarthropathy is covered in a separate section.

Frontal/Parietal Trauma

Blows to the front of the head over the dome of the calvarium directly injure the cerebral cortex adjacent to the point of impact.[2] Brain injuries are most severe when the overlying bone is fractured and pushed inward or if there is hemorrhage around or within the brain. Because of the violent distortions and movements of the cerebral hemispheres related to the impact, additional cortical injuries may occur diametrically opposite the point of collision (contrecoup) and caudally adjacent to the tentorium cerebelli. With the development of the secondary phase of cerebral injury and edema, the enlarging cerebral hemispheres herniate under the falx cerebri (asymmetric injury) and/or tentorium cerebelli to compress other parts of the brain. Horses may recover from the acute effects of calvarial fracture only to suffer recurrent seizures later. Horses that collide at speed with fixed objects are at risk for both head trauma and spinal cord injury.[3]

Impact to the Poll and Temporal Areas

When a horse flips over backward the point of contact is either the poll or the side of the skull.[4-13] Fifteen of thirty-four horses with neurologic signs due to head trauma were injured by flipping over backward.[14] Nine of these horses were younger than a year old. The force of impact is absorbed by the occipital protuberance and/or zygomatic arch and transmitted around the skull to the petrosal bones. Presumably because of the asymmetry of impact, only one side is usually injured. This may be either the upper or lower (i.e., impacted) side. There is hemorrhage into the middle and inner ear with or without fracture through the petrosal bone. The vestibulocochlear end organs in the inner ear are vulnerable to injury by both hemorrhage and the lacerating effects of fracture. In the latter case, the facial nerve may be damaged as it courses through the facial canal within the petrosal bone. When the point of impact is centered on the occipital protuberance, the basilar bones under the brainstem are subject to fracture and separation (Fig. 35-5). The basioccipital and basisphenoidal bones are pulled apart at their synchondrosis connection, at least in part by the strong distracting force of the rectus capitis ventralis muscles. Fragments of bone from the basisphenoid may be displaced ventrally and caudally by muscular attachments.[13] Because the synchondrosis is beneath the midbrain and flanked on each side by the foramina lacera and guttural pouches, basilar fractures are clinically serious. There may be life-threatening arterial hemorrhage between or into the guttural pouches; injury to cranial nerves IX (glossopharyngeal), X (vagus), XI (accessory), and the mandibular branch of V (trigeminal) as they pass through the foramen lacerum; and/or direct laceration and contusion of the midbrain and adjacent parts of the brainstem. Because the connection between the basilar bones ossifies and fuses by 2 to 5 years of age, this type of injury is probably more likely in young horses. In the most serious cases, fracture lines extend laterally and dorsally through the squamous temporal and occipital bones or rostrally through the sphenoidal bones (see next section).

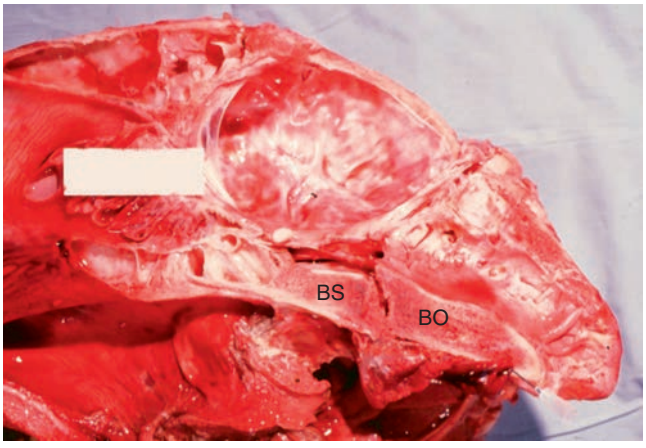


FIG. 35-5 Sagittal section of the skull of a 2-year-old colt that flipped backward during handling and suffered multiple skull fractures. Note separation/fracture in the region of the synchondrosis between the basioccipital *(BO)* and basisphenoid *(BS)* bones and hemorrhage in the region of the attachment of rectus capitis ventralis major.

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Other Cranial Nerve Injuries

The optic nerve(s) of one or both eyes can be stretched and damaged within the optic canals by the violent to-fro gyrations of the brain after impact to the head[11,15] and/or by fractures through the optic canals. Sphenoidal bone fractures also may involve cranial nerves III (oculomotor), IV (trochlear), and VI (abducens) or the ophthalmic and maxillary branches of V as they pass to the orbital foramen and foramen rotundum. Injury to the facial nerve proximal to the vertical ramus of the mandible causes full facial paresis. Proximal facial nerve trauma is usually caused by fractures of the petrosal bone, vertical ramus of the mandible, or stylohyoid bone or by fracture of the paracondylar process related to pulling back in a tied horse.[16] Distal facial nerve damage is usually due to direct injury from a blow or lateral recumbency or strangulation by a tight-fitting halter. Cattle whose heads are clamped in the head-catch on stanchions may present with "stanchion head" or ptosis and drooping ears caused by bilateral neurapraxia of the auriculopalpebral branches of the facial nerves. The nerve or its branches are often damaged as they cross the mandible and/or zygomatic arch. Facial paresis following recumbency during general anesthesia is common and usually involves only the nose and/or lips. When a horse pitches headfirst into the ground while traveling at speed, it is possible for components of a fractured atlas to be driven rostrally around the occipital condyles, where they may traumatize cranial nerve XII (hypoglossal) as it exits the hypoglossal foramen.

Skull fractures occur in cattle from blows to the top of the calvarium.[17] Most skull fractures are located in the center of the frontal bones, where the internal and external plates of the frontal sinus are fused into a single-layer dorsal wall of the cranial vault. This position can be located on the skull as the imaginary cross found by intersecting lines drawn between the medial canthus of the eye and the horn of the opposite side. Injuries in this area compress the frontal and parietal lobes of the cerebral cortex. The pressure changes result in loss of sensorium, sensory deficits, blindness contralaterally, or convulsions.

In young goats and horned sheep younger than 4 to 6 months of age, the calvarium can be inadvertently opened by removal of excessive bone during disbudding or dehorning. In goats, cerebrocortical burns can occur from overapplication of a hot iron or caustic dehorning paste. Cortical necrosis caused by bacterial infections after dehorning of calves has also been described.

Clinical Signs

Epistaxis is common after a blow to the head of sufficient severity to cause neurologic signs.[4,8] After frontal/parietal or poll trauma, blood may flow from either or both nostrils and is typically dark (venous) and of low to moderate volume. With poll trauma, epistaxis may be bilateral, copious, occasionally bright red, and may also issue from the mouth.[13] In such cases, the hemorrhage is from one (usually) or both guttural pouches and originates from adjacent veins and/or arteries.[18] If the tympanum is perforated, blood additionally may flow from the external ear. Profuse hemorrhage into the retropharyngeal area may cause obvious swelling behind the vertical ramus of the mandible and *inspiratory dyspnea,* which can be life threatening. Respiratory distress may also be associated with a poorly understood syndrome of noncardiogenic *pulmonary edema* that is reported to occur after serious head injury. Head trauma in humans is often complicated by *systemic arterial hypotension*. The cause is not completely understood but may be explained in part by *brain-heart syndrome* wherein myocardial damage is inflicted by the reflex actions of sympathetic nerves.

Immediately after impact to the frontal/parietal area, there is often a period of apparent concussion that may last minutes to hours. The most severely affected animals transiently lose all reflexes and are sometimes thought to be dead. Even after recovery of consciousness, such horses are typically obtunded for up to several hours. Altered behavior (i.e., dementia) is another characteristic of forebrain injury—there can be loss of affinity of a suckling foal for its dam; failure to respond to training cues; yawning; head pressing; compulsive walking, often in circles around the inside of an enclosure (usually toward the side of the injury); or, rarely, hyperexcitability or aggression. Because of damage to the visual centers in the occipital cortex, vision and *menace response(s)* may be impaired in the eye contralateral to the lesion; however, pupillary light reflexes should be intact. Injury to the somesthetic centers of the parietal cortex interferes with awareness of (and thus response to) touch on the opposite side of the head in a manner analogous to the way in which trauma can cause cortical blindness and abnormal menace response. This *perception of touch* is best evaluated by comparing the horse's reactions to tapping the nasal septal mucosa on either side. *Seizures* occurred in 7/34 cases of head trauma in one equine series.[14] These seizures are likely to be generalized, with loss of consciousness and uncontrolled autonomic activity (e.g., salivation, urination, defecation, pupillary dilatation, chewing movements) and abnormal motor function (e.g., muscular rigidity, followed by running and paddling movements of the limbs). In comatose horses with cerebral injury, the breathing pattern may be irregular with periods of either Cheyne-Stokes breathing or hyperventilation.

Fortunately, midbrain injury is a relatively uncommon but serious complication of head trauma of any type. It may occur immediately after the injury or be secondary to subtentorial herniation of forebrain components, rostral herniation of the cerebellum, or intraparenchymal bleeding. Because of involvement of the ascending reticular activating system (ARAS), affected horses are usually obtunded and may be comatose. Weakness of limbs is seen bilaterally or on the side opposite to an asymmetric midbrain lesion. In recumbent horses with severe midbrain injury, the neck, back, and limbs may be rigidly extended in a decorticate posture. If the nucleus of cranial nerve III (oculomotor) is involved, there is strabismus and a dilated, unresponsive pupil. With severe diffuse injury, bilateral pupillary miosis may be seen initially, followed by gradual progression to fixed, dilated pupils. Vision is normal unless there is involvement of other parts of the brain.

Vestibular dysfunction is seen commonly in horses after poll trauma or temporohyoid osteoarthropathy (THO). Clinical signs may arise because of injury centrally or, more commonly, because of involvement of the vestibular apparatus or vestibulocochlear nerve (VIII). With peripheral vestibular disease, there is head tilt, neck turn, body lean, and staggering in tight circles, all toward the side of the lesion. These signs can be revealed or exacerbated by blindfolding. With acute severe vestibular dysfunction secondary to THO, there may be sudden recumbency with flailing and thrashing movements. These signs of vestibular disease can easily be mistaken for seizures. The ipsilateral eye is usually rotated ventrally and laterally, especially when the horse's nose is elevated, and there may be horizontal or rotatory nystagmus, with the fast phase away from the side of the lesion. There may also be facial paralysis attributable to damage to cranial nerve VII as it passes close to the middle/inner ear. With central vestibular disease, signs are similar to those seen when the injury is peripheral; however, there will likely be additional signs suggestive of brainstem damage, including spontaneous vertical nystagmus, signs of other cranial nerve dysfunctions, obtundation, and limb ataxia and weakness. In horses, central lesions quite commonly result in a *paradoxical vestibular syndrome* in which the lesion (usually in the caudal cerebellar peduncle or the flocculonodular lobe of the cerebellum) is located on the side opposite to that which is expected from the clinical signs. An important clue to the presence of this syndrome is the finding of other signs of cranial nerve dysfunction (e.g., facial paralysis) on the side opposite to the direction of circling.

In horses with traumatic damage to the pons and medulla of the hindbrain, there is evidence of dysfunction of multiple cranial nerves in association with obtundation and limb ataxia/weakness. There may be reduced jaw tone or deviation of the jaw (Vm), reduced facial sensation (Vs), facial paralysis (VII), vestibular signs (VIII), dysphagia and respiratory stridor (IX and X), or tongue paralysis (XII). The gait may appear hypometric (spastic) like that seen in horses with compression of the cervical spinal cord. With severe hindbrain

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lesions, rapid deep breathing or other abnormal respiratory patterns are sometimes seen.

Signs of cerebellar injury occur rarely and are usually a result of poll trauma. Coarse head tremors are the most consistent sign; these are especially obvious during attempts to eat or suckle (intention tremor). The horse with cerebellar injury typically has a broad-based swaying stance, and limb movements may be spastic, clumsy, faltering, and jerky. Infrequent signs of cerebellar trauma include absent menace response(s) with normal vision and paradoxical vestibular syndrome (see earlier).

With traumatic optic neuropathy (usually after poll trauma), vision and pupillary light reflexes are impaired or absent and pupils are dilated immediately after the injury. Because the secondary phase of nerve injury continues for many hours after the initial trauma, visual function may progressively deteriorate during at least the first 24 hours post trauma. The signs of facial nerve injury depend on the site of damage. Complete unilateral facial paralysis is evident as deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelid, and ear. Reflexes involving cranial nerve VII such as the lip, eyelid, ear reflexes, and menace response are reduced or absent. Inability to close the eyelid causes minimal corneal problems unless there is also damage to the secretomotor fibers of the facial nerve at or proximal to the geniculate ganglion (keratitis sicca), in which case a deep horizontal corneal ulcer develops within hours of the injury. The tongue protrudes out of the paralyzed side of the mouth, often erroneously suggesting a problem with lingual function. Buccinator (cheek) paralysis causes a form of dysphagia, evident as dropping of and accumulation of feed between the teeth and cheeks (quidding). The peripheral parts of other cranial nerves are infrequently damaged with head trauma. The key to distinguishing central versus peripheral causes of neurologic deficits is that the former usually involve multiple cranial nerves and have additional features of obtundation, ataxia, and weakness that are not found with peripheral lesions.

Pathophysiology

Impact to the brain causes immediate damage to intracranial vasculature, neuronal cell bodies, axons, and glia.[19,20] Neuronal depolarization initiated at the site of impact may spread centrifugally throughout the cortex and cause the transient coma characteristic of severe concussion. In axons, a dramatic rise in intracellular calcium concentration activates processes that cause interruption of axoplasmic flow and result over hours to days in death of the distal axon. Diffuse axonal injury is thought to account for many of the permanent neurologic sequelae of head trauma. These early events constitute *primary* brain injury. Subsequent damage occurring during the response phase is termed *secondary* injury.

The surface and parenchyma of the brain may be lacerated by fracture fragments pushed inward from the calvarium. Significant bleeding at any site compresses the brain against the skull, thereby raising intracerebral pressure (ICP). Extravasated blood also elicits inflammatory responses in glial and other cells, initiating many of the autodestructive cascades that characterize the secondary phase of traumatic brain injury. Bleeding, ischemia, and mechanical damage to tissues evokes liberation and production of vasoactive and other mediators.[19,21] The production and action of damaging mediators is much affected by brain temperature—adverse effects are muted when there is hypothermia and are exacerbated by increased temperature.

Hemorrhage, increased permeability of damaged vasculature, and inflammatory edema all increase extravascular volume at the expense of brain volume. Exuberant swelling of the relatively mobile cerebral hemispheres may force portions under the falx cerebri (if asymmetric) or tentorium cerebelli.[19,20] In extreme cases, the pressure of subtentorial herniation in turn pushes the caudal cerebellum through the foramen magnum. The effects of reduced systemic blood pressure and increased ICP combine to choke off oxygen and glucose supply to cells and prevent removal of cellular metabolites such as lactic acid.[21] The consequent tissue hypoxia is more severe if there is also reduced blood oxygen content, as may occur after traumatic blood loss anemia or hypoxemia.

In the hypoxic environment of the traumatized brain, there is rapid depletion of neuronal adenosine triphosphate (ATP) and collapse of energy-dependent membrane homeostatic systems.[21] Calcium and sodium ions flux into cells in response to changes in membrane ion channel function associated with energy depletion, damage by ROS, and the actions of glutamate/aspartate. Brain damage that occurs during the primary traumatic event is irreversible; however, there is a window of minutes to days in which equally important secondary injuries theoretically can be prevented or treated.

Diagnosis

Changes in routine hemograms and chemistries are nonspecific. Collection of CSF from the atlantooccipital cistern is generally contraindicated in head trauma because of concern about inducing cerebellar herniation, but CSF can be collected via the lumbosacral space. Characteristic changes include yellow discoloration (xanthochromia), high RBC count, and protein with normal nucleated cell count.

Conventional diagnostic radiography is the best and most practical method for initial evaluation of skull trauma; however, radiographs significantly underestimate the extent of bony and soft tissue abnormality. Because the brain is not visible in plain radiographs, degrees of brain injury must be inferred from secondary changes in the skull. Fractures are visible as radiolucent lines within the calvarium, which may or may not be associated with normal suture lines. A step defect is visible when there is misalignment of the fracture fragments. Lateral views are most useful for detecting parietal/frontal and basilar fractures and for finding bone fragments originating from the basisphenoid or nuchal crest. On dorsoventral projections, a thickened stylohyoid or radiodense osseous bulla is most easily appreciated. Increased opacity of the affected bulla may reflect hemorrhage into the middle ear associated with petrosal bone injury or reactive thickening of the ventral bulla wall in cases of temporohyoid osteoarthropathy. Intracranial or spinal intrathecal gas shadows may be seen if there is a communication between the subarachnoid space and the skin surface, nasal cavity, paranasal sinuses, or middle ear. There may be radiographic evidence of bleeding into the paranasal sinuses, guttural pouches, or retropharyngeal area. In cases of frontal/parietal impact, it is also prudent to radiograph the cervical spine so as to detect fractures/dislocations caused by the axial compressive force of the original impact.

Computed tomography (CT) characteristics of brain trauma include change in ventricular size, shape, or position; deviation of the falx cerebri (falx shift); and focal change in brain opacity. Administration of iodinated contrast medium intravenously causes focal enhancement of areas of brain injury or hemorrhage. CT is particularly useful for identifying fractures of the bones that surround the caudal fossa—such fractures are often not well resolved by conventional radiography.[22] These include fractures of the petrosal bone, basilar and sphenoid bones, occipital condyles, and squamous temporal bone.[15] Blood in the middle ears, paranasal sinuses, guttural pouches, or retropharyngeal tissues and changes associated with temporohyoid osteoarthropathy are also easily seen. The principal disadvantage of CT in North America, apart from high cost and limited availability of necessary equipment, is the need for general anesthesia.

The main advantages of magnetic resonance imaging (MRI) over CT include lack of beam-hardening artifacts, ability to acquire images in any plane, and higher sensitivity for detection of early infarcts and edema. CT is more sensitive than MRI for detection of bony abnormalities, acute brain hemorrhage, and intracranial gas. The brain is not accessible to ultrasound imaging; however, the technique is sometimes useful for assessing fractures of the skull.

Clinical findings and historical information may form the sole bases for diagnosis in many cases.

Treatment

Relevant treatments for brain injury can be classified in two levels according to evidence-based support for their use. All applicable level 1 treatments should be used in every case of

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clinically apparent brain injury, whereas level 2 treatments are less clearly indicated and can be considered optional.

Level 1

TREAT OTHER INJURIES OR DISEASES. The normal principles of critical care medicine apply to the brain-injured patient—establish an airway, obtain vascular access, clean and dress wounds, stanch the bleeding, and sedate the horse if necessary and move to a cool, well-padded area. If necessary, a padded helmet can be used to minimize additional head trauma. A regimen of broad-spectrum antibiotics should be begun if there is an open wound or fracture.

TREAT HYPERTHERMIA. Hyperthermia after head trauma results from either a resetting of the hypothalamic temperature set point (fever) or excessive heat production in horses with normal set points. High brain temperature accelerates all of the destructive forces unleashed during the secondary phase of brain injury, so it must be detected and treated vigorously. Rectal temperature should be checked frequently, and efforts at cooling should begin when the temperature exceeds 101°F. In brief, ambient temperature can be reduced, the body can be clipped, ice water or isopropyl alcohol can be repeatedly applied to and removed from the skin (including the head), and overhead or box fans can be placed close by. Antipyretic medication (e.g., flunixin meglumine 1.1 mg/kg IV) is particularly useful when the horse has a fever but should be tried in all cases of hyperthermia. Nonsteroidal antiinflammatory drugs have the additional advantages of analgesic and antiinflammatory action.

PREVENT OR TREAT HYPOTENSION. Blood pressure must be at or close to normal to sustain adequate cerebral perfusion. The old notion that head trauma patients should be "kept a little dry" is no longer viable. Blood pressure should be monitored frequently, and heart base–adjusted systolic blood pressure should be maintained above 110 mm Hg.[23] Blood volume should be maintained or expanded by IV infusion of isotonic (Normosol-R; Plasmalyte-A; lactated Ringer solution) or hypertonic (hypersaline) crystalloid or colloid (plasma, hetastarch) solutions. Plasma possibly has additional useful effects including antioxidant and protease-inhibiting activities. In the case of significant blood loss, cross-matched whole blood is the fluid of choice. If volume resuscitation alone is inadequate to restore normal pressure, pressor/inotropic drugs may be used (e.g., dopamine, dobutamine, norepinephrine).[23] Remember that the effects of these drugs on cerebral vascular tone are difficult to predict.

OPTIMIZE OXYGEN CONTENT OF BLOOD. Oxygen is carried in blood either bound to hemoglobin (predominantly) or as free gas. Thus it is important that both hemoglobin concentration and Pa_{O_2} are at least in the normal range. Hypoxemia (arterial oxygen saturation <94% in this setting)[23] should be treated by establishing airway patency, treating underlying pulmonary disease (e.g., head trauma–associated noncardiogenic pulmonary edema), and beginning nasal or tracheal insufflation with oxygen. Foals may be intubated and manually or mechanically ventilated. At several equine hospitals, there are hyperbaric oxygen chambers that theoretically could be used to dramatically increase blood oxygen content in horses with brain injury. The efficacy and safety of this approach has not been established. Hemoglobin concentration must be kept above 7 g/dL (packed cell volume of 21%) and should probably be kept above 11 g/dL. Anemia can be treated with whole blood (preferable in the case of blood loss anemia) or packed RBCs.

ENSURE ADEQUATE PULMONARY VENTILATION. High P_{CO_2} has the potential to exacerbate CNS acidosis and cerebral edema. In foals, hypercapnia can be addressed by mechanical ventilation of the lungs. In all horses with head trauma, pulmonary ventilation must be optimized by ensuring a patent airway and treating lung disease. For example, acute pulmonary edema may be treated with furosemide (0.5 to 1 mg/kg IV q8h). Ventilation-induced hypocapnia has been advocated as a way to lower ICP[24]; however, low P_{CO_2} may cause reflex cerebral vasoconstriction and probably should not be used in foals with brain injury.

CONTROL PAIN. Alleviating pain in brain-injured horses is not only humane but also may reduce ICP.[25] A nonsteroidal antiinflammatory drug (e.g., flunixin meglumine, 1.1 mg/kg IV or PO bid) or opioid (e.g., morphine, 0.1 to 0.3 mg/kg IV or IM qid) can be used for this purpose. Useful analgesic effects have also been seen with constant-rate infusion of butorphanol or lidocaine.

REGULATE BLOOD GLUCOSE AND MAINTAIN NUTRITION. Experimental studies have shown that at least 140% of maintenance energy is expended by animals with severe brain injury.[26] Even during the first 24 hours after injury, nutrition (enteral or parenteral) probably should be provided to anorexic horses with head trauma. Blood glucose concentration ought to be kept greater than 80 mg/dL in order to provide adequate substrate for brain cells and less than 150 mg/dL so as to prevent hyperglycemia-induced exacerbation of CNS acidosis and apoptosis of brain cells. IV infusions of dextrose and regular insulin can be used as needed to maintain normal blood glucose concentration.

PREVENT OR TREAT BRAIN SWELLING. If possible, the neck should be free of constrictive wraps and only one jugular vein should be punctured or catheterized in order to prevent obstruction of venous flow from the head. Likewise, any recumbent horse should have its head elevated at least 10 degrees in order to facilitate blood flow. If the horse is significantly depressed (i.e., at least stuporous) or has signs of worsening brain function, a hyperosmolar infusion should be given to try to reduce the extravascular volume of the brain. The solution of choice is hypertonic saline (e.g., 1232 mmol Na/L), which is given as a continuous IV infusion of 1 mL (1.2 mmol)/kg/h for 6 hours and then 0.2 mL/kg for another 12 hours. Alternatively, boluses of 2 mL/kg can be given q4h for 5 infusions. Further treatment with hypertonic saline should be based on reassessment of clinical signs and plasma Na concentration (keep <150 mmol/L). Hypertonic saline has additional salutary actions including plasma volume expansion, antiinflammatory effect, and reduction of microvascular permeability. Mannitol (20% solution) can also be used for this purpose as a series of bolus infusions of 0.25 to 1 g/kg q4-6h. Craniectomy is not used yet for this purpose in horses, although the necessary surgical approaches have been described.[27]

TREAT SEIZURES. There is no justification for prophylactic antiseizure medication. Seizures should, however, be treated vigorously when they occur. They may be treated with diazepam phenobarbital or pentobarbital. Once a horse seizes for the first time, antiseizure medication (usually phenobarbital) should be continued for at least a week. If delirious thrashing or recurrent seizures remain a problem, the horse can be immobilized by continuous infusion of propofol or pentobarbital for up to 24 hours.

PERFORM EMERGENCY SKULL SURGERY. After initial stabilization of the patient, depressed fractures of the frontal/parietal area that impinge on the cerebral cortex may be carefully elevated and reduced under general anesthesia using techniques described in standard texts.[28-30] No surgical approach to basilar fractures has been described for the horse—such an approach would be extremely difficult and risky.

Level 2

Such treatments are supported by either strong anecdotal data from equine practice or convincing experimental data in other species. The downside of these treatments is that they do not meet the standard of evidence-based medicine.

TREAT WITH ANTIOXIDANTS. Oxidant damage is known to be an important part of the secondary phase of brain injury, yet clinical evidence supporting the therapeutic use of antioxidants is scant.

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Dimethyl sulfoxide (DMSO) is widely used by equine practitioners for treatment of CNS trauma (and almost everything else). The potential advantages of this drug's antioxidant and diuretic actions are obvious; however, there is virtually no evidence for effectiveness in the setting of brain injury. Common use suggests a protocol of 1 g/kg as a 10% solution in isotonic solution given IV or by NG tube q12h. Vitamin E (α-tocopherol, 50 IU/kg PO daily), vitamin C (ascorbic acid, 20 mg/kg PO daily), mannitol (see earlier), and allopurinol (5 mg/kg PO q12h) are all antioxidant therapies that can be used in the horse and can be rationalized as part of the overall approach to brain trauma.

GIVE CONVENTIONAL DOSES OF CORTICOSTEROIDS. High-dose steroids are harmful to humans with brain trauma[31] and should not be used in horses. Traditional antiinflammatory doses of dexamethasone (0.05 to 0.1 mg/kg IV or 0.1 to 0.2 mg/kg PO q12-24h) or prednisolone (1 to 4 mg/kg PO bid) likely inhibit production and action of injurious mediators in the brain and may be of some value.

GIVE MAGNESIUM SULFATE. Magnesium sulfate has the potential to inhibit several aspects of the secondary injury cascade including glutamate release, activity of the *N*-methyl-D-aspartate and calcium channels, and lipid peroxidation.[32] In light of these findings and its demonstrated safety in horses, it seems reasonable to give a single IV infusion of $MgSO_4$ at 50 mg/kg. This dose (25 g in a 500-kg horse) can be conveniently administered with the first 5 to 10 L of IV fluids.

Prognosis In one series, horses that had basilar fractures were 7.5 times more likely to die than those that did not.[14] Nevertheless, one horse with a basilar fracture returned to racing. Twenty-one of thirty-four horses survived to discharge. Most horses should recover completely, although residual vestibular and facial nerve signs are sometimes seen.

Facial nerve dysfunction due to neurapraxia should resolve over days to weeks. If there is morbid axonal injury (axonotmesis), the facial nerve may regrow via axonal sprouting along existing nerve sheaths. Regrowth of nerves occurs at a rate of about 1 cm per week, and reinnervation may continue for at least a year.

Traumatic Optic Nerve Blindness of Horses

Robert J. MacKay

Severe blunt trauma to the skull in horses may result in a rapid caudal displacement of the brain and avulsion or stretching of the peripheral optic nerves within the bony optic canals. Typical settings for such injuries are blows to the poll from flipping over backward and trauma to the frontal-parietal area from running into stationary objects such as posts or trees. The clinical signs include sudden blindness, loss of pupillary reflexes, and pupillary dilation. Ophthalmoscopic changes in the retina occur after 2 to 4 weeks and include pallor of the optic discs, reduction in the number and caliber of the retinal vessels, and linear peripapillary pigment disruptions (Fig. 35-6). The condition can be partial or complete, asymmetric or symmetric, and generally does not respond to treatment.[1,2] Because traumatic optic nerve injury likely progresses for many hours after the initial injury, there is a rationale for robust antiinflammatory treatment during the first 3 days after injury. This should include an NSAID such as flunixin meglumine at a dosage of 1.1 mg/kg q12-24h IV or PO and a corticosteroid such as dexamethasone, 0.05 to 1 mg/kg IV or IM sid or bid.

Thiamine Deficiency of Horses

Mary O. Smith

Horses may develop thiamine deficiency when fed diets that contain thiaminases. Common sources of thiaminases are bracken fern *(Pteridium aquilinum),* horsetails *(Equisetum arvense),* and amprolium (400 to 800 mg/kg). The clinical signs of thiamine deficiency are ataxia, conscious proprioceptive deficits, heart block, bradycardia, blindness, weight loss, dysuria, hypothermia of the extremities, and periodic muscular fasciculations. Terminally, affected horses develop convulsions. Electrolyte changes include hyperkalemia, hyperphosphatemia, hyperglycemia, and decreased glucose tolerance. Parenteral thiamine is effective treatment.[1,2]

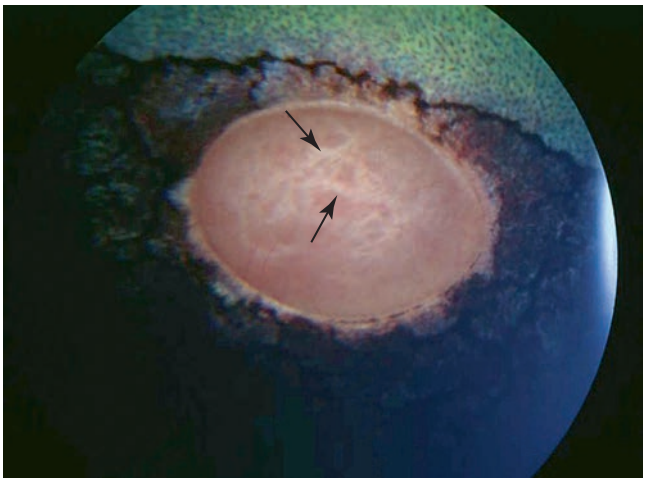


FIG. 35-6 Fundus of 4-month-old Thoroughbred colt that was blind as a result of severe bilateral nerve injury that occurred as a result of poll trauma 2 months earlier. Note absence of fundic blood vessels and exposure of the lattice-like lamina cribrosa *(arrows)* indicating demyelination.

Equine Leukoencephalomalacia

Robert J. MacKay

Equine leukoencephalomalacia (ELEM) is a fatal CNS intoxication of horses caused by ingestion of fumonisin toxins on corn or corn by-products.[1-3] Fumonisin toxins (B_1, B_2, and B_3), produced by the fungi *Fusarium verticillioides* and *F. proliferatum* (previously combined as *F. moniliforme*), interfere with sphingolipid metabolism, disrupting endothelial cell walls and basement membranes.[4] Although all three are toxic, B_1 is the most common and most thoroughly studied. See Chapter 54 for more details.

Clinical Signs The onset of ELEM is usually sudden. Previously healthy animals may be found dead, but most horses show abnormal neurologic signs for hours to days before death.[5,6] These include obtundation to the point of stupor and dementia manifested as compulsive walking in large circles, head pressing, and hyperesthesia. There is blindness and menace deficit, as well as reduced reaction to touch around the face. Movements of the muzzle, lips, and tongue may be weak and ineffectual. Signs are typically asymmetric. Muscle fasciculations occur over the neck and withers and in antigravity muscles, and limb ataxia and weakness are prominent terminally. Seizures are common after affected horses become recumbent, and animals often die while convulsing. The few horses that survive usually have permanent neurologic dysfunction. Hepatic involvement occurs in many cases, as evidenced by high serum liver enzymes, although hepatic failure is uncommon.[4,7] Signs of liver disease include icterus, petechiation on mucous membranes, and swelling of the muzzle or lips. Fatal outbreaks of liver disease without brain involvement have been reported.[4] Cardiovascular abnormalities are also described in horses with experimental ELEM and include decreased cardiac contractility, heart rate, arterial pulse pressure, and increased systemic vascular resistance.[8]

Fumonisin toxins cause a variety of clinical syndromes in other species including pulmonary edema in swine, but horses appear to

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be the most susceptible domestic animal species and can show signs when exposed to toxin concentrations as low as 5 to 10 ppm.[4] Regulatory guidance issued by the U.S. Food and Drug Administration calls for fumonisin (B_1+B_2+B_3) concentrations of no more than 5 ppm in horse feeds.

Clinical Pathology and Diagnosis ELEM has no unique findings on routine bloodwork. Serum liver enzymes (i.e., aspartate transaminase, γ-glutamyltransferase, and sorbitol dehydrogenase) and bilirubin are often high. Anemia, leukocytosis, and leukopenia all have been reported, but none is a consistent finding. Markedly high protein concentration (i.e., >100 mg/dL) with normal nucleated cell count typifies CSF analysis of affected horses.[9] High serum sphinganine, sphingosine, and sphinganine-to-sphingosine ratio suggest acute fumonisin toxicosis,[8] but these assays are only available at research laboratories. In practice, antemortem diagnosis relies on recognition and demonstration of fumonisin (B_1+B_2+B_3) concentrations greater than 10 ppm in feed. Fumonisin assays are widely available through diagnostic laboratories, and turnaround should be rapid.

Differential diagnoses include traumatic brain injury, the arboviral encephalitides, hepatic encephalopathy, equine protozoal myeloencephalitis, and botulism.

Epidemiology Leukoencephalomalacia occurs worldwide. Corn becomes contaminated during growth rather than in storage, and climatic factors that stress the plants, such as drought followed by high rainfall, contribute to the likelihood of mold development. The fungus is introduced into the growing corn by insects such as the western flower thrip, which enters the ear and damages the kernel as it feeds.[10] Most cases of equine disease occur during the winter and early spring.[1] Repeated exposure to the toxin, rather than a single large dose, seems to be associated with the development of clinical signs.[11] Experimental studies with infected corn demonstrated an onset of clinical signs on the ninth day after the beginning of the feeding period, but the reported delay between exposure and signs in outbreaks has ranged between 4 and 180 days. Older animals develop clinical signs of ELEM more rapidly than younger animals and thus appear to be more susceptible to the effects of the mycotoxin.

The rates of disease in exposed horses vary widely, from 14% to 100% in some reports; lethality is close to 100%.

Pathology The major pathologic features in the CNS result from the vascular damage caused by fumonisin toxins, including liquefactive necrosis and degeneration or malacia of the white matter of one or both cerebral hemispheres.[5,12] The size of the lesions may vary from grossly inapparent to complete subcortical cerebral necrosis. Flattening of the cortical gyri, enlargement of the cerebral cortex, vascular congestion, cortical softening, yellowish discoloration of the white matter, hemorrhage, and cavitation of the cerebral cortex may be present.[1] A gelatinous fluid can be seen in many of the cavitary lesions. Hemorrhage in the CNS has also been reported. Lesions in the visceral organs including hepatic congestion, centrilobular hepatic necrosis, hemorrhagic enteritis, and cystitis are found in some horses. The relationship between these lesions in the CNS and those in the liver, urinary bladder, and gastrointestinal (GI) tract is unknown.

Treatment Specific treatment is not available, and early euthanasia is usually the best option. Because there is cerebral edema, IV antiedema drugs including corticosteroids (e.g., dexamethasone 0.1 mg/kg daily), DMSO (1 g/kg as a 10% solution), hypertonic saline (4 mL/kg of 7.2% NaCl every 4 hours), or mannitol (1 g/kg as a 20% solution) can be rationalized. Nonsteroidal antiinflammatory drugs (e.g., flunixin meglumine 1.1 mg/kg PO or IV bid); antioxidants (DMSO, tocopherol, 20 IU/kg PO); ascorbic acid (25 mg/kg in IV fluids); and thiamine (5 mg/kg, slowly IV) can all be tried to limit secondary brain injury, but none of these treatments is likely to be effective.

Intracarotid Drug Injection

Robert J. MacKay • Mary O. Smith

Intracarotid drug injection is common in horses because the jugular vein and the common carotid artery are closely apposed in the caudal third of the neck. The condition is rarely seen in cattle because the omohyoideus muscle lies between the carotid artery and the jugular vein in the posterior part of the neck.[1] Hypertonic or caustic drugs including phenothiazine tranquilizers, chloramphenicol, chloral hydrate, barbiturate anesthetics, phenylbutazone, calcium gluconate, and sodium iodide cause cortical necrosis when injected into the carotid artery.[2-5]

The carotid artery provides blood supply to the circle of Willis via the internal carotid artery and thence to the thalamus and rostral and middle cerebrum. The internal carotid also provides arterial supply to the eyeball via the ophthalmic artery. By contrast, the blood supply to the caudal cerebrum, midbrain, pons, medulla, cerebellum, and inner ear is via the vertebrobasilar arteries and originates in the vertebral branches of the subclavian arteries. Thus the carotid artery injectate travels principally to the ipsilateral thalamus, cerebrum, and eye while relatively sparing the rest of the brain. The effect of the arrival in the forebrain of a bolus of irritant material is akin to a cerebral stroke of variable severity. There is intense vasospasm and physical endothelial damage with endothelial swelling, increased vascular permeability, mural necrosis, hemorrhage, intercellular edema, and thrombosis. As a result of ischemia there is glucose, oxygen, and energy starvation, progressing to Ca influx and anaerobic metabolism, and finally loss of function and accumulation of excitotoxic amino acids, free radicals, and eicosanoids. At necropsy, there is grossly evident ipsilateral brain swelling and hemorrhage.

When the drug is injected into the carotid artery, the animal recoils backward and falls over. Some horses strike or rear violently or run wildly, often in circles toward the injected side, without regard to obstacles. After falling, many horses convulse violently, whereas others become comatose without showing excessive motor activity. Severely affected animals may die after a variable period, but others regain their footing and recover completely. Milder and residual neurologic signs include contralateral (thalamic) or ipsilateral (retinal) blindness, contralateral facial hypalgesia, circling (toward the side of the injection), and contralateral conscious proprioceptive deficit.

If it can be done safely, seizing horses should be given IV antiseizure medications (diazepam, 0.2 to 1.0 mg/kg; pentobarbital, 2 to 10 mg/kg; xylazine, 0.2 to 1.1 mg/kg), which can be repeated as needed to control seizures. If possible, horses should be placed in a padded stall and treated with anti-inflammatories including dexamethasone (0.05 to 1 mg/kg IV or IM), flunixin (1.1 mg/kg PO or IV) or equivalent, and DMSO (1 g/kg IV as a 10% solution). The use of hypertonic antiedema drugs in this setting is controversial because of the possibility of active bleeding in the CNS and loss of the blood-brain barrier.

Intracarotid injection of drugs is best prevented by the use of large-bore needles or catheters for intravenous injections. In the horse, venipunctures should be performed in the anterior one third of the jugular furrow because the artery and vein are separated by the omohyoideus muscle in this area. The inexperienced phlebotomist may prefer to place the needle into the vessel without a syringe attached to confirm that the blood is dark and drips from the hub, indicating proper placement into the jugular vein. Conversely, intracarotid placement of the needle results in forceful, often pulsatile ejection of bright red arterial blood from the hub.

Brain Tumors

Mary O. Smith • Lisle W. George

Nervous system tumors of ruminants include medulloblastoma, ependymoblastoma, neurofibrosarcoma, angioblastoma, meningioma, meningeal hemangioma, neurofibroma, schwannoma, choroid

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plexus papilloma, pituitary adenocarcinoma, primitive neurectodermal tumor, and reticulosis.[1-5] CNS tumors of horses include pituitary adenomas, microgliomas, medulloepithelioma, choroid plexus papilloma, ependymoma, neurofibroma, meningioma, meningeal carcinoma, and reticulosis.[1,6-10] Secondary tumors that invade the CNS include melanoma, lymphosarcoma, adenocarcinoma, squamous cell carcinoma, hemangiosarcoma, and osteoma.[1,10-15] Of these, lymphosarcoma is most often encountered.[16,17] Metastatic invasion to the CNS occurs either by vascular routes or by extension along the peripheral nerve rootlets.[18] Local extension from adjacent tissue, such as the paranasal sinuses, can also occur.[11]

Clinical signs of brain tumors vary with the location and include abnormalities of gait (ataxia, paresis, hypometria/hypermetria); seizures; altered mentation (especially dullness); facial paresis or paralysis; facial anesthesia or analgesia; dysphagia; head tilt; strabismus; nystagmus; and loss of the menace reflex.[11,18-20] Migration of facial tumors (squamous cell carcinomas) into the cranial vault through the cranial nerve foramina may also result in facial swelling, exophthalmos, Horner syndrome, or asymmetric airflow through the nares.[17] Pituitary adenomas of aged horses (see Chapter 41) rarely cause neurologic disease, but they secrete melanocyte-stimulating hormone, which stimulates the adrenal cortex and causes Cushing disease. Some tumors are discovered as incidental findings at necropsy.

Antemortem diagnostic tests include radiographs of the skull (for tumors that spread locally and some metastatic tumors), and electroencephalography (EEG) to elucidate brain dysfunction.[11] Where available, CT or MRI can greatly facilitate diagnosis, but limited availability and considerations of cost restrict their use in most cases.[18,20-22]

Treatment of brain tumors in horses and livestock is generally not feasible because of limitations of cost, nursing care challenges after craniotomy, lack of access for large animals to radiation therapy, and considerations of safety for personnel handling animals with significant neurologic deficits. Palliative treatment such as corticosteroids may reduce clinical signs temporarily in some animals. Euthanasia is the choice for most large animals with brain tumors.

Cholinesteric Granuloma Encephalopathy

Robert J. MacKay • Mary O. Smith

Cholinesteric granulomas (CG) are found associated with the choroid plexuses of the fourth ventricles and lateral ventricles. Up to 20% of older horses have CGs in one or both lateral ventricles, usually without adverse effect.[1] CGs are thought to develop as a chronic inflammatory reaction to cholesterol released from extravasated degenerating RBCs within the choroid plexus. Syndromes of neurologic dysfunction in association with CGs have been described in horses from 7 to 23 years old.[2-5] The onset of signs is ascribed to combinations of attenuation and edema of cerebral tissue overlying a large CG, hydrocephalus secondary to obstruction by a CG of CSF efflux from the lateral ventricle through the foramen of Monro, and ependymitis/meningitis in response to proinflammatory substances released from CG.[2-5] In some cases there is a history of months to years of intermittent neurologic episodes presumably related to waxing and waning hydrocephalus and/or intermittent inflammation.

Signs can develop insidiously or present suddenly and are usually referable to forebrain dysfunction.[2,4] There may be dementia, manifested as irritability, aggression, yawning, head pressing, compulsive walking, drifting to one side when walking, circling, abnormal body posture, loss of learned skills, syncope-like attacks, seizures, blindness and menace deficit with normal pupillary light reflexes, and reduced response to tactile stimulation of the face.[2-5] With presumed CG-associated cerebral edema, signs suggestive of brainstem compression also have been described including stupor, limb weakness and ataxia, anisocoria, head tilt, stiffness at the walk, and facial paresis. Signs are typically asymmetric or unilateral, reflecting asymmetric involvement of the lateral ventricles.

CG should be suspected in any mature horse showing signs referable to waxing and waning forebrain dysfunction. Results of cerebrospinal fluid analysis may be normal, show high protein concentration with normal cell count, or show mild pleocytosis notable for the presence of nondegenerate neutrophils. The diagnosis is strongly supported by advanced imaging. CT in the standing[5] or anesthetized horse[2,3] is the diagnostic of choice, although MRI has also been used.[4] The finding by CT of heterodense, hyperattenuating, poorly contrast-enhancing masses in the lateral ventricles is tantamount to the diagnosis of CG. A technique for CG biopsy has been described and can be used to exclude the possibility of other choroid plexus tumors including papillomas and ependymomas.[3] At necropsy of clinically affected horses, CGs are found as brownish ellipsoid masses at least 3 cm in the smallest diameter attached to the choroid plexuses of one or both lateral ventricles. Histologically, these masses contain abundant cholesterol crystals interspersed with empty clefts, hemosiderin, and heavy infiltrations of macrophages and giant cells.

Traditionally, horses with CGs have been considered terminal and untreatable. It is clear, however, that all of the components of the pathophysiology of CG encephalopathy—namely, enlarging granulomas, hydrocephalus, and ependymal inflammation—are potentially treatable with antiinflammatory drugs. Horses with CG encephalopathy that were given antiinflammatory drugs, including dexamethasone, prednisolone, and phenylbutazone, have gained clinical remissions lasting from months to indefinitely. A reasonable treatment protocol includes seizure control as needed, induction of remission from clinical signs with dexamethasone (0.05 mg/kg IV or 0.1 mg/kg PO, once daily for 7 to 14 days), followed, if successful, by prednisolone, 1 mg/kg PO bid, to be given indefinitely except for intermittent trials designed to test the effect of tapering the dose. Hyperosmolar IV solutions (mannitol, 0.5 to 2.0 g/kg as a 22% solution; 7.2% saline, 1 to 2 mL/kg) can be given acutely to address cerebral edema and repeated as needed every 4 to 6 hours for the first 24 hours. More aggressive interventions including direct drainage of CSF from enlarged lateral ventricles and surgical removal of CG using techniques adapted from human brain surgery are also possible but not described. The prognosis for short- to medium-term (i.e., up to a year) maintenance of remission of clinical signs of CG encephalopathy should be regarded as fair.

Epilepsy

Robert J. MacKay

Epilepsy is defined as a persistent predisposition of an animal to repetitive seizures that has resulted in seizures on at least two different occasions.[1,2] For this purpose, a cluster of seizures occurring over hours to days is classified as a single seizure. Epilepsy may be primary or secondary. *Primary* epilepsy (also known as *idiopathic* or *true epilepsy*) occurs because of known or suspected genetic predisposition. This diagnosis is rare in large animals, but a few heritable epilepsy syndromes have been described including juvenile idiopathic epilepsy of Arabian foals of Egyptian lineage,[3] Arabian lavender foal syndrome,[4] and suspected familial epilepsy in cattle of various breeds.[5,6] *Secondary* epilepsy occurs as a result of known or suspected underlying brain dysfunction, termed *symptomatic* and *cryptogenic,* respectively. A systemic condition or chemical/drug may cause a normal brain to generate *reactive* seizures; however, these are not classified as epilepsy. Nevertheless, anything that lowers seizure thresholds including the use of epileptogenic drugs such as macrocyclic lactone anthelmintics (e.g., ivermectin) or the occurrence of estrus in females may compromise management of epilepsy.[2]

Seizure activity results from abnormal, synchronous, electrical discharges in the neurons of the forebrain that spread to the somatic and visceral motor areas to initiate spontaneous, paroxysmal, involuntary movements that may begin and end spontaneously. Each seizure (ictus) may be *generalized,* involving the entire cortex and resulting in generalized bilateral motor activity over the whole body, or *partial,* involving a focal cortical region with localized motor signs

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or sensations. Partial seizures may become generalized. Generalized seizures usually begin with tonic muscle contractions of the muscles of the neck and limbs but progress to rhythmic clonic limb thrashing, often accompanied by abnormal eye positions and movements. Affected animals usually fall and display various autonomic signs, such as salivation, urination, and defecation. Partial seizures begin as involuntary tonic or clonic contractions of groups of facial, jaw, or body muscles. These signs may stop spontaneously without progression but more typically spread from their initial focus to involve the whole body. Seizures may be preceded by an aura of up to several hours' duration, usually characterized by signs of restlessness or disorientation, and be followed by a period of stupor, restlessness, and central blindness that is usually short-lived but can last several days in foals.

Recurrent seizures in large animals are usually classified as secondary epilepsy with the majority of these of the cryptogenic type.[1] As diagnostic techniques improve, a higher proportion of such cases will be classified as symptomatic. In the horses of a recently published case series, epilepsy manifested in approximately equal numbers as either partial or generalized seizures.[1] Diagnoses in cases of symptomatic epilepsy in this series included intracranial neoplasia, cholesterol granuloma, congenital structural abnormalities of the brain, degenerative processes (white matter cavitation and focal neuronal dysplasia), and equine protozoal myeloencephalitis.

In large animals, the best characterized primary epilepsy syndrome is *juvenile idiopathic epilepsy* of Arabians of Egyptian lineage.[3] Seizures usually begin in foals by 2 months of age (range 2 days to 6 months), although onset as late as 18 months has been described. Seizures are usually symmetric and generalized, often with no preictus. After a brief period of whole-body myotonus and collapse into lateral recumbency, there are clonic ("galloping") limb movements, opisthotonos, sweating, retracted lips, and staring, unblinking eyes. Each seizure can last up to 5 minutes but typically is less than a minute. Postictal signs are usually profound and persistent and are often the first abnormality detected by the owner. There is obtundation, cortical blindness, loss of maternal bond and interest in suckling, and other variable behavioral signs. Blindness, the last sign to resolve, typically lasts several days (range: hours to 2 weeks). Injuries, especially to the skull, may occur during seizures or as a result of collisions during the period of blindness. Juvenile epilepsy responds well to anticonvulsant therapy and does not usually recur (see treatment section later). Untreated foals also may grow out of the condition by a year of age but are subject to cumulative seizure-associated injury and there are anecdotal reports of permanent behavioral abnormalities in untreated horses.

A diagnosis of epilepsy is supported by the finding of epileptiform discharges in interictal electroencephalograms (EEG), although this procedure does not appear to be highly sensitive.[7] Epileptiform discharges were identified in EEGs of only 9/13 foals with juvenile idiopathic epilepsy.[3] Artifacts induced by patient movement or sedative drugs limit the usefulness of traditional EEG in large animals. It has been suggested that ambulatory EEG recording, as is routinely used in human neurology, may be a more sensitive and reliable method for investigating suspected seizures in large animal patients.[7] In food animals, evaluation of seizure disorders may be performed using evocative drug challenges with pentylenetetrazol, ketamine, or other seizure-inducing agents and established techniques, but care must be taken to prevent injury to the animal.[8,9]

Specific drug therapies have not been established for most large animal species. However, most seizures are controlled acutely with diazepam (0.05 to 0.2 mg/kg IV) and long term with oral or IV phenobarbital (see following section). A simple approach to treatment of epileptic horses has been described and can be followed in other species.[2] This protocol is based on the use of oral phenobarbital at 5 mg/kg once daily, begun without a loading dose. Treatment at this dose is continued for at least 2 weeks. If signs are insufficiently controlled, the dose rate is increased by 1 mg/kg and continued for another 2 weeks. This cycle of incremental dosage increase is continued until adequate control is achieved or side-effects prevent further increase. Potassium bromide (90 mg/kg once daily PO, optionally after a loading course of 120 mg/kg/day for 1 week) can be added to phenobarbital in these cases to provide additional anticonvulsant effect. Therapeutic trough concentration of phenobarbital is 15 to 40 µg/mL. After 6 months of seizure-free therapy, the dose of phenobarbital can be tapered in increments of 1 mg/kg every 2 weeks. If the animal remains seizure-free for 6 months after anticonvulsants have been discontinued, the horse is considered by some to be no longer epileptic; however, it is prudent to continue to advise owners that such horses should never be ridden or used for sporting purposes. Foals with juvenile idiopathic epilepsy are usually given phenobarbital twice daily at 5 mg/kg, and tapering can be begun after 3 months of seizure-free treatment. All ruminants experiencing seizures should also immediately be treated with thiamine (10 to 20 mg/kg IV, IM, or subcutaneously [SC]).

Narcolepsy-Cataplexy

Robert J. MacKay

Definition and Etiology Narcolepsy is a CNS disorder characterized by excessive sleepiness, episodes of muscular weakness (cataplexy), and rapid eye movement (REM)-onset sleep.[1,2] The disorder is defined as an abnormal tendency to transition from wakefulness into REM sleep. Attacks of narcolepsy and cataplexy are considered a paradoxic form of sleep because the EEG is characteristic of an alert, awake animal, but the REM is characteristic of deep sleep.

Sleep-wake regulation is normally achieved through reciprocal interplay of consciousness-arousing and consciousness-depressing regions of the brain.[3] Included in the arousal system are cholinergic and monoaminergic (histaminergic, serotonergic, dopaminergic, and noradrenergic) neurons located in the caudal hypothalamus/brainstem regions that diffusely project to the forebrain to upregulate cortical function. Conversely, gamma-aminobutyric acid (GABA)-ergic neurons of the rostral hypothalamus play a critical role in sleep by inhibiting neurons of the arousal system. Recently, it has been shown that the novel neuropeptides, hypocretins 1 and 2 (also known as *orexins A* and *B*), produced exclusively by neurons in the lateral hypothalamus, are critically involved in the neuronal circuitry regulating sleep/wake states. Via numerous afferent connections, hypocretin neurons sense the body's external and internal environments and regulate wakefulness accordingly, mostly via stimulation of consciousness-arousing monoaminergic neurons. Multiple lines of evidence suggest that sporadic narcolepsy in humans is caused by a dysfunctional hypocretin system, usually as a result of degeneration of hypocretin neurons. Some familial cases are associated with nonfunctional hypocretin receptors. With removal of hypocretin neuronal function, monoaminergic and GABAergic neurons set up a poorly regulated mutually inhibitory circuit, resulting in unwanted and abrupt transitions between wakefulness and sleep recognizable clinically as narcolepsy and cataplexy.[3]

Narcolepsy has been reported in numerous horse and pony breeds, a Suffolk lamb, Spanish fighting bulls, a Guernsey bull, and a Brahman bull.[4-13] Most cases appear to be sporadic, but early-onset, probably familial occurrence has been reported in American Miniature Horse, Lipizzaner, Suffolk, Shetland pony, and Fell pony foals[2,4] and has been seen by the author in a family of Morgan horses. The collapse syndrome associated with squeezing neonatal foals traditionally has been viewed as a transient form of narcolepsy; however, a recent study found that the associated EEG patterns were slow waves consistent with non-REM sleep and thus were not narcolepsy.[14]

Clinical Signs The clinical signs of narcolepsy include staggering, lowered head and neck, buckling of the thoracic limbs, kneeling posture, flaccidity of the lips, closure of the eyes, loss of the menace reflex, stertorous breathing, and ataxia. During severe narcoleptic attacks the animal collapses into lateral recumbency and appears

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comatose. Only rarely is REM sleep observed after collapse. The sensorium returns to normal after seconds to minutes. In the periods between attacks, the animal appears normal, although repeated attacks result in trauma to the dorsal aspects of the fetlocks and the knees and to the face.[1,2] Cataplexy, a sudden episode of paralysis of the voluntary muscles, may be induced by strong emotions (usually positive) in the patient and can range from atonic, areflexic paralysis of all skeletal muscles, except those of the diaphragm and eyes, to slight transient buckling of the limbs without collapse into recumbency. Episodes of cataplexy last seconds to minutes. Environmental factors that can stimulate cataplectic attacks include active restraint, suckling, feeding, changing the stall environment, grooming, or cross-tie–related activities of horses like saddling, removal of tack, and washing. Despite this association, narcolepsy in adult horses usually occurs while horses are in stalls or at pasture without any obvious prior stimulation.[1] Most cases of narcolepsy in humans are associated with cataplexy, but sleep attacks without cataplexy also occur. Mild cataplexy and attacks of excessive sleepiness can be difficult to distinguish in adult large animals in that both may cause blank facial expression, hanging of the head and neck, and buckling of the limbs with or without collapse into recumbency.[1] Sudden arousal associated with the stimulation of collapse and ground impact also could terminate either type of episode. In light of diagnostic ambiguities based on observations of mild sleep attacks, cataplexy that persists after collapse is the most frequently recognized manifestation of sleep disorders in large animals.

Signs are generally stable and lifelong. The cataplexy component of juvenile cases usually improves as the animal gets older but rarely completely resolves.

Diagnosis Strict EEG criteria, including the early onset of waveforms typical of REM at the beginning instead of the middle of a sleep cycle, are in place for confirming the diagnosis and for distinguishing narcolepsy from narcolepsy without cataplexy. The EEG changes of narcolepsy and cataplexy have been reported in a Brahman bull.[5] The waveforms vary between low-voltage high-frequency (LVHF) and high-voltage low-frequency (HVLF) patterns, with LVHF corresponding to the actual period of narcoleptic attack. In horses, EEG waveforms may be normal or may reveal fast waves typical of REM activity.[1] Hypocretin concentrations in CSF are typically low in humans and dogs with sporadic narcolepsy but normal in familial forms associated with mutations in the genes for hypocretin receptors.[15,16] In CSF from a narcoleptic Icelandic foal, immunoreactive hypocretin concentration was comparable with those from two control horses.[17] It will be important to evaluate this diagnostic in both juvenile and adult-onset forms of the disease in large animals.

It is reported that cataplexy can be induced by IV administration of the centrally acting cholinesterase inhibitor physostigmine salicylate (0.05 to 0.1 mg/kg),[6] but attacks cannot be evoked in all animals. In one series of narcoleptic horses challenged, only 1/10 horses had a positive response.[11] Signs of narcolepsy can be reversed for at least 24 hours by atropine sulfate (0.02 to 0.1 mg/kg IV once).[11,17] Diagnostic drugs must be used with caution because of the possibility of inducing colic, especially in horses.

Syncope and seizures are important differentials for narcolepsy. In general, syncope is characterized by acute collapse without warning and, unlike narcolepsy, is not preceded by a gradual lowering of the head and drowsiness. Increased focal or generalized tonic-clonic muscle activity and postictal depression are typically seen with seizures, but not in animals with narcolepsy. In addition, excessive sleepiness can be seen in horses that have an underlying painful physical condition, environment, or social position that prevents them from lying down to sleep. Therefore a complete history and thorough physical examination are essential.

Treatment and Prevention The tricyclic antidepressant imipramine (0.5 to 1 mg/kg PO bid to qid) can be used to treat cataplexy but is ineffective in treatment of the sleepiness component of narcolepsy. This drug must be used with caution, and oral dosages in horses should not exceed 2 mg/kg.[8] Results of oral imipramine therapy are inconsistent; duration of effect is about 5 hours. Anecdotally, tyrosine has been of benefit in some, but not all, narcoleptic horses. Its presumed mode of action is by increasing dopamine neurotransmitter concentrations.[1]

Selective serotonin reuptake inhibitors are also used in humans for treatment of cataplexy but have not been evaluated in large animals for this purpose.[18] Sodium oxybate (the sodium salt of gammahydroxybutyrate) is widely used as a wakefulness-promoting drug in narcoleptic humans and may apply to the treatment of veterinary patients.[18]

Headshaking in Horses

Robert J. MacKay

Headshaking in the horse is an important cause of wastage among otherwise normal riding or driving horses. There is no obvious predilection for age, breed, or gender. Surveys have usually found more than 50% of headshakers are geldings, and mean ages for published series are from 7.3 to 12.8 years (range 1 to 28 years).[1,2] Most headshakers are either used for pleasure riding, dressage, or show jumping, but horses of any breed or discipline can be affected.[3,4] Signs of headshaking usually first occur while the horse is being ridden or driven (i.e., with the horse in a bit and bridle) and become more pronounced over time, both in severity and duration of headshaking episodes.[1] The condition usually renders a horse unsafe or at least unsatisfactory for riding and in severe cases may cause inhumane suffering to the affected horse. Once established, the condition occurs during any form of exercise and about 60% of affected horses eventually also headshake at rest.[1,3] Additional trigger factors that exacerbate or provoke headshaking have been identified. These include bright light, sun, heat, cold, stress, extreme neck flexion, riding on narrow roads, hearing people's voices, or riding near trees or water.[5] On average, approximately one half of cases from multiple series[5] are either partially or completely seasonal with signs beginning suddenly or getting worse in spring and ending in the late summer or fall.[1,6] Signs may stop for weeks only to recur for no apparent reason.

Headshaking is classified as either *symptomatic* or *idiopathic*. The former have an identifiable physical cause that, if removed, permanently resolves the problem. The remaining cases either have no discernable basis or continue after removal of a putative cause. Reported or postulated symptomatic causes have included skull lesions,[7] allergic rhinitis, vasomotor rhinitis, otitis externa or media/interna, *Trombicula autumnalis* (harvest mite) infection, fungal sinusitis,[8] temporohyoid osteoarthropathy, mites or ticks in the external ear canals, guttural pouch mycosis, *Onchocerca* dermatitis, dental problems, cervical arthritis, and ocular lesions including cystic corpora nigricans, "floaters" in the anterior chamber, and blocked lacrimal ducts.[9] Because horses are normally programmed for headshaking as, for example, for fly avoidance,[10] almost any unpleasant condition around the head (or possibly elsewhere on the body) seems to have the potential to amplify the behavior to abnormal levels. Despite the seemingly impressive (and incomplete) list of potential causes given earlier, no physical basis for headshaking was found in 89 of a series of 100 reported cases.[1] Headshaking does not appear to be associated with latent equine herpesvirus 1 infection.[11]

Headshaking may be defined as involuntary sudden violent repetitive movements of the head, either dorsally and ventrally in the median plane (most common), horizontally, and/or in a rotatory manner. Other signs, particularly in horses with idiopathic headshaking, have included snorting, sneezing, snoring breath sounds, rubbing the face on stationary objects, keeping the head low while trotting or even rubbing the nose along the ground, acting as if a bee has flown up the nose, excessive nasal and lacrimal discharge, hyperesthesia/hyperresponsiveness around the face, anxiety and agitation, hopping off the ground in one or both thoracic limbs, head pressing, shade-seeking, muscle fasciculations, sweating, and striking

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at the nose. Many of these signs seem directed by the horse toward noxious sensations coming from the nose or face. Anesthesia of the infraorbital nerves at the infraorbital foramina prevented headshaking in 3 of 19 horses,[12] whereas 24 of 27 horses stopped headshaking when the posterior ethmoidal nerves (branches of the ophthalmic nerves) were blocked.[13] The latter technique may also block the proximal aspect of the infraorbital nerve and even the maxillary nerve.[14] These results indicate that idiopathic headshaking is set off in the caudal parts of the nasal passages in most horses. Some cases of headshaking are almost entirely induced by bright light and appear to represent optic-trigeminal summation of stimuli arriving via both nerves.[2] It is not yet known how these clear-cut cases of *photic* headshaking relate to the much larger number of cases wherein light is not directly involved or is only a weak trigger factor. It may be that photoperiod (i.e., the proportion of the day that is light) is more important than light intensity in such horses and may explain the role of season in many cases.[2] Whatever the inciting cause, idiopathic headshaking appears to be a nasal/facial pain syndrome associated with hyperactivity of trigeminal pain pathways.[13] In humans trigeminal neuralgia is often caused by vascular impingement on the trigeminal ganglion or nerve adjacent to the brainstem. Such a possibility has not yet been investigated in equine headshakers.

Examination of horses with headshaking includes a complete physical examination; ophthalmic, otoscopic, neurologic, and dental examinations; endoscopic examination of nasal passages, pharynx, and guttural pouches; radiography of the skull, and a complete blood count and chemistry panel. When available, CT is the preferred imaging technique. No abnormalities are usually noted in these examinations.[15]

Treatment

PHYSICAL. Mild cases of headshaking can often be partially suppressed by the use of a muzzle net. About 30% of horses treated this way improved at least 70%, although the durability of any salutary effect has not been established.[16] There was no difference in the effectiveness of full face versus nasal nets. A number of organizations and jurisdictions now allow horses to be shown wearing a muzzle net. A few horses respond to a heavy hair net or a dangling device that makes contact with the nose area or upper forehead. This type of contact may prevent the nerve from firing, similar to blocking a sneeze by placing a finger under the nose and applying pressure.[15] Facemasks and contact lenses that substantially reduce ambient light are available and are very effective in preventing photic headshaking.[2] An argument has been made that bitless bridles may be helpful if there are headshaking trigger points related to the action of the bit.[17] These devices have not found wide application.[5]

SURGICAL. Surgical approaches to headshaking are controversial because considerable morbidity and even severe suffering are frequent side effects of the procedures.[5] Notwithstanding these problems, surgery does appear to achieve a permanent cure in some horses.[12-14,18] The objective of surgery is interruption of pain pathways in the trigeminal nerve or its branches. Two approaches have been used—infraorbital neurectomy and caudal infraorbital nerve compression. In the first procedure, a 2-cm section of nerve is removed just rostral to the infraorbital foramen.[12,18] To effect nerve compression, up to eight platinum embolization coils are introduced via the infraorbital foramen and packed around the infraorbital nerve within the caudal aspect of the infraorbital canal.[13,14] Five of twenty-six (19%)[12,18] and 26 of 57 (46%)[13] horses had long-term elimination of headshaking after infraorbital neurectomy and caudal compression, respectively. Additional horses had temporary remission of headshaking only to relapse weeks to months after surgery. Further long-term remissions were achieved when the procedure was repeated in some of the relapsed horses.[13,18] Exacerbation of headshaking and self-inflicted trauma around the muzzle and lips were problems in most horses after these procedures. These complications typically resolved within weeks but were persistent in some; four of these horses were euthanized because of the severity of signs. The results of nerve blocks did not completely predict response to surgeries; however, two of three horses that responded to infraorbital blocks achieved complete remission with infraorbital neurectomy.[12] Tracheostomy has been shown to be effective as a salvage procedure, presumably by bypassing the passage of air through the nasal passages.[5]

MEDICAL. It is unlikely that complete and permanent remission can be achieved medically. Cyproheptadine, 0.3 mg/kg PO twice daily, has been used with some success for photic headshaking[2] and with limited success in other cases of idiopathic headshaking.[3,12,19] Mild lethargy and colic are occasional side effects. Headshaking can be suppressed for variable periods by the potent analgesic antiseizure drugs carbamazepine and gabapentin, but effects are often not complete and signs return within several weeks of beginning treatment.[5,20] Cyproheptadine may potentiate the analgesic actions of carbamazepine. In one horse persistent 95% remission was obtained by the CT-guided injection of glycerol into the trigeminal ganglia.[21] Individual horses are reported to have responded to corticosteroids or antihistamines, perhaps indicating a role for allergic rhinitis in those few cases.[1,12] Nonsteroidal antiinflammatory drugs have not been effective. Melatonin is advocated as a way to suppress the neurologic responses to increasing photoperiod (i.e., seasonal effect), so it should be started before the anticipated seasonal onset of headshaking.[2] This has reportedly been effective in a few cases. A variety of other supplements and traditional or alternative products have anecdotal or conceptual support with (as yet) no evidence. At least most of them are inexpensive and nontoxic at recommended doses. There are protocols for chiropractic therapy and acupuncture for headshaking. These have not been successful in the author's experience.

Maedi-Visna Virus Infection (Ovine Progressive Pneumonia Virus Infection; Zwoegerziekte)

Mary O. Smith • David C. Van Metre • Lisle W. George

Definition and Etiology Maedi-visna virus, or ovine progressive pneumonia virus (OPPV), infection is a chronic disease of sheep caused by a retrovirus (subfamily Lentivirinae).[1-4] Visna virus is closely related to the many lentiviruses that cause immunodeficiency and neurologic disease in other species; these viruses include equine arteritis virus, caprine arthritis-encephalitis virus, and simian, feline, and human immunodeficiency viruses.[5] Caprine and ovine lentiviruses constitute a single virus group, termed the *small ruminant lentiviruses* (SRLVs), which can readily cross between species.[6-8] These agents are enveloped RNA viruses.[9] The respiratory aspects of the viral infection are discussed in Chapter 31.

Clinical Signs Neurologic disease caused by maedi-visna virus is relatively rare. Adult sheep and lambs as young as 4 months of age can be affected.[10] Nervous system signs may be characteristic of a diffuse encephalitis and include ataxia, twitching of the facial muscles, conscious proprioceptive deficits, normal gait along a straight path, staggering or stumbling when turned or forced to perform a complex maneuver, circling, and blindness. Coma, convulsions, and hyperexcitability may be seen in terminal stages. Other sheep have gradually progressive limb weakness and ataxia, often worse in the rear limbs; neurologic dysfunction localized to the spinal cord may be the sole clinical manifestation of maedi-visna.[11] Some sheep merely show emaciation without neurologic signs. Others may show nonsuppurative, progressive arthritis of one or more joints or symmetric enlargement of the mammary gland. The time between the onset of clinical signs and death is highly variable but can be as long as 1 to 2 years. The presence of antibody in the serum is usually considered evidence of active infection.[12,13]

Clinical Pathology The CSF of affected animals is characterized by pleocytosis, with the cell counts per deciliter ranging from 1012 to 1478 for animals infected for 1 month and 4 years,

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respectively.[14] The protein concentrations of CSF range from 50 to 100 mg/dL for 30 days after infection. Antiviral antibody and virus can be detected in CSF specimens.

Pathophysiology The lesions of maedi-visna virus infection are partly induced by the host's inflammatory response. Experimental immunosuppression of infected sheep ameliorates the severity of the clinical signs and reduces the CNS lesions without altering the amount of viral shedding.[15,16] The maedi-visna virus is immunosuppressive, and infections may lead to a variety of secondary bacterial infections.[17] Chronic viremia is typical.

Pathology Gross lesions of visna infection are seen only rarely, when inflammation and malacia are extensive. In such cases, areas of yellowish tan discoloration are present in white matter.[18] The microscopic lesions of visna are predominantly those of a diffuse, nonsuppurative, perivascular inflammation throughout the neuraxis, with white matter affected more severely than gray matter. The lesions include demyelination, gliosis, lymphocytic choriomeningitis, and focal necrotic areas that are infiltrated by macrophages.[19,20]

After exposure to the virus, sheep develop an asymptomatic infection for as long as 6 weeks. Replication of the virus occurs in circulating cells during this stage of the infection.[21] Once the disease has been recognized, the affected sheep should be culled or slaughtered. Control measures are discussed in Chapter 31.

Diagnosis and Epidemiology Spread of maedi-visna virus occurs through ingestion of infected milk by neonates, through in utero transmission, and horizontally within a herd.

The diagnosis of visna infection is made initially by recognition of the clinical neurologic disease in groups of animals in which the pulmonary, joint, or mammary form of the disease is also present. Agar gel immunodiffusion (AGID) testing has been superseded by more accurate ELISA and PCR tests.[22] The diagnosis and epidemiology of maedi-visna virus infection are discussed in detail in Chapter 31.

Treatment and Prevention No effective treatment for maedi-visna virus infection is available for field use. Prevention is based on herd hygiene and culling of affected animals, as described in Chapter 31.

Caprine Arthritis-Encephalitis Virus Infection (Infectious Leukoencephalomyelitis)

Definition and Clinical Signs The caprine arthritis-encephalitis (CAE) virus is a small ruminant lentivirus that belongs to the retrovirus group and is closely related to the virus that causes maedi-visna and ovine progressive pneumonia in sheep.[1] The systemic manifestations of the disease are thoroughly discussed in Chapter 38. The distribution is worldwide, but disease tends to be more common in regions with intensive goat-rearing operations. The leukoencephalomyelitis form of CAE is predominantly seen in young goats younger than 1 year of age; only occasional cases occur in older goats.[2] The clinical signs of leukoencephalomyelitis are highly variable but typically involve the spinal cord. Signs include progressive ataxia, paraparesis, paraplegia, tetraparesis, tetraplegia, hemiparesis, and hemiplegia. Goats with high cervical spinal cord lesions (L1 to L4) are recumbent and unable to raise their heads from the floor. They may show resistance to passive neck flexion. Spinal reflexes range from hypertonia and hyperreflexia to hypotonia and hyporeflexia. Intracranial signs may also develop; these include head tilt, nystagmus, tremors, torticollis, salivation, depression, coma, and opisthotonos.[3-9] Vision and pupillary light reflexes may be diminished. The neurologic deficits may be either symmetric or asymmetric. This diversity of signs is related to the variable location of lesions in the CNS.

Other signs that may be associated with CAE infection include fever (although this is highly variable), enlarged joints, mammary gland enlargement, vague and shifting leg lameness, weight loss, and tachypnea without significant auscultatory abnormalities.

The major differential diagnostic considerations for the neurologic form of CAE include head or spinal trauma, listeriosis, cerebrospinal nematodiasis (verminous meningoencephalomyelitis caused by the meningeal worm of the white-tailed deer, *Parelaphostrongylus tenuis*), and multisystemic infections with *Mycoplasma* spp. The CAE virus causes neurologic lesions in numerous regions of the CNS, whereas the lesions of listeriosis are generally restricted to the brainstem. Mycoplasmal infections typically affect kids ranging from 1 to 6 months of age, and affected animals are systemically ill and often display septic polyarthritis and polyserositis. *Mycoplasma* infections of goats are described further in Chapter 38. Verminous meningoencephalomyelitis can be differentiated from CAE by serologic or PCR testing for the virus, CSF analysis, season, and geographic distribution of the white-tailed deer host.

Diagnosis Previously, an AGID test was used for the diagnosis of CAE, but this has been superseded by ELISA and PCR tests.[10,11] The virus may also be cultured from infected tissue.[12] One study has reported an increase in total plasma protein and hypergammaglobulinemia in affected goats.[4] The results of other hematologic and blood chemistry analyses are normal. The changes in the CSF are characteristic only of a chronic granulomatous inflammation. Specific changes include an increased protein concentration and pleocytosis.[13] Cell counts in the CSF of affected goats range from 5 to 1800/dL, and the protein concentration ranges from 0 to 700 mg/dL.[2]

Pathogenesis When inoculated into goats, the virus causes a chronic infection characterized by demyelinating encephalomyelitis, arthritis, and interstitial pneumonia. The pathologic changes resemble those of an autoimmune process and are probably caused by interactions among the host's immunologic responses, denatured myelin, and the virus.[14] Macroscopic pathologic changes in the CNS of naturally infected goats include cloudiness of the meninges and tan discoloration of the white matter.[3] Microscopic changes include disseminated perivascular accumulations of mononuclear cells, demyelination originating in the subependymal region, astrocytosis, and mononuclear leptomeningitis.[3,7,10,14,15] Spinal cord lesions are most frequently observed in the thoracolumbar segments.[2]

Treatment No treatment is available for goats with leukoencephalomyelitis. Control measures are discussed in Chapter 38.

Border Disease (Hairy Shaker Lambs; Hypomyelogenesis Congenita)

Definition and Etiology Border disease is a congenital infection of sheep and goats caused by a noncytopathic togavirus (genus *Pestivirus*).[1] The border disease agent is antigenically similar to the bovine viral diarrhea (BVD) and hog cholera (classical swine fever) viruses. Once introduced into a flock, the border disease virus causes abortion, infertility, and deformed lambs. During pregnancy in a naive ewe, viral infection results in a variety of fetal malformations, including early embryonic death, abortion and stillbirth, and small, malformed lambs. A seroprevalence rate as high as 29% has been seen in a newly infected flock. It is important to note that lambs infected in utero become immunotolerant and remain viremic for life, similar to calves persistently infected with BVD virus.[2] Adult sheep that become infected with the border disease virus develop an inapparent, short-lived viremia and become immune to reinfection.

Clinical Signs The severity of clinical signs in affected lambs varies. Changes are most marked in newborn lambs infected in early gestation (before 50 days). The CNS, skin, and skeleton are the most seriously affected. The hairs of congenitally affected lambs are coarse, straight, and elongated and stand out from the body like a halo.[3] The

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coat is abnormally pigmented and may have a dark-gray appearance or hyperpigmented spots that are especially prominent over the top of the neck.[4] Animals that survive shed the abnormal hairs at 9 to 12 weeks of age and replace them with normal hair fibers. Affected lambs also have a short, thickened body; shortened legs; smaller orbital size; and doming of the frontal bone.[5,6]

Arthrogryposis occasionally occurs. Some infected lambs show neurologic symptoms such as ataxia and uncontrollable tremors; the latter sign, combined with the characteristic hair coat, gives affected lambs the common term of "hairy shakers." The tremors are coarse, involve the trunk and head, and disappear when the animal is asleep.[7,8] The lambs are often alert and appetent but initially need assistance to stand and nurse. Some animals walk normally but hop on the rear limbs when forced to run. The CNS signs usually disappear by 20 weeks of age, but the animals appear stunted. Affected animals have greatly decreased viability compared with uninfected herdmates and may die unexpectedly. Aside from neonatal death losses, economic burdens imposed by the viral infection include low birth weights, diminished weaning weights, lowered carcass quality, and infertility.[6,9]

Abortions that occur 9 to 106 days after inoculation were seen in 30% of experimentally infected sheep.[4,5,10] In field outbreaks the average gestational age of the aborted fetus is 63 days. Teratogenic effects are most often observed when lambs are infected at 50 to 90 days of gestation.[11] Fetal mummification may occasionally be seen.

The border disease virus is also pathogenic in goats.[12] As in sheep, inoculation of pregnant does results in fetal mummification and abortion. The spinal cords of infected kids are hypomyelinated, but the haircoat is normal.

The border disease virus has low pathogenicity for cattle. Abortions can be induced in cows inoculated with the virus at approximately 50 days of gestation, and affected calves have cerebral cavitations.[13] When comingled with infected sheep, natural infection of cattle can occur.[13a]

Diagnosis Identification of the viral antigens in tissues using fluorescent antibody tests is the most accurate method of diagnosing border disease. Tissues that most consistently contain viral antigens are those of the abomasum, pancreas, kidneys, thyroid, and testicles.[14,15] Serodiagnostic methods including serum neutralization (SN), AGID, and complement fixation tests have been developed.[16] In most cases the BVD virus has been used as the indicator antigen. Serodiagnosis of infected lambs is difficult because the lambs tend to be immunotolerant and therefore do not develop strong serologic responses. The presence of viral antibodies in the CSF suggests border disease virus infection.

Pathophysiology Hypomyelination is probably caused by a combination of virus-induced degeneration of the oligodendroglial cells (dysmyelinogenesis), persistent viral infection, and diminished secretion of the thyroid hormones L-3,3′,5′-triiodothyronine and thyroxine.[17] The diminished production of thyroid hormones is thought to be related to direct inhibition of the thyroid gland because the pituitary activity of these lambs appears to be normal. Lambs infected in utero have decreased white and gray matter in their spinal cords as a result of the decreased myelin content.[18] Depressed blastogenic activity of lymphocytes, a decrease in T-helper cell function, and an increase in T-suppressor cell function have been demonstrated in affected lambs between 4 and 7 months of age, indicating a viral immunosuppression.[19-21] Such lambs may succumb to parasitism, diarrhea, and bronchopneumonia.

Epidemiology Border disease is transmitted both vertically and horizontally.[19,22] As for BVD in cattle, the major reservoir in infected herds is the asymptomatic, congenitally infected, seronegative animal.[2,23] Sheep exposed to the virus as adults develop antibody responses and clear the infection. Asymptomatically infected animals may shed the virus through the placenta, infected offspring, saliva, respiratory secretions, urine, or feces.[10,19] In one seroepidemiologic study of infected ewes in the western United States, lambs were more often seropositive than ewes.[2] A large percentage of the seropositive lambs were born to seronegative ewes, indicating the presence of a large amount of virus cycling from asymptomatic carriers. Strain-related differences appear to exist in viral pathogenicity.[24]

Necropsy Findings The macroscopic changes associated with border disease virus infection are hydranencephaly, porencephaly, microcephaly, cerebellar hypoplasia, abnormal curvature of the ribs, brachygnathia, doming of the frontal bones of the skull, narrowing of the distance between the orbits, a decrease in orbital size, shortening of the crown-to-rump and diaphyseal lengths, retention of secondary hair fibers, and abnormal skin pigmentation.

Microscopic changes in lambs with congenital infection include hypomyelinogenesis and hypercellularity of the white matter with abnormal-appearing glial cells.[7,8,11] The CNS shows dysmyelinogenesis, secondary demyelination, and periarteritis. Viral antigen can be demonstrated in CNS arterioles.[25]

Differential diagnoses for border disease virus infections in sheep and goats include other causes of infectious abortion, copper deficiency (swayback), and other viral diseases that may result in hydranencephaly, such as those caused by the Cache Valley, bluetongue, and Schmallenberg viruses.

Treatment and Control In herd situations, virus isolation from whole blood or examination of skin biopsies by fluorescent antibody tests can be performed to identify carriers.[14] Serologic testing is not a reliable indicator of infection because congenitally, persistently infected animals may be immunotolerant of the virus. Noninfected pregnant sheep should be kept separated from others in the flock for the first 60 days of gestation to ensure that in utero infections do not occur.

Encephalitic Bovine Herpesvirus Infection

Clinical Signs Two herpesviruses, bovine herpesvirus type 1 (BoHV-1) and type 5 (BoHV-5), have been rarely associated with encephalitis in cattle.[1-4] BoHV-1 infection typically results in infectious bovine rhinotracheitis (IBR), an acute upper respiratory tract disease characterized by fibrinonecrotic white plaques of the nasal, pharyngeal, and tracheal mucosa and abortions (see Chapter 31). Other clinical conditions associated with bovine herpesvirus infections include epizootic conjunctivitis (Chapter 39) and infectious balanoposthitis or vulvovaginitis (Chapter 43). The clinical signs of encephalitis include depression, mild nasal and ocular discharge, conscious proprioceptive deficits, head pressing, aimless circling, bellowing, salivation, bruxism, paralysis of the tongue, head tilt, nystagmus, convulsions, blindness, coma, and death.[2,3] The seizure activity is characterized by a tonic-clonic convulsion with violent spasms or tremors of the head, with all four legs flexed and the head in opisthotonos. Rectal temperatures of 41°C to 42°C (106°F and 107°F) have been reported.[5] Encephalitic herpesvirus infection is frequently fatal, although asymptomatic cases have been induced experimentally.[5a] In experimental infection, signs develop 1 to 2 weeks after infection. A mononuclear pleocytosis is found on analysis of CSF.[5a] Encephalitis may be evident on histopathologic examination of fetuses from cows that abort from BoHV-1.[5b]

Differential diagnoses for encephalitic herpesvirus infections in cattle include almost all encephalitic, encephalopathic, and neurotoxic diseases of cattle, including rabies, polioencephalomalacia, salt poisoning, and lead toxicity. Accompanying respiratory disease raises the index of suspicion for herpesvirus. A rising serum neutralizing antibody titer in surviving animals can be used to confirm infection, although this does not distinguish between BoHV-1 and BoHV-5. Specific diagnosis is usually made at necropsy using a number of modalities including virus isolation, immunohistochemistry, and PCR.[6-8] Many of these tests do not distinguish between BoHV-1 and BoHV-5; more specific PCR tests can differentiate between these two virus types.[9]

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Epidemiology Bovine herpesviruses cause disease in cattle worldwide. Epidemiologic factors that appear to favor dissemination of herpesviruses among cattle include a high stocking rate, repeated introduction of animals from diverse backgrounds, and mass weaning of calves at a time when the passively acquired anti-IBR antibodies are waning.[2] BoHV-1 may survive in the environment for up to a month; cooler ambient temperatures and higher humidity promote virus survival.[10] Calves younger than 6 weeks old are most susceptible, but infection and resultant neurologic disease also have been described in adult cattle.[1,3-5,11-13] Animals that survive the disease become persistently infected; virus survives in the nasal and tracheal mucosa and the trigeminal ganglion.[13] Reactivation and virus shedding may occur during periods of stress.[4,10,13] Although clinical disease caused by reactivation of latent virus is usually mild and may go unnoticed, shedding of virus during such episodes provides a source for infection of in-contact animals. The viruses grow in the nasal and pharyngeal mucosa. Brain involvement results from centripetal spread along the sensory neurons of the trigeminal and olfactory nerves.[13]

Pathophysiology Encephalitic IBR infections cause a nonsuppurative meningoencephalitis that is widely distributed in the gray matter of the brain, primarily in the cerebrum and thalamus. Extensive lymphocytic meningoencephalitis is evident on histologic examination. Intranuclear inclusion bodies are rarely seen in bovine herpesvirus encephalitis. The virus can usually be isolated from affected calves.[5a] Signs of respiratory disease may precede or occur coincidentally with neurologic disease.[5a]

Treatment and Control No adequate therapy exists for the encephalitic form of BHV-1 infection. Treatment is symptomatic and supportive and should include oral or intravenous fluid support, NSAIDs, antibiotics in animals with respiratory signs, and nursing care. Diazepam or phenobarbital may be used for seizure control when necessary (Table 35-2). Animals with severe clinical signs may be euthanized for humane reasons.

Vaccines that protect against BoHV-1 have been considered potentially useful in the prevention of BoHV-5 infection because of the close antigenic relationship between the two viruses.[11,11a] However, more recent trials have shown that certain BoHV-1 vaccines may not confer protection to cattle challenged with BoHV-5.[11b,11c]

In some European countries, eradication programs that employ testing and culling of infected animals have been successful in eliminating BoHV-1. Bovine herpesviruses can be spread through fomites and by aerosol transmission for up to 4 miles (6.4 km).[10] Strict biosecurity procedures are therefore essential to developing and maintaining virus-free herds.

Bovine Spongiform Encephalopathy ("Mad Cow" Disease)

Christine F. Berthelin-Baker • David C. Van Metre

Definition and Etiology Bovine spongiform encephalopathy (BSE) is a transmissible spongiform encephalopathy (TSE) of cattle that was first described in 1987 in Great Britain (GB).[1] The TSEs are a group of slowly progressing, invariably fatal neurodegenerative diseases that can affect humans and animals. They are also called *prion diseases* because of the accumulation of prion in the CNS. Since the prion hypothesis was first formulated in 1982, prions have been widely accepted as the etiologic infectious agents of the TSEs.[2] The prion is an altered conformation (PrP-BSE) of the normal prion protein (PrP), a host-encoded membrane protein that does not carry any nucleic acid. PrP-BSE replicates by inducing a posttranslational conformational change in the normal protein PrP to form the abnormal prion PrP-BSE.[2-4] After a characteristically prolonged incubation period, the abnormal isoform of the protein aggregates and accumulates in the CNS of affected animals, creating progressive neurologic dysfunction.

Clinical Signs As with all TSEs, BSE has a long incubation phase. It occurs mostly in 4- to 6-year-old cattle (age range, 20 months to 18 years). The clinical signs of BSE are usually insidious in onset.[5,6]

The detection of clinical signs of BSE and the array of clinical signs reported are influenced by how closely the cattle are being observed and the handlers' awareness of the insidious and nonspecific nature of the clinical signs. Subtle early behavioral changes are unlikely to be observed in large herds. Cattle may become apprehensive, stay apart from their herdmates, and become fearful of their handlers. As the disease progresses, cattle often become extremely excitable,

TABLE 35-2

Recommended Drug Dosages for Treatment of Cerebrocortical Disease

	Dose	Route	Frequency
Anticonvulsant Drugs			
Diazepam	0.01-0.4 mg/kg	IV or IM	Twice daily or as needed
Pentobarbital sodium	2-10 mg/kg	IV	Three times daily
Phenobarbital	Loading dose 20 mg/kg	IV	One time
	Maintenance dosage 1-4 mg/kg	IV, PO, or IM	Divided twice daily
Antiinflammatory or Antiedema Drugs			
Methylprednisolone	1-30 mg/kg	IV	One time
Dexamethasone	1-4 mg/kg	IV or IM	Twice daily
Mannitol	0.25-0.5 g/kg 20% solution	IV	Twice daily
Furosemide	1 mg/kg	IV, IM, or SC	Twice daily
Flunixin meglumine*	1 mg/kg	IV or IM	Twice daily
Phenylbutazone†	2-4 mg/kg	IV or PO	Twice daily
Dimethyl sulfoxide (DMSO)	1-2 g/kg	IV	Twice daily
Acetylsalicylic acid (aspirin)	7-10 g/500 kg	PO	Twice daily

*Monitor for signs of gastric or abomasal bleeding (fecal occult blood).

†An initial loading dose of 10 to 20 mg/kg, followed by 2.5 to 5 mg/kg daily to every other day thereafter has been recommended for cattle. Because of the prolonged plasma half-life in ruminants, serial administration of the drug should be accompanied by careful monitoring of renal function and gastrointestinal bleeding.

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

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especially when restrained or placed in confined quarters or an unfamiliar environment. BSE cattle may refuse to move through previously familiar doorways and become impossible to restrain. Unprovoked aggression is less frequently seen. Hyperesthesia is most marked around the head and neck. A light touch on the hindlimbs may induce violent and often repetitive kicking, which may also be observed during milking. Animals may overreact in response to sudden visual, tactile, or auditory stimuli. The startle reaction may be gauged by a hand test (punching fist abruptly toward the animal's head without touching it), flashlight test, a hand clap, or a loud metallic "bang." Normal animals rarely startle in response to such stimuli, or they may startle once or twice when the stimulus is repeated. BSE cases will frequently startle in a violent and repeatable fashion, with no habituation to a repeated stimulus. In some cases the response may escalate to an extreme aberrant startle, with headshaking and seizure-like head bobbing, which may be followed by violent turning, running around, and falling.

Other possible clinical signs of BSE include ptyalism, increased head rubbing, muscle fasciculations, and excessive vocalization. Other behaviors seen in BSE may include frequent and repetitive head tossing, licking of the nostrils, yawning, flehmen, head butting, and restlessness.[7] A relative bradycardia (60 beats/min) may be observed in animals when a tachycardia is expected because of their hyperexcited state. Affected animals often lose weight and have reduced milk output. Ataxia and tremors are seen in more advanced cases. Tremors most often involve the head and neck and may become generalized, especially with exercise. Ataxia is most marked on turns, when going over steps, or on uneven terrain; it may also be accentuated with exercise. BSE animals may become recumbent and unable to feed if the disease is left to run its course. Recumbency may also be triggered by an intercurrent illness or an injury during a fall. The clinical signs of BSE may be more difficult to recognize in animals that have become recumbent than in less advanced cases,[8] and systematic targeted surveillance of downer cattle (fallen stock) have allowed for the detection of previously unsuspected cases of BSE in various countries.[9]

Pathophysiology The exact function of the prion protein is unknown, as are the mechanisms of neurodegeneration and CNS dysfunction in TSEs. On the basis of recent research in transgenic mice expressing bovine PrP, the prion is thought to undergo limited propagation in the distal ileum before spreading to the CNS, most likely by moving through the gut-associated lymphoid tissue (GALT) into the peripheral nerves.[10,11] Studies of naturally infected cattle, combined with experimental oral challenge studies in cattle, have revealed that BSE infectivity may exist in the brain; spinal cord; retinal tissue; optic nerve; cervical, thoracic, and trigeminal ganglia; facial and sciatic nerves; and the distal ileum. The skeletal muscles, spleen, and lymphatic tissues did not demonstrate infectivity.[12,13] Intracerebral inoculation of cattle has also been demonstrated to result in infectivity of the tonsillar tissue.[14] Following a prolonged incubation period, accumulation of PrP-BSE in the CNS creates progressive and irreversible neurologic dysfunction.

Epidemiology and Zoonotic Potential Current evidence indicates that BSE has resulted from a single agent.[15-20] BSE may have derived from feedstuffs containing rendered carcasses of scrapie-infected sheep, or it might have been a preexisting sporadic and rare disease unrecognized in the bovine population. The BSE epidemic was traced to the recycling of BSE-infected carcasses into cattle feed, which occurred mostly in the 1980s in the United Kingdom (UK).[16] Cattle in other countries were affected as a result of the importation of infected feedstuffs or cattle, followed by later recycling the agent in their own rendered ruminant feedstuffs. At present (early 2013), according to the World Organization of Animal Health (Office International des Epizooties [OIE]), BSE has been detected in 26 countries including the United States.[21,21a] From 1986 to December 2012, a total of 181,128 cases of BSE were confirmed in GB, according to the Department for Environment, Food, and Rural Affairs.[22] These cases have been distributed among 36,194 farms.[22] The cattle cohorts born in 1986 to 1989 had the highest incidence of BSE cases, and the peak of the outbreak occurred in 1992, when 36,680 cases were detected through scanning of suspect clinical cases (passive surveillance) in GB. Active surveillance has revealed a sustained and sharp decrease in the number of cases since 2001.[22] The decline in the GB epidemic is directly related to the successive bans on the feeding of ruminant-derived meat and bone meal to cattle. The initial 1988 ban took effect in 1989 in the UK and has been tightened and refined since then. Similar feed bans have been adopted by many countries around the world. A list of countries that have reported home-born or imported cases of BSE and the number of cases reported each year is available and regularly updated on the website of the OIE.[21]

Bovine spongiform encephalopathy has predominantly affected dairy cattle because of their longer lifespan and more intensive feeding and wider use of concentrate than beef cattle. No clear genetic predisposition to BSE has been demonstrated in cattle, unlike for scrapie in sheep. The disease is considered to be a food-borne disease of cattle, associated with the ingestion of meat and bone meal contaminated with the BSE prion. This is substantiated by the steady decline in the incidence rate of BSE in endemic countries following enactment of bans on feeding ruminant protein to ruminants.[21a]

Since the onset of BSE epidemic, new TSEs have been identified in animals other than cattle. Strain typing in mice showed that these new TSEs were caused by the BSE agent,[23,24] which has proven to be a relatively promiscuous TSE agent, capable of experimentally infecting mice, sheep, goats, pigs, cats, mink, and primates.[15] The disease in humans, termed *new-variant Creutzfeldt-Jakob disease* (vCJD), was first identified in 1996 in the UK, where it has affected 176 people as of January 2013.[25] Other countries have detected vCJD cases in people who had lived in the UK between 1980 and 1996, as well as in citizens who never traveled to the UK. The emergence of vCJD has put worldwide emphasis on the prevention and detection of TSEs in animals. The route of infection of people by BSE has not been clearly traced, but on the basis of a case-control study, the consumption of food that included infected cattle nervous tissue was demonstrated to be associated with increased risk of vCJD.[26] This and other evidence has led to successive "Specified Risk Materials" bans in many countries, aimed at preventing contamination of human food with nervous system or other specified high-risk tissues from ruminant animals.

Rigorous, active surveillance programs have been initiated in many countries to screen cattle and beef products for the BSE agent. This large-scale testing recently led to the detection of two extremely rare, novel prions based on protease resistance patterns and glycopatterns.[27-30] These novel agents have been termed *H-BSE* and *L-BSE,* and animals from which these agents have been identified have been termed *atypical BSE* cases.[15] These novel BSE cases have been detected in multiple countries by rapid prion detection tests conducted on aged (>8 years) cattle that were tested either during slaughter surveillance or through targeted surveillance of downer cattle. Investigations regarding the origin and pathogenesis of atypical BSE are ongoing. Owing to the advanced age of affected cattle and the low known prevalence of atypical BSE, it has been speculated that atypical BSE may arise spontaneously.[15]

Diagnosis No in vivo test is available for the diagnosis of BSE. Clinical suspicion can be confirmed only by postmortem examination. The diagnosis of BSE is based on microscopic brain examination or tests that identify the abnormal prion in brain or spinal cord tissue.[1,31] Rapid prion tests include Western blot, paraffin-embedded tissue (PET) blot, and ELISAs.[32-35] Rapid tests have enabled the detection of BSE through surveillance in targeted at-risk populations such as fallen (downer) cattle.

Histopathologically, BSE is characterized by neuronal degeneration and intraneuronal vacuolation in specific brain areas. The vacuolation is accompanied by or preceded by the accumulation of

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PrP-BSE.[16,17,36] The obex of the medulla is currently considered to be the tissue of choice for detection of the BSE agent.[37]

Differential Diagnosis Nervous system diseases that could be confused with BSE include viral encephalopathies (pseudorabies, rabies, Borna encephalitis, bovine immunodeficiency virus encephalitis), listeriosis, polioencephalomalacia, lead poisoning, CNS parasitic migration, brain tumors and abscesses, and vitamin A deficiency. Hepatic encephalopathy and other metabolic imbalances may also be confused with BSE. Because of the insidious nature of BSE, affected cattle may appear to recover coincidentally with blanket therapy for suspected metabolic imbalances and later relapse. This must be kept in mind whenever therapy for metabolic imbalances initially appears to be successful but is followed by one or more relapses.

Treatment and Prognosis BSE is always fatal, and no treatment is available.

Control Various measures have been taken to protect public health by removing potentially infected animals and tissues from the food chain. The disposal of BSE-infected tissues and the sourcing of bovine tissues and body fluids for the preparation of medicinal products must take into account the extreme resistance of TSE agents. All TSE agents remain infectious after exposure to a wide range of inactivating treatments and environmental changes such as autoclaving, rendering, storage for months to years, exposure to ultraviolet light, freezing, thawing, prolonged boiling, and incubation with formalin.[38-40] Because of the public health risk, the carcasses of animals suspected of having BSE should be disposed of in an alkaline-hydrolysis tissue digester designed to inactivate TSE agents.[41]

In countries that have had an outbreak of BSE, the complete exclusion of ruminant tissues from ruminant feed has aided progress toward eradication of BSE, as previously noted. In the UK the initial feed ban of 1988 was found to be insufficient and was reinforced by successive measures. The 1996 ban on feeding mammalian meat and bone meal to all farmed animals was introduced to prevent contamination of ruminant feed at feed mills and down the supply chain to the farm. Because of the long incubation period of BSE, a time lag has occurred between the implementation of feed control measures and reduction in the incidence of this disease.

Scrapie

Definition and Etiology Scrapie is a TSE that naturally affects sheep, goats, and mouflons. It is the oldest known TSE, described over 2 centuries ago. The causative agent is considered to be a prion (PrP-Sc) distinct from that of BSE.[1] At least three distinct types of the scrapie agent have been identified in the natural hosts.[1] Although sheep are susceptible experimental challenge with the BSE agent, natural BSE has not been reported in sheep.[1]

Clinical Signs Most animals with scrapie are 1 to 5 years old. The clinical course varies but is typically slow and may last several months. Early behavioral changes are often accompanied by weight loss. Scrapie cases may stay apart from the flock and become nervous and restless.[2] Pruritus of increasing intensity is a common feature; sheep may rub on fixed objects, scratch with their horns or hooves, and bite or lick at themselves excessively. The head, withers, flanks, back, rump, base of the tail, and lower limbs are typically affected, showing secondary wool loss, dermatitis, and skin infections or excoriations.[2,3] Head and face rubbing and shaking may also cause ocular lesions or aural hematomas. When scratching the pruritic areas (mostly the back and rump), the animal may display a "scratch reflex" (or "nibble reflex"), which may include reflex nibbling, lip licking, and rhythmic head movements. This reflex is often but not always present in scrapie cases. Importantly, this response may also be observed in other CNS diseases and in pruritic skin diseases, particularly ectoparasitism, so it should not be considered specific for scrapie.

Other clinical signs of scrapie include bruxism, ptyalism, and regurgitation. Tremors may start with the head and generalize to the whole body. Apathy, exercise intolerance, hypermetria, and ataxia may develop. The most severe and advanced cases show stupor, episodic collapse, and convulsions. Death may occur during a convulsion or as a result of starvation. The clinical signs of scrapie in goats are broadly similar to those in sheep.[3-7] Scrapie has been identified in fallen (down) sheep as well.

Pathophysiology In contrast to BSE, which is restricted to the gut-associated lymphoid tissue and nervous tissue, the scrapie agent can be identified in infected sheep in a variety of non-neural tissues such as the lymphoreticular system, kidney, and placenta.[8,9] This difference has facilitated the development of lymphoid tissue biopsy techniques to detect scrapie (described later). Most transmission of scrapie appears to take place during the birthing season.[1] The scrapie agent is most likely spread by the placentas and birthing fluids of infected animals,[10,11] and oral uptake is considered the most likely route of entry.[10-12] Transport of PrP-Sc to the CNS likely occurs along the vagus nerve from the GI tract,[13] and the agent can be demonstrated in most cases in the vagal nucleus of the brainstem early in the stage of neuroinvasion.[14] Spread into higher brain centers follows. Dysfunction of the CNS appears to correlate roughly with accumulation of PrP-Sc in the brain; however, subtle dysfunction can occur with little or no characteristic histologic changes. The exact mechanism(s) that cause neurologic dysfunction remain to be fully defined.[8]

Epidemiology Scrapie occurs endemically in sheep flocks worldwide, with the exception of Australia and New Zealand.[1] Sheep are the natural host of scrapie, but the infection can be maintained in goats that have no direct contact with sheep, indicating both lateral and vertical transmission of the agent in that species.[3,4,15] Scrapie cases occur sporadically in infected flocks. Only one or a few animals are affected at any given time. Outbreaks may occur if scrapie is introduced into a genetically sensitive flock.

Although there is no known breed predisposition to scrapie, the genetic makeup of the host controls differences in susceptibility and resistance to scrapie in various breeds.[1,16,17] The molecular basis of this resistance is largely controlled by the PrP gene.[18] Polymorphisms at three codons of this gene (171, 136, and 154) appear to be the main determinants of the susceptibility of sheep to scrapie.[1] According to current evidence, the genotype $VV_{136}RR_{154}QQ_{171}$ (or $AA_{136}RR_{154}QQ_{171}$ in some breeds) is most susceptible, and the genotype $AA_{136}RR_{154}RR_{171}$ is highly, but not completely, resistant.[1] Susceptibility is most clearly linked with variation at codons 136 and 171 in breeds studied to date; the genotype of a particular animal is often referred to as RR, QR, or QQ to designate the alleles at site 171. Selection of scrapie-resistant sheep flocks may be based on pedigree, phenotypic expression of the disease, or genetic testing to select sheep of "resistant" PrP genotypes. Genetic polymorphisms or the PrP gene may also influence susceptibility to and/or the incubation period for scrapie in goats.[19]

Treatment and Prognosis Scrapie is a fatal and irreversible disease for which there is no known treatment.

Diagnosis Because the scrapie agent can disseminate in lymphoid tissue before the development of clinical disease, immunohistochemistry may show PrP-Sc in biopsies, lymphoid tissue in the tonsils,[20] nictitating membranes,[21] retropharyngeal lymph nodes,[22] or rectoanal junction.[23,24] However, these tests have limited sensitivity, primarily because of variable lymphoid involvement among infected sheep, a phenomenon that may be associated with the host's genetic makeup.[25] Microscopic examination of the brain and spinal cord is the classic diagnostic method for scrapie. It is possible only when tissues are collected soon after death, before autolytic changes take place. Neuronal vacuolation and PrP-Sc deposits are found in specific

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brain nuclei.[26-31] At present, collection of brainstem (particularly the obex), tonsillar tissue, and medial retropharyngeal lymph nodes is currently recommended for testing suspect sheep in the United States.[32] In autolyzed tissues, PrP-Sc can be identified by immunohistochemistry testing, Western blot tests, or ELISA.[33-36] As for BSE, heightened active surveillance for scrapie has revealed at least one atypical strain of scrapie (termed *atypical scrapie*), and investigations into the host range and detection methodologies for this novel agent are ongoing.[37]

DIFFERENTIAL DIAGNOSIS. Nervous system diseases that could be confused with scrapie include pseudorabies, rabies, Borna encephalitis, listeriosis, polioencephalomalacia, lead poisoning, cerebrospinal nematodiasis, gid (coenurosis), brain tumors, brain abscess, maedi-visna virus infection, vitamin A deficiency, pregnancy toxemia, and other metabolic imbalances. When pruritus is the only clinical sign, skin diseases such as psoroptic and sarcoptic mange, ringworm, myiasis, pediculosis, and atopy may be considered as differential diagnoses. Because of the insidious nature of the illness, animals with early scrapie may initially appear to respond to a variety of treatments. This must be kept in mind whenever specific therapy for another suspected illness appears initially to be successful but is followed by relapse. When therapy of an alternate condition fails, the final diagnosis must rely on detailed examination of appropriate postmortem samples.

Control

Because there is no effective treatment for scrapie, control measures designed to prevent the spread of the disease are especially important. Scrapie is a reportable disease. Eradication measures vary from country to country. Animals suspected of having scrapie are slaughtered and destroyed. Contaminated pastures or paddocks may be left empty of livestock, but the scrapie agent is unlikely to be inactivated in the environment. Contaminated stalls, corrals, and sheds should be disinfected with sodium hypochlorite diluted at 4% available chlorine. In the United States and Canada, scrapie-affected and related animals are destroyed and their flocks are quarantined. Lines of sheep genetically resistant to the development of clinical scrapie have been selected,[38,39] and genotype testing is currently used to select for resistance to the disease.[1]

Public Health Considerations

Although scrapie has been endemic in various areas of the world for more than 2 centuries, epidemiologic studies have not shown any correlation between the incidence of Creutzfeldt-Jakob disease in humans and that of classical scrapie in sheep; the zoonotic potential of atypical scrapie remains under investigation.[1] It is nevertheless prudent to take precautions to minimize the potential for human exposure to scrapie, owing to the high fatality rate characteristic of TSEs and the potential for emergence of novel strains of prions with unknown host ranges.[1]

Pseudorabies (Aujeszky Disease, Mad Itch, Bulbar Paralysis)

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Definition and Etiology

Pseudorabies is an acute, severe, and usually fatal encephalitis caused by an encapsulated DNA virus, suid herpesvirus type 1 (Su-HV1), a member of the genus *Varicellovirus,* subfamily Alphaherpesvirinae, family Herpesviridae.[1,2] This virus can infect the CNS and other organs (e.g., respiratory tract) of virtually all mammals except humans and most primates. Domestic and feral swine are the natural hosts and may become latent carriers. The virus can also infect cattle, sheep, cats, dogs, goats, wildlife (e.g., raccoons, opossums, skunks, rodents), and, rarely, horses.[3-6]

Clinical Signs

The incubation period ranges from 90 to 156 hours, and the illness may last 8 to 72 hours, although some affected animals have been found dead without any observed clinical signs.[7,8] The initial clinical sign in ruminants is usually a manifestation of paresthesia, with acute and severe pruritus inducing self-trauma, dermal abrasions, swelling, and alopecia.[7] Other signs may include fever, bellowing, bloat, feet stamping, excessive salivation, twitching, chewing of the tongue, ataxia, circling, nystagmus, and strabismus.[9-11] Aggression may be seen, but most affected animals become depressed. As the disease progresses, there may be hyperesthesia, tenesmus, excessive licking of the nostrils, continuous mastication, vocalization, coma, convulsions, and opisthotonos.[12] Most cases are fatal. The clinical signs of pseudorabies in cattle closely resemble those of rabies, polioencephalomalacia, salt poisoning, meningitis, lead poisoning, hypomagnesemia, and enterotoxemia.

Clinical Pathology

The Aujeszky disease virus (ADV) can be isolated from the pharyngeal or nasal secretions of affected animals and can be easily cultured from infected nervous tissues. Strains of ADV are antigenically distinct from other herpesviruses but share common antigens with the infectious bovine rhinotracheitis (IBR) virus. Heterospecific antibodies to the IBR virus may cross-neutralize the pseudorabies virus and confound serologic tests. For virus culture, tissues should be collected from sensory ganglia or the dorsal horn of the spinal cord. Segments serving the pruritic sites should be collected preferentially because these areas contain the highest concentration of virus.

Pathophysiology

Ruminants are susceptible to pseudorabies infection after intradermal, subcutaneous, intranasal, or oral exposure to the virus. After subcutaneous, oral, or nasal infection, the virus spreads centripetally to the CNS by axonoplasmic transport. During the acute infection the virus may be present in the nasal mucosa, secretions, and saliva.

Epidemiology

Aujeszky disease has a worldwide distribution and, although cases occur only sporadically, is an economically important disease because of the regulatory quarantine and other restrictions imposed on animals from affected herds. Until recently, Aujeszky disease was endemic in the United States, but it has been successfully eradicated from domesticated swine. As of December 2006, all states are classified as free of pseudorabies in domesticated swine (OIE status V), although ADV remains present in feral pigs in parts of the United States.

The viral infection in cattle is perpetuated partly by the occurrence of latent infections in pigs, which can be recrudesced by stressful conditions.[13] Occasional spillover of the virus from swine into ruminants occurs because of the proximity of the two species in many livestock operations.[8,14] The natural routes of transmission include nose to nose, fecal oral, and venereal.[3,15] Indirect transmission usually occurs by inhalation of aerosolized virus. The virus may travel via aerosols up to 2 km (1.2 miles) in certain weather conditions and may survive up to 4 days in straw bedding. It is inactivated by drying, sunlight, and high temperatures (37° C). Dead-end hosts such as dogs, cats, and wildlife can transmit the virus between farms, but aside from feral swine, these animals survive only 2 to 3 days after becoming infected.

Latency of the viral infection in ruminants is not an important mechanism for perpetuation of an outbreak because most animals die within 48 hours of disease onset. In the few that survive longer, shedding in saliva occurs for up to 6 days after infection. Direct spread of the virus between infected and uninfected cattle is unlikely.[14] Wild mammals such as raccoons may play a role in pseudorabies survival and transmission; rats, however, develop transient infections and do not appear to transmit or perpetuate the virus.[16-18] The pseudorabies virus may survive in contaminated meat products for up to 7 weeks. The role of this prolonged survival in perpetuating outbreaks in ruminants is unknown.

Necropsy Findings

Gross findings include excoriation, alopecia, edema, and hemorrhage at the pruritic site. The neuropathologic changes include nonsuppurative encephalitis, neuronal

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degeneration, and eosinophilic intranuclear (Cowdry type A) inclusion bodies. The lesions are most pronounced in the dorsal nerve rootlets and the dorsal horn.

Treatment There is no treatment for pseudorabies, which is usually fatal in livestock, although rare recoveries have been reported.[10]

Prevention The most effective method of preventing pseudorabies virus infection in ruminants is eliminating their exposure to swine. Contaminated pens can be disinfected with 10% sodium hypochlorite solution, quaternary ammonium compounds, tamed iodine, or phenolic compounds.[19] At least 5 minutes of contact time should be allowed before the disinfectant is rinsed from the contaminated surfaces. Fumigation with formaldehyde for 6 hours effectively kills the virus, as does 360 minutes of contact with ultraviolet light.

Ovine Encephalomyelitis (Louping Ill)

Definition and Etiology Louping ill is an acute, fatal encephalomyelitis of sheep that occasionally infects humans, wild ruminants, horses, and cattle.[1-3] The disease has been reported in England, Scotland, Ireland, Norway, Turkey, and Bulgaria.[4-6] The etiologic agent of louping ill is a neurotropic, single-stranded RNA virus (flavivirus) that is transmitted by primarily the tick *Ixodes ricinus,* as well as by *Rhipicephalus appendiculatus, Ixodes persulcatus,* and *Hemaphysalis anatolicum.* Most outbreaks occur in swampy areas with dense populations of infected ticks and wild animals. Infection through blood contamination of hypodermic needles, other fomites, and blood products has been reported.[7] Minor genetic variations occur among viruses from different geographic areas, forming four subtypes.[8]

Clinical Signs In sheep, the initial clinical signs of louping ill include fever, anorexia, depression, constipation, and generalized muscular tremors. The ensuing signs are characteristic of CNS disease and include ataxia, conscious proprioceptive deficits, head tremors, hypermetria, and hyperexcitability. The hypermetria results in a characteristic "bunny-hopping gait," which gives the disease its name (to "loup" is to leap in vernacular Scottish). Further progression of clinical signs is associated with cerebrocortical dysfunction; these signs include head pressing, hyperesthesia, recumbency, convulsions, coma, and death. Survivors have residual neurologic deficits. The duration of the illness is approximately 12 days.

Clinical Pathology Both hemagglutination inhibition and complement fixation tests can be used to detect virus in infected animals.[7] High levels of virus-specific IgG and IgM can be detected in the CSF of affected animals.[9] Viremia peaks at approximately 3 days after inoculation and disappears by 7 days. Because animals are usually not viremic at the time the nervous system lesions develop, virus recovery is best done from the brain or spinal cord.

Pathophysiology Ticks become infected when feeding on a viremic host. The virus survives in the salivary glands of the tick and can overwinter there, being transmitted to a new host when the tick becomes active the following year.[7] After inoculation into susceptible sheep, the louping ill virus migrates into the regional lymph nodes and spleen and then replicates. Viremia occurs 6 to 20 days after the invasion of the lymphatic tissues.[2] Viral replication in the brain causes nonsupportive inflammation and neuronal degeneration. Rapid antibody production is associated with recovery.[10] Concomitant infection of sheep with the agent of tick-borne fever *(Ehrlichia phagocytophila)* results in a greater level of viremia and increased mortality from the louping ill virus.[11] The virus is transmissible in unpasteurized sheep and goat milk.[11a]

Epidemiology Louping ill principally affects yearling sheep in the spring, although lambs and adults can be affected. Maternal immunity wanes when lambs are about 3 months old. Infection develops weeks to months after sheep have been placed on pastures infected by *Ixodes ricinus.* In any outbreak the prevalence of clinical louping ill is low, but the seroprevalence of antibodies in adult sheep in endemic areas is high, indicating a continuous, low-level exposure to the virus, and many animals are asymptomatically affected. Factors such as climate, tick population, and immune status of the flock all play a role in the severity of an outbreak.[7] The attack rate may reach 60% of the population, whereas the mortality rate rarely exceeds 15%. Adults tend to be more heavily parasitized by the host ticks and thus play a major role in virus survival and transmission.[12] Pigs, goats, cattle, horses, and red deer also become infected with the virus and can develop similar clinical disease.

Sylvatic cycles of virus transmission occur in which viral amplification takes place through certain wild mammals and red grouse.[1,13,14] The hare serves as an important source of virus for the red grouse.[15,16] It has been demonstrated that the red grouse can be infected by ingesting the infected tick, rather than by being bitten by the tick.[17] The louping ill virus probably is maintained on pastures through infected sheep because grouse populations become unstable and die out whenever the virus is introduced.[18]

Mild occupational infections can occur in shepherds, veterinarians, and laboratory workers who cultivate the virus. The high incidence of louping ill in the spring and summer months probably corresponds to the peak activity of ticks. The virus may persist for long periods in the arthropod vector, but it is unclear if transovarial transmission of the agent occurs. *Ixodes ricinus* is a three-host tick with a life cycle of 3 years. The ticks do not walk, and dissemination requires animal transport. After a blood meal, the tick molts and then rests on vegetation until the next meal, approximately 12 months later. The activity of the ticks tends to increase greatly in the spring whenever the ambient temperatures are above 7° C (43° F).

Necropsy Findings Gross lesions are absent at necropsy. The histologic lesions of louping ill reflect meningeal inflammation with mononuclear cells.[19,20] Microscopic lesions are most severe in the Purkinje cells, motor nuclei, and ventral horn cells. The forebrain is spared.[21] Virus in tissue can be detected by virus isolation, immunohistochemistry, and RT-PCR.[7,22,23]

Prevention There is no treatment for louping ill encephalitis, but supportive care should be provided.

A formalin-inactivated vaccine given in the last trimester of pregnancy has been recommended for preventing louping ill encephalitis.[24] A single dose of the vaccine provides responses that are protective for at least 2 years. Other methods of preventing the disease include frequent acaricidal dipping of sheep and clearing of pastures to reduce the population of infected intermediate hosts.

Louping ill has not been detected in the United States, but it is a reportable disease. Any suspicion of this disease should be reported to state and federal authorities. The disease also has a zoonotic potential; infection of humans is rare but can occur through tick bites; unpasteurized, infected sheep or goat milk; or fomites.

Rabies

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Definition and Etiology Infection with rabies virus results in severe and usually fatal neurologic disease. Most mammals are susceptible and are infected through bites from other animals during or near the clinical phase of illness. The rabies virus and other highly neurotropic rabies-related viruses belong to the genus *Lyssavirus,* family Rhabdoviridae (bullet-shaped RNA viruses). Wildlife provides a natural reservoir for rabies, and each rabies strain is maintained in particular reservoir host(s). Although they can readily cause rabies in other species, wildlife-adapted strains of rabies usually die out when passed into species to which they are not adapted. Other "rabies-related" lyssaviruses can cause a neurologic disease identical

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to rabies. They include the Lagos and Duvenhage viruses of bats in parts of Africa, the Mokola virus of rodents and shrews in Africa, and the European and Australian bat lyssaviruses.[1-3]

Clinical Signs Livestock cases of rabies have been reported mostly in cattle and occasionally in horses, sheep, and goats.[3,4] Rabies should be included in the differential diagnosis of any unexplained acute, rapidly progressive intracranial disease, especially in the presence of autonomic instability, dysphagia, hydrophobia, paresis, or paresthesia.[3,5,6] The incubation period ranges from a few days to 6 months, depending on the pathogenicity of the inoculum and the distance from the site of inoculation to the brain. The shortest incubation periods are seen in animals bitten on the head, whereas the longest incubations have been reported after bites on the extremities of the pelvic limbs.

The disease is usually fatal after a clinical course of 1 to 8 days. Occasionally, an animal may be found dead without any previously observed clinical sign. Early clinical signs of rabies in livestock may be nonspecific sensory and behavioral changes including anorexia, restlessness, depression, separation from the herd, and mild ataxia. Rumination may stop. Horses often appear colicky. Affected animals may show regional paresthesia with pruritus, creating excoriation and hair loss. As the disease progresses, animals may become hyperexcitable, fearful, or enraged *(furious rabies)* or mentally depressed *(dumb rabies)*. Cattle rabies frequently manifests as dumb rabies with flaccid paraparesis, tetraparesis, and tetraplegia *(paralytic rabies)* as the disease progresses. Therefore, the examiner should consider appropriate personal protective equipment (coveralls, boots, gloves, mask, and eye protection) when examining downer cattle in rabies-endemic areas.

In an experimental study, all cattle and sheep infected with the rabies virus exhibited excessive salivation and behavioral changes, and the majority also displayed tremors, bellowing, aggression, hyperesthesia, and pharyngeal paresis/paralysis.[3] Tetraplegic animals may show frantic motor activity of the legs and bellow when stimulated. Animals with dumb rabies are depressed, inappetent, and often febrile (>39.4°C [103°F]), and they may have a drooped head and neck, ptosis, flaccid facial musculature, profuse salivation, and yawning. They may demonstrate repeated nibbling motions with the lips. Other signs include tenesmus, paraphimosis, priapism, odontoprisis, head pressing, circling, basewide stance, difficulty rising, and falling episodes. Flaccidity of the tongue, tail, anus, and urinary bladder may also be evident, as may blindness, strabismus, and nystagmus.

The first clinical sign of paralytic rabies in horses may be an unexplained ataxia or shifting leg lameness, soon followed by paraparesis or paraplegia.[7] Spinal reflexes and tone in the affected limbs may be decreased or absent. Most affected animals become recumbent in 3 to 5 days. Initially the recumbent animal may be able to eat and drink with help, but it soon becomes anorectic and develops encephalopathic signs, followed by generalized seizures and coma[8,9] (Fig. 35-7).

Regardless of the clinical manifestations, rabies is a rapidly progressive and fatal disease leading to cardiorespiratory failure, and death usually occurs within 10 days. In all disease forms of livestock, the clinical signs rapidly worsen over 1 to 3 days, until the patient becomes recumbent and comatose. Animals may develop a pharyngeal-laryngeal paralysis resulting in stertorous breath sounds, inability to drink (thus the common name of *hydrophobia*), and accumulation of frothy saliva at the commissures of the lips.[10]

One summary of 21 cases of rabies in horses enumerated the frequency of particular clinical signs seen as the presenting complaint (Table 35-3). Rabies can only be differentiated from other encephalitic disorders by specific postmortem tests or virus isolation, which is usually not possible before death occurs. In horses the clinical signs of rabies are often indistinguishable from other encephalopathies such as hepatoencephalopathy, leukoencephalomalacia, togaviral encephalitis, equine herpesvirus 1 (EHV-1), protozoal and other meningoencephalomyelitides, and space-occupying masses. In ruminants, rabies may resemble pseudorabies, herpesvirus encephalitis, infectious thromboembolic meningoencephalitis, nervous ketosis, grass tetany, hypocalcemia, polioencephalomalacia, nervous coccidiosis, or even focal spinal cord or peripheral nerve diseases. Most horses die of fatal encephalopathy within 5 days of the onset of signs, but cases lasting as long as 14 days have occasionally been observed.[11]



FIG. 35-7 Ten-month-old mixed-breed calf with terminal rabies virus encephalitis. The calf is comatose and showing opisthotonos.

TABLE 35-3

Occurrence of Particular Clinical Signs of Rabies in Horses

Clinical Signs	Frequency of Occurrence
Ataxia, paraplegia	11/21
Lameness	5/21
Pharyngeal paralysis	2/21
Recumbency	21/21
Colic	2/21
Hyperesthesia	17/21
Tail and anal paralysis	12/21
Fever	11/21

From Green S, Smith LL, Vernau W, et al. 1992. Rabies in horses: 21 cases. J Am Vet Med Assoc 200:1133.

Clinical Pathology There is no valid antemortem test to diagnose rabies in livestock. Rabies usually remains immunologically and serologically silent throughout the incubation and clinical phase of the illness. Clinicopathologic tests are not specific for rabies but may help rule out other, more common diseases. The CSF may be normal or may show moderate mononuclear pleocytosis (5 to 30 cells/μL) and increased protein (60 to 200 mg/dL), occasionally with neutrophils, eosinophils, or xanthochromia reported. Laboratory personnel should be warned that rabies is on the differential diagnosis list when CSF is submitted for analysis.

Pathology and Postmortem Diagnosis Rabies causes a nonsuppurative meningoencephalomyelitis. Microscopic changes include edema, meningeal congestion, focal areas of hemorrhage, perivascular cuffing, gliosis, neuronophagia, and neuronal degeneration. These changes are most severe in the dorsal root ganglia and can be seen in most CNS regions.

A definitive diagnosis of rabies may be based on the finding of Negri bodies on histologic examination of brain tissue (notably, these are not always present, especially in cases euthanized early in the disease course) or through a positive direct or indirect fluorescent antibody (DFA, IFA) test conducted on fresh smears of CNS tissues (thalamus, hippocampus, brainstem, pons, medulla, cerebellum).[12-14] If these tests are negative or inconclusive and there has been human exposure, additional testing can be done using intracerebral

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inoculation of mice with CNS tissue from the suspect case. The DFA test on brain tissue has become the standard by which the value of other rabies tests is evaluated.[12] In cases of human exposure, public health authorities should always be contacted before sample collection and submission. The diagnostic pathologist will usually accept the refrigerated head (or even whole body for small animals and bats) or refrigerated brainstem and cerebellum collected through the foramen magnum in mature cattle and horses. Care should be taken to prevent any human exposure to body fluids and CNS tissue of any animal with rabies on the list of differential diagnoses, especially in areas where rabies is known to be present in any domestic or wildlife species; open wounds or small healing sores may provide portal of entry for the rabies virus.

Pathophysiology After subcutaneous or intradermal inoculation, the rabies virus replicates locally. Subsequently, it binds to the acetylcholine (and other) receptors of the peripheral nerves and then migrates retrogradely to the CNS through peripheral nerves, spinal rootlets, and the spinal cord. After entry into the nerve cell rootlets, the virus travels to the brain along nerve tracts and into CSF. From there it spreads centrifugally along the rootlets of the cranial nerves to the salivary glands and the nasal epithelium. While inside cells, rabies evades the immune system by blocking certain signaling proteins necessary for those cells to respond to interferons.[15] The virus must replicate in the brain before it can reach the salivary and nasal secretions. Therefore whenever an animal bites a person, the attacking animal can always be sacrificed and tested for the potential of rabies virus transmission, and it not necessary to wait for disease progression before testing an animal for rabies, as recommended earlier when histologic examination for Negri bodies was the main diagnostic test for rabies. Negri bodies are aggregates of viral proteins and nucleic acids, most commonly seen on histologic examination of the hippocampus of rabies-infected animals. In humans, most cases become apparent within 1 to 3 months of infection, but a small proportion of cases have had incubation periods in excess of 6 months, extending to several years in rare cases.[1] The rabies virus replicates in the cell bodies (gray matter) of the CNS. Dysfunction of these neurons results in behavioral changes and variable abnormalities of the cranial and the peripheral nerves, with multifocal loss of lower motor neuron and autonomic function. Death results from cardiorespiratory paralysis as the virus infects the brainstem medullary centers.

Epidemiology Rabies is a reportable zoonosis that has been detected worldwide, with some exceptions (primarily islands). It does not presently occur in Sweden, Norway, the United Kingdom, Ireland, Australia, New Zealand, or Iceland.[1] The disease is endemic in other parts of the world including the United States, Canada, and Europe but remains epizootic in Central and South America, Africa, and parts of Asia, especially where a tropical climate and a high population of infected feral mammals favor viral propagation and transmission.[2,4] The rabies virus is shed in the saliva and does not survive when dried or exposed to ultraviolet (UV) light. The most common method of viral transmission to domestic animals is through the bite of an infected feral or wild mammal. Humans and laboratory animals have also developed fatal infections after respiratory exposure to viral aerosols. Low levels of rabies virus are also shed in the milk of infected animals and may occasionally infect offspring nursing infected dams.[16,17] Laboratory animals, foxes, and skunks can also be infected experimentally by ingestion of infected tissues from rabies cases.[16,17] In the United States, survival of the virus in the wild may depend on cycling of infections in skunks, bats, or raccoons, which are also common sources of livestock infections.[18,19]

Certain strains of rabies virus have low virulence in skunks and bats, resulting in asymptomatic carriers serving as reservoirs. The rabies virus is also transmitted directly among bats through aerosols in caves. The bats may die off from rabies during periods of high viral contamination. In the United States the most common wild reservoirs are foxes in Alaska and along the border of Mexico, raccoons in the East, and skunks in the central and western regions.[4] Mandatory vaccination of dogs has virtually eradicated canine rabies from developed countries, where rabies transmission from domestic dogs to livestock is rare.[1,20] Island nations have been able to remain free of rabies by imposing a 6-month quarantine on imported dogs and cats. In South America, rabies outbreaks in cattle often result from vampire bat bites, causing up to 50,000 cattle deaths annually. Human rabies cases may result from bites inflicted by infected pets, feral dogs and cats, bats, or wildlife. Cases resulting from contact with infected cattle or horses are rare.[4,20,21]

Prevention Although widespread rabies vaccination of livestock is neither economically feasible nor justifiable on public health grounds, vaccination of valuable livestock or animals that travel or are in regular contact with humans (e.g., petting zoos, animal shows) should be considered, particularly in or near rabies epizootic areas. A list of licensed rabies vaccines for the protection of animals against rabies is regularly updated by state veterinary authorities.[22] Strict adherence to label directions for use of these vaccines is mandatory. In some jurisdictions, immunization of large animals is considered by regulatory authorities to be valid only if the vaccine is administered by a licensed veterinarian.

The disposition of livestock that have been bitten by rabid animals depends on the animal's vaccination history, local and national regulations, and the value of the bitten victim. In the United States and Canada, the disease must be reported to the state public health department. Management of exposed livestock must be coordinated with public health officials. Any livestock bitten by a wild animal should be considered to have been exposed to rabies, regardless of the availability of the biting animal for testing. If a bitten horse had been vaccinated before the bite, it should be revaccinated immediately and kept under observation for 90 days. Other exposed, unvaccinated animals with a low economic value should be euthanized, or if the animal is valuable, the bite wound may be washed with copious amounts of water and iodine or quaternary ammonium disinfectants, after which the animal should be quarantined for at least 6 months and the brain should be examined if it dies.[22] The prolonged quarantine period is based on case reports of prolonged incubation periods in certain species.[1]

Vaccination of animals shortly after rabies virus exposure is not recommended because it is less effective than prophylactic vaccination, and idiopathic responses to the vaccine may complicate interpretation of the animal's disease status after exposure.[1] Whenever human exposure to rabies virus is suspected, the suspected animal must be euthanized and its brain must be examined for evidence of infection. A vaccinated or valuable animal may be quarantined for 6 weeks under veterinary supervision, and the brain must be examined if it develops clinical signs suggesting rabies during that period. The World Health Organization (WHO) publishes and regularly reviews its recommendations for vaccination and prophylaxis in humans after exposure or suspected exposure to the rabies virus.[2]

Control of rabies by immunization of susceptible wildlife using baits containing modified live vaccines has been successful in certain cases.[1,4,23,24] Such approaches may provide a means for large-scale immunization of wildlife or feral animal populations for eventual eradication of the disease.

Sporadic Bovine Encephalomyelitis (Buss Disease; Polyserositis; *Chlamydophila pecorum* Infection)

Sporadic bovine encephalomyelitis (SBE) is caused by *Chlamydophila pecorum* biotype 2, an organism previously named *Chlamydia psittaci* and *Chlamydia pecorum*.[1] The disease was first reported in the United States in 1940.[2] A similar but not identical viral disease occurs in cattle in Australia and has been named *bovine ephemeral fever*.[3-5] Outbreaks of SBE are rare, but the attack rate in an epizootic ranges from 5% in adults to 25% in calves. The mortality is highest in calves and approximates 30% for all age groups.[6]

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Infected cattle shed the organism in urine, feces, nasal secretions, and milk. It can also be found in the feces of asymptomatic calves exposed to clinically affected herdmates. The agent tends to remain endemic on a single farm, and sporadic outbreaks of disease may occur only on those premises. The pattern of these outbreaks varies, from a few cases annually to acute, recurrent epizootics with high case-attack rates that subside after 3 to 4 weeks.

Clinical Signs Affected animals show signs of a multisystemic disease. The initial clinical signs in cattle are fever (39° C to 41.5° C [102.1° F to 106.7° F]), diarrhea, anorexia, depression, and stiffness. Early cases may show signs of a respiratory disease characterized by nasal discharge, dyspnea, and cough. These animals occasionally have a painful response to percussion of the hoof, as well as swelling of the coronary band or polyarthritis and tenosynovitis.[2] Auscultatory abnormalities may include high-pitched wheezes and crackles over the lung fields or pleural and pericardial friction rubs. Because of the fibrinous peritonitis and pleuritis, the clinical signs in some affected animals may resemble those of hardware disease. These animals may grunt or groan when sudden pressure is applied to the xiphoid region. Progression of the disease is related to development of the meningoencephalitis and is characterized by ataxia and conscious proprioceptive deficits, circling, head tilt, opisthotonos, hyperesthesia, stiff neck, convulsions, and coma. Animals may die after 4 to 10 days.

Diagnosis The detection of reticulate bodies in the exudate cells of pleural and peritoneal effusions is highly suggestive of SBE. The agent can be most readily detected in clinical samples by PCR, although inoculation of laboratory animals may also be used.[1] Serologic testing is difficult to interpret, as antibodies to *C. pecorum* may cross-react with other species of *Chlamydophila* on certain serologic tests.[1]

Pathogenesis and Pathologic Lesions The mode of transmission and the genesis of pathologic lesions are unknown in natural cases, but postmortem lesions support the role of hematogenous dissemination of the organism to the CNS and other tissues. The extracellular form, termed an *elementary body,* is metabolically inert and can be shed in the feces and urogenital secretions of multiple animal species.[1] The pathogenesis of infection and invasion into the host's bloodstream is not well understood. Growth of the organism in the arteriolar endothelium causes vasculitis, hemorrhage, edema, and accumulation of fluid in the body cavities. Diffuse fibrinous pleuritis, peritonitis, and meningitis are also seen. Microscopic changes include perivascular mononuclear cell infiltration and neuronal degeneration.

Treatment Early cases of SBE can be treated with oxytetracycline (20 mg/kg/day for a minimum of 7 days). Efficacy is indicated by a reduction of fever within the first 24 hours of treatment.

Control There are no known effective control measures for the prevention of SBE. The chlamydial agent is susceptible to a number of disinfectants including 2% sodium hydroxide (NaOH), 5% cresol, and 0.3% quaternary ammonium compounds.

Meningitis (Suppurative Meningitis; Bacterial Meningitis)

Definition and Etiology Bacterial meningitis is defined as inflammation of the meninges surrounding the brain and/or spinal cord that results from bacterial invasion of these tissues.[1] If the infectious process extends into brain tissue, the condition is termed *meningoencephalitis;* if it extends into the ventricles of the brain, it is meningoventriculitis. Differentiation of meningitis from the other two conditions almost always requires advanced imaging techniques or histologic examination, but the conditions result in similar clinical signs.[2] It is a relatively rare condition in large animals. It is most often the result of hematogenous infection in neonates, as a consequence of septicemia with partial or complete failure of passive transfer of colostral antibodies, or with septicemia resulting from translocation of invasive bacteria from the gastrointestinal tract, respiratory tract, or umbilicus.[2,3] Hematogenous infection of the meninges and/or brain can also occur sporadically in adults; such events may be associated with septicemia from a primary focus of infection such as the udder, uterus, gastrointestinal tract, or other sites. As for neonates, underlying immunodeficiency may predispose adult animals to this disease.[4,4a]

Bacterial meningitis can also result from direct extension of infectious agents into the calvarium such as extension of pyogenic infections into the calvarium from infected skull fractures,[5,6] osteomyelitis from sinusitis or otitis media/interna,[7] or osteonecrosis caused by thermal cauterization during dehorning (particularly in goat kids).[8] Improper placement of trephination holes, cribriform plate fractures, and extension from infected coccygeal vertebrae are additional routes of meningeal infection. In horses, septic meningitis is a potential sequela to surgical removal of progressive ethmoidal hematomas and has also been reported as a consequence of local spread of infections of the paranasal sinuses, nasal cavity, periocular tissues, and submandibular lymph nodes.[9]

A multitude of bacteria have been isolated from the blood, meninges, brain, and/or spinal cord of affected large animals. In neonatal calves and foals, gram-negative enteric bacteria such as *Escherichia coli, Salmonella* spp., and *Klebsiella* spp. are considered common isolates.[1,2] *Mycoplasma* spp. may be isolated in goat kids. *Histophilus somni* is a potential cause of meningitis in juvenile cattle in feedlots and is reviewed later in this chapter, as are CNS infections caused by *Listeria monocytogenes*. A variety of gram-positive and gram-negative bacteria may be involved in adults, a fact that underscores the importance of cytologic examination, Gram staining, and aerobic and anaerobic culture of CSF samples obtained early in the clinical course of disease.[1,2,10] PCR assays of CSF may be used to identify specific organisms of high clinical suspicion, as was recently done for diagnosis of meningitis caused by *Borrelia burgdorferi* in a horse.[4a]

Clinical Signs The earliest clinical signs of meningitis are often nonspecific and may reflect the signs induced by a primary infection site (e.g., diarrhea in neonates with invasive bacterial enterocolitis). Fever is common, as is anorexia and/or loss of a coordinated suckle in a neonate.[3] Reluctance to lift or bend the neck may be evident, and manipulations by the examiner may induce responses suggestive of hyperesthesia.[2,3,11] Slight tactile stimulation of the skin may result in strong spasmodic extension of the limbs, fasciculations of the underlying musculature, or even generalized frantic motor activity. The patient's behavior may vary from extreme depression to hyperexcitability. A subtle intentional head tremor is often observed in foals. Dysfunction of one or more cranial nerves may result in facial muscular tremors, nystagmus, facial palsy, blindness, anisocoria, or strabismus. Progression of the clinical signs is associated with a decreased sensorium, propulsive walking, coma, seizures, and status epilepticus. Sequelae to septicemia such as septic arthritis or polyarthritis, uveitis, panophthalmitis, hypopyon, cardiac murmurs secondary to valvular endocarditis, and pyuria/proteinuria may be detected as well.

Differential Diagnosis The clinical signs of bacterial meningitis closely resemble those of viral encephalomyelitis caused by such agents as rabies, West Nile, and togavirus encephalomyelopathies (eastern equine encephalomyelitis, Venezuelan equine encephalomyelitis, and western equine encephalomyelitis, described elsewhere in this chapter). Metabolic encephalopathies may also mimic bacterial meningitis including hypomagnesemia, hypocalcemia, hypoglycemia (which may occur simultaneously with septic meningitis in neonates), hepatic encephalopathy, renal encephalopathy, and encephalomalacias (e.g., salt poisoning, polioencephalomalacia). Congenital neurologic disorders of neonates may be

considered; however, these disorders do not typically induce fever, inflammatory leukogram, or inflammatory changes in the CSF.

These numerous differentials are distinguished from bacterial meningitis by compilation of data obtained by physical examination, serum immunoglobulin measurement, serum biochemistry analysis, complete blood count, and most importantly, cytologic examination, Gram stain, and culture of CSF. Early clinical suspicion of bacterial meningitis and rapid administration of appropriate antimicrobials are necessary to improve survival and minimize long-term neurologic impairment,[1,2,10] In a human study of pneumococcal meningitis, a delay of antimicrobial treatment of more than 3 hours after arrival was associated with higher morbidity at 3 months after admission.[12] Therefore it may be prudent to initiate appropriate antimicrobial therapy if the animal shows signs compatible with bacterial meningitis, then withdraw or modify antimicrobial therapy if that diagnosis is subsequently refuted by ancillary diagnostic data.

Clinical Pathology Diagnosis of meningitis is based on examination of the CSF (for normal values, see Table 35-1). The CSF of animals with meningitis may be turbid and white to amber in color, may foam when shaken, and may clot. Xanthochromia may be observed in some specimens. The WBC counts in CSF of calves with purulent meningitis are typically greater than 100 neutrophils/μL, and protein concentrations range from 20 to 270 mg/dL.[12] The differential cell counts in the CSF are either predominantly neutrophilic or mononuclear. Owing to bacterial consumption of glucose in the CSF, the concentration of glucose in the CSF is often less than 50% of the corresponding concentration in the serum. Gram staining of CSF should be conducted in all cases. Abnormalities in the blood are inconsistent and reflect secondary conditions such as septicemia, diarrhea, or concurrent fluid therapy. These changes could include leukocytosis, left shift, toxic changes in the neutrophils, hyperkalemia, respiratory acidosis, hypoglycemia, and hyponatremia or hypernatremia.

Pathophysiology Bacterial proliferation in the CNS results in production of bacterial endotoxins, cytokines, and other products of inflammation that damage the neural parenchyma. Vascular sequelae of infection may include thrombotic or hemorrhagic infarcts. After several days, inflammation of the arachnoid trabeculae and choroid plexus can result in decreased CSF absorption and hypertensive hydrocephalus.[1,3]

Necropsy Findings Gross lesions of primary infection in other organs and/or lesions suggestive of generalized sepsis may be apparent. When meningitis occurs secondary to trauma, the site of organism entry may be detectable. The meningeal vessels appear to be congested, and the meninges are swollen, opalescent, and petechiated. The CSF is cloudy or amber and may contain fibrin clots. Microscopic changes of CNS tissues include infiltration by neutrophils and lymphocytes, inflammation of the meningeal vessels, scattered hemorrhages, and bacterial colonies around the blood vessels of the meninges and the brain parenchyma.

Treatment Treatment of bacterial meningitis is difficult, and the mortality rate is high, so treatment should be initiated only after owners are appropriately counseled. Early recognition and treatment are essential for adequate recovery. Antimicrobial sensitivity tests performed on isolates from CSF may provide valuable information on ideal drugs. Because prompt treatment of meningitis is critical, antibiotic therapy must be based on the Gram-staining characteristics of bacteria in CSF and the initial 24-hour cultures. When expert laboratory cytologists are not immediately available, CSF can be placed into microhematocrit tubes and centrifuged for 10 to 15 minutes. The tube can then be scored with a file and broken at the interface of the fluid with the clay sealant, and the cell-rich fluid from the two ends of the broken tube can be smeared for cytologic examination and Gram stain. In rabies-endemic areas, appropriate precautions should be taken when handling CSF.

Domestic animals have a well-defined blood-CSF barrier, and antibiotics that reach high plasma concentrations may not necessarily reach bactericidal concentrations in the brain. However, under conditions of local inflammation, this barrier becomes considerably more permeable to certain antimicrobials.[1,10] As a general rule, in order to maximize distribution of antimicrobials across this barrier into infected meningeal or neural tissue, the highest dosage of antimicrobial established for the species in question should be used.[1,10] Toxicity potential and/or excretory organ dysfunction may limit dose escalation of certain classes of drugs such as aminoglycosides. Intravenous administration is preferred in order to obtain peak blood concentrations and spur greater diffusion of drugs across this barrier. Owing to the lack of endogenous immune capacity in normal neural tissue, bactericidal antimicrobials have been considered superior to bacteriostatic drugs, although this is controversial because successful use of bacteriostatic drugs has been reported.[1,10] The primary factors influencing CSF penetration of drugs in the healthy state are the lipid solubility (increased penetration with more lipid solubility) and molecular size (increased penetration with smaller size). However, the penetration capacity of a given antibiotic is not the sole determinant of appropriate antimicrobial selection because the blood-CSF barrier is made more permeable in bacterial meningitis. In fact, high-dose therapy with certain β-lactams—some with limited lipid solubility—either as monotherapy or in combination with antimicrobials of other classes, is currently recommended for many bacterial agents that cause meningitis.[10]

At present, use of all antimicrobial agents in treatment of bacterial meningitis in food animals and horses represents off-label use, and due consideration of legal restrictions on use should be considered in all cases. Further, the paucity of clinical reports and the variety of treatments used in those reports complicates the goal of making evidence-based decisions for treatment of this disease in horses and food animals. Therefore guidelines from published reviews of treatment in horses,[1] cattle,[3] and human medicine[10] are presented here.

When possible, meningitis caused by the gram-negative enteric bacteria should be treated with specific third- (ceftazidime, ceftizoxime, ceftriaxone, cefoperazone, cefotaxime) or fourth-generation (cefepime) cephalosporins. For horses, ceftriaxone (50 mg/kg IV q6h) or cefotaxime (40 mg/kg IV q6h)[1] have been used. Owing to a high degree of protein binding in serum, ceftiofur (at 2 mg/kg IM) does not appear to distribute into the CSF of normal horses.[1] Its performance in penetration of the inflamed blood-CSF barrier remains to be determined. Alternatively, penicillin G sodium or potassium (20,000 to 40,000 IU/kg IV q6h) or sodium ampicillin (20 mg/kg IV q8h) may be used, with success considered to be highly dependent on the susceptibility of the causative organism, a parameter that is often unknown in the initial treatment decision process. If enteric organisms are suspected in a neonate and third- or fourth-generation cephalosporins are not available or are cost prohibitive for use, ampicillin is considered to have superior gram-negative spectrum over penicillin G. Coadministration of an aminoglycoside can be considered for such neonates, with due consideration of nephrotoxicosis potential and, in animals intended for food, withdrawal time.[1,10] Although aminoglycoside antimicrobials are highly effective against gram-negative bacteria and are bactericidal, their efficacy for the treatment of purulent meningitis is diminished by their polar characteristics and low attainable CSF concentrations. Nonetheless, combination therapy consisting of a β-lactam and aminoglycoside may be effective for achievement of broad-spectrum coverage[10]; it can be speculated that the latter drug may at the very least reduce the circulating burden of gram-negative bacteria in the bloodstream and elsewhere. Although still used on occasion, intrathecal administration of preservative-free aminoglycosides has not been shown to produce tangible clinical benefit when compared with intravenous use.[10]

Alternative treatments for meningitis caused by gram-negative enteric bacteria, based on anecdotal data, include enrofloxacin (5 mg/kg IV q12h, with due consideration to potential cartilage damage and reduction of seizure threshold[1]), or trimethoprim-sulfonamide

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(5 mg/kg based on trimethoprim component, q12h IV).[3] In horses, chloramphenicol (25 to 50 mg/kg PO q6h) may be considered for use.[1] If β-lactam–resistant organisms are suspected, imipenem (10 to 20 mg/kg IV q6h) may be used, but its efficacy for meningitis in foals remains undetermined[1] and it carries the potential to lower the patient's seizure threshold.[10]

Meningitis caused by gram-positive bacteria may be treated with high doses of intravenous penicillin, ampicillin, or trimethoprim-sulfonamide combinations as described earlier. Third- and fourth-generation cephalosporins can be considered because these retain activity against certain gram-positive organisms.[1] For humans, moxifloxacin penetrates the blood-CSF barrier and have greater gram-positive activity than earlier fluoroquinolones.[10] Other antimicrobials showing promise against specific gram-positive agents in human medicine include daptomycin and linezolid.[10]

Anaerobic infections are uncommon and most likely result from penetrating or necrotizing wounds of the skull bones. Such infections in horses should be treated with metronidazole (15 to 25 mg/kg PO q6h)[1]; penicillin or ampicillin would be appropriate therapy in food-producing animals. Treatment of meningitis caused by *Chlamydophila* or *Mycoplasma* spp. has not been critically investigated in large animals, but administration of oxytetracycline, doxycycline, fluoroquinolones, or florfenicol can be considered. In general, treatment for 2 weeks is considered to be an empiric standard[3]; however, if aminoglycosides are included in the treatment regimen, careful patient monitoring for nephrotoxicosis is recommended.

Adjunct therapy for bacterial meningitis includes analgesics/antiinflammatory/antipyretic agents, fluid therapy, anticonvulsant therapy for seizures, protection against self-induced trauma (including corneal trauma), and nutritional support. Maintenance of euvolemia and euglycemia is considered vital to success.[10] Hypoxemia and hypercapnea are deleterious and should be avoided whenever possible; mechanical ventilation of severely affected patients may be necessary. Osmotic diuretics such as mannitol or glycerol should be administered if CSF pressure, neurologic examination, and/or fundic examination are suggestive of cerebral edema. Use of narcotic agents for analgesia should be weighed against their potential to increase cerebral blood flow and therefore intracranial pressure. Although outcomes vary according to the causative organism, concurrent administration of dexamethasone may improve clinical outcome, although this remains controversial.[10] Nonsteroidal anti-inflammatory agents may be a preferred choice if avoidance of dexamethasone-related complications (e.g., laminitis) is a concern. Owing to limited food intake and the pain associated with this condition, the potential for gastric ulceration is real and prophylactic anti-ulcer medication should be considered. Treatments for seizures, cerebral edema, and inflammation are listed in Table 35-3.[13-17] The maximum desirable trough phenobarbital concentration is 40 μg/mL, and the minimum therapeutic level is 15 μg/mL.[14,15] After initial sedation, long-term control of convulsions in horses can be maintained by oral phenytoin (2.8 to 16 mg/kg three times daily) or IV phenobarbital (11 mg/kg once daily).[15-17] The trough plasma concentration of diphenylhydantoin should also be measured repeatedly during continuous drug therapy; the maximum desirable trough level is 10 to 20 μg/mL,[16] and optimum plasma concentration is 5 to 10 μg/kg. In critical care settings, constant rate infusions of selected anticonvulsive drugs and drug combinations can be considered. The concentration of plasma immunoglobulins should be measured in neonatal patients with bacterial meningitis, and plasma should be administered if those values are subnormal for the species.

Prognosis A guarded prognosis at best is warranted for most cases of bacterial meningitis. In a retrospective study of 32 calves with septic meningitis, only 5 (16%) survived until discharge and all 5 animals subsequently died or were euthanized.[2] In a recent case series from Spain, two of seven treated foals survived to discharge.[18] The survival rate may be higher for adult horses.[9] Early detection is considered pivotal for successful treatment; therefore a poor prognosis is warranted for animals with severe neurologic impairment. However, because concurrent metabolic derangements (e.g., hypoglycemia) may cloud the clinical picture, aggressive antimicrobial treatment including achievement of euvolemia, euglycemia, control of convulsions (if present), and normalization of acid-base, blood gas, and electrolyte status may be attempted for valuable animals, with the prognosis refined on the basis of response to therapy.

Pituitary Abscesses

Pituitary abscesses occur sporadically in ruminants and are rare in horses. *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is the most frequently isolated bacterium, but *Corynebacterium pseudotuberculosis,* as well as *Streptococcus, Staphylococcus, Actinomyces, Bacteroides, Fusobacterium, Acinetobacter, Pasteurella, Pseudomonas,* and *Actinobacillus* spp. have occasionally been isolated.[1]

The clinical signs of pituitary abscess occur suddenly and progress for 7 to 10 days before the affected animal dies.[1] The initial signs are ataxia, head-neck extension, basewide stance, inappetence, depression, head pressing, and recumbency.[1-3] Most affected animals have asymmetric deficits of one or more cranial nerves, resulting in dysphagia, blindness, anisocoria, absent pupillary light reflexes, mydriasis, and/or a flaccid tongue. Nystagmus, facial paralysis, facial hypalgesia, ventrolateral strabismus, or head tilt may also be seen.[1,4] Approximately half of the affected animals have bradycardia (pulse rate < 60 beats/min).

The CSF protein concentration in affected cattle ranges from 70 to 502 mg/dL, and nucleated cell counts range from 6 to 12,640/μL (6% to 84% neutrophils).[1] The antemortem diagnosis is based on the observation of bradycardia, blindness, and nonresponsive pupils in conjunction with evidence of pyogenic inflammation in the CSF.

Some authors have postulated that the infectious agent gains entry to the sella turcica hematogenously and then localizes in the rete mirabile, which is the complex of blood vessels encircling the pituitary gland.[1] A direct relationship exists between the complexity of the rete mirabile and the incidence of pituitary abscessation in different mammals. The horse and dog lack a well-defined rete and correspondingly have a low risk for developing a pituitary abscess, whereas the situation is reversed in cattle. One study reported that 55% of cattle with a pituitary abscess had pyogenic foci in other organ systems or in the sinuses, teeth, or soft tissues of the face,[1] indicating that the abscesses may result from a retrograde bacterial embolization through branches of the facial veins.

Ataxia is caused by interruption of extrapyramidal motor nuclei in the brainstem by the expanding abscess. Extension of the abscess into the communicating retroorbital rete may result in exophthalmos. Extradural extension of the abscess along the brainstem causes loss of the cranial nerve function. Bradycardia may be caused by interference with diencephalic cardioacceleratory centers.

Animals ranging in age from 9 months to 12 years have been affected, but most cases occur between 2 and 5 years of age.[5] Pituitary abscess appears to have a slightly increased prevalence in castrated and intact males.[1] Pituitary abscess has been related to infections that develop in bulls after insertion of a nose ring.[3] Prophylactic administration of penicillin and attention to aseptic procedure during insertion of the ring can reduce disease incidence. Because of the high mortality rate associated with pituitary abscesses, treatment is not usually attempted.

Brain Abscesses

Streptococcus equi is the most common cause of brain abscesses in horses, likely owing to the occurrence of strangles in this species.[1] *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is a common cause of brain abscesses in cattle by means of extension of a sinus infection through the calvarium. Brain infections of cattle with *Bacteroides* species have also been reported.[2] The neurologic dysfunction caused by brain abscesses typically has a slower onset and is more commonly asymmetric than that caused by meningitis. However, acute onset of signs can also occur.[1] Forebrain abscesses

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compress the cerebral cortex, causing a caudal displacement of the brain and functional loss of one or both occipital lobes, which may result in cortical blindness in one or both eyes. Because of the high proportion of crossed fibers in the optic nerve decussation, unilateral cortical abscesses may result in vision loss in the contralateral eye. Increased CNS compression by the mass may induce ipsilateral mydriasis caused by interference with the oculomotor nerve. Further increases in the size of the lesion cause more generalized cortical signs including blindness, propulsive walking, circling, head tilt (toward the lesion side), depression, coma, head pressing, or sudden unexplained mania (Fig. 35-8). Abscesses at the base of the brain may cause additional abnormalities of cranial nerve function including vestibular disease (Fig. 35-9). Ophthalmoscopic examination may reveal papilledema in the ipsilateral eye.[2] Advanced imaging studies such as CT and MRI may be helpful for antemortem diagnosis when these modalities are available.[3-5]

In later stages, animals may assume lateral recumbency and display a decerebrate posture characterized by hypertonicity, hyperreflexia, opisthotonos, coma, and convulsions. At this stage the disease is difficult to differentiate from septic meningitis. CSF findings in animals with brain abscesses are variable, ranging from normal to very abnormal, with high protein concentration and marked pleiocytosis.[1,6,5] Treatment of brain abscess includes antibiotics and supportive care (see Meningitis earlier in this chapter). In one clinical report a brain abscess in a horse was localized with CT scanning and successfully drained through a craniotomy.[7]



FIG. 35-8 Head pressing in a pony caused an abscess in the right cerebral hemisphere. *(Courtesy Dr. R.H. Whitlock.)*



FIG. 35-9 Severely obtunded bull that developed a brain abscess from extension of a frontal sinusitis. The abscess extended to the base of the brainstem and affected cranial nerves V and XII, resulting in dropped jaw and tongue paralysis. The bull was also severely depressed, blind, and ataxic and had facial analgesia.

Nervous Coccidiosis

Definition and Etiology Nervous coccidiosis is a neurologic syndrome of calves and yearling cattle, sheep, and goats that is associated with enteric infections by *Eimeria* spp. The condition is most often seen in western Canada and the northwestern United States and is particularly prevalent in feedlots. The incidence of nervous coccidiosis is highest in the winter months. In contrast to enteric coccidiosis, mortality from nervous coccidiosis is relatively high, approximately 70%.[1] The pathogenesis of the encephalopathy may be related to the elaboration of a labile neurotoxin by the parasite.[2] The clinical signs and history of nervous coccidiosis are similar to those of other neurologic diseases that affect the function of the cerebral cortex.

Clinical Signs The onset of the nervous system signs is usually preceded by diarrhea, tenesmus, and hematochezia. Some calves with severe diarrhea develop prolapsed rectums. Initial signs of CNS dysfunction include depression, incoordination, twitching, and hyperesthesia. As the clinical signs worsen, the animal becomes recumbent and develops numerous cerebrocortical signs including opisthotonos, periodic tremors, horizontal nystagmus, frothing at the mouth, bellowing, snapping eyelids, and muscular fasciculations.[3-6] Blindness is rarely seen. Stimulation of the patient may precipitate a tonic-clonic seizure.[3-6] The animal may die after 1 to 5 days of encephalopathy. Convulsive calves may regain consciousness but relapse days later.[7]

Clinical Pathology Fecal flotations from the patient and herdmates show a large burden of coccidial oocysts. Fecal egg counts of affected animals may range from 5000 to 4 million/g. To exclude the possibility of other neurologic diseases, blood should be collected for measurement of electrolytes (calcium, magnesium, potassium). The acid-base status, plasma glucose, and blood lead concentrations should be measured. Acute meningitis and salt poisoning may be ruled out by CSF analysis. The plasma vitamin A concentration should be measured in any animal that has not had exposure to green forage. Polioencephalomalacia, ethylene glycol poisoning, lead poisoning, rabies, pseudorabies, petroleum distillate poisoning, and clostridial enterotoxemia should be considered as possible differential diagnoses.

Pathophysiology The pathogenesis of the encephalopathy is unknown. The nervous form of coccidiosis cannot be transmitted to mice by injection of CSF from infected calves; however, a heat-labile neurotoxin has been identified in the serum of calves with nervous coccidiosis.[2] The coccidia do not directly invade the CNS.

Epidemiology Nervous coccidiosis occurs most frequently in feeder cattle, but dairy and pastured beef calves, lambs, and kids may also be affected on occasion. In one survey, the prevalence of nervous coccidiosis was 0.3% of the calves that were affected with the intestinal form of the disease. Nevertheless, outbreaks with a large percentage of calves developing CNS disease have been reported.[3] In western Canada, nervous system signs have been reported in 21% of

herd outbreaks of intestinal coccidiosis.[8] Most cases occur in mid to late winter.

Necropsy Findings No macroscopic lesions are seen in the CNS of calves with nervous coccidiosis. The microscopic lesions of the brain are mild and nonspecific and include edema, congestion, and occasional shrunken neurons. Parasitic invasion of the ileum, cecum, and colon results in lesions in these organs.

Treatment and Prevention Treatment should include supportive fluid, macromineral, and electrolyte therapy. The coccidial infection should be treated with sulfadimethoxine (55 mg/kg PO or IV, followed by 27.5 mg/kg PO or IV q24h). Alternatively, sulfamethazine (110 mg/kg PO q24h for 5 days, or 1 lb/100 gallons of drinking water) or amprolium (50 mg/kg/day PO for 7 days) can be administered. Treatment administered via drinking water will only be effective if animals are willing and able to drink. Diazepam, sodium pentobarbital, or phenobarbital may be used to control tonic-clonic convulsions (see Table 35-3). The response to treatment is poor, and the case-fatality rate can be high in calves that develop tonic-clonic seizures. Specific chemotherapeutic regimens and methods of preventing intestinal coccidiosis are described in Chapter 49.

Sporozoan Infections of Ruminants (*Sarcocystis* Infection)

Definition and Etiology The three recognized species of *Sarcocystis* that infect cattle—*S. cruzi, S. hominis,* and *S. hirsuta*—are sporozoan parasites with definitive hosts of dogs, primates, and cats, respectively.[1,2] Three other *Sarcocystis* species—*S. capricanus, S. ovicanus,* and *S. tenella*—have definitive hosts in dogs and secondary hosts in goats and sheep.[3]

When a carnivore ingests flesh from infected cattle, *Sarcocystis* cysts in muscle are broken down by digestive enzymes and motile bradyzoites are released. The bradyzoites infect the intestinal mucosal cell and differentiate into sexual stages. The gametes fuse to form an oocyst, which is shed onto pastures as sporocysts. When eaten by a ruminant, the sporocysts hatch in the proximal small bowel and penetrate into the medium-sized mesenteric arteries, where they enter endothelial cells and form sporozoites. The sporozoites then mature in three successive waves. Each wave of development spreads downstream. The third-generation merozoites finally enter the soft tissues and encyst as sarcocysts. The total period of development in the ruminant requires 10 weeks. The life cycle is completed whenever a carnivore ingests uncooked meat containing viable sarcocysts. Disease may develop in cattle during the maturation of the cyst in the muscles, at approximately 9 to 11 weeks after infection.

Clinical Signs Most cases of *Sarcocystis* infestation are asymptomatic in both definitive and secondary hosts. However, if a large number of sporocysts are ingested by a nonimmune ruminant, clinical illness may develop. Clinical signs include fever (>39.5° C [103.5° F]), anorexia, weight loss, symmetric lameness, and diarrhea. Neurologic signs include ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency, tonic-clonic seizures, leg biting, blindness, opisthotonos, and nystagmus.[4,5] Cattle may lose the hair of the tail switch ("rat tail"). Sheep may show a wool break.[1-5] Animals with chronic infections may develop edema of the limbs, poor weight gain, muscular atrophy, and pallor.[1-5] Second-trimester abortions may occur in cattle and small ruminants beginning 28 days after ingestion of infectious sporocysts.[6] The fetuses may appear either normal or autolyzed.

Clinical Pathology and Pathogenesis Serum activity of liver enzymes is increased. The packed cell volume (PCV) and the serum protein concentration are often decreased. During early infection there is a marked normocytic, normochromic anemia. The anemia is thought to be caused by extravascular hemolysis.[7]

Antibodies to solubilized freeze-dried *Sarcocystis* antigens have been detected by indirect hemagglutination, ELISA, and an agar gel immunodiffusion (AGID) test.[8-10] Immunoglobulin M (IgM) responses first occur by 3 to 4 weeks after infection and peak by 11 to 15 weeks.[8-10] The concentrations of *Sarcocystis*-specific IgG begin to rise by 5 to 6 weeks postinfection. Background titers of normal cattle range from 1:54 to 1:486, and titers of infected cattle often exceed 1:10,000.

Pathophysiology The pathogenesis of *Sarcocystis* is poorly understood. Pathologic changes in the skin and muscle and in serum chemistry are speculated to result from a combination of parasite-directed immunologic responses and diffuse vasculitis. Abortions probably occur because of luteolysis that results from the increased concentrations of prostaglandin $F_{2\alpha}$, caused by vascular infection by the parasite.[11]

Epidemiology Estimates of infection rates range from 70% to 98% in cattle in the United States.[1] When infected flesh is eaten by carnivores, the encysted sporozoites complete their life cycle.[1] The prepatent period of the parasite in the carnivore (primary host) ranges from 9 to 45 days. The primary host may shed the sporulated oocysts in the stool for as long as 2 months after a single infection. The oocysts withstand freezing but are rapidly killed by sunlight and drying.[1] Reexposure of previously infected canids results in a large fecal output of sporocysts. Ingestion of approximately 250 g of infected meat by a dog can result in an output of 100 to 6000 sporocysts per gram of feces. Wild canids are even more susceptible than domestic dogs and may serve as a major mechanism for propagation of *Sarcocystis* in range cattle in the western United States.

Pathologic Lesions The pathologic lesions of the CNS are similar for all species of sporozoans; they include granulomatous meningoencephalomyelitis, focal malacia, perivascular cuffing, neuronal degeneration, and gliosis. The changes are generally most severe in the cerebellum and midbrain but can occur anywhere in the CNS including the spinal cord. The pathologic diagnosis is based on finding meronts and merozoites in the affected sections of neural tissue.[12,13]

Pathologic lesions elsewhere include hemorrhages on the sclera, serous surfaces, and muscles; fluid in the body cavities; and lymphadenopathy. The muscles have alternating light and dark stripes. Macroscopic changes may not be evident in animals with chronic sarcocystosis. If changes are not evident, postmortem diagnosis is based on the finding of intravascular schizonts or intramuscular hemorrhages without significant inflammation. Ultrastructural examination of affected areas of CNS shows an intracellular colony with rosette orientation of agents in the cytoplasm of infected astrocytes.

Treatment Feeding monensin (100 mg/kg daily for 30 days) during the incubation period is prophylactic; however, the efficacy of the drug in symptomatic cattle is unknown. For maximum effectiveness, monensin should be administered continuously for 2 to 5 weeks after exposure. Treatment of infected sheep with salinomycin (1 to 2 mg/kg) has also been recommended.[14] Administration of amprolium (100 mg/kg once daily for 30 days) may reduce the severity of *Sarcocystis* infection[15] but may not completely eliminate the clinical disease.

Control The best method of controlling *Sarcocystis* infection is to protect the food supply of ruminants. Scavenging of carcasses by carnivores should also be prevented by deep burial or incineration. Feed bunks should be kept clean and raised approximately 1 to 3 feet (30 to 90 cm) off the ground. All carnivorous pets that have access to the feed or pastures should be fed cooked meat or processed dry food. In range pasture situations, prophylactic feeding of monensin or elimination of predatory or scavenging carnivores may be necessary.

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Neospora Infection of Cattle (Protozoal Abortion)

Definition and Etiology A cyst-forming protozoal parasite that closely resembles *Neospora caninum* has been identified in aborted fetuses from cattle in California. The condition is predominantly a disease of dairy cattle; however, sporadic abortions can occur in beef cows.[1-3] The predominant clinical sign of a *Neospora*-like agent is a midterm to late-term abortion (3 to 8 months of gestation). Fetal lesions consist of a focal nonsuppurative necrotizing encephalitis, nonsuppurative myocarditis and myositis, and mononuclear cell infiltrates disseminated in other tissues. Occasionally, calves are mummified. (See Chapter 43 for more on abortion).

Nonfatal infection in the fetus results in neurologic dysfunction of the newborn. The clinical signs of neurologic disease vary because of the randomly widespread distribution of the parasite within the CNS. Affected calves are often unable to stand and suckle and have abnormal spinal reflexes. Flexural contractions of the forelimbs, domed skull, and torticollis have also been reported in spontaneously occurring cases.[4,5] The calves are usually born with the CNS signs, which initially are mild but then progress after birth. Pathologic lesions associated with the fetal infection include focal areas of brain discoloration, focal cavitation with cyst formation, and reduction of gray matter. Microscopic changes in the CNS of affected calves include nonsuppurative inflammation of the gray and white matter, focal lymphocytic meningitis, and neuronal necrosis. Changes in other tissues include nonsuppurative myocarditis, myositis, and hepatitis. Protozoa can be seen in microscopic sections of the stained tissues.

Neospora organisms have been isolated in pure form using cultured cells.[6] Antibodies have been produced by intubation of laboratory animals, and the agent can be identified microscopically using immunoperoxidase staining on the fixed tissues. The CSF changes in affected calves range from normal to mild pleocytosis.[7] Similar conditions have been described in sheep[8,9] and goats.[10,11]

Babesia Encephalitis (Babesiosis; Piroplasmosis; Texas Cattle Fever; Tick Fever; Redwater)

Parasitemia of cattle caused by the protozoans *Babesia bovis, Babesia argentina,* and *Babesia bigemina* is usually subclinical but results in devastating economic losses worldwide.[1] The disease is transmitted to cattle by the cattle fever ticks *Boophilus annulatus, Boophilus microplus,* and *Boophilus decoloratus.* Babesiosis occurs in the Americas, Europe, Africa, Asia, and Australia. Ticks acquire *Babesia* infection from an infected animal and then pass the agent to their offspring through the ovaries. The protozoan is passed to susceptible cattle by adult ticks and nymphs. Most infections result in intravascular and extravascular hemolysis and kidney and liver failure. See Chapter 37 for more detail.

A small proportion of *Babesia* infections cause acute encephalitis.[2,3] CNS signs begin suddenly and include fever (41.7° C [107° F]), anorexia, depression, ataxia, conscious proprioceptive deficits, mania, convulsions, and coma. Sudden death is occasionally observed. The nervous system signs are accompanied by engorgement of the scleral vessels, icterus, proteinuria, and hemoglobinuria. Encephalopathic diseases that closely resemble babesiosis include rabies, nervous coccidiosis, polioencephalomalacia, lead poisoning, bovine herpesvirus encephalitis, theileriasis, heartwater disease, salt poisoning, and chlorinated hydrocarbon toxicity.

The pathogenesis of the CNS signs is unclear; however, possible causes include capillary thrombosis and infarction, disseminated intravascular coagulation (DIC), anoxic encephalopathy, and direct invasion of the CNS by the parasite. Thrombi are disseminated throughout the CNS. Expression of parasite proteins on the surface of infected RBCs facilitates binding of RBCs to capillary endothelial cells.[4] The proclivity of *Babesia*-infected RBCs for binding to brain capillaries, particularly those in the cerebellum, is supported by the high incidence of parasite-positive RBCs found in the brains of infected cattle.[5] These findings and the observation of increased prothrombin and partial thromboplastin times, thrombocytopenia, and decreased fibrinogen concentrations suggest that DIC may play a role in the pathogenesis of the CNS disease.[6-8] Vascular blockage in the CNS, caused by severe sludging of RBCs within brain capillaries, appears to be central to the pathogenesis of neurologic disease in infected animals.[9] Studies of *Babesia ovis* in sheep, in which neurologic disease did not occur, failed to demonstrate RBC blockage of brain capillaries.[10] This further supports the belief that CNS vascular pathology is key to the development of neurologic signs in bovine babesiosis.

Babesia encephalitis is a reportable disease in the United States. Suspect cases should be referred to the appropriate state and federal authorities.

Ehrlichia (Cowdria, Rickettsia) ruminantium Infection (Heartwater Disease)

Definition and Etiology *Ehrlichia ruminantium* is a rickettsial parasite that causes a fatal encephalitis in goats, sheep, and cattle.[1] The disease originated in sub-Saharan Africa and has spread to cattle in the West Indies (Guadeloupe, Antigua, and Marie Galante).[2] *E. ruminantium* is transmitted by *Amblyomma* ticks.[3,4] Although a number of *Amblyomma* species have been implicated in the transmission of heartwater disease, the most important agents are *Amblyomma hebraeum* and *Amblyomma variegatum.* The intermittent feeding behavior of the tick makes it particularly difficult to control. *Amblyomma* ticks require three separate blood meals to complete their life cycle. The gravid females fall from the host and lay the eggs in rotting vegetation, particularly in areas where the hosts are bedded for the evening. Recently hatched larvae crawl onto foliage and await a host. After their first feed the larvae detach, molt into nymphs, and await a second host. After refeeding, the nymphs detach and molt into adults. The adults remain under rotting vegetation until they are activated by carbon dioxide exhaled by a large mammal. They are further attracted to the host by pheromones from male ticks that remain permanently attached to the host. Animals that do not have male tick infestations are poor attractants for nongravid females. Once attached to the proper host, the females seek the male, breed, feed, and fall from the host when it lies down for the evening. Ticks that feed from *Ehrlichia*-infected hosts develop ovarian infections and transmit the agent to their offspring. This serves to perpetuate the agent over successive seasons.[5]

Many species of vertebrates including snakes, iguanas, lizards, and birds are reservoirs for *E. ruminantium* because these animals may serve as the first two hosts for the *Amblyomma* tick.[6] A vector-wildlife cycle facilitates the survival of *E. ruminantium* even when domestic livestock are absent from the environment.[7]

Clinical Signs Animals with the peracute form of *E. ruminantium* infection die suddenly without premonitory signs. The acute form of the disease is characterized initially by fever, anorexia, depression, and respiratory distress. Cyanosis may also be noted. Nervous system signs, which may appear within a few days, include hyperesthesia, snapping closure of the eyelids, rapid extension of the tongue, behavioral changes, muscular fasciculations, hypermetria, ataxia, conscious proprioceptive deficits, and head pressing. As the disease progresses, the animals become recumbent and comatose. Convulsions may occur terminally. These episodes are characterized by opisthotonos, nystagmus, chewing movements, and frothing at the mouth. Mild forms of the disease are characterized by transient diarrhea, malaise, and fever, with no CNS involvement. The mortality rate in sheep ranges from 6% to 80%. Animals that recover are immune to reinfection for at least 58 months.[8] Losses may reach 60% of susceptible cattle and 40% of goats. The mortality rate among

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Angora goats may exceed 90%. Enterotoxemia caused by *Clostridium perfringens* type D is an important differential diagnosis in small ruminants.

Pathophysiology After inoculation into a ruminant, the rickettsial agent infects reticuloendothelial cells and proliferates by binary fission within membrane-bound vacuoles.[9,10] Release of the parasite from degenerating macrophages and neutrophils causes successive waves of parasitemia that infect endothelial cells and cause vasculitis.[10,11] Nervous system lesions may be caused by permeability changes in the cerebral capillaries. Changes in the other soft tissues include hydropericardium, hydrothorax, and subcutaneous edema.[1]

Except for Angora goats, which are highly susceptible to *Ehrlichia* infection, animals reared in indigenous areas usually have a high level of immunity and do not succumb to the infection.[12] Animals that survive the initial infection become asymptomatic but remain rickettsemic for as long as 223 days (sheep), 246 days (cattle), and 8 days (goats). Calves younger than 3 weeks of age, lambs younger than 8 days of age, and kids younger than 6 weeks of age are inherently resistant to *E. ruminantium* infection, regardless of the amount of colostral protection they have received.[13,14]

Necropsy Findings Pathologic changes of heartwater disease include hydropericardium, hydroperitoneum, hydrothorax, pulmonary edema, perirenal edema, hemorrhages in the pleura and peritoneum, and hemorrhagic enteritis. Microscopic changes include microgliosis, necrotizing vasculitis in the brain, hemorrhage, edema of the neuropil, microcavitation, and focal necrosis of the granular layer of the cerebellum. In clinical cases the parasite can only be definitively diagnosed by biopsy of the cerebral cortex or by collection of the cortical tissues at postmortem examination.[15] Simple techniques for collection of such biopsy specimens have been described.[16-18] Squash preparations of the biopsied material should be stained with either methyl green pyronine or Giemsa stain before microscopic examination of the tissues.[19,20]

Diagnostic tests developed to identify infected livestock include an indirect fluorescent antibody (IFA) test using infected bovine aortic endothelial cells for indicators, several ELISAs, and tests using PCR methodology.[21-24] Of these, PCR is the most accurate.

Treatment The administration of oxytetracycline (6 to 10 mg/kg IV twice daily for 3 or 4 days) may be beneficial for treatment of the early stages of the disease. The long-acting formulation of oxytetracycline is also effective, but for best results it should be administered as soon as the animal becomes febrile. Treatment is usually futile if the first dose of oxytetracycline is administered after the onset of neurologic symptoms.[25] Despite the depository nature of the long-acting formulation, two or more doses 48 hours apart are necessary to achieve a good clinical response. Cattle should be retreated if they develop a fever after the first dose has been administered.[26] Animals with nervous system signs frequently die despite intensive antibiotic therapy. Angora goats are highly susceptible to heartwater disease. In South Africa, Angora producers routinely treat all animals every 14 days during the summer with oxytetracycline. Animals that remain essentially tick free never develop adequate immunity to the *Ehrlichia* organism.

A small degree of tick infestation and exposure of the animals to low numbers of the agent, combined with judicious oxytetracycline therapy, would seem to favor the development of immunity over time.[27] One method of immunization uses a controlled infection of a virulent strain (Onderstepoort Ball 3 strain) of the *Ehrlichia* organism and treatment with long-acting oxytetracycline (800 mg per adult goat) at the beginning of clinical disease and 10 days later.[28] Vaccination with this isolate produces immunity against exposure to homologous but not heterologous strains of *Ehrlichia*.[29-31] More recent strategies have included vaccines using inactivated organisms, live attenuated organisms, and fragments of *E. ruminantium* nucleic acid, but none has had great success.[32-36]

Prevention and Control Control of ticks on cattle pastures is the most desirable means of controlling heartwater disease. Complete eradication of the ticks in most regions of sub-Saharan Africa is neither possible nor desirable. Cattle that are reared in areas where *Ehrlichia* infection is endemic develop acquired immunity over time. In these areas the ticks should be sufficiently abundant to permit a low level of heartwater infections in most cattle yet not so populous as to introduce severe, overwhelming infections. Integrated methods for tick control have been recommended. These include exclusion of wildlife from paddocks, artificial induction of host resistance to ticks, application of insecticidal ear tags, and conventional acaricide application. Application of insecticides as the sole method of tick control has not proved highly effective. Resistance to the acaricides may develop with prolonged use.

Cerebral Theileriasis (Turning Sickness; Draaisiekte; East Coast Fever; Corridor Disease; January Disease; Tropical Fever)

Definition and Etiology Cerebral theileriasis is an encephalitic disease of cattle caused by the piroplasma parasites *Theileria annulata* and *Theileria parva*.[1,2] Theileriasis is seen mainly in Africa (Kenya and Tanganyika) and India, where it is characterized by a high mortality rate and is known as East Coast Fever. *Theileria sergenti* is found in Korea and Japan. *Theileria mutans,* a parasite of cattle in the southwestern United States, is relatively nonpathogenic.[3] A mild form of theileriasis, locally called "January disease," occurs in cattle in Mozambique. This condition is caused by the subspecies *T. parva bovis.* Corridor disease is caused by *T. parva Lawrence,* and *Theileria annulata* is the cause of Mediterranean Coast fever or tropical theileriasis.

European breeds of cattle *(Bos taurus)* develop a more severe disease than do comparably infected Indian breeds *(Bos indicus).* Both types of cattle appear to be equally susceptible to infection but differ in their ability to control the course of disease.[4] *Theileria* organisms are transmitted to susceptible cattle by the ticks *Hyalomma anatolicum, Hyalomma lusitanicum,* and *Amblyomma hebraeum.*[5]

Trypanosoma spp. manipulate the immune system both to evade destruction and to promulgate infection. Organisms escape the host immune response by altering immune system activation so that infected cells avoid recognition and destruction.[6-8] Clonal expansion of infected lymphocytes is promoted, and these cells disseminate throughout the body.[9]

Clinical Signs The clinical signs of *Theileria* infections include lymphadenopathy, nasal discharge, lacrimation, tachycardia, fever, subcutaneous edema of the face, gangrenous dermatitis, sloughing of facial skin, dyspnea, pallor, CNS disease, and emaciation.[10] The neurologic syndrome is characterized by ataxia, hypermetria, conscious proprioceptive deficits, depression, head pressing, hyperesthesia, blindness, nystagmus, circling, and aggressiveness. Terminally the animals become recumbent and develop opisthotonos, tonic-clonic seizures, and coma. In rare cases the parasite may localize in the spinal cord. The CNS signs result from vasculitis and lymphocytic inflammation of the brain.[11-13] Clinically recovered animals become persistently infected.

Necropsy Findings The postmortem lesions of theileriasis include capillary engorgement, scattered punctate hemorrhages on the surface of the brain, thrombosis of the meningeal vessels, hemorrhage in the cerebral ventricles, pulmonary edema, peripheral lymphadenopathy, and infarctions of the kidney and spleen. The brain of affected animals appears to have a yellow hue.[13] Microscopically, blue cytoplasmic inclusion bodies (Koch blue bodies) are seen in the lymphocytes adjacent to the hemorrhagic areas.

The nervous form of theileriasis is difficult to diagnose definitively because the parasite is only sporadically visible in sections of nervous tissue from the infected animals. Occasionally, parasitemia can be

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detected by microscopic examination of blood smears from infected calves. Reliable blood tests are not currently available. Biopsy of the cerebral cortex has been recommended as a confirmatory test for the disease. The CSF of affected animals is normal or has an increased protein concentration ranging from 1400 to 12,452 mg/dL, with normal numbers of WBCs.[12]

Treatment Parvaquone 10 to 20 mg/kg IM in two injections 48 hours apart and buparvaquone at a single dose of 2.5 mg/kg are approximately 90% effective for the treatment of theileriasis.[14] Some studies have found buparvaquone to be the most effective treatment.[15,16] Parvaquone can be combined with furosemide, which improves survival of cattle that develop pulmonary edema, a common consequence of theileriasis.[17] Menoctone (10 mg/kg IV or IM) is also curative. Single doses were effective, but repeating the treatment daily for 5 days eliminated posttherapeutic recrudescence.[18]

Prevention Prevention of *Theileria* infection has largely been based on the use of live attenuated vaccines, which produce a solid, cell-mediated immunity.[19] These vaccines are used in an "infection and treatment" manner, whereby vaccination must be combined with administration of long-acting tetracyclines.[20] Recent efforts at vaccine development have focused on the creation of subunit vaccines, using a variety of *Theileria* antigens.

The naphthoquinones are the preferred chemotherapeutic agents in vaccinated animals and include parvaquone, halofunginone lactate, and buparvaquone (see Treatment).

Tick control is vital for prevention. Weekly spraying with coumaphos and insertion of ear tags impregnated with cypermethrin (have been effective for controlling ticks and preventing *Theileria* infections in calves in Tanzania. The calves became infected with *T. parva* by 3 months after the tags were removed. Woodford[21] suggested that the intensive tick control could minimize the incidence of theileriasis until the calves could be successfully vaccinated. However, inadequate or incorrect application of products and tick resistance to chemicals present challenges to effective tick control. The disease is exotic to North America.

Cerebral Trypanosomiasis (Sleeping Sickness)

Definition, Etiology, and Clinical Signs Trypanosomiasis is a hemoprotozoan disease of African cattle that also infects the CNS. The disease is transmitted to cattle by the bite of the tsetse fly (*Glossina* spp.). The agents that infect cattle include *Trypanosoma vivax, Trypanosoma congolense,* and *Trypanosoma brucei.* An especially severe neurologic form of the disease has been caused by the inoculation of cattle with *T. congolense,* followed 1 year later by infection with *T. brucei,* or by simultaneous inoculation with the two agents.[1] The encephalitic signs develop 2½ to 5 months after infection and include ataxia, conscious proprioceptive deficits, knuckling, depression, circling, and head pressing. Some animals may show signs of behavioral change, lose the herd instinct, and develop hyperesthesia and constant repetitive movements. Other signs associated with progression of trypanosomiasis are semicoma, coma, recumbency, opisthotonos, and intermittent tonic-clonic convulsions, which occur 2 to 3 days before death. Affected animals are emaciated, anemic, and icteric at death.[2]

Experimental infection with trypanosomes causes a marked fever (as high as 40.5°C [105°F]). Other common nonneurologic signs are anemia, petechiation of the mucous membranes, occult fecal blood, melena, and epistaxis. Chronic weight loss without other clinical signs may be seen in some animals. Hematologic abnormalities include anemia, hypoalbuminemia, hyperbilirubinemia, and increased plasma concentrations of aspartate transaminase and urea nitrogen.

Acutely infected animals may develop a thrombocytopenia and prolongation of the prothrombin and partial thromboplastin times, indicating that disseminated intravascular coagulation (DIC) may be responsible for the vascular changes that occur before death. The anemia is characterized by increased mean corpuscular volume and mean corpuscular hemoglobin, with increased serum iron concentrations early in the infection.[3,4] One study did not demonstrate a change in the concentration of WBCs or protein in the CSF of animals with the encephalitic form of trypanosomiasis.[1] However, another study showed significant alterations in cattle infected with *Trypanosoma brucei*i.[5] These included an increase in total protein (range, 37 to 44 mg/dL) and pleocytosis (range, 0 to 3060 mononuclear cells/μL). The abnormalities in the CSF may be present in infected cattle not currently displaying clinical neurologic signs. Antitrypanosomal antibody may be found in the CSF of affected cattle using indirect fluorescent antibody (IFA) tests.

Pathology The pathologic lesions of trypanosomiasis are a nonsuppurative encephalomyelitis, serosanguineous pericardial fluid, serosal hemorrhages, pulmonary edema, centrilobular coagulative necrosis, splenomegaly, necrotizing myocarditis, and glomerulonephritis.[6] Macroscopic lesions of the CNS include subtle thickening and grayish discoloration of the meninges. The meningeal vessels are congested. Microscopic lesions of the CNS reflect moderate diffuse meningoencephalitis. The pathogenesis of the encephalitis is not understood.

Trypanosomes may be cultured from the blood and CSF of infected cattle. The number of hematogenous parasites is highest in animals with a dual infection by *T. congolense* and *T. brucei.* The clinical diagnosis of trypanosomiasis may be confirmed by inoculating blood or CSF specimens into laboratory mice and observing the recipients for parasitemia with direct darkfield examination of the patient's blood. Identification of motile trypanosomes in the buffy coat zone of a microhematocrit capillary tube using darkfield illumination is apparently the most accurate of all diagnostic methods. Trypanosomes can be differentiated by their morphologic features, manner of attachment to erythrocytes, and type of motility.[7] Species-specific antibodies can be detected in serum using either an antigen-capture ELISA or an IFA test. Infected cattle develop acquired resistance to homologous but not heterologous isolates of trypanosomes.

Treatment and Control Of the drugs available for the treatment of trypanosomiasis, isometamidium chloride is most often used. The recommended dosage ranges from 0.25 to 1 mg/kg IM; a single dose of 1 mg/kg exerts a protective effect for up to 6 months.[8] The higher dosage (1 mg/kg) was required to obtain increased weight gain and prevent recurrent infection. The treatment was particularly effective when combined with weekly surveillance, followed by treatment of confirmed infected animals.[9] Side effects of isometamidium include tachycardia, salivation, lacrimation, pollakiuria, muscle fasciculations, convulsions, diarrhea, and in rare cases, death. The drug apparently does not cause abortion in pregnant cows or otherwise affect the calf.[10]

Other drugs used include suramin sodium, diminazene aceturate (7 mg/kg), quinapyramine sulfate, and homidium chloride (1 mg/kg). These drugs provide residual protection from reinfection for approximately 2 months; however, recurrent infection and resistance, especially to diminazene, have been reported.[11-14] Combinations of these drugs (e.g., diminazene followed by isometamidium) reduce the number of resistance-related therapeutic failures. Relapses also undoubtedly occur because many of the chemoprophylactic drugs are unable to penetrate the blood-brain barrier in sufficient concentrations to eliminate the parasite in the CNS tissues.

Because of the variable responses to treatment and the ability of *Trypanosoma* organisms to develop drug resistance, all control programs must include methods of controlling the tsetse fly.[13] Because the tsetse fly prefers to feed from the ventral torso or the legs, insecticide-impregnated ear tags have been ineffective for preventing infection; other means of application of insecticide are necessary.[15] Other fly control methods include aerial spraying with endosulfan, ground-based spraying with 4% dichlorodiphenyltrichloroethane

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(DDT), or use of scented insecticidal traps.[14] However, cost and environmental concerns have limited the usefulness of these techniques.

Selection of resistant lines of cattle is possible. The taurine N'Dama and West African shorthorn breeds have innate resistance to trypanosomiasis and are the sole breeds of cattle in areas of tsetse fly range.[16] Resistant breeds of small ruminants include the Djallonke, Red Maasai, Blackhead Persian, and East African sheep and goats.[17] Imported breeds of livestock usually cannot be maintained, even in areas of low tsetse fly risk, without intensive drug therapy.[18]

Polioencephalomalacia (Cerebrocortical Necrosis)

Christopher Cebra • Guy H. Loneragan • Daniel H. Gould

Definition and Etiology Polioencephalomalacia (PEM) is a common and important neurologic disease of ruminants[1,2] with a worldwide distribution. An animal with clinical manifestations of PEM is often referred to as having "polio" or being a "sleeper" or "brainer." "

Polioencephalomalacia is a descriptive term for histologic lesions[1,3] that may arise from a variety of etiologies. Literally, the name means softening or necrosis (malacia) of regions of the gray matter (polio) of the brain (encephalo). Thus a definitive diagnosis of PEM requires appropriate histologic examination of brain tissue. The possible etiologies of PEM include (but are not limited to) excessive sulfur consumption,[4-6] presumably manifested through elevated ruminal sulfide production[7,8]; altered thiamine metabolism[9]; salt poisoning or water deprivation[10]; amprolium administration[11-13]; rations composed of molasses and urea[14]; and lead intoxication.[15] When an etiology can be established, most PEM cases involve excessive sulfur consumption and/or altered thiamine metabolism.

Clinical Signs PEM appears to manifest both subacutely and acutely.[1,8] In the subacute form, signs may develop within hours or over several days. In the early stages of the disease, the affected animals detach from the herd or flock, become anorectic, and stagger. Neurologic signs are symmetric. Affected animals are blind, walk with the head held erect, and demonstrate a slight hypermetric gait. Progression of the condition is associated with bilateral cortical blindness, head pressing, opisthotonos, bilateral dorsomedial strabismus, miosis, repetitive chewing, profuse ptyalism, and odontoprisis.[1,5,16-18] Despite the defective menace response, the animals usually have normal palpebral reflexes. Affected animals may also develop a variable nystagmus. The rectal temperature is normal unless excessive muscular fasciculations have developed. The pulse and respiratory rates are usually increased. An odor of hydrogen sulfide may be detected on the breath if the PEM is associated with excessive sulfur consumption.

Although most of these animals respond favorably to aggressive therapeutic intervention, clinical signs may progress to recumbency, tonic-clonic convulsions, and death. In facilities with certain types of fencing, such as cables, affected animals may push or press with such force that they die of asphyxiation.

In the acute form of PEM, animals are found recumbent and comatose.[1,8] These animals often experience episodic tonic-clonic convulsions, and they remain recumbent and hypertonic between seizures. The prognosis is poor for acutely affected animals or those with advanced subacute manifestations. Survivors may remain irreversibly decorticated and are culled because of poor performance, chronic anorexia and ataxia, or blindness. However, mildly affected animals may remain as productive members of the herd.

Because the clinical manifestations of PEM may be subtle and nonspecific, they can be confused with other disorders. PEM is often confused with lactic acidosis that develops after consumption of excessive amounts of readily fermentable carbohydrates. Animals with lactic acidosis may appear ataxic and obtunded in addition to having a foul-smelling, watery stool and a distended, fluid-filled rumen. Concurrent PEM may not be diagnosed, or producers may confuse PEM for lactic acidosis or primary ruminal tympany in acutely affected animals that have remained laterally recumbent for some time.

The major differential diagnoses for PEM include enterotoxemia type D (focal symmetric encephalomalacia in small ruminants), head trauma, bacterial meningoencephalitis, coccidiosis with nervous system involvement, vitamin A deficiency, ethylene glycol poisoning, locoism, rabies, and infectious bovine rhinotracheitis encephalitis.

Clinical Pathology Although a definitive diagnosis depends on histologic confirmation, a presumptive diagnosis may be made antemortem on the basis of the history and clinical signs or response to therapy. If a diagnosis of PEM is made, the investigation should proceed at the animal, herd, and environmental level to identify evidence supportive of sulfide toxicity, thiamine deficiency, lead toxicity, or water deprivation (salt toxicosis).

Sulfide concentrations in the ruminal fluid and gas cap in experimentally induced sulfur-associated PEM have been shown to be high.[19,20] However, unpublished data supported a finding of a decrease in gas cap sulfide concentrations in naturally developing PEM associated with increased sulfur consumption.[21] This is most likely caused by the rapid metabolism of sulfate to sulfide in the rumen and resultant absorption or eructation of hydrogen sulfide (H_2S). Animals with naturally developing PEM are likely to have been anorectic for some time, resulting in a decrease in oxidized and reduced forms of ruminal sulfur.

Estimation of the rumen gas cap H_2S concentration in clinically healthy penmates of affected cattle is an effective chute-side diagnostic procedure that can indicate excessive sulfur consumption.[8] This method provides real-time results that may aid direction of further animal and environmental investigations. In short, an area in the left paralumbar fossa is prepared for ruminocentesis. An 18-gauge, 3½-inch spinal needle is inserted through the body wall and into the rumen gas cap. A modified gas sampler is attached to the spinal needle by means of an extension set, and a known amount of gas is drawn through an H_2S detector tube.[20] It is important to adjust the values to account for any dead space of the sampling instrument, such as the extension set and other modifications. H_2S concentrations greater than 1000 ppm are indicative of excessive sulfur consumption.[22]

Appropriate blood samples may be analyzed for lead concentration and possibly estimation of thiamine status. Thiamine status is generally evaluated using one of several available methods including determining the total blood thiamine concentration using a thiamine-dependent *Lactobacillus* bioassay.[23] The erythrocyte thiamine pyrophosphate concentration may be measured by high-performance liquid chromatography (HPLC).[24]

Another method of evaluating thiamine status is determining erythrocyte transketolase activity.[25] This test compares the specific activity in the active (holoenzyme) and inactive (apoenzyme) forms with the activity of the two forms after addition of thiamine to the homogenates. A large increase in specific transketolase activity after addition of the thiamine pyrophosphate suggests thiamine deficiency. Theoretically, in animals with thiamine-associated PEM, the concentration of holoenzyme is decreased, and that of the apoenzyme is increased. If thiamine deficiency is identified in an affected animal, caution should be used in interpreting the results because a period of anorexia may result in a decrease in ruminal de novo synthesis.[26,27]

Changes in CSF of affected animals are usually vague. They include mild pleocytosis (5 to 50 WBCs/dL) with vacuolation and increased protein concentrations (>50 mg/dL).[9,28] Electrophysiologic studies of affected animals show a normal latency and decreased amplitude of the late peaks of the visual evoked potentials. These changes reflect a decreased population of neurons capable of responding to the photic stimulation.[29]

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Environmental investigations should include evaluation of all feed and water sources for sulfur concentrations or the possibility of lead contamination. The diet should also be checked for molasses, salt, and urea content.

Pathogenesis The fundamental lesion with PEM appears to be neuronal edema with necrosis. In most cases the edema is postulated to result from adenosine triphosphate (ATP) depletion and insufficient function of the sodium-potassium pump in cortical cells. The bony calvarium limits expansion and neuronal swelling leads to pressure necrosis.

The brain is susceptible to PEM because of its high energy and oxygen requirements. Brain tissue is only about 2% of body weight but accounts for 20% to 30% of body glucose utilization and 20% of oxygen utilization in adults.[30] More than 85% of glucose used by the brain is energy substrate, and the blood-brain barrier prohibits the switching to many alternate energy substrates. Compared with liver or muscle, the brain has relatively small glycogen stores, only about a 10-minute supply. It is entirely dependent on circulating oxygen, and under normal conditions, the extracellular fluid contains approximately 100 times as much glucose as the oxygen required for complete aerobic glycolysis. Thus oxygen delivery or utilization is much more rate limiting for ATP production under most circumstances than glucose availability,[31] and factors that inhibit oxygen utilization (e.g., H_2S, lead) could have profound effects on neuronal ATP production.

Much of the early work on PEM focused on the importance of thiamine (vitamin B_1, thiamin, aneurin). In adult ruminants, thiamine is produced by rumen microbes at a rate that is marginally faster than the rate of consumption; very little is stored.[32] Preruminants depend on dietary thiamine. Thiamine compounds play several important roles in the glycolytic pathways. Thiamine pyrophosphate (thiamine diphosphate) is an important coenzyme for transketolase, the rate-limiting enzyme in the hexose monophosphate pathway (pentose phosphate shunt) of glycolysis, and the α-ketoacid dehydrogenases of the Krebs cycle. The role of thiamine in the hexose monophosphate pathway was long thought to be key in the development of PEM, but this pathway actually accounts for less than 3% of cerebral glycolysis.[33] It is unlikely that impairment of this pathway alone could lead to such severe disease. However, decreased function of the Krebs acid cycle through inactivity of the α-ketoacid dehydrogenases could cause the necessary reduction in ATP production. Thiamine triphosphate may also play a role in neuronal function independent of its enzymatic function.

The dependence of ruminants on microbial thiamine production has led to investigation of factors that might decrease production, absorption, or function. The mechanisms proposed include ruminal production of bacterial thiaminases, production or ingestion of inactive thiamine analogs, ingestion of preformed plant thiaminases, decreased intake of preformed thiamine by preruminants, impaired absorption or phosphorylation of thiamine by rumen bacteria, increased fecal excretion of thiamine, and decreased ruminal production of thiamine diphosphate. The most frequently reported inactive thiamine analog is amprolium.[11-13] Two types of bacterial thiaminases have been described. Thiaminase I, which is produced by *Bacillus thiaminolyticus* or *Clostridium sporogenes,*[34] catalyzes the cleavage of thiamine at the methylene bridge between the pyrimidinyl and the thiazole ring. A basic cosubstrate is required to combine with the pyrimidinyl derivative to form a new compound[35] (any common feedlot medications, including benzimidazoles, levamisole, and promazines, appear to be able to serve as this cosubstrate). Several plants also appear to make a thiaminase similar to thiaminase I. These include bracken fern *(Pteridium aquilinum),*[36,37] horsetail *(Equisetum arvense),*[37] and Nardoo fern *(Marsilea drummondii).*[38] Of these, only the Australian Nardoo fern has been strongly linked to outbreaks of PEM.

Thiaminase II is produced by *Bacillus aneurinolyticus,* which proliferates in response to excessive grain intake.[39] The enzyme catalyzes the hydrolysis of the methylene bridge between the two ring structures of the thiamine molecule. The specific relationship of this thiaminase to the clinical syndrome of PEM as seen in the field is unclear.

Complete correlation has not been established among production of ruminal and fecal thiaminase, tissue and plasma concentration of thiamine, and development of clinical encephalopathy.[40,41] Some affected animals may show normal amounts of thiamine in the plasma but have greatly decreased levels in the erythrocytes and other tissues, supporting the diversity of causes of PEM.[42]

Dietary sulfur and sulfates are an important factor in the development of many cases of ruminant PEM. Beef cattle require 0.15% to 0.20% sulfur on a dry matter basis.[43] Sources of sulfur include elemental sulfur,[4] feed additives such as gypsum and ammonium sulfate,[5,44] feedstuffs such as corn-processing by-products,[43] cruciferous crops,[45,46] molasses,[14] and fertilizers. Water can be an important contributor to sulfur intake, usually in the form of sulfates.[7,47,48]

There are two primary metabolic pathways of sulfur in the rumen.[48-53] The *assimilatory pathway* involves reduction of sulfate to sulfides and incorporation into sulfur-containing organic compounds such as cysteine and methionine.[51] These are ultimately incorporated into microbial crude protein. The *dissimilatory pathway* is an energy-producing pathway in which microorganisms use sulfate as a terminal electron acceptor, similar to how mammals use oxygen.[54] The end product is liberated sulfide ion. At a ruminal pH of 5.2, 97.2% of sulfide ions are in the form of H_2S and move freely to the rumen gas cap.[50,55] H_2S is readily absorbed and transported to the liver and oxidized to sulfate.[55,56] Some H_2S may be lost through eructation,[19,56] but the significance of this route has been questioned.[57] Excess sulfur is excreted in the urine and large intestine[58,59] or recycled to the rumen.[60,61] A period of adaptation is required for maximum H_2S production after exposure to sulfur.[52,58,61-63]

Because sulfur and sulfate demonstrate low cellular toxicity, it is unlikely that sulfur-associated PEM results from a sulfate or sulfur toxicity. However, sulfides are highly toxic.[64-66] Sulfur-associated PEM is more likely to occur secondary to a sulfide toxicity.[6,8,19] It has been proposed that the pathogenesis of sulfur-induced PEM involves inhibition of cytochrome-*c* oxidase, an enzyme in the electron transport chain; this chain is important for regenerating the intermediaries of aerobic glycolysis and the final round of ATP production. With oxygen availability already limiting aerobic glycolysis in the brain, inhibiting the electron transport chain could have a profound effect on neuronal ATP production.

For highly toxic sulfide to reach the brain, it must escape hepatic oxidation. This might be achieved by two mechanisms. A surge in ruminal sulfide generation usually follows a period of adaptation to high-sulfur diets. This may overwhelm the hepatic detoxification capacity. As an alternative possibility, cattle inhale the majority of eructated ruminal gas.[67] These inhaled gases can contain high amounts of H_2S, and if absorbed via the pulmonary route, the H_2S would completely bypass the hepatic circulation. However, this concept has been questioned.[68]

In feedlot cattle, a summer peak in PEM cases was associated with consumption of water containing 2500 mg/L of sulfate.[7] The total sulfur intake of these steers was estimated to be 0.6% on a dry matter basis during the hottest days of the year. Most PEM cases occurred between 15 and 35 days after arrival in this feedlot. In another investigation, 11% of weaned calves consuming a diet containing 0.9% sulfur on a dry matter basis developed clinical manifestations of PEM.[8] Lesions were confirmed in one steer that died. Addition of gypsum (calcium sulfate) to feeder steer rations at a final concentration more than 2% organic sulfate results in a significantly greater risk of developing PEM. The addition of sodium sulfate (0.6% to 0.8%) to diets may induce PEM within 11 days.[19,62,69,70] High sulfur concentrations in well water in combination with accumulation in forage has been traced to an outbreak of PEM in Canada.[8] One survey described an outbreak of cerebrocortical necrosis in cattle eating diets containing 7200 mg/kg of sodium sulfate.[48]

The recommended maximum tolerance level of sulfur is 0.4% of dry matter intake.[43] Other effects of excessive sulfur intake are

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decreases in feed intake and weight gain. Accurate diagnosis of sulfur toxicity requires measurement of sulfur in all food and water sources. Sulfur from water must be included when calculating total sulfur intake. One third of the molecular weight of sulfate is sulfur. Accordingly, if an animal drinks 30 L of water a day containing 2000 mg/L of sulfate, this contributes 60,000 mg of sulfate, or 20 g of sulfur. Further, if this animal consumes an average of 10 kg of dry matter daily at 0.15% sulfur, the feed or forage contributes 15 g of sulfur, making the total sulfur intake 35 g, or 0.35% on a dry matter basis. Therefore water may be a substantial source of sulfur.

Some have suggested that sulfides result in thiamine destruction, thereby directly implicating a thiamine deficiency in the pathogenesis of sulfur-associated PEM. Rumen thiamine production was slightly reduced by the inclusion of excessive sulfur in the ration.[71] However, the authors deemed the reduction clinically insignificant. Apparently, sulfur-associated PEM occurs independent of thiamine status.

PEM induced by feeding of molasses and urea is thought to be related to the high sulfur content of the molasses and to the depletion of propionate and other glucogenic precursors induced by the foodstuff.[14] It is not considered to be caused by an underlying thiamine destruction. The tissue thiamine concentrations of animals with molasses-related PEM are normal,[72] and signs are preventable by concomitant feeding of glycerol, which is converted to glucose in the rumen. Outbreaks of PEM in range cattle have been associated with ingestion of the plant *Kochia scoparia*.[73,74] The pathogenesis of this condition is unknown; however, some have suggested that the plant has the capacity to accumulate sulfur.[48]

Some cases of PEM cannot be linked to either problems with thiamine or sulfur toxicosis. Other compounds, such as lead, affect electron transport in a manner similar to sulfides and therefore also impair ATP production. Water intoxication creates a similar histologic lesion, but the pathogenesis of edema relates more to the generation of osmotic compounds and fluid shifts with rapid fluctuations of blood and neuronal osmolality (see section in this chapter titled Salt Poisoning [With or Without Concurrent Water Deprivation]).

Epidemiology PEM has a worldwide distribution. The condition is seen both in individuals and as herd outbreaks. In one instance, approximately 2000 of 2200 sheep grazing were clinically affected with PEM.[4] No predilection by gender or breed is seen. The condition affects cattle, sheep, goats, deer, camels, and camelids.[5,11,75-78] Although PEM is seen predominantly in animals that eat a high-concentrate supplement, the condition can also occur in unsupplemented animals on pasture.

The age range for susceptibility to PEM has been reported as 3 weeks to 5 years in sheep, 3 weeks to 8 years in cattle, and 2 months to 2½ years in goats. The peak age of incidence is 18 months or younger in cattle and sheep, but this depends on the production system.[1,8,79] The incidence of PEM has been reported as high as 90% in some sheep flocks, with mortality of 1% to 10%.[4] The incidence of PEM can be high in sheep exported by sea from Australia to the Middle East. In these cases the underlying disturbance was thought to be associated with a thiamine deficiency caused by a lack of rumen synthesis secondary to the shipboard conditions.[80]

Necropsy Findings In cases of sulfur-associated PEM, rumen contents may have an odor of H_2S. In other cases there may be evidence of grain overload, coccidiosis, or respiratory disease. Some of these lesions relate to management conditions but may also relate directly or indirectly to PEM. The macroscopic pathologic brain lesions of PEM include cortical swelling, softening, flattening, and yellowish discoloration of the gyri. Necrotic areas of the cerebral cortex autofluoresce under ultraviolet light (365 nm).[81,82] Severe cases show herniation of the cerebellum through the foramen magnum or the occipital cortex under the tentorium cerebelli. Animals necropsied months after recovery may show cerebral atrophy and submeningeal cortical cysts. The major microscopic lesion is a diffuse laminar necrosis. Other changes include intracellular and intercellular edema, neuronal necrosis, and neuronophagia.[3,17]

Treatment and Prognosis Regardless of the underlying cause, animals with the subacute form of PEM often respond favorably to parenteral administration of thiamine hydrochloride. These animals may remain blind and may have depressed sensorium for weeks or months.[83] Thiamine should be administered at 10 to 20 mg/kg IM or SC three times daily. In severe cases, IV administration of the first dose might be warranted. If given intravenously, thiamine should be administered slowly to avoid adverse reactions. If no improvement occurs initially, the treatment should be continued for at least 3 days. In some patients, recovery may take as long as 7 days, but most patients show improvement by 24 hours. A single administration of sodium dexamethasone at 0.1 to 0.2 mg/kg IM or IV or 1 g/kg of mannitol in a 20% solution IV may be beneficial in reducing cerebral edema. Anecdotal reports indicate that feedlot animals that have recovered from PEM are at increased risk of respiratory disease; therefore prophylactic antimicrobial administration may be indicated. Convulsions may be controlled with phenobarbital, pentobarbital, or diazepam (see Table 35-2). Animals with the acute form of PEM usually have more severe cortical and deep gray matter lesions than animals with the subacute form.[8] These animals generally do not respond to therapeutic regimens. Ruminants with PEM secondary to the molasses-urea diet do not appear to respond to treatment with thiamine. They may respond more favorably to parenteral administration of glucose or enteral or parenteral administration of a glucose precursor.

Prevention and Control Ultimately, the best way to prevent outbreaks is to manage the dietary intakes of susceptible animals appropriately. Ruminants should be allowed an adequate period of adaptation to high-concentrate rations. All feedstuffs and water sources should be carefully analyzed on a routine basis with an estimate of total sulfur intake. If excess sulfur consumption is a factor, steps should be taken to remove sources such as high-sulfur hay, ammonium sulfate, and molasses. If the excess sulfur intake is unavoidable, steps can be taken to limit its effects. Older members of the cow herd could be used to graze the high-sulfur pastures, and younger, more susceptible animals could be kept to lower-sulfur pastures or given hay supplementation. Personnel should be trained so that animals with PEM can be identified early in the disease and treated appropriately.

Thiamine may be supplemented (3 to 10 mg/kg of feed) in rations in which the concentrate/fiber ratio is high, but this has little or no effect in preventing PEM. Other recommendations for preventing PEM include addition of brewer's yeast to the ration and gradual adaptation of ruminants (at least 2 weeks) to high-concentrate diets. If present as a feed-limiting additive, gypsum should be removed from the diet. Elimination of supplementation and rotation of pastures have been sufficient for controlling some outbreaks.[79] Supplementation with cobalt in trace-mineral salt mixes may be necessary in deficient areas.

Salt Poisoning (With or Without Concurrent Water Deprivation)

Lisle W. George • David C. Van Metre

Definition and Etiology Salt poisoning is a common CNS disease of livestock. Salt-rich solutions ingested over time can cause production-related losses and even death. Ingestion of water containing more than 7000 mg/L of total dissolved salts is likely to result in acute salt poisoning.[1,2] Water that contains less than 3000 mg/L of total dissolved salts is considered safe for consumption. Salt poisoning can be associated with water deprivation.[1,3,4] Provided that access to free water is constantly available, animals may tolerate up to 13% dietary salt intake.[5]

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The acute toxic dose of oral sodium chloride (NaCl) for cattle and horses has been reported as approximately 2.2 g/kg body weight and for sheep about 6 g/kg.[5] With water restriction, the toxic dose of salt is considerably less, and poisonings have resulted from ingestion of 0.9% NaCl in water-restricted cattle.[6] Chronic toxicity can occur at lower dietary salt levels than acute toxicity. Ingestion of water with salt concentrations above 1% uniformly results in toxicosis if no other source of ion-free water is provided.[7,8]

Ingestion of water containing 0.7% salt lowers the fertility of females,[8] and water containing 0.25% salt suppresses milk production in cattle.[9] Dairy calves have been poisoned by daily feeding of 4 L of milk replacer containing 2.6% NaCl.[10] Animals are most susceptible to salt poisoning during the summer because of the increased insensitive loss of water at that time. Salt poisoning in ruminants is most frequently a syndrome of concurrent "water intoxication": a period of restricted access to water, followed by unrestricted access to water.[1,3,4] In such cases, the dietary intake of sodium can be relatively modest, yet disease occurs once water enters the extracellular fluid and moves into the brain tissue.

Clinical Signs

Acute ingestion of large amounts of salt causes gastrointestinal and neurologic signs.[7,10-15] These include mucohemorrhagic diarrhea and colic, head-neck extension ("star gazing"), blindness, aggressiveness, hyperexcitability, psychomotor seizures (paddling and loss of consciousness), vocalization, ataxia, proprioceptive deficits, head pressing, constant chewing movements, nystagmus, muscle twitching, and coma. Death occurs as a result of respiratory failure. Before the onset of neurologic signs, cattle with chronic salt toxicosis may appear to be depressed and dehydrated. Table 35-4 summarizes the spectrum of clinical effects associated with different levels of salt intake.

Excessive salt intake may also interfere with productivity in the absence of acute neurologic signs. In one study, cattle were given either tap water (196 ppm of dissolved salts) or saline (2500 ppm NaCl), and their milk production was measured.[9] Cows given tap water had a greater fluid intake and a significantly greater lactational persistence and daily milk production than did cows given saline, despite the fact that the latter group showed normonatremia and normokalemia. This study illustrates the importance of provision of high-quality water for optimization of milk production.

The clinical diagnosis of salt poisoning depends on the demonstration of exposure to toxic concentrations (>7000 ppm or 0.7% of sodium), the presence of water deprivation, or the determination of serum or CSF sodium concentrations greater than 160 mEq/L (occasionally exceeding 200 mEq/L).[11] CSF/serum sodium ratios greater than 1 also suggest salt poisoning. The serum sodium concentration may vary, depending on whether the patient had recently been given ion-free water before measurement. Some animals with acute neurologic lesions may be normonatremic if they have recently drunk to repletion with ion-free water, whereas others that have not had ion-free water may be hypernatremic.

Ruminal sodium concentrations above 0.36% to 0.5% or brain sodium concentrations above 150 mEq/g or 1800 ppm[16] also suggest salt poisoning in cattle.[11,12,17] Rapid intake of low-sodium water during the rehydration phase of the disease may cause intravascular hemolysis with resultant hemoglobinuria; such findings raise the index of suspicion of salt poisoning.[2]

TABLE 35-4

Effects of Different Salt Concentrations in Drinking Water on Performance in Cattle[8]

Salt Concentration (mg/L or ppm)	Clinical Effect
<1000	No effect
1000-3000	Temporary diarrhea; reduced milk production
3000-5000	May reduce milk production and feed intake; may produce reproductive failures (failure to conceive)
5000-7000	Conception failures (abortion, infertility), reduced appetite
>7000	Unsafe, especially in hot weather; may produce encephalopathic signs, abdominal pain, mucoid diarrhea, thirst, salivation, polyuria, central nervous system signs; include knuckling, blindness, convulsions, coma, and abdominal pain

Pathophysiology

The pathogenesis of salt poisoning involves the deposition of sodium ions in the CNS parenchyma and the CSF, which occurs either acutely from ingestion of a large quantity of salt or chronically after long periods of reduced water consumption with low to moderate sodium intake. The ionic sodium accumulates in the brain cells by passive diffusion. The resulting hyperosmolality reduces energy-dependent sodium transport mechanisms and glycolysis.[18] These mechanisms normally provide energy by which the sodium ion is removed from the cell cytoplasm.[14] The thirst receptors are triggered in response to the hyperosmolality of the extracellular fluid (ECF). The animal is permitted to drink ion-free water to repletion, and the fluid is absorbed from the gastrointestinal tract, resulting in expansion of the extracellular fluid and an abrupt reduction in the ECF osmolality. Water then diffuses down its osmolar gradient from the ECF into the relatively hyperosmolar CSF and neurons, resulting in CNS edema, increased intracranial pressure, and acute encephalopathy.

Gastrointestinal signs may also be seen when animals ingest large quantities of salt over short periods of time. The hyperosmolality in the intestinal lumen results in saline catharsis and osmotic diarrhea.

Epidemiology

Animals are tolerant of high dietary salt levels if they have concomitant access to fresh drinking water. Feedstuffs that are common sources of excessive salt include whey, saline-preserved fish or fish meals, bakery by-products, and certain milk replacers.[19] Confined calves may be poisoned by improperly formulated milk replacers or oral electrolyte replacements.[11,19] Cattle eagerly ingest large amounts of oil well sludge, which is a potential source of salt for cattle in the western and southwestern United States.[15,20,21] Brine is used extensively as a flush during the drilling of oil wells. Effluents from drilling rigs may contain as many as 100,000 ppm of salt. The effluents are also contaminated by heavy metals and magnesium salts, which complicate the clinical syndrome of salt poisoning. Concurrent neurologic disease may predispose animals to reduced water intake, as occurred in a group of goats with locoweed (*Oxytropis* spp.) poisoning who became water deprived because of reluctance to move to a water source. They developed clinical and pathologic evidence of salt poisoning when moved subsequently to an area where water was easily available.[3] Salt poisoning caused by water restriction may occur either inadvertently from freezing of water sources in northern climates or from intentional water restriction of veal calves.[11] Ingestion of brackish or tidal water is a cause of salt poisoning in cattle pastured on the coastal regions of the world.

Necropsy Findings

The pathologic changes of salt poisoning include cerebral edema and softening and flattening of the cortical gyri. Microscopic lesions include laminar cortical necrosis, poliomalacia, and occasionally, meningeal or perivascular infiltration of eosinophils and/or mononuclear cells.

Treatment

Treatment of animals affected by salt poisoning is difficult. Many animals die even after intensive medical treatment. Prognosis depends on severity of clinical signs at the start of treatment: Animals that already have significant cerebral edema have a guarded prognosis. Therapy should be aimed at limiting the ingestion of nonionic water and attempting to remove intracellular solutes

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slowly from the brain while simultaneously controlling cerebral edema and attendant CNS signs. To prevent brain swelling and herniation of the brain through the foramen magnum or the tentorium cerebelli, slow reduction of the CSF and plasma sodium is imperative. Slow intravenous administration of normal or hypertonic saline is the mainstay of treatment.

Adult cattle should receive normal (0.9%) saline intravenously at maintenance rate (7% body weight in adult cattle, 10% in neonates).[2] Slight underestimation of fluids is preferable to excess fluid administration. Serum sodium should be monitored regularly and correction effected over 24 hours or longer. Oral fluids can be introduced gradually toward the end of the first day of treatment; salt should initially be added to oral fluids to make them isotonic to blood. When IV replacement is not feasible, isotonic to hypertonic oral fluids should be administered at a maintenance level divided into four to six feedings daily. Access to low-salt water is gradually allowed after 3 to 4 days. Any worsening of clinical signs is an indication to increase the salt level in fluids and may require IV mannitol (0.5 to 2.0 g/kg as a 20% solution) or oral glycerin (1 mL/kg diluted 50:50 with water) to reduce cerebral edema.[2]

High-sodium crystalloid solutions (HSCS) have been used for individual treatment of severe hypernatremia, as might develop in salt poisoning.[22] Sodium (as dry salt, or, if metabolic acidosis is present, as sodium bicarbonate) is added to normal (0.9%) saline to create a final sodium concentration in the HSCS that is 10-15 mEq/L less than the patient's serum sodium concentration. Dry table salt (17 mEq Na^+ and Cl/gram) is added to 0.9% saline to achieve the desired sodium concentration in the HSCS. The HSCS is administered at 1-3 mL/kg/h while the patient's neurologic status and serum sodium concentration are monitored carefully over the first 1-2 days of treatment; reduction of serum sodium concentration by 0.5-1 mEq/L/h is considered optimal.[23] Small volumes of water are subsequently offered to aid in gradual reduction of the ECF sodium concentration; this gradual decline in ECF sodium is thought to prevent development of an abrupt osmolar gradient favoring water entry into brain cells.

The use of solutions containing 5% glucose is dangerous and probably contraindicated because this represents ion-free extracellular fluid, which can exacerbate brain edema. Administration of corticosteroids (dexamethasone, 0.04 to 0.08 mg/kg by slow IV injection twice daily for 2 to 3 days) may be helpful in animals with acute cerebral edema. If the neurologic signs diminish and the plasma sodium level returns to normal, the animal may be given fresh drinking water. Thiamine (10 mg/kg SC) may be a useful adjunctive therapy.

Control Cattle should be fenced away from polluted ponds and oil wells. Cattle on coastal pastures should have access to fresh well water. The total daily dietary salt intake should not exceed 4% of dry matter intake. Drinking water must contain less than 7000 ppm of sodium unless the dietary sodium load is reduced correspondingly. Oral rehydrating fluids for calves should be dissolved in strict accordance with the manufacturer's recommendations. Assessment of water cleanliness and availability should be a component of a daily animal husbandry plan.

Vitamin A Deficiency

Definition and Etiology Vitamin A (retinol) is found in green plants and can be synthesized from plant carotenoid precursors in the liver and intestinal mucosa. Precursors of vitamin A are usually fed in cattle rations as β-carotene or as retinoids. Vitamin A deficiency occurs primarily in growing ruminants in feedlots. Deficiency develops under these conditions because the growing animal has a higher requirement for the vitamin, and feedlot-reared animals may have limited access to succulent plants. The vitamin is labile in foodstuffs and is depleted after several years of storage. Diets that are naturally low in vitamin A include cereal grains, beet pulp, and cottonseed hulls. Conditions in which the immune system is challenged, as when exposure to pathogens is high, also increase the requirement for vitamin A. Other scenarios conducive to vitamin A deficiency include prolonged grazing on dry pastures or cereal grains other than corn, exclusive feeding of cereal grains that have been stored at high temperature and humidity, or prolonged feeding of mineral oil as a preventive for frothy bloat.

Clinical Signs Signs in deficient calves include anorexia, illthrift, blindness, diarrhea, and pneumonia. The syndrome in adults is characterized by "star-gazing" posture, blindness, diarrhea, anasarca, nystagmus, strabismus, exophthalmos, loss of pupillary light reflexes, and intermittent tonic-clonic convulsions. The seizures may last for only a few minutes and can be followed by partial recovery.[1-3] Animals may die during seizures. Stimulation of the animals frequently precipitates seizures.[4,5] Death is often preceded by hyperesthesia and coma.[1,2,6] Inadequate vitamin A supplementation of calves is associated with unthriftiness, intermittent fevers, and a higher incidence of diarrhea.[7] Vitamin A–deficient adults appear to be in good body condition unless parasitism or some other nutritional deficiency is superimposed on the low vitamin A intake.[1,8] Secondary factors that can influence the appearance of the animals include concomitant nutritional deficiencies, parasitism, and pneumonia.

The ocular changes of vitamin A deficiency are characteristic. The pupils become dilated and unresponsive. As papilledema develops, the optic disc becomes pale and its borders become indistinct, particularly in the upper quadrants,[1,3,9] giving the appearance of an inverted heart. The swollen disc may cast a shadow on the adjacent retina. The color of the disc becomes faded. In advanced cases the disc may become atrophic and appear dull, gray, flattened, and smaller than normal.[10] The retinal blood vessels become tortuous or appear to be occluded as they course over the disc. Retinal detachment and subretinal hemorrhages are possible.[1]

Reproductive disturbances can occur, including malformed fetuses, abortions, loss of libido, testicular degeneration, and decreased sperm counts. Calves born to vitamin A–deficient dams are blind, have domed foreheads and thickened carpal joints, and are weak at birth.[11]

Vitamin A deficiency can be clinically differentiated from polioencephalomalacia (PEM) and salt poisoning by comparing the menace response with the pupillary light reflex. Calves with lead poisoning and PEM generally have intact pupillary light reflexes because of the proper functioning of the mesencephalon and optic nerves, whereas vitamin A–deficient cattle have absent pupillary light responses because of retinal degeneration and constriction of cranial nerve II at the level of the optic foramen.

Clinical Pathology Assay of vitamin A and carotene concentrations in the plasma and feed is the most direct method of diagnosing the dietary deficiency. The concentration of plasma vitamin A and β-carotene in normal animals ranges from 25 to 85 μg/dL and 150 and 397 μg/dL, respectively.[2] Plasma concentrations of vitamin A–deficient and β-carotene–deficient animals usually are less than 7 and 70 μg/dL, respectively. The hepatic concentration of vitamin A and carotene in normal calves ranges from 60 to 200 and from 4 to 800 μg/g of tissue, respectively. In deficient calves the hepatic concentrations of the vitamin A and carotene nutrients range from 2 to 14 and from 0.5 to 32 μg/g, respectively.[8] There are no consistent changes in the blood chemistry analysis or the hemogram of deficient animals. Changes in the CSF of vitamin A–deficient animals include a mononuclear cell pleocytosis (40 to 50 nucleated cells/dL) and an increased protein concentration (140 mg/dL)[12]; increased CSF pressure (>200 mm Hg) may also occur.[13]

Pathophysiology Vitamin A is responsible for the regeneration of rhodopsin in the retina and in normal function of osteoblasts and osteoclasts, epithelial tissues, the choroid plexus, and reproductive tissues. Vitamin A deficiency causes a thickening of the dura mater, resulting in diminished CSF absorption from the arachnoid

granulations and the nerve rootlets. Narrowing of all the bony foramina of the skull occurs in immature animals, although bone remodeling does not occur in adults. The combined effects cause an increase in CSF pressure.[8] Closure of the optic foramen may lead to transection of the optic nerve. The high CSF pressure is transmitted into the optic nerves and results in papilledema.

Three causes of blindness have been associated with vitamin A deficiency. Nyctalopia (night blindness) is presumably caused by the decreased formation of vitamin A aldehyde in the regeneration of the visual pigment rhodopsin; this type of blindness is usually reversible. Second, degenerative changes in the outer retinal layers also cause blindness; this is reversible if treated in the early stages. The third cause is associated with stenosis of the optic foramen and compression of the optic nerve; this condition is irreversible.[14]

Epidemiology The vitamin A requirement of all species ranges from 40 to 110 IU/kg daily.[15-17] The minimum recommended daily dose of vitamin A for growing calves up to 1 year of age, for pregnant sheep, and for growing horses is 40 IU/kg. Pregnant cattle and pregnant or lactating horses require 40 to 50 IU (13.76 to 17.2 µg/kg) of vitamin A daily.[16] Lactating cattle require 80 IU (27.5 µg/kg) of vitamin A daily. Horses are susceptible to vitamin A deficiency, but the condition is rarely seen in that species. This is thought to be the result of differing conditions of management rather than an inherent resistance to the deficiency. The daily dietary requirement for carotene is 0.12 mg/kg.[16] Pasture forage, silage, and properly cured hay (<1 year old) contain large amounts of carotene. Common constituents that have low concentrations of vitamin A are sorghum, brewer's grain, and wheat straw.

Livestock are protected from short-term deprivation of vitamin A by their ability to accumulate the vitamin in the liver; however, it is estimated that the intake required to initiate storage is at least three times the minimum daily intake.[16] Vitamin A–replete cattle fed a diet devoid of vitamin A require approximately 180 days before they begin to show clinical signs. During that time the cattle grow and fatten normally and show no adverse effects. Offspring born to these animals may show severe deficiencies. Papilledema and blindness develop rapidly after the hepatic stores are depleted.[16]

Vitamin A deficiency may be categorized as a primary or secondary condition. Primary deficiencies of vitamin A develop in cattle confined in drylot corrals or pasture on dry grass forage for prolonged periods or when cattle are kept indoors and fed unsupplemented, vitamin-depleted cereals and dry forage in which the activity of carotene has been destroyed. Also, there is a seasonal difference in the concentration of vitamin A in feedstuffs. For example, cattle grazed on green pastures are consistently replete with the vitamin, whereas those grazed on dry pastures at the end of summer may become marginally deficient. Approximately 80% of the vitamin A concentration of hay is lost during field curing.[18]

Destruction of carotene is hastened by many environmental and physical factors, including heat, sunlight, trace mineral supplements, and humidity.[19] Other factors that affect the stability of vitamin A in feedstuff include pelleting and exposure to rancid fat in the feed.

Secondary deficiencies of vitamin A result from interference with vitamin absorption, inhibition of the conversion of β-carotene to retinol (vitamin A) in the small intestine, or an increased requirement in the face of limited vitamin intake. The conversion of carotene to retinol is impaired in vitamin A–deficient patients.[6] Sheep may be more resistant to vitamin A deficiency because they convert β-carotene more efficiently than cattle.[6] Fever, lactation, high ambient temperatures, and inadequate dietary energy may increase the daily requirement for vitamin A.[19] Other factors that can affect availability of vitamin A or the requirement for the vitamin include diets with low forage content, high proportion of corn silage to hay in the diet, increased exposure of animals to pathogens, and periods where immunocompetence is reduced (e.g., the peripartum period).[17] Secondary deficiencies of vitamin A may be caused by impaired vitamin absorption, which may occur from long-term feeding of mineral oil.

Necropsy Findings The major pathologic changes in the fundus of vitamin A–deficient calves include papilledema, small flame-shaped hemorrhages around the optic disc, venous congestion in the area of the swollen optic disc, degeneration of the retinal ganglion cells, focal retinal thinning, and fusion of parts of the retina to the choroid plexus.[9] Other changes associated with vitamin A deficiency include doming of the frontal bones, enlargement of the carpi, cerebellar and cerebral compression, partial transtentorial herniation of the cerebellum, cystic dilation of the hypophyseal cleft, focal ruminal hyperkeratosis, and increased keratinization of the squamous epithelium of the penile and the preputial mucous membrane. Corneal ulceration and clouding have been observed in the eyes of calves with naturally occurring deficiencies.[12] Vitamin A deficiency also can cause anasarca, squamous metaplasia of the salivary ducts, degeneration of the germinal testicular epithelium, degenerative changes in the intestinal epithelium in lambs, and reduction in intramuscular fat in cattle.[20-22]

Microscopic changes in the CNS include attenuation of the optic nerve with necrosis and demyelination. Focal accumulations of phagocytic cells containing lipofuscin and hemosiderin are present in the necrotic area. The optic nerve is attenuated along its entire length. The meninges are thickened by fibrosis and mononuclear cell inflammation. The microscopic changes in the bones include wider than normal spacing of the central canals and reduction of osteoclastic lacunae.

Treatment and Control Cattle with severe blindness caused by damage to the retina or optic nerves do not regain their vision when treated with vitamin A; however, cattle with acute encephalopathy and simple papilledema may respond favorably after a short period of vitamin supplementation.[16] Affected cattle should receive 440 IU/kg (1 IU = 0.4 µg) of vitamin A parenterally and then 6000 IU/kg parenterally every 50 to 60 days until the diet has been enriched. High-dose oral therapy is important because carotene and oil suspensions of vitamin A are not efficiently utilized when administered by parenteral injection.[23] Administration of large doses orally is important because conversion of β-carotene to vitamin A is inhibited in deficient calves. The recommended concentration of vitamin A in milk replacers for preruminant calves is 11,000 IU/kg dry matter.[7]

Prophylactic dietary supplementation of vitamin A should be considered in all cattle that lack access to green feed. Dietary supplements could include leafy, freshly cured hay, green pasture, or alfalfa meal. Concentrate feeds formulated with exogenous, stabilized vitamin A are commercially available. Recommended concentrations (IU/kg dry matter) of vitamin A in feed are 2200 IU for feedlot cattle, 2800 IU for pregnant cows, and 3900 IU for lactating cows.[18]

Hydrocephalus and Hydranencephaly of Ruminants

Definition and Etiology Hydrocephalus/hydranencephaly is a common occurrence in large ruminants. It is underdiagnosed because many of the affected animals die of complications, and the primary condition is overlooked during clinical and pathologic examinations. One study reported that 97 of 155 calves with CNS lesions had hydrocephalus.[1] Hydrocephalus may be classified as hypertensive or normotensive.[2]

NORMOTENSIVE HYDROCEPHALUS (HYDRANENCEPHALY). Normotensive hydrocephalus that develops as a result of a failure of cell growth or cellular necrosis is called *hydranencephaly.*[2] Most cases of hydranencephaly in domestic livestock are caused by in utero infection of the fetus by viral pathogens such as bluetongue, bovine viral diarrhea (BVD), akabane, Cache Valley, aino, border disease, and the Schmallenberg virus.[1,3-13] The pathogenesis and epizootiology of the multisystemic virus infections bluetongue and BVD are discussed in detail in Chapter 32. The neurologic effects of border disease virus infection are discussed earlier in this chapter.

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The loss of fetal neurons in utero results in flexural contractions of the limbs (arthrogryposis), which may manifest as dystocia. Affected neonates may be stillborn or born alive but weak, blind, unable to stand, and unable to nurse. They may exhibit a dysphonia, which resembles a bark. Neonates that are unable to nurse are deprived of colostrum and often die from septicemia.

Akabane Virus Infection. The akabane virus is a member of the Sindbis serologic subgroup of the Bunyaviridae family.[3] It has been isolated from cattle in Africa, Japan, Israel, Korea, and Australia.[4-9] The host range of akabane virus includes sheep, cattle, and goats. Infection of pregnant, nonimmune dams results in hydranencephaly or arthrogryposis of the fetus.[14] The disease is thought to be transmitted to the cow by various *Culicoides* spp. Experimentally infected calves develop porencephaly and encephalitis when exposed to the akabane virus between gestational days 62 and 96.[15] Studies in naturally infected cattle showed that infection of calves between days 76 and 104 of gestation resulted in hydranencephaly or porencephaly, whereas infection between days 103 and 174 of gestation resulted in arthrogryposis.[16] Lambs are susceptible when exposed to the virus on gestational days 30 to 36.[9] The CNS lesions are apparently the result of a direct necrotizing effect of the virus on the developing neurons. The pathologic changes of the CNS in experimentally infected calves and lambs are similar to those of naturally acquired infections.[6,9] Adults occasionally abort when infected by the virus but do not develop clinical disease.

A syndrome of arthrogryposis, facial deformities, kyphoscoliosis, hydranencephaly, and hypoplasia of multiple regions of the brain and spinal cord has been described in Corriedale sheep in Australia. Although resembling the disorder caused by congenital akabane virus infection, breeding trials supported an autosomal recessive inheritance for the disease.[17]

Aino Virus Infection. The aino virus causes stillbirths, premature calving, and congenital malformations including arthrogryposis, cerebellar hypoplasia, and hydranencephaly in calves of Japan and Australia.[18-20] Aino virus is antigenically and biologically distinct from akabane virus, but the clinical syndromes of fetal infection by the two viruses are indistinguishable.

Chuzan Virus Infection. Hydrocephalus, hydranencephaly, and cerebellar hypoplasia have been attributed to infection of pregnant cattle with the Chuzan virus.[21-23] This virus is a relative of the akabane and aino viruses and is classified as a new member of the Palyam subgroup of the genus *Orbivirus*. The virus has been isolated from *Culicoides oxystoma,* which may serve as the major vector. The clinical signs are characteristic of hydrocephalus.

Cache Valley Virus Infection. A flock outbreak of arthrogryposis, myositis, hydranencephaly, and a variety of other brain malformations (micrencephaly, cerebellar hypoplasia, porencephaly) in newborn lambs in the southwestern United States was attributed to in utero infection with the Cache Valley virus (family Bunyaviridae).[24,25] Cache Valley virus was first isolated from mosquitoes from Utah and has since been isolated from caribou, horses, sheep, and cattle elsewhere. Antibodies have been found in white-tailed deer in the southwestern United States, but the role of this mammal in the survival of the virus and the transmission of the disease to livestock is unknown.[26] In one survey of sheep in the western United States, the seroprevalence for the Cache Valley virus was 19.1%.[24] Vectors for the virus include *Anopheles, Aedes, Culex,* and *Coquellettidia* mosquitoes.[27] Infection before 30 days of gestation may cause embryonic death, whereas infection between days 30 and 52 causes fetal malformations.[27]

Bluetongue Virus Infection. Hydranencephaly and/or arthrogryposis may occur in ruminants when the dam is infected at specific vulnerable windows during gestation; abortions or fetal resorption can also occur. Serotype 11 or serotype 17 of the virus is most frequently isolated from calf and lamb neonates in field epizootics.[28,29] Recently, bluetongue virus serotype 8 has caused devastating disease in ruminants in Central and Northern Europe; importantly, neonates infected in utero may be born viremic, thereby providing *Culicoides* spp. with more abundant viremic hosts during the subsequent spring.[30] Calves, lambs, and kids infected in utero may be born normal or develop one or more associated birth defects including hydranencephaly, arthrogryposis, brachygnathia, prognathia, and excessive gingival tissue (see Chapter 32 for additional information).

Bovine Viral Diarrhea Virus Infection. Hydranencephaly, hydrocephalus, and cerebellar hypoplasia have been associated with fetal infection of cattle with the BVD virus.[31-34] Precolostral serum antibody titers for the virus in affected calves vary; some titers range from 1:32 to 1:256, but other calves may have persistent viremias yet no demonstrable antibody.

Schmallenberg Virus Infection. The Schmallenberg virus (SBV) is an enveloped RNA virus belonging to the genus *Orthobunyavirus* in the family Bunyaviridae.[10] The Schmallenberg virus is a member of the Simbu serogroup, which includes the well-known teratogenic Akabane virus. It is named after a town in west-central Germany where, in the autumn of 2011, signs of this viral disease first emerged in local cattle. Diagnosticians at the Friedrich-Loeffler Institute (the Federal Research Institute for Animal Health Investigation) subsequently identified this virus as a cause of transient fever, depression, reduced milk production, and occasional diarrhea in cattle. The virus was subsequently detected in ruminants in France, Belgium, the Netherlands, Luxembourg, the United Kingdom, Italy, and Spain.[11] During the fall of 2011, infections in small ruminants in the region were predominantly asymptomatic; however, once ruminant birthing commenced in late 2011 and early 2012, it became apparent that the virus had induced significant fetal morbidity and mortality—primarily in sheep—but in goats and cattle as well.

Fetal infection with SBV may result in abortion, stillbirth, weak newborns, newborns with significant neurologic deficits, or normal, healthy neonates; on the basis of the pathophysiology of Akabane viral infections, the outcome of fetal infection with SBV is considered likely to depend on the timing of viral infection relative to the stage of fetal development.[10,11] Infection early in pregnancy, within the first trimester, appears to result in the most significant fetal deformities, with arthrogryposis of one or more limbs, torticollis, spinal malformations (scoliosis, kyphosis, and/or lordosis), brachygnathia inferior, and a multitude of CNS malformations.[10,11] Hydranencephaly, porencephaly, and hydrocephalus are among the more common neurologic malformations. According to the Office International des Epizooties (OIE, or World Organization for Animal Health) the clinical disease in ruminants can best be categorized as an *arthrogryposis/hydranencephaly syndrome.*[12] Fetal limb, neck, and spinal skeletal anomalies can result in dystocia. To date, there have been no reports of SBV causing human infections, and the virus is not presently considered to be a zoonotic threat.

As is the case with other members of the *Orthobunyavirus* genus, SBV is an arthropod-borne virus, with Culicoid midges (specifically, *Culicoides obsoletus*) currently considered to be the most likely vector in Europe.[13] Other vectors, however, may also be involved. Vertical transmission of the virus from infected ruminant dam to ruminant fetus is considered to be the primary means of spread within animals. Horizontal transmission is a possible but less likely means of transmission. The cause of SBV emergence in Europe remains undetermined. Current research efforts are aimed at screening banked sera for evidence of previous exposure to the virus in European livestock, characterizing the vector(s) that may transmit the virus, investigating potential means of animal-to-animal spread, and vaccine development.

Other Infectious Agents. A single case of hydrocephalus in a calf aborted at 7 months of gestation was associated with necrotizing encephalitis caused by *Neospora caninum.*[35]

HYPERTENSIVE HYDROCEPHALUS. An increase in CSF volume that results from compressive or obstructive lesions in the ventricular system or from decreased CSF absorption is called *hypertensive hydrocephalus.*[2] Obstructive lesions of the ventricular system trap the CSF in the ventricles, causing an increase in CSF volume and pressure. Ischemia and CNS degeneration result from the high CSF

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pressure. The sites of obstruction most often include the lateral apertures, mesencephalic aqueduct, lateral ventricles, interventricular foramina, and fourth ventricle. The obstructions may be either congenital or acquired. Causes of acquired obstructive hydrocephalus include cerebral abscess, cholesteatoma (equines), equine infectious anemia, *Coenurus cerebralis* infestation, meningitis, and lymphosarcoma. Hypertensive hydrocephalus may also be caused by acute inflammatory disease such as meningitis and vitamin A deficiency. In these diseases the increased pressure is the result of impaired CSF resorption.

CONGENITAL HYPERTENSIVE HYDROCEPHALUS. Congenital hypertensive hydrocephalus is a hereditary condition seen in Hereford, Charolais, Ayrshire, Dexter, Holstein, and Jersey calves.[36-38] The condition has also been recognized in Arabian foals.[39]

Clinical Signs Hydrocephalic animals are often born dead or are weak and die shortly after birth. The most obvious signs in animals that survive include failure to bond to the dam, depression, diminished learning ability, partial failure of suckling, droopy head and ears, muscular fasciculations, head tremor, conscious proprioceptive deficits, blindness, ventrolateral strabismus, nystagmus, dysphonia, tongue flaccidity or paralysis, retention of food material in the cheeks and lips, limb spasticity, hyperreflexia, psychomotor seizures, recumbency, and coma. Occasionally, doming of the calvarium or protrusion of fluid-filled cystic structures through an open fontanelle is seen. Affected neonates often do not ingest sufficient amounts of colostrum and frequently die of septicemia.

In virally induced cases of hydranencephaly, associated skeletal deformities including abnormally curved ribs, kyphoscoliosis, flexural deformities of the limbs, domed skulls, and brachygnathia may be observed. Patients with hydrocephalus caused by compressive lesions around the ventricular system may show unilateral or bilateral signs of increased intracranial pressure. The clinical signs of unilateral lesions include head tilt (toward the lesion side), ipsilateral mydriasis, and contralateral menace deficit. Signs of hydrocephalus in foals are similar to those in calves. The cause of the condition in horses is unknown.

Antemortem diagnosis of brain malformations has been facilitated by CT and MRI. However, these techniques are rarely warranted or available for use in large animal species. A more practical technique for using ultrasonographic imaging, transorbital echoencephalography, has recently been described and has proved effective for the diagnosis of hydranencephaly.[40]

Clinical Pathology The diagnosis of hydrocephalus in calves and lambs is typically based on the presence of characteristic clinical signs and a domed skull. Whenever hydranencephaly is suspected, blood should be collected for virus isolation, serologic testing, and quantitative immunoglobulin determination. Presuckle serum samples from neonates that have been infected by the akabane or bluetongue virus in the latter part of gestation may be seropositive.[26]

Necropsy Findings The pathologic lesions of hydranencephaly are similar regardless of the etiologic agent. They include microcephaly, cerebellar hypoplasia, hydrocephalus, hydranencephaly, and porencephaly of the cerebral and the cerebellar cortex. Microscopic lesions of hydranencephaly include segmental loss of dorsolateral ventricular ependyma, thinning of the periventricular white matter, porencephalic cysts, and nonsuppurative meningoencephalitis. Lesions in other parts of the CNS may include loss of ventral horn cells in the spinal cord and demyelination in the spinal cord. Nonsuppurative inflammatory changes may be seen in cases caused by viral infections. Polymyositis has been described in affected calves; however, it is unclear if these lesions are caused by viral infection or occur secondary to the denervation. The skeletal deformities associated with virally induced hydranencephalies include rigid extension or contraction of one or more limbs (arthrogryposis), abnormally curved ribs, domed skull, thickening of the calvarium, kyphoscoliosis, and brachygnathia. Important differential diagnoses include causes of normotensive hydrocephalus, vitamin A deficiency, and congenital infection with bovine viral diarrhea virus in cattle.

Treatment Except for one report of successful surgical intervention in a calf with a meningocele, no satisfactory therapy is available for the treatment of hydrocephalus or hydranencephaly in large animals.

Ammoniated Forage Toxicosis (Cow Bonkers)

Exposure of poor-quality forage to anhydrous ammonia improves the nutritional density of the material and reduces certain toxic fungal metabolites, specifically the prolactin-like toxins of the endophytic fungus *Acremonium coenophialum* in fescue hay.[1] Ammoniation increases dry matter intake, enhances digestibility, and increases the relative value of the protein content of the feed. However, overammoniation of the forage, at a rate exceeding 3% of the forage on a dry matter basis, may result in toxicosis. Studies now suggest that several dialkylimidazoles may be responsible for the neurotoxic effects of ammoniated feedstuffs, superseding previous theories that 4-methylimidazole is the primary neurotoxin.[2,3] Ammoniated foodstuffs containing high levels of molasses are more toxic than similarly treated grass hay. The toxin may be concentrated in milk; consequently, calves suckling from normal-appearing dams may show clinical signs of intoxication.

Affected animals are hyperesthetic and ataxic. At rest the animals assume a sawhorse stance, but when excited, they become hyperactive, appear to be blind, and circle propulsively. Other clinical signs include vocalization, dysphonia, and walking or running into objects. The periods of frenzy may result in recumbency and convulsions. The spasmodic episodes last for 15 to 20 minutes. Afterward the animals rest quietly, with occasional muscle tremors. Repeated occurrences of the mania may be precipitated by loud noises or other frightening experiences. The concentrations of ammonia in the blood and CSF may be increased. Although specific treatments have not been identified, one report indicated that affected calves benefited from acepromazine (0.045 mg/kg IV) and thiamine (1.14 mg/kg IM). Thiamine dosages higher than described in this report[4] (such as 10-20 mg/kg SC q12h) have been used for treatment of other neurologic diseases and may be considered for use in this disease.

Lead Poisoning

Definition and Etiology Lead poisoning in ruminants is characterized by an acute encephalopathy. In contrast, lead poisoning in horses is characterized by chronic polyneuritis. Blindness, ataxia, and depressed sensorium are significant clinical signs in cattle, sheep, and goats, whereas in horses the poisoning is associated with weight loss, dysphagia, and secondary aspiration pneumonia. Cattle are most often poisoned because of their tendency to lick or chew on foreign objects, their access to lead-containing materials, and their propensity to drink contaminated petroleum distillates.[1]

Clinical Signs The signs of lead poisoning in ruminants are characteristic of CNS derangement. During the first stages of lead poisoning, affected cattle stand alone and are depressed.[2] They may show hyperesthesia, muscular fasciculations, and rapid, spastic twitching of the eyelids or other facial muscles. Progression of the disease is associated with ataxia, conscious proprioceptive deficits, cortical blindness, head pressing, odontoprisis, coma, and convulsions.[3,4] Some animals may display episodic running, hyperesthesia, and bellowing. Others may die suddenly without premonitory signs. The more acute and severe the toxicity, the more acute, severe, and excitatory are the clinical signs.[5] Affected cattle may accumulate frothy saliva at the commissures of the lips. GI signs of bloat, diarrhea, rumen atony, and colic occur in about 60% of lead-poisoned

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cattle, and the presence of such signs increases the index of suspicion for lead toxicity versus other causes of cerebral dysfunction.[6] Infertility, abortions, and fetal malformations may result from exposure to lead.[5]

The clinical signs of lead poisoning in horses include weight loss, lack of coordination, laryngeal or pharyngeal paralysis, dysphonia, roaring, conscious proprioceptive deficits, loss of anal tone, facial paralysis, and difficulty with mastication.[7] Aspiration of pharyngeal debris caused by dysphagia may result in pneumonia. Fine muscular tremors occur intermittently. The poisoned animals die in psychomotor seizures. Horses with lead poisoning are emaciated at death.[8]

Clinical Pathology Diagnosis of lead poisoning is based on measurement of increased blood and tissue concentrations of lead. Tissue levels of lead in naturally poisoned cattle can reach 20 to 100 ppm in the liver, 30 ppm in the kidneys, and 5000 ppm in bone. When interpreting the results of a lead measurement, consideration of the reference ranges obtained with similar methodology is essential. Heparin is the anticoagulant of choice when collecting blood for lead measurement because it does not chelate the lead. The lead concentration of ruminal fluid from acutely poisoned cattle ranges from 0 to 11,875 ppm.[3]

Livestock that are chronically poisoned with low concentrations of lead may have a normal blood lead concentration but a high concentration in the bone. In these cases the poisoning can be diagnosed by administration of calcium disodium ethylenediamine tetraacetic acid (EDTA), which solubilizes the bone lead stores and increases the concentration of lead in the plasma. The soluble lead-EDTA complexes are excreted in the urine. The urinary lead concentration may rise by 40-fold over pretreatment levels within a few hours. In cases of chronic lead poisoning, radiographs of the abdomens of smaller patients may reveal lead-containing radiodense foreign material in the GI tract.[9] "Lead lines" may also be present in the long bones of young animals chronically exposed to lead.

When blood lead concentrations are normal in chronically poisoned animals, measurement of free erythrocyte porphyrins and erythrocyte concentrations of α-aminolevulinic acid (ALA) are the preferred methods of diagnoses. The concentration of porphyrins is increased in the blood, urine, and feces of animals with lead poisoning. The reference range of blood porphyrin concentrations in normal calves is 21.6 ± 11.6 to 45.6 ± 10.3 μg/dL for whole blood and 113 and 142.8 ± 32.4 μg/dL for erythrocytes.[4,10,11] In chronically exposed, asymptomatic cattle, the free erythrocyte porphyrin concentrations are frequently greater than 2000 μg/dL.

Reference ranges for ALA dehydrase are 45.8 ± 20.6 U, whereas activities ranging from 28 to 33 U have been reported in naturally exposed calves.[8] The urinary concentration of δ-ALA is increased and ranges above 500 μg/mL.[12,13] Measurement of ALA in the erythrocytes is more reliable than measurement in urine.[14]

Environmental sources of lead can be detected by direct measurement of the lead concentration of the soil or pasture forage. Forage from toxic pastures contains more than 30 ppm of lead, and in some cases the level may exceed 300 ppm.[13,15]

The hematologic abnormalities of lead poisoning are subtle. Most poisoned livestock have a normal hemogram. If present, lead-related changes are characteristic of a hemolytic anemia with an inappropriately robust regenerative response. The morphologic abnormalities of erythrocytes include anisocytosis, poikilocytosis, polychromasia, hypochromia, Howell-Jolly bodies, metarubricytes, and basophilic stippling.[3,16] The shape changes begin within hours after ingestion of the lead and peak by 100 days.[3,16] Blood changes do not occur in all cases of the disease and are not necessarily specific indicators of lead poisoning in cattle, in which elevated blood lead may be present without hematologic abnormalities.[17] However, hematologic abnormalities tend to be more consistent in chronic lead toxicity and in lead-poisoned horses.

Lead toxicity has a variety of effects on endocrine function in cattle. Elevated levels of serum T_3, T_4, estradiol, and cortisol have been demonstrated in cattle with elevated blood lead levels.[18] Parameters of liver function are also affected; serum alanine and aspartate transaminase (ALT and AST) levels are increased, whereas serum lipids, total protein, and albumin are decreased.

In poisoned animals the concentrations of protein and WBCs in CSF are increased, ranging from 50 to 100 mg/μL of protein and 5 to 50 mononuclear cells/mL, respectively. Such changes are relatively nonspecific and found with other causes of cerebral cortical necrosis.

Pathophysiology Lead enters the body through the GI tract or less often through the respiratory tract. Metallic lead and the sulfide form are less well absorbed than the acetate, phosphate, carbonate oxide, and hydroxide salts. Metallic lead is poorly absorbed and causes toxicity only when a lead foreign body becomes entrapped in the stomach for prolonged periods. Interaction between lead and other minerals may occur. For example, high levels of dietary calcium reduce the GI absorption of lead. Concomitant exposure to lead and cadmium results in a worsening of the clinical signs of lead poisoning.[19]

Acute toxic single doses of lead range from 200 to 600 mg/kg for calves and 600 to 800 mg/kg for adults.[20,21] Although intestinal absorption of lead is relatively inefficient, significant amounts can cross into the blood if sufficient quantities are ingested. Approximately 1% to 2% of the total oral dose of lead is absorbed by 24 hours.[3] Most of the lead absorbed from the digestive tract (90%) is bound to erythrocyte proteins, resulting in a low lead concentration in the plasma but higher concentrations in whole-blood specimens.[22] At the end of the erythrocytes' lifespan, the cell-bound lead is metabolized from the erythrocyte proteins and deposited in the bone as the triphosphate salt. The half-life of blood lead in adult cattle is extremely variable and unpredictable, ranging from 48 to 2507 days in one study.[23] Phenotypic or genotypic factors may affect metabolism and storage of lead. The variable time for clearance of lead has an obvious implication for public health because all carcasses of animals suspected or known to be exposed to lead must be tested before being cleared for human consumption.[24]

Lead also crosses the placental barrier and accumulates in fetal bone, liver, and kidneys but does not substantially accumulate in milk. However, cattle with higher blood lead levels may have greater concentrations in milk.[25]

The toxic effects of lead include inhibition of free sulfhydryl groups found in many enzymes, interference with zinc-containing metalloproteins, and steric inhibition of enzyme activity.[16] Enzymes of heme synthesis are particularly susceptible to injury. These include δ-ALA dehydratase and ferrochelatase. Interference with ferrochelatase inhibits the formation of heme from protoporphyrin, resulting in a buildup of unmetabolized porphyrins.

Because of the interference with heme metabolism and the altered function of other erythrocyte proteins, the erythrocyte half-life is shortened, which may result in a normochromic, normocytic anemia in a small proportion of chronically poisoned animals.[26] Iron is not adequately used and is stored in sideroblasts in the bone marrow.[11] Lead also interferes with the activity of pyrimidine-specific 5′-nucleotidase, resulting in basophilic stippling of red cells.[27]

After absorption, lead rapidly enters the brain at a dose-dependent rate. The lead deposition in the CNS results in acute cerebellar hemorrhage and edema from capillary dysfunction.[22] The pathogenesis of lead encephalopathy is multifactorial. Encephalitic signs probably originate from a combination of microvascular damage, cellular necrosis, brain swelling, neurotransmitter dysfunction, and decreased glucose uptake by the brain.[26]

Ingestion of lead also results in competitive inhibition of selenium uptake, thereby diminishing the absorption of selenium by up to 26%.[21] If selenium intake is marginal, lead toxicosis could manifest as overt selenium deficiency.

Epidemiology Sources of lead are legion including lead arsenate defoliants, batteries, used motor oil, linoleum, roofing felt, paint,

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machinery grease, caulking compounds, improperly compounded mineral supplements, and foliage near lead smelters and battery-recycling plants.[2,8,13,28-33] High lead levels have been reported in grasses growing near busy roadways, but the clinical significance of these findings is unclear.[30,34,35] Factors that can increase the likelihood of ingestion of lead-contaminated foodstuffs include lack of alternative feed, hunger, and phosphorus deficiency.[5] The single lethal dose of lead for cattle is estimated to range from 220 to 600 mg/kg for calves, 600 to 800 mg/kg for adult cattle, and 400 mg/kg for goats.[5,20] Lead poisoning has been reported in cattle exposed naturally to 6 to 7 mg/kg/day of lead on foliage and in calves given oral lead acetate at 2.7 to 20 mg/kg/day.[36] The interval for development of clinical signs ranges from 5 to 20 days and is related to the dose and ionic form of lead administered.[36] Ensiling of contaminated forage results in percolation and concentration of lead at the bottom of the silo.[37]

The toxicity of lead is apparently influenced by dietary factors. Calves on a milk diet are more susceptible to lead poisoning than calves fed hay and grain.[38] There appears to be a direct correlation between high levels of vitamin D and enhanced lead absorption, which may explain the greater occurrence of poisoning during the summer. Elevated copper concentrations in forage, such as may be found in pastures fertilized using pig slurry, may potentiate accumulation of lead in animals consuming it.[39]

The estimated cumulative toxic dose of lead for horses is 2.9 mg/kg/day.[40] Poisonings have been reported in horses grazing pastures contaminated with 320 to 440 ppm of lead from a metal smelter; this amounted to a daily intake of 2 g (≈6.4 mg/kg). Metallic lead and the "galena" (insoluble sulfide salt) are less toxic than the acetate and carbonate lead salts.[41]

Necropsy Findings The macroscopic brain lesions of lead poisoning are mild and include brain edema, congestion of vessels of the cerebral cortex, and yellowish discoloration and flattening of the cortical gyri. Lesions tend to be most severe in the occipital lobes. Microscopic changes in the brain include capillary prominence, endothelial cell swelling, edema of the Purkinje cell layer of the cerebral cortex, laminar cortical neuronal necrosis, and edema of the white matter.[42]

Treatment Therapy for lead poisoning should include removal of the lead from the digestive tract, chelation therapy with calcium disodium EDTA, and fluid and nutritional support of the patient. Treatment with calcium disodium EDTA (calcium versenate) has been shown to be superior to treatment with penicillamine or dimercaprol (BAL). The EDTA chelates osseous but not soft tissue–bound lead. After chelation, the unsaturated bone stores reequilibrate with the lead remaining in the soft tissues. In cases of acute lead poisoning, several days are required before reequilibration results in a decreased blood lead concentration. The dose of calcium disodium EDTA is 66 mg/kg/day, divided into several doses daily for 3 to 5 days.[43] After five daily treatments, a 2-day nontreatment period is recommended to reequilibrate the soft tissue and bone lead. After the 2 days' rest, daily treatments are given for another 5 days. The decision to continue therapy with EDTA should be based on the results of post-treatment blood lead analyses and renal function tests. Another recommendation is for administration of two IV injections of calcium disodium EDTA (110 mg/kg per dose) given 12 hours apart for 2 days.[44] Therapy is then withheld for 2 days, after which the EDTA treatments are reinstituted for 2 more days. The comparative efficacy of this regimen is unknown.

The EDTA also chelates other divalent cations. Consequently, prolonged administration of the drug results in trace-mineral deficiencies, especially of zinc. For this reason, after prolonged EDTA therapy, oral supplementation with zinc should be considered to prevent the development of parakeratosis.

Reports have indicated that thiamine therapy is an effective adjunctive treatment with EDTA in cases of acute lead poisoning of cattle.[20,45,46] Administration of 2 mg/kg thiamine daily was more effective than treatment with disodium EDTA (62 mg/kg twice daily for 4 days) or thiamine plus disodium EDTA in inducing remission of clinical signs of experimentally induced lead poisoning.[47] For clinical treatment of lead poisoning, thiamine dosages of 500 mg for small ruminants and 1 g for cattle weighing 300 kg have been recommended,[45] and alternatively, a dosage of 10-20 mg/kg SC q12h can be used. Administration of daily doses of thiamine (100 mg/calf/day or 5 mg/kg) has protected experimentally exposed calves from clinical signs of lead poisoning and reduced lead deposition in the soft tissues.[46,48,49] The nature of the protective effects of thiamine is unclear. Apparently, either lead interferes with thiamine synthesis or the tissue distribution and deposition of lead are reduced by the formation of rapidly excreted lead-thiamine complexes.

In ruminants, ingested lead is best removed from the digestive tract by means of a rumenotomy.[20] Magnesium sulfate laxatives are administered concomitantly to form insoluble lead sulfides. Patients that respond slowly to chelation and thiamine therapy should be given supportive care. These measures should include provision of 40 to 80 mL free water/kg/day for maintenance, oral hyperalimentation, and administration of diazepam or phenobarbital for convulsions (as discussed in the section on bacterial meningitis).

Prevention and Control Toxic pastures can be made safe by removing contaminated forage. This is best done by cutting, baling, and burying native grasses, then burning the stubble. The source of the lead should be established, and the affected animals should be carefully documented. In the United States, insurance liability responsibilities may be covered under homeowner or farm insurance.

Helichrysum argyrosphaerum (Golden Guinea Everlasting, Vaalsewejaartjie) Poisoning

Both naturally occurring and experimental poisoning of sheep and cattle in South Africa by plants of the genus *Helichrysum* results in blindness and a variety of CNS signs.[1,2] The clinical signs of intoxication include progressive tetraparesis, depression, nystagmus, mydriasis, blindness, intentional head tremor, and star-gazing attitude. Older sheep may develop lens cataracts 2 to 3 months after eating the plants. The case-attack rate ranges from 1% to 29%. Plants are toxic only in the flowering stage. *Helichrysum* spp. have been shown to contain substances that bind at the γ-aminobutyric acid (GABA)–benzodiazepine receptor, suggesting a mechanism for toxic effects on the nervous system.[3]

Pathologic findings include widespread status spongiosus of brain white matter, particularly in subependymal areas and in the cerebellar peduncles and brainstem.[2] Myelin edema is present in some cases. Edematous swelling of the optic nerve causes compression of the nerve in the optic canal, with secondary damage to nerve axons and myelin. The toxic principle in *Helichrysum* plants also causes a primary retinopathy in some animals.

Flatpea (*Lathyrus sylvestris, Lathyrus collis*) Poisoning

Ingestion of flatpea *(Lathyrus sylvestris, Lathyrus collis)* results in a CNS disorder. The condition may be seen by 5 days after consumption of a diet composed of 50% flatpea vines. Toxicosis has been induced in sheep ingesting forage of 35% flatpea vines.[1] Livestock can develop a tolerance for the plant through rumen microbial detoxification. Nevertheless, acclimatized animals can be rendered susceptible by treatment with monensin or by a change in rumen microflora.[2]

The toxic constituent of the plant, 2,4-diaminobutyric acid, is known to inhibit ornithine transcarbamylase, an enzyme responsible for urea detoxification. Consequently, the blood ammonia concentration in clinically affected animals is increased.

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The clinical signs of flatpea intoxication are depression, muscular tremors, and spasmodic torticollis. Affected animals become recumbent and are reluctant to rise. When stimulated to move, they display circling, head pressing, and odontoprisis. The urine may appear dark brown. The clinical disorder often culminates fatally in a seizure. During the interictal periods the animals may rest, rise, and resume normal behavior and gait. Treatment is empiric and supportive and could include 1 to 2 L of vinegar PO, IV diazepam, and removal from the offending forage.

L. sylvestris is a leguminous plant with a high protein content that might be an adequate substitute for alfalfa in areas where the latter grows poorly.[3] *L. sylvestris* harvested in the vegetative state has been fed to lambs in combination with alfalfa and as a sole diet without ill effect.[4] Similarly, when fed as part of a mixed silage in which the concentration of diaminobutyric acid was approximately 1%, *L. sylvestris* produced an acceptable weight gain in cattle without signs of toxicity.[5]

Nitrofurazone Toxicosis

Nitrofurazone is an antimicrobial that has been fed to cattle for the treatment and control of respiratory or gastrointestinal diseases. Treatment of food-producing animals with the nitrofurans is currently prohibited by the U.S. Food and Drug Administration. Nervous system signs of nitrofurazone toxicosis occur after 1 to 3 weeks of continuous feeding at dosages exceeding 15 to 30 mg/kg.[1,2] Lower dosages (7.1 mg/kg) reduce feed intake but do not result in neurologic signs. The nitrofurans inhibit enzymes of the oxidative glycolytic pathways and are thought to interfere with brain metabolism of carbohydrates.

Clinical signs of nitrofurazone toxicosis include hyperirritability, propulsive running, muscular tremors, blindness, convulsions, and death. At lower doses the convulsions may appear intermittently, but as the condition progresses, the signs become continuous.

Coenurosis (Sheep Gid; *Coenurus cerebralis* Infestation; *Taenia multiceps* Infestation)

Definition and Etiology Coenurosis is caused by invasion of the CNS by *Coenurus cerebralis,* the intermediate stage of the tapeworm *Taenia multiceps.* The adult worms live in the intestine of domestic dogs and some wild carnivores, where they shed eggs into the feces. Ruminants eat the eggs from contaminated pastures. The eggs hatch in the small intestine of the ruminant, and the larval stages travel through the blood to the CNS, where they mature into *C. cerebralis.* The life cycle is completed when the ruminant dies and the brain is eaten by a scavenging carnivore. *Coenurus* cysts then develop into sexually mature adults in the bowel of the carnivore host.

Many animals including sheep, goats, cattle, horses, wild ruminants, and humans are susceptible to *C. cerebralis* infestation.[1-3] Outbreaks of coenurosis may occur in previously uninfected sheep that are suddenly exposed to contaminated fecal matter from carnivores. Cases initially occur as early as 2 weeks after the sheep are exposed and continue for as long as 4 months.

Clinical Signs Signs can occur acutely, during the migratory phase of the larval stage in the intermediate host. Lambs 6 to 8 weeks old are most often affected by this form and develop fever, dullness, and mild neurologic deficits.[4] Occasionally, acute encephalitis occurs, leading to sudden onset of severe neurologic signs and death within a few days. More frequently, the clinical presentation of coenurosis is that of a space-occupying brain lesion; signs include depression, anorexia, ataxia, unilateral or asymmetric loss of vision, facial hemiplegia, head tilt, circling, high-stepping forelimb gait, and hyperesthesia. When the spinal cord is the site of cyst development, hindlimb ataxia and paresis to paralysis is the main clinical sign.[5] As the disease progresses, the sheep assume lateral recumbency and become comatose.[6,7] In advanced cases the calvarium directly over the parasite enlarges and softens.[3]

Pathophysiology Lesions of the CNS may result from three separate pathogenic mechanisms. These include encephalitis from invasion of the CNS by large numbers of larvae, hypertensive hydrocephalus resulting from interference with CSF drainage, and development of large cerebral cysts that increase intracranial pressure.

Necropsy Findings In the acute form of coenurosis, the main finding is coagulation necrosis and inflammation associated with the pathway of the larval form as it migrates through the CNS.[8] This may be visible grossly as yellow to red tracks through the brain parenchyma. Coagulation necrosis and surrounding inflammatory cells such as degenerate granulocytes, macrophages, and histiocytes are found microscopically. The mature cysts, up to 7 cm in diameter, are thin walled and contain clear fluid or, occasionally, purulent fluid. Protoscolices, up to many hundreds, can be visualized microscopically within the cysts, which are surrounded by severe and mainly nonsuppurative inflammation. The cysts deform and compress the underlying brain tissue.

Diagnosis The combination of a characteristic clinical syndrome and location in an endemic area supports a presumptive diagnosis. Radiographs in the lateral and posteroanterior planes may detect radiolucent areas in the calvarium. The optimum diagnostic views in the posteroanterior projection occur whenever the base of the nose is level with the upper margin of the orbit. When possible, CT effectively demonstrates the presence of cysts.[9]

Treatment Praziquantel (50 to 100 mg/kg PO q24h for 3 to 5 days) is effective for the treatment of coenurosis in sheep that do not yet have neurologic signs.[5,10] Concomitant administration of an NSAID or dexamethasone may enhance the posttreatment survival rate. The cyst can also be removed surgically by craniotomy.[11-15]

Prevention In endemic areas the carcasses of affected animals should not be fed to dogs, and dogs in endemic areas should be treated repeatedly with a vermifuge to minimize the possibility of pasture contamination. Appropriate management practices have virtually eliminated this disease from North American sheep flocks.

Ceroid Lipofuscinosis

Definition and Etiology Ceroid lipofuscinosis is a lysosomal storage disease that has been reported in South Hampshire, Swedish Landrace, and Rambouillet sheep; Nubian goats; Devon cattle; and horses.[1-5] The disease is known to be inherited as an autosomal recessive trait in many cases[7] and is believed to be so in others.[6] It is characterized by the intracellular accumulation of abnormal autofluorescent lipopigments in lysosomes of neurons and other cells throughout the body. The storage material has been shown to consist predominantly of the subunit *c* of mitochondrial *c* synthase.[8,9] Affected animals display progressive ataxia and postural abnormalities, blindness due to retinal involvement in many cases, sensory depression, and terminally, coma. Lesions seen on CT scans include enlargement of the lateral ventricles and reduced thickness of the cerebral cortex.[10]

Gross pathologic lesions in the CNS may include moderate enlargement of the lateral ventricles, flattening of cerebral gyri, and a yellow to brown discoloration of the brain parenchyma. Accumulation of protein storage material in neuronal lysosomes is evident on microscopic examination and is accompanied by neuronal necrosis and astrocytosis, which may be severe. The lesions sometimes have a lamellar appearance.[11] The disease is ultimately fatal, and no practical method of treatment is currently available.

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Diseases Presenting Principally with Brainstem and Cranial Nerve Dysfunction

Peripheral Vestibular Disease of Horses

Robert J. MacKay • Mary O. Smith

Definition and Etiology Vestibular disease of horses is an acute, usually asymmetric, condition with several major causes: bacterial or mycotic infection of the middle/inner ear, polyneuritis equi, viral/idiopathic labyrinthitis, remodeling and/or fractures of the petrous temporal bone associated with temporohyoid osteoarthropathy (THO), and external trauma to the skull with or without fracture of the petrous temporal bone.[1] Idiopathic labyrinthitis is probably an acute viral inflammation of the vestibular system that is severe, but complete recovery is common. Lightning strike is also an uncommon cause of vestibular signs in horses.[2,3] Staphylococci, streptococci, *Actinobacillus, Aspergillus, Enterobacter, Pseudomonas, Salmonella* spp., and *Corynebacterium pseudotuberculosis* have been isolated from cases of otitis media/interna in horses.[1,4] There has been speculation that THO results from extension of chronic low-grade bacterial otitis media to the adjacent temporohyoid joint[5]; however, remodeling and fusion of the temporohyoid joint is more likely the result of repeated trauma and/or chronic degenerative processes.[6,7] Primary otitis media/interna in horses is probably rare and, by contrast to ruminants, young age does not appear to be a risk factor. It is presumed that the middle ear is infected via the eustachian tube or hematogenously. With the exception of viral/idiopathic labyrinthitis, the proximity of the facial canal to the vestibular system means that the facial nerve (VII) is frequently involved in conditions causing vestibular signs.

Clinical Signs There is rotation of the poll (i.e., head tilt) toward the affected side, abnormal physiologic nystagmus, spontaneous horizontal or rotatory nystagmus with the fast phase away from the affected side, and vestibular strabismus with downward rotation (infraduction) of the eye ipsilateral to the lesion that can be exaggerated by elevating the horse's chin. There is usually a staggering, dysmetric gait, with a tendency, because of increased extension of the contralateral limbs, to lean or circle toward the affected side. Horses with any acute peripheral vestibular disease sometimes fall or even roll to the side of the lesion and may panic and thrash wildly in an effort to stand. Bilateral vestibular disease causes severe dysmetria and ataxia, and complete absence of normal vestibular nystagmus. The horse may have wide swinging movements of the head.

Signs of vestibular disease are markedly exacerbated by blindfolding. Deafness is also apparent with bilateral involvement of the cochlear division of cranial nerve VIII. With unilateral vestibular disease, visual accommodation often occurs over a period of weeks and affected animals may even return to racing. Signs of vestibular disease may still be elicited by blindfolding, however.

Concomitant ipsilateral facial paralysis is evident as deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelid, and ear. Reflexes involving cranial nerve VII such as the lip, eyelid, menace, and ear reflexes are reduced or absent. Inability to close the eyelid causes exposure keratitis, which is particularly severe and usually involves deep horizontal corneal ulceration when there is damage to the secretomotor fibers of the facial nerve at or proximal to the geniculate ganglion. With chronic facial paralysis, there is visible atrophy of the parotidoauricularis caudal to the vertical ramus of the mandible.

Horses with bacterial otitis media/interna may have other sites of infection including paranasal sinuses, guttural pouches, and the lower respiratory tract. Extension of infection along a fracture defect or from otitis media/interna into the meninges is associated with development of additional neurologic signs including obtundation, limb ataxia and weakness, and cranial nerve deficits, along with systemic signs of sepsis including fever, tachycardia, and tachypnea.

Diagnosis and Treatment A complete blood cell count (CBC) should reveal leukocytosis and increased fibrinogen concentration in cases of chronic otitis media/interna, whereas neutrophilic pleocytosis in CSF samples is evidence of secondary meningitis. Diagnostic procedures for horses with peripheral vestibular disease include skull radiography, CT, and endoscopic examination of the guttural pouch. Otoscopic examination in the horse is difficult,[5,8] and general anesthesia is required for transtympanic centesis of the middle ear, although this procedure can rarely be justified. The rate of tear secretion may be tested with a Schirmer tear test strip and should be greater than 17 mm/min. Brainstem auditory-evoked response testing may help to establish the location of vestibular pathology as peripheral versus central.[9]

Antibiotic treatment of peripheral vestibular disease due to otitis media/interna should, if possible, be guided by antimicrobial susceptibility testing of bacteria cultured from the middle ear or from related processes such as sinusitis, guttural pouch empyema, or pneumonia. In the absence of such information, coverage should be provided against gram-positive bacteria by penicillin G (22,000 units/kg bid IM as procaine penicillin or IV qid as potassium penicillin) or ceftiofur sodium (2.2 to 5 mg/kg IM sid to bid). Additional coverage (including for staphylococci) can be provided by the addition of enrofloxacin (5 mg/kg IV, or 8 mg/kg PO sid). Oral continuation of treatment can be conveniently provided by trimethoprim-sulfonamide drugs (30 mg/kg PO bid) or chloramphenicol (50 mg/kg PO qid). Treatment should continue for at least 30 days and ideally should be guided by results of repeated imaging of the affected petrous temporal bone.

Affected horses should be kept in a quiet, heavily bedded stall with good footing. Exposure keratitis may be treated or prevented under a partial tarsorrhaphy.

Equine Nigropallidal Encephalomalacia (Star Thistle Poisoning, Knapweed Poisoning)

Robert J. MacKay

Nigropallidal encephalomalacia (NPE) is a disease of adult horses characterized by facial and lingual dystonia, mild obtundation, behavioral signs, and ataxia. NPE is caused by ingestion of large quantities of the plants *Centaurea solstitialis* (yellow star thistle) or *Rhaponticum repens* (Russian knapweed; syn. *Acroptilon repens, Centaurea repens*).[1-4]

Clinical Signs The signs appear suddenly but always after long-term ingestion of large quantities of the plants. Characteristic signs of NPE include weight loss, mild to moderate obtundation, ataxia, yawning, lowered head, protruding tongue, tremor of the tongue and lips, and facial grimacing when feed is offered. The facial hypertonicity causes a retraction of the lips, resulting in a fixed grimace with the mouth and lips held half open. Although affected horses can grasp food between the incisors, prehension, chewing, and swallowing of food are uncoordinated and inefficient. There may be constant chewing movements and food retained in the mouth, and cheek pouches may protrude from the commissures of the lips. Affected animals may attempt to drink by immersing their muzzles deeply into the bucket to force the water into the back of the pharynx. There also may be a transient tendency to walk compulsively, often in circles. Occasionally, horses with NPE are hyperexcitable.

After several days of progression, signs stabilize and do not then progress. Affected animals usually do not recover and are euthanized or die of starvation or dehydration.

Diagnosis The CSF of affected horses may have high nucleated cell counts.[3] There are no characteristic changes in the CBC or the

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serum chemistries. MRI was used to make an antemortem diagnosis in one horse with NPE.[5]

Pathophysiology A toxic principle in yellow star thistle and Russian knapweed has been isolated and chemically characterized and named *repin*. Repin is a sesquiterpene lactone with high affinity for neural tissue.[6-8] Studies in rats suggest that repin exerts its neurotoxic effects by inhibiting dopamine release.[8] A role for neurotoxic amino acids, including aspartic and glutamic acids, has been proposed, but recent work could not confirm their presence in yellow star thistle.[9] Immunohistochemical staining of affected brains show that NPE is similar to environmentally acquired toxic parkinsonism of humans, with clinical findings attributable to lesions in the globus pallidus and substantia nigra pars reticulata rather than to destruction of dopaminergic neurons.[10]

Necropsy Findings At necropsy, sharply demarcated areas of yellowish malacia are visible grossly in the substantia nigra and globus pallidus (extrapyramidal system). Lesions are symmetric in most but not all cases. Lesions in other brainstem nuclei are found in a small number of animals.[2,9] Microscopic lesions include neuronal necrosis, vacuolation with gliosis, liquefactive necrosis, and cavitation in well-developed lesions.[11]

Epidemiology NPE has been reported in horses of the United States, Australia, and South America. Yellow star thistle is a common plant in unirrigated pastures in the arid regions of the western United States. The plant is resistant to the effects of saline or alkaline soil conditions and has a minimal moisture requirement. Russian knapweed belongs to the sunflower family and grows predominantly on flood plains, where it can extract deep subterranean moisture. In the United States the plants tend to remain green during the dry months, so most poisonings occur during the summer or late autumn. Most horses are reluctant to eat *Centaurea* and *Rhaponticum* plants unless other vegetation is unavailable, but some develop a craving and selectively seek it out. Horses that develop NPE are usually being fed a poor-quality, high-roughage diet. Affected horses range from 4 months to 10 years of age (median, 2 years).[11] The case-attack rates of yellow star thistle poisoning range from 3% to 31% of horses on infested pastures.[11] Feeding studies have reported that as much as 59% to 200% of the body weight of yellow star thistle and 59% to 63% of Russian knapweed must be eaten over 3 to 11 weeks to cause clinical disease.[2,11] Continuous protracted exposure to the weeds seems to be important for expression of clinical disease. The dried plants retain their toxicity.

Treatment and Prevention There is no known treatment for the poisoning. Prevention is best aimed at correcting the nutritional problem by daily supplementation with 10 to 15 lb of alfalfa hay and by not pasturing horses in areas where either of the responsible plants grows.

Temporohyoid Osteoarthropathy

Robert J. MacKay • Lisle W. George

Temporohyoid osteoarthropathy (THO) is a progressive syndrome involving periosteal reaction, enlargement and sclerosis of the stylohyoid bone, tympanic bulla, and petrous portion of the temporal bone (Fig. 35-10).[1] Ultimately, there is fusion between the skull and hyoid apparatus, stricture of the external ear canal, and obliteration of the lumen of the tympanic bulla. These changes are thought to represent a primary degenerative process in the temporohyoid joint (THJ), although it is conceivable that some cases are secondary to chronic otitis media.[1-3] The tympanic membranes of horses with this condition are usually not inflamed, and ruptures and associated discharges from the external ear are uncommon.[1] Horses from 6 months to older than 20 years of age have been affected with a mean or median age of 10 to 12 years reported in all studies.[1,4-8] Quarter Horse and Quarter Horse–type breeds accounted for more than 50% of cases in several but not all series.[4-7] Both joints are affected, albeit asymmetrically, in most horses with clinical THO.[4] In rare instances, there are associated clinical signs on both sides.[5,6] Fusion of the THJ causes interference with the interdependent coordinated movements of the tongue, hyoid apparatus, and larynx. Particular stress is placed on the fused joint(s) during chewing, swallowing, vocalizing, and combined head and neck movements. Veterinary procedures such as dental work and passage of a nasogastric tube also put unaccustomed pressure on the THJ. Any of these mechanical forces applied to the immobilized THJ may result in fractures through the petrous temporal bone or proximal stylohyoid bone. THO is also likely a risk factor for fracture of the petrous temporal bone during head trauma, especially in horses that flip over backward and strike the poll. The facial nerve (cranial nerve VII) and vestibulocochlear nerve (VIII) and apparatus are within the petrous temporal bone and can be impinged on by bony proliferation or lacerated by fracture. After fracture of the petrous temporal bone, there may also be extension of middle/inner ear infection around the brainstem with signs of meningitis or extradural abscess.



FIG. 35-10 Rostral view of left and right tylohyoid bones from a horse with left-sided temporohyoid osteoarthropathy. Note fusion of the temporohyoid joint on the affected side and extensive remodeling and enlargement of the stylohyoid.

Clinical Signs Two sets of clinical signs are associated with the evolution of this disease process.[1] Early in the syndrome, including the period before ankylosis of the temporohyoid joint, reluctance to chew, dysphagia, headshaking, ear rubbing, sensitivity to pressure at the base of the ear, facial hyperesthesia, wild tossing of the head and neck under tack, reluctance to take a bit, dropping of feed, or even weight loss may be seen, although most THOs are probably subclinical until development of neurologic signs. Fracture of the proximal stylohyoid bone increases the likelihood of pain-associated clinical signs. Because of bony proliferation around the ear canal, the external ear may be unusually narrow and difficult to examine by otoscope.

After fusion of the THJ, the disease may manifest as sudden onset of asymmetric signs of cranial nerve VII and/or VIII dysfunction. Almost all affected horses have degrees of facial paresis, with drooping of the ear, upper eyelid, and lower lip on the affected side and deviation of the muzzle to the contralateral side.[1,6,7] Buccinator weakness results in "quidding" (retention of feed material in the denervated cheek) and dropping of feed. Facial denervation may be

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evident as fine fasciculations of facial muscles and, after 2 weeks, obvious atrophy of the parotidoauricularis muscle behind the vertical ramus of the mandible. Facial paralysis may occasionally be bilateral.[5] Schirmer tear tests commonly disclose reduced tear production (i.e., values of 5 to 20 mm, normal >20 mm),[5] indicative of injury to the parasympathetic lacrimal branch of the facial nerve. By the time of presentation, most such horses already have a deep horizontal corneal ulcer with corneal edema and miosis. Because of facial weakness, affected horses cannot mount the typical response to corneal ulceration—namely, blepharospasm and epiphora, so ulcers often go undetected by horse owners. Signs of vestibular dysfunction accompany facial paresis in the majority of cases. Of 29 horses with THO that had involvement of VII, 23 (≈80%) had vestibular signs.[6] Typically, there is a sudden onset of head tilt, neck turn, body lean, and tight circling, all toward the affected side, and a staggering ataxic gait with preservation of limb strength. These signs may be revealed or exacerbated by blindfolding the horse. In the acute stages, there may be conjugate horizontal nystagmus, with the fast phase away from the side of the lesion. In a study of 11 horses with THO and neurologic signs, all had electrodiagnostic evidence of partial to complete hearing loss on the affected side; 5 also had partial hearing loss on the contralateral side.[5] Although it is unusual, vestibular signs can occur without concurrent involvement of the facial nerve. Rarely, horses may also have difficulty eating and swallowing due to either pain (e.g., because of acute stylohyoid fracture) or involvement of cranial nerves IX and X. A few horses have seizure-like convulsions at the onset of neurologic signs. Bacterial abscess adjacent to the brainstem or meningitis may be sequels to fracture of the petrous temporal bone and result in the death of the horse.

Diagnosis Endoscopic examination of the inside of the guttural pouches is the diagnostic imaging test of choice because of its convenience in standing horses and its high sensitivity for detection of THO.[6] Evaluation of the external contour of the THJ from within the guttural pouch can detect asymmetric enlargement and discoloration of the stylohyoid bone and THJ and, in some cases, hyperemia, edema, and/or hemorrhage in the guttural pouch lining surrounding the joint. Previously healed fractures of the stylohyoid bone may be evident as angulation and distortion of the bone close to the THJ. CT imaging of the THJ allows appreciation of changes not always evident by endoscopy (or plain radiographs) including involvement of both sides, enlargement of the ceratohyoid bone, fractures of the petrous temporal and stylohyoid bones, and the presence of fluid in the tympanic bullae.[4,9] A system has been developed to quantify the remodeling changes found in THO cases.[4] The main disadvantage of CT is the expense and requirement for general anesthesia. In Europe, where standing CT units are available in some referral practices, this is less of a concern, although adequate positioning can be difficult in horses with severe vestibular dysfunction.[8] Radiographic examination of the skull using ventrodorsal, lateral, and lateral oblique views detects those cases in which the bony proliferation has progressed to cause osteitis and fusion of the temporohyoid joint. Optimal images are obtained with the horse under general anesthesia and in dorsal recumbency; however, adequate views can be taken using a dorsoventral projection with the horse standing but heavily sedated. Sensitivity for detection of THO by plain radiography in one series was 20/24 (83%).[6] MRI and nuclear scintigraphy are imaging techniques that have been applied successfully to THO diagnosis but have not found wide application.[6,8,10]

Brainstem auditory-evoked response (BAER) testing of vestibulocochlear nerve function has been described for horses with THO and is the only way of evaluating auditory function in these horses.[5] It is also a sensitive method for detecting involvement of the contralateral side.

In horses with neurologic signs other than dysfunction of CNN VII and VIII, CSF tap, analysis, and possible culture are recommended. Two of four horses tested in one report had increased nucleated cell counts or protein concentrations suggestive of septic or nonseptic meningitis.[6] Xanthochromia and increased RBC counts are also expected in acute cases.[3]

Treatment and Prognosis Medical and surgical approaches to THO have been described.[1,3,11] Conservative medical therapy involves prolonged rest and treatment with an NSAID (e.g., 2 mg/kg phenylbutazone PO, or 1.1 mg/kg flunixin IV or PO twice daily for 3 days, then once daily for 1 to 2 weeks more) and broad-spectrum antibiotics (e.g., trimethoprim-sulfa, 30 mg/kg PO twice daily for 30 days). The lever action of the hyoid apparatus on the petrous temporal bone can be removed surgically by complete removal of the ipsilateral ceratohyoid bone or removal of a 1- to 2-cm section from the middle of the stylohyoid bone.[3,11,12] Because midbody stylohyoid ostectomies tend to heal,[12] the ceratohyoid procedure is now favored. If necessary, this surgery can be done bilaterally and the procedure can be performed in the standing sedated horse. With facial nerve paralysis and keratitis sicca, corneal ulcers are a medical emergency and must be treated or prevented with topical antibiotics, artificial tears, and, preferably, a multifocal partial split-thickness tarsorrhaphy.[3] For this purpose, shallow 3- to 5-mm-long incisions are made in the tensed lid margins of each eyelid immediately posterior to the line of tarsal gland openings. Using 5-0 absorbable suture, a bite is taken in each eyelid deep in the incision, in the plane of the eyelid, and then the suture is carefully tied so that margins evert away from the corneal surface.[3] One or two shallow horizontal mattress sutures are then placed in the everted lid margin. The eyelids are joined in this manner at two or more sites, leaving open the nasal third of the palpebral fissure. The tarsorrhaphy is maintained permanently or until resumption of lacrimal and eyelid function, which may take up to 18 months.

Both medical and surgical approaches reportedly have returned most treated horses to athletic activity after a period of weeks to months, so there is not yet clear evidence to support the need for surgery in all cases.[1,6,7] On theoretical grounds, however, it is clear that a horse with THO will remain at risk for catastrophic relapse of neurologic signs as long as the hyoid apparatus and skull remain connected through a fused THJ. Relapse is particularly likely if there is a temporal bone fracture. In one series 20 of 30 horses treated medically (18) or surgically (2) survived, with 19 of 20 returning to athletic function albeit with persistent mild residual facial and/or vestibular dysfunction in most cases.[6] Four horses in this series died or were euthanized because of fractures along the base of the skull, complications that should be preventable by ceratohyoidectomy.

If possible, the management of convalescent horses should be adjusted to minimize stress on the remaining THJ(s). Cribbing collars can be tried for crib biting, bitless bridles can be used for riding, and dental work and other professional procedures can be minimized and done cautiously.

Horner Syndrome

Robert J. MacKay • Lisle W. George

Definition and Etiology Horner syndrome results from interruption of ocular sympathetic pathways. Sympathetic pathways to the head originate as first-order neurons (upper motor neurons) in the tectum of the midbrain. Axons descend to the first to third thoracic (T1 to T3) segments of the spinal cord, where they enter the gray matter of the dorsal horn, synapse on second-order (preganglionic) sympathetic motor neurons, and exit in the ventral spinal nerve roots. From there the nerves pass through the cervicothoracic and middle cervical ganglia (combined as the stellate ganglion) and ascend in the cervical sympathetic trunk (part of the vagosympathetic trunk) to the cranial cervical ganglion (CCG), where they synapse on the third-order (postganglionic) sympathetic nerve. In the horse, the CCG is part of a neurovascular bundle in the caudodorsal aspect of the guttural pouch; in ruminants the CCG is located under the petrous temporal bone. The third-order fibers are distributed with the blood supply via canals through the petrous

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temporal bone to the sweat glands of the head, ciliary muscles, and periorbital smooth muscles including the eyelid levator, Mueller muscle, and periarteriolar musculature. The sympathetic supply of the head thus can be damaged within the brainstem or spinal cord (first order), cranial thoracic nerve roots or spinal nerves or cervical sympathetic trunk (second order), or the CCG, the skull, or behind the eye (third order).

Specific causes of Horner syndrome include mycotic guttural pouch infections; traumatic lesions of the basisphenoid area; otitis media; cervical trauma; abscesses, tumors, or space-occupying lesions in the anterior aspect of the thorax; periorbital abscesses or tumors; parotid duct obstruction and inflammation; esophageal rupture; and complications associated with surgical ligation of the carotid artery.[1-7] Lesions involving first-order sympathetic neurons in the ipsilateral brainstem are rare but have been reported as a consequence of metastatic neoplasia or with equine protozoal myeloencephalitis in horses.[8,9] Horner syndrome has also occurred after intravenous injection of certain drugs including xylazine, vitamin E or selenium, and phenylbutazone.[10-12] The sympathetic supply to the eye may rarely be involved in the inflammatory polyneuropathy characterizing horses with polyneuritis equi (cauda equina neuritis) syndrome.[13,14] Tumors that have resulted in Horner syndrome include sclerosing respiratory epithelial carcinoma, squamous cell carcinoma, lymphoma, mesothelioma, and melanoma.[2,4-6,10,15,16]

Clinical Signs The clinical signs of Horner syndrome in horses vary but include miosis, ptosis, regional hyperthermia, excessive sweating on the ipsilateral side of the face, congested mucous membranes, inspiratory stridor, and dermatitis caused by chronic sweating. Although enophthalmos is reported to be a reliable sign of equine Horner syndrome, many (most?) affected horses do not prolapse the nictitans and thus are probably not enophthalmic. The presence of this sign is apparently variable among species: Enophthalmos is not part of Horner syndrome in humans and ruminants[17] but is so in cats and dogs.[9] Ptosis is caused by the combined effects of loss of the eyelid levator function of Mueller muscle and variable enophthalmos. It is most reliably detected by comparison of the eyelash angles on each side. On the affected side the eyelashes slope at a relatively downward angle. The palpebral reflex and the menace response are normal. Facial sweating may begin to decrease 6 to 14 days after sympathectomy.[10] If there is concomitant damage to the vertebral nerve or its cervical sympathetic branches, sweating of the skin of the neck may also be seen. Regional hyperthermia results from cutaneous and mucosal vasodilation, which results from removal of sympathetic vasomotor tone. Sweating is thought to be caused by vasodilation and increased delivery of epinephrine to sweat glands.[18,19]

In cattle, there is *dryness* of the ipsilateral planum nasale. This can be explained by the mediation of normal sweat gland secretion by postganglionic sympathetic fibers and α-adrenergic receptors in cattle.[19] The other signs seen in cattle are similar to those in horses. The clinical signs of experimentally induced Horner syndrome in sheep and goats are limited to mild ptosis.[19] Retrobulbar tumors may cause both exophthalmos and Horner syndrome.[15] On cold days, while exhaled breath from the external nares of cattle normally contains a mist of condensed water vapor, breath from the relatively warm nostril on the affected side may be mist free.[9]

Diagnosis The level of sympathetic interruption can be determined by pharmacologic testing.[9] Hydroxyamphetamine (1% solution) instilled into the eye will result in release of norepinephrine from intact postganglionic sympathetic neurons, causing pupillary dilation, but no response when the postganglionic neurons are damaged. A positive response to this test indicates a preganglionic sympathetic lesion, and a lack of response indicates a postganglionic lesion. In animals with a postganglionic lesion, topical administration of 0.1 mL of 1:1000 epinephrine solution directly activates the iris musculature and produces mydriasis by 20 minutes, whereas the onset of dilation occurs at about 40 minutes in animals with preganglionic lesions. Similarly, 2.5% to 10% phenylephrine solution will produce pupillary dilation in an eye with a postganglionic sympathetic lesion, but not in a normal eye. The increased sensitivity to these direct-acting sympathomimetics in animals with postganglionic sympathetic lesions results from the phenomenon of denervation hypersensitivity, with numbers and sensitivity of norepinephrine receptors in the iris muscle increasing over days to weeks after postganglionic nerve injury. A positive response therefore is not seen until several days after the injury. Parenteral administration of 1 mL of 1:1000 epinephrine solution causes affected horses to sweat profusely over the affected side of the face.[10] However, this test does not differentiate between preganglionic and postganglionic lesions.

The guttural pouches of horses and the pharynx of all patients should be examined endoscopically to exclude the possibility of pharyngeal or laryngeal paralysis or guttural pouch disease. The jugular furrows should be palpated for swellings. Insertion of a nasogastric tube during palpation may be helpful for detecting subtle lesions on the left side of the neck. The thorax should be examined using auscultation and ultrasound and, if indicated, radiographs should be taken. Cranial ribs can be evaluated for lesions by scintigraphy.[20] A neurologic examination should be performed to evaluate the function of the spinal cord. The skin temperature may be measured using thermography[1,6,21]; on the affected side it is 1° C to 3.5° C higher than normal.

Treatment The treatment for Horner syndrome depends on the underlying cause of the denervation. Except for Horner syndrome related to IV injection of xylazine, the signs are often irreversible, even if the primary cause of the condition has been eliminated. With xylazine-associated Horner syndrome, the condition disappears spontaneously. The necrotizing effects of perivascular drug injections can be minimized by immediate dilution and/or irrigation with large volumes of saline infiltrated into the perivascular tissues. Antiinflammatory doses of flunixin and dexamethasone can be given systemically. Abscesses should be drained, and fungal infections of the guttural pouch should be treated as described in Chapter 31.

Guttural Pouch Mycosis

Robert J. MacKay

Definition and Etiology The clinical signs occur because fungal infections invade vital vascular and neural structures in the roof of one, or occasionally both, guttural pouches. There is no apparent age, sex, breed, or geographic predisposition to this disease.[1] Foals as young as 3 months of age have been affected.[2] *Aspergillus fumigatus* and *Emericella nidulans* (also known incorrectly as *Aspergillus nidulans*) are the fungi most commonly identified in pure or mixed culture.[3,4] Lesions are typically diphtheritic membranes of variable size, composed of necrotic tissue, cell debris, a variety of bacteria, and fungal mycelium (Fig. 35-11).[1]

The guttural pouch is partially separated into two compartments by the stylohyoid bone and occipitohyoideus muscle. Cranial nerves IX through XII, the cranial cervical ganglion and postganglionic sympathetic nerve, and the internal carotid artery are located in a fold that traverses the dorsomedial aspect of the medial compartment. For unknown reasons, this site is susceptible to colonization and destruction by invasive mycotic infections.[5] In about one third of cases, the fungal lesion is located in the lateral compartment, sometimes after extension from a primary site in the medial compartment.[1] At this location, the fungal mycelium may invade the wall of the external carotid artery or any of its branches and affect the facial nerve (VII). Facial nerve paralysis has also been observed as a result of direct invasion by a fungal guttural pouch infection into the overlying parotid lymph node and salivary gland.[6] Fungal plaques may also spread from one guttural pouch to the other by eroding through the apposed medial walls of the pouches.

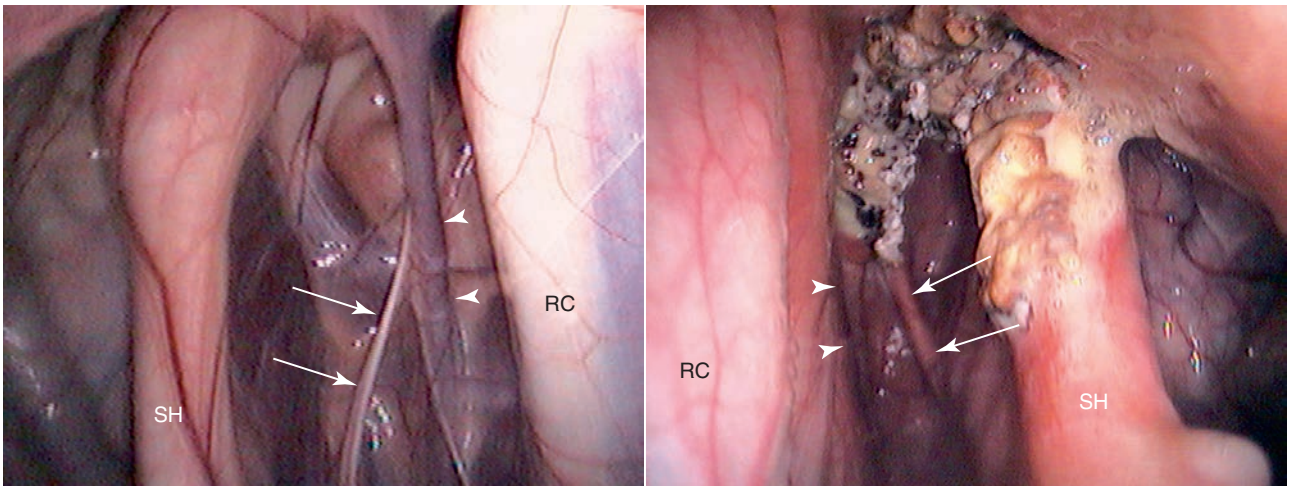


FIG. 35-11 Endoscopic views of the caudal aspects of the left guttural pouch with a mycotic plaque over the neurovascular structures of the medial compartment of left guttural pouch (right) and normal right guttural pouch (left). There is also thickening of the left stylohyoid bone secondary to temporohyoid osteoarthropathy. *Arrows* point to the glossopharyngeal nerves and arrowheads are pointing to the internal carotid arteries. *RC,* Rectus capitis ventralis major muscle; *SH,* stylohyoid bone.

Clinical Signs Initial signs are headshaking and unilateral nasal discharge. There is a tendency to hold the head in extension or lower to the ground than normal. Additional clinical signs are nasal discharge, dysphagia with nasal return of feed-stained saliva, head shyness, stridor, dysphonia, protrusion of the tongue from the mouth, and epistaxis.[6,7] Epistaxis may be bright red, high volume, and life threatening. Other clinical signs include sensitivity to pressure over the parotid salivary gland; Horner syndrome (sweating, miosis, and ptosis on the side of the lesion); paralysis of the tongue on the affected side; and facial paralysis.[6-10] Atrophy of the brachiocephalicus and trapezius muscles has been described in a few cases secondary to denervation of the spinal accessory nerve (XI). Horner syndrome occurs secondary to damage of the cranial cervical ganglion and postganglionic fibers. The sensorium is intact unless aspiration pneumonia develops or the fungus spreads into the brain.[11,12] Affected horses may die peracutely as a result of exsanguination from ruptured internal or external carotid arteries or their branches. Endoscopic examination of the larynx of affected horses may reveal dorsal displacement of the soft palate, inability to swallow, and laryngeal hemiplegia. Mycotic guttural pouch infection can be diagnosed definitively endoscopically by identifying the characteristic fungal mass in the caudodorsal aspect, usually of the medial compartment. Radiographic examination of the pouches shows a poorly defined border of the pouch in the abnormal area.

Treatment Before the onset of neurologic signs, the affected artery or arteries may be occluded on each side of the lesion(s) by ligation/balloon-tipped catheter, embolization coils, or nitinol plugs.[1] Arterial occlusion prevents fatal epistaxis, but it is not clear whether or not it affects fungal growth. Some studies have shown excellent, albeit delayed, rates of resolution of mycotic lesions in horses that underwent the procedure with or without additional antifungal therapy,[13,14] but in other animals the lesion may progress despite complete arterial occlusion.[8] Because a proportion of such lesions resolve spontaneously over time, the role of surgery in their resolution remains controversial.[1] Optic neuropathy and blindness of the ipsilateral eye are occasional sequelae of occlusion of the external carotid artery and its branches.[1] Lesions may be treated topically through an endoscope with povidine-iodine or triazole antifungal agents such as enilconazole, voriconazole, and itraconazole. Itraconazole is also affordable and safe when used systemically. Nystatin, natamycin, miconazole, and fluconazole have little activity against *Aspergillus/Emericella* spp. Amphotericin is effective, although systemic administration is limited by its toxicity. Topical treatment may be repeated daily (or as frequently as is practicable) for up to several weeks. As the fungal mass degenerates, pieces can be carefully removed endoscopically with biopsy forceps in horses that have previously undergone arterial occlusion. Dysphagic horses may be fed via an indwelling esophagostomy tube while lesions are being treated.[15] Neurologic signs may be permanent, although improvement or recovery over many months has been reported in some horses.[14] Affected horses are often euthanized for humane reasons. (See Chapter 31 for more on treatment of guttural pouch mycosis.)

Listeriosis (Circling Disease; Silage Disease; *Listeria monocytogenes* Infection)

Lisle W. George

Definition and Etiology Listeriosis is an acute meningoencephalitis caused by the gram-positive bacterium *Listeria monocytogenes.* The disease has a worldwide distribution but occurs most often in temperate climates. Listeriosis typically affects ruminants, fowl, and humans but is rare in horses. The prevalence of listeric meningoencephalitis in infected herds does not usually exceed 1% of the adult animals at risk.[1]

Clinical forms of listeriosis include septicemia of neonates, abortion, neonatal death, ophthalmitis, uveitis, septicemia and diarrhea of ewes, and neurologic disease.[2] Neurologic listeriosis may manifest as a multifocal brainstem disorder, diffuse meningoencephalitis, or myelitis. The condition usually affects individual animals but occasionally can affect several members of a herd.[3] Asymptomatic intramammary infections apparently occur and may be responsible for outbreaks of listeriosis in humans. Repeated intramammary inoculation of 10^6 to 10^7 colony-forming units (CFUs) of *L. monocytogenes* into cattle resulted in 500 to 50,000 CFUs of *Listeria* in the milk for as long as 12 months.[4]

Clinical Signs The neurologic signs of listeriosis in adults reflect dysfunction of the caudal brainstem, cerebellar peduncles, or spinal cord.[5] Fever may be present early in the clinical course, and poor appetite and depression are common. Central nervous system signs are usually asymmetric and include conscious proprioceptive deficits, head pressing, and cranial nerve deficits. Depressed consciousness is the result of lesions of the reticular activating system. Conscious proprioceptive deficits are caused by interference with the descending motor pathways and the ascending proprioceptive fibers in the brainstem and may precede or accompany cranial nerve

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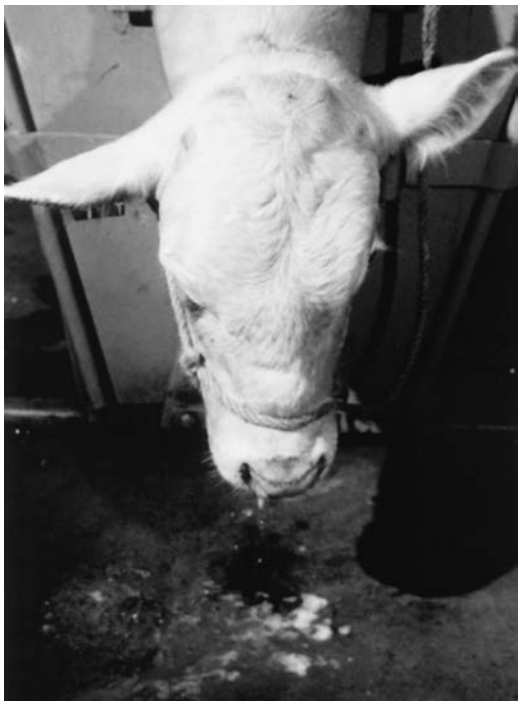


FIG. 35-12 Clinical appearance of the neurologic form of listeriosis in a Charolais bull. Note the dropped right eye and ear and the drooling of saliva from the right side of the mouth. *(Courtesy Dr. W.D. Wilson.)*

dysfunction. Head pressing and propulsive walking or compulsive circling are caused by lesions of the basal ganglia. Severely affected animals may be recumbent and may display torticollis, head tilt, or other unilateral vestibular signs.

Cranial nerves (CNs) V through XII are usually dysfunctional in listeric animals. Patients with loss of the trigeminal nerve (CN V) show dropped jaw or asymmetric jaw closure and facial analgesia or anesthesia. Facial analgesia is best detected by stimulation of the nasal septum with a pencil or piece of straw. Animals with lesions of CN VI exhibit a medial strabismus on the ipsilateral side of the lesion. Animals with lesions of CN VII have ptosis, loss of menace response, absent palpebral reflex, drooped ear, loss of levator nasolabialis muscle function, and decreased lip tone (Fig. 35-12). Small ruminants with CN VII loss have a deviated philtrum. The paralysis of the orbicularis oculi muscle results in exposure keratitis.[6] The loss of levator nasolabialis function is best detected by observation of the muscular contraction on the dorsum of the nose during inspiration. Loss of lip and cheek muscle tone is best detected by observation of drooling of saliva from the ipsilateral side of the mouth and by palpation of the lips and nostrils.

Animals with CN VIII lesions display a nystagmus that changes as the position of the head is altered. Other signs include a head tilt toward the side of the lesion and a tendency to circle or fall to the lesion side. The nystagmus may be horizontal, vertical, or rotatory and is usually inconstant. If the spinal reflexes can be tested, the affected animals show a mild to moderate hypertonia and hyperreflexia in the limbs opposite the side of the lesion. Animals with acute loss of CNs IX, X, and XII develop stertorous breathing and dysphagia. Animals with dysfunctional CN XII have paresis or paralysis of the tongue. With unilateral lesions the tongue protrudes from the side of the mouth ipsilateral to the lesion. Progression of listeriosis is associated with decreased consciousness, coma, and convulsions.

Lambs may selectively develop spinal myelitis without brainstem disease. This condition results in flaccid paraparesis or hemiparesis without attendant signs of brainstem dysfunction.[7] The clinical signs of myelitis include tetraparesis, tetraplegia, paraparesis, paraplegia, conscious proprioceptive deficits, and recumbency. The sensorium and appetite are normal in some affected animals and greatly depressed in others.[8] Primary ocular disease caused by *L. monocytogenes,* manifesting as keratitis, conjunctivitis, or uveitis, may occur in cattle or horses with no signs of neurologic disease.[9]

Clinical Pathology The clinical signs of multifocal, particularly unilateral, brainstem disease with inconsistent fever in a ruminant are suggestive of listeriosis, head trauma, or aberrant parasite migration. Examination of the CSF should be helpful for confirming a diagnosis of listeriosis, but the cell and protein concentrations of the specimens do not correlate with the severity of the clinical signs or prognosis. The protein concentration in the CSF may be more than 40 µg/dL, and the CSF WBC counts may be more than 12 mononuclear cells/µL.[1,10,11] Many cattle with advanced signs of listeriosis develop metabolic acidosis as a result of salivary bicarbonate loss.

Pathology Pathologic confirmation of listeriosis is based on identification of multifocal microabscesses in the brainstem and isolation of *L. monocytogenes* from infected brain tissue. The agent is only rarely isolated from CSF and is best recovered from refrigerated nervous tissues. Enrichment of the *Listeria* organisms may be accomplished by refrigerating slices of brain at 4°C (39.1°F) for 3 months while culturing the tissues weekly. In contrast to septicemic listeriosis of monogastric animals, peripheral monocytosis is not observed in infected ruminants.

Pathophysiology *Listeria* organisms produce a hemolysin, listeriolysin-O, a thiol-activated toxin (molecular weight, 58 kD) that is correlated with pathogenicity. The molecular role of the toxin in dissemination of the infection and in cell death is not known.

It is unclear whether infection of the brain by *L. monocytogenes* occurs hematogenously or by ascent from the cranial nerve rootlets.[12] Morphologic studies of naturally occurring cases of encephalitic listeriosis have demonstrated the bacterium in the axons of the trigeminal nerve rootlets, indicating a possible centripetal migration.[12,13] Similar findings have been reported in animals infected experimentally.[14] Younger animals may be susceptible because eruption of the permanent teeth may expose trigeminal nerve rootlets. A model for experimental induction of listeriosis by inoculation of the bacterium into the pulp cavity of sheep has been described.[15] Infection of the CNS without bacteremia has been detected, indicating that centripetal migration of the bacterium is possible.[16] Some investigators consider axonal migration as an unlikely mode of pathogenesis because of a lack of nutritional dependency of *L. monocytogenes* for nervous tissue and the ready ability to produce multifocal brain microabscesses by intravenous inoculation of the bacteria into susceptible hosts.[12,17]

Epidemiology In untreated cases the fatality rate is almost 100%.[5] The survival rate in treated animals is considerably higher than in untreated patients. The disease in sheep and goats tends to be more acute and results in a higher case-fatality rate than in cattle. Occasional outbreaks of listeriosis may occur in sheep without access to silage.[5,18] In these cases the source may be the feces of carrier animals or rotting vegetation on the pastures or feed bunks. During an outbreak of listeriosis, the bacterium can be isolated from the feces of a large percentage of normal animals.[19] It is unclear whether this high rate of asymptomatic infections represents a true carrier state or is simply the result of a high environmental contamination by nonpathogenic isolates.[19] The agent infects the udder but rarely causes clinical mastitis. In sheep, excretion of the bacterium in the milk is greatest during the immediate postlambing period.[20,21]

L. monocytogenes can survive for long periods in the environment and in asymptomatic carriers. The bacterium can multiply at low environmental temperatures and is resistant to environmental influences. *L. monocytogenes* is shed in the feces of asymptomatic carriers, especially at the end of pregnancy and at lambing. Once in the environment, the bacterium can survive for 2 years in dry soil. It is

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resistant to freezing and thawing in the soil but does not survive for more than 1 to 2 weeks in properly preserved silage. The bacterium proliferates in rotting vegetation in which aerobic conditions exist and the pH is above 5.4.[22-24] Common sources of contaminated forage include spoiled silage at the ends of trench silos, decaying forage at the bottom of feed bunks, or rotting hay at the periphery of hay stacks.[22,25] The incidence of listeriosis may be increasing because of the greater use of trench silos and bulk handling methods that result in a greater amount of spoilage than in conventional upright silos. Although *L. monocytogenes* can be isolated from silage with a pH below 4, fewer bacteria are found in well-preserved forage.[26]

A selective enrichment medium has been developed for identifying and enumerating the *Listeria* organisms in silage. This medium permits semiquantitative enumeration of *Listeria* bacteria in 10 g of silage. Hemolysin production is measured by overlaying the colonies with bovine blood agar and reincubating the plates. Using this method, outbreaks of listeriosis have been correlated with silage containing 1 million *Listeria* organisms and more than 1 million enterobacteria per gram of silage. The pH of such silage is characteristically above 7.8.[27]

There is a significant public health concern about *Listeria* contamination of milk products. The 4b serotype of *L. monocytogenes* is most often responsible for infections in humans.[28] Outbreaks have been traced to ingestion of pasteurized milk, cole slaw, and soft, ripened cheese. Recent foodborne listeriosis outbreaks have also been linked to contaminated fruit and vegetables.

Pathologic Lesions The lesions of listeric meningoencephalitis are most common in the pons and trapezoid bodies, but they can be located anywhere in the brainstem. Neurologic structures most often affected include the reticular formation and CNs V and VII to X. Macroscopic lesions are limited to mild meningeal congestion and clouding of the CSF. Microscopic lesions include perivascular cuffing with mononuclear cells, multifocal asymmetric brainstem microabscesses, and mononuclear cell meningoencephalitis.[28] The microabscesses are composed predominantly of neutrophils. Other microscopic changes include degeneration of the neuropil and neuronophagia.

Treatment The recovery rate is best if treatment is administered early in the disease course. Animals that are recumbent, comatose, or convulsive rarely survive despite intensive antibiotic and supportive therapy. In most cases, treatment must be administered for a prolonged period because recovery may take as long as 1 month. *L. monocytogenes* is susceptible to most of the common antimicrobial drugs. Recommended treatment is either oxytetracycline, 10 mg/kg IV twice daily, or penicillin G.[6] Specific recommendations for penicillin therapy include an initial dosage of 40,000 IU/kg (IV potassium penicillin G) three or four times daily for 7 days and then 22,000 IU/kg (procaine penicillin) IM once daily for 14 to 21 additional days.[6]

The plasma concentrations of bicarbonate and potassium should be measured, and specific corrective fluid therapy should be administered as indicated by acid-base and electrolyte assays. Good footing and nursing care are also beneficial.

Prevention Serologic responses to flagellin and listeriolysin-O develop after oral administration of virulent *L. monocytogenes* and correlate with protection against listerial bacteremia.[16] Vaccines of attenuated or killed bacteria have been used successfully to protect sheep and goats. Although these vaccines reduce the incidence of listeriosis in vaccinated flocks, they are not commercially available in the United States.

Although the case-attack rate of listeriosis is low, occasional epizootics may occur in cattle, sheep, or goat herds, invariably associated with high rates of environmental contamination. In such cases the hay and silage should be cultured for *L. monocytogenes*. Rotten vegetation should be discarded, and cattle should be fenced from contaminated areas.

Thromboembolic Meningoencephalitis (*Histophilus somni* [formerly *Haemophilus somnus*] Infection; Sleeper Calves)

Definition and Etiology Thromboembolic meningoencephalitis (TEME) is a fulminant neurologic disease of cattle that arises from septicemia caused by the pleomorphic, nonencapsulated, gram-negative bacterium *Histophilus somni* (formerly *Haemophilus somnus*).[1] Owing to its capacity to disseminate via the bloodstream, this organism can incite infection in multiple organs. In addition to TEME, *H. somni* can cause pleuropneumonia, myocarditis, laryngeal abscesses, polyarthritis, polyserositis, and infections of the ear, eye, udder and urogenital tract.[1-6]

Clinical Signs Only the neurologic syndrome (TEME) is discussed here. Descriptions of other clinical syndromes of *H. somni* infection are discussed in Chapters 31, 39, and 43. The initial signs of TEME are fever (40° C to 41.6° C; 104° F to 107° F), anorexia, depression, and ataxia.[7-9] In addition to depression, affected animals show a number of conscious proprioceptive deficits including knuckling, circumduction, crossing over, and interference. Affected animals may fall while attempting to walk. Signs specifically associated with lesions of the cerebellum and caudal brainstem include head tilt, nystagmus, strabismus, blindness, muscular tremors, opisthotonos, coma, and convulsions.[10] Signs of infection in other organ systems (e.g., pneumonia, arthritis) may be present in the affected animal or in cohorts. Death may occur within 36 hours after the onset of neurologic signs.

Clinical Pathology Examination of CSF may be helpful in substantiating a clinical diagnosis of TEME. Specific CSF changes characteristic of hemorrhage include high erythrocyte counts, xanthochromia, and increased concentrations of protein (>100 mg/dL) and neutrophils (>500 WBCs/μL). In untreated cases of TEME, the bacterium may be isolated from the brain, kidney, pleural fluid, lung sections, aspirated tracheal exudate, urine, blood, and preputial washings. Standard transport swabs containing Amies media are appropriate for culturing of clinical samples. Isolation of *H. somnus* from joint fluid and CSF is usually unsuccessful.[11] The kidneys and brain should be collected at postmortem examination because these tissues contain the highest concentrations of *H. somni*.[11]

Initial changes in the peripheral WBC count include neutropenia, left shift, and toxic changes in the neutrophils. Cattle that develop acute TEME invariably have agglutinating antibody titers greater than 1:400 and show a fourfold increase by 2 to 4 days after infection.[12] Serum agglutination titers greater than 1:1024 are seen in convalescent cattle; lower titers may be seen with inapparent infection or vaccination.[13]

Pathophysiology Infection of cattle by *H. somni* probably occurs through the respiratory tract. Bacterial proliferation in the lungs and other soft tissues by serum-resistant isolates results in bacteremia. *Histophilus* possesses multiple virulence factors including the capability to induce apoptosis of endothelial cells.[6] Exposure of subendothelial collagen occurs subsequently, resulting in microthrombus formation and organ damage through hypoxia and inflammation. The sites of the body most affected by the thrombosis are the brainstem, spinal cord, synovial membranes, pleura, and lungs. Although the name *thromboembolic meningoencephalitis* implies the passage of solid material in the vasculature to a downstream occlusion site (embolism), thrombus formation likely occurs directly at the site of the vascular lesion.

Epidemiology Although TEME occurs most frequently in feedlot cattle,[9] outbreaks in the western United States and Canada have been reported in both pasture and dry-lot environments.[7,14] In a serologic study of feedlot cattle, seroconversion to *H. somni* occurred early in the feeding period (soon after placement).[15] This may be reflective of the role of stressors (e.g., comingling of animals

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from different sources, transport, changes in feed) in the pathogenesis of this disease. Chapter 31 includes further details on the epidemiology of *H. somni* infections in cattle.

Necropsy Findings Macroscopic pathologic lesions of the CNS include disseminated multifocal hemorrhages and infarctions in the spinal cord, brainstem, and cerebral cortex. Bacterial colonies are frequently observed in thrombosed blood vessels and the surrounding infarcted tissues. Ocular lesions are characterized by conjunctivitis, multifocal retinal hemorrhages, and areas of retinal edema. The CSF is cloudy and xanthochromic. A focal fibrinous meningitis is seen, and suppurative otitis may be seen in some cases.

The earliest microscopic lesion of TEME is a vasculitis that progresses to septic infarction and abscess formation. The lesions are usually found in the CNS but in severe cases may be disseminated throughout the body.

Non-neurologic lesions of *H. somni* infection include suppurative arthritis, synovitis, myocarditis, suppurative pleuritis, urogenital infections, and bronchopneumonia. Changes associated with the bronchopneumonia include infarction, cranioventral pulmonary consolidation, and hemorrhagic interstitial pneumonia. Other lesions include ecchymotic to petechial hemorrhages over the serous surfaces, purulent exudate in the joints, and ulceration of the laryngeal and tracheal mucosa with diphtheritic membrane formation.[16]

Treatment and Prognosis During an outbreak, cattle must be examined frequently and should be treated when the neurologic signs first appear. *H. somni* is susceptible to many antibiotics and antimicrobial drugs. Drugs that have been reported to be effective for the treatment of TEME include tetracyclines, penicillin, aminoglycosides, and ampicillin. Parenteral oxytetracycline is regarded as the most cost-effective treatment for infected commercial cattle; dosage is 10 mg/kg of a conventional formulation given IV twice daily for 3 days or 20 mg/kg of a long-acting formulation given SC. Some advocate the addition of chlortetracycline (2.2 mg/kg) to the feed for 10 successive days.[17]

Prevention and Control Antibody responses protective against respiratory challenge have been generated by vaccinating cattle with anionic, heat-stable proteins derived from the bacterial cell wall.[18] Vaccination of cattle with commercial products affords substantial protection from experimentally induced *H. somni* septicemia and neurologic disease for more than 3 months.[18-20] (See Chapter 48 for more information about vaccines.) Mass prophylactic treatment of affected cattle with a parenterally administered, long-acting oxytetracycline formulation may be efficacious for preventing TEME in high-risk cattle.[21]

Otitis Media/Interna of Ruminants

Otitis media/interna is a common bacterial disease of cattle and sheep; it is less commonly observed in goats. The condition usually occurs as a sequela to upper or lower respiratory infections caused by *Mannheimia haemolytica, Pasteurella multocida, Corynebacterium pseudotuberculosis, Histophilus somni,* or *Mycoplasma* spp.[1-5] Subclinical otitis media/interna is common in feedlot-reared animals, particularly early in the feeding period.[1,3] Although viral infections are the cause of a large proportion of otitis media/interna cases in children,[5] the role of viral infections in ruminant otitis media/interna remains speculative; it is possible that viruses play a similar role in facilitating otitis media interna as they do in facilitating lower respiratory tract disease. Recently, the detection of *Mycoplasma* spp. in clusters or outbreaks of otitis media/interna on dairies has justified the consideration of contaminated milk as an important potential source of this organism to young stock.[4,6] Chapter 31 includes more detailed discussion on the role of *Mycoplasma* in the bovine respiratory disease complex.

Otitis media/interna is considered to most commonly result from ascending infection of the middle ear from the nasopharynx via the eustachian (auditory) tube.[5] Infection that progresses from the external ear into the middle ear is less common but may occur secondary to aural infestation by ectoparasites. Once infection is established in the middle ear, extension into the inner ear may occur as a result of erosion of bone or extension of the infection through the round and/or oval windows. The constellation of clinical signs of otitis media/interna results from damage to the peripheral vestibular apparatus residing in the tympanic bulla and petrous temporal bone. In chronic cases, the peripheral vestibular apparatus can be damaged beyond repair and neurologic deficits may be permanent. Rarely, extension of infection into the central nervous system can occur, resulting in subdural abscess formation, meningoencephalitis, or brain abscess formation.[5] The vast majority of cases shows clinical signs of unilateral peripheral vestibular disease; however, subclinical inflammatory lesions may be present in the contralateral, clinically normal side. Bilateral, clinically apparent peripheral vestibular disease is rare. Additional signs of multisystemic disease caused by *Mycoplasma bovis, Pasteurella multocida,* or *Histophilus somni* may be present (e.g., pneumonia, polyarthritis).

Clinical Signs Headshaking (possibly producing an aural hematoma), an ear droop, and reduction in appetite may precede the clinical vestibular signs. Fever is inconsistent.[6] Patients with vestibular signs display unilateral head tilt (toward the side of the lesion), continuous horizontal nystagmus (fast phase away from the side of the lesion), and imbalance, manifested as a tendency to stumble, fall, or circle tightly (walk in a tight circle) toward the side of the lesion. If the tympanic membrane ruptures, or in the rare case of otitis externa as a preceding condition, purulent exudate may be evident in one or both ears.

Animals may become recumbent and lie with the lesion side toward the ground; if turned, they return to the same position. Many animals with otitis media also develop ipsilateral facial nerve dysfunction, which results in ptosis, drooped ear, and flaccid lips and nostrils. In small ruminants, facial nerve paralysis results in deviation of the philtrum toward the normal side. Deviation of the philtrum does not occur in cattle because of the large amount of connective tissue surrounding the planum nasale. Occasionally, affected animals develop subtle or pronounced signs of cortical or brainstem disease as a result of extension of infection from the middle ear into the meninges. Cerebrospinal fluid analysis may reveal increased leukocyte counts in such cases.[6]

Although the clinical signs of peripheral vestibular disease are characteristic, it is important to differentiate this condition from that of central vestibular disturbance. Animals with peripheral vestibular disease are usually appetent, alert, and aware of their surroundings and do not have a significant deficit of postural placement. The nystagmus of these animals is constantly horizontal. In comparison, animals with central vestibular disturbances are depressed, have a nystagmus that varies in direction, and show marked conscious proprioceptive abnormalities.

Treatment Treatment of bacterial otitis with procaine penicillin (44,000 IU/kg IM or SC daily) may be effective. Importantly, however, given the potential for involvement of bacteria that do not have a cell wall (*Mycoplasma* spp.), initial treatment with an antibiotic other than a member of the β-lactam class might be warranted (e.g., tetracyclines, florfenicol, macrolides, and where legal, fluoroquinolones), unless bacterial culture and sensitivity results or clinical response directs the veterinarian to treat with a β-lactam class antimicrobial drug.[6] Relapses may occur, warranting prolonged treatment (3-6 weeks). Treatment is effective in obtaining a complete cure in animals with acute otitis but is less so in the chronic form. In chronic cases, infection may irreversibly damage middle or inner ear tissues, causing neurologic deficits that can persist despite resolution of infection with antimicrobial therapy. Osteomyelitis of the petrous temporal bone, abscess formation in the tympanic bulla, or a noninfectious etiology (e.g., neoplasia) are other considerations for affected animals that do not respond to antimicrobial therapy.

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Ear Mite Infestations of Ruminants

The ear mite of cattle is *Raillietia auris,* and that of small ruminants is *Psoroptes cuniculi.* Severe infestations perforate the tympanum and result in vestibular disease, facial paralysis, and ataxia.[1-4] Infestation can be recognized by observation of ulceration and purulent debris in the auditory canal next to the tympanum. Mites may or may not be visible during otoscopic examination. Malodorous discharge on the side of the face under the ear canal may be seen in some affected animals.

The accumulation of purulent debris and swelling of auricular tissues block the transmission of sound to the tympanum.

Ear mite infestations in cattle are common and in some herds may affect most of the adults. The biologic importance of the infestation may be related to changes in the herding or mothering behavior of range cattle. The economic significance of the infestation is unknown.

Ear mites have been successfully treated in goats using eardrops containing rotenone once daily for 5 to 10 days. Good clinical responses can be obtained in cattle with the same treatment. Fenthion drops have also been used successfully. In cases of parasitic otitis in which the discharge has been inspissated, lateral resection of the ear canal should be considered to establish adequate ventral drainage.[5] A single subcutaneous injection of ivermectin at 0.2 mg/kg has been shown to be an effective treatment for *P. cuniculi* otitis in both sheep and goats.[6,7]

The life cycle of the mite involves two free-living stages, the protonymphs and deutonymphs. These forms molt in the vegetation and reinfest cattle as they graze or bed during the evening.[8] Therefore tilling the soil of the infested pastures or retreating cattle every 14 to 21 days with insecticide should be considered as part of an eradication scheme.

Diseases Producing Tremors and Ataxia; Cerebellar Diseases

Cerebellar Abiotrophy of Arabian Foals

Robert J. MacKay

The most commonly reported cerebellar neurodegenerative conditions of horses are inherited abiotrophies. A distinct apparently inherited cerebellar condition of Oldenberger foals is characterized by multifocal cerebellar degeneration and an invariably fatal outcome.[1] A syndrome of progressive ataxia associated with cerebellar degeneration was identified in one American Miniature Horse foal, and anecdotal evidence for an additional two cases was cited.[2] An unusual case of neuroaxonal dystrophy with cerebellar signs was reported in a Pony of the Americas foal.[3] Cerebellar degeneration and lipofuscin accumulation associated with presumed toxicosis has been described in Gomen disease of horses in New Caledonia.[4] Induced mannosidosis with neurovisceral degeneration involving the cerebellum has been reported for poisoning by swainsonine-containing plants in the United States, Australia, and Brazil.[5-7]

Cerebellar Abiotrophy

The term *abiotrophy* refers to spontaneous premature degeneration resulting from an inborn error of development.[8] Syndromes of cerebellar abiotrophy (CA) have been described for Arabian[9] and Gotland Pony[10] foals. In Arabians with CA, degeneration only begins after formation of the cerebellum and is characterized by apoptosis of Purkinje cells.[11] The likely genetic basis for CA in Arabians was recently identified as a single-nucleotide polymorphism (SNP) upstream of the *mutY* homolog gene (MUTYH), in a region involved in transcriptional upregulation of the gene.[12] MUTYH encodes for a DNA glycosylase involved in repair of oxidative damage to genomic DNA during organogenesis and mitochondrial DNA during postnatal life. This gene is abundantly expressed in the cerebellums of normal horses; expression is significantly reduced in CA foals.[12]

The mode of inheritance of CA is simple autosomal recessive.[9,12,13] The CA allele was found in 19.7% of approximately 4200 Arabian horses and is well represented in Egyptian, Spanish, and Polish lineages.[12,13] Among tested horses, 1.4% of were homozygous for the allele. Nine of these were clinically normal, which, taken together with the observed range of ages of onset, is evidence for variable expression of the CA trait. The allele was also present at low frequency in the Bahkir Curly Horse, a breed that used Arabians as foundation stock, and in Welsh Ponies and Trakehners, breeds that allow out-crossing with Arabians.[14]

Signs of CA typically begin in foals between 6 weeks and 4 months of age; however, foals may be affected at or shortly after birth. Among 18 confirmed or suspected cases, signs were present at birth in 4 (22%) and began at 3 months of age or younger in 10 (56%), 3 to 6 months in 2 (11%), and older than 6 months in 2 (11%).[1,15-17] The first signs noticed are incoordination, basewide posturing in the thoracic limbs, and head tremors. The head tremor is usually a coarse bobbing in either the horizontal or vertical plane. When the head is extended (e.g., toward the dam's udder or toward offered food), the head tremor becomes more pronounced. Although CA foals can see normally, the menace response cannot be elicited in most cases. Foals walk with a swaying, lurching gait and may even wobble side to side or back and forth while standing still. Thoracic limbs may appear stiff, or there may be exaggerated flexion ("paddling") during the protraction phase. Gait abnormalities are most obvious when movement is initiated and during turns. Normal strength is preserved even in severely ataxic foals, and blindfolding does not exacerbate clinical signs. All clinical signs are exaggerated by stimulation of affected foals. Such hyperresponsiveness means CA foals are difficult to halter-train and lead; even normal handling often causes an affected foal to pull away or even flip over backward. Severely affected foals that fall often panic and struggle for some time before standing.

The diagnosis in an Arabian foal with compatible clinical signs is strongly supported by demonstration of homozygosity for the CA allele. This test requires submission of 20 to 30 hairs with roots and is submitted to the Veterinary Genetics Laboratory at the University of California, Davis (http://www.vgl.ucdavis.edu/services/horse.php). Hematologic and serum chemistry findings are usually normal. Some foals have high CSF protein concentration and creatine kinase activity, consistent with active neurodegeneration at the time of CSF collection.[16] Magnetic resonance, and possibly CT, imaging of affected foals reveal atrophy of the cerebellum in foals with CA.[18]

Signs may be stable after onset or get worse for up to several months. It is rare, however, for CA foals to become persistently recumbent. Modest improvement has been noted in some mildly affected horses once they become adults.[1] Foals with CA seldom succumb to direct effects of the condition but most are euthanized because of severe clinical signs and poor prognosis.

Gross appearance of the affected brain is usually described as normal; however, the ratio of cerebellar to whole brain weight is usually less than 8%, whereas normal ratios are 8% or higher. The characteristic histologic lesion is thinning of the cerebellar cortex affecting both granular and molecular layers.[1,9,15-17] There is marked reduction in the number of Purkinje cells in the granular layer, and some of those remaining show degenerative changes (swelling, shrinkage, and hyperchromasia of the perikaryon). There is relative sparing of the Purkinje cells of the nodulus and flocculi.[16] Vacuolation may be noted in the olivary nuclei.[15] Mineralized neuronal cell bodies may be found in the thalamus adjacent to the third ventricle.

Cerebellar Hypoplasia Caused by Congenital Bovine Viral Diarrhea Virus Infection

Lisle W. George • David C. Van Metre

A complete discussion of bovine viral diarrhea–mucosal disease (BVD-MD) can be found in Chapter 32. BVD virus infection of

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FIG. 35-13 Characteristic head position and basewide stance of a calf with cerebellar hypoplasia.

susceptible pregnant cattle from 90 to 170 days' gestation results in abortion or stillbirth, hydranencephaly, or cerebellar hypoplasia in the fetus.[1,2] The BVD virus infects the developing germinal cells of the cerebellum and kills Purkinje cells in the granular layer, resulting in necrosis and inflammation.[3] The microscopic lesions include necrosis of the external germinal cells, focal parenchymal hemorrhages, and folial edema.

The signs of cerebellar dysfunction are usually present at birth and include truncal ataxia, falling backward, opisthotonos, basewide stance, coarse intentional head tremors, hypermetria, hyperreflexia, and nystagmus or strabismus (Fig. 35-13).[4,5] If severely affected, the animal may be unable to stand or lie in sternal recumbency. Excitatory stimuli in these animals precipitate wild oscillations and side-to-side movements of the head, which can be mistaken for convulsions. The affected calves may have a deficient menace response and appear to be blind, especially with concomitant hydranencephaly or microphthalmia. The neurologic condition rarely improves after birth. Other fetal changes that may be induced by the BVD virus include thymic atrophy, retinal degeneration, corneal opacity, failure to grow, and abortion.[1,4] The diagnosis of cerebellar hypoplasia is based on identification of the specific clinical signs and the recognition of BVD antibodies in precolostral blood specimens. The virus may be cultured from the blood of some affected calves, but this appears to be dependent on whether or not an immune response to the virus has developed in the affected calf.

Storage Diseases and Inborn Errors of Metabolism

Inherited Myoclonus of Peruvian Paso Foals

Robert J. MacKay

Inherited myoclonus is a disorder described in two Peruvian Paso foals that is characterized by myoclonic contractions of the musculature in response to auditory or tactile stimuli.[1] These contractions are sustained with repeated stimulation. One foal could not stand without assistance, and the other had a "bunny-hopping" gait in the pelvic limbs. Analeptic drugs and tranquilizers are ineffective for controlling this condition. Inherited myoclonus is associated with a specific deficiency of spinal glycine receptors, which are responsible for synaptic inhibition in the CNS. Glycine is a major inhibitory transmitter providing reciprocal inhibition via Ia afferents and interneurons, as well as recurrent inhibition on motor neurons via Renshaw cells.

Congenital Encephalomyelopathy in Quarter Horses

Robert J. MacKay

Congenital encephalomyelopathy has been described in Quarter Horse foals.[2] The condition occurred in three foals born to two different mares and three unrelated stallions. Signs were present at birth and included recumbency and coarse tremors of the pelvic limbs. When foals were assisted to stand, the hindquarters bounced off the ground. Thoracic limb function appeared normal; however, patellar reflexes were exaggerated. Affected foals are bright, alert, and responsive and have intact pain perception. There are no gross CNS lesions. Microscopic lesions include spongiform degeneration and axonal swelling of the spinocerebellar spinothalamic tracts within the medulla and spinal cord.

Lavender Foal Disease (Coat Color Dilution Lethal)

Robert J. MacKay

Lavender foal syndrome (LFS), also known as coat color dilution lethal (CCDL), is an autosomal recessive disorder of Arabian foals that has been recognized for many years but only recently reported.[3,4] LFS is characterized by a dilute coat color, episodes of opisthotonos, hyperresponsiveness to touch, limb paddling, and rapid, uncontrolled eye movements. Affected foals are unable to assume sternal recumbency or stand. Despite the incapacitating neurologic signs, LFS foals are able to vocalize and usually have a strong suckle response. The important feature of this condition that distinguishes it from neonatal encephalopathy and other causes of neonatal neurological dysfunction is the dilute hair color. In a few cases, the color is the striking iridescent silver to pale lavender hue suggested by the name. *Coat color dilution lethal* may be a more appropriate name, however, because many affected foals exhibit other dilute coat colors including pewter (pale slate gray) and pale chestnut (pink). Complications from neurologic abnormalities invariably lead to death or euthanasia by around 72 hours. Abnormal findings at necropsy are nonspecific and minimal. A single base pair deletion in the *MYO5A* gene is responsible for LFS.[5,6] This deletion results in a frame shift and truncation of the protein at a premature stop codon 12 amino acids beyond the deletion. Loss of *MYO5A* disrupts melanosome trafficking and endoplasmic reticulum transport in cerebellar Purkinje cells, thus leading to the clinical signs of cerebellar seizures. Reported allelic frequencies are 5.2% among Egyptian Arabians in the United States[6] and 1.62% among European Arabians and 0% among European Thoroughbreds and Standardbreds. Testing for the *MYO5A* gene mutation is available commercially and is performed on plucked mane and tail hairs.

Overo Lethal White Syndrome

Robert J. MacKay

Overo lethal white syndrome (OLWS) is an inherited syndrome of American Paint foals from parents with the frame overo coat pattern.[7,8] Affected foals are totally or almost totally white and die within days from complications due to intestinal aganglionosis.[7] Aganglionosis is characterized by a complete lack of submucosal and myenteric ganglia from the distal small to large intestine. Foals with OLWS are homozygous (designated OO) for a dinucleotide mutation, which causes an isoleucine to lysine substitution at codon 118 in the gene for endothelin receptor B.[9,10] Although heterozygotes for the

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lys118 mutation (nO) are mostly frame overos, the mutation is also found at lower frequency in other white patterned horses including tobianos and solid pattern breeding stock.[11] The mutation should not be found in breeds without white pattern variants, although OLWS was reported in the offspring of a registered Quarter Horse. Genetic testing is the only reliable method for detecting carriers. Plucked mane or tail hairs are submitted to commercial laboratories for testing.

Locoism (Swainsonine Toxicity)

Robert J. MacKay • Lisle W. George

Definition and Etiology Chronic ingestion of a variety of plants worldwide can result in an acquired neurovisceral storage disease. Plants incriminated so far include members of *Astragalus* and *Oxytropis* genera (locoweeds) in the western United States (Table 35-5), Canada, Africa, Asia, and Australia; *Ipomoea carnea* in Mozambique; the darling pea in Australia (*Swainsona* spp.); and *Ipomoea* spp., *Turbina cordata,* and *Sida acuta (carpinifolia)* in Brazil.[1-8] The disease was also diagnosed in a horse in Belgium; however, the causative plant was not identified.[9] Horses are most susceptible, but cattle, sheep, goats, and deer can also be affected.[10]

Conditions that promote locoweed poisoning are hot, dry weather and a scarcity of alternative forage. Horses may be more prone to graze on locoweed than cattle, particularly when other green forage is scarce, and may increase their consumption over a single season.[10] Chronically exposed livestock become addicted to locoweeds and feed selectively on the plant over successive grazing seasons.[11]

Locoweeds represent only a small proportion of the species in the *Astragalus* or *Oxytropis* genera; many *Astragalus* spp. contain nitrotoxins or are selenium-accumulators, and many other members of both genera are nontoxic. The indolizidine alkaloid *swainsonine* (also known as locoine) has been identified as the cause of locoism. Swainsonine acts by potent inhibition of mammalian α-D-mannosidase and of Golgi mannosidase II.[5,12] The source of swainsonine in *Astragalus* and *Oxytropis* plants is the fungal endophyte *Undifilum oxytropis* or closely related *Undifilum* spp.[13,14] Swainsonine, along with slaframine (slobber toxin), is also produced by *Rhizoctonia leguminicola,* a fungus that causes black patch disease of red clover.[15] Whether or not plants other than *Astragalus* and *Oxytropis* spp. are also colonized by swainsonine-producing fungus has not yet been clarified. Other toxins identified in locoweeds have included β-galactosidase and β-glucosidase; aminonitrile, a toxin that causes abortion and teratogenesis; and miserotoxin, a cause of respiratory disease.

Oxytropis and *Astragalus* plants are legumes that have herbaceous stems and alternate pinnately compound leaves.[16] The fruits are characteristic leguminous pods that contain kidney-shaped seeds with pods marked by characteristic longitudinal grooves. The plant is eaten because it is the first vegetation available in the spring. Neurologic signs do not usually develop in cattle until 3 weeks after the animals first begin grazing the plant and may not occur until long after ingestion of the plant has stopped. In parallel with changes in the concentration of endophyte in locoweeds, toxicity may vary from year to year and even within one season.[17]

TABLE 35-5

Species of *Astragalus* and *Oxytropis* Found in the Western United States[16]

Scientific Name	Common Name
Oxytropis sericea	White locoweed, point locoweed
Oxytropis lambertii	Purple locoweed
Oxytropis campestris	Yellow locoweed
Astragalus argillophilus	Half-moon locoweed
Astragalus bisculatus	Two-grooved milk vetch
Astragalus earlei	Earles locoweed
Astragalus lentiginosus	Speckled, spotted locoweed
Astragalus mollissimus	Wooly locoweed
Astragalus mothoxys	Sheep locoweed
Astragalus wootnii	Wooton locoweed

Clinical Signs Experimentally and naturally poisoned horses show clinical signs by 2 to 3 weeks after continuous ingestion of locoweed.[10,18] The clinical signs include ataxia and obtundation alternating with periods of frenzied or manic activity.[7] There is sometimes a high-stepping gait suggestive of cerebellar dysfunction.[7] At rest, there is intention tremor of the head; flaccidity of the nose and lips; repetitive, dystonic movements of the lips and tongue; and dysphagia. The clinical signs worsen when affected horses are handled or transported. Signs in goats are similar including ataxia, hypermetria, hyperesthesia, and muscle tremors.[1,2] When the chin is raised for 30 seconds and then suddenly released, even mildly affected goats fell into recumbency with additional signs of nystagmus, opisthotonos, tetanic spasms, and seizures. Sedation is usually ineffective for controlling the hyperexcitability of locoism. Horses that survive locoweed poisoning retain altered behavior and an irregular gait. Abortions, stillbirths, and neonatal deaths can occur in all species exposed to these toxic plants, regardless of whether the dams have clinical signs of neurologic disease.[2,3,19]

Neurologic signs in adult cattle include ataxia, limb hypermetria and weakness, obtundation, dull staring eyes, and loss of herding instinct. Heavy losses from abortions or malformed calves have also been described. The indolizidine alkaloids are secreted in the milk and may cause unthriftiness and weak suckling behavior in calves. Calves that have been exposed to the toxin in utero are weak and fail to thrive. Some may have flexural contractions of the limbs and lateral rotation of the carpus.[8,20,21] Ingestion of locoweed by certain cattle at high altitudes may result in the development of cor pulmonale.[22] Many cattle with mild signs of locoweed poisoning recover completely by 60 days after removal from the offending pastures. Poisoned sheep have a star-gazing attitude and appear to be blind, nervous, and stiff. The normal flocking behavior is absent.[12] Affected sheep may salivate excessively. Testicular atrophy has been reported in rams.[23] The immunosuppressive actions of swainsonine predispose affected animals to pyogenic infections such as pneumonia, keratoconjunctivitis, and foot rot.

Clinical Pathology Microscopic examination of stained blood smears may reveal cytoplasmic vacuolation of lymphocytes. These changes are found in the majority of lysosomal storage disorders but might be considered diagnostic of locoweed poisoning in animals with characteristic clinical signs and historical evidence of exposure. Serum activities of alkaline phosphatase (ALP) and aspartate transaminase (AST) are high; elevated concentrations reflect liver dysfunction associated with prominent vacuolation of hepatocytes.[24] Definitive diagnosis can be established by assaying blood from affected animals for α-D-mannosidase activity and swainsonine concentration. The half-life of swainsonine in the serum is 16 to 20 hours.[25] This means that an animal suspected of locoweed poisoning must have a blood sample taken within 2 days of eating locoweed for swainsonine to be detected.

Pathology The microscopic abnormalities of the soft tissues of acutely poisoned animals are similar to those of the inherited lysosomal storage diseases of cattle including cytoplasmic vacuolation of neurons, particularly cerebellar Purkinje cells, and cells in various other tissues.[7,18,26] Paraffin-embedded tissues can be examined using lectin photochemistry to characterize the stored material within the vacuoles.[27] Vacuolation of renal tubular epithelial cells may occur as early as 4 days after the start of daily feeding of 0.34 kg of locoweed to horses and may be present in animals exposed to toxic plants but clinically normal.[28] Pulmonary lesions associated with chronic ingestion of locoweed that may predispose to high-altitude disease (brisket disease) in cattle include alveolar emphysema, bronchiolar constriction and hypertrophy, and interlobular edema and fibrosis. Pyloric or gastric ulcers have been reported in affected cattle.[8,28] Placental

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edema, fetal ascites, and hydrops allantois have been described in exposed pregnant cattle.

Treatment There is no known effective long-term therapy for locoweed poisoning. Animals remain affected for a prolonged period or even permanently after removal from the plants. One author recommends tranylcypromine (60 mg PO), a monoamine oxidase inhibitor, and protryptyline (60 mg PO) or reserpine (1.25 mg PO per animal once daily) for treatment of chronically affected animals.[29] The efficacy of these treatments is unknown. Addition of a mineral supplement and a natural clay (clinoptilolite) to the diet of cattle ingesting locoweed did not prevent toxicity.[30]

Prevention Nonaddicted livestock normally do not eat locoweed if other forage is available. The condition may be prevented by supplemental feeding during the early spring and late summer. One report has described conditioning aversion to locoweed in horses using lithium chloride administered simultaneously with grazing of *Oxytropis sericea*.[31] Whether this is a practical management tool in large numbers of animals has yet to be determined.

Staggers Syndromes (Grass Staggers)

Robert J. MacKay

Forage-associated staggers syndromes are common and have been associated with protective fungal secondary metabolites, bacterial antibiotic corynetoxins, or neurotoxic chemicals produced by the forage itself. Some associated plant or fungal toxins also induce other physiologic effects including agalactia, fever, and low productivity because of a prolactin-like effect.

Tremorgenic Mycotoxicoses

There are at least 20 known tremorgenic mycotoxins, produced by several different fungi, that have the same biologically active moiety and give rise to similar clinical manifestations.[1,2] Indole-diterpenoid tremorgens are secondary fungal metabolites that act by blocking potassium outflow from cells via inhibition of cell membrane large-conductance Ca-activated potassium (BK) channels.[3,4] The most important classes of tremorgens are the *lolitrems* (perennial ryegrass staggers) and *paspalitrems* (*Paspalum* staggers, Bermudagrass staggers). Other indole-diterpene tremorgens that may be elaborated on moldy feeds by saprophytic fungi and occasionally cause staggers in livestock include penitrems, janthitrems, aflatrems, and verruculogen. The major tremorgenic mycotoxicoses are similar or identical clinically; therefore clinical signs are only discussed in detail in the Perennial Ryegrass Staggers section.

Perennial Ryegrass Staggers

Perennial ryegrass staggers (PRS) is a syndrome of tremors and ataxia resulting from ingestion of endophyte-infected perennial ryegrass *(Lolium perenne)* by horses, cattle, sheep, deer, goats, and alpacas.[5] PRS is an important condition of livestock in New Zealand and Australia and occurs occasionally as outbreaks in Northern Europe, the northwestern United States, South America, and Europe.[6-9] The case-attack rate may reach 100%, but mortality is generally low and attributable only to accidents. Substantial economic losses may be incurred, however, when production animals with PRS cannot be safely moved. For example, herd- or flock-wide outbreaks have prevented milking of dairy cows and mustering of sheep for necessary procedures such as anthelmintic treatment, shearing, or breeding.[5] Conditions that increase toxicity of perennial ryegrass pastures include high proportion of endophyte-infected plants; late seasonal growth; hot, dry summer and fall after wet spring; ryegrass domination of pastures; ambient temperatures over 23°C; ryegrass that is allowed to flower before consumption; and close grazing.[9] Endophyte is most abundant in the leaf sheath and florets and lowest in the blades. The disease is seen from June to September in the northern hemisphere and December to June in the southern hemisphere.

PRS typically appears acutely 5 to 10 days after introduction of livestock onto endophyte-rich pastures; onsets as early as 48 hours and as late as 2 weeks after exposure have been recorded. The source of tremorgenic toxins is the symbiotic endophytic fungus *Neotyphodium lolii*.[5] The fungal infection confers resistance to predation of grass by insects including the Argentine stem weevil, so there is selective pressure for expansion of toxigenic cultivars. *N. lolii* produces three classes of alkaloids with approximately parallel profiles of production, namely *tremorgens, ergopeptides,* and *peramine*. The most abundant and active indole-diterpene tremorgen produced by endophyte-infected plants is lolitrem B.[10] Concentrations of more than about 2 mg/kg (ppm) dry matter of lolitrem B in forage reliably cause staggers in sheep, cattle, and horses.[11] The concentration of lolitrem B in pasture increases from spring through fall. Plant infection rates below 25% (typical in northern hemisphere pastures) are associated with sporadic cases, whereas plots with 90% infection rates are common in Australasian pastures and are associated with outbreaks of PRS.

Ergovaline and other ergopeptide alkaloids (also see Chapter 54) produced by endophytes cause signs comparable to heat stress syndrome, a condition seen in cattle in the U.S. Southwest that are grazing tall fescue infected with the endophyte *Neotyphodium coenophialum*.[9] The resulting clinical signs are diarrhea, hyperthermia, high heart and respiratory rates, poor weight gain, and reduced milk production. The high mortality rates (up to 30% of affected sheep) reported during PRS outbreaks in Australia in 1986, 1993, and 2002 have been attributed to heightened susceptibility to heat stress caused by ergopeptides in endophyte-infected perennial ryegrass.[9] Horses experimentally fed endophyte-infected *L. perenne* seeds during cool conditions in New Zealand developed limb edema and exudative heel lesions, signs that reflected the vasoconstrictive fescue footlike effects of ingested ergopeptides.[11] Peramine, a pyrrolopyrazine alkaloid, is a potent insect-feeding deterrent with substantial protective effects against the destructive Argentine stem weevil. Strains of endophyte-free perennial ryegrass have been propagated but are difficult to maintain without extensive insecticide use. Cultivars of *L. perenne* that are infected with strains of *N. lolii* have been produced that contain peramine but not tremorgen or ergopeptide. These cultivars (e.g., AR1, AR37) therefore have multiple advantages, compared with traditional endophyte-infected strains, in that they do not cause staggers or ergopeptide-associated production loss and substantially protect against stem weevil predation.[12] AR1 is not as broadly insect resistant as wild-type *N. lolii,* however, and root aphid infestation is notably unaffected.

Clinical signs first occur about 5 to 10 days after introduction of livestock to infected pasture (or after eating infected ryegrass seeds or straw[7,11]) and become progressively more severe until animals are removed from the endophyte source. It is useful to review the carefully observed signs recently reported for experimentally induced PRS in horses because these are typical of mild to moderate signs shown by animals of all affected species during natural PRS outbreaks.[11] Initially, there were fine, then coarse, fasciculations and tremors of skeletal muscles, particularly those of the shoulders, chest, and thoracic limbs. Tremors were particularly apparent during eating, after exercise, or in a thoracic limb that was offloaded by the horse and rested. Fine tremors of the eyeballs were evident during ophthalmoscopic examinations but otherwise difficult to appreciate.[11] Other early clinical signs included a basewide gait, truncal sway, both at rest and during walking, and rapid, stumbling, corrective foot placements. Blindfolding or elevation of the chin exaggerated these signs, consistent with bilateral vestibular dysfunction. Horses were hyperresponsive to the withers slap used to test the laryngeal adductor ("slap") reflex. With progression, signs of general proprioceptive ataxia became apparent including delayed limb protraction, interference between pairs of limbs, and circumduction of pelvic limbs on the outside of circles. The gait also became jerky and more interrupted, but hypermetria, a characteristic cerebellar sign, was not seen

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in these mildly and moderately affected horses. The authors speculated that signs reported in severely affected livestock—namely, limb stiffness and unpredictable, inconsistent limb movements, hypermetria, head tremor, falling, and generalized tetanic convulsions[6,13]—are consistent with cerebellar involvement.[11] They therefore propose a time- and dose-related progression through the three "qualities" of ataxia (vestibular, general proprioceptive, then cerebellar) during the course of PRS in an individual animal.[11] Note that normal muscle strength is preserved in affected animals and they remain bright and alert.

In all cases, signs are exacerbated by handling. Attempts to force affected animals through gates or onto trailers may precipitate recumbency. While down, animals have rigid extension of the legs with occasional flailing with opisthotonus and tonic-clonic convulsions. Frothy exudate from the mouth has also been described. After approximately 10 to 20 minutes, the animal recovers if left undisturbed, stands, and walks back to the herd or flock.

Recovery occurs over days to weeks with longer recoveries typical of severely affected animals. Most animals are normal within a week of removal from toxic pasture. Treatment is not usually necessary, but it is important not to disturb or frighten tremoring animals and to handle them as infrequently and carefully as possible. If practicable, they should be kept on level ground in an area free of potential hazards, especially water hazards. If handling is necessary, hyperresponsiveness can be controlled by sedation. Tremors can temporarily be suppressed by diazepam (0.02 to 0.1 mg/kg IV for horses or 0.1 to 0.2 mg/kg IV for small ruminants).

Paspalum Staggers

Claviceps paspali ergots parasitize *Paspalum* spp. grasses and produce paspalitrems, indole-diterpene tremorgens that cause staggers syndromes in livestock similar or identical to that described earlier for perennial ryegrass staggers. Susceptible grasses include dallisgrass *(P. dilitatum),* bahiagrass *(P. notatum),* water couchgrass *(P. distichum),* and knotgrass *(P. paspaloides).*[14-16] *Paspalum* staggers has been recognized in the United States, South Africa, Great Britain, Australia, and New Zealand.[15,17-19] Natural outbreaks occur most commonly in cattle, but *Paspalum* staggers has been reported in three foals and two adult horses grazing dallisgrass in Australia[20] and sporadic cases are seen regularly by the author in horses on bahiagrass pastures in Florida.

C. paspali first attacks the pistil of the grass flower and replaces the ovary with a sclerotium (ergot). The fungus secretes a sticky fluid, the "honeydew," which contains a large number of spores but little toxin. The fluid hardens into a mature sclerotium containing high concentration of tremorgenic metabolites. Toxic stands of dallisgrass or other *Paspalum* grasses can be recognized by the presence of numerous small, reddish brown or black sclerotia measuring 3 to 5 mm in diameter on the seed head of the plant. The most abundant indole-diterpene metabolite in sclerotia is paspalitrem B, but paspalitrems A and C, paspaline, and paxalline are also produced.[15,21] *C. paspali* sclerotia also produce ergot alkaloids, albeit at low concentrations (on the order of 10 µg/kg dry weight compared with 150 mg/kg for paspalitrem B in one report[22]). Notable ergot alkaloids are ergonovine and ergine (lysergic acid amide). Particular animals apparently develop a craving for the infested seed heads and graze them selectively. Toxin production is greatest when there is a wet period after formation of the seed heads. The toxin remains active in cured hay. Mowing the toxic pastures and removing or burning the infested seed heads is effective for preventing further exposure to the tremorgen.

Clinical diagnosis is made by observation of clinical signs, visible detection of the toxic agent in the feed, or detection of indole-diterpenes by thin-layer chromatography (TLC). Animals recover spontaneously within days to several weeks after being removed from the pasture.

Bermudagrass Staggers

Bermudagrass *(Cynodon dactylon)* occasionally may become toxic for livestock.[19] Cattle are considered most susceptible, followed by sheep, goats, and horses. As is the case for *Paspalum* staggers, bermudagrass staggers results from ingestion of paspalitrems in grass parasitized by fungal ergots, in this case *Claviceps cynodontis*. *C. cynodontis* is closely related to *C. paspali,* and the profiles of indole-diterpenoid and ergot alkaloids produced by the sclerotia of these two fungi are similar. The clinical and epidemiologic aspects of bermudagrass staggers and *Paspalum* staggers are likewise similar.[22]

Animals may develop clinical signs as early as 36 hours after consuming toxic forage. Experimentally poisoned goats have developed clinical signs 8 days after being fed 772 g/head/day of toxic hay.[23] The toxin survives drying, and hay that is cut from offending pastures may remain toxic for as long as 9 years.[24] Pastures that are toxic remain so for successive seasons unless the vegetation is burned off and the ground is tilled and reseeded. The clinical signs occur suddenly, usually simultaneously, in several animals in the herd. In some cases, most of the animals on a single pasture may be affected, whereas animals on an adjacent pasture remain normal. The mortality rate is low, and deaths usually occur from self-inflicted trauma. Affected animals recover 2 days to 2 months after removal from the affected pasture or hay. Management is as for perennial ryegrass staggers.

Tremorgenic Mycotoxicoses Associated with Saprophytic Fungi

Most tremorgenic mycotoxins are synthesized by common saprophytic fungi of the genera *Penicillium* and *Aspergillus* that elaborate mycotoxins onto improperly harvested or stored livestock feeds. Some *Penicillium* spp. can also act as opportunistic plant pathogens, most notably as a cause of ear rot in corn. Ingestion of moldy cornstalks is probably the most common source of fungal tremors in livestock. The fungi proliferate in the corn but do not produce tremorgens until the stalks touch the ground. After production at or near the soil surface, the toxins translocate in plants through root absorption.[25] Cases associated with *Aspergillus* molds (usually *A. clavatus*) have occurred worldwide, linked to feeding sprouted grains and the by-products of beer production, both of which provide an environment for growth of the mold.[26,27] Clinical signs are indistinguishable from those of *Paspalum,* perennial ryegrass, and bermudagrass staggers.[16,25,28,29] Indole-diterpenoid tremorgens produced by *Penicillium* and *Aspergillus* spp. can be classified into four major groups: the aflatrem-paxilline group, verruculogen-fumotremogen group, territrem group, and tryptoquivaline group. Of these, the most important fungal tremorgens are aflatrem, penitrem A, fumotremogen B, and verruculogen. In some cases, additional non-indole-diterpenoid mycotoxins elaborated by these fungi cause a wider spectrum of clinical signs. For example, *A. clavatus* caused a highly fatal mycotoxicosis of cattle in South Africa, associated with widespread degeneration and necrosis of skeletal muscle and CNS motor neurons.[15]

Diagnosis is by demonstration of indole-diterpenoid tremorgens by thin-layer chromatography (sometimes in combination with a mouse tremorgen assay). Mycelial elements of *Penicillium* and *Aspergillus* molds may survive degradative conditions in the gastrointestinal tract and can be identified and cultured from the feces of affected animals.

Corynetoxicoses (Annual Ryegrass Toxicity, Flood-Plain Staggers, Blown Grass Staggers)

Corynetoxicoses are severe, often fatal neurologic disorders of livestock in Australia and South Africa.[30] A related syndrome was seen in Oregon from the 1940s through the 1960s but apparently has not been seen since.[31,32] Corynetoxins are produced by plants of several genera including *Lolium rigidum* (annual ryegrass), *Polypogon monspeliensis* (annual beard grass), and *Lacnagrostis filiformis* (blown grass) that are colonized by a nematode (*Anguina* sp.) and a bacterium *(Rathayibacter toxicus).*[33-35] Affected sheep and cattle with the same clinical syndrome in Oregon had been fed a fescue *(Festuca negrescens)* infected with a grass seed nematode and a *Rathayibacter*-like organism.[31,32] Corynetoxin-producing *R. toxicus* is transported

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into host plants by nematode L2 larvae and ingested by sheep, cattle, and occasionally horses.[30] The colonized plant forms a hollow gall in response to larval invasion of the seed. Bacteria are thus carried into the galls, where they proliferate into a distinctive yellow to orange mass.[30] *R. toxicus* organisms produce a series of closely related corynetoxins that are glycolipids in the tunicaminyluracil class of antibiotics. Corynetoxins potently inhibit lipid-linked *N*-glycosylation of glycoprotein, and their toxicity in animals probably results from the depletion of essential *N*-glycosylated proteins. It takes up to 15 years after introduction of the nematode-bacterial complex to a pasture before clinically significant amounts of toxin are produced.[36] A method of evaluating toxic pastures based on both enumeration of contaminated seedheads and ELISA to quantify *R. toxicus* has been developed.[37]

Although the serum half-life of corynetoxins in livestock is only about 4 hours, repeated exposure leads to an accumulation of the toxin and onset of clinical disease may take up to 12 weeks of continued ingestion.[30] Also, the concentration of the toxin increases in the seedheads during the summer and is greatest as the plant dries and the seeds ripen. Outbreaks associated with the feeding of hay made from toxic pasture may occur at any time. Stock losses are highest in sheep, although cattle deaths can be substantial. Outbreaks in horses occur occasionally and generally involve only a few horses.[38,39] Clinical signs appear to reflect the cerebellar and thalamic lesions that are evident histologically.[39] All ages are affected, and morbidity and mortality are usually high. When an affected flock is driven or cattle rounded up or otherwise stressed, some animals collapse in sternal or lateral recumbency. They often have muscle tremors, opisthotonos, head nodding, tetanic and clonic convulsions, limb extension, hypermetria, teeth-grinding, nystagmus, and ptyalism. Animals may regain their feet after several minutes and stagger away with a stiff-legged, jumping, or swaying gait. These animals often wander aimlessly, exhibiting stupor and ataxia. In mildly and moderately affected animals, clinical signs usually resolve within a week of removal from affected pasture, although relapses may occur in animals that appear to have recovered and it may take several months for severely affected animals to recover. Treatment with magnesium sulfate solution (50 to 100 mg/kg, IV in horses, SC in ruminants, repeated as needed) is reportedly effective in some cases.[38,40] The most practical strategy for controlling annual ryegrass toxicity is to break the nematode's life cycle by killing the ryegrass for two or three growing seasons. Otherwise, pastures remain perpetually toxic. Integrated control measures that have been recommended for prevention of annual ryegrass toxicity include applying herbicides in the spring, seeding the pastures with legumes, burning the infected pasture grasses during early autumn, and applying ryegrass-selective herbicides in the summer months, combined with heavy winter grazing.

Pathologic changes associated with corynetoxin poisoning include widespread petechial hemorrhages and a yellow, friable liver. Histologically, CNS changes are surprisingly mild and nonspecific. Most lesions are cerebellar with proteinaceous fluid around vessels, especially in the meninges. There is diffuse vacuolation of hepatocytes and bile duct proliferation.

Kikuyu Grass Poisoning

A multiorgan disease characterized by peracute onset obtundation, ataxia, drooling of saliva, sham drinking, ruminal distention, and colic occurs in cattle and, to a much lesser extent, sheep and goats of New Zealand and Australia that are grazing kikuyu grass *(Pennisetum clandestinum).*[41] A review of 9 reports involving 2719 cattle at risk reported a 23% morbidity rate and 70% case-fatality rate.[41] The cause and pathogenesis are poorly understood.

Canarygrass Staggers (*Phalaris* Staggers)

Phalaris poisoning has been reported in Australia, New Zealand, South Africa, Norway, Argentina, and the United States, in association with the ingestion of *Phalaris* spp. grasses by sheep and cattle, most notably *P. aquatica* (bulbous canarygrass or hardinggrass) and *P. arundinacea* (reed canarygrass).[42] These outbreaks have involved either sudden death due to peracute brain dysfunction (termed *polioencephalomalacia-like sudden death*) or myocardial dysfunction (termed *cardiac sudden death*).[43,44] Sheep are considered to be the most susceptible species, but cattle are also affected.[45] Only the cardiac sudden death syndrome has been reported in horses.[46,47] In the United States, outbreaks of canarygrass staggers have been reported in sheep and feedlot lambs in California *(P. aquatica),*[48,49] as well as sheep and cows in Louisiana *(P. caroliniana)*[50] and cows in West Virginia *(P. arundinacea).*[45]

It has been suggested that phenylethylamines or derivatives of tyramine are involved in sudden death syndromes.[42,51] Staggers occurs as either an acute and reversible or a chronic, irreversible, and typically lethal form. The latter, more common, presentation usually occurs as outbreaks. Delayed or chronic *Phalaris* staggers is associated with tryptamine alkaloids produced by the plant that structurally resembles serotonin.[42,51] These alkaloids act as serotonergic receptor agonists, and accumulation within serotonergic tracts of the CNS eventually results in staggers signs. Rapid growth of canarygrass favors the formation and accumulation of toxin. Other factors that enhance the toxicity of canarygrass pasture include fog, humidity, or rain, followed by sunny, warm weather or sunshine on nitrogen-fertilized pastures.[52] Grazing animals are not usually affected until *Phalaris* spp. grasses comprise more than 50% of the diet.[53] The concentration of tryptamine alkaloids may be reduced by curing the forage as hay. By contrast, ensiling canarygrass does not reduce the amount of toxin.[54]

Staggers occurs after exposures of from 5 days to 33 weeks. Signs may be delayed for as long as 4 months after removal from the toxic grass.[50] Characteristic early clinical signs in sheep are constant anxious observation of handlers and continuous twitching ear movements. Signs progress to include hyperexcitability, exaggerated responses to auditory or tactile stimuli, fine muscular fasciculations (particularly of masseter muscles), licking of the lips, wrinkling of the facial muscles, repetitive chewing, inability to swallow, flaring of the nostrils, ptyalism, nystagmus, intention tremor of the head, ear and tail twitching, basewide stance, reduced menace response, and deficient pupillary reflexes.[55] The gait of affected sheep is described as stiff legged, with both hindlimbs moving in unison at gaits above the trot ("bunny-hopping"). Affected sheep and cattle may buckle at the knees and assume sternal recumbency with the hindquarters elevated.[45,53] They then fall into lateral recumbency and flail wildly while attempting to stand. Poisoned cattle also become uncoordinated and may have distinctive stabbing movements of the tongue and inability to prehend forage.[56] They salivate profusely and drop feed from the mouth. Eventually the animals die from starvation. There may be increased protein concentration (40 to 100 mg/dL) and nucleated cell count (up to 50 mononuclear cells/μL) in CSF of affected animals.[48] Animals may survive the initial signs but have neurologic signs that wax and wane for up to 10 months. For confirmation of a diagnosis, tryptamine alkaloids in suspect grasses can be quantified by ELISA.[57] Concentrations greater than 30 to 50 mg/100 g dry weight of forage are considered toxic for sheep.[52,55]

The pathologic lesions in the CNS of affected animals are characteristic and include focal, demarcated, blue-green or slate-gray discoloration in the brainstem and corticomedullary junction of the kidney; intracytoplasmic accumulations of yellow-brown pigment in the dorsal root ganglia, brainstem nuclei, and ventral horns of the gray matter of the spinal cord; neuronal loss; focal gliosis; and swelling of axonal sheaths in the ventromedial aspect of the spinal cord.[45,48,53] The pigment is thought to originate from deamination of the toxic alkylamines, but their presence does not correlate well with the development of neurologic deficits.[55]

Administration of cobalt to animals on toxic grass pastures is protective. In the presence of cobalt, rumen microflora inactivate toxic alkaloids. Weekly administration of 28 mg of cobalt to each animal was required experimentally to prevent clinical signs in

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exposed sheep.[58,59] Additional recommendations include removal of affected animals from the offending pasture, sedation with a phenothiazine tranquilizer, and administration of sodium pentobarbital or diazepam to convulsive animals. *Phalaris* plants may also contain potentially toxic concentrations of nitrate or cyanide. In any outbreak of suspected *Phalaris* toxicosis with acute signs of sudden death, cyanide and nitrate poisonings should also be considered.[43]

Differential Diagnoses for Staggers Syndromes

Grass staggers is easily recognized by clinical signs. The specific plant involved must be identified by examination of the pasture forage. Tremorgenic diseases of adult cattle are common throughout most of the world. In addition to the syndromes discussed earlier, plants that may cause staggers syndromes include toxic storage syndromes including locoism induced by the swainsonine-containing plants *Swainsona luteola, Swainsona galegifolia, Astragalus,* and *Sida* spp. and the tremor syndrome induced by *Solanum dimidiatum, Solanum fastigiatum,* and *Solanum viarum*. Hypomagnesemia causes grass staggers and has been reported to cause cerebellar degeneration under some circumstances. The genetic storage diseases α- and β-mannosidosis, generalized glycogenosis, globoid cell leukodystrophy, and neuronal lipodystrophy may also be important differential diagnoses for ataxic animals with tremor and cerebellar signs.

Multiple Congenital Central Nervous System Defects

Multiple congenital defects that are suspected or documented to have a heritable (genetic) basis have been described in large animals. Many, but not all, of these disorders involve signs referable to cerebellar dysfunction; others may have signs referable to spinal cord dysfunction. These defects along with others are presented at this point in the textbook in Table 35-6.

Diseases Presenting Principally with Spinal Cord or Peripheral Nerve Signs

Equine Herpesvirus Myeloencephalopathy

Robert J. MacKay

Equine herpesvirus 1 is a member of the Alphaherpesvirinae subfamily of Herpesviridae. Along with another alpha herpesvirus EHV-4, it is a common cause of upper respiratory disease in horses (see Chapter 31); more importantly, because of a predilection for cell-associated viremia and vasculitis, EHV-1 infection is associated with late-term abortion, death of neonatal foals, and spinal cord disease. There is a strong perception that outbreaks of the last of these syndromes, known as *equine herpesvirus myeloencephalopathy* (EHM), have over the past 20 years become more frequent and severe. The U.S. Department of Agriculture has suggested that EHM is an emerging disease on the basis of the following criterion: "A disease changes in severity, type of animal that can be infected, or other changes in pathogen behavior."[1]

Clinical Signs Acute onset of ataxia and tetraparesis of variable severity most often characterizes the neurologic form of EHV-1.[2,3] Signs usually appear between 6 and 10 days after infection. The severity of clinical signs can range from subtle pelvic limb ataxia and weakness to complete recumbency without limb or head movement. Nonneurologic signs including nasal and ocular discharge, limb edema, colic, ocular lesions, and anorexia may also be seen.[2-7] Horses may be febrile at presentation, but most are normothermic. Fever, often biphasic in profile, is the most consistent premonitory sign of neurologic disease, although not all febrile horses develop myeloencephalopathy. Coughing and nasal discharge or abortion sometimes accompany the neurologic signs or may have occurred during the preceding 2 weeks.[5,8,9]

The neurologic signs reflect injury to the white and gray matter of the spinal cord and include limb and truncal ataxia and paresis, bladder distention, urinary incontinence, weakness of the tail and anus, and reduced perineal sensation. There may be either penile paresis or persistent erection (priapism) during the first several days of clinical signs. Pelvic limbs are more severely affected than thoracic limbs, and signs are usually symmetric. In mild and moderately affected horses with EHM, there is often bladder distention with spastic detrusor tone without urethral relaxation (dyssynergia). Bladder atony and incontinence also occur, particularly in recumbent horses, and the associated dribbling of urine leads to secondary perineal scalding. Bladder rupture has occurred in such horses. Anal sphincter and caudal rectal tone may also be reduced, with consequent obstipation and gaping of the anus.

Signs of brain dysfunction including seizures, blindness, and cranial nerve dysfunction have been reported in a few cases of EHM.[10] Ocular lesions such as mydriasis, hypopyon, uveitis, and optic neuritis may also be present. The occurrence of multifocal chorioretinopathy, visible several weeks after onset of neurologic signs as foci of depigmentation, appears to be a particularly sensitive indicator of previous EHV-1 viremia.[11]

The clinical signs typically stabilize within 48 hours, and in most instances recumbency, if it occurs, begins during this period. Some horses continue to deteriorate and eventually die or are euthanized. In survivors, improvement begins within the first 5 to 7 days and may continue for weeks or even months. Many horses make a full clinical recovery; however, an unknown proportion still have residual signs of limb weakness or ataxia. Obviously, a horse that does not become recumbent during the first 2 days has a much better prognosis for survival.

Diagnosis A tentative diagnosis of EHM can be made on the basis of characteristic neurologic signs, history, and supporting findings on physical examination. A CSF analysis that shows a xanthochromic fluid with high protein concentration and normal or slightly high nucleated cell count (albuminocytologic dissociation) is typical and almost pathognomonic for EHM,[10,12] although cases with normal protein concentration and/or mononuclear pleocytosis occur occasionally.

Conventional, nested, or quantitative PCR amplification of EHV-1–specific gene sequences (usually glycoprotein B) in nasal swabs and EDTA-anticoagulated blood is the diagnostic technique of choice for horses with suspected EHM.[12] Both nasal swab and blood should be submitted at the acute stage of disease; nasal swabs alone are sufficient to monitor for release from quarantine in some jurisdictions. Nasal swabs are more likely to collect virus than are nasopharyngeal swabs.[13] Swabs for this purpose should be about 6 inches long with a synthetic shaft. After collection, the swab should be placed in viral transport medium and sent to the diagnostic laboratory. If transport media are not available, the swab can be broken into a sterile tube and transported. Positive samples can separately or simultaneously be analyzed for a single nucleotide variant in the viral DNA polymerase gene, DNA_{pol} D_{572}, that defines the best known and most important neuropathogenic strain of EHV-1. Real-time PCR provides quantification of viral DNA load and allows additional interpretation of the relevance of positive results.[12] It should be noted that these molecular diagnostic tests confirm active EHV-1 infection (and viremia when blood is positive) but do not per se confirm the diagnosis of EHM.

Additional aliquots of nasal swabs and anticoagulated blood should also be submitted for traditional virus isolation in tissue culture. Virus isolation is important to allow full characterization of outbreak viruses including susceptibility to candidate antiviral drugs.[14]

A fourfold or greater increase between acute and convalescent serum virus neutralizing (VN) or complement-fixation (CF) antibody titers in samples taken 7 to 21 days apart is presumptive

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TABLE 35-6

Congenital Diseases of Large Animals with CNS Signs and Mode of Inheritance, Where Known

Diseases with Predominant Intracranial Signs	Species and Breed(s) Affected	Clinical Signs/Ancillary Tests	Age of Onset	Mode of Inheritance	References
Ceroid lipofuscinosis	Ovine: South Hampshire, Swedish Landrace, Rambouillet Caprine: Nubian Cattle: Devon Horses: breeds not described	Progressive ataxia, blindness, depression, coma	Variable	Autosomal recessive	1-10
Citrullinemia	Cattle: Holstein	Progressive depression, bellowing, abnormal tongue and facial movements, convulsions, death Increased blood ammonia and citrulline concentrations	Newborns	Autosomal recessive	11-19
Exophthalmos and strabismus	Cattle: Jersey, Holstein, Brown Swiss, Shorthorn	Protrusion and crossing of the eyes	>6 mo	Unknown	20, 21
Cerebellar abiotrophy	Cattle: Holstein, Angus, Limousin	Intention tremors, hypermetria, basewide stance; may or may not progress	Variable	Suspected autosomal recessive	22-26
Bovine familial convulsions and ataxia	Cattle: Angus, Charolais, Polled Hereford, Angus Cross	Stillbirth/abortion with occasional dorsiflexion of the spine Intermittent cerebellar signs and convulsions	Variable, may improve with age	Autosomal dominant with incomplete penetrance	27-33
Cerebellar abiotrophy/ hypoplasia	Horses: Arabians, Arabian cross	Head tremor, ataxia, hypermetria	>2 mo	Autosomal recessive	34-39
Familial ataxia	Cattle: Hereford	Ataxia, abnormal head posture, pupillary dilatation	Newborns	Unknown	40
Micrognathia/cerebellar hypoplasia	Cattle: Angus	Stillbirth, brachygnathia, cerebellar hypoplasia	Stillborn	Suspected autosomal recessive	41
Alpha mannosidosis	Cattle: Angus, Murray Grey, Simmental, Galloway, Holstein	Stunted growth, ataxia, head tremor, hypermetria	1 wk-15 mo	Autosomal recessive	42-49
Beta mannosidosis	Cattle: Salers Goats: Anglo-Nubian	Recumbency, deafness, narrow palpebral fissures, intentional head tremor, rotatory head movements, ocular defects, joint abnormalities, domed skull	Newborns	Autosomal recessive	50-71
Generalized glycogenolysis (beta-galactosidase deficiency, GM1 gangliosidosis)	Sheep: multiple breeds Cattle: Holsteins	Lethargy, anorexia; head carried low and extended; blind, collapse when head moved	>1 mo	Suspected autosomal recessive	72-83
Bovine generalized glycogenosis (type II glycogenosis, Pompe disease)	Cattle: Shorthorn, Brahman	Weakness, tremors, ataxia, right-sided heart failure	2-3 mo	Autosomal recessive	84-93
Globoid cell leukodystrophy (Krabbe disease)	Sheep: Polled Dorset	Depression, head tremor, ataxia, hyperesthesia	>4 mo	Unknown	94, 95
Neuronal lipodystrophy	Cattle: Angus, Beefmaster Sheep: Breeds not described	Depression, blindness, circling, seizures, coma	>10 mo	Unknown	96-98
Shaker calf syndrome	Cattle: Horned Hereford	Recumbency, hypermetria, hypertonia, hyperesthesia, muscle tremors	Newborns	Unknown	99
Maple syrup urine disease	Cattle: Hereford, Polled Shorthorn	Viscous, dark, malodorous urine; fever, depression, opisthotonos, myoclonus, convulsions; spongiform changes in brain	Newborns	Autosomal recessive	100-116

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TABLE 35-6

Congenital Diseases of Large Animals with CNS Signs and Mode of Inheritance, Where Known—cont'd

Diseases with Predominant Intracranial Signs	Species and Breed(s) Affected	Clinical Signs/Ancillary Tests	Age of Onset	Mode of Inheritance	References
Hereditary neuraxial edema	Cattle: Polled and Horned Herefords, Hereford × Friesian	Inability to rise; hyperesthesia, myoclonus, extensor rigidity, and apnea/dyspnea when stimulated	Newborns (may be stillborn)	Suspected autosomal recessive	117-125
Epilepsy	Cattle, horses	See text			
Narcolepsy/cataplexy	Horses, cattle, sheep	See text			
Diseases with Predominant Spinal/Motor Nerve/Muscle Signs					
Inherited myoclonus	Horses: Peruvian Paso	Myoclonus in response to stimuli, bunny-hopping gait; may not be able to stand without assistance	Newborns	Unknown; deficiency of receptors for the inhibitory neurotransmitter GABA	126
Congenital encephalomyelopathy	Horses: Quarter Horse	Inability to stand; when assisted to stand, hindlimb tremors cause the hindlimbs to bounce off the ground; increased patellar reflexes		Unknown	127
Systemic neuraxonal dystrophy	Sheep: Suffolk	Progressive hindlimb ataxia leading to recumbency	>1 mo	Suspected autosomal recessive	128-129
Weaver syndrome (bovine progressive degenerative myeloencephalopathy)	Cattle: Brown Swiss, Angler	Progressive paraparesis, hindlimb ataxia with proprioceptive deficits, muscle tremors, recumbency	>5 mo	Autosomal recessive	130-146
Progressive spinal myelinopathy	Cattle: Murray Grey	Unable to stand; progressive hindlimb hypertonia and proprioceptive deficits	Newborns	Autosomal recessive	147-148
Bovine spinal muscular atrophy	Cattle: Brown Swiss, Red Swiss, Braunvieh, Holstein	Progressive muscle atrophy leading to recumbency	>2 wk	Autosomal recessive	149-157
Spinal dysmyelination	Cattle: Braunveih, Braunvieh Cross	Unable to stand, generalized tremors, muscle atrophy	Newborns	Autosomal recessive	158-160
Neuropathy/myopathy/glomerulopathy	Cattle: Gelbveih	Progressive hindlimb ataxia and paraparesis, muscle atrophy, reduced anal tone; proteinuria	Few weeks-1 yr	Unknown	161-162
Progressive ataxia	Cattle: Charolais, Charolais Cross	Progressive paraparesis and hindlimb ataxia, proprioceptive deficits; muscle/tail tremors on rising	>6 mo	Suspected autosomal recessive	163-172
Spastic paresis (Elso heel)	Cattle: multiple breeds	Intermittent extensor spasticity and hypertonia of one or both hindlimbs; hyperextension of hock during weight bearing	>3 wk	Unknown	173-195
Inherited periodic spasticity (crampy syndrome, barn cramps, Krampfigkeit)	Cattle: dairy breeds	Intermittent muscular spasms of hip and upper hindlimb muscles, simultaneous kyphosis	>3 yr	Suspected autosomal dominant with incomplete penetrance	196-200
Hereditary lethal spasms (Doddler syndrome)	Cattle: Jersey	Unable to stand, head and neck spasms when stimulated, convulsions, death	Newborns	Suspected autosomal recessive	201-202
Congenital abnormalities of the vertebrae and/or spinal cord	Multiple species	See text			

evidence of EHV-1 infection.[12] These tests are of limited value, however, because they do not distinguish between EHV-1 and EHV-4 responses and results are delayed several weeks. An ELISA that distinguishes between infections with these two viruses is available commercially outside the United States[15] and is the serologic diagnostic of choice. A practical approach to an outbreak that may involve many horses is to submit serum from both clinical and in-contact/cohoused horses for serology and samples for PCR only from horses with clinical signs of fever and/or EHM. Such an approach provides additional support for the diagnosis and defines the extent of exposure to the virus during the outbreak.

Pathophysiology After initial colonization of the epithelia of the upper respiratory tract, EHV-1 spreads to and amplifies in regional lymph nodes before circulating in the blood within leukocytes. The magnitude and duration of the leukocyte-associated

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viremia are positively related to the risk for EHM.[12,16] Virus is presumed to enter endothelial cells of small arterioles of CNS after binding to its surface MHC-1 receptor. Endothelial infection incites destructive innate and specific immune inflammatory responses, which in turn initiate coagulation and widespread arterial microthrombosis and hemorrhage. Viral replication within neurons has not been demonstrated in EHM; rather, neuronal injury is secondary to ischemia secondary to vasculitis and thrombosis.

Epidemiology Herpesvirus infection is enzootic in the horse population. Infection usually occurs through the respiratory epithelium when the animal comes in contact with the virus in aerosolized droplets or via fomites contaminated with fluids from an abortion or in ocular, nasal, or other respiratory tract secretions.[3,10] Foals likely become infected with virus shed from their dams during recrudescence of latent infections.[12] Most horses first become infected before 1 year of age and remain infected with latent virus in the trigeminal ganglia or in lymphoid tissues around the head.[12,14] Surveys of necropsied adult horses indicate that more than 50% of normal horses are latently infected by EHV-1 in one or both of these sites.[12]

EHM is rare, but cases have been reported worldwide. Outbreaks occur more commonly in Europe and the United States than they do in Australia and New Zealand.[12] Viral polymorphism undoubtedly accounts for differences in neurovirulence. Viruses with one allele of a single nucleotide polymorphism in the viral DNA polymerase gene, D_{752},[17] were found to be 162 times more likely to cause EHM than were viruses with the alternative allele N_{752}.[18] The mechanism for enhanced neuropathogenicity of D_{752} partly relates to higher-order viremia in infected horses compared with that in horses infected with N_{752} but is not due to greater neurotropism. It is common for horses to be latently infected with both variants (D_{752} and N_{752}), and there is no evidence that horses latently infected with the neuropathogenic strain pose a higher risk of being the source of future EHM outbreaks.[12] Polymorphism elsewhere in the genome likely also modulates neurovirulence.[9] During outbreaks, the virus appears to be spread readily and both morbidity and mortality can be high.

Horses of any age, gender, or breed are susceptible. In some studies females in general, or mature pregnant or lactating mares, are most often affected.[7,16,19] The principal risk factor for development of EHM is fever, especially the second peak of a biphasic fever.[6] The onset of neurologic signs often follows closely the decline from peak temperature. Additional purported risk factors in at least some outbreaks were older age,[6,7] cooler seasons (all but summer), introduction of horses to a herd,[7,8] and inconsistent outbreak-specific breed susceptibilities.[7,8,12] Foals are rarely affected. Mules and donkeys are infected and shed virus but apparently do not develop EHM.[20] Frequent (up to four times annually[6,19]) and recent[19] vaccination against EHV-1 have been reported as risk factors; however, age was an important covariable in the former study and confounded interpretation of any role of vaccination.[12] Stress-associated recrudescence of latent infections and subsequent shedding without clinical signs has been difficult to confirm experimentally but undoubtedly is important in the initiation of some outbreaks, especially those occurring after long-distance transportation or in closed herds. Experimentally infected horses may nasally shed virus for 3 weeks or longer after infection; however, viral shedding was not found after 9 days after onset of clinical signs in 20 horses with EHM.[21]

Primary attack rates, as judged by occurrence of fever (usually defined as rectal temperature >101.5° F) among at-risk horses may be up to 90%; an average of 10% of these infected horses develop EHM, and mortality rates for horses with EHM are typically between 20% and 80%, with 50% a typical rate.[3,12] There is no report of EHM caused by modified live virus vaccines currently approved for use in horses.

Necropsy Findings Gross and histologic lesions are not always limited to the CNS. Ocular lesions including hypopyon, iritis, and chorioretinitis have been reported. Cystitis and scrotal edema may be present. Focal areas of hemorrhage may be found throughout the brain and spinal cord parenchyma and meninges. Vasculitis and thrombosis of the small arteries and veins of the spinal cord and brain results in ischemic lesions in the CNS.[22,23] Equine herpesvirus is infrequently cultured from the CNS, but PCR, in situ hybridization, and immunohistochemistry can be performed on CNS tissues obtained postmortem to confirm the presence of the virus.[12]

Treatment Acyclovir is guanosine analog with in vitro activity against EHV-1 that has been used successfully for treatment of herpes simplex encephalitis in humans. Adequate blood levels of acyclovir can be achieved in horses by oral dosing of valacyclovir (30 mg/kg q8h for 2 days and then 20 mg/kg q12h) or IV administration of acyclovir (10 mg/kg q12h) but not by oral acyclovir.[24] Valacyclovir is now available as a generic but still costs $150 to $300 daily to treat a 500-kg horse. Unfortunately, on the basis of limited experimental and anecdotal clinical reports, valacyclovir, although safe, is not effective in horses with EHM.[25] In light of the scant evidence available, however, valacyclovir treatment is still worthwhile when economic circumstances permit. Ganciclovir may be more effective than valacyclovir in preventing clinical signs in horses experimentally infected with EHV-1 (see Prevention section later),[25] but its efficacy in treating horses with EHM has not been evaluated.

Supportive care is the most important aspect of treatment for equine herpes myeloencephalopathy. Measures include bladder decompression by sterile catheterization at least twice daily for horses with bladder distention and/or incontinence, evacuation of the rectum, administration of intravenous or oral fluids, and enteral or parenteral nutritional support. Recumbent horses must be appropriately padded, and decubital lesions must be prevented or treated. Horses that are recumbent but able to support their weight when lifted should be managed with an abdominal sling.

Administration of antiinflammatory drugs soon after the onset of neurologic signs may be beneficial. NSAIDs (e.g., flunixin meglumine 1.1 mg/kg IV q12-24h) should be used if the horse is febrile or there is clinical suspicion of a painful condition, but there is no evidence that NSAIDs affect the course of neurologic signs. Corticosteroids are often used because of presumed suppression of vasculitis, and although no objective data for their efficacy are available, there is a solid theoretical basis for their use.[12] Dexamethasone (0.05 to 0.1 mg/kg IV or IM) can be given q12-24h for 3 to 5 days, with the dosage then tapered for 1 to 3 days. There are unquantifiable risks related to steroid-induced immunosuppression including increased susceptibility to bacterial infection of the urinary tract and reactivation of latent virus. Because of uncertainties as to its benefits and risks, steroid treatment should be reserved for horses that are recumbent or in imminent danger of becoming so. Dimethyl sulfoxide (DMSO; 1 g/kg as a 10% solution in polyionic fluids by slow IV infusion) every 12 to 24 hours is often used, although its efficacy has not been documented.

Use of antibiotics should be considered if the horse is recumbent or has urinary tract or respiratory tract involvement. Chronic cystitis, sometimes associated with bacteria resistant to common antimicrobials, is a common complication of urinary incontinence and bladder catheterization in horses with EHM. Management of such cases is discussed in Chapter 34.

The lesions of EHM are characterized by both microvascular thrombosis and hemorrhage, so there is as of yet no compelling rationale for the use of anticoagulant therapy in horses with EHM.

Control and Prevention Vaccines currently used to prevent EHV-1 respiratory and abortion syndromes do not claim to prevent EHM, and there is no reliable evidence that they do. A small study concluded that modified live virus vaccine provided modest albeit significantly better protection against experimentally induced EHM than did a killed low-antigen vaccine,[26] although the duration and robustness of such protection, if any, are not yet clear. Vaccination with inactivated "high-antigen" vaccines (i.e., those with a label claim

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for prevention of herpesvirus abortion), enhanced adjuvant vaccines, or modified live vaccine does have the important effect of reducing nasal shedding and thus potentially limiting the spread of infection during an outbreak. This rationale has also been used to justify booster vaccination of at-risk horses during an outbreak. Because of persistent evidence-based concerns about inducing or exacerbating EHM by excessive and recent vaccination, however,[6,19] this practice remains controversial.

Immunostimulants are sometimes administered to horses at risk for EHM on the basis of the theory that immune system activation will prevent viral reactivation or replication,[12] but supportive evidence is lacking. Provision of nutritional supplements containing zinc protected horses exposed during an EHM outbreak from developing the disease according to a retrospective study of horses involved in the 2011 Ogden, Utah, outbreak.[19]

Valacyclovir and valganciclovir are prodrugs of the antiviral agents acyclovir and ganciclovir that have adequate bioavailability in horses when given orally.[24] Although these agents have in vitro activity against EHV-1, valacyclovir and ganciclovir were not effective at preventing EHM when either one was 4 to 6 days after viral inoculation (i.e., at the onset of the second temperature rise).[25] Ganciclovir, but not valacyclovir, reduced the severity of ataxia. Therefore if these drugs are tried as preventatives, they should be used no later than the onset of the initial febrile period with the understanding that there are no data for preventive efficacy in this setting.

Protocols for management of premises with EHM cases are now well established and tested. The reader is referred to the comprehensive and regularly updated guidelines available from the American Association of Equine Practitioners (AAEP; http://www.aaep.org/). In addition, the British Horserace Betting Levy Board publishes Codes of Practice on Equine Diseases (http://codes.hblb.org.uk/). In brief, the essentials of these protocols are (1) isolate affected horses; (2) monitor temperatures twice daily on all quarantined horses; (3) submit diagnostic samples; and (4) implement robust biosecurity procedures.[12] There is still uncertainty about the length of quarantine required after the last occurrence of fever in any horse. AAEP guidelines currently call for 28 days. A workable but expensive alternative is to require 14 days after the last fever in any quarantined horse, then test all horses for nasal shedding by PCR on swabs taken on 2 to 4 successive days.[12] It is essential that all guidelines are followed meticulously; each new fever resets the quarantine clock for another month. Biosecurity procedures for EHM caused by neuropathogenic and nonneuropathogenic strains should be the same.[11] Additional guidelines are available for measures designed to prevent or reduce the likelihood of outbreaks and to lessen the impact of those outbreaks that do occur.[12]

Equine Protozoal Myeloencephalitis

Robert J. MacKay

Equine protozoal myeloencephalitis (EPM) is the most common infectious neurologic disease of horses in the United States, and *Sarcocystis neurona* is the usual cause, with sporadic cases caused by *Neospora hughesi*.[1,2] Species of *Sarcocystis* have an obligatory definitive host such as a dog, cat, opossum, skunk, or raccoon, which passes the oocysts (sporocysts) to the herbivore via fecal contamination.[3] Sexual reproduction occurs in the lining of the small intestine of the definitive host, the opossum (*Didelphis virginiana* in North America and *Didelphis albiventris* in South America), while asexual proliferation occurs in the intermediate host and culminates in the formation of sarcocysts in muscle. The nine-banded armadillo, striped skunk, raccoon, and domestic cat are natural intermediate hosts that cover the geographic range in which EPM occurs.[4-7] The hosts for *N. hughesi* are not known. The horse usually functions as an aberrant dead-end intermediate host. With the exception of a single foal with *S. neurona* muscle sarcocysts,[8] only precystic stages (i.e., merozoites and schizonts) have been found in the CNS of horses with EPM.

Pathogenesis

The pathophysiology and immunology of *S. neurona* infection in horses is not completely understood. Horses ingest the infective sporocyst stage of *S. neurona* in food and water that has been contaminated by opossum feces. The mechanism of entry into the CNS of the horse is likely related to leukocyte-associated parasitemia. Once in the CNS, *S. neurona* can localize and replicate in any region, from cerebrum to spinal cord. Peripheral nerves and nerve roots are not infected. The location and extent of the lesions determine the character and severity of clinical signs. Histologically, protozoa are usually associated with mixed inflammatory cellular responses and neuronal destruction. Schizonts (multicellular proliferative bodies) or free merozoites are seen commonly in the cytoplasm of neurons or mononuclear phagocytes and in capillary endothelial cells or rarely in other inflammatory or CNS cells.[3]

Both cellular and humoral immunity are thought to be important for control of infection by *S. neurona*. Because of the intracellular location of the parasite, competent cell-mediated adaptive immune responses are considered essential for its elimination.

Epidemiology

Equine protozoal myeloencephalitis is a disease of horses that have spent time in North or South America. There are isolated reports of horses diagnosed with EPM elsewhere that have no travel history to the Americas, and the nature of infection in these cases remains unclear. [9,10] Horses of all breeds can be affected by EPM and there is no gender bias. There is only one report of EPM in a pony and one describing *N. hughesi* in a mule, suggesting that these equids may be less susceptible to EPM than are horses. Ages at onset have ranged from 2 months to at least 30 years, although it is rare in horses younger than 2 years old. One study identified an increased risk of EPM in horses aged 1 to 4 years and older than 14 years.[11] EPM typically occurs as individual cases, but clusters of cases have occasionally been reported.[12]

The reported prevalence of *S. neurona* infection as evidenced by *S. neurona* antibodies in horses in various locations throughout the U.S. varies from 0% to 89.2%.[13,14] Generally high rates are found in areas with dense human populations, abundant water sources, and moderate rainfalls; low seropositivity rates are found in arid, sparsely populated regions. The geographic variation in prevalence is accounted for by the still-expanding range of the definitive host, the opossum. Despite the high rate of infection by *S. neurona,* there is probably only about a 1% lifetime risk of a horse developing EPM in these areas (estimated from the mean 0.14% one-year incidence reported in the *National Animal Health Monitoring System 1996* survey[11]).

The factors that influence the relationship between infection with *S. neurona* and development of EPM are not well understood. Although *S. neurona* lacks the genetic diversity found among *Toxoplasma gondii* isolates, it may still be capable of *T. gondii*–like clonal expansion of virulent strains,[15] although conclusive evidence for this has not yet been found. Results of risk factor analysis for EPM vary by study, but factors likely to increase exposure to opossums, their environment, and their feces are consistently identified.[11,16-18] Other risk factors include previous diagnosis of EPM on the premises; primary use of the horse, with showhorses and racehorses at increased risk; recent transport; and recent adverse health events including medical problems, parturition, and management changes. Collectively, these risk factors indicate that physiologic stress may play an important role in the onset of EPM.

Diagnosis

Antemortem diagnosis of EPM remains challenging. Criteria for diagnosis include finding clinical signs consistent with EPM, ruling out other differential diagnoses, and finding *S. neurona*–specific antibodies through immunodiagnostic testing. Proof of diagnosis postmortem is demonstration of protozoa in CNS lesions, often done with immunohistochemical staining or polymerase chain reaction. Even when the organism is not seen, the diagnosis is frequently made presumptively if characteristic inflammatory changes are found.[19,20]

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Two types of immunodiagnostic tests are available for EPM: those that rely on threshold values of serum anti–*S. neurona* antibody (indirect fluorescent antibody test, ELISAs for antibody against various *S. neurona* surface antigens) and those that purport to detect specific antibody made within the CNS (Western blot, serum-to-CSF antibody ratios, *C* values). Blood samples for serum tests are easily obtained, but the diagnostic assays are based on the yet-to-be validated principle that horses with EPM have distinctly higher serum antibody concentrations than do exposed/subclinically infected horses.[21] The rationale for tests of the second type, each of which requires a clean CSF sample, is that identification of CNS-origin antibody is the only way to discriminate EPM cases from exposed horses. The most popular test of each type—namely, serum IFAT and snSAG2,4/3 ratio, both have reported good (i.e., >80%) sensitivity and specificity for diagnosis of EPM among horses with solid postmortem diagnoses.[22,23] One drawback of the IFAT is that it is unable to differentiate between antibodies against *S. neurona* and *S. fayeri* (a nonpathogenic species),[24] but an advantage is that submitted samples are tested for both *S. neurona* and *N. hughesi* antibodies. A recent study used samples from necropsy-confirmed EPM positive and negative cases to specifically compare results of serum IFAT and snSAG2,4/3 serum-to-CSF ratio tests. Sensitivity, specificity, and accuracy values were 59%, 71%, and 68% for the serum IFAT and 88%, 100%, and 97% for the snSAG2,4/3 ratio test.[20] Further large comparative clinical studies are necessary to determine clearly the relative utilities of these two approaches, although the lack of a gold standard for diagnosis in horses that are not subjected to necropsy makes this challenging. What is clear, on the basis of both flawed concepts and unsupportive clinical data, is that neither CSF Western blot nor serum SAG-1 ELISA is a robust diagnostic test for EPM.[25-27] In contrast to the situation with Western blots, snSAG ratio test results are relatively robust in the presence of a small amount of contaminating blood; however, false positives do occur in cases of moderate or severe blood-brain barrier (BBB) injury. For samples from horses with BBB injury (as detected by high CSF albumin concentrations or high albumin quotient values[28]), additional total IgG testing is performed on the serum/CSF sample and a C value is calculated.[29] CNS antibody production is indicated by C values greater than 1.

At the time it was last investigated more than a decade ago, PCR testing of CSF had high specificity but low sensitivity for the diagnosis of EPM.[30] False negatives are common because free parasitic DNA is destroyed by enzymes in the CSF and merozoites rarely enter the CSF. Testing by PCR of tissue samples is useful for postmortem diagnosis.

Ancillary procedures including survey cervical radiographs, lameness examination, and serology may be required to rule out competing differential diagnoses. In horses with signs of brain involvement, suggestive lesions may be seen with advanced imaging techniques.[31] Consistent abnormalities are not found in complete and differential WBC counts and serum chemistry panels in horses with EPM. Abnormal CSF values occur in some horses with EPM. It has been reported that up to 35% of horses at a referral hospital have increased protein concentration (>65 mg/dL) or nucleated cell count (>6 cells/μL).[32] In the author's experience, in horses with mild clinical signs of EPM (i.e., those that typically are encountered in practice), a low percentage have any abnormality on routine CSF analysis. Creatine kinase (CK) activity may be high in CSF, reflecting diffusion of the BB isoenzyme from damaged CNS gray matter.[33] Unfortunately, inadvertent inclusion of a small plug of epidural fat or dura during CSF collection can dramatically elevate CK activity, thus reducing the specificity of the test.

Clinical Signs Protozoa may infect any part of the CNS, making almost any neurologic sign possible. The disease usually begins insidiously but also may present acutely and be severe at onset. Signs of spinal cord involvement are seen much more commonly than signs of brain disease. Horses with EPM involving the spinal cord have asymmetric (usual) or symmetric truncal and limb weakness and ataxia. If all lesions are behind the second thoracic spinal cord segment (T2), only the pelvic limbs are affected. If a lesion (or lesions) is located in front of T3, all four limbs may be affected. In the rare instance when the spinal cord behind the second sacral spinal cord segment (S2) is involved, there are signs of cauda equina syndrome, which may include degrees of rectal, anal, bladder and penile paralysis, and reduced sensation of the skin of the tail and perineum. When gray matter of the ventral horn of the spinal cord is damaged for more than 1 to 2 weeks, there may be obvious focal muscle atrophy and electromyographic changes in denervated muscle. Common locations for atrophy in horses with EPM are the gluteal, biceps femoris, and infraspinatus/supraspinatus and serratus ventralis muscles. Lesions in the spinal cord may also result in demarcated areas of spontaneous sweating or loss of reflexes and cutaneous sensation.



FIG. 35-14 Obtundation, right-sided head tilt neck turn and body lean in a 3-year-old Thoroughbred colt with peracute-onset equine protozoal myeloencephalitis.

Neurologic signs noticed at the walk or during neurologic examination include any to all of the following: asymmetric stride length, toe dragging, circumduction of pelvic limbs, and hypometria (also described as floating or marching) of thoracic limbs. Other signs are noted only when the horse is ridden. There may be difficulty maintaining a specific lead, cross-cantering or cross-galloping, and difficulty negotiating turns. Some signs that are usually attributed to primary musculoskeletal disease, such as back soreness or upward fixation of the patella(s), can be caused by weak or asymmetric use of muscle groups in horses with EPM that are in training.

The most common manifestation of brain disease in horses with EPM is a brainstem syndrome with signs of obtundation and asymmetric vestibular (VIII) nerve dysfunction (Fig. 35-14). There may also be facial paralysis (VII); dysphagia (X); tongue paralysis (XII); laryngeal paralysis (X); strabismus (III, IV, IV); failure of globe retraction (VI); and deviation of the mandible (Vm). With involvement of the rostral brainstem or cerebrum, EPM may manifest as seizures, visual deficit/abnormal menace response, reduced perception of touch on the opposite side of the face, or behavioral abnormality.

Without treatment, EPM usually progresses. Progression to recumbency occurs over hours to years and may occur steadily or in a stop-start manner.

Treatment Since 2000, the folate inhibitor combination sulfadiazine/pyrimethamine (SDZ/PYR), the triazine coccidiostats

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ponazuril (PNZ) and diclazuril (DCZ), and the nitrothiazole nitazoxanide (NTZ) have all been licensed by the U.S. Food and Drug Administration (FDA) for the treatment of EPM and commercial products have been launched.[34] NTZ was withdrawn in 2009. Multicenter studies of SDZ/PYR, PNZ, NTZ, and DCZ reported improvement rates of 57.1% to 61.5%.[34]

Many dosage permutations and combinations of these products and the use of pharmacologically similar products occur in clinical practice, although efficacies have not been investigated. A loading dose of 15 mg/kg PNZ (three times the normal dose) achieves steady-state concentrations of PNZ several days earlier than is the case with conventional dosing.[35] A sodium salt formulation of diclazuril has been shown to have good oral bioavailability and may have potential as a feed additive.[36] Some veterinarians use a compounded form of diclazuril IV, although there are no published data for its safety or efficacy. There is experimental support for the enhanced antiprotozoal effect of combinations of PYR with either DCZ or PNZ in treatment of other coccidian infections,[37] so the author routinely combines PNZ and SDZ/PYR when treating horses for clients with the necessary financial resources. Such treatments constitute unapproved and/or extra-label use, albeit of FDA-approved products.

Another drug used commonly as an anticoccidial in calves, decoquinate, was evaluated in horses with presumptive EPM, at dosage of 0.5 mg/kg daily for 10 days, in combination with the immunomodulator levamisole, 1 mg/kg daily.[38] Success rates of 93.6% and 89.3% were reported on the basis of improved neurologic gait score at the end of treatment and reversion of serum snSAG1,5,6 titers, respectively. Decoquinate was also shown to have potent inhibitory and cidal activity in vitro against two different isolates of *S. neurona*.[39] If this drug combination continues to perform well in wider use, it will obviously become an important treatment option.

Horses may relapse soon after the initial course of treatment is discontinued, or up to several years after improvement or apparent resolution of signs. Although there is no consensus on how to treat relapses, the authors prefer to change or add antiprotozoal drugs. If a horse relapses twice, the author usually recommends indefinite intermittent therapy with SDZ/PYR, 2 days/week at double the standard dose. A similar rationale can be used to treat horses only around stressful events that may predispose to relapses.

Of the available drugs, only PYR has significant adverse side effects. Toxicity reflects inhibition of mammalian dihydrofolate reductase by PYR, inducing folate deficiency. Signs include reproductive and neonatal disorders, glossitis, and bone marrow suppression including anemia, leukopenia, neutropenia, and thrombocytopenia in decreasing frequency.[40,41] Horses treated with SDZ/PYR should be kept on good-quality green forage (e.g., alfalfa hay or pasture), which is likely to be rich in folate. There is no advantage to supplementation with folic acid during treatment, and some evidence from other species indicates that this practice could increase the possibility of toxicity.[41] Most cases of bone marrow suppression resolve if treatment is suspended for 1 to 2 weeks. Folic acid (100 mg daily) is appropriate for treatment of folate deficiency once PYR is discontinued. If signs are severe, treatment with folinic acid (100 mg PO daily for 1 month, then every other day for 1 month) is indicated.

In mild acute cases of EPM (grade 1), additional therapy is unnecessary. In horses with moderate or severe disease, antiinflammatory and antioxidant treatment is usually provided for the first 1 to 2 weeks. If the horse is grade 3 or worse, a corticosteroid may be added. Vitamin E is often given empirically throughout the period of antiprotozoal treatment for additional antioxidant effect. Oral administration of vitamin E has been shown to result in increased concentrations of alpha-tocopherol in serum and CSF. As a relatively crude way to address putative immunodeficiency and "boost" cellular immunity, immune stimulants are sometimes given to horses with EPM.

Prognosis On the basis of drug efficacy studies and clinical experience, it is reasonable to expect that about 60% of moderately or severely affected horses will improve at least one grade after treatment. Only 10% to 20% of such horses will completely recover, and 10% to 20% of successfully treated horses will suffer at least one relapse. The outlook for mildly affected horses (grade 1) is considerably better, particularly if treatment is begun promptly. Although there are no published data for the latter, more common class of treated horse, at least 80% of such cases can be expected to improve and at least 50% should recover completely, with low possibility of recurrence.

Prevention An inactivated vaccine was marketed under conditional approval by the U.S. Department of Agriculture. The conditional license lapsed in March 2008, and the vaccine is no longer available. There was no published evidence for or against preventative efficacy for this product.

Prevention of EPM by antiprotozoal agents is probably effective but probably cost prohibitive. Prevention of infection by *S. neurona* may be possible by daily administration of a drug such as DCZ or PNZ.[42] The disadvantage of this approach is that normal immune responses to the organism may be prevented. An alternative approach is metaphylaxis, wherein intermittent doses of drug are given to allow an initial round of protozoal proliferation and normal immune responses to take place but prevent invasion of the CNS. Ponazuril given at 20 mg/kg every 7 days but not every 14 days significantly reduced *S. neurona* antibody in the CSF of *S. neurona*–challenged horses, suggesting the potential utility of such an approach.[43]

Common-sense measures can be instituted to prevent contamination of feed with *S. neurona* sporocysts. Opossums can be trapped and removed or kept away by free-ranging dogs. Spilled grain, fallen fruit, and animal or bird feed should be removed, and horse food sources should be monitored and secured. The utility of controlling intermediate hosts in an effort to reduce environmental sporocyst load is doubtful; however, if there are heavy populations of host animals on a problem premise, then such animals should be trapped and removed. Products useful for cleaning of areas potentially contaminated with sporocysts have been described.[44]

Cervical Vertebral Stenotic Myelopathy

Robert J. MacKay

The term *wobbler* (also wobbler syndrome) describes horses with ataxia caused by any of a group of developmental anomalies and degenerative conditions involving the cervical vertebrae.[1] Several more or less descriptive abbreviations are used in wobbler terminology. The most important of these are CVM (cervical vertebral malformation and malarticulation), CSM (cervical stenotic myelopathy), and the inelegant but descriptive CVSM (cervical vertebral stenotic myelopathy). CVSM is the most common noninfectious neurologic disease of horses. The prevalence of CVSM among 1289 Thoroughbred horses born on four breeding operations was 1.3%.[2]

Two overlapping CVSM syndromes are recognized, differing greatly in developmental histories. *Type I:* There is focal or multifocal stenosis of the vertebral canal, principally between C1 and C6, that is worse on flexion (*dynamic* stenosis). Affected horses are typically younger than 2 years of age. *Type II:* There is bony and soft tissue impingement into the vertebral canal resulting from remodeling of the articular facets of the caudal cervical vertebrae (usually C5 to T1) and stenosis of the cranial vertebral orifice. This impingement is present in all positions of the neck (*static* stenosis) but may also have a dynamic component with worsening during hyperextension. Horses with static stenosis are usually young to middle aged at the onset of wobbler signs.

Both syndromes likely involve some combination of aberrations in cartilage and bone development and external trauma that may precede clinical ataxia by many months (perhaps even in utero in the case of type I CVSM[1]).

Pathogenesis Type 1 CVSM is another manifestation of the group of disorders of endochondral ossification (i.e., osteochondroses) that occur in young, growing horses and include physitis,

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contracted tendons, osteochondritis dissecans (OCD), subchondral bone cysts, and malformation of the cuboidal bones of the carpus and tarsus.[3] Study of wobbler matings has indicated a propensity for rapid growth and superior performance among offspring but no clear evidence that CVSM was genetically predetermined.[4] Interestingly, other developmental orthopedic diseases were overrepresented. There is clearly a genetic predisposition to development of CVSM, but because it is probably genetically and environmentally multifactorial, pure genetic influences have been difficult to discern. Because rapid growth and large size appear to be risk factors for foal osteochondrosis,[5] it is not surprising that studies have tentatively implicated high protein and caloric intake in the development of CVSM.[1] Marginally low levels of trace minerals such as copper may come into play during rapid growth.

As a result of presumed genetic, physical, and dietary factors, there is early osteochondrosis of the articular facets and metaphyseal growth plates of foals. Genetic predisposition, rapid growth, maternal nutrition, calcium/phosphorus imbalance, low dietary copper, and high dietary zinc all have been implicated as developmental orthopedic diseases in foals, but their roles as risk factors for CVSM are not clear.[6-9] Osteochondrosis of the vertebral physes of rapidly growing foals and weanlings results in multiple vertebral abnormalities including flaring and enlargement of the caudal metaphyses and epiphyses of the vertebral bodies (equivalent to physitis of the limbs) and disparity of longitudinal growth of the vertebral bodies and dorsal laminae. These deformities cause focal stenosis (narrowing) of the vertebral canal and susceptibility to dynamic compression, respectively. In severe form, the latter abnormality forces pairs of vertebrae into a permanently flexed, malarticulated, kyphotic position in which severe vertebral canal stenosis (both static and dynamic) is likely. Flaring of the caudal metaphyseal-epiphyseal unit contributes to the narrow caudal orifice of the canal within an affected vertebra that is commonly seen in horses with CVSM.

Osteochondrosis of the articular facets may result in joint instability and later osteoarthritis and remodeling of the dorsal intervertebral joints. Associated with degenerative joint disease of the dorsal intervertebral joints are gross enlargements due to osteophyte development. Affected facet pedicles may be relatively brittle and susceptible to trauma. Fractured facets are found quite frequently in diseased intervertebral joints at postmortem, although the fractures often cannot be seen in lateral radiographs. Pedicle fractures caused by trauma likely contribute to the massive asymmetric remodeling and enlargement seen in some of these joints. The canals within affected vertebrae may deform to a funnel shape with a small stenotic cranial orifice. There may also be hypertrophy and fibrosis of the synovial membrane and joint capsules of the dorsal intervertebral joints, and fibrovascular proliferation of the ligamentum flavum. These soft tissue structures or fluid-filled cysts associated with them may cause static stenosis and compression of the spinal cord and spinal nerves. Synovial and epidural cysts are prone to cause dramatic waxing and waning of clinical signs of spinal cord compression.[1]

Necropsy Findings

Horses with CVSM have one or more focal compression–type lesions in the cervical spinal cord.[10] Grossly, such lesions may appear as flattening and palpable softening of the cord. Histologically, they are characterized by swollen and disrupted axons and phagocytosis of myelin in white matter. Mild hemorrhages are sometimes seen in acute lesions. In the white matter of chronically affected animals, there is continued degeneration of neuronal fibers, proliferation of capillaries with prominent fibrous coats, and astrofibrosis. More severely affected horses also have neuronal necrosis, loss of cell bodies, and sometimes astrofibrosis in the gray matter. Massive focal lesions also occur with cavitating necrosis of white matter, particularly in lateral funiculi and occasionally in gray matter. Markedly asymmetric lesions are found in horses with prominently asymmetric clinical signs. Cranial to the focal lesions, there is secondary degeneration of neuronal fibers (axons and myelin) in ascending (proprioceptive) tracts for variable distances, depending on the extent and age of the focal lesion. Caudal to the lesion, there is secondary fiber degeneration in descending (motor) tracts. This fiber degeneration is the result of neuronal fibers being severed from their cell bodies by the focal lesion. It is most prominent in dorsolateral funiculi cranial to the lesion and deep lateral and ventromedial funiculi caudal to the lesion.

Clinical Signs

Most animals with type I CVSM are 6 to 18 months old, whereas those developing type II CVSM are typically 18 months to 5 years, although there are many exceptions to these ranges and both conditions can occur in a single animal. In four large breeding farms, the onset of type I CVSM occurred in horses aged 202 to 986 days (average 434 days), whereas type II CVSM cases began at 1085 to 1299 days (average 1188 days).[2] A recent study of 811 horses in the United States indicated that horses of the Thoroughbred, warmblood, and Tennessee Walking Horse breeds were significantly more likely to have CVSM than were Quarter Horses; Standardbreds and Arabians were significantly less likely to have CVSM.[11] Large warmblood breeds are notably affected by type II CVSM.[12] Males are over-represented among horses with CVSM.[12,13] Affected horses are often well grown, and some have a history or signs of other developmental orthopedic diseases such as osteochondritis dissecans or physitis.

Clinical signs of ataxia and paresis typically begin insidiously but may present suddenly. In the latter case, there is often a history of some minor fall or training incident that confuses the diagnosis (was the fall a precipitating cause or a result of the disease?). After they have been recognized, signs typically progressively worsen for a period of months and then may stabilize or even regress. Spontaneous complete recovery is rare, although it does occur[1]; waxing and waning signs are frequent. In general, horses with CVSM appear physically normal; however, enlarged intervertebral joints in the caudal cervical spine and severe flexion angulations, particularly at C2-C3 and C3-C4, are occasionally externally visible and palpable. Pain in response to pressure over the transverse processes, or reluctance of the horse to flex its neck laterally are common findings in horses with type II CVSM. Rarely, impingement on caudal cervical spinal sensory nerves by enlarged intervertebral joints in type II horses is sufficient to cause signs of thoracic limb lameness.

The principal neurologic signs are ataxia, weakness, and spasticity of the limbs. These signs reflect involvement of axons of upper motor neurons and general proprioceptive tracts in the white matter of the spinal cord underlying the site(s) of compression. Because of the more superficial location of general proprioceptive tracts from the pelvic limbs, the pelvic limbs are generally more affected than the thoracic limbs.[1] Dynamic stenosis is usually associated with symmetric signs, whereas static stenosis may cause asymmetric signs. Occasionally, severe arthrosis of the joints between C6-7 or C7-T1 causes signs more severe in the thoracic than in the pelvic limbs. The first sign noticed may be stumbling or clumsiness when the horse is moving into or out of a box stall. During exercise gallops, the rider may comment on a feeling of looseness or "losing the back end" around turns. Reluctance to change leads, cross-cantering or cross-galloping, or even falls after stumbling are other early signs in horses being ridden. With progression, affected horses may have an obviously stiff uncoordinated gait at the walk; the prominent truncal sway; or "wobble" explains the common name for horses with CVSM. Because of pelvic limb extensor weakness, some wobblers catch their patellas or have persistent upward patella fixation.

In addition to the signs already mentioned, careful neurologic examination usually discloses some to all of the following: (1) Abnormal pelvic movements during walking best observed from behind including excessive swiveling of an imaginary line on the median plane from between the tuber sacrale to the tailhead, excessive rotation of the pelvis around its long axis (seen as exaggerated amplitude of the rise and fall of the tuber coxae), and side-to-side truncal sway; (2) decreased resistance to lateral pressure exerted by pulling the tail while the horse is walking; (3) apparent stiffness of the limbs during the swing phase of the stride in the thoracic and/or pelvic limbs. This may be associated with scuffing of the toes. When the horse's head is

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raised during walking, especially down a gentle slope, the stiff hypometric gait in the thoracic limbs may be exaggerated and is sometimes described colloquially as a "marching," "floating," or "tin-soldier" gait; (4) circumduction of each outside pelvic limb when the horse is walked in small circles; (5) interference between the thoracic limbs and pivoting around the pelvic limbs when the horse is moved in tight circles; and (6) absence of the thoracolaryngeal ("slap") reflex. In horses with markedly asymmetric compression (usually horses with asymmetric caudal intervertebral arthritis), there also may be marked asymmetry of stride length between the pelvic limbs.

Diagnosis

Radiography of the cervical spine is the most important diagnostic tool. A presumptive diagnosis of CVSM can usually be obtained from plain laterolateral radiographs of the cervical spine by finding focal narrowing (stenosis) of the vertebral canal. The diagnosis is buttressed by additional demonstration of malformation, osteochondrosis dissecans, or degenerative joint disease of the facet joints, metaphyseal and epiphyseal flaring of the caudal aspect of vertebral bodies, relative elongation caudally of the dorsal laminae, or angulation between pairs of vertebrae.

Intravertebral sagittal ratios for vertebrae behind C2 are calculated as the ratio [minimal sagittal diameter of the vertebral canal] ÷ [maximal sagittal diameter of the cranial half of the vertebral body].[14] Both measurements are made perpendicular to the long axis of the vertebral canal. The denominator normalizes for variations in horse size and object-film distance. A value for sagittal ratio (SR) of less than 0.52 from C4 to C6 and less than 0.54 at C7 predicts spinal cord compression with 89% sensitivity and specificity for diagnosis of spinal cord compression according to the original description.[14] In practice, cutoff values of 0.50 for C3-C6 and 0.52 for C7 are typically used.[1] Even horses with static stenosis, which may have predominantly transverse compression from large joints, usually have at least one abnormal intravertebral SR.[14]

Intervertebral sagittal ratio measurements are made between pairs of vertebrae in order to capture the effect of *fixed* flexion or extension angles on the diameter of the vertebral canal.[15] For a pair of vertebrae fixed in a kyphotic angle, the primary measurement (numerator) is the shortest distance between the caudal aspect of the dorsal lamina and the craniodorsal aspect of the vertebral body of the caudal-adjacent vertebra. For a fixed lordotic intervertebral joint, the corresponding measurement is the shortest distance between the caudodorsal aspect of the vertebral body and the most cranial point on the dorsal lamina of the caudal-adjacent vertebra. The intervertebral SR is calculated by dividing this measurement by the maximal sagittal diameter of the cranial half of the vertebral body of the cranial-adjacent vertebra.[15] Normal values for means and lower bounds of the 95% confidence intervals for intravertebral and intervertebral SR from C3 to C7 have been published.[1,15] Any value below these lower bounds is highly predictive of spinal cord compression.

A semiquantitative scoring system has been developed for use in foals 3 to 7 months of age to predict the risk of developing CVSM.[16] Intravertebral and intervertebral sagittal diameters are recorded as described earlier but rendered as ratios by using vertebral body length (rather than sagittal diameter) as denominator.[16] Up to 10 points are assigned for decreased sagittal ratios and up to 5 points for each of the following signs of cervical vertebral malformation: dorsal flaring of the caudal vertebral body, caudal extension of the dorsal lamina, angulation between adjacent vertebral bodies, delayed ossification, and enlargement of articular processes. A score of 12 or higher (maximum, 35) predicts the development of CVSM. Interestingly, this study revealed a strong tendency for the diameter of the vertebral canal to be greater in female foals than it was in males.[16] A multi-component and detailed system of measurements in plain and myelographic studies has been devised by Japanese workers[17,18] This system accurately identifies foals and yearlings with CVSM but has not been widely adopted in other countries.

When plain radiographs are abnormal, contrast myelography may be used to support the diagnosis, establish the number and locations of sites involved, and the severity of lesions in each, and to define the soft tissue contribution to spinal cord compression. These factors are especially important if surgical stabilization is contemplated because a different site may be revealed by myelography than was suspected in plain films. Under general anesthesia, 30 to 50 mL iohexol (Omnipaque) or iopamidol (Isovue) radiocontrast solution are injected slowly into the atlantooccipital subarachnoid cistern after a similar volume of CSF has been removed. After injection has been completed, the head is raised for 5 minutes to encourage caudal flow of dye and then the head is lowered and radiographs are taken.

Laterolateral views of the cervical spine are taken in neutral, flexed, and extended positions. Spinal cord impingement due to dynamic compression is clearly defined in lateral views if the dorsal and ventral dye columns are completely extinguished at diametrically opposed sites in flexed views. When there is less than complete compression of the dorsal column, several different diagnostic criteria have been used, none of which is completely satisfactory.[19,20] The traditional standard of complete compression of the ventral dye column and greater than or equal to 50% compression of the dorsal column at diametrically opposed sites is sensitive but has poor specificity (i.e., there are many false positives). Other likely, more accurate alternatives are (1) comparison with reference ranges for minimal dural diameters and minimal flexed dural diameters for horses either above or below 320 kg and (2) 20% or greater reduction in dural diameter in neutral views at the site of interest (usually intervertebral) compared with the midbody dural diameter in the cranial-adjacent vertebra. Sites affected in order of frequency are C3-C4, C4-C5, and C5-C6. Multiple sites may be affected in a single horse. The typical myelographic feature of *static* stenosis is focal spinal cord compression throughout the full range of vertebral motion. Any dynamic component at these caudal sites is relieved by flexion of the spine. The C6-C7 articulation is most frequently involved, and C5-C6 and C7-T1 to a lesser extent. At these sites, absolute narrowing of the minimal dural diameter or 20% reduction in comparison with the cranial-adjacent midbody measurement are the best diagnostic criteria.[1] In those cases in which the plane of compression is transverse rather than dorsoventral, the dural diameter is usually abnormal; however, less objective criteria may have to be considered when measurements are normal. These include widening of the spinal cord diameter and fading of the dye columns over the area of lateral compression. Unfortunately, the diagnostic accuracy of plain radiographic or myelographic diagnoses of CVSM has been unimpressive when compared against the gold standard of postmortem spinal cord histopathology.[13]

Advanced imaging by CT[21] or MRI[22] techniques have been described but in mature horses are limited by gantry dimensions to vertebrae in front of C4, so currently these techniques have little application to the workup and diagnosis of horses with CVSM.

A technique has been described for endoscopic evaluation of the epidural and subarachnoid spaces of the cervical spinal cord, and this procedure was applied to a horse with CVSM.[23,24] Although the technique may have application in selected cases, it has no place in the routine diagnosis of CVSM.

Because needle electromyography is most useful for investigation of muscles deprived of lower motor neuron activity, it has little application to the diagnosis of CVSM. The most promising electrodiagnostic testing application in this setting is transcranial magnetic stimulation.[25,26] Descending motor tracts are stimulated by current pulsation from a coil placed on the scalp. The onset latency of electromyographic responses in limb muscles is related to the integrity of spinal motor pathways. Latencies for horses with CVSM were significantly longer than those for normal horses.[27]

CSF analysis is generally normal. At most there are xanthochromia and elevated protein (70 to 130 mg/dL).

Treatment

MEDICAL. Corticosteroids and NSAIDs may provide transient improvement of the signs of CVSM but do not treat the underlying problem.

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Large degenerative intervertebral joints can be seen ultrasonographically, and corticosteroid (e.g., triamcinolone or methylprednisolone acetate) can be injected intraarticularly under ultrasound guidance, as has been described.[28] The theoretical applications for this procedure include relief from pain of arthritis and reduction in the soft tissue components of arthritic joints so as to provide at least temporary reversal of their impingement on the spinal cord and spinal nerves in the case of CVSM and thoracic limb lameness, respectively. Although descriptive support for all of these possibilities was provided in a recent observational series,[29] no fully objective evidence has been provided for reversal of the signs of CVSM, and it is inconceivable that permanent relief could be provided.

Some mildly affected horses can stabilize and even improve both radiographically and clinically if confined and placed on restricted but nutritionally complete feed.[1] There are reports of complete recoveries with this conservative approach.[30] Horses younger than a year of age (and preferably younger than 6 months of age) can be tried on a restrictive "paced-growth" diet in order to retard growth rate and prevent CVSM in clinically normal foals with radiographic evidence of stenosis of the vertebral canal or to treat foals with mild clinical signs of CVSM.[31] This diet reduces energy intake to 65% to 75% of National Research Council recommendations and increases trace minerals. The essential elements are as follows: (1) immediately wean if still suckling; (2) feed free-choice grass hay (e.g., coastal Bermuda hay) plus 3.5 lb daily of a ration balancer that is high in micronutrients and low in calories (e.g., Buckeye's Gro 'n Win). At 1 year of age (based on birth date), the supplement is reduced over 1 week to 1 lb daily. Foals should be confined in a stall except for limited round-pen or equivalent turnout time, certainly without access to pasture. Good results are claimed for slightly affected foals, although breaking, training, and racing are set back several months and the foals look poor as yearlings.[31]

SURGICAL. Ventral interbody vertebral fusion is the principal procedure. In this surgery, pairs of vertebrae are fused in extension by implantation of a cylindrical stainless steel or titanium basket (Cloward Bagby basket) filled with autogenous cortical bone fragments.[32,33] Osseous union of the vertebral bodies and stabilization of the dorsal intervertebral joints occurs after this surgery, although nonunion is an occasional postoperative problem. A recent modification uses a threaded titanium implant that screws into a prepared circular, threaded kerf around an isthmus of preserved bone. By leaving the isthmus and its blood supply intact, it is expected that complete bony fusion occurs more quickly. A plate may be secured over the implant, but this does not prevent retrograde migration of the implant.

The surgery provides immediate relief from dynamic stenosis and may improve static stenosis over months by causing atrophy of arthritic intervertebral joints. In the latter case intraarticular administration of corticosteroid may hasten atrophy of the enlarged joint. The surgery results in improvement in neurologic status in 44% to 90% of horses with dynamic compression, and 12% to 62% of treated horses return to athletic function.[32-35] Overall, the success rate offered by most surgeons is about 60% with normal myelographic columns expected by 2 months after surgery and complete osseous union by 1 year postoperatively. On average an improvement of 1 to 2 grades is expected.[34] Results of surgery for dynamic compression were significantly better than those for static compression in one published series.[36] Although there is a general impression that increasing time since onset of signs, higher neurologic grade, and multiple surgical sites are negative indicators for response to stabilization surgery, published results are not consistent on any of these issues.[32] Even three-site surgeries can be successful, although neck mobility is diminished.[37] The use of a locking compression plate has been described with initial promising results.[32] If the results of locking plate surgeries continue to be positive, such surgeries may become more widely available, obviating the need for the specialized equipment needed for implant surgery.[32]

Dorsal subtotal decompressive laminectomy is described[38] and provides immediate relief for static compression but technically is extremely difficult and fraught with severe postoperative complications.

Equine Degenerative Myeloencephalopathy

Robert J. MacKay

History and Epidemiology Since the original description in 1976,[1] equine degenerative myeloencephalopathy (EDM) and the related condition neuroaxonal dystrophy (NAD)[2] have been reported throughout the world in horses and ponies of many different breeds and in other equids including a donkey, Przewalski's Horses, and zebras.[3,4] The clinical signs of EDM and NAD are identical, and the associated CNS lesions are thought to be on a continuum with EDM lesions more widely distributed than are those of NAD.[3,4] For the rest of this section, both conditions will be referred to as EDM.

Clinical signs usually begin within the first year of life and, with only a few reported exceptions, have begun by 3 years of age.[5] A hereditary basis for the condition has been strongly suggested by the results of breeding studies or pedigree analyses in Morgan, Appaloosa, and Lusitano horses.[4,6,7] The mode of inheritance was suspected to be polygenic or dominant with variable expression.[4,6] A familial basis has also been suspected because of clustering of cases among the progeny of particular Standardbreds, Paso Finos, Norwegian Fjord horses, Arabians, Welsh ponies, Haflingers, and Quarter Horses.[8,9]

Overcrowding, lack of access to fresh green forage, pelleted feed, and poor-quality hay were thought to be risk factors on two affected premises.[10] In another study, significant risk factors were exposure to insecticides/repellents, exposure to wood preservatives such as creosote, and time spent on dirt lots.[5] Time spent on green pasture was a protective factor. By contrast, several clusters of cases in Oregon and California occurred in horses on pasture.[7,9] In the latter case, the pasture was growing on volcanic soil that was deficient in selenium and vitamin E.[9]

With rare exceptions,[5,11] there has been a consistent association reported between EDM and marginal or low serum/plasma vitamin E concentration. Published normal ranges for α-tocopherol vary with age, location, season, diet, and use; however, a commonly accepted scheme classifies results greater than 2 μg/mL as normal, 1.5 to 2 μg/mL as marginal, and less than 1.5 μg/mL as deficient.[10,12] Healthy horses sharing feedstuffs and environment with affected horses usually also have low vitamin E, although foals in an Appaloosa family with hereditary EDM had significantly lower plasma vitamin E than did age-matched normal pasturemates.[13] This effect was continuous from 6 weeks to 10 months of age. During the approximately 15 years after it was first recognized, EDM was one of the most prevalent causes of spinal cord disease in horses presented to teaching hospitals in the United States.[5] Although no statistics on prevalence have been published in recent years, prevalence of EDM in the United States may have declined over the past 20 years.

Cause and Pathogenesis EDM most closely resembles vitamin E deficiency of humans and other animals.[4,9,12] The neuroprotective effects of vitamin E relate to inhibition of oxidation of CNS membrane lipids and facilitation of axonal transport of macromolecules.[12] Although familial isolated vitamin E deficiency of humans is caused by mutations in the α-tocopherol transfer protein (α-TTP) gene, expression of α-TTP mRNA was similar between one unaffected horse and two horses with EDM from a group of related Quarter Horse weanlings and yearlings.[9] Low serum vitamin E in horses with EDM is not explained by impaired intestinal absorption: oral vitamin E tolerance tests were normal in affected horses.[13] It is reasonable to speculate that a defect in some component of vitamin E metabolism such as a lipoprotein carrier, hepatic transfer protein, or vitamin E receptor site may be involved in the pathogenesis of EDM.[12,13]

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Clinical Signs EDM is an acute to occasionally insidious-onset symmetric ataxia and paresis of the trunk and limbs. The onset of clinical signs typically occurs between 1 and 12 months of age but has been seen in neonates and mature horses.[3,4] Posture and gait are wide based. There is notable hypometria (spasticity) in affected limbs. Signs are typically considerably more severe in the pelvic limbs, and the thoracic limbs may be clinically normal. In two recent reports, it was noted that limb weakness was only seen in horses with moderate or severe ataxia and was not recognized in many horses that were mildly ataxic.[4,9] Some horses with EDM adopt a two-beat lateral ("pacing") gait at walking speed. Long spinal reflexes such as the cervicofacial, laryngeal adductor (slap), and cutaneous trunci may be reduced or absent, especially in long-standing cases. Neurogenic muscle atrophy is not seen in horses with EDM, and recently reported cases occurred in horses with body condition scores of 5 to 6 out of 9.[4,9] Signs of brain dysfunction were not reported until recently. Among a group of Quarter Horses with EDM (NAD), 77/88 were described as dull or obtunded and minimally responsive to light flashes, sudden movement, or loud noises.[9] An electroencephalogram performed on one affected horse revealed dominant states of drowsiness to slow-wave sleep. Reduced or absent menace responses were noted in 33/88 Quarter Horses and 4/6 Lusitanos with EDM.[4,9] Vision, pupillary light reflexes, ophthalmologic examinations, and electroretinograms were normal.

Signs may not worsen after initial onset; others progress for days to months before stabilizing. Only rarely does the condition progress to recumbency.

Laboratory Findings There is no antemortem diagnostic test for EDM. Plasma/serum vitamin E concentrations of EDM horses and pasturemates are often marginal or low. Because vitamin E concentrations within individual horses vary considerably over time (especially if they are low), it is recommended that three blood samples be taken over the course of 24 hours.[12,13] Samples must not be visibly hemolyzed and should be stored so that the blood is not in contact with the rubber stopper. Plasma CK and AST activities may be slightly to moderately high because of increased recumbency.[7]

Diagnosis Diagnosis antemortem is presumptive only and is made primarily by suggestive signalment and clinical signs with exclusion of competing diagnoses. EDM should be suspected in horses with symmetric limb ataxia that began within the first year of life and for which results of standard neurologic workups (cervical vertebral radiographs, CSF analysis, immunoassay for *S. neurona* antibody) have not implicated another diagnosis. Low or marginal serum/plasma vitamin E concentration (≤2 μg/mL) is supportive of the diagnosis.

Necropsy Findings There are no abnormal gross necropsy findings. Histologic changes develop in the spinal cord and brainstem.[4,7,9,11] In horses with NAD there are lesions in the lateral and medical cuneate, gracilis, and thoracic nuclei characterized by spheroid formation with vacuolation, loss of somata, astrogliosis, and lipofuscin pigment accumulation. Additionally, in horses with EDM, axonal necrosis and demyelination involve the dorsal and ventral spinocerebellar tracts and ventromedial funiculi of the cervicothoracic spinal cord. No histologic lesions were found to explain observations of dull mentation[14] and abnormal menace responses[4,9] in recently reported case series.

Treatment and Prevention It is unlikely that EDM can be cured even if treated early. Slight to no improvement was seen in affected horses supplemented with 2000 to 8000 IU vitamin E daily.[7,10] The type of vitamin E and the method of supplementation have important effects on its bioavailability. Natural vitamin E (RRR-α-tocopherol) is up to twofold more active than synthetic vitamin E (d,l-α-tocopherol or all-rac-α-tocopherol). Absorption requires fat, so bioavailability of vitamin E is negligible or low unless given with feed or vegetable oil.

Consistent with the notion that EDM is associated with some interaction between metabolic defect and vitamin E deficiency, vitamin E supplementation appears to be at least partially effective prophylaxis and is recommended in circumstances in which there are familial predisposition, processed feed, lack of access to pasture, and exposure to insecticides or wood preservatives. In one study, the incidence of EDM was reduced from 36% over 3 years to 9% in the following year by supplementation of foals with 1500 IU vitamin E daily.[10] Similar results were seen in two other outbreaks.[9,10] Obviously, sensible genetic, nutritional, and other management practices alone could greatly reduce or eliminate the risk of EDM.

Spinal Cord Trauma

Robert J. MacKay • Lisle W. George

Vertebral trauma is a relatively common cause of spinal cord dysfunction in both ruminants and horses. The spinal cord is normally protected by a complex of bones and ligaments that can be conceptualized in biomechanical terms as two columns: dorsal and ventral.[1] The ventral column consists of the vertebral bodies, intervertebral disks, and dorsal and ventral longitudinal ligaments, whereas the dorsal column consists of alternating bony (arches, dorsal articular processes, and dorsal spinous processes) and ligamentous (supraspinous ligament, interspinous ligaments, ligamenta flava, and joint capsules) complexes. According to biomechanical models that have been used for assessment of spinal trauma in humans and small animals, acute spinal instability occurs when there is disruption of *both* of these columns by external mechanical forces. The corollary is that a single intact column provides stability. This two-column system has not been validated for large animals. Fractures of vertebral transverse processes and dorsal and ventral spinous processes and partial fractures of vertebral bodies or arches (i.e., stress fractures) do not cause spinal instability or neurologic signs.[2]

Most, but not all, traumatic spinal cord injuries are accompanied by vertebral fracture, subluxation, or dislocation.[3] Conversely, many spinal injuries are associated with pain, reduced mobility, and abnormal neck position but do not cause acute neurologic signs. In large animals, cervical spinal cord trauma is usually caused by hyperextension or hyperflexion of the spine in the sagittal plane with superimposed vectors of compression, distraction, rotation, and/or shear. With vertebral hyperextension, compressive force is applied to the dorsal column and distractive force to the ventral column, whereas the reciprocal forces apply to hyperflexion injuries. In all cases, the likelihood of associated spinal cord compression is higher in animals with abnormally narrow vertebral canals. Disk prolapse and fibrocartilaginous embolization of the spinal cord are rare in large animals, and when they occur are usually associated with degenerative changes rather than with acute trauma, as may occur in dogs.[4-6] Young animals are subject to fractures involving epiphyseal or growth plates (i.e., Salter-Harris fractures). Vertebral infections may be seeded hematogenously along these cartilaginous plates or by direct traumatic implantation, and osteomyelitis may progress to the point of pathologic vertebral fracture. Poorly balanced nutrition or undernutrition decreases bone density and increases susceptibility to vertebral fractures.

Horses

In racehorses, cranial or vertebral fractures have accounted for 2.5% to 3% of deaths at flat races and 16% to 23% of deaths at chase and hurdle starts.[7] In a 3-year study of fatal fractures/dislocations in the spine of 125 horses at racing events in Britain, 23% involved the cervical vertebrae, whereas the remainder involved the thoracolumbar vertebrae.[8] Of 60 horses with vertebral trauma that were necropsied in Australia, 33 involved cervical, 10 thoracic, 10 lumbar, and 2 sacral vertebrae.[9] In general, cervical vertebrae are more prone to fractures during accidents at jumping events (e.g., cross-country, showjumping, foxhunting, steeplechasing, and hurdling). The occipitoatlantoaxial region is most often involved in the following

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situations: (1) when there is broad forehead impact as in collisions with the ground, other horses, or fixed objects; (2) when a horse rears and flips over backward; or (3) when major traction forces are applied to the head as occurs in tied horses jerking backward on a halter. The atlantal ring or body of the axis may be fractured, the dens may fracture transversely anywhere along its length (including at physes in young horses), and/or the dens may subluxate or dislocate from its usual position in the fovea dentis of the atlas. Fracture of a single articular process is the most common fracture from C3 to C7. In young horses (especially those younger than 2 years), a characteristic and spectacular hyperextension fracture results in severe extension angulation of the intervertebral joint.[10,11] On the more cranial of the affected vertebrae, the dorsal lamina and caudal articular processes are fractured and lifted dorsally. It is thought that this "deroofing" lesion provides natural decompression of the spinal cord while the surprisingly sturdy dorsal half of the intervertebral disk provides residual stability of the ventral column of the cervical spine.

In the thoracolumbar spine, T1 to T3, T10 to TI6, and T18 to L6 appear to be relatively susceptible. Foals and young horses at pasture are prone to collide with fixed objects or other horses, get kicked by adult horses, or pitch forward headfirst into the ground, all while running at high speed. Such accidents often occur at night. Typical hyperflexion and hyperextension injuries of the cervical spine result from these falls, and cranial thoracic and midback fractures result from striking solid objects or being kicked. Horses may suffer contiguous or noncontiguous injuries of multiple vertebrae after high-speed impacts. Any horse that falls backward or struggles violently against a caudal barrier (e.g., in a trailer) may sustain sacrococcygeal fractures with damage to the cauda equina. There are reports that avulsion of the cauda equina can be caused by lifting or dragging a recumbent horse by its tail. It is worth noting that horses may have serious spinal injuries while alone in a stall, without observed or external evidence of an accident, so trauma should always be considered in cases of acute onset of spinal cord signs, regardless of the environment.

Ruminants

The common sites of spinal fractures in calves are C2 to C4, T10 to T13, and L3 to L6 vertebrae. Vertebral fractures (particularly compression fractures) are especially common in 3- to 6-month-old ruminants as a result of nutritional problems including vitamin D, calcium, and copper deficiency or low calcium-to-phosphorus ratio.[12] Nutrition-related fractures usually involve several animals and may also involve the ribs and long bones. Traumatic cervical vertebral fractures of cattle and small ruminants may be caused by injuries sustained in falls, roadway accidents, butting of other animals, collisions with moving farm machinery, predation, or accidents in tie-stalls, stanchions, or squeeze chutes.[12-14] Spinal injury is especially likely if the head is restrained in the chute or stanchion when the animal falls. Fractures or dislocations of the lumbar or sacrococcygeal spine frequently occur in cattle that slip in wet cemented areas.[13] Many of these fractures occur during mounting by herdmates exhibiting estral behavior. Spontaneous fractures of vertebrae weakened by congenital defects (e.g., hemivertebrae) or osteomyelitis also are common problems in calves.[15] Traumatic dislocations, subluxations, or fractures of the atlantooccipital and atlantoaxial joints of pygmy goats may occur when the horns are held during restraint. Thoracolumbar fractures, particularly with epiphyseal separation of the middle to caudal thoracic vertebrae, may occur in calves transiting the birth canal during correction of a dystocia.[16-18] These fractures are mainly related to excessive traction and rotational force.[19] Luxation of a sacroiliac joint in the dam may occur with the use of extreme force during manual extraction of a calf. Mature Holstein bulls and rams may have a fused thoracolumbar spine and stenotic vertebral canal because of ankylosing spondylitis. This condition results in progressive pelvic limb paresis and ataxia.[20] These animals are at risk for traumatic lumbar vertebral fracture, spinal cord injury, and recumbency if they are required to mount for semen collection or breeding.[21] As was described for horses, vigorous traction on the tail (e.g., when trying to assist a downer cow to stand) has the potential to cause stretching or avulsion of the cauda nerve roots and signs of cauda equina syndrome.

Pathophysiology

The primary phase of spinal cord injury is the direct effect of the mechanical events of the original trauma.[22] The primary phase is irreversible, but additional rounds of primary injury can be prevented or minimized by surgery and external stabilization of the spine. The principal mechanical forces that are involved in acute traumatic injury are concussion, compression, shear, laceration, distraction, and contusion of the spinal cord. The secondary phase of spinal cord damage refers to the injurious molecular and biochemical events that are set in motion by the primary injury and occur in the first few hours after initial injury. The goal of medical therapy is to limit the damage that occurs from secondary injury. The most important events during this phase of injury are vascular damage with hemorrhage and microthrombosis, loss of autoregulation of blood flow, excessive release of the excitotoxic neurotransmitters aspartate and glutamate, increased neuronal intracellular calcium concentration, cellular damage from reactive oxygen species, and acute neutrophilic inflammation.

Clinical Signs

The most common sign of vertebral trauma in all large animal species is localized pain and limited mobility of the affected part. The atlantoaxial vertebral canal of horses is subject to fractures, subluxations, and dislocations, many of which do not cause signs of neurologic dysfunction, presumably because of the large cross-sectional area of the vertebral canal at this level of the spine.[23] There are two quite rare disorders that result from spinal cord trauma and confound the rules of neuroanatomic localization: spinal shock and Schiff-Sherrington syndrome. *Spinal shock* refers to loss of muscle tone and segmental spinal reflexes caudal to a focal severe transverse spinal cord injury, usually between T3 and L3.[24] Although seldom described in the veterinary literature, it does occur in large animals but, in contrast to the situation in humans, areflexia usually lasts less than 30 minutes after which there is progressive recovery of segmental reflexes with persistence of signs referable to a focal spinal cord lesion. With such a lesion, the thoracic limbs may be hypertonic, reflecting release from the inhibitory effect of tracts originating in the lumbar segments. This combination of paraplegia and thoracic limb stiffness is known as *Schiff-Sherrington syndrome*.[25] At least in small animals, signs regress by about 10 days. Spinal shock and Schiff-Sherrington syndrome may occur together or separately.

Diagnosis and Treatment

The first priority is the safety of attending personnel, which means that large thrashing disoriented patients may need to be heavily sedated or anesthetized to allow for initial assessment, IV catheter placement, and treatment of any life-threatening conditions. Small ruminants theoretically can be taped to a backboard to immobilize them in lateral recumbency during initial procedures. Handlers must be careful not to exacerbate cervical vertebral trauma when restraining injured animals via lead rope and halter.

An indwelling IV catheter should be inserted and secured and IV fluids and initial treatment provided as needed. Volume support and maintenance of normal arterial pressure and hematocrit are essential in all forms of CNS injury.[26] Any animal with spinal injury and neurologic signs should be provided with full doses of analgesics. Nonsteroidal antiinflammatory drugs (e.g., flunixin meglumine 1.1 mg/kg IV or PO) have the dual advantages of analgesic effect and inhibition of potentially injurious cyclooxygenase activity.[22] Additional analgesia can be provided if necessary by doses of butorphanol, morphine, or lidocaine or ketamine constant-rate infusions. The use of methylprednisone sodium succinate in this setting in human medicine remains highly controversial, although slight long-term benefits have been reported for a regimen of 30 mg/kg, followed by 5.4 mg/kg/h for 23 hours.[27,28] Patients are at an increased risk for pneumonia, sepsis, and hyperglycemia. Because more recent data indicate a trend away from the routine use of methylprednisolone because the risks

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of complications outweigh the potential benefits,[29] high-dose MPSS is not recommended in large animals with acute spinal cord injury. As is the case for brain injuries, the use of routine antiinflammatory doses of dexamethasone (0.05 mg/kg IV or IM once or twice daily) is reasonable.

As soon as possible, a careful neurologic examination should be performed to localize the lesion. It is important that this examination be complete even if the site of injury seems obvious because multiple discontinuous spinal cord segments and/or the brain may be injured in a single traumatic incident.[30]

When technically possible, it is prudent to radiograph the entire vertebral column. In large animals under field conditions, views are generally restricted to lateral projections of the cervical vertebrae. Remember that radiographs show the amount of spinal displacement at the time they are taken, not the amount of displacement that occurred at the time of injury. The two-column model can be used to assess spinal instability.[1] Myelography is usually not necessary if it is determined that the spinal injury can be treated conservatively or if there is a substantially displaced fracture or luxation that is an obvious candidate for surgery. Myelography should be performed in animals with marked neurologic deficits and normal or equivocal radiographs. Additional information can be obtained from oblique and ventrodorsal radiographic views, C-arm fluoroscopy, CT, MRI, and osseous-phase nuclear scintigraphy. Techniques that require general anesthesia in a large animal with spinal instability generally should be avoided unless there is an immediate surgical option.[10]

After these initial evaluations, the clinician has sufficient information to make recommendations for euthanasia, conservative treatment, or surgical management. Obviously, economic considerations and the intended use of the patient are driving considerations in this situation. In all cases, if there is quadriplegia and loss of deep pain and/or radiographic evidence of likely spinal cord transection, early euthanasia is appropriate. Otherwise, keeping paramount the issues of handler safety and humane treatment, it is reasonable to wait 12 to 24 hours to allow time for recovery of function before delivering a hopeless prognosis and euthanasia recommendation. Once the decision has been made to continue treatment, most large animals are still managed conservatively with surgery an option in selected cases.

Conservative Management

For large animals with vertebral column injury, 1 to 2 months of each of the following is recommended: full-time stall confinement; stall confinement with daily hand-walking; turnout into a small paddock or roundpen during the day with stall confinement at night. Pain control and sedation should be provided as needed. In horses that have difficulty getting to their feet, frequent use of an abdominal sling is essential. Such horses must be able to support their own weight once in the standing position. In cattle, a flotation tank can be used for the same purpose.

Surgery

In the absence of evidence-based guidelines for surgical intervention in large animals, it is worth considering the potential adverse consequences of *not* doing surgery. Although conservative management has often been successful, the following negative outcomes have been observed in horses with spinal injuries managed conservatively: (1) sudden recumbency days to weeks after dens fracture, subluxation, or dislocation[2,31]; (2) limb ataxia and weakness after callus formation and joint remodeling around a fractured articular process[11]; (3) progressive torticollis and/or head tilt after articular process and vertebral body fractures in the midcervical region; (4) limb ataxia and weakness after fibrous proliferation at the site of previous atlantoaxial subluxation; (5) abnormal head position and stiffness of the upper neck after upper cervical injury; and (6) a domino effect wherein there is progressive stenosis of the vertebral canal at the intervertebral joint(s) immediately caudal or cranial to a traumatized intervertebral joint that has healed with a marked flexed or extended angle.[11,18] In light of the foregoing, reasonable indications for surgical intervention in horses are (1) prevention of neck stiffness or deformity; (2) prevention of callus formation or joint remodeling that may impinge on the spinal cord; (3) decompression and/or stabilization of the atlantoaxial joint after dens fracture, subluxation, or dislocation[23,31,32]; and (4) decompression or reduction and stabilization of vertebral fractures/subluxations in response to deteriorating neurologic signs. Techniques have been described for each of these surgical procedures (generally with successful outcomes) in the cervical spine of horses.[10,33,34] Canine surgical techniques can be adapted for use in the lumbosacral spine of valuable small ruminants, calves, and foals. In particular, the use of polymethylmethacrylate and Steinmann pins and plating of the dorsal spinous processes have wide potential application to thoracolumbar injuries in animals less than 70 kg.[35] Surgical decompression of the cauda equina by dorsal laminectomy of the sacrum has been described. In adult horses, the tuber sacrale of the pelvis interferes with the approach to the first and possibly the second sacral vertebra, but decompression of the caudal part of the sacrum is possible.[36] In foals and heifers, sacral fractures may be reduced and stabilized with plates and screws.[37]

Prognosis For horses with spinal trauma without neurologic dysfunction that are treated conservatively, there is a fair to good likelihood that neurologic signs will not develop; however, there is also a fair chance that the neck will remain stiff and/or become deviated or rotated. The prognosis for horses with spinal cord trauma associated with luxations or fractures of the vertebral body, arch, or articular processes must remain guarded to poor for return to use. Healing of such fractures frequently results in some degree of vertebral malalignment, sometimes with lordosis, kyphosis, scoliosis, or torticollis. Even after apparent healing and resolution of neurologic signs, delayed callus formation and degenerative changes in adjacent articulations can result in delayed spinal cord compression. When the injured spine is appropriately stabilized, improvement may continue for up to a year. It is estimated that even 10% survival of axons across a lesion site in the spinal cord may be compatible with walking in a small quadruped. The limbs behind a permanent spinal cord lesion will be ataxic and weak to lateral pressure but spastic and stiff during walking and able to resist dorsal pressure.

Ankylosing Spondylitis of Holstein Bulls

Lisle W. George

Ankylosing spondylitis is an inflammatory disease of joint tissue associated with fusion of lumbar vertebrae in Holstein bulls. Approximately 4% of all Holstein bulls used for artificial insemination are culled each year because of spondylitis.[1] The clinical onset of the condition is insidious. The first signs of the disorder are a stilted gait, reluctance to move, and dragging of the toes of the rear limbs. Affected bulls are slow to mount teaser dummies for collection. The condition is progressive, and over several months the animals develop paraparesis and ataxia. With mounting, the ankylosed area of the spine may fracture, leading to acute recumbency. Pathologic changes associated with the condition include calcification of the ventral vertebral ligaments between the T11 and L3 vertebrae. The condition appears to be hereditary. All bulls with the condition possess the class I major histocompatibility complex (MHC) BoLA A8 phenotype. In comparison, the phenotypic frequency of BoLA A8 in the general population of normal Holstein bulls is only 44%.[2]

Spinal Tumors

Robert J. MacKay • Lisle W. George • Mary O. Smith

With the exception of lymphosarcoma in cattle, tumors involving the spinal cords of domestic animals are rare. In the horse, tumors within the spinal cord or dura (i.e., intramedullary or extramedullary-intradural) have included meningioma, ependymoblastoma, angioma, angioblastoma, ganglioglioma, schwannoma, and neurofibroma.[1] Reported extradural tumors are lymphosarcoma, plasma cell

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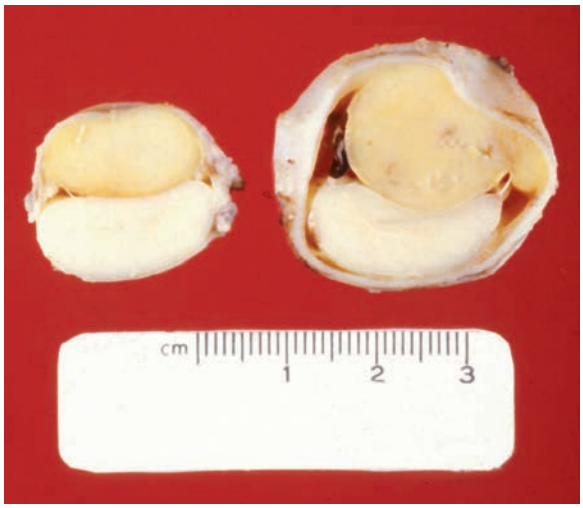


FIG. 35-15 Epidural lymphosarcoma in a 5-year-old Holstein dairy cow. The tumor had spread from neoplastic periaortic lymph nodes and had expanded to compress the caudal lumbar and cranial sacral spinal cord segments, resulting in signs that resembled bilateral sciatic paresis. Tumorous masses are above the compressed spinal cord in the two transverse sections shown.

myeloma, neurofibroma, fibrosarcoma, melanoma, hemangiosarcoma, and carcinoma.[1-4] The most common tumor affecting the spinal cord of ruminants is lymphosarcoma, but others such as histiocytic sarcoma, glioma, neuroblastoma, and embryonal neuroectodermal tumors have been reported.[5-9]

Clinical Signs The clinical signs of tumorous invasion are usually referable to a single-site spinal cord lesion, although extradural tumors such as lymphoma can extend over multiple spinal cord segements.[9] The rate of onset of the neurologic dysfunction varies. Some neurofibromas, melanomas, and lymphosarcomas invade centripetally along the peripheral nerve rootlets. These patients develop slowly progressive limb ataxia and weakness caudal to the location of the lesion, leading eventually to tetraplegia or paraplegia. In rare cases the onset of tetraplegia may be peracute and unaccompanied by prodromal neurologic signs. Lymphosarcoma has a predilection for the lumbar segments of the spinal cord and the cauda equina in cattle older than 5 years of age (Fig. 35-15). A diagnosis of spinal cord tumor should be considered in cases of progressive neurologic disease characterized by flaccid tail and anus, dysuria, urine scalding, distended bladder, perineal analgesia or anesthesia, and paraparesis. Although most animals with spinal tumors are mature to older adults, immature animals can be affected rarely, mainly by embryonal tumors.[8-11]

Clinical Pathology Examination of CSF may be useful when the tumor has infiltrated the cauda equina and is located in the lumbosacral cistern. In these cases, tumor cells may be biopsied as the needle is inserted into the lumbosacral space. In other cases the CSF may be normal, or albuminocytologic dissociation can be expected (elevated CSF protein with normal to mildly elevated nucleated cell count) with or without variable degrees of hemorrhage and xanthochromia. After necropsy, various immunohistochemical techniques can be used to identify the tumor type when routine histologic examination is insufficient.

Treatment There is currently no treatment for most spinal cord–associated tumors of large animals; however, protocols could be adapted from those used for other forms of lymphoma in horses or for other solid tumors in small animals. One study reported survival of a cow for 57 days after three treatments with L-asparaginase at 10,000 IU/m^2 surface area. The nearly 2-month period of survival allowed the investigators to successfully superovulate the cow. When treating food animals with L-asparaginase, the benefits of the antimetabolite drug must be weighed against the potential for teratogenicity of the fetus, toxicity for humans, and the certainty of relapse in the patient.[12]

Verminous Meningoencephalomyelitis

Robert J. MacKay

Verminous meningoencephalomyelitis is caused by the meanderings of one or more parasites through the CNS and is, therefore, an extremely variable clinical entity. Depending on the number, size, and location of the parasites and the duration of their migration through the brain or spinal cord, a spectrum of signs is possible, ranging from a nonprogressive localizing neurologic deficit to rapidly fatal, diffuse encephalitis. Verminous meningoencephalomyelitis usually occurs sporadically and has been associated with strongylid *(Strongylus vulgaris),* metastrongylid *(Angiostrongylus cantonensis, Parelaphostrongylus tenuis),* filarid (*Setaria* spp.), tylenchid (formerly rhabditid) *(Halicephalobus gingivalis),* and spirurid *(Draschia megastoma)* nematodes, as well as warble fly larvae (*Hypoderma* spp.).

Strongylus vulgaris

Verminous myeloencephalitis due to *S. vulgaris* in the CNS is a rare aberrant event resulting from embolization to the CNS of L4 or L5 larvae from verminous thrombi in the left ventricle, proximal aorta, or any of the aortic branches that supply the CNS.[1,2] Upstream subintimal migration of *S. vulgaris* larvae in the aorta occurs from locations in the proximal cranial mesenteric artery.[2] Disintegration of thrombi in these aberrant locations sends clot fragments and larvae to the CNS. Three differing outcomes are possible: (1) acute massive infarction, ischemia, and edema of the brain; severe neurologic dysfunction; and death after a brief clinical course; (2) nonlethal or even subclinical embolization of the CNS is followed by entry of a larva (or larvae) into the CNS parenchyma and wanderings therein for up to several months with associated neurologic signs; or (3) subclinical embolization and parasite migration. Subclinical larval migration occurs in relatively forgiving parts of the cerebral hemispheres and ends when the parasite dies or migrates out of the CNS. A single larva can migrate through many levels of the CNS; in one case an L5 *S. vulgaris* larva was estimated to have traveled 8 cm per day for several days along the spinal cord of a donkey.[3] Virtually any clinical sign is possible, and signs are likely to change dramatically over time or even stop and then restart or spontaneously resolve. A larva may exit the CNS only to reenter at a different location and continue its migration. The donkey mentioned earlier was paraparetic and dog-sitting because of larval damage through the midlumbar spinal cord; signs improved for a few days when the larva migrated out of the spinal cord, then the animal collapsed into recumbency when the larva reentered and migrated within the cervical spinal cord.[3] Thrombosis, infarction, and serpiginous hemorrhagic or discolored tracts may be evident grossly. Microscopic findings include linear tracts of hemorrhage lined by neutrophils, macrophages, occasional eosinophils, and reactive glial cells. CSF changes associated with *S. vulgaris* migration include xanthochromia, protein concentration ranging from 32 to 550 mg/dL, and increased nucleated cell count (42 to 10,000/μL).[1-4] The differential counts range from 70% to 80% neutrophils, 12% to 19% mononuclear cells, and 1% to 2% eosinophils. Verminous myeloencephalitis due to *S. vulgaris* virtually disappeared after the introduction of the macrocyclic lactone anthelmintics in the 1980s; however, the increasing practice of selective deworming may allow the reemergence of large strongyles.[5]

Hypoderma lineatum and *Hypoderma bovis* (Cattle Grubs)

Hypoderma lineatum (common cattle grub) and *Hypoderma bovis* (northern cattle grub) are parasites of cattle that occasionally migrate in the horse (also in goats and deer). In the late spring or early summer, adult *Hypoderma* spp. flies (known as warble flies or heel

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flies) deposit eggs on hairs on the limbs or lower body. First-stage larvae hatch in 5 to 7 days, penetrate the skin, and migrate in a dorsal direction along fascial planes, often following the paths of blood vessels or nerves.[6] Over about a year migrating larvae moult once or twice and arrive in subcutaneous tissues along the back. Their dorsally directed path may sporadically take larvae through the foramen magnum or other foraminae of the skull to penetrate and meander in the brainstem. Because of the large size of *Hypoderma* spp. larvae and their propensity for migration within the caudal fossa of the skull, resulting neurologic signs are usually severe, progressive, and fatal.[6,7] Typically, there is profound obtundation and signs of asymmetric cranial nerve dysfunction (e.g., head tilt and circling) that worsen quickly and lead to recumbency and death. Since the advent of pour-on and injectable systemic organophosphate insecticides in the 1950s and macrocyclic lactones in the 1980s for systematic treatment of cattle, *Hypoderma* populations have decreased dramatically in the United States and have been eradicated in several European countries, so intracranial myiasis is now unlikely in developed countries. *Hypoderma diana,* a parasite of deer, has also infested horses and presumably has the potential for CNS invasion.[8]

Halicephalobus gingivalis

Halicephalobus gingivalis (previously *Halicephalobus deletrix, Micronema deletrix*) is a free-living microbivorous tylenchid nematode that feeds on bacteria in rich organic environments such as decaying vegetation, compost, or manure.[9,10] Cases of meningoencephalomyelitis caused by *H. gingivalis* occur sporadically worldwide in equids (including zebras) and occasionally humans.[11-16] The nematode opportunistically enters the body through breaks in the mucous membranes (and possibly skin) of the nose, mouth, prepuce and mammary gland of horses and invades and proliferates locally to cause clinically apparent granulomas.[17-22] Such masses can be locally invasive and destructive, particularly in the jaws, nasal cavity, and paranasal sinuses.[17,23] In one case a foal was apparently infected by suckling from its dam who had *H. gingivalis* mastitis.[24] From these superficial sites larvae or adults may enter lymphatic or venous drainage and be distributed hematogenously to various organs and tissues. *H. gingivalis* has a propensity to invade and proliferate in the kidneys (Fig. 35-16), CNS, and eyes, although lesions have also been found in long bones, heart, lungs, liver, uterus, testes, lymph nodes, and the walls of the aorta and pulmonary arteries.[22,25-27] The brain is the usual site of CNS infection with lesser involvement of the spinal cord or, in one instance, the cauda equina.[28] The typical severe progressive neurologic signs are due to massive proliferation of nematodes adjacent to blood vessels and the associated florid perivascular granulomatous inflammation.[9] Only female nematodes are present in lesions, and reproduction is by parthenogenesis.[9] Clinical signs of *H. gingivalis* infection of the CNS depend on the location of the lesions and include asymmetric ataxia, hypermetria in the thoracic limbs, obtundation, behavioral changes, compulsive walking, head pressing, head tilt, circling, nystagmus, recumbency, convulsions, and coma.[11-16,29-31] *H. gingivalis* meningoencephalitis is invariably fatal, regardless of treatment; affected horses die or are euthanized within several days of onset.[25,32] CSF analysis in affected horses ranges from normal to xanthochromic appearance with increased protein and mild to moderate pleocytosis of nucleated cells. Differential analyses reveal mostly mononuclear cells with lesser numbers of neutrophils and occasional eosinophils. In many (most?) cases of *H. gingivalis* meningoencephalitis there are also characteristic renal lesions.[25] The latter are usually multifocal large nodules in the renal parenchyma of one or both kidneys.[25,33] Of potential diagnostic significance in such cases, there may be a history of weight loss, hematuria, and/or polyuria and findings at initial examination of nematodes in the urinary sediment, high serum creatinine and calcium concentrations, and ultrasonographically evident renal masses.[34-37] Severe progressive, usually unilateral verminous chorioretinitis or panophthalmitis may precede or coincide with the onset of signs of encephalitis.[36,38,39] Efforts to eliminate subcutaneous or renal *H. gingivalis* infections by surgery and anthelmintics are occasionally successful[20] but, unfortunately and unpredictably, are often followed within several days to weeks by the onset of encephalitis.[18,38,40-42]



FIG. 35-16 Kidneys from a horse with disseminated *Halicephalobus gingivalis* infection including fatal meningoencephalomyelitis.

Parelaphostrongylus tenuis

Parelaphostrongylus tenuis (the meningeal worm) is a ubiquitous parasite of white-tailed deer in the eastern United States (north of a line through the middle of the states along the Gulf of Mexico[43]). Infective larvae are ingested within infected snails and slugs, exit through the abomasum, and then migrate to the dorsal horn of the gray matter of the spinal cord, where they mature to adults before traveling along the dorsal nerve roots to the venous sinuses and subarachnoid spaces over the cerebral hemispheres.[44] *P. tenuis* is increasingly a cause of verminous meningoencephalomyelitis due to aberrant larval migration in the CNS of other cervids, goats, sheep, and New World camelids within the same geographic range. In 2003 a series of six equine cases with cervical scoliosis were described.[45] In each case, there was a unilateral multisegment contiguous lesion involving the dorsal horn of the gray matter on the convex side of the neck. In one case, cross-sections of a metastrongylid nematode were seen associated with the characteristic lesion and the presumption is that all cases were caused by aberrant migration of *P. tenuis*. Five of the horses were younger than 1 year of age and, in each case, there was acute onset of severe scoliosis after a variable prodrome with degrees of hypalgesia of the neck and cranial thorax and limb weakness and ataxia, all on the side of the cervical convexity. Treatment with anthelmintics and antiinflammatories had no effect, and affected animals were all euthanized for humane reasons. An additional case, also in a young horse, was reported in 2007, this time with signs of obtundation, head tilt, circling, quadriparesis, and ataxia in all four limbs.[46] There were numerous larval stages, eggs, and occasional adults of both sexes associated with granulomatous eosinophilic inflammation in the cerebellum and adjacent brainstem. These nematodes were shown by PCR of specific DNA sequences to be *Parelaphostrongylus* species.[44] A *P. tenuis* nematode was extracted from the anterior chamber of a horse with signs of anterior uveitis.[47]

Angiostrongylus cantonensis

Angiostrongylus cantonensis is a neurotropic metastrongylid parasite with a life cycle in rats closely analogous to that of *P. tenuis* in white-tailed deer.[48] It has long been endemic in the Pacific islands and Southeast Asia but has spread its range into Australia, the United States, and the Caribbean. It is now well established among the wildlife of Louisiana.[49] The definitive hosts are species of wild rat that become infected by ingesting the infective larva in slugs or snails. The larvae migrate to the CNS to continue development before finishing the life cycle via the pulmonary vasculature. Inadvertent ingestion of infective larvae by atypical hosts such as humans, dogs, and horses may lead to aberrant migration in the CNS and signs of verminous meningomyeloencephalitis similar to those described earlier for

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S. vulgaris. Equine cases have been reported for two foals in Australia and an American Miniature Horse foal in Louisiana.[50,51] Larvae migrated in the gray and white matter of the spinal cord and brainstem. CSF analysis revealed mild pleocytosis with small numbers of neutrophils and eosinophils. Specific ELISA tests are available for testing of CSF in humans and dogs.[48]

Draschia megastoma

Draschia (Habronema) megastoma is a spirurid nematode that has been found in the brainstem of a horse from the southern United States.[52] The adult worm is normally embedded in benign pyogranulomatous masses in the equine stomach, but larvae can invade wounds to cause granulating summer sores and have been reported to cause pulmonary nodules. The two unusual features of the solitary report of encephalitis are, first, the parasite found at necropsy was an adult gravid female and, second, there was a quiescent period of 6 weeks during the clinical course when clinical signs improved before again progressing.

Setaria spp.

Setaria spp. are long threadlike filarid nematodes that live without adverse effect in the peritoneal cavities of animals worldwide.[53] Microfilariae are released into the blood of the host and acquired by feeding mosquitoes in which they undergo development to infectious larvae. Bovids outside the Americas are hosts to several setarial nematodes including *Setaria digitata, Setaria labiatopapillosa,* and *Setaria marshalli*.[54-56] When inserted by mosquitoes into atypical hosts such as horses, goats, and sheep, immature *S. digitata* may migrate aberrantly through the CNS and other organs of atypical hosts.[55,57] This parasite has also migrated aberrantly in the CNS of cattle.[58] Outbreaks of so-called epizootic cerebrospinal nematodiasis, lumbar paralysis, or kumri occur during the summer or autumn when mosquito intermediate hosts are active. Outbreaks have been reported in Japan, Taiwan, China, Korea, Sri Lanka, Burma, India, Nepal, Iran, Israel, and Saudi Arabia.[57,59,60] Cases in horses are sporadic and often involve older horses; in goats, young animals are usually affected and morbidity and mortality is up to 100%.[55] *S. digitata* apparently does not occur in the United States[54]; however, a single case of verminous encephalomyelitis due to *S. labiatopapillosa* has been reported in this country.[61]

Clinical signs are variable and are related to mechanical and inflammatory destruction along the tracks left in the brain or spinal cord by one or more larvae.[57,62] In this respect, the pathology of setarial meningoencephalomyelitis is identical to that described earlier for *Strongylus vulgaris*. Changes in the CSF associated with *Setaria* infestation include xanthochromia, pleocytosis (25 to 84 cells/dL), and a slightly increased protein concentration. The cells of one horse contained a small proportion of eosinophils and basophils, but this finding was inconsistent with other reports.

Treatment and Prevention When single or a few migrating larvae are involved, there have been successful outcomes using combinations of anthelmintics and vigorous antiinflammatory treatment. The latter component is likely important to prevent the effects of strong inflammatory responses against killed parasites.[48] Because penetration of the blood-brain barrier by anthelmintics is limited, high-dose benzimidazoles are often used for this purpose. Typical protocols are 10 to 60 mg/kg fenbendazole one to five times daily by mouth or nasogastric tube with 0.05 mg/kg dexamethasone (or equivalent) IV or IM, once or twice daily for 3 days. Ivermectin was effective in goats with early signs of setarial myeloencephalitis[55] but has not been effective in treatment of *P. tenuis* or *H. gingivalis* cases in horses, even when used against *H. gingivalis* at a potentially toxic dose of 1.2 mg/kg (6× the recommended dose).[34] Diethyl carbamazine citrate at 40 to 100 mg/kg daily was effective in natural and experimental setarial cases in horses.[63] Most types of verminous encephalitis are unlikely in horses on a regular deworming program; however, *H. gingivalis* cases regularly occur in horses on any of a variety of regular anthelmintic regimens.

Postanesthetic Myelopathy and Encephalopathy

Mary O. Smith • Robert J. MacKay

A sudden-onset myelopathy has been described in horses and in a single calf after anesthesia.[1-6] Most of the horses were large, young, and in dorsal recumbency under halothane anesthesia. There is a tendency for affected animals to be hypotensive during anesthesia. Paraparesis, ataxia, recumbency, or paraplegia is usually apparent during recovery from anesthesia but may be delayed as long as several days. Other reported signs include cutaneous hypalgesia and areflexia of the hindquarters and occasionally the thoracic limbs. Lesions occur mainly in the lumbosacral spinal cord, although cervicothoracic segments also may be involved. There is malacia predominantly within gray matter (poliomyelomalacia), with associated mild to severe hemorrhage in most cases.

Rare cases of postanesthetic encephalopathy have been described in horses.[5,7] Clinical signs included dementia, pacing and circling, cortical ("central") blindness, ataxia, hypermetria, and recumbency. In mild signs, blindness may be the only clinical sign. The onset of signs ranged from a few hours after recovery to several weeks later. The major pathologic finding in affected horses that did not survive was cerebrocortical necrosis, particularly in regions of the cortex supplied by terminal arterial branches ("watershed zones").

Although the pathogenesis of postanesthetic myelopathy is incompletely understood, it is proposed that compromise to the blood supply to the spinal cord is caused by hypotension or pressure from the abdominal viscera on the great veins (caudal vena cava, azygos vein). Systemic hypoxia, hypovolemia, and hypercapnia may underlie postanesthetic encephalopathy.[7] Factors suspected to increase the risk of postanesthetic encephalopathy include positioning in dorsal recumbency during anesthesia, multiple anesthesias, use of halothane anesthesia, endotoxemia, and shock. Differential diagnoses for myelopathy include orthopedic conditions such as limb fractures, spinal fracture, myopathy, and peripheral neuropathy secondary to recumbency. Differentials for encephalopathy include numerous metabolic, infectious, and toxic disorders. Prognosis for recovery in cases of myelopathy is poor or hopeless. By contrast, most horses with encephalopathy recover completely. The risk of these complications probably can be reduced by supporting adequate blood pressure and ventilation in patients under anesthesia, minimizing anesthesia duration, and avoiding dorsal recumbency whenever possible.

Occipitoatlantoaxial Malformation

Robert J. MacKay • Mary O. Smith

Occipitoatlantoaxial malformations are a heterogeneous group of cranial cervical spinal abnormalities.[1] They occur in cattle, sheep, goats, and horses.[2-5] At least five different types of defects have been reported in horses, as follows[6-12]:

1. A heritable condition in Arabians characterized by symmetric atlantooccipital fusion, atlantalization of the axis, and hypoplasia of the atlantal wings.[1,11,12] A similar disorder has been reported in an Arabian-cross colt.[13]
2. A nonfamilial disease of Quarter Horses with spinal lesions similar to those in Arabians.[6,14]
3. Asymmetric malformations of the occipitoatlantoaxial area in Morgan horses and Standardbred foals.[1]
4. Atlantal duplication in Arabian and Arabian crossbred horses.[8,15]
5. Asymmetric occipitalization of the atlas and symmetric atlantalization of the axis.[1]

Malformations common to the five forms include loss or flattening of the occipital condyles, asymmetric flattening of the articular surfaces of the axis, and shortened dens. The pathogenesis of the vertebral defects is unknown, but a familial form has been demonstrated in the Arabian horse.[11]

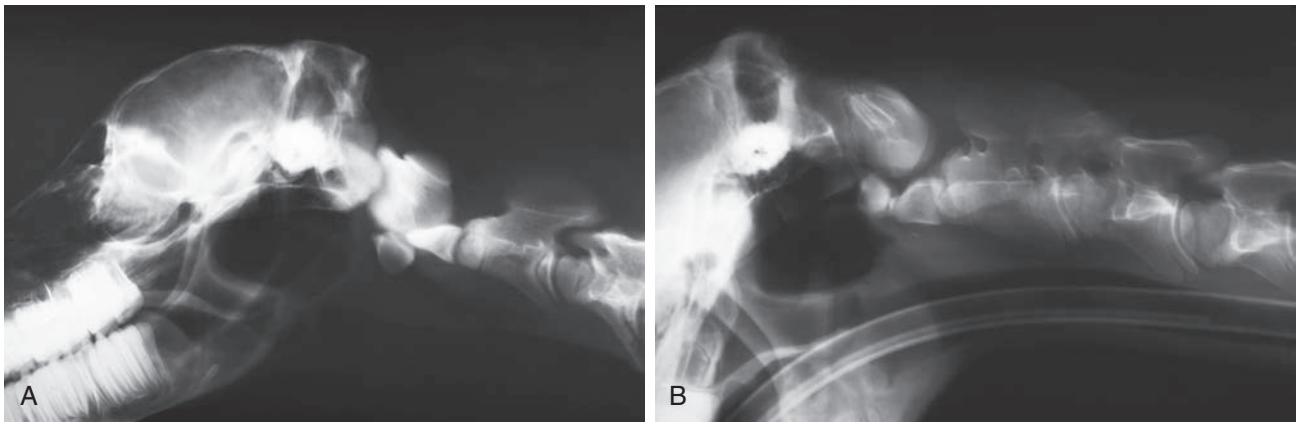


FIG. 35-17 Occipitoatlantoaxial malformation (OAAM). Radiographs of the craniocervical region of a normal neonatal foal **(A)** and a 3-week-old Arabian foal with OAAM **(B).** Note slightly shortened dens, ventral luxation of the dens, cranioventral movement of the body of the atlas to encroach on the guttural pouch, and fusion of the atlas to the occiput with occipitalization of its caudal surface, in the foal with OAAM. *(Images courtesy Dr. I.G. Mayhew, Massey University.)*

The clinical signs range from normal with or without torticollis to brainstem compression, sudden unexpected death, and stillbirth.[1] In typical cases, signs of tetraplegia or tetraparesis begin at or shortly after birth and progress at variable rates. Foals may become suddenly tetraplegic, appear to stabilize for several days, but then die suddenly.[16] In rare cases, horses may not show nervous system signs until 3 years of age.[10]

The signs are symmetric in most affected animals and include hyperreflexia, hypertonia, weakness, and ataxia in all 4 limbs. There may be reluctance to move the neck and head and resistance to manipulation of the area. A click or crepitation may be palpated over the cranial cervical spine when the head is moved.[1,4] With asymmetric bone lesions there often is torticollis, whereas patients with symmetric lesions hold their heads in extension and frequently display the "weather vane" attitude. Neurologic deficits may not be seen despite moderate torticollis.

The malformations are readily apparent radiographically (Fig. 35-17) and by CT can further elucidate the anatomic abnormalities.[14] There may be subluxation of the atlantoaxial joint, ventral displacement of C2 relative to C1, nonunited ossification center of the dens, shortened or elongated dens, shortened transverse process of the atlas, fusion of C1 with the occipital condyles, atlantal duplication, and deviation of the basioccipital bone.[1,17] In sheep, additional malformations of the cervical vertebrae have been seen concomitantly.

Suggested approaches to treatment are surgical fusion of the atlantoaxial joints, with or without a laminectomy.[10,18] Laminectomy alone has been used to alleviate spinal cord compression and clinical signs caused by occipitoatlantoaxial malformation.[19] However, long-term results of surgical intervention have been poor, with neurologic deficits persisting. Closed reduction of the luxated atlantoaxial joint has been similarly unsatisfactory.[14,20] If treated, Arabian horses must not be bred because of the hereditary nature of the disease in that breed.

Congenital Vertebral Anomalies

Mary O. Smith • Robert J. MacKay

A large number of spinal deformities have been reported in domestic livestock including the following:

- *Spina bifida.* Failure of closure of a vertebral neural arch; spina bifida usually occurs together with myelodysplasia.[1]
- *Spina bifida cystica.* Spina bifida associated with a cerebrospinal fluid-filled cyst at the site of the bony defect.
- *Hemivertebra.* A unilaterally incomplete vertebral segment; spina bifida and hemivertebrae have been described in calves, and spina bifida has also been reported in sheep and foals.[1-4]
- *Arnold-Chiari syndrome.* A complex disorder that has been reported in lambs, calves, and a foal[4-6] and is characterized by a group of changes including herniation of cerebellum through the foramen magnum, caudal overgrowth and displacement of the brainstem, internal hydrocephalus, polymicrogyria of the cerebral cortex, malformation of the base of the skull, and enlargement of the foramen magnum. The strong correlation between the occurrence of spina bifida and Arnold-Chiari syndrome of calves indicates that the pathogenesis of the two conditions may be interrelated.[1,4,6]

Animals with spina bifida may be asymptomatic or, in reverse order of frequency, may have signs involving only the hindquarters, pelvic limbs, and hindquarters or all four limbs and the hindquarters. Affected animals that are ambulatory often have a peculiar "bunny-hopping" gait and some or all of the elements of cauda equina syndrome (tail paralysis, perineal and tail analgia, and anal, bladder, and penile paralysis). The clinical signs are often present at birth or develop during the first 2 months of life and are nonprogressive.[7,8] Kyphoscoliosis and abnormalities of the rib cage may be seen at birth in some animals.[8] The skin over the abnormal vertebrae may be smooth and hairless.[9] When examined microscopically, this tissue resembles leptomeninges or ependyma.[2]

Spina bifida and hemivertebrae are easily diagnosed by examination of plain radiographs or CT images. The specific site of central nervous system stenosis can be detected by performing a myelogram, CT, or MRI. The etiology of spina bifida is unknown; genetic and toxic etiologies have been suggested.[10-12]

Arthrogryposis occurs secondary to the spinal cord changes. Spina bifida and myelodysplasias are not the only causes of arthrogryposis, however, and clinicians should attempt to differentiate between these and other diseases that interfere in utero with motor neuron development in the spinal cord. Nongenetic arthrogrypotic conditions of cattle include perosomus elumbis, hydranencephaly, manganese deficiency, and ingestion of lupines or *Nicotiana glauca* (40 to 60 days of gestation).[12,13]

See also Chapters 51 and 52.

Myelodysplasias (Syringomyelia; Spinal Dysraphism; Hydromyelia)

Mary O. Smith • Robert J. MacKay

The following types of myelodysplasia occur in livestock[1-13]:

1. *Spinal dysraphism.* A general term denoting arrested development of the spinal cord before complete differentiation of gray and white matter; the areas of agenesis form longitudinal cystic

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structures instead of differentiated nervous tissue. Most of these anomalies are neural tube defects.
2. *Syringomyelia.* Longitudinal cavitations of the spinal cord.
3. *Hydromyelia.* Abnormal dilation of the central canal.
4. *Diastematomyelia.* Duplication of the gray matter at one or more segments.
5. *Rachischisis.* Complete failure to close the neural tube; the central canal remains open and communicates with the integument.
6. *Meningocele.* Herniation of the dura mater through a vertebral defect (usually spina bifida).
7. *Meningomyelocele.* Herniation of the meninges and spinal cord through a spinal column defect.

Associated abnormal neurologic signs are as described earlier for spina bifida.[14]

Myelodysplasia has been related to genetic factors in Charolais and Hereford calves, although the mode of inheritance is unknown.[3,15] The condition has also been recognized in foals of several breeds.[16-18] In addition to genetic factors are intrauterine BVD infection, hypovitaminosis A or copper deficiency, maternal fever, or exposure to teratogens including substances in species of *Solanum* and *Veratrum*.[19]

The neurologic deficits of myelodysplasia are difficult to differentiate from other spinal diseases unless the disorder is accompanied by spina bifida. Clinical recognition of myelodysplasia is usually based on the historical findings of paraplegia in a newborn calf without radiographic evidence of spinal fractures and with no myelographic evidence of spinal cord compression.

Acquired Torticollis

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Primary acquired torticollis with or without neurologic disease occurs in all species of domestic livestock. Causes include fracture or subluxation of the cervical vertebrae, basilar skull fractures, dystrophic muscle degeneration, unilateral cicatricial muscular contracture from injections, lupinosis, traumatic rupture of the cervical muscles, parasitic migration through the cervical spinal cord, hydranencephaly, asymmetric neurodegeneration, and congenital vertebral deformity.[1-6] One study hypothesized that physical constraint within the narrow tips of uterine horns caused acquired torticollis and a variety of other deformities such as head scoliosis and limb malformations in more than 200 foals.[7] Draft horses may be predisposed to this problem, which frequently results in severe dystocia in horses. Provided the spinal cord is intact, no neurologic deficits result. The current epizootic of fetal Schmallenberg virus infections has caused torticollis with other malformations in calves, kids, and lambs.[8]

Treatment of traumatic torticollis should be directed at reducing the edema, relieving pain, and immobilizing the damaged structures. Muscular tears may be treated by incorporating the head, neck, and proximal thorax in a fiberglass cast. Ancillary supportive treatment may include dexamethasone (0.04 to 0.08 mg/kg IM or IV daily for 2 to 3 days), methocarbamol (8 mg/kg IV daily for 5 days), and NSAIDs (e.g., phenylbutazone PO or IV or flunixin meglumine IV for 3 to 5 days after injury). A method of surgical correction of cervical muscle contractures using a muscle-splitting procedure has been described[9]; however, this seems unnecessary because most animals recover with only medical treatment. When torticollis is the cause of equine dystocia, delivery of the foal by cesarean section is often followed by rapid and complete anatomic and functional recovery.[7]

Tetanus

Robert J. MacKay

Tetanus is characterized by muscular rigidity and spasms. Death is common and results from respiratory compromise or tetanic convulsions. Clinical signs are caused by tetanospasmin (TeNT), an exotoxin produced by the anaerobic, spore-forming, gram-positive bacterium *Clostridium tetani*. Horses are exceptionally sensitive to TeNT; cattle are relatively resistant, and small ruminants have intermediate sensitivity to the toxin. Spores are long-lived and resistant to most disinfectants and environmental extremes. They are not completely destroyed by boiling but can be eliminated by autoclaving at 115° C (239° F) for 20 minutes.[1] *C. tetani* is a ubiquitous soil inhabitant and can be isolated from feces of herbivorous domestic animals, with highest frequency in horses.[2,3] Tetanus is usually a disease of individual animals, but herd outbreaks of tetanus in livestock have been described.[4-8]

Pathogenesis

The most common route of infection is inoculation of wounds with *C. tetani* spores. Deep puncture wounds contaminated by manure, soil, or rusty metal are especially likely to cause tetanus. In horses, such wounds are typically in the lower limb, although contaminated surgical sites, the postpartum uterus, injection abscesses, and infected umbilical structures are also potential sites for *C. tetani* infection.[9-11] Causative wounds are not found or reported in up to 50% of equine cases. Dairy cattle are infected most frequently after bacterial contamination of the uterus postpartum. Reestablishment of anaerobic conditions in the involuting uterus favors germination and proliferation of *C. tetani* spores. Other sites for growth of *C. tetani* in livestock include lesions caused by elastrator bands, sharp castration or tail docking, dehorning or disbudding, insertion of bull rings or ear tags, shearing, fly strike, intramuscular injection of anthelmintics or vaccines, and umbilical infections.[4,5,7,8] Outbreaks of "idiopathic tetanus" occur occasionally in young cattle, usually in association with the grazing of rough, fibrous feed, and it is likely that this is analogous to the pathogenesis of toxicoinfectious and forage poisoning forms of botulism wherein toxin is produced in wounds in the mouth or gastrointestinal tract or ingested preformed in contaminated feed.[12,13]

The crucial event in development of tetanus is germination of *C. tetani* spores followed by vegetative growth and elaboration of exotoxins. Factors that enhance the germination and growth of *C. tetani* include necrotic tissue, pus, concomitant bacterial infection, and foreign bodies. Spores inoculated into the tissues are highly resistant to normal host defenses and may remain dormant for months or years before germinating. *C. tetani* produces at least two exotoxins: *tetanospasmin* and *tetanolysin*.[14] *Tetanolysin* damages viable tissue, thereby lowering the redox potential and creating favorable conditions for expansion of the anaerobic infection.[3] The neurotoxin tetanospasmin (TeNT) is a 150-kD polypeptide that is immediately cleaved by tissue proteases into active heavy and light chains connected by a single disulfide bond. It diffuses from the site of production into the vascular system and is distributed hematogenously to somatic neuromuscular junctions and autonomic ganglia, where it binds to nerve terminals. Once bound, the toxin is internalized and transported retrograde in axons of both somatic and autonomic motor neurons at 75-250 mm/day.[15] After 1 to 14 days the toxin enters the CNS, reaches the neuronal cell body, traverses the synaptic cleft, and binds irreversibly to presynaptic inhibitory interneurons. Intact toxin is internalized, and then light chain is released into the cytosol, where it acts to inhibit membrane fusion and recycling, events crucial in the release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA).[14] The resulting disinhibition of motor neurons is the proximate cause of muscle rigidity and spasms.[3]

Preganglionic autonomic motor neurons in the lateral column of the gray matter and parasympathetic centers in the brainstem are affected by a similar mechanism but with delayed kinetics compared with somatic motor neurons.[16] Both a basal increase in sympathetic activity and episodes of intense hyperactivity ("autonomic storms") occur, involving α-adrenergic and β-adrenergic receptors. During autonomic storms there is up to a 10-fold increase in the concentration of circulating epinephrine. The resulting sympathetic overactivity causes hemodynamic instability and is an important cause of death in ventilated human tetanus patients.[17] Its significance in large animal patients is unclear.

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Neuronal binding of toxin is thought to be irreversible.[18] Recovery requires sprouting and growth of new nerve terminals, a process that is completed in weeks to months.

Diagnosis Routine blood work is unhelpful, and abnormalities found are nonspecific. Gram stain of wound exudates reveal the characteristic drumstick-shaped gram-positive bacilli in about 30% of human tetanus patients,[19] but Gram stain and culture are seldom attempted in large animals with tetanus. With the development of a real-time PCR assay for the TeNT gene,[20] timely confirmation of *C. tetani* wound infection is now theoretically possible and may have application to veterinary cases.

Necropsy findings of animals with tetanus are nonspecific with secondary signs of musculoskeletal trauma and pulmonary congestion, atelectasis, and edema most common.[9,10] The diagnosis can theoretically be confirmed by detection of TeNT antigen in spinal cord ventral or intermediate horn cells by immunohistochemical staining with antibody directed against tetanus toxin.[21]

Clinical Signs Signs occur 1 to 60 days after wound inoculation by *C. tetani* spores with most animals affected between 7 and 21 days.[9,10] The incubation period varies depending on the size of the wound, redox potential of the contaminated tissue, number of spores inoculated, and host's antitoxin titer. Probably because cranial somatic nerves are shorter then nerves to the limbs, the first signs of tetanus are associated with rigidity of muscles around the head and neck. These signs are commonly missed in livestock that are not closely watched but are usually recognized in horses. Increased tonus of the masticatory muscles (trismus), rigidity of facial expression (risus sardonicus), and neck stiffness are typical early signs.[9,22] Prolapse of the membrana nictitans begins during this phase and may be a prominent sign in the horse but is inconsistent in cattle and usually not seen in sheep.[12] The head and neck are held in an extended position, and the face has a fixed anxious expression. The ears and commissures of the lips are retracted caudally, and the upper eyelids are elevated. Often the mouth is clamped shut and the jaws cannot be pried apart manually (lockjaw). Hyperthermia (usually <102.5° F) occurs in some animals during the early stages, and rectal temperature may rise further after tetanic convulsions.

In mildly affected animals, signs may be restricted to the head and neck; however, in most cases, generalized spasticity is evident within the first 2 days. The limbs, back, and neck are held in a characteristic rigid extended posture that resembles the legs of a sawhorse (i.e., "sawhorse" stance).[9] The tail is elevated from the ischiorectal fossa (i.e., "pump handle"). Affected animals display a stiff, toe-scuffing gait and an extended head posture. Gas bloat usually begins during the first 24 hours in ruminants and camelids, and colic is occasionally an early sign in horses.

In all cases of generalized tetanus, tonic muscle spasms develop shortly after the onset of rigidity. These can be initiated by external tactile, visual, emotional, or auditory stimuli or by voluntary movements such as posturing to acquire food or water, urinate, or defecate. The limbs and head are resistant to passive flexion and dramatic responses to even minor stimuli manifest as hyperresponsiveness or hyperesthesia. When the face is touched, there is reflex retraction of the eye and prolapse of the nictitans.[12] This is inconsistent in cattle and sheep. Attempts to chew or suckle set off rounds of masseter contractions that are easily visible under the skin. Unmasticated feed is lodged in the cheeks or between the teeth. Even if ingesta can be moved to the pharynx, reflex pharyngeal and laryngeal spasms result in nasal regurgitation, drooling of saliva, and stridor. Aspiration pneumonia may develop as a result of impaired swallowing.

Disturbances of autonomic function have not been well documented in large animals but are presumed to occur after the development of muscle spasms, as is the case in humans with tetanus.[17] There may be increased or dramatically fluctuant heart rate and blood pressure with profuse sweating in horses.[9,11] It is not clear whether these signs represent TeNT-induced sympathetic overactivity or are physiologic responses to the pain of and anxiety caused by muscle rigidity and spasms. Signs of sympathetic overactivity are usually overlooked until after muscle spasms have been controlled. It is reported in humans that hypersalivation, increased respiratory secretion, and late-onset hypotension occur because of parasympathetic overactivity.[23]

Severely affected animals are at high risk of falling to the ground, especially during spasms. Once recumbent they lie in lateral recumbency with the head and legs in full extension and the ears held almost parallel to the back. Frothy saliva accumulates at the commissures of the lips because the animals are unable to swallow. Spontaneous deaths are usually due to respiratory failure because of laryngeal spasm and asphyxia; contractions of the chest wall, diaphragm, and abdomen; accumulation of excessive respiratory secretions; and aspiration pneumonia. Autonomic overactivity may cause fatal cardiac dysrhythmia or heart failure and death secondary to hypertension. Ventrolateral strabismus and dilated, fixed pupils may occur in advanced tetanus of cattle. Animals often die during a tetanic convulsion.

Treatment The general principles that guide tetanus treatment of large animals are as follows: provide muscle relaxation, ensure good footing, eliminate the infection, neutralize the unbound toxin, maintain hydration and nutritional status, and establish active antitoxic immunity.[24]

PROVIDE MUSCLE RELAXATION. All possible external stimuli including light and noise should be minimized. Packing the ears with cotton to minimize auditory stimulation can also help reduce muscle spasms. Sedatives and muscle relaxers are used for control of muscle spasms and rigidity.[25] The cornerstone of this approach is the combination of a phenothiazine-based ataractic sedative such as acepromazine with a GABAergic agent such as pentobarbital or diazepam.[18] An IV catheter should be placed to minimize treatment-associated stimulation. In mild to moderately affected animals, acepromazine (or chlorpromazine) produces obvious muscle relaxation within minutes of treatment that lasts for hours. Acepromazine additionally has α-adrenergic antagonist and anticholinergic actions that may help suppress autonomic overactivity.[26] Pentobarbital sodium provides additional muscle relaxation in cattle but in horses must be titrated carefully in order to avoid recumbency.[9,27] Phenobarbital, at a dose of 10 mg/kg IV and then by NG tube q8h, provided effective muscle relaxation for a neonatal foal with tetanus that had not to that point been controlled by high and frequent doses of diazepam.[28] Large doses of diazepam or midazolam by repeated injection or constant rate infusion (CRI) are effective for control of muscle rigidity, but these drugs are expensive and impractical in many settings. The direct muscle relaxant dantrolene is used in horses for prevention of myopathy and might have application to the treatment of tetanus. This drug has been used successfully in human tetanus.[29] Methocarbamol, glycerol guaiacolate, mephenesin, and d-tubocurarine have all been used for muscle relaxation in horses with tetanus but have not found wide application.

Magnesium infusion has multiple potentially useful actions against spasms and autonomic dysfunction and is inexpensive. It blocks neuromuscular transmission, interferes with catecholamine release from nerves and the adrenal medulla, reduces receptor responsiveness to released catecholamines, antagonizes the actions of calcium, and is an anticonvulsant and vasodilator.[30,31] Magnesium has been shown to reduce the requirements for other drugs used to control muscle spasms and cardiovascular instability in human tetanus patients.[30] Interestingly, electromyographic studies show that magnesium tends to spare the respiratory muscles, which is a marked advantage. Effective serum/plasma Mg concentrations are 5 to 10 mg/dL. An electrocardiogram should be monitored continuously and infusion discontinued if the width of the QRS complex increases by more than 25%.

ENSURE GOOD FOOTING. The affected animal should be moved carefully to a large well-bedded stall. Feed and water should be hung

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so that the animal does not need to lower its head. Horses and, theoretically, cattle, in danger of falling may be maintained in a body sling, tackle and girdle, stocks, or walking frame. Appropriate caution must be exercised to ensure that such procedures do not cause the patient to become frantic.

ELIMINATE THE INFECTION. Because *C. tetani* grows in nonvascularized sites, the infection is best eliminated by surgical débridement of the affected area. If a recent wound or other infection can be identified, it must be opened, cleaned, débrided, and flushed. Penicillin (22,000 IU/kg as procaine penicillin G IM bid) traditionally has been given to kill remaining *C. tetani* organisms and remains the drug of choice for food animals; however, there is a theoretical concern that penicillin has anti-GABA and proconvulsant activities.[32] Metronidazole is now the preferred antimicrobial[26] and has outperformed penicillin in two clinical trials of human patients. It can be given at 20 to 30 mg/kg PO every 12 hours (q12h) for 3 to 5 days. If the horse's condition precludes oral medication, give 40 to 60 mg/kg per rectum, or 10 to 20 mg/kg IV q6-8h (neonates).

NEUTRALIZE THE UNBOUND TOXIN. Tetanus antitoxin (TAT) can be infiltrated into the tissues around the lesion, although this procedure is not recommended in protocols for treatment of human tetanus.[3] Despite the lack of evidence for efficacy of large TAT doses, it is prudent to ensure neutralization of any residual unbound toxin by administration of at least 20 IU/kg IV, IM, or SC, repeated daily for up to 5 days. The results of intrathecal therapy as reported in small case series in horses have been inconclusive.[9,10,33] Although the data for human studies prior to 1991 were not supportive, meta-analysis of 12 more recent studies of both neonatal and adult cases detected a statistical survival advantage for intrathecal versus intramuscular TAT.[34] A suggested protocol is 400 to 1000 IU/kg by slow installation via the lumbosacral space including frequent cycles of aspiration of CSF into the loaded installation syringe in order to dilute the biologic before delivery. Alternatively, TAT can be infused into the AO cistern, but this route requires general anesthesia. Because of severe reactions to intrathecal equine serum in ruminants, intrathecal administration of equine-origin tetanus antitoxin is contraindicated.[24] Administration of TAT has been associated with acute hepatic necrosis in horses.[35,36] The first clinical sign of this potentially fatal adverse reaction may appear 4 to 10 weeks after administration of TAT and has been reported in horses that received TAT for treatment of clinical tetanus (see Acute Hepatitis in Horses, Chapter 33).

MAINTAIN HYDRATION AND NUTRITIONAL STATUS. The patient's hydration and food intake should be monitored daily. Food should be placed off the ground in an elevated feed bunk or hay net to allow easier access. Intravenous fluids should be administered as needed to correct dehydration and electrolyte abnormalities. Alimentation via a nasogastric tube may be attempted in horses with tetanus, but because of adverse reactions, supplementation via an indwelling esophagotomy tube or IV may be necessary. A 5- to 10-cm-diameter rumenostomy should be created in cattle with anything more than mild tetanus.[37] This has the dual advantage of relieving bloat and providing a portal for water and feed (usually alfalfa pellets).

ESTABLISH ACTIVE ANTI-TOXIC IMMUNITY. Clinical tetanus does not elicit a protective immune response. Affected animals should begin a primary toxoid series (see Prevention later).

Prognosis

The fatality rate for adult dairy cattle is up to 50% and, for horses, was 75% and 68% in the most recent North American and European series, respectively.[9,10,24] Outbreaks of tetanus associated with contaminated procedure wounds in small ruminants usually have high mortality rates (>80%). Most animals that die are recumbent by 24 to 48 hours after admission. In survivors, there is usually stabilization of signs by 2 to 7 days, with gradual recovery over the next several weeks. However, one horse reportedly remained stiff at 6 months but was normal at 9 months after onset of signs.

On the basis of various prognostic scoring systems used for human tetanus[26] and the few small large animal series published, negative prognostic indicators are incubation period less than 7 days, period of onset (time from first sign to first spasm) less than 2 days, umbilical or uterine entry site, no vaccination within the previous year, and presence of comorbid disease. Severe signs at presentation, recumbency, or initial rapid progression of clinical signs are all predictive of poor outcome.

Prevention

Because cattle are more resistant to tetanus than horses and small ruminants, they are not routinely immunized against the disease unless outbreaks have occurred previously.[24] Nonvaccinated adult horses should be given an initial two-dose series of tetanus toxoid administered 3 to 6 weeks apart. Protective responses are usually attained within 2 weeks after the second dose. Current recommendations are to give booster doses annually thereafter or additionally at the time of injury or surgical procedure.[38] Broodmares should be revaccinated 4 to 6 weeks before foaling to provide for colostral transfer of immunity to their foals. Passively transferred antibody suppresses the IgG response of foals to toxoid vaccination at 3 months but not 6 months of age.[39] Therefore it is recommended that foals from vaccinated mares be given a three-dose initial series beginning at 4 to 6 months of age, with a second dose 4 to 6 weeks later and the third dose at 11 to 12 months. Foals from nonvaccinated mares are vaccinated three times at 4-week intervals beginning at 1 to 4 months of age. Pregnant ewes and does should be boostered with *C. perfringens* types C and D/tetanus toxoid trivalent vaccine approximately 4 weeks before parturition to cover lambs and kids during the early high-risk period around common husbandry procedures.[40] Young replacement animals can be given a primary series of inoculations at 1 and 2 months of age and annual boosters thereafter.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of one vial of antitoxin (1500 IU) to a nonvaccinated horse provides immediate protection that lasts for 2 to 3 weeks. Antitoxin is indicated in foals from nonvaccinated mares and in any wounded horse that has not been vaccinated within the previous year. In these cases, antitoxin and toxoid should be administered concurrently, with separate syringes at separate sites. Because the use of antitoxin is associated with hepatic necrosis (serum hepatitis) in a small number of horses, antitoxin should not be given in horses that are adequately covered by toxoid vaccination.

Spinal Abscesses

Lisle W. George

Definition and Etiology

Most abscesses of the spinal cord originate from a preexisting vertebral body osteomyelitis. The bone is usually infected hematogenously. Extension of bacteria from the lungs, heart, or a septic injection site is common. Neonates frequently develop vertebral abscesses secondary to septicemia.[1,2] Bone lesions may develop from sequestra broken from fractured vertebrae. Epizootics of spinal abscesses can result from injection of contaminated vaccines or mineral supplements near the spinal column. Similarly, spinal abscesses may be seen along with other diseases in groups of animals that are immunocompromised.[3] Infectious agents isolated from spinal abscesses of ruminants include *Corynebacterium pseudotuberculosis, Arcanobacterium pyogenes, Mannheimia haemolytica, Staphylococcus aureus,* and *Fusobacterium necrophorum.*[1,4-6] Agents typically found in vertebral infections of foals include β-hemolytic streptococci, *Salmonella* spp., *Actinobacillus equuli, Escherichia coli, Rhodococcus equi,* and *Klebsiella pneumoniae.*[6-10] In rare cases, septic arthritis of the atlantooccipital joint may result from extension of a mycotic guttural pouch lesion.[11,12]

If the infectious agent remains localized in the vertebral body, the patient usually shows signs consistent with a transverse myelopathy. If the infection erodes through the dura mater, the animal develops signs of septic meningitis. If the bone infection is extensive, the

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vertebrae may fracture suddenly, resulting in signs characteristic of spinal trauma.

Clinical Signs The neurologic deficits of animals with vertebral body abscesses without pachymeningitis are similar to those described previously for spinal fractures.[5] Animals with mildly compressive cervical abscesses show a characteristic "weather-vane" attitude, appear stiff, and are reluctant to eat food from the ground.[5,7,8] Ruminants with this lesion hold the neck in extension and attempt to prehend the food from the ground by using their tongue.[5] Additional signs of spinal abscess include heat, pain, swelling, or crepitus over the affected areas and associated signs of bacteremia. Abscesses in the thoracolumbar spine cause hindlimb weakness and ataxia of variable severity, from mild gait abnormalities to complete recumbency. Stud males may be unable to breed because of weakness and pain.[13] Differential diagnoses include trauma, aberrant parasite migration, tumor and pathologic fractures, hemorrhage into or around the spinal cord (e.g., postanesthetic myelopathy), myopathies, caprine arthritis-encephalitis, and fibrocartilaginous embolism.[14] Spinal abscesses can be mistaken for other painful conditions such as orthopedic disorders or traumatic reticuloperitonitis.[15]

Clinical Pathology and Radiographic Findings Radiographs are the best method for obtaining a definitive diagnosis of spinal abscess. A random pattern of lucency and increased bone density characteristic of osteomyelitis is seen in the affected vertebrae, with or without adjacent soft tissue mass lesions indicative of abscess formation.[16] Diskospondylitis usually results in detectable osteolysis in the intervertebral joints.[7] Nuclear scintigraphy can be used when the bone lesions are not well defined in plain film radiography.[17] In addition, myelography can be used to detect the specific site of the spinal cord compression.

A CBC may indicate the presence of a chronic inflammatory focus. Specific changes in the CBC include hyperfibrinogenemia, neutrophilia, monocytosis, nonresponsive anemia, and left shift. The plasma globulin levels are often increased in adults but may be increased or decreased in neonates, depending on the adequacy of colostral immunoglobulin transfer.

The changes in the CSF depend on the location of the abscess in the nervous system tissue and the meninges. In most cases the abscess does not infiltrate through the meninges, and the CSF is normal or shows xanthochromia and mild increases in the protein concentration (60 to 120 mg/dL), with mild to no increase in nucleated cell count.[18] The CSF of animals with pachymeningitis contains high numbers of WBCs (>100 neutrophils/μL) and a greatly increased protein concentration (>200 mg/dL). The CSF may clot after collection because of high concentrations of fibrinogen. Bacteria may be observed in a Gram-stained smear of CSF sediment. Spinal abscesses have been associated with *Brucella abortus* and *Mycobacterium bovis* in horses, so affected horses should be tested for exposure to these organisms.[19,20]

Pathophysiology Hematogenously derived abscesses arise because of embolization of septic thrombi into the metaphyseal arteries. These vessels have a sluggish blood flow because they become tortuous as they approach the physis. The metaphyseal vessels communicate with the ventral vertebral plexus, which in turn drains into the post cava, portal vein, and pulmonary veins. The ventral vertebral plexus does not have valves; blood flow reverses with an increase in abdominal or pleural pressure. Regurgitated blood from infected sites in the body cavities may shower the vertebrae and spinal cord with bacteria.[4,17]

Necropsy Findings The most common sites of involvement are the costovertebral and intervertebral articulations and the vertebral body epiphyses.[21] Lumbar vertebrae are frequently involved. The bone is uneven, deformed, and softened. The abscessed area is interspersed with calcified trabeculae and pockets of necrotic debris. Sequestration of necrotic bone may be seen in some cases. The meninges may be adherent to the abscessed site, and occasionally a fistulous tract may be seen from the center of the abscess pocket to the subarachnoid space. In other cases the abscess is compartmentalized away from the CSF, but the proliferating bone impinges on the spinal cord.

Treatment and Prevention If spinal abscessation is recognized early, prolonged antimicrobial therapy is generally effective. Selection of the appropriate antimicrobial agents should be based on the results of cultures from the patient's blood, urine, feces, and CSF. When bacteriologic culturing is inconclusive, a broad-spectrum antimicrobial should be chosen. Phenylbutazone, flunixin meglumine, or aspirin may be administered for pain relief. Immobilization of the head and neck in a fiberglass cast extending from the thorax to the nose may provide support to smaller patients with a cervical abscess. Surgical drainage of the abscess and curettage of the necrotic bone may be feasible in animals with sufficient economic value to justify the procedure.[10,22] Surgical intervention in adult cattle and horses is usually difficult because of the size of the epaxial musculature and inaccessibility of the spine in large animals.

Triaryl Phosphate Poisoning (Chronic Organophosphate Poisoning; Dying-Back Axonopathy)

Ingestion of lubricants containing triaryl phosphates causes a neurologic disturbance of livestock characterized by a delayed neuropathy resulting in incoordination and paralysis. Common sources of the triaryl phosphate esters include motor lubricants, hydraulic oils, industrial solvents, plasticizers, and automotive brake fluid. Chronic organophosphate poisoning also occurs in some families of sheep after treatment with organophosphorous anthelmintics.[1]

Triaryl phosphates have few effects on the glial cells,[2] but they have profound neurotoxicity for the longest axons.[3] These fibers degenerate first at the distal, nonterminal areas. The degenerative lesions then spread proximally from the terminal nerve rootlets into the spinal cord until the cell body dies (dying-back axonopathy). Dosages of triaryl phosphate ranging from 5 to 10 g/kg cause paralysis by 19 to 36 days after exposure.[4]

Clinical Signs The onset of slowly progressive neurologic signs occurs about 10 days to a few months after exposure.[5-7] The clinical signs of chronic organophosphate intoxication are rough hair coat, bloat, dyspnea, muscular weakness, and incoordination of the rear legs. The animals may slip on their hindlimbs and assume a dog-sitting posture. The limbs are circumducted and lack normal conscious proprioceptive responses. Affected animals become recumbent. When they attempt to rise, they do so incompletely and fall. Muscular tone and flexor reflexes may be normal, or flaccid paralysis may be evident.[6] The tail, bladder, and rectum are often paralyzed, and affected animals show signs of incontinence, constipation, and perineal scalding. Slight ventrolateral strabismus has been described, and some animals have been reported to become mute.[7,8] Most animals retain a normal appetite and sensorium during the development of the paralysis. Electromyographic changes in experimentally poisoned animals include increased insertional activity, positive sharp waves, and fibrillation potentials in the muscles of the hindlimb, consistent with denervation of affected muscles.[9] Organophosphate-induced neuropathy has also been reported in horses, where the most striking clinical sign was bilateral laryngeal paralysis.[10,11] Degeneration similar to that caused by delayed organophosphate toxicity in other species was most severe in the recurrent laryngeal nerves, but milder changes were present in other peripheral nerves.

Pathology Laboratory confirmation of the condition is usually based on histopathologic detection of a dying-back axonopathy. Clinical pathologic parameters are usually normal. The RBC

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cholinesterase is low or undetectable at clinical onset but may return to normal concentrations by the time the animals display profound paralysis. The specific concentration of cholinesterase depends largely on the type of organophosphate and the patient's genetic ability to metabolize the toxic compounds. Whole-blood cholinesterase concentrations in haloxon-treated esterase A–deficient animals remain significantly lower than in controls for at least 27 days after administration of 375 mg. In comparison, the enzyme concentrations in the plasma of normal sheep do not decrease after drug treatment.[12] Cholinesterase levels in exposed animals are not predictive of the later onset of delayed neurotoxicity.[7]

Macroscopic lesions are not usually seen. Microscopic lesions are found exclusively in the central nervous system, and their severity appears to be dose dependent. The lesions begin distally and progress retrograde along the long, unsynapsed proprioceptive and motor tracts. The dorsospinal, cerebellar, gracile, and cuneate tracts are most susceptible to the effects of the toxins.[9] Specific lesions include demyelination, internodal axonal swelling, and Wallerian degeneration. There is also a vacuolation of the large neurons of the ventral motor nucleus of the spinal cord. The mechanism of neurotoxicity is unknown, but alteration of a cell membrane protein found in neurons and some other cells has been implicated.[12-14] This protein has been designated a "neuropathy target esterase" and is thought to be "aged" by phosphorylation induced by the toxicosis.

Newer compounds in the triaryl phosphate group are less capable of causing delayed neurotoxicity, which offers some hope that the incidence of this type of toxicity may decline in the future.[14] Delayed organophosphate toxicity is not treatable and is irreversible.

Motor Unit and Cauda Equina Diseases

Botulism

Robert J. MacKay

Botulism is a highly fatal disease characterized by muscle flaccidity and progressive generalized paralysis. Death results from euthanasia or respiratory failure. Clinical signs are caused by the potent botulinum neurotoxin (BoNT), an exotoxin produced by the anaerobic, spore-forming, gram-positive bacterium *Clostridium botulinum*. Eight distinct antigenic types have been identified: A to G, with C1 and C2 subgroups.[1,2] All but C2 are BoNT toxinotypes. Two other clostridial species, *C. barati* and *C. butyricum,* also produce BoNT. Mosaic recombinant toxins, with either type C or type D light chains, designated BoNT/CD and BoNT/DC, have increasingly been identified in outbreaks of bovine botulism in Asia and Europe and likely are the dominant toxinotypes of animal botulism in Europe.[3,4] *C. botulinum* spores are ubiquitous in the soil and marine sediments of most regions of the world. In general, soil-origin botulism in large domestic animals in the United States is caused by BoNT/A and BoNT/B (and occasionally BoNT/C), whereas botulism caused by contamination of feed by animal carcasses is BoNT/C and BoNT/D. Botulism caused by *C. botulinum* type B is endemic among horses in Kentucky and in the mid-Atlantic states and accounts for most cases in the United States.[5] Almost all type A equine cases and outbreaks in the United States have occurred in western states, with Oregon and Idaho overrepresented.[6] Type C cases occur sporadically throughout the country, and type D botulism has rarely been reported in horses.[5] BoNT is acquired either by ingestion of preformed toxin (forage poisoning), germination of ingested spores in the GI tract (toxicoinfectious botulism), or contamination of wounds with spores and subsequent vegetative growth and toxin production (wound botulism).[6] Forage poisoning is the most common route of infection, although shaker foal syndrome, a form of toxicoinfectious botulism caused by *C. botulinum* type B, is endemic in the United States.[5]

Horses are much more susceptible to the effects of botulinum toxin than are cattle.[5] In fact, horses and humans are among the most sensitive mammals.[1] Botulism in horses typically affects one or a few members of a group. By contrast, the disease in cattle is usually in the form of outbreaks.[5] Increasingly, these outbreaks in cattle have been associated with ingestion of poultry litter.[7-10]

Pathogenesis The seven authentic BoNTs, BoNT mosaic toxins, and tetanus neurotoxin (TeNT) are closely related 150-kDa proteins that differ in receptor and substrate specificities.[1] Unlike TeNT, which is released alone, BoNTs are associated with a variable number of accessory proteins. It is believed that these proteins stabilize BoNTs during transit of the stomach and then may facilitate transport across intestinal epithelial cells. BoNTs are distributed hematogenously to bind to presynaptic cholinergic nerve terminals, most importantly at the somatic neuromuscular end plate. Tissue proteases activate the toxin by cleavage into light and heavy chains connected by a disulfide bridge. After receptor-mediated internalization of BoNT in endosomes, the light chain, which is a zinc endopeptidase, is released into the cytosol, where it inactivates the SNARE complex and thereby prevents docking and fusion of synaptic vesicles.[1] Vesicles containing acetylcholine are thus prevented from undergoing exocytosis and release of neurotransmitter at the neuromuscular junction. Flaccid paralysis of striated muscle is the main clinical result; however, there is also paralysis of smooth muscle and failure of parasympathetic effector functions. Once toxin is bound at the motor end plate, recovery is only possible by the sprouting of new axons and formation of new motor end plates, a process that requires weeks to complete.

Soil contamination of forage (including pasture) is the usual cause of botulism affecting one to several animals in the United States. In endemic areas of the United States this is almost always caused by BoNT/B; cases associated with type BoNT/A are also reported.[5,6] In small outbreaks or individual cases involving types C and D (or mosaic toxins), it is often not clear whether the source is carrion or soil contamination. Birds may play a role in carrying spores from a carcass to feeding areas.[5,11-13] Large outbreaks of food-borne botulism are of two types: germination of *C. botulinum* spores and bacterial growth in spoiled or moldy forage and point contamination of feed (forage or concentrate) by animal carcasses. Spoiled forage can be in the form of hay (especially large bales) or chaff or even grass clippings stored improperly or left out to rot, but usually it involves some type of improperly fermented forage.[5,14-16] Conditions of high pH, low oxygen, and high water content favor spore germination and toxin production.[17] Traditionally, small-grain silage (i.e., rye, wheat, oats, and barley) has been a common source of botulism for cattle,[18] but corn silage has also been implicated in several outbreaks.[13] The use of plastic film or bags to envelop (or encircle in the case of round bales) partially dried cut forage has become a popular way to produce and preserve silage and haylage for both cattle and horses. Unfortunately, plastic-wrapped forage has been the source of numerous outbreaks of botulism in both species.[5,18-20] These outbreaks have usually involved *C. botulinum* types B or A. In many cases, the plastic on the offending bale is found to be torn.[5] Accidental incorporation of an animal corpse into feed can have devastating consequences. For example, a single cat carcass that contaminated feed caused the deaths of 420 cattle.[5,21] Carcass-origin botulism is usually BoNT/C, BoNT/D, or, perhaps more often, either of the mosaic variants BoNT/DC or BoNT/CD.[14,22] Rodents can be caught in a grain auger and contaminate cereal grain or killed by hay mowers and incorporated into the center of bales. Poultry litter has become by far the most important source of carrion-based botulism. Processed broiler litter is widely used as a cheap source of nonprotein nitrogen in feed for beef cattle and as a fertilizer for pastures and hayfields. Accidental incorporation of chicken or rodent carcasses into these litter products has resulted in botulism outbreaks all over the world affecting up to 5500 steers in a single outbreak.[7-9,23,24] For this reason, feeding of poultry litter to cattle is now banned in Australia and guidelines are provided for resting of pasture after litter fertilization. Even free-ranging poultry were suspected as a source of botulism in outbreaks in dairy herds in the Netherlands.[25] Type D botulism in cattle has

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been associated with osteophagia (chewing on bones of decaying carcasses) by cattle deficient in phosphorus.[17]

C. botulinum can colonize the GI tract of normal infants or adult humans whose intestinal microflora has been disrupted by intercurrent disease or antimicrobial treatment. Shaker foal syndrome, an endemic form of toxicoinfectious botulism caused by *C. botulinum* type B, is of this type.[26] The peak age of occurrence of shaker foal syndrome is 4 weeks, with 70% of cases occurring between 2 and 6 weeks of age.[5] The juvenile equine GI tract, possibly influenced by putative risk factors such as a high milk intake, gastric ulceration, and heightened stress, is relatively hospitable to colonization and toxin production by the organism.[27,28] Toxin is detectable in the feces of approximately 30% of shaker foals, but only in the acute clinical phase of the condition.[5] Normal intestinal flora of mature horses presumably are inhibitory to colonization by *C. botulinum*.

Diagnosis Routine bloodwork is unhelpful, and abnormalities found are nonspecific.

Demonstration of botulinum toxin or spores is required for diagnosis. The level of diagnostic support ranges from definitive to presumptive for detection of the following: (1) botulinum toxin in serum, GI contents, or wounds; (2) antibodies against botulinum toxin in the serum of convalescent animals; or (3) *C. botulinum* spores in the GI contents or suspect feed materials. Toxin is detected by the sensitive mouse lethality bioassay and typed by mouse protection experiments. With mosaic toxins, mice may be protected by both type C and type D antisera, likely explaining why many outbreaks are recorded as involving both toxinotypes.[29] Detection of toxin in serum is only possible in animals with peracute onset and rapidly progressive clinical signs and is more likely in cattle than horses.[17] Spores are detected by inoculation of mice with culture filtrate after incubation of samples anaerobically for several days in enrichment media.[6] ELISA and real-time PCR tests have been used on enriched samples to detect and distinguish botulinum toxins or toxin genes, respectively.[3,30,31] Spores are found in the feces of approximately 34% of adult horses and 70% of foals affected with endemic type B botulism but are rarely detected in samples from normal foals or adult horses.[5] The presence of toxin antibodies in survivors has been used diagnostically in outbreaks of type C and D botulism in cattle in Australia[32] but lacked sensitivity when used in similar outbreaks in England and Wales.[33]

Needle electromyography and decremental responses to repetitive nerve stimulation can be used to support the diagnosis.[34,35] Typically, no obvious gross or histologic lesions are associated with botulism in most species.

Clinical Signs The severity and rate of progression of clinical signs are dose dependent. Horses given low (e.g., 10^3 mouse lethal dose units) or very high (e.g., 10^8 units) doses of BoNT display the extremes of the clinical spectrum of botulism.[36] The low dose may only cause dysphagia with some progression over 5 to 7 days, then recovery with minimal treatment. By contrast, the high dose causes recumbency within 8 to 12 hours and death within 48 hours of the first detectable signs. After high experimental doses, signs may begin as soon as 12 hours after toxin challenge, whereas cases may continue to develop for up to 14 days after removal of the suspect feed source when low amounts of toxin have been ingested.

Signs of dysphagia, lethargy, and generalized muscle weakness are the first indications of most naturally occurring cases. In horses, an early sign that can be exploited diagnostically is slow, clumsy prehension and swallowing of concentrates. Normally, bright horses require less than 2 minutes to eat 250 mL of sweet feed from a shallow pan; horses with botulism might take at least twice as long. Efforts to swallow are made with the head extended and seem exaggerated and prolonged; mixtures of food and saliva are retained in the cheeks, between the teeth, or drop out of the mouth. There are often thin trails of green-stained saliva from each nostril. Endoscopic examination of the nasopharynx usually reveals persistent displacement of the soft palate and aspiration of feed into the trachea. With progression, water runs freely from the nostrils during attempts to drink. Drooling of saliva in cattle is continuous, although the volume is usually not great, perhaps because of inhibition of saliva production by BoNT. In foals, dysphagia is evident during attempts to suckle as spillage of milk from the mouth and regurgitation through the external nares. Some horses present with colic, and most have reduced auscultable borborygmi. Affected cows have decreased strength and frequency of rumen contractions and firm feces.

Although animals showing the first signs of botulism may appear obtunded, it is facial muscle weakness and lack of facial expression that creates this impression. Even mildly affected animals tend to lie down more frequently than usual. With stimulation, such an animal may stand and initially walk quite normally before moving in a progressively more stilted and hypometric manner. When the patient is made to stand in one place, tremors may be apparent in the triceps muscles. As the disease progresses, tremoring spreads to other antigravity muscles and increases in intensity until the animal collapses into recumbency. Prominent, generalized tremors of this type in foals in the United States with endemic toxicoinfectious botulism gave rise to the descriptive name "shaker foal syndrome."

Tongue weakness is an important and consistent early clinical sign and, at least for type B botulism, a reliable indicator of impending limb weakness in at-risk cattle and horses. Tongue tone is assessed for this purpose as the ability of the animal to withdraw its tongue back into the oral cavity after the tip has been pulled out several inches through the interdental space. Another sign of myasthenia around the head is jaw "looseness," evaluated in cattle as lack of resistance to forced lateral movements of the lower jaw. Mydriasis and sluggish pupillary light reflexes are variable early signs; the prominence and persistence of these signs likely corresponds well with the dose and type of botulinum toxin ingested.

Between episodes of recumbency, moderately affected animals walk with a slow, shuffling, toe-scuffing gait and the head is held progressively lower.[22] Recumbent animals mount increasingly more ineffectual attempts to stand and often adopt unusual positions while recumbent; severely affected cattle often lie in sternal recumbency with both pelvic limbs extended caudally. Other animals lie in lateral recumbency with intermittent weak voluntary limb movements. Heart and respiratory rates rise during these struggles and, in some cases, respiratory efforts may seem labored, with a prolonged expiratory lift. Animals often die within 3 days of becoming recumbent. In survivors that remain standing, signs of limb weakness, dysphagia, and slow pupillary light reflexes completely reverse over several days to several weeks. Most persistently recumbent horses die, but in those that live and in the larger proportion of cattle that survive after becoming recumbent, efforts to stand typically resume after 1 to 4 weeks. Once such animals have successfully regained their feet, they remain standing for increasingly longer periods until recovery is complete weeks to months later. Generalized but reversible muscle atrophy may be evident in long-standing cases.

Differential diagnoses for horses include any disease associated with muscular weakness and dysphagia including infectious encephalomyelitis (equine protozoal myeloencephalitis; eastern, western, and Venezuelan equine encephalomyelitis; equine herpesvirus myeloencephalopathy; West Nile); generalized myopathy (nutritional, seasonal pasture, polysaccharide storage myopathy); equine motor neuron disease (EMND); grass sickness; hyperkalemic periodic paralysis; and heavy metal toxicity. Diagnostic ruleouts for cattle include hypocalcemia, hypokalemia, sulfur toxicity, listeriosis, epidural lymphosarcoma, and organophosphate toxicity.

Treatment Treatment involves nursing care and the use of specific anti-BoNT. Early treatment with specific antitoxin is a critical determinant of survival in horses. Eighty-nine of ninety-one untreated horses of various ages died with presumptive type B botulism,[36] whereas 27 out of 28 foals[26] and more than 70% of adults[36] survived when treated early with antitoxin. The trivalent antitoxin commercially available in the United States (*Clostridium botulinum* A, B, C TRIVALENT Antitoxin, Lake Immunogenetics, Ontario,

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N.Y.) covers cases typically seen in this country. Only one dose of antitoxin is necessary because the half-life of botulinum antitoxin (equine origin) is about 12 days in normal horses.[5] Unfortunately, antitoxin has minimal efficacy if used after the onset of recumbency in adult horses. The dose of antitoxin is 200 mL (≈20,000 IU) for a foal and 500 mL (≈50,000 IU) for an adult horse.[36] Clinical signs may progress for 12 to 24 hours after antitoxin administration. Horses with mild, slowly progressive disease may survive without antitoxin, as long as they are confined to stalls to restrict activity as much as possible.

Recumbent animals need to be kept on deep clean bedding and, if in lateral recumbency, need to be rolled to the opposite side several times daily. Bony prominences need to be padded with pillows or circular inflatable tubes in an effort to prevent decubital ulcers. Standing horses with prominent neck weakness may suffer life-threatening edema of the head and upper respiratory tract as a result of persistently hanging their heads near to the ground. This was noted to be a feature of the presentation during an outbreak of type C botulism in horses.[22] These horses need to have their heads supported above the level of the heart for several hours daily to allow mobilization of tissue fluid. Adults that are dysphagic can be fed and watered via an indwelling stomach tube. Thoroughly soaked and suspended complete pelleted feed (e.g., Equine Senior, Purina Mills, St. Louis, Mo.) can be fed indefinitely by this route. It is important to establish the patient's tolerance for bolus feedings and adjust volume and frequency of feedings accordingly. A reasonable starting point is 50% maintenance caloric requirement in 50 mL/kg water divided over 4 to 6 feedings. Caloric intake is progressively increased, and feeding frequency decreased as the animal's GI motility permits. Foals are initially fed at least 100 mL/kg of milk daily via this route, in 6 to 12 feedings, increasing to 200 mL/kg if tolerated. All recumbent animals must be in sternal position during feeding and remain sternal for at least 30 minutes after feeding. Patients without auscultable or other evidence of GI motility may be hydrated intravenously and may also be given intravenous parenteral nutrition. Recumbent adults that are being fed by nasogastric tube are at increased risk for large intestinal impactions and should be given 1 to 2 L mineral oil daily with feedings (or equivalent twice weekly) in an effort to lubricate digesta. Recumbent male horses including foals are prone to retention of urine and bladder distention and must be catheterized with meticulously clean technique at least twice daily to prevent pressure necrosis and failure of the bladder wall. Animals that are able to support their own weight when assisted to a standing position should be lifted several times daily by an abdominal sling and allowed to stand with sling support for brief periods (or simply helped to their feet in the case of small ruminants). Flotation tanks may be used intermittently for this purpose in recovering cattle, especially those that are limited by recumbency-associated peripheral neuropathies.

A minimal database of laboratory monitoring in recumbent horses with botulism should include daily hematocrit and total solids for hydration status, twice-weekly urine dipstick and specific gravity measurements to detect urinary tract infections and monitor hydration, and twice-weekly chemistry panels to assess organ function and electrolyte homeostasis. Total CO_2 values should be accorded particular attention. Values below 18 mEq/L indicate metabolic acidosis, whereas values above 35 mEq/L indicate significant metabolic alkalosis. The latter finding suggests compensation for chronic respiratory acidosis caused by respiratory paralysis or aspiration pneumonia and may prompt management changes such as improved sternal body position, frequent monitoring of respiratory function via arterial blood gas testing, or even initiation of mechanical ventilation. Foals with PaO_2 persistently below 65 mm Hg should be given humidified oxygen by nasal insufflation; those with $PaCO_2$ persistently above 60 mm Hg need to be mechanically ventilated. Of thirty foals with type B toxicoinfectious botulism admitted to a referral hospital and given antitoxin, 16 required nasal insufflation with oxygen and 8 of these foals also required mechanical ventilation.[26,37]

Antibiotics are generally used only to treat known infections (e.g., aspiration pneumonia or cystitis) or to prevent or treat bacterial sepsis in heavily instrumented foals. In cases in which wound botulism is suspected, the responsible wound must be opened, drained, cleaned, and débrided, following the same approach as is used for wounds associated with tetanus. Antibiotics such as metronidazole and penicillin G that are clostridiocidal are generally not recommended for treatment of wound or infant botulism in humans, out of concern that lysed organisms will release another pulse of BoNT into the circulation.[38] Presumably, pretreatment of large animal patients with antitoxin would remove this theoretical risk. Aminoglycosides should also be avoided if possible because they may potentiate the action of BoNT and were a significant risk factor for a subsequent requirement for ventilation in cases of infant botulism.[38] Because gastric ulcers were an important feature of the original postmortem descriptions of shaker foals,[27,28] such foals are usually on a regimen of acid suppression (e.g., omeprazole, 4 mg/kg PO once daily) and sucralfate (40 mg/kg PO every 6 hours), although the importance of this approach is unknown.

The rate of recovery from botulism depends on the toxin type and dose, the species and body weight of the patient, and the dose and timing of antitoxin. Dysphagic horses that are able to stand and are given antitoxin will gradually regain the ability to swallow over 1 to 14 days, with most cases resolving within 7 days.[5,36] Mydriasis usually resolves within several days, but the pupillary light reflexes may remain sluggish for weeks. Return to full limb strength often takes more than 1 month.[5,36] Few adult horses that become persistently recumbent recover unless they are provided meticulous nursing care, and most such horses should be euthanized. Decubital ulcers and secondary respiratory problems are the major complications. Recumbent foals that were treated with antitoxin and intensive care at a referral hospital were able to stand in an average of 7 days if they did not need ventilation and 10 days if they did.[26,37]

Prevention

BoNT/B toxoid (BotVax B, Neogen Corporation, Lexington, Ky.) is a safe and highly effective vaccine. The primary series is three inoculations, each 4 weeks apart, and then annual revaccination of broodmares 4 to 6 weeks before foaling to provide passive immunity to their foals. Although multivalent and BoNT/C toxoid vaccines for horses and cattle are available in many parts of the world, no vaccine of this type is licensed for horses in the United States.

Equine Motor Neuron Disease

Robert J. MacKay

Equine motor neuron disease is an acquired neurodegenerative disorder of the ventral horns of the gray matter of the spinal cord and selected brainstem nuclei.

History and Epidemiology

Equine motor neuron disease (EMND) was first reported in 1990 in 11 horses from 4 northeastern states.[1] Hundreds more cases occurred in the northeast section of the United States over the subsequent 20 years with many fewer cases scattered elsewhere across the country.[2,3] Additional solitary cases or outbreaks of EMND were reported in Great Britain, Canada, Ireland, Switzerland, Belgium, Japan, Brazil, and the Netherlands.[2-5] Annual incidence of EMND cases in the United States peaked in about 1997 and has now declined to low levels with less than one new admission annually to Cornell University College of Veterinary Medicine's Equine Animal Hospital.[6]

The disease usually occurs sporadically, with only one case on a given premise at any time; however, one or more additional cases have occurred on the same premise within 2 years of the original diagnosis.[2] An unusual cluster of more than 80 cases was seen among horses in a city police cavalry in Brazil during the 1990s.[2] The age range of reported cases is 2 to 27 years[3,7] with a mean of 9 years and estimated maximal risk at 16 years of age.[8,9]

In the United States, Quarter Horse breed and age,[8] duration of residence, lack of recent rabies vaccination, exercising in a dirt

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paddock, a history of cribbing or coprophagia, use of pelleted feed (alone or with sweet feed), and frequent supplementation with vitamin/mineral supplements lacking vitamin E/selenium were significant nutritional risk factors in multivariate logistic regression models.[9] Most important, after controlling for other significant risk factors, a strong negative association was demonstrated between vitamin E concentration and EMND risk.[10] Interestingly, 13/32 cases in Europe had part- or full-time exposure to pasture, yet all had low plasma vitamin E, suggesting that bioavailability of ingested vitamin E was low in these horses.[7] A horse in Finland developed EMND despite supplementation with 300 mg α-tocopherol daily for the previous 10 years.[11] In that case, daily supplementation with excessive amounts of iron was suggested as a possible cause. In the United States, horses with EMND that had normal access to pasture had enteric or hepatic disease, presumably resulting in malabsorption of vitamin E.[3,12]

Cause and Pathogenesis

EMND is a spontaneous, progressive, sporadic, even solitary, condition that closely resembles progressive spinal muscular atrophy, a variant of amyotrophic lateral sclerosis (ALS; Lou Gehrig disease) of humans.[8] Although sporadic ALS is likely multifactorial, it is widely believed that oxidative stress is involved in the final common pathways of neuronal injury. Evidence of systemic oxidant stress in horses with EMND includes the dominant involvement of oxidatively active type 1 myofibers in atrophied skeletal muscles and the abundant deposits of ceroid lipofuscin found in the retinal pigmented epithelium and in the endothelium of spinal cord capillaries.[3,13] Such deposits are thought to be the end products of peroxidation of membrane polyunsaturated fatty acids.[14]

In addition to the epidemiologic evidence for an association between hypovitaminosis E and EMND, the disease has been reproduced experimentally by prolonged feeding of vitamin E–deficient diets. After 21 to 28 months on a diet deficient in vitamin E but high in the pro-oxidant transition elements Fe and Cu, 4 of 8 horses developed clinical signs of EMND that were confirmed histologically.[15] In a separate experiment, 4 of 10 horses on the vitamin E–deficient diet but with normal Fe and Cu developed clinical signs of EMND after 18 to 37 months, and the remaining horses had histologic confirmation of the disease via peripheral nerve biopsy and/or necropsy.[16] Taken together, the results of these experiments and epidemiologic studies confirm that a diet low in vitamin E is a strong risk factor for EMND. Left unresolved is whether or not vitamin E intake is the *only* responsible nutritional or management factor influencing the development of EMND in these experimental horses and in other affected horses around the world.

Clinical Signs

The clinical signs of EMND reflect denervation of skeletal muscles. Signs of muscle weakness and atrophy dominate the clinical presentation.[2-4,12,15] Weakness may occur acutely in horses with (common) or without (uncommon) noticeable muscle wasting. In four horses that developed EMND when fed a vitamin E–deficient diet, there was mean weight loss of 92 kg at the time signs of limb weakness occurred.[2] In rare cases, the atrophy may advance insidiously without sudden weakness. Typically, there is acute onset of trembling in antigravity muscles and generalized sweating. Episodes of recumbency are frequent. When standing in one place, horses with EMND adopt a characteristic "horse-on-a-ball" stance with the limbs gathered close together under the body (Fig. 35-18).[17] Affected horses lack the strength necessary to engage the stay apparatus of the limbs when standing still; thus they constantly shift weight between limbs and have great difficulty standing in a confined area such as stocks. Acutely affected horses are more comfortable walking than standing, although even brief walking exercise may cause signs of distress such as sweating, tachypnea, and nasal flaring. Typically, at the walk, protraction phases appear somewhat short and hypometric. Horses with EMND do not have signs of ataxia such as interference between limbs or circumduction of the pelvic limbs.

In most horses with EMND, the head is carried below the shoulders, usually reflecting obvious wasting of the neck muscles.[2] The tail head is elevated in many cases because of atrophy and contracture of the dorsal coccygeal muscles.[2] If not present at presentation, widespread muscle atrophy develops quickly (days to weeks) and is most obvious in the quadriceps, triceps, and gluteal areas.



FIG. 35-18 Equine motor neuron disease in a 13-year-old Quarter Horse mare showing characteristic stance in which feet are placed close together under the body in a "horse on a ball" stance. Also note the generalized muscle atrophy, extended tail, and flared nostrils (indicative of severe exercise intolerance).

Despite the frequent occurrence of pathologic changes in the motor nuclei of cranial nerves V and XII, noticeable atrophy of the masseters or tongue has not been reported. The only clinical signs possibly ascribable to cranial nerve involvement are weak palpebral tone, dilated pupils, and sluggish pupillary light reflexes reported in a horse examined in the United Kingdom.[18]

In some 40% of cases, fundoscopic examination reveals a horizontal band of pigment above the optic disc at the tapetal-nontapetal junction.[2,14] The pigment may be brown-black to yellow-brown and has a reticulated or mosaic appearance. Surprisingly, problems with vision have not been reported even in EMND horses with severe pigment retinopathy.[14]

Laboratory Findings

Typical cases have below-range plasma/serum vitamin E concentration. However, as a stand-alone test, vitamin E is quite nonspecific[17]: Normal pasturemates of experimentally induced[15] or naturally occurring[12] EMND horses often also have low vitamin E. In healthy pasture-fed horses, vitamin E concentrations are variable during the day and often drop transiently below the normal range.[19] For this reason, it is recommended that plasma (or serum) from serial blood collections throughout the day be combined for the purpose of vitamin E assay.[19]

Mild to moderate increases in plasma or serum creatine kinase (CK) and aspartate transaminase (AST) activity are found during the initial rapid progression of clinical signs, but muscle enzyme activities may be normal in chronic stable cases.

Changes in cytology of cerebrospinal fluid are not seen in EMND; however, there may be increased total protein concentration and CK activity.[3,15] IgG index is high in many cases, suggesting the presence of intrathecally produced IgG.

Ancillary Tests

NEEDLE ELECTROMYOGRAPHY. Needle electromyography (EMG) can be performed in the standing or recumbent, anesthetized horse. Horses with EMND often have abnormal EMG findings including prolonged insertional activity and pathologic spontaneous activity such as fibrillation potentials and trains of positive sharp waves.[17] Signs of denervation are found in facial muscles, as well as appendicular and epaxial muscles.[3] Standing EMG is preferred in order to avoid anesthesia in weak compromised animals; however, interpretation of these studies is difficult because of movement

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artifacts associated with reluctance of affected horses to stand in one place. The use of sedation and caudal epidural anesthesia (lidocaine, 0.2 mg/kg) was reported to facilitate the procedure in a horse with EMND.[18] Techniques for quantitative analysis of motor action potentials have been published, and results are abnormal in horses with EMND.[20,21] Regardless of the EMG technique used, abnormal results are nonspecific as to cause, suggesting only denervation or myopathy.[17]

GLUCOSE ABSORPTION/METABOLISM. Oral glucose tolerance tests in horses with EMND were abnormal in approximately 50% of reported cases, whereas results of oral xylose absorption tests were normal or slightly low.[2,12,21] It appears that increased glucose metabolism, possibly associated with increased glucose sensitivity, rather than reduced intestinal absorption, is the cause of abnormal oral glucose tolerance in horses with EMND. Euglycemic clamp results from one horse showed a 5.4-fold increase in insulin sensitivity compared with control horses.[22]

NERVE BIOPSY. Biopsy of the ventral branch of the spinal accessory nerve allows reliable antemortem diagnosis of EMND, at least in subacute and chronic cases.[3,23] A 5-cm section of the nerve is excised as it courses over and into the medial belly of the sternocephalicus muscle. The procedure can be performed either in the standing or recumbent, anesthetized patient and does not induce visible muscle atrophy at the surgical site. A positive histologic result is evidence of mild to severe Wallerian degeneration of axons and Schwann cell proliferation. Chronic cases are marked by loss of myelinated fibers, presence of compact Büngner's bands, and increased endoneurial collagen. Positive predictive value of nerve histology for EMND was 77.4%, and negative predictive value was 90%.[23] False-negative results appeared to be most likely in acute cases (<2 weeks). Nerve biopsy has largely been supplanted as an initial test by evaluation of sacrocaudalis dorsalis muscle biopsies (see next section).

MUSCLE BIOPSY. The initial invasive procedure of choice is biopsy of the sacrocaudalis dorsalis tailhead muscle.[3,24] This muscle is rich in type I myofibers, a fiber type that is highly sensitive to the effects of denervation. The muscle sample is obtained under local anesthesia, placed on a tongue depressor, and sent chilled or in 10% formalin for histologic examination. There is neurogenic atrophy characterized by variable numbers of angular atrophied fibers. Atrophied muscle fibers are of both types, but type I fibers predominate. The use of muscle biopsy has high sensitivity for EMND (>90%) but relatively low specificity.[3] In chronic EMND cases, histology of nerve biopsy may have higher sensitivity for diagnosis than muscle histology.[3]

Diagnosis

Antemortem diagnosis of EMND is not usually difficult. It is based on typical clinical signs, age of 2 years or older, and diet low in green forage and high in carbohydrates. Needle EMG findings of denervation, especially in the deep limb muscles, are difficult technically because of movement artifact in weak horses but are supportive of the diagnosis as are mild to moderate increases in plasma CK and AST activity and low plasma vitamin E concentration. Finally, evidence of denervation in muscle or nerve biopsies in the context of the preceding clinical and laboratory findings is tantamount to a definitive diagnosis of EMND. Occasionally, in cases of insidiously progressive EMND, especially in nonendemic areas, diagnosis is only made postmortem.

Necropsy Findings

Although there is obvious weight loss in horses with EMND, fat deposits noted postmortem are usually within normal limits.[1,4,24] In acute cases, there is widespread degeneration and loss of somatic motor neurons in the ventral horns of the spinal cord accompanied by degenerative axonal changes in the ventral roots and peripheral nerves. All brainstem cranial nerve somatic motor nuclei, except those of cranial nerves III, IV, and VI, are variably involved. Most affected neurons are swollen, markedly chromatolytic, and diffusely argyrophilic while severely affected neurons are shrunken or vacuolated. In chronic burnout cases, there are glial scars consisting of astrocytes and lipofuscin-laden microglia. Additional deposits of ceroid lipofuscin are found in the retinal epithelium and occasionally in the liver and intestine. Relatively minor neurodegenerative changes may be found in dorsal root ganglia. By contrast with grass sickness, there are minimal or no lesions in the autonomic nervous system. In skeletal muscles, there is angular atrophy of all myofiber types with some selectivity for type I fibers. Atrophied fibers are intermingled among normal fibers and fascicles. Involvement of the deeper muscles of the limbs may be grossly evident as pale discoloration.

Treatment

The only treatment recommended for horses with EMND is vitamin E. This can be supplied in good-quality grass and alfalfa hay or by vitamin E supplementation (at least 10 IU/kg). Natural vitamin E (RRR-α-tocopherol) has higher bioavailability and potency than synthetic vitamin E (all-rac-α-tocopherol acetate or dl-α-tocopherol). Although vitamin E treatment appears logical, there has been no clinical trial that has evaluated the efficacy of treatment.

The frequent clinical observation that many EMND horses have increased appetite may be explained by an estimate that daily caloric requirement of horses could be doubled.[17] Thus as part of the convalescent program of surviving horses, high quantity and quality of pasture, hay, and concentrate is recommended.

Clinical Course

Within 6 weeks after onset of signs, approximately 40% of horses progressively deteriorate and are euthanized while a similar number undergo marked improvement in clinical signs (usually following relocation to another premise and /or administration of antioxidants).[2] These "recovered" horses look normal but may recrudesce under the pressure of intensive training or competition.[1] In the remaining 20%, the disease appears to "burn out" and such horses survive with permanent and obvious muscle wasting and emaciation.

Acquired Equine Polyneuropathy (Scandinavian Knuckling Syndrome)

Robert J. MacKay

A disease characterized by bilateral knuckling of pelvic limbs has been observed in Sweden, Norway, and Finland and is sometimes referred to as *Scandinavian knuckling syndrome*.[1,2] Polyneuropathy with inflammatory demyelination and Schwann cell inclusions has been reported in affected horses.[2] The cause of the disease is unknown, although an ingested neurotoxin is considered most likely. Clinical signs appear mainly in late winter to spring, and almost all affected horses have been fed wrapped forage (haylage/silage). Affected horses in Sweden and Norway have clustered within farms and all cases on a particular farm occurred within 100 days of the index case on that farm.[1] As of 2012, no outbreak had occurred in Sweden since 2009, whereas several outbreaks every year have occurred in Norway. The clinical signs are bilateral pelvic limb weakness, with hyperflexion and collapse of the limb and knuckling, such that the dorsum of the hoof contacts the ground. Surprisingly, there is no or only slight atrophy of digital extensor muscles. Mild and inconsistent thoracic limb weakness has been described in a few cases. Apparently there is no cutaneous sensory or proprioceptive component to the disease, and cranial nerve abnormalities are not found. Approximately one third of affected horses become recumbent and do not recover. Survivors in a recent case series fully recovered in a median 7 months, and all horses recovered within 19 months.[1] Acquired equine polyneuropathy was less prevalent in horses older than 12 years, and young horses had a higher chance of survival than older horses. An apparently similar syndrome, termed *idiopathic peripheral*

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polyneuropathy, has been reported in horses in Japan.[3] Affected horses are severely affected in all limbs.

Polyneuritis Equi (Neuritis of Cauda Equina)

Robert J. MacKay • Mary O. Smith

Definition and Etiology Polyneuritis equi (PNE) is a progressive granulomatous polyradiculoneuritis involving the cauda equina and, less commonly, cranial nerves and other spinal nerves.[1-4] The disease usually occurs in adult horses,[2] although it has been described in a yearling filly.[5] No breed or gender predilection has been noted.[6]

The cause of PNE is unknown. The lesions are characterized by heavy infiltrations of cytotoxic T cells and macrophages with lesser populations of helper T cells, B cells, and plasma cells.[1,7] This pathology is similar to experimental allergic neuritis of rats, coonhound paralysis of dogs, and Guillain-Barré syndrome in humans, all of which are suspected of having an autoimmune basis.[1,8] Other proposed etiologies include a hypersensitivity reaction after systemic infection, aberrant migration of helminth larvae, and association with equine herpesvirus type 1, equine viral arteritis, or adenovirus infections.[5,6,9,10] However, conclusive evidence for any of these theories is lacking.

Clinical Signs The clinical signs of PNE reflect destruction of somatic and autonomic lower motor neurons and sensory neurons at the level of the nerve roots and dorsal root ganglia. Vague signs of dysuria and tail rubbing may precede the neurologic syndrome.[1] The onset of acute signs is marked by cutaneous and muscular hyperesthesia around the hindquarters, focused on the tailhead. Rubbing and chewing of this area is characteristic. Over days to weeks, there is progressive desensitization of previously hyperesthetic areas until the skin over the caudal rump, tail, perineum, and caudal thighs becomes anesthetic. At least initially, there may be a zone of residual hypersensitivity around the margins of the desensitized skin. There is progressive paresis of the tail, bladder, rectum, anal sphincter, and penis with neurogenic atrophy of the muscles of the tail. Fecal retention and overflow urinary incontinence reflect paralysis of rectal and detrusor muscles, respectively. Urine dribbling causes scalding and staining of the perineum (in mares) and hindlimbs. In males the penis may remain dropped out of the sheath, although penile and preputial sensation is preserved. Impotence resulting from incomplete erection and inability to achieve intromission was the presenting complaint in one stallion with PNE.[11] In some cases, involvement of the lumbosacral nerve roots causes variable weakness and ataxia of the pelvic limbs and atrophy of muscles of the rump or legs. Any spinal nerve root may be affected symmetrically or asymmetrically, so discrete areas of muscle atrophy, cutaneous desensitization, and sweating are possible anywhere along the spine. Weakness and ataxia have been observed in all four limbs of a few horses.[12-14]

Cranial nerves can be involved. The signs depend on the individual nerves affected and the severity of the disease. The nerves most often affected are the motor division of the trigeminal (atrophy of chewing muscles), the facial (facial paralysis), and the vestibular (head tilt and ataxia), although signs due to involvement of cranial nerves XII (tongue weakness and atrophy), III (reduced pupillary light reflex), IX, and X (dysphagia) have also been reported.[9,12-14] Signs of cranial nerve involvement are usually asymmetric.

Any disorder that affects the cauda equina may cause similar signs. These include instabilities of the caudal spine caused by luxations or fractures, EHM, sorghum-sudan intoxication, rabies and other infectious diseases that involve the cauda equina or sacrocaudal spinal cord segments, and some primary diseases of the lower urinary tract.

Diagnosis CSF may have a moderate mononuclear pleocytosis with lesser numbers of nondegenerate neutrophils and high protein concentration. Electromyographic abnormalities occur in PNE as a result of denervation of affected muscles. Horses with PNE have high circulating antibodies to P2 myelin basic protein, but this test is not available commercially and is reported to be nonspecific.[15,16] The diagnosis was supported in one case by the finding of an intense mononuclear neuritis in a biopsy from the sacrocaudalis dorsalis muscle.[1] Thickened sacral nerves were also imaged by transrectal ultrasonography in this horse.

Necropsy Findings The cauda equina is thickened, discolored, and covered with edematous tissue and fibrous material. There may be adhesions of the nerve roots or the spinal cord to the meninges and the periosteum of the vertebral canal. Subdural or epidural petechiation and hemorrhage are sometimes seen.

At the microscopic level the major finding is granulomatous inflammation of the extradural and intradural parts of the nerve roots. The nerve sheaths are thickened and infiltrated to varying degrees by lymphocytes, plasma cells, lymphoblasts, macrophages, giant cells, eosinophils, and, in rare cases, neutrophils. Nerves are obliterated by intraneural inflammation, necrosis, and endoneurial thickening. Axonal degeneration and demyelination are present in surviving nerves. Nerve bundles are separated by large amounts of fibrous tissue. There is minimal to moderate evidence of nerve regeneration.

Treatment and Prognosis Treatment with corticosteroids at antiinflammatory doses early in the course of the disease may be palliative but is not curative. Immunosuppressive gold salts and cytotoxic drugs such as azathioprine have been used for the treatment of PNE, but the efficacy of such approaches has not been reported. General supportive care should be given including fluid therapy when necessary, and the rectum and bladder must be emptied manually and by catheter, respectively. With careful management, affected horses can be kept alive for months but the prognosis for extended life is still regarded as hopeless with the usual cause of death being euthanasia for humane reasons.

Sorghum Toxicity

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Definition and Etiology A syndrome of ataxia and cystitis in horses, cattle, and sheep has been linked to the consumption of annual grasses of the genus *Sorghum*.[1-4] Incriminated species have included *Sorghum bicolor* (sorghum), *Sorghum sudanense* (sudangrass), sorghum-sudan hybrids, and *Sorghum halepense* (Johnson grass, oxgrass). The causative toxin is not known, although there is evidence supporting a role for chronic cyanide toxicity.[5] This disease does not appear to be linked to the breed, gender, or age of an animal.[3]

Clinical Signs The first sign observed is usually ataxia of the pelvic limbs, followed by urinary incontinence. Affected animals have a swaying pelvic limb gait and a tendency to knuckle in the fetlocks. Occasionally, affected horses may walk with a hopping gait, in which both pelvic limbs are lifted off the ground simultaneously. Signs in horses tend to worsen on backing, and animals may fall or even become recumbent.[3] During an outbreak of the disease in cattle, 3 of 54 affected cows became recumbent and 2 died.[6] The perineal muscles are relaxed, and urine dribbles from a flaccid, distended bladder.[4,6] In mares the vulva opens and closes repeatedly; in stallions and geldings the penis is relaxed and protrudes from the prepuce.[7] There may be paresis of the tail in affected horses and cattle. Loss of skin sensation over the hindquarters has been described in a cow, suggesting involvement of both sensory and motor nervous pathways.[6] Headshaking, ataxia, weakness, recumbency, opisthotonos, and death have been reported in sheep, and mortality can approach 50%.[8]

Cystitis in affected animals may be severe and occurs secondary to urine retention. Dribbling of urine onto the skin of the perineum

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and pelvic limbs results in scalding of the skin and dermatitis. Pyelonephritis is a common sequela to chronic cystitis and may be fatal.[2,3] Sometimes the clinical signs may be chronic; in one outbreak, horses had been showing signs for as long as 3 years.[3]

Abortion in mares, arthrogryposis as a congenital deformity of foals and lambs, and neurologic abnormalities in newborn lambs have also been linked to the feeding of *Sorghum* plants.[3,8]

Clinical Pathology Diagnosis of sorghum toxicity is made by the presence of typical clinical signs in association with a history of feeding *Sorghum* plants. No specific diagnostic test is available. Cystitis and pyelonephritis are identified by typical findings on routine urinalysis, serum biochemistry, and urine culture.

Pathophysiology The precise nature of the toxic substance in *Sorghum* plants that causes this syndrome is unknown. Most *Sorghum* spp. are cyanogenic plants that contain the cyanogenic glycoside surrina, which, when hydrolyzed, releases hydrocyanic acid at potentially toxic concentrations.[1] Acute, sometime fatal, cyanide toxicosis has been described in cattle that ingest large amounts of rapidly growing sorghum.[9,10] Chronic exposure to cyanide has been suggested as the cause of the neuropathologic changes found in animals with ataxia-cystitis syndrome.[3] Experimental long-term dosing of potassium cyanide to goats caused histologic changes in the CNS that were comparable with those seen in the natural disease.[5] It has also been suggested that the toxic principle in *Sorghum* plants may be a lathyrogen-like substance.[2]

Epidemiology The cyanide content of *Sorghum* plants is increased by rain after drought and higher in new shoots and wet plants.[1] In one survey of the disease in horses, most cases occurred during the wet season and involved young, growing plants.[3] The period of grazing before the onset of signs ranges from 1 week to many months.[3,6]

Necropsy Findings Wallerian degeneration, swelling of axons and myelin sheaths, and demyelination in a small number of nerve fibers throughout the length of the spinal cord and in the cerebellum, cerebellar peduncles, and pons have all been described, together with the presence of phagocytic gitter cells. In lambs grazing sorghum, there were also lesions in the ventral horn gray matter of the spinal cord.[3,6,8] These changes are not associated with specific tracts. Ultrastructural studies of brains and spinal cords of affected sheep have revealed that the axonal swelling (spheroids) are composed of aggregates of neurofilaments, mitochondria, vesicular bodies, and dense bodies, enclosed within a thin myelin sheath.[8]

Treatment and Prognosis Withdrawal of *Sorghum* plants from the diet of affected animals results in a gradual improvement in the clinical signs over weeks to months, although recovery may not be complete.[6,8] Death is a potential outcome, however, and mortality can be high in some cases.[8] There is no specific treatment for affected animals. Supportive therapy includes antibiotics for treatment of bacterial urinary tract infections.

Control Avoidance of feeding *Sorghum* plants as a predominant part of the diet or the sole diet is the only method of control. This plant has considerable feed value and should not present a major hazard when used as part of a diversified feeding regimen.

Stringhalt

Robert J. MacKay

Stringhalt is a condition of horses characterized by sudden exaggerated flexion of one or both pelvic limbs during the swing phase of locomotion. Two distinct syndromes are recognized: *classical stringhalt,* a persistent condition of individual horses involving only one limb, and bilateral or Australian stringhalt, which involves both pelvic limbs and occurs in outbreaks in horses at pasture. Both forms occur worldwide, but *bilateral stringhalt* is most common in Australasia, South America, and the western United States.[1-5]



FIG. 35-19 Bilateral hyperflexion of the pelvic limbs in a horse with pasture-associated (Australian) stringhalt.

Clinical Signs The defining clinical sign of stringhalt is abrupt hyperflexion of the hock and stifle during attempted movement. In classical stringhalt only one limb is affected; by contrast, Australian stringhalt is almost always bilateral, although signs may be asymmetric (Fig. 35-19). Stringhalt is most evident during backing, sharp turning, when going down a slope, after a sudden stop, and during the transition from standing still to walking forward.[2,6] Signs may be exacerbated by excitement, cold weather, or hard exercise.[2,7] The clinical presentation of stringhalt varies greatly, even among horses with bilateral stringhalt grazing the same pasture. In mild cases flexion is only slightly exaggerated and pelvic limb action may be completely normal at gaits above the walk. Such horses are able to perform without impairment. At the other end of the spectrum, the upper joints of the limb flex so violently that the dorsum of the fetlock slaps against the horse's abdomen with each stride.[6] When the condition is bilateral, the result is a bouncing bunny-hopping gait in which "progression can only be accomplished with a series of bounds and plunges extremely painful to witness."[4,8] In the most severe cases, movement is impossible. An atypical bilateral stringhalt syndrome is described wherein the forelimbs are also involved and there are signs of generalized weakness.[1,2,4,9,10] Nine of seventy horses with stringhalt studied in France had signs of obtundation or increased aggressiveness.[11] A variable proportion of horses with bilateral stringhalt have abnormal laryngeal movement, stridor, or abnormal vocalization.[4,5,11,12] Onset of stringhalt is usually sudden. Signs may fluctuate but tend to worsen over several weeks in horses with bilateral stringhalt, before plateauing, often for several months, then beginning to improve.[2] Within 2 weeks after onset of severe bilateral stringhalt, atrophy of the muscles of the gaskin and, less obviously, the thigh and other parts of the body, becomes apparent.[2,13] Horses with severe or atypical bilateral stringhalt may develop profound generalized neurogenic muscle atrophy that results in marked weight loss despite normal appetite and food consumption.[10]

Clinical Pathology No abnormal clinical pathologic findings are associated with stringhalt. Electromyography of affected muscles reveals increased insertion activity and abnormal spontaneous activity such as fibrillation potentials and positive sharp waves consistent with denervation.[2,12] Nerve conduction velocity is slowed in the peroneal nerves of affected limbs, indicating demyelination, and improves as animals recover clinically.[2]

Pathophysiology The cause of classical stringhalt is unknown. Foot conditions and articular lesions of the hock or stifle are possible

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risk factors.[4,6,14] Trauma to the proximal dorsal metatarsus, particularly over the digital extensor tendons, often precedes classical stringhalt and likely is an important factor in the development of this form of stringhalt.[2,4] Months may elapse between injury and the onset of stringhalt.[15]

Since 1884,[8] most reports of bilateral stringhalt have implicated the common pasture weed *Hypochaeris radicata* (also known as flatweed, castear, cat's ear, or false dandelion).[†] Most outbreaks occur in late summer or autumn among horses grazing drought-damaged pastures heavily infested with *H. radicata*. Cases often occur following weeks to months of grazing on suspect pastures.[8,11] Interestingly, some affected horses are thought to have developed a taste for flatweed, to the exclusion of other forage.[11] Several outbreaks have been associated with "true" dandelion *(Taraxacum officinale),* and one has been associated with mallow *(Marva parviflora).*[1,4,16] Attack rates during bilateral stringhalt outbreaks are usually less than 50% but vary widely.[2,7,11] Some attempts at producing bilateral stringhalt by feeding cut *H. radicata* to horses have been unsuccessful; however, recently, stringhalt was induced in a 6-month-old colt fed a daily average amount of nearly 10 kg *H. radicata* harvested from a pasture where the disease had occurred.[3]

Bilateral stringhalt is a distal neuropathy primarily affecting large myelinated axons of the peripheral nervous system.[13,17] The longest nerves in the body—namely, the recurrent laryngeal nerves and the peroneal and tibial branches of the sciatic nerve—appear to be most severely affected. This also explains why tall horses are more prone to the condition than young horses, ponies, or small native Chilean breeds.[16] Shetland ponies have been affected, however.[7] The lesions of bilateral stringhalt are consistent with ingestion of a neurotoxin produced by either pasture weeds such as *H. radicata* or, less likely, by associated fungi.

It is likely that bilateral stringhalt and some cases of classical stringhalt result from interference with myotatic reflexes.[15] The immediate cause of pelvic limb hyperflexion in bilateral stringhalt is presumably progressive degeneration of large myelinated axons in tibial and peroneal nerve branches including α motor neurons to skeletal muscle, 1A and 1B sensory neurons from muscle spindles and Golgi tendon organs, and γ-efferents to muscle spindles. Classical stringhalt may be the final common sign for a variety of insults: besides interference with limb reflexes, mechanical effects of adhesions involving the muscles and tendons of the digital extensors of the pelvic limb may be important, as well as painful conditions of the hock or distal limb.

Pathology In long-standing cases of bilateral stringhalt there is variable, often severe, atrophy of the muscles of the pelvic limbs, especially distally, and atrophy of the muscles of the larynx supplied by the recurrent laryngeal nerves.[1,10,17] In peripheral nerves there are decreased numbers of myelinated fibers, perineural fibrosis, and accumulation of myelin debris. Evidence of nerve regeneration including regenerating nerve clusters, onion bulbs, and Schwann cell proliferation is usually found. Recurrent laryngeal nerves, branches of the sciatic nerves, and variably other nerves are affected with a proximal to distal gradient of severity.

Treatment Care should be taken to identify sources of pain (e.g., arthritis, hoof abscess, recent hoof trimming) that might account for stringhalt-like signs. Signs of stringhalt were blocked in one horse by intraarticular anesthesia of the distal tarsal joints; use of intraarticular corticosteroids permanently resolved the problem.

Several skeletal muscle relaxants have been investigated in horses with bilateral stringhalt. Phenytoin, an inhibitor of voltage-gated sodium channels, gives partial to complete remission of signs in horses given 10 to 15 mg/kg PO, once or twice daily.[2,10,12] Mephenesin, which acts in the spinal cord to specifically inhibit polysynaptic reflexes, suppressed signs in a horse with chronic bilateral stringhalt[6] but was ineffective in an outbreak of bilateral stringhalt.[1] Baclofen, an analogue of the inhibitory neurotransmitter GABA, had no effect in a horse with severe stringhalt.[7,12] Taurine (10 mg PO q24h) may help behavioral abnormalities.[11]

Although the results of the procedure are unpredictable, surgical removal of the distal muscle belly and tendon of insertion of the lateral digital extensor effects a clinical cure in a proportion of horses with either classical stringhalt or bilateral stringhalt.[3,4] Of four horses with classical stringhalt treated with lateral digital extensor myotenectomy, two resolved and the other two improved partially. The surgery was precluded in two other horses because of adhesions involving the tendon.[15] Responses to a survey of veterinarians in Australia indicated that more than 50% of over 100 lateral digital extensor surgeries had been successful in eliminating signs of stringhalt.[2] Even more impressively, 11 of 13 horses with bilateral stringhalt were normal within 12 days of surgery.[5] The surgery can be performed standing or in lateral or dorsal recumbency. An initial skin incision is made over the lateral digital extensor tendon immediately proximal to its junction with the long digital extensor, and the tendon is isolated and exposed. A second incision is made over the muscle belly proximal to the hock, and the muscle belly is dissected free of overlying fascia. The tendon is severed through the distal incision and then the tendon is pulled through its sheath into the proximal incision by exerting traction on the muscle. The muscle belly is then incised 2 cm proximal to the musculotendinous junction. A modification of the technique, which may improve success rate, removes 7 to 10 cm of muscle. After the fascial and skin layers have been closed, a bandage is applied over the surgical site and maintained, with box stall rest, for 2 to 3 weeks.

Prognosis There is almost no information on outcomes for horses with classical stringhalt; however, it is commonly supposed that most cases persist, although they may improve with time. Of one series of four cases that developed after proximal dorsal metatarsal trauma, one recovered, two improved, and one was unchanged for at least 6 months after onset of signs.[15] Many cases of bilateral stringhalt recover normal gait and muscle mass if removed from toxic pasture. In a series of 70 cases followed over several years in France, 36 recovered in an average of 8 months, with 6 deaths, and 14 still had stringhalt signs at least 2 years after onset.[11] The few reported deaths are in horses that are either unable to stand or unable to move to sources of water and feed and are euthanized for humane reasons. Recovery times of 3 days to 3 years have been recorded, with most horses taking 6 to 12 months.[2,6] It is unclear to what extent athletic performance returns after clinical recovery from severe bilateral stringhalt. There is evidence that laryngeal dysfunction may persist beyond the time of recovery from gait abnormalities.

Tick Paralysis

Robert J. MacKay

Definition and Etiology An ascending lower motor neuron paralysis has been described in foals, a Miniature Horse adult, sheep, calves, and pigs in Australia, associated with feeding by ticks of the genus *Ixodes,* especially *Ixodes holocyclus.*[1-6] In the United States a similar disease occurs in dogs, humans, cattle, New World camelids, and wild animal species as a result of infestation with several *Dermacentor* spp.[7,8] A similar problem occurs in small ruminants in Africa, where *Ixodes rubicundus* and *Rhipicephalus evertsi* are the tick species implicated.[9-11]

Clinical Signs Progressive generalized flaccid paresis develops over one to several days, terminating in recumbency. Death from respiratory paralysis may occur in as little as 24 hours in severe cases.[6] Animals may be found recumbent or may be paraparetic and ataxic in the early stages of disease. When signs are mild to moderate, differential diagnoses include a variety of neurologic and nonneurologic diseases such as botulism, rabies, colic, uterine torsion, trauma,

[†]References 1, 3, 4, 7, 10, 11, 14.

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myelopathies, myopathies, and metabolic disorders. Of these, only botulism progresses to the profound muscular flaccidity seen in tick paralysis. Reflex withdrawal from a noxious stimulus and the blink reflex are both reduced to absent, although sensory function appears normal.

Tick paralysis may be fatal when caused by *I. holocyclus* even when ticks have been removed. By contrast, paralysis caused by *Dermacentor* spp. is usually reversible if the ticks are removed before the animal is moribund.

Diagnosis Diagnosis is made on the basis of the clinical signs and finding ticks on the affected animal. There are no pathognomonic findings in affected animals except for the presence of ticks on the patient. Electromyography in tick paralysis in dogs in North America reveals minimal spontaneous activity and lack of evoked compound muscle action potentials in response to motor nerve stimulation.[12] Findings in large animals can be expected to be similar. Cerebrospinal fluid is normal in tick paralysis, helping to differentiate it from some, but not all, myelopathies.

Pathophysiology The cause of tick paralysis is believed to be a neurotoxin in the saliva of female ticks that is inoculated into the host when the tick feeds. Nymphs and larvae in large numbers may also cause the disease. In the case of *I. holocyclus* the toxin has been named *holocyclotoxin.*[13] The toxin(s) elaborated by *Dermacentor* spp. has (have) been less well characterized. The toxin acts by inhibiting release of acetylcholine from nerve terminals at the neuromuscular junction.

Epidemiology The disease occurs worldwide, associated with different tick species in different areas. In North America the region from the Pacific coastal range to the Continental Divide provides especially favorable conditions for the proliferation of *Dermacentor andersoni.*[8] Tick paralysis in the United States and Canada occurs mainly in the Pacific Northwest and the Rocky Mountains, although the geographic range of the responsible tick species is much larger. The disease tends to be seasonal in North America, with most cases occurring in the spring, when ticks are most active. Smaller animals such as sheep and New World camelids are more often affected than cattle, probably because they receive a larger dose of the tick neurotoxin relative to their body size.[14] Tick factors probably influence disease severity, and genetic variation within *I. holocyclus* may play a role in toxin potency.[15] A short-lived immunity has been demonstrated in dogs exposed to ticks. Tick paralysis is most common in the early part of the season and in younger animals, suggesting that a similar phenomenon may occur in other species.[14]

Necropsy Findings There is no pathognomonic finding at necropsy, although the presence of ticks should increase suspicion of this disease. Death usually results from respiratory paralysis.

Treatment and Prognosis Treatment is symptomatic after removal of the tick(s), which is essential. Lack of improvement suggests that ticks remain on the animal, except in cases of *I. holocyclus* infestation, where signs persist and may worsen for 1 to 2 days after removal of all ticks. Spraying or dipping affected animals facilitates tick removal. In small animals, shaving the hair coat may be necessary to ensure detection and removal of all ticks. Areas such as the axillae and groin, in particular, provide good sites of attachment for ticks. The prognosis is good in the case of *Dermacentor*-induced paralysis when tick removal and supportive care are instituted before animals are moribund. Fatalities occur in cases of *Ixodes*-induced paralysis despite removal of ticks. Cooling of the patient has been suggested in treatment of *I. holocyclus* toxicity, but this practice is controversial and a better approach may be to avoid warming the patient excessively.

Administration of hyperimmune serum has been shown to be beneficial in the treatment and prevention of this disease in dogs and in one llama.[16] Adverse reactions such as anaphylaxis, bradycardia, and hypotension occur in a small number of dogs and cats treated with hyperimmune serum, but these can be avoided by premedication of atropine.[17] No report of such treatment in other species was found.

Control Environmental control to reduce tick populations and routine use of acaricides may decrease the incidence of tick paralysis.

Equine Grass Sickness

Robert J. MacKay

Grass sickness is a debilitating, often fatal, dysautonomia of equids associated with full-time access to pasture.[1] Because lesions are also found in somatic lower motor neurons, it has been suggested that it is more accurate to describe grass sickness as a polyneuropathy rather than a dysautonomia. A comparable fatal polyneuropathy has also long been recognized in the Patagonia region of South America, where it is known as "mal seco."[2] Equine grass sickness (EGS) is endemic in Scotland, England, and Wales and has also been reported from Western Europe, Cyprus, the Falkland islands, and Colombia with isolated cases in Australia, Ethiopia, and the United States.[1,3-5]

Epidemiologic studies conducted since the early 1970s have identified high horse density, full-time grazing, a recent change in pasture or premises, previous occurrence of the disease on the premises, lack of hay in the diet, pasture disturbance, mechanical removal of horse manure from pastures, sandy or loamy soils, recent deworming with ivermectin, and good bodily condition as risk factors.[1,6-13] Cases occur throughout the year with peak numbers in the spring and a smaller peak in the autumn. The risk of disease was highest in horses aged 2 to 7 years (peak 5 to 6 years), although cases have been reported in horses from 2 months to 27 years of age. Horses of all breeds, ponies, donkeys, Przewalski's horses, and zebras are all affected. Males and females are equally represented in recent surveillance data. Protective factors included contact with previous cases, daily feeding of hay or haylage, chalky soil, manual removal of feces from pastures, pasture grass mowing, and co-grazing with ruminants.

Cause and Pathogenesis Theories as to the cause of EGS have included mineral or vitamin deficiencies or exposure to toxic plants, secondary metabolites and trace minerals in pasture grass, insects, mycotoxins, viruses, or bacterial toxins.[14,15] Although the clinical syndrome of EGS has not been reproduced experimentally, the characteristic neuropathology has been induced by administration of serum from acute cases into the peritoneal cavity or parotid salivary gland.[16,17] The activity was found in a greater than 30-kD fraction of serum but was not further characterized.

Since the 1990s, a hypothesis has been developed that EGS is a toxicoinfectious form of botulism involving a type C strain commonly carried by birds.[18] Strong support for this hypothesis has been (1) the demonstrated association between EGS and the presence in ileal contents of *Clostridium botulinum* type C and type C1 neurotoxin (BoNT/C)[18]; (2) the observation that horses with EGS have significantly lower serum antibodies to *C. botulinum* and BoNT/C than do pasturemate controls[19,20]; and (3) presence of rising titers of specific IgG antitoxin in chronic EGS cases. *C. botulinum* type C is unique among clostridial organisms in that its major toxin, BoNT/C, possesses potent and nonspecific neurotoxicity in vitro, probably via action on cellular syntaxin.[18] It has been hypothesized that toxin production and absorption occur in the ileum due to overgrowth from normal intestinal flora and/or to spore germination in association with *nutritional or environmental triggers* involving factors such as changes in feed, pasture, and weather conditions and parasite status.[1,3] An EGS pilot study involving use of a *C. botulinum* type C vaccine in 100 horses is under way, and its results will be used to design a larger trial of approximately 1000 horses, beginning in 2013.

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Clinical Signs The major clinical signs of grass sickness reflect dysfunction of the autonomic nervous system, particularly of the gastrointestinal tract.[1,21] There is dysphagia, gastric and small intestinal dilation, nasogastric reflux, colonic impaction, and colic. Clinical presentations are classified as acute (course of <48 hours), subacute (2 to 7 days) and chronic (>7 days).[22] Since 2000, 66% of reported cases have been acute or subacute, with 34% classified as chronic.[1] Acutely affected horses may be found dead or in abdominal crisis with signs of colic, tachycardia, generalized sweating, nasogastric reflux including spontaneous nasal regurgitation of stomach contents, absence of intestinal borborygmi, and abdominal distention. Rectal palpation and transabdominal ultrasonography reveal distended loops of small intestine and gas-filled large bowel. Affected horses are unable to swallow food or water, and thick ropy saliva may drool from the mouth. Fine muscle fasciculations similar to those seen with equine motor neuron disease may affect the triceps and quadriceps. Horses with subacute EGS survive long enough to develop colonic impactions and secondary large intestinal tympany. Chronic EGS may develop insidiously, and only a minority of these cases show mild, intermittent colic. There is patchy sweating and/or piloerection on the neck, flanks, and behind the shoulders. Typically, the appetite is reduced and there are varying degrees of difficulty in chewing and swallowing; however, salivation, accumulation of fluid in the stomach, and impaction are not usual features. There is often bilateral ptosis with ventral deviation of the eyelashes secondary to loss of sympathetic eyelid tone. Because of suppression of normal nasal secretions there is a characteristic dry crusty nasal exudate (rhinitis sicca). Fecal production is reduced, and feces are unusually firm and small. There is rapid and severe weight loss.

Acute and subacute cases are invariably fatal. Death occurs from gastric rupture, circulatory compromise, cardiopulmonary failure, or, most commonly, euthanasia. Before the 1980s, it was thought that chronic EGS was usually fatal or associated with hopeless emaciation. EGS is unlikely to recur in recovered horses.[12]

Diagnosis Definitive diagnosis requires histopathologic examination of autonomic neurons for chromatolytic changes.[1] Antemortem, the sample of choice is an ileal biopsy, which is typically obtained during exploratory celiotomy of horses presenting with signs of colic. Nasal and rectal biopsies have been investigated for diagnostic accuracy but are currently regarded as unreliable for diagnosis in the live horse.

There is no confirmatory blood test for EGS. Nonspecific abnormalities are consistent with severe dehydration, hypovolemia, stress, loss of GI secretions, and anorexia.[23] Peritoneal fluid protein concentration may be high, although nucleated and red cell counts are usually normal. Serum concentrations of numerous acute phase proteins including α2 macroglobulin, serum amyloid A, ceruloplasmin, haptoglobin, and orosomucoid are high, but such changes are not specific to EGS.[24]

In EGS cases with ptosis, topical application of 0.5 mL 0.5% phenylephrine eyedrops results in normalization of the eyelash angle within 30 minutes and is supportive of the diagnosis.[25]

Treatment and Prevention All cases of acute and subacute EGS are considered incurable and therefore require euthanasia on humane grounds as soon as possible after diagnosis. Treatment of selected chronic cases involves excellent nursing care and provision of palatable, easily swallowed food and high energy concentrates. Clinical recovery occurs in about 70% of preselected treated cases.[1]

Current efforts at prevention involve minimization of known risk factors and introduction of suspected protective practices. Thus in endemic areas, horseowners are advised to avoid exposure to pastures where previous cases have occurred, minimize disturbance of pasture or soil, prevent overgrazing of pasture, and avoid the "overuse" of ivermectin dewormers. On the other hand, owners are encouraged to co-graze horses with ruminants, mow pastures regularly, remove feces by hand, and supplement pasture feeding with hay or haylage. These practices are particularly important during seasonal and climatic risk periods, as well as for young horses in good bodily condition, especially those recently imported.

Necropsy Findings Gross necropsy findings in horses with EGS include esophageal ulceration, fluid distention of the stomach and small intestines, impaction of the large colon and/or cecum, and the presence of inspissated mucus within the small colon and rectum. Subacute and chronic cases do not have gastric and small intestinal distention but do have variable degrees of large intestinal impaction and often rhinitis sicca.[21] Histologic lesions of neuronal degeneration are most evident in the autonomic ganglia, gut wall nerve plexuses, brain, and spinal cord.[22,26] There is chromatolysis, nuclear eccentricity, nuclear degenerative changes, cell death and neuronophagia, cytoplasmic vacuolation, and spheroid formation.

Peripheral Nerve Disorders

Robert J. MacKay • Lisle W. George

Most peripheral nerve disorders of large animals are traumatically induced, but injections, abscesses, tumors, and parasitic invasion of the nerves may occur in rare cases. Damage to nerves fall into two major functional categories.[1] Type 1 injury refers to loss of function without loss of axonal continuity. Type 2 injury represents damage to axonal structures such that Wallerian degeneration of the axon ensues distal to the site of injury; the proximal axonal segment and the cell body remain intact. Retrograde degeneration of the proximal nerve occurs if connectivity is not reestablished.

Type 1 or *neurapractic* lesions are characterized by a failure of conduction of the action potential across the injured axonal segment. The pathologic basis for these reversible injuries could be nerve compression, damage to the myelin sheath, or alteration of the functions of the axonal cell membrane or its channel proteins. Type 2 injuries are characterized by axonal interruption, or *axonotmesis*. If there is also disruption of components of the connective tissue sheath and axon, the process is termed *neurotmesis*. Immediately after axonotmetic injury, the distal axonal segment is competent to conduct action potentials; however, within 3 to 8 days after injury, the distal segment degenerates and no longer responds to electrical stimulation. In this way, *neurapractic* (type 1) and axonotmetic (type 2) injuries of greater than 8 days' duration can be theoretically distinguished. After axonotmesis of motor nerves, muscle reinnervation occurs by two separate mechanisms: collateral sprouting and axonal regrowth. If there is incomplete loss of axons to a muscle, surviving motor axons generate sprouts from their nerve terminals, which can establish competent junctions with adjacent denervated muscle units. Reinnervation of muscle units by this process occurs within days to weeks. However, if the motor axons to a muscle are severed, reinnervation occurs by growth of collateral sprouts from the proximal stump. Axonal sprouts grow at a rate of 1 mm per day (≈1 inch per month). Because of progressive fibrous replacement of denervated muscle and retrograde degeneration of the proximal parts of affected motor neurons, it has been suggested that reinnervation may not be possible if more than 12 months have elapsed since the original injury. However, reinnervation surgery has been successful when performed on human patients 20 years or more after denervation.[2]

Large-diameter myelinated fibers are most sensitive to compression forces. The largest axons (sensory axons) including afferent fibers conveying touch-pressure, vibration, and proprioception are usually damaged first (resulting in ataxia or inappropriate limb placement); second, the large myelinated motor axons are compromised; third, the smaller axons are affected, which carry cutaneous and deep mechanoreceptor sensory information; last to be lost are the smallest-diameter fibers transmitting pain sensation.

The following section discusses the peripheral nerves most often damaged in large animals.

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FIG. 35-20 Sweeney (neurogenic atrophy) of the left supraspinatus and infraspinatus muscles in a Quarter Horse gelding. The lesion was caused by trauma related to running into a fencepost 2 months previously.

Suprascapular Nerve

Mechanical damage to the suprascapular nerve results in paralysis of the infraspinatus and supraspinatus muscles.[3] Such injuries occur most commonly when the animal collides at speed with gateposts, trees, or other objects.[4] Acute injury or local anesthesia of the suprascapular nerve is characterized by outward bowing and/or "popping" of the scapulohumeral joint as weight is placed on the limb. Neurogenic atrophy develops after 2 to 4 weeks, and the scapular spine becomes prominent (Fig. 35-20). The common name for this condition is "sweeney."

Brachial Plexus

Damage to the brachial plexus may result in any combination of dysfunction of the radial, pectoral, axillary, musculocutaneous, median, and ulnar nerves, although radial nerve signs usually dominate.[5,6]

Lesions of the brachial plexus are caused by trauma to the shoulder with or without scapular or rib fracture, deep penetrating axillary wounds, neoplasia or bacterial cellulitis, or forced extraction of a fetus to relieve a dystocia.[7] Because of their tendency to move at high speeds, horses are most susceptible to brachial plexus injuries. The condition may occur in small ruminants after automobile accidents, carnivore attacks, or blows from larger animals.

Avulsion of the brachial plexus results in complete flaccidity, lack of reflexes, and desensitization of the affected thoracic limb. Disruption of the origins of the cervical sympathetic trunk in the caudal aspect of the plexus results in ipsilateral Horner syndrome. With lesser injuries there may be abduction of the elbow (pectoral nerve), dropped shoulder (subscapular), hyperextension of the elbow (musculocutaneous), or signs of radial paralysis (next section).[8]

Radial Nerve

The radial nerve provides motor input to a flexor of the shoulder and extensors of the elbow, carpal, and digital joints. The nerve courses over the lateral aspect of the elbow joint and is vulnerable to traumatic insult at that point. Radial nerve paralysis arises from injury to the T1 nerve root or nerve from vertebral or rib fracture, as part of a brachial plexus injury, as a result of humeral fracture, from direct trauma to the nerve over the elbow, as part of an ischemic myoneuropathy during prolonged anesthesia, or during restraint in lateral recumbency with inadequate padding of the forelimb.[7,9-11]

With radial paralysis, the limb position varies, depending on the location of the lesion in the radial nerve. Lesions at or near the elbow joint are characterized by dropped elbow, inability to protract the limb, scuffing of the toe, and flexion of all distal limb joints (Fig. 35-21). The foot is knuckled over at rest, and the animal is unable to bear weight on the leg. Lesions distal to the elbow cause knuckling of the carpus, fetlock, and pastern joints, but the animal can support weight on the affected limb if the metacarpus and distal limb are held in extension. The triceps reflex is depressed to absent. After weeks of radial denervation, there is atrophy of the extensor muscles of the thoracic limb. Detectable sensory deficits resulting from radial nerve paralysis tend to be vague and probably vary from patient to patient.



FIG. 35-21 High radial nerve paralysis in a horse showing knuckling of the carpus and digit and dropped elbow.

Kangaroo Gait in Sheep

A locomotor disorder predominantly involving the thoracic limbs of lactating ewes has been reported in New Zealand, Australia, Scotland, and northern England.[12,13] There is knuckling and paresis of the thoracic limbs suggestive of radial paresis and a high-stepping forelimb gait. In advanced cases the pelvic limbs are also involved. Limited necropsy data suggest both CNS and peripheral nerve involvement.[14,15] Affected ewes are usually of large breeds and nursing twins. Most recover after weaning their lambs. Affected sheep are usually grazing mixed forage, often with some concentrate supplementation. A clinically identical condition has been reported in Israel and in Australia among sheep grazing the legume fenugreek.[16] A causative toxin or nutritional deficiency is suspected for both kangaroo gait and fenugreek staggers, but no toxin has yet been identified.

Femoral Nerve

The femoral nerve is distributed to the quadriceps femoris muscles and the skin of the rear limb over the medial thigh. Traumatic overextension of the hip and stifle joint from a fall or other injury or forced posterior delivery of a fetus can damage the femoral nerve(s).[17] The nerve courses too deeply to be directly affected by an external blow to the pelvic limb; however, it can be damaged by ilial, femoral, or vertebral fractures. Ischemic injury caused by prolonged stretch or increased tissue pressure during anesthesia in dorsal recumbency may cause bilateral femoral neurapraxia.[18] A similar presentation, presumably caused by compression of lumbar spinal branches by the foal in the birth canal, is seen in mares after severe prolonged dystocia.

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The clinical signs of femoral nerve paralysis are related to an inability to extend and fix the stifle.[3] The reciprocal apparatus is unable to fix the stifle and hock, resulting in collapse of the limb during weight bearing and constant flexion of all distal digital joints. The hoof usually remains flat on the ground. Chronic femoral denervation causes atrophy of the quadriceps femoris muscles. The patellar reflex is absent or depressed, and the patella is often displaced laterally. There is hypoesthesia to anesthesia of the medial part of the rear limb extending from the proximal thigh to the medial malleolus of the tibia.

Sciatic Nerve

The sciatic nerve is the largest nerve in the body and innervates the extensor muscles of the hip, flexor muscles of the stifle, and most of the muscles of the distal limb. Sciatic nerve paralysis occurs most often in postpartum cows after forced fetal extraction.[19] Injury to the sixth lumbar nerve proximal to the lumbosacral plexus is the usual cause of so-called calving or obturator paralysis syndrome. Injection of irritating drugs into the space between the greater trochanter and the ischial tuberosity may cause a sciatic neuritis.[20] This occurs most frequently in young animals but can occur rarely in adult cattle and small ruminants. Other causes of sciatic nerve damage are pelvic fractures, sacroiliac or coxofemoral dislocations, tumors, or abscesses located along the course of the nerve. Sciatic neuropathy is a rare complication of sacroiliac joint injections in horses.

The sciatic nerve innervates most of the musculature of the rear limb, so the motor deficits associated with denervation are profound. At rest the limb hangs behind the animal. The stifle is dropped and extended, and the hoof rests on its dorsum (Fig. 35-22). If the limb is positioned properly, the animal usually can bear some weight because of the normal function of the quadriceps muscles and the action of the reciprocal apparatus. Chronic sciatic denervation results in neurogenic atrophy of the caudal thigh muscles and all of the muscles distal to the stifle.

The sciatic nerve divides into the tibial and the peroneal nerves in the distal limb. Therefore except for the medial part of the thigh and gaskin, there is hypoesthesia and anesthesia of the entire limb distal to the stifle.



FIG. 35-22 Characteristic posture of a foal with partial sciatic nerve paralysis. The condition pictured here was induced during correction of a severe dystocia. Not the flexion of the hocks, fetlocks, and stifle. The signs were the result of an intramuscular injection in the gluteal area.

Peroneal Nerve

The peroneal branch of the sciatic nerve is distributed to the flexor muscles of the hock joint and the extensor muscles of the digit. The nerve becomes superficial and is exposed to damage as it crosses over the lateral condyle of the fibula immediately distal to the stifle. Peroneal paralysis of this type is seen in all species of large animals and is common in postpartum dairy cattle that have been recumbent as a result of hypocalcemia or other causes and in horses because of postanesthetic ischemic myoneuropathy. There is hyperextension of the hock joint and flexion of the fetlock and pastern, and the dorsum of the hoof usually rests on the ground[3,21,22] (Fig. 35-23). Affected animals can bear weight when the limb is manually placed in the proper position. There is desensitization of the skin over the craniolateral aspect of the limb extending from the stifle to the hoof.

Tibial Nerve

The tibial nerve supplies the extensor muscles of the hock joint (i.e., the gastrocnemius) and the digital flexors. Tibial paralysis is most often observed in periparturient cattle or neonates that have been given an injection of an irritant drug in the caudal leg at the level of the stifle. Tibial paralysis is also seen in sheep and goats and is a common sequela to dog-bite injuries. The resting limb is held more flexed than is normal, and, although the foot contacts the ground in normal position, the metacarpophalangeal (MCP) joint often partially collapses into a flexed position (i.e., "knuckles"). The limb moves in stringhalt-like fashion, with exaggerated flexion of the tarsus and stifle during protraction, followed by sudden extension to the weight-bearing phase of the stride. At rest the pelvis is asymmetric, with the affected side held lower than normal.[3] Chronic loss of tibial nerve function results in atrophy of the gastrocnemius and digital flexor muscles. There is anesthesia of the skin of the caudomedial aspect of the leg.

Obturator Nerve

The obturator nerve supplies the adductor muscles of the pelvic limb. The nerve is well protected in the horse and small ruminants, so injury is rare in these species. By contrast, because the cow has a relatively shallow acetabulum and poorly developed round ligament, the obturator nerve and the lumbar branches that supply it are vulnerable to injury during forced extraction of a calf to relieve a dystocia. Reports of obturator nerve paralysis of cattle accompanied by



FIG. 35-23 Calf with peroneal nerve paralysis. Note the flexed fetlock and digit and the hyperextended carpus. This condition was caused by injection of antibiotics into the peroneal nerve on the caudolateral aspect of the leg.

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FIG. 35-24 Cow with obturator nerve paralysis caused by relief of a difficult dystocia. Note the basewide stance, yet the apparent ease with which the cow is able to stand on the deep bedding. Note also that rope hobbles are being applied to prevent further abduction and trauma.

knuckling and inability to support weight on the rear limbs probably represent a combination of sciatic and obturator nerve dysfunction. Coxofemoral dislocation is a common complication of obturator paralysis in cattle housed in stalls with slippery flooring.

Obturator nerve paralysis is most common in cattle and is almost exclusively a result of dystocia. The nerve injury is located in the pelvis at the level of the obturator foramen. Of all dystocias in dairy cattle, 9.2% result in paraplegia.[23] The obturator nerve innervates the adductor, pectineus, and gracilis muscles. Only minimal effects are seen if the cow is placed on a surface that has good traction. Clinical signs of an obturator nerve injury include a hopping pelvic limb gait when the animal attempts to run and severe pelvic limb abduction or splay-leggedness when the animal stands on a slippery surface (Fig. 35-24). In severe cases the cow may be sternally recumbent with the pelvic limbs extending laterally to each side. Experimental studies have indicated that the so-called calving paralysis syndrome is actually a result of a combination of injuries to the obturator nerve and to the sixth lumbar spinal nerve (L6), a major contributor to the sciatic and obturator nerves. Experimental sectioning of the obturator nerve alone does not produce paralysis, provided the animal has secure footing.[3,19,24] Obturator nerve paralysis does not result in a cutaneous sensory deficit.

Compression damage to one or more peripheral nerves during parturition or milk fever is a frequent factor in the so-called downer cow syndrome (see later discussion). The incidence of the condition ranges from 4% to 28% of all cases of milk fever and, before the advent of flotation tanks for treatment, was associated with a mortality rate of 20% to 67%.[25,26]

Peripheral Facial Nerve Paralysis

Facial paralysis is common in horses but uncommon in other large animals. Depending on the site of damage, some or all of the facial muscles can be affected. Complete unilateral facial paralysis in horses is evident as deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelid, and ear. Reflexes involving cranial nerve VII, such as the lip, eyelid, menace and ear reflexes, are reduced or absent. Inability to close the eyelid causes exposure keratitis, which may be particularly severe when there is damage to the secretomotor fibers of the facial nerve at or proximal to the geniculate ganglion (keratitis sicca). The tongue protrudes out of the paralyzed side of the mouth, often erroneously suggesting a problem with lingual function. Because of paralysis of the buccinator cheek muscle, boluses of feed accumulate between the cheek and teeth from where they may be dropped from the mouth. With chronic facial denervation in horses neurogenic atrophy of the parotidoauricularis muscle becomes apparent as a groove behind the vertical ramus of the mandible. In cattle, because of the rigid structure of the planum nasale, muzzle deviation is not seen. In small ruminants, subtle muzzle deviation can usually be appreciated.

Injury to the facial nerve proximal to the vertical ramus of the mandible causes full facial paresis. Proximal facial nerve trauma in horses is usually caused by fractures of the vertical ramus of the mandible, stylohyoid bone, or petrous temporal bone (after a blow to the head or as a complication of temporohyoid osteoarthropathy). Damage within the facial canal is often associated with concurrent signs of vestibular nerve damage such as head tilt, nystagmus, and circling. Tear production may also be reduced or absent. Hemorrhage into the middle/inner ear, otitis media/internal guttural pouch mycosis, and parotid lymph node abscessation each can involve the adjacent facial nerve, causing ipsilateral facial paralysis. Distal facial nerve damage is usually due to direct injury from a blow or lateral recumbency or strangulation by a tight-fitting halter. The nerve or its branches are often damaged as they cross the mandible and/or zygomatic arch. Facial paresis following recumbency during general anesthesia is common and usually involves only the nose and/or lips. Similar conditions occur in goats and are caused by excessive pull on neck chains while the animal is being led onto the milk stand or tied with the neck chain. In cattle, facial nerve paresis is usually the result of space-occupying masses at the caudal aspect of the mandibular ramus.

Most animals with facial nerve paralysis caused by trauma have neurapractic (type 1) nerve injury and recover within 2 weeks; those with type 2 (axonotmetic) injuries regrow axons from the site of injury at the rate of about 1 inch per month, so several months may be required for full resolution. Occasionally the paralysis is permanent. In chronic cases, food should be removed from the cheek pouches twice daily and the tongue and fauces should be routinely examined for ulcers. If present, oral ulcers should be treated by flushing the mouth.

Treatment

The objectives of medical treatment of peripheral nerve injury are (1) reduction of swelling and inflammation at the site of injury, (2) support and stabilization of the denervated area, and (3) maintenance of the general health of the animal.

In the case of lacerating trauma, the general principles of wound management apply. The wound should be cleaned, irrigated, débrided, and dressed and ventral drainage established. If severed nerve ends are visible, they can be tagged for later identification and surgical repair. Medical therapy for inflammation and swelling should be initiated, especially if there is obvious tissue swelling. This may include any combination of a cyclooxygenase inhibitor (e.g., flunixin meglumine, 1.1 mg/kg IV, IM, or PO once or twice daily); dimethyl sulfoxide (DMSO; 1 g/kg as a 10% solution IV or by nasogastric tube once or twice daily); and a glucocorticoid (e.g., dexamethasone, 0.05 mg/kg IV or IM once daily). An additional antiinflammatory effect can be provided by cold water hydrotherapy or local application of skin-permeant drugs such as DMSO or diclofenac. In the presence of an open wound or other risk for bacterial infection, broad-spectrum antimicrobial therapy should be initiated. This can be directed by culture results, if available. Fractured or dislocated bones that have the potential to further injure nerves must be reduced and stabilized. Stall rest is helpful to prevent further injury. In the case of paralyzed limbs, a protective wrap may be necessary to prevent damage caused by dragging or improperly placing the limb. A support wrap, splint, or light cast should be maintained on a leg

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affected with radial paralysis so as to prevent limb contracture. A heavy support wrap, possibly with additional fetlock support, should also be placed on the opposite limb to protect against breakdown caused by prolonged increased weight bearing. If the horse has difficulty alternating between recumbency and standing, it should be supported as needed in an abdominal sling (horses and small ruminants) or flotation tank (cattle) until it is able to rise unassisted. Because of the buoyancy provided by water, affected animals (usually horses) may be able to exercise affected limbs in swimming pools. Skin over bony prominences should be padded to prevent decubital injury; such injuries must be treated aggressively if they occur.

If possible, passive range-of-motion exercises should be performed on paralyzed limbs in an attempt to preserve joint flexibility and prevent contracture. Faradic or galvanic electrical muscle stimulation, acupuncture, and hyperbaric oxygen therapy are other procedures advocated for treatment of peripheral nerve injury. Calcium gluconate can be given empirically to down cows (500 mL SC daily), as may potassium chloride (100 g in 20 L of water given daily by stomach tube). Abduction of the rear limbs may be prevented in cattle by application of a hobble around the metatarsus. The distance between the legs should be approximately 35.6 to 50.8 cm (14 to 20 inches) when the legs are tied together and held abducted. It is important to apply the hobbles with a nontightening bowline knot to prevent strangulation of the foot.

Surgical procedures for repair of peripheral nerves are beyond the scope of this text but are described elsewhere. External neurolysis refers to the dissection of the nerve from a bed of scar tissue.[1] This is indicated if there is obvious compression from fibrous tissue, and it is performed routinely in horses with suprascapular neuropathy.

Down Cows (Alert Downers)

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Down cows, downer cows, or downers are cattle that are recumbent and cannot stand; those that can maintain sternal recumbency while continuing to eat and drink are classified as "alert downers." Common underlying causes of recumbency in cattle include severe mastitis, metritis, musculoskeletal disease (primary musculoskeletal injuries including fractures and torn muscles/tendons), neuropathies secondary to pelvic trauma (calving paralysis), spinal cord compression (e.g., secondary to lymphosarcoma), and metabolic disease (hypocalcemia, hypokalemia, hypophosphatemia, hypomagnesemia).[1] Following the initial episode of recumbency, secondary muscle and nerve injury caused by extended periods of recumbency on a firm surface may further exacerbate the recumbency. Heavy cattle down on concrete are particularly susceptible to pressure ischemia of the muscles and nerves and to muscle and ligament tearing secondarily to repeated struggling and slipping. The severity of pressure damage depends on the nature of the surface on which the animal is recumbent and the duration of compression.

Identifying underlying causes for recumbency in downer cattle represents a diagnostic challenge for the practitioner. Assessing prognosis and determining reversibility of the underlying condition are necessary for practitioners to assist producers in making treatment decisions, as well as to conform to laws and abide by ethical norms surrounding humane handling of down animals. In short, dragging of down livestock is considered inhumane, and down livestock that are in distress or that do not respond to treatment should be humanely euthanized.

Pathogenesis and Laboratory Findings Laboratory testing for metabolic causes of recumbency would be ideal in all circumstances, but this is often not feasible or possible. As such, many downer cattle are treated empirically for suspected metabolic abnormalities and response to treatment aids in establishing the diagnosis. Periparturient downer cows should be treated for hypocalcemia with one or more doses of calcium. Animals that become more alert but that are not standing after one or two doses of calcium are classified as alert downer cows. It is reported that 3.8% to 28.2% of all milk fever cases become alert downers,[2-5] with a mortality rate of 20% to 67%.[3-7] The incidence of downers (24 hours or longer) was 21.4 cases per 1000 cow-years in Minnesota dairy herds, with a 33% recovery rate.[7] Fifty-eight percent of downers occurred within a day of calving, and 97% occurred within the first 100 days after calving.[7] Because the pressure damage done to muscles and nerves is aggravated by recumbency, it is desirable to have the animal on soft bedding (e.g., sand, grass) and to have the animal stand as soon as possible. Eight of 16 normal cows anesthetized for 6 to 12 hours in sternal recumbency with the right hindlimb under the body were unable to stand on recovery and became alert downers.[8] Those that could stand exhibited swelling and stiffness and peroneal nerve deficits and paresis in the right hindlimb.[8] These signs are typically seen in cows that have been recumbent for several hours on a hard surface. As pressure applied to a nerve increases, nerve conduction is impaired and eventually lost.[9]

Serum CK values in experimental downer cows increased, starting at 12 hours and continuing up for the first 48 hours, and then decreased, even though the cow remained down.[8] The CK values at 12 and 24 hours did not differ statistically for the cows that could rise after anesthesia and the downers. After 48 hours and 96 hours, the downers had higher mean CK values than the ambulatory group, but there was a great range in values.[8] The clinical difference between cows that recovered and those that remained downers was attributed to damage to the sciatic nerve or its branches, particularly the peroneal nerve.[8] Peroneal nerve damage results in knuckling over at the fetlock. In another study of downers, AST levels were greatly elevated on days 4 to 7, even after CK levels fell.[10]

Serum levels of creatine phosphokinase, AST, and lactate dehydrogenase have been examined to determine whether these indices of muscle damage can predict recovery of recumbent dairy cattle. Of the three enzymes, AST has been shown to be most useful in predicting nonrecovery. Dairy cattle with an AST level greater than 171 IU/L are 80% more likely not to recover than a dairy cow with an AST level less than 171 IU/L.[11]

Treatment Devices that aid and promote standing traditionally include hip lifters (hip clamp), slings, and inflatable bags. Although these devices help less severely affected animals to stand temporarily, they do not allow the animal to stand comfortably for hours and may even cause further trauma in animals that struggle. For these reasons, the use of water flotation has been explored as a tool in the management of downer cows. Rasmussen[12] first reported on the use of a warm-water flotation system in Denmark in 1982. Commercial flotation systems practical for cows (Aqua Cow Rise System, St. Johnsbury, Vt.; www.downcow.com) are marketed in the United States.

For flotation therapy to allow the best chances for recovery, the animal should first be examined to determine that it is a good candidate for flotation, by ruling out fractures, severe spinal cord compression, and severe systemic illness. Identifying and correcting electrolyte disturbances (e.g., hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia) are required for successful application of flotation therapy. Once metabolic or systemic illnesses have been addressed and the cow is considered strong enough to stand once supported by water, the cow is placed in the flotation tank as follows: (1) the water tank is positioned near the down cow; (2) the wheels and tongue are detached, and both ends of the tank are removed; (3) a mat is pulled from the tub to a position beside the cow, and the down cow is rolled or slid onto the mat; (4) the mat is winched or otherwise pulled into the tub, and the ends of the tub are put in place; they seal with rubber gaskets and large turnbuckles; and (5) the cow's head is held up a few inches by a rope halter, and a hose is inserted into the tub, which is filled with water as quickly as possible; the water temperature should be 37.7° C to 38.7° C (100° F to 102° F). Cows in lateral recumbency on the mat become sternal when 12 to 24 inches of water fills the tub and usually attempt to stand beginning when the tub is one-half to two-thirds full. If no hot water

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is available near the cow, or if the tub is not next to dirt or grass suitable for the cow to exit on, the wheels can be put back on and the cow easily trailered to a better location. In addition, it is helpful to have an assistant support the tail or have a means to pull the tail once the cow attempts to rise. This helps the cow maintain a sternal position during early efforts at struggling before the cow is actually standing. Before flotation of lactating cattle at the University of California, Davis, cows are milked and teat ends sealed with a rubber teat sealant; this is removed once the cow is removed from the tank before milking. The sealant is reapplied after milking in preparation for the next flotation.

Once the cow is standing in warm water, it is possible to determine which limb or limbs are paretic or painful by observing which limbs the cow is using to support weight. Most cows calm down and relax in a standing position within 5 minutes. Most will eat hay, and even first calf heifers that have not been handled much seem to be remarkably calmed by the warm water. Unlike horses, cattle do not panic or attempt to jump out. The cow can be left in the water for 12 to 24 hours. If the water temperature drops below 35° C (95° F), some water should be released from the discharge valve and replaced with hot water; this is especially recommended in cold weather. When the decision is made to remove the cow from the tub, the water is drained, and the end of the tub facing the dirt, sand, or grass is opened. The cow is encouraged to exit *slowly* into a pen with good footing. Some cows fall as the water is let out, and others collapse once they try to walk. By observing how a cow is ambulating on exit, it is possible to determine whether hobbles should be placed onto the cow before the next flotation. If cows are considered at risk for splaying out while exiting the tank, it is recommended to apply hobbles before placing the cow in the tank.

Careful observation as the cow moves can be helpful in trying to locate anatomic or functional problems. The animal that collapses can be pulled out on the mat and left on suitable bedding, dirt, sand, or grass until refloated after a period of rest. Advanced planning on location is important for successful use of flotation therapy. Cows that can walk out into a pen may or may not be able to stand by the next day and may need to be refloated. Cows may need to be floated for up to 10 consecutive days before they can arise by themselves. If cases are carefully selected to rule out fractures, severe traumatic stifle injuries, septic arthritis, and spinal cord compression, a recuperative success rate of 46% to 90% can be expected.[12,13]

Flotation is most effective if applied early, before a downer cow develops serious myopathy and neuropathy. Studies have shown that water flotation is practical and effective, even when cattle have been down for 24 hours or longer.[1] The sooner a postparturient alert downer cow can be floated after onset of recumbency, the shorter the time to stand. In one study of postparturient alert downer cattle treated with flotation therapy, the mean time to stand was shorter for cattle floated within 1 day of going down (mean, 2.8 days to stand) than for cattle floated after being down for 2 or more days (mean, 5.3 days to stand).[13]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Helichrysum argyrosphaerum (Golden Guinea Everlasting, Vaalsewejaartjie) Poisoning

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Thromboembolic Meningoencephalitis (*Histophilus somni* [formerly *Haemophilus somnus*] Infection; Sleeper Calves)

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Diseases Producing Tremors and Ataxia; Cerebellar Diseases

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• CHAPTER 36

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Mammary Gland Health

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Specialized mammary glands to feed progeny are a defining characteristic of mammals, but the milk of several breeds of cattle, goats, and sheep has such excellent nutritional qualities, dairy herds are bred to produce milk for human consumption. Mammary gland diseases in these animals thus have important repercussions not only for the animals' health but also for human well-being.

Mammary Gland Health of Dairy Cattle

The global dairy industry has changed dramatically in the past quarter century. Volatile milk prices, increasing herd size, reliance on hired labor, more complex feeding and housing systems, and increased pressure for environmental stewardship have fostered greater diversity among dairy enterprises. Bovine mastitis is the most common and economically important disease of dairy herds in developed countries[1-3] and hinders realization of optimum farm productivity, milk quality, and supply of dairy foods. Mastitis remains the most common cause of antimicrobial drug therapy for cows on U.S. dairy farms.[4] An important and often unrecognized obstacle to implementation of mastitis control practices is the behavior and attitude of farmers and employees.[5] Veterinarians can play a critical role in controlling this disease as part of a quality milk team that targets drug use, environment, milking practices, and the epidemiology of mastitis within each dairy herd. Successful implementation of quality milk programs within dairy herds will increase productivity for dairy producers, supply milk processors with superior raw milk, offer consumers better-quality dairy foods, improve cow health and well-being, establish the dairy industry as advocates for antimicrobial stewardship, and promote a global sustainable market for U.S. dairy products.

Economic Impact of Dairy Cattle Mastitis

Decreased milk production in affected mammary glands is the primary economic loss associated with mastitis. Inflammation causes pathologic changes in milk-secreting epithelial cells that results in decreased functional capacity. Depending on the type of pathogen, losses may continue into subsequent lactations. Most infections result in local inflammation, or relatively mild clinical cases.[6,7] However, chronic infections can lead to agalactia in the affected quarter, or in the case of severe clinical cases, profound systemic involvement that occasionally results in death.

Somatic cells in milk are indicators of leukocytosis and primarily due to infection of the mammary gland. Bulk tank somatic cell counts (BTSCCs) strongly correlate with the proportion of infected cows within a dairy herd[8] and are an indication of milk quality. Substantial economic loss may be incurred when regulatory or processor limits for BTSCCs are exceeded. Many milk processors routinely monitor BTSCCs, and dairy producers may be paid considerable monetary premiums for low BTSCCs or be penalized for high BTSCCs. Premium and penalty programs vary widely by location, but in some cases, penalty payments or unearned premiums account for the greatest loss associated with subclinical mastitis.[9]

Milk from cows with subclinical mastitis is not usually withheld from the bulk tank and may result in increased BTSCC and reduction in milk quality. Proteolytic and other changes in milk due to subclinical mastitis adversely affect organoleptic qualities and shelf life of milk and milk products. BTSCCs greater than 100,000 cells/mL are associated with decreased productivity per cow, shorter shelf life of fluid milk, and reduced yield of products like cheese.[1,10,11] Individual cow milk yield is estimated to decrease 0.5 to 0.6 kg/day for each twofold increase in SCC over 50,000 cells/mL.[12,13] However, the magnitude of the milk decrease relative to SCC increase has been reported to be higher in later lactation and older cows.[13] Thus, a cow with subclinical mastitis and a SCC of 800,000 cells/mL is potentially losing 2 to 2.5 kg of milk each day relative to having a SCC of 50,000 cell/mL.

High-BTSCC milk also has a greater risk of condemnation because of violative antimicrobial residues.[14-16] In a retrospective study, the rate of antibiotic residue violations increased as herd SCC increased, and the relative risk of antibiotic residue violations (compared to herds with SCC < 250,000 cells/mL) was 2.4, 2.8, and 7.1 times greater for herds with SCCs of over 400,000, over 550,000, and over 700,000 cells/mL, respectively.[14]

Cows with chronically increased SCC caused by intramammary infections (IMIs) are often culled prematurely as a consequence of decreased milk production. The cost of premature culling depends on the perceived value of the cow, market prices for culled cows and replacement heifers, and the potential value of the replacement heifer.[9] Cows with average SCCs above 700,000/mL were twice as likely to be culled than cows with SCCs under 250,000/mL, especially in herds with low BTSCCs.[17] Cows that are not culled may be segregated or require use of milking procedures that increase labor costs. For example, cows with chronic IMI caused by *Staphylococcus aureus* or *Mycoplasma* may have to be housed separately and milked last.

The incidence of clinical mastitis averages between 15% and 25% of lactations, although some herds may have rates greater than 45%.[18-20] Estimates of lost milk production from a case of clinical mastitis over an entire lactation range from 110 to 552 kg, depending on the parity and stage of lactation when the case occurred.[21] Further losses from clinical mastitis can result from subsequent repeated episodes during the same or later lactations. In a study of seven New York dairies, milk losses in the first 50 days following onset of clinical mastitis were 304, 128, and 92 kg for cases caused by gram-negative, gram-positive, and other pathogens, respectively.[22] Clinical mastitis also results in additional economic losses beyond milk production. In a 1700-cow dairy, cows with clinical mastitis lost 341 kg of saleable milk, compared to projected yield, during the first 60 days after case onset.[23] Nearly 75% of the milk loss was discarded because of treatment, with the remainder accounted for by lost production. Cows in their second or later lactation or more than 150 days in milk incurred greater losses, although the type of causative pathogen was not

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associated with differences in losses.[23] The average total costs per case (in U.S. dollars) of gram-positive, gram-negative, and other pathogens were estimated to be $133, $211, and $95, respectively.[24] Premature culling resulting from unresolved clinical mastitis cases or subsequent suboptimal milk yield of the affected cow may increase these costs to as much as $600 per case.[25]

The occurrence of both subclinical and clinical mastitis has been associated with reduced reproductive performance. In a preliminary field study, cows were almost two times more likely to have altered interestrus intervals following an episode of clinical coliform mastitis compared to herdmates without clinical mastitis.[26] Conception rates for cows with clinical mastitis between 3 weeks before and 5 weeks after insemination have been reported to be lower compared to cows without clinical mastitis.[27,28] Clinical mastitis due to gram-negative bacteria has a more detrimental effect on the probability of conception than clinical mastitis caused by gram-positive bacteria or other organisms.[28] Additionally, the days to first service, services per conception, and the days to conception were all increased in cows with clinical mastitis as compared to non-mastitic cows.[29] Cows with a case of clinical mastitis in the first 45 days of gestation are nearly three times more likely to abort within the next 90 days than non-mastitis cows.[30] Cows with increased SCC (>150,000 cells/mL) also have decreased conception rates compared to cows with lower SCC, and as the SCC increases the odds of pregnancy decreases.[31,32] Inflammatory mediators released in response to IMI likely play a role in oocyte and embryonic degradation.[33,34] For example, lipopolysaccharide endotoxin in cattle induces a prolonged release of inflammatory mediators including $PGF_{2\alpha}$, leading to uterine smooth muscle contraction and luteolysis, a gradual decline in plasma progesterone, and thus abortion, especially in the first trimester of pregnancy.[33]

The total cost of mastitis is impossible to quantify accurately, varies over time, and is herd dependent. Nationally, the cost of mastitis has been estimated at $200/cow/yr, or $1.5 to $2 billion.[9,35] Costs associated with implementation of mastitis control programs can be substantial. In one survey the cost of mastitis prevention accounted for 50% of the cost for preventing all diseases.[36] Return on investment in mastitis control is more important than the absolute cost and ranged from −$20 to $275/cow/year in a review of 9 studies.[37] However, this return depends on the prevalence and type of mastitis in the herd, existing control measures, and producer compliance.[38] Although the costs incurred by producers to control mastitis are significant, the benefits of reducing mastitis include improved cow health and productivity, a superior raw milk supply for processors, better quality and safer dairy foods for consumers, and a more sustainable global market for dairy products.

Anatomic Structures of the Bovine Mammary Gland

Cattle have a single udder composed of four independent mammary glands that are referred to as *quarters*. Suspensory ligaments attach the udder to the pelvic bone and abdominal muscles of the ventral body wall. The four quarters are independent and have no direct connections among them.[39] Each mammary gland consists of a teat with a single opening, small cisterns (also called *sinuses*) in the teat and base of the gland, a system of ducts, and secretory tissue. The secretory tissue is organized into lobes composed of lobules containing hundreds of microscopic alveoli lined by mammary epithelial cells that synthesize and secrete milk.[40] Nutrients required for milk synthesis are delivered to each mammary gland by the circulatory system and transported into epithelial cells or directly into the alveolar lumen. Milk components (e.g., casein, lactose, fat) are synthesized within epithelial cells and secreted into the alveolar lumen, where they combine with other constituents to form milk. Production of milk is continuous, and during the interval between milkings, about 20% of the milk accumulates in the larger spaces of the udder like the teat cistern, gland cistern, and large ducts *(cisternal fraction)*. However, about 80% of the milk remains fixed by capillary forces within the alveoli *(alveolar fraction),* and removal of this fraction is dependent upon achieving successful milk ejection *(milk letdown).*[41]

Milk letdown occurs in response to tactile stimulation of teats, which triggers a neurohormonal reflex, causing the pituitary gland to release *oxytocin* into the bloodstream.[41] Milk is ejected from the alveoli into the cisterns when the surrounding myoepithelial cells contract after binding oxytocin. Milk flows through the teat orifice after resistance of the teat canal (also called the *streak canal*) is overcome owing to pressure of milk in the teat, suckling by offspring, or through the process of milking. Activation of the sympathetic nervous system during periods of stress or excitement can inhibit oxytocin release from the pituitary gland or oxytocin binding to myoepithelial cells, thus preventing milk ejection.[42]

The teat canal and surrounding musculoelastic tissue provide the primary physical barrier to microbial invasion and also prevent milk leakage between milkings.[43,44] The teat canal is a narrow, longitudinally folded cylinder lined with stratified squamous epithelium. The tortuous shape of the canal provides physical protection against infection, as does protein-rich *keratin,* which is continually produced by the epithelial cells and lines the canal. Lack of keratin in the teat canal greatly increases the risk of IMI, because keratin physically plugs the teat canal, traps invading microbes, and contains bactericidal fatty acids and proteins.[45-47] Hyperkeratosis of the teat end, trauma-associated abrasion of the teat orifice, or teat damage from ineffective pulsation, excessive milking vacuum, or poorly fitting teat cup liners can also increase the risk of IMI.[48-50]

Because of the importance of the teat in mammary gland defense, dairy producers should routinely monitor teat condition and use a combination of genetic selection and management practices to promote teat health and sound conformation of the udder. However, it must be emphasized that cows that are housed on wet or soiled bedding or have udders and teats exposed to excessive water during milking preparation are at high risk for IMI, despite good teat end health.[51-53] Additionally, lack of aseptic preparation of teat ends before cannula insertion or use of multiple-dose drug preparations that are not intended for intramammary infusion can result in outbreaks of infection caused by opportunistic pathogens.[54]

Immunologic Response to Intramammary Infection

Preventing exposure to pathogens is the foundation of controlling infectious disease, including mastitis. When exposure to pathogens is sufficient to traverse the teat canal and multiply in milk, the ensuing host immune system response initiates inflammation of the mammary gland, which is recognized as subclinical or clinical mastitis. If the innate and acquired immune systems effectively eliminate the invading microbes, the mastitis will be mild and transient. However, when defense mechanisms are compromised (e.g., during the periparturient period or following transportation and comingling of new animals in the herd) or when the pathogen expresses virulence factors that resist phagocytosis or intracellular destruction, severe or chronic mastitis may develop. The intensity of the inflammatory response determines whether mastitis is subclinical or clinical.

With *subclinical mastitis,* the inflammatory process does not result in visible abnormalities in the milk, mammary gland, or cow, although leukocytosis and other soluble changes in milk occur. With *clinical mastitis,* milk from the affected quarter is visibly abnormal, the gland may undergo marked inflammation, and the cow may exhibit signs of systemic illness. Although mastitis can result from trauma, the vast majority of mastitis is caused by IMI via the teat canal. As stated earlier, limiting exposure to pathogens at the teat end remains the primary means to prevent infection, but mastitis will occur even in well-managed herds.

MAMMARY INFLAMMATION. If invading pathogens overcome the teat canal barrier and gain entry into the gland, a series of innate host defenses help limit bacterial growth. Since bovine mastitis is essentially a disease of bacterial (and occasionally mycotic or algal) pathogens, the primary effectors of mammary immunity are polymorphonuclear neutrophils. However, as in other tissues, these

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phagocytes rely on a complex system of soluble and cellular mediators that recognize pathogen presence and subsequently recruit and activate phagocytes to eliminate the microbes. This system is called the *innate immune system*. Soluble factors include complement, lactoferrin, and acute-phase proteins (e.g., mannose-binding lectin, C-reactive protein). Lactoferrin is an iron-binding glycoprotein produced by mammary epithelial cells and found in neutrophil granules.[55] By sequestering iron, lactoferrin prevents multiplication of iron-dependent microorganisms like coliform bacteria.[56] Mannose-binding lectin and C-reactive protein will bind to molecules specific to pathogen cell walls and help activate the complement cascade.[57] Innate host defenses differentiate host tissue from pathogens by recognizing molecules that are universal to many microbes but not present on the body's own cells.[58] These pathogen-associated molecular patterns (PAMPs) are recognized and selectively bound by serum proteins and receptors in host cells called *pathogen recognition receptors* (PRRs).[58]

Toll-like receptors (TLRs) are an important class of PRRs that reside both on cell surfaces and within host cells. These receptors invoke gene expression and release of inflammatory cytokines (e.g., interleukins [ILs], tumor necrosis factor [TNF]-α) from the host cells and act as the critical link between recognition of foreign agents and initiation of the host response.[58,59] Examples of specific pathogen targets bound by TLRs include peptidoglycan and lipoteichoic acid of gram-positive bacteria (TLR-2), gram-negative lipopolysaccharide (LPS [TLR-4]), bacterial flagellin (TLR-5), and bacterial DNA as CpG oligonucleotides (TLR-9).[60] Much of the local inflammation and systemic signs (when they occur) associated with mastitis are due to this response. Numerous cell types, including epithelial and endothelial cells, macrophages, and other phagocytic cells, possess TLRs that can contribute to an inflammatory response.[61] The inflammatory response is further modulated by activation of eicosanoid (arachidonic acid) metabolites such as prostaglandins and leukotrienes, as well as endocrine and adipose mediators.[62]

Milk from healthy mammary glands contains a low concentration of cells, the majority of which are macrophages. However, when microbial ligands (molecules) are detected by TLRs on macrophages and epithelial cells, these cells release proinflammatory cytokines like IL-1, IL-6, and TNF-α.[58] These mediators cause vasodilation and expression of adhesion molecules on endothelial cells, which in turn triggers an influx of neutrophils.[60,63] Circulating blood neutrophils must adhere to the vascular endothelium before migrating into the milk. Vascular neutrophils loosely bind and roll along the endothelium, using a surface adhesion molecule (CD62L or L-selectin).[64] L-selectin is highly expressed on the surface of normal circulating neutrophils, whereas similar molecules, E-selectin (CD62E) and P-selectin (CD62P), are expressed on vascular endothelial cells at the site of inflammation.[64,65] Neutrophil CD62L is responsible for making initial contact between fast-flowing blood neutrophils and the vascular wall, which rapidly slows neutrophil movement in small postcapillary vessels, whereas endothelial CD62E and CD62P direct slow-moving neutrophils to the specific site of inflammation. Additional proinflammatory mediators like IL-8, leukotriene B-4, and complement component 5a serve as neutrophil chemotactic agents and promote expression of surface receptors on endothelial cells.[64] This in turn causes neutrophils to express the β_2-integrin adhesion complex CD11b/CD18. The CD11b/CD18 complex firmly anchors neutrophils to vascular and intercellular adhesion molecules.[64,66,67] Once bound, neutrophils migrate between the endothelial and mammary epithelial cells into the milk *(diapedesis),* traveling along a chemotactic gradient to the site of infection.[64] During infection, neutrophils often exceed concentrations of 1 million cells/mL. Both the speed of recruitment and extent of neutrophil influx into milk influence microbial clearance and are critical determinants of infection outcome.[60,68-70]

During migration and under the influence of proinflammatory cytokines (e.g., TNF-α and interferon [IFN]-γ), neutrophils are further activated to become focused killer cells.[64] In this way, the leukocytes arrive at the infection site ready to recognize, phagocytose, and kill infecting pathogens. Phagocytosis is accomplished through a variety of specialized receptors on the surface of neutrophils, which are generally upregulated in response to the proinflammatory signals received during diapedesis and chemotaxis. Expression of CD14 receptors enables neutrophils to bind bacterial lipopolysaccharide (LPS) in the presence of LPS-binding protein (LBP); this binding facilitates nonopsonic phagocytosis of gram-negative bacteria.[71] At the same time, soluble CD14 is shed into the milk, where it neutralizes free LPS and binds to epithelial cells, enhancing chemoattractant release.[70] The most important neutrophil receptor for opsonic phagocytosis is the Fc receptor, which binds the Fc region of immunoglobulins (Ig), particularly IgG2 and IgM, enabling the phagocytosis of antibody-coated pathogens.[72,73] Complement component 3b is also opsonic for bovine neutrophils.[66]

Receptor binding stimulates the neutrophil to extend pseudopods and engulf the adhered pathogen into a phagosome. The phagosome fuses with cytoplasmic secretory granules to form an intracellular vesicle (phagolysosome), where degranulation and microbial killing take place. Neutrophil granules contain cationic peptides called *defensins* that have broad-spectrum antibacterial and antifungal activities.[55,60] These proteins, along with lactoferrin and hydrolytic enzymes, contribute to O_2-independent killing of engulfed pathogens.

To effectively respond to pathogen invasion, the lactating mammary gland of ruminants must overcome numerous deficits. The number of somatic cells in milk, which in lactating dairy cattle are primarily leukocytes, is typically less than 100,000 cells/mL in uninfected glands—about 100-fold lower than in blood. Concentrations of factors like lactoferrin and complement are also lower in milk relative to plasma.[74] The ability of circulating macrophages in milk to reenter tissue for antigen presentation remains speculative, but compared to blood, macrophages and neutrophils in milk have decreased phagocytic ability.[75,76] Neutrophils engulf fat globules and casein, which reduces subsequent pseudopod formation as well as intracellular killing capacity.[70] Host-adapted pathogens (e.g., *S. aureus*) often have numerous virulence factors to help evade recognition and phagocytosis, which further compromises the ability of host defenses to eliminate the infection.

Specific Immune Responses. If a pathogen survives innate host defenses, the specific (also called *acquired*) immune system is triggered. This branch of the immune system recognizes specific antigens of pathogens, and if repeated exposure occurs, an immunologic "memory" initiates a faster and more intense response with longer duration. As with neutrophils, mammary macrophages ingest and kill microorganisms.[77] Macrophages appear to be particularly important in chronic IMI and during involution (dry-off) of the mammary gland. In addition to initiation of inflammation and pathogen killing, macrophages and dendritic cells play a key role in processing and presenting antigen to T lymphocytes. Antigen presentation is critical to activating T cells ($CD4^+$), thus enabling cytokine secretion, activation of B lymphocytes, and cytotoxic ($CD8^+$), suppressor, and memory functions.[78] To date, the role of the $CD4^+$ (helper), $CD8^+$ (cytotoxic and suppressor), and CD17 (phagocyte agonist) subsets in bovine mammary immunity are best understood.[79,80] B-lymphocytes are also critical for antigen processing and serve as precursors to immunoglobulin-producing plasma cells.

Concentrations of immunoglobulin are low in normal milk but rise in response to IMI. This increase is partly a result of local Ig production but is mostly due to increased permeability of vascular endothelial cells and mammary epithelial cell tight junctions, which allows an influx of plasma Ig (and other plasma proteins) into milk. Influx of opsonizing Ig (IgM and IgG2) enables efficient phagocytosis of microorganisms by neutrophils.[72,73,81] Nonopsonizing Ig (IgG1 and IgA in cattle) has other beneficial functions like neutralization of bacterial toxins, agglutination of bacteria, and prevention of bacterial adherence to epithelial cells. Immunoglobulins in milk also mediate antibody-dependent cell-mediated cytotoxicity by leukocytes.[78,82]

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DEFENSE MECHANISMS IN THE PERIPARTURIENT PERIOD. Mammary gland defense mechanisms are greatly reduced in the periparturient period, increasing the animal's vulnerability to IMI. Indeed, both the incidence and severity of mastitis are greater in the periparturient period than during other periods of lactation.[64,83-85] Phagocyte diapedesis and killing and lymphocyte mitogenic responses are markedly decreased during the periparturient period.[79,82,86-88] Cows infected with *S. aureus* have a subpopulation of $CD8^+$ lymphocytes within the mammary gland that suppress proliferation of $CD4^+$ lymphocytes, and this class of $CD8^+$ cells is preferentially trafficked into the gland during the postpartum period.[80]

The immunosuppression accompanying parturition is partly caused by increased circulating cortisol concentration, which impairs neutrophil margination and recruitment.[64] Neutrophils of periparturient cows also undergo apoptosis more rapidly than neutrophils of cows in later lactation, and early onset of apoptosis reduces phagocytic and intracellular killing activity.[70] Low circulating concentrations of insulin-like growth factor (IGF)-1 in periparturient cows may reduce neutrophil viability and impair cytokine secretion.[85]

Nutrition of cows during the transition period can also play a critical role in mammary immunity. Recently a critical link between negative energy balance and immune function in dairy cattle has been elucidated. Nonesterified fatty acids (NEFAs) are released from adipose tissue in response to negative energy balances that are typical for cows in the transition period from late gestation through peak milk production. Particularly before calving, cows with excessive negative energy balances and high serum NEFAs are more at risk for culling and diseases during early lactation.[89,90] Additionally, elevated serum NEFAs lead to undesirable expression of proinflammatory mediators, adhesion molecules, and reactive oxygen species.[91] The altered plasma fatty acid profile in cattle during periods of negative energy balance also changes the phospholipid content in membranes of endothelial and mononuclear cells.[92] Fatty acids from membrane phospholipids are the precursors for numerous arachidonic acid metabolites, the control of which is critical for the magnitude of inflammatory responses.

Antioxidant supplementation has also been shown to play an important role in mammary immune function. Vitamin E, selenoenzymes, and zinc-dependent superoxide dismutase protect cells and membranes from oxidative damage that could result from expression of reactive oxygen species during phagocyte killing.[93] Compared to selenium-supplemented cows, cows that were selenium deficient showed reduced neutrophil phagocytosis and killing.[94] Selenium deficiency also resulted in more severe outcomes in cows with coliform mastitis.[95] In one herd, vitamin E supplementation above National Research Council (NRC) guidelines (4000 IU/day) to dry cows in the last 14 days before calving was reported to decrease clinical mastitis in the first 7 days of lactation.[96] However, in a larger field study in five herds, feeding dry cows 3000 IU/day of vitamin E (which exceeds NRC recommendations) was found to increase both subclinical and clinical mastitis in the first 3 months after lactation.[97] In this field study, antioxidant status in cows fed high levels of vitamin E varied, which may reflect the dependency of plasma α-tocopherol concentrations on lipid mobilization, which itself varies with individual cow energy balance.[98] Although antioxidant supplementation is critical for mammary health, there is no compelling evidence to feed selenium, vitamin E, or any other nutrient of this type above NRC guidelines.

Diagnosis and Detection of Mastitis

Definitions Technically, *mastitis* can be defined as any inflammation of the mammary gland (including inflammation caused by injury), but almost all mastitis occurring in dairy cows is caused by pathogenic organisms that are mostly of bacterial origin but can also include yeasts, fungi, and algae.[6] Like infections occurring in other tissues, mastitis begins with invasion of a pathogen, followed by a brief latent period, and then progression to either subclinical or clinical states or resolution of the infection as a result of the cow's immune response.[99] Detection of mastitis is almost never based on identifying the precise moment of infection but rather on observing the resulting inflammation. Recognition of mastitis is dependent on pathogen and cow characteristics that govern the magnitude of the immune response and the intensity and accuracy of the detection methods used on the farm.

Subclinical mastitis is characterized by inflammation of the udder that is usually detected by enumeration of inflammatory cells in the milk. By definition, milk obtained from mammary gland quarters of cows experiencing subclinical mastitis appears normal but contains an abnormal number of somatic cells with or without the detectable presence of mastitis-causing bacteria.[100] In most instances, detection of subclinical mastitis is based on evaluation of the SCC in an appropriate milk sample. The SCC can be measured using milk collected from individual quarters or composite milk samples that are a mixture of milk from all functional glands of an individual cow. Composite milk samples are routinely used in Dairy Herd Improvement Association (DHIA) programs for monitoring SCCs of individual cows. When composite SCC values are used, some subclinical infections will not be detected because the SCC of the composite milk will be reduced by dilution with milk from healthy quarters that contain few somatic cells.[101] When cows are not routinely tested for individual SCC, veterinarians cannot determine important epidemiologic characteristics of subclinical infections (e.g., prevalence, incidence) necessary for implementing mastitis control programs.

The distribution of cell types found in bovine milk varies depending on infection status and milk fraction.[102] The SCC of healthy quarters is quite low and usually remains well below 100,000 cells/mL.[103] However, based on detection of IMI (microbiologically positive milk samples), a threshold of less than 200,000 cells/mL is usually considered the optimal value to define a mammary quarter as healthy.[100,104-106] Selecting the appropriate threshold for defining subclinical mastitis depends the goal of the control program. Lower thresholds will identify more animals with subclinical infections (increased sensitivity and fewer false negatives), whereas higher thresholds (increased specificity) will result in fewer false positives.[106] Regardless of the threshold selected, reviewing the history of SCC values for a cow is much more informative than observing a single monthly value.

A SCC above 200,000 cells/mL in milk does not mean bacteria will be recovered from milk samples obtained from the affected gland. The immune response reflected by the influx of leukocytes can be quite effective at reducing the number of bacterial colonies in milk, and about 10% to 25% of quarters that are above a threshold of 200,000 cells/mL will be apparently bacteriologically negative.[100,104-107] When historically important contagious pathogens (e.g., *Streptococcus agalactiae* and *S. aureus*) have been controlled, the rate of apparent "false negatives" (inability to recover bacteria from quarters that exceed the SCC threshold) is often even greater. These culture-negative samples do not always indicate that the quarter is cured, but merely that the immune response has reduced the number of bacteria to below normal laboratory detection limits. It is useful to educate clients that about 30% to 50% of milk samples collected from mammary glands with high SCCs will be culture negative, so sufficient samples should be collected to ensure meaningful diagnostic test results.

The duration of the subclinical phase of IMIs will vary depending on etiology. In most herds, a greater proportion of subclinical mastitis is caused by gram-positive than by gram-negative pathogens (Table 36-1). Usually, gram-negative opportunistic pathogens like *Escherichia coli* have a shorter subclinical phase than gram-positive pathogens like *S. aureus* or most IMIs caused by *Streptococcus* spp.[108,109] In general, some 25% to 35% of cows experiencing chronic subclinical mastitis caused by gram-positive pathogens may eventually exhibit clinical symptoms.[110] For opportunistic environmental pathogens, the likelihood of a clinical episode occurring in a cow with subclinical IMI varies among pathogens. For example, about

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TABLE 36-1

Common Mastitis-Causing Bacteria*

Country	Herds	Milk Samples†	*Staphylococcus aureus*	Other Staphylococci	*Streptococcus agalactiae*	Other Streptococci	Coliforms	Other	No Growth
Milk Samples Collected from Clinical Cases									
Holland[109]	274	2737	18%	6%	0%	25%	28%	NR‡	22%
United Kingdom[135]	90	480	3%	13%	0%	25%	21%	11%	27%
New Zealand[149]	28	1332	19%	7%	0%	45%	NR	4%	27%
Canada[136]	106	2850	11%	6%	0%	16%	15%	5%	47%
United States[7]	51	706	3%	6%	0%	14%	35%	13%	29%
Milk Samples Collected from Cows with Visibly Normal Milk									
Finland[187]	216	12,661§	3%	17%	<1%	<1%	<1%	15%	62%
Germany[188]	80	9910	6%	9%	<1%	2%	<1%	13%	74%
United States[190]	40	5227	4%	16%	2%	8%	2%	16%	57%
Italy[189]	101	13,124	2%	19%	21%	12%	3%	6%	37%

*Results of selected studies that describe the distribution of bacteria recovered from milk obtained from cows with clinical and subclinical mastitis in modern dairy herds located in developed countries.

†Results characterized as contaminated and mixed infections were excluded.

‡NR indicates that the study did not report that outcome.

§Contaminated cases are included.

50% of IMIs caused by streptococci progress to clinical signs, but over 80% of coliform infections will exhibit clinical signs.[108]

It is important to diagnose the prevalence and incidence of subclinical infections within a dairy herd. Cows with subclinical mastitis infections are known to produce considerably less milk and maintain a reservoir of infection that can result in increased exposure to potential pathogens of otherwise healthy cows.[111] Subclinical infections that persist for long durations are especially costly. For example, cows that maintain subclinical mastitis across the dry period (SCC > 200,000 cells/mL at the last test of the completed lactation and first test of the subsequent lactation) have been shown to produce 9.1 kg (20 lb) less milk at their first DHIA test day.[106]

In diagnostic laboratories, SCCs of milk can be determined using methods like direct microscopic observation or, more commonly, electronic counting of dyed cells in either fresh, preserved, or frozen milk.[112,113] About half of U.S. dairy farms subscribe to monthly DHIA testing and have access to SCC values determined using composite milk samples collected from individual cows.[114] SCC values are not usually normally distributed, and many DHIA centers report the SCC using a linear score transformation that is calculated using a simple formula ($LS = \log_2 [SCC/100] + 3$). This transformation results in a normal distribution of the values and a linear association of the transformed data with estimates of losses in milk yield that are caused by subclinical infections.[115] Review of monthly summarized SCC values at the herd level is a critical component of udder health programs and should be part of routine veterinary activities on dairy farms.

Laboratory-based methods for identification of subclinical mastitis are considered to be accurate, but because they are removed from the farm, they are sometimes criticized as too slow for making cow-side decisions. To overcome this hurdle, a number of indirect measures of SCC have been developed. The California Mastitis Test (CMT) is an example of an indirect test that has been used for more than 50 years to help guide mastitis control programs.[116] The CMT was developed to test milk from individual quarters but has also been used on composite milk samples and bulk milk samples.[116] The CMT reagent is a mixture of a detergent plus bromcresol purple (used as an indicator of pH). The degree of reaction between the detergent and the DNA of cell nuclei is a measure of the number of somatic cells in milk. The CMT test is generally read using a five-point scale that begins with "negative" (SCC range of 0 to 200,000 cells/mL) and "trace" scores (SCC range of 150,000 to 500,000 cells/mL) and ends with a maximum score of 3 (SCC > 5,000,000 cells/mL). The CMT was developed during an era when many cows had very high SCCs as a result of chronic subclinical infections caused by *S. agalactiae* and *S. aureus*. Adoption of standardized best management practices has decreased the prevalence of these pathogens,[117] and SCC values of cows infected with other pathogens are typically much less. Although the CMT continues to have considerable utility, it is important to note that even "trace" scores indicate the presence of subclinical mastitis, and the test may be difficult to read when used on milk obtained from cows in the first few days of lactation.[118,119]

In addition to increased SCC, a number of changes in milk composition are due to the immune response to infection. Compositional changes include reduced casein, lactose, and α-lactalbumin concentrations; an influx of sodium, chloride, and plasma proteins; increased proteolytic and lipolytic activity; an increase in lactoferrin concentration and enzyme activities; and a rise in pH.[120] Many of these changes can be used as indicators of subclinical mastitis. Among the more common milk tests are those that detect albumin, sodium, chloride, lactose, or adenosine triphosphate (ATP) concentration; *N*-acetyl-β-D-glucosaminidase (NAGase) activity; antitrypsin activity; or pH. Plasma tests detect α-lactalbumin, casein, or lactose concentration.[120,121-125] Milk concentrations of the acute-phase proteins amyloid A and haptoglobin are also used to distinguish healthy quarters from those with subclinical mastitis.[121,125] With increases in diagnostic technology and increased emphasis on production of high-quality milk, considerable research has been focused on producing tools for continuous in-line monitoring of milk quality. The increased use of automatic milking systems (robotic milking) has led to the search for automated methods that can consistently and accurately detect abnormal milk.[126] Current testing technology generally gives accurate results, but the ultimate value of the test depends on the value of the management decision that is based on the test result; veterinary practitioners should continuously review how such tests can be best used on dairy farms.

Clinical mastitis is usually defined as the production of abnormal milk with or without secondary symptoms. Detection of clinical mastitis is based on observation of foremilk prior to attaching the milking unit, but the working definition of clinical mastitis varies greatly among farm personnel. Many farms do not routinely remove or observe foremilk of all cows, so detection of clinical mastitis is limited to cases with more severe signs.[114,127] To better understand the incidence of mastitis, veterinarians should ask milking technicians to describe their individualized definition of clinical mastitis symptoms. Clinical signs of mastitis result from inflammation and may include abnormal appearance of milk (presence of clots or serum); swelling, redness, or edema of one or more quarters; or severe systemic signs

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such as anorexia, fever, or agalactia. Compared to subclinical mastitis, a much greater proportion of clinical cases are caused by gram-negative pathogens (see Table 36-1). Like other bacterial diseases, many cases of mastitis occur as a syndrome, with the infected quarters alternating between a clinical state and a subclinical state.[108] The disappearance of clinical signs simply indicates that inflammation has decreased and does not always coincide with bacteriologic cure.[128] The ability to achieve a bacteriologic cure depends on the etiology, case severity, variation in immune response among cows, efficacy of the treatment protocol, and promptness of initiating treatment.[129]

Recording the standardized severity scores can help veterinarians to better define the pattern of clinical mastitis on individual farms.[128,130-132] One severity scoring system uses a three-point scale that combines the appearance of milk with the progression to additional clinical signs. A score of 1 (mild mastitis) = abnormal milk only; 2 (moderate mastitis) = abnormal milk and abnormal udder; 3 (severe) = systemic symptoms.[128] This system is practical, simply recorded, and can be an important way to assess detection intensity. In most herds, the distribution of clinical mastitis by severity is approximately 40% to 50% mild cases, 40% to 50% moderate cases, and 5% to 15% severe cases.[7,128,130,132,133] Veterinarians are rarely asked to treat mild and moderate cases of clinical mastitis and therefore may not understand the true incidence of clinical mastitis on many dairy farms.[134] Veterinarians need to promote the use of clinical mastitis records that allow them to monitor the occurrence of mild and moderate cases and also the ability to evaluate outcomes of mastitis treatments.

Identification of Etiologic Agents

Treatment and prevention of mastitis is based on understanding the etiology of mastitis. As dairy farms increase in size, an increasingly diverse group of pathogens have been associated with the occurrence of mastitis.[7,134-136] Clinical signs may be suggestive of some pathogens, but it is impossible to diagnose the etiology based on the appearance of the milk, gland, or animal.[137,138,139] Some practitioners erroneously believe they can recognize coliform infections based on severity of the symptoms, but researchers have consistently shown that the majority of clinical cases caused by coliform bacteria present with only mild or moderate symptoms,[7,131,133] and misdiagnosis of coliform infections is common.[139] Submission of an aseptically obtained milk sample to a laboratory qualified to perform appropriate microbiological or molecular testing is necessary to determine etiology.

MILK SAMPLES COLLECTED FROM INDIVIDUAL ANIMALS. Milk samples may be individually collected from affected quarters (quarter milk samples) or combined from all four glands into a single vial (composite milk samples). Quarter milk samples collected from affected glands are more sensitive than composite samples in detecting bacteria from subclinical infections, but the sensitivity of composite samples increases with the number of infected glands per cow.[140,141] Sampling the cow on more than one occasion also increases the likelihood of detecting glands that are intermittently shedding some pathogens.[142] The concentration of bacteria per milliliter of milk varies among pathogens. Some pathogens (e.g., *S. agalactiae* and most other *Streptococcus* spp.) consistently shed large numbers of bacteria in milk. For these pathogens, composite milk samples may be acceptable because concentrations of bacteria will more consistently exceed the microbiological detection limit.[143] For other pathogens (e.g., *S. aureus* and *Mycoplasma* spp.) composite samples will often result in apparently culture-negative samples, because these pathogens are often shed in fewer numbers, and dilution with milk from healthy quarters will result in samples that contain less than the limit of detection in most laboratories (100 colony-forming units [CFU]/mL of milk).[144]

Composite milk samples are often used in an attempt to reduce the cost of routine screening of high-risk animals for the presence of existing subclinical infections with potentially contagious mastitis pathogens. Pooling 5 to 10 aseptically collected milk samples is another strategy used in some herds to further reduce costs. When either of these strategies is used, it is important to recognize that the potential for false-negative outcomes is increased. The sensitivity of composite milk samples for detection of *S. aureus* and *Streptococcus dysgalactiae* was estimated to be about 73% to 77%, in contrast to about 60% to 62% for *Streptococcus uberis* and coagulase-negative staphylococci (CoNS).[145] In all instances, sensitivities increase as the number of infected mammary gland quarters increases.[145] When using pooled or composite samples, veterinarians should routinely review cow histories to identify cows with increased SCCs that are typical of cows with subclinical infections.

Mastitis is usually caused by a single type of bacteria, and the National Mastitis Council (NMC) has developed standards that specify that recovery of more than two types of bacteria from an aseptically collected milk sample is indicative of contamination.[6] Before collection of milk samples, technicians should be trained in aseptic collection techniques. To maximize the possibility of recovering bacteria from the sample, milk should be collected after the teats have been prepared for milking (application of pre-milking disinfectant and drying) but before the units are attached.[146] Sampling before milking is usually easier because cows are generally more likely to stand still and there is less pressure from farm workers to release the cows. Before obtaining the sample, the udders should be clean, and dry-wiping the udder with a paper or cloth towel is often helpful in reducing the possibility of contamination. Milk should be collected in sterile vials by technicians who are wearing disposable nitrile or latex gloves and using a standardized process. After thoroughly drying the teat using a cloth or paper towel, the teat end should be vigorously scrubbed using 70% ethyl or isopropyl alcohol. If composite samples are collected, a separate alcohol swab must be used for each teat. Sanitation is not complete until the surface of the swab remains clean after it is used.

The cap should be removed from the sample vial without touching the inside, and it should be held so that the inner surface faces down. Milk from the teat to be sampled can be directed at an angle into the sampling vial. A sample size of 3 to 5 mL is usually adequate. The cap should be immediately replaced after the sample is obtained. When sampling multiple teats, the far teats should be scrubbed before the near teats, and the near teats sampled first to avoid contamination by the sampler's arm or hand. Samples must be immediately cooled, refrigerated at 4° C, held on ice, or frozen until cultured. Failure to use aseptic technique or mishandling after collection can produce erroneous results. If samples are to be submitted to a diagnostic laboratory, they should be submitted within 24 hours of collection. If samples cannot be processed within 24 hours, they should be frozen until transported to the lab. Freezing for periods of less than 2 weeks has minimal effects on recovery of most mastitis-causing bacteria but can reduce recovery of *Mycoplasma* spp.[147]

When proper sampling and laboratory techniques are used, recovery of bacteria from milk samples is highly specific for mastitis. However, microbiological examination of milk obtained from glands affected with clinical or subclinical mastitis is not very sensitive.[148] Failure to recover bacteria from a milk sample obtained from a gland with a high SCC does not usually mean that bacteria are not the causative agent for mastitis. When a single milk sample is obtained from dairy cattle exhibiting clinical or subclinical mastitis, approximately 35% to 50% of milk samples will be culture negative (see Table 36-1).[7,117,149] Repeated sampling of affected quarters can increase the probability of reaching a diagnosis.[142,144]

Laboratory Methods. Standardized laboratory methods for identifying mastitis pathogens have been well defined by the NMC.[6] In general, technicians inoculate media that contain nutrients required for bacterial growth, and the inoculated media are placed in an incubator that contains the appropriate atmosphere and temperature to encourage growth of the target organisms. After 24 to 48 hours, the plates are examined for growth, and the bacteria are identified using a variety of specific test methods that depend on observable bacterial characteristics. In most mastitis laboratories, 10 to 100 µL of each milk sample are inoculated onto a portion of a blood agar plate (5%). The inoculum volume determines the lower limit of

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detection. For example, one colony observed on a plate inoculated with 0.01 mL (10 µL) is equivalent to roughly 100 CFU/mL of milk, whereas one colony observed using a 0.1-mL (100-µL) inoculum is equivalent to about 10 CFU/mL. The use of larger (0.05- or 0.10-mL) volumes of inocula increases recovery rates for pathogens shed in low concentrations *(E. coli, S. aureus)*.[151] Other ways to increase recovery are preculture centrifugation,[150] incubation,[141,152,153] or freezing[152] of the milk, or a combination of these methods. The optimal method is pathogen dependent. Augmented methods are most useful for detecting subclinical *S. aureus* infections and reducing false-negative results for clinical mastitis samples.

After inoculation, agar plates are incubated at 37° C (98.6° F) and observed for growth at 24 and 48 hours. There is no absolute definition of IMI, but the presence of at least 100 to 300 CFU/mL is usually required to define an infection. Bacterial identification is based on phenotypic characteristics of the colonies and the result of additional laboratory tests. *S. aureus* is usually differentiated from other staphylococci based on a positive coagulase reaction and other typical phenotypic characteristics (e.g., hemolysis).[6] *Streptococci* are usually identified using the Christie-Atkins-Munch-Petersen (CAMP) test and esculin reactions. When milk samples originate from cases of clinical mastitis, MacConkey agar is usually also inoculated to facilitate rapid identification of gram-negative, lactose-fermenting organisms (coliforms). Additional biochemical tests are required for final identification at the species level. Identification of *Mycoplasma* spp. requires use of media containing specific nutrients not found in general media and incubation in a CO_2-enhanced environment.

On-Farm Culturing. As farms have increased in size, on-farm culture (OFC) programs have been developed.[153] Methods used for OFC are not usually the same as those used in professional diagnostic laboratories, and are often performed by farm personnel who may have some technical expertise but lack formal training in microbiological methods. On most farms, OFC methods are based on using laboratory shortcuts and have a goal of rapidly reaching a presumed diagnosis to guide treatment. The most basic OFC method uses biplates, triplates, or quadplates that contain selective media.[154] Growth on a selective medium is used to differentiate cases caused by gram-positive or gram-negative bacteria, culture-negative cases, or in some instances specific pathogens. After 24 hours of incubation, culture plates are observed, and the treatment protocol is specified based on the culture outcome.[153,155,156] Typically used agars include MacConkey agar (selective for growth of gram-negative bacteria), TKT agar (selective for growth of streptococci) and Factor, Baird-Parker, or KLMB media (selective for growth and differentiation of some staphylococci). Studies show that using selective media in OFC systems is about 80% accurate in differentiating gram-positive and gram-negative pathogens when compared to diagnostic laboratories.[157-160] Using OFC to make more specific pathogen diagnoses is not as accurate and requires additional training of farm personnel.

Most smaller herds do not have sufficient cases of mastitis to develop the expertise needed for OFC, so one alternative is to offer in-veterinary clinic culturing (IVCC). In these instances, farmers usually collect a milk sample and immediately initiate treatment, but they may stop or modify treatment duration or the drug after receiving a preliminary microbiological diagnosis from their veterinarian within 24 hours. Development and oversight of a culture program (either OFC or IVCC) is an ideal way for veterinarians to increase involvement in mastitis control programs. The use of veterinary technicians to supervise these programs may also increase veterinary involvement and oversight of mastitis treatments. When OFC is used, veterinary technicians can visit farms to restock supplies, train farm personnel, and provide oversight and quality control.

MICROBIOLOGICAL ANALYSIS OF BULK TANK MILK. Depending on the objective of the testing, microbiological examination of bulk tank milk samples is performed using a variety of laboratory techniques.[101] Enumeration of the total number of aerobic bacteria in bulk milk is routinely performed by milk processors as part of the regulatory requirements for milk production. Standardized methods for counting bacteria may be based on culture or performed using automated counting of stained bacterial cells.[113] Processors also commonly perform additional laboratory tests to assess hygienic conditions of milk harvest and storage and may use results of these tests to determine premium payments.[161] Comparison of the number of psychotropic, thermoduric, or coliform bacteria from various milk samples can be used to identify problems with dirty udders, poor premilking preparation, cleanliness of milking equipment, or problems with cooling stored milk.[162] Methods that count bacteria are simply quantitative and do not identify specific microorganisms.

Qualitative bulk tank cultures (BTCs) are usually performed with the objective of identifying specific pathogens shed by cows being milked while affected with subclinical mastitis.[101,163] Methods of sampling, types of laboratory techniques, and the reporting format have not been standardized, making it difficult to compare BTC results among laboratories. Because of the variation in laboratory methods, it is best to submit bulk tank milk samples to a specialized laboratory that tests several dilutions using selective media for isolating and counting colonies.[6] The laboratory should be informed if identification of *Mycoplasma* spp. is of interest so that proper media and incubator conditions are used.

Interpretation of BTC results can be confusing because bacteria can originate from teat skin, subclinical mastitis infections, failure of milking technicians to exclude milk from cows that have clinical mastitis, poor hygienic conditions, failure to adequately cool milk, and the use of inadequately cleaned milking equipment. Interpretation of BTC is based on knowledge of the expected reservoirs of the organisms found in the milk.[163,164] A few organisms *(S. agalactiae, S. aureus, Mycoplasma bovis)* are known to originate primarily from infected cows, but many organisms have multiple potential sources. Pathogens such as CoNS originate from infected udders, poorly disinfected teat skin, and udders that have been contaminated by bedding sources. Non-*agalactiae* streptococci are commonly found in the dairy farm environment and are associated with dirty udders, but these organisms can also cause subclinical mastitis. The natural duration of subclinical IMI caused by *E. coli* is short, and there are multiple environmental sources of this organism.[108] Thus, when many *E. coli* are found in bulk milk, the most likely source is contamination during the milking process. When organisms that have environmental niches are found in bulk tank milk, sources other than IMI should first be investigated before assuming infected cows are the cause of the increased count.

The sensitivity of a single BTC for detecting herds with infected cows is generally considered fairly low, so results should not be used to estimate the prevalence of infected cows.[163-166] However, the positive predictive values of BTC (detection of at least one positive cow when the organism was found in BTC) are estimated to be better than 97% for *S. agalactiae* and *S. aureus* and better than 80% for *Mycoplasma* spp.[166] Because of this low sensitivity, inability to isolate contagious pathogens from bulk milk does not necessarily mean infected cows are not present; negative bulk tank cultures routinely occur in herds with some infected cows. The relatively low sensitivity of a single bulk tank culture for screening herds for contagious pathogens can be improved by using enhanced laboratory techniques or by increasing the frequency of sampling. The use of commingled samples that have been independently collected for 3 to 5 consecutive days is recommended to reduce false-negative results that are due to variations in bacterial shedding.[163]

MOLECULAR TESTING. The continued development of molecular techniques has the potential to improve diagnosis of mastitis, but a full review of these technologies is beyond the scope of this chapter. A variety of molecular methods have been used to diagnose mastitis pathogens, identify potential zoonotic agents in milk, and investigate mastitis outbreaks and milk quality problems.[167-169] Some molecular methods are used to identify specific strains of bacteria to determine the likely source of transmission of mastitis pathogens.[170] Other methods are used to improve diagnosis of pathogens for which biochemical methods for identification of species are known to be

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inaccurate[171,172] or to more rapidly arrive at a diagnosis.[173] In general, genotypic methods of identifying bacteria are based on identifying unique sections of DNA that are compared to characteristics of known library strains. Several polymerase chain reaction (PCR)-based methods of identifying bacteria have been developed,[173-175] and at least one real-time (rt)PCR method for diagnosis of bovine mastitis pathogens is widely commercially available (PathoProof [Thermo Fisher Scientific]). PathoProof can accurately detect the presence of bacterial DNA of at least 11 mastitis pathogens but requires aseptically collected milk samples to limit the number of false-positive results.[176,177] In one study, this test resulted in identification of bacterial DNA of potential mastitis pathogens in 43% of culture-negative milk samples.[178] However, 31% of the culture-negative milk samples contained DNA from two or more types of organisms, and major mastitis pathogens were grown from a few of the PCR-negative samples.[176] Thus, the use of molecular testing for making individual cow decisions is not yet well defined.

Use of the PathoProof test to evaluate milk quality of bulk tank milk has also been investigated.[179] As expected, rtPCR testing is useful to detect the presence of obligate udder pathogens (e.g., *S. agalactiae*) in bulk milk, especially when there is a low prevalence of infected cows within the herd.[179] However, interpretation of rtPCR test results for other bacteria found in bulk milk is difficult. PCR test results are interpreted relative to the cycling threshold (Ct) values, which indicate the number of PCR cycles required to reach a signaling threshold. In general, the lower the Ct value, the greater the amount of the specified DNA in the sample. When using PCR on bulk milk samples, there is limited understanding of how to interpret Ct values for bacteria that can originate from either the environment or from IMI, and validated guidelines for interpretation at the herd level are unavailable.

Decision making for management of milk quality based on PCR results is complicated because DNA from both live and dead bacteria is detected. Just as the occurrence of a few colonies of environmental pathogens on a blood agar plate would not be sufficient evidence to initiate treatment,[6] identification of bacterial DNA from milk is not always sufficient evidence on which to base a treatment protocol. To improve the utility of diagnostic methods based on DNA, aseptic samples should be collected,[177] and the medical history and SCC of the cow should be reviewed before making treatment or culling decisions. For some pathogens (e.g., *Mycoplasma* spp., *S. agalactiae, S. aureus*) the cow's history will generally support the presumed diagnosis; for other pathogens the relationship may be less apparent. The cost of using molecular methods will likely decrease and their use likely increase, but continued research is warranted to help define practical ways of best using these methodologies.

Epidemiology of Mastitis Pathogens

TRANSMISSION AND RESERVOIRS. Mastitis is an infectious disease that occurs when udders become infected with pathogens, most of which are bacteria. With the exception of infections caused by a few unique microorganisms (e.g., *Mycoplasma* spp.), exposure of the teat sphincter to bacteria is the primary route of almost all mammary gland infections. Microorganisms that can potentially cause mastitis are typically categorized as either environmental or contagious based on the likely reservoir on the farm and the most probable source of the initial exposure.

Opportunistic organisms found in the cow's surroundings are generally considered to be primarily environmental pathogens. Transmission occurs when teats are exposed to bacteria found in environmental sources like fecal material, bedding, soil, and contaminated water.[53] Contamination of teat skin with environmental pathogens increases the probability of IMI, especially when defense mechanisms (e.g., teat sphincter patency) are compromised. IMI with environmental pathogens can also occur when teat ends are insufficiently disinfected before infusing antibiotics, or when a contaminated infusion preparation or cannula is used.[53,180,181] Gram-negative bacteria (e.g., *E. coli* and *Klebsiella* spp.) are the most commonly isolated environmental pathogens,[7] but many gram-positive organisms (e.g., *S. uberis, S. dysgalactiae*) can be found in the cow's surroundings, and initial infection with these pathogens is often from an environmental source. Although coliforms and streptococci are commonly isolated, many other organisms are found in the environment of cows and capable of causing mastitis. The diversity of environmental mastitis pathogens is increasing as management of dairy farms intensifies and a variety of bedding sources are used.[53,133,135] Reducing exposure to environmental pathogens is based on improving hygiene of cows, housing areas, and the milking process.

Mammary glands with chronic subclinical infections are the predominant reservoirs of contagious mastitis pathogens. Transmission occurs when teats are exposed to bacteria present in milk that came from an infected gland. In many instances, exposure to infected milk occurs during the milking process. Infected milk droplets can be found in teat cup liners, hands of milking technicians, towels used to wash or dry teats, or in milk droplets that leak onto bedding surfaces. The presence of these organisms on teat skin increases the probability of infection. In some cases, abrupt vacuum fluctuations within the milking cluster (reverse-pressure gradients) can propel contagious pathogens from the milk of an infected gland into the teat canal of a healthy gland.[183] The most common contagious mastitis pathogens are host-adapted bacteria that cause long-term subclinical infections. Historically, *S. agalactiae* was considered one of the most important causes of contagious mastitis,[6] but this obligate udder pathogen is controlled in most developed dairy regions, and it is not commonly isolated from bulk milk of U.S. dairy herds.[117,184,185] In recent years, *S. aureus* and *M. bovis* have been the most prevalent contagious mastitis pathogens found in U.S. dairy herds.[184] Most organisms that cause chronic subclinical mastitis are introduced by contagious transmission, so successful control programs for pathogens must reduce the prevalence of subclinically infected cows to reduce the probability that healthy cows are exposed to milk that originated from infected udders.

Classifying organisms as contagious or environmental is a broad characterization of the most common sources of initial exposure to pathogens and does not preclude other potential routes of transmission.[133] Such classifications were developed prior to the development of molecular tools that allow differentiation among bacterial strains of the same genus and species.[167,191] Historically, contagious pathogens were considered to be caused by highly contagious identical clones that were transmitted only among cows, whereas environmental bacteria were often considered to consist of diverse strains found only in the environment. However, DNA fingerprinting has demonstrated that several different strains of contagious organisms like *S. aureus* can be present in cows on a single farm.[192] Similarly, a single dominant strain of *Klebsiella* spp. isolated from multiple cases of mastitis has been reported as evidence of contagious transmission of a supposedly environmental pathogen.[170] Molecular methods have demonstrated that microbes are continually evolving in response to control measures and changes in farm management. Although the traditional categories still provide a reasonable basis for initiating control programs, veterinarians should be aware of the possibilities of additional routes of transmission and the necessity for comprehensive control programs that may exceed typical recommendations.

PREVALENCE OF MASTITIS PATHOGENS. More than 130 organisms, including bacteria, algae, yeasts, and fungi, have been documented to cause mastitis.[193] Some regional differences in prevalence have been demonstrated, but the distribution of pathogens that cause clinical and subclinical mastitis on modern dairy farms is remarkably consistent (see Table 36-1). In recent years, widespread adoption of standardized mastitis control procedures in developed dairy regions has resulted in decreased prevalence of mastitis caused by contagious pathogens such as *S. aureus* and *S. agalactiae* (see Table 36-1).[117,135,194] Failure to control these herd pathogens is typically a consequence of failure to effectively implement well-known mastitis control procedures like postmilking teat dipping and comprehensive use of antimicrobial dry-cow therapy.[185,186] On most dairy farms, about 25% to 30% of milk samples obtained from cows secreting

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abnormal milk result in no significant growth of bacteria (see Table 36-1), usually because of an effective immune response to infection by opportunistic environmental pathogens. Coliform bacteria and environmental streptococci are the most common pathogens identified from milk samples collected from cases of clinical mastitis (see Table 36-1). In contrast, when milk samples are collected from cows with subclinical infections, few coliform bacteria are identified, indicating the short duration and clinical nature of most of these infections.[108,187-190] In regions that have controlled *S. aureus* and *S. agalactiae,* CoNS are the most prevalent pathogen group associated with subclinical infections (see Table 36-1). Although epidemiologic studies of mastitis pathogens within regions have resulted in consistent recovery of typical groups of pathogens, pathogen distribution often varies among farms, based on individual risk factors. Implementing effective control programs and correct treatments must be based on understanding the etiology of mastitis, and sufficient diagnostic testing should routinely be used by veterinary practitioners who are working to control mastitis.

CHARACTERISTICS OF PATHOGENS. The pathogenesis, virulence, and prognosis of IMI is influenced by important characteristics that vary among pathogens. General characteristics of the most common mastitis pathogens are described in Table 36-2. Depending on specific virulence factors, organisms infect different locations in the mammary gland, have differing abilities to cause systemic symptoms, vary in the expected duration of subclinical phases of infection, and differ in the expected rate of spontaneous bacteriologic cure (see Table 36-2). Understanding these differences is fundamental to developing effective control programs.

MASTITIS CAUSED BY STAPHYLOCOCCAL SPECIES

Staphylococcus aureus. The genus *Staphylococcus* contains at least 47 species and 24 subspecies (available at http://www.bacterio.cict.fr/s/staphylococcus.html), and the initial differentiation of this genus is based on its ability to coagulate plasma.[6] Of staphylococci associated with bovine mastitis, *S. aureus* and *Staphylococcus hyicus* are coagulase positive, but *S. hyicus* is considered a minor mastitis pathogen and is usually grouped with CoNS. *S. aureus* is considered a major mastitis pathogen because of its impact on SCC and widespread prevalence. *S. aureus* has been isolated from bulk tank milk of about 40% of U.S. dairy herds,[184] but the prevalence and economic impact vary tremendously among herds. Most IMIs caused by *S. aureus* are chronic and subclinical, with periodic bouts of mild clinical mastitis. However, clinical mastitis caused by *S. aureus* can result in systemic signs, or the affected mammary gland can become gangrenous. Herds with a large proportion of cows with *S. aureus* mastitis tend to have higher BTSCCs and many cows with chronically increased SCCs (see Table 36-2).

IMI caused by *S. aureus* is diagnosed by isolating coagulase-positive staphylococci from milk samples of cows. When grown on appropriate media, colonies usually demonstrate hemolysis and other typical phenotypic characteristics.[6] Some *S. aureus* strains are coagulase negative,[195] and other *Staphylococcus* spp. (e.g., *S. hyicus*) can be catalase positive,[196] so definitive identification requires additional diagnostic testing. There are many different strains of *S. aureus*. When DNA fingerprinting is used, some herds may have a predominant strain while other herds may exhibit diverse strains.[192,197] Strains of *S. aureus* differ in contagious transmission, virulence, and antibiotic susceptibility, leading to variable responses to treatment and control measures among herds and among cows.[198-200] In some cases, multiple strains of *S. aureus* co-inhabit a gland or cow.[201] Resolution of infection with one strain can be followed by infection with another strain.[202]

S. aureus adheres to and invades mammary epithelial cells and interstitial tissue.[203-205] The organism also resists phagocytosis by neutrophils. Antiphagocytic mechanisms include a capsule that inhibits opsonization and a surface protein (protein A) that binds the Fc portion of host Ig. Leukotoxin production enables some *S. aureus* strains to kill phagocytes.[206] Other mechanisms allow *S. aureus* to survive within leukocytes and epithelial cells and induce apoptosis.[205,207,208] *S. aureus* strains produce a variety of enzymes and exotoxins that damage mammary cells and result in fibrosis and abscess formation.[209] Some strains produce β-lactamase, conveying resistance to antibiotics such as penicillin and amoxicillin. Others convert to L-form or small-colony variants that can persist with antibiotic therapy.[210-212] Certain *S. aureus* strains form adherent colonies surrounded by a biofilm, making them inaccessible to phagocytes and antibiotics[213,214]; biofilm-associated proteins are associated with persistent *S. aureus* mastitis.[213] For these reasons, *S. aureus* IMIs seldom resolve spontaneously and are difficult to treat with antibiotics.

Herds where replacement heifers or lactating cows are purchased without screening the animals or source herds often have a greater prevalence of *S. aureus* mastitis and more *S. aureus* strains than closed herds, illustrating the importance of biosecurity in mastitis control.[197] The prevalence of infected cows within a herd is an important risk factor for new infections. Cows with chronic *S. aureus* infections or characteristics that predict a low likelihood of cure should either be culled as soon as economically feasible or segregated and milked last.[185,215] Alternatives are simply to stop milking the infected gland or induce cessation of lactation in an individual gland.

Coagulase-Negative Staphylococci. In most studies, CoNS are the most prevalent bacteria isolated from milk samples obtained from cows with subclinical infections and from mammary secretions of dry cows and prepartum heifers (see Table 36-1).[216] Based on use of traditional microbiological methods of identification, at least 10 species of CoNS have been isolated from IMIs of dairy cows.[135,216-218] Epidemiologic differences among various infective species have not been well defined, and control programs are not currently based on differentiation among species.[219] Thorough understanding of epidemiologic characteristics and differences in pathogenesis among species of CoNS has been limited by the relatively poor discriminatory ability of diagnostic tests that are based on phenotypic or biochemical features.[171] Accurate identification of CoNS associated with bovine mastitis is greater for genotypic methods, and use of these methods in research will likely result in better understanding of potential differences among CoNS species.[171,220]

Staphylococcus chromogenes, S. hyicus, and *Staphylococcus simulans* are the most common species associated with bovine mastitis.[154,217] Staphylococci are the most common organisms recovered from mastitis in heifers, and a variety of CoNS species have been recovered from teat skin, the streak canal, and precalving udder secretion obtained from heifers.[216,221-223]

Because IMIs due to CoNS typically cause subclinical infection associated with only modest increases in SCC,[217] they are often referred to as "minor" mastitis pathogens despite their widespread prevalence.[220] Most infections caused by CoNS remain subclinical with SCCs less than 500,000 cells/mL.[105] However, when CoNS infections persist, they may be characterized by greater increases in SCC.[224] Some researchers have suggested that CoNS infection protects the mammary gland against infection with major pathogens[225,226] or shortens the duration of infection with other pathogens.[227] However, other researchers have demonstrated either no protective effect or that IMI caused by CoNS increased the risk of infection with other pathogens.[228,229] Current research is not definitive, but current information suggests that IMIs caused by CoNS are not protective against other infections and should not be considered as a management strategy that will result in reduced mastitis or improvements in milk quality.

Although CoNS account for about 15% to 20% of subclinical IMIs, they are recovered from a relatively small proportion of cases of clinical mastitis, and clinical signs are usually mild (see Table 36-1).[7,133] The rate of spontaneous cure is often high,[230] but intramammary treatment used for cases of clinical mastitis caused by CoNS usually results in bacteriologic cure rates that exceed 80%.[217,220] Use of β-lactam intramammary antibiotics at dry-off is often successful in treating subclinical IMI caused by CoNS. Treatment of subclinical IMI caused by CoNS during lactation is unlikely to be profitable because a potential increase in milk yield after treatment has not been

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TABLE 36-2

Summary of Characteristics of Common Mastitis Pathogens

Pathogen	Most Common Point of Infection in Mammary Gland	Duration of Subclinical Phase	Clinical Cases That Develop Systemic Signs (%)	Typical SCC Response (Cells/mL)	Common Source of Infection	Risk of Cow-to-Cow Transmission	Expected Rate of Spontaneous Bacteriologic Cure	Key Preventive Strategies
Gram-Positive Organisms								
Staphylococcus aureus	Adheres to and invades mammary parenchyma	Long	10%-20%	Variable, ranging from 250,000 to >1,000,000	Exposure to milk from infected cows	Moderate to high	Very low	Cull or segregate infected cows, five-point plan, good biosecurity
Coagulase-negative staphylococci (CoNS)	Usually mucosal surfaces	Short to moderate	2%-10%	<500,000	Teat skin	Low to moderate	Moderate to high	Teat dipping and hygiene
Streptococcus agalactiae	Mucosal surfaces of ducts and cistern	Long	<1%	>800,000	Obligate udder pathogen	High	Negligible	Identify and treat infected cows, dry-cow therapy, five-point plan, good biosecurity
Other *Streptococcus* spp. (*S. uberis, S. dysgalactiae,* others)	Variable depending on species	Moderate to long	10%-20%	>500,000; varies by spp.	Environment and milk from infected cows	Varies by spp.	Low to moderate	Improve environmental hygiene
Corynebacterium bovis	Teat canal		<1%	<200,000	Exposure to milk from infected cows	Moderate	Moderate to high	Teat dipping
Gram-Negative Organisms								
Escherichia coli	Mucosal surfaces	Short	25%-30%	>1,000,000	Environment	Low	Usually high	Improve hygiene; vaccination
Klebsiella spp.	Variable by strain	Moderate to long	25%-30%	>500,000	Environment and milk from infected cows	Varies by strain	Low to moderate	Improve hygiene; vaccination
Serratia spp. (*S. marcescens, S. liquefaciens,* others)	Can invade mammary parenchyma	Moderate to long	<15%	>500,000	Environment, chlorhexidine teat dips	Moderate	Moderate	Change to iodine dip, cull or segregate infected cows
Other Commonly Isolated Organisms								
Mycoplasma bovis and other spp. (*M. californicum, M. bovigenitalium,* others)	Distributes throughout udder and other organs	Long; often multiple glands affected	Variable depending on herd	>500,000	Infected cows; aerosol transmission among cows infected with respiratory disease is common	High	Low	Cull or segregate infected cows, five-point plan, good biosecurity, control respiratory disease
Prototheca spp. (*P. zopfii, P. blaschakeae, P. wicherhamii,* others)	Epithelial layer of mammary alveoli	Often long	Few	>500,000	Environment and milk from infected cows; poor hygiene during IMM treatments	Moderate	Low to moderate	Cull or segregate infected cows, five-point plan, reduce exposure to water, improve hygiene for IMM infusions

IMM, Intramammary.

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documented. There are no specific control measures for CoNS mastitis. Effective pre- and postmilking teat dipping, use of comprehensive antibiotic treatment of cows at dry-off, and attention to udder and milking hygiene are recommended.

MASTITIS CAUSED BY STREPTOCOCCAL SPECIES

Streptococcus agalactiae. *S. agalactiae* is considered an obligate udder pathogen, and control measures focused on reducing the prevalence of infected cows are highly effective.[5,231] This organism is rarely isolated from individual cow milk samples (see Table 36-1) or bulk tank milk obtained from U.S. dairy farms.[184] However, without proper attention to biosecurity and milking procedures, *S. agalactiae* can be introduced and spread rapidly throughout a herd, resulting in substantial economic loss. Mastitis caused by *S. agalactiae* is usually subclinical and if not treated can persist for months or years (see Table 36-2). Subclinical infection may be interspersed with bouts of mild clinical mastitis, but only rarely will cows exhibit systemic signs.

S. agalactiae adheres to epithelial cells in the mammary gland and localizes primarily in the ducts. Milk production declines when ducts become blocked with cells and debris and the associated alveoli involute. Early treatment can result in increased milk production because the superficial nature of the infection results in minimal damage to the milk secretory cells.[231] However, tissue damage, fibrosis, and a permanent decrease in milk production can occur if infection becomes chronic. *S. agalactiae*–infected glands tend to shed high concentrations of bacteria and SCCs in milk, and this organism should be suspected when BTSCC exceeds regulatory limits.[18]

S. agalactiae is easily isolated from milk samples and is diagnosed when esculin-negative, CAMP-positive streptococci are identified in milk samples obtained from bulk tanks or individual cows. Because *S. agalactiae* is an obligate udder pathogen, rt-PCR is a useful diagnostic tool for rapid diagnosis of infected cows.[173,232-235] When the organism is found in bulk milk or milk samples of affected cows, a sampling plan should be developed to screen the herd to identify and treat all infected cows. Control programs for *S. agalactiae* are based on eradication through identification, treatment, culling, and biosecurity.[185,231]

Environmental Streptococcal Species. A number of streptococci and closely related organisms are frequently isolated from milk samples collected from cows with clinical and subclinical mastitis (see Table 36-1). *S. uberis* and *S. dysgalactiae* are the most common streptococcal species recovered from IMI, but other species such as *Streptococcus parauberis, Streptococcus equinus, Streptococcus saccharolyticus, Streptococcus salivarius,* and *Streptococcus canis* have also been associated with mastitis.[236] A number of gram-positive, catalase-negative cocci such as *Enterococcus faecalis, E. faecium, Aerococcus viridans,* and several species of *Lactococcus* have similar reservoirs and are often grouped with streptococci.[172] Because the primary reservoir of these opportunistic pathogens is bedding materials in cow housing areas, they are collectively referred to as *environmental streptococci.* Many IMIs caused by environmental streptococci result in subclinical infections, and strains that become chronic may be contagiously transmissible among cows.[237-239]

Environmental streptococci are shed in cattle feces and are often ubiquitous in the dairy farm environment.[240] Infected dogs and cats can carry *S. canis* in their respiratory and urogenital tracts and serve as potential sources of infection for cows.[237,239] *S. uberis* is found in the vagina of cows,[240] but genital tract secretions probably play little role in transmission of infection. Teats are often exposed to environmental streptococci that are present in bedding contaminated with feces and urine[241]; straw is well known to support growth of *S. uberis.* *S. uberis* also affects cows in pastures and is the most frequent cause of mastitis in New Zealand dairy herds.[149,194] High-traffic cow lanes and areas of pastures or lots where cows congregate and defecate harbor *S. uberis* and serve as reservoirs.[240]

Roughly 50% of environmental streptococcal infections are initiated during the dry period.[242] The mammary gland is highly susceptible to environmental streptococcal infection during the early and late stages of the dry period, when mammary secretions accumulate and host defense mechanisms are compromised.[243-246] However, infection may develop at any stage of lactation. Infection is accompanied by a rapid influx of neutrophils into the mammary gland and a resultant increase in SCC. Based on experimental inoculation studies with *S. uberis,* the recruited neutrophils are unable to fully prevent bacterial multiplication.[210,241] Ineffective host response probably explains the prolonged infections and persistently high SCCs seen in some cases.

Environmental streptococcal infections often remain subclinical and induce large increases in SCC.[105] A high prevalence of IMI caused by environmental streptococci may result in increased BTSCCs and loss of quality premium payments. In rare instances, the number of environmental streptococci in bulk tank milk may result in bacterial counts that exceed the regulatory limit of 100,000 CFU/mL.[248]

Although many IMIs caused by environmental streptococci spontaneously cure within 30 days, about one third of infections persist for long periods, sometimes more than a lactation. Up to 50% of IMIs caused by environmental streptococci may result in clinical signs,[242] but only about 10% to 20% of those cases will become systemically ill.[7,130,133] Control of IMI caused by environmental streptococci is based on reducing exposure in housing areas and ensuring that cows remain healthy, clean, and dry.

MASTITIS CAUSED BY COLIFORMS

Characteristics Shared Among Coliform Bacteria. *Coliform bacteria* are defined as gram-negative rod-shaped organisms that can ferment lactose.[6] These organisms are fairly easy to identify because growth on MacConkey agar results in a characteristic pink colony. *E. coli* and several other genera, such as *Klebsiella, Enterobacter,* and *Serratia* (some are non–lactose fermenting), are commonly associated with bovine mastitis (see Table 36-1), while other coliforms such as *Citrobacter* spp. only rarely cause mastitis. Coliform organisms include both pathogenic and non-pathogenic strains that are ubiquitous in the dairy farm environment and are frequently shed in feces. Within individual bacterial species, a wide variety of strains are capable of causing mastitis.[249] Teats are initially exposed to these organisms in housing or pasture areas, so coliforms are considered primary environmental pathogens. Organic bedding materials like straw, wood chips, sawdust, recycled manure or solids from methane digesters, pelleted corncobs, and newspaper support the growth of coliform bacteria, particularly under warm, wet conditions.[250] Environmental conditions like increased ambient temperatures and increased rainfall influence the growth of bacteria and thus the extent of teat end exposure and risk of IMI. Likewise, management decisions such as increased housing density, poor stall design, failure to use sufficient bedding materials, or poor pasture management can increase the probability that teats will be exposed to coliform bacteria in manure.

In early lactation, clinical mastitis caused by coliforms may be the result of IMI acquired during the dry period.[246,251] However, coliform infections can be acquired at any time during lactation, particularly if the exposure is great and primary defense mechanisms (e.g., teat sphincter patency) are compromised.

After coliform bacteria infect the mammary gland, they multiply rapidly, but most do not adhere to or invade the epithelial cells.[252] If the cow's immune response is rapid and efficient, infection will be quickly eliminated and there will be little long-term impact on cow health or productivity. Although the majority of clinical cases of mastitis caused by coliform bacteria are mild, up to 30% of cases may result in systemic signs like anorexia, fever, or a marked drop in milk production.[7,120,130,131,133] On most farms, IMI caused by coliform mastitis accounts for the majority of mastitis cases accompanied by systemic signs.[247,248] Development of systemic signs and severe disease is primarily associated with characteristics of the cow that influence her ability to respond to the infection.[252] When influx of neutrophils is delayed or phagocytosis or intracellular killing mechanisms of neutrophils impaired, bacterial multiplication continues, resulting in greater concentrations of inflammatory mediators and more severe

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clinical disease.[253] Severe cases occur most frequently in the periparturient period and early lactation.[69,254,255]

The outcome of clinical mastitis caused by coliform bacteria depends on the severity of the case, which is usually dependent on the balance between the dose (relative degree of exposure) and the ability of the cow to respond immunologically. Increased or subnormal rectal temperature, reduced rumen contraction rate and amplitude, marked dehydration, and marked depression are associated with increased risk of death, culling, or poor return to milk production.[131,256] Severe neutropenia[131] and high bacterial concentration in the milk[131,257] are also indicative of a poor prognosis. Cows in early lactation do not develop neutropenia to the extent observed in later lactation, so the leukogram is not a good indicator of mastitis severity in early lactation.[258,259]

In contrast to environmental streptococcal mastitis, intramammary antibiotic treatment at dry-off is considered less effective in preventing coliform infections during the dry period.[260,261] The spectrum of activity of many antibiotics (β-lactams and macrolides) used for dry cows in the United States is primarily directed toward gram-positive pathogens. Infusion of internal teat sealant at dry-off reduced the incidence of new *E. coli* infections compared with infusion of antibiotics (cephalonium) in one study.[262] However, the risks of new gram-negative IMIs during the dry period and clinical mastitis during early lactation were similar when quarters were treated with teat sealant plus antibiotics (cloxacillin) or antibiotics alone.[263] The use of internal teat sealant combined with appropriate intramammary antibiotics has been shown to result in reduced frequency of new IMI caused by coliform bacteria.[264]

Control of mastitis caused by coliform bacteria is based on reducing teat end exposure to these organisms. This is especially true for periparturient cows that may have compromised immune responses. Improving hygienic conditions of the cows' surroundings and during the milking routine, reducing cow density, and ensuring that cows have access to an adequate diet are fundamental steps used for reducing the incidence of coliform infections. Although coliforms are often referred to as a group, there are some important differences in pathogenicity and expected outcomes of IMI among the coliform genera.

***Escherichia coli*.** Most IMIs caused by *E. coli* are of short duration, and these organisms are rarely isolated from cases of subclinical mastitis.[265] Although many producers may believe *E. coli* typically causes severe mastitis, research demonstrates that about one third of cases of clinical mastitis will present with mild symptoms (only abnormal milk), one third will present with moderate symptoms (abnormal milk accompanied by local signs in the udder), and one third will present with systemic signs.[7,133] Most cases of clinical mastitis caused by *E. coli* are preceded by low SCC values, and the transient nature of most *E. coli* infections is evidenced by the rapid return of SCC to relatively normal levels within weeks of occurrence of a clinical case.[109] As expected for opportunistic pathogens, a large number of *E. coli* strains have been demonstrated to cause bovine mastitis, and most of these strains lack known virulence markers.[266] However, about 10% of *E. coli* cases can result in persistent infections that may result in recurrent clinical mastitis in the same or another quarters.[267,268] Persistent strains have been shown to be able to invade and replicate within mammary epithelial cells, and the ability to survive in an intracellular reservoir is likely a survival mechanism of some *E. coli* strains.

***Klebsiella* Species.** *Klebsiella oxytoca* and *Klebsiella pneumoniae* are the two most common species associated with bovine mastitis. Recent molecular studies have shown that some organisms previously identified as *Klebsiella* spp. are actually *Raoutella* spp.[170,269] The clinical presentation and management of mastitis caused by *Raoutella* spp. are identical to recommendations for control of mastitis caused by *Klebsiella* spp.[269] The distribution of symptom severity is similar for clinical mastitis caused by *Klebsiella* and *E. coli,*[7] but the impact of *Klebsiella* spp. mastitis on milk yield is significant and long lasting.[128,263] In contrast to *E. coli,* IMIs caused by *Klebsiella* spp. are often of much longer duration[259] and are often accompanied by longer-lasting increases in SCC. Initial IMI may be environmental, but between-cow transmission can occur during periods of subclinical infection. Sawdust bedding has been implicated in outbreaks of *Klebsiella* mastitis,[270] but *Klebsiella* spp. can proliferate rapidly in other bedding materials, and fecal shedding from healthy dairy cows has been documented.[271]

***Serratia* Species.** *Serratia marcescens* and *Serratia liquefaciens* are the species most commonly associated with bovine mastitis. Many *Serratia* spp. produce bright red colonies on blood agar, but they are easily outcompeted by other pathogens, and prevalence may be underestimated unless special media and cultural conditions (e.g., incubation at 20° C) are used.[272,273]

In contrast to mastitis caused by other coliforms, IMI caused by *Serratia* spp. often persists in a subclinical form for many months. Field observations and experimental infections have demonstrated that *Serratia* spp. are less pathogenic than most other coliform infections, probably because they stimulate a less profound immune response.[274] In contrast to other coliform bacteria, few cases of mastitis caused by *Serratia* result in severe clinical signs.[275,276] However, *Serratia* infection persists longer than *E. coli.* A mean duration of 55 days has been reported,[275] but many infections persist for 6 to 10 months.[272,276] Substantial SCC increases in cows and bulk milk are often associated with herd outbreaks of mastitis caused by *Serratia* spp.[272,273]

Serratia IMI can originate during lactation or the dry period. In one longitudinal study, 48% of *Serratia* infections were acquired during the first half of the dry period and 31% during the second half, with only 21% initiated during lactation.[275] IMI caused by *Serratia* can originate from environmental reservoirs like organic bedding material,[272,273] but *Serratia* mastitis is frequently associated with contaminated chlorhexidine teat dips or teat dip cups.[269,277-279] In one outbreak that used molecular analysis to identify a source, the diversity of *Serratia* strains identified indicated that chlorhexidine teat dips became contaminated with unique strains at each farm.[270] Antibiotic therapy is usually ineffective,[275,276] but up to 50% of infected quarters may eventually self-cure.[269,275] Segregation of chronically infected cows may help contain an outbreak.[272] Culling is recommended for cows with recurrent cases of clinical mastitis or persistently high SCCs.

MASTITIS CAUSED BY OTHER ORGANISMS

***Mycoplasma* Species.** *Mycoplasma* spp. are well-known dairy cow pathogens that infect a number of organs and cause a variety of cattle diseases.[280] *Mycoplasma* spp. are associated with otitis media in calves, infections of the urogenital tract, arthritis in calves and cows, pneumonia, and mastitis. Infections caused by *Mycoplasma* spp. can be recognized in disease outbreaks that present with a variety of symptoms and result in significant economic losses for dairy farms. *Mycoplasma* has been isolated from bulk tank milk of less than 4% of U.S. dairy herds,[184] but the prevalence is strongly associated with herd size and region. In 2007, *Mycoplasma* was isolated from some 14% of bulk tank milk samples obtained from herds that contained over 500 cows.[184] Risk factors for mycoplasmal mastitis include co-mingling of cattle from multiple herds, off-site rearing of calves, and stressors like overcrowding, unhygienic milking practices, and insufficient biosecurity programs.

A number of *Mycoplasma* spp. are considered pathogenic for cattle, but the most common species associated with mastitis include *M. bovis, Mycoplasma californicum,* and *Mycoplasma bovigenitalium.*[281] *M. bovis* is the most common species associated with bovine mastitis. *Mycoplasma* spp. can be isolated from a variety of mucosal surfaces of both normal and ill cattle, but increasing evidence suggests that *M. bovis* is an important cause of chronic nonresponsive pneumonia in cattle.[282] Although *Mycoplasma* spp. can be isolated from the nares of clinically normal cattle, several researchers have noted that the prevalence of nasal shedding is greater in herds that have problems with mycoplasmal mastitis than in herds that have not identified a mycoplasmal mastitis problem.[281] Colonized cattle may remain asymptomatic or may develop bronchopneumonia, otitis, polyarthritis, or mastitis. Because of the unique nature of

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carriage and transmission of this organism, veterinarians should review detection, diagnosis, and treatment of bovine respiratory disease as part of an investigation into mastitis outbreaks associated with *Mycoplasma* spp. In dairy herds with mycoplasmal mastitis, otitis media-interna, respiratory disease, or swollen joints may be seen in calves, especially if unpasteurized milk is ingested.[182,280,283]

Transmission of *Mycoplasma* spp. is unique in that multiple routes of infection of the mammary gland are possible. Asymptomatic carrier animals may infect herdmates by shedding the organisms in nasal or vaginal secretions, feces, or milk. Infection can occur at milking time when teats are exposed to fomites infected with *Mycoplasma* organisms that originated from the udder of another cow. However, IMIs can also occur when *Mycoplasma* spp. are spread from other infected body sites like the respiratory tract.[281] In one study, intramammary inoculation of *Mycoplasma* spp. into a single mammary gland was followed by detection of phenotypically identical *Mycoplasma* spp. in extramammary body sites, blood, and noninoculated mammary glands.[284,285] Biddle and associates[286] found that isolates of *Mycoplasma* species from the milk, mammary gland parenchyma, and supramammary lymph nodes of infected cows all had the same pulse-field gel electrophoresis pattern, and that all cows had at least one extramammary isolate with the same pattern. These findings suggest that cows with mycoplasmal mastitis frequently have disseminated infections, and that internal transmission may occur.

The presentation of mastitis outbreaks caused by *Mycoplasma* spp. is extremely variable among farms.[281] On many farms, most IMIs caused by *Mycoplasma* result in persistent subclinical infections. However, clinical mastitis often affects multiple glands (as a result of internal transmission of infection) and will not respond to antibiotic therapy. Many outbreaks of disease caused by *Mycoplasma* are not recognized because diagnosis is dependent on the use of appropriate laboratory methods. *Mycoplasma* spp. have unique growth requirements and must be cultured using appropriate media and incubation under specific conditions such as 10% CO_2. Prolonged freezing of milk samples reduces the concentration of viable organisms and may result in false-negative diagnoses, but broth enrichment before culturing can enhance detection of *Mycoplasma*.[147] When culture is used for diagnosis, the plates must be allowed to incubate for up to 7 to 10 days, because some colonies grow very slowly. Identification of *Mycoplasma* DNA in milk is indicative of an IMI, so diagnosis using PCR is useful because a diagnosis can be achieved more rapidly. PCR-based diagnostic methods have acceptable limits of detection (<100 CFU/mL) and use primers that differentiate among several *Mycoplasma* spp.[168] Although PCR-based methods will be increasingly used, it is important to review the health and SCC history of PCR-positive cows to ensure that identification based on DNA is indicative of active infection.

The recovery of *Mycoplasma* spp. from bulk tank milk is strongly suggestive of the occurrence of at least one infected animal in the milking herd,[144] but failure to find *Mycoplasma* does not necessarily mean the herd is free of infection. Infected cows may not be contributing to the bulk tank, they may be culled, or they may be not be shedding sufficient numbers of bacteria to be detected using typical culture methods. After identification of an infected herd, the next step is to identify the infected animals by obtaining milk samples from high-risk cows. It is possible to collect samples of milk from each string during milking to narrow sampling of individual cows to groups that test positive. Individual milk samples can then be collected and pooled to identify individuals for further testing. Cows with clinical mastitis and those with high SCC are good candidates for testing, but some infected animals may not exhibit clinical mastitis and may maintain relatively low SCC values, so diagnostic testing should continue until the bulk tank tests negative and symptoms of an outbreak subside.

Mycoplasma organisms lack a cell wall, so most antibiotics approved for use in dairy cattle are not effective. Antibiotic treatment during lactation or at dry-off is not useful for control of mycoplasmal mastitis. Although some IMIs may resolve spontaneously, infected cows should be considered permanently infected. Even if repeated culturing of milk from an individual quarter yields negative results, infection might persist in an extramammary site and spread to the mammary gland later. For this reason, the most commonly and least risky control strategy is based on an aggressive test and culling program for all cows diagnosed with mycoplasmal mastitis.[287] However, even aggressive diagnosis and culling programs may not prevent periodic mycoplasmal mastitis incidents if infections persist asymptomatically in extramammary sites. Controlling mycoplasmal mastitis in a herd is possible without aggressive culling if within-herd segregation, effective biosecurity, and excellent milking techniques are implemented.[281] This strategy is risky, however, because even with these practices, airborne transmission among cows may still occur. Vaccination against *M. bovis* is possible because bacterins are available, but their efficacy for control of mastitis has not been demonstrated. Vaccination against *M. bovis* is hindered because of variable expression of a diverse and ever-changing set of genes encoding variable surface lipoproteins (Vsps).[288]

Overall, control of *M. bovis* is based on identifying infected cows, preventing transmission through excellent biosecurity, and implementing milking and management programs that prevent new infections.[281] As with other pathogens that can be transmitted in a contagious manner, effective postmilking teat dipping is required. *Mycoplasma* spp. are susceptible to most germicides found in teat dips.[289] Effective premilking and postmilking teat dipping and other measures used to prevent the spread of contagious pathogens in the milking parlor help limit mycoplasmal mastitis transmission. Care must be taken to ensure that hospital pens do not become a source of transmission either through direct contact with infected cows or through fomites or airborne transmission.[290] Control of respiratory disease and provision of housing with excellent ventilation are also necessary. Pasteurization of waste milk reduces the risk of *Mycoplasma* transmission to milk-fed calves.[283]

Pasteurella multocida. *Pasteurella multocida* is found in the upper respiratory tract of cattle and can be considered both normal flora and a contributor to bovine respiratory disease complex. This organism is occasionally associated with bovine mastitis. Most episodes are sporadic, but herd outbreaks can occur.[291,292] Mastitis caused by *P. multocida* can be recognized by increased incidence of clinical mastitis and BTSCC increases indicative of cows with subclinical infections.[291] Hematogenous or lymphatic spread of *P. multocida* from the respiratory tract to the mammary gland has been proposed, and *P. multocida* has been isolated from the blood of cows with severe coliform mastitis.[293] However, it is unlikely that hematogenous or lymphatic spread is responsible for herd outbreaks. Contamination of teats by nasal secretions (e.g., from nursing calves or intersucking cows), cow-to-cow spread at milking time, or inappropriate infusion practices may contribute to outbreaks.[291] Antibiotic treatment has historically been unrewarding, and infected cows are often culled. However, spontaneous resolution appears to occur in some cases.[291] Control of herd outbreaks associated with *P. multocida* should be directed at reducing the possibility of cow-to-cow transmission at milking time and improving ventilation of cow housing areas.

***Prototheca* Species.** *Prototheca* species are unicellular algae that are widespread in nature and occur throughout the world in habitats that contain moisture and organic matter.[52] *Prototheca* have been frequently isolated from feces of cows and other warm-blooded animals such as pigs and rodents.[294,295] On dairy farms, several different *Prototheca* spp. have been found in moist areas like soil, mud, vegetation, and water.[294] *Prototheca blaschkeae* and *Prototheca zopfii* genotypes 1 and 2 have all been associated with bovine mastitis,[296] but *P. zopfii* genotype 2 is the main species associated with herd outbreaks of *Prototheca*-related mastitis.[297,298] Initial IMI is likely due to environmental reservoirs, but several risk factors for *Prototheca* mastitis have been identified.[54] Important risk factors include the use of intramammary infusions of unapproved products and use of internal teat sealants at dry-off. On many farms, *Prototheca* is ubiquitous in the environment, and these risk factors illustrate the importance

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of hygienic technique when performing intramammary infusions. When *Prototheca* is identified as a cause of mastitis, veterinarians should investigate treatment practices and ensure that teats are thoroughly cleaned before infusion and that intramammary products are not warmed by being placed in potentially contaminated farm water before infusion into the udder.

P. zopfii will grow on blood agar and can be detected on microscopic examination of colonies stained with Gram stain, but the colonies are easily overgrown and may be underdiagnosed. Diagnosis can be improved by culturing milk on selective media. *Prototheca* Isolation Medium (PIM) contains inhibitory substances that facilitate identification of the organism and is often used in mastitis laboratories. Identification of specific genotypes is not routinely performed but can be done for research or epidemiologic purposes using several molecular techniques.[299,300]

IMI with pathogenic *Prototheca* can result in both subclinical and clinical symptoms, and infections can occur sporadically, endemically, or acutely.[52] Most clinical cases are of mild or moderate severity. Infected cows may become chronically infected and experience persistently increased SCC.[301] Shedding of *P. zopfii* in milk can be persistent or intermittent.[302] Most *Prototheca* IMIs are probably acquired from the environment, but the possibility of contagious transmission among cows should be recognized and prevented as part of a control program.

Treatment of mastitis caused by *Prototheca* is not recommended.[52] *P. zopfii* is resistant to antimicrobial therapy, and infection can persist through the dry period.[302] Therefore, identification, segregation, and progressive culling of infected animals are required to control *Prototheca* mastitis. On most farms, searching for point sources of environmental contamination will not be useful, but hygienic conditions of the environment should be improved. Culling of infected cows should be coupled with identifying and avoiding contaminated environmental sites, enhanced cleaning of feed bunks and watering devices, and use of milking procedures that ensure clean teats and minimize contagious spread of infection.

Corynebacterium bovis. *Corynebacterium bovis* is commonly found in the streak canal and can cause occasional IMIs that result in mild increases in SCC and very little impact on milk yield.[6] It is rarely a cause of clinical mastitis. *C. bovis* can be cultured on routine media like blood agar, but colonies may not be apparent until after 48 hours of incubation. *C. bovis* can be a frequent contaminant in milk samples, and DNA from this organism is frequently identified in association with other bacteria when PCR testing is used on milk samples.[176] This organism can be transmitted from cow to cow at milking time, but effective use of pre- and postmilking teat germicides is effective in controlling transmission.

Trueperella pyogenes. *Trueperella pyogenes* is the current name assigned to an organism that was formerly known as *Arcanobacterium pyogenes;* in the past, this organism was identified as *Actinomyces pyogenes* or *Corynebacterium pyogenes*. IMI with this organism usually results in acute purulent symptoms of clinical mastitis. In most instances, treatments are ineffective, and mastitis caused by this organism has a poor prognosis.[6] Few cases remain subclinical; identification of this organism in bulk tank milk is usually a result of failure to detect and divert milk from cows with clinical symptoms. The outcomes of most cases occurring in lactating cows is loss of the quarter or culling of the cow.[303] Transmission among cows can occur by flies or through environmental exposure of teat skin, especially if teat ends are damaged.[6]

Historically, this organism was considered one of the etiologic agents of "summer mastitis," a condition of prepartum heifers and nonlactating cows that has been recognized mainly in Europe and Japan during summer months.[304] In most cases, anaerobic bacteria (e.g., *Peptococcus indolicus, Bacteroides* spp., *Fusobacterium necrophorum*) and facultative anaerobes (e.g., *S. dysgalactiae*) are also involved.[304,305] Summer mastitis is characterized by a swollen, hard, painful mammary gland containing purulent, foul-smelling secretion. Acutely affected animals typically demonstrate systemic signs ranging from lethargy and reduced feed intake to high fever, severe depression, abortion, and death. Systemic administration of procaine penicillin G often resolves systemic illness, but neither systemic nor intramammary antibiotics are effective at eliminating IMI.[305] The outcome of most episodes of summer mastitis is chronic clinical mastitis or a nonfunctional quarter. Horn flies are believed to be responsible for transmitting summer mastitis. Because *T. pyogenes* is often found in the environment on farms and on body sites of cattle, teat skin contamination may predispose to infection, as occurs with coliform or environmental streptococcal mastitis, particularly if teat defenses are compromised.

Control of summer mastitis is accomplished by fly control, infusion of mammary glands with antibiotics at dry-off, appropriate environmental hygiene practices and stocking density, prevention and treatment of teat lesions, and prompt recognition and segregation of infected cows. Amputation of the teat, which facilitates drainage of secretions, increases environmental contamination and should not be done unless the cow can be segregated.

Yeast Mastitis. Yeasts are microorganisms that are ubiquitous in the environment of dairy farms, and they can cause opportunistic IMIs. Sources of exposure of teats include contact with soil, plants, and water and feedstuffs such as total mixed rations (TMR).[306] *Candida* spp., *Trichosporon beigelii,* and other yeast organisms can cause clinical mastitis in individual cows or herds.[6] Yeast infection usually follows intramammary antibiotic treatment or teat skin injury. Outbreaks often occur when homemade infusion products or associated equipment (e.g., needles, syringes, bottles, cannulas) are contaminated or when the teat is not adequately disinfected before infusion.[180,307] In one study, six cows treated with a homemade intramammary antibiotic solution contaminated with *T. beigelii* all developed fever, hypogalactia, and swollen mammary glands within 2 weeks, and two of the six died. When the producer continued to use homemade solutions, an additional 23 cows (over half the herd) became infected, and the herd was dispersed.[307] Yeast can be cultured from towels or teat cup liners used on infected cows, suggesting that contagious transmission may occur.[307,308]

On blood agar, yeast colonies appear similar to CoNS colonies, so it is important to examine the colonies microscopically. Sabouraud dextrose agar with antibiotics is a common alternative medium that selects for yeasts. Yeast infections are not susceptible to antibiotic treatment, and infusion of antibiotics may potentiate infection. Use of antifungal agents is prohibited in the United States, but experimental use has not been demonstrated to be effective. Infection (especially with *Candida* spp.) often resolves spontaneously within 2 to 4 weeks,[306,308] but cows with severe or recurrent clinical mastitis, reduced milk production, or persistently high SCC should be culled.[307] Control of yeast mastitis includes aseptic intramammary infusion procedures, use of single-dose commercially prepared antibiotic infusion products, segregation of infected cows at milking time, and use of individual rather than shared towels. Feeding contaminated silage or TMR can promote fecal excretion of yeast and has been blamed for outbreaks of yeast mastitis in some instances.[306,308]

***Pseudomonas* Species.** *Pseudomonas* is considered an environmental pathogen and is commonly isolated from water sources on dairy farms.[6] *Pseudomonas* spp. typically appear on blood agar as white or gray hemolytic colonies and may produce a grapelike odor. *Pseudomonas aeruginosa* is the most common spp. isolated from milk of mastitic cows. IMI with *Pseudomonas* spp. can result in severe clinical mastitis that may develop into gangrene.[309] However, chronic subclinical mastitis with periodic bouts of mild clinical mastitis is the more common presentation.

After IMI with *Pseudomonas* spp. is established, it usually persists, and antibiotic therapy is unsuccessful. This is due in part to production of factors (e.g., biofilm) that inhibit host defenses and reduce antibiotic efficacy.[71] Cows with persistently high SCC or repeated bouts of clinical mastitis should be culled, or individual glands may be dried off.[310]

IMI of cows usually occurs when teats come in contact with contaminated water, and the use of water to wash teats before milking has frequently been implicated in outbreaks of *Pseudomonas*

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mastitis.[311] Water sources should always be investigated when *Pseudomonas* spp. are responsible for mastitis outbreaks on dairy farms. The use of predipping for teat disinfection rather than washing with water reduces the risk of infections caused by contaminated water sources. Similar to IMI caused by *Prototheca,* mastitis caused by *Pseudomonas* has also been attributed to use of contaminated intramammary infusion products[312] or teat cannulas, inadequate teat end sanitation before drug infusion, contaminated teat wipes,[313] and exposure of cows to stagnant water. Investigation of a herd problem should focus on hygienic practices for intramammary infusion practices and reduction of exposure to water in the environmental and milking process.

***Nocardia* and *Mycobacterium* Species.** *Nocardia* spp. and mastitis-causing *Mycobacterium* spp. are saprophytes and therefore may cause IMI when teats are exposed to unhygienic environmental conditions. However, both *Nocardia* and *Mycobacterium* spp. are uncommon causes of mastitis that have typically been associated with unhygienic use of intramammary infusions or with use of contaminated intramammary products.[6,314] Both of these organisms have been associated with sporadic cases or herd outbreaks of mastitis. Symptoms are variable and can range from greatly increased SCC[315] to death. A tentative diagnosis can be made by observing acid-fast rods or gram-positive rods with branching filaments in a milk smear, but culture of aseptically obtained milk samples is required to diagnose and differentiate *Nocardia* and *Mycobacterium* spp. Prolonged freezing can reduce recovery of *Nocardia* from milk samples.[6] Antibiotic therapy is futile. *Nocardia* is a potentially zoonotic pathogen, and affected animals should be segregated and culled. Control of mastitis caused by these organisms involves proper intramammary infusion practices and general environmental hygiene.

Prevention and Control of Mastitis

Prevention of Intramammary Infection

At the herd level, the prevalence of mastitis is a function of the incidence and duration of IMI. Control programs are directed toward implementing management programs that can influence either duration of IMI or development of new infections. After an infection is acquired, duration of IMI is influenced by the inherent characteristics of the pathogens involved (see Table 36-2), treatment efficacy, and culling decisions. Management practices that focus on limiting IMI duration typically occur after infection-related financial losses have already been incurred. In contrast, control programs that focus on preventing development of new infections are profitable because they reduce mastitis-related losses. Thus, the emphasis on controlling mastitis should be directed toward implementation of management practices that prevent new infections.

Prevention is based on knowledge of where the exposure to pathogens is occurring. In general, contagious transmission occurs when teats of healthy cows are exposed to bacteria that originated from subclinically infected udders of other cows. The primary principle of reducing exposure to pathogens that can be transmitted in a contagious manner is to reduce the possibility of contact with milk that came from subclinically infected cows. Successful implementation of the five-point plan is the basis for control of pathogens that can be transmitted contagiously.[316] The components of the five-point plan are discussed throughout this chapter and include:

1. Postmilking teat dipping
2. Comprehensive use of intramammary antimicrobial therapy at the end of every lactation
3. Appropriate therapy of clinical cases
4. Proper maintenance and functioning of milking equipment
5. Appropriate culling of chronically infected cows

The components of the five-point plan are now widely viewed as standard management procedures and are highly adopted in many developed dairy regions.[127,186] As a result, many regions have dramatically reduced the prevalence of IMI caused by organisms that are primarily transmitted in a contagious manner.

To address the increased incidence of mastitis caused by environmental pathogens, the NMC has added five additional components focused on implementation of a comprehensive mastitis control program (available at www.nmconline.org/docs/NMCchecklistna.pdf). The 10-point mastitis control program incorporates all the components of the five-point plan and is organized in the following checklist:

Point 1: Establishing goals for udder health. As with management of reproduction, nutrition, and production, it is difficult to improve udder health without having clear goals. Although establishing goals seems intuitive, few farmers set aside sufficient time to develop an udder health plan that includes herd-specific goals. Surveys of veterinarians and other professionals who work with dairy producers suggest that barriers to improvement in milk quality are often related to motivation and implementation rather than lack of technical knowledge or skills.[127,317-319] Several studies have shown that many dairy veterinarians are only marginally involved in mastitis control programs. Upon beginning a team-based milk quality improvement program, only 24% of dairy farmers ($n = 180$) indicated that they used their herd veterinarian to plan milk quality programs.[127] In a companion survey, most dairy veterinarians ($n = 42$) interested in participating in a mastitis control program reported that they spent less than 10% of their professional time actively working to improve milk quality.[317] Increased involvement in the development of annual udder health plans is an area of opportunity for dairy veterinarians, and the initial step can be to begin a discussion of herd-specific goals.

Point 2: Maintaining a clean, dry, comfortable environment. Exposure to pathogens that have environmental reservoirs is strongly associated with facility and animal hygiene. Numerous hygienic practices on dairy farms have been associated with the incidence of clinical mastitis.[320-322] The rate of clinical mastitis occurring in dairy cows has been shown to be strongly associated with the cleanliness of animal housing and bedding sources.[320] The number of bacteria on teat skin is associated with bacterial count in bedding,[323] and a linear relationship between the rate of clinical mastitis and the number of gram-negative bacteria in bedding has been demonstrated.[182] Nutritional management can have an indirect influence on hygiene. High-concentrate diets have been associated with looser feces and reduced facility cleanliness.[324] Cow cleanliness can be evaluated using several scoring systems.[322,325] A four-point udder hygiene scoring (UHS) system for assessing udder hygiene has been described by Schreiner and Ruegg.[322] Cows that are scored as having dirty udders were at increased risk of IMI and increased SCC.[322] Similarly, Reneau's group used hygiene scores to evaluate five body areas on dairy cows.[325] The udder and hindlimb scores were significantly associated with SCC.[325] Research has demonstrated that neither UHS nor the rate of new IMI is improved by the use of tail docking, and this practice should not be encouraged.[326,327]

Mastitis control programs should be focused on reducing bacterial exposures by improving facility hygiene. In many herds, clean or recycled sand will be the recommended bedding material because it does not support as much growth of coliform bacteria as organic bedding materials.[182,328,329] In some herds, bacterial counts can be reduced by adding lime and other bedding conditioners, or using other methods to reduce bacterial counts, but the effect is generally short lived.[330,331] Use of dried manure solids as bedding is a risky strategy because these substances are ideal to support growth of bacteria found in the intestinal tract of dairy cows.

Point 3: Proper milking techniques. Milking hygiene and the risk of new IMI can be improved by ensuring that milking technicians wear disposable nitrile or latex gloves.[127,332-334] Essential aspects of an effective premilking routine include effective teat disinfection, examination of foremilk, sufficient stimulation to allow for effective milk letdown, complete drying of the teats, and timely attachment of the milking unit. Research has definitively established that the gold standard for premilking teat disinfection is applying an effective disinfectant for a sufficient contact time, then drying the teat using a single cloth or paper towel for each cow.[335-337] To ensure that clinical mastitis

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is detected and abnormal milk does not reach the human food chain, two or three streams of foremilk should be removed and examined before attaching milking units. Teat drying has been demonstrated to reduce bacterial counts of teat ends,[335] reduce the number of colonies of spore-forming bacteria in bulk milk,[338] and effectively reduce the risk of contaminating milk with iodine residues from predips.[339] Separate drying cloths or paper towels should be used for each cow. Using towels to dry teats on multiple herdmates has been associated with a greater monthly rate of clinical mastitis than using a single towel per cow.[127]

Modern dairy cows in high-producing herds have been selected to milk rapidly, and removal of foremilk is often sufficient stimulation to achieve milk letdown. The period of time between stimulation and attachment of the milking unit should be about 60 to 90 seconds, but disturbances in milk flow and yield have not been reported until lag times have exceeded 3 minutes.[340,341] To prevent bimodal milk flows, premature attachment of the milking unit should be avoided.[340] To minimize stress on teat ends, milking units should be removed when milk flow rates drop to a level that indicates most milk has been harvested. In most high-producing herds, milking units are removed when milk flow rates fall below 0.5 to 1 L/min. Automatic take-off units are encouraged because they increase consistency of milking and allow milking technicians to focus more on premilking preparation.

The purpose of postmilking teat disinfection is to reduce contagious transmission of pathogens.[185,342,343] The principle is to kill pathogens deposited on teat skin during the milking process before they colonize the teat orifice and invade the gland. Effective application of postmilking teat dips can result in over 50% reduction in new IMI.[343] Postmilking teat dipping is a highly adopted practice,[127,186,344] but it is not always properly implemented. Milking technicians should be trained to use an application method (e.g., use of a dip cup) that ensures that at least 75% of the teat skin is covered with an approved, commercially formulated teat disinfectant. Efficacy of the postmilking teat dip should have been demonstrated through properly performed scientific trials. The NMC maintains a list of peer-reviewed publications about efficacy trials of teat dips (available at www.nmconline.org/docs/Teatbibl.pdf).

Point 4: Proper maintenance and use of milking equipment. The impact of machine milking on development of new IMI is well known, and veterinarians should be aware of how to evaluate key indicators of milking equipment function. Improper functioning of milking machines can result in reduced resistance of the teat canal to IMI; vacuum fluctuations and liner slips may provide forces that overcome the resistance of the teat canal to bacterial invasion or dispersion of bacteria within the udder; and milking equipment parts can serve as fomites to transfer bacteria among cows.[345] Provision of stable teat end vacuum is a central objective of a properly functioning milking system.[346] A high rate of liner slips has been demonstrated to be associated with increased rates of clinical mastitis and increased risk of IMI.[183] Improperly functioning machines may cause congestion in the teat wall, which can result in slower closure of the teat canal and development of IMI.[345]

Point 5: Good record keeping. Measuring outcomes is an integral part of effective management.[347] Mastitis is a bacterial disease that occurs in individual animals, but mastitis control programs must be implemented at the herd level. Successful mastitis control is dependent on effective detection, accurate diagnosis, evaluation of appropriate treatment options, and implementation of preventive practices that address herd-specific risk factors associated with exposure to mastitis pathogens. Veterinarians who wish to reduce mastitis should regularly review herd records for SCC and clinical mastitis and evaluate key performance indicators relative to herd goals.[347] The program should be structured to allow for the evaluation of cow factors, environmental factors, and milking machine factors that can contribute to exposure to mastitis pathogens. An effective surveillance system for mastitis includes clear case definitions and effective mechanisms to detect both clinical and subclinical mastitis, use of recording systems that allow for timely evaluation of risk factors, and feedback mechanisms that allow management personnel and veterinarians to develop goals and evaluate actions.

Points 6 and 7: Appropriate management of clinical mastitis during lactation and effective dry cow management. These topics are discussed later in this chapter.

Point 8: Maintaining biosecurity of contagious pathogens and marketing of chronically infected cows. Biosecurity programs are designed to reduce the risk that healthy cows will be exposed to bacteria originating from other animals. The goal of mastitis biosecurity programs is to reduce the probability that teats of healthy cows will be exposed to infected milk and to enable the cow to have an effective immunologic response if exposure occurs (see section on immunization later in this chapter). Many farmers arrange the milking order so that lower-risk animals (first-lactation cows or cows with lower SCCs) are milked first to reduce the risk of transmission of mastitis pathogens during the milking process. Physical segregation of chronically infected cows has been shown to be an effective method of reducing the new-infection rate[348,349] but depends on diagnostic methods that can accurately detect infected cows. Use of automated disinfectants to backflush teat cups between cows has been demonstrated to reduce the risk of developing new IMI caused by *S. aureus*,[350] but the cost-effectiveness of these systems depends on the prevalence of infection within the herd.[108] Use of an automated teat dipping and backflush system was shown to result in reduced bulk tank SCC, fewer cows with elevated SCC, and fewer cows with newly increased SCC, but the effect became more significant after 6 to 18 months of use.[351]

The prevalence of chronically infected cows is a strong predictor of risk of new infection with pathogens that can be transmitted in a contagious manner. One study demonstrated that the odds of a cow becoming infected with *S. aureus* doubled with each 5% increase in the herd prevalence of existing infection.[332] Chronically infected cows must be identified through routine testing of individual cows' SCCs, and microbiological analysis should be performed to identify the causative pathogens. Cows that develop chronic infections with pathogens that are refractory to treatment should be culled to reduce the risk of transmission to healthy animals.

When animals from outside sources are purchased, they should be bought from recognized individual herds (rather than sale barns), and historical information such as bulk tank culture results and individual cow SCC histories should be reviewed. Animals should be screened for *Mycoplasma* spp.; a history of recent respiratory disease should be viewed as an important risk factor for this infection.

Point 9: Regular monitoring of udder health status. Udder health recording systems must include monitoring programs that allow assessment of both clinical and subclinical disease. Animal health recording systems for mastitis should consist of both temporary cow-side records that are used for day-to-day decision making and permanent records (e.g., cow cards, computerized records) that are used to summarize trends over time.[352,353] The recording system should be accessible and allow the veterinarian to determine important risk factors and epidemiologic trends.[353] The first step in monitoring subclinical mastitis is to ensure that SCC values are routinely obtained from all cows on a regular basis. Generally, all cows with SCC values above 200,000 cells/mL (linear somatic cell score ≈ 4.0) are considered to have subclinical mastitis. SCCs should be reviewed monthly at both the herd level and the cow level. At herd level, evaluation of monthly SCC patterns can be highly diagnostic for troubleshooting subclinical mastitis problems. Several recommendations for key performance indicators for monitoring udder health are available.[347,353]

Point 10: Periodic review of mastitis control programs. Dairy farming is a complex process that involves interactions among animals, nature, and people. Like other research-based businesses, the growth in knowledge about dairy management practices is extraordinary. Dairy farmers acquire information about animal health from a variety of sources, including veterinarians, nutritionists, other producers, dairy magazines, and consultants. Veterinarians visit multiple farms, see results from a wide variety of management decisions, and bring an outside perspective to farm decisions.

On-farm management teams can be formed to troubleshoot specific farm issues or to meet periodically and review farm performance. A properly formed management team can aid the farmer by bringing together advisors with a range of experiences. Management teams also allow for dialogue between consultants (e.g., veterinarians and dairy plant personnel) that have shared interest in specific outcomes. The management team format is extremely successful in problem-solving mastitis problems. Farms that participated in a team-based milk quality program in Wisconsin increased adoption of best management practices and improved mastitis control.[354]

Prevention through Immunization

The 10-point mastitis control plan includes an emphasis on biosecurity and immunization as aspects of ensuring effective control of mastitis. Understanding the principles of the immunologic response is necessary to successfully implement an effective vaccination program.

Lymphocytes will respond to a specific microbial antigen only if the antigen (protein) is combined with a major histocompatibility complex (MHC) molecule on the surface of host cells, a process referred to as *antigen presentation*.[61] Cells like macrophages and dendritic cells are particularly efficient in antigen processing by phagocytizing, digesting, and presenting antigens on their membrane surface in conjunction with an MHC molecule. In response to antigen presentation, naïve lymphocytes then undergo clonal expansion and differentiation. A specific antigen can only be presented to a lymphocyte that solely recognizes that antigen.[58] Thus, successful immunization against a pathogen must link the invasion of the pathogen with recruitment of innate phagocytic cells that recognize and digest the microbe and subsequently present one of potentially hundreds of different protein antigens from the pathogen on the cell surface to attract and activate a matching lymphocyte that specifically recognizes the antigen. T helper cells play a central role by (1) enhancing B-lymphocyte clonal expansion and differentiation to antibody-producing plasma cells, and (2) completing the inflammatory response loop by releasing cytokines like IL-17 and IFN-γ that stimulate phagocytes to more efficiently phagocytize and kill ingested microbes. Antigen-specific antibodies that arise from the acquired immune response also enhance phagocyte function by opsonizing microbes, thus assisting in target recognition and ingestion.

The decision to employ a vaccine as part of a mastitis control program should be founded on the practitioner's ability to access peer-reviewed studies and compare incidence and severity of natural infections between vaccinated animals and unvaccinated controls. Studies should encompass a diversity of herd management practices and geographic regions. Unfortunately, such trials require a large number of animals and long duration. Alternatively, challenge-exposure trials are often performed to assess vaccine efficacy. This type of trial requires fewer animals and less time, and many variables (e.g., different strains of bacteria, challenge dose, physiologic and lactation status of the animal) can be uniformly standardized. More comprehensive outcomes (e.g., bacterial shedding in milk, physical examination of the cow, changes in biochemical parameters of serum and milk) can also be reliably measured. Unfortunately, these studies may have limited application to the diversity of dairy farm management and environment, as well as among pathogens.

As with therapeutics, appraisal of vaccine efficacy should *not* be made on testimonials, especially herd-level impressions of "before-and-after" responses. Assertions are often made on perceptions that initiating a vaccine program decreased the incidence and severity of mastitis cases, lowered SCC, increased milk production, and so forth, without employing a concurrent non-vaccinated control group for comparison. This is a frequent flaw in the evaluation of autogenous bacterins, in addition to a lack of quality control standards that are rigorously followed in commercial production. Mastitis incidence and SCCs within a herd can rise and fall from many factors, including weather, changes in proportion of younger to older animals in the herd, history of herd additions, correction of milking techniques or deficiencies in equipment, and culling decisions.

IMMUNIZATION AGAINST SPECIFIC MASTITIS PATHOGENS

Gram-Negative Core Antigen (J5 *Escherichia coli*) Bacterins. Gram-negative core antigen bacterins are used on many dairy herds. The most extensively studied variants are formulated with a mutant strain of *E. coli* O111:B4 (Rc mutant, commonly termed *J5*) lacking the "O" antigen capsule of the cell wall but with the core lipopolysaccharide, membrane proteins, and lipid A antigens intact. These core antigens are highly conserved among gram-negative bacteria[355-357] and elicit cross-reactive anti–gram-negative antibodies in J5-vaccinated cows.[357-359] Dairy cattle immunized with these bacterins develop immune resistance against a wide variety of gram-negative bacteria, including mastitis-causing coliforms.

Initial studies in California determined that higher serum anti-J5 *E. coli* IgG correlated with a lower incidence of clinical coliform mastitis.[360] A subsequent field trial demonstrated that compared to unvaccinated cows, animals administered three immunizations (at drying off, 30 days after drying off, and in the postpartum period) had a fivefold decrease in the rate of clinical coliform mastitis in the first 100 days of lactation.[361] A field trial in Ohio using a similar dose regimen reported that J5 immunization did not reduce the prevalence of gram-negative IMIs at calving, but 67% of the infections present at calving in unvaccinated cows developed clinical mastitis, compared to only 20% of the J5-vaccinated cows.[362] In a comparison with unvaccinated controls, cows vaccinated with J5 bacterin demonstrated increased anti-J5 *E. coli* IgG in serum and milk,[362-364] although anti-J5 *E. coli* antibody titers in milk are orders of magnitude lower than in serum. Following intramammary challenge of *E. coli,* J5 immunization reduced the severity of infection but did not prevent infections.[362]

The pathogenesis of severe coliform mastitis is dependent upon LPS-induced immune mediator responses, and a high proportion of severe coliform mastitis cases become bacteremic.[293] J5 bacterins may likely have a greater impact on the systemic effects of coliform mastitis than on local mammary inflammation. This concept is supported by a field trial from New York that determined two doses of J5 bacterin decreased the proportion of clinical mastitis cases that resulted in culling or death by threefold, but did not reduce the overall incidence of clinical mastitis cases.[365] However, coliform mastitis cases contracted during the first 50 days of lactation resulted in less milk production loss among J5-vaccinated cattle.[366]

Gram-negative bacterins are regarded as weakly immunogenic in dairy cattle because they elicit poor amnestic IgG1 and IgG2 responses.[76] An Ontario study found that a substantial population of cows given two J5 bacterin doses during the dry period had poor antibody responses and a higher incidence of mastitis in the subsequent lactation.[367] This relatively short duration of immune protection is supported by several trials.[368-370] A New York study determined that compared to unvaccinated cows, cows vaccinated with two doses of J5 bacterin lost less milk production following clinical mastitis and survived longer. However, this protection, as well as anti-J5 antibody titers, declined as lactation (and time since vaccination) progressed and did not exist by 75 days in milk.[368] In a Michigan study, hyperimmunization of cows with six doses of J5 bacterin resulted in a threefold decrease in severe clinical coliform mastitis from 42 to 126 days in milk, compared to cows that received three doses. This suggested that supplemental immunizations extended protection beyond that offered by traditional vaccination regimens.[369] A subsequent Michigan study determined that cows immunized with five doses of J5 bacterin had elevated anti-J5 *E. coli* antibody IgG1 and IgG2 titers, relative to unvaccinated cows, for up to 60 to 90 days longer than cows administered three doses of J5 bacterin only.[370] The best response to immunization in terms of intensity and duration of antibody response was gained when multiple immunizations were given as a series in different anatomic locations on the cow.[370]

Use of J5-type bacterins relies on five principles:

1. Diagnose if coliform organisms cause a substantial portion of clinical mastitis within a herd.
2. Determine the severity and incidence of clinical coliform mastitis cases.

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TABLE 36-3

Guidelines for Core Antigen Gram-Negative Bacterin Use in Dairy Herds

1. Diagnose the cause of clinical mastitis.	Does bacteriology of clinical mastitis cases frequently yield coliforms (gram-negative)?	Bacterin ineffective for gram-positive pathogens.
2. Determine the incidence of severe mastitis caused by coliforms.	Are >1% clinical mastitis cases?	Bacterin reduces severity, not incidence of infection.
3. Describe affected animals.	What are the risk factors associated with animals with severe coliform mastitis in the herd?	Determine whether stage of lactation, age, or season are associated with the problem.
4. Decrease risk factors of exposure.	Are there other critical risk factors for coliform mastitis prevention that should be addressed?	Bacterin effects are diminished in herds with poor sanitation, cow comfort, intramammary infusion techniques, teat end health, or milking preparation.
5. Develop a protocol that best fits the herd.	Will the compliance of the protocol likely be followed? Is it likely to offer the best return on investment?	Immunization programs should be designed to reduce unnecessary doses and target affected animals.

3. Describe the epidemiology of the problem in the herd.
4. Decrease other herd risk factors that may contribute to clinical coliform mastitis.
5. Develop a vaccination protocol that best integrates immunology with herd needs and practical limitations (Table 36-3).

Veterinarians should review these steps when developing a protocol for dairy herds and periodically review progress and changes in the herd that may lead to a reevaluation of the immunization protocol.

Use of *Staphylococcus aureus* Bacterins. Considerable effort that encompasses numerous antigens, virulence factors, and bacterial strains has been made to develop an efficacious and practical *S. aureus* vaccine; interest has focused on vaccination of primiparous heifers. A bacterin containing a lysed culture of polyvalent phage types, including a variety of capsular serotypes, is commercially available in many regions (Lysigin). This product originated from work in Louisiana that determined two initial doses 2 weeks apart, followed by doses at 6-month intervals, reduced IMI at calving caused by both CoNS and *S. aureus*.[371] However, a subsequent challenge-infection study determined that this bacterin did not prevent IMI, accentuate clearance of IMI, or affect SCC or milk yield post challenge.[372] Lysigin-vaccinated heifers did have improved clinical scores and shorter duration of clinical mastitis.[372] Although immunization with Lysigin increased serum anti–*S. aureus* IgG1 in heifers, milk concentrations of IgG1, IgG2, or IgM were not affected.[373] In a subsequent report in lactating cows, representing multiple parities, two doses of Lysigin administered 14 days apart did not reduce the number of mammary quarters that developed new *S. aureus* or CoNS IMI, the time after vaccination to develop new IMI, SCC, or milk antibody isotype sample-to-positive (S:P) ratio.[374] The authors speculated that the bacterin may have induced insufficient opsonizing antibodies in milk to promote phagocytosis.

S. aureus vaccines would likely have limited use in many dairies, especially in herds with a low prevalence of IMI, as is typical for herds with SCCs below 200,000 cells/mL. In herds where contagious mastitis is successfully controlled by practicing excellent milking techniques and maintaining milking equipment, *S. aureus* bacterins are unlikely to have a significant impact. Conversely, immunization in lieu of good management practices is likely to produce disappointing results. Investigators have administered *S. aureus* bacterins in an attempt to augment antimicrobial therapy, with conflicting results.[375,376]

Mastitis Therapy Using Antimicrobial Drugs

General Concepts

Mastitis remains the most common cause of antimicrobial drug therapy for cows on U.S. dairy farms. In 2007, 16.4% of cows were treated for this disease.[114] If this use represents the majority of all U.S. dairy herds—with approximately 9 million dairy cows—nearly 1.5 million mastitis cases are treated annually. Surveys from Wisconsin and Canada estimated that between 2 and 4 doses of intramammary infusions are used per cow per year, or for a 1000-cow dairy, an average of 5 to 10 doses of intramammary antimicrobials would be administered daily.[190,377] Antimicrobial therapy benefits animal health and well-being, but economic losses associated with antimicrobial therapy of mastitis include drug and veterinary expenses, extended labor, and most importantly, discarded milk.[2,378] Unwarranted antimicrobial use in dairy cattle can result in residue violations in milk and meat, eroding consumer confidence in food safety. Culled dairy cows account for 65% of residue violations among all marketed animals in the United States, and 80% of the residues in these animals arise from antimicrobial use.[379]

To date, the risk of emerging antimicrobial resistance among bovine mastitis pathogens has been low, particularly for drugs with high therapeutic value in human medicine.[380-382] Nonetheless, prudent administration of antimicrobials is necessary on dairy farms, similar to stewardship of antimicrobial resources as advocated in human medicine.[383] Responsible antimicrobial stewardship minimizes the emergence and dissemination of antimicrobial resistance among pathogens and preserves the therapeutic integrity of the drugs.

In human medicine, physician behavior when administering antimicrobial therapy is altered by cultural and economic factors that include lack of information, desire to satisfy patient demand, and pressure from managed care organizations to speed throughput.[384] These same behavioral pressures are germane to veterinarians who design therapeutic regimens for dairy farms, although farm personnel, not managed care organizations, drive the desire for economic and labor efficiency. Mastitis therapy is often initiated empirically without consideration of case risk factors for efficacy and as a substitute for an integrated mastitis control program.[385] Standardizing mastitis therapeutic protocols should diminish spontaneous cow-side biases and establish uniformity for therapeutic regimens. However, farmers' therapeutic decisions often differ from veterinary recommendations.[386] Risk factors that decrease therapeutic efficacy include increasing age of the cow, preexisting SCC before treatment, duration of infection, number of quarters infected, and *S. aureus* infections.[128,215,387] In particular, chronic infections have poor therapeutic outcomes and may require extended duration of antimicrobial therapy.[378-389] To reduce antimicrobial use associated with mastitis, we need to change behaviors and attitudes of farm personnel to (1) utilize bacteriology to the best of herd labor abilities, (2) determine the history of the cow, and identify cow-level risk factors that may impact the efficacy of therapy, and (3) apply standardized therapy protocols that are based on sound pharmacology.

A small proportion of cows can be responsible for a large proportion of clinical mastitis episodes in a herd; antimicrobial therapy is unlikely to cure infections in glands with repeated bouts of clinical mastitis episodes. As mentioned previously,[128,215,387] chronic

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non-responsive IMIs are poor choices for therapy. Unnecessary losses of time and money are incurred by treating "repeat offender" clinical mastitis cases. When coupled with the lack of bacteriologic culture, thus opening the door for treatment of unresponsive pathogens, a majority of clinical mastitis may be treated unnecessarily on many dairy farms. Veterinarians should direct not only drug selection and protocols for mastitis therapy on dairy farms, but more importantly establish selection criteria for cows to be either included or excluded for treatment.

Alternatives to antibiotic treatment include euthanizing or culling the cow, drying off the cow or gland, administering supportive treatment alone, or doing nothing. The cow's welfare (i.e., minimizing pain and suffering) must be considered when choosing among these options. If supportive treatment or no treatment is chosen, the cow should be milked after healthy cows and the milk withheld from sale as long as it is visibly abnormal. If a single gland is dried off, antibiotics should not be infused; this may result in antibiotic residues in milk from the other glands.

LIMITATIONS OF ANTIMICROBIAL SUSCEPTIBILITY TESTING. Antimicrobial susceptibility test results should not be used as the primary basis for antibiotic selection. In most cases, susceptibility cut-points for zone diameters (for the disk diffusion test) or minimum inhibitory concentration (MIC) values are based on antibiotic concentrations in human serum or interstitial fluid after oral (PO) or intravenous (IV) dosing; these are not equivalent to concentrations achieved in milk or mammary tissue after intramammary or systemic dosing.[390] The absolute MIC value is more useful than a dichotomous result (susceptible or resistant) based on an irrelevant cut-point. However, the reported MIC value may not reflect the MIC in milk because MICs in milk are often higher than in blood, especially for non–β-lactam drugs.[391] The newest intramammary antibiotics have MIC or disk diffusion cut-points that are relevant to treatment of mastitis, but the cut-points have to be validated in vivo. Recent studies have determined that susceptibility test results (susceptible vs. resistant) had no impact on the outcome (clinical cure, bacteriologic cure) of clinical mastitis episodes.[230,392-394] Interestingly, *S. aureus* isolates that are penicillinase-producing strains are less responsive to treatment even if penicillinase-resistant antibiotics are used.[200]

Treatment of Mild and Moderate Cases of Clinical Mastitis

TREATMENT OF CLINICAL MASTITIS CAUSED BY STREPTOCOCCI AND STAPHYLOCOCCI. The effectiveness and selection of antibiotic therapy depend on the pathogen causing clinical mastitis. Cows with cases of mild (severity score 1) or moderate (severity score 2) clinical mastitis and no bacterial growth in the milk are unlikely to benefit from antibiotic therapy, as are cows with a low concentration of *E. coli* in the milk. Cows with mycoplasmal mastitis or mastitis caused by opportunistic pathogens like *P. aeruginosa, S. marcesens, P. zopfii,* or *Candida* spp. are unlikely to respond to antibiotic therapy.[52,281,311,378] Antimicrobial therapy for mastitis cases caused by these pathogens should be avoided and may lead to unnecessary risks for drug residues.

On the other hand, antimicrobial drugs can enhance resolution of many cases of streptococcal or staphylococcal mastitis episodes. The prototype for therapeutic success is treatment of IMI caused by *S. agalactiae*. This organism tends to be highly susceptible to intramammary therapy with β-lactam drugs, with cures of 85% to 90% often reported.[185,231,395] This organism is essentially an obligate udder pathogen in dairy cattle, remains superficial in mammary tissue, and has a high level of susceptibility to therapy. Thus, *S. agalactiae* can essentially be eradicated from a herd by simultaneously treating all infected cows, including subclinical infections.[231,395,396] This can be economical for a dairy, but only if proper prevention programs (e.g., postmilking teat dipping, dry cow treatment) are in place to prevent new infections after herd treatment.[185,231] For this and other gram-positive pathogens, systemic administration of antimicrobial drugs is not likely to attain any better cure rates than intramammary infusions. In one study, cure rates for *S. agalactiae* following intramammary infusion was 91% of treated cows, as opposed to only 9% for cows administered intramuscular (IM) ceftiofur.[395] This outcome also reflects the relatively poor distribution of most drugs used in dairy cattle into the mammary gland, particularly β-lactams, sulfonamides, and aminoglycosides.[385]

Therapeutic efficacy of other gram-positive cocci, with the exception of *S. aureus,* can also be efficacious in many cases. About 10% to 20% of clinical mastitis caused by environmental streptococci are severe.[397] Similarly, the vast majority of clinical mastitis caused by CoNS is mild to moderate. Intramammary infusion of commercial products is the treatment of choice, although some strains of streptococci have been reported to be resistant to cloxacillin and pirlimycin.[200,398,399] Treatment of experimental infections with intramammary therapy attained 90% bacterial cures, compared to no cures in untreated controls.[400] Likewise, studies of naturally occurring clinical streptococcal mastitis determined that intramammary pirlimycin or amoxicillin therapy attained bacterial cures of 70% to 75% of infected quarters, compared to 29% to 39% in untreated quarters.[398,401] However, results can vary depending on the herd, and as mentioned earlier, the duration of infection at the time of treatment has a significant impact on outcome. Cures following pirlimycin therapy for CoNS did not differ from untreated controls in one study (≈45% for both groups).[398] Similarly, about 66% of subclinical quarters infected with streptococci or staphylococci cured whether treated with two doses of intramammary pirlimycin or not treated.[392]

Several studies have described the potential benefits of extended intramammary therapy (beyond the traditional two doses) for the treatment of mastitis caused by streptococci and *S. aureus*.[402-404] This may be appropriate from a pharmacodynamic standpoint because all antimicrobial drugs that are labeled for intramammary use in dairy cattle (U.S.) rely on time-dependent inhibition of bacterial growth. Inhibitory action of the drug is more likely to be efficacious if the concentration of the drug is maintained above the MIC for extended periods of time at the site of infection, as opposed to peak concentrations. Experimental *S. uberis* infections treated for 2, 5, or 8 days (q24h) with intramammary ceftiofur attained bacterial cures in 43%, 88%, and 100% of the infections, respectively.[389] Similar results were obtained for chronic streptococcal and *S. aureus* infections treated with intramammary pirlimycin.[402] In naturally occurring subclinical mastitis, two doses of intramammary ceftiofur cured 39% of infections (including all gram-positive cocci), as opposed to 66% cured in quarters treated with eight doses; however, the sample was insufficient to determine pathogen-specific effects.[404]

The decision to use extended therapy as part of a herd mastitis therapy protocol should be made carefully and when possible should be based on microbiological diagnosis (see earlier section about OFC). The success of therapy with conventional dosing should first be considered. If deemed unsatisfactory, extended therapy may be a viable choice. To date, the benefits of extended therapy have best been determined for infections caused by streptococci and *S. aureus*. One study has determined that extended treatment of mild cases of clinical mastitis caused by a variety of coliform bacteria increased bacteriologic cures and reduced culling but did not influence posttreatment milk yield or SCC, although the outcomes were highly herd dependent.[405] The ability of herd personnel to perform aseptic infusions into the teat canal is critical. Extended therapy is associated with an increased risk of infection from opportunistic pathogens, and herds with poor infusion techniques are not good candidates for multiple doses of intramammary tubes.

S. aureus IMIs often result in deep-seated abscesses. Therapy is difficult because resistance to antibacterials (particularly β-lactams) is more common than with streptococci, and *S. aureus* may survive intracellularly following phagocytosis, where antibacterial concentrations are reduced.[378] Additionally, *S. aureus* has numerous extracellular substances that impart an ability to survive in the presence of a hostile host immune system. Consequently, elimination of IMIs caused by this pathogen is often not as successful as with other gram-positive pathogens.

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Cure rates of 25% to 55% of infected quarters have been reported in experimentally induced *S. aureus* IMIs when evaluated for 21 to 60 days after infection.[406] However, the pretreatment duration of natural infections is usually longer before detection and subsequent therapy and thus more refractive to therapy. The importance of duration of infection was evident in a study that determined that intramammary penicillin-novobiocin cured 70% in quarters that had been infected for 14 days or less, compared to only 35% in chronically infected quarters.[388] Similarly, Barkema and colleagues[215] reported a wide variation in the success of therapy: near 60% for younger, newly infected animals but less than 5% in older animals with chronic infections. Even modest results of efficacy reported in the literature may be optimistic, since relapses occurring more than 30 days after treatment are common.[210,404,406] This not only reaffirmed the difficulty in attaining successful therapy but also suggests a poor correlation between in vitro culture and susceptibility and therapeutic outcome in chronic IMI caused by this organism.[407]

Consequently, combinations of parenteral and intramammary treatment regimens may be helpful to eliminate a higher proportion of *S. aureus* infections. In experimental infections in lactating cows, the combined use of IM procaine penicillin G and intramammary amoxicillin achieved a better cure rate (18/35 infected quarters) than intramammary amoxicillin did alone (10/40 infected quarters).[408] Dry cows with *S. aureus* IMI had improved cure rates when administered 11 mg/kg of oxytetracycline IM in addition to intramammary antibacterials as compared to cows administered intramammary infusions only.[409] Other studies have not found any benefit from systemic antimicrobial use to eliminate chronic infections caused by *S. aureus*.[410,411] Additionally, systemic therapy for mastitis is an off-label drug use, and milk and meat withholding periods must be determined judiciously. Therapy should be administered for periods long enough (7 to 10 days) to allow effective elimination of the pathogen and would be more economical and less likely to result in residues in milk if this therapy were administered to dry cows. Depending on susceptibility testing, lipophilic antibacterial drugs that distribute well into mammary tissue (e.g., oxytetracycline) are the best candidates for systemic administration. Cure rates may not be much better than those attained from spontaneous cure, especially in chronic IMI, and efficacy must be defined critically. Affected quarters should be monitored by culture or SCC for at least 60 days to encompass the refractory period when bacteria may not be isolated.

USING BACTERIOLOGY AS A CRITERION FOR THERAPY. Microbial culture of milk is a practical tool to identify causative agents and the foundation to better target therapeutic regimens for mastitis. In a large Michigan dairy, cows with mild to moderate clinical mastitis were sampled for on-farm bacteriologic culture of milk samples. Cows that were infected with gram-positive cocci were included, but cows with no organism isolated or gram-negative organisms were excluded from therapy. This reduced the number of treated cows by 80%.[153] A recent multistate study further demonstrated that culture-based therapy of gram-positive and mixed isolates only, compared to empirical therapy of all mild mastitis cases, reduced antimicrobial use by 50%.[155] No differences were found between mastitis cases assigned to the empirical therapy or culture-based treatment program in recurrence of clinical mastitis (35% vs. 43%), linear somatic cell count (4.2 vs. 4.4), daily milk production (30.0 kg vs. 30.7 kg), and culling or death (28% vs. 32%) for the rest of the lactation after the clinical mastitis case.[156]

Thus, selective treatment of mild clinical mastitis based on culture results does not affect long-term outcomes but does decrease antibiotic use. If farms do not routinely culture milk from cows with clinical mastitis, it is still important to determine the most frequent clinical mastitis pathogens in the herd to make appropriate treatment and prevention recommendations. It is particularly important to determine whether *Mycoplasma* spp. or opportunistic pathogens that are unresponsive to antibiotic therapy are contributing to clinical mastitis.

TREATMENT OF SEVERE CLINICAL MASTITIS. Clinical mastitis cases that include systemic involvement are termed *severe* (severity score 3).[128] Coliform organisms are the most common cause of severe mastitis in most dairy herds and are the common cause of cases that result in loss of a cow from death or agalactia (see Tables 36-1 and 36-2).[412,413] Thus, primary therapy for severe clinical mastitis should be directed against coliform organisms, although secondary consideration must be given for other pathogens. From a cow-side appraisal, treatment of severe clinical mastitis is a forced decision (i.e., empirical treatment is indicated). Although the basis for antimicrobial therapy is knowledge of the causative pathogen, this is not attainable for some hours after initial case recognition, so the practical problem is to design a therapeutic regimen on clinical impression. In addition, systemic antimicrobial therapeutic regimens currently are not labeled by the U.S. Food and Drug Administration (FDA). As a result, veterinarians often formulate therapeutic management of severe mastitis with off-label drug use.

Experimental challenge models have clarified much of the pathophysiology of mastitis resulting from infection with gram-negative organisms.[95,363,414] Following infection, bacterial numbers in milk rapidly increase, and depending on the size of the challenge, peak bacterial concentrations in milk often occur within a few hours. Typically, a subsequent rapid decline in bacterial concentration follows neutrophil migration into the gland. Though often severe, experimental IMIs caused by *E. coli* usually clear spontaneously and rarely last more than 10 days. The resulting inflammation and leukocytosis in the affected quarter may persist for several weeks, or the quarter may become agalactic, despite the inability to isolate bacteria on culture. Although useful for determining the pathogenesis of coliform IMI, experimental challenge models should not be universally applied for therapeutic decisions. Most challenge infections do not include recently calved cows, use strains of bacteria that may not be as virulent as some of the wild types of pathogens, and are generally not administered if other possible immune stressors (metabolic or heat) are present. All these variables could reduce the severity of clinical outcome for experimental (compared to natural) infections. Herd factors like nutrition and housing can also affect the outcome of naturally occurring infections, and host-adapted strains that may persist in affected cows have been identified.[269]

Many of the inflammatory and systemic changes that occur during severe coliform mastitis result from the release of lipopolysaccharide (LPS) endotoxin from the bacteria, which is released from the bacterial cell wall following phagocytosis and killing by neutrophils. As previously mentioned in the discussion of host defenses, LPS is a potent stimulator of the inflammatory cytokine response through the action of TLRs.[415-418] This results in subsequent activation of the cyclooxygenase (COX) and lipoxygenase pathways, releasing prostaglandins, leukotrienes, and thromboxanes, compounds that are potent mediators of local inflammatory and systemic circulatory events.[91] Also, endotoxin-induced cytokines initiate a wide range of systemic responses, including fever, leukocytosis, protein synthesis and release by hepatocytes, and serum iron sequestration, collectively termed the *acute-phase response*.[417,419,420] Although LPS concentration in milk may be high, LPS is usually undetectable or in low concentration in plasma.[421] This suggests that the fever, tachycardia, reduced rumen motility, and signs of shock that accompany severe coliform mastitis are not a consequence of endotoxemia, but production and absorption of inflammatory mediators like TNF-α. The concentration of TNF-α in milk is positively correlated with coliform mastitis severity, and a high concentration of TNF-α in blood is seen only in severe responders.[69,421-423] Hematologic and plasma biochemical changes that often accompany clinical coliform mastitis include leukopenia (neutropenia, lymphopenia, monocytopenia), hypocalcemia, and reductions in plasma concentrations of zinc, copper, and iron.[258,424]

To reduce the severity of acute coliform mastitis, either bacterial growth must be inhibited to reduce exposure of the quarter and the cow to LPS, or the effects of LPS release must be neutralized. From a practical standpoint, therapy of severe coliform infections cannot

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begin until clinical signs appear. Clinical recognition of coliform mastitis usually occurs after peak bacterial numbers have been attained, so by the time therapy is initiated, maximal release of LPS has likely occurred. This raises concerns regarding the advantages of antibacterial therapy in alleviating the effects of acute coliform mastitis. The primary therapeutic concern should be treating endotoxin-induced shock with fluids and other supportive care.

Antibacterial therapy may be of secondary importance relative to immediate supportive treatment of endotoxic shock, but it remains an integral part of a therapeutic regimen for severe mastitis. Because of low MICs for gram-negative rods relative to other antimicrobials, aminoglycosides were considered for many years to be a drug of choice for coliform mastitis. However, cows experimentally challenged with *E. coli* and dosed with 500 mg of intramammary gentamicin q12h did not have lower peak bacterial concentrations in milk, shorter duration of infection, lower convalescent SCC or serum albumin concentrations in milk, or decreased rectal temperatures compared to untreated challenged cows.[425] Additionally, gentamicin readily diffused through the milk-blood barrier, evidenced by detectable concentrations in serum throughout the treatment period and the first 12 hours after the last dose. Consequently, urine gentamicin concentrations were detectable 14 days after the last infusion, and concentrations of 1 µg of gentamicin/g in renal tissue were detected in cows 6 months after the trial.[425] IM gentamicin was not more efficacious in preventing agalactia or death resulting from severe coliform mastitis, or in improving other clinical outcomes, than IM erythromycin or no systemic antimicrobial therapy.[426]

Considering the lack of efficacy in controlled studies, increased sophistication of drug residue testing among regulatory agencies, zero tolerance for residues in renal tissue of culled cows, the 30- to 45-day half-life for clearance in the bovine kidney, and extended milk withdrawal periods following use of aminoglycosides, use of this class of drugs in adult dairy cattle has little merit.

Seminal research from Colorado found that bacteremia occurs in nearly half of severe coliform cases and increases with the severity of clinical signs.[293,427] Numerous pathogens, in addition to mammary-derived coliforms, that are likely opportunistic invaders from the respiratory and gastrointestinal tract, were also isolated from blood.[293] This is likely a consequence of the profound neutropenia that occurs in many severe coliform cases.[258] Cows that remain neutropenic for 4 or more days or have high metamyelocyte and myelocyte concentrations in their blood are more likely to be bacteremic than cows with a normalizing leukon.[427] Bacteremia is a very poor prognostic indicator, and these cows are at greater risk of death or culling.[293] Thus, a primary target of antimicrobial therapy for severe coliform mastitis should be highly perfused tissue and selecting drugs that remain in the plasma compartment and have low MICs for gram-negative rods.

Three doses of parenteral sulfadiazine-trimethoprim failed to achieve clinical improvement in experimental *E. coli* infections.[428] In another study that compared cloxacillin or ampicillin use to three IM doses of cefquinome, a fourth-generation cephalosporin that has better distribution into mammary tissue than sulfonamides, cefquinome improved clinical outcomes of experimentally infected cows.[429] Further research confirmed the possible benefits of systemic antimicrobial administration; IV oxytetracycline improved clinical outcomes of cows with coliform mastitis (not necessarily severe), compared to cows that did not receive systemic antibacterials.[430] Ceftiofur sodium, a third-generation cephalosporin, has been reported to have excellent activity against gram-negative pathogens, with a suggested MIC for *E. coli* of 0.25 to 1.0 µg/mL. Mammary tissue and milk concentrations of ceftiofur following systemic treatment remain below these concentrations.[431,432] This is probably due to low bioavailability as a result of a high degree of protein binding. However, in a study of naturally occurring cases in Michigan, cows with severe coliform mastitis that were administered IM ceftiofur at a dose of 2.2 mg/kg once daily for 5 days were three times less likely to be lost from the herd and had significantly higher marketed milk than cows not receiving systemic antimicrobial therapy.[413] This strongly emphasizes the inclusion of possible bacteremia in therapeutic considerations for severe coliform mastitis.

Intramammary antimicrobial therapy should be administered for most severe mastitis cases, at least until bacterial culture results are determined. Numerous severe mastitis cases are caused by gram-positive cocci and can be difficult to distinguish from cases caused by coliforms at initial presentation. Chronic IMI caused by pathogens such as *S. aureus* can become acutely gangrenous at times of neutropenic dysfunction (e.g., parturition).[433] Bacterial culture of cases can also help identify other causative agents unlikely to respond to antimicrobial therapy, including *M. bovis,* mycotic organisms, and *Prototheca* spp. Severe overwhelming IMIs that lead to bacteremia can occur from *S. marcesens, P. aeruginosa,* and *Bacillus cereus*.

Therapeutic regimens for severe clinical mastitis should (1) administer supportive care, especially for those cows displaying shock, (2) target antibacterial therapy to maintain effective concentrations in plasma with a drug that has a broad-spectrum of activity, and (3) administer intramammary antibacterial drugs to reduce the effects of a gram-positive IMI, unless bacteriology results suggest otherwise.

Summary of Antimicrobial Therapy

Judicious antibiotic use is necessary for successful mastitis treatment programs. Case selection is critically important to avoid unnecessary antibiotic use, which is costly to the producer and of concern to the public. When producers are unwilling or unable to use culture results as the basis for treatment determination, a decision may be necessary to avoid treatment completely, or alternatively, treat all cows empirically. In some herds, complete avoidance of antibiotics resulted in increased streptococcal mastitis prevalence and reduced milk quality,[434] but this will vary depending on the herd. Antibiotic selection and the timing, dose, frequency, and duration of treatment impact the outcome. Therefore, antibiotic treatment protocols should be designed with veterinary input and monitored for efficacy. Monitoring requires that farm personnel record the incidence, severity, and duration of clinical mastitis, as well as the treatments administered. The occurrence of relapses, SCC, and targeted milk bacteriology also facilitate assessment of treatment efficacy.

SUPPORTIVE MASTITIS THERAPY. A variety of supportive measures are used in cows with severe clinical mastitis, often in conjunction with antibiotic therapy. Fluids and electrolytes are administered to correct circulatory and electrolyte disturbances. Steroidal and nonsteroidal antiinflammatory agents are used to reduce pain, inflammation, and fever. Dairy producers and veterinarians use many other systemic and local treatments, most of which have not been scientifically evaluated or shown to be effective. This section discusses the most frequently used supportive treatments.

FLUID AND ELECTROLYTE THERAPY. Cows with severe clinical mastitis can develop fluid and electrolyte disturbances as a result of decreased feed and water intake, rumen stasis, ileus, and diarrhea. Severely affected cows, particularly those with coliform mastitis, may develop septic or endotoxic shock; death or organ damage can result from decreased effective circulating volume.

The hydration status of an adult cow is assessed subjectively by observing skin tent duration on the neck or eyelid and position of the globe in the orbit. Unfortunately, findings can be influenced by the body condition of the cow. Objective criteria for estimating the extent of dehydration have been reported for dairy calves but have not been established for adult cows.[435] Extrapolating from calves, a healthy cow should have cervical skin tenting of 2 seconds or less and no recession of the eyeball. Skin tent durations of 4, 6, or 8 seconds and eyeball recession of 2, 4, or 7 mm would correlate with 4%, 8%, and 12% dehydration, respectively. Indicators of reduced peripheral perfusion are cold extremities (ears, tail, fetlocks (only reliable at moderate ambient temperatures) and a dry muzzle or mouth.[436] Hematocrit and plasma protein concentration are not reliable indicators of hydration status in an individual cow because of the wide

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range of normal values and the effects of inflammation and stage of lactation on total protein concentration.

Most cows with clinical mastitis, even severe mastitis, have normal acid-base balance or metabolic alkalosis; metabolic acidosis is uncommon and associated with a poor prognosis.[427,437] Therefore, there is no need for routine IV administration of alkalizing agents like bicarbonate or lactate. Oral products containing magnesium hydroxide or sodium bicarbonate likewise should not be administered.

Fluids can be administered by the oral (intraruminal) or IV route. The oral route is least expensive and is often adequate for cows with mild to moderate dehydration. Oral fluids should be hypotonic or isotonic and should contain sodium to create an osmotic gradient between rumen fluid and blood, and enable sustained absorption of fluid and electrolytes; hypertonic oral fluids should be avoided.[438] A 600-kg cow that is 6% dehydrated needs to absorb 36 L of fluid to replace her deficit. This volume can be safely administered orally, but administration of larger volumes of hypotonic fluid might lead to intravascular hemolysis.[439] Oral fluids are not sufficient for cows with severe dehydration, because they do not cause rapid resuscitation.

Ringer's solution, which is an isotonic (isosmotic), mildly acidifying solution that contains physiologic concentrations of sodium, chloride, potassium, and calcium, is the fluid of choice for rapid IV resuscitation of adult ruminants.[438] Isosmotic (0.9%) sodium chloride is an alternative that can easily be constituted using table salt and distilled water in a sterile carboy. However, administration of isosmotic crystalloid solutions is impractical in many situations because of the large volume of fluid required and the need for IV catheterization. A 600-kg cow that is 10% dehydrated requires 60 L of fluid to replace her deficit.

A more practical (although inferior) alternative to isosmotic IV fluid therapy for on-farm treatment is IV administration of hypertonic (7.2%, 2460 mOsm/L) saline. Hypertonic saline is administered through a large-bore needle at 4 to 5 mL/kg body weight over 4 to 5 minutes, in conjunction with oral administration of water (5 gal). Rapid administration of hypertonic saline is required to effectively create an osmotic gradient that draws fluid from the intercellular spaces and gastrointestinal tract (mainly rumen) into the vasculature. Although hypertonic saline does not have a sustained effect and will not completely correct a large fluid deficit, it rapidly increases plasma volume and improves cardiac output and tissue perfusion. Hypertonic saline has been shown to be safe in cows with endotoxic mastitis.[440,441]

Mild to moderate hypocalcemia often accompanies clinical mastitis, with the odds of hypocalcemia increasing with the severity of mastitis,[131] although other serum electrolytes are variable. Affected cows may show muscle tremors or weakness but are seldom recumbent. Calcium supplementation can be by the PO, subcutaneous (SC), or slow IV route, depending on the severity of clinical signs and product used. Anorexic cows often become hypokalemic, especially if anorexia persists for several days. Hypertonic saline administration also causes a transient reduction in serum potassium concentration. Potassium chloride can be supplemented orally at a rate of up to 240 g divided two to three times daily, with lesser amounts (30 to 120 g) satisfactory for mild to moderate hypokalemia.[442] Sodium and chloride derangements are usually mild and can be addressed by administering balanced PO or IV fluids or hypertonic saline. Blood glucose concentration is usually normal or high in cows with clinical mastitis, so dextrose should not be administered routinely. However, IV dextrose treatment may be warranted in cows with concurrent ketosis.

ANTIINFLAMMATORY DRUGS. Most of the physiologic and pathologic changes associated with clinical mastitis are a result of the inflammatory response to infection, so it is logical to administer antiinflammatory agents. Also, antiinflammatory agents can reduce the pain associated with clinical mastitis.[443] However, the inflammatory response is necessary for resolving IMI, and antiinflammatory agents can produce detrimental side effects. Many of the agents used in other countries are not labeled for use in lactating dairy cows in the United States. The choice of antiinflammatory agents in the United States is limited to three approved drugs: dexamethasone, isoflupredone acetate, and flunixin meglumine.

Dexamethasone and isoflupredone acetate are inexpensive steroidal antiinflammatory agents that have no milk-withholding requirement. Glucocorticoid drugs inhibit the production of inflammatory molecules and the adhesion molecules that facilitate transport of inflammatory cells from the bloodstream to the site of inflammation.[444] Glucocorticoids also help maintain microcirculation and cell membrane integrity, interfere with dissolution and disruption of connective tissue, decrease formation of histamine by injured cells, and antagonize toxins and kinins.[444] These actions of glucocorticoid drugs could be expected to benefit mastitic cows, particularly those with mastitis caused by endotoxin-producing coliform bacteria. Glucocorticoids prevent arachidonic acid release by stabilizing cell membranes and inducing lipocortin production. Lipocortin prevents phospholipase A_2 from contacting cell membrane–associated arachidonic acid and effectively limits the precursor needed for eicosanoid production.[445] Endogenous cortisol release has also been identified as playing an important role in down-regulating neutrophil trafficking into the site of infection and production of inflammatory cytokines.[64,446]

Data on the efficacy of steroidal antiinflammatory agents for treatment of clinical mastitis are limited to experimental mastitis trials. A single 30-mg IM dose of dexamethasone given at the time of *E. coli* inoculation reduced local signs of inflammation, tachycardia, rumen motility impairment, and 14-day milk production loss, compared with untreated controls.[447,448] A large IV dose of dexamethasone (0.44 mg/kg) given to goats 12 hours after *E. coli* infusion reduced fever and appetite suppression but had no effect on heart rate, rumen contractions, serum biochemical parameters, SCC, milk yield, or histopathologic changes.[449] Isoflupredone acetate (20 mg IV) administered to endotoxin-challenged cows after the onset of clinical mastitis had no beneficial effect on systemic parameters, mammary gland swelling, or milk production, compared with untreated controls.[450] However, each of these agents has potential adverse effects. Dexamethasone can cause abortion in pregnant cows, especially after 5 months of gestation, although this would be less of a concern for cows in early lactation. Repeated dosing (0.04 to 0.08 mg/kg IM for 3 days) of cows with subclinical IMIs resulted in increased bacterial shedding and development of clinical mastitis.[451] Perhaps more problematic is the use of isoflupredone acetate, because this drug reduces plasma potassium concentration, and repeated doses can lead to severe hypokalemia and recumbency.[452-454]

The above studies suggest that the most likely benefit of corticosteroid treatment would be for severe coliform mastitis, and delays in therapy relative to the onset of infection may hamper efficacy. Nonetheless, dexamethasone is a potent antiinflammatory agent, and it is difficult to extrapolate the benefit for cattle in terms of improved attitude and shock mitigation from experimental mastitis trials to naturally occurring clinical mastitis. Because of mineralocorticoid effects on serum potassium, dexamethasone may be preferred over isoflupredone. Additionally, corticosteroid use in chronic IMI is contraindicated.

A variety of nonsteroidal antiinflammatory drugs (NSAIDs) are used to treat clinical mastitis worldwide,[443] but only flunixin meglumine is approved for use in lactating dairy cows in the United States. Dipyrone and phenylbutazone are banned, and other NSAIDs can be used off-label only if appropriately justified. NSAIDs are not immunosuppressive but carry a risk of abomasal ulceration and renal damage. These complications are not well documented in cattle and presumably are minimized if treatment is of short duration, hydration is maintained, and appetite is restored. The primary mode of action of NSAIDs is to inhibit synthesis of prostaglandins and thromboxanes through COX inhibition. NSAIDs also inhibit formation of prostaglandin (PG)E_2 in the brain, which effectively reduces fever.[455]

Treatment of cows with flunixin meglumine at 0 and 3 to 5 hours after *E. coli* inoculation abolished fever and improved rumen motility

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compared with untreated controls, but it had no effect on gland or milk appearance, heart rate, or respiratory rate.[456] Similarly, administration of flunixin meglumine every 8 hours beginning 2 hours after endotoxin infusion reduced fever and improved gland appearance and attitude compared with untreated controls, but it had no effect on milk appearance, heart rate, rumen motility, SCC, or milk production.[457] When administered after the onset of fever and gland swelling, flunixin meglumine (2.2 mg/kg IV) reduced heart rate and rectal temperature and increased rumen motility in cows with endotoxic mastitis but had no effect on milk production or mammary gland inflammation.[458] As with the steroids, the relevance of these trial results to cows with naturally occurring clinical mastitis is uncertain. Meloxicam, although not available for use in U.S. cattle, was shown to reduce pain associated with clinical mastitis.[459]

Other studies found that increased survival and improved milk production did not occur following treatment of clinical cases of acute mastitis with flunixin meglumine.[460,461] Additionally, withdrawal times are significantly increased for milk and meat if this drug is administered IM rather than IV. In summary, it appears that NSAIDs can improve well-being and outcome in cows with clinical mastitis, but specific criteria for instituting NSAID therapy, timing of therapy relative to infection onset, and optimal duration of treatment remain to be determined.

OXYTOCIN AND FREQUENT MILKING. Oxytocin is administered to stimulate milk ejection and facilitate removal of secretions from mastitic mammary glands. Frequent milk-out (stripping) reputedly augments the removal of pathogens, toxins, and inflammatory mediators from the mammary gland. Although seemingly logical practices, no solid evidence exists to support their routine use, and some data suggest they can be detrimental. Oxytocin (20 IU IM twice daily for 3 days) at milking time prevented development of clinical mastitis in only two of eight cows experimentally inoculated with *S. uberis;* once clinical mastitis developed, oxytocin was ineffective at resolving the *S. uberis* infections.[462] When initiated at the onset of clinical *S. uberis* mastitis, oxytocin (80 IU IM, followed by 20 IU IM twice daily) resulted in no clinical or bacteriologic cures by 3 or 6 days.[463] In contrast, clinical and bacteriologic cure rates of 91% and 64%, respectively, were achieved by intramammary antibiotic administration by 3 and 6 days. When oxytocin was used in conjunction with intramammary antibiotics, clinical and bacteriologic cure rates at 6 days dropped to 10%, implying a significant adverse effect of oxytocin and stripping. Frequent milk-out (every 4 to 6 hours) in conjunction with oxytocin administration did not shorten the time to clinical or bacteriologic cure or resolution of systemic illness in cows with experimentally induced coliform mastitis, compared with no treatment.[464] When oxytocin administration (100 IU IM twice daily for 1 week) was compared with no treatment (udder massage only) in cows experimentally inoculated with *S. aureus,* oxytocin administration reduced bacterial concentrations in the milk but did not improve the bacteriologic cure rate or reduce SCC.[465] Oxytocin administration increases the permeability of mammary epithelial cell tight junctions in a dose-dependent manner, which can alter milk composition in non-mastitic glands, particularly if high doses (100 IU) are administered repeatedly.[466]

Oxytocin and frequent milk-out have not been evaluated extensively in the field. In a California study, oxytocin (100 IU IM twice daily for three treatments) at milking time resulted in clinical and bacteriologic cure rates similar to intramammary antibiotics, although an untreated control group was not evaluated.[467] However, no overall benefit resulted, because the oxytocin-treated cows had a higher recurrence rate of clinical mastitis, particularly environmental streptococcal mastitis.[468] In a Virginia study, frequent milk-out (six times daily) in conjunction with oxytocin administration (20 IU) did not improve clinical or bacteriologic cure rates, time to cure, or return to milk production compared with no treatment.[469] In an Illinois herd, cows treated with supportive therapy alone (oxytocin administration [all cases], frequent milk-out [moderate and severe cases], antiinflammatory therapy [severe cases], and fluid therapy [severe cases]) had lower clinical and bacteriologic cure rates and a higher recurrence rate than cows given antibiotics in addition to the same supportive therapy.[470] Furthermore, two studies showed that 50 IU of oxytocin q12h for 19 or 22 days increased residual (non-harvested) milk by 15% each milking.[471,472] From their study, Bruckmaier and colleagues[471] noted, "Cows increasingly refused to enter the milking parlor voluntarily and had to be fetched by the milker, and cow entry into the parlor remained disturbed for up to one week after the end of injections."

In summary, oxytocin administration and frequent milk-out are unlikely to be effective stand-alone treatments for clinical mastitis, particularly mastitis caused by streptococci, and may even be detrimental. In certain circumstances, when a cow clearly will not eject milk or when garget in the milk prevents effective milk removal, these practices might be of some benefit. Otherwise, unnecessary administration of oxytocin injections and frequent milking of painful teats should be avoided for welfare reasons. Sustained use of this drug as a routine therapy is a poor substitute for good milking preparation and will likely incite cows to be reluctant to enter the milking parlor and milk out effectively, which is the opposite of therapeutic intentions with this drug.

Prevention and Treatment of Mastitis during the Dry Period

The dry (nonlactating) period of the lactation cycle is a critical time for udder health in dairy animals. The major proportion of calf growth occurs during this time, and metabolically this is the most critical time for the cow to prepare for the next lactation. Prevention of new infections during the dry period hinges on prevention of teat end exposure to environmental pathogens. Rates of new IMI of coliforms are thought to be greater in dry periods than during lactation.[53] Thus the same management practices that prevent infections from these organisms in lactating cows apply to dry cows (i.e., maintaining cows in clean, dry, comfortable housing).[53] The importance of dry cow management is apparent from studies that found that (1) nearly two thirds of clinical coliform mastitis cases in the first 2 months of lactation were newly acquired infections during the dry period,[108] and (2) the rate of environmental streptococcal IMI was 5.5-fold greater during the dry period than during lactation.[246]

During involution, the mammary gland undergoes marked biochemical, cellular, and immunologic changes. Involution of the mammary parenchyma begins 1 to 2 days after the end of lactation and continues for 10 to 14 days. During this time, the gland is particularly vulnerable to new IMI and, in conjunction with the periparturient period, constitutes the times of greatest risk for new IMI in the lactation cycle of the cow.[473] The most important defense, as with lactating cows, remains the teat canal. When a cow is dried off at the end of lactation, the teat canal does not fully fill with keratin for days to months. This contributes to the risk of infection during mammary involution, and cows that have higher milk production at dry-off are more at risk to have teats remain open throughout the dry period.[243,474] Leukocytes increase to millions per milliliter as involution progresses and then decrease prepartum. Macrophages are predominant in lacteal secretions, followed by lymphocytes and neutrophils.[473] Lactoferrin is also associated with resistance to infection during the nonlactating period.[74,473] Lacteal immunoglobulins increase throughout involution and function by opsonizing bacteria, neutralizing toxins, and preventing bacterial adherence.[473] Consequently, the dry period is an ideal time to attain synergy between antibacterial therapy and immune function to eliminate pathogens from the gland, and not incur the extensive costs of milk withholding typical of lactating cow therapy.

Intramammary administration of antibacterials at the end of lactation (dry-cow therapy) has been a standard of dairy mastitis management for 40 years, particularly as a tool to help reduce the prevalence of contagious mastitis.[18,260] Cure rates for IMI caused by all gram-positive cocci (those IMIs that existed prior to the dry period but were not detected following calving), as with lactational therapy, vary from farm to farm and are pathogen dependent. A New

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Zealand study determined that dry-cow therapy eliminated 85%, 90%, and 90% of IMI caused by *S. aureus, S. uberis,* and *S. agalactiae,* respectively, as opposed to spontaneous cures of 31%, 50%, and 29% in untreated controls.[475,476] Cures for chronic *S. aureus* IMI or gram-negative organisms may be considerably less.[410] However, a ceftiofur dry-cow therapy is now labeled for use in North America. A previous dry-cow therapy study that compared cows treated with cloxacillin to cows treated with a product with significant activity against gram-negative bacteria (100 mg framycetin, 100 mg penethamates, and 300 mg procaine penicillin) showed decreased clinical coliform mastitis in the framycetin-penethamate-penicillin–treated cows during the dry period and early lactation.[261]

Because of concern regarding overuse of antibacterial drugs and potential effects on antimicrobial resistance of bacteria, selective dry-cow therapy (treatment of infected cows only) versus total or blanket dry-cow therapy (treatment of all cows) is debated. Decisions should be made on an individual herd basis, and results monitored to determine the success of a dry-cow mastitis program based on numbers of new IMIs during the dry period, cures of existing infections, and impact on the rate of clinical mastitis, particularly in early lactation.

In addition to the role dry-cow therapy plays in eliminating existing IMI, one dry-cow therapy is also thought to prevent new IMI. Early studies suggested that dry-cow therapy reduced new IMI during the dry period by 50%.[476] Overall rates from multi-institution studies reported new IMI rates during the dry period as 11% to 25% of quarters in herds that practiced blanket dry-cow therapy.[263,477] Intramammary infusion of tilmicosin reduced new infection rates by more than 33% in a Canadian study.[477] Selective dry-cow therapy can also result in more clinical mastitis in the dry period, more new IMI during the dry period, and subsequently more clinical mastitis in early lactation than blanket dry-cow therapy.[478] A technology consisting of a bismuth subnitrate paste in a paraffin base is being applied in many dairies, with the intent to create a barrier in the teat canal during the dry period. This is an inert product with no activity or food residue risks. When infused into the teat following intramammary cloxacillin at dry-off, investigators determined that the combined use of the teat sealant and antimicrobial infusions resulted in 30% fewer new IMIs during the dry period and 33% fewer clinical mastitis cases from drying off until 60 days in milk, compared to quarters that were infused with cloxacillin only.[263]

As with lactational therapy, systemic administration as an adjunct to intramammary administration has stimulated interest in potential alternative therapeutic regimens. Subcutaneous norfloxacin nicotinate administered at the start of the dry period achieved a better cure rate and lower new infection rate over the dry period for *S. aureus* infections, as compared to untreated cows and cows administered intramammary cephapirin benzathine preparations.[479] However, in a Michigan study, cows administered IM oxytetracycline and intramammary cephapirin did not have better cure rates for quarters infected with *S. aureus* than cows treated with cephapirin only, although this study was performed in a herd where 50% of cows were infected with *S. aureus* with a history of long duration of infection.[410] Systemic therapy should be reserved for use in dry cows for animals of exceptional value and for infections deemed to be difficult to attain cures (i.e., chronic). However, success rates are likely to be low and in most cases will not be worth the injection and withholding time risks, especially with off-label drug use.

Epidemiology and Management of Mastitis in Heifers

Mastitis in heifers is rarely apparent prior to calving, but few farms actively look for mastitis before parturition. Many farms raise healthy dairy heifers, but in some studies, bacteria have been isolated from more than 50% of quarters of prepartum heifers.[480-482] Reviews of heifer mastitis studies indicate that the prevalence of mastitis pathogens recovered from mammary secretions obtained before the first parturition ranged from 29% to 74%, while the prevalence of infection at first calving ranged from 12% to 57%.[483] Recovery of *Mycoplasma* organisms from milk samples was not included in these studies.

Staphylococci (primarily CoNS but also *S. aureus*) are the most frequent isolates recovered from heifers, but environmental pathogens like streptococci are also frequently recovered.[484] CoNS are the most common pathogens recovered from heifers, and a variety of CoNS species have been recovered from teat skin, the streak canal, and precalving udder secretion obtained from heifers.[221,222] CoNS are the most common group of bacteria recovered from postpartum heifers, but many apparent IMIs spontaneously disappear within the first week after calving. One study reported that 41% of mammary quarters had CoNS infections between days 1 and 4 post calving, but 46% of those infections had spontaneously disappeared by days 5 to 8 post calving.[485] However, some herds may experience persistent infections with CoNS in heifers, resulting in increased SCC values and potentially decreased milk production. These herds require interventions to limit long-term effects on milk quality and production.

Detection of *S. aureus* in dairy heifers usually indicates that a significant number of lactating cows are infected. Although *S. aureus* has been controlled in many herds, regional differences in the prevalence of infected dairy heifers have been reported.[483] The exact mechanism of how nonlactating heifers develop *S. aureus* infections is unknown, but studies have demonstrated that teat canals of heifer calves can become colonized at very young ages.[486] *S. aureus* can spread to heifers when they are fed unpasteurized milk or colostrum or when calves come in contact with objects contaminated with infected milk.[487] Ingested milk is not transmitted directly from the digestive tract to the mammary gland, but it is possible calves may lick their udder or legs and colonize the teat skin, eventually leading to increased risk of infection. *S. aureus* can also be transmitted to heifers during the immediate pre- or postpartum period. Comingling ill animals with periparturient heifers may result in exposure to infected secretions (milk, blood, feces, etc.) from sick animals. These secretions may remain infectious for variable periods of time (depending upon the characteristics of the organism, type of bedding, and environmental conditions) and serve as a point of exposure. Milking heifers using equipment that has been previously used on infected cows is also a common route of exposure. Several studies have demonstrated that biting flies can play a role in the transmission of *S. aureus* between infected and healthy heifers.[222] It is thought that flies congregating on teat ends of infected cows can become contaminated with bacteria present in milk droplets and mechanically transfer the bacteria when they land on the teats of uninfected animals.

M. bovis is an important pathogen that often affects heifers. This organism is associated with respiratory disease, ear infections, joint infections, mastitis, and other diseases of dairy calves and cows.[488] *M. bovis* dwells primarily in the respiratory tract of cattle, often without causing apparent clinical disease in the host.[280] This organism is unique in that respiratory infections can spread through the lymphatic and bloodstreams to infect other mucosal tissue such as the udder. Animals colonized with *M. bovis* can develop long-term infections and infect other animals. *M. bovis* is usually introduced into herds by clinically healthy cattle that are carriers of the organism.[488] *M. bovis* has been demonstrated to colonize developing udders of prepubertal heifers and eventually cause mastitis.[489] The feeding of waste milk from infected cows has long been considered a primary route of infection with *M. bovis.* One study demonstrated that 100% of 50 calves fed milk experimentally contaminated with *M. bovis* became colonized in their respiratory tract.[490] Comingling of calves from different sources has consistently been identified as a risk factor for infection with this organism. Control of *M. bovis* in heifers is based on reducing the potential for contact with potentially infected shedders of the organism and ensuring calves never receive unpasteurized milk. The organism's ability to colonize the respiratory tract of cattle also requires strict attention to limiting the potential for airborne transmission, so adequate ventilation, isolation of calves from older animals or ill calves, and reduced stocking densities are commonsense precautions.

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RISK FACTORS FOR MASTITIS IN HEIFERS. Most risk factors that contribute to the development of mastitis in heifers are related to exposure of heifers to mastitis-causing organisms. The exception is the occurrence of udder edema. Calves that are group housed have the opportunity for cross-suckling, resulting in increased risk for transmission of contagious pathogens.[491] Several studies have shown that contact of heifers with older cows before calving (even housing in the same barn) increases the risk of clinical mastitis after calving, and separation of heifers from older cows is generally recommended.[492] The hygiene of the environment is also an important determinant of the risk of developing mastitis in heifers, and this is true for heifers raised on pasture as well as heifers raised in confinement.[228]

PREVENTION OF MASTITIS IN HEIFERS. Prevention of mastitis in heifers is based upon reducing exposure to mastitis pathogens and enhancing the ability of the heifer's immune system to respond to exposure. Strategies for preventing mastitis in heifers include:

1. Controlling the prevalence of mastitis in the existing adult herd. Exposure to contagious mastitis is more likely in herds where many animals are infected than in herds with few animals infected.
2. Use individual stalls for preweaned calves.
3. Cull calves that persist in suckling other calves.
4. Feed milk replacer or pasteurized milk from healthy uninfected cows rather than waste milk.
5. Control flies—especially important in the control of *S. aureus*.
6. Milk fresh heifers first, using clean milking equipment.
7. Calve heifers in clean pens that have not been used to house sick cows.
8. House growing and prepartum heifers in an adequately bedded area that is clean and dry and provides sufficient space for all animals.
9. Feed a well-balanced diet that enhances heifers' immune systems. Recommended values include 1000 IU/day vitamin E during the prefresh period and adequate selenium.
10. Boost the immunity of heifers by using gram-negative J5 vaccines. These vaccines work to reduce the severity of infections caused by gram-negative bacteria like *E. coli*.
11. In problem herds, prepartum teat dipping several times a week[493] or use of internal teat sealants administered about 1 month precalving can be considered.[494]

PREPARTUM TREATMENT OF HEIFERS. Intramammary therapy with antibiotics is one of the tools used to control mastitis in heifers.[486] Intramammary treatment of prepartum heifers is generally considered efficacious in reducing the prevalence of infection, can result in a reduction of SCCs, and in some cases has been shown to increase milk production in the subsequent lactation.[495-499] However, research shows that the production response is highly variable among herds, and this strategy should only be routinely recommended for herds that have demonstrated problems with heifer mastitis.[221] Oliver and associates[500] reported cure rates of 84% and 97%, respectively, for heifers infected with CoNS that received intramammary treatment using 200 mg of either sodium cloxacillin or cephapirin sodium; the spontaneous cure rate was 27% for heifers in an untreated control group. Research has shown that administration of intramammary antimicrobial treatments during late gestation is generally highly effective, and cure rates for staphylococcal infections frequently exceed 90%.[498] Intramammary products designed for both lactating and nonlactating cows (dry-cow products) have been evaluated for use in precalving heifers.[486] In virtually all instances, high rates of bacteriologic cure have been reported. No significant difference in treatment efficacy was found based on treatments given during the first, second, or third trimester of pregnancy, but fewer new *S. aureus* infections were reported for animals treated in the third trimester.[497-501] To minimize the potential for residues after calving, treatments should be administered at least 60 days before the expected due date, and milk should be checked for residues after calving. Unlike intramammary treatments, systemic antibiotics administered to heifers have not been shown to be effective in reducing the prevalence of mastitis.[502] The effect of precalving treatment on production of heifers appears to be variable among herds[481] and is not performed without introducing the risk of infections caused by improper administration of the intramammary tubes. Internal teat sealants or intramammary antibiotics should only be given under hygienic conditions and following effective sanitation of teat ends. This practice is generally only recommended for herds that have demonstrated problems with mastitis in heifers.

Other Conditions of the Mammary Gland

UDDER EDEMA. Dairy cattle frequently develop physiologic edema of the udder during the periparturient period, and heifers have increased incidence of this disorder. Physiologic udder edema must be differentiated from pathologic edema, which can accompany mastitis and diseases of other body systems. Physiologic udder edema is symmetric, cool to the touch, and pits on palpation. It can be limited to the udder or extend cranially along the ventrum or into the perineal region. In contrast, the edema that accompanies mastitis is more focal, asymmetric, and accompanied by abnormal milk and an inflamed mammary gland. Intermandibular and brisket edema, which are often observed in cows with congestive heart failure or severe hypoproteinemia, do not occur in cows with physiologic udder edema.

In most cases, physiologic edema is of little consequence and resolves spontaneously after parturition. However, treatment is recommended if the udder becomes excessively large and heavy, because this threatens the integrity of the udder suspensory apparatus and predisposes to teat injury and mastitis. Severe edema also can hinder ambulation or impair milking or nursing of the teats. If the edematous udder impinges on the skin of the thigh, moist dermatitis and secondary infection may develop and the skin may slough; this condition is referred to as *udder scald*.

The mechanism(s) of physiologic udder edema is uncertain. Supplementing the ration of prepartum dairy cows with high concentrations of sodium or potassium salts significantly increases the incidence and severity of edema.[503] However, serum biochemical values and fractional clearance of electrolytes are similar in affected and unaffected cows.[504] Increased capillary hydrostatic pressure (resulting from changes in mammary blood flow and intramammary pressure that occur around parturition) might be involved, as might incompetent valves in the cranial superficial epigastric veins draining the udder. Cows with udder edema have higher blood pressure in the cranial superficial epigastric veins than unaffected cows, and blood pressure is inversely related to mammary blood flow.[505] Poor udder suspension can also predispose to physiologic udder edema.

First-calf heifers and high-producing cows are at greatest risk of developing udder edema. Other risk factors are not well documented. In a case-control study of heifers in Florida, the risk of udder edema increased as height of the heifer increased, was higher if calving occurred in winter than in summer, and was higher if the fetus was male rather than female.[506] Heifers with udder edema in the first lactation were more likely than unaffected heifers to develop edema in subsequent lactations.[506]

Treatment of udder edema includes preventing excessive salt intake and administering a diuretic. In the United States, furosemide is labeled for use in dairy cows, has 48-hour milk-withholding and slaughter-withholding times, and is the diuretic of choice for treating udder edema. In one study, high cranial superficial epigastric venous pressure in cows with udder edema was reduced by IV administration of furosemide (500 mg) but not hydrochlorothiazide (250 mg) or acetazolamide (500 mg).[501,505] Repeated administration of furosemide for several days should be avoided, but if repeated dosing is necessary, cows should be monitored for signs of electrolyte imbalance. Although corticosteroids have been recommended for treatment of udder edema, their efficacy is questionable. Prepartum milking reduces the severity of edema[507] but also decreases colostral immunoglobulin concentration at calving, so an alternative source of colostrum is needed. Prepartum milking of affected heifers has also

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been shown to reduce the risk of developing mastitis, but care should be taken to manage energy balance to prevent development of ketosis.[491] Increased milking frequency has not been demonstrated to reduce udder edema. Milking first-lactation animals four times daily neither reduced nor increased udder edema scores.[508] Udder massage, exercise, and hydrotherapy are empirically justified treatments for udder edema. Udder supports are available for cows with excessively pendulous or heavy udders.

BLOODY MILK. It is not uncommon to observe blood in postpartum mammary secretions. Small vessels may rupture as a result of trauma or in conjunction with udder edema. The milk is usually light pink to red or brown and may contain small blood clots. Antibiotic treatment is not indicated. Bloody milk can also accompany severe clinical mastitis or gangrenous mastitis, both of which have a poor prognosis, but physical examination of the animal will identify these conditions.

Bloody milk should be withheld from sale for human consumption. The milk usually returns to normal appearance within 1 week. However, because blood contains natural antimicrobial inhibitors, bloody milk may cause false-positive antibiotic residue test results. The IgG1 concentration of bloody colostrum is similar to that of normal-appearing colostrum, meaning it is unnecessary to discard colostrum simply because it contains blood.[509]

TEAT AND SKIN CONDITIONS. Several noninfectious diseases of teats are recognized to occur.[510] The color and condition of teats can be influenced by milking equipment, overmilking, use of caustic chemicals, or environmental conditions. The development of hyperkeratosis of the teat ends is not uncommon and occurs more commonly during winter months. *Hyperkeratosis* is a thickening of the skin that lines the teat canal and is the result of a localized hyperplasia of the stratum corneum.[511,512] Mild hyperkeratosis is a normal physiologic response to forces applied to the teat during milking and does not increase the risk of IMI. However, moderate and severe hyperkeratosis can become a problem. Various scoring systems have been developed to assess teat end health. In general, teats are scored on a 1 (N = no ring) to 4 (VR = very rough ring) scale based on the teat end callosity observed. It is recommended that herds should have less than 20% of scores of 3 (R = rough ring) and 4 and less than 10% of scores of 4.[512] Rough teat ends are not only difficult to clean but also provide a surface for pathogenic bacteria to harbor.[511] Hyperkeratosis is a multifactorial problem, and risk factors must be determined and addressed for individual farms. Areas to investigate that may resolve a problem with hyperkeratosis include liner compression, excessive teat end vacuum or overmilking, environmental conditions, and use of teat dips that do not provide sufficient skin conditioning.

Infectious lesions of teats have been associated with several viruses.[511,513] Pseudocowpox is caused by a paravaccinia virus that can cause acute infection in cattle. This disease results in lesions that include center vesicles that ulcerate to form scabs. As the lesions heal, they result in a characteristic ring or horseshoe-shaped scab. This virus can also affect the hands of milking technicians. Diagnosis is based on observation of lesions on hands of milking technicians and animals' teats. The condition is generally self-limiting within 3 to 5 weeks.

Bovine herpes mammillitis has been associated with both herpesvirus type II and herpesvirus type IV.[511,513] The resulting lesions appear similar and can occur either sporadically or in an outbreak. These viruses can present with a wide range of symptoms ranging from mild edema to development of vesicles that result in severe ulceration and formation of painful scabs. This condition appears to be more common during winter months. Diagnosis is based on observation of clinical signs and can be confirmed by histopathology. There is no effective therapy, but teat dipping using an effective germicide is recommended. This virus can spread among animals, so affected animals should be segregated and milked with separate milking equipment.

Teat warts are not uncommon and can be caused by several different papillomaviruses. The appearance of the warts is variable, ranging from small, smooth lesions to large frondlike protuberances.[511,513] Younger animals are often more susceptible and will develop immunity. Warts are generally self-limiting and will resolve within several months. No therapy is recommended.

Mastitis in Beef Cows

Several surveys have demonstrated that about 15% to 40% of beef cows have IMI in at least one mammary gland.[514-516] Similar to heifers and small ruminants, CoNS are the predominant bacteria that are generally isolated, but *S. aureus* has been recovered from 7% to 10% of milk samples. Milk from infected glands has significantly higher SCC than milk collected from healthy glands.[514,515,517,518] Clinical mastitis occurs rarely and is diagnosed and treated when economically feasible, but most mild cases of clinical mastitis likely go undetected.

Several modes of transmission of mastitis pathogens have been proposed for beef cattle. Flies are believed to serve as vectors for staphylococci, and fly-induced teat scabs of beef heifers have been shown to harbor staphylococci.[519] Calves may also serve as vectors by transmitting oropharyngeal organisms to the teats or carrying bacteria-laden milk from teat to teat. Unsanitary housing conditions probably increase the risk of infection with environmental pathogens.[515,519] As with dairy cows, poor udder conformation and teat injuries may predispose to mastitis.

Several studies have demonstrated numeric or significant decreases (up to 40 kg) in weaning weights of calves from beef cows with subclinical mastitis,[514-516,518] probably as a result of reduced milk production.[517] The adverse effect on weaning weight appears to increase with the number of infected glands.[515] Use of dry-cow antimicrobial therapy has been associated with decreased IMI in the subsequent calving and increased body weight gain of calves.[518] However, the economic justification for routine use of antibiotic treatment at dry-off is lacking. Selective intramammary antibiotic treatment at weaning based on CMT reaction has been suggested, but CMT score is unlikely to be an accurate predictor of infection. Sanitary housing conditions, appropriate stocking density, and good fly control should help minimize mastitis risk in beef cattle.

Mastitis in Small Ruminants

General Concepts

The udders of sheep and goats differ from cows in that they have only two mammary glands, which are logically referred to as *halves*. With the exception of the relative proportion of the cisternal cavities, anatomic structures, milk secretion, and milk letdown of small ruminants are similar to cattle. Both goats and sheep have much larger cisterns than dairy cows, and the cisternal fraction of milk may approach 50% to 75% for these species.[520]

Just as in dairy cows, mastitis of small ruminants is a bacterial disease that occurs in either a subclinical or clinical state. Subclinical mastitis is an important and underrecognized disease in small ruminants. In two separate studies, an Israeli research group compared milk production and composition of healthy and CoNS-infected half-udders in ewes.[521,522] These studies demonstrated large increases in SCC and 30% to 50% reductions in milk yield of infected half-udders. Subclinical mastitis is generally defined by the migration of neutrophils into the mammary gland in response to bacterial infection. This response occurs in all dairy species, but the magnitude of the response and distribution of cell types in the healthy mammary gland differ considerably among species.[523-525] In both sheep and cows, a significant increase in somatic cells occurs almost exclusively in response to bacterial infection of the mammary gland. The SCC response in dairy goats is not as specific to infection, so different interpretation criteria are necessary. The proportion of neutrophils (PMNs) and the number of cytoplasmic particles present in milk are

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very different in milk produced by goats, compared to milk produced by ewes or cows. Part of this difference is generally attributed to different milk secretion mechanisms. Both goats and sheep are thought to produce milk using a largely apocrine process, where the apical portion of the secretory cell is excreted into the milk. Despite similar secretory processes, the number of cytoplasmic particles found in milk obtained from both healthy and infected glands is approximately 10- to 20-fold greater for goats (≈70,000 to 300,000 cells/mL) than for sheep (≈15,000 cells/mL).[523] The large number of cytoplasmic particles necessitates use of DNA-specific counting mechanisms to accurately enumerate somatic cells in goat milk.[523] Similar to dairy cows, microbiological analysis of milk samples obtained from affected glands is the only way to determine the etiology of mastitis.

As noted, enumeration of SCC of goat milk must be performed using DNA-specific methods.[523] The CMT test is based on reaction of the detergent with DNA in cells and is also considered accurate. When enumeration of SCC in goat milk is properly performed, IMI is a well-known cause of increased SCC, but the threshold used to determine infection must be determined relative to stage of lactation.[526] Milk samples obtained from infected udder-halves of goats generally exhibit SCC values over 500,000 cells/mL (first 90 DIM) and over 1,000,000 cells/mL (later stages of lactation). Important factors that must be considered when evaluating SCC of goats include parity, stage of lactation, breed, and estrus.[523,526,527] In does, the ability of estrus to stimulate increased SCC in the absence of IMI has been demonstrated in a controlled study using induced estrus.[517] In one part of the trial, the day after inducing estrus, SCC values were 1,778,000 cells/mL for does in estrus versus 363,000 cells/mL for does in the control group; both values have been converted from the reported log values. These physiologic increases were not associated with IMI or decreased milk production, but the mechanism behind the increase was not elucidated. Overall, while several noninfectious causes for increased SCC are observed in goats, IMI remains an important cause of increased SCC. Although it is more complex to use SCC values to investigate mastitis problems in goats, the large variation observed among herds indicates that control of mastitis can result in lower bulk-tank SCC, and veterinarians should work with producers to understand the factors that influence SCC in their herd.

The types and proportions of cells present in sheep milk are more similar to dairy cows than goats, and standard methods used to count somatic cells in cows' milk are considered accurate for counting somatic cells in ewes' milk. Evaluation of SCC data is considered an effective tool for diagnosing IMIs in dairy sheep.[528,529] In an uninfected half-udder, the SCC count is generally lower than 200,000 to 400,000 cells/mL.[526,529] Higher counts are almost always associated with bacterial infections and indicate the presence of subclinical mastitis. Individual gland SCC values increase in response to IMI in ewes, so bulk-tank SCC values are an indication of milk quality and increase when the prevalence of subclinical mastitis increases. Dairy sheep producers should monitor bulk-tank SCC and manage the flock to maintain SCC less than 300,000 cells/mL.

Mastitis in Dairy Sheep

In North America, most sheep are kept for production of meat, and most research literature discusses symptoms of mastitis occurring in ewes that are nursing lambs. In this population, only severe clinical mastitis is likely to be diagnosed. This lack of emphasis on milking ewes has led to an overemphasis on the occurrence of clinical mastitis and a lack of appreciation for subclinical mastitis. There are no national studies assessing the incidence of clinical mastitis in dairy ewes milked in the United States, but based on research in other regions, clinical mastitis is thought to occur in less than 5% of ewes per year.[526] Limited U.S. data are available to define the prevalence of subclinical mastitis, but researchers believe that up to 30% of ewes in some flocks may be affected.

In almost all instances, mastitis is caused by a bacterial infection. Although most bacteria can cause both clinical and subclinical mastitis, *S. aureus, Pasteurella hemolytica,* and various yeasts and molds are organisms frequently reported to be recovered from milk samples of ewes affected with clinical signs. Bluebag (clinical mastitis with a hard, cold, swollen udder) is typically caused by either *Pasteurella hemolytica* or *S. aureus*. CoNS are considered to be minor pathogens in dairy cows but behave as major pathogens in dairy sheep and have been frequently reported to be the most commonly isolated pathogens recovered from cases of subclinical mastitis of dairy ewes.[530-532] Subclinical infection caused by CoNS and other mammary pathogens has been associated with increased SCC.[529,530] Other pathogens typically recovered from subclinical mastitis infections in ewes include *Corynebacterium* spp., yeast, *Streptococcus* spp., Enterobacteriaceae, and *S. aureus*. Yeast and mold infections in ewes are often associated with unhygienic administration of intramammary treatments, and great care must be taken when these treatments are used.[533]

In rare instances, the lentivirus that causes ovine progressive pneumonia (OPP) has been associated with mastitis in sheep,[534] but there is no evidence this virus has influence on SCC of sheep milk.[526] Mammary gland symptoms are associated with lesions in secretory tissue. Although it is known that this virus has an affinity for mammary glands, the disease is slowly progressive and results in weight loss, greatly reduced milk production, and other clinical signs that make it unlikely to become widespread in flocks used for dairy production.

Risk factors for subclinical mastitis are not well defined for intensively managed milking sheep in North America. European research in Mediterranean countries has indicated that most of the variation in mastitis is associated with differences in herd management.[535] In the same study, higher-producing breeds were at greater risk of mastitis, and the use of dry-off treatment resulted in less mastitis.[536] Practices that improve udder hygiene and reduce teat exposure to bacteria are likely to result in less mastitis.

Ewes that develop clinical mastitis are often seriously ill and should be treated immediately according to protocols that have been developed in consultation with the flock veterinarian. Most treatments for severe clinical mastitis are administered systemically, and the ewe may require supportive therapy. No antibiotic compounds are FDA-approved for treatment or prevention of mastitis in milking sheep, and off-label use of drugs for these purposes must be prescribed and supervised by a licensed veterinarian. Administration of a drug approved for treatment of another sheep disease (e.g., ceftiofur for treatment of pneumonia) to treat mastitis is also considered off-label use. It is important to recognize that systemic administration of ceftiofur will not achieve effective inhibitory levels in the mammary glands of cows, sheep, or goats.

Intramammary dry-off therapy has been shown to positively influence milk yield and SCC in the subsequent lactation, and is recommended.[533,536] However, administration of intramammary treatments does increase the risk of mastitis caused by yeast, and selective dry-off treatment can be recommended in flocks that have a relatively low prevalence of subclinically affected ewes. Milk samples obtained from ewes with three or more monthly SCCs of 400,000 or more cells/mL in the previous lactation were six to eight times more likely to be positive for mastitis pathogens in the next lactation than milk from ewes with SCCs below that threshold. That threshold may be appropriate to identify ewes that should receive dry-off treatment.[537]

Mastitis in Dairy Goats

Similar to ewes, the incidence of clinical mastitis is generally reported to be less than 5% of lactating does per year.[526] A recent study that surveyed about 90% of all goat dairy farms in Holland (≈300 farms) reported the incidence of clinical mastitis was 2% per year, and about two thirds of the farms culled the majority of affected does rather than treat them.[538] One interesting study conducted in Spain linked the incidence of clinical mastitis to selenium deficiency.[539] Spanish researchers reported that for does consuming a selenium-deficient diet, the incidence of clinical mastitis was 3.8% and 15.4%, respectively, for does that had been treated with slow-release barium selenite or were enrolled in a nonsupplemented control group.[539]

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There are neither national surveys nor comprehensive reviews that describe the prevalence of subclinical mastitis in dairy goats in the United States or Canada. Review of existing data about the prevalence of subclinical infection is further complicated by the lack of a uniform SCC threshold and the influence of intervening factors (e.g., estrus) on SCC. When recovery of bacteria from milk samples is used as the gold standard to identify subclinical mastitis, several studies have indicated that half-udder prevalence of subclinical mastitis varies between about 15% and 40%.[540] When using the SCC threshold of 500,000 cells/mL as a threshold for defining subclinical mastitis, researchers have estimated sensitivity (probability of recovery of pathogen when the SCC is > threshold) as ranging from 0.69 to 0.90, and specificity (probability of not recovering pathogen when the SCC is < threshold) of about 0.35 to 0.77.[540] Although some high SCC values are likely associated with physiologic changes, some reflect IMI, and it is likely that the prevalence of subclinical mastitis in many goat herds is greater than commonly recognized.

Similar to dairy sheep, researchers have consistently reported that CoNS are responsible for the greatest proportion of subclinical mastitis infections occurring in this species.[526,527,541] Infections with CoNS are especially prevalent in goats at parturition, with recovery of CoNS from up to 17% of goats reported.[527] Similar to ewes, the early lactation spontaneous cure rate is only about 50% for IMI caused by CoNS, and up to 25% of does may remain infected 6 weeks after parturition.[527] SCC values of infected half-udders of does are always significantly greater than SCC values of healthy half-udders.[527] Other pathogens frequently recovered from goats with subclinical mastitis include *Corynebacterium* spp., *Streptococcus* spp., and *S. aureus*. The relationship between lentiviral infections (caprine arthritis-encephalitis virus [CAEV]) and SCC has been reviewed,[526] and herds with greater prevalence of seropositive does have been shown to have greater SCC values. However, this relationship is considered weak and may have been a result of immunosuppression caused by CAEV infection.

Clinical mastitis in goats is often associated with infection by *S. aureus, Streptococcus* spp., *Pseudomonas,*[542] or miscellaneous pathogens like yeast. In many regions of the world, IMIs are associated with infection by a variety of *Mycoplasma* spp., and milk samples obtained from goats with chronically increased SCC should be submitted for *Mycoplasma* culture. When clinical mastitis cannot be explained by bacterial or fungal infection, *Mycoplasma* infection should be suspected. A variety of *Mycoplasma* spp. can cause clinical mastitis outbreaks in small ruminants. *Mycoplasma mycoides* subspecies *mycoides,* large-colony type, is an important mastitis pathogen in goats in the United States, especially in California.[543,544] *Mycoplasma putrifaciens* is involved in some outbreaks,[458] and *Mycoplasma agalactiae* is isolated on rare occasions.[545] Does with mycoplasmal mastitis often exhibit severe clinical illness and reduced milk yield, in addition to an inflamed udder and visibly abnormal milk, but subclinical IMIs can occur. Adult goats and kids in herds with mycoplasmal mastitis may experience polyarthritis and pneumonia, and pregnant does may abort. Morbidity and mortality can be very high, with more than 90% of goats dying or euthanized in some herds.[545]

Because all mastitis treatments involve off-label drug usage, treatment of clinical mastitis should be performed using protocols developed by the veterinary practitioner who has a valid veterinary-client-patient relationship. Treatment of systemically ill animals should be focused on supportive care and appropriate antimicrobial therapy. Treatment of animals with local signs of clinical mastitis generally involves administration of commercial intramammary products, and should be accompanied by microbiological assessments of at least some cases. Treatment of subclinical mastitis is unlikely to be pursued by most farms, and aggressive culling of affected animals has been shown to be associated with herds that have lower bulk-tank SCCs.[538] At least one study has demonstrated that treatment of subclinical mastitis in early lactation based on CMT resulted in increased bacteriologic cure but was not economically beneficial.[538] Thus, treatment of subclinical infections during lactation is not currently recommended. However, the use of dry-off therapy has been shown to effectively cure CoNS infections and result in lower SCC in early lactation.[546] As with sheep, producers should be taught to use extreme care when disinfecting teat ends to prevent the iatrogenic development of IMI caused by yeast.

Mastitis is an important disease of small ruminants used in dairy production, and its prevalence varies with management. Most mastitis occurs in a subclinical form, and producers who do not routinely measure individual animal SCCs will be unable to determine the impact of subclinical mastitis on production and milk quality. Most subclinical mastitis in small ruminants is caused by CoNS, which should be considered major mastitis pathogens in these species. Prevention of infection is the key to mastitis control, and good hygienic housing and milking practices are a necessity to minimize the impact of this disease. As in all dairy species, exposure of the teat end to bacteria is the mechanism for development of mastitis, and control programs are based on principles that improve hygiene and reduce exposure to potential pathogens. The prevalence of subclinical mastitis has been shown to be decreased in goat herds that practice good teat dipping and premilking teat sanitation.[547]

Mastitis in Horses

Mares have a uniquely different anatomic structure of the udder. Similar to cows, the equine udder is composed of four independent glands, but the pairs of glands on either side of the midline share a single teat and are referred to as *halves.*[548] Mastitis occurs uncommonly in horses, in part because of the relatively small size and inguinal location of the udder, which minimizes exposure to potential pathogens. Little research has been done on the prevalence of subclinical mastitis in horses, but it is not recognized to be a serious problem. In one study, no pathogens were grown from the milk of 11 mares sampled repeatedly during the first 2 months of lactation, and average SCC was less than 50,000/mL at most sampling times.[549]

Clinical mastitis occurs sporadically in lactating and nonlactating mares; signs range from mild to severe. The most common clinical mastitis pathogen is *Streptococcus zooepidemicus,* but a variety of aerobic bacteria have been isolated from the milk of affected mares.[550,551] In a retrospective study of 28 cases, gram-negative bacteria (coliform bacteria, *Pseudomonas, Actinobacillus, Pasteurella*) were isolated from 42% of milk samples.[550] Streptococci and staphylococci constituted most of the gram-positive isolates. Rarely, mastitis is caused by nonbacterial pathogens. For example, one mare developed unilateral mastitis as a component of disseminated coccidioidomycosis.[552] Verminous mastitis has even been reported.[553]

Clinical signs of mastitis in horses include an enlarged, firm, warm, painful mammary gland and edema of the udder and surrounding tissues. The mare resists milking, and secretions are abnormal in appearance (color, viscosity, consistency). About half of all mares with clinical mastitis are systemically ill, with signs such as fever, tachycardia, tachypnea, anorexia, depression, or agalactia. The mare may be reluctant to move or may adopt an abnormal gait to minimize contact between the hindlimb and the painful gland. Sedation or anesthesia is necessary to achieve a thorough examination of the udder and collection of milk in some horses.[551]

Culturing of the milk is required to definitively identify the causative pathogen of equine mastitis and confirm that antibiotic selection is appropriate. However, bacteria can often be observed on cytologic examination of the milk.[550,554] A differential diagnosis for a firm, enlarged, painful mammary gland is adenocarcinoma, particularly if the udder skin is ulcerated and the secretion is serosanguineous.[555] With adenocarcinoma, neoplastic cells may be seen during cytologic examination of the secretion, or a mammary biopsy may be required. Because bacterial mastitis and adenocarcinoma can occur simultaneously, it is important to reevaluate mares that do not respond as expected to antibiotic treatment. Fescue toxicosis should be included in the differential diagnosis for agalactia. With fescue toxicosis, the udder is not inflamed, and mares may sweat profusely, have prolonged gestation, or give birth to weak or dysmature foals.[556]

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Treatment of bacterial mastitis in horses consists of intramammary and systemic antibiotics to combat infection; NSAIDs to reduce pain, inflammation, and fever; and fluids to correct dehydration. Hot packing, hydrotherapy, and frequent stripping of the affected gland are empirically justified supportive measures but may be difficult to accomplish. Furosemide can be administered if edema is substantial.

Broad-spectrum antibiotics should be given until results of cytologic examination or culture of the milk are available. Potentiated sulfonamides, or a combination of penicillin and an aminoglycoside, are reasonable systemic antibiotic choices. Because no antibiotics are labeled for intramammary administration in horses in the United States, intramammary infusion products for cattle are used. Infusion products containing ceftiofur, cephapirin, amoxicillin, or hetacillin are appropriate until the cause of the mastitis is determined. A commercial intramammary infusion product is preferable to a homemade solution, because the latter carries a greater risk of unintentional contamination. Intramammary infusion of antibiotics can be difficult to accomplish in horses because of the small size of the teat orifice and the presence of two distinct lobes within each udder half. One or both lobes can be infected, so antibiotics must be directed appropriately. Antibiotic treatment should be continued for at least 5 days to avoid relapse.

The prognosis for survival of horses with bacterial mastitis is good, but milk production may be transiently or permanently reduced. Fortunately, mastitis is usually unilateral, and recurrence is rare.[550] Most mares respond rapidly to antibiotic treatment. Although spontaneous recovery is possible, it is unethical to withhold treatment from a mare that is ill or in discomfort. The prognosis for mammary adenocarcinoma is poor, even with surgical removal of the affected mammary gland(s) and local lymph nodes, because of the high rate of metastasis.[555]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 37

Diseases of the Hematopoietic and Hemolymphatic Systems

JOHANNA L. WATSON, *Consulting Editor*

Diseases Associated with Blood Loss or Hemostatic Dysfunction

Johanna L. Watson • Debra Deem Morris

Blood loss may be acute or chronic, and the clinical and laboratory manifestations are widely different because physiologic adaptation occurs in the chronic state.

Acute Blood Loss

Common causes for acute blood loss include trauma (e.g., severe lacerations), surgical procedures (e.g., dehorning, castration), and erosion of the carotid artery by guttural pouch mycosis in horses. External hemorrhage is immediately obvious, but hemorrhage into a major body cavity may be occult (e.g., spontaneous rupture of the middle uterine artery, splenic rupture resulting from trauma or erosion of a major vessel by abscess, aneurysm, or neoplasia). Hemoperitoneum may induce signs of colic, and hemothorax is generally attended by dyspnea. Acute massive blood loss induces hypovolemic shock characterized by tachycardia, tachypnea, cold extremities, pale mucous membranes, muscle weakness, and eventual death resulting from cardiovascular collapse.

Acute blood loss does not initially cause a change in the packed cell volume (PCV) or total plasma protein, although rapid mobilization of extracellular fluid to maintain circulating blood volume causes PCV and total plasma protein to decline within 12 to 24 hours. The severity of blood loss may be partially masked by splenic contraction, because shock causes activation of the sympathetic nervous system. Icterus is absent, and bone marrow erythroid hyperplasia is delayed by 3 to 4 days. Peripheral signs of erythroid regeneration in horses are limited to mild anisocytosis with a variable increase in mean corpuscular volume. Ruminants show erythrocyte polychromasia, basophilic stippling, Howell-Jolly bodies, and occasionally nucleated erythrocytes within 4 days of hemorrhage onset.

Diagnosis Diagnosis of acute blood loss is based on clinical signs, evidence of recent hemorrhage, and anemia accompanied by hypoproteinemia. Hemoperitoneum and hemothorax may be suggested by ultrasound and abdominocentesis and thoracocentesis, respectively.

Treatment Treatment of acute blood loss should initially be aimed at stopping the hemorrhage. External hemorrhage may be managed by pressure wraps or appropriately placed ligatures, but attempting to control internal hemorrhage when the patient is a poor risk for general anesthesia may be inadvisable, and the source of hemorrhage may not be found. Hypovolemic shock should be treated by prompt intravenous (IV) administration of 40 to 80 mL/kg of sodium-containing crystalloid solutions. Studies indicate that a small volume of hypertonic saline (2 to 4 mL/kg 7.2% sodium chloride) may temporarily reverse the pathophysiologic sequelae of severe hemorrhagic shock.[1,2] The total volume of crystalloid solution required is usually much greater than the volume of blood lost, because crystalloid solutions distribute throughout the extracellular space. The clinical response to fluid administration should be evaluated in light of ongoing losses to determine the necessary replacement volume.

If anemia becomes life threatening, whole blood transfusion must be considered. A PCV less than 20% in an animal with acute blood loss suggests depletion of erythrocyte reserves, and persistent reduction of the PCV over a period of 24 to 48 hours to 12% or less indicates the need for blood transfusion. A low but stable PCV (12% to 20%) does not necessitate transfusion, because transfusion should be reserved for instances in which oxygen delivery to the tissues is inadequate to support life. Blood transfusion can only be viewed as a temporary therapeutic procedure because even crossmatch-compatible allogeneic erythrocytes are removed from the circulation by the mononuclear phagocyte system (MPS) within 2 to 4 days of transfusion.[3] Horses and cattle display a high degree of blood type polymorphism, and minor antigenic incompatibilities are only delineated by blood typing.[4] Serum antibodies against nonhost erythrocyte antigens (erythrocyte alloantibodies) probably mediate the short lifespan of transfused erythrocytes. Compatibility testing is used to avert life-threatening antigen-antibody reactions caused by major blood group mismatching.

The routine crossmatch involves incubating washed erythrocytes from donor (major) and recipient (minor) with serum from the other. Gross and microscopic examination for clumping demonstrates serum agglutinins in horses. Sensitized cattle erythrocytes do not become clumped in saline solution but do lyse in the presence of rabbit complement, so only a hemolytic crossmatch can be performed in this species. Not all equine erythrocyte alloantibodies act as agglutinins, and hemolysins must be detected by adding complement to the reaction mixture. Pooled rabbit serum must first be absorbed with equine erythrocytes to remove naturally occurring antibodies. The necessity for special handling and storage of rabbit serum makes hemolytic crossmatch procedures impractical for most veterinarians. These tests are best performed by veterinary

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hematology laboratories (e.g., Veterinary Genetics Laboratory, School of Veterinary Medicine, University of California, Davis), which usually require serum and whole blood in sodium citrate or acid-citrate-dextrose (ACD) to crossmatch.

The first transfusion of whole blood to a horse or ruminant not previously transfused or sensitized by immunization or pregnancy is usually well tolerated because natural alloantibodies are of low concentration and weak activity. After incompatible transfusions, alloantibodies develop rapidly, making subsequent transfusions more hazardous.

Blood for transfusion should be collected aseptically into sterile containers containing sodium citrate (2.5% to 4%) or ACD solution and used immediately. The necessary dosage can only be estimated, but in most instances replacing 20% to 40% of the calculated blood loss is sufficient to maintain life until the bone marrow can respond. A drop in PCV from 36% to 12% in a 500-kg animal (8% body weight blood) represents a loss of 27 L of blood. In this case, 6 to 8 L of whole blood would be therapeutic and easily donated by another 500-kg individual. Blood warmed to 37° C (98.6° F) should be administered through an in-line filter to remove clots. After pretransfusion vital parameters have been recorded, 0.1 mL of blood/kg body weight is given over 5 to 10 minutes and the evaluation is repeated. If parameters and attitude are unchanged, the transfusion can be continued at a rate not to exceed 20 mL/kg/h. The recipient should be continuously monitored so the transfusion can be stopped if adverse reactions like tachypnea, dyspnea, restlessness, defecation, tachycardia, piloerection, muscle fasciculations, or sudden collapse occur. Although these signs may not indicate anaphylaxis, severe reactions should be treated with epinephrine (0.01 to 0.02 mL/kg, 1:1000). Mild signs may respond to a slowed transfusion rate or administration of corticosteroids or flunixin meglumine. Because it is often impossible to delineate the cause of transfusion reactions, the safest approach is to discontinue the blood and administer isotonic crystalloid solutions.

The prognosis is good for most cases of acute blood loss if hypovolemic shock is quickly treated and bleeding stops. Normal bone marrow begins to replace lost cells within 5 days. Sequential PCV analysis will be necessary to determine whether blood loss is controlled. Examples of specific disorders follow.

Guttural Pouch Mycosis

See Chapter 31 for an in-depth discussion of this and other respiratory diseases.

Hemoperitoneum in Horses

Monica Aleman • Johanna L. Watson

Hemoperitoneum is accumulation of blood in the abdominal cavity and can be a life-threatening problem. In the horse, associated causes are trauma, postoperative abdominal hemorrhage, neoplasia, complications from pregnancy and foaling (utero-ovarian, middle uterine, and external iliac artery rupture), organ rupture, mesenteric injury, coagulopathies, ovarian hematoma, systemic amyloidosis, and idiopathic hemoperitoneum.[5-11] The underlying cause is identified in the majority of cases (78%).[11] Trauma (spleen and in mares, reproductive tract with associated vessels) and neoplasia are the most common causes of hemoperitoneum.[7,11]

A recent retrospective study of 67 horses with hemoperitoneum revealed that Thoroughbreds and Arabians were overrepresented breeds.[11] Middle-aged and older horses (>13 years of age) and females may be overrepresented.[10,11] The most common clinical signs include abdominal discomfort, lethargy, hypovolemic shock, pale mucous membranes, prolonged capillary refill time, tachycardia, and tachypnea.[10,11] Other clinical signs are anorexia, reluctance to move, weakness, trembling, cool extremities, and abdominal distention.[10]

Clinicopathologic abnormalities include anemia, neutrophilia, lymphopenia, thrombocytopenia, hypoproteinemia, hypocalcemia, and azotemia.[10] Abnormalities in clotting parameters may be observed, depending on the cause. Hemorrhagic abdominal effusion is characterized by high red blood cell (RBC) count (>2,400,000 RBC/μL), PCV (≥18%), and total protein (≥3.2 g/dL), with a normal to high leukocyte count.[10] Central venous pressure and blood lactate concentration appear to be early indicators of hypovolemia due to acute blood loss.[12] Fluid swirling and site of hemorrhage may be evident on abdominal ultrasound.

Primary goals of therapy are treating hypovolemic shock, restoring perfusion and oxygen delivery to tissues, correcting fluid deficits, stopping further blood loss, and preventing complications. Blood transfusion should be considered if anemia becomes life threatening. The use of antifibrinolytic and procoagulant agents have been reported in the literature, but controlled studies on efficacy and safety in the horse with acute blood loss are lacking. Physical activity must be restricted in affected patients.

The short-term outcome is strongly associated with the underlying cause.[11] Horses with neoplasia, uterine artery rupture, mesenteric injury, or disseminated intravascular coagulation (DIC) have a greater risk of not surviving. The survival rate has been reported to range from 51% to 74%.[10,11] Poor short-term outcome was significantly associated with high respiratory rate in one study.[11] Prepartum hemorrhage appears to be associated with a poorer prognosis than postpartum hemorrhage (100% vs. 20% mortality, respectively).[11]

Hemothorax

Hemothorax may occur secondary to trauma (including lung biopsy), neoplasia, and strenuous exercise (see Chapter 31).[13] Hemothorax in neonatal foals may be the result of lacerated lungs and vessels from fractured ribs (see Chapter 20).[14]

Exercise-Induced Pulmonary Hemorrhage

Exercise-induced pulmonary hemorrhage (EIPH) has not been identified as a major cause of blood loss. EIPH is associated with high-intensity exercise in horses. An estimated 14% to 75% of racehorses examined by endoscopy have EIPH.[15] Based on bronchoalveolar lavage analysis, a study suggested that 100% of horses performing strenuous exercise have EIPH.[16] EIPH has been reported in various breeds. A recent study reported that the frequency of EIPH is associated with race type, distance, gender, and age. In one study, epistaxis was more common in females, older horses (vs. <2 years of age), following steeplechase races (vs. flat races), and at shorter distances (≤1600 m long).[17] Recurrence rate in that study was reported to be 4.64%. The pathophysiology of EIPH is not completely known. For a complete description of this disorder, see Chapter 31.

Chronic Blood Loss

Johanna L. Watson • Debra Deem Morris

A number of diseases can result in chronic loss of blood that is insidious until clinical signs of anemia develop. Physiologic adaptation to gradually developing tissue hypoxia generally masks signs of anemia until the PCV is less than 15%. Causes for chronic blood loss include bleeding gastrointestinal (GI) lesions, certain renal diseases, hemostatic dysfunction, bloodsucking external parasites, and haemonchosis (especially in goats and sheep).

GI hemorrhage is usually caused by neoplasia (especially gastric squamous cell carcinoma in horses and abomasal lymphoma in cattle), parasitism, or mucosal ulceration (e.g., abomasal ulcers in cattle and nonsteroidal antiinflammatory drug [NSAID] toxicity in horses). Significant hemorrhage may occur in ruminants heavily infested with *Haemonchus contortus* shortly after they are treated with an anthelmintic. Generally, GI hemorrhage is best detected by chemical determination of fecal occult blood, because melena rarely occurs in horses, and bleeding abomasal ulcers cannot be excluded in cattle when melena is absent. Because of the low specificity of tests for fecal occult blood, the diagnosis of chronic GI blood loss is usually supported by strong clinical suspicion and ruling out other sources of hemorrhage.

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Although both renal calculi and renal papillary necrosis due to NSAID therapy cause hematuria, anemia rarely results. Renal neoplasia and congenital renal vascular anomalies are rare causes of chronic blood loss anemia. Other causes of blood loss include idiopathic hematuria and idiopathic recurrent hematuria of Arabian horses.

Disorders of hemostasis can cause internal or external hemorrhage that leads to anemia if enough blood is lost. Qualitative or quantitative abnormalities of blood vessels, platelets, or coagulation factors result in hemostatic dysfunction (see next section). Loss of erythrocyte iron secondary to chronic severe blood loss may result in iron deficiency anemia. Hypoferremia or reduced serum ferritin develops with increased total iron-binding capacity and reduction in marrow iron.

The key to managing chronic blood loss is determining the primary cause; treatment of the anemia per se is rarely indicated. Iron deficiency may be alleviated by oral (PO) supplementation with ferrous sulfate, although good-quality forages contain more than adequate amounts of iron. Parenteral iron supplementation as iron dextran should be avoided because it has been associated with anaphylactoid reactions in large animals. Examples of specific disorders follow.

Gastric Ulceration

Monica Aleman • Johanna L. Watson

Gastric ulceration is also known as *equine gastric ulceration syndrome* (EGUS). Although EGUS is not an important cause of blood loss, it has a high prevalence among adult horses. Thoroughbred racehorses have the greatest prevalence (range, 82% to 93%), followed by endurance horses (67%), show horses (58%), hospitalized horses (49%), and geriatric patients with abdominal pain (18%).[18-22] Gastric ulcers were found in 66.6% of pregnant and 75.9% of nonpregnant mares on a Thoroughbred breeding farm.[23] Clinical signs may include poor hair coat, decreased appetite, poor performance, nervous disposition, abdominal pain, teeth grinding, and salivation among others. Proposed causes of gastric ulceration include exercise, transportation, grazing deprivation, alternating periods of feeding and fasting, diets with high-concentrate content, and confinement. For a complete description of gastric ulceration see Chapter 32.

Right Dorsal Colitis

Right dorsal colitis (RDC) is an enteropathy associated with NSAID administration, most commonly phenylbutazone.[24,25] Other factors that may predispose to RDC are infection, immune-mediated response, genetics, and stress; pathogenesis is unknown. NSAIDs act by inhibiting cyclooxygenase (more inhibition of constitutively expressed COX-1 than inducible COX-2 expression during states of inflammation), which will cause inhibition of prostaglandin E production, resulting in hypoxic or ischemic GI mucosal damage and delayed mucosal healing.[25]

Ponies and young performance horses appear to be predisposed. Clinical signs include inappetence, lethargy, intermittent or episodic colic, diarrhea, and weight loss. Clinicopathologic abnormalities may include mild anemia, moderate to severe hypoproteinemia with hypoalbuminemia, hypocalcemia, and in some cases azotemia. Although mild anemia is seen in most cases, horses occasionally present with severe anemia and hematochezia. RDC often develops over a period of days or a few weeks. The complete discussion of diagnosis and treatment is included in Chapter 32.

Hemostatic Dysfunction

Johanna L. Watson • Debra Deem Morris

Basic Physiology of Normal Hemostasis

The basis for understanding the pathogenesis and manifestations of hemostatic disorders is a thorough understanding of the normal physiologic mechanism of hemostasis. Hemostasis can be viewed as two interrelated components—coagulation and fibrinolysis (both with their respective inhibitors)—which function to arrest bleeding from a damaged blood vessel and maintain nutrient blood flow.

Coagulation is mediated by blood vessels, platelets, and blood procoagulant proteins. When a blood vessel is damaged, vasoconstriction occurs, followed by rapid adherence of platelets to subendothelial collagen. Platelet adhesion causes membrane conformational changes that trigger aggregation, contraction, and granule secretion (the basic platelet reaction). Platelet phospholipoprotein (platelet factor 3) provides the necessary surface to catalyze interactions among the activated coagulation proteins that result in thrombin formation. Coagulant proteins are localized to this hemostatic plug because the platelet surface protects them from plasma anticoagulants. Through an incompletely understood mechanism, platelets also prevent spontaneous hemorrhage into the skin and mucous membranes by maintaining vascular integrity.

Procoagulant proteins circulate in the blood as precursor forms (zymogens) that must be altered during coagulation to become active. Numerous communications exist between the traditional extrinsic and intrinsic pathways, although initiating mechanisms remain distinct.[26] The extrinsic system is initiated when lipoprotein tissue factor (TF) gains access to the bloodstream. TF is widely distributed in most tissues, including endothelial cells and monocytes, and it may be increased or secreted in response to numerous pathologic stimuli like bacterial endotoxin. Intrinsic coagulation is initiated when blood is exposed to a negatively charged surface (e.g., activated platelets). Because of reciprocal activation between factor XII and prekallikrein, the intrinsic coagulation pathway stimulates formation of numerous inflammatory mediators such as kinins and complement. Both coagulation pathways culminate in the formation of activated factor X (Xa) by which thrombin is generated. In addition to catalyzing the conversion of fibrinogen to fibrin, thrombin promotes platelet aggregation, enhances cofactor activities of factors V and VIII, and activates factor XIII and protein C.[27] Mechanisms to localize coagulation to the site of vascular injury are critical to protect against generalized thrombosis.[28] Plasma anticoagulant proteins include the serpins, which inhibit activated coagulation factors, and the protein C system, which is directed against cofactors V and VIII.[29] Antithrombin III (AT III), the main physiologic inhibitor of thrombin and Xa, normally provides 70% of the anticoagulant activity of plasma. Although not absolutely necessary, heparin accelerates AT III action by 2000-fold.[30] Activated protein C destroys factors V and VIII, ultimately limiting its own activation, which depends on thrombin and endothelial cofactor, thrombomodulin. Protein S enhances the anticoagulant ability of protein C.

The fibrinolytic system is activated at the same time as coagulation and functions to prevent tissue ischemia by limiting the extent of fibrin clot formation. Plasmin, primarily responsible for degradation of fibrin, exists in the plasma as the zymogen plasminogen. Plasminogen has a high affinity for fibrin, as does tissue plasminogen activator (tPA); because clots contain the necessary components to allow lysis from within, systemic plasmin formation is avoided. α_2-Antiplasmin (α_2-AP), the main physiologic inhibitor of plasmin, competes with the binding of plasminogen to fibrin, and the clot contains equal amounts of both glycoproteins. Because of this molar balance between α_2-AP and plasminogen, a normal blood clot does not lyse spontaneously, despite fixation of tPA. Physiologic plasminogen activator inhibitors (PAIs) are found in plasma, platelets, and endothelial cells; platelet-derived PAI protects a blood clot against premature lysis. Clot lysis is initiated if additional tPA is taken up from the surrounding tissues, and stasis upstream from the occluded vessel is a potent stimulus for release of endothelial tPA. Conversion of plasminogen to plasmin allows partial digestion of fibrin and exposure of additional plasminogen binding sites. When this additional plasminogen is converted to plasmin, the inhibitory effect of α_2-AP is overcome, and clot lysis is accelerated. Plasmin hydrolyzes fibrinogen and fibrin with equal affinity, as well as numerous other procoagulants, and it can activate complement and kininogen. The

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physiologic actions of plasmin are limited to the fibrin clot by the affinity between the latter and plasminogen and the presence of α_2-AP in blood. Because of multiple interactions between the coagulation and fibrinolytic systems, the most important factor that determines the rate of fibrinolysis is the rate of fibrin formation.[31]

Inherited Coagulation Disorders

Jeffrey W. Norris

The presentation of patients with reductions in protein levels or activity associated with the traditional coagulation pathways may range from asymptomatic to severe prolongation of bleeding subsequent to trauma, including that associated with diagnostic procedures, surgery, and parturition. Other signs of pathologic hemorrhage associated with coagulation factor deficiency include subcutaneous hematomas, hemarthroses, epistaxis, melena, or hematuria. Several coagulation factor deficiencies have been described in domestic herd animals.

Prekallikrein, or Fletcher factor, deficiency has been described in both Miniature[1] and Belgian horses.[2] Conversion of prekallikrein to kallikrein is traditionally thought of as initiating the intrinsic pathway of coagulation through activation of factor XII. Recent studies have demonstrated that prekallikrein and factor XII are critical factors in thrombosis but not hemostasis.[3,4] This subtle role of prekallikrein in the coagulation system is consistent with observations that many patients with prekallikrein deficiency are asymptomatic, but bleeding in response to trauma (e.g., surgery) is possible.[2] The inheritance pattern of this deficiency and the causal mutation have not been determined.

The second step of the intrinsic pathway of coagulation is activation of factor XI by activated factor XII. Factor XI deficiencies have been reported in Holstein,[5] Holstein-Friesian,[6] and Japanese Black cattle.[7] The deficiency has been reported in Canada,[5] Britain,[6] the United States,[8] Poland,[9] Turkey,[10] and Japan.[7] Factor XI deficiency in cattle is transmitted as an autosomal recessive trait.[11] Most cases result from a 76–base pair (bp) insertional mutation in exon 12 of the F11 gene,[8] but a 15-bp insertional mutation in exon 9 of the F11 gene has also been identified in a group of Japanese Black cattle.[7] Estimates of the prevalence of the former mutant gene allele are approximately 1.2%,[8,12] but the latter mutant allele may have a prevalence as high as 23.1% in Japanese Black cattle.[13] Cattle with factor XI deficiency may be asymptomatic or present with a range of signs that includes prolonged bleeding, reduced resistance to infection (particularly mastitis, metritis, and pneumonia),[11,14] and an increased prevalence of repeat breeding, possibly due to a slower estrus cycle.[15] Distribution of this deficiency within a family group is best determined by genetic analysis because there is poor segregation in factor XI plasma levels between normal and heterozygous cattle.[16]

Factor VIII deficiency, or hemophilia A, has been reported in a range of breeds, including Quarter Horses,[17] Japanese Brown cattle,[18] and Hereford cattle.[19] Congenital factor VIII deficiency is X-linked and recessive, with clinical disease occurring predominantly in males, although homozygous females or heterozygous females with X inactivation may also be affected. A leucine-to-histidine mutation leading to the deficiency was recently found in the F8 gene of Japanese Brown cattle.[20] Factor VIII levels of 5% or less are considered to be moderate to severe hemophilia and may predispose patients to spontaneous hemorrhage; a less severe deficiency may lead to excessive hemorrhage only after trauma.

Factor VIII is stabilized in circulation via non-covalent association with von Willebrand factor, which also promotes platelet-endothelial adhesion at sites of vascular injury. Deficiency of von Willebrand factor has been reported in a Quarter Horse filly that had hemorrhage from mucosal surfaces following trauma.[21]

A combined deficiency of the vitamin K–dependent coagulation factors (factors II, VII, IX, and X) was reported in a family of Rambouillet sheep.[22] Signs included excessive subcutaneous bleeding and bleeding from the umbilicus in newborn lambs following parturition. Evidence that (1) affected lambs were consistently produced by a single sire in the flock and (2) failure to identify a known vitamin K antagonist in affected lambs was consistent with an inherited disorder. Breeding data from the study supported an autosomal recessive mode of transmission. The molecular defect underlying this coagulopathy is unknown, but mutations leading to altered vitamin K metabolism or γ-glutamyl carboxylase function are possible.

A second combined deficiency with moderate decreases of factors VIII, IX, and XI was reported in an Arabian colt.[23] Factors VII and prothrombin were also moderately reduced in this colt, but no abnormalities were apparent in plasma from the sire, mare, or other half-siblings, raising the possibility of an acquired coagulopathy. Additional differential diagnoses for coagulation factor deficiencies include DIC, warfarin toxicosis (horses), moldy sweet clover toxicosis, and acute hepatic disease.

The heritable clotting factor deficiencies involve proteins in the intrinsic pathway, and prolonged activated partial thromboplastin time (APTT) is the primary hemostatic abnormality. However, multifactor defects in the vitamin K–dependent coagulation factors (e.g., that described in Rambouillet sheep[22]) and acquired coagulation factor deficiencies also involve proteins in the extrinsic or common pathways of coagulation, which will cause a trend toward prolongation of both the prothrombin time (PT) and APTT. Except as noted for factor XI deficiency in cattle, the definitive diagnosis of heritable clotting factor deficiencies is based on specific quantitative assays of those factors.

Heritable clotting factor deficiency is treated by replacing the factors through the administration of fresh plasma. Specific clotting factor concentrates are not commercially available for large animals, and development of such products is unlikely because of the rarity of these disorders. The expense of therapy and potential for complications makes the long-term prognosis poor for horses with hemophilia A or animals with multiple congenital coagulation factor defects. Cattle with factor XI deficiency apparently have a normal lifespan but may require treatment for secondary diseases like infection, owing to their increased susceptibility.

Thrombasthenia in Horses

Jeffrey W. Norris • Monica Aleman

GLANZMANN THROMBASTHENIA. Glanzmann thrombasthenia is a rare, inherited platelet defect caused by either a quantitative or qualitative change in the platelet glycoprotein complex IIb-IIIa (integrin $\alpha_{IIb}\beta_3$). This complex is made from two subunits encoded by separate genes that must both be expressed to form stable, functional heterodimers on the platelet surface. This complex is the receptor that binds fibrinogen and mediates platelet aggregation. Glanzmann thrombasthenia has been documented in humans and dogs.[1,2] Of the six reports of thrombasthenia in the horse,[3-7] four have been confirmed to be Glanzmann thrombasthenia by genetic analysis.

Interestingly, mutations associated with Glanzmann thrombasthenia in horses have only been found in the α_{IIb} subunit. An 18-month-old Oldenburg filly was shown to be homozygous for a G-to-C mutation of codon 72 in exon 2 that causes an arginine-to-proline substitution.[8] A similar G-to-C mutation, also causing an arginine-to-proline substitution, was identified at codon 41 in exon 2 of both a 7-year-old Thoroughbred cross gelding that was homozygous for the mutation, and a 4-year-old Quarter Horse mare that was heterozygous.[9] Both arginine-to-proline mutations occur in a single highly conserved portion of the α_{IIb} gene and are expected to destabilize the protein structure, leading to an absence of the complex on platelet surfaces.[9] Further analysis of the Quarter Horse mare revealed a 10-bp deletion in the second α_{IIb} allele that spanned the distal (5′) exon 11 splice site and likely led to decay of the mRNA transcribed from the allele.[10] This deletion was also identified in a 17-year-old Peruvian Paso that was homozygous for the mutation.[7]

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The prominent clinical sign of Glannzman thrombasthenia in the horse is chronic intermittent epistaxis unrelated to exercise. Other signs include petechial and ecchymotic hemorrhages in the nasopharynx.

Conclusive diagnosis usually requires nonstandard testing procedures. Clinical biochemistry may indicate mild anemia in the face of normal platelet count, activated coagulation time, partial thromboplastin time (PTT), PT, thrombin time, fibrin degradation products, and plasma concentration of von Willebrand factor. However, gingival bleeding time is prolonged (>60 minutes, control horses <2 minutes), clot retraction is markedly reduced, and platelet aggregation in response to various agonists as measured by aggregometry is markedly impaired. Closure time measured using a PFA-100 analyzer with collagen/ADP cartridges is markedly prolonged.[6] Also, the amplitude of thromboelastograph (TEG) tracings may be reduced, consistent with weakened tensile strength of kaolin- or tissue factor–induced clots.[6] Flow cytometric studies using CD41/CD61 monoclonal antibodies have revealed a reduction in $\alpha_{IIb}\beta_3$ integrin on platelet surfaces.[5]

Currently, no treatment is available. Superficial cauterization of bleeding sites in nasal mucosa using silver nitrate swabs and a CO_2 laser has been attempted but provided only temporary hemostasis.[7] Clients have been advised to be observant for signs of bleeding requiring supportive care; regular monitoring for anemia is recommended.[7]

HERITABLE BLEEDING DIATHESIS (OTHER THAN GLANZMANN THROMBASTHENIA). Severe intermittent bleeding was reported in a 2-year-old Thoroughbred filly subsequent to minor insults.[11] Platelet concentration, PT, PTT, antithrombin III, and the coagulation factors (von Willebrand, VIII, IX, XI, and XII) were unremarkable. Several integral platelet membrane glycoproteins involved in aggregation and clotting, including GPIb, GPVI, and $\alpha_{IIb}\beta_3$, were present on platelets from this filly. The filly's template bleeding time was over 120 minutes, compared to 5.5 minutes in control horses. Platelet-rich plasma aggregated normally in response to a range of agonists (ADP, thromboxane A_2) but was prolonged in response to thrombin and collagen.[12]

Consistent with the reduced aggregation in response to thrombin, fibrinogen binding to platelets from the filly was markedly decreased in comparison to control platelets.[12] Platelets from this filly also had reduced prothrombinase activity, which reflects decreased thrombin activation and catalysis of fibrinogen polymerization. Reduced fibrinogen binding and prolongation of the template bleeding time was also observed in one of two offspring from the affected mare. In a screen of 444 randomly selected horses from a single breeding facility, a normal distribution of fibrinogen binding was established for equine platelets, and 0.7% of the population was found to have reduced levels of fibrinogen binding (67.6% to 83.4% reduction) that were comparable to the affected mare and offspring.[13]

Unlike Glanzmann thrombasthenia, in which platelets lack the ability to bind fibrinogen entirely, the $\alpha_{IIb}\beta_3$ integrin on platelets from horses with this bleeding diathesis functions normally. Therefore, acute bleeding in established cases has been managed by stabilization of clotting through inhibition of fibrinolysis using ε-aminocaproic acid.

Acquired Hemostatic Disorders

Monica Aleman • Johanna L. Watson

Acquired defects of hemostasis may be divided into those involving blood vessels, platelets, and coagulation factors, although some diseases affect more than one component.

VASCULITIS. Vasculitis is a clinicopathologic process that involves inflammation and necrosis of blood vessel walls, regardless of size, location, or cause.[1] Vasculitis in large animals is generally a secondary manifestation of a primary infectious, toxic, or neoplastic disorder and has characteristics of hypersensitivity vasculitis in humans. The predominant involvement of small vessels in the skin (e.g., venules, arterioles) is the hallmark of hypersensitivity vasculitis.

Clinical manifestations of vasculitis include demarcated areas of dermal or subcutaneous edema that may progress to skin infarction, necrosis, and exudation.[2] Hyperemia, petechial and ecchymotic hemorrhages, and ulceration of mucous membranes are common. Although the skin and mucous membranes are predominantly involved, hemorrhage and necrosis may occur in any organ system, resulting in conditions like lameness, colic, dyspnea, and ataxia. Subclinical renal disease is not uncommon. Vasculitis is often attended by a number of adverse sequelae such as cellulitis, thrombophlebitis, laminitis, and pneumonia. Characterized vasculitis syndromes with predominant cutaneous involvement include equine purpura hemorrhagica (EPH), equine viral arteritis (EVA), equine infectious anemia (EIA), and equine granulocytic ehrlichiosis (EGE). There are also a number of vasculitis syndromes in horses for which cause, pathogenesis, and clinical course are poorly defined.[3,4] Vasculitis is apparently uncommon in ruminants but may accompany certain septicemic diseases (e.g., malignant catarrhal fever of cattle, bluetongue of sheep).[5] Hematologic and serum biochemical findings in vasculitis are determined by the underlying disease, length of illness, organ involvement, and secondary complications. Chronic inflammation may be attended by neutrophilia, mild anemia, hyperglobulinemia, and hyperfibrinogenemia. Some horses with EPH develop a moderate anemia (PCV 20% to 25%) that is thought to be caused by increased erythrocyte destruction.[6] The platelet count is generally normal. Muscle damage may be reflected by increased serum concentrations of creatine phosphokinase (CPK) and aspartate aminotransferase (AST). The creatinine may be elevated, and urinalysis may rarely show trace hematuria or proteinuria if there is glomerulonephritis.

Definitive diagnosis of vasculitis is made by demonstration of the characteristic histopathology of involved vessels. Full-thickness punch biopsies (at least 6 mm in diameter) of skin in an affected area should be obtained and preserved in 10% formalin and Michel's transport medium. Multiple biopsies from different sites may be necessary to reach the diagnosis. The most common inflammatory pattern is neutrophilic infiltration of venules in the dermis and subcutaneous tissue, with nuclear debris in and around involved vessels (leukocytoclasis) and fibrinoid necrosis. Immunofluorescence on biopsies preserved in Michel's medium may reveal immune complexes. Considerable evidence suggests that most vasculitis syndromes are mediated by immunologic mechanisms—that is, a hypersensitivity reaction to a microbe, drug, toxin, or protein.[1] In some instances an exogenous stimulus cannot be identified, and an autoimmune pathogenesis is suspected. Immune complex deposition in vessel walls, with subsequent complement activation and chemoattractant production, seems to be the major pathogenic mechanism. Infiltrating neutrophils and macrophages release proteolytic enzymes that cause vessel wall necrosis with subsequent edema, hemorrhage, and infarction of supplied tissues. Size and physiochemical properties of immune complexes, blood flow turbulence in sites of vessel bifurcation, and hydrostatic forces in dependent areas account for preferential formation of lesions in certain disease states and anatomic locations. Horses and cattle with idiopathic vasculitis may have incomplete response to therapy with an unpredictable poor prognosis.[5,6]

Equine Purpura Hemorrhagica. Purpura hemorrhagica (PH) is a noncontagious disease of horses characterized by vasculitis leading to extensive edema and hemorrhage of the mucosa and subcutaneous tissue. The disease has been recognized as a sequela to infection with or exposure to *Streptococcus equi, Streptococcus zooepidemicus, Rhodococcus equi, Corynebacterium pseudotuberculosis*, and others, and vaccination against *S. equi*.[2,7]

Young to middle-aged horses are commonly affected (mean, 8.4 years of age; range, 6 months to 19 years).[7] Clinical signs usually develop acutely within 2 to 4 weeks of a respiratory infection.[8]

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Predominant signs are well-demarcated subcutaneous edema of all four limbs, lethargy, anorexia, hemorrhages on mucous membranes, fever, and tachycardia. Other signs are tachypnea, reluctance to move, serum exudation from the skin, colic, and epistaxis.

The predominant laboratory abnormalities include anemia, neutrophilia, hyperproteinemia, hyperfibrinogenemia, hyperglobulinemia, and elevated muscle enzymes. Thrombocytopenia is rarely detected in horses with PH.

Skin biopsy shows evidence of acute leukocytoclastic or nonleukocytoclastic vasculitis with necrosis of blood vessels. The lesions are marked dermal and subcutaneous hemorrhage, protein-rich edema, and multifocal areas of dermal infarction. Small arteries and capillaries are swollen and infiltrated by degenerate or nondegenerate neutrophils. Hyaline thrombi may be observed.[7] Immune complexes have been demonstrated to be primarily composed of immunoglobulin (Ig)M or IgA and streptococcal M protein and may be present in capillaries and small blood vessels of horses with PH, leading to a type III hypersensitivity reaction.[9] Deposition of immune complexes in vessel walls and subsequent complement activation may result in cell death. Extensive hemorrhages in the dermis, subcutis, skeletal muscles, lungs, kidneys, spleen, intestinal walls, and blood vessels have been observed in postmortem examination.

Horses with infarctive PH can present with colic, lameness, muscle swelling, and stiffness.[10] Extensive GI infarction results in severe colic signs. Significant findings in these horses include leukocytoclastic vasculitis and necrosis of various tissues, neutrophilia with a left shift, hypoalbuminemia, and high serum creatine kinase.[10]

Treatment should aim to address the primary cause if identified, reduce the immune and inflammatory response, initiate antimicrobial therapy in cases of active infection or prevent infection if indicated, provide supportive care, and prevent complications. Horses with known streptococcal infection should receive penicillin (22,000 IU/kg of intramuscular [IM] procaine penicillin G twice daily, or IV potassium penicillin G q6h) or other antibiotic with excellent efficacy against streptococcal organisms for at least 2 weeks. Hydrotherapy, limb bandages, and light exercise (hand walk) have been helpful in reducing limb edema. Fluids administered IV or via nasogastric tube may be necessary for animals that become severely lethargic and fail to drink or those that develop dysphagia from laryngeal edema. Stridor and dyspnea may indicate the need for tracheostomy. Prolonged treatment with corticosteroids (2 to 4 weeks) has resulted in favorable outcome and low relapse rate. However, some horses may require a longer course of therapy than 4 weeks. Depending on severity of clinical signs, proposed dosages are 0.04 to 0.2 mg/kg of dexamethasone (IV, IM, or PO) once (morning) or twice a day, or 0.5 to 1 mg/kg of prednisolone PO once (morning) or twice a day (0.05 to 1 mg/kg), with gradual reduction of the dosage.[7] It has been suggested that antimicrobials be used throughout the course of corticosteroid therapy to reduce the occurrence of secondary sepsis.[2]

Outcomes will depend on early detection, early aggressive treatment, and extent of organ involvement. Skin sloughing, laminitis, cellulitis, pneumonia, and diarrhea are common and may significantly prolong convalescence. The prognosis is fair with early aggressive therapy and supportive care; a recent retrospective study of 53 horses with purpura hemorrhagica reported a mortality rate of 7.5%.[7]

Equine Viral Arteritis. Equine viral arteritis (EVA) is an infectious disease characterized by panvasculitis, edema, hemorrhage, and abortion in pregnant mares. EVA is caused by an enveloped, spherical, positive-stranded RNA virus with a diameter of 50 to 70 nm. Equine arteritis virus (EAV) is a nonarthropod-borne virus classified as a member of the new order Nidovirales within the family Arteriviridae.[11] EAV was first isolated from fetal lung collected during an epizootic of abortion in Bucyrus, Ohio.[12] Clinical signs may be absent or may develop 1 to 10 days after infection and include pyrexia, lethargy, anorexia, limb edema, stiffness, rhinorrhea, epiphora, conjunctivitis, rhinitis, and abortion. Edema of several regions can be observed, including periorbital, supraorbital, ventrum, mammary gland, scrotum, and limbs.[13] Other signs include urticarial rash, abortion, respiratory signs, ataxia, mucosal eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema. EAV can present as epidemic abortion, with occasional fatalities in foals and adults. With natural exposure, abortion rate varies widely (<10% to >60%) and can occur from 3 to 10 months of gestation.[14] Infected mares do not become EAV carriers or chronic shedders and do not appear to have fertility problems.

Laboratory abnormalities are variable and not diagnostic for EVA. Experimentally infected mature horses had a consistent leukopenia due to neutropenia and lymphopenia.[15] After infection, EAV can be localized in macrophages and lymph nodes within 24 and 48 hours, respectively. Various tissues are affected, but blood vessels are the principal target of EAV. Within vessels, EAV localizes in endothelium, medial myocytes, and pericytes. The virus causes vasculitis with fibrinoid necrosis of the tunica media, abundant vascular and perivascular lymphocytic and lesser granulocytic infiltration with karyorrhexis, loss of endothelium, and formation of large fibrinocellular stratified thrombi.[13] Body cavity effusion is common.

The virus is mainly transmitted through aerosols from respiratory, urinary, or reproductive tract secretions of acutely infected animals. The other route of transmission is via semen from shedding stallions; the virus remains viable in fresh, chilled, and frozen semen.[14] Horizontal transmission via fomites is possible.[16] Natural EAV exposure results in long-term immunity to the disease. Mares and geldings eliminate virus within 60 days, but 30% to 60% of acutely infected stallions will become persistently infected, temporarily or permanently shedding virus in semen.[13] The virus is maintained in the accessory organs of the male reproductive tract (ampullae, vasa deferentia).[14] Seroprevalence for EAV is very common in the Standardbred and warmblood breeds and, more recently, EAV infection has been established within some Quarter Horse populations.[17]

Laboratory diagnosis of EVA can be based on virus isolation, viral nucleic acid detection (polymerase chain reaction [PCR] assay), or serology. In the case of serology, a fourfold or more increase in serum neutralizing antibodies between acute and convalescent samples (3 weeks apart) is required for diagnosis. Stallions with positive titers of 1 : 4 should be tested for persistent infection by virus isolation from sperm-rich ejaculate.[14] Viral isolation and PCR can be attempted from respiratory secretions or fetal and placental tissues. Semen can be tested for viral shedding by culture, isolation, or PCR. Identification of carrier stallions is crucial in preventing dissemination of EAV. A modified live vaccine is commercially available (Arvac [Fort Dodge Animal Health, Livestock Division, Overland Park, Kan.]). Vaccination will result in development of a serum titer that will be detected on EVA testing and cannot be distinguished from active infection. Horses vaccinated for the first time should have serum submitted to a U.S. Department of Agriculture (USDA)-approved laboratory to confirm seronegative status. After vaccination, these animals should be isolated because they may temporarily shed the modified virus.

Equine Infectious Anemia. See section on hemolytic anemia.

ANAPLASMA PHAGOCYTOPHILA INFECTION IN HORSES

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Definition and Etiology Equine granulocytic ehrlichiosis (EGE) was first reported in the late 1960s in the foothills of Northern California.[1] The disease is caused by *Anaplasma phagocytophila*. This organism was formerly known as *Ehrlichia equi,* but it was reclassified in the *Anaplasma* genus based on genetic analysis.[2] Recently, the agents of human granulocytic ehrlichiosis (HGE), *Ehrlichia phagocytophila* and *E. equi,* were grouped into a single species and named *A. phagocytophila*.[2] These organisms are identical based on 16S rRNA gene sequences, and they have similar morphology, host cell tropism, and indirect fluorescent antibody (IFA) response.[3]

The organism is found within vacuoles (1.5 to 5 μm in diameter) in the cytoplasm of infected granulocytes, primarily neutrophils and eosinophils. These vacuoles or inclusion bodies are pleomorphic and

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contain one or more coccobacillus or large granular aggregates called *morulae*. The organisms are visible under light microscopy as deep blue to pale blue gray with Giemsa or Wright-Leishman stains.

Epidemiology Since the disease was first reported in California,[4] cases have been diagnosed in Colorado, Connecticut,[5] Florida, Illinois, Minnesota, New Jersey, New York, Oregon, Washington, Wisconsin, Canada, Brazil, northern Europe, and Israel. Equine cases occur during late fall, winter, and spring. There is no apparent gender or age predilection, but the disease appears to be less severe in younger horses. Persistent, chronic, or latent infections or carrier status have not been demonstrated and are unlikely to occur, since the presence of *A. phagocytophila* is limited to the acute phase. Therefore, it is also unlikely that infected horses could serve as reservoirs. The disease is not contagious but could be readily transmitted through the administration of infected blood. The vectors of granulocytic ehrlichiosis are *Ixodes pacificus* in California, *Ixodes scapularis* in the eastern and midwestern United States, and *Ixodes ricinus* in Europe.[6-9] Potential or proposed reservoirs are white-footed mice, chipmunks, white-tailed deer, dusky-footed wood rats, cervids, lizards, and birds.[9]

Pathogenesis The pathogenesis of the disease is unknown. Entry of the organism occurs after inoculation from a biting tick and is presumed to be spread via blood and/or lymph. The organism has cell tropism toward neutrophils and eosinophils, where it replicates within vacuoles, forming characteristic morulae. Presumed cytolysis, induction of inflammation, cell sequestration, consumption, or destruction result in the observed clinical signs and pancytopenia.[10] Cell- and humoral-mediated immune responses develop in affected animals. Antibody titers peak at 19 to 81 days after the onset of clinical signs, and immunity likely persists for a long period of time (>2 years).[11]

Clinical Signs Clinical signs include reluctance to move, fever ranging from 39.4° to 41.3°C (102.9° to 106.3°F), mild to moderate tachycardia (50 to 60 beats/min [bpm]), lethargy, decreased appetite, limb edema, petechiation, icterus, weakness, ataxia, and recumbency (reported in one case). Secondary trauma may result from falling in severely ataxic horses. These clinical signs appear to be less profound in younger horses. The incubation period after natural infection is believed to be less than 14 days. The prepatent period after experimental exposure to infected ticks or inoculation with infected blood is 8 to 12 days and 3 to 10 days, respectively. The disease is self-limiting and nonfatal provided no complications develop. However, affected horses may be predisposed to secondary bacterial, fungal, and viral infections.[1] Abortions and laminitis have not been reported in affected horses.

Clinical Pathology Laboratory alterations include anemia, leukopenia characterized by granulocytopenia and lymphopenia, and thrombocytopenia. Morulae may be observed within the cytoplasm of neutrophils and eosinophils during the acute phase of the infection.

Diagnosis Definitive diagnosis is based on the presence of characteristic morulae (minimum of 3) within the cytoplasm of neutrophils and eosinophils, or positive PCR assay for *A. phagocytophila* in peripheral blood (buffy coat).[12] Morulae may be observed in less than 1% of cells in the initial stages of the infection, rising to 20% to 50% of cells a few days later. A fourfold or greater increase in IFA titer of paired samples confirms recent exposure.[13]

Pathologic Findings Petechiae and ecchymosis of subcutaneous tissues, and edema of the ventral abdomen, limbs, and prepuce are characteristic in infected animals. Proliferative and necrotizing vasculitis, thromboses, and perivascular cuffing in subcutaneous tissue, fascia, kidneys, heart, brain, lungs, ovaries, and testes have been reported.[1,10]

Treatment, Prognosis, and Prevention The treatment of choice is IV administration of oxytetracycline at 7 mg/kg, or oral administration of doxycycline at 20 mg/kg of body weight once a day for 5 to 7 days. Prompt response to treatment is seen within the first 24 hours. Supportive therapy may be necessary in some cases. The disease can be self-limiting in 2 to 3 weeks if untreated. Prognosis is excellent provided no secondary complications develop. At present, prevention is limited to tick control.

THROMBOCYTOPENIA

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Thrombocytopenia (platelet count < 100,000/μL) can result from one or more of three basic mechanisms: (1) decreased or ineffective platelet production; (2) abnormal sequestration (usually in the spleen); or (3) shortened platelet survival (consumption or destruction). Thrombocytopenia causes a hemorrhagic diathesis characterized by multiple sites of small vessel bleeding. Petechial hemorrhages with or without ecchymotic hemorrhages are generally found on the oral, nasal, or vaginal mucous membranes, as well as on the nictitans and sclera. Epistaxis, melena, hyphema, or microscopic hematuria may occur, but spontaneous hemorrhage is unusual unless the platelet count is less than 10,000/μL. Prolonged bleeding from wounds, injections, or surgical procedures and the propensity to form hematomas after minor trauma are quite common when the platelet count drops below 40,000/μL. The platelet count below which bleeding occurs varies among individuals and seems to be determined by concurrent diseases.

The interaction of blood platelets with a discontinuous vascular surface constitutes the basis for primary hemostasis. In addition, platelets provide the phospholipoprotein surface necessary to catalyze interactions among the activated coagulation proteins that culminate in fibrin formation. The platelet surface also protects activated clotting factors from destruction by plasma anticoagulants, thereby localizing coagulation to the hemostatic plug. Platelets maintain vascular integrity through mechanisms involving immunoreceptor tyrosine activating motif (ITAM) signaling and prevent spontaneous hemorrhage into the skin and mucous membranes. Severe thrombocytopenia produces prolonged bleeding time and abnormal clot retraction without affecting clotting times or plasma fibrinogen.

Persistent life-threatening hemorrhage caused by thrombocytopenia may be treated with a transfusion of compatible fresh whole blood or, preferably, platelet-rich plasma. The latter may be produced by centrifugation thrombocytopheresis[1] or by centrifugation of freshly collected blood, 3 to 5 minutes at 250 *g*.[2] Blood or plasma must be used immediately, and contact with glass must be prevented to avoid platelet adhesion and activation. Platelet transfusion is a very transient life-saving measure, and the ultimate prognosis for thrombocytopenia depends on the cause.

Decreased production of platelets may occur secondary to replacement of the normal marrow architecture by neoplastic or inflammatory tissue (myelophthisic disease) or bone marrow aplasia. Both conditions are characterized by peripheral pancytopenia of variable severity and are extremely unusual in large animals. Myelophthisic disease with thrombocytopenia has been described in horses with various forms of myelogenous neoplasia[3-5] and eosinophilic myeloproliferative disorder.[6]

Hypoplastic anemia with leukopenia and thrombocytopenia has been reported in horses and cattle and is discussed later in the chapter in the section on aplastic anemia. Shortened platelet lifespan is by far the most common cause of thrombocytopenia in large animals. Increased platelet consumption accompanies DIC (discussed in the next section) and rare cases of vasculitis. Immune-mediated mechanisms result in platelet destruction.

Immune-mediated thrombocytopenia (IMTP) may be primary (idiopathic) or secondary to drug administration, infections, neoplasia, or other immunologic disorders.[2] This disease is most common in horses and has been reported secondary to EIA,[7] lymphoma,[8] and autoimmune hemolytic anemia.[9] The clinical signs of IMTP include

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mucosal hemorrhages and the propensity to bleed from small blood vessels. Horses with idiopathic IMTP are usually bright, afebrile, and without overt hemorrhage despite severely reduced platelet numbers. Thrombocytopenia in a horse with obvious primary disease should prompt a thorough hemostatic workup to rule out DIC.

Alloimmune thrombocytopenia of neonates has been recognized as a spontaneous disease of human infants, piglets, foals, and possibly mule foals.[10] Clinical signs include depression, loss of suckle, a bleeding tendency, blood loss, and rapidly developing anemia due to a profound thrombocytopenia. The condition occurs in multiparous dams, and immunoglobulins from the mare, found in her plasma, serum, and milk, bind to the foal's platelets. Alloimmune thrombocytopenia should be considered in neonates with severe thrombocytopenia when other causes can be excluded, and platelet antibody assays should be used to support this diagnosis. Differential considerations include neonatal sepsis, neonatal maladjustment syndrome, and neonatal isoerythrolysis. Laboratory findings of IMTP include severe thrombocytopenia (<40,000/μL), prolonged bleeding time, and abnormal clot retraction with normal thrombin time (TT), PT, APTT, and plasma fibrinogen. Fibrin(ogen) degradation products (FDPs) may be mildly increased, and anemia accompanied by hypoproteinemia develops if there is ongoing blood loss. In most cases of IMTP and other causes for shortened platelet lifespan, megakaryocytic hyperplasia is evident on examination of bone marrow aspirates or biopsies. Megakaryocytic destruction by the immunologic process could induce megakaryocytic hypoplasia, although this is apparently rare in horses. The definitive diagnosis of IMTP requires demonstration of increased quantities of platelet-associated IgG or C3 or antiplatelet activity in the serum. Flow cytometric methods to detect platelet surface–associated IgG (PSAIgG) have been adapted for horses.[11] Without PSAIgG testing, the diagnosis of IMTP must be based on small-vessel hemorrhagic diathesis and severe thrombocytopenia in a horse with normal coagulation times and no other evidence of DIC. Response to therapy (see next section) supports the diagnosis. A tentative diagnosis of IMTP in the horse should prompt a thorough search for an underlying disorder, especially lymphoma.

Platelet destruction in IMTP is apparently mediated by antibodies coating the platelet surface that cause premature platelet removal from circulation by the mononuclear phagocyte system (MPS).[12] In primary IMTP the platelet-associated Ig is directed against a membrane antigen, is usually of the IgG class, is produced in the spleen, fixes complement, and can be absorbed from serum by platelets from a normal individual of the same species. Autoantibodies may attach to megakaryocytes, but the latter are not necessarily destroyed because they do not circulate through the spleen or liver. In secondary IMTP the Ig bound to the platelet surface is part of an immune complex composed of antibody directed against a drug, microbe, or neoplastic antigen that is nonspecifically attached to the platelet Fc receptor. For secondary IMTP to be perpetuated, the foreign antigen must be constantly replenished or difficult to excrete. Drug-induced IMTP generally subsides within a few days of drug discontinuation, although thrombocytopenia secondary to chrysotherapy (gold therapy) may persist for weeks to years. Because gold is occasionally used to treat pemphigus foliaceus in horses, thrombocytopenia should be considered as a potential side effect. The spleen is the major site of platelet phagocytosis because (1) much antiplatelet antibody is secreted locally, (2) more than 30% of circulating platelets are normally stored there, and (3) the stagnant splenic blood flow allows sensitized platelets to pass slowly through a dense network of phagocytic cells. The mean cell life of circulating platelets and the platelet count are inversely proportional to the quantity of platelet-associated IgG.

When any unexplained case of thrombocytopenia is treated, all current medication should be stopped. If a drug is absolutely necessary, it must be replaced by the chemically most dissimilar substitute. Drug-induced IMTP usually responds within 14 days of drug withdrawal. Most animals with suspected IMTP improve when treated with corticosteroids. Although their precise mechanisms of action are speculative, corticosteroids improve capillary integrity, impair clearance by the MPS, decrease the number and avidity of macrophage Fc receptors, impair antiplatelet antibody production, impede platelet-antibody interactions, and increase thrombocytopoiesis.

Dexamethasone (0.04 to 0.2 mg/kg IV or IM) given once daily generally results in an elevation in the platelet count within 4 to 7 days. Once the platelet count is greater than 100,000/μL, the dose of dexamethasone can be reduced by 10% to 20% daily while the platelet count is monitored for a relapse. Occasionally, animals with IMTP are refractory to dexamethasone, in which case prednisolone (0.5-1 mg/kg IM twice daily) may be tried. Treatment with corticosteroids can usually be discontinued after a period of 10 to 21 days, provided the platelet count has been normal for at least 5 days. Most horses with IMTP have a favorable prognosis, and the disease resolves within 14 to 21 days. This suggests that many cases may be secondary, yet the initiating cause is rarely found. Chronic or recurrent IMTP requiring prolonged corticosteroid therapy has been reported.[13] Alternative treatment modalities for IMTP are largely unproven in horses, because most cases are responsive to corticosteroids.[14-16]

DISORDERS OF COAGULATION FACTORS

Johanna L. Watson • Debra Deem Morris

Normal blood coagulation proceeds in an integrated sequence that can be simplistically viewed as three key reactions: formation of activated factor X, formation of thrombin, and formation of fibrin. Other protein interactions serve to accelerate or inhibit the reaction rates of coagulation factors. Excessive use or inhibition of these proteins produces a relative deficiency that causes hemorrhagic diathesis. Alterations in the coagulation cascade, including thrombocytopenia and procoagulant and anticoagulant effects, can be observed with snakebite (e.g., rattlesnake) envenomation (see Chapter 54).

Disseminated Intravascular Coagulation. The most common form of hemostatic dysfunction in large animals is a syndrome known variously as *DIC, consumption coagulopathy, defibrination syndrome,* or *intravascular coagulation fibrinolysis.*[1,2] The pathologic process is characterized by widespread fibrin deposition in the microcirculation (with subsequent ischemic damage) and development of a hemorrhagic diathesis caused by the consumption of procoagulants and hyperactivity of fibrinolysis. Never a primary disease entity, DIC represents an intermediary mechanism of underlying disease. In large animals, DIC has been described in association with forms of localized or systemic septic processes,[2-5] neoplasia,[2] GI disorders,[6] renal disease,[6] and hemolytic anemia.[5,7] Diffuse activation of the hemostatic system is particularly prevalent in horses with acute GI disorders that cause colic[5,6] and is a likely initiating factor for laminitis.[8,9] Because of the dynamic nature of DIC, clinical manifestations may fall anywhere on the spectrum from diffuse thrombosis leading to ischemic organ failure to severe hemorrhagic diathesis. The most important determinants are the rate of thrombin generation (which depends on the triggering disease), the adequacy of fibrinolysis, and the functional state of the MPS, which is largely determined by peripheral circulation. Coagulopathy usually occurs in a compensated form in horses and cattle and is rarely attended by overt hemorrhage; however, microvascular thrombosis and subsequent ischemia to vital tissues leads to organ malfunction (e.g., renal failure), which contributes to the morbidity and mortality of the primary disease process.

Renal involvement is common in DIC, which produces ischemic cortical necrosis followed by acute tubular necrosis. Renal disease may be manifested by oliguria, depression, and ileus caused by azotemia and electrolyte imbalances. GI microthrombosis may induce colic as a result of submucosal necrosis and superficial ulceration. Spontaneous GI hemorrhage caused by DIC may cause melena in ruminants and occult fecal blood loss in horses. Pulmonary function may rarely be compromised by microvascular thrombosis in DIC, causing tachypnea and variable hypoxemia. Altered consciousness, delirium, convulsions, or coma may follow cerebral microvascular thrombosis, although these signs are not common in DIC in large animals. Although reported in both horses[10] and cattle,[7]

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microangiopathic hemolysis is rare in large animals with DIC because of their small erythrocyte size.

Digital ischemia frequently accompanies DIC in horses and may play a role in the development of acute laminitis. Laboratory evidence of DIC has been documented during the developmental phase of equine laminitis,[9] and digital microvascular thrombosis occurs in horses that develop laminitis with colic or septic conditions.[8] The tendency for thrombosis of major peripheral veins is another prominent manifestation of coagulopathy in horses. Venous thrombosis occurs in horses and is associated with needle- or catheter-induced intimal trauma, nonsterility during catheterization, blood sampling or treatment procedures, and thrombogenic catheter materials. However, the strong clinical impression remains that severely ill horses with diseases known to induce coagulopathy have a greater tendency toward venous thrombosis. Spontaneous thrombosis of smaller cutaneous vessels also occurs.

As the thrombotic stimulus continues or intensifies, the tendency for hemorrhage develops because of clotting factors and platelet depletion or generation of excessive fibrinolytic by-products (FDPs). Petechial or ecchymotic hemorrhages on mucosae and sclerae and a tendency to bleed from venipuncture or after minor trauma are the principal signs. Spontaneous life-threatening hemorrhage is very rare, but trauma or surgery may induce uncontrollable hemorrhage. Once signs of blood incoagulability develop, the prognosis is poor.

Horses may develop a chronic compensated form of DIC that is attended by few or no clinical signs. This entity develops in patients with illnesses that produce a low-grade or intermittent procoagulant stimulus that allows used coagulant proteins and platelets to be partially or totally replenished, and activated clotting factors and FDPs to be cleared by the MPS. Localized sepsis (e.g., pleuritis), neoplasia, protein-losing enteropathy, and immune-mediated disorders (vasculitis, anemia) are common initiating diseases. This compensated state may become imbalanced by stress, concurrent diseases, or worsening of the primary process, resulting in clinically obvious DIC. Diseases that must be differentiated from DIC include IMTP, warfarin toxicosis (horses), moldy sweet clover toxicosis, and inherited coagulation abnormalities.

Numerous laboratory tests of hemostasis may be abnormal during DIC, but no one test consistently or specifically provides a definitive diagnosis. Lack of test sensitivity results from the dynamic nature of DIC, the laboratory reflection of which is determined by the balance between coagulation and fibrinolytic forces, as well as MPS integrity at the time of blood sampling.

The most widely used hemostatic function tests in large animals include platelet count, plasma fibrinogen, PT, APTT, and serum FDPs. Because clinical manifestations of DIC vary widely, clarification of the most frequent laboratory abnormalities in large animals with DIC is hindered by lack of a definitive diagnosis in most instances. A disseminated coagulopathy is characterized by multiple hemostatic abnormalities, and serial analyses should reveal reduced platelet numbers and a trend toward prolongation of PT, APTT, and TT. Repeated hemostatic testing is advised when there is strong suspicion for DIC. Serum FDPs are most often elevated by DIC, but they are usually normal in the early or compensated form of the disease. Hypofibrinogenemia is an uncommon manifestation of DIC in large animals and, when present, should strongly suggest concomitant liver dysfunction. Hemostatic function tests are totally unreliable unless blood samples are collected and handled properly.

Criteria used for diagnosis of DIC are extremely arbitrary, and laboratory results must be interpreted in light of the patient's underlying disease. The combination of thrombocytopenia with mild to moderate PT or APTT prolongation strongly suggests DIC. The clinician should seek laboratory assistance when considering the diagnosis of DIC, but appreciate that the findings are often not helpful. Clinical signs and specific situations suggest the possibility of DIC, and laboratory tests are only used to provide support.

Diseases initiate DIC by two major mechanisms: (1) generation of excessive procoagulant activity within the blood or (2) contact of blood with abnormal surfaces. Many diseases act by more than one mechanism to induce the overwhelming stimulus needed to trigger DIC. The nature and intensity of the procoagulant force (which determines the rate of thrombin formation), the concentration of natural coagulation inhibitors, and the functional capacity of the MPS determine whether an individual with a given disease process develops DIC, as well as the clinical manifestations. Many diseases that produce DIC have the propensity to cause endotoxemia. The intestinal tract in large animals normally contains large quantities of endotoxins, only a small part of which is absorbed through the portal vein and removed by the liver. Conditions that cause intestinal mucosal edema or disruption allow endotoxins to gain access to the peripheral circulation and initiate many morbid sequelae, one of which is DIC. Intestinal strangulating obstruction, thromboembolic infarction, and severe colitis induce mucosal abnormalities, allowing endotoxemia to occur. The proliferation of gram-negative bacteria within tissues and the blood is also accompanied by endotoxemia.

Gram-negative endotoxins are capable of direct factor XII activation. However, most studies indicate that the procoagulant effects of endotoxin are primarily mediated by cytokine production by mononuclear phagocytes.[11] After endotoxin stimulation, phagocytes produce a platelet-activating factor (PAF), tissue factor, prostaglandins, interleukins (ILs), tumor necrosis factor (TNF), and other mediators with procoagulant activity.[12]

The net result of any triggering mechanism for DIC is exaggerated generation of systemic thrombin, which causes widespread microcirculatory thrombosis. In addition to the cleavage of fibrinogen to produce fibrin monomers, thrombin activates factor XIII to render fibrin more resistant to fibrinolysis, enhances the cofactor activity of factors V and VIII, and induces platelet aggregation and exposure of platelet phospholipid. Circulatory obstruction produces organ hypoperfusion, leading to ischemic necrosis.

The counterbalance fibrinolytic system is also activated by DIC, and plasmin contributes to factor consumption by destroying factors V, VIII, XIIa, IX, and XI, in addition to fibrin and fibrinogen. FDPs contribute greatly to the hemorrhagic manifestations of DIC because they have antithrombin activity, interfere with fibrin monomer polymerization, and cause platelet dysfunction. Paradoxically the combination of consumption and anticoagulation predisposes to hemorrhage at the same time disseminated thromboses occur.

The MPS plays a vital role in the pathogenesis of DIC. The tissue-fixed macrophages of the spleen and liver normally remove FDPs and activated clotting factors from the peripheral circulation, and FDPs only increase when their rate of formation exceeds the ability of the MPS to clear them. Shock and hypoperfusion of the liver and spleen or diseases associated with excessive tissue debris that must be removed by the MPS (e.g., sepsis, metastatic neoplasia) reduce its ability to function effectively and predispose to or perpetuate DIC.

Therapy for DIC is highly controversial, and the only noncontended modalities are those directed toward identification and treatment of the primary disorder, along with general supportive measures to combat shock and maintain tissue perfusion.[13,14] IV fluid administration helps prevent organ dysfunction after microvascular thrombosis and can correct existing acid-base or electrolyte imbalances. Septic conditions should be treated with appropriate antimicrobial agents, and necrotic tissue or purulent exudate removed whenever possible (e.g., immediate surgical intervention to resect nonviable bowel). Flunixin meglumine mitigates the deleterious effects of endotoxin caused by eicosanoids and is used in horses at a dosage of 0.25 mg/kg IV q8h). Corticosteroids may worsen DIC because they reduce the phagocytic action of the MPS and potentiate the vasoconstrictor effects of catecholamines.

Significant life-threatening hemorrhage is rare in large animals with DIC, but if it occurs, fresh plasma should be administered (15 to 30 mL/kg) to replace used coagulant and anticoagulant proteins. The use of heparin in DIC has been recommended in various regimens to stall the disseminated microvascular thrombosis that precipitates organ failure; there is still controversy regarding its efficacy.[14] In dogs, minidose heparin therapy (50 to 75 units/kg subcutaneously [SC] three times daily, or 5 to 10 units/kg/h) is commonly used with

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blood products to treat DIC.[13] Efficacy of heparin for DIC in horses is unproven. Heparin in all species can predispose to hemorrhage, thrombosis, and thrombocytopenia[15] and causes anemia and erythrocyte agglutination in horses.[16] If heparin therapy is considered, one must ensure there is adequate plasma AT III, which is necessary for heparin action. Because AT III is often depleted by DIC, plasma may be necessary. Clinical trials in humans have not shown therapeutic benefit of anticoagulants in chronic DIC.

The prognosis for DIC in large animals depends largely on the nature and severity of the underlying disease and how effectively the latter is treated. Once DIC has progressed to the stage where signs of blood incoagulability predominate, the prognosis is generally very poor.

Warfarin Toxicosis. Horses may develop a hemorrhagic diathesis due to warfarin toxicosis.[17] This coumarin-derivative anticoagulant is used by some to treat horses with navicular disease.[18] Rarely, horses and other animals may be exposed to coumarins used as rodenticides in grains or other feedstuffs. Therapeutic concentrations of warfarin can have a cumulative toxic effect if the diet is altered to contain less vitamin K or if there is concurrent protein-bound drug therapy. The clinical signs of warfarin toxicosis include hematomas, ecchymoses of mucous membranes, epistaxis, and hematuria. The earliest laboratory indication of warfarin toxicosis is prolongation of the PT, because the plasma half-life of factor VII is shorter than the other clotting factors.[19] As the disease progresses, the APTT becomes prolonged, and the animal may develop blood-loss anemia and hypoproteinemia. The diagnosis of warfarin toxicosis is based on a history of exposure, clinical signs of large-vessel hemorrhagic diathesis, and prolonged PT with or without APTT and with no other abnormalities of the clotting profile.

Warfarin acts through competitive inhibition of vitamin K, which is necessary for liver production of clotting factors II, VII, IX, and X.[18] Factor activity is reduced in the blood at a rate dependent on its individual half-life. In most species, factors VII, IX, X, and XI have increasingly greater half-lives, accounting for the greater sensitivity of PT for the early diagnosis of warfarin toxicosis. After GI absorption, warfarin is highly bound to plasma proteins. Drugs that are normally protein bound (e.g., phenylbutazone, chloral hydrate) can enhance warfarin's toxicity by allowing a greater proportion of the administered drug to be unbound and active.[20] In the same manner, hypoalbuminemia may increase the likelihood of warfarin toxicosis. Corticosteroids and thyroxin can lower the necessary therapeutic dose of warfarin by increasing both receptor affinity and clotting factor catabolism. Drugs that induce hepatic microsomal enzyme activity (e.g., barbiturates, rifampin, chloramphenicol) can accelerate warfarin metabolism and reduce therapeutic response to a given dose. Any reduction in hepatic function or content of vitamin K in the diet can also precipitate warfarin toxicosis.

Treatment of warfarin toxicosis depends on clinical signs. Warfarin therapy should be stopped if the PT exceeds twice the pretherapeutic value. Vitamin K_1 (0.5 to 1 mg/kg SC) must be given every 6 hours until the PT is again normal and stable. Significant hemorrhage can be controlled by giving fresh plasma to provide necessary clotting factors. If the anemia is life threatening, whole blood transfusion should be considered. Although warfarin is eliminated rapidly, some potentiated coumarins have a prolonged half-life, requiring a longer course of vitamin K therapy. With early diagnosis and prompt vitamin K treatment, the prognosis for warfarin toxicosis is good. However, it is imperative that vitamin K_3 *not* be used because it has poor therapeutic action and is highly nephrotoxic for horses.[21]

Prevention of warfarin toxicosis is based on limiting access of livestock to rodenticides and carefully monitoring the therapeutic use of warfarin in horses. Warfarin's benefits for horses are highly controversial, and many question whether its advantages outweigh the risks.

Sweet Clover Toxicosis. Sweet clover (*Melilotus* spp.) toxicosis is caused by ingestion of moldy sweet clover hay or silage containing dicoumarol. Natural coumarins in sweet clover can be converted to dicoumarol when hay or silage is improperly cured and mold forms. The toxin persists in moldy hay or silage and is palatable. This disease can occur in all species but is most commonly seen in cattle fed sweet clover hay in the northern plains states. Early signs include epistaxis and melena, with the development of subcutaneous hematomas and periarticular swellings as the disease progresses. Visible swellings occur at points of trauma such as the brisket, tuber coxae, or carpi and are not hot or painful, although they may cause stiffness and disinclination to move. Accidental and surgical wounds cause severe hemorrhage and may precipitate fatal blood-loss anemia.

Clinical pathology is similar to that described for warfarin toxicosis, with prolonged PT being the earliest abnormality (detected before clinical evidence of hemorrhage). The platelet count remains normal, which differentiates this syndrome from DIC and bracken fern toxicosis. Other diagnostic ruleouts include mycotoxicosis and toxicosis from trichloroethylene-extracted soybean meal. In the absence of fever and anorexia, coagulopathy should make moldy sweet clover toxicosis a strong tentative diagnosis in animals with a history of access. Chemical analysis for dicoumarol in suspected feed or in the blood and liver of affected animals aids in the diagnosis,[22] but the disease cannot be excluded if dicoumarol is not detected.

The pathogenesis of moldy sweet clover toxicosis is identical to that of warfarin toxicosis. Dicoumarol interferes with hepatic synthesis of clotting factors II, VII, IX, and X by inhibiting vitamin K. Usually the syndrome appears in cattle 2 to 7 days after they ingest the moldy hay. Lower levels of dicoumarol (<70 mg/kg) in feed may prolong the onset of signs for up to 3 months.

The succulent nature of sweet clover creates a high incidence of molding in hay. Grazing the crop is not dangerous. Because of its high forage yield, sweet clover is usually harvested as silage, which should carry less danger of molding when properly cured. The toxic level of dicoumarol in sweet clover feed samples is 10 mg/kg of feed.[22]

Treatment of sweet clover toxicosis involves discontinuing the use of contaminated feed and administering vitamin K_1.[20] Dosages between 0.5 and 1 mg/kg of body weight should be administered IM every 6 hours; response occurs within 24 hours. Animals with severe blood-loss anemia or ongoing hemorrhage should be treated with plasma or whole fresh blood. Sweet clover toxicosis can be prevented by careful forage preparation, followed by the inspection of hay and silage before feeding. When the disease is suspected, questionable feed should be removed from the diet.

Diseases Associated with Increased Erythrocyte Destruction (Hemolytic Anemia)

Gary P. Carlson

Hemolytic disorders are characterized by an increased rate of red cell destruction. Anemia results when the rate of red cell destruction exceeds the bone marrow capacity for increased proliferative response. Although intravascular hemolysis occurs in some circumstances, these anemias are primarily due to an increased rate of extravascular erythrocyte destruction and shortened intravascular lifespan.

Hemolytic anemias are associated with a wide range of systemic disease processes. The mechanisms responsible for the enhanced red cell destruction also vary markedly. A list of differential considerations for possible causal factors of hemolytic anemia in large animals is presented in Box 37-1. Clinical manifestations of hemolytic anemia vary with the degree of anemia, rate of red cell destruction, and primary or underlying disease process. However, several common clinical signs are seen in animals with severe hemolytic anemia, regardless of the cause: mucous membrane pallor, fatigue, depression, and anorexia. Clinical icterus can be quite variable depending on the rate of red cell destruction and the liver's ability to excrete bilirubin. Icterus is a characteristic feature in hemolytic anemia, but intense icterus is noted only after massive red cell destruction and is often

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BOX 37-1

Causes of Hemolytic Anemia

Infectious Causes

Parasitic

Anaplasmosis
Babesiosis
Hemobartonellosis
Eperythrozoonosis
Theileriasis
Trypanosomiasis

Bacterial

Leptospirosis
Bacillary hemoglobinuria

Viral

Equine infectious anemia (EIA)

Immune-Mediated Hemolytic Anemia

Autoimmune hemolytic anemia
Neonatal isoerythrolysis (NI)
Drug induced: penicillin, trimethoprim-sulfamethoxazole

Heinz Body Hemolytic Anemia

Phenothiazine toxicity
Wild onion poisoning
Red maple leaf poisoning

Other Causes

Severe cutaneous burns
L-Tryptophan-indole intoxication
Water intoxication
Postparturient hemoglobinuria
Copper poisoning
Hemolytic syndrome in horses with liver failure
Erythropoietic porphyria in Holstein cattle

transient. With continued low-level hemolytic processes, the liver may be able to excrete bilirubin at a rate sufficient to avoid clinical icterus. Hemolytic icterus must be differentiated from other potential causes like liver disease or anorexia in horses. If icterus is caused by hemolytic processes, clear clinical and hematologic evidence of anemia should exist. Massive intravascular hemolysis may result in an orange to reddish discoloration of the mucous membranes. Modest to marked and often variable febrile responses are frequently encountered in hemolytic anemias caused by infectious agents and during periods of active erythrocyte destruction. With advanced anemia the pulse and respiratory rates are elevated at rest. Death losses may occur, and neurologic abnormalities ranging from bizarre behavior to mania, collapse, and death may be associated with handling animals with a severe anemia.

The hematologic manifestations of hemolytic anemia also vary with the rate of red cell destruction, time course of the anemia, and primary or underlying disease process. Anemia may be modest to severe, and after the first few days in all species except the horse, there is usually hematologic evidence of enhanced erythropoietic response seen as increased anisocytosis, polychromasia, reticulocytosis, and the presence of nucleated red blood cells in the circulation. Morphologic abnormalities of diagnostic significance (e.g., intracellular or epicellular parasites, granulocytic inclusion bodies, Heinz bodies, spherocytes, schistocytes, or poikilocytes) may be noted on examination of stained blood smears. Responsive anemias often are accompanied by neutrophilia and a regenerative left shift. Bone marrow usually shows an active erythropoietic response with a decreased myeloid/erythroid (M:E) ratio. The serum concentration of haptoglobin is decreased, and serum lactate dehydrogenase enzyme activity may be elevated during acute hemolytic episodes. An increase in serum bilirubin concentration caused primarily by an increase in indirect reacting bilirubin is a reflection of active red cell destruction. Specific serologic diagnostic procedures are available for many of the infectious causes of hemolytic anemia. Immunohematologic procedures like the direct and indirect Coombs test provide an indication that immune-mediated processes contribute to enhanced erythrocyte destruction. It should be noted that the principal mechanisms responsible for the increased rate of red cell destruction associated with many infectious causes of hemolytic anemia (parasitic, bacterial, viral) are immunologically mediated, and affected animals may be transiently Coombs positive.

Infectious Causes of Hemolytic Anemia

Bovine Anaplasmosis

Guy H. Palmer • Kristin A. Clothier

Definition and Etiology In livestock medicine, *anaplasmosis* traditionally refers to disease characterized by progressive anemia caused by intraerythrocytic infection with *Anaplasma marginale* in cattle and *Anaplasma ovis* in sheep and goats. In addition, a subspecies of *A. marginale, A. marginale* subsp. *centrale* (also referred to as *A. centrale*) causes mild disease in cattle and has been used as a live vaccine to induce partial protection against *A. marginale*.[1,2]

Molecular characterization and genetic analysis of *Anaplasma* and *Ehrlichia* have resulted in identification of six species in the *Anaplasma* genus: *Anaplasma phagocytophilum* (formerly called both *Ehrlichia equi* and *Anaplasma equi*), which infects granulocytes in a wide range of mammalian species including dogs, horses, and humans; *A. marginale, A. ovis,* and *A. centrale,* which infect erythrocytes of wild and domestic ruminants; *Anaplasma bovis,* which infects monocytes of cattle and related species; and *Anaplasma platys,* which primarily affects platelets in small animal species.[2,3,4] Although many species become infected and demonstrate symptoms of disease due to *A. phagocytophilum* infection, there is no evidence *A. marginale* or *A. ovis* are capable of infecting humans or any non-ruminant mammalian species. This discussion primarily addresses bovine and, to a lesser degree, ovine and caprine anaplasmosis.

Clinical Signs and Differential Diagnosis Clinical signs are highly variable, from acute severe disease to subclinical infection, and reflect variation in virulence among pathogen strains, breed resistance, and age-related host susceptibility.[1,6] The typical incubation period ranges from 15 to 30 days. Primary exposure in calfhood often produces asymptomatic or mild clinical disease resulting in slight lethargy and anorexia for 24 to 48 hours. In contrast, acute anaplasmosis in adult cattle is typified by fever with rectal temperatures ranging from 39.5° to 41°C (103° to 106°F). Within 12 to 24 hours the fever subsides, and the temperature may become subnormal before the animal dies. Anorexia, lethargy, and in dairy cows, a dramatic decrease in milk production are often observed. Concurrently there is suppression of rumination, dryness of the muzzle, and lethargy. Cattle may stagger or become aggressive as a result of cerebral hypoxia associated with anemia. Care must be taken not to stress severely anemic cattle, since this may result in collapse and death. Mucous membranes are pallid, or icteric if an animal has survived for 2 to 3 days past the acute crisis. Additional clinical signs include constipation characterized by dark brown feces covered with mucus, pollakiuria with dark yellow urine, and abortion in late-gestation animals. Hemoglobinuria does not occur. If an animal survives the acute crisis, the convalescent period is protracted (3 to 4 weeks) depending on the severity of the anemia, and icterus and weight loss are common. Recovered animals remain infected for life and serve as a reservoir for ongoing transmission. Persistent infection is not associated with any disease or decrease in production status, so there is no basis for the diagnosis of "chronic anaplasmosis." Although *A. ovis* infection in sheep and goats is often asymptomatic, anemia occasionally becomes severe enough to produce signs similar to those seen during *A. marginale* infection of cattle.

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Definitive diagnosis of acute anaplasmosis requires identification of *A. marginale*– or *A. ovis*–infected erythrocytes by microscopic examination of blood smears, concomitant with a significant decrease in hematocrit (see Clinical Pathology and Serology). Differential diagnoses include diseases that can produce anemia and/or icterus (babesiosis, bacillary hemoglobinuria, leptospirosis); hepatotoxic plant poisonings *(Senecio),* chemicals, and other causes of liver disease; and copper poisoning in sheep.

Clinical Pathology and Serology Because acute bovine anaplasmosis is characterized by anemia, a falling hematocrit provides an estimate of the severity of infection. PCV may drop precipitously within 24 to 48 hours. Death can occur during this period despite a PCV above 20%. In other cases, the PCV may decrease below 10% before death. During this acute phase, *A. marginale* can be detected within the erythrocytes by microscopic examination of blood smears stained with Wright's, new methylene blue, or Giemsa stain. The inclusion is composed of a small morula of 2 to 8 individual organisms, and over 5% (as many as 20% to 70%) of erythrocytes may be infected. After several days of anemia the percentage of infected erythrocytes decreases dramatically, and evidence of erythrocyte regeneration can be detected. Blood smears demonstrate anisocytosis, basophilic stippling, poikilocytosis, polychromatophilia, and reticulocytosis.

Following recovery from acute disease, cattle and sheep remain persistently infected with 0.000001% to 0.1% of erythrocytes affected. Detection of organisms in erythrocytes at this stage is unreliable; persistently infected animals that serve as reservoirs for transmission have to be detected serologically. Serologic diagnosis is most commonly by competitive enzyme-linked immunosorbent assay (cELISA [VMRD Inc., Pullman, Wash.]), which provides both high specificity and, unlike the complement fixation (CF) test, high sensitivity in detecting persistently infected carrier cattle.[1,5] The cELISA test, approved as an official test by the USDA and the Office of International Epizootics (OIE), is conducted by most if not all state diagnostic laboratories. Currently, negative status with the cELISA is required for importation of live cattle into Canada. Although cattle will seroconvert by cELISA during acute infection, organism-based assays, including PCR, are more reliable for diagnosing acute anaplasmosis.[1]

Pathophysiology *Anaplasma* spp. are naturally transmitted by ixodid species ticks, most commonly *Dermacentor* in the U.S. mainland and *Rhipicephalus* spp. (including tick species previously classified in the genus *Boophilus*) in tropical and subtropical regions worldwide. Organisms can be transmitted transstadially (from larvae to nymphs and nymphs to adults), indicating that ticks can become infective and transfer *Anaplasma* spp. to a new host after only a single molt.[2] Direct mechanical transfer of infected erythrocytes by biting flies, as well as iatrogenic spread through management practices (contaminated needles, dehorning, castrating, hormone implanting, and ear tagging instruments), can result in transmission.[1,2] Bacteria replicate within parasitophorous vesicles in the red blood cells; similar invasion mechanisms are used within tick cells to propagate infection.[6] Sequential rounds of bacterial invasion of mature erythrocytes, replication, and egress result in a progressively increasing cell-associated bacteremia, with a doubling time of roughly 24 hours. Depending on the strain of *Anaplasma* and host susceptibility, 10% to 90% of erythrocytes may become infected; clinical signs appear when over 15% of erythrocytes are infected.[1,6] Anemia is due to splenic and hepatic macrophage-mediated phagocytosis of both infected and uninfected erythrocytes, reflecting induction of autoantibodies against the erythrocyte surface, as well as activation of acute-phase reactants, including complement activation, during high-level rickettsemia. The regenerative response to anemia can be vigorous and does not appear to be suppressed by the infection.

Protective immunity appears to require induction of both antibody against the outer membrane proteins and macrophage activation for enhanced phagocytosis and bacterial killing.[7,8] Although the immune response controls the acute phase of infection, organisms are not completely cleared from the blood, owing to emergence of antigenic variants.[8] These variants are responsible for persistent infection, characterized by recurring waves of bacteremia that reflect sequential emergence and then immune control of antigenically variant organisms.

Epidemiology *A. marginale* is the most prevalent of the tick-borne diseases of cattle worldwide and remains as a serious constraint to livestock production in tropical, subtropical, and even temperate regions. In the United States, infection is endemic in much of the West and occurs episodically in at least 40 states, but Canada is considered to be free of widespread anaplasmosis. Endemic regions are maintained by the prevalence of both competent arthropod vectors and persistently infected carrier cattle. These carrier cattle, which are typically asymptomatic, are efficient reservoirs for tick-borne transmission.[1,2,8] Vector activity varies by region, but outbreaks of anaplasmosis occur most frequently in the late spring and summer when arthropod activity is highest. In contrast, iatrogenic transmission can occur anytime and can be controlled by avoiding blood contamination during veterinary medical procedures. Although wild ruminants (deer, elk, bison) rarely have clinical disease and are generally asymptomatic persistently infected carriers, their overall importance in the epidemiology of infection is unclear. Currently, wild ruminants are thought to play at most only a minor role in natural transmission.

Pathology At necropsy, there are no pathognomonic lesions for the diagnosis of disease. In acute anaplasmosis the blood is thin, watery, and fails to clot readily. Mucous membranes, subcutaneous tissues, and skeletal musculature are pale; in later stages of acute disease, the same tissues may be icteric. Splenomegaly is a consistent finding; hepatomegaly and gallbladder distention are commonly but less frequently observed. Urine is deep yellow, but neither hemoglobinuria nor hematuria occurs, which helps differentiate anaplasmosis from other hemolytic diseases (babesiosis, bacillary hemoglobinuria, leptospirosis, onion toxicity, copper poisoning in sheep). Occasionally petechiae may be found in the subepicardium, subendocardium, and other serous membranes. Detection of *A. marginale*–infected erythrocytes within capillaries of Giemsa-stained histologic sections can be used to confirm a diagnosis of anaplasmosis.

Treatment Tetracyclines are the antibiotic of choice for treating acute disease, and therapy is aimed at minimizing or preventing the effects of *A. marginale* infection; however, treatment does not eliminate persistent infection.[1,9] In acute anaplasmosis, oxytetracycline 11 mg/kg IV q24h for 3 to 5 days may be effective. One to two administrations of long-acting oxytetracycline at 20 mg/kg IM at 72-hour intervals is an alternative treatment regimen. In addition to antibiotic therapy, supportive therapy is important to maximize the chance of survival. If the PCV is 12% or below, whole blood transfusion (4 to 8 L) may be indicated to prevent death and shorten the convalescence period. A PCV of 8% or below indicates an unfavorable prognosis, and death often occurs despite appropriate antibiotic and supportive therapy. Evaluations of a variety of chemical compounds and treatment regimens have determined that chemosterilization for *A. marginale* infection is rarely successful.[1,10] If required for exportation, clearance should be confirmed by conversion to seronegative status.

Prevention and Control The control measures used vary depending on the geographic region and type of livestock production system. In endemic regions with high transmission rates, beef cattle are often allowed to become naturally infected at a young age and remain asymptomatic carriers with minimal risk of later acute disease. In regions with lower transmission rates, live blood-based vaccines may be used to ensure infection of cattle at a young age. This is exemplified by the use of trivalent *(A. marginale, Babesia bovis, Babesia bigemina)* live vaccine in Australia. Similarly, live vaccines

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TABLE 37-1

Babesia Species (Babesiosis)

Organism	Livestock Affected	Principal Geographic Distribution	Morphology of Organism	Tick Vectors
B. bigemina (B. bovis)	Cattle	Americas, Europe, Africa, Australia, Middle East	4.5 × 2.5 µm (large, round, and pyriform; acute angle)	*Boophilus annulatus, B. decoloratus, B. microplus* spp.
B. bovis (B. berbera, B. argentina)	Cattle	Americas, Europe, Russia, Africa, Asia, Australia	2.4 × 1.5 µm (small and more rounded; obtuse angle)	*B. annulatus, B. microplus, Ixodes* spp.*
B. divergens	Cattle	Europe	1.5 × 1.4 µm (small, narrow, and obtuse angle)	*Ixodes ricinus*
B. major	Cattle	Europe, Russia, North Africa, Middle East	2.6 × 1.5 µm (similar to *B. bigemina* but smaller)	*Haemaphysalis punctata*
B. jakimovi	Cattle	Asia	2-4.6 × 1.5-2.1 µm (large, round, and pyriform)	*I. ricinus*
B. ovate	Cattle	Japan	4.5 × 2.5 µm (large, round, and pyriform)	*Haemaphysalis longicornis*
B. caballi	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	3 × 2 µm (large, pyriform; acute angle)	*Dermacentor, Hyalomma, Rhipicephalus* spp.
Theileria equi (B. equi)	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	1-2 µm (small and rounded; Maltese cross is characteristic)	*Dermacentor, Hyalomma, Rhipicephalus* spp.
B. motasi	Sheep and goats	Europe, Russia, Asia, Middle East	3 × 2 µm (large, pyriform; acute angle)	*D. silvarum* (?), *Haemaphysalis* spp., *R. bursa*
B. ovis	Sheep and goats	Europe, Russia, Asia, Middle East	1.5 × 1 µm (small and more rounded; obtuse)	*I. ricinus* (?), *R. bursa, D. reticulatis* (?)
B. trautmanni	Swine	Europe, Africa, Russia	3.5 × 2 µm (large, narrow, and long; acute angle)	*R. sanguineus* (?), *Dermacentor* spp. (?) *Boophilus* spp. (?) *Hyalomma* spp. (?)
B. perroncitoi	Swine	Europe, Africa, Asia	0.7-2 µm (small and more rounded)	Vectors unknown

*Suspected vector.

From Kuttler KL. 1984. Foreign animal diseases, p 77. United States Animal Health Association, Richmond, VA.

based on *A. centrale* or weakly virulent strains of *A. marginale* are commonly used in Africa, Asia, and Central and South America. However, these are not licensed for use in the United States, largely because of the risk of transmitting known or newly emergent pathogens contaminating the blood-based vaccine. The exception to this is the licensing of a live vaccine for use in California (AnaVac [PHL Associates, Davis, Calif.]). Importantly, these live vaccines should only be used in young animals and are contraindicated for pregnant and older animals. Killed vaccines are less efficacious and require multiple immunizations but can induce at least partial protection against severe morbidity and mortality. Unfortunately, none of the federally licensed killed vaccines previously marketed in the United States is currently available. However, an experimental killed vaccine (Experimental Anaplasmosis Vaccine [University Products LLC, Baton Rouge, La.) has been licensed for use in 14 states and Puerto Rico. In the absence of immunoprophylaxis, anaplasmosis is usually controlled by preventing transmission. While it is difficult to absolutely prevent the contact of ticks and biting flies with cattle grazing on open ranges or farm pastures, strategic use of acaricides and insecticides can reduce transmission during periods of high vector activity. Periodic spraying for tick control and the use of insecticide-impregnated ear tags or insecticide dust bags for biting fly control are cost-effective for controlling both anaplasmosis and pinkeye and directly reduce irritation and increase weight gain. Appropriate sanitary measures to prevent mechanical transmission should be implemented when injections or surgical procedures are performed.

Maintenance of an *A. marginale*–free herd in nonendemic areas can be accomplished by quarantine and serologic screening of all additions using the USDA-approved cELISA. Control within endemic regions requires extreme vigilance in screening and prevention of both direct contact and sharing pasture with other domestic and wild ruminants that may result in vector-borne transmission. The risk of maintaining a fully susceptible herd within an endemic region should not be taken lightly.

Babesiosis

Jerry L. Zaugg

Babesiosis is a tick-borne intraerythrocytic disease of domestic and wild mammals and humans caused by protozoan parasites of the genera *Babesia* and *Theileria*. The acute disease is characterized by fever, hemolytic anemia, icterus, hemoglobinuria, and death. Although both morphologic and serologic differentiation is required for specific identification of the various disease-producing species, all can be categorized as being either "large" or "small" in size. A list of the commonly encountered *Babesia* spp., *Theileria equi,* their usual biological vectors, and livestock hosts is presented in Table 37-1. Babesiosis has a wide geographic distribution, particularly in the tropics and subtropics, largely related to the distribution of vector ticks. Of the different diseases, the economically most important infections of livestock are those of cattle and horses.

BABESIOSIS IN THE BOVINE

Etiology Known variously by such names as *bovine babesiosis, piroplasmosis, Texas fever, redwater, tick fever,* and *tristeza,* the disease may be caused by at least six *Babesia* spp. (see Table 37-1). Some animals other than cattle known to be susceptible to agents of bovine babesiosis include white-tailed deer, American bison, water buffalo, reindeer, and the African buffalo. Infections in these species are nominal, and except under unusual conditions, such hosts are probably not significant reservoirs.

Of greatest concern in the western hemisphere are *Babesia bigemina* and *Babesia bovis. B. bigemina* is a large *Babesia* characteristically appearing within mature erythrocytes as nonpigmented, paired, pear-shaped bodies joined at an acute angle. Irregularly shaped, round, or amoeboid forms are also seen. *B. bovis* is a small, pleomorphic *Babesia* often identified as a single round body or as paired pear-shaped bodies joined at an obtuse angle within mature erythrocytes. Of the two species, *B. bovis* is usually considered the most virulent.

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Natural transmission of both species occurs primarily by the feeding of various stages of the one-host ticks of the genus *Boophilus*. Ticks are most commonly infected transovarially (vertically). The female tick becomes infected by the ingestion of parasites during engorgement. After it drops off the host, the babesial organisms reproduce within the tick's tissues. Some of the reproducing organisms are incorporated within developing tick embryos, and the disease agents are transmitted to new vertebrate hosts by the feeding of ensuing tick larvae, nymphs, or adults. Larval ticks may transmit *B. bovis,* but *B. bigemina* is not transmitted until the larvae have molted into the nymphal or adult stages. Both *Babesia* spp. may also be transmitted iatrogenically through blood-contaminated fomites as described under anaplasmosis.

Clinical Signs Clinical signs manifest 2 to 3 weeks after tick infestation. The incubation period following blood inoculation may be less than 5 days to more than 3 weeks, depending on the volume of inoculum. Clinical signs of fever (40° to 42°C [104° to 107.6°F]), depression, icterus, anorexia, tachycardia, tachypnea, anemia, hemoglobinemia, hemoglobinuria, abortion, and death are seen. Anemia is caused by intravascular destruction of erythrocytes by escaping merozoites following intraerythrocytic reproduction of the babesias by binary fission. In addition, the osmotic fragility of the whole erythrocyte population increases terminally, such that massive lysis occurs even though the parasitemia may be less than 1%.[1] Additionally, as also seen with anaplasmosis, an autoimmune condition may result in which the spleen removes damaged and apparently healthy erythrocytes from circulation. Thus the degree of anemia may exceed that expected with a low parasitemia. Anemia may occur very rapidly, with 75% or more of erythrocytes destroyed in just a few days. The exit of *B. bigemina* and *B. bovis* parasites from infected erythrocytes releases two or more parasite-associated proteolytic enzymes into the plasma. These enzymes and other parasite metabolic products are believed to interact with blood components and are responsible for such clinical signs as metabolic acidosis and anoxia. Tachycardia may be dramatic and heart sounds pronounced.

Cerebral babesiosis, characterized by hyperexcitability, convulsions, opisthotonos, coma, and death, may be observed in cattle infected with either *B. bigemina* or *B. bovis,* but especially with the latter. Central nervous system (CNS) signs are due to brain anoxia resulting from severe anemia and/or erythrocyte blockage of cerebral capillaries.

Death is caused by a shock-like syndrome associated with the accumulation of toxins, release of vasoactive substances, and anemic anoxia. Most cases with cerebral involvement are fatal, but mortality is extremely variable and depends on the *Babesia* strain, host susceptibility, and management and environmental stress factors. Many cattle that survive the acute phase recover but become chronic carriers. Other survivors often experience episodes of recrudescence, eventually succumbing to the disease, or they may die from secondary infections contracted during their debilitated state.

Cattle of all breeds are susceptible to babesiosis, but *Bos indicus* breeds exhibit a definite degree of resistance to both *B. bigemina* and *B. bovis* and the tick vectors.[2] Calves possess a natural immunity to babesiosis. Such immunity was believed to be reinforced by colostral antibodies for calves born to previously infected dams.[3] However, erythrocytes of young bovines may contain factor(s) independent of antibody that provide an innate resistance to severe babesiosis.[4] Thus calves infected up to the age of 9 months experience a minimum reaction to the disease, becoming asymptomatic carriers. Carriers remain resistant to clinical disease for at least 4 years.[5] The carrier state can be overcome, however, by such stresses as calving, malnutrition, or concurrent disease.[6]

Clinical Pathology Clinical signs observed in cattle located in enzootic areas where *Boophilus* ticks occur may provide sufficient data for a presumptive diagnosis. Other conditions that may exhibit some of the same signs as babesiosis are anaplasmosis, trypanosomiasis, theileriosis, leptospirosis, chronic copper toxicity, and bacillary hemoglobinuria. The cerebral signs may be confused with rabies and other encephalitides. A positive diagnosis requires identification of *Babesia* on Giemsa-stained thin blood smears, positive serologic tests, or inoculation of splenectomized calves with infective blood. In acute infection, *Babesia* spp. can usually be detected in smears made from peripheral blood. In chronic cases the numbers of parasitized erythrocytes diminish, becoming so sparse as to make detection difficult. This is especially true with *B. bovis,* which shows a marked tendency to accumulate in capillaries, particularly those of the brain. *B. bovis* may favor capillaries in the brain and kidney because the major energy-producing pathway of *Babesia* appears to be anaerobic glycolysis. The blockage of cerebral and renal capillaries by parasitized erythrocytes results in an anaerobic condition that enables the parasites to absorb preformed substrates by pinocytosis and diffusion through their surface membranes. PCV values drop rapidly from a normal of 35% to below 10% in less than a week after the onset of clinical signs.[7] Serum potassium levels decrease in some infected animals, whereas urine potassium levels increase in nearly all cases.[8]

Specific anti-*Babesia* antibodies are detectable in cattle sera in fewer than 7 days following infection.[9] Such antibodies also exist for at least 252 days after the disappearance of detectable parasites.[10] The CF and IFA tests are the most widely used.[9,11] The CF test follows the same basic procedure used in anaplasmosis CF testing,[11] but with a *Babesia* antigen.[12] The test is effective, but about 100 days after infection, CF antibodies drop below a reliable diagnostic level.[9] The IFA test uses the whole intraerythrocytic parasite as antigen rather than an extract, and commercially prepared rabbit antibovine γ-globulin conjugated to fluorescein.[9] Other serologic tests include gel precipitation,[13] latex particle agglutination,[14] rapid card agglutination,[15] and enzyme-labeling immunoassay (EIA).[16] It should be noted that the immunologic assays are indirect methods and do not detect the causal organisms in samples obtained from a suspected infected animal. Recombinant DNA techniques using selected clones containing inserts of *Babesia* genomic DNA sequences are now available to be utilized as specific, highly sensitive DNA or RNA probes to detect the presence of the hemoparasite DNA in an infected animal or tick vector.[17]

Necropsy Findings Postmortem findings in cattle that die peracutely are characteristic of an acute hemolytic crisis. Such findings include a generalized pallor or icterus throughout the carcass; an enlarged icteric liver; gallbladder distended with thick, dark green bile; and a markedly enlarged dark, soft spleen. Hydropericardium and subepicardial/subendocardial petechiation may be seen. The blood is thin and watery. The urinary bladder is frequently distended with dark red urine. There may be subserosal ecchymotic hemorrhages in abomasal and intestinal mucosa, and the lymph nodes are edematous. The carcass of an animal that dies after a prolonged illness is generally emaciated and icteric. The blood is thin and watery, and the intermuscular fascia is edematous. The kidneys are pale and edematous, and the bladder may contain pink-tinged or normal urine. The liver is enlarged and jaundiced, and the bile may contain flakes of semisolid material.

Treatment and Prognosis After the onset of hemoglobinuria or cerebral signs, the prognosis is poor. Acute cases with PCV values above 12% usually respond well to treatment. The prognosis decreases for cases with PCV values below 10%. Successful treatment depends on early diagnosis and prompt therapy. In addition to specific treatment, supportive therapy such as blood transfusions (4 L of whole blood per 250 kg of body weight), fluids, hematinics, and prophylactic antibiotics are important. However, wild excitable cattle may best be left alone. With severe hemolytic anemias, any exertion associated with restraint and treatment may precipitate an anoxic crisis.

The small *Babesia* spp. are more resistant to chemotherapy and may require increased dosages or additional treatments. The

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most commonly used, effective, and relatively less toxic specific babesiacides are diminazene diacturate (Berenil [Intervet Inc., St. Millsboro, Del.] or Ganeseg [Squibb & Sons de Mexico, Mexico City]) at 3 to 5 mg/kg; phenamidine diisethionate (Lomidine [May and Baker Ltd., Dagenham, England]) at 8 to 13 mg/kg; imidocarb dipropionate (Imizol [Pittman-Moore, Middlesex, England]) at 1 to 3 mg/kg; and amicarbalide diisethionate (Diampron [May and Baker Ltd., Dagenham, England]) at 5 to 10 mg/kg.[18] Generally, treated cattle become chronic carriers and are resistant to further clinical episodes of the disease. However, treatment of *B. bigemina* may be so effective that sterilization occurs, eventually leaving the animal susceptible to reinfection. Imidocarb has both therapeutic and prophylactic activities. In enzootic areas its use prevents clinical infection for as long as 2 months, but at the same time allows mild subclinical infections to occur, resulting in premunition immunity.[19,20]

Prevention and Control Eradication of *Boophilus* tick vectors has provided effective control in the United States. Other such projects attempted elsewhere have not been successful owing to such diverse reasons as tick resistance to acaricides, ability of some ticks to infest alternate non-bovine hosts, failure to obtain 100% cooperation of cattle producers, and lack of financial resources to sustain a prolonged program.

Most procedures aimed at reducing tick infestations (i.e., acaricide applications [on host or over environment], controlled range burning, cultivation, prolonged pasture rest, and use of repellents) are beneficial. Care should be taken to prevent accidental transfer of blood from one animal to another in routine surgery (e.g., dehorning, castration, ear marking, hormone implanting) and vaccination procedures.

The most common form of immunization consists of inoculating live organisms (virulent or attenuated) into susceptible calves to induce a state of premunition. Inoculation of older animals is followed by nonsterilizing chemotherapy as needed to modify clinical effects.[21] Although a premunition approach is useful in endemic areas, it is less desirable in areas with low infection rates, because the premunized carriers provide a large reservoir of infection. In vitro cell cultivation techniques have yielded highly immunogenic soluble antigens of *B. bovis*. Subunit vaccines were proven effective in protecting against severe clinical disease.[22,23] Subunit vaccines may not prevent disease, but they may moderate the effects of infection and do not directly produce carriers.

BABESIOSIS IN THE HORSE

Etiology Babesiosis/theileriosis of the horse (piroplasmosis) is a febrile tick-borne disease of equids caused by *Babesia caballi* and *Theileria equi*. Until recently *T. equi* was known as *Babesia equi,* but because the organism more closely resembles members of the genus *Theileria,* with its exoerythrocytic (lymphocytic) stages within the vertebrate host and development of microschizonts and macroschizonts, it is now classified as *T. equi*[24] (see Table 37-1). *B. caballi* is a large *Babesia* resembling *B. bigemina,* which affects cattle. Although *T. equi* is not a member of the genus *Babesia,* for practical purposes it is still considered a "small" parasite somewhat like *B. bovis* in stained thin blood smears. However, a unique characteristic of *T. equi* is that the intraerythrocytic parasites divide into four cells to form a Maltese cross.[25]

Equine piroplasmosis is widely distributed throughout the tropics and subtropics and to a lesser extent in temperate regions. The distribution roughly corresponds to those of the tick vectors. Both species are naturally transmitted by ticks of the genera *Dermacentor, Hyalomma,* and *Rhipicephalus. B. caballi* is passed transovarially (vertically) from one tick generation to the next. Transmission of *T. equi* apparently only occurs transstadially (horizontally); that is, one tick stage (larvae or nymphs) becomes infected, and the disease agent is passed to the next vertebrate host in the next tick stage (nymph or adult). Because of the widespread prevalence of potential tick vectors in the United States *(Dermacentor albipictus, Dermacentor ieus, Dermacentor variablis),* equine piroplasmosis could become a problem in the United States at any time.

Clinical Signs Apparently, all equids are susceptible to both parasite species. The zebra in Africa is naturally infected with *T. equi* but not with *B. caballi*. Once infected, survivors remain chronic carriers. At least *T. equi* can be transmitted transplacentally. Clinical features following an incubation period of 5 to 28 days are fever (39° to 42° C [102° to 107.6° F]), hemolytic anemia, jaundice, hemoglobinuria, and death. Generalized signs of depression, anorexia, incoordination, lacrimation, mucous nasal discharge, swelling of the eyelids, and frequent lying down are seen. *T. equi* is considered the most pathogenic of the two species and is responsible for a greater incidence of hemoglobinuria and death. *B. caballi* causes a more persistent fever and anemia. Differential diagnoses include equine monocytic ehrlichiosis, EIA, liver failure with hemolytic anemia, and other hemolytic anemias of the horse.

Clinical Pathology A fever associated with anemia, jaundice, and hemoglobinuria, with the detection of parasite-infected erythrocytes in Geimsa-stained blood smears, is diagnostic. A significant increase in relative and absolute numbers of monocytes and absence of eosinophils may be observed in horses infected with *T. equi*. Hemoglobinuria is rare in animals infected with *B. caballi,* but urine is often dark yellow in color. The official testing method is the cELISA test. There is also a PCR test for both equine diseases. As with the bovine infections, both *B. caballi* and *T. equi* infections can be specifically detected with nucleic acid probes.[17]

Necropsy Postmortem features are similar to those seen in bovine babesiosis, but jaundice is even more prominent throughout the carcass. There is excessive fluid in the body cavities, especially the pericardial sac. Pulmonary edema is evident. The liver is swollen, and hepatic vessels contain large yellowish clots. The spleen in enlarged, with rounded edges.

Treatment and Prognosis Generally both *B. caballi* and *T. equi* respond to the same babesiacidal drugs used to treat bovine babesiosis, but *T. equi* is more refractory to treatment than *B. caballi*. If diagnosed early and treated promptly, recovery is the rule. The drug of choice for eliminating the carrier state of infected animals is imidocarb. Imidocarb at the level of 2.2 mg/kg given two times in 24 hours is effective against *B. caballi*. A 4-mg/kg dose given four times over 72 hours is effective against *T. equi* of eastern hemisphere origin.[26] However, donkeys receiving similar treatment died from drug toxicosis.[26] The higher doses of imidocarb often produce transient colic in horses. To date, attempts to consistently eliminate the carrier state of *T. equi* of Eastern European origin have been unsuccessful.[27] However, an earlier proposal[28] suggested that irregular chemical sterilization success could be obtained with concurrent IV administration of buparvaquone (Butalex [Coopers Animal Health Ltd., Hertfordshire, U.K.]) at 4 mg/kg and IM imidocarb at 4 mg/kg.

Prevention and Control Control of tick infestations does much to reduce disease incidence, as does care to prevent blood transfer during such routine surgical procedures as castration. No vaccines effectively prevent equine babesiosis. Although premunition as used in bovine babesiosis is of limited value in some enzootic areas, it is not widely practiced. This is because early treatment without sterilization is effective, and the resulting chronic carriers resist further disease challenge.

Haemobartonellosis (Eperythrozoonosis)

Gary P. Carlson

Haemobartonella bovis is an epicellular organism closely associated with the surface of erythrocytes. It may appear as a rod shape, an ovoid, or in chains with conventional stains. Haemobartonellosis is

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primarily of academic interest in North America; it is rarely a cause of anemia. The organism has been found in association with other rickettsial diseases and has been experimentally transmitted in splenectomized calves. The agent may be visualized as delicate ovoid, rod, or dumbbell forms arranged in chains or tight groups or randomly distributed epicellularly throughout appropriately stained blood smears.

EPERYTHROZOONOSIS IN CATTLE. The causal agent is *Eperythrozoon wenyonii (Mycoplasma wenyonii).* Infection is usually latent, producing no clinical signs in normal cattle, but it may become apparent in animals that have been severely stressed by some other systemic disease. The disease can be produced experimentally if infected blood is administered to splenectomized calves. Even under experimental circumstances, clinical signs consist of mild depression, fever, and modest anemia. The disease in cattle is of little clinical consequence except for the potential for confusion should the organism be seen on stained blood films. Occasionally cattle may have swollen and tender teats and legs.[1]

EPERYTHROZOONOSIS IN SHEEP AND GOATS. The causal organism in sheep and goats is *Mycoplasma ovis (Eperythrozoon ovis),* which appears to be very similar morphologically and serologically to that found in cattle. The disease can produce more prominent clinical signs in sheep, with profound depression, anemia, and significant death losses in young lambs.[2] Red cell destruction is thought to be caused by intravascular hemolysis and erythrophagocytosis.

Theileriasis

Gary P. Carlson

Theileriasis is caused by a small hemoparasite of the genus *Theileria* that infects lymphocytes and erythrocytes of ruminants and is most common in tropical and subtropical climates. The organism is spread by bloodsucking arthropods, particularly ticks of the Ixodidae family. *Theileria parva* is the cause of East Coast Fever, a highly fatal disease of cattle in Africa. Other members of the genus *Theileria* (spp. *annulata, mutans, hirci,* and *ovis*) tend to be less pathogenic and produce diseases with a wider geographic distribution.[2] *Theileria cervi* has been seen in North American deer. *Theileria mutans* has been seen in erythrocytes of both cattle and deer in North America. Theileriosis due to an agent indistinguishable from *Theileria buffeli* has been described in cattle from Texas and North Carolina with parasitemia, but clinical signs were not reported.[3] Recently *T. buffeli* was reported as the cause of hemolytic anemia in a 6-month-old Simmental calf.[4] There was serologic evidence of a high herd prevalence of *Theileria* infection, and the agent was transmitted to splemectomized calves that developed mild anemia. The organism produces a brief illness characterized by mild fever, anorexia, and modest anemia, followed by rapid recovery.

Trypanosomiasis

Gary P. Carlson

Trypanosomes are flagellated protozoal organisms that can produce a variety of serious diseases of humans and animals, although many are nonpathogenic. Nagana, a disease of cattle in Africa, is caused by *Trypanosoma congolensi. Trypanosoma evansi* is the cause of Surra, a disease of cattle in India, and *Trypanosoma equiperdium* produces Dourine in horses. In North America, *Trypanosoma theileri (Trypanosoma americanum)* is the only agent reported and is principally of academic interest, since it is relatively nonpathogenic. On stained blood films from cattle, small numbers of the organism can occasionally be seen free in plasma, appearing as large flagellated protozoa with undulating membranes.[30] *Trypanosoma* is best visualized in buffy coat smears, which tend to concentrate it. *T. theileri* rarely produces clinical signs, but occasionally a fulminating parasitemia may develop, resulting in fever, depression, and decreased milk production.

Leptospirosis

Gary P. Carlson

Leptospira infections produce disease in several species including cattle, sheep, swine, horses, dogs, and humans, but the acute hemolytic syndrome associated with these infections is seen most commonly in calves and lambs. *Leptospira interrogans* serovars *pomona* and *icterohaemorrhagiae* are the serotypes usually involved in the hemolytic syndrome. Clinical signs of the hemolytic syndrome vary but generally include fever, lethargy, icterus, anemia, and petechial hemorrhages. The anemia is brought about at least in part by immune-mediated mechanisms. Cold-reacting IgM antibodies have been implicated in the hemolytic anemia seen in lambs. The degree of anemia is variable but can be severe, with evidence of erythropoietic response apparent in the peripheral blood within 4 to 7 days. A moderate leukocytosis and elevation in plasma fibrinogen are often associated with the hemolytic anemia. The diagnosis is generally made on the basis of demonstration of the organism in the urine, PCR, and an increase in serum antibody titer. Discussion of leptospirosis as a reproductive, renal, and ocular problem can be found in other chapters.

Equine Leptospirosis

Monica Aleman

Leptospirosis is a bacterial zoonotic disease that is prevalent worldwide.[1] The organism can be readily transmitted between mammalian species (cattle, pigs, horses, dogs, and humans) through infected urine, body fluids, and contaminated soil or water.[2] In horses from North America, infections are primarily caused by *Leptospira pomona kennewicki*.[3] There are various maintenance hosts for this serovar, with the skunk being the most common host. *Leptospira bratislava* has been considered to be the host-adapted serovar of the horse, but this has been controversial. Some researchers believe this serovar is also pathogenic to the horse, and when infected, the organism can be shed indefinitely in urine and possibly the reproductive tract.[3]

L. pomona can cause uveitis, placentitis, abortion, stillbirth, renal disease, and hemolysis. Clinical signs include fever, jaundice, anorexia, and lethargy. Leptospirosis is a sporadic cause of abortions; in endemic areas it may account for 13% of bacterial abortions.[4] In general, abortions occur during late-term gestation. The organism can be found in the placenta, umbilical cord, kidney, and liver of the aborted fetus. *L. pomona* can be shed in urine for up to 14 weeks post infection. *Leptospira grippotyphosa* and *Leptospira hardjo* are also known to cause equine abortions.[3]

Renal disease, tubulointerstitial nephritis, pyuria, and rarely acute renal failure have been reported in horses with leptospirosis. More commonly, two ocular disorders appear to be associated with *L. pomona* in horses: equine recurrent uveitis (ERU) and immune-mediated keratitis. It has been postulated that the immune-mediated response results from the cross-reaction between leptospiral antigens and uveal tissue, cornea, lens, vitreous body, and retina.[5] Recent reports have confirmed the presence of live *Leptospira* in the uveal tissue of horses with uveitis through isolation of the organism, positive PCR, or high antibody titer in the aqueous humor.[5]

Diagnosis Variable serologic results make a diagnosis of leptospirosis challenging. Microscopic agglutination titer (MAT) in serum and/or fluorescent antibody titer (FAT) in infected tissues have been routinely used. Sensitivity and specificity of FAT in tissues of aborted fetuses is nearly 100%.[4] In cases of uveitis, high antibody titers in aqueous humor may be found despite variable serum titers,

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suggesting local antigenic stimulation.[5] Serum titers of 1:6400 are considered significant and consistent with infection.[6] Serum titers of 1:3200 that are stable for a period of 2 to 3 weeks are not considered significant. Rising titers after a 2- to 3-week period are considered significant, and the patient should be isolated and treated. Other diagnostic modalities are PCR, histology, and bacterial isolation. Recently, genes of two surface proteins of *L. pomona* (Ig-like protein A and B) that are only expressed during active infection were isolated by Divers and collaborators.[4] These proteins may improve diagnostic testing and potentially lead to future development of a protective vaccine for leptospirosis.

Treatment Treatments advocated for leptospirosis include ampicillin, amoxicillin, procaine penicillin (22,000 IU/kg IM q12h), oxytetracycline (5 to 10 mg/kg IV q24h, slowly administered in fluids not containing calcium) or doxycycline (10 mg/kg PO q12h) for 7 days. The inflammatory response in horses with ERU and immune-mediated keratitis has been managed with corticosteroids and cyclosporine, but this may provide only temporary relief. Affected horses tend to develop ocular complications like cataracts, glaucoma, blindness, and intractable pain that may result in the need to consider enucleation. The inability to cure many cases of ERU may be due to lack of treatment of the potential active infection; treatment should be directed toward controlling the ocular inflammatory response and ongoing infection if indicated. An intact blood-ocular barrier may render systemic antimicrobial therapy unsuccessful despite the local inflammation.[4]

Prevention Prevention must be aimed at controlling exposure to shedding hosts, infected animals, and contaminated fomites. Thorough cleaning and disinfection of contaminated areas and proper disposal of infected material are essential measures to minimize exposure. Pregnant mares should be isolated from other animals because bacterial shedding may last several weeks. If abortions occur in endemic areas, testing horses for leptospiral antibodies and isolating those with a serum titer of 1:6400 or higher is recommended.[6] Horses with a negative or low titer should be retested in 2 to 3 weeks. Horses with rising titers should be isolated. Attempts to decrease shedding with oxytetracycline, penicillin G, and streptomycin in horses has not been effective.[4] Vaccination is sometimes performed on farms with endemic abortions or a high rate of uveitis.[4]

Bacillary Hemoglobinuria (Red Water)

Gary P. Carlson

Bacillary hemoglobinuria is an acute hemolytic disorder caused by *Clostridium haemolyticum* (*Clostridium novyi* type D). Also known as "Nevada red water," it has been reported as a naturally occurring disease in cattle and experimentally produced in sheep. Clinical signs develop rapidly, and death losses are often seen. Affected animals may manifest severe depression, anorexia, fever, hemoglobinemia, and hemoglobinuria. The disease is endemic in certain poorly drained areas of the western United States and is caused by ingestion of infectious spores. The organism finds a favorable environment for development in areas of preexisting liver damage that most often have been produced by migrating liver flukes. The hemolytic syndrome is produced by toxins elaborated by the organism, which also produce a characteristic focal liver lesion. The anemia produced may be marked, and both icterus and evidence of erythropoietic response may be seen in animals that survive for more than a few days. For a complete description of the disease, see Chapter 33.

Equine Infectious Anemia

Brett A. Sponseller

Equine infectious anemia virus (EIAV) is an RNA virus, a member of the Retroviridae family, belonging to the lentivirus genus. It has a structure and genome organization similar to other animal and human lentiviruses and uses virally encoded *reverse transcriptase* to convert the RNA genome to a DNA intermediate that is integrated into the host's genome by another virally encoded enzyme, *integrase*. The integrated DNA intermediate, or provirus, usurps the host cell to replicate its genome, manufacture viral proteins, and assemble the virally encoded proteins into virions that subsequently bud from the cell. Thus, infection by a lentivirus results in lifelong persistent infection. EIAV causes equine infectious anemia, first described in 1843 by Lignée.[1] In 1904, Vallée and Carré determined that EIA was associated with a filterable agent, making it the first animal disease determined to be caused by a virus.[2]

IDENTIFICATION OF EQUIDS SEROPOSITIVE FOR EIAV. EIA is a USDA-regulated disease. In 2003, the USDA estimated that serosurveillance of nearly 2 million samples cost U.S. horse owners in excess of $48 million. USDA-accredited laboratories use a testing scheme that detects the presence of serum antibody to the virus. The Coggins test, developed by Dr. Leroy Coggins in 1970, provided the first efficient serologic test for detection of EIAV-infected animals and remains a USDA-accepted test.[3,4] There are also four licensed ELISAs, one of which is a cELISA. These ELISAs detect antibody directed at the transmembrane glycoprotein (gp45) and/or the p26 antigen.[5] All U.S. states, Canada, and Mexico accept either the Coggins test or one of the licensed ELISAs when EIA testing is required for entry. Equids that cross state lines or attend many equestrian events (e.g., shows, races, etc.) have to be seronegative for EIA. The required period of seronegativity between tests varies state by state, however. No tests based on detection of viral nucleic acid are currently USDA approved for EIA diagnosis.

Serosurveillance can lead to detection of horses infected with EIAV that otherwise appear healthy. Indeed, most horses infected with the virus are inapparent carriers. However, blood transferred from an inapparent carrier to another horse, either through instruments (needles, nasogastric tubes, dental equipment, etc.), blood products, or by insect vectors (primarily tabanids) can lead to infection and a fatal outcome.

EQUINE INFECTIOUS ANEMIA. The clinical form of the disease is characterized by three defined temporal stages: acute, chronic, and inapparent. The acute stage occurs with the initial burst of viremia and is characterized by high fever, thrombocytopenia, and nonspecific signs of malaise, including lethargy and inappetence. In experimentally infected horses, thrombocytopenia inversely correlates with virus load and occurs slightly in advance of onset of fever. Ecchymoses and petechiae may also be detected on mucous membranes. During the chronic stage, similar clinical features occur during recurrent episodes of viremia, which are interspersed with periods of clinical quiescence and low viremia. Throughout the chronic stage, clinical episodes tend to gradually diminish in severity and duration. The inapparent stage occurs once levels of viremia are immunologically contained and no clinical signs are detected. Horses experiencing clinical disease at any point may develop DIC and die. In addition, episodes of stress (e.g., transportation, racing, extreme temperatures, etc.) may precipitate clinical disease. Corticosteroids have been experimentally used to induce recrudescence of clinical disease.[6] Other chronic manifestations of EIA include development of dependent edema, weight loss, anemia, and other signs of ill thrift. Rare manifestations that may develop include leukoencephalitis and enterocolitis.[7] Expression of clinical disease, particularly during acute infection, likely involves multiple factors, including inoculating dose, virulence factors of the inoculating viral strain, immune status, and immunogenetics of the host, age, stress, and so forth. Indeed, clinical disease occurs concomitantly with high-titered viremia. Horses with high-titered viremia pose the biggest risk of transmission to uninfected horses.

Lentiviruses have a DNA-dependent RNA polymerase (reverse transcriptase) that misincorporates nucleotides, resulting in changes in the viral genome.[8] This mechanism allows for generation of viral

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variants that differ genetically from preexisting ones. As a result, genetic and antigenic variation of epitopes for neutralizing antibody and cytotoxic T lymphocytes allows viral escape from adaptive immune responses.[9,10] Antigenic variation plays a central role in clinical disease recurrence throughout the chronic stage of infection and thwarts attempts to develop an effective vaccine.[8]

EIAV can replicate effectively in monocytes, dendritic cells, and tissue macrophages[11-13] and has been shown to replicate in endothelial cells. EIAV replication in endothelial cells may play a role in the development of DIC by viral damage to endothelial cells, with subsequent exposure of subendothelium.[14] This in turn could lead to platelet aggregation and formation of thrombi.[15] In addition, damaged endothelium may lead to development of dependent tissue edema by transudation of fluid through compromised small vessels.[14]

Pathology and Clinical Pathology Necropsy examination of horses that die of EIA may demonstrate splenomegaly, lymphadenopathy, hepatomegaly, pronounced hepatic lobular architecture, ecchymoses of the mucosa and viscera, dependent subcutaneous edema, and thrombotic disease of small vessels. Histologic findings may include a mononuclear cell infiltrate of periportal regions of the liver, adrenals, spleen, lymph nodes, meninges, and lungs. Hemosiderophages are frequently detected in the spleen, lymph nodes, liver, and bone marrow. Glomerulonephritis due to immune complex deposition is commonly observed.

Clinicopathologic abnormalities will vary depending on the stage and severity of infection. During clinical disease, a frequently profound thrombocytopenia develops concurrently with each successive episode of fever. Platelet function of EIAV-infected horses has been demonstrated to be hypofunctional, possibly exacerbating bleeding tendencies and the progression to DIC in clinically affected equids.[16] Anemia due to intravascular hemolysis, extravascular hemolysis, and depression of bone marrow erythropoiesis may progressively develop during the chronic stage of infection.[17] During the inapparent stage of infection, horses typically have increased plasma total solids and globulin concentrations, mild anemia, and decreased albumin concentration.[18] Polyclonal B-cell activation is also evident, suggesting chronic antigenic stimulation despite clinical quiescence.[18] Concomitant fever and thrombocytopenia should prompt immediate consideration of EIA. A history of recurring fever is also suggestive of EIA, particularly when other causes of fever have been ruled out.

Prevention, Control, and Regulatory Considerations It is well recognized that seroprevalence varies with the region of the United States.[17] States considered at a high risk include Texas, Oklahoma, Louisiana, and Arkansas, whereas the mid-Atlantic area, New England, Alaska, and Hawaii are considered low-risk regions. The remaining states are classified as being at intermediate risk. Despite regional differences in risk to noninfected horses, sporadic outbreaks do occur. Veterinarians should encourage all horse owners to annually test for EIAV, test new arrivals, and maintain good fly control, and the veterinary community should encourage organizers of equestrian events to require proof of seronegativity of attending horses.

Once a seroreactor is identified, all contact horses are quarantined and undergo testing until two negative test results at 30- to 60-day intervals are obtained for all individuals in the quarantined herd.[15] The required interval is based on the need to allow recently infected horses to seroconvert. Seroreactors may be either quarantined or euthanized, depending on state regulations. Quarantined horses must be at least 200 yards from seronegative animals, the distance shown to be sufficient to obviate viral spread by insect vectors. In addition, seroreactors remaining in permanent quarantine must be permanently identified. A USDA code number followed by the letter *A* is assigned to the quarantined horse and permanently applied to the horse in the form of a brand or lip tattoo.

Because an EIA eradication program has never been implemented in the United States, persistence EIAV-infected horses can be expected. The vast majority of horses in the United States are not tested annually, so to encourage horse owners to voluntarily maintain vigorous surveillance testing, the veterinary community must educate them about the consequences of EIAV infection. Horse owners are often unprepared to deal with the financial and emotional losses associated with detection of a horse seropositive for EIAV.

Immune-Mediated Hemolytic Anemia

Autoimmune Hemolytic Anemia

Gary P. Carlson

Definition and Etiology Autoimmune hemolytic anemia is associated with production of autologous antibodies directed against the patient's own red cells. These antibodies combine with complement and antigens on the red cell membrane, leading to rapid removal of affected red cells from the circulation and their accelerated destruction. Autoimmune hemolytic anemia occurs rarely as a primary idiopathic disorder[1,2] but more commonly is found secondarily associated with some other primary disease process.[1] An idiopathic immune-mediated hemolytic anemia (IMHA) was recently reported in a calf[2] and pony.[3]

Clinical Signs and Differential Diagnosis The presenting clinical signs of autoimmune hemolytic anemia are quite variable depending on the degree of anemia and the animal's primary disease. Marked anemia (PCV < 15%) manifests signs typical of those seen in any animal with a severe hemolytic anemia (i.e., depression, pale mucous membranes, variable icterus, elevated heart and respiratory rate, and variable to intermittent fever). Secondary autoimmune hemolytic anemia in horses has been associated most often with some other primary problem like purpura hemorrhagica, lymphoma, other neoplasms, protein-losing enteropathy, or chronic bacterial infections.[4,5] Clinical features are typical of the primary problem, with additional findings of a hemolytic anemia. In humans, exposure to a wide variety of drugs has been causally associated with development of autoimmune hemolytic anemia. There are a number of reports of an association between procaine penicillin and autoimmune hemolytic anemia in horses.[6-10] Autoimmune hemolytic anemia was recently reported in a 10-year-old horse that was treated with trimethoprim-sulfamethoxazole.[11] This apparently occurs rarely, perhaps only in specific individuals, but drug history should be ascertained in all animals with an otherwise unexplained hemolytic anemia.

It should be noted that the anemia in cattle with anaplasmosis and babesiosis or that in horses with equine infectious anemia, piroplasmosis, or ehrlichiosis is largely the result of an immune-mediated hemolytic process. These diseases are discussed fully elsewhere in this book.

Clinical Pathology The hemolytic process is often rapid and persistent, leading to a pronounced anemia. Hematologic features are those typically expected for a responsive hemolytic anemia. The anemia is often progressive and may become severe, even life threatening (i.e., PCV < 10%). Erythrophagocytosis and autoagglutination may be noted on blood smears. Spherocytosis may be difficult to recognize in large animals, owing to the relatively small erythrocyte cell size and lack of a clear area or central pallor. If the process has gone on for 4 days or more, hematologic evidence of active erythropoietic response may be seen in the peripheral blood of all species except the horse. This evidence of bone marrow response is a favorable prognostic indicator, even when anemia is quite advanced. A moderate neutrophilic leukocytosis is a common feature, and thrombocytopenia may be noted in some individuals if the autoimmune process is directed at platelets and megakaryocytes in addition to erythrocytes.

Diagnosis The direct Coombs test can detect the presence of antierythrocyte antibodies and/or complement on the red cell

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membrane, whereas the indirect Coombs test detects antierythrocyte antibody in the serum. It is important to remember that the Coombs test is based on species-specific reagents. These reagents are commercially available in the United States for small animals and horses, but not all diagnostic laboratories will have suitable Coombs reagents for other species. Special procedures may be necessary to adsorb these reagents to avoid nonspecific reactions. Multivalent Coombs reagent directed against IgG, IgM, and complement is most commonly used. The Coombs test is usually conducted at body temperature and also in the cold. A positive reaction at body temperature indicates that the antibodies are primarily IgG. These warm antibodies are associated more commonly with anemia, generally produce a more severe anemia, and tend to be more responsive to corticosteroids than cold-reacting antibodies. Cold-reacting antibodies detected with the saline agglutination test (run at 25° and 4°C [39° and 77° F]) are primarily of the IgM class. Exposure to a cold environment may be necessary to produce clinical signs associated with cold agglutinin disease. Both warm- and cold-reacting antibodies are capable of fixing complement. Unfortunately the Coombs test is not always positive in affected animals. In humans and the dog, approximately one third of patients with autoimmune hemolytic anemia have a negative direct Coombs test, possibly because of low concentrations of antibody or low binding to the red cell membrane. The diagnosis in these cases is contingent on ruling out other causes of a responsive hemolytic anemia and on the response to corticosteroid therapy. Recently, direct immunofluorescence flow cytometry was used to determine the classes of antibody bound to erythrocytes in three horses and 12 dogs with IMHA. The three horses had surface-bound IgG, including a horse with suspected penicillin-induced IMHA, a foal with neonatal isoerythrolysis, and a foal with clostridial septicemia.[12]

A substantial proportion of otherwise normal horses have small amounts of cold-reacting Coombs antibodies, and spontaneous agglutination may be noted in blood sample tubes exposed to the cold. In most instances these cold agglutinins appear to occur naturally, and in low levels are of little clinical significance. Prior treatment with corticosteroids may inhibit antibody production and could lead to a false-negative Coombs test.

Pathophysiology Autoimmune hemolytic anemia has rarely been reported as a primary or idiopathic process in large animals, but immune-mediated anemia occurs more commonly as a secondary problem (1) in association with certain types of neoplasia; (2) with a variety of viral, bacterial, rickettsial, and protozoal infections; (3) following exposure to certain drugs; or (4) in association with other immune-mediated disorders like systemic lupus erythematosus.[13] The initiating factors for this autoimmune disorder are not completely understood but may be related to alterations in the red cell membrane through direct or indirect injury, which elicits an abnormal response by the immune system. The red blood cell membrane is no longer recognized as self but is treated as a foreign antigen. Alternately, alterations in the immune system or stimulation by some other antigenic source may result in production of antibodies with a misdirected cross-reactivity with the patient's own normal red cells. Structural and functional changes in the red cell membrane are induced by the antigen-antibody reaction and complement fixation. The complement-fixing IgG or IgM antigen-antibody reaction may produce sufficient erythrocyte damage to result in intravascular lysis of erythrocytes, but more commonly, affected cells are removed from the circulation at a rapid rate by the reticuloendothelial system of the liver and spleen. Partial phagocytosis of affected cells may result in spherocyte formation. Although the presence of spherocytes on blood smears is a characteristic diagnostic feature in human and canine patients with autoimmune hemolytic anemia, the relatively small size of red cells of most large domestic animals may make it difficult to recognize spherocytes.

Treatment and Prognosis The approach to treating autoimmune hemolytic anemia depends on causal factors. If the animal has a history of drug therapy, it is advisable to discontinue medication or change to another class of drug. Patients with primary or idiopathic autoimmune hemolytic anemia may be the best candidates for treatment. IMHAs that are secondary to other diseases can only be managed if the primary problem is amenable to treatment. Thus treatment of an IMHA in a patient with extensive lymphoreticular neoplasia is likely to be unrewarding, and thorough diagnostic efforts should precede case selection for treatment. Although immune-mediated processes are responsible for hemolytic anemia in a number of infectious diseases, therapy must be directed at the primary agent, and corticosteroids are contraindicated in these diseases. Corticosteroids can cause recrudescence of viremia in horses with EIA, and a negative Coggins test should be a prerequisite to treating horses with an autoimmune hemolytic anemia of undetermined cause.

Treatment of autoimmune hemolytic anemia is directed at providing supportive care and interrupting the immune response responsible for antibody production. This is usually accomplished with systemic glucocorticoids. For a 450-kg horse, parenteral dexamethasone is recommended at an initial dosage of 30 to 40 mg/day This dosage is continued for 3 to 5 days and then decreased gradually over a period of 7 to 14 days, depending on response to therapy. The hematologic response to therapy should be closely monitored. If there has been no response in 5 to 7 days, the diagnosis of autoimmune hemolytic anemia should be reviewed, and potential causes of bone marrow suppression should be evaluated. Once the hemolytic process is well under control, treatment can be switched to oral prednisolone, 0.8 to 1 mg/kg daily. Human patients and small animals with IMHA that is unresponsive to corticosteroids are often treated with cyclophosphamide. One case of successful management of a horse with cyclophosphamide and azathioprine when anemia failed to respond to corticosteroids has been reported.[14] Supportive care consists of providing a quiet, restful environment and good nutrition, including vitamin supplementation. Iron- and copper-containing hematinics are generally of little benefit; neither of these elements is lost with hemolytic anemia. Blood transfusion is also of little benefit, since it is often impossible to find a compatible donor, and transfused cells are rapidly removed from the circulation. Blood transfusion should not be administered unless anemia is life threatening and the immune response can be controlled with corticosteroids.

Neonatal Isoerythrolysis in Horse and Mule Foals

Monica Aleman

Neonatal isoerythrolysis (NI) is the most common alloimmune disease in neonatal foals 7.5 hours to 12 days old (median age, 2.5 days).[15] NI is characterized by hemolytic anemia, icterus, and hemoglobinuria. Clinicopathologic abnormalities include anemia, high serum indirect and direct bilirubin concentrations, and sorbitol dehydrogenase activity. NI is caused by a blood group incompatibility between the foal and dam. The foal inherits from the sire and expresses an erythrocyte antigen (alloantigen) that is not present in the mare. The hemolytic syndrome is mediated by maternal antibodies against foal erythrocytes (alloantibodies) absorbed from colostrum. Blood factors associated with NI in horse foals are Qa, Qb, Qc, Aa, Pa, and Dg, and donkey factor in mule foals.[15] The most common antigens are Qa and Aa. Foals with NI may also present with alloimmune thrombocytopenia. For a complete description of NI, see Chapter 53.

Heinz Body Hemolytic Anemia

Gary P. Carlson • Monica Aleman

Definition and Etiology An acute hemolytic anemia can develop following exposure to a variety of oxidizing agents. These include chemicals such as phenothiazine, methylene blue, acetylphenylhydrazine, or plants like wild or domestic onions, members of the *Brassica* family (rape or kale), and wilted or dried leaves of the

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red maple *(Acer rubrum)*.[1-7] Red maple toxicosis (RMT) has been reported in horses, zebras, and alpacas.[5,8-10] Heinz body hemolytic anemia also occurs in sheep on specially formulated diets that are low in molybdenum, which results in chronic copper toxicity; as herd problems in cattle grazing rye grass *(Secale cereale)*[11] or selenium-deficient pastures in Florida[12]; and in association with selenium deficiency as a contributing factor in postparturient hemoglobinuria in cattle in New Zealand.[13] These agents produce or allow oxidative denaturation of hemoglobin and resultant aggregation of the protein globin, which appears as Heinz body inclusions within the red blood cells. Heinz body anemia has been seen in association with lymphoma in a horse and was possibly due to failure of the reticuloendothelial system to remove Heinz bodies, as has been reported in horses with EIA.[14]

Clinical Signs and Differential Diagnosis Clinical signs vary with the species involved, specific toxin or toxic metabolites, amount of toxin ingested, time course of the disease process, and occurrence of complicating secondary factors like hemoglobin nephrosis and acute renal failure. Weakness, lethargy, anorexia, and exercise intolerance are the usual presenting complaints, and death losses can occur. Mucous membranes are generally pale with variable to marked icterus. Heart and respiratory rates are generally elevated, but rectal temperature is usually within normal limits. Horses with RMT may be subclinical or may present with lethargy, muddy or cyanotic mucous membranes, tachycardia, inappetence, weakness, colic, icterus, brown discoloration of the blood, and pigmenturia. Rarely, sudden death occurs.[10] Most horses develop clinical RMT during summer and fall, and the high mortality rate may relate to the combination of a rapidly progressive hemolytic anemia and the formation of methemoglobin. Urine output may be reduced, and the presence of hemoglobin, methemoglobin, or bilirubin may make urine appear dark.

It is not possible to differentiate Heinz body hemolytic anemia from other potential causes of hemolytic anemia without laboratory evaluation. The absence of fever may help differentiate these anemias from infectious causes of hemolytic anemia. History of exposure to potential oxidizing agents and the fact that these toxic plants may produce death losses or clinical signs in multiple animals at the same time should help differentiate these cases from autoimmune hemolytic anemia.

Clinical Pathology Poisoning or intoxication resulting in Heinz body formation usually causes acute and profound anemia. In the early stages a very high percentage of erythrocytes may have Heinz body inclusions. Later, as these cells are removed from the circulation and replaced by young cells from the bone marrow, the relative number of affected cells may decrease markedly. Heinz bodies are round, oval to serrated, refractile granules usually located near the cell margin or protruding from the cell. They are best visualized with vital stains like crystal violet or new methylene blue applied to unfixed blood smears. Heinz bodies appear as bluish-green inclusions with new methylene blue stain. Fixing blood smears with methanol in preparation for staining with the classic Wright stain interferes with stain uptake, and Heinz bodies appear as a pale area within or projecting from the cell margin and can easily be missed. After the first 3 or 4 days the anemia is usually associated with hematologic evidence of an active erythrogenic response in all species except the horse. Total plasma protein usually remains within normal limits, and the Coombs test is negative. Red maple poisoning also results in depletion of red cell mass, reduced glutathione, methemoglobinemia, increased osmotic fragility, and modest elevations of liver-derived serum enzyme activities.

Rapid and profound erythrocyte destruction may lead to hemoglobinemia and hemoglobinuria. Development of renal failure secondary to hemoglobin nephrosis is a definite risk in these animals and is reflected by modest to marked increases in the BUN and creatinine, as well as changes in the urinalysis.[6,7] These parameters should be monitored in severely affected animals. As with other causes of hemolytic anemia, serum bilirubin, particularly indirect-reacting bilirubin, is elevated.

The clinicopathologic abnormalities of horses with RMT include anemia (PCV as low as 7.5%), eccentrocytes, Heinz bodies, and elevated plasma methemoglobin concentration.[10] Other significant findings are an inflammatory leukogram and renal insufficiency (75% and 40% of cases, respectively).[10] Mild serum total bilirubin elevation is observed in most cases, and hemoglobinuria is seen in all affected patients.

Pathophysiology Heinz bodies are formed by precipitation of oxidatively denatured hemoglobin. The hemoglobin contained within the red blood cell is constantly undergoing mild oxidative stress associated with oxygen transport, as well as generation of superoxide radicals and hydrogen peroxide within the cell. There are a number of reducing mechanisms within the red cell to counteract these oxidative processes through production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and reduced glutathione. The occurrence of Heinz body hemolytic anemia could be viewed as a consequence of exposure to oxidative stresses that simply overwhelmed the cells' reductive capacity. Selenium deficiency results in a decrease in glutathione peroxidase, a selenium-containing enzyme, and selenium deficiency may in special circumstances contribute to Heinz body formation by impeding the ability of the cells to respond to oxidative stress. There are substantial species variations in the rate of Heinz body formation that relate to the chemical structure of hemoglobin and the efficacy of erythrocyte-reducing mechanisms in the face of oxidative stress.[1] Red cells with Heinz bodies are less deformable than normal cells and are rapidly removed from the circulation by the reticuloendothelial system in the spleen, where they are phagocytized and broken down. Splenectomy or corticosteroid therapy may alter Heinz body clearance mechanisms, allowing significant numbers of affected red cells to remain in the circulation of otherwise normal animals.

Gallic acid is a strong oxidant present in red maple leaves. Gallic acid has been implicated in the oxidation of hemoglobin, methemoglobin formation, and Heinz body anemia.[5,6,15] Methemoglobin results from the oxidative change of hemoglobin iron to the nonfunctional ferric state (see discussion of nitrate poisoning in Chapter 54). This is normally prevented by glutathione reductase, ascorbic acid, and reduced glutathione. Methemoglobin cannot load or transport oxygen and, when present in sufficient quantities, results in a brown color of peripheral blood and mucous membranes. An estimation of methemoglobin concentration in a blood sample can be made by comparing the hemoglobin concentration measured by the cyanmethemoglobin method, which measures all forms of hemoglobin, and the oxyhemoglobin method, which only measures oxyhemoglobin but not other forms (e.g., methemoglobin). Methemoglobinemia and hemolytic anemia have been reported in a mare and her dam in association with decreased levels of red cell glutathione and glutathione reductase, presumably as a result of an inherited enzymatic defect.[16]

Treatment Treatment is largely a matter of removal from the source of toxicity and provision of supportive care. Blood transfusion can be very beneficial in severely anemic patients, particularly when there is insufficient evidence of active erythropoietic response. Iron-containing hematinics are of little benefit. IV fluid therapy is indicated in animals with hemoglobinuria or azotemia to reduce the potential for further renal damage. High doses of vitamin C (ascorbic acid, 50 to 100 g IV daily), together with fluids and transfusion, were thought to aid recovery in two horses with red maple poisoning.[17] A recent report suggests that vitamin C therapy may have little impact on survival of affected horses, and when methylene blue was used to treat the associated methemoglobinemia in two horses, both died.[18] Therapeutic goals should be to improve tissue oxygenation and perfusion and control inflammation and pain (e.g., with NSAIDs). Horses treated with corticosteroids have an increased likelihood of death.[10]

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Prognosis Prognosis in animals with modest anemia and evidence of response is good if the inciting factor can be controlled or eliminated. The mortality rate of experimental and naturally occurring cases of RMT in horses is said to be 60% to 65%.[18] In animals with rapidly progressive and profound anemia, prognosis is poor unless blood transfusion is undertaken. Complications are associated with hypoxia, hypoperfusion, and inflammation. Horses may develop acute renal failure, colic, pyrexia, and laminitis. A retrospective study of 32 horses reported a fatality rate of 59% but failed to show an association between mortality and severity of anemia.[10]

Other Causes of Hemolytic Anemia

Intravascular Hemolysis Following Cutaneous Burns

Monica Aleman

Intravascular hemolysis has been reported in horses following severe cutaneous burns affecting more than 25% of their body surface. Plasma on admission showed hemolysis along with abnormal RBC morphology, increased osmotic fragility, hemoglobinuria, azotemia, and hemoglobin pigment nephropathy.[1] The pathophysiology of hemolysis is unclear but suspected to be associated with the production of hydroxyl radicals by complement-activated neutrophils. Abnormal findings reported in humans include intravascular hemolysis, increased RBC osmotic fragility, decreased membrane deformability, RBC crenation, eccentrocytosis, spherocytosis, bud formation, fragmentation, and vesiculation.[2] These abnormalities are dependent on severity of burn trauma.[2] Pseudothrombocytosis has been reported and is presumably due to the incorrect recognition by automatic counters of red cell microvesicles as platelets.[2] Early fluid therapy and free radical scavengers have been beneficial for burn treatment in humans, along with supportive and wound care, control of pain and inflammation, and sepsis prophylaxis. A recent study in mice suggested that the level of plasma free hemoglobin is related to the size and depth of burn injury, which may be difficult to determine in some cases.[3]

L-Tryptophan-Indol Intoxication

Gary P. Carlson

Experimental studies in ponies have demonstrated an acute hemolytic process associated with orally administered L-tryptophan, which is converted to indol in the GI tract.[4] Intoxication was associated with an acute onset of restlessness, tachypnea, intravascular hemolysis, and hemoglobinuria. At necropsy there was evidence of hemoglobinuric nephrosis and bronchiolar degeneration in some ponies. Similar clinical signs were noted following oral administration of tryptophan at 0.35 to 0.60 g/kg, and indol at 0.1 to 0.2 g/kg.[4,5] Intravascular hemolysis was associated with increased osmotic fragility and with Heinz body formation in a few of the experimental ponies.

Water Intoxication

Gary P. Carlson

Massive water intake may produce marked hypotonicity of body fluids, with subsequent intravascular hemolysis of erythrocytes.[6] This problem has been described as a naturally occurring entity in milk-reared calves when they are first given access to unlimited quantities of water.[7,8] Severe neurologic signs may be seen (e.g., depression, convulsions, coma). Respiratory distress, hemoglobinuria, and death losses occur in some cases. Clinicopathologic features include hemolytic anemia, hypoproteinemia, hyponatremia, hypochloremia, hyposmolality, hemoglobinuria, and hyposthenuria. A sudden decrease in serum osmolality is believed to result in osmotic lysis of erythrocytes.[9] Erythrocytes are most susceptible to osmotic shock when calves are between 4 and 5 months of age. Treatment is primarily a matter of temporarily restricting water and providing supportive care. Calves with marked hyponatremia (sodium of 110 mmol/L) that are manifesting neurologic signs may benefit from hypertonic saline, mannitol, and corticosteroids. The goal of treatment is restoring serum sodium to 120 to 125 mmol/L without overcorrection. Death losses can occur in as little as 2 hours, but most calves recover without long-term adverse effects.

Postparturient Hemoglobinuria

Gary P. Carlson

A syndrome of intravascular hemolysis, hemoglobinuria, and anemia has been recognized in postparturient dairy cattle around the world.[10] The disease occurs sporadically, and the incidence is relatively low. Affected animals are most often high-producing multiparous cows that develop clinical signs during the first month after calving.[11] Depression, decreased feed consumption, and decreased milk production are associated with hemoglobinuria, anemia, and icterus. The anemia is often marked and after 4 or 5 days is associated with evidence of a marked erythropoietic response. The precise mechanism by which the intravascular hemolysis occurs has not been fully elucidated. The condition has been related to the marked hypophosphatemia commonly found in affected cows and moderately low phosphate levels in unaffected herdmates. Hypophosphatemia is brought about by inadequate dietary phosphorus intake in animals grazing phosphorus-deficient soils or fed fodder grown on such soils. Low intracellular phosphate concentration may interfere with energy metabolism, thus affecting cell viability and the ability of the red cells to deal with potential hemolysins (e.g., saponins from sugar beets or alfalfa). A postparturient hemolytic problem associated with copper deficiency and Heinz body formation has been described as a herd problem in New Zealand (see previous section).

Blood transfusion and supportive IV fluids are indicated in valuable cows with severe life-threatening anemia. Correcting hypophosphatemia consists of providing phosphate, initially as sodium acid phosphate ($NaH_2PO_4H_2O$), 60 g/300 mL of water IV, followed by oral phosphorus supplementation. Correction of dietary imbalances is indicated.

Copper Toxicosis

Lisle W. George

Copper is an essential nutrient for domestic animals, but excessive supplementation can result in toxicity. Copper poisoning is a common intoxication in ruminants. Reviews of the toxicodynamics and clinical syndromes have been published.[1-3] Lambs are most susceptible to the toxic effects of copper, but poisonings have occurred in adult sheep, goats, and cattle; Merino sheep are more resistant than British breeds.[4] Cattle have been poisoned by ingesting diets containing 37 mg of copper/kg of feed for 2 years.[5] Cattle fed 12 mg or more of copper/kg of body weight have been reported to develop subclinical hepatic disease.[6]

Elemental copper is an essential trace mineral with a narrow therapeutic window. Dietary requirements for growing sheep range between 4 and 6 parts per million (ppm), yet toxicity can occur whenever sheep are exposed to diets containing as little as 10 to 20 ppm.[7-9] Phytogenous copper poisoning results from concomitant ingestion of copper at 20 ppm of food, molybdenum, and sulfate. Ingested salts of copper are absorbed through enterocytes by carrier proteins and transported to blood in loose complexes with albumin and amino acids.[10] Roughly 20% of total plasma copper is ionized copper. Between 70% and 90% of this ionic copper is internalized by hepatocytes, where it is redistributed to bile, packaged in lysosomes in protein complexes, or used for the formation of ceruloplasmin.[10] Accumulation of copper occurs because daily hepatic biliary copper

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excretion amounts to less than 1% of ingested copper in ruminants.[11] Hepatic storage can buffer high levels of copper intake until the sites become saturated. At that time, hepatocytes die spontaneously or in response to environmental stress or dietary changes. Hepatocyte death causes the release of large amounts of cuprous copper into the blood. Animals that have preexisting hepatitis from pyrrolizidine alkaloids store less copper and are more susceptible to the hemolytic crisis.[4,12]

Free inorganic copper is an oxidant and can participate in the Fenton reaction. Cellular damage is related to production of oxidative hydroxides and peroxides, not to copper oxidation. These reactive intermediates are thought to initiate lipid peroxidation and oxidative denaturation of proteins within erythrocytes. Oxidation of heme protein produces Heinz bodies, and oxidation of hemin produces methemoglobinemia. Oxidized erythrocytes either lyse spontaneously intravascularly or are sequestered in the spleen and degraded to constituent amino acids. Vitamin E is also denatured. This latter reaction removes a potent antioxidative protective factor and enhances cellular susceptibility to additional oxidants. Differences in genetic susceptibility to copper poisoning are unknown.

The hemolytic phase of copper poisoning is often initiated by noxious stimuli that could include shipping, hierarchal change, administration of oxidative drugs, starvation, or change of housing.[13] High-protein diets have increased resistance to the hemolytic crisis in sheep, but the role of extra molybdenum intake in these supplemented animals was unclear.[9,14] The mechanistic relationship between stressful events and hepatocyte release of copper is unknown.

Sources of copper that have been responsible for copper accumulation in animals include trace mineralized salt, inappropriately formulated cereal grain mixtures, forages from pastures that have been fertilized by swine or chicken manure,[15] orchard pastures that have been contaminated by copper-containing fungicides, rations containing more than 20% chicken litter, or diets that contain high concentrations of palm kernel oil. Other potential sources of copper include fencing and copper piping and overdoses of parenterally administered copper salts. In one recent case at our institution (University of California, Davis), dairy goats were poisoned by supplementation of trace minerals that were formulated for dairy cattle.

The toxic dose of copper for each species is variable and depends on duration of exposure, the animal's genetics, and the amount of molybdenum being fed. Diets with copper/molybdenum ratios over 6:1 are more likely to result in copper poisoning than diets with lower ratios. The interaction between the two minerals may occur in the solid phase of rumen ingesta, where insoluble and nonabsorbable complexes between copper, sulfur, molybdenum, and large-molecular-mass protein complexes are formed. The highly complexed copper is unabsorbed and hence not toxic. High dietary intake of zinc and iron also inhibit absorption of copper, and although the precise mechanism of antagonism is unknown, the elements share a competitive affinity for metallothionein.[16-18] Competition for this protein could alter the storage capacity for copper. Soil sulfates reduce molybdenum absorption by plants, increasing the potential for pathologic accumulation of copper in herbivores.

The respective single toxic doses of copper for sheep and cattle range between 20 and 110 mg/kg and 220 to 880 mg/kg of body weight. Most poisonings occur after long-term, low-dose ingestion of the element. Copper poisoning can occur in sheep after 2 months of daily dosing of 3.5 mg/kg of copper, feeding a ration that contains 20 ppm of copper for several months, or after a single SC injection of copper EDTA salt at a dose of 2 mg/kg.[19] Sheep have been poisoned by subcutaneous injection of 3 to 4 mg/kg of copper-calcium EDTA but remained normal after 6 mg/kg of copper methionate.[20] Sheep have died after single injections of 2 mg/kg of diethylamine copper oxyquinoline sulfonate.[20] One study that fed 3.7 mg/kg of copper daily for 84 days reported peak hepatic copper levels that ranged between 258 and 375 mg/kg wet weight by 26 days after the final copper feed.[21] A single dose of 50 mg of copper caused acute hemolytic crisis in sheep when treated during mid-pregnancy. The largest incidence of hemolytic anemia occurred in Welsh sheep, and the lower cumulative incidence in Cheviot sheep.[22] Single doses of copper calcium ETDA at 25 mg/animal has killed lambs.[23] Cumulative doses of copper ranging between 12.8 and 22 g have produced hemolytic anemia in Suffolk lambs by 42 days.

Goats may show signs of copper poisoning by 144 days after daily feeding of a ration that contains 80 mg copper/kg. Placental transfer of copper occurs, but concentrations in the tissues of lambs are not toxic even during the hemolytic phase in the dam.

Adult cattle may be poisoned by feeding 5 g of copper sulfate daily for as long as 4 months. Calves may be poisoned after 6 to 8 weeks of feeding milk replacer containing 115 ppm of copper.[10,24] Horses are resistant to high dietary concentrations of copper and may remain clinically normal after prolonged feeding of diets containing levels as high as 791 ppm. In those horses, hepatic concentrations of copper at the end of the feeding period reached 4000 ppm. Adult ponies that were treated once with an oral dosage of copper of 40 mg/kg did not develop hemolytic anemia.

Clinical Signs

Animals exposed to high levels of copper are asymptomatic for weeks until the onset of hepatic necrosis.[25,26] Signs develop rapidly thereafter and are reflective of coexisting anemia, myopathy, and neurologic, renal, and hepatic disease. Clinical signs include inappetence, lethargy, weakness, recumbency, cool extremities, pallor, and greyish discoloration of the mucous membranes. Affected animals have a markedly increased pulse rate, tachypnea, hypotension, and hypothermia. The pulse amplitude of the linguofacial artery is decreased. Urine is dark red from the presence of free hemoglobin products. Feces are dark or have yellowish discoloration but are normally formed and do not contain hemoglobin unless secondary abomasal ulceration has occurred. Animals may have marked petechiation of the conjunctival mucosa. Pregnant animals often abort secondary to hypoxemia. Recumbent patients usually expire without struggling. Exposed ewes that survive copper poisoning tend to have dystocia and dilation failure in subsequent lambing periods.

Pathology

The tissues of hemolyzing animals are pale and icteric, and serous surfaces are covered by petechial and ecchymotic hemorrhages. The liver is often pale and yellow, and the lungs are firm. Kidneys turn black and have a metallic sheen due to entrapped hemoglobin. The urinary bladder of copper-poisoned animals is filled with serosanguineous urine. Microscopic changes include hemoglobinuric and tubular nephrosis, and necrosis of the splenic follicles and hepatocytes. There is also biliary ductular proliferation and pericholangitis.[21,27] Hepatic necrosis may be detectable by microscopic examination for as long as 412 days post poisoning. Microscopic brain changes in poisoned animals include spongy degeneration of the pons and brainstem.

Diagnosis

Normal hepatic concentrations in sheep have been reported as 173 ± 130 (mean ± SD) and 129 ± 59 ppm (wet matter) for adults and lambs, respectively.[28] Wet matter hepatic concentrations of copper in poisoned animals were 429 ± 249 (mean ± SD) ppm. Dry weight concentrations may be greater than 3000 ppm. Hepatic concentrations are usually high prior to and after the hemolytic episode, but normal hepatic copper concentrations in hemolyzing animals have been reported.[19] The correlation between plasma and hepatic copper concentrations in prehemolytic animals is poor.[29-30] Copper poisoning in animals with normal plasma concentrations and near-toxic liver levels have been reported.[31] Normal plasma copper concentrations range from 13 to 20 µmol/L (0.8 to 1.2 µg/mL).[21] Serum copper concentrations range between 0.60 and 1.50 µg/mL (0.6 to 1.5 ppm). Plasma copper concentrations that range between 2.4 and 20.0 µg/mL (2.4 to 20 ppm) are diagnostic for acute toxicosis.

Clinical Pathology

There are no consistent hematologic changes until 24 hours prior to the hemolytic crisis, when sudden

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concentrations of cytosolic hepatic enzymes rise coincidentally with a sharp rise in plasma copper concentration. Plasma copper concentrations fall rapidly following the hemolytic crisis and are often near normal by 4 days after hemolysis.[25] Copper concentrations within erythrocytes remain high.

Hepatic concentrations of 16 mmol copper/kg of dry matter are the threshold for development of hemolytic anemia. The half-life of copper in the liver of untreated poisoned sheep has been estimated to be 175 ± 91 days,[21] and high copper concentrations in hepatic tissues can be found for as long as 100 days after initiation of the hemolytic episode.[29]

Kidney concentrations of copper in animals with hemolytic crisis are 15 and 50 ppm for dry and wet weight volumes, respectively. Sheep may have increased plasma concentrations of γ-glutamyltransferase (GGT) and AST for 3 days prior to the onset of hemolysis, and glutamate dehydrogenase may be increased for as long as 700 days after cessation of copper ingestion.[21,32] Fecal copper concentrations may exceed 10,000 ppm during the hemolytic episode.

Clinicopathologic changes that occur during the acute hemolytic crisis include Heinz body formation, intravascular hemolysis, methemoglobinemia (as much as 5%), decreased PCV, and increased concentrations of plasma bilirubin, AST, GGT, alkaline phosphatase, total bilirubin, creatine kinase, creatinine, plasma urea nitrogen, and plasma ceruloplasmin. Urine is dark brown to black and contains high concentrations of protein, blood, and hemoglobin casts. Microscopic examination of urine may detect erythrocytic casts and inflammatory cells.[33] Sheep that survive the hemolytic episode develop reticulocytosis by 4 days after the onset of clinical signs.[34]

Treatment Animals with acute hemolytic syndrome should be insufflated with oxygen and treated with vitamin E (3 to 5 daily doses consisting of 3000 IU/dose). If PCV is below 8%, animals should be given packed washed homologous erythrocytes. Additional therapy should include D-penicillamine (Cuprimine [Merck Sharp & Dohme, Rahway, N.J.] at 52 mg/kg of body weight daily for 6 days), anhydrous sodium sulfate (1 g/sheep daily for 6 days) and ammonium molybdate (100 mg/sheep daily for 6 days). Treatment with D-penicillamine increases urinary copper excretion by 10- to 20-fold.[35] Single-dose therapy with D-penicillamine (28 mg/kg body weight) increases copper excretion, but the effect is transient and insignificant for reducing the total hepatic copper load.[36]

Dietary supplementation with 7.7 ppm ammonium molybdate also results in hepatic copper concentrations that are 40% lower than in unsupplemented controls. Addition of 7 or 15 mg molybdenum for 80 days to experimentally poisoned sheep has reduced hepatic copper concentration in sheep by 34% and 46%, respectively.[37] Copper-poisoned cattle have been successfully treated with oral sodium molybdate (3 g daily) and sodium thiosulfate (5 g daily). When introduced into the sulfur-rich rumen contents, molybdenum salts complex with high-molecular-weight proteins in the solid phase of the digesta.[38] The protein-bound thiomolybdate aggregates strongly chelate copper in insoluble and indigestible complexes. Molybdenum salts also enhance biliary copper excretion and selectively remove copper from hepatic metallothionein.[16,39,40] For poisoned cattle, top dressing food with 500 to 1000 mg ammonium molybdate daily for 18 days markedly reduced the amount of hepatic copper.[41]

Parenterally administered ammonium tetrathiomolybdate has been recommended for treatment of acute hemolytic crises due to copper poisoning. IV administration of ammonium tetrathiomolybdate reduces both lysosomal and cytosolic copper in hepatocytes. The drug has been given as a 5% solution in sterile saline with an IV dosing schedule of either 50 to 100 mg twice weekly for up to 11 weeks, or as 3 doses consisting of 3.4 mg/kg of body weight on alternate days and beginning at the onset of hemolytic crisis.[42-46] Concomitant administration of 36 mg of xylazine IV increased copper excretion in bile by as much as 2.25-fold over controls that were treated with thiomolybdate only.[47] Parenteral administration of thiomolybdate results in transient increases of copper concentrations in blood for as long as 24 hours. Because copper is acid insoluble, the effect is to protect copper-exposed animals from hemolytic crises and reduce tissue damage during a hemolytic event.[48,49] Biweekly injection of 100 mg molybdenum as tetrathiomolybdate increased daily hepatic biliary copper excretion by a factor that ranges between 150% and 300%.[50]

Prevention Owing to the sporadic nature of copper poisoning and lack of signs during the accumulative phase, it can be difficult to prevent. Clients should be counseled to purchase concentrates with label claims for the species being supplemented. Copper-supplemented salts should be restricted, especially in sheep. Pastures heavily contaminated by copper can be top dressed with molybdenum phosphate (113 g molybdenum/acre). Fencing and plumbing that contain copper sulfate or metallic copper should be removed from the environment. One study in sheep receiving 36 mg copper/kg daily for 18 months controlled the hemolytic crisis and associated mortality due to copper poisoning by SC injection of sterile ammonium tetrathiomolybdate (containing 3 to 4 mg molybdenum) on alternate days for three injections.[45] The sheep in this study were given either IV or SC molybdenum at dosages that amounted to 1.7 and 3.4 mg/kg of ammonium tetrathiomolybdate. Addition of ammonium molybdate at 7.7 ppm and sodium sulfate at 4200 ppm reduced liver copper and decreased plasma ceruloplasmin in experimentally exposed lambs.[30]

Feeding experimentally poisoned lambs sodium molybdate and sodium sulfate at respective daily dosages of 20 mg and 6 grams reduced hepatic copper content after 90 days.[51] Molybdenum and sulfur protect sheep by converting ingested copper to nonabsorbable thiomolybdate complexes in the rumen. The antagonistic effects are most marked at times of rapid hepatic accumulation of copper. Addition of 3 mg/kg of food (dry matter) molybdenum in the form of tetrathiomolybdate reduced hepatic copper accumulation by as much as 33-fold.[44] Lambs fed diets containing 7.7 ppm of ammonium molybdate after weaning until 14 weeks of age had reduced hepatic copper and decreased ceruloplasmin concentrations.[30] Cattle can tolerate indefinite periods of ingesting copper at dosages of less than 0.6 mg/kg daily.[31] Addition of 220 to 420 ppm of zinc may be protective against copper poisoning in sheep, but this is not put into practice in clinical situations.[38]

Hemolytic Syndrome in Horses with Liver Failure

Gary P. Carlson

A fulminant intravascular hemolytic syndrome has been reported as a near-terminal event in horses with either acute or chronic liver failure.[1] Marked hemoglobinemia and hemoglobinuria are associated with intense icterus, and the sclera and conjunctiva often take on a distinctive deep reddish-orange color. The onset of intravascular hemolysis is sudden and rapidly progressive. The prognosis is highly unfavorable; nearly all horses that develop this syndrome die or must be euthanatized because of clinical deterioration.[2] IV fluids, corticosteroids, and supportive care do not appear to alter the clinical course or unfavorable outcome.

The cause of this syndrome is unknown, but release of hepatic copper stores does not appear to be a factor. The hemolysis seems to be associated with increased erythrocyte osmotic fragility. Human patients with liver cirrhosis develop a hemolytic syndrome associated with alterations in the exchangeable lipoproteins of the red cell membrane. A similar mechanism has not been shown in horses, but morphologic alterations in these horses' red cells resemble the burr cells described in human patients.[3] Bile acids and their salts are markedly increased in liver failure and could play a contributing role in the hemolytic process. At necropsy, widespread hemorrhagic lesions that resemble those described for DIC are often present.[3] It may be that DIC and activation of various mediators may play a role in the terminal stages of this almost invariably fatal process.

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Congenital Erythropoietic Porphyria

Gary P. Carlson

A rare congenital disorder of hemoglobin production that is inherited as an autosomal recessive has been recognized primarily in Holstein cattle, but has also been reported in Shorthorns and Jamaican cattle.[4-6] Commonly called "pink tooth," the disorder is characterized by slow growth rates in calves, photosensitization and exfoliation of nonpigmented skin when exposed to sunlight, reddish-brown teeth, and modest anemia. The teeth and bones exhibit a pink fluorescence under ultraviolet light, and the presence of uroporphyrin turns urine a brownish-red color. The condition is present at birth, and the metabolic defect is a hereditary deficiency of the enzyme uroporphyrinogen III synthase (UROS), which catalyzes an essential step in the synthesis of the porphyrin structure of hemoglobin. This leads to accumulation of uroporphyrin and coproporphyrin, which deposit in the teeth where they are concentrated in the dentin, bones, and other tissues. The anemia seen in these cattle is variable among individuals, and several factors contribute to it. Reduced intravascular red cell lifespan is related to the high concentration of uroporphyrin and coproporphyrin within the cells. Porphyrins may induce hemolysis and delay red cell series maturation in the bone marrow, although there is often evidence of active erythropoietic response in peripheral blood.[5]

There is no treatment for this inherited disorder, but genetic counseling is advisable. Substantial efforts have been made to reduce the incidence of this disease in the Holstein breed. It may be possible to detect carrier animals. Affected cattle have much lower levels of UROS than normal cattle, and carrier animals have intermediate levels of this enzyme. Despite their rather serious problems, these cattle do reasonably well if housed indoors out of direct sunlight. The principal differential consideration is chronic fluorosis, which also produces brown discoloration of the teeth, but they do not fluoresce under ultraviolet light.

Another form of altered porphyrin metabolism, erythropoietic porphyria, has been described in humans and cattle.[5] In humans the mode of inheritance is autosomal dominant, whereas in cattle the disorder appears to have a recessive pattern of inheritance and may be sex linked, since it is only seen in females. The disease does not produce anemia, porphyrinuria, or teeth discoloration, but ferrochelatase (heme synthase) deficiency leads to high concentrations of erythrocyte and fecal protoporphyrins.

Porphyria has also been reported in swine, where it exhibits a dominant pattern of inheritance.[5] Health effects are minimal and there is no photosensitivity, but the pigs' teeth have reddish-brown discoloration. There are similarities with bovine congenital erythropoietic porphyria, but the precise defect in pigs has not been found.

Finally, animals may develop acquired toxic porphyrias. This can occur with heavy metal poisonings, principally lead, but has also been produced experimentally with hexachlorobenzene and other chemicals. Lead inhibits several key enzymes of heme synthesis. Inhibition of aminolevulinate dehydrase leads to accumulation of aminolevulinic acid, and decreased aminolevulinate dehydrase activity is a sensitive indicator of lead poisoning. Lead also inhibits ferrochelatase and leads to marked elevation of erythrocyte zinc protoporphyrin IX, making measurement of zinc protoporphyn IX levels a means of monitoring lead exposure.[5]

Depression Anemia

Gary P. Carlson

The most common form of anemia in domestic animals is associated with inadequate erythropoiesis or bone marrow depression. Depression anemia can be caused by (1) deficiencies of vitamins or minerals essential for erythrocyte production, (2) systemic disease processes that interfere with normal erythropoiesis, or (3) processes that damage or displace normal bone marrow elements. Common causes of depression anemia are listed in Box 37-2. Depression anemia is often mild to moderate in severity and generally is only slowly progressive. Depressed erythropoiesis is occasionally associated with processes that also result in blood loss and/or an increased rate of erythrocyte destruction. When this occurs, a profound rapidly progressive and potentially life-threatening anemia can develop. With the possible exception of chronic iron or copper deficiency, depression anemia tends to be normocytic and normochromic. Bone marrow evaluation is an extremely useful diagnostic tool in animals with nutritional deficiencies or when bone marrow damage or dyscrasia is suspected. A thorough clinical evaluation and vigorous application of appropriate diagnostic procedures are necessary to establish a diagnosis of depression anemia and determine the factors responsible.

BOX 37-2

Causes of Depression Anemia

Nutritional Deficiency

Iron deficiency
Copper deficiency
Cobalt deficiency
Vitamin B_{12} deficiency
Folic acid deficiency

Anemia of Inflammatory Disease

Chronic infection
Chronic inflammation
Fractures and severe trauma
Neoplasia

Anemia Secondary to Organ Dysfunction

Chronic liver disease
Chronic renal disease
Chronic gastrointestinal disease
Parasitism (trichostrongylosis)

Bone Marrow Damage/Dysplasia

Myeloid and megakaryocytic bone marrow hypoplasia in Standardbred horses
Bracken fern poisoning
Congenital dyserythropoiesis and keratosis in polled Hereford calves
Trichloroethylene-extracted soybean meal toxicity
Myelophthisic disorders (myeloproliferative disease, lymphoma)
Aplastic anemia

Iron Deficiency Anemia

Gary P. Carlson • Monica Aleman

Iron is present in most forages and grains. In neonates, the major source of iron is colostrum (≈0.79 mg/L in mare's milk).[1] Soil, dam's feces, and milk are other important sources of iron.[1] Iron deficiency is most commonly associated with chronic blood loss due to internal or external parasitism, bleeding GI lesions, or hemostatic defects. Dietary iron deficiency is seldom the sole cause of anemia, even in neonates on an all-milk diet, unless they are raised on cement or in barns or hutches with no access to the soil. A modest anemia is anticipated in veal calves. The anemia seen in some young calves during the first few days to weeks of life is apparently the result of congenital iron deficiency,[2] but the causal factors have not been determined. Altered immune functions, high incidences of infection, and reduced growth performance are reported in veal calves on low-iron diets.[3] Alterations in GI pH may alter absorption of iron by the small intestine. States of inflammation and infection cause iron sequestration, not deficiency, by the reticuloendothelial system and lactoferrin. Iron deficiency has been well documented in calves and

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piglets housed exclusively indoors or in hatches with no access to soil.[4] Absolute iron deficiency anemia is not commonly reported in horses.[5-8]

Circulating erythrocytes account for about two thirds of the total iron reserves found in the body. The remaining iron stores are distributed in the liver, spleen, and bone marrow. With chronic blood loss anemia, iron depletion is first indicated by decreased marrow iron, which can be appreciated with special staining of the bone marrow with Prussian blue stain for iron. As blood loss continues and iron deficiency progresses, serum iron is decreased, whereas iron-binding capacity may actually increase. Late in this process, iron-deficient erythropoiesis results in the typical microcytic, hypochromic erythrocytes generally thought to be characteristic of iron deficiency anemia (decreased PCV, hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin concentration). Other laboratory findings include echinocytosis, keratocytosis, schistocytosis, acanthocytosis, ovalocytosis, hypoferritinemia, and hypoferremia.[5-8] The observed RBC morphologic abnormalities are thought to be due to oxidative damage. Normal serum iron and iron-binding capacity for most domestic animals is 100 and 300 µg/dL, respectively. There is one report of a neonatal foal with iron deficiency with refractory anemia and severe abnormal RBC morphology but no microcytosis and hypochromasia.[8]

Treatment Treatment of iron deficiency anemia is contingent on evaluation of the cause and correction or resolution of the process responsible for chronic blood loss. Iron is usually supplied as an oral supplement or feed additive, and many commercial preparations are available. Injectable iron dextran intended for use in baby pigs should be avoided in horses and cattle, because it can induce anaphylaxis, especially if administered repeatedly.[9] Iron cacodylate was a safe parenteral iron preparation for use in horses but is no longer readily available. An injectable iron preparation intended for use in horses was reported to result in acute iron overload, massive hepatic necrosis, and severe death losses in a group of young cattle.[10] Iron overload has resulted in acute death losses in neonatal foals fed an iron-containing microbial supplement. Iron accumulation resulting in hemochromatosis and extensive liver damage has also been reported in adult horses, although the mechanism responsible for the iron accumulation has not been explained.[11]

Copper Deficiency

Gary P. Carlson

Copper deficiency can occur as a primary problem in milk-fed animals or in pastured animals in copper-deficient areas. More commonly, copper deficiency occurs secondarily in association with other trace mineral imbalances such as dietary molybdenum excess and is influenced by the sulfur and zinc content of the diet. Copper is an essential cofactor for a wide variety of enzymatic reactions, and copper deficiency produces a constellation of clinical signs related to impairment of these reactions.[12] Clinical signs of copper deficiency are most prominent in young, growing animals and may include reduced growth rate, rough and depigmented hair, diarrhea, osteoporosis with spontaneous fractures, and anemia. In lambs, copper deficiency can produce a demyelinating syndrome known as *swayback* or *enzootic ataxia*. Copper deficiency has also been associated with hemolytic anemia in postparturient dairy cattle in New Zealand.[10] Copper plays an important role in iron transport from the gut to the marrow, and in the incorporation of iron into the heme moiety. The anemia produced by copper deficiency is generally moderate, slowly progressive, and closely resembles iron deficiency in that it is usually a microcytic, hypochromic anemia. Bone marrow evaluation often reveals intracellular accumulations of iron known as *sideroblasts*. This finding indicates that the principal problem is a function of altered incorporation of iron into the erythrocyte hemoglobin rather than an actual deficiency of iron. Copper deficiency can be documented by measuring serum copper as ceruloplasmin, erythrocyte superoxide dismutase, or the copper content of hair, liver, or kidney. Serum iron tends to be low in animals with copper deficiency. Copper can be supplied as a dietary supplement or as an injectable copper glycinate preparation.

Vitamin B_{12} and Folic Acid Deficiency

Gary P. Carlson

Nearly all of the vitamins are necessary for normal erythropoiesis, but in ruminants and horses only deficiencies of vitamin B_{12} and folate have been associated with development of anemia. These two vitamins play essential roles in DNA synthesis. When deficiency of both vitamins coexists, as has been experimentally produced in pigs, a marked macrocytic anemia with hypersegmented circulating neutrophils and giant metamyelocytes and neutrophils in the bone marrow may be found. In ruminants, vitamin B_{12} deficiency has been associated with grazing cobalt-deficient pastures. A macrocytic to normocytic anemia may be noted in these animals. Folate deficiency has been reported as a cause of a mild seasonal decline in erythrocyte parameters in horses.

Anemia of Inflammatory Disease

Gary P. Carlson

A depression anemia associated with characteristic disturbances of iron metabolism is often found in animals with conditions that result in a chronic inflammatory response.[13,14] These conditions include chronic internal or cutaneous infections, infectious diseases, or immune-mediated processes that result in chronic inflammation, severe traumatic injury or fractures, and active malignant neoplasia. The anemia tends to be mild, slowly progressive, and of little clinical consequence. Clinical signs relate to the primary disease process, and hematologic features are those of a mild, unresponsive anemia, often with indications of a chronic inflammatory response (neutrophilic leukocytosis and monocytosis with elevated fibrinogen, total protein, and globulin). Serum iron and iron-binding capacity are decreased, but marrow iron reserves and serum ferritin are increased.[14] Anemia in these animals is partially due to a modest decrease in circulating red cell lifespan, but it is primarily caused by major alterations in iron metabolism and depressed bone marrow response to the anemia. These alterations represent part of the body's response to inflammation, which includes release of interleukin and other mediators and production and release of a variety of acute-phase proteins from the liver. The body tends to sequester iron from the circulation into storage forms, primarily in the liver and bone marrow, where it is retained and relatively unavailable for erythropoiesis. This general reaction may play a protective role by denying readily available iron to potential bacterial pathogens that require iron for rapid growth and multiplication. Iron supplementation is not indicated to treat the anemia of chronic inflammation; therapeutic effort should be directed at resolving the primary disease process.

Anemia Secondary to Organ Dysfunction

Gary P. Carlson

A mild to moderate unresponsive anemia can develop in patients with chronic endocrine, hepatic, renal, or GI diseases. These disorders can produce bone marrow depression by reducing production or absorption processing and distribution of elements essential for erythropoiesis, by allowing elaboration or accumulation of toxic compounds, or by interfering with the production or action of erythropoietin.[15,16] These effects can occur independently of the alterations in iron metabolism that characterize the anemia of inflammatory disease.[14] However, should inflammatory processes be responsible for the specific organ damage or dysfunction, the same pattern of anemia

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as described in the previous section would apply. Specific therapy for anemia in these patients is not indicated, and resolution of the anemia depends on successful management of the primary disease process.

Internal parasitism, particularly that associated with *Trichostrongylus* spp. in ruminants, can result in a marked anemia that is primarily the result of bone marrow depression in which failure to absorb iron, copper, and essential amino acids plays a major role.

Myeloid and Megakaryocytic Bone Marrow Hypoplasia

Gary P. Carlson

Myeloid and megakaryocytic bone marrow hypoplasia has been reported in eight young Standardbred horses sired by the same stallion.[17] Clinical signs were variable and in some individual horses included nonhealing wounds, unresponsive fevers, pleuritis, pneumonia, ataxia, hemoperitoneum, and bleeding into the bowel. Seven of eight horses died or were euthanized. The principal laboratory findings were a variable red cell count from normal to modest to marked anemia, moderate to profound neutropenia, and intermittent thrombocytopenia in most of the horses. There appeared to be a cyclic variation in neutrophil and platelet counts. A bone marrow microenvironment or growth factor defect are suspected causes of this problem; myeloid progenitor cells were present, and cells were able to respond to exogenous growth factors. A familial basis for the disease is suspected.[17]

Aplastic Anemia

Debra Deem Morris

Aplastic anemia is a stem cell disorder characterized by reduced marrow production of all blood components in the absence of a primary disease process infiltrating the bone marrow or suppressing hematopoiesis.[18,19] Peripheral pancytopenia secondary to marrow aplasia is apparently very uncommon in horses, although idiopathic hypoplastic anemia has been reported,[20-22] as well as rare cases associated with phenylbutazone use.[15-23] Hemorrhagic diathesis caused by thrombocytopenia is often the first indication of disease, manifested by epistaxis, mucosal petechiae, or prolonged hemorrhage after trauma or injections. Pallor may be present, with other signs of anemia (e.g., reduced exercise tolerance) depending on the severity and rapidity of aplasia progression. Neutropenia causes increased susceptibility to infections, which may result in intermittent fever or weight loss. Lymphocyte production is reportedly not impaired, but absolute lymphopenia is common in aplastic anemia. Circulating lymphocytes are often highly reactive, producing the suspicion of neoplasia or a preleukemic syndrome.[15]

Marrow aplasia in humans is generally termed *idiopathic,* although some cases are associated with exposure to a drug, chemical, ionizing radiation, or presence of another disease.[19] Marrow failure results from damage to the hematopoietic stem cell compartment. This may be in the form of DNA damage to stem cells or depletion of later progenitor cells by a cycle-active agent. Some cases of marrow aplasia appear to be immune mediated, either genetically determined or incited by a particular viral infection or drug exposure.

The diagnosis of aplastic anemia is based on the combination of peripheral pancytopenia and bone marrow hypoplasia with fatty replacement. Because the normal erythrocyte lifespan in horses is roughly 140 days and in cattle exceeds 160 days,[24] neutropenia with no left shift and thrombocytopenia are earlier hematologic manifestations.

The major aims in treatment of aplastic anemia are to remove the animal from suspected causative agents and provide supportive care, in the hope spontaneous remission will occur. Broad-spectrum antimicrobials are necessary to control infections. Blood transfusions are rarely indicated, and platelet transfusion should be reserved for severe bleeding episodes, which rarely occur. Bone marrow transplantation is used with some success in humans, although graft-versus-host disease poses significant risk. The latter would presumably limit this therapy in horses; too few horses with aplastic anemia have been studied to give a clear indication of prognosis.

Bracken fern toxicosis in ruminants causes bone marrow depression and subsequent pancytopenia.[24] Most field outbreaks of the disease occur in cattle. The toxic effects of the plant are cumulative, and clinical signs occur suddenly 2 to 8 weeks after cattle gain access to the plant. Clinical signs include fever, melena, epistaxis, hematuria, mucosal petechiae, hyphema, and bleeding from the eyes and vagina. Hematology reveals a platelet count less than 40,000/μL and profound leukopenia with essentially no neutrophils present. Death may follow in 1 to 3 days as a result of the combined effects of multiple internal hemorrhages and bacteremia. The aplastic anemia factor in bracken fern has not been identified, although ptaquiloside has been suggested.[24] Necropsy of cattle with bracken fern toxicosis reveals multiple hemorrhages throughout most tissues, necrotic GI tract ulcers, and pale bone marrow. Antibiotics and blood and platelet transfusions may be appropriate, but cattle with advanced bracken fern toxicosis (platelet count < 50,000/μL, leukocyte count < 2000/μL) usually die.

Paradoxical Erythroid Hypoplasia

Monica Aleman

Recombinant human erythropoietin (rhEPO) has been used in racehorses to enhance their athletic activity by stimulating erythrocyte production in the bone marrow. Mild to moderate anemia and paradoxical erythroid hypoplasia based on bone marrow cytology were reported in two Standardbred racehorses following rhEPO administration.[25] Serum from these horses inhibited the rhEPO-induced activity of mouse bone marrow in vitro. The degree of inhibition was inversely proportional to the amount of exogenous rhEPO added to the serum, suggesting the presence of anti-rhEPO antibodies. Anti-rhEPO antibodies to exogenous rhEPO likely cross-reacted with the horses' endogenous rhEPO. These horses were treated with dexamethasone and returned to their usual athletic activity.

Erythrocytosis (Polycythemia)

Debra Deem Morris

Absolute erythrocytosis is caused by increased erythropoiesis that creates a circulating erythrocyte mass above normal for the species. Relative erythrocytosis caused by hemoconcentration, endotoxemia, and splenic contraction (horses) must be ruled out because these conditions are much more common in large animals than absolute erythrocytosis. Diagnosis of absolute erythrocytosis is based on persistently elevated PCV, hemoglobin, and erythrocyte count without clinical evidence of shock or dehydration and without response to IV fluid therapy. Primary erythrocytosis is associated with normal arterial oxygen tension and reduced plasma erythropoietin, whereas secondary erythrocytosis is due to increased production of erythropoietin.

All disorders characterized by an absolute erythrocytosis share clinical manifestations caused by expanded blood volume and increased blood viscosity. Generalized vascular expansion and venous engorgement cause the characteristic "muddy" hyperemia of mucous membranes. A marked decrease in cardiac output accompanies blood hyperviscosity and ultimately impairs tissue oxygenation, producing the vague signs of lethargy and weight loss. There may be an increase in thrombotic complications like laminitis and renal failure.

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Congenital Erythrocytosis

Familial erythrocytosis, described in cattle[1] and humans,[2] is due to autonomous erythropoietin production without a demonstrable lesion. Congenital erythrocytosis is thus a form of inappropriate secondary erythrocytosis. Chronic hypoxia should be ruled out by measuring arterial oxygen concentration. The only way to definitively differentiate secondary erythrocytosis from primary erythrocytosis is by determination of serum erythropoietin.

Acquired Erythrocytosis

Primary Erythrocytosis

Polycythemia vera, an idiopathic myeloproliferative disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic elements, has not been reported in large animals.

Secondary Erythrocytosis

PHYSIOLOGICALLY APPROPRIATE ERYTHROCYTOSIS. In domestic animals, absolute erythrocytosis is usually secondary to chronic diseases that produce tissue hypoxia. Chronic tissue hypoxia that attends residence at high altitude, congenital heart defects that produce right-to-left shunting, and some forms of chronic pulmonary disease induce a compensatory increase in plasma erythropoietin that results in absolute secondary erythrocytosis.[3]

The partial pressure of oxygen (P_{O_2}) in capillaries must be maintained close to 40 mm Hg to ensure adequate off-loading of oxygen to tissues. At elevated altitudes, diminished atmospheric oxygen tension produces a much smaller alveolar capillary P_{O_2} gradient and an inadequate driving force for tissue oxygenation. Erythropoietin production in response to hypoxia causes erythrocytosis to increase the oxygen-carrying capacity of circulating blood. Cattle are most susceptible to the effects of high altitude, and some develop polycythemia at 1800 m above sea level. Horses develop an increased erythrocyte mass above 2200 m, especially when in training. Sheep are similar to cattle, but goats are apparently least susceptible to elevation hypoxia.

Congenital cardiac disorders that produce right-to-left shunts are a common cause for absolute erythrocytosis in large animals. Tetralogy of Fallot is the most common defect to cause shunting of unoxygenated blood into the peripheral circulation, although a number of other defects (ventricular septal defect [VSD] being the most common) may eventually result in right-to-left shunting and secondary erythrocytosis.[4]

Chronic impairment of alveolar ventilation may eventually cause erythrocytosis, although most chronic pulmonic diseases in large animals are not associated with significant hypoxemia. Chronic obstructive pulmonary disease in horses may produce enough ventilation/perfusion mismatching to reduce the pressure of arterial oxygen below normal, but the resultant hypoxemia is insufficient to induce erythrocytosis.

PHYSIOLOGICALLY INAPPROPRIATE ERYTHROCYTOSIS. Inappropriate elaboration of erythropoietin (i.e., normal P_{O_2} and secondary erythrocytosis) may rarely accompany renal, hepatic, or endocrine disorders, especially those caused by neoplasia. Secondary erythrocytosis may accompany nonmalignant renal disorders, in which local intrarenal ischemia is believed to mediate increased erythropoietin production. Paraneoplastic erythrocytosis with normal serum erythropoietin is due to tumor production of androgenic steroids or a protein with erythropoietin-like action.[5] Increased plasma erythropoietin and secondary erythrocytosis has been identified in horses with hepatocellular carcinoma.[3,6] Erythrocytosis was described in a horse with hepatoblastoma[7,8] and in another with lymphoma,[9] but serum erythropoietin levels as measured by a human assay were normal in both instances. In the horse with lymphoma, erythropoietin gene expression was identified in the lymphoma tissue. Typically, the diagnosis of inappropriate secondary erythrocytosis is based on elevated serum erythropoietin in the absence of hypoxemia. Elevated serum erythropoietin may not be demonstrated because of the nature of the assay or other compounds causing erythrocytosis.

Treatment of Erythrocytosis

When erythrocytosis is not in response to an appropriate physiologic stimulus (e.g., primary erythrocytosis and inappropriate secondary erythrocytosis), phlebotomy to keep PCV below 50% is the mainstay of treatment to control hypervolemia and blood hyperviscosity. Initially 2 to 4 L of blood may have to be removed every 2 to 3 days, but as iron deficiency supervenes, the frequency of phlebotomy may be reduced. The myelosuppressive drug hydroxyurea, used in humans and dogs with *polycythemia vera,*[2,10] has not been tried in large animals.

Appropriate management of secondary erythrocytosis is more complex because there is a need for increased oxygen-carrying capacity of the blood. The beneficial effect of expanded red cell mass is ultimately offset by the detrimental effect of increased blood viscosity on oxygen delivery. Oxygen delivery is impaired when PCV exceeds 60%, although continued erythropoietin output may result in overcompensation. Phlebotomy is indicated when PCV is over 60%, but the optimum PCV for patients residing at high altitudes or those with right-to-left cardiac shunts must be determined by trial and error.

The long-term prognosis for patients with erythrocytosis is determined by the severity and cause of the disorder. Congenital cardiac defects, neoplastic diseases, and chronic organ insufficiency carry a guarded to poor prognosis. Familial or primary erythrocytosis may be managed by phlebotomy, although there are no long-term follow-ups for large animals with these disorders.

Proliferative Disorders of Lymphoid and Myeloid Systems

The lymphoproliferative disorders reported in large animals are lymphoma, lymphocytic leukemia, and plasma cell myeloma. The myeloproliferative disorders are myeloid leukemias and malignant histiocytosis.[1] The following sections will describe lymphoma, leukemia, and myeloma.

Bovine Lymphoma

John A. Angelos • Mark C. Thurmond

Bovine lymphoma (lymphosarcoma) is characterized in terms of the frequency of occurrence (sporadic or endemic/enzootic), age at onset, organ involvement, and associated etiologic agent. Sporadic bovine lymphoma occurs as generalized lymphadenopathy in calves (calf or juvenile form), as thymic involvement in cattle between 6 months and 2 years of age (thymic or adolescent form), and as a cutaneous form in cattle between 1 and 3 years of age. Lymphoid tumors of cattle with sporadic bovine lymphoma are of the B- or T-cell lineage.[1] The most common form of lymphoma appears endemically in adult cattle (>2 years of age) and is associated with *bovine leukemia virus* (BLV) infection and typically involves multiple organ systems; BLV-associated lymphomas of adult cattle are of the B-cell lineage.[2] BLV is classified in the genus *Deltaretrovirus,* subfamily Orthoretrovirinae, and family Retroviridae.

Sporadic Lymphoma

CALF OR JUVENILE FORM. The prevalence and cause of juvenile lymphoma are unknown, but this form of lymphoma is rare and does not appear to be associated with BLV infection. Age at onset ranges from 3 to 6 months, but juvenile lymphoma can be seen in calves as young as 1 month or in cattle as old as 3 years. There have been reports of fetal involvement with the calf form.[3] Calves generally

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present with a history of slight to moderate depression, weight loss, weakness (mainly in older calves and despite good appetite), or lymphadenopathy (mainly in younger calves). The onset of signs can be sudden (within a week).

Physical examination may reveal generalized bilateral enlargement of lymph nodes, particularly the deep cervical and parotid nodes and occasionally the popliteal and hemal lymph nodes. Moderate to marked enlargement may be noted for the iliac and mandibular nodes. Rarely, node enlargement is not generalized but restricted to a regional anatomic site. Enlarged nodes tend to be smooth and firm but are not hot or painful. Mucous membranes are usually pale as a result of anemia. Tachycardia, tachypnea, hyperpnea, cough, and harsh respiratory sounds may be evident on auscultation. Less frequently reported signs include fever, ruminal tympany, enlarged liver, ataxia, and diarrhea.

Hematologic features include a microcytic, hypochromic anemia, low hemoglobin (<7 g/100 mL), low PCV (typically mid-20s), and leukocytosis primarily caused by lymphocytosis. Bone marrow examinations may reveal an elevated myeloid/erythroid ratio with massive neoplastic infiltration in some calves. Affected calves also tend to have low serum globulin and elevated AST. Neoplastic involvement of a variety of organs—spleen, heart, kidney, liver, pancreas, uterus, and thymus—may occur. Less thymic involvement occurs than with the thymic form of lymphoma; neoplastic tissue is found only as small, microscopic nodules. Subperiosteal neoplastic infiltration may produce spinal cord compression and result in paresis. The disease is rapidly progressive and usually fatal within 2 to 8 weeks of onset.

THYMIC OR ADOLESCENT FORM. The thymic form of lymphoma is very rare. The disease is usually seen in cattle 6 to 24 months of age but may occur in newborn calves and cattle up to 4 years of age. Clinical signs are produced by space-occupying lesions in the neck or thorax. Metastatic mammary lymphoma along with thymic lymphoma was reported in a 3-year-old beef heifer.[4] Cattle with thymic lymphoma typically present with brisket enlargement or firm swelling in the presternal area of the brisket, associated with pitting edema.[5] Loss in body condition, rumen tympany, and dysphagia are common. A space-occupying lesion around the esophagus can cause bloat secondary to the animal's inability to eructate rumenal gas. Although generalized lymphadenopathy is uncommon, enlarged superficial cervical and prescapular nodes are usually observed. Jugular veins are distended and nonpulsating; there may be muffled heart sounds and diminished resonance on thoracic percussion. Tachycardia, dyspnea, coughing, or respiratory distress may be present. Hematologic features are generally unremarkable. Anemia is not a consistent feature, and lymphocytosis is only seen occasionally. The course of the disease from the time of recognition is generally from 2 to 9 weeks, but poor condition may have been present for several months before presentation. The disease is fatal, often as a consequence of bloat.

Although thymic lymphoma is not associated with BLV infection, there has been one report of a BLV-positive 18-month-old heifer with thymic lymphoma. In situ PCR was used to detect the presence of BLV proviral DNA in lymphocytes of the thymus and in liver and kidney epithelium.[6]

ATYPICAL FORMS. A 7-month-old Holstein heifer with diffuse swelling over the left thigh, difficult ambulation, and peroneal and tibial nerve deficit had an infiltrative B-cell lymphoma involving the semitendinosus, semimembranosus, and gluteal muscles.[7] This heifer was serologically positive for BLV antibody, but the possibility of maternally derived antibody could not be ruled out. In another case report, the external and internal surfaces of the trachea of an 18-month-old Friesian heifer with cutaneous lymphoid tumors also had extensive lymphoid nodules covering the external and luminal surfaces of the trachea.[8] An 8- to 9-year-old beef cow with weight loss was reported with pleural and pericardial invasion with a lymphoid tumor of T-cell lineage; the animal tested negative for BLV by PCR.[9] Four of 10 cattle 3 years of age or less diagnosed with sporadic lymphoma had BLV provirus in tumor DNA as detected by PCR, and a possible role for BLV in some cases of sporadic lymphoma of cattle has been suggested.[10]

CUTANEOUS FORM. Cutaneous lymphoma is not as age specific as the other forms of sporadic lymphoma and may affect cattle between 1 and 3 years of age. The history may reveal an initial period of 1 to 3 months, during which cutaneous swellings are observed around the anus, vulva, escutcheon, shoulders, or flank. These signs may regress and subsequently recur. Lesions tend to be raised and can be ulcerated. They are generally about 2 to 3 cm in diameter with necrotic centers and may be painful on palpation. Other clinical signs depend on additional organ system involvement of the tumor and may include cardiac insufficiency, with brisket edema extending along the ventral abdomen and jugular pulsation. Pulse and respiration may be elevated as a result of anemia. Hematologic features include anemia and presence of atypical lymphocytes. The mandibular, prescapular, prefemoral, and supramammary lymph nodes are usually enlarged.

At necropsy, a variety of organs may be involved, including heart, brain, skin, spinal cord, liver, lung, kidney, and abomasum. The massive lymphoid infiltration of the skin resembles the clinical manifestations of mycosis fungoides of humans. In a report of a 12-month-old red Holstein heifer with cutaneous T-cell lymphoma, serum activity of lactate dehydrogenase (LDH) was moderately increased despite normal to minimally increased activities of liver- and muscle-specific enzymes.[11]

HEMONODE ENLARGEMENT (HEMAL LYMPH NODE). A lymphoproliferative condition associated with hemonode enlargement and some generalized lymphadenopathy has been described for cattle infected with a lentivirus[12] that is now called *bovine immunodeficiency virus* (BIV). BIV belongs in the genus *Lentivirus,* subfamily Orthoretrovirinae, and family Retroviridae. BIV has molecular similarity to human immunodeficiency virus and is associated with persistent lymphocytosis, lymphadenopathy, CNS lesions, progressive weakness, and emaciation. Infected calves may develop enlarged superficial nodes (hemonodes), mainly in the cervical region anterior and dorsal to the prescapular lymph node, over the spine of the scapula, in the paralumbar fossa, and dorsal to the prefemoral lymph node. Lymphocytosis is possibly related to an increase in B lymphocytes. In utero transmission of BIV has also been documented.[13]

Adult Lymphoma (Bovine Leukemia Virus)

The adult, or enzootic, form of lymphoma is the most common neoplastic disease of cattle and is associated with BLV infection. Rates of lymphoma in cattle vary considerably, probably reflecting variation in BLV infection rates. In 1978 the U.S. condemnation of carcasses because of lymphoma was reported to be 170 per 100,000 head slaughtered.[14] A high condemnation rate, sometimes exceeding 1%, was reported for slaughtered California dairy cows,[15] and about 1.73% of BLV-infected cattle had lymphoma.[16] The rate of lymphoma-associated cattle condemnations appears to have increased over time.[15]

Epidemiology The epidemiology of adult lymphoma is not completely understood. Herd size might be positively correlated with a high rate of lymphoma, which may reflect higher rates of BLV infection in large herds or a preponderance of susceptible pedigrees in some of the herds studied.[16,17] Susceptibility to BLV infection is associated with BoLA type,[18,19] which may explain why higher rates of lymphoma are found in certain families of cattle. The progression of disease to lymphocytosis in some BLV-infected cows may also be influenced by BoLA type, suggesting a genetic predisposition to development of lymphoma through the antigens of the major histocompatibility complex (MHC) encoded at closely linked loci. Polymorphisms at the MHC class II BoLA-DRB3.2 gene have been

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associated with differing circulating proviral loads in blood of Argentinian Holstein cattle and can be used to define BLV-resistant versus susceptible genotypes in these cattle.[20] Other potential contributing factors (e.g., nutrition, concurrent infections, environmental/meteorologic stressors) have not been explored sufficiently. There is no evidence for a seasonally associated pattern to appearance of clinical lymphoma.[15] Antigenic and molecular evidence for the presence of BLV in mammary glandular epithelium has been demonstrated.[21] The effect of BLV persistent mammary infection on the mammary gland is not completely understood. Although one study identified increased average milk production in BLV-infected versus uninfected cattle,[22] others report negative associations between milk production and BLV status.[23,24]

Economics The economic importance of adult lymphoma varies according to production type.[24,25] Producers incur losses from lymphoma associated with death of cattle (particularly genetically valuable livestock), loss of milk production, costs of treatment and diagnosis, and premature replacement costs for cattle dying or culled as a result of lymphoma. The latter may explain, in part, an observed increased rate of culling found for BLV-infected dairy cattle.[22,26] Besides premature culling and replacement costs, losses due to failure to retain salvage value of cows condemned for lymphoma at slaughter are also incurred.[15] A hidden cost may also be in the perpetuation of BLV-infected cattle via in utero infection of calves born to cows with lymphoma.[27,28] Although economic losses are associated with morbidity and mortality of cattle that develop lymphoma, estimates of production losses associated with BLV infection are variable. BLV positivity, as determined by serum BLV ELISA or milk ELISA, has not been associated with production losses in dairy cattle in Canada or Turkey.[29-31] In Michigan dairy herds, an increased prevalence of BLV was associated with decreased herd milk production and decreased cow longevity.[32]

Diagnosis Cattle presented with the adult or enzootic form of lymphoma usually are older than 4 years of age but may be as young as 2 years. Cattle are often presented with a history of loss in condition, an abrupt drop in milk production (over a period of a few days), enlarged peripheral nodes, exophthalmos, or partial to complete anorexia, particularly with regard to grain or concentrates. Because dry cows are not observed as closely as lactating cows and are not monitored for milk yield, lymphoma is less likely to be recognized until they freshen. Subclinical lymphoma may be diagnosed in cows submitted for routine reproduction examinations; other signs may include diarrhea, ataxia, paresis, ketosis, and infertility.

Physical examination often reveals an organ system failure resulting from tumor involvement. Thoracic auscultation may reveal cardiac dysrhythmia, tachycardia, tachypnea, and hyperpnea. Common sites of lymphoid tumor predilection in adult lymphoma include heart (usually right atrium), abomasum, uterus, kidney, and spinal cord (epidural space); other common sites include the retrobulbar space and rumen/reticulum.[33] Epicardial lymphosarcoma has been described in three dairy cows 3 to 19 months after diagnosis and treatment for idiopathic hemorrhagic pericardial effusion; at the time of initial presentation with pericardial effusion, none of the three had cytologic evidence of neoplasia in pericardial fluid.[34] Dependent pitting edema is common when cervical or supramammary lymph nodes are involved. Involvement of intestinal lymphatics is often associated with generalized dependent edema anterior to the udder. Peripheral lymph nodes typically found to be enlarged are the prescapular, femoral, and supramammary nodes. Feces may be scant, pasty, or watery, probably reflecting the presence of lesions within the GI tract. Melena may be present in animals with ulceration of the abomasum and lymphoid cell infiltration in the abomasal wall. The main ultrasound finding in a case of abomasal lymphosarcoma was enlargement of lymph nodes caudal to the reticulum, as well as severe enlargement of the abomasum with thickening of the abomasal wall.[35] Rectal palpation can be useful in cases lacking peripheral node enlargement or exophthalmos. Tumor masses palpated in the abdomen typically are multiple and range in size from only slightly enlarged lymph nodes to massive lesions half a meter in diameter. The internal iliac nodes are involved in most cattle with abdominal tumors.

Tumors tend to be firm but not hard and may feel slightly lobulated. Differentiation by palpation of lymphoma tumors from other masses is highly subjective. Carcinomas tend to be of similar consistency but are seldom larger than 15 cm in diameter and are usually associated with intestinal tissue. Lymph nodes of cows with carcinoma are not usually enlarged unless a secondary infection is present. Melanomas are generally less than 15 cm in diameter and hard, sometimes with protrusions 1 to 2 cm high along the surface, and not usually found associated with lymph nodes. Masses of fat necrosis tend to be firm and are usually associated with omental tissue. Internal abscesses are often single and associated with the uterus, as a consequence of uterine tear and infection during parturition, or with gluteal muscles of the pelvic ceiling, as a consequence of injection-related infections. Exploratory laparotomy may be indicated as an additional diagnostic tool in difficult cases, particularly in valuable cattle.

The hemogram of cattle with lymphoma is often unremarkable. A microcytic, hypochromic anemia may be present in cattle with GI hemorrhage. Because fibrinogen levels have been inconsistent in lymphoma, measurement may be helpful only in differentiating an abscess. Some 30% of cattle with BLV infection develop persistent lifelong lymphocytosis, composed mostly of B cells.[36,37] Lymphocytotic cattle have higher BLV proviral loads in peripheral blood lymphocytes than nonlymphocytotic cattle, but some nonlymphocytotic cattle may have high BLV proviral loads and could represent obstacles to successful eradication efforts.[38] Low antibody response to the BLVp24 antigen was observed in cattle with low BLV proviral loads.[38] In a majority of calves that were experimentally infected with BLV, calves became PCR positive sooner than they seroconverted (as determined by a commercial BLV antibody test).[39]

Cytologic analysis of aspirates of tumors or tumorous nodes may not always be a reliable diagnostic tool, although it can be helpful. Discrimination cannot be made between a normal node responding to an infectious agent and a node involved with neoplastic lymphocytes; in both situations, cells resembling young, poorly differentiated lymphocytes may be present. Examination of nontumorous active lymph nodes may reveal an elevated proportion of large, young lymphocytes that could resemble those of lymphoma. In a retrospective study, the sensitivity of antemortem diagnostic testing found peripheral lymph node biopsy to be 100% sensitive while fine-needle aspirate was only 41% sensitive.[33] When compared to core needle biopsy of peripheral lymph nodes, fine-needle aspiration is more specific and more predictive for a positive test.[40] Cytology and culture of aspirates can be helpful in differentiating a tumor from an abscess. Failed attempts at collection of cerebrospinal (lumbosacral) fluid in cattle with recumbency or rear limb weakness may be associated with the presence of lymphoid tumors in the vertebral canal; cytologic examination of cells from the collection needle in such cases may reveal abnormal lymphoid cells.

Standard serologic testing for BLV involves identification of antibody against the 51-kD envelope glycoprotein (gp51). BLV diagnosis historically involved use of the agar-gel-immunodiffusion (AGID) test, but that method has been shown to be less sensitive than ELISA.[41] Commercially available ELISA test kits (e.g., HerdChek Bovine Leukemia Virus Antibody Test Kits [IDEXX Laboratories Inc., Westbrook, Me.], Bovine Leukemia Virus Antibody Test Kit, ELISA [VMRD Inc., Pullman, Wash.], SVANOVIR BLV gp51-Ab ELISA [Svanova Biotech AB, Uppsala, Sweden]) can detect antibodies to gp51 in serum and/or milk. A recombinant p24 antigen ELISA has been developed.[42] Diagnosis is also possible with PCR to detect BLV nucleic acid,[43-45] as well as by a combined PCR-ELISA that is more sensitive than staining of PCR amplicons with ethidium bromide.[46] ELISA-positive cattle that were not detected by PCR testing have been reported; this is most likely related to a low number of infected circulating lymphocytes at the time of sample collection.[47] PCR by

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itself is considered unreliable for routine detection of BLV in herds with a high prevalence of disease.[48] The ability of PCR to detect a BLV-infected animal is improved by means of a nested PCR, which was reported to be effective in diagnosing infection when seroconversion had not yet occurred.[49] A loop-mediated isothermal amplification (LAMP) assay has been developed to diagnose BLV infection in cattle; this test has sensitivity at least as good as the conventional single PCR and has the advantage of not requiring specialized thermal cycling equipment.[50]

The presence of antibodies to gp51 is generally considered to be a prerequisite to a diagnosis of lymphoma, except for cows during the periparturient period, when circulating antibodies may fall below the level detectable by a serologic test.[51] The mere presence of BLV antibodies does not necessarily mean an animal has lymphoma, which is found in only about 1.7% of BLV-infected cattle.[52] However, serology can be helpful in predicting the chance of lymphoma in cattle seropositive to the gp51 antigen. Sera from cattle with lymphoma generally have high titers to the gp51 antigen (a score of 3 or 4 on AGID) compared with those of infected cattle without lymphoma (score of 1 or 2 on AGID). Cattle that do not have lymphoma tend not to have antibodies to the p24 antigen of BLV, as detected by AGID. The percentage of cattle with histologically confirmed lymphoma but in which lymphoma was not diagnosed by a gp51-positive and p24-negative test result (false-negative rate of the diagnostic test) has been found to be only 0.21% using the AGID test.[16] Unfortunately, most diagnostic laboratories do not have the capability to perform the test using the p24 antigen.

At necropsy, tumors are found enclosed in a capsular-like tissue that, when sectioned with a knife, results in an eversion of tumor stroma. Cut tumor tissue is cream colored and friable, with little binding structure. Centers of tumors may appear necrotic and mushy, whereas peripheral regions are firmer and pink to white. Histopathologic analysis provides the only definitive diagnosis. Tissue should be biopsied by surgical removal of as much of the node (or mass) as possible.

Control No curative treatment for lymphoma exists. Supportive therapy may be indicated to reduce discomfort and prolong life long enough to remove valuable ova/embryos or calves or to harvest semen.

Until more information is available on the epidemiology of lymphoma, control and eradication hinge on success of efforts to eradicate BLV from a herd. No vaccines presently offer effective protection from BLV infection.[53-56] Control and eradication of BLV require reduction of blood transmission through iatrogenic means and through physical contact among cattle.[57] Transmission associated with physical contact between infected and susceptible cattle can be reduced by segregating infected and uninfected cattle.[58,59] Separation of cattle by 10 feet is preferred, but a single fence may sufficiently reduce the degree of contact necessary for transmission. Transmission after physical contact may be via inhalation of BLV shed in nasal secretions.[60-63] Experimental studies have found that under extreme conditions of blood contamination and mucosal irritation, BLV can be transmitted rectally.[64-68] Under conditions typical of routine palpation during pregnancy examination, however, BLV does not necessarily appear to be transmitted to any measurable degree.[66,68] If potential for rectal transmission is a concern, palpation sleeves may be rinsed or replaced between cows. Although insect transmission of BLV is theoretically possible[69] and has been demonstrated experimentally by interrupted feeding of tabanids from cattle with persistent lymphocytosis to uninfected cattle,[70] studies of natural infection have not linked flies to new natural infections.[71,72] Several studies have failed to demonstrate transmission after use of a common needle.[73-75] However, infection after use of a tuberculin needle dipped in blood of a BLV-infected animal could be prevented by wiping the needle with cotton before injection.[76] Although data have not shown the use of common needles to be an important means of BLV transmission, it would be prudent to use individual sterile needles for treatment, testing, or vaccination.

Transmission of BLV has not been shown in cows inseminated artificially using commercially prepared frozen semen.[77-81] However, infection by an infected bull during natural breeding may be possible.[82,83] Semen of 27 bulls that were BLV PCR positive in peripheral blood had no evidence of BLV by PCR.[84] Embryo transfer recipients should be tested for BLV before transfer.[85] Embryo transfer using uninfected recipients offers a means of producing phenotypically preferred cattle from BLV-infected cows and controlling in utero infection,[71,77,86,87] because at harvesting, embryos are not infected.[79] Through a washing procedure, it is possible to produce transferable in vitro–fertilized embryos that are free of BLV provirus from oocytes that are exposed to BLV during maturation, fertilization, or after fertilization.[88]

For most herds, control and eradication of the infection would require modification of facilities, alteration of management practices, and serologic surveillance at least annually. Planning a control program should include a cost/benefit analysis to evaluate potential return on the investment. Financial benefit of a BLV control program has been documented in herds where prevalence of BLV infection is 12.5% or higher.[89] Selective culling of BLV-infected cattle based on positive lymphocyte BLV antigen expression in vitro was reported to be effective in preventing transmission of BLV infection.[90]

Feeding colostrum from BLV-positive cows to calves known to be BLV negative at birth was shown to decrease the risk of BLV exposure that presumably occurred during calving.[91] In Japan, feeding colostrum from the dam was also found to be protective against within-farm BLV transmission.[92]

Lymphoma in Horses

Monica Aleman • Johanna L. Watson

Lymphoma and *lymphosarcoma* are terms that have been used interchangeably to describe a group of neoplasias originating from the lymphoid system, such as nodal (lymph nodes) or extranodal lymphoma (thymus, spleen, mucosal-, conjunctival-, or skin-associated lymphoid tissue). The mucosal-associated lymphoid tissue includes mucous membranes lining the digestive, respiratory, and urogenital systems. Metastasis can occur to other organs, including primary lymphoid tissues like bone marrow. Based on its embryologic origin, lymphoma is classified as a mesenchymal neoplasm. Although the suffix *-oma* indicates a benign neoplasm, whereas *-sarcoma* indicates a malignant mesenchymal neoplasm, the Leukemia and Lymphoma Society determined that *lymphoma* is the appropriate term because all neoplasms of the lymphatic system in humans are malignant. In veterinary medicine, lymphomas are also malignant, so the term *lymphoma* has been adopted. It is important to emphasize that *lymphoid hyperplasia* is not synonymous with lymphoma.

Lymphoma is one of the most common malignant neoplasias in the horse; in postmortem studies, its prevalence is estimated to be 2% to 5%.[1,2] In contrast to other species, there is no proven viral etiology for development of lymphoma in the horse. Virus-like particles in lymph nodes of neonatal foals with lymphoma have been described, but no causal relationship has been proven.[3,4] Lymphomas can occur at any age, with reports as early as in an aborted equine fetus to horses older than 30 years,[4-6] but the average age of onset of all forms of lymphoma has been reported to be between 5 and 10 years of age. Studies of intestinal lymphoma report the mean age of onset to be 16 years.[6,7] There is no apparent breed or sex predilection. Clinical signs vary depending on tumor location, but the most common include lymphadenopathy, lethargy, weight loss, edema, and pyrexia. Affected lymph nodes tend to be firm, cool, and nonpainful. In one retrospective study of 79 horses with lymphoma, 21 cases had ocular involvement.[8] Paraneoplastic pruritus and alopecia were described in a horse with diffuse lymphoma.[9] Neurologic alterations, lameness, osteolysis, and pathologic fractures have been described as the result of lymphoma.[10-15]

Although the hematologic features of lymphoma vary, anemia is a relatively common finding and is thought to be due to suppression

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of erythropoiesis, bone marrow infiltration, blood loss, or IMHA. Frank leukemia is rare, but when present, neoplastic cells are generally found in the bone marrow.[16] More often the lymphocyte count is within reference range or low. Atypical lymphocytes may be noted in the blood smears of 20% to 50% of affected horses, especially late in the disease course.[17-20] A modest neutrophilic leukocytosis with an elevated fibrinogen is often seen. This inflammatory response can be confounding when attempting to differentiate neoplasia from internal abscessation.[21] Serum biochemistry profiles may provide indication of internal organ involvement. Serum protein alterations are frequently observed and include hypoalbuminemia, hyperglobulinemia with polyclonal gammopathy (most cases), and decreased albumin/globulin ratio. However, deficiencies in IgG and IgA concentrations were reported in a horse.[22] Neoplastic lymphocytes may arise from reactive B-cell clones producing antibodies responsible for gammopathies and immune-mediated processes (hemolytic anemia, neutropenia, lymphopenia, thrombocytopenia). Although low serum IgM concentrations and hypercalcemia have been reported in few cases, these are not consistent features of lymphoma in the horse.[20,22-24]

Lymphomas in horses have been classified based on anatomic distribution, morphology, and cell lineage.[24-27] Based on anatomic distribution, lymphoma classification in the horse is as follows: multicentric, generalized, alimentary or intestinal, splenic, mediastinal, thymic, and cutaneous.

Morphologically, lymphocytes are classified as small-cell type if their nuclear diameters are 1.5 times the diameter of erythrocytes or less; cells are classified as large if their nuclei average 2 times or more the diameter of erythrocytes.[26] Small-cell–type lymphoma consists of 60% or more of small cells. Large-cell lymphoma consists of 60% or more of large cells. A lymphoma designated as "mixed" is a tumor that contains both small and large neoplastic cells of the same immunophenotype.[26]

Immunohistochemical classification of lymphomas can be determined using monoclonal antibodies such as CD79a (mb-1) and B29 for B-cell lymphomas and CD3 and CD5 for T-cell lymphomas. All three—B-, T-, and mixed B- and T-cell lymphomas—have been reported in the horse.[26,27] The monoclonal antibody proliferating cell nuclear antigen (PCNA) has been used to determine the proliferative status of the cells.[26] Frequently, lymphomas are described as T-cell–rich B-cell lymphoma or vice versa. T-cell–rich, large B-cell lymphoma is a neoplastic proliferation of large B cells associated with a prominent component of non-neoplastic reactive T lymphocytes that constitute a significant percentage of the cellular population.[26] The presence of large numbers of non-neoplastic T cells within a B-cell lymphoma could result in erroneous diagnosis of a T-cell tumor. Neoplastic cells are characterized by large cell size, large vesicular and irregularly shaped nuclei with coarse chromatin, atypical mitotic figures, and positive immunostaining to PCNA markers. Non-neoplastic cells are identified by their normal morphology and lack of immunoreactivity to proliferation markers. However, discriminating between neoplasia and chronic inflammation with reactive lymphocytes can be difficult. Molecular clonality assays can be used to make this determination. Clonality assay results indicating a polyclonal population of lymphocytes support a classification of inflammation, whereas results indicating a monoclonal population support a diagnosis of neoplasia. Accurate lymphoma characterization and staging in humans has been critical to establishing effective therapeutic management plans and accurate prognoses.

Multicentric Lymphoma

Multicentric lymphoma involves lymph nodes (veterinary oncology terminology: nodal = lymph node; multiple lymph nodes = multinodal = multicentric), regardless of location. Extranodal lymphoid tissue (lymphoid tissue other than lymph nodes) is not involved, but multicentric lymphoma may metastasize to extranodal areas, in which case it will be classified as generalized (diffuse) lymphoma. In veterinary medicine, the terms *multicentric* and *generalized* have been used interchangeably.

Generalized Lymphoma

Generalized lymphoma is considered an end-stage disease characterized by involvement of both nodal and extranodal lymphoid tissue. This form is more common than the intestinal (extranodal) and mediastinal (nodal) forms alone. Horses often present with severe lethargy, emaciation, anorexia, generalized lymphadenopathy, and edema due to impaired lymphatic drainage.[6,29] Anemia is common, and hypoproteinemia due to hypoalbuminemia may be found. Although leukemia is rare, it is generally associated with this form of lymphoma.[16] In addition to lymphoid tissue involvement, infiltration of neoplastic lymphocytes has been reported in the spleen, liver, bladder, kidney, lung, heart, nasopharynx, eye, ovary, uterus, brain, and spinal cord.[4,16,22] Multifocal eosinophilic granulomas have been identified in neoplastic lymph nodes and are hypothesized to be a response to paraneoplastic production of IL-5 and granulocyte-monocyte colony-stimulating factor (GM-CSF).[15]

Alimentary or Intestinal Lymphoma

Alimentary tract lymphoma involves the GI tract, more frequently the small intestine.[27,30] Lymphoma is the most common neoplasia of the intestinal tract in horses.[6] The mean age of onset of intestinal lymphoma is 16 years (range, 2 to 30 years). Arabian horses are the most common breed affected.[6] Lymphoma arises from the lymphocytes of the lamina propria (extranodal lymphoid tissue) of the intestinal tract, resulting in diffuse or segmental thickening, focal masses, or scattered crater-like ulcers with raised margins on the intestinal wall.[27,28,30] Lymphadenopathy is generally not present. Metastases to mesenteric lymph nodes, liver, and spleen have been reported.[28] Transabdominal ultrasound may be very useful for detecting intestinal thickening and cecal lymphadenopathy. Clonality analysis of tissues from affected horses reveals that T-cell lymphomas are more common than B-cell lymphomas in the intestinal tract.[6] This neoplasia is usually associated with malabsorption, protein-losing enteropathy (hypoalbuminemia), weight loss, edema, abdominal effusion, mild recurrent colic, and diarrhea.[30-33] Affected horses frequently have abnormal glucose or xylose absorption tests, indicating small intestinal malabsorption. In one study, cytologic analysis of abdominal fluid provided support for the diagnosis of intestinal neoplasia of any kind in 38% of the cases examined.[6]

Thoracic Lymphoma: Mediastinal/Thymic

Lymphoma is the most common thoracic neoplasia in horses, and it may involve mediastinal lymph nodes and the thymus and/or lungs.[34,35] Exclusive involvement of mediastinal lymph nodes is called *mediastinal lymphoma,* whereas exclusive involvement of the thymus is called *thymic lymphoma.* Its prevalence varies from 18% to 29% of all forms of lymphoma.[32,36] Primary and secondary (metastatic) mediastinal lymphomas have been reported, with metastatic being more common.[34] Primary mediastinal lymphoma is usually seen in adult horses (mean age, 10 years; range, 2 to 30 years); however, the disease has been reported in a 1-month-old foal with a 1-week history of respiratory distress.[5] Metastasis from primary mediastinal lymphoma often occurs. In the early stages of the disease, minimal clinical signs may be observed. Common clinical signs include nasal discharge, adventitious lung sounds, pleural effusion, thoracic ventral and limb edema, and regional lymphadenopathy at the thoracic inlet.[32,34] Other signs may include cough, pyrexia, pleurodynia, and in some cases respiratory distress.[34,37] Temperature, pulse, and respiratory rate are often elevated. Dysphagia may be observed in cases with retropharyngeal lymphadenopathy.[38] An elevated nucleated cell count of several thousands per µL, with a large percentage of abnormal lymphocytes, may be evident in pleural fluid cytologic analysis. However, collection of multiple pleural fluid samples may be necessary to establish a definitive diagnosis.[37] Cytologic abnormalities include the presence of prolymphocytes, lymphoblasts, nuclear blebbing, indented and cleaved nuclei, amorphous nuclei, altered nuclei/cytoplasm ratio, and mitotic figures.[37] Thoracic lymphomas may

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be of B-, T-, or mixed-cell origin, but T-cell lymphomas are most common.[26,37]

Cutaneous Lymphoma

Cutaneous lymphomas are confined to the skin-associated lymphoid tissue. Single or multiple subcutaneous firm, nonpainful nodules ranging from less than 1 cm to greater than 20 cm in diameter can develop rapidly or slowly, regionally or over most of the body surface.[39,40] The nodules are usually covered with hair. In some cases, the lesions tend to wax and wane spontaneously, or in association with sex hormone levels, seasonality, or steroid therapy. There is one report of complete regression of cutaneous lymphoma following surgical removal of an ovarian tumor.[41] Depending on the anatomic location, cutaneous lymphomas may cause mechanical lameness and limb edema secondary to vascular and lymphatic obstruction. In most cases, there are no associated hematologic abnormalities, and generalized lymphadenopathy and internal organ involvement is rare. Cutaneous lymphomas are usually of B-cell origin. A far less common form of cutaneous lymphoma, mycosis fungoides, is characterized by diffuse infiltration of neoplastic T lymphocytes in the epidermis, dermis, and subdermis. Mycosis fungoides has been reported in a mare with a vulvar mass that infiltrated the skin of the perineum and ventral abdomen.[42] This type of lymphoma may involve mucocutaneous junctions and carries a poor prognosis if deeper tissues are involved.[42]

Angiotrophic Lymphoma

This neoplasia, also known as *endotheliotropic lymphoma* or *intravascular lymphangiomatosis,* has been described in humans, dogs, and cats.[43-45] There is a single report in a 12-year-old pregnant Thoroughbred mare with anorexia, tachycardia, and mild fever.[46] The significant laboratory abnormalities were profound anemia (PCV 12%), decreased RBC count, marked anisocytosis, mild lymphopenia, low IgM, and marked erythroid hyperplasia and erythrophagocytosis on bone marrow biopsy. Triglycerides, cholesterol, and total bilirubin were elevated on serum biochemistry. Coombs and Coggins tests were negative. Postmortem examination revealed generalized icterus and moderately enlarged mediastinal and mesenteric lymph nodes. Histologic examination revealed thickened pulmonary alveolar septae and vessels crowded with atypical lymphoid cells with scattered mitoses. Similar atypical cells were evident within renal vessels. The neoplastic cells were determined to be of T-cell origin based on immunohistochemical staining. Angiotrophic lymphoma may represent an antemortem diagnostic challenge owing to the lack of circulating neoplastic lymphocytes and identifiable masses.

Chemotherapy for the Treatment of Lymphoma

There is limited information about chemotherapy for lymphoma in horses. One protocol used in two pregnant mares with lymphoproliferative disease consisted of a combination of cytarabine (200-300 mg/m^2 SC or IM q7-14d), chlorambucil (20 mg/m^2 PO q14d) or cyclophosphamide (200 mg/m^2 IV q14-21d), and prednisolone (1.1 to 2.2 mg/kg PO q48h).[47] Vincristine (0.5 mg/m^2 IV q7d) can be added if no clinical improvement is noticed in the first month of therapy. This protocol was continued for 2 to 3 months, then followed by a maintenance protocol consisting of gradual decreases of prednisolone and extending by 1 week the administration of other chemotherapeutic agents for the next 2 to 3 months. This was followed by extending the administration interval by another week for 2 to 3 months for a total of 6 to 9 months.[47] Other protocols include drugs used alone or combined such as L-asparaginase (10,000-40,000 U/m^2, IM q14-21d), doxorubicin (50 mg/m^2 IV), vincristine (1.4 mg/m^2 IV), and rituximab (375 mg/m^2 IV). A horse with thoracic lymphoma was treated with cytarabine (170 mg/m^2 IM) 2 weeks apart, alternating with cyclophosphamide (142 mg/m^2 IV) 7 days after each dosage of cytarabine.[37] In addition, the horse received prednisolone (86 mg/m^2 PO q48h) and was discharged 1 month after the initiation of chemotherapy with instructions to continue prednisolone at the previous dosage every 48 hours for the remainder of its life. Eight months after discharge, the horse was in good health and resumed light exercise. Therapy may be attempted with dexamethasone (0.2 mg/kg IV or PO q24h for 5 days) followed by prednisolone (1 to 2 mg/kg PO q24h).

Complications associated with chemotherapeutic agents in horses may include anorexia, lethargy, thrombosis, arrhythmias, laminitis, bone marrow damage, GI and genitourinary toxicoses, urticaria, and immunosuppression. Anemia, thrombocytopenia, leukopenia, and secondary infections may occur.[48] Successful management of cutaneous lymphomas has been achieved with glucocorticoids like dexamethasone, prednisolone, and betamethasone. Controversy exists regarding the nature of cutaneous nodules (i.e., possible lymphoid hyperplasia, not true lymphomas). Other treatment modalities that have been tried include autologous tumor vaccines and radiation therapy.[49-51] Although periods of remission have been reported with chemotherapy,[37,47] the long-term prognosis has been poor for the majority of horses.

Leukemia in the Horse

Monica Aleman

Leukemia is a rare neoplasia of the hematopoietic system that originates from the bone marrow (primary leukemia). A leukemic phase (secondary leukemia) has rarely been reported in horses.[16,18,19] Based on the cell of origin, the major forms of leukemia include myeloid and lymphoid leukemias, which can have an acute or chronic clinical course. According to the Leukemia and Lymphoma Society, *acute leukemias* are rapidly progressing disorders that affect mostly primitive or immature cells that lack normal function, whereas *chronic leukemias* progress slowly, allowing some growth and cell maturation that may preserve limited normal function. Reported leukemias in the horse include myelomonocytic, monocytic, granulocytic, eosinophilic, and lymphocytic forms.[16,18,51-66] Based on the presence and numbers of cells in blood, other terms used are *leukemic, subleukemic,* and *aleukemic leukemia.* Leukemic leukemia is characterized by an increase in cell numbers in peripheral blood; subleukemic leukemia is defined by an increase in abnormal blast cells in blood, with a total white cell count within the reference range or low; and aleukemic leukemia is characterized by the presence of abnormal cells in the bone marrow but not in peripheral blood.

There is no apparent breed or gender predisposition, based on the few reported cases.[16,18,52-66] The age at onset of clinical signs ranges from 2 to 25 years. The most common clinical signs are weight loss, lethargy, anorexia, pyrexia, and lymphadenopathy if associated with lymphoma. Other signs are weakness, ventral edema, exercise intolerance, colic, and recurrent or concurrent infections.

At the initial stages of disease, laboratory features may show mild hematologic abnormalities and include one or more of the following: anemia, neutropenia, lymphopenia, thrombocytopenia, hyperproteinemia, and hyperfibrinogemia. As the disease progresses (days to months), marked leukocytosis (counts may be >200,000 WBC/μL) and hyperproteinemia will be observed in leukemic leukemias.[16] Thrombocytopenia is a common hematologic feature.[16,62,63,66] Pancytopenia and high blast cell counts (up to 1.6×10^9 cell/μL) were reported in a lactating mare with myeloblastic leukemia.[66] Pancytopenia due to severe infiltration of leukemic cells in the bone marrow, ineffective hematopoiesis, and myelofibrosis has been reported.[62] Horses with multicentric lymphoma, pancytopenia, severe leukocytosis (more than expected for severe inflammation), or presence of atypical or blast cells in peripheral blood should prompt the collection of a bone marrow aspirate or biopsy. Bone marrow aspirates may have normal to altered myeloid/erythroid ratio (reference range, 0.5 to 3.76) with a disproportion of atypical or poorly differentiated blast or mature cells of certain lineage. Decreased or absent megakaryocytes is a common observation.

Hyperproteinemia due to hyperglobulinemia is a consistent finding. Serum electrophoresis typically shows a polyclonal increase of β_2- and γ-globulin fractions, and in some cases α-globulin fraction.

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TABLE 37-2

Monoclonal Antibodies for Specific Equine Leukocyte Antigens (ELAs)

ELA Marker	Specificity
EqCD2	T cells
EqCD3	T cells
EqCD4	Helper T cells (T_H cells)
EqCD5	T cells
EqCD8	Cytotoxic T cells (T_C cells)
EqCD11a/18	Panleukocyte
EqCD13	Myeloid cells
CD21	Most B cells
CD79a	B cells
EqWC1	Large T-cell and neutrophil subsets
EqWC2	T cells and neutrophils
EqWC4	Minor T-cell subset
MHCI	Nucleated cells
MHCII	B cells, macrophages, dendritic cells, and a large T-cell subset
IgM	B cells

CD, Cluster of differentiation; *Eq,* equine; *IgM,* immunoglobulin M; *MHC,* major histocompatibility complex; *WC,* white cell.

Marked increases in serum IgG and IgA concentrations have been detected in horses with lymphocytic leukemias.[16] Deficiencies in IgA and IgM have been reported in a single horse with chronic lymphocytic leukemia.[59]

Necropsy findings may include mucosal ulceration, edema, thrombosis, and hemorrhages of various organs due to intravascular leukostasis (aggregates of leukemic cells in blood vessels), disseminated intravascular coagulopathy, and thrombocytopenia secondary to decreased production of megakaryocytes. Leukemic-induced cell lysis may occur as the result of mediators released by neoplastic cells. Peripheral and internal lymphadenopathy may also be observed.

The diagnosis is based on results of a complete blood cell count (CBC) and chemistry panel, with cytologic and histopathologic evaluation of bone marrow, immunocytochemical analysis, flow cytometry, and immunophenotyping. Previously, leukemic cells in peripheral blood and bone marrow were described based on their morphology. However, this may result in leukemia misclassification, especially in acute leukemias where mononuclear blast cells comprise the leukemic clone, which may lack specific morphologic identifying features. Numerous cytologic and cytochemical stains (e.g., Wright, Giemsa, Sudan black B, peroxidase, periodic acid-Schiff, alkaline phosphatase, acid phosphatase, various esterases, and surface glycoproteins) have been used to determine leukemia type. Leukemic cells may lack specific cytochemical properties, however. Currently, the various types of leukemias are identified by specific cellular antigens, using a panel of monoclonal antibodies and flow cytometry to analyze peripheral blood and/or bone marrow. Examples are B-cell/IgM-positive, B-cell/IgM-negative, CD3/CD4/CD5-positive T-cell, CD3-negative/CD4-positive T-cell, and CD13-positive/myeloid leukemias.[16,59,63] The various monoclonal antibodies for specific equine leukocyte antigens are shown in Table 37-2.

The prognosis is grave, resulting in death within days to a few months after its diagnosis. Treatment of leukemia in horses has been attempted with cytosine arabinoside, cytarabine, and prednisolone, but without much success.[55,59,65]

Myeloma in the Horse

Monica Aleman

Myeloma is a neoplastic proliferation of plasma cells that primarily originates in the bone marrow but may have an extramedullary source.[67] Both forms have been reported in the horse.[68-70] Accumulations of neoplastic plasma cells outside the marrow is called *extramedullary plasmacytoma.*[67] Plasmacytomas can form in several organs and tissues, including the skin. The most common extraosseous sites in horses are lymph nodes, kidneys, spleen, and liver.[68,70,71] Multiple myeloma involves bone marrow at multiple locations and other tissues, and it is the most common form of myeloma in humans.[72] In human medicine, causes of myeloma include chromosomal translocation, irradiation, and chronic antigenic stimulation.[67]

Myeloma is a rare neoplasia of the horse (only 16 cases reported in the literature), with a median age of 14 years and a range of 3 months to 25 years of age.[68-71,73-83] Almost half of the horses were Quarter Horses, but various breeds including draft horses and ponies were represented. There is no apparent gender predilection. Clinical signs vary with the degree of plasma cell infiltration, extent, and location. The most common clinical signs are weight loss, anorexia, fever, pale mucous membranes, lethargy, limb edema, and recurrent infections.[68-71,82,83] Bone pain due to osteolytic disease is the most common early sign of myeloma in humans.[72] Four horses from the literature were reported to have osteolysis. The clinical signs in these horses included paresis, cervical pain, and lameness.[71,74,76,79]

Laboratory features are anemia, hyperproteinemia due to hyperglobulinemia, hypoalbuminemia, and proteinuria. Anemia results from reduced erythropoiesis secondary to myelophthisis, blood loss, and as a result of the osmotic effect of paraproteins. Pancytopenia is observed if myelophthisis develops. Hypercalcemia has been reported in a few cases.[68,70,71] Significantly different features have been reported (hypoproteinemia, hypoglobulinemia, hypoalbuminemia, hypocalcemia) in a gelding with systemic amyloidosis and multiple myeloma, thought to be the result of severe protein-losing enteropathy.[83] Concurrent systemic amyloidosis and multiple myeloma is common in humans but extremely rare in domestic animals, with only one cat and one horse reported in the literature.[83,84] Serum parathyroid hormone–related protein concentration was mildly elevated in one horse with multiple myeloma.[71]

In secretory myelomas, neoplastic plasma cells are responsible for overproduction of a monoclonal Ig called *M protein* or *paraprotein.* M protein may be fragments (mainly light chains also called *Bence Jones protein*) or a complete Ig. Subclasses of IgG are the predominant paraprotein associated with myeloma in horses,[68,82] but there are three reported cases with IgA paraprotein.[70,71]

Plasma cells are relatively sparse in normal bone marrow. Involvement of marrow is usually focal rather than diffuse, requiring multiple marrow aspirates in some cases to confirm plasmacytosis. The diagnosis of multiple myeloma in humans is based on the presence of at least 10% of plasma cells in the affected tissue, monoclonal protein in serum or urine, and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions). Renal insufficiency has not been reported in horses with myeloma.[68,70] Bleeding and blood hyperviscosity syndrome are common complications of multiple myeloma in humans.[72] These complications have been reported in four horses.[68,77]

The median length of survival after diagnosis in humans is approximately 3 years.[72] Owing to poor prognosis or deterioration of condition, most reported horses were euthanized within a few days to months of diagnosis. However, two horses survived for 1 and 2 years, respectively.[78,81] One horse was euthanized 3.5 years after the diagnosis for deteriorating condition.[70]

Lymphangioma in the Horse

Monica Aleman

Lymphangioma is a rare tumor in horses that originates from lymphatic vessels. Morphologically, lymphangiomas are classified into three types: simplex or capillary, cavernous, and cystic.[85] This tumor may involve cutaneous tissues of the mammary gland, thigh and inguinal regions, pleural cavity, and intestines and has only been observed in young horses.[86-88] Clinical signs vary depending on tumor location. At diagnosis, these tumors were extensive; surgical

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removal was not attempted, and all horses were reportedly euthanized.

Other Diseases of the Hemolymphatic System

Anthrax

Kristin A. Clothier*

Anthrax is a soil-borne bacterial disease primarily affecting herbivores and most often presenting as acute septicemia with high mortality. Other animal species, including humans, can be infected. Anthrax occurs worldwide and is noteworthy both because of its impact on agriculture and its potential to cause zoonotic infections. *Bacillus anthracis,* the etiologic agent of anthrax, has been classified by the Centers for Disease Control and Prevention (CDC) and the USDA as a "select agent" because it is one of the microbes most likely to be used as a bioterrorism agent. Dissemination of genetically modified *B. anthracis* spores through the U.S. Postal Service (USPS) in 2001 demonstrated its usefulness in this capacity.[1] Possession of this organism is under federal jurisdiction and is highly regulated.

Etiology

In the vegetative form, *B. anthracis* is a large, rectangular-shaped, gram-positive rod. Vegetative cells are predominantly found in tissues of infected animals, but *B. anthracis* exchanges genetic information with other *Bacillus* spp. in the environment, indicating vegetative cells can exist outside animal hosts.[2] Under nutritionally limiting conditions, vegetative cells are induced to form spores. Sporulation is an oxygen-dependent process and does not occur under anaerobic conditions. The spore form of *B. anthracis* is highly stable and resists many chemical and heat treatments, as well as adverse environmental conditions.[3] Spores can survive and remain infectious in the environment for decades.

Pathogenesis

Exposure of animals occurs primarily from grazing contaminated pastures and ingestion of spores.[4] Forage grown on anthrax-positive premises and animal by-products containing spores are other sources for infection. In swine, consumption of contaminated animal by-products in feed is the usual source of infection.

Ingested anthrax spores cross mucosal barriers, are phagocytosed by macrophages, and traffic to regional lymph nodes. As spores convert to their vegetative phase, they are able to avoid the antimicrobial action of the phagocyte, kill the host cell, and escape into the extracellular environment. Plasmid-encoded virulence factors, particularly a poly-D-glutamic acid capsule and a three-component toxin, are keys to survival in the host.[4] Production of the capsule by vegetative cells enables the bacterium to resist phagocytosis and mask surface antigens, resulting in evasion of the host's phagocytic defenses.[5] The three components of the toxin are protective antigen (PA), lethal factor (LF), and edema factor (EF). Protective antigen attaches to host cells through surface receptors, polymerizes to form a prepore, and binds one or both of the other two toxin components, LF and EF. This entire complex enters the cell by endocytosis. In the endosome, the polymerized prepore becomes a functional pore and allows LF and EF to enter the host cytoplasm.[6] The enzymatic effects of EF and LF disrupt host cell functions including innate and adaptive immune responses.[7] EF increases cyclic adenosine monophosphate (cAMP) production, leading to tissue edema and suppression of phagocytic capability. LF causes cell death by interrupting signal transduction pathways and inducing expression of numerous proinflammatory cytokines. The result is rapid proliferation of *B. anthracis* in the host and an overwhelming septicemia. Death is due to toxic shock with hypotension and multiorgan failure.

*Previous contributions by Richard L. Walker (deceased) are acknowledged.

Epidemiology

Anthrax occurs worldwide. Frequency of outbreaks depends on geographic location. Some parts of the world (sub-Saharan Africa, central and south Asia) with high concentrations of spores in the soil are referred to as "anthrax zones." In the United States, anthrax occurs more frequently in certain states or geographic regions (e.g., Texas and the plains regions). Some areas with greater incidence of disease follow old cattle trails, which may have been the primary source for contaminating those environments.[8,9]

Environments favorable for anthrax spores include soils with elevated pH and concentrations of selected cations (Ca^{++}, Mn^{++}) and soils rich in organic material.[4] Droughts followed by heavy rainfall or flooding often precede outbreaks, as do earth-disturbing activities like excavations. Topography that favors collection of runoff and establishment of temporary water storage areas (seasonal ponds) may promote the concentration of spores.[8,9] Outbreaks usually occur during warmer months of the year.

Bites from bloodsucking insects can spread anthrax organisms from infected septicemic animals through mechanical transmission.[10] Scavenging animals can also disseminate organisms.[9] Carcasses of affected wildlife are an additional source for contaminating environments, because they are unlikely to be disposed of properly.

Clinical Presentation

Susceptibility to infection depends on the individual animal species and the route of infection (respiratory, GI, cutaneous).[11] Ruminants (cattle, sheep, and goats) are most susceptible to peracute infections, and clinical signs prior to death may not be observed. If present, nonspecific clinical signs include fever, depression, respiratory distress, congestion of mucous membranes, and convulsions.[12] In more protracted cases, bloody diarrhea, hematuria, and localized tissue swelling may be observed.

Horses develop an acute intestinal form. Associated clinical signs include colic, diarrhea, fever, and depression followed by a fatal septicemia. A more localized form, possibly initiated by insect transmission, typically involves massive edema in the neck region. A dependent edema may result, involving the thorax, abdomen, prepuce, or mammary gland.

Swine are less susceptible to infection. Oropharyngeal involvement with swelling of the head and neck is the most common presentation; edematous tissue may obstruct breathing and swallowing.[4] Cervical lymph nodes are prominently involved. An intestinal form may present as dysentery. Pregnant animals may abort.

Pathology

Animals that die of anthrax sometimes produce bloody exudates from body orifices and show incomplete rigor mortis. Blood often will not clot. Carcasses undergo rapid decomposition. If a carcass is opened, the spleen is frequently enlarged and has a "blackberry jam" consistency. Lymph nodes and internal organs may be edematous and hemorrhagic. Localized exposure may result in enteritis, regional lymph node involvement, or peripheral tissue edema.[12] Histologically, large numbers of bacilli are observed in affected tissues. Spleen and lymph node architectures are obscured by massive hemorrhages.

Diagnosis

Initially, anthrax may be confused with clostridial infections, lightning strikes, plant poisoning (e.g., oleander), other intoxications, or mineral deficiencies. To prevent sporulation of vegetative cells and further contamination of the environment, carcasses of animals suspected to have died of anthrax should not be opened. Definitive diagnosis is based on microscopic exam of blood or tissue smears and bacteriologic cultures performed in the laboratory, particularly for index cases. Samples that minimize potential for environmental contamination and maximize diagnostic accuracy include unclotted blood collected from superficial veins or ocular fluid collected in a sterile syringe using a large-gauge needle. An intact eye can also be removed and submitted to the laboratory for diagnostic evaluation. In the more localized form of anthrax, samples from regional lymph nodes may be required. Tissue samples containing normal bacterial flora (e.g., ear, skin, intestinal content) are not

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recommended for testing, because recovery of normal flora may obscure the presence of *B. anthracis* in culture. Anthrax carcasses undergo rapid putrefaction, and vegetative *B. anthracis* cells are destroyed during decomposition, so the time between death and sample collection can substantially affect the recovery rate of *B. anthracis*. To ensure specialized diagnostic and safety procedures are followed, always notify laboratory personnel whenever a case of anthrax is suspected. Gram stain of direct smears demonstrates typical large, gram-positive, squared-ended rods found singly or in chains of two to four cells. A polychrome methylene blue (M'Faydean) stain confirms the presence of the *B. anthracis* capsule surrounding organisms. Anthrax bacilli must be distinguished from postmortem invading clostridial species, which have more rounded ends and are acapsular when examined with M'Faydean stain. *B. anthracis* also stains well with other common laboratory stains, including Wright and Giemsa.

Isolation of *B. anthracis* is readily made on standard sheep blood agar. Many organisms grow on this media, so cultures of samples from sterile sites are more likely to identify *B. anthracis* if it is present. With a doubling time of 30 to 60 minutes, colonies are apparent after as little as 6 hours of incubation.[11] Typical *B. anthracis* colonies after 24 hours incubation are large, gray-white in color, have a rough, dry texture, and are usually nonhemolytic. Gram stains of young colonies show very long chains (10 or more cells) of large, square-ended, gram-positive rods often described as having the appearance of a row of "railway boxcars."

Verification of isolates as *B. anthracis* is based on lack of motility, lysis by a specific bacteriophage (gammaphage), protoplast formation in the presence of penicillin (string of pearls test), and confirmatory PCR.[13] Capsules are induced in culture by growing isolates on bicarbonate agar under an increased CO_2 atmosphere. Spores that are centrally located and do not cause the cells to bulge develop in cultures after approximately 48 hours of incubation. Care should be taken to prevent exposure to air and inadvertent spore dissemination from culture plates. Other available molecular- and antigen-based rapid screening tests are primarily used by first responders in potential bioterrorist events and to discriminate between vaccine and wild-type strains. Definitive diagnosis of a *B. anthracis* isolate must be made at a CDC Laboratory Response Network (LRN) confirmatory lab. All positive samples must be destroyed within 7 days of diagnosis.[14]

Treatment, Control, and Prevention Any suspected anthrax case should be reported to appropriate local or state veterinary regulatory officials as soon as possible. The peracute nature of many anthrax infections can make early intervention impossible and treatment unrewarding. Penicillin and tetracycline remain the drugs of choice for treating animals. Treatment should be continued for a minimum of 5 days. Rare *B. anthracis* strains resistant to these antibiotics have been reported.

Carcass management is critical in controlling anthrax outbreaks. Carcasses should not be opened or moved from the area where they are discovered and should be destroyed either by burning or deep burial. Burning carcasses is preferred to burial, because it is more effective at destroying spores, but may not be permitted in certain areas. Any contaminated bedding or soil should be handled similarly.

In the face of an outbreak, regulatory officials will likely quarantine affected premises. All potentially exposed animals should be closely observed for clinical signs of infection. Clinically normal animals should be vaccinated using a commercially available live acapsular vaccine (Sterne) strain (Anthrax Spore Vaccine [Colorado Serum Co., Denver, Colo.]). Prophylactic antibiotic treatment of unaffected herdmates is sometimes practiced, but concurrent use of the live, attenuated product with antibiotics may lessen effectiveness of the vaccine and should be undertaken only after consultation with local veterinary public health or regulatory officials. Vaccination of neighboring herds should be initiated to prevent new infections due to either exposure to similar predisposing environmental conditions or through spread from initial outbreak sources. Controlling insects and both avian and mammalian scavengers will aid in preventing dissemination to neighboring premises.[9]

Prophylactic vaccination of animals in endemic areas should be performed annually 4 weeks prior to turning animals onto pastures where outbreaks have occurred. A single dose of vaccine is given subcutaneously in the neck. In heavily contaminated areas, a second dose may be given 2 to 3 weeks later to enhance protection. Follow vaccine manufacturer's recommendations or local regulatory officials' instructions regarding postvaccination market withholding time for meat and discard time for milk. Localized swelling may occur at the site of vaccination. Goats and llamas may exhibit serious adverse reactions to the vaccine.

Insuring that pastures are of good quality so that grazing close to the soil is avoided will minimize exposure to spores. Avoiding rough feed that might traumatize mucosal surfaces will also decrease incidence rates. If possible, avoid grazing animals on highly contaminated pastures altogether and encourage alternate uses for the land.

Public Health Anthrax is a zoonotic disease. Humans develop three forms of anthrax: cutaneous, inhalational, and gastrointestinal.[4] Occurrence of the different forms depends on the route of exposure. Naturally acquired anthrax cases in humans in the United States are rare. When they occur, the cutaneous form is most common. Veterinarians are included among at-risk individuals because of the potential for contact with organisms while handling infected carcasses. If anthrax is suspected, proper personal protective equipment, including physical barriers (e.g., gloves) and respiratory protection, should be used when collecting diagnostic samples and during carcass disposal. Naturally acquired inhalational anthrax in humans is rare because of the relatively high LD_{50} (8000 to 10,000 spores) required for infection and because spores carry static charges. These charges result in spores binding to larger particles, making aerosolization of spores more difficult.[8] Contact with *B. anthracis* should always be taken seriously, and owners of affected animals should be advised to consult with their physician for advice on medical care.

Lyme Disease

Monica Aleman • John E. Madigan

Lyme disease, also known as *borreliosis,* is one of the most important arthropod-borne bacterial infections in the United States. It is caused by the spirochete *Borrelia burgdorferi* and affects humans, horses, dogs, and cats.[1-4] Because Lyme borreliosis was first identified as the causative agent of an epidemic of juvenile inflammatory arthritis in children and adults in Old Lyme, Lyme, and East Haddam, Connecticut,[5,6] medical references commonly cite "Lyme disease" when referring to *B. burgdorferi* infection.

Epizootiology *B. burgdorferi* is widely distributed in the northern hemisphere all over the world. Prevalence of infection or exposure in horses has been reported to be high in the northeastern United States (50%), Midwest, Texas, and California.[7] Lyme borreliosis has been extensively reported in Europe, England, the Soviet Union, China, Japan, Southeast Asia, and South Africa.[8] *B. burgdorferi* is transmitted from ticks to humans and animals by ticks belonging to the *Ixodes ricinus* complex.[9] These ticks each feed three times during the larval, nymphal, and adult stages.[5] The larvae and nymphs feed on wild animals, and adults are found most commonly on deer.[9] On the east coast, *Ixodes scapularis* ticks are the principle vector, whereas on the west coast *Ixodes pacificus,* the western black-legged tick, is the main vector identified.[10] *I. scapularis* is seen from the Atlantic coast to Oklahoma and Texas.[11] A much higher percentage of *I. scapularis* ticks (12% to 99%) will carry the spirochete compared with *I. pacificus,* in which the maximum number of infected ticks is 4% to 5%.[10,11] *I. scapularis* larval ticks principally acquire the

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spirochete from *Peromycus leucopus,* the white-footed mouse, and the nymphal stages are the major transmitters of disease to animals and humans.[12] With *I. pacificus,* the California kangaroo rat, *Dipodomys californicus,* and the dusky-footed wood rat, *Neotoma fusicipes,* are the likely enzootic reservoirs of *B. burgdorferi.*[13]

B. burgdorferi is found in many arthropods, but the major route of transmission to animals and humans is believed to be limited to *Ixodes* spp. ticks. Experimental studies have demonstrated that ticks may harbor and transmit several pathogens, the human granulocytic ehrlicheal agent, and *B. burgdorferi* at the same time.[14] Exposure to ticks infected with *B. burgdorferi* produced seroconversion without detectable histopathologic changes except for skin lesions in experimental horses.[15] *B. burgdorferi* is maintained in a 2-year enzootic cycle that involves *Ixodes* spp. ticks and mammals. Ticks are usually attached for at least 24 hours for *B. burgdorferi* transmission.[15] Birds are frequently infected with *B. burgdorferi* and may be responsible for disease spread to new areas.[9]

Public Health Considerations

The CDC initiated surveillance for Lyme disease in 1982, and in January 1991 it became nationally reportable. Cases have been reported from 46 states, and the annual number of Lyme disease cases has increased 18-fold, from 497 to 8803. It is now the most common tick-transmitted disease in the United States.

B. burgdorferi organisms have been recovered from the urine of feral white-footed mice *(P. leucopus).*[16] Contact transmission has been reported between white-footed mice,[16] further complicating the understanding of transmission. Lacking any proof to the contrary, it is generally believed that any potential increased risk to humans from infected animals is due to animals bringing ticks into areas of human habitation, rather than any animal transmission.[17]

Molecular Biology

Immunochemical analysis of North American strains of *B. burgdorferi* reveal two abundant surface proteins termed *outer surface protein A* (OspA, 30 to 32 kD) and *outer surface protein B* (OspB, 34 to 36 kD).[18] The 41-kD antigen is located on the flagellum and is similar to the flagellar antigens of other spirochetes.[19] All isolates to date have four to nine pieces of extrachromosomal plasmid DNA. Plasmid may code for proteins that are important in pathogenicity, because the loss of infectivity of isolates that have been heavily passaged in the laboratory correlates with the loss of particular plasmids in culture.[20] Recent work suggests that *B. burgdorferi,* like the relapsing fever–causing *Borrelia* (e.g., *Borrelia hermsii*), can vary its antigenicity, although by a different mechanism and using subtle alterations in the genome.[21]

Clinical Signs

EQUIDS. Clinical signs are nonspecific but may include low-grade fever, stiffness, lameness in more than one limb, muscle tenderness, hyperesthesia, swollen joints, and behavioral changes.[22,23] The most common signs are lameness and hyperesthesia. These signs have been more commonly reported in performance horses. *Borrelia* may be found concurrently with *A. phagocytophilum* in *Ixodes* ticks, resulting in dual infection in the horse.[14]

Horses from endemic areas have serologic evidence of exposure.[24-27] Attempts have been made to correlate individual cases of arthritis, uveitis, or brain infection with this organism.[26,28,29] Experimental infection has produced seroconversion and shedding of the organism in the urine and seroconversion in contact controls.[30] In the United Kingdom, most seropositive horses do not show clinical signs of disease.[31]

RUMINANTS. Although there are some reports in the literature of seropositive animals with arthritis, the evaluation performed on these patients makes it difficult to determine whether *B. burgdorferi* was the cause of the signs.[32] It appears many ruminants are seropositive to *B. burgdorferi* but do not have clinical signs. Whether these tests lack specificity in the ruminant or represent a host-adapted strain of the *Borrelia* organism is unknown.[33] A recent report correlates exposure of *I. scapularis* ticks in dairy cattle with titers to *B. burgdorferi.*[34] An attempt to develop a more specific test in cattle using the 41-kD flagellin antigen has been reported.[35]

Diagnosis

A number of diagnostic methods are available, including IFA, ELISA, indirect complement fixation, and Western blot.[29,32] Culture of the organism requires special media (BSK) and is difficult but may be possible from blood, urine, or cerebrospinal fluid. Diagnosis of recent or active *Borrelia* infection has been based on high ELISA titers (>300 kinetic ELISA [KELA] units), positive Western blot, or PCR.[36] In an experimental infection study, *I. scapularis* ticks infected with *B. burgdorferi* were placed in healthy ponies for 7 days. These ponies developed detectable antibody at 5 to 6 weeks.[36] KELA units were elevated at 3 to 4 months post exposure and remained elevated for several months until euthanasia. Western blot became positive at 10 to 12 weeks post exposure.[36] Throughout the duration of the study, the organism was isolated from the skin where infected ticks were attached. Histopathologic examination revealed lymphohistiocytic nodules in the dermis, lymph node enlargement, and perivascular and perineural lymphocytic infiltrates in the skin, fascia, and perisynovial membranes. PCR was useful for detecting organisms in the skin, lymph nodes, skeletal muscle, fascia, and synovial membranes. Less commonly, organisms were detected in the heart, pericardium, kidney, bladder, and meninges.[36] More recently, detection of serum antibodies to *B. burgdorferi* in horses was improved (84% detection) by using an ELISA based on whole-cell and recombinant antigens.[37]

Treatment

Antibiotic susceptibility of *B. burgdorferi* has been reported but may lack appropriate standardization.[38] *B. burgdorferi* is sensitive to tetracycline and moderately sensitive to penicillin. Amoxicillin, ceftriaxone, and imipenem are highly active against *B. burgdorferi.* Aminoglycosides, ciprofloxacin, and rifampin lack activity.[39] Doxycycline twice daily in humans has been frequently used. Probenecid and ampicillin or amoxicillin also have been used.[38] When CNS involvement is present, ceftriaxone or IV penicillin G has been used. The appropriate duration of therapy is unknown but is related to the stage of infection.

Three different antimicrobials that included ceftiofur sodium (2.2 mg/kg/day IM), doxycycline (10 mg/kg/day PO), and tetracycline (5 mg/kg/day IV) were used for a 28-day period in experimentally infected ponies.[40] High KELA titers and *B. burgdorferi* isolation from skin biopsies confirmed infection. Antimicrobial therapy was initiated 3 months post exposure. Tetracycline was the most effective antimicrobial; it decreased KELA antibody titers (<110 units) during and months after treatment, and bacterial isolation became negative in tissues. However, tissues were still positive for the spirochete on PCR.[40] The efficacy on decreasing titers of tetracycline in the clinical setting has not been highly successful.[41] Proposed treatment for *Borrelia* infection includes tetracycline (6.6 mg/kg IV q12h), doxycycline (10 mg/kg PO q12h), or ceftiofur (2.2 mg/kg IM q12h) for 3 to 4 weeks.[36]

A recombinant outer surface protein A (rOspA) subunit vaccine was shown to be effective in preventing infection in challenged horses with infected ticks.[14,42] Specific recommendations for its use in the clinical setting are lacking.

Tularemia

Bradford P. Smith

Tularemia, an infectious disease of humans, wild animals, livestock, and pets throughout the northern hemisphere, is caused by *Francisella (Pasteurella) tularensis.* There are four major subspecies: *tularensis, holarctica, mediaasiatica*, and *novicida*, with *tularensis* being the most virulent.[1] The organism is a facultative, intracellular, non–spore-forming, gram-negative coccobacillus that survives frozen or in mud and water for a period longer than 1 year,[2] but it only survives for hours in carcasses. The natural hosts are rabbits and rodents, and

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transmission to livestock occurs chiefly through ticks, fleas, deerflies, and other insects.[3] Sheep are the most frequently affected livestock species, along with dogs, cats, and humans. Massive epidemics with high mortality in range sheep have been reported.[3] One paper describes three late-term abortion outbreaks, with one also including sick/dead ewes, between 1997 and 2007 in Wyoming and South Dakota.[4]

Humans are stricken with a plague-like illness when bitten by infected ticks, fleas, or insects and from handling infected rabbits or other infected animal carcasses.[5] The disease has also been called *rabbit fever, deer fly fever,* and *meat cutter's disease.*[6] Sheep shearers may become infected by bites of parasites from the sheep. Disease in horses has also been documented.[7] Oral infection from contaminated water occurs, so fresh water should be provided.[3]

The disease causes an acute septicemia, with localization and granulomatous lesions in the organs (particularly the liver and spleen). Signs are very nonspecific, as expected with bacteremia, and include fever, anorexia, lethargy, and in some cases cough, rapid respiration, or diarrhea. Stiffness and edema of the limbs may be seen. The course of disease is usually 2 to 14 days.

Agglutination titers in recovered affected sheep range from 40 to 5000. Agglutination titers persist for very short periods (21 days) in horses,[3] probably because they measure mainly IgM. Diagnosis is based on culture of the organism from blood or organs. Samples must be specially handled and tests done in BSL-3 laboratories.[6] Diagnosis can also be made by IFA testing or PCR[8] or ELISA.[6]

Necropsy usually reveals ticks on the carcass. Often, reddened or necrotic areas appear in and under the skin at the site of infected bites. Regional lymph nodes may be swollen and congested. Congestion and edema of the lungs are common. Fetal lesions from abortions have multifocal pinpoint necrosis of the liver, spleen, and lung.[4] Differentials include other bacteremias such as *Mannheimia (Pasteurella) haemolytica* in sheep, *Histophilus somni* (formerly *Haemophilus somnus*) in cattle, *Mycoplasma mycoides* subsp. *mycoides* in goats, and anthrax in all livestock. Treatment early in the course of infection is effective. Aminoglycosides, tetracyclines, cephalosporins, chloramphenicol, or quinolones all are probably beneficial initially until results of antimicrobial susceptibility testing are available. Insecticide removal of ticks from affected animals and herdmates is important. No vaccine is currently available, so insect and tick control in endemic areas remains the major prevention. Because oral infection from contaminated water has also been documented, fresh water should be provided.

Corynebacterium pseudotuberculosis Infection

Monica Aleman • Sharon Jane Spier

Definition

Corynebacterium pseudotuberculosis infections occur worldwide and cause external and internal caseous lymphadenitis in sheep and goats; cutaneous excoriated granulomas and mastitic, visceral, or mixed infection in cattle; and ulcerative lymphangitis and external and internal abscesses in horses.[1-4] Subacute to chronic lymphadenitis and pneumonia have been reported in humans handling infected sheep.[5,6] Several zebras in the United States developed severe or multiple internal abscesses and died weeks after being exposed to horses in California.[7] There have been reports of the disease in camels, alpacas, and buffalo.[8,9]

Microbiology

C. pseudotuberculosis infection is caused by a 2-µm gram-positive, intracellular, nonmotile, pleomorphic, rod-shaped facultative anaerobe.[10] *C. pseudotuberculosis* grows well at 37°C on blood agar in 24 to 48 hours, and it forms small, pinpoint in diameter, whitish, opaque colonies that are surrounded by a weak zone of hemolysis. Because of the high lipid content in the bacterial cell wall, particularly corynomycolic acid, the colonies spatter in a flame pushed across the agar surface.[11] High lipid content may facilitate survival of the organism in macrophages.[12] Two species-specific biotypes of *C. pseudotuberculosis* have been identified based on differences in nitrate reduction[5] and DNA fingerprinting techniques.[11,13,14] Strains isolated from small ruminants are nitrate negative, strains from horses are nitrate positive (except for two horses that were nitrate negative), and both strains have been isolated from cattle.[1,5,13,15] From the results of DNA studies, the terms *biovar equi* for nitrate-positive and *biovar ovis* for nitrate-negative strains were proposed.[11] Recent studies revealed that there is more heterogeneity of the isolates of *C. pseudotuberculosis* from small ruminants and from horses[13,14,16] and concluded that nitrate reduction may not absolutely distinguish between the isolates, as does ribotyping.[13] On the basis of ribotyping, sheep and goats have specific isolates throughout the world, and horses and cattle have two distinct groups of isolates depending on geographic location, one from the United States and the other from South Africa and Kenya.[13] Natural cross-species transmission does not seem to occur.

C. pseudotuberculosis produces various exotoxins: phospholipase D (PLD), sphingomyelinase, inhibitory factor of staphylococcal β-hemolysin, hemolysis factor, dermanecrotoxins, and mouse lethality toxins.[17] Phospholipase D and sphingomyelinase are important in the pathogenesis of the disease, because they hydrolyze lysophosphatidylcholine and sphingomyelin, respectively, enabling degradation of the endothelial cell wall and increasing vascular permeability.[18] The synergistic activity of sphingomyelinase with the exotoxin of *Rhodococcus equi* in lysing red blood cells in agar forms the basis for the synergistic hemolysis inhibition (SHI) test.[19]

Molecular characterization of *C. pseudotuberculosis* isolates from four different states (California, Colorado, Kentucky, and Utah) was determined by random amplified polymorphic DNA (RAPD) PCR.[20] The identity of *C. pseudotuberculosis* in these isolates was confirmed by the presence of the gene encoding the PLD toxin by PCR. Ten distinct genotypes (I to X) were identified. Types IV to VIII and X were isolated only from horses, whereas types III and IX were isolated from horses and cattle. This study also found differences in genotypes among states as follows: California (III, IV, V, VI, IX, X), Colorado (III, VI, VII, IX, X), Kentucky (III, IV, V, VI, VIII), and Utah (III). In horses, types III, VI, and X were isolated from internal abscesses from California and Kentucky; types III to VI and VIII to X were isolated from external abscesses from one or more states.[20] More recently, the complete genome of *C. pseudotuberculosis* causing an abscess in a horse was reported.[21]

Clinical Signs and Differential Diagnosis

SHEEP AND GOATS. *C. pseudotuberculosis* causes caseous lymphadenitis (CLA) in sheep and goats worldwide. Caseous lymphadenitis is a major cause of poor production, premature culling, and mortality. There are two forms of CLA: external and internal abscesses.[22] The infection in small ruminants is primarily characterized by suppuration and necrosis of the large superficial lymph nodes. External abscesses are found more commonly involving the mandibular, parotid, prefemoral, or prescapular lymph nodes. The exudate present in those abscesses is thick or inspissated and may appear white in sheep and greenish in goats.[4] A breed association with the type of CLA cutaneous lesion was observed in an outbreak in a commercial ram stud in Scotland.[23] The disease is commonly known as "cheesy gland" in Australia. Differential diagnosis should include abscesses caused by other organisms, trauma, seroma, hematoma, foreign body, injection reaction, and less commonly, tumors. *C. pseudotuberculosis* infection represents a major herd health problem, so abscess culture to determine the precise causative agent is important. Mastitis occasionally develops.[2]

Internal abscesses can be found in the lungs, kidneys, and mediastinal, bronchial, mesenteric, and lumbar lymph nodes.[22] Chronic weight loss is the most common presenting complaint. Other clinical signs are related to the organ or tissues affected. Other diagnostic procedures may be necessary for the differentiation of internal abscesses as the cause of weight loss. Signs of spinal cord compression by vertebral abscesses have been seen in lambs born in unsanitary

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conditions.[4] Knowledge of the local prevalence can aid diagnosis of the infection when uncommon anatomic locations are affected. The prevalence in large breeding operations in endemic areas is estimated to be between 5% and 10%.

CATTLE. *C. pseudotuberculosis* infection in cattle occurs as a herd problem with sporadic incidence. The most common clinical form affecting cattle is cutaneous excoriated granulomas; other forms are mastitis, visceral, and mixed infections.[2] In the most common form, the lesions do not occur as abscesses but as ulcerative, exuding granulomatous lesions as large as 20 cm in diameter, with necrotic areas that are easily surgically removed, leaving granulation tissue underneath.[3,4] Lesions are usually located in the lateral exposed areas of the body: face, neck, thorax, and flanks. The exudate varies from bloody to thick greenish in color. Lesions heal spontaneously in 2 to 4 weeks and do not appear to cause significant illness or decrease milk production in cattle in California.[4] However, monthly milk production was decreased by 6% in Israeli cattle.[3] The prevalence of the infection has been reported to be up to 10% in California dairies.[4] Morbidity was reported to be up to 35% in Israeli herds.[3] Management problems like broken posts or exposed wires traumatize the skin of cattle, allowing penetration of the organism. Young cattle appeared to be less susceptible to the disease than older cattle in Israel.[3] Differential diagnoses include trauma, foreign body, and other masses like tumors. Cutaneous lesions and mastitis were seen in 6%, and cutaneous lesions with concurrent visceral involvement in 1.6% of the Israeli cases.[3] The rest of the cows (92%) only had the cutaneous form.[3] The most affected organ in the visceral form was the lung.[3] The infection has been reported in bison from Egypt, resulting in severe emaciation and edema in the ventral areas and flanks.[24]

CAMELS AND CAMELIDS. Caseous lymphadenitis has been reported in alpacas in South America.[25] A recent study documented five young alpacas (aged 22 days to 14 months old) in North America with caseous lymphadenitis or subcutaneous abscesses that developed during late summer and early fall.[9] The alpacas did not appear clinically ill but developed swellings that progressed to abscesses. The abscesses (1 to 3 per alpaca) were located in the submandibular and cervical areas, and in one case adjacent to the eye. Abscess excision appeared to be the most effective treatment in those cases. Differential diagnoses include abscesses caused by *Streptococcus* spp., *Corynebacterium* spp., and *A. pyogenes*.[26] Severe lymphadenitis was reported in camels in Asia.[8] A study of experimental infection of adult alpacas resulted in abscesses at the inoculation site and renal lymph nodes.[27]

HORSES. Three forms have been described in horses: ulcerative lymphangitis and external and internal abscesses. In a previous study of *C. pseudotuberculosis* infection in horses from California, ulcerative lymphangitis was diagnosed in 1%, external abscesses in 91%, and internal abscesses in 8% of the cases.[28] There appears to be no breed or sex predilection for development of infection. Ulcerative lymphangitis appears as a severe cellulitis, where the lymphatics are affected in one or more limbs, with multiple draining ulcerative lesions. Horses often develop a non–weight bearing lameness, fever, lethargy, and anorexia. This form of the disease occurs worldwide and often becomes chronic, resulting in limb edema, lameness, weakness, and weight loss.[4] The differential diagnosis should include blunt trauma, fracture, foreign body, puncture wounds, nonseptic cellulitis, staphylococcal cellulitis, and other septic cellulitis. Musculoskeletal infection can result in marked lameness (grade 4 to 5 out of 5) and most commonly involves the axillary and triceps areas, followed by the stifle area.[29] Besides diffuse lymphangitis of the limbs, it can also cause osteomyelitis and septic arthritis.[28,29]

The median age for horses with external abscesses is 5 years (range, 3 months to 28 years).[28] Young horses appear to be predisposed to infection; 52% of the cases in a large retrospective study were 5 years old or younger.[28] Few cases involved foals younger than 6 months of age, suggesting that foals born to mares in endemic areas may be protected for several months by colostral antibodies.[28] External abscesses located primarily in the pectoral and ventral abdominal regions are common in geographically restricted areas of the western United States (Texas, New Mexico, Nevada, California) and Brazil.[1,4,28,30] However, the infection has been diagnosed in other states, such as Arizona, Colorado, Kentucky, Utah, and Wyoming.[20,31] This form of infection is commonly known as "pigeon fever" because of the large size of pectoral abscesses, giving the appearance of a pigeon's breast. "Dryland distemper" is another name that reflects its geographical distribution primarily in arid areas. Other common anatomic locations are the prepuce, mammary gland, axilla, inguinal region, limbs, and head.[28] Abscesses involving the head include the ears, eyelids, forehead, maxillary, and mandibular regions.[28] Severe facial suppurative cellulitis and panniculitis with skin sloughing have also been reported.[32] Other less common areas are the thorax, neck, parotid gland, guttural pouches, larynx, flanks, umbilicus, tail, and rectum.[28] CNS infection has also been reported.[28,33] A large area of edema develops in the area of abscess formation. While the abscess matures, the area becomes hard and painful, and some get very large, particularly in the pectoral area. These abscesses typically have a thick capsule measuring up to 10 cm, and can cause severe lameness if located in the axillary or inguinal region.[1,28] Maturation can be slow and drainage difficult to establish if the abscess lies deep to muscle. Once drainage is established by spontaneous rupture or lancing, the majority of cases resolve within 10 to 14 days without complications. Abscesses may contain from 5 to 400 mL of thick, tan, purulent exudate.[1] The majority of affected horses present with a single abscess rather than multiple abscesses.[28] Fever up to 40° C develops in about 25% of cases. Other signs are nonhealing wounds, lameness, ventral dermatitis, and (less commonly) depression, anorexia, mastitis, and other problems, depending on abscess location.[28] In the majority of horses (91.4%), complete recovery occurred, with no recurrence of infection in subsequent years, implying a long-lasting immunity. However, 8.6% of the horses' infections persisted for longer than 1 year or recurred as external or internal abscesses.[28] In sheep and goats, humoral and cellular immune responses develop following infection, and macrophages acquire the ability to kill the organism.[6] The case fatality for horses with external abscesses is very low (0.8%).[28] The differential diagnosis for external abscess, particularly pectoral, should include trauma, seroma, hematoma, foreign body, or abscess due to a different organism.

In a large retrospective study of *C. pseudotuberculosis* infection in the horse, 8% of 538 horses developed internal abscesses.[28] In two different studies, almost half to 63% of horses that had internal abscesses also had concurrent (or a history of) external abscesses.[28,34] In a study of 30 horses with internal abscesses, a female predilection (70%) was apparent.[34] Mean age is 8 years, with a range of 10 months to 23 years.[28,34] The most common clinical signs are anorexia, lethargy, fever (up to 41.1° C), tachycardia, and weight loss. Other signs are colic, pale mucous membranes, ventral and/or limb edema, ventral dermatitis, ataxia, hematuria, nasal discharge, and abortion.[28] The most commonly affected anatomic location is the liver, followed by mesentery, mediastinum, lungs, kidneys, diaphragm, spleen, pericardium, blood, and uterus.[1,28,34] A postmortem examination was performed on an aborted fetus from a mare with pneumonia and revealed *C. pseudotuberculosis* abscesses in the liver, lungs, spleen, diaphragm, kidney, and bladder.[34] Bacteremia may also occur. Both single and multiple organ involvement have been documented.[34] The case fatality for horses with internal abscesses ranges from 30% to 40%.[28,34] The differential diagnosis should include other types of abscesses, such as *Streptococcus, Actinomyces, Staphylococcus, R. equi* in foals, *Coccidioides immitis,* anaerobes, neoplasia, and other causes of weight loss. The clinical signs and differential diagnosis will depend on the location of the abscess.

HUMANS. Human infection may result from consumption of unpasteurized infected milk or milk products, continued close contact with infected animals, handling contaminated equipment,

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and exposure to wounds with exudates.[6,35] Human infection has been reported from strains of small ruminants.[6] Transmission from horses to humans has not been reported, but precautions should be taken when handling infected horses. Infection in humans occurs as a subacute to chronic lymphadenitis and pneumonia.[6]

Clinical Pathology and Laboratory Diagnosis Common findings include anemia of chronic disease.[28,29,34] Leukocytosis with neutrophilia and elevated fibrinogen are common features of developing bacterial infections, particularly in the case of internal abscesses.[28,29,34] Leukocytosis with neutrophilia was seen in 36% and 76% of horses with external and internal abscesses, respectively.[28] Hyperproteinemia due to increased globulins was observed in 38% and 59% of horses with external and internal abscesses, respectively.[28] Similarly, infected cattle and small ruminants had increases in white cell counts.[2,3]

Peritoneal fluid from 93% of horses with abdominal abscesses was abnormal.[28] The remaining horses with abdominal abscesses and normal peritoneal fluid had abscesses located retroperitoneally in the kidneys, without involvement of other abdominal structures. *C. pseudotuberculosis* was isolated in 32% of the samples of peritoneal fluid.[28] Failure to isolate the organism from peritoneal fluid does not rule out the disease. The organisms could be located retroperitoneally, sequestered within a thick capsule, or suppressed by local factors or nucleated cells.[36]

The ELISA test for detection of cell wall antigens is somewhat inaccurate in horses.[4,17] It appears to be more useful for detecting infection in sheep.[37-40] The synergistic hemolysis inhibition (SHI) test measures IgG response to exotoxin in the patient's serum by detecting the highest dilution that will prevent hemolysis of *R. equi* exotoxin–sensitized bovine red cells when mixed with *C. pseudotuberculosis* exotoxin of a known concentration.[19,41] The IgG response to the exotoxin depends on the chronicity and severity of the infection and antibody availability.[4] It has been reported that a serum antibody titer of 1:128 indicates exposure, while 1:512 or higher indicates the presence of infection.[4] Studies in goats have demonstrated that most animals have serum antibody titers that correlate with bacterial culture results.[42] The SHI test can be used in sheep and goats to monitor prevalence and exposure of incoming animals and to detect subclinical infections.[4,41] Only 40% of horses with external abscesses (infection confirmed by culture) had serum antibody titers over 256. However, a low SHI titer does not rule out the disease. Possible reasons for lack of titers include acute onset of infection and rapid maturation of the abscess prior to developing an Ig response, presence of a thick capsule isolating the organisms and preventing a serologic response, consumption of antibody during active infection, or horses with compromised immune systems.[4,28] Many horses that are seronegative at the time an external abscess is drained seroconvert later. In contrast, almost all horses with confirmed *C. pseudotuberculosis* internal abscesses have SHI titers of 512 and higher.[28,34] The high titers in horses with internal abscesses probably reflect the chronicity of the disease and the resulting prolonged immune stimulation. However, high titers can be seen with both internal and external abscesses.[28,34,43] Further, in the presence of external abscesses, an SHI titer higher than 512 may not necessarily indicate internal infection.[43] Exposed herdmates can also have SHI titers in the absence of clinical infection. Prolonged seropositivity has been observed in horses and goats.[28,41,44] Other serodiagnostic tests used in sheep and goats are tube agglutination, complement fixation, and gel immunodiffusion.[17,45]

A presumptive diagnosis can be made based on history, local prevalence, time of year, clinical signs, and exudate characteristics.[4] For the diagnosis of internal abscesses, the previous features must be considered as well as the presence of an inflammatory leukogram with elevated fibrinogen, serum chemistry abnormalities, abnormal peritoneal fluid or transtracheal wash, positive blood culture, SHI titer of 512 or higher, and ultrasonographic and/or radiographic evidence of masses.[28,34] A definitive diagnosis is established by isolating the organism from abscesses or draining wounds. The organism is readily isolated and grows well in blood agar in 24 to 48 hours, even when contaminant bacteria are present.[28]

Pathophysiology and Epidemiology *C. pseudotuberculosis* is a soil-borne organism that survives for long periods of time, months to years, even in direct sunlight at environmental temperatures.[6,46,47] The incidence of infection in horses varies considerably from year to year. External and internal abscesses in horses can present at any time of the year, but are more commonly observed during the fall and early winter months, with the highest incidence in September, October, and November.[28] However, internal infections are more frequently seen in November through January, 1 to 2 months following the peak number of cases with external abscesses.[34] The largest numbers of equine cases have been observed during the dry months of the year, following heavy rainfall, which may result in optimal breeding conditions for insects.[1,28,30] The seasonal incidence in horses has been associated with the presence of biting insects like *Haematobia irritans* (horn fly); this insect's feeding pattern causes ventral midline dermatitis. Insect vectors involved in transmission of disease in horses (e.g., *H. irritans, Stomoxys calcitrans, Musca domestica*) were identified by detecting the PLD exotoxin gene of *C. pseudotuberculosis* in an endemic area.[48] Results of a recent study suggest the disease could be transmitted by horse-to-horse contact, vectors, or contaminated soil.[49] Temporal and spatial analysis indicated an incubation period of 3 to 4 weeks in horses.[50] There is no breed or sex predilection.[28] However, a retrospective study indicated a predilection for internal abscesses in females.[34] A case-control study in an endemic area revealed young adult horses (<5 years of age) had increased risk of infection.[49] Horses housed outside or with access to an outside paddock or in contact with other horses on pasture appeared to be at higher risk than stabled horses.[49]

The disease in cattle from Israel occurred during the spring and summer dry season (March to October) when the housefly population is high.[3] *C. pseudotuberculosis* was isolated from houseflies collected over an Israeli cow lesion.[51] The infection in cattle may spread by direct contact or indirectly by houseflies or fomites.[3] The disease in sheep and goats is not seasonal, and transmission is through contact of exudate from a draining abscess from animal to animal or via contaminated equipment.[1] Lambs born in contaminated surroundings can be infected through the umbilicus, mouth, or inhalation.[4] Sheep that acquire the organism orally or from shearing wounds tend to have parotid, submandibular, prefemoral, or thoracic abscesses.[4] Goats can be infected when wounds are exposed to contaminated milking equipment. The incubation period is long and variable. In experimental infections in small ruminants, the incubation period was from 2 weeks to several months.

The pathogenesis of the disease in horses is unclear, but it has been speculated that the organism enters the equine host through skin or mucous membrane abrasions or wounds, as has been confirmed in sheep.[52,53] Experimentally induced infections in small ruminants revealed that once *C. pseudotuberculosis* gains access via wounds or abrasions, the organisms spread to subcutaneous or submucosal lymphatics, where they are phagocytosed by macrophages that migrate to the invasion site to engulf them.[54] The organism survives intracellularly because of its high lipid content (corynomycolic acid), resisting the action of lysosomal enzymes.[10,54] *C. pseudotuberculosis* replicates in the phagolysosome; if large numbers of organisms are engulfed, phagocytic cells die. Experimental inoculation of the organism in sheep revealed a massive infiltration with polymorphonuclear leukocytes,[55] which are believed to carry the bacteria to regional lymph nodes.[4] A PLD toxin of approximately 31.5 kD, produced by all *C. pseudotuberculosis* isolates, increases vascular permeability, causing spread of the organism regionally and systemically.[6,42,56] Development of abscesses at secondary locations in horses can occur in up to 25% of cases.[28] PLD toxin can cause lymphatic necrosis and thrombosis and may enhance survival and multiplication of the organism via complement depletion and inhibitory effects on phagocytic cells.[6] Corynomycolic acid and PLD toxin contribute to inflammation, edema, and pain during abscess development.[57] The profound

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reaction of these compounds is probably responsible for the formation a thick abscess capsule that develops as phagocytes accumulate in the abscess core. The abscess eventually matures and drains, but if removal of infected material is incomplete, recurrence may be expected, particularly in small ruminants.[4] The development of internal abscesses in horses is unclear but has been postulated to result from hematogenous or lymphatic spread of bacteria from more superficial sites.[4,28,34]

Treatment and Prognosis Important features to consider when treating external abscesses are to (1) allow the abscess to mature, (2) establish drainage, (3) collect and properly dispose of the infective exudate, and (4) lavage the wound with an antiseptic solution. In a retrospective study in horses, the majority of external abscesses were incised to establish drainage, then some received antimicrobials after drainage in an effort to decrease cellulitis.[28] Many horses received no treatment; abscesses broke and drained without clinical intervention.[28] Other horses were only treated with antimicrobials.[28] Outcomes were successful for 99% of horses with external abscesses.[28] Horses with abscesses in the axillary region or deep within muscles have considerable pain, necessitating incision and drainage. Ultrasound is useful for localization of deep abscesses.[34]

In one report, median resolution time for horses with external abscesses that did not receive antimicrobial therapy before abscess drainage was 18 days, versus 30 days for horses that received antimicrobials.[28] These data suggest that systemic antimicrobial therapy before abscess drainage in horses with external abscesses may prolong the disease course.[28] However, when abscesses recur, drainage and concurrent antimicrobials may improve the chance of resolution. Conversely, long-term (minimum 4 to 6 weeks) antimicrobial therapy is necessary for the treatment of internal abscesses and ulcerative lymphangitis. Median resolution time for horses with internal abscesses treated with antimicrobials was 36 to 42 days, with a maximum duration of 97 days.[28,34] The case fatality for horses with internal abscesses treated with antimicrobials was 30% to 40%, but 100% if not treated.[28,34] A study describing 35 horses with musculoskeletal infection reported surgical drainage in 60%, antiinflammatories in 97%, and antimicrobials in 86%.[29] In vitro, *C. pseudotuberculosis* is susceptible to nearly all commonly used antimicrobials, including penicillin, trimethoprim-sulfonamide, tetracyclines, cephalosporins, chloramphenicol, doxycycline, erythromycin, and rifampin.[58,59] Most isolates are resistant to nitrofurans, cycloheximide, and nalidixic acid.[59] Bacitracin has marked activity against the bacterium.[60] In selecting an antimicrobial, the following features must be considered: the intracellular location of the organism, presence of a thick abscess capsule and purulent exudate, the lengthy course of treatment that may be required (e.g., internal abscesses, persistent or recurrent external abscesses), risk of complications (e.g., diarrhea), and cost. Antimicrobial-associated diarrhea was seen in 6% of horses receiving antimicrobials for *C. pseudotuberculosis* infection in a retrospective study.[28] The antimicrobials associated with diarrhea included rifampin, trimethoprim-sulfas, and penicillin.[28] Additional therapies include marsupialization of internal abscesses if location allows. NSAIDs like phenylbutazone or flunixin meglumine may be used to control the pain and/or fever while waiting for external abscesses maturation.

The prognosis for external abscesses is good. Most resolve in 3 weeks from the day of drainage.[4] The prognosis for horses with internal abscesses and ulcerative lymphangitis is guarded but improves if infection is detected early and appropriate long-term therapy is administered. Horses with musculoskeletal infection tend to have a favorable prognosis, but osteomyelitis and septic arthritis can complicate recovery.[29]

In a study in cattle, skin lesions on individual cows healed (on average) in 23 days after local or parenteral treatment; 17% of severely affected cattle were culled.[3] Simple drainage in small ruminants does not usually result in resolution of the disease and can become a potential source of infection. Dilute iodine solutions can be used for abscess lavage. Complete excision of the abscess under general anesthesia may be necessary to keep the abscess from draining and prevent spread of the infection to other animals.[4] The treatment of choice in small ruminants is complete surgical removal of affected lymph nodes.

Prevention and Control Even though *C. pseudotuberculosis* infection is one of the most commonly diagnosed infectious diseases in California, little is known about its prevention and control. General recommendations to prevent its spread are isolation of infected animals, fly control, good sanitation, careful shearing practices, disinfection of contaminated fomites, and careful disposal of bedding. On small-ruminant farms, morbidity can reach 100%, with depopulation being the most economic option. Because *C. pseudotuberculosis* can survive in soil and fomites, the potential for environmental contamination is very high.[46,49]

Immunization trials utilizing whole cells, cell wall toxoids, and bacterin-toxoid combinations have been used to prevent CLA in small ruminants.[61-65] These vaccines have been shown to provide a high degree of protection, decreasing the number of infected sheep and the number of abscesses per sheep.[61-65] *C. pseudotuberculosis* toxoids are commercially available for sheep and goats (e.g., Caseous D-T [Colorado Serum Co., Denver, Colo.], Glanvac [Australia]). The use of autogenous bacterin-toxoid in horses resulted in fewer abscesses and less postchallenge pain in experimentally inoculated horses but did not reduce the incidence of infection on one farm, owing to the low prevalence of disease.[66] Use of an experimental bacterin-toxoid demonstrated increased SHI titers following two injections; however, the protection remains to be established.[67]

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• CHAPTER 38

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Diseases of the Bones, Joints, and Connective Tissues

ROBIN M. DABAREINER, *Consulting Editor*

Physitis (Epiphysitis)

A. Berkley Chesen

Definition and Etiology *Physitis* is a term used to describe a developmental orthopedic condition where there is a disturbance in endochondral ossification at the physis, or growth plate. Of the developmental orthopedic diseases (osteochondrosis, physitis, subchondral bone cysts, flexural limb deformities, cuboidal bone malformation, acquired angular limb deformities, and juvenile arthritis), physitis is the most common.[1,2] In one study of 1711 Irish Thoroughbred foals, 67% had signs of developmental orthopedic disease.[2] The term *physitis* may better be defined as physeal dysplasia, since there is typically no evidence of an inflammatory process.[3] Physitis due to copper deficiency and interactions with molybdenum, zinc, and sulfates, as well as in calves raised on slatted floors, has been seen in growing cattle.[4] Two common antagonists of copper include zinc, which when prevalent at high levels prevents absorption of copper by the body, and molybdenum, which is found in alfalfa.[5] Other animals in which physitis has been reported include show rams being heavily fed and sheep and goats with pregnancy-associated ephiphysitis.[4] Physitis typically affects the given physis during its active growth phases. Many factors have been implicated as causes of physitis in horses, including[4]:

1. A genetic component for faster-growing horses and for specific conformation (e.g., an upright pigeon-toed appearance)
2. Overweight foals
3. Growth spurts in foals
4. Intake of high levels of carbohydrates, causing hormonal changes affecting the physis
5. Improper mineral balance (e.g., copper or zinc deficiencies)
6. Excessive or deficient calcium intake
7. Excessive exercise, especially on hard ground, may cause strain on maturing cartilage

More recently, physitis has been implicated as a complication after treatment with a transphyseal screw for angular limb deformities in the distal radius. It was shown that the single transphyseal screw had a significantly higher complication rate of physitis when compared to the technique using screws and wires.[6]

Clinical Signs Physitis in horses is seen mainly in three specific locations at certain ages. Foals ranging in age from 3 to 6 months most commonly have signs of physitis at the distal metacarpal/metatarsal growth plate (with or without involvement of the proximal physis of the first phalanx).[7] Older foals (8 to 24 months) may have signs of physitis at the physis of the distal radius.[7] Less frequently, the distal physis of the tibia may be involved. Physitis is characterized by firm swellings that may be warm and painful upon palpation. Typically the swellings are medial and due to increased weight bearing on this portion of the limb.[7] Foals may or may not be lame. Radiographic changes include a sclerotic, roughened physis with an irregular metaphyseal shape.[2] If physitis continues, the growth plate may close prematurely, leading to an irreversible angular limb deformity (usually a varus deformity due to decreased growth on the medial physis).[2]

Diagnosis A diagnosis of physitis is usually made by appreciation of the clinical signs, including warm, sometimes painful, firm swellings in the locations mentioned. Physitis at the fetlock may appear to have an hourglass appearance if the proximal physis of the first phalanx is affected.[7] A convex appearance just proximal to the distal tibial and radial physis may be seen early in the disease process.[7] Recently a quantitative method for detecting physitis was investigated in Thoroughbred foals.[2] This method was based on the observation that when the physis is enlarged, both the metaphysis and ephiphysis are more concave.[8] Results of this study showed that epiphyseal concavity may indicate the degree of physeal swelling by using the maximum second-derivative value of that contour.[2] Radiographically, physitis is characterized by a growth plate that is irregularly thickened with sclerotic adjacent bone.[2]

Treatment and Prognosis Treatment of physitis should begin with management changes. Special attention should be given to the nutrition of these foals and weanlings. Ensuring a proper balance of minerals, especially calcium, phosphorus, and adequate amounts of trace minerals like copper and zinc, is necessary. Copper is required for successful cross-linking of collagen. When a copper deficiency exists, the cartilage matrix weakens and microfractures occur.[5] Because mare's milk is very low in copper, foals rely on hepatic stores gained during the last trimester of gestation.[5] One study showed that supplementation of mares with copper during gestation significantly reduced radiographic signs of physitis in their foals at 150 days of age.[9] Supplementation of foals did not affect the incidence of physitis in the same study. The results of this study strongly suggested that on farms with a high incidence of physitis, copper supplementation of mares during the second half of gestation may be beneficial in preventing physitis in their foals.[9] A general reduction in energy is necessary to slow growth rates and, when necessary,

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decrease body weight. Total concentrate for nursing foals should be 0.5 to 0.75 kg/100 kg body weight, 1 to 1.5 kg/100 kg for weanlings, and 0.5 to 1 kg/100 kg for yearlings.[9] Physitis involves varying degrees of discomfort. For horses with very painful, warm physes, judicious use of nonsteroidal antiinflammatory drugs (NSAIDS) is indicated. Exercise restriction—specifically stall rest—is indicated in affected horses. Without exercise restriction, these horses continue to load the physes, which may lead to permanent conformational changes like angular limb deformities. With early detection and treatment, the athletic prognosis for physitis is good.

Osteochondrosis

Jason C. Mez

Definition and Etiology Osteochondrosis is a developmental orthopedic disease characterized by failure of, or a defect in, endochondral ossification; it can lead to cartilage flaps, osteochondral fragments, or subchondral bone cysts. It is classified as a developmental orthopedic disease (DOD) along with physitis, angular limb deformities, subchondral bone cysts, flexural deformities, incomplete ossification of the cuboidal bones, and juvenile arthritis.[1] *Chondrodysplasia* and *dyschondroplasia* are more descriptive terms because they imply a primary defect in cartilage maturation, but their use is generally reserved for abnormalities of limb and vertebral development. The terms *osteochondrosis, osteochondritis,* and *osteochondritis dissecans* have all been used synonymously in discussing the condition. To maintain consistency and avoid confusion, the following designations are used here: *osteochondrosis* refers to the disease, *osteochondritis* refers to the synovial inflammatory response caused by the disease, and *osteochondritis dissecans* refers to the condition when a cartilaginous flap is identified.[2]

Osteochondrosis has been recognized in most domestic species, including horses, swine, and less often in cattle, sheep, and goats. The main focus has been in horses, owing to the economic impact and performance-limiting characteristics of the disease, and in swine, owing to effects on production traits[3] and development of comparative models for study of the disease.[4]

Clinical Signs and Differential Diagnosis Osteochondrosis can present with a variety of clinical signs that are frequently recognized in juvenile animals. Effusion of the affected joint with or without accompanying lameness is common. The tarsocrural and femoropatellar joints are most often affected, but the condition can be seen in any joint. In young animals, physitis (i.e., inflammation at the physeal plate) can have a similar appearance, with generalized enlargements adjacent to synovial structures. Osteomyelitis can cause a periosteal reaction that, if located in the area of a joint, can have a similar appearance. Septic arthritis can closely mimic the signs of osteochondrosis, but the associated lameness is often much more severe. Physitis, osteomyelitis, synovitis, and septic arthritis should all be considered in the differential diagnosis of osteochondrosis in juvenile animals. In older animals the clinician should consider synovitis, osteoarthritis, and trauma in the differential diagnosis.

Osteochondrosis is generally diagnosed in horses when they are started into training programs or begin athletic activity. They often present with a complaint of joint effusion that can be acute or insidious. Lameness is usually nonapparent to mild, except in cases with large osteochondral fragments or subchondral bone cysts. Severe cases seem to be more common in the stifle, and associated clinical signs may be present in foals as young as 6 months. Warmblood horses generally present later, at 3 to 4 years of age, because it is common practice to delay training until this stage.

Reports in cattle indicate that young, intact male, purebred animals are most often affected. The typical clinical signs are lameness with associated joint effusion. Osteochondrosis in swine has been associated with a syndrome known as "leg weakness." Affected animals can show a range of signs from mild lameness to inability to rise and inability or refusal to mount.[5] Evaluation of performance data from swine herds can be a useful indicator of osteochondrosis, because it has been shown to have a significant effect on production traits.[3,6] Being that production animals are usually slaughtered prior to 2 years of age, recognizable clinical signs of the disease in cattle and swine may only be apparent in breeding animals.

Sites of Predilection Osteochondrosis can be found in any diarthrodial joint, but sites of predilection exist in all species affected. In horses the stifle and hock are most frequently affected. In the stifle, in order of frequency, the lateral trochlear ridge of the femur, medial trochlear ridge of the femur, trochlear groove, and distal end of the patella are affected.[7] The medial femoral condyle is the site of predilection for subchondral cystic lesions. In the hock, in order of frequency, the distal intermediate ridge of the tibia, lateral trochlear ridge of the talus, and the medial malleolus are affected.[7] Predilection sites in cattle are similar to those in horses, with the hock and stifle most often affected and similar distribution in the joints.[8] Swine show a slightly different pattern, with the medial condyle of the humerus and femur most frequently affected.[6]

Diagnostic Tests Animals presenting with signs of joint effusion and lameness should undergo a thorough physical examination. A compete blood cell count (CBC) indicating a septic process, along with radiography, help differentiate osteomyelitis, septic physitis, or septic arthritis from osteochondrosis. In cases with any indication of a septic process, appropriate cultures should be taken. Horses should be observed in motion and given flexion tests, using local and intraarticular anesthesia to localize the site of lameness. Swine and cattle can be observed in their normal surroundings for signs of lameness. Once localized, the affected joint should be radiographed, as should the corresponding joint on the contralateral limb in the tarsocrural and femoropatellar joints, because lesions are often bilateral (Fig. 38-1). If lesions are detected in the metacarpophalangeal or metatarsophalangeal joint, the remaining three limbs should be radiographed because these can occur quadrilaterally.[9]

Lameness and effusion are more reliably seen in cases of osteochondritis dissecans and subchondral bone cysts than in osteochondrosis. Intraarticular anesthesia of the affected joint will alleviate the lameness, localizing the source. After the lameness has been localized, appropriate radiographs of both the affected area and the contralateral or quadrilateral limbs should be obtained (Fig. 38-2), as described previously.

Swine and cattle will often present with signs of lameness and mild joint effusion. Careful physical examination of the restrained animal should allow the affected area to be localized and appropriate radiographs to be obtained. As with equine patients, the lesions are rarely unilateral, and corresponding limbs should be radiographed. Reviewing production records of finishing or breeding swine herds may also be of diagnostic value, because osteochondrosis has been shown to cause significant reductions in performance and production traits.[3]

The manifestation of osteochondrosis may not be adequately represented by clinical signs and radiographs. Clinical signs of lameness and joint effusion have been shown to precede changes within the joint, and serial radiographs may be needed to diagnose the condition.[10] Radiographic abnormalities consistent with osteochondrosis of the distal intermediate ridge of the tibia and lateral trochlear ridge of the femur can return to a normal appearance by 5 and 8 months, respectively, in warmblood foals.[11] Radiographs often underrepresent the severity or size of the lesion seen at surgery.

Pathophysiology Endochondral ossification is the process of bone formation that begins with a cartilage scaffold arranged in zones that are gradually replaced by bone. It occurs at the articular/epiphyseal and metaphyseal growth plates and secondary centers of ossification, such as the carpal and tarsal bones. Directly beneath the articular cartilage is a zone of resting chondrocytes that divide to form the next zone, the proliferating chondrocytes. These

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FIG. 38-1 Osteochondrosis in the tarsocrural joint of a horse. Note the characteristic osteochondral fragments located at the distal intermediate ridge of the tibia.



FIG. 38-2 Osteochondrosis in the femorotibial joint of a horse. Note the large subchondral cystic lesion in the medial distal femoral condyle, a typical location for a bone cyst in the stifle.

proliferative cells divide rapidly, organizing into columns perpendicular to the long axis of growth. The cells progress to the hypertrophic zone, where they swell and become vacuolated, and the columns become more organized. The chondrocytes in this zone also become surrounded by increasing amounts of extracellular matrix, which becomes mineralized in the zone of calcification. These columns of chondrocytes are invaded by metaphyseal blood vessels supplying nutrients from below, and bone forms on these calcified cartilage columns, creating the primary spongiosa, which is subsequently remodeled into mature bone.

The exact pathogenesis of osteochondrosis is still undefined. The traditional theory is that the process of endochondral ossification is disrupted, resulting in areas of thickened cartilage. The deeper layers of these retained cartilage plugs do not receive adequate nutrients, and necrosis of the cells develops along with failure of proper ossification. These retained cartilage plugs have less structural integrity than normal cartilage and are prone to damage. Shear forces acting on the abnormal cartilage can lead to fissure formation. These fissures can then form dissecting cartilage flaps, free flaps, or fragments of cartilage and subchondral bone. When compressive forces predominate on an area of thickened cartilage, it can cause infolding of the cartilage plug. Normal endochondral ossification proceeds around the infolded plug, forming a subchondral bone cyst.

This traditional theory of defective endochondral ossification is still well accepted, but recent literature suggests this may be a simplistic view of a multifactorial condition. Limited reparative responses of bone and cartilage make it difficult to determine whether the origin of a lesion is developmental or traumatic. A recent report failed to distinguish articular cartilage differences in naturally occurring osteochondrosis versus healing osteochondral fragments.[12] Arthroscopic observations of normal-thickness cartilage defects and normal subchondral bone, as well as lesions occurring preferentially at single sites at the limits of articulation, suggest causative factors other than defective endochondral ossification.[9] The development and spontaneous regression of osteochondrosis lesions suggest that the condition is a dynamic process that can be affected by numerous intrinsic and extrinsic factors, and a "window of susceptibility" may exist whereby lesions are repaired and normal articular development proceeds.[13] These findings and observations suggest that multiple pathologic pathways exist and that a single etiologic explanation of osteochondrosis is unlikely.

Etiology

As with its pathophysiology, the exact etiology of osteochondrosis is unclear and likely multifactorial in origin. Several factors, including biomechanical forces, failure of vascularization, nutrition, growth rate, genetics, and hormones, have been implicated and are likely interrelated in the etiopathogenesis of the disease.

The consistent distribution of lesions at specific anatomic sites within the joint implicates trauma as a causative factor. The bilateral or quadrilateral nature of the disease would indicate that trauma or biomechanical stress is a necessary factor rather than direct cause. It has been established in pigs that microtrauma or disruption of the metaphyseal blood vessels supplying the developing cartilage canals causes ischemic necrosis, failure of mineralization, and a retained cartilage plug.[14] The same vascular pattern has been shown to be present in young foals, with the arterial supply crossing the ossification front from metaphyseal blood vessels to nourish the developing cartilage canals.[15-17] There is little doubt that failure of vascularization, resulting in ischemic necrosis of the cartilage canal and retention of a cartilage plug, plays a role in the development of osteochondrosis in both swine and horses.[18] To date, these mechanisms have not been studied in cattle.

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Nutritional influences have been extensively studied in relationship to osteochondrosis. Studies have focused mainly on dietary energy levels and mineral composition (copper and zinc). The growth rate of the animal is directly affected by energy intake as well as the genetic predisposition of the animal for growth and size. Animals fed high-energy levels for accelerated growth rates have a much higher incidence of osteochondrosis than those fed for lower rates of growth.[4,19,20] When looking at growth characteristics in pigs, it was shown that for every 100-g increase in average daily gain during the weaning and finishing period, a 20% increase in cartilage lesions or osteochondrosis in the humeral condyle occurred.[21] This is important when considering ration planning and growth rates of replacement animals, where longevity is a greater concern than in the production animal.

Low copper levels and increased zinc concentrations have both been implicated in the etiology of the disease. Low copper is thought to exert its effect through lysyl oxidase, a copper-dependent enzyme essential in the cross-linking of collagen molecules. Increased levels of zinc antagonize copper and could work indirectly through a similar mechanism. There is conflicting evidence on the causative nature of low copper levels, and lesions seen in copper-deficient animals do not always mimic those of naturally occurring osteochondrosis. More recently, evidence suggests that neonatal copper levels exert a positive effect on the resolution of osteochondrosis lesions but are not directly involved in the pathogenesis of the disease.[22]

Genetics have been shown to be at least partially responsible in the etiopathogenesis of osteochondrosis in different species. Landrace and Yorkshire breeds of swine show a high frequency of osteochondrosis, whereas domestic pigs crossed with wild hogs do not develop the disease.[4] Heritability has also been demonstrated in Standardbred trotters in the tibiotarsal and metacarpal/metatarsal phalangeal joints.[23,24] A genetic component is also likely interrelated with nutrition levels because an animal must have the genetic capacity for increased growth rate and size while on high planes of nutrition.

Alterations in hormone concentrations have been implicated in the etiology of osteochondrosis, but the mechanisms remain in question. Numerous hormones (e.g., insulin, somatotropin, thyroxine) are involved in the process of endochondral ossification. Physiologic or iatrogenic alterations of these hormones or their derivatives could theoretically lead to the development of osteochondrosis. The contribution of these factors to the etiology of osteochondrosis will likely not be elucidated until the molecular mechanisms of endochondral ossification are better understood.

The current focus of research has been on the molecular mechanisms involved in the development of the disease. Much has been published in this area, but no definitive conclusions have yet been reached. The exact molecular mechanisms of normal endochondral ossification are not yet fully understood, making comparison to a normal process difficult to impossible. Also, the reparative process in lesions begins almost immediately, and it was shown that there is no difference between tissue types in healing, naturally occurring osteochondrosis lesions compared to surgically created fragments.[12]

Treatment and Prognosis Treatment of osteochondrosis should take several factors into account: clinical signs; lesion severity; species, age, intended use, and relative value of the animal; and owner expectations. Treatment options include both nonsurgical and surgical management.

Nonsurgical management should consist of rest, controlled exercise, and dietary evaluation. Dietary mineral and carbohydrate levels should be evaluated carefully and any deficiency or excess corrected. Systemic NSAIDs and intraarticular medications like corticosteroids, hyaluronic acid, and polysulfated glycosaminoglycans (GAGs) can all be administered, but minimal clinical evidence exists to support their use. In food-producing animals the clinician must take into consideration that these are not approved treatments and that withdrawal times may not be established. Given the nature of the disease, nonsurgical management may provide a favorable outcome only in very young animals with regenerative capacity or in those with very mild lesions and minimal to no clinical signs.

Animals with osteochondritis dissecans are best treated with arthroscopic surgery. Cases with no radiographic evidence of degenerative joint disease (DJD) before surgery and minimal articular damage at arthroscopy carry a favorable prognosis. Animals that show radiographic evidence of DJD before surgery or considerable damage to the articular surfaces at arthroscopy carry a guarded prognosis. Arthroscopic approaches to the joints of cattle have been described, but the procedure is more difficult than in the horse.[8] In selected cases, reattachment of large cartilage flaps with absorbable poly-*p*-dioxanone pins may be warranted.[25] Dietary evaluation of surgical patients should be included and appropriate adjustments made.

Treatment of subchondral cystic lesions is still controversial, and many options are available. Nonsurgical management can be attempted and should consist of rest, controlled exercise, and intraarticular injection of corticosteroids along with hyaluronic acid or polysulfated GAGs. The prognosis is guarded except in cases with very narrow openings into the synovial cavity, and alternate treatments should be considered in refractory cases. Cysts can be treated with ultrasonographically or arthroscopically guided intralesional deposition of corticosteroids.

Arthroscopic guided injections into the fibrous lining of the cyst carries a 67% success rate in horses without preexisting secondary radiographic changes.[26] Arthroscopic débridement and curettage of the cystic lesion is another option with similar success rates, and horses younger than 3 years of age carry a better prognosis. Recent investigations show promise for arthroscopic débridement and curettage of lesions followed by packing the remaining defect with either a cancellous bone graft covered by a chondrocytic growth factor or with various bone substitutes, even in older horses and those with preexisting osteoarthritis.[25,27] Cysts located in the proximal interphalangeal joint (PIP) are generally unresponsive to conventional treatment, and arthrodesis of the joint offers the best prognosis.

Treatment of osteochondrosis in food animals is generally limited by the economic value of the animal. Show animals or valuable breeding animals may be treated by any of the methods described, and the surgical options will offer a better prognosis than nonsurgical treatment. In production herds, ration evaluation and genetic predisposition may be the only variables that can be addressed. Because production animals are slaughtered at an early age, treatment is generally unnecessary. A review of production records and estimates of monetary loss will indicate whether intervention is necessary in herd situations.

Angular Limb Deformities

Jeffrey P. Watkins

Definition, Etiology, and Clinical Signs Angular limb deformities are deviations in the axis of the forelimbs or hindlimbs in the frontal plane. *Valgus deformity* denotes a lateral deviation of the limb distal to the origin of the deformity; *varus deformity* denotes a medial deviation. The deformity is further described by naming the joint adjacent to the origin of the deformity; for example, *carpus valgus* describes an angular deformity arising in the carpal region, with lateral deviation of the metacarpus (knock-kneed conformation) (Fig. 38-3).

Angular limb deformities may be either congenital or acquired. In general, they are due to laxity of periarticular supporting structures, incomplete ossification, or asynchronous growth rate. Although the underlying cause of these abnormalities remains undefined, potential causes include intrauterine malpositioning, relative immaturity, hereditary predisposition, rapid growth, dietary imbalances, osteochondrosis, and trauma.[1-3]

Congenital angular deformities are frequently attributed to intrauterine malpositioning and laxity of periarticular supporting

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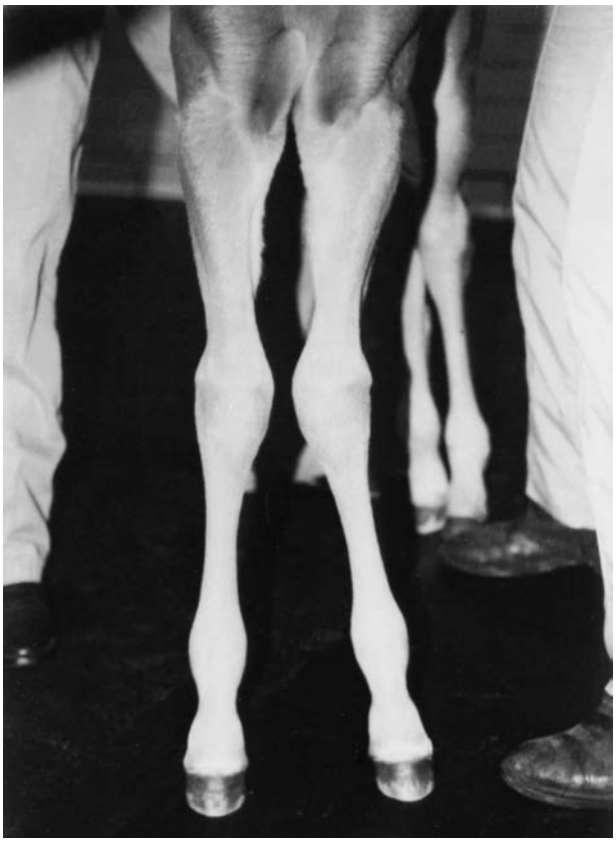


FIG. 38-3 Carpus valgus deviation.

structures. They typically originate in the region of the carpus and tarsus, resulting in bilateral valgus deformity. It is also common to identify a "windswept" foaling in which valgus deformity of one limb is accompanied by varus deformity of the contralateral limb. Acquired angular deformities usually occur secondary to asynchronous growth. A foal born with incomplete ossification may acquire an angular deformity secondary to crushing of the cartilaginous precursors of the cuboidal bones. A hereditary angular limb deformity of Suffolk, Suffolk crossbred, and Hampshire sheep is known as *spider lamb syndrome* (see later discussion).

Pathophysiology Incomplete ossification is an important cause of angular deformities originating at the carpus and tarsus. The epiphyses and cuboidal bones of the carpus (ulnar, third, and fourth carpal bones) and tarsus (central and third tarsal bones) are primarily affected.[1] Ossification of the cartilaginous precursors of these bones occurs in late gestation; prematurity or relative immaturity results in the birth of a foal before these precursors are completely ossified (Figs. 38-4 and 38-5). If laxity of the periarticular supporting structures accompanies incomplete ossification, the deformity is congenital and may progressively worsen with weight bearing. If laxity is not present, the foal may be born with straight legs and later acquire an angular deformity after deformation of the precursors of the cuboidal bones during weight-bearing activity.

Foals can acquire an angular limb deformity as a result of asynchronous growth at the metaphyseal and epiphyseal growth cartilages.[2,3] An important cause of asynchronous growth is trauma to a portion of the growth cartilage of the physis.[4] In many foals this trauma is in the form of nonphysiologic compression of the growth cartilage. Excessive exercise in foals with mild angulation and normal activity in foals with moderate to severe preexisting angular deformity may cause sufficient trauma to the growth cartilage to cause progressive deformity.

Asymmetric loading also occurs when severe lameness is present. With the change from a rectangular stance with four weight-bearing limbs to a triangular stance with three weight-bearing limbs, asymmetric, nonphysiologic loading of the weight-bearing limb occurs, which predisposes it to developing an angular deformity. Because compressive forces are concentrated along the medial aspect of the growth cartilages, a varus deformity usually develops in the overloaded limb. Abnormalities of the growth cartilage that affect ossification (e.g., osteochondrosis) may also be responsible for angular deformities caused by asynchronous growth. Foals with a predisposition for rapid growth or those exposed to nutritional imbalances appear to be at greatest risk for developing the disease. Rapid growth may also result in a foal with a large body size disproportionate to its skeletal structures. This condition may cause increased compressive forces, nonphysiologic loading of the growth cartilages, and angular deformity.[4]



FIG. 38-4 Premature foal with incomplete ossification of the cuboidal carpal bones, showing marked bilateral carpal valgus.

Ruminants raised in confinement may experience endochondral dysplasia and angular limb deformities if dietary iron is high or dietary vitamin D is low[5] (rickets). Elevated dietary iron results in elevations in serum phosphorus, which may in turn inhibit 1,25-dihydroxycholecalciferol synthesis by the kidney, resulting in rickets.[5] Pregnancy-associated epiphysitis in primiparous dairy goats[6] can also result in angular limb deformities.

Evaluation and Radiographic Findings When evaluating a foal with an angular deformity, important historical information includes age, onset and progression of the deformity, and intended use of the foal. The foal should be observed carefully while standing and walking to characterize the degree of deformity and

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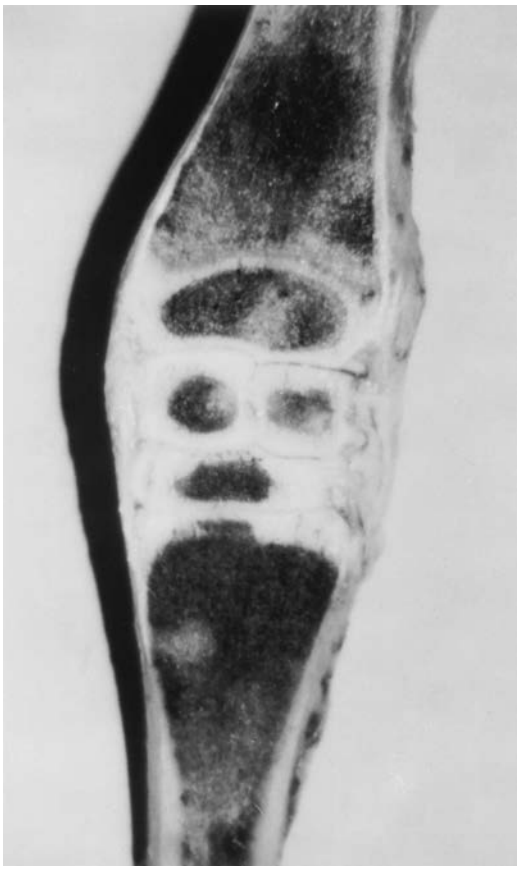


FIG. 38-5 Specimen from a foreleg of the premature foal in Fig. 38-4, cut in the frontal plane. Note the thick cartilage surrounding the centers of ossification of the cuboidal bones of the carpus.

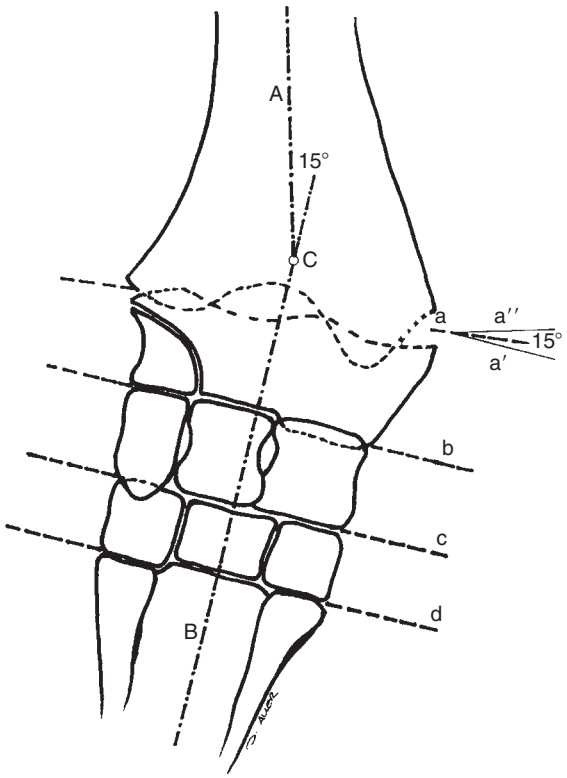


FIG. 38-6 Two methods for geometric evaluation of an angular deformity at the carpus. Lines A and B are drawn through the long axis of the radius and metacarpus, respectively. The angle of incidence is 15 degrees. Lines a, b, c, and d are drawn through the distal radius physis, antebrachiocarpal (radiocarpal), middle, and carpometacarpal joints, respectively. Line a′ is drawn parallel to line b, and line a″ is perpendicular to A. Their angle of incidence is 15 degrees. *(Reprinted with permission from Compend Contin Educ Pract Vet 4:S330, 1982.)*

determine the presence of compensatory problems or lameness. Physical examination includes careful palpation of the affected limb and a determination of whether the deformity can be corrected by manual manipulation of the limb. If the foal is examined before ossification has progressed, deformities resulting from laxity of periarticular supporting structures and incomplete ossification can be corrected manually. On the other hand, if deformities in foals born with incomplete ossification are left untreated and the cuboidal bones are in a collapsed configuration, or if deformities are the result of asynchronous growth, they cannot be corrected manually.

An arthropathy should be suspected if lameness is present. Collapse of incompletely ossified cuboidal bones may result in deformation of articular surfaces and subsequent DJD. When this occurs in the carpus, the prognosis for athletic performance is guarded to poor. If the cuboidal bones of the tarsus are affected, mild collapse may not adversely affect performance, but with significant collapse, degenerative change is likely. A less common cause of lameness in foals with angular limb deformity is osteochondrosis. The prognosis for athletic performance in foals with osteochondrosis-associated angular limb deformities is guarded, depending on the severity of the cartilage lesions.

The importance of early radiographic evaluation of foals with angular deformity cannot be overemphasized. If a diagnosis of incomplete ossification is delayed, irreparable damage may occur. In fact, a strong argument can be made for radiographic evaluation of all foals shortly after birth before uncontrolled exercise is allowed. Radiographic evaluation is mandatory to determine the degree of ossification in premature foals, twins, foals that appear to be relatively immature at birth, and foals born with angular deformities.

Radiographic evaluation allows the examiner to identify the origin of the deformity and determine its severity. Dorsopalmar views for the carpus and fetlock using 7 × 17-inch film cassettes and a lateromedial view of the tarsus are recommended. In the carpus and fetlock the origin of the deformity may be subjectively determined by two geometric methods (Fig. 38-6). One is to draw longitudinal lines bisecting the long bones above and below the joint. Where these lines intersect is the *pivot point,* which is considered the origin of the deformity; the angle of incidence of these lines is an estimation of the degree of deformity. Another method, which we prefer for the carpus and fetlock, is to draw lines through the joints and adjacent physes. These lines should be parallel to each other and perpendicular to the long axis of the long bones proximal and distal to the affected joint. The origin and degree of deformity are estimated by determining where and by what degree these lines deviate from normal. Both asynchronous growth and incomplete ossification can occur concurrently, which is most easily determined with the latter method of geometric evaluation[1] (Fig. 38-7). Geometric examination to determine the degree of deformity in the tarsus is less reliable because the tibia and third metatarsus are not in the same frontal plane. The severity of the angular deformity in this location is best determined by a careful visual assessment.

Radiographic examination of foals with incomplete ossification reveals a rounded contour to the affected bones instead of their normal angular appearance. The width of the radiolucent cartilage is increased, appearing radiographically as an increase in the width of the joint space (Fig. 38-8). As ossification progresses, the bones may appear wedge shaped or crushed because of deformation of the cartilage during weight bearing. This phenomenon often is noted in the ulnar, fourth, and lateral aspect of the third carpal bones in the forelimb and the central and third tarsal bones in the hindlimb. In severe cases the affected bones may be grossly deformed and appear to be partially extruded from the joint (Fig. 38-9). In the tarsus, lateromedial radiographs are used to determine whether ossification is complete (Fig. 38-10).

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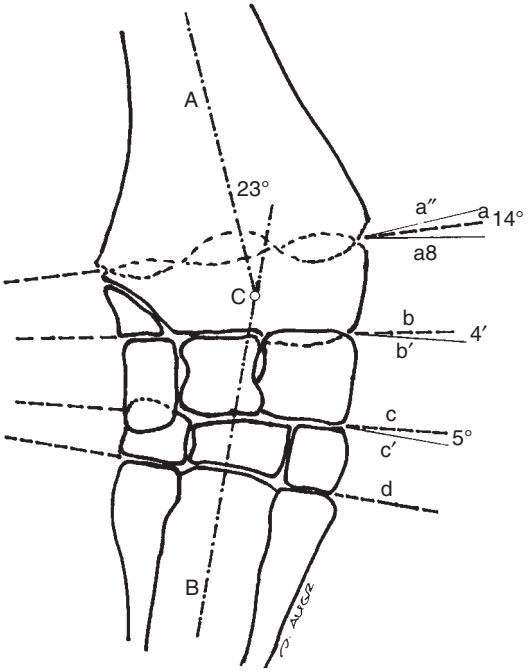


FIG. 38-7 Geometric evaluation of an angular deformity at the carpus caused by a combination of asynchronous growth and incomplete ossification. The pivot point, C, identified by lines A and B, indicates that the origin of the deformity is in the distal radial physis. However, lines a, b, c, and d are not parallel to each other, and lines a, b, and c are not perpendicular to the long axis of the metacarpus and radius. Their orientation indicates that the deformity is in the distal radial physis and the cuboidal bones as well. Note that the sum of angles a-a′, b-b′, and c-c′ equals the angle of incidence of lines A and B. *(Reprinted with permission from Compend Contin Educ Pract Vet 4:S330, 1982.)*

Radiographic evaluation of foals with angular deformity caused by asynchronous growth may show wedging of the epiphysis (Fig. 38-11), widening of the physis, and sclerosis adjacent to the physis. Geometric evaluation places the deviation in the metaphysis or the epiphysis of the long bone proximal to the affected joint. The joints are parallel to each other and perpendicular to the longitudinal axis of the adjacent long bones.

■ ***Treatment and Prognosis*** Neonatal foals with an angular deformity should be confined to a stall until clinical and radiographic examinations are completed. If the deformity is 10 degrees or less and radiographs reveal normal ossification, stall confinement with periods of controlled exercise is recommended. This regimen promotes continued development of the supporting structures while minimizing trauma to growth cartilages that could result if the foal were allowed uncontrolled exercise.

Foals with a congenital angular deformity of more than 10 degrees accompanied by incomplete ossification or ligamentous laxity failing to improve with controlled exercise should be externally supported. If incomplete ossification is present and the limb is not supported in axial alignment, continued weight bearing can cause deformation of the cartilaginous structures. Subsequent ossification results in permanent deformity of the affected bones (see Fig. 38-9).

Methods of externally supporting the carpus and tarsus vary from tube casts or rigid splints to custom-made orthotic devices. Tube casts have been recommended and used successfully for several years,[1-3] but although they provide the rigid external support required to maintain axial alignment while ossification progresses, several potential complications are associated with their use. The most serious is the potential for coxofemoral luxation when tube casts are used on the hindlimbs. In addition, foal skin is easily traumatized by a poorly fitting cast, and deep ulcerations may occur. Other considerations include the cost of materials and necessity for constant monitoring to detect signs of a poorly fitting cast. Monitoring the status of a cast requires daily evaluation by a trained individual, and owners are seldom capable or willing to take on this responsibility; hospitalization is recommended. Rigid splints are an alternative method of support. The leg is protected with a padded support bandage, and the splint is applied with nonelastic tape while the limb is held in alignment by an assistant. These splint bandages are changed every third or fourth day. Pressure sores beneath the splint bandage are a concern and must be prevented. A splint for the tarsus may be fashioned from synthetic casting material molded lengthwise over the cranial aspect of a padded bandage centered at the joint. Once the material has dried, the splint is taped to the dorsal surface of the bandage.



FIG. 38-8 Dorsopalmar radiograph of a foal with mild incomplete ossification of the cuboidal carpal bones. Note the difference in width of the medial aspect *(a)* and the lateral aspect *(b)* of the third carpal bone. Normally, width a should be approximately three-fourths the width of b. Also note the appearance of an increase in the width of the joint space *(c)* as a result of incompletely ossified joint cartilage.

Regardless of the means of external support used for the carpus or tarsus, it should not extend beyond the distal metacarpus or metatarsus. Continued weight bearing by the suspensory apparatus of the fetlock helps prevent development of fetlock hyperextension after removal of the external support. A degree of carpal hyperextension is usually present immediately after removal of external support from the forelimb, and exercise should be controlled until the tendons and periarticular supporting structures regain their normal tone.

Foals with an angular deformity resulting from asynchronous growth should also be confined to a stall and allowed only controlled

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FIG. 38-9 Dorsopalmar radiograph of a foal with incomplete ossification that was not externally supported. Severe deformation and collapse of the fourth and third carpal and proximal fourth metacarpal bones have occurred.



FIG. 38-10 Lateromedial radiograph of a tarsus from a foal with incomplete ossification. Note the lack of an angular appearance of the central tarsal bone and incomplete ossification of the third tarsal bone.

exercise to minimize the magnitude of asymmetric loading at the growth cartilages and encourage spontaneous correction. In these cases, reducing the magnitude of the forces acting asymmetrically at the growth cartilage should encourage compensatory growth to occur and correct the deformity. Additional therapy consists of corrective hoof trimming. Because foals with valgus deformity typically have a toe-out conformation, emphasis in the past has been to lower the lateral hoof wall of the affected limb. If this mode of therapy is vigorously pursued, compensatory varus deformity may develop in the fetlock region. This form of corrective trimming concentrates forces asymmetrically on the medial aspect of the distal metacarpal and proximal phalangeal growth cartilages. Currently, trimming the hoof level and squaring the toe to promote breakover at the toe are recommended. If the lateral hoof wall is to be lowered, only a few millimeters should be removed each week.

Foals with angular limb deformities that fail to respond to stall confinement are candidates for surgical therapy. Animals with angular deformities arising distal to the physis were not considered candidates for surgical therapy in the past, but it has been shown that they can respond favorably to surgery.[7,8]

The decision for surgery should take into account the amount of correction required (degree of deformity) and the age of the foal. The more severe the deformity, the earlier the surgical intervention should be. Timing of surgery should consider the periods of rapid and predictable growth at the physis. The most rapid and predictable rate of growth occurs from birth to 10 weeks of age.[9] In the distal radius, continuous but declining growth occurs until 60 weeks of age. In the distal third metacarpal and metatarsal bones, growth rate slows dramatically by 10 weeks of age and stops shortly thereafter.

Surgical manipulation of physeal growth is intended to asymmetrically alter the elongation occurring at the physis, thereby realigning the axis of the limb. Growth at the physis can be altered surgically in one of two ways: retardation or acceleration. Growth retardation is accomplished by bridging the physis with metallic implants. When applied to the convex side of the affected physis, growth is disallowed on the long side of the bone while continued growth on the opposite of the bone brings the limb into alignment. As long as the implants are in place, the effect continues and is limited only by the amount of growth remaining at the physis. If the physis is still active once the limb is aligned, it is extremely important that the implants be removed, or overcorrection will occur. Techniques of transphyseal bridging include stapling, screw and wire implants, use of a small bone plate, and more recently, a single transphyseal screw. Indications for transphyseal bridging include deformities that present after the period of rapid and reliable physeal growth, severe angulations, and based on the author's experience, deformities of the carpus and tarsus resulting from cuboidal bone malformations.

In the second surgical approach to altering physeal growth, periosteal transection and elevation (stripping) is aimed at promoting growth acceleration on the concave side of the bone.[10] Reported advantages include rapid correction without the potential for overcorrection.[7,10] Because periosteal transection does not require implants, the likelihood of infection and excessive fibrosis are reduced. Implant failure is not a consideration, and a second surgery for implant removal is unnecessary. The procedure does not require specialized equipment and is technically easy to perform. In one series of foals, correction of the deformity occurred in 22 of 25 limbs treated with periosteal transection.[10] In a second series of 23 foals,

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FIG. 38-11 Dorsopalmar radiograph of a foal with angular deformity caused by wedging in the distal radial epiphysis, the result of asynchronous growth of the epiphysis growth cartilage.

83% had straight limbs and were sound for their intended use at long-term follow-up.[7] The success rate was not affected by the origin of the deformity, degree of deviation, or presence of mild to moderate morphologic changes in the involved bones.[10] Indications include mild to moderate deformities present during the rapid, reliable growth at the involved physis. The periosteum will reestablish itself, so the surgical effect is short-lived, and if correction is not adequate within 4 to 6 weeks, additional therapy is indicated.

Ovine Hereditary Chondrodysplasia (Spider Lamb Syndrome)

Juan E. Romano, Sr.

Ovine hereditary chondrodysplasia, also known as *spider lamb syndrome* (SLS), is an inherited semilethal musculoskeletal disease primarily affecting lambs of Suffolk or Hampshire breeding. The clinical signs are characterized by deformities affecting the appendicular and axial bones, with elongated extremities, scoliosis, abnormal ribs, and sternum concavities.[1] Other signs include extreme height, fineness of bones, Roman nose with facial deformities, lack of body fat, and scarcity of muscling. At present, it is the most common skeletal inheritable disorder in sheep.[2] Males and females are affected equally[3] and called *spider lambs, spiders, monkey lambs,* and *crooked-legged* or *corkscrew lambs*.[4] This disease was first described in 1980 in the United States in the Suffolk breed[5,6] and then in the Hampshire breed. The disorder was also reported in Shropshire, Texel, Southdown, and Oxford breeds.[7] It has now been disseminated into several sheep breeds that used Suffolk for breeding purposes and has been



FIG. 38-12 Twin Suffolk lambs (12 weeks old), with normal lamb (78 lbs) at left and spider syndrome lamb (37 lbs) at right. Note extreme height, narrow chest, scoliosis, kyphosis, and facial deformity of the affected lamb.

propagated worldwide in the United States and Canada,[7] Australia,[8] New Zealand,[9] Brazil,[10] and Germany.[11] The frequency of this disorder was reported to be 4% in Germany by detecting the mutation using blood samples.[11]

Transmission Pedigree analyses and breeding studies have established that the gene responsible for this disease has a simple autosomal recessive mode of inheritance.[12-15] The breeding of carrier animals will produce 25% of offspring with the genetic disorder.[14,15] The breeding of a spider ram in a population of carrier females produces 50% of offspring with spider lamb syndrome.[6,13] The breeding of a carrier ram with his daughters also produced offspring with this disorder. The transfer embryos produced between a spider ram and spider donor females to normal recipients' ewes resulted in all the offspring having spider syndrome.[16]

Etiology Genetic linkage between SLS and several microsatellite makers was detected. Mapping the SLS locus was suggested to be the telomeric end of ovine chromosome 6.[7] The causative mutation was identified after positional cloning of the ovine fibroblast growth factor receptor 3 (FGFR3).[7,17] A transversion at nucleotide position 69 of ovine FGFR3 exon 17 causes a non-conservative amino substitution of nonpolar valine (V) to charge glutamate (E) at residue 700 in the second tyrosine kinase domain of the receptor. The mutation leads to loss of receptor function in homozygotes. FGFR3 acts as a negative bone growth regulator by restricting chondrocyte proliferation and endochondral bone elongation.[17,18] Heterozygous (Ss) animals are phenotypically indistinguishable from unaffected normal (SS) animals. The genotypes of presumed heterozygous carriers of SLS are detectable only after test-mating of suspect animals to proven heterozygous carriers, with subsequent evaluation of all resulting progeny or by using blood or hair follicles to detect the mutation in the FGFR3.

Clinical Signs Clinical presentation of the syndrome is also highly variable, with some lambs severely affected at birth and others developing the condition in the first 6 weeks after lambing.[1] External symptoms characteristic of the disease included extreme height, fineness of bones, and lack of muscling and angular deformities of the limbs (Fig. 38-12) along with kyphoscoliosis. Affected lambs tend to be thin and arthritic, with poor muscling and insufficient weight gain. The affected individuals rarely survive and are an economic liability in market lamb production.

The order of frequency of the abnormalities was in the forelimb (81% to 87%), hindlimb (63% to 69%), spine (52% to 62%), and skull (19% to 35%).[19] No differences between Suffolk and Hampshire

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FIG. 38-13 Rotation and deviation of front legs (carpal valgus) characteristic of spider lamb syndrome in a 16-week-old Suffolk lamb.



FIG. 38-14 Lateral radiograph of front leg of a lamb with spider syndrome. Note thick growth plates and multiple ossification centers near the olecranon and distal humerus.

lambs were detected in the type, extent, or incidence of lesions.[19] The forelimbs and hindlimbs were characterized by mild to severe carpus (Fig. 38-13) and tarsus valgus, respectively. The most common spine abnormality was kyphoscoliosis. SLS was observed in aborted fetuses, stillborn viable neonates, and lambs younger than 6 weeks of age.[19]

Detection of this abnormality during pregnancy, either by radiography or transabdominal ultrasonography, even at the second or third tiers was not possible.[16] Diagnosis was possible only by direct examination of the fetus.[16]

Laboratory Analyses No differences in hematologic and biochemical analyses between chondrodysplastic lambs and normal flock mates were detected. Serum levels of vitamin A and E and liver levels for selenium and vitamin E were within normal parameters.[4] Serum trace element levels for iron, magnesium, zinc, and copper were no different than in normal lambs.[4] Serum alkaline phosphatase activity has been reported either high or low in affected lambs compared with healthy lambs.[1] The only difference was a trend in a high level of skeletal muscle enzymes in serum.[4]

Some data suggest that the regulation of insulin-like growth factor (IGF)-1 and IGF-binding proteins may be involved in this disorder. SLS lambs between 50 and 80 days of age showed a significant decrease in serum IGF-1 levels and an increase of IGF-binding proteins compared with a control group of lambs of the same age.[20]

No differences in the number of morphologic features of the chromosome were detected, and there was no evidence of deletions, duplications, translocations, or inversions observed when lymphocytes from clinically normal lambs and lambs affected with ovine hereditary chondrodysplasia were cultured, G-banded, and karyotyped.[21]

Necropsy The primary lesions affect the musculoskeletal system. The gross lesions observed were similar to the changes noted radiographically. Lesions were observed in the skull, sternebrae, atlas, elbows, other vertebrae, and physes of the long bones, as well as other areas. The lesion noted in all locations was an excess of cartilage.[4] Marked muscle atrophy was also present. The principal lesions in bones are an increase in the width of the zone of proliferation and hypertrophy and an unevenness of the growth cartilage. A cartilage column disorder, with failure to form or maintain orderly columns of chondrocytes, is characteristic.[1] The chondrocytes and cartilage matrix appear histochemically normal and have proper ultrastructure.[22]

Radiography Chondrodysplastic lambs have characteristic radiographic patterns in the elbow, sternum, shoulder, and spine, with multiple irregular islands of ossification.[1] Radiography may be the technique of choice for identifying affected lambs prior to detecting clinical signs or when in doubt.[23] A flexed lateral radiograph of the elbow of a suspect lamb appears to be diagnostically reliable when there is suspicion of the syndrome (Fig. 38-14).[1]

Control The mode of inheritance for SLS is autosomal recessive, making identification and culling of carrier (heterozygous) animals difficult owing to their normal phenotype. Eliminating these heterozygous animals from an affected sheep flock is possible by identifying individuals that are carriers of the mutation. This can be done by collecting peripheral blood or hair follicles and performing polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis. The best approach is performing this test in males, but depending on the objectives of the program, the test can also be run in females. Genetic testing by using blood and then PCR-RFLP permits a quick and accurate detection of heterozygotes. The presence of a lamb spider is an indication that both parents are heterozygous for the disorder, so no test is required. Since the introduction of this test in the year 2000, a significant reduction in the incidence of heterozygous animals in New Zealand and the United States has been reported.[24,25]

Another possibility is to run breeding tests, which is time consuming, costly, and requires adequate numbers of breeding animals to be accurate. In addition, correct identification of the animals is paramount. A ram can be progeny tested by breeding with females

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that produced spider lambs or his own daughters. The number required to be highly accurate is 16 normal offspring from mating with a known carrier's ewes or 32 normal lambs from breeding with his own daughters. However, for these numbers the probability the ram is a carrier is 1% or less of the cases.[26]

Differential Diagnosis Some of the lesions seen in SLS require differentiation from abnormalities produced by viruses, chemicals, and toxic plants. Infection with blue tongue and Akabane virus may result in arthrogryposis and hydrancephaly. Border disease can cause abnormalities of the nervous system, skin, fleece, and skeleton. Cache Valley virus and blue tongue can also produce such anomalies.[27] Benzimidazoles, antiparasitic drugs, have been implicated as a cause of skeletal deformities when used in pregnant ewes during specific periods.[28] Toxic plants such as locoweeds are known to cause limb deformities in utero.[29] Deficiency of vitamin D or phosphorus can cause skeletal deformities or rickets.[30]

Septic (Infectious) Arthritis and Osteomyelitis

Joanne Hardy

Incidence and Risk Factors Septic arthritis can result from extension of a periarticular wound infection, traumatic inoculation, iatrogenic inoculation, or hematogenous inoculation. The hematogenous route is the most common avenue of inoculation of organisms in a joint in foals, and bacteremia and septicemia are the most important risk factors for septic arthritis in foals. In one study, septicemia was the most common cause of death (30%) in foals younger than 7 days of age; septic arthritis was identified as the cause of death in 12.5% of foals aged 8 to 31 days.[1] In adults, articular wounds are reported to be the most common cause of joint infection, followed closely by iatrogenic intraarticular injection; postsurgical infection and idiopathic (unidentified cause) are also reported in association with septic arthritis in adult horses.[2-4] Although uncommon, hematogenous spread from a distant focus is possible in adult horses.[5]

Establishment of infection depends on several factors, including size of inoculum, host defense, virulence of the organisms, and local joint factors. In foals, host defense is mainly associated with passively acquired immunity. Failure of transfer of passive immunity (FTPI) is the greatest risk factor for development of septicemia in foals.[6] The incidence of disease resulting from FTPI has been reported to be as high as 78%. Organism virulence is related to the ability to establish infection. Attachment factors, ability to resist phagocytosis, and resistance to cell killing all contribute to the establishment of infection. Local joint factors that may predispose to establishment or maintenance of infection include low blood flow, particularly in end-loop capillaries, and poor blood supply, more prominent in bone. In adults, certain intraarticular medications (e.g., corticosteroids, hyaluronate, polysulfated GAGs) have been associated with a higher risk for septic arthritis, potentially by decreasing articular defense.[7,8]

In calves, septic arthritis is associated with FTPI and septicemia and with feeding of mastitic milk *(Mycoplasma)*.[9,10] In older cattle, direct spread from a perisynovitis is the most common cause, and the distal interphalangeal joint (DIJ) is most often involved.

Pathogenesis Articular blood supply is provided through a main arteriole that branches to the synovial membrane and epiphysis. Blood supply to the metaphysis is provided by the nutrient artery, but in young foals, transphyseal vessels exist that connect the metaphyseal and epiphyseal blood supply.[11] Experimental intravenous (IV) injection of bacteria results in rapid inoculation of articular and periarticular capillaries. Five types of hematogenous articular infection have been described: *type S* (synovial), where a septic arthritis results from inoculation of the synovial membrane; *type E* (epiphysis), where subchondral bone infection is present (Fig. 38-15); *type P* (physis), where infection of the physis occurs on the metaphyseal side of the growth plate (Fig. 38-16); *type T,* observed in premature foals, with infection of the small tarsal or carpal bones (Fig. 38-17); and *type I,* where joint invasion occurs after a periarticular soft tissue abscess (Fig. 38-18).[12] In young foals, functional transphyseal vessels allow communication of the metaphysis and epiphysis, such that bacteria localize preferentially in the synovial membrane and subchondral bone. Thus, young foals predominantly have infectious arthritis types S and E. Closure of transphyseal vessels occurs after about 7 to 10 days of age, such that localization of infection to the metaphyseal vessel loops occurs in older foals.[11] Although bone inoculation can occur simultaneously with synovial inoculation in young foals, determination of bone involvement can be delayed until radiographs identify the lesions. In foals the hock, carpus, and stifle are frequently involved in hematogenous joint infection, but it is important to remember that any joints, including those of the vertebral column, can be affected. In young foals, *Actinobacillus equuli, Salmonella* spp., *Escherichia coli,* and other Enterobacteriaceae are often involved; in older foals, *Streptococcus* spp. and *Rhodococcus equi* are common isolates. In foals with type P (physeal) involvement, *Salmonella* and *Rhodococcus* spp. are typically involved.



FIG. 38-15 Radiograph of a foal with type E septic arthritis, showing involvement of the distal femoral epiphysis *(arrows).*

In adults, inoculation of the joint from an articular wound is the most common cause of joint sepsis. The establishment of infection will depend on size of the inoculum, pathogenicity of the bacteria, and duration before treatment. In one study, 53% of horses examined within 24 hours of an open joint wound developed septic arthritis, versus 92% of horses examined within 2 to 7 days of injury and 100% of horses examined after 7 days.[13] However, two studies failed to find a relationship between interval before admission and outcome.[14,15] This suggests that there are many other factors that influence the prognosis following joint infection. Joints of the lower limb (fetlock, coffin joint) are often involved in open joint injuries because of the poor tissue coverage in those areas.[3,16] Organisms frequently

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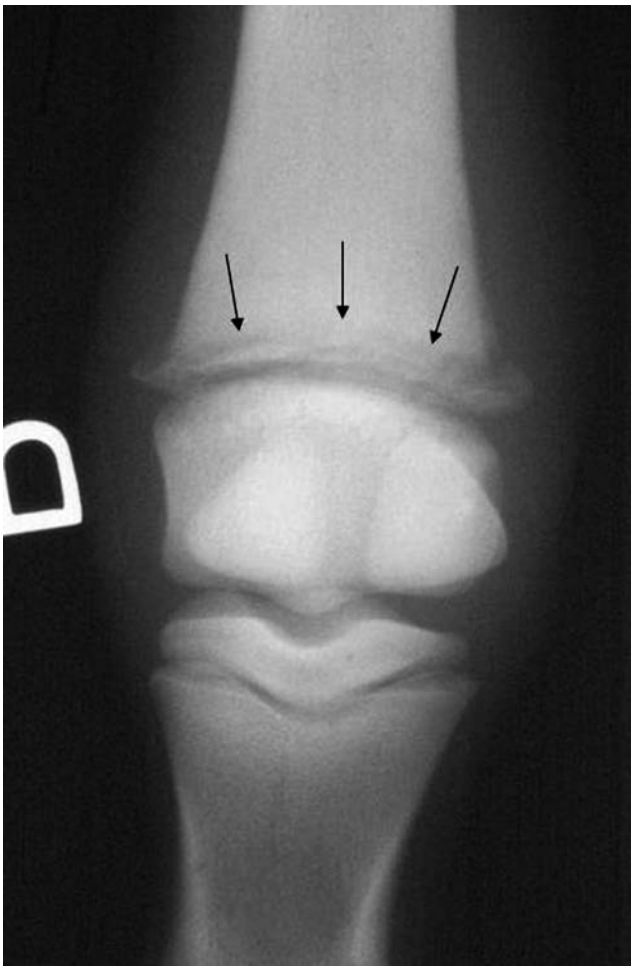


FIG. 38-16 Radiograph of a foal with type P septic arthritis, showing involvement of the distal metacarpal physis *(arrows).*



FIG. 38-17 Radiograph of the tarsus of a premature foal with type T septic arthritis, showing involvement of the distal tarsal bones *(arrows).*



FIG. 38-18 Photograph of a foal with Type I septic arthritis where a soft tissue abscess *(arrow)* dissected down into the coxofemoral joint.

encountered in open joint wounds include Enterobacteriaceae, streptococci, and staphylococci.[3,16] These injuries are also likely to have multiple bacterial infections. Wounds near the hoof are more likely to have anaerobic infection, and *Clostridium* is the most common isolate. Fungal organisms are a rare cause of septic arthritis in horses but should be considered if isolated in pure culture more than once.[5]

Iatrogenic joint injection is the second most common cause of septic arthritis in adults, followed by postoperative infection. The tarsus is the joint most often involved in septic arthritis after joint injection, whereas the carpus is the most common joint involved after surgery.[2,3] Staphylococci, particularly *Staphylococcus aureus,* are the most common organism isolated after iatrogenic joint injections or surgery. When *S. aureus* is isolated from a joint infection, care should be taken to determine the possibility of methicillin resistance.[17,18] The risk of septic arthritis after arthroscopic surgery is low, 8 of 627 joints (1.3%) in one study.[19] Interestingly in these horses, clinical signs did not develop until several days after discharge.

In adult cattle, common pathogens involved in septic arthritis include *Mycoplasma bovigenitalium, Mycoplasma mycoides, Brucella* spp., and *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), which is most often involved.[20] In sheep, goats, and calves, *Chlamydia psittaci* polyarthritis can occur as an endemic or epidemic disease and may be accompanied by keratoconjunctivitis.[21,22] In lambs, *Erysipelothrix rhusiopathiae* is also a cause of polyarthritis, gaining systemic entrance through the stump of docked tails or a castration site. Improving hygiene during these procedures helps prevent the disease.[21]

Diagnosis

Septic arthritis, osteomyelitis, or physitis should be ruled out in any lame foal. Foals with septicemia are at high risk of developing septic arthritis, which generally is noted clinically hours to days after the initial signs of septicemia. Although owners often complain of external trauma, septic arthritis is the most common cause of lameness in foals. In young foals with types S and E arthritis,

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inoculation of the synovial membrane is the first event, which the astute clinician can identify as periarticular edema. Joint effusion rapidly follows. Involvement of multiple joints is common, and identification of all affected joints is essential for successful management. Because effusion of the shoulder, elbow, or hip joints is more difficult to detect by palpation, arthrocentesis of these joints should be performed in foals with an unidentified lameness. In the stifle, femoropatellar joint involvement results in marked effusion, but femorotibial joint effusion is usually more difficult to discern. Because of the usual communication between the femoropatellar and the medial femorotibial joint, both are usually involved concurrently. Lateral femorotibial infection is more subtle to identify and can occur separately. Distention of the long extensor pouch is often present in lateral femorotibial infection and suggests involvement of that joint. In foals older than 7 days, physeal infection may be observed. With physeal infection, presence of concurrent synovial effusion depends on the intraarticular or extraarticular localization of the growth plate. For example, distal metacarpal physeal infection results in periphyseal edema, initially without joint effusion. The infection can break through the skin rather than involving the joint. In foals with septic arthritis, the CBC is consistent with an inflammatory response and includes a neutrophilic leukocytosis and hyperfibrinogenemia. In one study in foals, a plasma fibrinogen concentration of 900 mg/dL or higher (as measured by the heat precipitation method) was useful as an indicator of physeal or epiphyseal osteomyelitis, with a positive and negative predictive value of 84.2% and 98.2%, respectively.[23]

Adult horses usually show minimal changes on the CBC and little change in systemic signs, so development of or increasing lameness after a wound, joint injection, or surgery indicates the need for further examination. In one study, the mean and median times for readmission for septic arthritis following an elective arthroscopic procedure were 47 and 20 days, respectively.[19] In that study, the authors speculated that the delay in onset of septic arthritis following surgery was an indication that joint inoculation occurred in the postoperative period rather than intraoperatively, supporting careful joint closure and continued aseptic technique when changing bandages in these horses.[19] Because of their potent antiinflammatory properties, corticosteroids may delay the onset of clinical signs of septic arthritis after joint injection. In one study of experimentally induced septic arthritis, changes in synovial fluid were present before the onset of clinical signs, and clinical signs of lameness were delayed for 3 days in these horses.[24]

Arthrocentesis is the mainstay of diagnosis of septic arthritis.[24] Table 38-1 lists the characteristics of synovial fluid according to conditions in large animals. A high protein concentration (>2.5 g/dL) and high white blood cell (WBC [leukocyte]) count are observed. Classic counts diagnostic for septic arthritis in foals exceed 30,000 cells/μL, with greater than 80% neutrophils; cell counts above 10,000/μL may indicate early infection. Neutrophils are not always degenerate. Gram stain is a useful diagnostic tool because it may identify the etiologic agent in up to 25% of cases in which culture results are negative.[25] In foals with a separate physeal infection where the physis is extraarticular, sympathetic joint inflammation and effusion can occur.[26] This manifests as a moderate increase in WBC count, with less than 90% neutrophils. The presence of such cytologic findings should alert the clinician and practitioner to the presence of physeal sepsis. Several studies have examined the usefulness of synovial fluid markers to predict joint sepsis. In one study, synovial fluid D-dimer concentration was markedly increased in septic joints, and this was not influenced by the presence of septicemia.[27] However, inclusion criteria for the study included the presence of a synovial fluid analysis consistent with sepsis, so it is not known whether D-dimer concentration would be a useful marker earlier in the disease process or when results of synovial fluid analysis are equivocal. In another study, synovial fluid equine myeloperoxidase (MPO) activity was compared in different forms of joint disease. In cases of septic arthritis, MPO activity in synovial fluid was significantly increased compared to control. Although the study concluded that synovial fluid MPO may be useful as a marker of septic arthritis in horses, further studies are needed because horses were included in the study when they already had synovial fluid analysis indicative of septic arthritis.[28] Serum amyloid A (SAA) is an acute phase protein that is markedly increased (>1000 mg/dL) in horses with septic arthritis.[29] Interestingly, SAA concentration was not increased in synovial fluid collected after repeated intraarticular injections of amikacin in healthy horses.[30] Intraarticular injection of various substances such as antibiotics, saline, or therapeutic agents often cause a transient inflammatory reaction where total protein and nuclear cell counts are consistent with sepsis.[31] The use of SAA to differentiate inflammation from infection would definitely warrant further study.

In adult horses with a wound localized near a synovial structure, it is crucial to identify as early as possible whether there is synovial involvement. The most convincing evidence is demonstration of synovial communication with a wound by injecting a sterile solution into the synovial structure and observing fluid exiting the wound. For this purpose, a site remote from the wound and covered with normal skin should be prepared aseptically, and depending on the structure involved, 20 to 200 mL of a sterile solution (e.g., saline, balanced electrolyte) is injected after collecting synovial fluid samples using aseptic technique.[32] If synovial involvement is detected, therapy is immediately instituted.

Radiographs of all affected joints are essential. The presence of osteomyelitis may affect prognosis and dictate prolonged antibiotic therapy. Radiographs should be repeated weekly until resolution of clinical signs, or any time there is deterioration in the clinical condition. Radiographs are also indicated whenever a change in therapy is planned (e.g., from IV to oral antibiotics).

Nuclear scintigraphy has been used to diagnose infectious foci in odd localizations in foals. For example, vertebral and atlantooccipital involvements have been diagnosed using this imaging modality. It

TABLE 38-1

Characteristics of Synovial Fluid According to Condition in Large Animal

Characteristic	Normal	Septic	Degenerative Joint Disease	Inflammatory*
Color	Clear	Yellow/green, serosanguineous	Yellow	Yellow to iridescent
Clarity	Transparent	Turbid	Transparent	Translucent
Fluid volume	Low	Increased†	Low	Increased
Viscosity	High	Low	Variable	Low (usually)
WBCs/μL	<500	>30,000	<5000	2000-10,000
PMNs (%)	<25	>75	25	>75
Total protein (g/dL)	<1	>2.5	<1	>1
Glucose	Equal to blood	<25 mg/dL	Equal to blood	25-50 mg/dL lower than blood
Gram or other stain	No bacteria seen	Bacteria may be seen	No bacteria seen	No bacteria seen

*May include low-grade sepsis in which bacteria are not found.

†Unless there is an open joint injury, in which fluid may be difficult to obtain.

PMNs, Polymorphonuclear leukocyte neutrophils; *WBCs,* white blood cells.

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FIG. 38-19 Computed tomography scan of a foal with septic arthritis of the left coxofemoral joint, showing osteomyelitis of the acetabulum *(arrows)* that was not radiographically evident.

must be remembered that local bone infarcts, which are often present in osteomyelitis, will result in areas of decreased rather than increased uptake. Scintigraphy using technetium-99m (^{99m}Tc)–labeled WBCs or ciprofloxacin labels has potential uses in foals with multiple-limb involvement and warrants further investigation as an imaging modality for septic arthritis.[33]

Computed tomography (CT) is a useful imaging modality to identify osteomyelitis (Fig. 38-19). It is particularly useful for imaging areas that are difficult to detail with radiography.[34] The main disadvantage is that it is currently limited by the size of the animal.

Magnetic resonance imaging (MRI) has been used in foals and adults with septic arthritis.[35,36] In a limited series comprising six foals with infectious arthritis, four of the six had infectious lesions on MRI indicative of osteomyelitis, and only four of 19 lesions were detected on digital radiographs. Osseous lesions in the T2-weighted, short tau inversion recovery (STIR), and proton density MRI sequences appeared as hyperintense foci.[36] In addition, joints with infectious arthritis had heterogeneous signals within the synovial fluid, whereas all nonseptic joints had homogeneous fluid signals.[36] In adult horses with septic arthritis, MRI findings included diffuse hyperintensity within bone and extracapsular issue on fat-suppressed sequences (Fig. 38-20). The study concluded that MRI may allow earlier and more accurate diagnosis of septic arthritis in horses, particularly when the clinical diagnosis is challenging.[35]

Identification of the organism should be attempted in all cases of septic arthritis. Gram stains, culture of synovial fluid in blood culture bottles, and culture of synovial biopsies have been suggested to increase the likelihood of identification of the organism. In general, the positive culture rate from synovial fluid samples is approximately 50%, and synovial biopsy culture has a low yield to increase this figure.[37] Appropriate culture techniques should be used for organisms such as *Chlamydia* or *Mycoplasma* spp., and special stains may be required. In foals, because bacteremia or septicemia precedes the local signs, blood cultures should be obtained. In addition, any other local sites of infection should be cultured. In cases of septic physitis, needle aspiration of the affected site under radiographic or fluoroscopic guidance can be performed. In the future, other techniques for early identification of synovial sepsis may become available.[37]

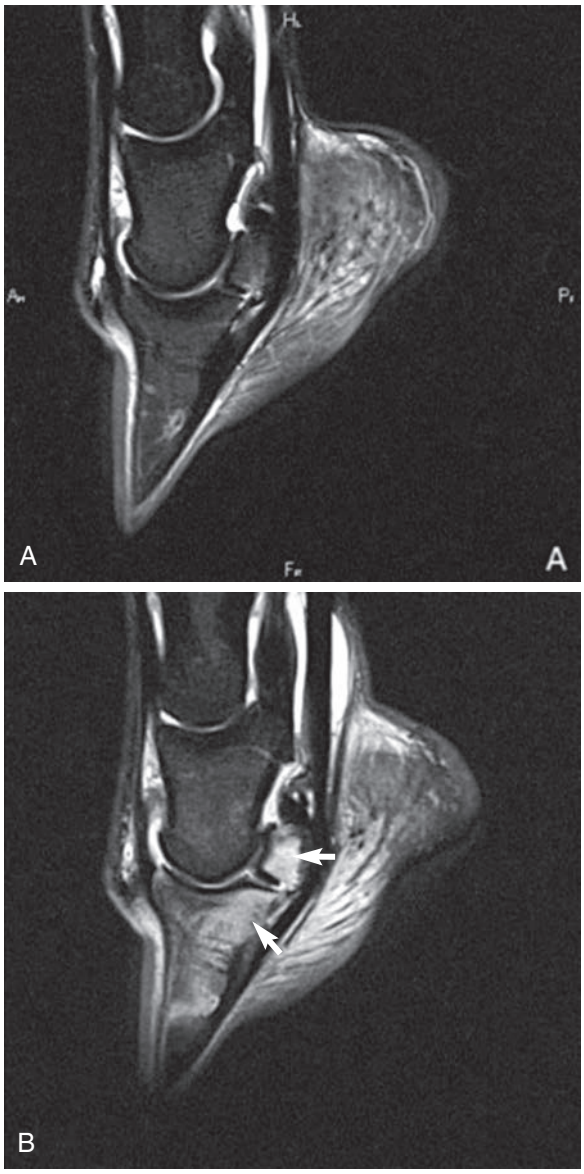


FIG. 38-20 Sagittal short T1 inversion recovery weighted magnetic resonance imaging sequence of the left **(A)** and right **(B)** feet of a horse with septic navicular bursa and septic navicular bone, showing severe hyperintensity of the navicular bone and distal phalanx *(arrows)*.

Treatment Septic arthritis is an emergency. Immediate assessment followed by institution of treatment should be done as soon as possible after problem identification. The principles of treatment of septic arthritis include systemic broad-spectrum antibiotics, local joint lavage and débridement, and local antibiotic delivery. Systemic antibiotics are best administered intravenously to ensure adequate tissue concentrations. Most often the combination of a β-lactam and an aminoglycoside or fluoroquinolone is used in adults; a β-lactam and aminoglycoside combination is most often used in foals because fluoroquinolones may have detrimental effects on articular cartilage in young animals. In open joint injuries, particularly if an anaerobic organism is suspected, metronidazole may be added to the antibiotic regimen. Gram-positive organisms can be isolated from blood cultures in up to 33% of foals with sepsis, so gram-positive coverage is also important.[38,39] In foals with physeal involvement, Gram stain and culture of a physeal aspirate are helpful to identify the causative agent. The most common organisms isolated from septic physitis are *Salmonella* spp. and *R. equi*. If *R. equi* is identified, appropriate therapy with erythromycin, azithromycin, or clarithromycin and rifampin should be instituted, keeping in mind that resistance to rifampin and erythromycin has been reported; obtaining susceptibility patterns may be warranted.[40] Intestinal uptake of clarithromycin is significantly impaired when administered in combination with rifampin, so use of that combination should be questioned.[41] The presence of osteomyelitis warrants an antibiotic combination that reaches effective bone levels; rifampin with another antibiotic is often used. Rifampin should not be used as the sole antimicrobial, because resistance is acquired rapidly with this antibiotic. Other antibiotics that reach effective bone concentrations include tetracyclines,

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chloramphenicol, fluoroquinolones, and cephalosporins. If cephalosporins are chosen, third-generation agents (e.g., ceftiofur, cefotaxime, ceftriaxone, ceftazidime) are preferred because they are more effective against gram-negative bacteria. In foals, fluoroquinolones should be reserved for organisms that are only susceptible to this class of drugs, because evidence shows cartilage lesions developing in immature animals with their use.[42,43]

Local lavage of the joint or synovial structure is an important component of therapy; removal of debris, fibrin, and inflammatory mediators helps minimize damage and eliminate the organism. In foals, joint lavage can be performed under heavy sedation or short-term general anesthesia. In adults, sedation and a regional block can be used or short-term general anesthesia. Joint lavage can be performed using through-and-through needle technique; use of a pressure bag or a pump will facilitate efficient lavage of several liters of fluids through the joint. This technique may be sufficient in joints where the diagnosis was made early, where the infection is not severe, and in simple joints (fetlock, carpus). If there is poor response to treatment after one or two sequential joint lavages, arthrotomies should be performed without hesitation. Often, fibrin accumulation in the affected joint precludes effective lavage and allows sequestration of bacteria. Once arthrotomies have been performed, the affected joint will have to be covered with a sterile bandage. During subsequent lavages, a teat cannula inserted in the arthrotomies may be used to lavage the joint. The arthrotomies are left to heal by second intention; the joint will have to remain bandaged until the arthrotomies are closed. Occasionally, delayed closure of the arthrotomies is necessary, particularly in arthrotomies localized over high-motion joints. In joints with multiple compartments (stifle, hock), in severe infection or osteomyelitis, in cases of longer duration, or in animals with poor response to joint lavage, arthroscopic débridement is indicated.[15] Arthroscopy has several advantages over simple needle lavage. It allows thorough débridement, removal of fibrin, and lavage of all compartments, evaluation and débridement of cartilage and underlying bone lesions, and in the case of wounds, identification and removal of foreign material. In one study, foreign material was identified on arthroscopy in 41 of 121 (43%) horses and 34% of joints with wounds involving synovial structures; these were predicted in only 15% of cases, suggesting that endoscopic evaluation is important diagnostically in wounds involving synovial structures.[15] In addition, arthroscopy may have prognostic value when radiographic lesions are equivocal. The arthroscopic portals can be left open for drainage and subsequent lavage but must be kept under a sterile bandage.

Local or regional delivery of antibiotics is advocated for the management of septic arthritis.[44] Delivery of local antibiotics to the affected joint can be achieved by intraarticular injection, isolated IV or intraosseous (IO) infusion, isolated retrograde venous injection, continuous antibiotic delivery, or implantation of antibiotic-impregnated biocompatible materials. Intraarticular injection is the simplest method but requires repeated injections. Aminoglycosides (gentamicin, amikacin) and ceftiofur have been shown to maintain levels above the minimum inhibitory concentration (MIC) for 24 hours after a single intraarticular injection.[45,46] Intrasynovial catheter placement and repeated antimicrobial injection was described successfully in one study where a modified over-the-wire catheter system was placed directly in the synovial structure and used for antibiotic injection and lavage of the synovial structure.[4] Continuous infusion of antibiotics can also be accomplished by placing a small catheter into the affected synovial structure and attaching it to an infusion system, providing constant rate infusion of the antibiotic.[47,48]

Isolated regional IV perfusion or IO perfusion techniques are also advocated for the treatment of septic arthritis.[49,50] Although the term *perfusion* is often used in the veterinary literature, the term *infusion* should probably be used because in most studies a single injection of the antibiotic is made at the start of the treatment period, whereas perfusion techniques establish an extracorporeal bypass system for the extremity or organ under treatment.[51] Isolated limb infusion techniques are based on isolating the area of interest with a tourniquet, followed by a single IV or IO injection of the antimicrobial. These techniques rely on transient pressure and concentration gradients to distribute a drug to the tissues. The type of tourniquet used is important; escape into the systemic circulation must be avoided during the treatment period. Wide rubber or pneumatic tourniquets are recommended.[52] An Esmarch tourniquet has also been shown to be effective.[51,53] Tourniquets should be 20% wider than the diameter of the limb on which they are used.[54] After tourniquet placement, a regional vein is catheterized using a 23-gauge butterfly catheter for isolated limb infusion. Alternatively, a long-term indwelling catheter can be placed in the vein to facilitate treatment and avoid repeated injection and possible damage to the vein.[55,56] The antibiotic is diluted in a volume of sterile fluid (20 to 120 mL have been reported) and is subsequently injected and the tourniquet left in place for 30 to 45 minutes. In theory, the increased volume serves to increase the vascular pressure and therefore antibiotic distribution, but it remains unknown whether distribution of the antibiotic is a result of a pressure gradient or a concentration gradient. The increased pressure generated after a single infusion of 60 mL returned to baseline after 10 minutes in one study.[51] For IO infusion, a tourniquet is placed in a similar manner, and an intraosseous screw is placed in the medullary cavity and used to inject the antibiotic. Alternatively, a sterile infusion line can be placed in a hole drilled into the medullary cavity. In one study, the IV infusion method had fewer complications than the IO route.[57] Several drugs have been used for IV infusion, including aminoglycosides, cephalosporins, erythromycin, enrofloxacin, vancomycin, and amphotericin B.[49,58-62] The irritating property of drugs like enrofloxacin makes their repeated use undesirable unless no alternative is available.[63]

Intravenous retrograde venous injection (ILRVI) was compared to isolated limb infusion (ILI).[51] The ILRVI technique was similar to that reported for regional limb perfusion in horses. The ILI consisted of catheterization of one digital artery and vein followed by application of a tourniquet. The antibiotic was then injected over 3 minutes, followed by circulation of infusate and blood from the venous to the arterial circulation in 5-minute aliquots for 25 minutes. In the ILI technique, high pressure within the venous system was sustained for the duration of treatment, compared to the ILRVI technique. There was no difference in pharmacokinetics of synovial fluid amikacin in the metacarpophalangeal joint between the two techniques, but significantly higher amikacin concentration was measured in the DIJ.[51] The authors concluded that either ILRVI or ILI may be used for antibiotic delivery, but the technically less demanding ILVRI technique may be more practical.[51]

Antibiotic-impregnated polymethylmethacrylate (PMMA) beads can also be used, although direct implantation into a joint can result in cartilage damage.[64-66] PMMA implants are fabricated by mixing the desired antibiotic with the powder before adding the polymerizer. Antibiotics evaluated for inclusion in PMMA include gentamicin, metronidazole, vancomycin, ceftiofur, cefazolin, and amikacin.[67-74] Antibiotic combinations have also been used, but combining antibiotics can change their elution properties. For example, cefazolin or amikacin elute at concentrations greater than MIC for 30 days in vitro, but the combination elutes above MIC for only 6 days.[73,74] Antibiotic-impregnated biodegradable implants include synthetic and natural carriers. The advantage of these implants is that a separate procedure for their removal is unnecessary.[75-77] Synthetic carriers are degraded by hydrolysis, which may affect the antibiotic prior to its implantation.[44] Although synthetic biodegradable carriers have been evaluated in an experimental model of synovial membrane sepsis, they are not currently clinically available.[75] Gentamicin-impregnated collagen sponges consist of highly purified cattle collagen; the gentamicin molecules are embedded within the pores of the collagen. No stabilizing agents or foreign substances are added. Clinical use of successful treatment of septic arthritis in horses and cattle has been reported.[77-79] However, a recent study performed in healthy horses failed to detect sustained antibiotic release beyond that obtained with a single intraarticular injection.[80]

As high levels of antibiotics are reached within the targeted tissues with these techniques, it remains unknown whether systemic

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antibiotics are still required. In addition, the best dosing interval between treatments is unknown; for example, with concentration-dependent aminoglycosides, there is a transient reversible adaptive resistance for some bacteria to a second dose of aminoglycoside up to concentrations 128 times MIC. These same bacteria revert to original susceptibility when exposed to drug-free media.[51,81] Another unknown is the potential interaction of aminoglycosides and β-lactam combinations, which depending on the drug combination, can be synergistic or antagonistic. Although inactivation of certain β-lactam antibiotics by certain aminoglycosides in vitro has been documented, several studies document in vivo synergism.[82,83] Significant postantibiotic effects were detected with several antibiotic combinations.[84]

With extensive physeal lesions in foals, curettage, autologous bone grafting, and external coaptation may be required.[85,86] The addition of tricalcium phosphate granules or bioresorbable paste may be considered.[87] Angular limb deformities may result from growth disturbances or collapse of the physis on the affected side. In adults with septic arthritis and osteomyelitis, curettage of the bone lesion followed by bone grafting and external coaptation may also be indicated.[88] Adjunctive therapies that may help alleviate inflammation include sodium hyaluronate, polysulfated GAGs, and dimethyl sulfoxide (DMSO). Sodium hyaluronate and polysulfated GAGs can be used systemically or locally, but local use should be reserved for when infection is under control, because these agents decrease joint defense mechanisms.[8,89] Although DMSO has significant antiinflammatory properties in joints, it should be used with caution because of its negative effects on cartilage metabolism.[90]

In addition to specific therapies, management of pain, stress, and other metabolic disturbances are indicated. Pain can be managed by judicious use of NSAIDs, using the smallest dose that will keep the animal comfortable. If a foal continues to show severe pain despite appropriate treatment, it is important to ensure that other joints in the limb are not involved. Other pain management modalities (e.g., opiates, fentanyl patches, epidural analgesia) can be used. It is important to remember that in foals, continued pain in one limb may result in development of a varus deformity in the contralateral weight-bearing limb owing to the tripod stance these foals acquire to maintain the weight-bearing limb under the center of gravity. Application of a lateral extension to the contralateral foot may help increase the weight-bearing surface and prevent development of this complication. Continued pain is a negative prognostic indicator in the affected foal. In adults, continued pain in one limb may result in the development of contralateral limb laminitis.[91] When continued pain in the treated limb is a problem, preventive measures (e.g., hoof support, therapeutic shoeing) should be undertaken.

Antiulcer agents are indicated in foals and adult horses that are in pain, stressed, and receiving high doses of NSAIDs. Omeprazole is currently the only medication that has been shown to significantly prevent formation of gastric ulcers and promote healing of existing ulcers in adult horses. Although evidence for its efficacy in preventing and treating NSAID-induced ulcers is lacking, omeprazole is still indicated when NSAIDs are used in stressed animals.

In cattle, facilitated ankylosis is a reasonable alternative when the disease is too advanced, and it is a particularly good option for involvement of the DIJ. Articulations of the distal limb in general are well suited to facilitated ankylosis. In brief, the involved joint is opened and débrided of all debris, all infected tissue is curetted and removed, and a cast is applied and maintained until ankylosis is achieved.[92] Alternatively, the digit may be amputated, although a reduced production life should be expected.[93]

Prognosis

In clinical studies, treatment is often limited by economic considerations, so the true long-term outcome of treatment is unknown. Outcome variables used in clinical studies range from discharge from the hospital to pasture soundness to racing potential. Owner expectations should be clear, keeping the animal's welfare in mind. The prognosis for septic arthritis should always be guarded, and owners should be informed of the high cost of treatment. In foals, factors that will influence prognosis are systemic condition of the foal, number of joints involved, localization of joint involvement, severity of the infection, early versus delayed identification and institution of treatment, presence of osteomyelitis, and virulence of the organisms. In one study, 73 of 93 (78%) foals survived to discharge, but only a third reached racing performance.[94] Isolation of *Salmonella* spp. and presence of multisystem diseases were negatively associated with survival and ability to race.[94] A multidrug-resistant *Enterococcus* sp. was associated with unresponsive septic arthritis in three horses.[95] In another study, 58 of 69 (84%) foals survived to discharge, although signs were present for less than 24 hours in 74% of foals, only five foals had more than one joint involved, and only one foal had osteomyelitis.[96] This population of foals therefore appeared less severely affected. Of the affected foals, only 40.5% started in one race, and of the affected foals that were discharged, only 48.3% raced versus 66.2% in the control (sibling) group. This study concluded that even if foals are successfully discharged from the hospital, they are significantly less likely to start in at least one race than their siblings. Furthermore, these foals took significantly longer to appear on the track than their siblings. In another study of foals with osteomyelitis of hematogenous origin, 87 of 108 (80.6%) foals were discharged from the hospital, and 79 of 87 reached racing age.[97] Overall 52 of 108 foals (48%) raced. Of the 21 non-survivors, only one died; the other 20 were euthanized, but none were euthanized for economic reasons. Factors associated with non-survival in that study included foals less than 30 days of age, critical illness, multisystem disease, multiple bone lesions, lesions of the proximal phalanx, concurrent septic arthritis, multiple septic joints, and involvement of the coxofemoral, stifle, hock, or navicular bursa. In that study, the bacterial isolate involved had no significant effect on short-term outcome.[97] In a study evaluating the factors associated with survival and racing performance in 423 neonatal Thoroughbred foals with bacteremia, the presence of septic arthritis increased the likelihood of non-survival by 4.54 times.[98]

In adults with open joint injuries, the prognosis can be favorable if the joint is contaminated but not yet infected, and if aggressive treatment is immediately started. However, with established infection, the prognosis should always be guarded. In one study of horses with open joint injury, 53% of those examined within 24 hours developed septic arthritis, and overall survival was 65%. In horses presented within 2 to 7 days of injury, septic arthritis developed in 92%, and survival was 38.5%; in horses examined more than 7 days after injury, septic arthritis developed in all, and survival was 50%.[13] In one study of 101 horses with heel bulb lacerations, those with involvement of synovial structures had worse outcomes then those that did not; 5 of 17 horses with synovial involvement were euthanized.[16] Horses with contaminated or infected synovial structures treated by arthroscopic débridement appeared to have a better long-term outcome, with 106 of 118 (90%) surviving and 96 (81%) returning to previous use.[16] In a study of horses with septic tenosynovitis, 40 of 51 horses (78%) were discharged, and 37 of 40 (73%) survived long term, with 21 (57%) returning to intended use.[99] Surgical technique did not influence outcome in this study. One study reported on the use of matrix metalloproteases 2 (prommp2) and 9 (prommp9) and WBC count to monitor treatment and predict outcome in horses with septic arthritis.[14] In that study, survivors had a significantly lower WBC count, prommp9, and ratio of prommp9:prommp2, with the latter being the best predictor for survival.

In cattle the prognosis for septic arthritis is generally better than in horses, probably because of the lack of expectation for athletic use. Prognosis depends on time of presentation, degree of bone involvement, and degree of extracapsular ankylosis. In two studies the success rate was reported as 72% and 85%; cattle with septic tarsi had a worse prognosis.[100,101] In another study, arthroscopic lavage and implantation of gentamicin-impregnated collagen sponges resulted in recovery in 12 of 14 cattle.[102] After arthrodesis of the DIJ, 85% success was reported.[93] For carpal arthrodesis, 87% success was reported if no carpal bone was removed, 72% success if one row of carpal bones was removed, and 35% if both carpal rows were

removed. Tarsal arthrodesis has a reported success rate of 87% in cattle.[93]

Mycoplasmal Polyarthritis in Goats

Piper Lambard Norton

Definition and Etiology There are numerous species of *Mycoplasma,* but not all are pathogenic. The contagious agalactia syndrome of sheep and goats causes mastitis in lactating does and septicemia in kids, leading to polyarthritis and keratoconjunctivitis. This syndrome was originally thought to be attributed to only *Mycoplasma agalactiae* but has also been attributed to *Mycoplasma capricolum, M. mycoides* subsp. *capri, M. mycoides* subsp. *mycoides* (caprine or large colony type), and *Mycoplasma putrefaciens* and has been documented in many different countries.[1] Each of these species has been described as causing septic arthritis in kids as well as mastitis in does.[1,2]

Of these species, *M. mycoides* subsp. *mycoides* is the most common in the United States.[3] Documented infected goats are usually housed at large U.S. dairies, and infection follows introduction of asymptomatic carrier animals into a herd.[4]

M. mycoides subsp. *mycoides* (small colony) is the etiologic agent of contagious bovine pleuropneumonia and was eradicated from the United States in 1892.[4] Since that time, goats in this country have been affected by mycoplasmas that are serologically indistinguishable from the bovine strain.[1] *M. mycoides* subsp. *mycoides* that affects goats is known as *caprine* or *large colony type* rather than the small colony type that affects cattle.

Clinical Signs and Differential Diagnoses The majority of cases of *Mycoplasma* spp. mastitis are observed during the spring, although one large U.S. outbreak was documented in the fall.[5] Adults may be asymptomatic carriers, have mastitis, or have more severe systemic infections like pneumonia. Does with mastitis may have clinical signs of an elevated temperature, anorexia, interstitial fibrosis of the mammary gland, and decreased milk production. Milk has the appearance of white liquid glue, progresses to being curdled and thick, and then becomes thin and watery.[5] In addition, goats may exhibit pneumonia (interstitial or fibrotic), arthritis or polyarthritis, conjunctivitis, lymphadentitis, peritonitis, abortions, pericarditis, or septicemia.[3] Differential diagnoses in adults with mastitis include a large number of other bacteria such as coliforms, *S. aureus,* fungal organisms, and other bacteria.

Goat kids most frequently demonstrate clinical signs of fever (102° to 107° F), polyarthritis, pneumonia, anorexia, and lethargy due to mycoplasmal septicemia.[6] Infections with *M. putrefaciens* may be less likely to be associated with temperature elevations in goat kids and adults.[5] Meningitis and sudden neurologic signs may also be observed in goat kids.[3] Experimentally inoculated kids demonstrate clinical signs of anorexia, lethargy, and painful enlarged joints within 3 to 5 days of inoculation.[7,8] Differential diagnoses in kids with septic arthritis include chlamydial infections and other bacterial etiologies secondary to septicemia.[4]

Clinical Pathology and Diagnosis Hematologic abnormalities in kids may include decreased red blood cell (RBC) counts, increased platelets, and increased fibrinogen. Neutrophilia may be observed, but the finding is inconsistent.[5] Chemistry panels may show decreased albumin levels.[3]

Arthrocentesis of effusive joints may be grossly hemorrhagic or dark yellow and turbid with increased total protein.[9] Mean total protein in normal joints was 1.8 ± 0.2 g/dL, whereas mean total protein in joints of affected kids was 3.2 ± 0.2 g/dL.[9] Cytologic analysis of synovial fluid may reveal increased neutrophil, lymphocyte, and erythrocyte counts in addition to decreased glucose concentrations.[9] Synovial fluid also has very poor mucinous precipitate quality (mucin clot test).[9] Culture of *Mycoplasma* requires special medium and up to 14 days of incubation.

Pathophysiology and Epidemiology Transmission of the organism from the infected doe to a kid is through infected colostrum.[3] The organism penetrates the gut wall and leads to septicemia. Transmission in adults has been speculated to be through direct contact, the milking process, venereal transmission, or through vectors such as ear mites or fleas.[3,10,11] Most sources say *Mycoplasma* is not very contagious if milk sources are not contaminated.

Chronic carriers of the bacteria have been noted following treatment for the disease, and asymptomatic carrier does and bucks have been documented.[10] In one outbreak of *M. putrefaciens,* clinical signs were documented to occur within 3 weeks of the introduction of new animals into the herd.[5] In another outbreak in Spain, a drought was implicated as a possible predisposing factor, suggesting environmental stress may play a role.[8,11] Recommendations should be made to ensure that sanitary milking, kidding, and housing environments are established to decrease the risk of contagion.

Necropsy Findings Gross necropsy findings in does with mastitis include enlarged, firm udders with thick, chunky to putrefactive milk. Histopathology of the udder may show severe chronic mastitis with a mononuclear infiltrate and enlarged mammary lymph nodes.[5,12] Lungs may have a diffuse interstitial pneumonia or consolidation with areas of focal necrosis.[7,8] A thickened pleura may be observed, with fibrinous exudate in the thoracic cavity.[7,8] The arthritis is characterized by a fibrinopurulent polyarthritis.[8] Some animals may show ulcerated synovium with an infiltration of macrophages and neutrophils.[3]

Treatment and Prognosis Mortality rates in kids may surpass 90%, and mastitis may affect 25% to 33% of does in a herd, or more if unsanitary conditions are present.[3,5] Most sources state that there is no effective treatment for mycoplasmal infections, although many antibiotics have been tested in vivo and in vitro. It is important to recognize that individual isolates of *Mycoplasma* spp. may be more or less susceptible to certain antibiotics, and susceptibility patterns may be regionally dependent.[13] Mycoplasmal organisms lack a cell wall, making cell wall synthesis inhibitors ineffective as treatment, but they are generally susceptible to antibiotics that inhibit protein or DNA synthesis. Antibiotics used to treat this condition in goats include oxytetracycline, florfenicol, macrolides (tulathromycin), and tylosin.[13,14] Only antibiotics with established milk withdrawals should be used in dairy goats. Prognosis for response to treatment is poor, and oftentimes carrier animals persist despite treatment.[3]

Prevention and Control Maintenance of a closed herd is the simplest method of prevention.[3] Modification of milking practices and kid rearing is necessary to prevent mycoplasmal spread.[3] When does with mycoplasmal mastitis are identified, they should be culled or isolated from the remaining herd. Kids born to mastitic does should be isolated from infected does and raised on milk replacer or heat-treated milk.

Whole-herd milk culture can be used to identify *Mycoplasma* in a herd. Polymerase chain reaction (PCR) assay of milk, synovial fluid, or tissues can also be used to identify *Mycoplasma.* Asymptomatic bucks in a herd can be detected using cultures of ear swabs or semen.[10,15]

Caprine Arthritis-Encephalitis Virus

Kevin Washburn

Definition and Etiology Caprine arthritis-encephalitis virus (CAEV) is an RNA-enveloped lentivirus from the Retroviridae family that infects cells of the monocyte-macrophage lineage, with clinical manifestations ranging from subclinical disease to severe encephalitis. Time from viral infection to clinical disease may vary from months to years, and because infection is lifelong, efforts to eradicate

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and control its prevalence and incidence are paramount to maintaining successful goat herds. Loss of productivity, death, and restrictions on the export of dairy goats are some of the economic impacts of this disease on U.S. herds and the goat industry.

Clinical Signs Only about 20% of CAEV-infected goats display clinical signs of disease during their lifetime, but recognized forms of disease include a leukoencephalomyelitis, interstitial pneumonia, chronic mastitis, and debilitating polysynovitis-arthritis.[1] Leukoencephalomalacia is observed primarily in kids 2 to 6 months of age, but reports have been noted in adults.[1] This form is characterized by an ascending paresis leading to paralysis, beginning in the rear limbs and sometimes involving the forelimbs. These signs may or may not be accompanied by a mild interstitial pneumonia. Goat kids may continue to be bright, alert, and appetent. The most severe manifestation of this form of CAEV infection is progressive paresis to paralysis to urinary retention and bloating. Chronic interstitial pneumonia with progressive weight loss and dyspnea is another recognized form of CAEV infection. Primary ruleouts for this form should include lung worms, pulmonary abscessation, and chronic bronchopneumonia. The mammary gland is a target organ for the virus, resulting clinically in a firm udder with decreased milk production. Although quantity of milk is reduced, there are no apparent gross abnormalities.

The most common form of CAEV infection is polysynovitis-arthritis, which can be recognized in goats as young as 6 months but more frequently is observed in mature goats. Lameness caused by this form is intermittent and insidious in onset, but eventually affected joints become painful and enlarged. Enlargement of the joints is most typically due to hyperplasia of the synovial tissues and their associated sheaths rather than increased volume of joint fluid. The carpus is most frequently involved, but the stifle, coxofemoral, atlantooccipital, and hock joints are also potential locations. Affected goats have a stiff, stilted gait and progress to walking on their carpus or recumbency. Range of motion (ROM) is greatly affected, contributing to chronic soft tissue contracture. This polysynovitis-arthritis form can be accompanied by a chronic interstitial pneumonia and weight loss and typically is also associated with some form of mammary involvement.[1]

Clinical Pathology and Laboratory Aids Arthrocentesis to confirm suspicion of the polysynovitis-arthritis form of CAEV infection usually yields a brown to red-tinged fluid with an increased cell count and decreased protein. Joint fluid cell counts in affected joints are dominated by mononuclear cells, differing from bacterial synovitis, where cells consist predominantly of neutrophils. This predominance of mononuclear cells in CAEV infection is also seen in the cerebrospinal fluid (CSF) of goats affected with the leukoencephalomyelitis form. Radiographs may be a useful diagnostic tool for CAEV polysynovitis-arthritis; early cases display soft tissue swelling dorsal to the carpus. As the disease progresses, mineralization can be observed in the periarticular tissue, tendon sheaths, joint capsules, and ligaments. Roughened bone proximal and distal to the joint becomes apparent, as does periosteal reaction. The U. S. Department of Agriculture (USDA) recognizes an agar gel immunodiffusion (AGID) test using ovine progressive pneumonia virus antigen as the official test for CAEV. However, an enzyme-linked immunosorbent assay (ELISA) has been developed for detection of whole virus, core, or envelope proteins. Both AGID and ELISA are considered reliable enough to be incorporated into prevention and control programs. The AGID test is reportedly more specific but less sensitive than the ELISA.[2] Detection of antigen in milk, tissue, and blood can be facilitated through PCR techniques. A positive AGID or ELISA in adults is synonymous with lifelong viral infection. Generally, time from infection to seroconversion ranges from 4 to 16 weeks, but some infected goats shed virus for long periods of time without seroconversion.[3] Goat kids may be transiently positive for the presence of antibodies during the first 8 to 16 weeks of life after consuming CAEV antibody–containing colostrum, but because of the nonprotective nature of maternal antibodies, such kids may seroconvert to true viral infection due to viral shedding from the infected dam.

Pathophysiology The characteristic granulomatous inflammatory pathology produced in affected tissues is thought to be due to immune complexes generated by the interaction of non-neutralizing antibodies produced by lymphocytes and associated virus-infected macrophages. Localization of such inflammatory lesions occurs where tissue-associated macrophages are found. Tissues of importance for CAEV localization include the synovium, mammary gland, and central nervous system (CNS), so the clinical manifestations of the disease are logical.

Epidemiology Transmission involves the transfer of virus-laden cells from one animal to the next. Transfer of CAEV to neonates through colostrum and milk is a highly efficient natural mode of transmission.[4,5] Transmission has also been reported through direct contact, so herd owners who do not practice segregation of seropositive animals continually have difficulty controlling and eradicating the disease.[4-7] Complete separation of kids from dams immediately following parturition and during the periparturient period is necessary; evidence exists that even kids not allowed to nurse become infected. Caprine arthritis-encephalitis virus proviral DNA has been recently detected in the caprine genital tract,[8] and experimental infection of goat embryos with CAEV has been reported.[9] Additionally, intramammary and in utero transmission have been described.[7,10] All the described means of acquiring the virus are potential explanations for continued transmission in herds where segregation and sound colostrum and milk management are practiced.

Maedi-visna virus (MVV), also known as *ovine progressive pneumonia,* is another lentivirus that together with CAEV is commonly referred to as *small ruminant lentivirus* (SLV). Although sheep are most likely to display clinical signs of MVV, and goats signs of CAEV, studies have shown that these viruses can be transmitted from sheep to goats and vice versa.[11] Therefore, eradication programs aimed at eliminating SLV from herds and flocks should not allow contact between sheep and goats.

A study examining the prevalence of antibody to CAEV in the United States found that 31% of all goats tested were seropositive, and 73% of herds had at least one seropositive member. Serum samples in this study were obtained from 28 states. Prevalence was highest in the western Pacific and northern plains regions on family-owned farms, and increased with age. Prevalence in this study was lowest in the Angora breed.[12]

Necropsy Findings Grossly, goats affected with the polysynovitis-arthritis form of CAEV have thickened, sometimes folded synovium consistent with synovial hyperplasia due to chronic inflammation. Microscopically, synovial hyperplasia is characterized by mononuclear infiltration of lymphocytes, plasma cells, and macrophages. Synovial spaces contain fibrin, and synovial villi and collagen are necrotic.[1]

No gross lesions are apparent in the CNS of goats affected with the leukoencephalomyelitis form of CAEV, but microscopically, perivascular infiltration of lymphocytes, macrophages, and plasma cells are observed. Perivascular infiltration is often accompanied by malacia of the brain and spinal cord, in addition to loss of myelin. Occasionally, degenerative lesions are seen in the gray matter.[13]

Treatment and Prognosis Prognosis for CAEV infection varies because most goats do not show clinical disease; once signs begin, however, rapid deterioration ensues. Arthritis and accompanying weight loss progress, and there is no treatment. Kids or mature goats affected with the leukoencephalomyelitis form do not survive and should be euthanized for humane reasons. Reportedly, a genetically determined predisposition for development of CAEV arthritis exists and can be identified with DNA fingerprinting.[14]

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Prevention and Control Prevention and control centers upon colostrum and milk management, but kids should also be prevented from any contact with the dam following parturition. Heat treatment of colostrum by holding it at 45°C (113°F) for 1 hour effectively inactivates the virus.[7] Kids can then be fed pasteurized milk until weaning. Unpasteurized goats' milk from seronegative dams is a risky substitute for heat-treated milk because some seronegative goats shed virus for long periods before seroconversion occurs. Pooling of colostrum increases the prevalence of disease in goat dairies, so this practice should be restricted. Kids should be tested serologically at periodic intervals to detect and remove infected individuals. Seronegative goats should be isolated from seropositive ones by a minimum of 6 feet.[7] Sharing of feed and water troughs should not be allowed, nor should use of common needles during routine vaccination or administration of medication. During breeding, seronegative does should not be housed with seropositive bucks, but they can be hand mated and quickly re-isolated. New additions to the herd should be tested and isolated until seronegative status is confirmed prior to entry into the herd.

Despite diligent prevention and control programs based on elimination of colostrum and milk transmission, isolation of seronegative goats, and serologic monitoring, obstacles to a CAEV-free herd are often encountered. Detection of virus has been reported in properly treated colostrum.[4] Overheating colostrum denatures immunoglobulin, thereby preventing effective passive transfer of immunity, but not heating colostrum long enough or at high-enough temperatures fails to inactivate the virus. Feeding overheated colostrum may also cause diarrhea in kids.[15] Attention to time and temperature details during heat treatment of colostrum and pasteurization of milk are of the utmost importance for effective colostrum and milk management. Some farms routinely feed cow colostrum, but neonatal isoerythrolysis has been reported in kids consuming cows' milk, and the lack of goat-specific immunoglobulin transfer is less than ideal.[15] Serologic monitoring can be complicated by the fact that viral shedding precedes seroconversion, so all goats should be tested a minimum of twice yearly to ensure any new cases are detected and managed accordingly. Unfortunately, no vaccine is currently available for CAEV.

Osteoarthritis

Melinda H. MacDonald

Definition The term *osteoarthritis* (OA) encompasses a large group of joint disorders characterized by progressive, permanent deterioration of the articular cartilage.[1-4] Cartilage damage is often accompanied by changes in the adjacent bone and soft tissue structures, including subchondral bone sclerosis, periarticular new bone formation, and synovial inflammation. Unfortunately, some confusion and debate surround the best term to use for this broad group of disorders. *Osteoarthritis, DJD, osteoarthrosis,* and *secondary joint disease* have been used almost interchangeably in veterinary medicine,[1,2] but *osteoarthritis* emphasizes the characteristic synovial inflammation detected in most patients, so this term is used here.

Interestingly, OA is one of the oldest documented orthopedic conditions. In fact, the fossilized remains of early dinosaurs suggest that OA predates the evolutionary development of mammals. Unfortunately, however, questions remain regarding the etiopathogenesis of OA, and this condition is still regularly diagnosed in most large animal species, including horses, cattle, and small ruminants. In goats, OA is frequently associated with CAEV (see previous discussion).[5,6] In pigs, OA is a common debilitating sequela of infectious arthritis or osteochondrosis.[7] Although not routinely diagnosed in sheep, OA has been reported to develop in individuals infected with ovine progressive pneumonia.[5] In contrast, joint disease is a common and expensive problem in the equine industry, and a wide variety of athletic injuries can progress to a common endpoint with stereotypic features of chronic OA.[1-3]

Etiology and Classification Many factors, including athletic performance, repetitive trauma, and age, are thought to influence cartilage homeostasis and contribute to degenerative changes in the joint. Contrary to the traditional view of articular cartilage as a passive bystander subjected to overexertion and traumatic wear-and-tear damage, it is now recognized that both resident and infiltrating articular cells have a critical role in the development of OA. Cartilage degeneration is an active process ultimately resulting from the inability of resident cells to maintain a normal balance between matrix synthesis and degradation. This occurs when chondrocytes and synovial cells are exposed to various nonphysiologic stimuli, including trauma and inflammation. Once the balance is disrupted, proteoglycans within the hyalin cartilage matrix are depleted and reduced in size, while the collagen meshwork progressively deteriorates. These changes in turn alter the mechanical properties of articular cartilage. A variety of different joint problems can initiate an imbalance between the rates of cartilage degradation and repair and, if left untreated, will ultimately progress to a common endpoint of OA.

Although a number of initiating and predisposing conditions have been identified, it is generally thought that trauma, either a single severe injury or low-grade repetitive damage, is the most important basis for the development of OA in large animal species.[1-3] In many cases the traumatic damage is augmented by abnormal weight bearing, poor-quality cartilage, or congenital joint instability, such as that seen with hip dysplasia in calves. In addition, OA frequently develops in joints that have unresolved or untreated osteochondrosis, subchondral bone collapse, or septic arthritis. In all these cases, the link between the cause and the end result of OA is a series of complex biochemical and metabolic events that are not yet fully understood. Regardless of the inciting etiology, advanced OA is characterized by fibrillated and ulcerated cartilage, eburnation and sclerosis of the subchondral bone, hyperplasia of the synovial membrane, and development of periarticular osteophytes.

Several classification schemes have been proposed to group clinical OA conditions in both human and veterinary medicine. One useful classification developed for equine OA defines three main categories of disease based on predisposing causes and clinical findings.[6] The categories include OA associated with synovitis and capsulitis (type 1), OA secondary to other identified injuries or disorders (type 2), and incidental or nonprogressive articular cartilage erosion (type 3).[2] For example, type 2 OA would include the chronic degenerative changes typically associated with intraarticular fractures, septic arthritis, osteochondrosis, and traumatic cartilage or ligament injuries. All three categories are routinely identified in equine athletes, but this simple scheme can easily be applied to other large animal species as well. Cattle most often develop type 2 OA as a consequence of septic arthritis, cruciate rupture, osteochondrosis, or nutritional deficiencies.[7]

A second way of classifying OA is based on the possible deleterious effects of biomechanical forces on normal and abnormal joints.[3] According to this scheme, the first of two major causes of OA is the concentration of abnormal forces on a previously normal joint. For example, OA can develop when there is increased weight bearing on one limb to protect a painful contralateral limb. The second major cause is the concentration of normal forces on an abnormal articulation, such as the joint damage that occurs when normal weight-bearing forces are applied to cartilage previously exposed to infection.

Pathology and Pathogenesis Despite the many pathways by which OA may develop, the resulting changes in the joint are essentially indistinguishable regardless of the initiating cause. By definition, this condition has a characteristic picture of cartilage damage with variable amounts of hypertrophic cartilage and bone remodeling. Pathologic features include different degrees of cartilage splitting and fragmentation, extending to complete erosion and loss of articular cartilage.[1-3] Typically the rate of disease progression and severity of OA are related to the nature and severity of the primary

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insult, the animal's age at the time, the joint location, and the animal's type and level of activity.

The pathogenesis of these changes is only partially understood. Several explanations have been proposed for the failure of resident chondrocytes to maintain the extracellular matrix. Mechanical trauma to the joint surface could initiate matrix damage, and repetitive microtrauma could damage chondrocytes and physically disrupt the joint surface. Leukocytes in an inflamed joint release destructive enzymes that can degrade the cartilage surface. Recent work has also demonstrated that various polypeptide mediators released in inflamed joints can stimulate chondrocytes to degrade their surrounding matrix. Regardless of the initiating factor, once the balance of chondrocyte-matrix turnover shifts toward degradation, proteoglycans are rapidly depleted from the extracellular matrix, and collagen fibers are exposed to direct traumatic and enzymatic breakdown. Unfortunately, hyaline cartilage has no effective intrinsic repair mechanism.

Articular cartilage damage is accompanied by changes in the adjacent subchondral bone (e.g., sclerosis), joint capsule (e.g., synovial hyperplasia, thickening of fibrous joint capsule), and joint margin (e.g., osteophyte formation, enthesophyte formation at joint capsule and ligament insertions).[3] Subchondral bone sclerosis may develop from an abnormal distribution of forces under damaged articular cartilage, or it may actually precede the cartilage damage. It is now known that bone remodeling and subchondral bone sclerosis occur in response to repetitive cyclic compression during exercise and, in certain cases, could result in trauma to the overlying articular cartilage and predispose to the development of OA (e.g., third carpal bone disease in horses). Joint margin changes occur as a result of progressive cartilage deterioration and subchondral remodeling (osteophytes) or joint instability (enthesophytes).

Clinical Signs

History and occupation are important for identifying animals at risk for developing OA. Typically the first sign an owner or caretaker recognizes in an affected animal is lameness or stiffness. Whereas the pain and dysfunction may develop insidiously, the owner will often report a sudden onset of clinical signs. Flexion and extension of an involved joint frequently exacerbates the lameness or elicits a pain response. Because articular cartilage is aneural, pain is thought to result from joint inflammation and secondary changes in adjacent tissues. Pain receptors are abundant in joint capsules, articular ligaments, and subchondral bone. Joint stiffness may be associated with guarding of a painful joint. Decreased ROM with joint capsule inflammation is also common. Osteophytes and enthesophytes may be palpable in chronic cases of bone spavin and ringbone. A postural deformity may be evident if articular degeneration progresses to ankylosis. It is also important to remember that OA may exist in the absence of any clinical signs.

Gait abnormalities compatible with OA include shortened stride length, limb abduction, and dragging the toe. Increased lameness after sustained flexion of a single joint suggests the joint is involved. Horses with OA often present early in the course of disease with a primary complaint of poor performance. These individuals can warm out of the lameness or temporarily improve with rest and are often difficult to diagnose. In contrast, food animals typically present in the advanced stages of OA. Rams and bulls may stand post-legged and appear weak in the rear when the hindlimbs are severely affected. In all species, the severity of signs varies with the joint affected, stage of disease, amount of inflammation, cartilage degeneration, and periarticular changes.

Diagnosis

Regional nerve blocks and intraarticular anesthesia can be useful for determining the origin of lameness. Unfortunately, standard synovial fluid analysis typically shows only minimal nonspecific changes. Although not useful for determining the severity of cartilage destruction, cytologic analysis is often useful for differentiating OA from other causes of synovial inflammation (e.g., septic arthritis). A variety of synovial fluid markers have been evaluated as possible diagnostic aids for evaluation of equine synovitis and joint disease (e.g., cytokines, eicosanoids, GAG concentrations, immune complexes, collagen type-specific antibodies and propeptides, cartilage wear fragments, free-radical oxidation products, polymerization of hyaluronate, chondroitin sulfate epitopes). Current detection techniques for cytokines and eicosanoids may prove useful diagnostically and prognostically.

After identification of an involved joint, radiographs are used to determine the severity and extent of disease. Articular cartilage is not visualized but may be indirectly assessed by evaluating joint space width. In contrast, the associated subchondral and periarticular bone reaction can be directly evaluated. Radiographic signs of OA develop gradually, affect opposing joint surfaces, and may include destructive as well as productive lesions. Changes typical of advanced OA include marginal osteophyte proliferation, periosteal new bone production at sites of joint capsules and ligamentous attachments (enthesophytes), narrowing or obliteration of the joint space, subchondral bone sclerosis, and occasionally subchondral lysis. Early in the disease, no bony lesions may be detected, and clinical findings from the entire examination must be considered. Radiographic changes associated with OA must be differentiated from similar bone reactions caused by active infection, fractures, osteochondrosis, and invasive tumors. Infectious arthritis classically causes rapid widespread osteochondral destruction. Minimally displaced fractures may mimic OA but are usually discrete isolated lesions. Knowledge of the characteristic site distribution and site-respective appearances of osteochondroses in each species is useful for differentiation from OA. The presence of OA in joints with osteochondrosis usually worsens the prognosis.

Scintigraphy is particularly valuable in early disease states when conventional diagnostic methods have not revealed bone or soft tissue changes. Increased scan activity is associated with soft tissue inflammation or increased bone remodeling, but alone it is not diagnostic for OA. Arthroscopy is the best method for gross evaluation of articular cartilage and is most useful when lameness has been localized to a specific joint but no bony changes are detected radiographically. This technique provides the added therapeutic benefit of simultaneous joint lavage. Although arthroscopy was initially promoted for diagnostic and therapeutic use in equine patients, these techniques are gaining popularity in food animal practice as well.[8]

Treatment

The choice and efficacy of treatment depend on the inciting cause of OA, stage of cartilage degradation, joint involved, and degree of active inflammation. In general the treatment of OA should be directed at eliminating any primary causes, reducing active joint inflammation, and treating articular cartilage loss or degeneration.[1,2,9] Early treatment of primary problems minimizes the extent of secondary joint damage. For example, fractures and osteochondritis dissecans can often be managed successfully with arthroscopic surgery; however, early intervention is essential to avoid the secondary changes of OA.

Many therapeutic options are designed to treat active soft tissue inflammation and prevent progression of articular cartilage damage. Rest is the simplest but often the most difficult recommendation to enforce, especially when dealing with elite performance horses. There are also valid concerns that complete rest may result in resorption of subchondral bone and predispose the horse to subsequent injury. Other treatments for soft tissue disturbances in the joint include physical therapy and controlled exercise, systemic NSAIDs (e.g., phenylbutazone, flunixin meglumine), joint lavage, and topical application of antiinflammatory products.

Numerous medications have been specifically designed and marketed for treating OA in human and veterinary patients. However, many of these products remain controversial in terms of their safety and efficacy in large animals. The most popular formulations include intraarticular corticosteroids, intraarticular and intramuscular (IM) polysulfated glycosaminoglycans (GAGs), intraarticular and IV hyaluronan, and oral GAG supplements.

Intraarticular steroids are the most potent antiinflammatory agents available, but they have been associated with progressive cartilage damage.[9,10] Nevertheless, investigations critically evaluating the

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effects of corticosteroids in equine joints suggest that when administered at physiologic doses, these drugs may have beneficial protective effects.[9,10] Current recommendations emphasize the need for appropriate caution and encourage use of low doses of steroids in conjunction with other antiinflammatory medications. Hyaluronan (sodium hyaluronate) is currently used both intravenously and intraarticularly to treat synovial inflammation and OA in the horse.[9,11] The intraarticular products vary in molecular weight and cost and include cross-linked hylans, which may prolong intraarticular retention. Clinical reports document the efficacy of hyaluronan for mild to moderate synovitis, and some research supports an inhibition of proteoglycan degradation and inhibition of synoviocyte release of various inflammatory mediators. Other studies failed to demonstrate beneficial effects in joints with significant articular cartilage damage or osteochondral fragmentation.

Intraarticular administration of polysulfated GAG has been reported to reduce progressive degenerative changes in articular cartilage, but is controversial in terms of its ability to augment the chondrocyte repair response.[9,12] IM use is advocated because intraarticular use has been associated with adverse reactions and potentiates the risk of iatrogenic joint infection.[9,12] Intraarticular regenerative medications (platelet-rich plasma and stem cell therapy) are currently under investigation and used in specific clinical cases, but clinical research data are lacking.

There is still great interest in the use of nutritional supplements to prevent and treat OA, with a proliferation of products promoted as beneficial to joint health and cartilage regeneration.[13] Among the most popular are oral glucosamine sulfate and chondroitin sulfate preparations. However, oral absorption of chondroitin sulfates has not been documented in the horse, and although clinical reports suggest a beneficial effect from these supplements, additional controlled studies are necessary to confirm these effects. Methylsulfonylmethane (MSM), a dietary derivative of DMSO, is also being used as a dietary supplement to control the inflammation associated with OA. Again, minimal documentation exists regarding its value in treating joint disease in large animals. Other compounds to treat OA include *S*-adenosyl-L-methionine (SAMe) and various vitamins known to provide antioxidant protection.

The most challenging aspect of OA management is treating existing articular cartilage degeneration and loss. Partial-thickness cartilage defects do not heal, and full-thickness defects heal with inferior fibrocartilaginous tissue. Some surgical techniques (e.g., curettage, subchondral bone drilling, microfracture) facilitate defect repair by enhancing fibrocartilage ingrowth from the underlying subchondral bone; however, fibrocartilage is biomechanically inferior to normal hyaline cartilage. Grafting cartilage defects with periosteum, perichondrium, and sternal cartilage has not been encouraging. More recent work focuses on transplantation resurfacing using chondrocyte grafts and growth factors to stimulate repair.[14]

Prognosis

Prognosis for animals with OA depends on the initiating factor(s), extent of the secondary disease, joint affected, and intended use of the animal. With early and aggressive treatment, many animals can return to soundness and athletic performance. In other cases, salvage in the form of surgical arthrodesis may provide the most favorable outcome.

Sprains, Subluxations, and Luxations

Will C. Jordan • Robin M. Dabareiner

Definitions

Sprains and luxations have been classified as type 2a traumatic arthritides.[1] These injuries have been categorized in three forms: mild, moderate, and severe. *Mild sprains* constitute injuries that involve the tearing or disruption of a minimal number of ligament fibers with no loss of integrity to the ligament. Hemorrhage and edema are typically present in the ligament. Injuries that involve a portion of the ligament, with loss of integrity, are considered *moderate sprains*. Laxity of the joint is often present with moderate injury, but complete separation of the ligament from the bone or complete separation of the body of the ligament is not seen. Significant hemorrhage and edema are present in the ligament. Injuries that involve tearing of the ligament, resulting in either complete separation from the bone or widening of the tendon fibers, are considered *severe sprains.* These injuries will result in some form of joint instability, especially when the affected joint is manually stressed.



FIG. 38-21 Dorsopalmar radiograph of a subluxated metaphalangeal joint after the joint has been manually stressed.

Luxations and subluxations are usually the result of severe sprains of periarticular or articular ligaments. *Luxations* represent the complete dislocation of the articular surfaces, with *subluxations* having only partial and incomplete disarticulation (Fig. 38-21).

Etiology and Pathophysiology

Sprains can be associated with acute injuries in which there is excessive strain on the ligament fibers, on ligamentous attachments, or secondary to repetitive actions on the ligament. The latter results when there are maximal or near-maximal loads repeatedly applied to the ligaments and associated structures, causing a degenerative type of lesion. Age can also be a contributing factor in these degenerative changes. Muscle fatigue can contribute to the weakening of adjacent structures, increasing the stresses applied to the supporting ligaments. Luxations and subluxations are usually of traumatic origin, such as stepping in a hole or entrapment of a limb in a gate or fence.[1]

Typically, hemorrhage and edema form within the ligament(s) surrounding the joint capsule, or in severe lesions the hemorrhage can be periligamentous or intraarticular. Inflammation ensues, and the ligamentous or capsular lesion heals through fibrosis, forming a scar, with the predominant production of type III collagen. Type III collagen contains smaller-diameter fibrils and has fewer cross-links than type I collagen, which is the predominant collagen type in normal tendons and ligaments. As the lesion matures, both fibril diameter and number of cross-links increase, in addition to the proportion of type I collagen. This will increase the strength of the injury, which can take weeks to months to heal but will ultimately be weaker than normal tissue.[2] Often the affected joint capsule and surrounding ligaments become fibrotic as healing occurs, resulting in decreased ROM in the affected joint. Secondary calcification of the affected soft

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tissue structures may occur and also adversely affect the joint's mobility.

Luxations of the coxofemoral joint in calves may be associated with calving injuries during dystocia or in cows being ridden while in estrus, or with a traumatic fall in the immediate postpartum period.[3,4] Shoulder joint luxations are usually the result of trauma.[5,6]

Clinical Signs and Differential Diagnosis Clinical signs vary depending on the severity of the sprain and time since the initial injury. The animal may have a history of mild lameness or decreased performance, as well as a history of a positive response to NSAIDs or stall rest. Patients with moderate to severe sprains will typically have a more pronounced, acute lameness or may be non–weight bearing on the affected limb. There may also be localized swelling, heat, increased joint effusion, or pain elicited on palpation or manipulation of the affected joint. Other signs may include abnormal limb positioning, decreased ROM, crepitus, and joint laxity. Injuries may present after an acute or traumatic insult as chronic lameness, or a chronic mild injury can present acutely with severe lameness if the collateral ligament completely ruptures. Chronic injuries are characterized by joint capsule thickening or enthesophyte formation at the origin and insertion of the affected collateral ligament.

Subluxations and luxations result in loss of joint function and mobility and may present with a varus or valgus deformity. Complete luxations in the horse are most common in the pastern, fetlock, and hock joints.[1] Luxations can occur in the shoulder, carpus, and coxofemoral joint, but these luxations are less common in horses. Coxofemoral luxations are the second most common type of luxation in cattle.[4]

Differential diagnoses vary depending on the region affected and duration of injury but may include soft tissue contusion, synovitis and capsulitis, osteoarthritis, bursitis, musculotendinous injuries, fractures, physeal fractures, septic arthritis, tenosynovitis, and flexural or angular limb deformities.

Diagnostic Tests A thorough history and physical examination should be performed at presentation. The exam should include assessment of pain, swelling, heat, joint effusion, and joint instability. Patients presenting with only mild lameness should have a thorough lameness examination including perineural anesthesia to localize the affected region or joint. The clinician should be cautious if there is any evidence of joint laxity or instability or severe lameness, since perineural anesthesia could exacerbate the extent of joint damage.

Radiographs should be obtained to assess the joint's bony structures because concurrent factures are common, with traumatic insults resulting in luxation. Stress views can be performed to assess the level of joint instability (see Fig. 38-21). One study reported on 17 horses with luxation or subluxation of the metacarpalphalangeal (MCP) or metatarsalphalangeal (MTP) joints.[5] All had rupture of at least one collateral ligament (CL) of the joint. In those horses, radiographs showed that 8 of 17 horses sustained fractures, 6 of which were avulsion fractures located at the origin of the CL. Other types of fractures identified in that study were splint bone fractures and small articular chip fractures. Fractures of the proximal or middle pastern bones can cause luxation or subluxation of the proximal or distal interpastern joint. Nuclear scintigraphy can also be used to evaluate insertional desmopathies that may not be radiographically apparent.

Ultrasonography is very useful in localizing and depicting the severity of ligamentous lesions and for confirming the association of fracture fragments identified radiographically. In acute cases, ultrasound evaluation often shows hemorrhage within the joint capsule (Fig. 38-22). MRI is becoming more readily available in the veterinary field and has been found useful in identifying and characterizing lesions in ligaments. In addition, there may be concurrent damage to adjacent structures of the joint or avulsion fractures that might not be ultrasonographically or radiographically detectable but that can significantly influence the prognosis.[3,7-9]

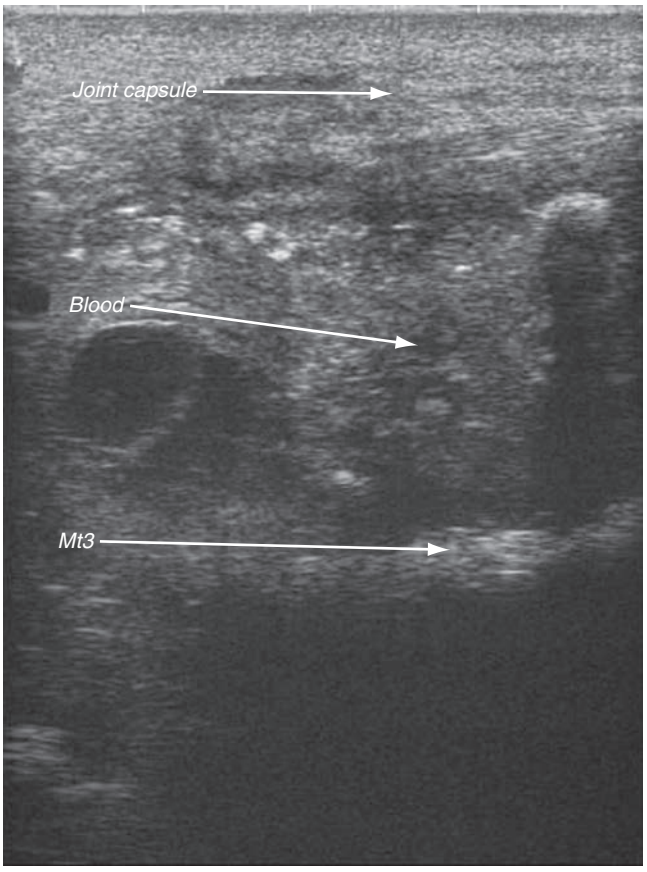


FIG. 38-22 Ultrasound image of a metacarpophalangeal joint from a horse with an acute sprain. Note the hemorrhage accumulation within the joint capsule. *Mt3,* Third metatarsal bone of fetlock joint.

Treatment Treatment is largely based on the severity of the lesion and the associated structures involved. Mild sprains can be treated conservatively with support bandages, NSAIDs, polysulfated GAGs, and rest for 3 to 4 weeks, followed by a controlled exercise program before returning to normal activity. Adjunctive physiotherapies may also be considered, such as hydrotherapy or shock wave treatment. Moderate sprains involving significant ligament damage may necessitate use of a cast or splint to provide joint stability during the initial healing process. Distal limb immobilization with a fiberglass cast and stall confinement was the initial treatment for 10 of 17 horses with MCP or MTP luxation and CL rupture. Duration of cast immobilization ranged from 14 to 132 days (mean, 71 days).[5]

In acute cases, hemorrhage is often present within the affected joint. This hemorrhage usually resolves after 7 to 10 days, but it can also subsequently form a fibrinous clot within the joint capsule, resulting in a chronic mild synovitis that can be treated with intraarticular medications such as sodium hyaluronic acid, triamcinolone, and amikacin antibiotic. Diagnostic arthroscopic surgery should be considered to evaluate articular cartilage integrity and remove persistent fibrin accumulation. If arthroscopic surgery is performed, a cast or splint should be applied to the affected limb during recovery from anesthesia to prevent luxation of the affected joint and further injury. Severe sprains may require some form of internal coaptation (surgical implants) or arthrodesis of the joint, depending on the degree of joint instability. Support of the contralateral limb should be considered for non–weight-bearing injuries.

Luxations of the coxofemoral joint in cattle can be repaired by open or closed techniques, and success depends on duration of the luxation, concurrent fractures or soft tissue injury, and age. Open reduction was reported as being more successful than closed reduction, although closed reduction should be attempted immediately after the injury if possible.[4] Shoulder joint luxations can also be

reduced by closed and open techniques.[5] Open reduction with internal stabilization seems to result in a better survival outcome for the animal.[5]

Prognosis Prognosis depends on the severity of damage to the intraarticular cartilage and surrounding soft tissue structures. Horses sustaining mild joint or ligamentous strains have a good prognosis for returning to previous athletic use. Horses sustaining moderate or severe sprains or joint luxations usually develop secondary DJD in the affected joint, which may require intraarticular medications and NSAIDs to return to previous use. The long-term prognosis for returning to athletic performance in many cases is poor. Eight of 17 horses with MCP or MTP joint trauma resulting in joint instability and rupture of the CL returned to riding and one returned to jumping activity after limb immobilization and stall confinement.[5] Simple shoulder luxations in large animals generally carry a guarded to poor prognosis. Simple coxofemoral luxations in cattle have a fair to good prognosis, with calves having a better prognosis than adult cows.



FIG. 38-23 Arthrogryposis as a result of Schmallenberg infection in a live lamb *(right)* in the United Kingdom. Its unaffected twin is on the left.

Arthrogryposis

Philippa Sprake

Arthrogryposis, or multiple congenital contracture, is a syndrome of persistent contracture present at birth.[1] In this condition, the limb cannot be straightened manually, and there is improper articular alignment or rotational deformity.[2] Arthrogryposis is one of the most common congenital defects of cattle and more commonly affects the forelimbs. It should be differentiated from other types of contractures, such as congenital tendon contracture or contracture secondary to articular fracture, ankylosis, septic arthritis, agenesis, or dysgenesis of joints.[2]

Etiologies for arthrogryposis include genetic, infectious, and toxic. A congenital syndrome comprising forelimb arthrogryposis, spinal dysraphism, and cleft palate has been documented in calves of primarily Charolais origin.[3] Arthrogryposis was documented to be part of the clinical findings in Holstein calves with the inherited complex vertebral malformation syndrome.[4] Various other congenital syndromes have been reported in cattle, including vertebral agenesis and arthrogryposis of the pelvic limbs in a Holstein heifer calf[5] and arthrogryposis in Herefords.[1] Arthrogryposis multiplex, or "curly calf syndrome," is an autosomal recessive defect in Angus cattle where kyphoscoliosis and decreased muscling are also observed.[6] While not as common as in ruminants, arthrogryposis has been reported in equines, including Norwegian Fjords[7] and a Thoroughbred foal.[8] Arthrogryposis has been documented as an autosomal recessive condition in Suffolk[9] and Corriedale sheep.[10] There are no documented case reports of arthrogryposis in camelids.

Viruses of the family Bunyaviridae have a common tropism for fetal tissues and result in abortion, stillbirths, and arthrogryposis.[11] The viruses include Akabane virus, primarily found in Australia, Asia, and the Middle East,[11] and Cache Valley virus in the United States.[12] Both wild and domesticated ruminants and horses are susceptible to the Akabane and Aino viruses.[11] Concurrent defects include hydranencephaly or microencephaly, cerebellar hypoplasia, and irregular neuromuscular development.[11,13,14] More severe defects are found with infection earlier in gestation.[11,14] In 2011, a syndrome consisting of fever, decreased milk yield, diarrhea, and abortion or stillbirth was reported in adult dairy cattle in northwestern Europe.[15] Abortions, stillbirths, and live births with congenital malformations were reported in calves, lambs, and kids (Fig. 38-23).[16] Congenital defects included arthrogryposis, brachygnathia inferior, spinal curvature, hydrocephalus, hydranencephalus, porencephaly, and cerebellar hypoplasia primarily. The syndrome was found to be caused by a novel virus of the Simbu serogroup of the genus *Orthobunyavirus,* and was named Schmallenburg after the town in Germany where it was first detected.[15] The virus is currently diagnosed by real-time polymerase chain reaction (RT-PCR).[15,17] No vaccine is currently available. In utero infection with bluetongue virus in cattle and sheep primarily presents with hydranencephaly, although arthrogryposis, prognathia, brachygnathia, and excessive gingival tissue have been reported.[18] The pestivirus causing border disease in lambs was shown to result in several congenital abnormalities when experimentally inoculated into pregnant ewes (arthrogryposis, tremors, brachygnathism, prognathism, and lateral deviation of joints).[19]

Arthrogryposis has been associated with ingestion of toxic alkaloids during pregnancy, including plants of the genera *Conium, Lupinus,* and *Nicotiana*.[20] All three have also been shown to result in cleft palate deformities when fed to goats during days 30 to 60 of pregnancy.[20] Arthrogryposis due to lupine toxicity has been termed "crooked calf disease." Congenital contractures have also been reported with the grazing of sorghum pastures in sheep[21] and feeding *Veratrum californicum* at day 29 of gestation in sheep.[22]

The pathogenesis of arthrogryposis is thought to be a result of denervation resulting in muscle atrophy with the functional opposing muscles resulting in contracture.[23] Reduced numbers of ventral horn cells have been reported in cases of multiple congenital contracture.[24] Restriction of fetal movement in utero has also been proposed.[24]

Animals with arthrogryposis may be aborted, stillborn, or born alive. The prognosis for survival, however, is poor. Treatment has been attempted by tenotomy of the ulnaris lateralis and flexor carpi ulnaris followed by stall confinement and bandaging.[25] In that study, a straight palmar carpal angle was achieved in 70% of treated limbs at 8-month follow-up. Outcome was improved in less severely affected limbs.[25] Arthrogryposis in aborted or near-term fetuses commonly results in dystocia, leading to the necessity for manual removal of the fetus by fetotomy or caesarian section.[2,14] Death of the dam has also been reported.[11] Severely affected animals commonly have secondary problems including sepsis and metacarpophalangeal deformities.[25] Surviving animals should not be retained in the herd as breeding animals.

Ankylosis

Ricardo Loinaz

Definition and Etiology *Ankylosis* refers to the abnormal fusion of bones in a joint, which can occur naturally or as a desired end result of treatment. *Facilitated ankylosis* refers to a medical fusion and thus is different from *arthrodesis,* or surgical fusion, of two or more bones into a single structure.[1] Naturally occurring ankylosis is often the result of disease or trauma to the joint and bones involved. Septic arthritis with subsequent DJD and associated prolonged

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therapy, including joint immobilization, are often the inciting factors for ankylosis. *Congenital ankylosis* is the absence of an articulation, and it is a rare condition in horses and cattle, often associated with other congenital abnormalities.[2] Congenital ankylosis of the DIJ in both hindlimbs, with concurrent dysplasia of the distal sesamoid bone in all four limbs, has been reported in a 2-year-old Arabian horse.[3] In calves and foals, congenital ankylosis may occur between vertebrae or in multiple joints of the limbs, resulting in dystocia related to musculoskeletal inflexibility.[2]

Joint fusion is initiated by biomechanical and biochemical factors, leading to instability and degeneration of cartilage and chondrocytes.[2] Periarticular contracture, joint capsule fibrosis, and chronic muscle spasm all contribute to joint immobility, which leads to synovitis and cartilage destruction. Ossification of periarticular soft tissues develops, resulting in partial bone bridging across the joint. The final stage of ankylosis is complete bone bridging with trabecular bone and joint obliteration.

Common sites of ankylosis in horses include the distal hock joints (distal intertarsal [DIT] and tarsometatarsal [TMT]), the thoracolumbar intervertebral articulations, and the PIP. These low-motion joints are more likely to achieve complete bone bridging without surgical intervention. In high-motion joints (antebrachiocarpal, midcarpal, metacarpophalangeal, scapulohumeral, and distal interphalangeal), naturally occurring complete bone bridging is rare, and the resulting cartilage degeneration leads to severe lameness. In these cases, surgical fusion or arthrodesis using internal fixation techniques is required if treatment is to be attempted.[4] Large animals with vertebral ankylosis may show neurologic deficits caused by bony impingement on the spinal cord or by dynamic compression leading to abnormal motion or spinal ligament hypertrophy.[2]

Clinical Signs and Differential Diagnosis Indications for ankylosis include stiffness of a joint and associated immobility, degenerative joint changes, decreased range of joint motion, and varying degrees of lameness. Decreased ROM is most obvious if high motion or multiple joints are involved. Degree of lameness can range from mild to severe, particularly in the acute phase where local inflammation contributes to the degree of lameness. Enlarged and thickened periarticular structures, conformational abnormalities, disuse atrophy of muscles or disuse osteopenia of bones, and gait stiffness may also be identified. Once bone bridging is complete and no articular cartilage remains, the condition is no longer painful and the articulation is immobile.

Differential diagnoses include soft tissue injuries or contracture, intraarticular or periarticular adhesions, joint luxation, neoplasia, arthrodesis, spondylosis, an intraarticular mass, osteomyelitis, and fracture. Diagnosis of ankylosis should be based on a complete physical and musculoskeletal examination, lameness evaluation, and radiography. Multiple radiographic views should be available for definitive diagnosis, but additional imaging techniques such as ultrasonographic evaluation of relevant soft tissues and joint spaces, CT, and MRI may be useful and provide more detailed information that may influence the treatment option elected.

Treatment and Prognosis Treatment in the acute phase focuses on providing comfort to the animal, because ankylosis is a chronic and progressive disease process. A complete treatment plan should be tailored to the specific case and is often determined by the presence or absence of infection or severe joint instability. Antiinflammatory medications (phenylbutazone, firocoxib, flunixin meglumine, intraarticular corticosteroids) are necessary in most cases. Additional oral joint supplements, hyaluronic acid, and polysulfated polysaccharides (Adequan) may also be beneficial as chondroprotectants. Although joint immobilization and a decrease in exercise are often necessitated, low-level exercise appears to be beneficial in some cases because it helps increase and stimulate development of new bone formation, promoting faster and more complete ankylosis.[2] Unstable joints or actively septic joints, however, require immobilization with splints or casts to allow the fusion to progress and improve the animal's comfort level. Animals that remain lame, have end-stage joint disease, or are not completing ankylosis naturally require surgical or chemical arthrodesis to improve the comfort level and chances of returning to performance activity.

Different methods of facilitated ankylosis can be used to promote joint fusion. The speed at which complete bone bridging occurs may be enhanced through the use of chemical chondrocyte destruction or surgical obliteration of the articular cartilage. Chemical methods of ankylosis include the use of sodium monoiodoacetate (MIA) and ethyl alcohol, but MIA has been associated with considerable morbidity and signs of severe pain.[1] In addition, postinjection soft tissue swelling, progression of osteoarthritis to adjacent unaffected joints, severe soft tissue necrosis, variable length of convalescence, and inconsistent outcomes are why MIA-mediated ankylosis can no longer be recommended.[5] Ethyl alcohol ankylosis works via nonselective protein denaturation and cell protoplasm precipitation and dehydration. One of the first controlled studies investigating the use of ethyl alcohol in horses found that 70% ethyl alcohol injected in the TMT joint of healthy horses with no radiographic evidence of joint disease resulted in a pain-free fusion by 4 months in 8 of 16 horses and complete fusion by 12 months post injection in 15 of 16 horses.[6] A recent study evaluated the safety and efficacy of ethyl alcohol–mediated ankylosis of the DIT and TMT joints in horses with lameness localized to those joints and found a significant reduction in posttreatment lameness in all treated horses but evidence of joint collapse and progressing ankylosis by 3 months post injection.[1] Another study looked at 24 horses that received ethyl alcohol injections in the distal hock joints, and 52% had improved lameness scores at 6- and 9-month follow-up, whereas 19% had deteriorated.[7] A recent study looked at 70% ethyl alcohol injection alone or in combination with lag screw placement for PIP fusion, and in both instances alcohol treatment failed to produce reliable fusion of PIP joints.[8] Another recent study looked at facilitated ankylosis of PIP joints using ethyl alcohol and reported that 50% of horses were sound and 34% were improved but not sound at time of follow-up.[9] The median time for horses to become sound enough to return to work in this study was 8 months, suggesting that ethyl alcohol–facilitated ankylosis may be more effective and work faster in DIT and TMT joints than in PIP joints.

Facilitated ankylosis via surgical débridement of articular cartilage and use of casts or transfixation casts is recommended in the initial treatment of septic PIP joints instead of surgical arthrodesis in the acute phase.[5] Laser-facilitated ankylosis using a neodymium:yttrium-aluminum-garnet (Nd:YAG) or a diode laser to destroy articular cartilage by superheating and vaporizing synovial fluid, resulting in chondrocyte death, can also be used for facilitated ankylosis. Experimental studies using laser-facilitated ankylosis in DIT joints found that partial ankylosis was achieved in 5 to 12 months.[5] Transarticular drilling has been used as a method for ankylosis of the DIT and TMT joints, alone or in combination with laser application, and estimates of outcomes suggest that this technique is 47% to 85% successful.[5]

Ankylosis may require 6 to 12 months for complete bone bridging after surgical or chemical treatment methods. This process can take several years if left to natural ankylosis. Prognosis depends on which joint is involved and the expectations for use of the animal. Low-motion joints have a good prognosis for returning the horse to soundness and athletic performance once the fusion process is completed. High-motion joints have a poor prognosis for return to use in horses.

Osteomyelitis

Justin Dominick McCormick

Definition and Etiology Osteomyelitis is an infectious inflammatory disease process of bone and its marrow cavity, causing bone destruction. Infection may be localized to a single region of

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bone or may involve several structures including marrow, cortex, periosteum, and surrounding soft tissue.[1,2] If only bone is affected, it is classified as osteitis. The majority of osteomyelitis cases, both acute and chronic, are bacterial in origin, though myotic infections have been reported. This disease process begins hematogenously, secondary to adjacent soft tissue infection, or by direct inoculation (e.g., trauma, internal fixation).

Clinical Signs and Differential Diagnosis Clinical signs will depend on the severity and duration of infection and the organism involved. Diagnosis is based on a complete history, physical examination, identification of microorganisms, and results of diagnostic imaging.

In the neonate, acute osteomyelitis is most commonly of hematogenous origin. Translocation of bacteria from the umbilicus or other sites of infection (e.g., respiratory or gastrointestinal) results in infection of synovial structures and bone.[3] In the foal, common anatomic locations of established infections have been described.[4] *S-type infections* only involve the synovial membrane. *E-type infections* are located around areas of growth (i.e., articular epiphyseal complex). A *P-type infection* is a primary infection of the long-bone physis. Early detection of acute osteomyelitis in young animals can be difficult. Clinical signs of S- and E-type infections include persistent lameness and joint effusion with fever. P-type infections present without synovial effusion, but edematous soft tissue swelling secondary to osteomyelitis of the metaphysis is often seen. The femoropatellar and tarsocrural joints are most commonly affected, followed by the carpal and fetlock joints. Persistent lameness that is unresponsive to antiinflammatory treatment often precedes diagnosis, but lameness can be subtle during the early stages of osteomyelitis and easily mistaken for musculoskeletal injury.[5] There is often a history of failure of passive transfer, pneumonia, septicemia, gastroenteritis, or omphalophlebitis.[6] Osteomyelitis in the neonate is typically localized to areas of growth near the distal femur, radius, tibia, and metacarpal/metatarsal regions (Fig. 38-24).[3] Joints of lame foals should be evaluated thoroughly to localize pain and swelling.

Osteomyelitis in adults is usually associated with traumatic infection (e.g., puncture wound or laceration) or open fracture reduction. In mature animals it is difficult to differentiate between infection and postoperative inflammation in cases of acute osteomyelitis. Lameness may be mild initially then progresses rapidly to non–weight-bearing lameness. Local swelling, painful response to digital palpation, fever, and inappetence are clinical signs often associated with acute osteomyelitis in the adult.[2] Clinical signs of infection related to injury or following orthopedic surgery may be present as early as 7 days or be delayed up to 3 to 4 weeks.[6] Chronic osteomyelitis becomes more localized as the disease progresses and often results in a firm swelling over the affected area. Persistent drainage from an incision or area of granulation tissue, mild to severe lameness, or a non-healing wound are also often seen with disease progression in chronic cases. Drainage may be persistent or intermittent and is generally characterized as purulent. Osteomyelitis in conjunction with septic arthritis or tenosynovitis may result in only mild lameness if the wound is open and able to decompress.

Osteomyelitis is difficult to diagnose with radiography in the acute stages. Soft tissue swelling with or without gas opacities adjacent to the area of infection may be the only abnormalities noted in early infections. Ultrasonography can aid in early diagnosis of osteomyelitis by detecting purulent fluid in soft tissues and irregular bone echoes near affected sites.[2] Osteolysis does not appear on radiographs until 30% to 50% of bone mineral is lost, which may take up to 10 to 14 days after infection is established.[6] Radiographic signs of chronic osteomyelitis include soft tissue swelling with bone destruction and new bone formation (Fig. 38-25).[8] Infection of bone may result in the formation of an *osseous sequestrum,* a piece of radiodense cortical bone that has lost local vascular supply.[9] The sequestrum is well defined by an outline of radiopaque productive new bone formation called an *involucrum,* which forms as the body attempts to wall off infection.[8] An opening to the sequestrum, the *cloaca,* is usually present and allows drainage of purulent exudate out to the skin surface.[9] Fistulography can be useful in determining the extent of draining tract communication with bone or joints.[8]

Advanced imaging modalities provide greater diagnostic capabilities than radiography and may help in the early detection of osteomyelitis. CT gives superior imaging of bone in three planes and can be used to identify purulent material in the medullary cavity, adjacent soft tissue abscesses, intraosseous gas, decreased bone density, and presence of foreign bodies.[2] CT can also provide additional



FIG. 38-24 Osteomyelitis and septic physitis of the distal radius of a 3-week-old foal. There is a large area of lysis over the distomedial radius involving the metaphysis, physis, and epiphysis with marked soft tissue swelling.



FIG. 38-25 Lateromedial radiograph of a horse with chronic osteomyelitis of the third metatarsus. A sequestrum is identified at the level of the proximal metaphyseal region. An involucrum is outlined by an area of medullary sclerosis. There is periosteal new bone formation over the dorsal cortex.

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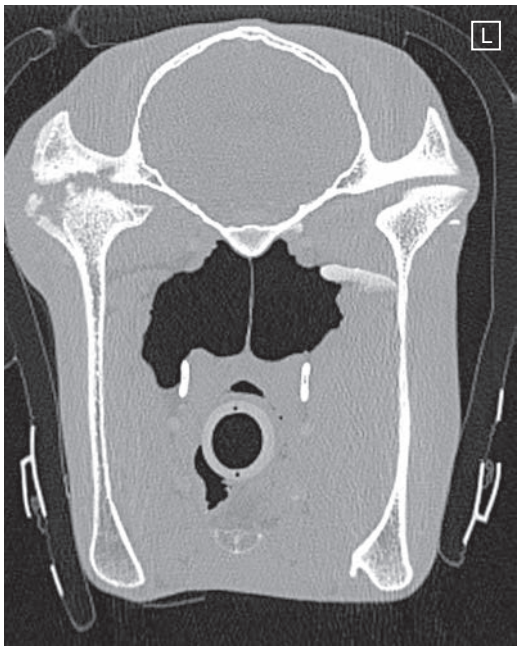


FIG. 38-26 Computed tomography image of a septic temporomandibular joint with osteomyelitis of the right mandibular and temporal bones. There are multiple small subchondral lytic lesions of the medial aspect of the condyle and temporal bone. Periosteal reaction is associated with the temporal bone at the level of the temporomandibular joint.

information in anatomic locations where images on radiographs and ultrasound are difficult to interpret (e.g., skull) (Fig. 38-26).[2] MRI is useful in determining lytic changes in the medullary cavity but less effective than CT in defining cortical bone involvement.[2]

Development of osteomyelitis following fracture repair decreases stability of the affected limb and increases healing time. Signs related to orthopedic infection are subtle in the acute stages, making primary recognition difficult. Fever, malaise, and a slight increase in lameness are nonspecific signs of immediate postoperative infection. Risk factors associated with orthopedic procedures include use of implants, length of surgery, location of injury, and the amount of soft tissue damage related to the initial injury.[2,10] Open reduction and internal fixation during fracture repair require extended duration of surgery, increasing the exposure time of soft tissues to air.[10] Early radiographic evaluation when infection is suspected is beneficial to ensure structural stability of the construct.[5] Bone lysis around implants with periosteal reaction unrelated to fracture healing can be seen later on radiographs (Fig. 38-27).[5] Implant loosening secondary to bone lysis increases motion across the fracture gap and decreases stability of the repair. Healing is prolonged or improbable when rigid internal fixation is lost. In addition, motion across the fracture together with osteomyelitis adds to patient discomfort and reluctance to bear weight on the affected limb. Overloading the contralateral limb increases the risk of laminitis or breakdown of the support limb.

Microbial culture and sensitivity testing should be performed to confirm a diagnosis of osteomyelitis. Ultrasonography can be useful in aspirating fluid samples proximal to suspected bone lesions. A WBC count should be performed to differentiate between serous and purulent aspirates.[2] Culture may also be performed on surgically removed sequestra, necrotic tissue from the area, biopsy of affected bone, and infected metallic implants. Samples should be collected aseptically and inoculated directly into culture media to improve chances of obtaining bacterial growth.[2] Swabs taken from an open draining sinus tract may include nonpathogenic microorganisms and yield misleading results.[1] Arthrocentesis is indicated to measure WBC count, cytology, and total protein in cases of septic arthritis and osteomyelitis.[2] Both aerobic and anaerobic culture testing should be performed on samples when osteomyelitis is suspected. Blood culture may be useful in isolating the infectious organism in the neonate.



FIG. 38-27 Dorsoplantar **(A)** and lateromedial **(B)** radiographic projections of implant-associated osteomyelitis and nonunion of a comminuted fracture of the third metatarsus in a horse. The fourth most distal screw of the lateral plate is retracting. There is increased lucency surrounding the screws involving the medial plate, suggestive of implant loosening and instability secondary to implant failure associated with osteomyelitis.

Clinical Pathology A peripheral WBC count is generally considered unreliable in determining the presence of osteomyelitis. In the acute stage, increased fibrinogen and a degenerative left shift in the leukogram should raise the index of suspicion that bone or synovial infection may be present.[3] In chronic cases of osteomyelitis, a leukogram is often within normal range.

Arthrocentesis is the preferred diagnostic test for septic arthritis in both the adult and neonate. Synovial sepsis should be suspected if the nucleated cell count is greater than 10,000 cells/dL or if the polymorphonuclear cell count is over 90%.[3] Gram stain of synovial fluid immediately following arthrocentesis can be useful in narrowing selection of antimicrobial treatment before results of culture and sensitivity become available. Nuclear degeneration and bacteria are

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not always observed on cytologic analysis of acutely infected joints. The absence of these markers should not be delay treatment if suspicion of joint sepsis high.[3] The most commonly isolated gram-negative bacteria from foals include *E. coli, A. equuli,* and *Salmonella* spp. Gram-positive isolates include *Streptococcus* spp., *Staphylococcus* spp., and *R. equi*.[7] Neonates exhibiting signs of lameness should be monitored closely for synovial sepsis until the definitive cause of clinical signs can be determined (e.g., musculoskeletal injury). In the adult horse, members of the Enterobacteriaceae family, *Streptococcus* spp., and *S. aureus* are the most commonly isolated microorganisms in cases of osteomyelitis, septic arthritis, and tenosynovitis.[13] In a retrospective of 192 cases of postoperative infections involving orthopedic implants for repair of long-bone fractures or arthrodesis, the most common gram-negative and gram-positive bacteria cultured were *Enterobacter cloacae* and gram-positive coagulase-negative *Staphylococcus,* respectively.[14]

Pathophysiology Development of osteomyelitis is related to host microbial factors.[1] Injured bone forms a sequestrum if the periosteum is damaged, local blood supply is disrupted, or soft tissue covering is lost, leading to compromise of normal defense mechanisms. As the body attempts to contain the infection, inflammatory cells are released into the area and engulf bacteria. Proteolytic lysosomal enzymes are released as phagocytic cells are lysed, resulting in damage to local tissues and bone.[2,11] If the host is unable to eliminate the infection, a purulent exudate begins to accumulate. As the infection persists, bacteria colonize adjacent periosteal, cortical, and medullary regions of bone. Bacteria attach to the surface of dead bone or implants through adhesins and produce a polysaccharide extracellular matrix known as *biofilm*.[2,11] Within this biofilm, microcolonies develop, mature, and continue to produce matrix material.[11] Inflammatory molecules, phagocytic cells, and antimicrobials are unable to effectively penetrate the biofilm matrix, providing a protective environment through evasion of host immune responses and effects of antimicrobial therapy.[2,11] Granulation tissue forms over the devitalized tissue, and new bone is laid down, forming an involucrum as the body attempts to isolate the infection.[9] As exudate accumulates, it may eventually form a draining sinus tract through the cloaca out to the skin.

Hemotogenous osteomyelitis is most often localized to the metaphyseal region in young, developing animals. The nutrient artery ends in the metaphysis, capillaries close to the growth plates make loops to enter large venous sinusoids, and blood flow subsequently slows.[12] The slowing of blood flow in this area allows bacteria to accumulate, leave the vasculature, and initiate an inflammatory response.[12] It has also been shown in the developing embryo that osteogenic cells and vascular endothelium are a continuous network, suggesting that the relationship between bone and circulation is closer in the developing animal than in the adult.[3] The metaphyseal capillaries in this region lack phagocytic cells, allowing further growth of microorganisms.[12] The inability of young animals to mount an adequate immune response against bacteria is a key factor in the development of hematogenous osteomyelitis in areas of bone growth.

Tremendous forces are sustained during fractures of long bones in large animal species, often leading to soft tissue injuries that compromise vascular supply to the wound. Reduced perfusion to the area increases oxidative damage to healthy tissues, decreases delivery of immunogenic and proinflammatory cells during the acute stages of healing, and increases the probability of developing infection. In addition, certain locations (e.g., distal limb) have limited soft tissue covering, making closure over implants difficult. Inadequate soft tissue covering over implants can lead to cast sores and if left undetected may cause exposure of implants.

Treatment Early diagnosis and aggressive therapy are critical in preserving normal function to the limb in neonates affected by osteomyelitis.[5] Left untreated, irreversible damage to the growth plate or articular cartilage may cause lifelong debilitating lameness in the affected limb. Antimicrobial treatment during the acute stages may resolve bone infection, but medical treatment is often unsuccessful once osteomyelitis is established, and surgical intervention is required.[9] Treatment goals are to physically remove bacteria, inflammatory debris, and devitalized tissue. Long-term medical therapy is directed at controlling inflammation in the area and preventing recurrence.[2] Supportive therapy should be considered to improve the overall systemic health of the neonate, especially in cases of failure of passive transfer. Broad-spectrum IV antimicrobials should be considered until culture results are available.[5] β-Lactams and an aminoglycoside provide activity against gram-negative and gram-positive bacteria.[5] Metronidazole can be added when anaerobic infection is suspected.[5] In cases of septic arthritis without osseous involvement, joint lavage, arthroscopic débridement of synovial proliferation and concurrent articular damage, arthrotomy portals to facilitate drainage, intraarticular antimicrobial administration, and IV regional limb perfusions should be considered, along with systemic antimicrobial therapy targeted against the causative organism.[3] Radiographs may be helpful in determining whether osteitis or osteomyelitis are present. Débridement of the bone defect is indicated if infection has been seeded in bone. Use of antimicrobial impregnated beads can facilitate sustained delivery of high concentrations of antimicrobials to infected tissues.[3] IV antimicrobials should be selected based on culture and sensitivity results and be continued for 1 week following resolution of lameness in the neonate, followed by at least 2 weeks of oral antimicrobials.[3]

Medical management, including parenteral antimicrobials and topical wound dressings, may reduce drainage and contain infection to a single area, but is rarely successful as a single treatment of osseous sequestra.[9] A sequestrectomy with effective débridement can resolve infection rapidly and decrease the duration of antimicrobial therapy.[5] The goal of surgical treatment is to increase efficacy of antimicrobial treatment and host defenses by breaking down the biofilm matrix, removing necrotic debris with infected tissue, promoting vascularization of compromised tissues, and in most cases, establishing drainage. A tourniquet placed proximal to the affected site at the time of surgery decreases hemorrhage and facilitates visualization between healthy and devitalized tissue.[5] Infusion of the sinus tract with diluted methylene blue or use of a metallic probe may help identify areas of sequestered bone when location is difficult to determine.[5] Successful treatment depends on removing necrotic tissue lining the draining tract, opening the cloaca to access and remove the sequestered piece of bone, and aggressive débridement of all infected bone and exudate. Cancellous bone graft or antibiotic-impregnated beads can be used to fill in large defects following sequestrum removal. Autogenous bone grafts provide structural support by filling in gaps and providing a large volume of viable cells and increased osteogenic potential.[15]

Local delivery of high concentrations of antimicrobials has been described using various methods. Choice of antimicrobial delivery methods should be based on results of culture and sensitivity testing and the antimicrobials chosen. Continuous local infusion (e.g., indwelling pumps) may be the best method of delivering time-dependent drugs, and concentration-dependent antimicrobials (e.g., aminoglycosides) can be given intermittently in high doses via IV regional limb perfusions.[5] Wound location and duration of antimicrobial treatment should also be considered when choosing the best method of delivery.

Regional limb perfusion of antimicrobials is an effective way to deliver a high dose of antimicrobials to an isolated area. For regional limb perfusion to be effective it is critical to have adequate venous access, appropriate tourniquet application, and control of limb motion during the procedure. The tourniquet should be placed just proximal to the area of infection, where adequate venous access can be attained. A pneumatic tourniquet or a broad rubber tourniquet have been shown to be the most effective at achieving vascular occlusion and adequate delivery of antimicrobial concentrations distal to the tourniquet site.[17] An indwelling or 25- to 27-gauge butterfly catheter is used to establish venous access distal to the tourniquet. A 4.5-mm hole drilled into the medullary cavity can be used to deliver

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a regional limb perfusion when venous access cannot be attained. Dosage of antimicrobials varies between one third and a full systemic dose, depending on drug selection.[5] Careful attention should be paid to ensuring the regional limb perfusion dose combined with the systemic dose does not exceed nephrotoxic levels, especially in the neonate. It has been suggested that in horses the dosage of antimicrobials should be diluted to a total volume of 60 mL when the tourniquet is placed above the carpus or tarsus, and 30 mL if the tourniquet is placed at the level of the distal limb.[5] The injection should be given over 5 to 10 minutes, checking periodically for blood-tinged back pressure to make sure venous access is maintained throughout the injection. The tourniquet is removed after 25 to 30 minutes once the infusion is complete, and pressure is applied over the injection site to prevent hematoma formation. The animal should be properly restrained (and sedated if necessary) to prevent movement during the procedure.

Antibiotic-impregnated biomaterial allows for sustained continuous release of antimicrobials to the area of bone and soft tissue infection. Antibiotic-impregnated polymethyl-methacrolate (PMMA) beads provide sustained delivery of antimicrobials up to 80 days at 200 times the concentration obtainable in a systemic dose.[16] Traditionally, gentamicin-impregnated PMMA beads were used for their broad-spectrum bactericidal coverage and water- and heat-soluble characteristics. However, additional antimicrobial PMMA bead choices have since been determined to have suitable elution rates.[2] Selection of appropriate drugs and withdrawal times depend on the species treated. Antibiotic-impregnated PMMA beads are routinely used in orthopedic procedures when dealing with open fractures, plate luting, and placement around orthopedic implants at the time of closure. When managing septic synovial structures, there is concern that using rigid implants like PMMA beads may cause cartilage damage or mechanical lameness if the implant moves to the joint surface.[2] Collagen sponges and indwelling synovial catheters may be viable options for managing septic synovitis without causing inflammation or damage to articular cartilage. Antibiotic-impregnated plaster of Paris biodegrades faster and is often used in the neonate to deliver high concentrations of antimicrobials for a short period of time.[5]

In the presence of infection, fractures can only heal if adequate stability is maintained through internal fixation, although healing is often delayed. Débridement of infected bone and tissue, in addition to implant replacement, can be performed in an attempt to resolve infection.[5] Antibiotic-impregnated PMMA beads placed around sites of orthopedic infection, along with regional limb perfusion and establishing dependent drainage, may slow the rate of infection and allow additional time for fracture healing, increasing stability before removing implants.[5] If infection persists, implant removal maybe indicated in addition to alternative methods of fracture management (e.g., transfixation casting, external fixator).[5] In cases of open contaminated fractures, external fixation is often necessary to keep animals comfortable until infection is resolved and internal fixation can be performed. Maintaining use of the affected limb is important in preventing support limb breakdown and should be considered when making management decisions while treating orthopedic infections.

Prevention and Control Early recognition and aggressive medical therapy are critical in preventing acute hematogenous osteomyelitis in high-risk neonates. Hyperimmune plasma and prophylactic antibiotics are indicated when failure of passive transfer is suspected. In open wounds, débridement of necrotic and avascular tissue, eliminating gross contamination, controlling ongoing infection, and reestablishing vascular supply are the foundations of preventing osteomyelitis. Sharp dissection of devitalized tissues to reestablish viable soft tissue margins and copious lavage of the wound can help reduce the level of contamination in open wounds. If availability of soft tissues is inadequate for closure, a bandage should be used to cover exposed bone until granulation tissue fills in the area. Osteostixis or curettage of superficial cortical bone can be performed to access endosteal blood supply to reestablish vascular supply to exposed bone in an attempt to prevent sequestrum formation.[9]

Risk of developing postoperative infection following open reduction and internal fixation of fracture repair is relatively high compared to other orthopedic procedures, so strict adherence to aseptic technique should be followed to reduce the possibility of this complication. Extended-period postoperative antimicrobial use is often warranted after long-bone fracture repair because of the increased risk of postoperative infection due to prolonged surgery times, use of metallic implants, and injuries to soft tissue structures at the time of fracture occurence.[10] In addition, orthopedic patients are often placed in a rigid cast following internal fixation, which prevents daily monitoring of the affected limb for subtle changes suggestive of implant infection. Antimicrobials are generally administered until the first cast change (i.e., 2 weeks), and daily regional limb perfusions can be given when indicated.

Navicular Disease (Palmar Foot Pain)

Robin M. Dabareiner

Roughly a third of all forelimb lameness in horses originates from the caudal third of the foot and has generally been associated with pain arising from the navicular bone and its related structures, although other foot structures can also cause lameness. Any one or a combination of the following should be considered when evaluating horses that exhibit lameness localized to the posterior aspect of the foot:

1. Injury to the navicular bone itself
2. Desmitis of the navicular suspensory apparatus, which includes the sesamoid impar ligament (IL) distally and the collateral suspensory ligament (CSL) proximally
3. Inflammation of the synovial membrane of the navicular bursa; navicular bursitis or inflamed tissue (adhesions) between the navicular bursa and deep digital flexor (DDF) tendon
4. Desmitis of the DDF at (a) the insertion, (b) palmar to the navicular bone, or (c) proximal to the navicular bone
5. Laminar tearing in the heel region
6. Solar bruising in the heel region
7. Pain arising from some aspect of the palmar region of the distal phalanx
8. Pain arising from synovial structures located in the distal interphalangeal (DIP) joint
9. Structural damage to the hoof capsule in the heel region (e.g., underrun heels, collapsed foot)
10. Desmitis of the distal digital annular ligament

Diagnosis The diagnosis of heel pain is not difficult when a horse's lameness resolves with a palmar digital nerve block. However, determining which foot structure is the source of pain and establishing correct treatment can often be challenging. It seems the more we learn about diagnostic anesthesia, the more clouded the picture becomes. Horses with navicular or heel pain can be a diagnostic and therapeutic challenge to the owner, clinician, and farrier.

Diagnosis is based on historical data, clinical findings, and both routine and advanced imaging techniques to localize the structure causing pain within the hoof capsule. Our approach to horses with lameness originating from the heel region is to determine which structure in the foot is causing the pain and then develop a therapeutic plan. Severity and duration of the lameness, the horse's activity, potential owner compliance, and the farrier's experience should be considered. The horse's hoof wall quality, conformation, environment, and occupation will all affect therapy.

HISTORICAL DATA. Common complaints reported by owners of a horse exhibiting chronic foot pain include intermittent unilateral or bilateral forelimb lameness and increased severity of lameness for several days immediately after shoeing or at the end of the shoeing

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period (when the toes are long). Occasionally the horse may point the affected forelimb, stumbling with a short, choppy gait and increased lameness when ridden on hard ground.

Horses sustaining acute injuries to soft tissue structures in the caudal aspect of the foot (e.g., impar or CSL of navicular suspensory apparatus, distal DDFT), laminar tearing, or severe bruising of the heel region may have a history of becoming acutely lame during or immediately after a performance event. Historical data are often overlooked but may suggest which foot structure is damaged.

Clinical Findings and Diagnostic Evaluation

Signalment can be helpful in the diagnosis of chronic heel pain. Middle-aged Quarter Horses and Thoroughbred and warmblood horses in general are often affected by navicular disease. Arabians, draft horses, ponies, donkeys, and mules are rarely affected with palmar foot pain. A hereditary predisposition may be related to the development of navicular disease. Many Quarter Horses are heavily muscled and have relatively small hoof size. Poor hoof conformation plagues many Thoroughbred and warmblood horses. Since 1978, Dutch Warmblood stallions with grade 4 classification on navicular bone radiographs (0 = excellent, grade 4 = poor) have not been certified for breeding. The incidence of grade 3 or 4 navicular radiographs decreased from 11% in 1997 to 3% in 2002.[1] Although hindfeet can be affected with navicular disease, it is predominantly considered a forelimb problem.

Observation of limb conformation, as well as hoof size and shape and hoof-pair asymmetry, can aid in the diagnosis and treatment of palmar foot pain. A broken back hoof-pastern axis is frequently seen in horses with navicular or heel pain, but a small subset of horses with navicular pain will have a broken forward or normal hoof-pastern alignment. In one report of horses diagnosed with navicular disease, 72% had a broken back hoof-pastern axis and 8% a broken forward axis.[2] Horses having a long toe/low heel hoof conformation or underrun heels (defined as >5 degrees difference between heel and toe angle of foot) accounted for 77% of a group of horses with chronic heel pain.[2] Atrophy of the frog and contracted heels (defined as frog width < two-thirds its length) can be seen in horses with palmar foot pain and have been attributed to lack of weight bearing in the posterior portion of the foot, which reduces the dynamic movement of the frog.[2] Hoof-pair asymmetry in which one foot is smaller, narrower, and has a higher heel length is also common in horses with navicular area pain. The smaller and more upright foot is usually the lamest limb.

A thorough musculoskeletal examination should include palpation and comparison of the digital pulses in the feet and assessment of the hoof capsule for increased heat. Of 23 horses diagnosed with navicular area pain, 97% had an increased digital pulse in the most severely affected limb.[3] Hoof-tester evaluation can be beneficial in determining pain location. Pain involving the navicular area is identified by application of intermittent hoof-tester pressure over the middle third of the frog, which results in persistent nonfatigable reflex withdrawal of the hoof from the examiner. It is important to assess whether the withdrawal reflex is due to real pain and not a whimsical reaction by the horse. Both front feet should be tested and results from each foot compared. A positive hoof-tester response over the wall of the foot across the ends of the navicular bone may occur in horses with radiographic evidence of proliferative new bone on the abaxial margins of the navicular bone. Horses that have sustained an injury to the impar ligament or insertion of the DDFT seem particularly sore with hoof-tester pressure near the junction of the middle and anterior thirds of the frog. Horses with underrun or bruised heels or damaged laminae in the heel area will often have more pain over the affected heel. It is important, if possible, to differentiate peripheral from central hoof pain with a thorough hoof-tester examination. Many horses with heel pain will land toe first and may bruise the sole in the toe region, resulting in pain from hoof testers in this area. The hoof-tester exam is a useful diagnostic tool, but horses can have navicular area pain and not respond to hoof-tester pressure. This will occur more often during periods of dry weather, when the horse's feet are excessively hard, or in horses with thick soles and hard frogs.

LAMENESS EXAMINATION. Horses with bilateral forelimb involvement have a stiff, shuffling, short-strided gait that owners often perceive as shoulder lameness. The horse should be observed at a slow trot in a straight line and circled in both directions. A smooth, hard surface is optimal. Lameness will often be exacerbated when horses with heel pain are trotted on hard ground. The severity of lameness should be assessed before and immediately after application of hoof-tester pain. Horses with navicular area pain may have increased severity of lameness when trotted after the hoof-tester application in the central frog area. Several tests may exacerbate lameness in horses with navicular pain, such as allowing the horse to stand for 60 seconds on a small block of wood centered over the frog before trotting, or elevating the toe with a block of wood. A 30-second lower-limb fetlock flexion test may also exacerbate lameness in horses with navicular area pain.

DIAGNOSTIC ANESTHESIA. Perineural anesthesia of the palmar digital nerves (PDNs) with 1 to 2 mL of mepivacaine placed axial and distal to the proximal limits of the medial and lateral collateral ligaments will desensitize the palmar half of the foot, entire sole, and palmar aspect of the coffin joint. This block is performed just below the proximal limits of the collateral cartilages to avoid desensitizing the dorsal nerve branches. One study demonstrated that lameness secondary to solar pain created by a setscrew-induced pain model was eliminated 10 minutes after anesthesia using 2 mL mepivacaine over each PDN.[4] In the past, coffin joint (DIP) anesthesia was thought to be helpful in diagnosing navicular area pain, but investigators have recently demonstrated a lack of specificity with this block. DIP anesthesia has been shown to eliminate lameness associated with pain in the navicular bone itself, navicular suspensory apparatus, navicular bursa, and sole of the foot, because the sensory nerves to the navicular area are close to the DIP joint, and passive diffusion of the anesthetic occurs to the PDNs. Solar pain in the toe region was eliminated before solar pain in the heel region after DIP anesthesia, and a maximum 6 mL of anesthetic was recommended for analgesia of the DIP joint. This suggests that horses with heel bruises or laminar tearing in the heel region should not improve after DIP analgesia using low-volume anesthetic and evaluating the horse after 10 minutes.

The navicular bursa is a thin synovial structure located between the navicular bone and distal aspect of the DDFT. Analgesia of the navicular bursa may be more specific for navicular area pain. A positive response to navicular bursa analgesia probably reflects pathology in the navicular bursa, navicular bone, or supporting ligamentous structures. The normal navicular bursa has a 3-mL capacity, which may be reduced in horses with inflamed tissue or adhesions between the navicular bursa and DDFT. Synovial fluid is obtained infrequently when performing navicular bursa analgesia.

Horses that improve but do not have total resolution of the lameness until after a high palmar digital or abaxial nerve block may have pain associated with a desmitis of the DDFT within the hoof capsule or desmitis of the DIP joint collateral ligament. Horses with DDFT desmitis may also improve after DDFT digital tendon sheath analgesia.

RADIOGRAPHIC EXAMINATION. A minimum of three high-detail radiographic views should be used to evaluate the navicular bone; additional views are needed to evaluate the entire foot. Latero-medial (LM), 60-degree dorsoproximal-palmarodistal oblique with grid (D60Pr-PaDiO), and palmaroproximal-palmarodistal oblique (Pa45Pr-PaDiO) views of the navicular bone are obtained. Some clinicians also include two oblique views of the navicular bone. Abnormal radiographic changes include variation in size and shape of synovial foramina on the D60Pr-PaDiO projection; cystic changes within the navicular bone; enthesophyte formation at the attachment of the CSL ligament on the LM projection; flexor cortex erosions and

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loss of corticomedullary distinction, best viewed on the Pa45Pr-PaDiO projection; calcification of the flexor surface and distal DDFT; and osseous fragments associated with avulsion of the impar ligament. Previous studies have shown that abnormal synovial fossae correlate poorly with lameness, rarely progress over time, and are inconclusive for the diagnosis of navicular disease. Radiographic abnormalities more strongly associated with lameness are flexor cortex defects, medullary sclerosis, proximal border remodeling, and loss of medullary trabecular pattern.

Although radiographic evaluation is important in the diagnostic work-up of a horse showing palmar foot pain, it is not very sensitive in defining the actual pathologic condition of the navicular bone. Radiographs often underestimate the extent of pathology seen on necropsy in horses with navicular lesions.

NAVICULAR BURSOGRAPHY. Administration of a 3-mL mixture of 1:1 contrast media and anesthetic into the navicular bursa, followed by a Pa45Pr-PaDiO radiographic view, is used to evaluate pathologic changes on the flexor surface of the navicular bone and adhesions or scarring of the DDFT. The advantage of this technique is confirming pathologic changes on the flexor surface of the navicular bone, which may not be apparent on survey radiographs, and injection of the anesthetic into the navicular bursa. Navicular bursography identified pathology in the flexor region of the navicular bone 60% more often than plain radiographs.[5] The disadvantages are that some horses are not very tolerant of needle penetration of the DDFT and insertion into the navicular bursa, and the procedure carries risks like trauma to the navicular bone, sepsis, acute synovitis of the bursa, and possibly DDFT damage secondary to needle penetration.

NUCLEAR SCINTIGRAPHY. Nuclear scintigraphy offers higher sensitivity than radiography but equal specificity for the diagnosis of navicular disease. For detecting abnormal bone activity within the hoof, nuclear scintigraphy is a sensitive but rather nonspecific imaging method; it detects increased ^{99m}Tc uptake in areas of active osteoblastic activity. However, because of the proximity of anatomic structures in the caudal third of the foot, specific structural location of the source of pain in a horse with palmar foot pain is limited. The reliability of scintigraphy in diagnosis of foot pain has been criticized because of common false-positive and false-negative results. Lateral bone-phase images were found to be less sensitive than palmar images, and views taken 1 hour after radioisotope administration were as diagnostic as those taken 2 to 4 hours after administration.

ULTRASONOGRAPHY. Diagnostic ultrasonographic images can be obtained for some structures in the foot region. Ultrasonographs of the collateral ligaments of the DIP joint are obtained by positioning a 7.5- or 10-MHz transducer on the firm part of the dorsolateral and dorsomedial aspects of the coronary band. The normal DIP joint collateral ligament for a large horse is about 0.66 cm.[2] The distal aspect of the DDFT can be visualized from between the heel bulbs in the palmarodistal aspect of the pastern joint. The frog of the foot can also be used as a window to image the DDFT and impar ligament near the flexor surface of the navicular bone. Before imaging, the frog should be trimmed to pliable tissue and the foot soaked in a water bath overnight. Limitations of ultrasound are that the images are restricted to the axial midline, and off-incidence artifacts can confuse image interpretation. If the frog is excessively hard or has deep sulci, poor contact between the frog and transducer may prevent propagation of the ultrasound beam. Variation in cross-sectional area and width of the DDFT and impar ligament both within and between limbs of normal horses also may make image interpretation difficult.

COMPUTED TOMOGRAPHY. CT is the best modality for detecting and evaluating bone pathologies in the cortex or trabecula and can also provide an accurate three-dimensional assessment of soft tissue structures of the foot. Although less expensive than MRI, CT is less versatile. Special contrast studies are needed to evaluate articular cartilage with CT, but not with MRI. One advantage over MRI is that CT can be used to assess accurate needle or scalpel placement for specific treatment options. One disadvantage for CT in horses is the need for general anesthesia and special equipment designed to accommodate the horse.

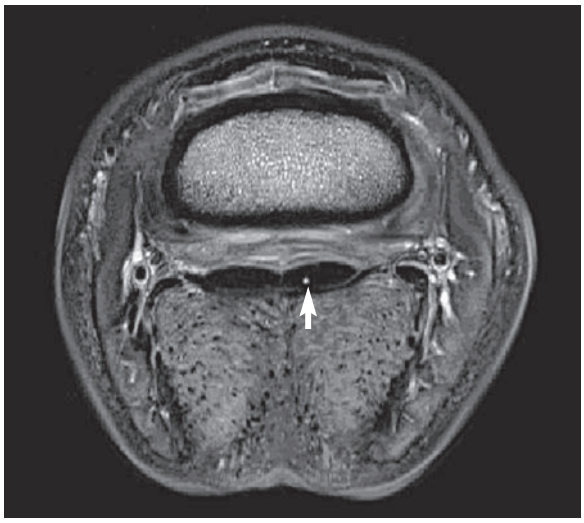


FIG. 38-28 Transverse magnetic resonance imaging section showing deep digital flexor tendon tear *(arrow). (Courtesy Dr. Chad Marsh.)*

MAGNETIC RESONANCE IMAGING. MRI offers a superior diagnostic tool to image soft tissue structures in the foot, and its use to evaluate equine lameness has provided valuable insight into the pathologic problems occurring in horses with palmar foot pain. MRI is particularly useful in the recognition of abnormally high signal (fluid) in structures such as the DDFT, IL, and collateral ligaments (Fig. 38-28). It can also detect navicular bone edema and articular cartilage damage in the navicular region. MRI can be performed under general anesthesia or in the standing horse, depending on the equipment available. In one study of 199 horses with lameness localized to the foot by clinical signs and perineural anesthesia, MRI was found to be superior to nuclear scintigraphy, ultrasound, or radiology in identifying the specific foot structure causing the pain. The most common injury was DDFT desmitis (59%), followed by desmitis of the DIP collateral ligament (31%); 17% of horses had injuries to multiple structures. Only 28% of horses with DDFT or collateral ligament injuries of the DIP joint returned to previous use.[6] A recent study evaluated 101 horses with clinical signs of navicular syndrome; the animals underwent MRI evaluation and had the navicular bursa (NB) medicated with 40 mg methylprednisolone and 10 mg hyaluronate at the time of the MRI.[7] Response to treatment was dependent on which specific structure(s) were damaged, supporting the value of MRI as a superior diagnostic tool in horses with foot pain.

NAVICULAR BURSOSCOPY. Endoscopic evaluation of the navicular bursa has recently been described in 92 horses.[8] This surgical procedure allows direct visualization of pathology within the navicular bursa and digital flexor tendon sheath. It is recommended for horses with lameness localized by regional anesthesia to the foot and absence of significant radiographic abnormalities.

Etiology

The exact etiology of navicular pain is unclear, but two theories exist. Initially, vascular occlusion of the navicular arteries was believed to result in ischemic necrosis of the navicular bone, but this theory lacks experimental support. The biomechanical theory suggests that the degenerative changes in the navicular bone result from abnormal forces exerted on the bone and its supporting ligaments. Compression of the navicular bone by the DDFT is an important aspect of this theory. Peak compressive forces of the DDFT

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on the navicular bone are about 0.77 times body weight during a slow trot and occur at approximately 70% of the stance-phase duration.[2] In addition, the navicular bone suspensory apparatus (IL and CSL) is under excessive tension and possibly compression when the horse has dorsopalmar hoof imbalance (broken back hoof-pastern axis or long toe/low heel hoof conformation). Faulty conformation and improper hoof balance resulting in abnormal biomechanical forces in the navicular area cause pathologic changes in the navicular bone that appear similar to those seen in clinical cases. Pain presumably results from interosseous pressure in the navicular bone or from strain of the supporting soft tissue structures. The biomechanical force applied to the navicular bone depends on hoof conformation and is negatively correlated ($P < 0.05$) to both the angle between the distal phalanx and the ground and the ratio between heel and toe length. Experimental studies seem to support the biomechanical theory.

Treatment

There are numerous treatment regimens for horses with palmar foot pain, and no one treatment can be recommended in all cases. Factors to consider in determining a treatment plan include prior treatment, duration of clinical signs, structure injured, severity of disease, use of horse, hoof conformation, and shoeing. Treatment options include variable periods of rest, therapeutic trimming and shoeing, antiinflammatory medications, intraarticular therapy, systemic osteoarthritis-modulating drugs, and surgery.

MEDICAL THERAPIES

Rest. Taking the horse out of work and confining it to a small area like a stall and small run allow it freedom of movement without opportunities to run and buck, which could exacerbate the lameness. Controlled exercise at a walk and trot for 15 minutes daily has been shown to increase blood flow to the feet by 15%. Although the duration of the rest period is variable, 3 to 6 weeks will allow soft tissue inflammation to subside and the horse to adjust to changes in trimming and shoeing. If the lameness has resolved after the rest period, a gradual increase in exercise is recommended before returning to normal use. An exception is the horse with an acute ligamentous injury to the navicular suspensory apparatus or distal DDFT injury. These injuries are usually severe and require 6 to 12 months of rest and confinement.

Although rest may be beneficial as part of the treatment regimen, the owner's situation may not allow for a rest period. Other treatments are then required to minimize the pain while allowing the horse to continue working, as often preferred by many professional horsemen.

Farriery. Therapeutic trimming and shoeing to reduce biomechanical forces on the navicular/heel area is the cornerstone of treatment for horses with palmar foot pain. Many horses respond to this without further need for medical or surgical therapy. Other horses improve after corrective shoeing but still require additional treatments. Horses with poor hoof conformation or inappropriate shoeing often respond best to corrective shoeing, whereas horses with good farrier management and good hoof conformation may show minimal or no improvement after therapeutic trimming and shoeing. The goals are to (1) restore hoof balance, (2) improve existing problems such as underrun heels, (3) reduce biomechanical forces on the navicular region, and (4) protect injured areas of the hoof. Although there is no standard shoeing technique for horses with heel/navicular pain, observing abnormalities in the hoof and lower-limb conformation and following basic principles can often accomplish these four goals. Proper trimming alone may restore correct hoof balance such that special shoes or pads are unnecessary; even with proper trimming, however, many horses still require special shoes or pads to achieve the desired hoof conformation. Many horses benefit greatly from therapeutic shoeing, but some have permanent structural problems that cannot be corrected. The veterinarian, farrier, and owner must work together and consider the horse's hoof shape and hoof wall quality, environment, conformation, use, and severity of disease.

Basic Principles for Proper Hoof Balance. The configuration of the hoof capsule reflects the stresses applied to the foot during the previous months. *Hoof balance* refers to both mediolateral and dorsopalmar balance. *Dorsopalmar balance* refers to proper hoof-pastern alignment. Ideally, when viewed from the side, a line drawn through the central aspect of the first phalanx should bisect the hoof capsule, and the toe angle and heel angle should be parallel to this line. A broken back hoof-pastern axis is common in horses with long toe/low heel conformation and results in increased stress on the phalangeal joint capsules, navicular suspensory apparatus, and distal DDFT and increases pressure between the navicular bone and DDFT.

Breakover (break-over point) of the foot is the terminal part of locomotion when the heel loses contact with the ground surface, followed by the toe. Tension of the DDFT over the navicular area and flexion of the coffin joint occur during breakover. A low hoof angle or long toe is associated with prolongation of breakover time. A high heel angle reduces breakover, causing a reduction of forces exerted on the caudal structures of the foot and limb (e.g., navicular suspensory apparatus, DDFT, suspensory ligament). Breakover should be made as easy as possible by decreasing toe length.

Corrective trimming is often more important but can be more difficult than corrective shoeing. The toe is shortened as much as possible, and the heels are trimmed back to the widest aspect of the frog. One of the most common problems we see in our practice is allowing the heels to grow forward, decreasing heel support and contributing to dorsopalmar hoof imbalance (Fig. 38-29). The heels lose mechanical strength and often collapse, and the bars of the hoof flatten out and lose support. Proper heel trimming back to the widest aspect of the frog increases the functional weight-bearing surface of the foot. The ground surface of the properly trimmed foot has a more



FIG. 38-29 Hoof with the heels allowed to run too far forward. The heels are located at the end of the pointer but should be back at the widest aspect of the frog.

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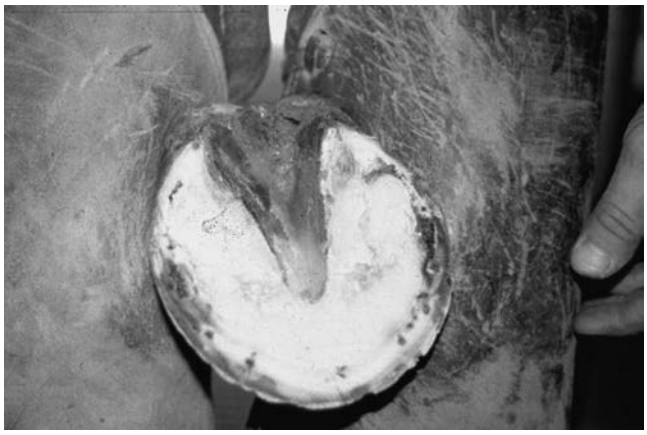


FIG. 38-30 Hoof from Fig. 38-29 after trimming the heels back to the widest aspect of the frog. Note the larger, rounder shape to the hoof and increased heel support.

rounded appearance (Fig. 38-30). Palmar hoof support is essential for horses with navicular/heel pain. Full-fitting shoes provide more support hoof by increasing the weight-bearing surface. Ideally, the shoe should fit about 1/16 inch wider than the hoof behind the last shoe nail to allow heel expansion. The nails should be placed in a line parallel to the ground approximately 1 inch (2.5 cm) proximal to the shoe, and no nails should be placed behind the widest aspect of the hoof.

Using a wedged shoe or pad to elevate the heels by 2 to 3 degrees after the foot is properly trimmed decreases tension in the DDFT, reducing pressure applied to the navicular region. The effect of raising the heels is helped by rolling or rockering the toe to quicken the breakover of the foot. The use of an egg-bar shoe is controversial. Although horses with long toe/low heel hoof conformation may gain caudal foot/heel support from the shoe, egg-bar shoes had no effect on reducing forces between the DDFT and navicular area.

When selecting a particular corrective shoe or shoe/pad combination, the horse's use is an important factor because the desired corrective shoe for the individual hoof conformation may not be suitable for the horse to perform its intended use. A compromise must be made between shoeing for the ideal and shoeing for athletic performance, taking into consideration such factors as weight of the shoe, traction, and interference of other limbs. Another important factor is hoof quality. The ideal shoe/pad selected for proper hoof balance may be impossible to apply if the hoof wall is thin or damaged. In these cases, a secondary shoeing regimen is selected that will accomplish similar results until hoof quality improves. Although no standard shoeing technique exists for horses with navicular pain, the following suggestions may be beneficial.

A *rim shoe* or *half-round shoe* has a rounded edge that will enhance breakover. The rim shoe has good traction and is useful in western performance horses (e.g., roping horses, barrel racers, cutting horses). The Natural Balance Shoe (Anvil Brand Shoe Co., Lexington, Ill.) has a rockered toe and, because of its design, artificially shortens the toe length and enhances breakover. It is made of aluminum or steel; owners of some western performance horses seem to prefer the steel shoe, which is thought to provide better traction than the aluminum shoe.

Acute ligamentous injuries involving the distal aspect of the DDFT or navicular suspensory apparatus require extended periods of rest. During the rest period, application of a 3- to 4-degree wedge pad to the shoeing regimen may decrease tension of these soft tissue structures. Controlled exercise is important in treating these injuries. Our group often begins with a 3- to 4-degree pad, depending on the horse's hoof conformation, and gradually decreases the quantity of heel elevation over time.

Different shoeing techniques will accomplish the same goals of easing breakover, supporting the heels, and protecting injured areas of the foot.

Nonsteroidal Antiinflammatory Drugs. Phenylbutazone is the most common NSAID used to treat navicular/heel pain. It reduces pain by inhibiting the enzyme cyclooxygenase and the subsequent cascade of prostaglandins. It also inhibits platelet aggregation, which may theoretically increase blood flow to the foot. Phenylbutazone can break the pain cycle and allow adjustment to new hoof angles and shoeing changes. The recommended dosage depends on individual horse needs and severity of disease. An initial dosage of 4.4 mg/kg once daily for 5 to 7 days seems appropriate to allow adjustment to shoeing changes. Many horses will require additional treatment during competition. Gastric and right dorsal colon ulceration has been associated with phenylbutazone administration in some horses.

Isoxsuprine Hydrochloride. This β-agonist, α-antagonist is a peripheral vasodilator working to increase blood flow to the foot. Its absorption after oral (PO) administration in the horse is erratic, and it usefulness is questioned. The recommended dose of isoxsuprine is 0.6 mg/kg PO twice daily for 3 weeks; if no response is seen, the dose is increased to 1.2 mg/kg PO twice daily for 3 weeks, then once daily for 3 weeks, then every other day for an additional 3 weeks. No adverse drug reactions have been reported. Isoxsuprine's efficacy appears to be horse-dependent.

Intraarticular Medications. Intraarticular medication of the DIP joint can be beneficial in horses with navicular area pain. Some horses fail to respond adequately to corrective shoeing, rest, and NSAID therapy, or the horse may have responded initially but no longer. If the lameness has been previously localized to the caudal aspect, intraarticular anesthesia of the DIP joint is performed at the recheck examination. If significant improvement is seen in the lameness, the client is offered intraarticular medication as a treatment option. Alternately, if the horse improves after PDN anesthesia in one limb and becomes lame in the opposite limb, anesthesia of the DIP joint is performed. If significant improvement is seen, medication of the DIP joint is offered as an initial treatment option. It is important to remember that DIP joint anesthesia is not specific for navicular area pain, as discussed earlier.

Selection of intraarticular medication varies with the clinician, severity of disease, and client. We usually inject 20 mg of sodium hyaluronate and 6 to 9 mg of triamcinolone (Vetalog), which often alleviates clinical signs of lameness for 6 to 12 weeks. In severe cases of navicular disease, 20 to 40 mg of methylprednisolone acetate (Depo-Medrol) in combination with the sodium hyaluronate may provide a slightly longer duration of effect. Hyaluronate is used for joint lubrication and to increase the hyaluronan content of synovial fluid. Corticosteroids interact with steroid-specific receptors in the cytoplasm of cells and inhibit inflammatory infiltration into the joint and neutrophil function by impairing lysosomal enzymatic release. Corticosteroids also inhibit phospholipase A_2, preventing both cyclooxygenase and lipoxygenase inflammatory pathways.

The two primary reasons not to use intraarticular corticosteroids in horses with joint disease are risk of sepsis and potential adverse effects on articular cartilage and subchondral bone. Using aseptic technique and combining intraarticular antimicrobials with the injection medication should decrease the risk of synovial infection. We prefer to use 50 to 100 mg of amikacin sulfate for joint injections. To minimize the negative effects of intraarticular corticosteroids, the lowest clinically effective dose is used. Minimal research has been performed in this area, so clinician experience and empirical information are often consulted. Both systemic and intraarticular corticosteroids have been associated with laminitis in horses. DIP joint medication is injected using a 20-gauge sterile needle placed approximately 1 cm dorsal to the hoof capsule on midline, penetrating the extensor tendon while entering the DIP joint. The angle of needle insertion is about 45 degrees from perpendicular to the ground surface. Synovial fluid is usually obtained.

About 30% of horses with pain localized to the navicular area either do not improve or may improve but remain lame after DIP joint anesthesia, which may be associated with different diffusion properties of the local anesthetic versus the intraarticular medication. Drug treatment of the navicular bursa may be beneficial in some

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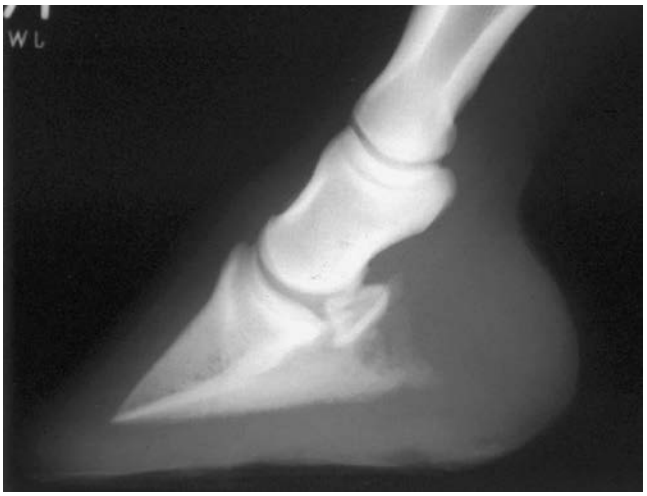


FIG. 38-31 Lateralomedial radiograph of foot, showing an enthesophyte at the proximal aspect of the navicular bone where the collateral suspensory ligament attaches. Horses with this type of radiographic abnormality usually respond better to navicular bursa medication than distal interphalangeal medication.

of these horses. We recently reported on 25 horses with pain localized to the navicular region that did not respond to corrective shoeing, phenylbutazone, or DIP joint medication.[3] These horses did improve after navicular bursa injection with 40 mg methylprednisolone and remained sound for a mean of 4 months. Most of the 25 horses had moderate to severe radiographic changes involving the navicular bone. About half had an enthesophyte located at the proximal aspect of navicular bone at the attachment of the CSL, possibly indicating chronic CSL desmitis (Fig. 38-31). The technique for navicular bursa injection has been previously described.[3]

A recent study evaluated 101 horses with clinical signs of navicular syndrome that underwent MRI evaluation and had the navicular bursa (NB) medicated with 40 mg methylprednisolone and 10 mg hyaluronate at the time of the MRI.[7] Seventy-six (75%) of 101 horses returned to their intended use for a mean of 9.6 months. Horses that had been lame less than 6 months before treatment had a significantly better chance of returning to intended use than horses that were lame more than 6 months before treatment. Horses with primary DDF tendinitis responded best to NB medication and 6 months rest. If the DDF tendinitis extended proximal to the navicular bursa in these horses, the digital flexor tendon sheath was also medicated with 100 mg methylprednisolone acetate and 20 mg hyaluronic acid. Horses with primary navicular bursitis returned to work within 2 days after NB medication. Horses with scar tissue and adhesions between the DDFT and CSL or horses with adhesions between the navicular bone and DDF tendon were treated with pressurization of the navicular bursa with 30 to 50 mg of hyaluronate to create high pressure within the bursa in an attempt to break down some of the adhesions.[7]

Navicular bursoscopy was performed in 92 horses with navicular area pain.[8] Injuries of the DDF tendon within the navicular bursa were evaluated and débrided. In addition, fibrillated fibrocartilage seen on the navicular bone was also débrided. Fifty-three of 92 (63%) horses returned to soundness.[8]

Systemic Joint-Modulating Drugs. Hyaluronan (HA) is a normal component of synovial fluid and functions as a joint lubricant. It also appears to have some antiinflammatory properties, but the exact mechanism is unknown. Exogenous HA inhibits chemotaxis and phagocytosis of granulocytes, reduces the stimulation of lymphocytes, and may decrease prostaglandin synthesis. The antiinflammatory properties of HA appear to be dose dependent, and HA with a molecular weight greater than 500,000 daltons may be more effective. Systemic HA may be more effective in horses with mild synovitis/capsulitis and less effective in horses with chronic osteoarthritis. The recommended dose is 40 mg HA IV once weekly for 3 weeks, then once monthly for maintenance. Some horses with mild navicular pain improve after systemic HA administration, but its use is usually combined with other treatments.

Polysulfated GAGs like Adequan are referred to as *chondroprotective agents* and are used to prevent, attenuate, or reverse morphologic cartilaginous lesions associated with osteoarthritis. Adequan is made from bovine lung and trachea extracts containing mainly chondroitin sulfate. Previous studies have shown that the antiinflammatory effect of GAGs involves inhibition of enzymes and cytokines associated with osteoarthritis, such as interleukin (IL)-1, a potent chemotactant agent, metalloproteinases (MMs), and prostaglandin E_2 (PGE_2). Both in vivo and in vitro equine studies have been performed, with conflicting results. More recently, a survey of 1522 equine veterinarians assessing the efficacy of systemic polysulfated GAGs resulted in the subjective conclusion that their use was more effective than HA for treatment of subacute DJD and less effective for acute synovitis. IM GAG administration was shown to improve lameness in horses diagnosed with navicular syndrome in one double-blind study.[9] The dose was 500 mg IM every 4 days for eight treatments. In our hospital we see many middle-aged western performance horses with chronic navicular problems. IM Adequan (500 mg) every 1 to 2 weeks subjectively seems to benefit these cases, although no scientific studies support the change in frequency of its use.

The oral chrondromodulatory nutraceutical Cosequin has been evaluated in the treatment of 10 horses with navicular syndrome.[10] The nutraceutical consisted of 9 g glucosamine, 3 g chondroitin sulfate, and 600 mg manganese ascorbate and was given PO twice daily for 60 days. The clinical impression from the owners was that the horses' lameness showed improvement. Glucosamine has been shown to reduce expression of MMPs and increase expression of natural inhibitors of MMPs in the joint when studied in vitro. The ability of the horse to absorb these oral nutraceuticals has been questioned, however, and recent work suggests that doubling the dose currently recommended by the manufacturer improves product efficacy, although 4 to 6 weeks of treatment is often needed before a response is seen. We have found that nutraceutical use is variable in horses with navicular area pain, with some showing improvement with daily administration and some showing no effect. Empirically, the benefit of oral nutraceuticals seems inferior to systemic administration of IV hyaluronan or IM Adequan.

Other Medical Treatments. Tiludronate, a biphosphonate, is used in human medicine to reduce bone resorption. It has been used to treat navicular area pain in horses with promising results.[11]

Investigated as a treatment for navicular disease in horses, extracorporeal shock wave therapy (ESWT) directs a pressure wave to a specific area of the body to increase osteogenic activity in bones and induce neovascularization at the tendon-bone junction. Human patients have variable duration of analgesic effect after treatment with ESWT. The equine study reported that a single ESWT treatment had no effect on horses with navicular disease.[12]

SURGICAL OPTIONS

Palmar Digital Neurectomy. Neurectomy of the palmar digital nerves is occasionally required to allow horses with chronic heel or navicular pain to remain athletically sound. Despite aggressive medical treatment with corrective shoeing, NSAIDs, and intraarticular/intrabursal injections, many horses fail to respond or only improve temporarily, which leaves palmar digital neurectomy as a final treatment option. Before surgery the horse should improve greater than 90% after palmar digital nerve perineural anesthesia. Palmar digital neurectomy resulted in improvement in lameness for a mean of 2 years in one study evaluating 59 horses with navicular disease. Diligent postoperative care is critical to achieve prolonged soundness. After surgery, a padded pressure bandage is applied to the limb and changed every 4 to 5 days for 2 weeks. The horse remains in a stall for 30 days, followed by 30 days of light riding and resumption of normal activity 60 days after surgery. The limited activity and diligent bandaging after surgery may reduce the inflammatory response and reduce scar tissue formation around the nerve stumps.

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Navicular Suspensory Desmotomy. This procedure has been recommended for horses with navicular syndrome in the past and applied to a number of cases, without favorable long-term results. Therefore, we are not currently using this procedure and believe it has fallen out of favor as a treatment for horses with navicular pain.

PROGNOSIS. Prognosis depends on which structure(s) are affected and severity of the damage. After NB medication, horses with primary DDF tendinitis and navicular bursitis had a good outcome, especially if lameness was present less than 6 months before treatment. Horses with adhesion of the DDF tendon to the CSL and horses with adhesions from the DDF tendon to the navicular bone had a better (60%) chance of returning to previous use. Horses with significant scar tissue in the proximal aspect of the navicular bursa or those with multiple lesions were less likely to return to intended use (25% to 50%).[7]

SUMMARY. No single treatment option is suitable for all horses with heel or navicular area pain. Each horse must be evaluated individually to determine which structure in the palmar aspect of the foot is injured, severity of disease, horse and hoof conformation, and horse use and level of performance expectation before a treatment plan can be developed. Many treatment options are available to help these horses to perform. Horses having the best outcomes are those that have an accurate diagnosis of which structure(s) are affected within the navicular region of the foot so that proper treatment can be recommended. MRI appears to be the best diagnostic tool in identifying specific structural damage, thus dictating treatment.

Spondylitis/Diskospondylitis

Sarah M. Reuss

Definition

Spondylitis is inflammation of the vertebral body, whereas diskospondylitis is an inflammatory lesion that includes the intervertebral disk and its adjacent vertebrae. The etiologic agent may be difficult to isolate, but infection is the most likely cause. Thus, *vertebral osteomyelitis* and *spondylitis* are often interchangeable terms, and if the disk is involved, *diskospondylitis* is the most appropriate term. Both spondylitis and diskospondylitis are rare in large animals but are potentially career and life threatening when they occur. Diskospondylitis is described in swine,[1] horses, cattle,[2] goats,[3] and sheep. Neonates of all species are especially at risk for spondylitis. Diskospondylitis in large animals is most commonly reported in adult horses and cows in the cervical vertebrae.[4-6] Lesions have been less commonly identified in the thoracic,[7,8] lumbar,[9] and sacral[10] regions.

Clinical Signs and Differential Diagnoses

The earliest signs of spondylitis may include fever, lethargy, stiffness, and localized spinal pain. Soft tissue swelling may be evident with paravertebral abscessation.[11] Muscle atrophy has also been reported.[8] Diskospondylitis most commonly affects the cervical and thoracic vertebrae, so neck pain and reluctance to lower the head to graze are common signs. Animals may develop an abnormal stance with one forelimb forward and the other back to graze.[7] Vertebral osteomyelitis may progress to spinal cord compression with variable degrees of ataxia, paresis, sensory and proprioceptive deficits, and recumbency. Neurologic signs are dependent on the vertebral section affected and the amount of spinal cord compression. Once present, clinical signs are usually progressive.

Clinical signs in ruminants are similar. Early signs include abnormal behavior, decreased appetite, and weight loss. Difficulty in extending the head and neck ventrally is often the reason for presentation to a veterinarian.[2] Varying degrees of neurologic deficits are reported, from occasional stumbling[2] to tetraparesis[12] and paraplegia.[3]

Differential diagnoses for spinal pain include spondylosis, vertebral fracture, muscle strain, dorsal spinous process impingement, vertebral subluxation, vertebral infarcts, and aberrant parasite migration.[13] Additional differentials for spinal cord ataxia in horses include cervical vertebral stenotic myelopathy, equine protozoal myeloencephalopathy, herpes myeloencephalopathy, and neoplasia.

Etiology/Pathogenesis

Both spondylitis and diskospondylitis are thought to be septic conditions, although etiologic isolation is not often successful. Even in cases where bacteria are not isolated, response to antimicrobials may indicate a bacterial pathogenesis.[7] Bacterial infection is more common than fungal infection, and the hematogenous route of infection is the most common. Spondylitis occurs most frequently in neonates, which may be due in part to failure of passive transfer leading to sepsis.[1] In general, spondylitis is often secondary to a preexisting focus of infection elsewhere in the body.[1] Tail docking wounds,[14] umbilical infections,[1,12] pneumonia,[10] and lung abscesses[1] are possible sources of infection. Septic thrombi embolize into the metaphyseal arteries of the vertebrae, where flow is sluggish and bacteria can colonize.[14] In adults, direct injury to the intervertebral disk and/or the vertebral endplate may contribute to the formation of diskospondylitis. The injury disrupts the vasculature, increasing susceptibility to infection. Diskospondylitis is also reported to occur secondary to spread of local infection[5] and traumatic injury.[4] Infection results in destruction and remodeling of affected bone. Inflammation of the disk and vertebrae leads to spinal cord compression and the associated neurologic dysfunction. The intervertebral disk may actually prolapse into the spinal canal.[5] Lesions are usually confined to one intervertebral space. The neurologic signs may also be secondary to the infection eroding into the meninges and causing a suppurative meningitis.

Pathogens that have been cultured from adult horses with vertebral osteomyelitis include *Brucella abortus,*[15] *Aspergillus* spp., *Streptococcus zooepidemicus,*[1] *Staphylococcus* spp.,[6,9] and *Mycobacterium bovis.*[16] Vertebral osteomyelitis isolates in foals include *R. equi,*[10,11,17] *Streptococcus* spp., *Actinobacillus* spp., *Eikenella corrodens,*[18] *E. coli, Salmonella typhimurium, Staphylococcus* spp., and *Corynebacterium pseudotuberculosis.*[13] Isolates from cattle with vertebral osteomyelitis include *Aspergillus fumigatus, Bacteroides nodosus, Clostridium perfringens, Streptococcus* spp., *Staphylococcus* spp.,[2] *E. coli,*[14] *Actinomyces pyogenes, Fusobacterium necrophorus,* and *Pseudomonas* spp.[19] *Staphylococcus* spp. and *T. pyogenes* (formerly *A. pyogenes*) were cultured from the intervertebral disk of a goat.[3]

Diagnosis

Diagnosis is based on clinical signs and imaging modalities. Clinicopathologic findings may include anemia, leukocytosis, neutrophilia, and hyperfibrinogenemia.[1] One retrospective study, however, found that 80% of affected horses had a normal WBC count.[20] Hyperproteinemia due to hyperglobulinemia may also be seen.[7] CSF is usually normal unless the osteomyelitis has progressed to meningitis. Blood and urine cultures should be obtained but are often not diagnostic.

Radiography is often the basis of diagnosis. Radiographic signs of spondylitis include bony proliferation, lysis, sclerosis, and localized soft tissue swelling.[1] Radiographic abnormalities in diskospondylitis include osteolysis of adjacent endplates, with surrounding sclerosis and collapsed intervertebral disk space[9] (Fig. 38-32). Contrast radiography may be used to delineate spinal cord compression.[9] Radiographic changes may lag at least 2 to 8 weeks behind clinical signs, hampering the ability to make an early diagnosis.[1] With vague clinical signs, the neuroanatomic location within the vertebral column may be difficult to identify, making targeted radiographs impossible. Nuclear scintigraphy may help localize the lesion to a specific vertebral section that can then be radiographed.[1] Scintigraphy may also allow earlier detection, owing to the lag time in radiographic changes. Ciprofloxacin and white cell–labeled scintigraphy may also prove useful in the diagnosis of vertebral osteomyelitis. Ultrasonography is becoming increasingly used as a diagnostic imaging modality. Abnormalities include irregular endplates or bone surfaces, wide or narrow disk spaces, vertebral step formation, and associated abscessation or muscle involvement.[9] Transrectal ultrasonography of the

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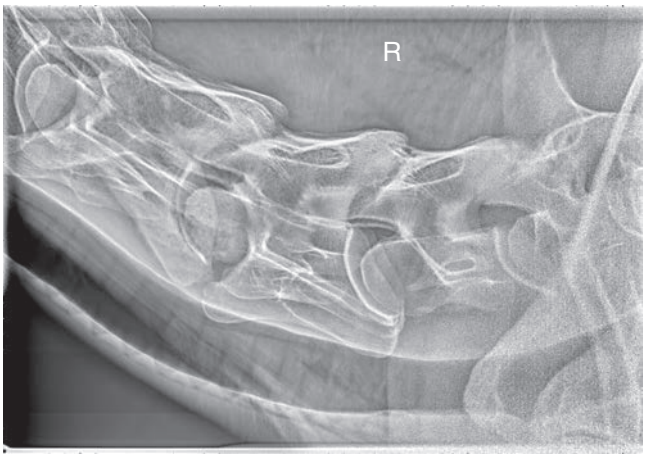


FIG. 38-32 Eleven-year-old Arabian cross gelding with fever and neck pain. The cortical margins of the caudal endplate of C5 and the cranial vertebral body of C6 are markedly thin and ill defined. Additionally, there is osteolysis and sclerosis associated with the cranial vertebral body of C5. The C5-C6 intervertebral disk space is narrow.

lumbar vertebrae may be performed, and transcutaneous studies can image the rest of the vertebral column. Advantages to ultrasound are that it can be done in the field, it can be used for needle-guided aspirates of potentially infectious lesions, and it can be used as a screening tool to localize lesions.[9] Depending on the size of the animal and availability of equipment, MRI and CT may also be considered because these modalities can be used to assess the vertebral endplates, disk, and spinal cord.[3] CT has been used in a goat to diagnosis diskospondylitis. Bone lysis, bone proliferation, mineral opacity within the intervertebral disk, and spinal cord displacement were seen.[3]

Treatment Long-term antimicrobial therapy is indicated for cases of vertebral osteomyelitis. Blood, urine, or tissue cultures and sensitivities may be used to guide antimicrobial choices. When that is not possible, broad-spectrum bactericidal antimicrobials should be used. Long-term treatment is necessary and may extend to 3 to 6 months.[10] NSAIDs can be used for pain control. In unresponsive cases, curettage of infected bone may be necessary.[6,10] This also provides an opportunity to collect material for bacterial culture.[10] In horses with instability and spinal cord compression, surgical decompression and stabilization may be indicated.

Prognosis The prognosis for horses with diskospondylitis is guarded. If there are no neurologic deficits, and thus presumably no spinal cord compression, the prognosis is more favorable. Early diagnosis and long-term treatment is essential. In one retrospective study, 13 of 19 adult horses survived to discharge, with 7 returning to their previous level of performance.[20] Foals may have a worse prognosis, with only 7 of 15 surviving to discharge.[21]

Spondylosis

Sarah M. Reuss

Definition Spondylosis is a degenerative condition of the intervertebral joints. In middle-aged and older horses and cattle, the thoracic and lumbar vertebrae are susceptible to chronic progressive development of enthesophytes within the ventral longitudinal ligament or the ventral margins of the anulus fibrosis. Osteophytes extend across the intervertebral space toward osteophytes on the adjacent vertebrae, resulting in partial bridging, where a lucent line persists between the two. Complete bridging, or *ankylosis,* can occur without significant loss of intervertebral disk width. A variety of terms are used in veterinary medicine to describe vertebral enthesophyte formation: *spondylosis deformans, vertebral osteophytosis,* and *ankylosing spondylosis.*[1]

Spondylosis in horses is most common in mature animals and reportedly in a higher proportion of mares.[2] The most common location in horses is from the tenth to fourteenth thoracic vertebrae, and most horses with spondylosis have lesions at more than one intervertebral space. In the thoracic region, the osteophytes are usually ventrolateral; osteophytes are more lateral when found in the lumbar region.[3]

Middle-aged and older bulls have a higher prevalence of vertebral enthesophytes than other cattle. Bulls used for artificial insemination are especially at risk, with over 49% of those 8 years and older having spondylosis.[4] Middle-aged bulls also have significant pathology, with 21 of 21 dairy bulls aged 65 to 90 months in one study having some degree of lumbar vertebral osteophytes; 13 had complete ankylosis of at least one intervertebral space.[5]

Etiology/Pathogenesis The exact cause of spondylosis is unknown but is apparently related to altered biomechanics and inflammatory mediators. One hypothesis is that spondylosis is a result of excessive dorsiflexion when the back muscles fatigue. There is then mechanical stress and tearing of the ventrolateral anulus fibrosus.[6] Chemical mediators act on the periarticular ligaments and joint capsules, leading to metaplastic change. Ossification occurs within the anulus fibrosis and ventral longitudinal ligament, leading to partial bridging. The cycle may continue until complete ankylosis and a continuous medullary cavity exists.[1] Partial or complete ankylosis at one site puts more stress on adjacent segments, so there is more active bone remodeling elsewhere in the vertebral column.[3] One study found that 60% (14/23) of horses with radiographic evidence of spondylosis had involvement of more than one site.[7] Secondary DJD of the dorsal articular facets may also develop as a result of the altered biomechanics.

The enthesophytes and then the ankylosed vertebral bodies are both at higher risk for fracture because of their inability to absorb normal forces; 3% of bulls at artificial insemination centers have vertebral fractures.[8]

Spondylosis in bulls is not related to force of ejaculatory thrust at service, frequency of semen collection,[9] or high-calcium diets. Despite previous thought, limited dietary calcium does not reduce the prevalence of spondylosis in bulls.[8]

Nerve roots may be compressed as they exit the intervertebral foramen, and spinal cord compression may occur if the bony proliferation extends dorsally into the vertebral canal. This results in neurologic deficits including progressive ataxia and paralysis.

Clinical Signs and Differential Diagnoses Spondylosis can be an incidental finding in animals with no history or clinical signs of back pain. Spondylosis can, however, account for acute, recurrent, and chronic back pain in some animals. Pain is due to inflammation, impingement, and fracture. Palpation of the spine may be resented. Horses may "guard" their vertebral column by using muscle contraction to not allow ventroflexion. Resentment of girthing and mounting may be noticed. Riders may report poor performance, vague lameness, or altered gait.[6] Spondylosis is rarely the cause of back pain, however; only 3.4% (23/670)[7] and 2.7% (8/443)[2] of horses presenting for back pain were found to have spondylosis in two separate studies.

Bulls with spondylosis will have a good appetite and be afebrile, but they may have difficulty rising, be reluctant to move, and have difficulty mounting.[1] Once clinical signs are present, they are slowly progressive. Lameness becomes more severe, and neurologic deficits may develop with nerve root impingement or spinal cord compression. Abnormalities include bilateral proprioceptive deficits of the hindlimbs with hoof dragging, excessive hindlimb flexion, and incoordination. Hindlimb ataxia can progress to paralysis in some animals, especially older dairy bulls.[5]

Differential diagnoses for spinal pain include muscle strain, vertebral fracture, diskospondylitis, dorsal spinous process

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impingement, vertebral infarct, and aberrant parasite migration. Additional differentials for cattle with hindlimb neurologic deficits include lymphosarcoma, encephalopathy, progressive degenerative myeloencephalopathy, and "downer cow" syndrome.[1]

Diagnosis Diagnosis is suggested by clinical signs. Palpation of the dorsum may elicit signs of pain. Rectal palpation may reveal ventral osteophytes if they are located on the caudal lumbar vertebrae. A thorough neurologic examination is indicated if there are hindlimb deficits. CSF is usually normal.

Standing lateral radiographs are the mainstay of diagnosis, but diagnostic radiographs can be difficult to obtain, given the depth of the vertebrae in the thoracolumbar region. If one suspects spondylosis, targeting radiographs to areas of predilection is helpful. Spondylosis in horses is typically in the midcaudal thoracic vertebrae, commonly T10-T14, but may also affect the lumbar vertebrae.[2] In bulls, the most common locations are C3-C5, T2-T6, and T11-L5. The largest osteophytes occur in older bulls at the thoracolumbar junction.[4,9] Radiographic changes include smooth bone that blends with the vertebral body and bridges apparently normal intervertebral disks. A grading system has been developed, with grade 0 being normal, grade 1 having an osteophyte from one vertebral body, and up to grade 5 having complete bridging of the intervertebral space.[7] The clinical significance of radiographic change must also be determined based on history and clinical signs, as spondylosis can be an incidental finding. Nuclear scintigraphy can be useful for determining the activity and potential clinical significance of a lesion based on the radiopharmaceutical uptake. Scintigraphy may also helpful in localizing the lesion for targeted radiography and is an option if diagnostic radiographs cannot be obtained owing to size constraints. Subjective assessment of scintigraphic images had 21.7% sensitivity but 95% specificity in a recent study using radiographic change as the standard.[7]

Treatment and Prognosis Treatment for clinical spondylosis consists of palliative care. Systemic antiinflammatories, cryotherapy (ice packs, cold hosing), and stall rest are recommended during the acute phase. Some horses may respond to intervertebral injection of corticosteroids and/or systemic chondroprotectants such as IM Adequan. Once complete fusion occurs, clinical signs should improve. However, if vertebral fractures or neurologic deficits are present, the prognosis is poor.

Laminitis

Michelle C. Coleman

Definition *Laminitis,* defined as inflammation of the laminae of the hoof wall, results in degeneration, necrosis, and inflammation of the dermal and epidermal laminae in the hoof wall of equids and ruminants.

Etiology and Pathogenesis Laminitis has a complex and multifactorial etiology ultimately resulting in lamellar degradation of the suspensory apparatus of the distal phalanx. Disease states thought to be associated with laminitis include sepsis and systemic inflammation, equine metabolic syndrome, pituitary pars intermedia dysfunction, and mechanical or traumatic overload. Septic processes including endotoxemia, gastrointestinal disease, pneumonia, and septic metritis are frequently associated with the development of laminitis. Laminitis has also been noted secondary to systemic inflammation resulting from an overload of carbohydrates, such as from overgrazing lush pastures or unrestricted access to concentrates. Excess weight bearing as a result of a contralateral limb lameness and trauma to the distal phalanx following exercise on hard ground can result in laminitis. Exposure to a water-soluble toxin in black walnut shavings[1] and administration of corticosteroids have also been associated with the development of laminitis.[2]

In cattle, overweight heifers fed excess concentrates and housed on concrete surfaces appear to be at higher risk.

Pathophysiology The pathophysiology of laminitis has not been fully elucidated, but it appears to involve a combination of events that lead to lamellar degeneration, impaired biomechanical function, and debilitating pain. There are several experimental models for induction of laminitis, including carbohydrate overload, fructan overload, black walnut extract administration, and hyperinsulinemia. These models support several similar and possibly interconnected theories on the pathophysiology of laminitis: digital hemodynamic events, enzymatic events, inflammatory events, endocrinopathic events, and mechanical/traumatic events.

Clinical signs of acute laminitis include bounding digital pulses and elevated temperature, supporting a vascular component of the disease. It is thought that increased capillary pressures secondary to venoconstriction of the digital microvasculature result in laminar edema, increased arteriovenous shunting, and capillary collapse.[3] Thrombi have been identified in laminar microcirculation of laminitic horses, with unknown effect on laminar ischemia. Through release of vasoactive and inflammatory mediators, leukocyte activation, and platelet-neutrophil activation in the lamella, platelets are likely involved in vascular disturbance and inflammation in the acute stages of laminitis.

The enzymatic theory postulates that increased digital blood flow results in delivery of cytokines to the digit, which induce production and activation of matrix metalloproteinase (MMP) enzymes. Active lamellar MMPs are important in the separation of lamellar cells from their basement membranes, resulting in separation of epidermal and dermal laminae. MMP-2 and MMP-9 have been isolated in increased quantities from lamellar tissue affected by laminitis,[4] and affected lamellar tissue has been shown to increase transcription of MMP.[5] MMP-9 has also been associated with neutrophil migration into the lamellae.[6]

Experimental models of equine laminitis have displayed a number of inflammatory events. In the early stages of laminitis, endothelial activation, leukocyte extravasation, inflammatory signaling, and activation of degradative enzymes like MMP occur.[7] These inflammatory events in the laminae of laminitic horses closely resemble inflammatory events that occur in human sepsis. Proinflammatory cytokines IL-1β and IL-6 have increased laminar expression in laminitis. There is also increased expression of IL-8, GRO-α, and MCP-1, which play a role in leukocyte activation and chemotaxis. Increased expression of inducible cyclooxygenase, COX-2, suggests that prostaglandins may play a role in laminar dysfunction.

The role of endotoxemia in the development of laminitis remains unclear. Although systemic inflammation is a risk factor for development of laminitis, experimental endotoxin administration fails to induce the disease. This could be explained by the fact that endotoxin does not act alone but in combination with several factors including bacterial toxins, necrotic cell products, and proinflammatory cytokines. Endotoxin has been detected in the blood of horses following experimental carbohydrate overload[8] and is known to affect digital vascular function and platelet activation. Recent studies have hypothesized that the proinflammatory state of carbohydrate overload models is driven by an immune response to the rapid overgrowth of gram-positive and gram-negative cecal bacteria.[9]

Several conditions in the horse that have been associated with insulin resistance are pituitary pars intermedia dysfunction (PPID), equine metabolic syndrome (EMS), and iatrogenic corticosteroid administration. To help better understand the underlying relationship between insulin resistance and laminitis, the metabolic profiles of laminitic ponies and a cohort of non-laminitic ponies were compared in one study.[10] Body condition score, measures of insulin resistance, and serum insulin concentration were predictors of development of laminitis in 11 of 13 ponies in that study. Laminitis can be induced in healthy horses by maintaining a high plasma insulin concentration with normal glucose,[11] but insulin at lower

concentrations has resulted in changes within the laminae that were suggestive of laminitis.[12]

Laminitis has long been associated with mechanical overload on the distal phalanx, such as excessive concussion (road founder) and supporting-limb laminitis. The mechanism of insult to the laminae is thought to be direct damage to the lamellae and/or altered blood supply.

These theories of the pathogenesis of laminitis are extremely complex and likely interconnected. Much research has been performed on experimental models, but the relationship of these models to the naturally occurring condition is unknown.

Clinical Signs Laminitis can affect all four feet but is most commonly noted in the front feet of horses (likely due to an increased load on the forelimbs) and the hind feet of ruminants. Supporting-limb laminitis occurs on the supporting forelimb or hindlimb opposite the non–weight-bearing limb. Clinical signs of acute laminitis include lameness, depression, and anorexia. The lameness may vary in severity from subtle to prolonged recumbency due to digital pain. Because of the variability in lameness, the Obel grading system was developed.[13] Grade 1, the least severe classification, is characterized by shifting weight with no apparent lameness at the walk but a short-stilted trot. Horses with grade 2 lameness are willing to walk but have a stilted gait and are willing to lift a foot off the ground. Grade 3 is characterized by reluctance to ambulate and resistance to having a foot lifted off the ground. The most severe classification is grade 4, in which the horse refuses to move.[13] Other clinical signs consistent with laminitis include bounding digital pulses, sensitivity to hoof testers over the sole at the toe, sensitivity to tapping of the hoof wall at the toe, heat over the dorsal surface of the hoof wall, swelling of the coronary band, and shifting of weight, often to the hindlimbs if laminitis affects the forelimbs. More severe clinical signs consistent with rotation or distal displacement of the distal phalanx within the hoof wall include palpation of a depression over the coronary band and a dropped sole.

Chronic laminitis results in lameness and deformation of the hoof capsule that vary with duration of disease and type of displacement. In these cases, the sole is flat or dropped, the white line is widened, and the hoof wall shows signs of uneven growth. Irregular rings of growth may be noted around the hoof wall, more widely spaced at the heels. The abaxial white line develops apparent hemorrhages, and fissures of the hoof wall may be noted parallel to the coronary band. In ruminants the sole softens and assumes a light yellow discoloration.[14]

Clinical Pathology and Radiology There are no clinical pathologic findings specific to acute or chronic laminitis. If clinical pathologic findings are present they may reflect an underlying disease process such as endotoxemia, enteritis, colitis, pleuropneumonia, or metritis. Changes may also be seen as a result of glucocorticoid and catecholamine release in response to pain and stress. One study showed that horses euthanized for chronic laminitis had higher WBC counts when compared to control horses and horses with less severe disease.[15] Baseline values for creatinine and total protein should be obtained because they are important parameters to monitor for NSAID toxicity.

Radiographic examination is critical for diagnosis of suspected cases, monitoring progress, and guiding appropriate therapy. Radiographs, including lateromedial and 65-degree dorsoproximal-palmarodistal views, should be taken of all suspected digits in acute disease to serve as a baseline for subsequent radiographic studies and to determine whether prior radiographic changes are present. Using a consistent technique is important to achieve a true lateral image and allow accurate evaluation of radiographic parameters for comparison of serial studies. For both views, the foot should be thoroughly cleaned and placed on a wooden block such that the x-ray beam can be centered on the solar margin of the distal phalanx. A radiopaque marker placed on the mid-dorsal hoof wall starting at the coronary band and extending distally can be useful in determining the position of the distal phalanx in relation to the surface marker.

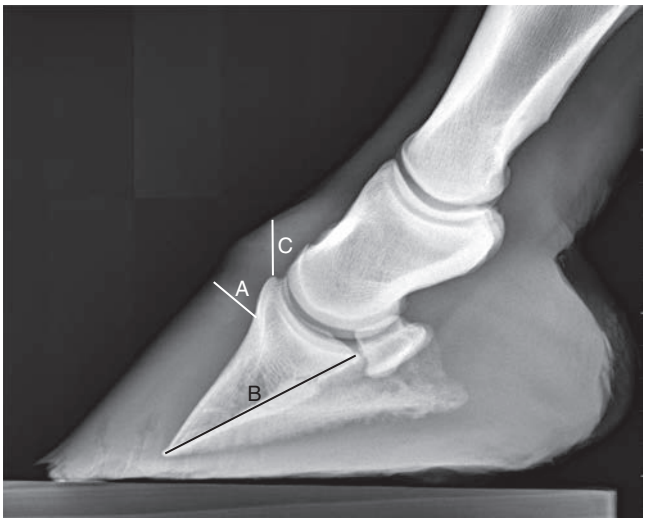


FIG. 38-33 Lateromedial radiograph of a horse with acute laminitis. *(A)* Distance from the dorsoparietal surface of the distal phalanx to the dorsal surface of the hoof capsule, *(B)* length of the palmar cortex of the distal phalanx, and *(C)* distance from the extensor process to the proximal aspect of the hoof wall distal to the coronary band.

Primary radiographic changes in acute laminitis include thickening of the dorsal hoof wall as a result of inflammation and separation of the laminae and separation of the distal phalanx from the hoof wall. When the suspensory apparatus of the distal phalanx fails, the distal phalanx rotates away from the hoof wall or displaces distally, increasing the distance between structures. This distance can be measured as a line vertical to the parietal surface of the distal phalanx and distal to the extensor process. In normal horses, this distance should be less than 18 to 20 mm (Fig. 38-33, *A*). The ratio between this dorsal measurement and the palmar cortical length of the distal phalanx measured from the dorsodistal tip of the bone to its articulation with the navicular bone (see Fig. 38-33, *B*) can be used to account for changes in magnification and size of the foot. This ratio should be less than 28% in normal horses and greater than 32% in horses with displacement of the distal phalanx. Sinking of the entire distal phalanx within the horny capsule can be assessed by measuring the vertical distance between the coronary band and the extensor process of the distal phalanx (see Fig. 38-33, *C*). Soft tissue swelling of the coronary band may be apparent. Palmar/plantar rotation of the distal phalanx away from the hoof wall greater than 5 degrees is indicative of capsular rotation (Fig. 38-34, *A*).

In chronic cases, a radiolucent line may appear between the distal phalanx and the sole or hoof wall; this is due to accumulation of serum between the dermal and epidermal laminae. The angle of the solar margin of the distal phalanx to the ground surface may be a more accurate assessment of rotation in chronic cases (see Fig. 38-34, *B*). Radiographic evidence of a previous episode of laminitis may be evident in clinically normal horses. Changes may include increased thickness of the dorsal hoof wall, a radiolucent line in the dorsal hoof wall, modeling of the toe of the distal phalanx, and/or uncorrected rotation of the distal phalanx.

Positive contrast venography is useful in identifying filling defects in the digital vasculature, including the lamellar vessels, circumflex area, and terminal arch. Venographic studies are most valuable in early disease and may reveal damage in the hoof before radiographic changes are evident.[16]

Epidemiology Epidemiologic studies into the risk factors for naturally occurring laminitis in horses are limited; a few studies report inconsistent results. A recent systematic review of publications assessing the risk factors for naturally occurring laminitis revealed

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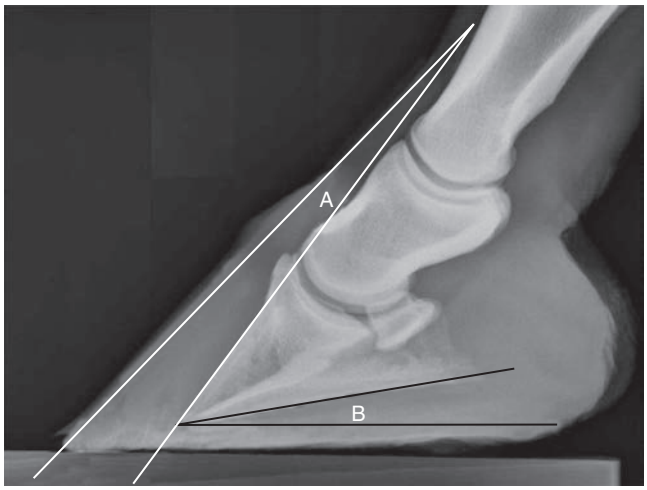


FIG. 38-34 Lateromedial radiograph of a horse with acute laminitis. *(A)* Measurement of the degree of capsular rotation, and *(B)* measurement of the angle of the solar margin of the distal phalanx to the ground surface of the foot.

only an association with chronic laminitis and increasing age. Results for other horse-level factors like gender, breed, and body weight were inconsistent. No consistent associations have been identified with other factors, including exercise and seasonality.[17] Associations between health conditions and laminitis have been investigated, with endotoxemia the only variable for which an association has been noted.[18] This finding has not been reproducible in experimental models.[19] Many studies describe concurrent pituitary pars intermedia dysfunction and laminitis, but no association has been identified.[18] Likewise, no scientific evidence of an increased risk of laminitis from a supporting limb has been identified despite widespread concern. Further evidence-based studies on the risk factors for development of laminitis are clearly indicated.

Necropsy Necropsy findings depend on the duration and severity of the disease. Separation of the primary epidermal laminae of the hoof wall and the collagen fibers of the corium occurs as a result of complete degeneration of the secondary epidermal laminae. The distal phalanx may sink, rotate ventrally, or penetrate the sole. Necrotic laminae are prone to abscessation. Severe changes include fractures of the solar margin, osteomyelitis, or resorption of the distal phalanx.[14]

Treatment Incomplete understanding of the pathophysiology and progression of laminitis limits our ability to successfully prevent and treat the disease and results in considerable controversy regarding appropriate treatment regimens. Therapy is often empirical and based on the clinician's experience. Advancement in our knowledge of the complex pathophysiology of laminitis may result in more effective preventive and therapeutic approaches. Acute laminitis should be considered an emergency, and therapy should be initiated before or immediately following the onset of clinical signs. General principles of therapy include minimizing or eliminating predisposing factors, decreasing pain and inflammation, promoting digital circulation, reducing tension on the laminae, and reducing platelet activation and coagulation.

ELIMINATING CAUSES. Predisposing factors to the development of laminitis should be minimized or eliminated. Following ingestion of large amounts of grain, laxatives or purgatives (e.g., mineral oil, activated charcoal) may be administered via nasogastric tube. Exhaustion, dehydration, and hypovolemia may be treated with appropriate IV fluid therapy. Appropriate therapy for endotoxemia and septic processes like colitis, enteritis, pleuropneumonia, metritis, and retained placentas should be initiated.

Preventive measures in suspect cases may include placing the horse in a deeply bedded stall, frog support, and corrective shoeing or trimming.

DECREASING PAIN AND INFLAMMATION. Antiinflammatory therapy is recommended to decrease lamellar inflammation, edema, and pain associated with laminitis. The most common NSAID used in horses is phenylbutazone at a dose of 2.2 to 4.4 mg/kg IV or PO q12h. The dose and frequency are tapered as quickly as possible. Flunxin meglumine can be administered at a dose of 0.5 to 1.1 mg/kg PO or IV q8-12h for its antiinflammatory effects, or at a dose of 0.25 mg/kg IV q8h to interrupt eicosanoid production associated with endotoxemia. Ketoprofen and firocoxib are also labeled for use in horses. DMSO is a free radical scavenger that aids in reduction of edema and may reduce ischemia-reperfusion injury. DMSO is typically administered at 0.1 to 1 g/kg IV diluted in a polyionic fluid to a concentration of less than 10% to avoid hemolysis. Pentoxifylline, a phosphodiesterase inhibitor, alters RBC membranes to improve blood flow. It has been shown both in vivo and in vitro in horses to have antiinflammatory effects,[20] and preliminary data indicate a decreased incidence of laminar failure in horses treated with pentoxifylline at the time of experimental carbohydrate overload.[21] In a recent study, the analgesic effects of tramadol hydrochloride administered in combination with ketamine hydrochloride were evaluated in horses with naturally occurring chronic laminitis. Tramadol provided little analgesic effect, but analgesia was enhanced by administration of subanesthetic doses of ketamine.[22]

PROMOTING DIGITAL BLOOD FLOW. Venous vasoconstriction is involved in the pathogenesis of laminitis, but several therapeutic agents that have been suggested for increasing blood flow to the digit (i.e., isoxsuprine, nitroglycerin paste) have not proven effective. Acepromazine, a phenothiazine tranquilizer, has been shown to increase digital blood flow in clinically normal horses, with a short duration of efficacy of about 30 minutes.[23] Acepromazine has been recommended at a dose of 0.03 to 0.06 mg/kg IM or IV q6-8h.

Continuous application of cryotherapy to the distal limbs for 48 hours effectively ameloriated induced acute laminitis during the developmental stages of experimental models.[24-25] Filling a 5-L fluid bag with ice and water was shown to be as effective as using wader boots at laminar and digital venous cooling.[26]

REDUCING TENSION ON THE LAMINAE. Because laminar deformity is likely due to tension placed on the suspensory apparatus of the distal phalanx, reduction of mechanical force and stabilization of the distal phalanx are essential in the treatment of acute laminitis. Horses should be confined to strict stall rest and not be exercised in the acute stages of the disease. The horse should be encouraged to lie down, and bedding in the stall (ideally sand) should be deep. Redistributing weight from the hoof wall to the bars, sole, and frog may decrease laminar tension. Various methods have been suggested, including silicone impression material (EquiFlex-Pak [Sound Horse Technologies, Unionville, Pa.]), styrofoam insulation board, Lily Pads (Nanric Inc., Lawrenceburg, Ky.), the Steward Clog (Equine Digit Support System Inc., Penrose, Colo.), and Soft-Ride boots (Soft Ride Inc., Vermillion, Ohio). Regardless of the method of weight redistribution, it is important to remember that once the distal phalanx displaces, increased pressure over the sole where the distal phalanx displaces may cause severely increased discomfort. Various methods of distal limb casts have also been used to improve stability to the distal phalanx.

Decreasing tension on the DDF tendon will also help decrease tension on the laminae. This can be accomplished by elevation of the heels with a wedge (i.e., the Redden Modified Ultimate Wedge [Nanric]) or transection of the DDF tendon to reduce caudal pull on the coffin bone.

Depending on the degree of rotation and/or distal displacement in chronic laminitis, various methods of hoof care and shoeing have

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been employed. More radical past approaches (e.g., hoof wall resection, coronary band grooving) offered varying efficacy.

ANTICOAGULANT THERAPY. Heparin has been recommended in the treatment of laminitis to reduce microthrombi and platelet-platelet or platelet-neutrophil aggregates that are thought to form. Heparin was recently reported to have potential antiinflammatory effects on equine endothelium exposed to neutrophil-derived myeloperoxidase.[27] When administered prophylactically, unfractionated heparin was shown to reduce the proportion of horses with proximal enteritis that develop laminitis,[28] and low-molecular-weight heparin reportedly reduced the incidence and severity of laminitis in postoperative colics.[29]

Prognosis

There is little evidence-based research on prognosticating laminitic horses, but it is likely the prognosis of laminitis depends largely on the severity of the pathology, type of displacement, clinical signs, and underlying diseases or conditions. Prognosis may also be influenced by financial constraints, owner expectations, and owner compliance. In general, rotation is considered to have a more favorable prognosis than distal displacement, which is considered to have a more favorable prognosis than unilateral displacement. The degree of rotation and distance from the proximal margin of the extensor process of the distal phalanx to the proximal margin of the hoof were reported to be important factors in return to soundness and prognosis for survival.[30] General guidelines based on degree of lameness and rotation and progression of clinical findings proposed by Redden in 1988 can be found in the previous edition of this textbook.[14] In one study, 75% of horses referred to a university veterinary hospital with acute laminitis did not return to athletic function, and a majority were euthanized within 1 year because of poor response to therapy or development of complications.[31]

Prevention and Control

Preventive measures are aimed at decreasing risk factors for development of the disease, but our poor understanding of the etiology and pathophysiology of the disease makes prevention challenging. In general, suspected risk factors such as uncontrolled grazing on lush pastures, unrestricted access to grain or concentrates, factors contributing to gastrointestinal upset including rapid changes in diet, and retained placentas should be avoided when possible.

Fluorosis

John Maas

Definition and Etiology

Ingestion of excessive fluoride by cattle, sheep, and horses can result in toxicosis. Acute fluoride toxicosis is relatively rare and is the result of accidental massive ingestion of fluoride compounds such as sodium fluoride or sodium fluorosilicate. Signs of acute fluoride toxicosis include restlessness, stiffness, anorexia, agalactia, salivation, vomiting or regurgitation, urinary incontinence, diarrhea, clonic convulsions, hyperemia, weakness, severe depression, and cardiac failure. Necrosis of the gastrointestinal mucosa and high concentrations of fluoride in plasma and urine are present in acute fluoride toxicities. Chronic fluoride toxicosis is most often referred to as *fluorosis,* a general term that includes osteofluorosis and dental fluorosis. Common sources of excess fluorides in the diet are (1) water with a naturally high fluoride content, (2) forages contaminated with fluorides from nearby (upwind) industrial plants (e.g., phosphate-processing plants, aluminum plants, and aluminum smelters), (3) mineral sources (nondefluorinated rock phosphorus) and feed supplements with excessive fluoride content, (4) forages contaminated by soil or water (particularly sprinkler irrigation water) with a high fluoride content, and (5) volcanic activity, which can deposit fluoride-containing ash on soil, plants, or in water used for agriculture.

Recent outbreaks of fluorosis have been attributed to environmental fluoride contamination by superphosphate fertilizer plants,[1] ingestion of a commercial mineral supplement containing a contaminated phosphorus source,[2] fertilizer-grade phosphorus supplements (containing large amounts of fluoride) fed to cattle for lameness attributed to a phosphorus deficiency,[3] and fluorosis in sheep and cattle attributed to water with excess fluoride used for irrigation and drinking water.[4]

Clinical Signs, Differential Diagnosis, and Pathophysiology

Clinical signs of fluorosis are usually first recognized as either dental fluorosis or osteofluorosis. Developing teeth are very sensitive to the ingestion of excess fluorides. The deciduous teeth rarely show signs of dental fluorosis because a partial placental barrier to the accumulation of fluorides appears to be present in the fetus. During tooth development, excess fluorides cause ameloblasts to reduce in size prematurely and the enamel epithelium to form an irregular matrix. This matrix does not calcify normally, producing defects in the mature teeth. Cattle are susceptible to dental fluorosis during enamel matrix formation, from approximately 6 months to 3 years of age. Excess fluoride intake after 3 years of age does not result in the typical fluoride-induced dental lesions. Changes in incisor teeth are observed most frequently and include chalkiness, mottling (striations or patches in enamel), hypoplasia (defective enamel), and hypocalcification. Clinical lesions can be graded from normal to excessive.[5] Factors that influence dental fluorosis include the amount of fluoride ingested, the animal's age, the duration and consistency (intermittent vs. continuous) of exposure to fluoride, and the source and chemical form of fluoride ingested. Although clinically important, dental lesions should not be used as the sole criterion to determine the degree of fluorosis.

Fluoride accumulation in bone occurs over a prolonged time; osteofluorosis can eventually develop if excessive fluoride is ingested. In cattle the first palpable lesions occur on the medial surface of the proximal third of the metatarsal bones. Later, lesions can be palpated on the mandible, metacarpal bones, and ribs. Radiographically, osteofluorotic bones are thickened with a chalky, roughened, and irregular periosteal surface.

The presence of osteoporosis, osteosclerosis, hyperostosis, osteophytosis, or osteomalacia depends on the amount of fluoride ingested and the duration of exposure to fluorides. The articular surfaces are not involved in osteofluorosis and can be used to differentiate osteofluorosis from osteomyelitis, osteoarthritis, and septic arthritis. The osseous lesions eventually cause intermittent lameness and stiffness, which may affect feed intake, body condition, milk production, and reproduction. Severe dental fluorosis causes reduced feed intake and efficiency, and affected animals are sometimes reluctant to drink cold water.

Clinical Pathology and Diagnosis

Diagnosis of fluorosis is difficult and complicated by many factors that affect fluoride intake and deposition. Fluorosis may be suspected by history, clinical signs, and physical examination. Radiographic findings of bone disease without evidence of joint involvement are highly suggestive of fluorosis in the live animal. The fluoride concentration in the urine of cattle may help to approximate recent fluoride exposure. The diagnostic value of urine fluoride analysis increases as the duration of excess fluoride ingestion increases. Normal cattle have a urine fluoride concentration of about 2 to 6 mg/L (2 to 6 parts per million [ppm]) or less than 10 mg/L (ppm).[6] Cattle exhibiting moderate fluorosis have urine fluoride concentrations of about 15 to 20 mg/L (ppm). Cattle with urine fluoride concentrations of 40 mg/L (ppm) or greater or a urinary fluoride/creatinine ratio of 0.025:1 or greater could be suspected of ingesting a diet with a fluoride concentration of 60 ppm or greater.[5,7] The concentration of fluoride in bone is also quite helpful in the diagnosis of fluorosis (Table 38-2). Fluoride content in cancellous bone (e.g., rib, pelvis) is greater than in cortical bone. In addition, fluoride concentrations may vary in different areas of the same bone.

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TABLE 38-2

Fluoride Concentration in Bones of Dairy Cattle Fed Various Levels of Sodium Fluoride[8,9]

Fluoride in Feed (ppm*, Dry Matter Basis)	Fluoride in Bone (ppm*; Dry, Fat-Free Basis)		
	2 years	4 years	6 years
0-15 (Normal conditions)	401-714	706-1138	653-1221
15-30 (No adverse effects)	714-1605	1138-2379	1221-2794
30-40 (Borderline fluorosis)	1605-2130	2379-3138	2794-3788
40-60 (Moderate fluorosis)	2130-3027	3138-4504	3788-5622
60-109 (Severe fluorosis)	3027-4206	4504-6620	5622-8676

*ppm = mg/kg

TABLE 38-3

Long-Term Tolerances of Dietary Fluoride for Cattle[11]

Animal	Dietary Fluoride (ppm*, Dry Matter Basis)
Dairy or beef heifers	30-40
Mature dairy cows	40
Mature beef cattle	40-50
Feedlot cattle	100

*ppm = mg/kg

Fluoride concentration of bone is usually expressed as mg/kg (ppm) of dry, fat-free bone. However, some bone samples are ashed before fluoride determination, so it is critical to note precisely which bone was sampled, how it was prepared, and what part of the bone was analyzed. The metatarsus and metacarpus are typically analyzed for fluoride content. For all practical purposes, fluoride concentration is equal in either of these bones from the same patient.[8] Using sawdust from a longitudinal section of bovine metatarsus (dividing the bone into lateral and medial halves or dorsal and palmar halves) yields virtually the same fluoride concentration as the whole bone.[8] The fluoride concentration of the fourteenth coccygeal vertebrae (ash basis) is approximately twice that of the metacarpus (dry, fat-free weight basis).[9] This can be a practical tool for clinical diagnosis in the live animal.

Analysis of dietary fluoride is a valuable adjunct to the diagnosis of fluorosis. The upper safe limit of fluoride in water for livestock is 2 mg/L (ppm).[10,11] This safe limit may not protect against fluorosis in all field situations because of the large number of variables involved in the pathogenesis of fluorosis. Table 38-3 lists the long-term dietary tolerances for cattle. Under field conditions, the clinician must consider all possible sources of fluoride ingestion in evaluating total intake. Because fluoride intake may be intermittent, a low dietary intake at one time may not necessarily eliminate a diagnosis of fluorosis.

Treatment and Prognosis No specific treatment is known for ruminants with severe fluorosis, and the prognosis is poor for cattle lame from extensive bony lesions. Animals removed from the offending diet or water may lose 50% of the fluoride from bone within 2 to 5 years,[12] but severe dental damage is irreversible.

Prevention and Control Prevention involves avoiding feeds, water, and supplements with excessive fluoride concentrations. Feeding aluminum sulfate at 0.5% of the total diet reduces bone fluoride storage by 30% to 40%. However, additional phosphorus must be supplied in the diet, or osteoporosis and possibly spontaneous fractures may occur. Aluminum chloride or calcium aluminate also can be fed to cattle to reduce fluoride absorption. Calcium carbonate added to soils high in fluorides aids in reducing fluoride in forages. Cereal grains do not accumulate fluorides and thus can be helpful in reducing overall fluoride consumption. In circumstances of high fluoride concentrations in water, use of flood irrigation rather than sprinkler irrigation decreases the fluoride content of crops such as alfalfa hay.

The effects of varying levels of dietary protein on long-term fluoride exposure have been examined. In this study the feeding of low-protein diets (75% of recommended amounts) increased the bioavailability of fluoride, but there was no significant influence on the susceptibility to fluorosis by varying the dietary protein concentration from low (75%) to normal (100%) to high (125%).

Hypertrophic Osteopathy

M. Keith Chaffin • Robin M. Dabareiner

Definition and Etiology Hypertrophic osteopathy (HO), also known as *Marie's disease,* is an uncommon condition in horses and is characterized by symmetric proliferation of connective tissue and subperiosteal bone along the diaphyses and metaphyses of the bones of the distal extremities.[1-3] The skeletal manifestations of HO are usually secondary to a primary underlying disorder elsewhere in the horse's body, often involving a space-occupying mass.[1-4] Most often, intrathoracic disorders are the primary cause[2]; intraabdominal and intracranial lesions have been less frequently associated with HO.[2,4,5] In addition to horses, HO has also been described in humans, dogs, cats, cattle, deer, and fowl. In humans the term *hypertrophic osteoarthropathy* is used because the articular surfaces are usually affected; in animals, however, HO apparently does not frequently affect the articular surfaces.[1-3]

In the horse, HO has been associated with a number of primary intrathoracic disorders, including mycobacterial pneumonia,[2,6] lung abscess,[1,2] suppurative pneumonia,[1,2,7] granulomatous pneumonia, systemic granulomatous disease,[2,3] fibrosing pneumonia,[8] primary and metastatic lung neoplasia,[7,9-12] pulmonary infarction,[13] rib fracture,[14] pleural adhesion,[2] and pericarditis.[15] Recently a 5-year-old warmblood was diagnosed with HO secondary to equine multinodular pulmonary fibrosis.[16] Reported primary extrathoracic disorders associated with HO include ovarian neoplasia,[17-19] pituitary adenoma,[5] and gastric squamous cell carcinoma.[4] There is one report of HO in a mare that was thought to be associated with pregnancy; signs of HO developed during three different gestational periods and regressed each time after parturition.[7] In occasional cases, HO may develop in the absence of an identifiable underlying disorder.[2]

Pathophysiology The pathophysiology of HO is not completely understood. Initially, blood flow to the distal limbs is increased, followed by proliferation of connective tissue, then bony proliferation along the inner aspect of the periosteum.[1-3] The periosteal proliferation results in the bony enlargements seen clinically. The link between the primary lesion and the skeletal abnormalities is poorly understood. Proposed explanations include hormonal abnormalities, hypoxia, arteriovenous shunting, and neurologic mechanisms.[1-3] The neurologic theory is based on increased vagal stimulation, and the endocrine mechanism involves a variety of local and systemic hormones increasing the production of vascular endothelial growth

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factor (VEGF) and platelet-derived growth factors (PDGF), causing release of megakariocytes from the pulmonary circulation, resulting in platelet clumping in the periosteal capillaries.[16] No single theory offers a completely satisfactory explanation.

Horses of any age or breed and either gender can be affected with HO. Some evidence suggests that HO may be more common in male horses and large-breed horses.[2] Ponies, donkeys, cattle, and sheep can also be affected.[7,10] The condition appears to be most common in mature horses.[7]

Clinical Signs Common clinical signs of HO include lameness, stiff gait, and reluctance to move or trot.[1-3] Firm bony enlargements are present on the distal extremities. In some cases, there may be soft tissue swelling or edema adjacent to the bony enlargements. In some horses the limb swelling is warm and painful to palpation, whereas in others the swelling is cold and painless.[2] Pain can frequently be elicited by forced flexion of the major joints. Bony enlargements are usually bilateral and symmetric and often affect the cranial, lateral, and medial aspects of the affected bones.[1,2] All four limbs are usually affected.[2] The metacarpal and metatarsal bones are most often affected; other sites that can be affected include the phalanges, carpus, tarsus, radius, and tibia, as well as the maxilla, mandible, and nasal bones.[2]

Affected horses may or may not show signs related to the primary underlying disorder, such as cough, fever, weight loss, ventral edema, tachypnea, or colic.[2] Clinicopathologic features are highly variable and depend on the underlying primary disease process. Generally, there is increased serum activity of alkaline phosphatase, associated with increased osteoblastic activity at the sites of periosteal proliferation.[2,3]

Radiographically, the bony enlargements are characterized by periosteal proliferative new bone formation of the diaphysis and metaphysis of affected bones.[2] The periosteal reaction often exhibits an irregular palisade pattern of osteophyte formation.[1,2] The bony reaction may extend to the chondrosynovial junctions; the articular surfaces are usually not affected.[3] In a few cases, nuclear scintigraphy revealed focal areas of intense uptake of radiopharmaceutical at the sites of bony enlargement.[1,15]

Treatment and Prognosis The prognosis for horses with HO is guarded and depends on the underlying disorder. In one study, 71% of horses with HO were euthanized.[2] Gradually progressive limb swelling and pain are the typical clinical course in most affected horses for which an underlying cause is either not identified or effectively managed. Thus, management of HO should be directed at identification and treatment of the underlying primary disorder if possible. Common methods to help identify the underlying disease include hematologic studies, serum chemistries, fibrinogen, thoracic radiography, thoracic and abdominal ultrasonography, abdominocentesis, thoracocentesis, gastroscopy, and rectal examination. Successful management of the primary underlying disorder has resulted in partial or complete regression of the skeletal disease in a limited number of equine cases.[1,2,15,16] Regression of HO is characterized by a decrease in limb swelling and lameness, and a return to athletic performance is possible if bony lesions are not advanced.[1] In a few idiopathic cases in which an underlying disorder was not identified, bony reactions decreased with rest, phenylbutazone, or corticosteroid therapy.[2]

Fescue Foot

Eric W. Davis

Definition and Etiology Fescue foot is a toxicosis of cattle grazing pastures that contain tall fescue grass (*Festuca arundinaceae* Schreb). The condition is characterized by lameness, particularly of the rear limbs, progressing to dry gangrene of the feet and lower legs. The end of the tail and the ear tips occasionally may be affected.

Fescue pastures also cause three other syndromes. "Summer slump" is characterized by reduced gain and milk production, dull hair coat, and poor heat tolerance. Abdominal fat necrosis also has been reported in cattle on fescue pasture.[1] Equine reproductive problems, including prolonged gestation and agalactia, as a result of grazing tall fescue late in gestations have also been described.[2]

The earliest description of fescue foot appeared in 1949 in Australia. It has been reported in Europe, New Zealand, and the United States, particularly in the Southeast. The etiologic agents in fescue have not been definitely established, although several toxins have been identified.[1,3-7] Chemicals produced by the grass itself (e.g., loline, perloline, several organic acids) could be toxic agents contributing to fescue foot and other syndromes, but mycotoxins produced by endophytic fungi that infect tall fescue are generally accepted as being the most important agents. The endophytic fungus of tall fescue, *Acremonium coenophialum* (formerly *Epichloe typhina*), produces ergovaline, ergonine, ergosine, and lysergamide.[1,3,7] All these toxins are capable of producing vasoconstriction similar to that caused by ingestion of the ergot fungus *Claviceps purpurea.* In fact, the symptoms of fescue foot are identical to gangrenous ergotism. Pastures not infected with *Acremonium* produce none of the symptoms of fescue toxicosis in animals.[7]

Environmental factors also play a role in the development of fescue foot. Although the disease can occur over a range of seasons, symptoms usually occur during colder months. Another factor is the level of pasture fertilization. High levels of nitrogen in soil, regardless of the form applied, increase pasture toxicity. Certain strains of fescue, particularly Kj-31, seem to be more toxic.[8] Finally, because the endophyte imparts a selective advantage on the infected plant by increasing growth rate and disease resistance, the number of toxic plants in a pasture increases. The infestation rate of the fescue endophyte is high; more than half the forage samples from states in which fescue foot occurs are infected with *A. coenophialum.*[9]

Clinical Signs and Differential Diagnosis Clinical signs of fescue foot usually begin as hindlimb lameness. Affected cattle are underweight and have a dull, "rough" hair coat. The feet and pasterns become cold to palpation, and the coronary bands become reddened and swollen. Hair may be rubbed from the pastern area with the fingers, and limb edema may be present. As the condition progresses, the classic signs of fescue foot appear, including a sharp line of demarcation at the level of the pastern or fetlock, distal to which the skin becomes dry and gangrenous and eventually sloughs. The tips of the ears and tail also may necrose. Affected animals lose condition initially and eventually are unable to stand or to walk. Susceptibility to the toxin in animals on a given pasture seems to vary considerably. Generally, morbidity is low, although 20% to 30% of the herd may be affected in some circumstances.

The diagnosis is made on the basis of characteristic signs and gross lesions, as well as the presence of tall fescue in the pasture. As mentioned, gangrenous ergotism is clinically identical except that it occurs in the presence of the easily recognizable "ergot" fungus *C. purpurea,* which grows on rye grass. Similarly, chronic selenium toxicosis ("alkali disease") mimics fescue foot, except that this disease does not occur on fescue pastures, and affected animals have elevated tissue selenium concentrations. Both ergot and selenium poisoning affect animals other than cattle, whereas fescue foot has been described only in the bovine.

Early in the course of the disease, mechanical foot injury, foot rot, or laminitis can resemble fescue foot, especially because only a few animals in a herd are affected. Close inspection of the foot, however, reveals lesions that are typical of these diseases. Necrosis due to freezing may be difficult to distinguish from fescue toxicosis, because both occur at the same time of year.

Pathophysiology Pastures that contain tall fescue infected with *A. coenophialum* produce toxins responsible for vasoconstriction. Peripheral vasoconstriction causes blood stasis, endothelial damage, and thrombosis in peripheral vessels. Impaired circulation

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causes tissues of the distal extremities to become ischemic and gangrenous. By decreasing peripheral circulation, cold ambient temperatures exacerbate the condition.

Necropsy Findings At necropsy the principal finding is a characteristic line of demarcation between normal and gangrenous tissues. Generalized loss of condition is also found because of the animal's inability to ambulate and eat. Vascular thrombosis and necrosis of the tissues of the lower limbs are found microscopically.

Treatment and Prognosis When animals with fescue foot are recognized early in the disease course, they should be removed from pasture as soon as possible. Antibiotic treatment to prevent bacterial invasion of injured skin and hooves is valuable; recovery can occur in 2 weeks. Once the extremities have necrosed, however, treatment is unsuccessful, and euthanasia is recommended.

Control Unlike *C. purpurea,* which grows only on the seed head of grasses, the toxins causing fescue foot are contained in the leaves and stems. As a result, mowing contaminated pastures is not an effective control measure. Growing strains of tall fescue with low toxicity, mixed with legume forage plants, seems to be the best management technique for controlling fescue foot. In cold weather, feeding hay to cattle when the pasture contains tall fescue decreases the ingestion of toxins.

Interdigital Necrobacillosis (Foot Rot) in Cattle

Jared J. Janke

Definition and Etiology Interdigital necrobacillosis is an infectious disease of cattle that is a leading cause of lameness in feedlots and confinement dairies. The condition can affect cattle at any age, although most cases are in mature or weaned animals. Sporadic cases are encountered with pastured beef and dairy animals. A variety of names have been used to describe this condition, including "foul-in-the-foot," "foot rot," and "interdigital phlegmon" (phlegmona interdigitalis). The condition is characterized by inflammation and tissue necrosis of the soft tissues of the interdigital space.[1] Deep structures (e.g., tendons, ligaments, synovium, bone) may be involved in severe cases. *Fusobacterium necrophorum,* a gram-negative anaerobic rod, has classically been considered the etiologic agent associated with foot rot, but multiple anaerobic organisms are likely to be synergistically involved. Typical foot root lesions could be induced 5 days after inoculation of the interdigital cleft with *F. necrophorum* alone.[2] *Prevotella melaninogenicus* and *Porphymonas levii* (both previously classified in the genus *Bacteroides*) have been reported to play an important role.[1] The presence of *Dicylobacter nodosus,* the agent associated with contagious foot rot in small ruminants and interdigital dermatitis in cattle, may facilitate penetration of the skin with *F. necrophorum*. Wet, unsanitary conditions and rough environmental flooring are important factors in precipitating infection.

Clinical Signs Early in the course of foot rot, symmetric swelling and heat of the interdigital space are noted, progressing to the coronary band and possibly extending proximally to the level of the fetlock. The claws begin to spread as a result of severe cellulitis, leaving a widened interdigital space. Soft tissue swelling leads to necrosis and fissure formation within a few days,[3] starting at the dorsal interdigital space and spreading toward the heels. The edematous skin margins protrude and roll outward (Fig. 38-35). Exudation and pseudomembrane formation are seen, but significant purulent drainage is not evident. A characteristic foul odor accompanies the necrotic lesion. Acute and progressive lameness in one limb is typical, with the hindlimbs more frequently involved than the forelimbs.[4,5] Septic synovitis, osteomyelitis, or tendon involvement is more likely to result in non–weight-bearing lameness and limb carriage. Mild to moderate elevation of the body temperature (39.4° to 40°C [103° to 104°F]) may be recorded. The associated pain leads to reduced ambulation, feed intake, and milk production, as well as weight gain. Affected animals may spend a significant amount of time lying down, predisposing them to injury from herdmates. Systemic effects of inflammation and infection can result in reduced fertility in breeding bulls. Differential diagnoses for lameness of the foot include trauma, interdigital dermatitis, verrucose dermatitis, and laminitis.[6]

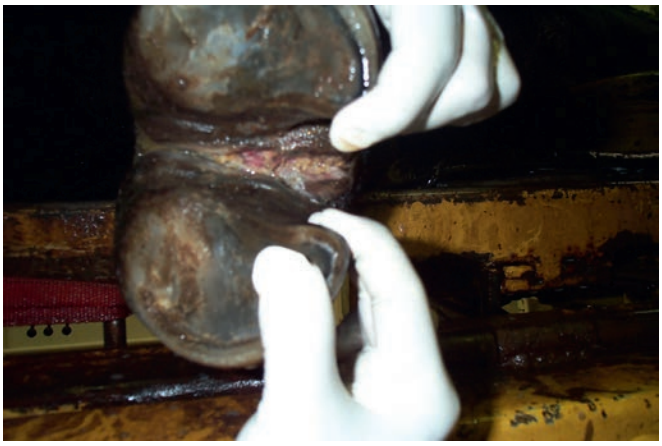


FIG. 38-35 Bovine foot rot lesion present in the interdigital space. *(Photo courtesy Dr. Kevin Washburn, Texas A&M University.)*

A previously described severe form of foot rot is peracute in onset and refractory to conventional treatments.[4,7] Severe interdigital swelling is noted in multiple limbs and most often in the hindlimbs. The condition is rapidly progressive, leading to recumbency and a rapid extension to deeper structures. Euthanasia may be warranted on animal welfare grounds.[8] Penicillin/sulfonamide-resistant *F. necrophorum* has been isolated from several cases.[7] Concurrent infection with bovine viral diarrhea (BVD) virus and the resultant immunosuppression have been suggested as an etiology.[9]

Clinical Pathology Laboratory analysis of blood is not typically done, although a normal or inflammatory leukogram may be encountered. Serum haptoglobin levels were found to be increased in foot rot–infected cattle, but this finding is not specific to foot rot. Researchers also noted a decrease or normalization within 1 to 5 days after treatment.[10] Collection of samples for microbial culture is seldom done because of the ability to diagnose the condition through typical clinical findings. Lesional swabs or biopsy samples may be submitted for bacterial culture. A mixed population of environmental and fecal contaminants is likely, but isolation of *F. necrophorum* and other anaerobes suggests true foot rot. Microscopic evaluation of biopsy samples may identify spirochetes, although this is not a consistent finding. Serodiagnosis has been reported with indirect ELISA (rL-ELISA) for the detection of leukotoxin A (lktA) antibodies using the recombinant protein PL2, yielding relatively high sensitivity and specificity.[11]

Pathogenesis The mechanisms of interdigital necrobacillosis are complex and incompletely understood. Compromise of the skin barrier is critical for invasion of the offending pathogens. Chronic exposure of feet to wet and dirty conditions leads to softening and maceration of the skin. Exposure to sharp gravel and stones, excessive stubble, irregular concrete, and other forms of mechanical trauma can result in significant abrasions and damage to the interdigital skin, particularly in wet environments. The combination of these two factors can result in penetration of the offending pathogens and resultant infection. Initial microbial flora may reduce tissue oxygen tension, allowing anaerobes and ideal environment to proliferate.[6,12] Once the organisms colonize the subcutaneous tissues, multiple

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mechanisms likely promote growth and evasion of the host defense systems.

The two subspecies of *F. necrophorum* currently recognized are biotypes A and B. Biotype A appears to be more virulent and is more frequently isolated.[13,14] Others have described differentiation of virulent strains by colony morphology,[15] and PCR differentiation of strains is available.[16] New Zealand researchers evaluated lktA PCR analysis of foot rot lesion swabs from cattle, sheep, and goats and found a lack of evidence for lktA strain variability within the same animal. This is contrary to the strain variability that is common with *Dicylobacter nodosus* in small ruminant foot rot cases.[17]

Although *F. necophorum* is also a human pathogen, differences exist between human and animal strains.[13] *F. necrophorum* is a normal inhabitant of the gastrointestinal tract of ruminants, although isolation from the feces is generally rare.[13,18] Oral administration of some antimicrobials has been shown to increase fecal shedding of *F. necrophorum*.[19] The increased number of organisms in exudate from necrotic lesions may provide an important source of transmission to other animals. Major virulence factors associated with this organism are a high-molecular-weight leukotoxin and lipopolysaccharide (LPS).[20,21] The leukotoxin is cytotoxic to ruminant neutrophils and, when combined with LPS, may protect the organism from phagocytosis.[13]

Findings suggest that *P. levii* did not stimulate a significant chemotactic response in bovine macrophages in vitro, and suppression of phagocytosis occurred when the organism was present in low numbers.[1] These properties of *P. levii* may facilitate a local tissue environment that allows other anaerobic organisms, including *F. necrophorum,* to colonize and evade host defense mechanisms.

Epidemiology Interdigital necrobacillosis has been recognized worldwide for centuries.[22] Wet and humid climates predispose to disease, and foot rot has been associated with rainy seasons.[12,23] The risk of the disease is higher in management systems that expose animals to traumatizing ground underfoot, such as concrete confinement with water and excrement accumulation, irrigated pastures, muddy lots, high stocking densities, and stony walkways. As noted, cattle of any age are susceptible, but mature animals account for most cases. *Bos indicus* breeds appear to be have a lower incidence than *Bos taurus,* and Jersey cattle may be overrepresented in the dairy breeds.[23]

Necropsy Findings Postmortem examination is rarely performed. Characterization of the lesions reveals subcutaneous and soft tissue necrosis, with suppurative inflammation of the foot. In severe cases, evidence of osteomyelitis, tenosynovitis, and septic arthritis may be identified.

Treatment and Prevention Most animals are responsive to parenteral antimicrobial therapy. Local treatment (e.g., topical preparations, wound care, bandaging) is probably not necessary for minor cases identified early, although local therapy may reduce the number of infectious organisms spread to the environment.[10] The organisms are typically susceptible to a variety of antimicrobials.[4] Procaine G penicillin (22,000-44,000 IU/kg IM once or twice daily) has been used successfully when infection is detected early.[10] These dosages of penicillin are considered off-label, and the clinician must take appropriate steps to ensure meat- and milk-withdrawal periods. A number of drugs have been approved to treat foot rot in the United States,[4,8] including amoxicillin (6.6 to 11 mg/kg IM or subcutaneously [SC] for 5 days), oxytetracycline (10 mg/kg IM or SC), sulfadimethoxine (55 mg/kg PO or IV loading, then 27.5 mg/kg PO or IV daily for 5 days), erythromycin (2.2 to 4.4 mg/kg IM daily for 3 to 5 days), ceftiofur hydrochloride/sodium (1.1 to 2.2 mg/kg SC or IM daily for 3 to 5 days), tylosin (18 mg/kg IM daily for up to 5 days), sulfamethazine (30 g/100 kg PO, repeated in 72 hours), florfenicol (40 mg/kg SC once), and tulathromycin (2.5 mg/kg SC once).[4,6,8,10] A comparison of ceftiofur crystalline free acid (6.6 mg/kg SC in the base of the ear once) and ceftiofur sodium daily for 3 consecutive days revealed no statistical difference in recovery rates; however, the ceftiofur sodium resulted in more labor and time required for multiple administrations.[24]

Early recognition and treatment can produce clinical improvement in 2 to 4 days.[4] The antimicrobial of choice can be tailored to suit the needs of the farm in terms of withdrawal times, number of treatments, route of administration, and familiarity with the product. Investigators found that 5 mg/kg of off-label tilmicosin SC at the onset of lameness resulted in a 74% cure rate, significantly higher than with placebo.[25] Antiinflammatory therapy, including flunixin meglumine or aspirin, may reduce fever and provide analgesia, resulting in improved appetite and ambulation.[8]

When topical therapy is warranted, wound cleansing and curettage of the necrotic tissue are beneficial. A variety of topical antimicrobial or astringent preparations can be placed under a foot bandage. The main objectives of bandaging are to keep the wound clean and prevent further contamination from fecal organisms for several days. Moving treated animals to clean, dry areas is recommended.[6] Dressing the foot to prevent further spreading of the digits helps protect the interdigital space. Bandaging infected feet may also reduce the amount of exudate that could infect herdmates.[10]

Spontaneous recovery is possible, although the risk of complications is increased and recovery may take several weeks.[6] Animals with significant deep structure involvement may require prolonged therapy and repeated wound management. Animals with evidence of septic arthritis of the digital joints or other synovial structures may require amputation of the digit to allow drainage. Claw amputation has been described.[8,26]

Metaphylaxis, or the mass treatment of animals, may be warranted in some circumstances. Methods to mass-treat animals include topical treatment in the form of footbaths or the addition of feed-grade antimicrobials and supplements to diets. It is prudent to inform owners that no feed additives are currently approved for the prevention or treatment of foot rot.[27] Off-label use of feed additives, as governed by the Animal Medicinal Drug Use Clarification Act, is strictly prohibited.[4,27] The only food-additive antimicrobials approved for nonenteric disease are chlortetracycline and oxytetracycline.[27] Ethylenediamine dihydriodide (EDDI) has been used to reduce the severity and incidence of foot rot,[28] although high doses are toxic in cattle. EDDI used for this purpose is prohibited, based on the present regulation of feed additives.[4,27]

Footbaths are an appealing alternative for many producers, but proper use is important. Contact time and efficacious ingredients are sometimes difficult to ensure. Footbath additives often are rapidly contaminated with organic material, eventually leading to inactivation.[27] Antibacterial agents and astringents have been traditionally used, including 3% formalin, 2% copper sulfate, oxytetracycline, and lincomycin-spectinomycin formulations. Dry footbaths have also been reported and include 10% copper sulfate and slaked lime.[6] Practitioners must check state and local laws that may prohibit use of some substances that could cause environmental contamination and might be unsafe for handlers.

Vaccination against *F. necrophorum* has been available for some time, but firm evidence of its efficacy in peer-reviewed publications is limited.[4] One study evaluating the incidence and severity of hepatic abscess and foot rot suggested a positive response to vaccination of feedlot cattle compared with controls, although the significance was evident only in the free-choice forage program. The same positive result was not evident when the analysis included all the cattle, particularly the limit-feed grain program. The benefit of vaccination may not overcome the challenge of diets that promote rumenitis.[29]

Infectious Foot Rot in Sheep and Goats

Jared J. Janke

Definition and Etiology Infectious foot rot is a highly contagious foot disease of sheep and goats and the leading cause of

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infectious lameness in these species.[1,2] The essential pathogen is the anaerobic bacterium *Dicylobacter nodosus*.[1-12] Synergistic activity with other microbes, primarily *F. necrophorum,* plays an important role in pathogenesis.[1,4,5,12] Equally important are the roles environmental moisture and climate play in transmission from animal to animal.[1,4-6,10,12] The infection has been reported in a variety of species including cattle, horses, pigs, deer, and mouflon but is generally considered a sheep- and goat-specific disease.[8]

Epidemiology Foot rot accounts for significant economic losses in sheep-producing countries[3,5,7,8] and has often resulted in government control programs.[2,6] Reduced body and fleece weight and increased costs of management, treatment, and culling make control of this disease important. Infectious foot rot is found worldwide wherever sheep and goats are reared, although it is primarily a problem in warm, humid climates.[1,4-6,10,12] Sheep raised on improved pastures in arid regions may also develop the disease.[5] Prolonged periods of moisture are required to facilitate transmission; short periods of heavy rainfall do not lead to significant increases in clinical disease.[1,4,5]

Consistent temperatures above 10° C (50° F) are considered favorable for disease transmission.[1] Incidence rates are likely to correspond with the seasons that favor these conditions and may vary between geographic regions. Using pastures with ground cover that promotes trauma to the foot is likely to increase the risk of disease. The natural herding behavior of sheep and goats is likely to propagate the spread of the organism within a flock. Traditionally, routine hoof trimming was thought to reduce the incidence by improving general foot health, but others have not made this association and have actually proposed trimming as a risk factor.[1,2,5,10]

Sheep are the primary species of concern, although other ruminants can be infected. An association with increased severity in lambs from aged ewes has been suggested.[5] The Merino breed appears to be the most susceptible, whereas British breeds demonstrate less severity.[4,5] Clinical disease is more often diagnosed in adults, although lambs may also be affected. Age and breed have been identified as risk factors, with an increase in incidence with age. Breed genetics and heritability may play important roles in resistance to disease, and reducing matings from chronically infected sheep may be an important step in propagating less susceptible breeding lines.[2,5] Introduction of the organism to a native flock is almost exclusively by the addition of asymptomatic chronic carrier animals that may harbor the organism on their feet for years.[4,5] Animals exposed to pastures or housing facilities immediately contaminated by infected feet are at risk of contracting the organism. *D. nodosus* is an obligate parasite of the hooves and survives only a short time in the environment, but it may remain viable for up to 2 weeks in favorable conditions.[4,5] Chronic subclinical infections of the interdigital skin or small cryptic lesions within the hoof can allow for persistence of the organism within the flock for months.[12] This finding is a critical point when considering flock biosecurity.

Pathogenesis and Clinical Signs The interdigital skin is typically an adequate barrier to infection. In prolonged wet conditions, however, the skin becomes macerated and weakened. Initially, *F. necrophorum* invades the skin and superficial soft tissues, resulting in ovine interdigital dermatitis (OID). This organism may produce a local tissue environment that promotes invasion of *D. nodosus*. These two organisms work synergistically to allow *F. necrophorum* to invade into deeper tissues and allow bacterial proteases produced by *D. nodosus* to eventually cause horn separation. Both organisms are essential for true foot rot to occur.[1] The lesion associated with foot rot is characterized as exudative inflammation and necrosis of the epidermal tissues of the foot.[8] A characteristic foul odor is almost always present.[3,5] Both claws of multiple limbs are typically involved. The interdigital skin becomes moist and swollen, and the soft horn is pale, pitted, and may be separated from the skin.[4]

Disease associated with *D. nodosus* infection is highly dependent on the virulence of the organism, resistance of the animal, and environmental conditions. All these factors are extremely variable; a relatively low virulent strain in wet conditions may contribute to more severe disease than a highly virulent strain in dry weather. Virulence is associated with the keratinolytic ability of a strain and occurrence of type IV fimbriae.[1,3,5-8] The fimbrial subunit gene fimA appears to be essential for virulence.[5] Heat-stable protease production is characteristic of virulent strains. Infectious foot rot is categorized into two clinical syndromes, benign or virulent, based on the clinical severity and the ability to transmit through the flock. Some have included a third, intermediate syndrome for cases that are clinically more involved than the benign form but are not associated with the appreciable production losses that occur with the virulent form.[1] Foot rot accounted for a 10% decrease in body weight and wool production in one report.[8] It may be difficult to clearly define each case early in the disease process; what appears to be benign may be the early onset of the more virulent form. Benign foot rot may progress into separation of the soft horn from the underlying hard horn, but it does not progress beyond this point. Virulent foot rot is characterized by severe interdigital lesions, with separation of the soft and hard horn from the sensitive laminae. Separation of the axial surfaces of the heels progresses in a dorsolateral direction.[4,5] Underrunning of the sole occurs, and in the most severe cases, the entire hoof may be sloughed. When confronting acute multiple-limb lameness in several animals in a flock, a practitioner should strongly consider virulent foot rot.

The spread from animal to animal is generally rapid, and multiple stages of the infection are present within the flock. Inspection of the flock is indicated to categorize the severity of the infection. In some flocks, only a small portion needs to be examined to determine the classification of the disease, whereas evaluation of the majority of the flock is required in other cases. If uncertainty exists, 2 weeks is usually adequate to allow lesions to progress to a stage that will accurately allow classification of the clinical syndrome.[1] Affected animals may graze on their knees to relieve the foot pain or remain recumbent in severe cases. Systemic signs of infection may include fever, anorexia, and weight loss.[4] Complications of the foot wounds include blowfly strike and secondary bacterial infection.[4,5] Although susceptible, the clinical course in goats is often less severe. Interdigital dermatitis is a more prominent clinical finding than separation of the horn in this species.[4]

Differential diagnosis for foot rot include traumatic injury, laminitis, foot abscesses, OID, and contagious ovine digital dermatitis (CODD). The presence of interdigital dermatitis increases the risk of the development of foot rot, and the prevalence may be high in the early stages of foot rot infection. It may be impossible to clinically distinguish between interdigital dermatitis and benign foot rot.[1]

Identified in the United Kingdom in the mid-1990s, CODD was initially thought to be a severe form of virulent foot rot. The disease shows clinical similarity to infectious foot rot, but initial involvement of the interdigital space is usually absent with CODD. Ulcerative lesions involving haired skin adjacent to the coronet are more common. This condition responds poorly to traditional foot rot treatment strategies. The complete pathogenesis of CODD is unclear, but one report isolated *D. nodosus* in 74% and a spirochete in 70% of affected feet. The spirochete was from the genus *Treponema,* which has been associated with similar lesions in cattle.[11]

Clinical Pathology, Diagnostic Tests, and Necropsy Findings Samples collected by swabs or lesion material can be submitted for anaerobic microbial culture. The mixed bacterial population present and the fastidious growth of *D. nodosus* make isolation difficult and time consuming.[3,8] Collection of samples in anaerobic transport containers and rapid submission to the laboratory are required. One report found that *D. nodosus* could not be isolated from field samples if they remained longer than 3 hours in transport.[3] Routine growth media found in most laboratories is not usually sufficient to grow this organism; selective media and techniques are helpful in isolating this microbe.[3] Microscopic examination of

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D. nodosus organisms by Gram stain reveals large, barbell-shaped, gram-negative rods.[4,8] Some investigators have reported colony morphology and correlation with virulence, but others have been unable to make this correlation.[3]

Biochemical testing for elastase activity and thermal stability of bacterial proteases has been used to differentiate benign from virulent strains. Thermal stability of bacterial proteases can be measured by the gelatin gel test,[5,6,7] although false-positive results have been reported. Advanced molecular techniques, including PCR and DNA sequencing, have recently become available for detecting gene sequences that encode for virulence, particularly fimA.[3,6,7] These advanced techniques have expanded the classification and number of strains and serotypes identified[3,6,7] and allow a rapid and sensitive diagnostic tool for use in control programs.[5] Serum antibody detection using an ELISA is available, but its specificity may be lacking.[5] Serology may be helpful in determining flock involvement. Infectious foot rot is usually diagnosed on clinical findings, and postmortem examination is not typically necessary.

Treatment and Prevention Once *D. nodosus* infection is identified in a flock, treatment to control and potentially eradicate the organism should be initiated. Eradication may not be possible in all flocks, and the severity of the disease, management practices, strain virulence, and environmental factors likely play a critical role. Separation of animals confirmed to have lesions could reduce transmission to uninfected flockmates, but this may not be possible under some management strategies. When possible, planning pasture rotation to allow 2-week dormancy periods enables producers to have infection-free zones. Improving pastures to prevent areas of standing water, excrement, and mud will theoretically reduce the potential for transmission. Routine flock hoof trimming has been a mainstay in the prevention of foot rot, although supportive clinical data are lacking.[1,2] Regions having consistent problems with foot rot have discontinued this practice because of the lack of evidence and the increase in time and labor.[2] However, judicious hoof trimming for the treatment of foot rot is probably beneficial on an individual basis and when topical treatments are employed.[2,4,5] Researchers found an increase in prevalence of foot rot following routine hoof trimming in one study, leading to concerns that excessive foot paring should be avoided.[12] Meticulous paring of the hoof may be necessary if the disease has produced overgrown and misshapen feet that promote hiding places for *D. nodosus*. Disinfection of knives and shears between each animal is important to reduce iatrogenic transmission. Treatment is typically more successful during dry periods of the year, when transmission is reduced.

Medical treatment methods for foot rot include topical therapy, including footbaths and topical medications, and parenteral antimicrobials. Although bandaging individual feet may increase the contact time of medications and reduce the spread of infectious material, this is not practical and does not allow the foot to dry. Topical 5% oxytetracycline tincture has been used successfully.[5] Chemicals used in footbath solutions include 5% copper sulfate, 3% to 5% formalin, and 10% zinc sulfate.[1,4,5] When used properly, these agents are usually highly effective, but caution must be used with each chemical to prevent adverse effects. All these agents are potentially toxic to varying degrees if ingested, and copper sulfate will stain the fleece. Comparison of formalin and zinc sulfate in footbath preparations yields similar results.[5] Formalin is more resistant to contamination by organic material, but higher concentrations and frequent application are extremely irritating to the skin. Additionally, considerable human health concerns and government health regulations may prevent formalin use in some flocks. Efficacy and improved safety make zinc sulfate an ideal agent for use in footbaths. Improved chemical penetration of the hoof can be achieved when the surfactant sodium lauryl sulfate is combined with the footbath solution, reducing the need for hoof trimming before treatment. The use of footbaths requires facilities and construction (6 to 12 m [20 to 40 ft] long) that ensure all feet on each animal are treated. The ideal contact time has not been established in clinical studies, but brief walk-through or soaking for up to 1 hour has been shown to be successful.[1] The frequency of treatment is also not clearly defined and may be dictated by the contact time. Because of its irritating properties, formalin should not be used more than once a week.[5] Although the response is likely multifactorial, cure rates of 50% to 80% have been reported with foot bathing. Separate footbaths for infected and noninfected animals reduce the risk of inadvertent transmission. Washing the feet by walking animals through a plain-water bath and allowing the feet to dry 2 hours before and at least 1 hour after treatment is ideal.[1] Once treated, the groups should be immediately moved to clean, dry pastures or lots that have not held livestock for at least 2 weeks.

No antimicrobial drugs in United States are presently labeled for use against infectious foot rot in sheep, so use is off-label. One-time treatment without hoof trimming can produce similar results to foot bathing. Parenteral antimicrobials have produced recovery rates of 85% after one dose when sheep were kept on dry floors for 24 hours after treatment.[1] Although *D. nodosus* has been reported to be sensitive to many antimicrobials in vitro, this gives no indication of sensitivity when used clinically.[5] Medications used successfully have included penicillin procaine G (20,000 to 30,000 IU/kg IM twice daily),[4] long-acting oxytetracycline (20 mg/kg SC once, or repeated in 72 hours),[4,5] erythromycin (10 mg/kg once, or 3 to 5 mg/kg IM twice daily),[4,5] florfenicol (20 mg/kg IM, repeated in 48 hours),[4] and linomycin (5 mg/kg SC once) in combination with spectinomycin (10 mg/kg SC once).[5] Maintaining dry footing for 24 hours, yielding meat- and milk-withdrawal times, and the potential of reinfection are important considerations when using parenteral antimicrobials.[1] In an observational study, producers that treated with parenteral antimicrobials and topical antibacterials early in the course of disease had a lower prevalence of lameness and increased profitability when compared to later treatment with hoof trimming and topical antibacterials.[13] Parenteral and topical oxytetracycline therapy yielded a 75% recovery in 5 days in a randomized clinical trial, while those animals receiving foot trimming and topical oxytetracyline had the longest recovery times.[14]

Recent work has found an association with decreased whole blood selenium levels and foot rot in sheep. Clinical cases receiving parenteral selenium as a component of their control program recovered more rapidly and demonstrated a more robust immune response.[15,16] Flunixin meglumine may be administered for analgesia, but there was no significant effect on recovery in one study.[14]

Vaccination against *D. nodosus* is available, and its use to treat and control foot rot has been reported.[1,2,4,5,9] A reduction in disease severity and quicker response to treatment may be evident when this is used as a treatment modality. Several strategies have been used for classifying *D. nodosus* strains based on fimbrial types, and at least 10 serogroups with 19 serotypes have been identified.[1,3-5,7,8] Fimbrial gene variation undoubtedly plays an important role in vaccine efficacy.[5] The currently available commercial vaccine contains 10 serotypes, and antigenic competition is likely to impede additional serotypes.[1,5] Identifying the most prominent strain or fimbrial type in a geographic region or flock may facilitate vaccine selection and development. Eight strains of *D. nodosus* have been reported to infect one foot.[5] Response to vaccination appears to be strain specific, with poor cross-protection between strains. Successful resolution of clinical signs by using autogenous vaccine without other treatments has been reported.[9] The use of adjuvants in killed vaccines is required to produce an adequate antibody response, and the addition of adjuvants, particularly oil based, has led to a high incidence of injection site reactions.[1,4,5] The response to vaccination is likely short lived (≈8 to 12 weeks[1]) and requires multiple doses. A split-flock randomized treatment trial revealed a significant increase in recovery (92% vs. 82%) and reduction in new infection rates (12% vs. 27%) at 9 weeks in the vaccinates versus the non-vaccinates. In that study, both groups received concurrent parenteral antimicrobial therapy.[17] Vaccination of animals during the dry period, several weeks before the optimal transmission period, is likely beneficial in a control program.

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Control and eradication can potentially be achieved in regions where the climate allows a break in the transmission period, but the investment in labor and cost of medical therapy may be high. A combination of topical treatment, parenteral antimicrobials, and vaccination is likely to be employed. Careful observation for early signs of infection and quarantine of any new animals are critical to controlling or preventing a flock outbreak. Some researchers have indicated aggressive culling practices may be necessary in an eradication program.[12] Using a weekly zinc sulfate footbath for 2 to 4 weeks, along with vaccination and culling of severe and unresponsive cases, has been suggested.[4] Based on the evidence of resistance heritability, careful breeding programs should be explored.[2,5] Complete eradication from a farm can be achieved if the entire flock is removed, the facilities are left dormant for at least 2 weeks, and the flock is repopulated with noninfected animals.[1]

Other Infectious Conditions of the Foot

Robin M. Dabareiner

Infections involving the foot of horses and cattle are common and almost always caused by contamination from the environment gaining access to the soft tissue or bony structures of the foot within the hoof capsule. Typically the animal has an acute, progressive lameness such that the animal is almost non–weight bearing on the affected limb or will bear weight on the toe region of the foot but resist putting the heel on the ground. Other clinical signs include increased digital pulse pressure, heat, and sensitivity to hoof-tester pressure over the affected area. Regional nerve blocks can be used to localize the lameness to the foot but frequently are unnecessary. Because the foot is encased in a shell of horny tissue, exudate from an infectious process often accumulates between the soft tissue and horn. The exudate then spreads or dissects along that plane until it reaches a soft tissue surface like the coronary band, especially near the bulbs of the heels, where rupture and drainage can occur.

Problems Associated with Horseshoe Nails ("Nail Prick")

History and Clinical Signs *Nail prick* ("quicking") refers to penetration of the sensitive hoof structures, usually the sensitive laminae, by a driven horseshoe nail. The horse will usually react as the farrier drives or clinches the nail by jerking the foot from the farrier. In some cases, blood may appear on the nail or leak from the nail hole. It is important to realize that nail pricks occur for many reasons and are not always caused by a misdirected nail. Poorly made shoes, nails that are too large, poorly placed nail holes, and faulty nails can also result in a nail prick. Horses with poor hoof quality, thin hoof walls, or flaring hoof walls can be difficult to nail and thus are at greatest risk. Fractious horses and young horses not previously shod may lean on the farrier or repeatedly pull the foot from the farrier, making nail driving difficult. Damage from an improperly driven nail can vary from minimal to serious infection.

Diagnosis Diagnosis of a misdirected nail warrants great diplomacy from the veterinarian, because many owners become unjustifiably upset with the farrier. Some horses will repeatedly stomp the affected foot or paw the ground immediately after shoeing. Others may point the affected limb after shoeing. Lameness may not be apparent immediately after shoeing and may occur days later when the nail hole becomes infected and the trapped pus begins to exert pressure. The horse usually becomes acutely lame and worsens over time unless treated. Some infected nail holes will travel up the lamellae (white line) and create an abscess or soft spot at the hairline of the coronary band. The abscess will be directly aligned with the hoof wall tubules, leading to the infected nail hole, which is an important diagnostic aid. Hoof-tester examination, paying particular attention to pressure over the driven nails, is an essential diagnostic tool to locate the offending nail. Using a hammer to strike the outside hoof wall may also elicit a painful response over the nail. Increased digital pulse and heat may be present.

Treatment Pricks from nails can be potentially serious and require immediate treatment. If the nail prick is discovered by the farrier at the time of shoeing, the nail is removed. The nail should be examined for moisture or blood. The nail hole can be irrigated with DMSO, povidone-iodine (Betadine) solution, or hydrogen peroxide. The nail hole is packed with iodine-soaked cotton and the nail hole left open. Often the nail is redirected, and no further treatment is needed. If the horse's immunization status is not current, a tetanus vaccine is given.

If the offending nail cannot be localized or the nail hole is infected, the shoe is removed. Hoof testers are then used to localize the painful nail hole. Frequently the pressure from the hoof testers will cause black, malodorous liquid pus to exit from the hole. The basis of treatment is to establish drainage. The infected nail hole often requires enlargement with a loop hoof knife or curette. Ideally a cone-shaped hole is made, with the larger opening at the bottom of the hoof. The hole is irrigated or the entire foot soaked in an Epsom salt/Betadine footbath for 20 to 30 minutes twice daily until the infection is gone. It is important to protect the foot from the environment (e.g., mud, dirt) by keeping the foot bandaged between foot soaks. Additional medications are usually unnecessary unless involvement is extensive. Antiinflammatory medications may be beneficial to decrease pain. Once the infection has cleared, the shoe is replaced. The affected nail hole can be packed with iodine-soaked cotton and the horse reshod with a plastic pad covering the sole. Alternately, a hole can be drilled into the shoe over the affected nail hole and the shoe replaced, leaving access to the infected area for daily irrigation and povidone-iodine packing.

Prognosis Prognosis is usually good provided that minimal damage occurs to vital structures of the foot. Establishing drainage for sepsis is important to avoid potential complications, such as third phalanx osteomyelitis or coffin joint sepsis.

Subsolar Abscess

Subsolar abscess is one of the most common causes of lameness in the horse and cow, but it is relatively rare in sheep and goats. In one study in cattle, 88% of cases of lameness were caused by problems in the hoof.[1] Most often, lameness is caused by a hole or crack in the horny sole, which then becomes packed with dirt, and eventually contamination extends to and is trapped within the sensitive soft tissue beneath the sole. Animals that are housed in filthy or muddy conditions and that have inadequate hoof care or overgrown feet are more prone to this problem. Horses taken from a very dry to a very wet environment, and vice versa, also tend to have a higher incidence of sole abscesses, apparently because of the sudden change in the moisture content of the hoof and the resultant cracking of the sole. Cattle with "corkscrew claw" (a hereditary condition) or other growth deformity in the claw are more prone to sole abscess. Puncture wounds or any form of trauma that introduces contamination to the soft tissue of the sole also may result in abscessation.

History and Clinical Signs Subsolar abscess is a common cause of acute lameness seen in all horses. There is no signalment or breed disposition. "Gravel" is a lay term describing the assumed etiology in which a piece of gravel migrates proximally from the white line to coronary band, leaving an infected tract. Subsolar abscesses may originate from a penetrating wound in the white line, a nail hole, or a deep subsolar bruise. Lameness is usually acute and severe (grade 3 to 4 of 5) and may worsen over time until drainage

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is established. The horse will often point and may not bear full weight on the affected limb. Distal limb swelling often accompanies a subsolar abscess that has not had drainage established. Systemic signs of infection (fever, lethargy) usually are not associated with subsolar abscesses unless deeper structures are involved. The infected tract may migrate and open at the coronary band. Before breaking open, a soft painful area can be located by digital palpation of the coronary band.

Diagnosis Digital pulses are usually increased, and the hoof capsule may radiate heat. A focal painful area can usually (but not always) be located with careful hoof-tester examination. Careful paring of the sole and frog may be helpful in locating the abscess, but the clinician must be careful not to damage good healthy tissue looking for the infection site. Foot poultices and hot-water footbaths with Epsom salts will eventually help to localize the affected area. Gray or black malodorous liquid will leak from the infected tract (Fig. 38-36). Radiographs are useful to rule out other causes, such as third phalanx and navicular bone fracture. In some cases a gas or fluid pocket can be identified on radiographs.

Treatment Treatment is aimed at establishing adequate drainage. If an opening in the tract is present at the solar surface, it should be enlarged just enough for good irrigation and drainage. This may or may not require sedation or peripheral anesthesia of the foot. If pink tissue or blood is encountered, débridement is discontinued. Large holes should be avoided to prevent solar corium protrusion, which can be a painful sequela to overzealous hoof paring. If drainage occurs at the level of the coronary band and solar surface, through-and-through lavage is beneficial. Débridement at the coronary band level should be minimal to prevent iatrogenic coffin joint contamination. Once drainage is established, a foot bandage can protect the foot from the environment and recontamination. Continued foot soaks in warm-water povidone-iodine and Epsom salt footbaths should be continued until sepsis and inflammation are eliminated. The shoe is replaced when the affected area is dry and cornified. Large areas may require a plastic pad under the shoe for solar protection. Antibiotics and NSAIDs are rarely needed except in severe cases or if penetration of deeper structures has occurred. The patient's tetanus immunization should be checked and a booster injection administered if needed.

Prognosis Prognosis for simple subsolar abscess is excellent but worsens if complications develop in which deeper structures of the foot become involved.



FIG. 38-36 Horse's hoof with a recently opened subsolar abscess, demonstrating gray exudate.

Deep Penetrating Injuries to the Sole

History and Clinical Signs Most animals' environments are filled with sharp objects that can penetrate the sole, causing severe damage to structures deep within the hoof capsule. All puncture wounds should be considered potentially serious, but those involving the solar white line or caudal frog area require special attention because of potential navicular bursa, digital tendon sheath, DDF tendon, or distal phalanx involvement.

The clinical signs of a penetrating wound to the sole vary with the anatomic structure involved and chronicity of the injury. The animal may show minimal lameness initially at the time of injury, but severe lameness once sepsis is established days later. Animals with penetrating wounds to the podotrochlear bursa or DDF tendon attachment to the third phalanx are in considerable pain and are reluctant to bear weight on the heel region.

Diagnosis If owners find a foreign body in the bottom of the animal's foot, they usually should be instructed to leave the object in the foot unless there is danger of further penetration. A radiograph is taken immediately to determine depth of penetration. Digital pulses are increased, and the foot is usually warm to the touch. Hoof testers are useful to determine the focal point of pain, but often the entire surface of the foot is reactive. Systemic sedation and peripheral anesthesia using an abaxial sesamoid nerve block may be needed to thoroughly examine the penetrated foot. Light paring of the sole and frog areas with a hoof knife may reveal a black spot indicating the penetration site. Often, however, the entry is not discovered because of the elastic nature of the hoof structures and collapsing of the penetration site. Regional IV anesthesia (Bier block) using a tourniquet is the method of choice for producing local anesthesia in cattle. Paring should be performed carefully so the solar corium is not injured with the hoof knife. Because the corium represents the horn-producing epithelial covering of the foot, injuries to it heal the same way as skin injuries. If an entry wound is discovered, the foot is scrubbed and prepared for further diagnostic testing. A sterile flexible probe can be gently inserted into the hole and a radiograph taken to determine its depth and direction. The clinician must take care that inadvertent force or horse movement does not cause the probe to penetrate previously unaffected structures. Alternately, a less invasive and preferred method is to catheterize or place a sterile teat cannula into the hole and inject sterile radiopaque material to determine which structures are involved (Fig. 38-37).

If sepsis of the podotrochlear bursa, DIJ, or digital tendon sheath is suspected, paracentesis and joint fluid cytologic analysis and culture and microbial sensitivity should be performed. Synovial fluid with an abnormal color, viscosity, elevated number of degenerative neutrophils, and high total protein concentration should suggest sepsis. If distal limb swelling is present, arthrocentesis should be delayed until the cellulitis subsides.

A series of radiographs should be taken to include a lateromedial, 60-degree dorsopalmar view of both the navicular bone and the third phalanx, and flexor (tangential) view of the navicular bone. Repeat examination 1 to 2 weeks after the original injury may be necessary because bony lysis takes time to develop and may not be apparent at the initial radiographic examination.

Treatment Broad-spectrum systemic antibiotics, antiinflammatory medications, and tetanus prophylaxis are administered if penetration of deep hoof structures is suspected. Depending on the severity of the lameness, the animal may require an NSAID such as phenylbutazone (4 mg/kg twice daily in horses; 10 mg/kg once daily in cattle) to reduce pain and lameness in the initial stages. Antibiotic therapy should be continued for 2 weeks after resolution of clinical signs of infection in most cases. Preferably, antibiotics are initiated after a culture and microbial sample has been obtained. Establishment of drainage, copious lavage with sterile ionic fluid, and débridement of all necrotic tissue are indicated. Involvement of the podotrochlear bursa warrants use of navicular bursoscopy and

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FIG. 38-37 Radiograph of a foot after injection of contrast dye to determine the path of the penetrating wound. Note dye in the navicular bursa and digital flexor tendon sheath.

aggressive medical therapy consisting of daily lavaging of the bursa under general anesthesia and local treatment using antibiotics instilled within the bursa and regional limb perfusion. Surgical treatment such as the "street nail" procedure, which opens a window through the central frog and DDF tendon in the bottom of the foot to reach the navicular bursa, is a drastic and aggressive method of therapy. This is usually a salvage procedure and reserved only for animals not responding to aggressive medical therapy.

If the DDF tendon is involved (septic tendinitis), débridement and removal of frayed and infected tendon fibers may be performed in the standing, sedated horse using a tourniquet and peripheral anesthesia, or under general anesthesia, depending on horse temperament and owner financial constraints. After débridement, placing the horse in a 4- to 8-degree wedge shoe decreases weight-bearing forces on the DDF tendon and provides some pain relief. The wedge shoe angle is gradually decreased over several months as the DDF tendon begins to heal and strengthen. The bottom of the foot requires protection with a bandage or hospital plate until the surgical site granulates in and cornifies.

Deep penetrating wounds to the sole, especially the solar/white line junction, can result in infectious osteitis of the distal phalanx. The horse usually presents with a chronic recurrent draining tract at the coronary band or solar surface and varying degrees of lameness. Infection of the distal phalanx often results from undetected soft tissue infection or dissecting subsolar abscesses. Septic pedal osteitis may also be a sequela to laminitis secondary to recurrent abscessation and ischemia at the toe region. As the bone infection progresses, blood supply to the area is compromised, and the area of avascular bone separates from the parent bone, forming a sequestrum. Localized third phalanx septic osteitis and sequestrum formation may not become radiographically evident for weeks after the initial penetration injury. Radiology often reveals a radiolucent area within the margins of the third phalanx, with or without sequestrum formation.



FIG. 38-38 Treatment (hospital plate) for medicating an open wound in the bottom of a horse's foot.

Débridement and curettage of all soft and necrotic bone can usually be performed in the standing, sedated animal if its temperament permits. The foot is desensitized with peripheral anesthesia, cleaned with a hoof knife and steel brush, then prepared for aseptic surgery using standard techniques. Hemostasis is achieved by wrapping a roll of Vetrap firmly around the fetlock joint to compress and occlude the palmar digital arteries. Access to the infected bone is made by removing sequential layers of sole using either a motorized Dremel tool or a Galt trephine with a retractable pilot bit.[2] The infected bone is usually discolored and soft and should be curetted to healthy bone margins. The infected bone should be cultured and undergo microbial sensitivity testing. A postoperative radiograph should be taken to ensure complete débridement. After surgery the site is packed with sterile gauze sponges soaked in antiseptic or antimicrobial solutions, and then the foot is bandaged. Disposable diapers and duct tape are inexpensive materials for a waterproof foot bandage. The bandage is changed every 1 or 2 days for the initial few weeks. Application of a bar shoe and hospital plate provides solar protection and decreases the labor and cost of daily bandage changes (Fig. 38-38). The bolts and metal plate are removed so that the surgical site can be cleaned and treated, and then the hospital plate is bolted back in place.

After surgery the horse is confined to a small area until the hole granulates in and cornifies, usually 4 to 6 weeks. If granulation tissue becomes excessive at the surgical site, application of 2% tincture of iodine will hasten healing. If severe infection is present, the site can be packed lightly with antibiotic-impregnated beads for continued antibiotic release at the infected site. Regional limb perfusion with antibiotics is also beneficial in severe cases.

In cattle, simple sole abscesses may heal quite satisfactorily without bandaging. In cows, use of a wooden block on the unaffected claw of the affected foot elevates the affected claw to a non–weight-bearing level and greatly reduces lameness. The block is attached with an epoxy such as Technovit and allowed to wear off over a period of weeks.

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Prognosis Prognosis depends on severity of injury, structures involved, and chronicity of the problem before initiating treatment. Horses with acute penetration wounds that receive immediate and aggressive treatment have a good chance of returning to athletic use. Penetration injuries that have an established infection involving the podotrochlear bursa, digital tendon sheath, or DIJ have a poor prognosis. In one study, only 12 of 38 horses with sepsis of the navicular bursa had a satisfactory outcome.[3] Chances of survival increased if treatment was started within a week of the penetration injury. Osteomyelitis of the navicular bone and DDF tendon rupture are common complications of a septic navicular bursa.

Prognosis for infectious osteitis of the distal phalanx is good if sepsis is not caused by laminitis. In one study, up to 24% of the distal phalanx was removed, and the horse returned to athletic soundness.[4]

Thrush

Definition and Etiology Thrush is a bacterial infection characterized by an accumulation of black, malodorous, necrotic material usually originating within the central or collateral sulci of the frog of the hoof. This degenerative condition may spread to involve deeper structures of the foot, such as the digital cushion, hoof wall, and heel bulb region of the foot, causing inflammation and breakdown of these structures.[5] Many keratolytic organisms may be present, but *F. necrophorum* is often isolated. Thrush is most often caused by poor environmental conditions; animals standing in soiled stalls, deep mud, swampy land, or wet pastures are at risk for developing thrush, especially if the feet are not cleaned daily. Another predisposing factor is poor hoof conformation. Saddlebreds, Tennessee Walkers, and other gaited horses have long feet with naturally deep frog sulci and are at risk of thrush.[6] Horses with sheared heels or acquired frog deformity are also predisposed. Horses shod with full pads may develop thrush secondary to moisture and dirt collection under the pad. Other well-kept, clean horses can develop thrush for no apparent reason.

Clinical Signs and Diagnosis Lameness may or may not be present, and severity can vary. Diagnosis is based on the presence of black, malodorous discharge, most often within the frog sulci. The central frog sulcus is often malformed and very deep. A painful response may occur when the affected sulci are cleaned, because the degenerative process may extend to sensitive structures of the foot. If structural damage has occurred, the heels may move independently of each other, causing pain on manipulation. Horses with mechanical instability of the heels may show caudal heel pain.

Treatment The basis for treatment is removing the predisposing cause of the thrush. The horse should be moved to a clean, dry environment and have the feet cleaned daily. Any necrotic debris and undermined tissue are carefully débrided and cleaned using a hoof knife. Foot bandages may be necessary if the débridement is extensive. Systemic antibiotics may be necessary in severe cases that involve deep or more proximal tissues. Infection is usually managed by topical medication. Several caustic materials have been recommended, including a combination of phenol, tincture of iodine and 10% formalin, Kopertox solution, or methylene blue. Others have recommended soaking the foot in chlorine bleach (1 oz bleach per gallon water). If poor hoof conformation is the cause, proper farrier management should be pursued to correct existing problems. If heel instability is present, a bar shoe may be necessary to stabilize the caudal aspect of the foot. Exercise is important to strengthen the caudal aspect of the foot and will naturally clean the feet. The best treatment for thrush involves prevention by educating the client on proper hoof hygiene.

Prognosis Prognosis is favorable if the cause of thrush can be identified and eliminated and if the condition is treated before extensive hoof damage has occurred.

White Line Disease ("Seedy Toe")

History and Clinical Signs The white line, visible at the sole, is created by the junction of the insensitive laminae of the hoof wall and the horn of the sole. White line disease has historically described the separation of the hoof wall from its laminar attachments. A crack or opening occurs within the white line, allowing a bacterial or fungal infection to invade the stratum medium close to the laminae, causing cavities to develop between the laminae and outer hoof wall. In environmental conditions with too much moisture (continuous wet pastures) or in drought conditions producing excessively dry feet, animals are at risk of developing a crack or opening in the white line. Horses with poor-quality hoof walls that split or crack may develop white line disease. In addition, horses with chronic laminitis having a thickened or stretched white line in the toe region ("seedy toe") are predisposed (Fig. 38-39).

The hoof wall separation is usually a chronic condition beginning weeks or months before presentation. Horses with white line disease often show little or no lameness and therefore are not perceived as an immediate concern by many owners. Hard ground may exacerbate any lameness seen.

Diagnosis Visual examination of the white line, assisted by a probing instrument, will reveal a cavity with separation of outer hoof wall from the laminae. Radiographic evaluation will determine the full extent of hoof wall separation. Often the cavity is either dry or filled with necrotic debris, which may involve a bacterial or fungal infection. The cavity is usually not painful to probing.

Treatment Treatment begins with removal of the separated outer hoof wall using a hoof nipper, hoof knife, and motorized tools. It is important to remove any unattached or loose hoof wall to reveal cracks or crevices that could harbor bacteria. The Dremel tool burr is useful to smooth any cracks in the insensitive laminae that are exposed after hoof wall removal. After thorough débridement, large



FIG. 38-39 Stretched white line secondary to chronic laminitis.

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FIG. 38-40 Hoof with white line disease after the undermined hoof wall has been removed.



FIG. 38-41 Horse's hoof with an infected collateral cartilage.

defects usually exist in the hoof wall and require protection (Fig. 38-40). A heart-bar shoe redistributes weight-bearing forces to the frog and caudal region of the foot and away from damaged and weakened areas. The hoof wall defects prevent normal nailing procedures, and shoe clips can help secure the shoe to the hoof. After hoof wall removal, the exposed laminae may still have an active infectious component. With the heart-bar shoe in place, the owner is instructed to keep the horse in a clean, dry stall and topically treat the exposed laminae with iodine or methiolate daily for 10 days or until the exposed laminae are dry and inactive. At this point, the horse may be a candidate for prosthetic hoof wall repair using a product such as Equilox. The plastic acrylic is trimmed and shaped to the horse's natural hoof wall at the next shoeing. The owner should keep the hoof dry to avoid losing the acrylic patch. The horse may return to normal activity once the prosthetic patch is in place.

Prognosis Prognosis depends on response to treatment and cause of the original white line problem. Horses with poor hoof quality or seedy toe will often have disease recurrence. If the horse responds to original treatment and environmental conditions improve, prognosis is good.

Quittor

Quittor is a term used to describe chronic infection of the medial or lateral collateral cartilage of the distal phalanx in the horse. This condition is characterized by local inflammation and necrosis of the affected cartilage, with subsequent formation of draining tracts proximal to the coronary band. The infection is usually caused by a wound, and the horse often presents with moderate to severe lameness and a history of chronic or recurrent drainage. Obtaining a dorsopalmar radiographic view after injecting contrast dye into the draining tract helps demonstrate the infected collateral cartilage (Fig. 38-41).

Although this condition occasionally responds to medical therapy, the treatment of choice is surgical débridement with the horse under general anesthesia, the foot in full extension, and a tourniquet around the pastern. An elliptical section that includes the draining tract should be incised above the coronary band and discarded. All underlying infected soft tissue and necrotic cartilage should be excised. If the case has not become chronic and only a small amount of cartilage has to be removed, the wound may be packed and partially sutured. The pack can be removed in 24 to 48 hours and the wound flushed twice a day until it has healed. If the condition is chronic with extensive cartilage necrosis or multiple draining tracts, the infectious process usually extends below the level of the coronary band. In this case it is best to trephine a hole in the hoof wall at the lowest point of the infection. This procedure provides better drainage, facilitates débridement of the necrotic cartilage, and allows for complete closure of the surgical incision above the coronary band. The wound should be packed through the trephine hole and treated as an open wound until it heals. In cases with extensive cartilage necrosis, care should be taken to avoid accidental opening of the coffin joint. If débridement is complete, the prognosis for the return to soundness is fair to good.[7]

Fistulous Withers

Sarah M. Reuss

Definition Fistulous withers is a chronic inflammatory condition of the supraspinous bursa and associated tissues in horses, mules, and donkeys. The supraspinous bursa is located dorsal to the dorsal spinous processes of the second through fifth thoracic vertebrae. The normal bursa may extend laterally to the scapular cartilage, and it may be asymmetric. Normal bursal volumes range from 30 to 90 mL.[1]

Clinical Signs Affected horses may show nonspecific signs that include lethargy, fever, and generalized muscle stiffness. These may progress to the more specific signs of pain, heat, and swelling of the withers and cervical area. Over days to weeks, these swellings mature and rupture at one or more locations, releasing serous or mucopurulent drainage. The classically described discharge is yellowish-brown with white, yellow, or red flakes ("rice bodies").[2] Fistulous tracts may extend to the dorsal spinous processed of the vertebrae, as well as to the scapula, ribs, and occasionally the thoracic cavity. Lesions and drainage may wax and wane.

Etiology/Pathophysiology There are two forms of fistulous withers: idiopathic (or typical) and traumatic (or atypical). The more common idiopathic form results from the spread of inflammation and infection of the supraspinous bursa to surrounding structures like the nuchal ligament and/or dorsal spinous processes. Organisms reported to be the primary cause of fistulous withers include *Brucella abortus, Actinomyces bovis,* and *Onchocerca cervicalis*. *B. abortus* has a predilection for synovial structures and is often associated with septic supraspinous bursitis in addition to septic atlantal bursitis ("poll evil"). In 1937, *B. abortus* was isolated from 80% of fistulous withers cases; 92% of affected horses had contact with cattle, and 65% were from farms with *Brucella*-positive cattle.[2] Geographic variability is evident. In New York, where the prevalence of *B. abortus* infection in cattle is low, *B. abortus* is rarely isolated from equine cases of fistulous withers. In 1988, the prevalence of *B. abortus* in horses presented to the New York State College of Veterinary Medicine had

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apparently decreased, with only 2 of 14 horses (14%) having positive titers.[3] However, in Texas, where seropositive cattle are still prevalent, 9 of 28 (37.5%) horses with fistulous withers were seropositive for *B. abortus,* and these horses were more likely to be pastured with seropositive cattle.[4] Researchers have also experimentally produced fistulous withers via injection of *B. abortus* and *A. bovis* into the supraspinous bursa.[5] *O. cervicalis* has also been proposed as an etiology for fistulous withers, especially in Australia. This parasite migrates through the nuchal ligament and causes inflammation that can extend to the supraspinous bursa. Fibrous and calcified tracts develop around dead and viable parasites, causing necrosis and degeneration of the nuchal ligament.[6] *Streptomyces* spp. have also been incriminated as the etiology of fistulous withers in donkeys.[7]

The traumatic form of fistulous withers is preceded by an open wound or blunt trauma to the withers and then secondary infection. Infection may result from external contamination or from hematogenous spread to devitalized tissue. Secondary contamination of open wounds with *Streptococcus equi* subsp. *zooepidemicus*[3] or environmental microorganisms is reported.

Diagnosis A careful history that includes duration and severity of clinical signs and response to previous treatment must be obtained. Physical examination with careful palpation over the withers may reveal pain, swelling, or draining tracts. CBC may show leukocytosis due to neutrophilia, as well as hyperfibrinogenemia, indicating chronic inflammation.

If the swelling is encapsulated and not draining, needle aspiration should be performed to obtain a sample for culture and sensitivity. Once tracts are open and draining, secondary bacterial contamination will make the validity of cultures questionable. Negative cultures can also be misleading because *B. abortus* is difficult to grow in culture and may be overgrown by other bacteria. Biopsy of inflamed tissue may also be obtained for culture and histology. Blood cultures may also be diagnostic in febrile animals.

Because of public health implications, serologic testing for antibodies against *B. abortus* should be performed in all animals with fistulous withers. The plate agglutination test is more sensitive and specific than the card test. *Brucella* titers are considered negative when they are less than 1:50. Ideally paired titers should be performed, with any rise in titers 2 weeks apart indicative of current infection.[8] Chronic infections may not show a paired titer increase, so a single high titer with compatible clinical signs should be considered diagnostic. Animals should be isolated while awaiting test results, and public health officials should be contacted if *Brucella* is suspected.

Radiographs should be obtained to determine the extent of the lesions, presence of osteomyelitis of the dorsal spinous processes, and/or presence of a foreign body. There may also be swelling or granular opacity of the soft tissue in the withers region.[3] Horses with positive *B. abortus* titers are more likely to have radiographic evidence of osteomyelitis of the dorsal spinous processes than seronegative horses.[4] A positive-contrast fistulogram may help determine the extent of any draining tracts. Ultrasonography can also help delineate draining tracts or foreign bodies.

Treatment Medical treatment may be attempted but is often unsuccessful alone. Antimicrobial selection should be guided by culture and sensitivity results. In the absence of a culture, systemic broad-spectrum antimicrobials may be used and should be combined with lavage of the draining tracts. Systemic antiinflammatories are also indicated to control pain.

Brucella vaccination with the S19 strain has been reported in *Brucella*-confirmed cases as an effective off-label treatment in horses. The vaccination regimens described varied from single-dose SC injection to a series of three SC injections 10 days apart. Success rates of 70% have been reported in horses treated with strain 19 vaccine.[2] However, SC injection reportedly causes severe local and systemic reactions, including fever, depression, and local abscessation.[8] IV administration of strain 19 vaccine has also been reported, but it resulted in death in 3 of 4 horses.[4] At this time, there are no approved vaccinations for use in horses, and the RB51 vaccine has not been used in equids. The apparent decline in frequency of *Brucella* infection in fistulous withers now makes vaccination of questionable value.

Medical management alone is rarely effective and usually has to be combined with aggressive surgical débridement. Reportedly, 80% of traumatic fistulous withers treated conservatively will have recurrent lesions.[9] Standing drainage and débridement has been performed, but general anesthesia and aggressive débridement is the preferred treatment.[3] Ostectomy and curettage of the dorsal spinous processes may be necessary. Primary closure is difficult to achieve but will provide a better cosmetic result and quicker healing time. Wounds left open to heal by second intention may take months to heal.[3]

Prevention and Control *B. abortus* infection, if present, carries great public health implications. Horse owners and veterinary staff must be notified of the possible exposure and take appropriate precautions. Brucellosis in humans may cause acute fever with pneumonia, spondylitis, orchitis, or pyelonephritis, and chronic brucellosis causes a transient fever.[1]

Parasite control is an important aspect of prevention of fistulous withers. Horses should be kept separate from *Brucella*-positive cattle. Proper saddle and harness fit will also decrease the incidence of traumatic fistulous withers.

Flexural Limb Deformities

A. Berkley Chesen

Definition Flexural limb deformities are defined as hyperflexion or hyperextension of a limb. Flexural deformities are described by the joint involved and occur in the sagittal plane, typically the DIJ, metacarpophalangeal/metatarsophalangeal joint, carpus, and rarely the tarsus. Although commonly referred to as "contracted tendons," the tendons themselves are not truly contracted but functionally short relative to the adjacent bone. Flexural limb deformities can be classified as either congenital or acquired and are very common in horses and cattle. Small ruminants and camelids are much less commonly affected.

Pathogenesis Congenital flexural deformities (present at birth) are likely due to a multitude of factors. Although intrauterine positioning has been suggested, it is probably an uncommon cause of flexural limb deformities. Disease and teratogenic exposures of pregnant mares are more likely causes of congenital flexural limb deformities. Evidence behind an absolute inciting cause is lacking, but the following have been implicated in contributing to flexural limb deformities: transient glycogen branching enzyme deficiency in Quarter Horse foals, ingestion of locoweed and hybrid Sudan grass, equine goiter, defective cross-linking of collagen and elastin formation from lathyrism, neuromuscular disorders, and viruses.[1-5] Foals with congenital flexural deformities commonly have other anatomic abnormalities like spinal deformities, which may result in dystocia.

Acquired flexural deformities are seen typically from 4 weeks to 4 months of age and in yearlings to 2-year-olds. These deformities have been implicated as part of the developmental orthopedic disease complex. Two general theories explain how acquired flexural deformities occur. The first is that the tendon unit is unable to passively elongate relative to the bone.[6] In the case of the DIJ, the rigid DDF tendon and its accessory ligament causes a palmar rotation of the foot (clubbed foot) (Fig. 38-42). Flexural deformities in the metacarpophalangeal joint often occur during rapid growth in the distal radius, leading to a functional shortening superficial digital flexor (SDF) tendon unit. The second theory is that longitudinal bone growth cannot create a functional shortening of tendons and that increased tension within the tendon induces pain, leading to the deformity.[7]

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FIG. 38-42 Flexural deformity of the distal interphalangeal joint (clubbed foot).



FIG. 38-43 Flexural deformity of the metatarsophalangeal joint.

Acquired deformities often have a very acute onset (24 hours), adding validity to the latter theory. Pain may initiate the deformity, but this can become a permanent condition if not addressed promptly, and contracture can occur. Contracture results from fibrodesis of the joint capsule and periarticular structures.[6]

Diagnosis

CONGENITAL DEFORMITIES. Digital hyperextension deformities in neonates are due to lack of tension in the flexor muscles. These deformities typically correct without intervention after a few weeks. In severe cases, the palmar or plantar surfaces of the foal's pastern and fetlock area may become ulcerated from contact with the ground if not protected.

Contractural deformities may involve one or a combination of the SDF tendon, DDF tendon, or suspensory ligament and most commonly affect the carpus and metacarpophalangeal/metatarsophalangeal joint (Fig. 38-43).[8] Flexural deformities of the DIJ and the tarsus occur less frequently. In some pony breeds and Miniature Horses, lateral luxation of the patella results in the stifle showing a flexural deformity. This is usually due to a hypoplastic trochlear groove. Depending on the severity of the deformity, if the metacarpophalangeal joint is affected, the foal may or may not be able to stand.[6] Although not truly a flexural deformity, rupture of the common digital extensor tendon results in a similar appearance. This can result secondary to flexural deformities. These foals have a characteristic swelling on the dorsolateral aspect of the carpus and often bow at the carpus owing to the lack of support over its lateral aspect.[2,9] More importantly, foals with ruptured common digital extensor tendons should be checked for incomplete ossification of cuboidal bones; these conditions often occur together.[6]

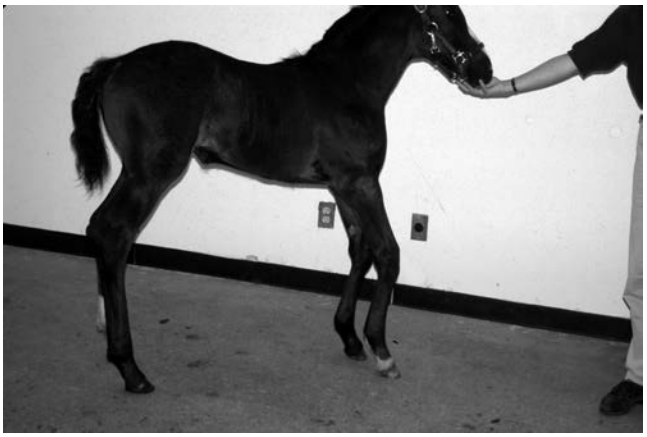


FIG. 38-44 Bilateral mild carpal flexural deformity.

ACQUIRED DEFORMITIES. The most common acquired flexural deformity involves the DIJ and typically occurs within the first 4 months of life. The affected limb will have a more vertical hoof wall angle and a shorter toe than the unaffected limb, but the condition is often bilateral. The heel will get longer on the affected limb, the metacarpophalangeal joint will concurrently begin to hyperextend, and the toe will undergo more wear, potentially causing issues with the white line. Two stages have been described for flexural deformities of the DIJ: *stage I* is defined as an angle of less than 90 degrees between the dorsal hoof wall and the sole; *stage II* is defined as a dorsal hoof wall that exceeds vertical.[10]

Early detection of flexural deformity of the metacarpophalangeal joint is characterized by a straight fetlock angle, or upright conformation. More severe deformity of this joint is evident by buckling at the fetlock. By placing pressure in a dorsopalmar direction on the fetlock, the flexor tendons are stretched, allowing the practitioner to determine which structure is tightest, which is important for selecting an appropriate treatment.[6] It is also important to palpate the limb while the animal is not bearing weight to detect any adhesions.

Carpal flexural deformities tend to occur within the first 6 months of life. These foals tend to be fast-growing, heavier foals (Fig. 38-44). Although not as common, flexural deformities of the PIP also occur; they are usually bilateral and affect the hindlimbs.[6] The exact mechanism is unknown, but it is thought that as the musculotendinous unit of the DDF complex shortens, the SDF tendon becomes more lax.[11] This can lead to a dorsal subluxation of the joint. Often a clicking sound is appreciated when the foal walks. This condition is most often seen in weanlings with a high growth rate.[6]

Flexural deformities also occur after foals or horses are non–weight bearing for a period of time. These deformities can be permanent if the joint undergoes contracture or fibrodesis (fixed without osseous ankylosis).[6]

Treatment

CONGENITAL DEFORMITIES. Hyperextension deformities require exercise to hasten recovery, but excessive exercise is contraindicated because it leads to fatigue and possible injury. Treatments include swimming, corrective shoeing, and light bandaging when indicated. Swimming allows muscle tone to increase without bearing weight on the limbs. If the foal's toe lifts off the ground when weight bearing, glue-on shoes with a heel extension may be indicated. It is important that glue-on shoes not be left on a growing foal for an extended period, because they may prevent the foot from expanding normally; changing them every 10 days is indicated. Bandaging is only necessary to prevent ulcerations of the skin in cases where the palmar/plantar surface of the pastern or fetlock is in contact with the ground; bandages should not be supportive of the structures. Excessive bandaging and support will only cause more laxity and should be avoided.

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Treatment for congenital flexural deformities should include pain management by judicious use of NSAIDs (e.g., phenylbutazone, 2.2 mg/kg daily, or flunixin meglumine, 1.1 mg/kg daily). Use of gastroprotectants such as omeprazole (4 mg/kg PO daily) is strongly suggested to help avoid the ulceragenic effects of NSAIDs.

Oxytetracycline at a dose of 44 mg/kg diluted in physiologic saline given slowly IV has been used for many years in foals with flexural deformities.[12] Renal function of the foal should be taken into consideration prior to administration of oxytetracycline. There are many proposed mechanisms for how oxytetracycline works to achieve a decrease in the angle of the metacarpophalangeal joint. One mechanism proposes the chelation of calcium, resulting in muscle contraction.[12] Oxytetracycline has been shown to be a neuromuscular blocking agent, but this mechanism does not explain why other muscle groups are unaffected.[12] An in vitro study showed that oxytetracycline also works through matrix metalloproteinase (MMP)1 mRNA expression to inhibit tractional organization of collagen fibrils by myofibroblasts; this interaction may cause relaxation of the musculotendinous unit.[13] Regardless of the mechanism of action, foals treated with oxytetracycline should also undergo forced exercise to make the improvement permanent. Without exercise, the angle of the metacarpophalangeal joint tends to return to its previous value within 96 hours.[14]

Toe extensions benefit the foal in two ways: they help protect the toe from being overworn, and they lengthen the breakover of the foot, adding strain to the flexor tendons, potentially helping stretch them. Toe extensions may be made using acrylic hoof products or glue-on shoes with built-in extensions. In severe cases, the dorsal hoof wall should be incorporated into the shoe to prevent excessive strain at the toe and separation of the white line. Shoes and extensions should be removed within 2 weeks because they can prevent the hoof from growing and expanding naturally in a young foal; typically, 2 weeks is enough to achieve correction. For foals with deformity of the DIJ, frequent rasping of the heels will help stretch the DDF tendon.

Splints and casts have been used to treat flexural deformities by giving support to the limb, thereby allowing the muscle-tendon unit to relax. When using splints, it is vital to use plenty of padding on the limb and change the padding every time the splint is changed to ensure pressure sores are not developing. Pressure sores can be very serious and even life threatening. Splints are made from a variety of materials, but the most common is polyvinyl chloride (PVC) pipe that has been cut an appropriate length and width; commercially made splints are also available. Splints are applied by placing the splint over the padding on the palmar or plantar surface of the limb. If the flexural deformity involves the DIJ, the splint should touch the ground. If the deformity is in the carpal region, the splint should end at the fetlock. Splints are left in place from several hours to 2 or 3 days, depending on the individual patient's condition.[6,8] One major advantage of splints over casts is that they may be removed every few hours if desired. Casts used for the lower limb are typically half-limb casts that incorporate the foot. The exception is the carpal region, where a tube cast ending at the fetlock is more appropriate. Casts should never be left in place longer than 2 weeks at a time in rapidly growing foals. Cast sores are a very serious complication and a legitimate disadvantage to using them.

A combination of conservative treatments should be considered when treating foals with flexural deformities. If nonsurgical management does not correct the problem, surgical intervention may be necessary, but foals with severe congenital contractural deformities have a poor prognosis. Surgery is more often attempted for foals with carpal contracture. Other congenital contractural deformities usually respond to nonsurgical treatments. Surgical correction for contractural deformities in the carpal region involves transection of the tendons of the flexor carpi ulnaris and ulnaris lateralis, as well as transection of the palmar carpal fascia.[6,8] The prognosis for mild to moderate congenital flexural deformities is good for an athletic future if the foal improves over the first 2 weeks and is able to stand and nurse.[8] Flexural deformities that can be manually straightened have a better prognosis than those that cannot.

Foals with ruptured common digital extensor tendons are best treated nonsurgically. Affected foals should be confined to stall rest, and a well-padded splint should be applied.[9] The splint will provide support to the limb and help protect immature cuboidal bones, which often accompany this condition.[6]

ACQUIRED DEFORMITIES. Conservative management for acquired flexural deformities is very similar to that for congenital flexural deformities. Other conservative therapies include dietary restrictions, including early weaning. Surgical management is selected for those cases unresponsive to nonsurgical treatments.

For flexural deformities of the DIJ, desmotomy of the accessory ligament of the DDF tendon is indicated. This surgery has an excellent prognosis for full athletic potential for stage I horses. For more severe flexural deformities of this joint (stage II) a tenotomy of the DDF tendon may be necessary.[15] This procedure is not performed to promote an athletic career. It is acceptable for pasture soundness, breeding animals, and for some, light riding. Gradual rasping of the heels should be combined with any treatment for flexural deformities of the DIP joint.

Acquired flexural deformities of the metacarpophalangeal joint are treated nonsurgically with a combination of NSAIDs, corrective shoeing (raising the heel with or without using a vertical bar shoe with rubber dorsal tubing), and splints. Physical therapy has been used to help stretch the tendons by having the horse hop on one leg while the other is held up in a flexed position, moving in a lateral direction toward the down limb.[6] If surgical correction is needed, it is important to first determine which structure is creating the tension. Most commonly, the SDF tendon is involved, but the DDF tendon and even the suspensory ligament may also be involved. For treatment of contracture of the SDF tendon, desmotomy of the accessory ligament of the SDF tendon is performed. If the DDF tendon is the most taut, desmotomy of the accessory ligament of the DDF tendon is completed. Both accessory ligaments may be cut when indicated. In very severe cases, the suspensory branches may be transected, but this procedure is done for salvage because it usually leads to subluxation of the PIP.[6]

Carpal flexural deformities are treated with splints and controlled exercise. Early weaning should be considered in these foals. If surgery is necessary, a tenotomy of the flexor carpi ulnaris and ulnaris lateralis in addition to splints may yield good results.

Flexural deformities of the PIP are not as common but can be very serious to the future athletic potential of the horse. Over time, the soft tissues around the joint will fibrose, and the PIP may undergo DJD. At this stage, a pastern arthrodesis may be necessary to achieve a pain-free and potentially sound limb. Desmotomy of the accessory ligament of the DDF tendon, as well as the tendon of the medial head of the DDF tendon (level of the chestnut), may benefit affected horses early in the disease process.[6,11]

Tendinitis

Elizabeth J. Davidson

Definition and Etiology Tendinitis is one of the more common musculoskeletal injuries in athletic horses. Of the two flexor tendons, the SDF tendon is more commonly injured than the DDF tendon. SDF tendon injuries occur in the forelimb far more frequently than the hindlimb, and most injuries are in the midmetacarpal region. The prevalence of SDF tendinitis in Thoroughbred racehorses ranges from 7% to 43%.[1] SDF tendon injury also occurs in Standardbred racehorses, upper-level event horses, and is less commonly diagnosed in other performance horses. DDF tendinitis is typically diagnosed in older (aged 9 to 10 years) English sport horses, and injury to the distal portion of the DDF tendon is a major contributor to lameness in horses with foot pain.[2] DDF tendon injury

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also occurs in the fetlock or pastern regions within the digital flexor tendon sheath (DFTS) and infrequently in the metacarpal/metatarsal region.[3,4] Desmitis of the accessory ligament of the DDF tendon[5] and the accessory ligament of the SDF tendon[6] are unusual injuries in performance horses.

The function of a tendon is to transfer activity from its associated muscle to its bony attachments on the opposite side of a joint. This allows for joint movement and locomotion. During normal weight bearing, the palmar/plantar situated digital flexor tendons act to support the fetlock joint. During locomotion, the elastic properties of tendons give them the ability to act like a spring, storing and releasing energy during movement. To withstand high tensile forces during exercise, tendons contain a high proportion of type I collagen, and its fibers are longitudinally aligned. When loaded, these fibers deform elastically by stretching. Substantial elongation, up to 20% increase in length, has been reported.[7] Tendon injury occurs when fibers are stretched beyond physiologic limits, which can be due to cumulative fatigue failure or a single sudden overloading event. In Thoroughbreds, normal SDF tendons have strains reaching up to 16% when galloping,[7] suggesting that at maximal exercise the SDF operates close to its physiologic limit, which may explain the high incidence of injury. Tendon injury also appears to be related to age and exercise matrix deterioration. Other factors like hard ground or a rider's weight can also contribute to tendon injury by increasing the peak load of the SDF tendon. Landing from a jump, for example, increases the peak forces in the SDF tendon[8] and accounts for the higher incidence of SDF tendinitis in Grand Prix jumpers and event horses than in those competing at lower levels.

Response to tendon injury is similar to other tissue healing and includes inflammation, repair, and remodeling. During the acute inflammatory phase, hemorrhage and edema occur, and the degree of the response is determined by severity of the injury. Angiogenesis quickly follows, and recruited fibroblasts produce new type III collagen. A fibrinous scar of weak, haphazardly arranged collagen fibrils is formed. At this stage, the tendon is prone to reinjury. Scar tissue remodels over several months, converting type III collagen to type I collagen. Controlled loading of the tendon promotes this conversion and alignment of the collagen fibrils in the direction of force (longitudinally). In a severely injured tendon the entire process can take 12 or more months. The healed but scarred tendon is stiffer than its original state; reinjury is common.

Clinical Signs The classic appearance of metacarpal/metatarsal SDF tendinitis is a convex or bowed profile of the tendon when viewed from the lateral aspect. In acute injury, swelling and heat of the tendon and peritendinous tissues can be noted but may be mild in the earliest stage of injury. A painful response to direct digital palpation is often appreciated and is best performed by holding the leg and palpating the tendon between thumb and forefinger. Unless the injury is severe, most horses with SDF tendinitis are not lame.

Horses with DDF tendon injuries within the DFTS are moderately lame and more lame after distal limb flexion.[3,4] Most horses have DFTS distention and thickening, making accurate palpation of the DDF tendon difficult. Injuries are usually unilateral and occur more commonly in the hindlimbs.[3,4] Horses with DDF tendon injuries within the hoof capsule have unilateral or bilateral lameness without any palpable abnormalities.[2] Horses with desmitis of the accessory ligament of the DDF tendon have obvious swelling and are acutely moderately to severely lame.[5] Thickening and effusion in the carpal canal may be noted in horses with desmitis of the accessory ligament of the SDF tendon.

Diagnosis Ultrasonography is the technique of choice to confirm the diagnosis and assess the severity of the injury. The entire palmar/plantar area of the metacarpus/metatarsus should be examined in transverse and longitudinal planes. The commonly measured variables include cross-sectional area, echogenicity, and fiber alignment. The severity of the injury is determined by the length of the lesion, cross-sectional area of the tendon, cross-sectional area of the lesion, lesion echogenicity, and fiber alignment of the lesion.[9,10] The severity rating score has been correlated with successful outcome. The most common type of SDF tendon injury is a central core lesion, which appears as an anechoic lesion.[9]

Diagnostic analgesia may assist the clinician in localizing the tendon injury if clinical signs are subtle or absent. This is particularly true for DDF tendon injury within the hoof capsule. Pain from DDF tendon injury in the distal metacarpal/metatarsal region usually improves after intrathecal analgesia of the DFTS.[4] Antebrachial or proximal metacarpal analgesia alleviates pain from the accessory ligament of the SDF tendon.[6]

MRI, either with the horse under general anesthesia or in a standing horse, offers the best method of diagnosing DDF tendinitis within the hoof capsule.[2,11,12] Injury types include core lesions, sagittal tears, and fibrillation along the dorsal border; most lesions occur at or near the navicular bone.[2] Transcuneal (through the sole) ultrasonography[13] has been reported but is not easy. Successful imaging requires meticulous foot preparation and clinician expertise.

Treatment Proper treatment of tendinitis includes assessment of the injury using ultrasonography, control of the acute inflammatory episode, controlled return to function, and adjunct medical and/or surgical therapy. In acute injury, a combination of systemic NSAIDs (e.g., phenylbutazone, flunixin meglumine) and topical therapy (e.g., cold water hydrotherapy, poultice, distal limb bandage) are recommended. DMSO and antiphlogistically impregnated gauze bandages may also be beneficial. Box stall rest is essential during the acute phase of injury.

A variety of intratendinous and peritendinous injections have been advocated. Intralesional corticosteroids dramatically decrease the swelling and pain but cannot be recommended due to delayed tendon healing and the risk of continued injury and catastrophic injury in horses that remain in training. Historically, intralesional β-aminoproprionitrile fumarate (BAPTEN), a plant-derived toxin that temporarily blocks collagen cross-linking, improved tendon healing and postinjury performance, but there is currently no commercially available source of BAPTEN, and its use has largely ceased in North America. For metacarpal/metatarsal DDF tendon injuries, intrathecal injections of sodium hyaluronon into the DFTS are beneficial.[14] Intralesional sodium hyaluronon for SDF tendinitis has been advantageous,[15] but other reports failed to document any significant improvement.[16,17] IM polysulfated GAG has a positive effect on tendon healing in a collagenase-induced model,[18] but no difference in return to racing or recurrence of SDF tendinitis has been demonstrated with intralesional and/or IM polysulfated GAG.[16] The therapeutic role of regenerative medicine (e.g., stem cells derived from fat or bone marrow and platelet-rich plasma) in equine tendinitis is not fully understood. Marketing and availability of such products are ahead of evidence-based research, and long-term clinical efficacy has yet to be determined, but early clinical results are encouraging.

Surgical treatments include tendon splitting,[19] desmotomy of the superior check ligament,[20-23] and desmotomy of the palmar/plantar annular ligament.[23] Tendon splitting is believed to enhance revascularization and has a tendency to improve tendon repair. It is used in horses with core lesions to decompress areas of hemorrhage. Disadvantages of tendon splitting include the risk of damaging normal tendon fibers, so this procedure can no longer be recommended. Superior check desmotomy may improve the likelihood that horses return to racing and is clearly beneficial in Standardbred racehorses.[20,21] In Thoroughbred racehorses, postoperative success was initially promising, but no difference between horses treated conservatively and horses treated with desmotomy has been reported.[22] In addition, desmotomy may predispose horses to desmitis of the suspensory ligament.[21,22] Annular desmotomy has been successfully performed in horses with signs of annular ligament constriction and is usually combined with superior check desmotomy.[23] Immediate decompression and improved gliding function are presumed benefits. Complications of annular ligament desmotomy include DFTS sepsis and subsequent tendon sheath adhesions.

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Other therapies for SDF tendinitis include therapeutic ultrasound, low-power laser treatment, and extracorporeal shockwave therapy. Counterirritation (internal or external blisters) and pin firing in combination with controlled exercise or turnout in a large pasture are time-honored treatments, but their effects on tendon healing have been questionable. These practices can no longer be recommended.

Controlled exercise in combination with the treatments described guides the repair process in hopes of producing a functional tendon or tendon substitute. If exercise is excessive, fibrous tissue is produced rather than remodeled. If no stress is applied, the tendon is more adapted to pasture exercise than to performance. Therefore, a controlled incremental exercise program is advocated. The program should be flexible and adjusted based on the severity of injury and the quality of healing. Typically, stall rest coupled with gradually increasing amounts of hand walking and trotting are recommended. Horses are monitored by regular clinical and ultrasonographic assessment until they have returned to their previous athletic function or have failed to do so. As the tendon heals, its echogenicity increases, and short linear echoes are detected. With continued healing, longer linear echoes and improved fiber alignment appear. Decrease in cross-sectional area is good indication that the tendon is healing and remodeling. Ideally, complete repair will occur, and the tendon will no longer have a discretely visible area of injury because it has filled in with tissue that is isoechoic with normal tendon, and fiber alignment is parallel to normal.

Successful treatment of DDF tendon injuries within the foot remains a challenge. Long-term follow-up indicates a high rate of recurrent lameness despite prolonged periods of stall rest and corrective shoeing.[2] Other treatments include surgical débridement via navicular bursoscopy,[12] CT-guided intralesional injections,[24] and navicular bursa injection with corticosteroids and hyaluronan.[11]

Prognosis Prognosis for horses with SDF tendinitis depends on lesion severity and the type of athletic work performed. In Thoroughbred racehorses, only 60% will return to successfully race, and reinjury rates are high.[25] Standardbreds and English sport horses have a better prognosis. Most horses treated with superior check desmotomy returned to racing, but recurrence and suspensory desmitis may develop.[21,22] Horses with DDF tendon injuries remain problematic; prognosis is fair to poor.[2-4,11,12,24] Prognosis for horses with desmitis of the accessory ligament of the DDF tendon is good.[5] Prognosis for horses with uncomplicated desmitis of the accessory ligament of the SDF is fair, but horses with concurrent injuries are likely to suffer recurrent lameness.[6]

Suspensory Ligament Desmitis

Elizabeth J. Davidson

Definition and Etiology The suspensory ligament (SL), also known as the *interosseous muscle,* is a strong, flat, tendinous band that contains a variable amount of muscle fibers.[1,2] The SL originates from the palmar carpal ligament and the proximal palmar aspect of the third metacarpus (MCIII) and in the hindlimb from the proximal plantar third metatarsus (MTIII). Coursing distally, it descends between the second and fourth metacarpal/metatarsal bones and divides into the medial and lateral branches before inserting on the abaxial aspect of the proximal sesamoid bones. The suspensory apparatus continues distally as the straight, oblique, cruciate, and short distal sesamoidean ligaments, which originate from the base of the sesamoid bones and insert in the palmar pastern. Similar to tendons, the SL acts like a spring, storing and releasing energy during locomotion. Its main function is to prevent hyperextension of the fetlock joint.[1,2] Its branches also help stabilize the rotational forces on the joint.[2] Injury to the SL occurs when it is overloaded with stress (overstretched) and its structural integrity is compromised. Like tendons, the repair process is characterized by inflammation (desmitis) and fibroplasia. Healing occurs over many months, and repaired tissue is subject to reinjury. SL desmitis is a common injury in all breeds of performance horses. Both forelimb and hindlimb injuries occur, and bilateral desmitis is not uncommon. Desmitis of the SL can be divided into three regions of interest: the proximal (origin) portion, the body, and the branches. Proximal SL desmitis is likely due to hyperextension of the carpus/tarsus in conjunction with severe overextension of the fetlock joint.[1] Straight hock conformation, hyperextension of the fetlock joint, and a long toe/low heel conformation may be predisposing factors in the hindlimbs.[2] Jumping and/or working horses in deep soft footing may also increase risk of injury.[1,2] Avulsion fracture, bone sclerosis, and/or enthesophyte formation in the proximal palmar/plantar MCIII/MTIII can also occur. Proximal SL desmitis occurs most frequently in sport horses, racehorses, and western performance horses.[1,2] Injury to the body of the SL is less common and occurs predominantly in racehorses, specifically Standardbreds.[1,2] Desmitis of the SL branches is most common in Standardbreds and jumping horses.[1] In the SL branches, injury is frequently associated with fetlock lameness, which suggests that the twisting motion of the fetlock predisposes horses to injury.

Catastrophic traumatic disruption of the suspensory apparatus occurs almost exclusively in the forelimbs of Thoroughbred racehorses and is the most common cause of breakdown injuries.[3] Fatigue and high speed are components of this career-ending injury. Degenerative suspensory ligament desmitis (DSLD) is a disorder characterized by progressive degeneration and enlargement of the SL, resulting in excessive fetlock hyperextension (dropping). Affected horses are generally dropped in both hind fetlocks. The condition occurs sporadically in many breeds, usually older horses and broodmares.[1,2] Peruvian Paso[4] and Andalusion horses may be at risk and often are affected in all four limbs. The pathogenesis is unknown.

Clinical Signs Horses with proximal SL desmitis frequently have no localizing clinical signs. Heat, swelling, and edema are transient or absent, and lameness is variable. Horses with bilateral injury, especially in the hindlimbs, may have subtle gait abnormalities that are only apparent when ridden or at speed. Lack of impulsion, resistant behavior, and loss of action are frequent complaints. In horses with desmitis of the body and branches of the SL, heat, pain, ligamentous enlargement, and lameness are common. Associated fetlock effusion and concurrent distal splint bone fractures may also be noted. Acute severe traumatic disruption of the suspensory apparatus results in obvious swelling, grade 4 to 5 lameness, and a hyperextended fetlock. Affected horses require first-aid treatment by application of a splint for weight-bearing stability. DSLD is characterized by bilateral chronic lameness, painful and enlarged SLs, dropped fetlocks, prolonged periods of recumbency, and reluctance to move.[1,2,4]

Diagnosis Perineural analgesic techniques help localize the site of lameness pain to the SL. For proximal SL desmitis, analgesia of the lateral palmar nerve[1,2,5] or lateral plantar nerve just distal to the tarsus[1,2,6] will alleviate lameness in the forelimb or hindlimb, respectively. Desmitis of the SL body and branches is localized using low palmar/plantar analgesia.

Ultrasonography is the imaging modality of choice. Lesion severity is assessed by obtaining cross-sectional and longitudinal views of the ligament and cross-sectional area measurements. Ultrasonographic changes include cross-sectional area enlargement, focal or diffuse areas of hypogenicity, core lesions, loss of normal fiber pattern, and periligamentous thickening. Mild injuries to the SL may be difficult to identify because of the wide variation in its normal ultrasonographic appearance. This is especially true in the proximal SL, since its origin is more heterogeneous than other tendons and ligaments owing to variable amounts of muscle tissue. Comparison between the affected and nonaffected limb in the same horse are recommended because of individual variations and the large variation between breeds.[1,2]

Radiographic examination should be performed to identify concurrent bony lesions. Subchondral sclerosis, avulsion fracture, and

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enthesophyte formation have been identified in the proximal palmar/plantar MCIII/MTII regions of horses with proximal SL desmitis.[1,2,7,8] Axial exostosis along the second and fourth metacarpal/metatarsal bones[9] or fractures can contribute to SL body desmitis. Sesamoiditis and sesamoid fractures may be noted in horses with desmitis of the SL branches. In acute traumatic disruption of the suspensory apparatus, comminuted fractures of both sesamoid bones is common.

Nuclear scintigraphic findings are normal in the majority of horses with SL desmitis.[1,2,10] Increased radiopharmaceutical uptake associated with the proximal palmar/plantar MCIII/MTIII can be identified in horses with avulsion fractures and other stress-related bone injuries seen in complex SL desmitis.[7,8] MRI is not necessary but should be considered if no ultrasonographic abnormality is identified. MRI has identified fibrous adhesions between the SL and the small splint bones.[9]

Treatment Treatment of acute SL desmitis is aimed at reducing inflammation with systemic NSAIDs, local cold hydrotherapy, limb bandages, and controlled exercise. Initial clinical signs dissipate quickly even when there is significant SL fiber disruption, so it is strongly recommended to assess the ligament using ultrasonography. In uncomplicated desmitis, a controlled graded exercise program is recommended. The duration of rehabilitation will depend on the extent and severity of the desmitis. Fractures of the small metacarpal/metatarsal bones or sesamoid bones should be removed prior to rehabilitation. Horses are confined to a stall and hand walked daily. Ligamentous healing should be monitored every 60 days using ultrasonography. Ideally there should be a progressive reduction in cross-sectional area, improved echogenicity, and fiber alignment. Gradual increase in exercise can be prescribed depending on healing. The reparative process is slow, and return to competition or racing may not be possible for 12 months.

Damaged SLs have been injected with a wide assortment of corticosteroids, iodine compounds, sodium hyaluronate, and polysulfated GAGs in an effort to reduce inflammation and promote a more rapid return to function. Pin firing, blistering, and cryotherapy with liquid nitrogen have also been used. Although these therapies may treat the initial inflammation, they do not restore normal fiber architecture and can put the SL at increased risk from overuse of the horse, based solely on reduction of clinical signs. Extracorporeal shockwave therapy[1,2,11] and surgical splitting of the branches[1,2] may be beneficial. The effects of intralesional platelet-rich plasma[12] and autologous stem cells[13] are currently under investigation, and clinical results are promising. These regenerative medicine therapies could be the recommended treatment of the future, but their long-term effects and clinical efficacy have yet to be proven.

Successful treatment of proximal hindlimb SL desmitis is particularly challenging. Plantar metatarsal neurectomy,[1,14] desmotomy,[15] and fasciotomy[13-15] may be beneficial in these horses. Fasciotomy surgery allows decompression of the compartment-like syndrome that occurs when the damaged proximal SL becomes edematous and swells within the surrounding retinaculum. The accessory plantar nerve within the damaged SL becomes inflamed and damaged, so a neurectomy of this nerve is performed at the same time as the fasciotomy surgery.

For horses with acute traumatic suspensory desmitis, it is crucial to place the affected limb in a protective splint that aligns the metacarpus with the phalanges in a straight column to prevent fetlock bending. Surgical management involves fetlock arthrodesis using dorsal plating. Treatment for horses with DSLD is palliative. Restricted activity and extended-heel or large egg-bar shoes may improve comfort. Humane euthanasia is recommended for affected horses with deterioration of clinical signs despite treatment.

Prognosis Prognosis of SL desmitis depends on the location and severity of the injury. Uncomplicated cases with minimal disruption of the ligament can recover and resume preinjury athletic function; 90% of horses with acute proximal SL desmitis in the forelimb will return to full athletic function.[2] Complicated, chronic, or recurrent desmitis has been associated with a worse prognosis; only 14% of horses with hindlimb proximal SL desmitis treated conservatively return to full work.[2] Adjunctive medical and surgical treatments can improve prognosis in these problematic horses. Most horses with traumatic disruption of the SL can be salvaged for breeding after surgical repair. Prognosis for horses with DSLD is extremely poor.

Fractures

Tamara M. Swor

The ability to treat fractures in large animals depends largely on rapid and correct diagnosis, appropriate first-aid treatment and stabilization of the injured limb, and safe transportation to a referral surgical center. Emergency treatment administered by a veterinarian in the field is crucial to provide the most treatment options and enhance the prognosis. Accurate knowledge of available treatment options and the prognosis for various fracture types is critical during discussions with clients. The surgeon receiving a patient with a fracture should be contacted early and involved in the decisions regarding limb stabilization, transportation, and owner financial commitments. Treatment options are discussed in this section; specific surgical principles related to fracture repair can be found in surgical textbooks.

Definition and Etiology A *fracture* is defined as a break or rupture of a bone. In large animals, fractures are usually classified as complete or incomplete, articular or nonarticular, displaced or nondisplaced, open or closed, simple or comminuted, and transverse, oblique, or spiral. Classification by location is also common and includes terms such as *physeal, metaphyseal,* and *diaphyseal.*

Fractures in large animals are typically associated with an acute traumatic event followed by sudden severe lameness. Horses may have a history of falling or running into a solid object, receiving a kick from another horse, being hit by a car, or flipping over backward (typically young animals). In another common scenario, the owner hears a loud pop or cracking sound while the horse is being lunged or is participating in an athletic activity.

Stress fractures may also occur and are often a result of cyclic loading over time, with corresponding fatigue leading to bone microfracture. Intensive training schedules create a high number of loading cycles with insufficient time to remodel and repair local areas of stressed bone (e.g., racehorse training). Specific locations of stress fractures include the distal end of the scapular spine, caudoproximal humeral head, craniodistomedial aspect of the humerus, medial humeral diaphysis, caudal aspect of the radius, dorsal middiaphyseal and distodorsolateral third metacarpal, caudal border of the ilial wing and adjacent to the pubic symphysis, proximolateral tibia, and caudal diaphysis of the tibia.[1]

Less common causes of large animal fractures include nutritional deficiencies, neoplasia, and infectious causes leading to pathologic fractures. Fractures related to difficult parturition events are seen in neonatal foals and calves.

Clinical Signs and Differential Diagnosis An animal with a long-bone fracture will typically present with an acute non–weight-bearing lameness of the affected limb. Moderate to severe soft tissue swelling and inability to control the limb often accompany other clinical signs of distress, agitation, and pain. Because of the horse's "fight or flight" reaction to traumatic situations, the patient will often continue attempts to place weight on the fractured limb. Fractures in locations with limited soft tissue coverage are often open (e.g., third metacarpal). Severe hemorrhage or laceration of large vessels is uncommon but may occur.

Complete catastrophic fractures are often easily identified based on limb instability and soft tissue trauma or swelling. Proximal limb fractures may be difficult to palpate but have adjacent severe soft tissue inflammation and edema, crepitus, and difficulties in limb

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function. Nondisplaced or incomplete fractures may be associated with a wound or may be painful to manual palpation. Focal pain on palpation, a corresponding lameness, and a history of trauma or being kicked by another animal warrants radiographic evaluation in search of an incomplete fracture. An unrecognized incomplete fracture may progress to a complete fracture with time and exercise. Physeal fractures should be considered in young animals.

Stress fractures often present with a history of acute severe lameness followed by a rapid decrease in the degree of lameness. There may also be reports of intermittent lameness that improves with stall rest. Palpation of the limb often reveals a focal area of pain, heat, and swelling. The horse may resist manipulation of the limb.

Differential diagnoses should include hoof and sole abscesses, joint subluxation, joint luxation, nerve damage, soft tissue injury, and septic synovial structures.

Clinical Evaluation A complete physical examination should be performed on initial evaluation. Animals that are not immediately identified as having a fractured limb may be in need of systemic support. Fluid therapy, pain control, antiinflammatory medications, and antimicrobials should be used as necessary.

Definitive diagnosis is made by taking multiple radiographic views; nuclear scintigraphy, ultrasonography, CT, and MRI may also be used. Information from imaging studies will provide fracture configuration details essential for determining prognosis. The bone involved, degree of comminution, articular involvement, physeal involvement, and condition of the bone fragments all affect potential repair attempts and long-term prognosis. Incomplete fractures may not be readily identified at the time of injury, and radiographs should be repeated in 10 to 14 days if a fracture is suspected.

Stress fractures are also diagnosed using radiographic evaluation and may be identified as an incomplete cortical fracture, endosteal callus, or periosteal callus.[2] As with incomplete fractures, it may be difficult to identify a stress fracture by conventional radiography in the acute stages. Radiographs should be repeated in 10 to 14 days if a fracture is suspected. Other imaging modalities, especially nuclear scintigraphy or CT, may be useful in stress fracture identification.

Emergency Treatment The goals of emergency treatment include preventing further soft tissue damage, stabilizing the injured limb to decrease the patient's anxiety, minimizing further damage to the fractured bone ends, keeping the fracture closed, and preventing further injury and stretching to the surrounding vessels and nerves.[3] A large animal with a fractured limb should be immediately restrained and calmed. Sedatives and tranquilizers should be used with caution, however, because the desired result may be difficult to achieve if the animal is agitated or in shock. The goal of sedation should be to allow manipulation of the limb and placement of external coaptation. Common sedatives should be used with caution to avoid creating additional ataxia; butorphanol should not be used if the horse has sustained a front limb fracture, because it will make the horse lean onto the forehand. If a soft tissue wound is present, the clinician should assume the fracture is open. The wound should be cleaned, topical antimicrobials used, a bandage placed to prevent further contamination, and the animal started on systemic antimicrobials. Antiinflammatory medications should be used as necessary.

Appropriate external coaptation and stabilization of the fracture for transport can greatly influence the options available for fracture repair and the prognosis for success. Table 38-4 outlines specific emergency splints for different fractures in bones.[3,4] Splinting techniques are designed to be placed on the standing horse and attempt to neutralize forces acting on the fractured limb. Splints should be made of a strong, lightweight material like PVC pipe or wooden boards. Bandages over fractures should be placed tightly over the injured area to decrease soft tissue swelling and minimize slippage. A layer of cotton padding should be followed by a layer of gauze or a self-adhering bandage. Multiple layers can be placed if needed (e.g., Robert Jones–type bandage). The splint should not end at the level of the fracture. In general, splinting techniques can be divided into categories based on fracture location.

DISTAL LIMB FRACTURES (PHALANGES, DISTAL METACARPUS/METATARSUS). A light cotton bandage should be placed on the affected limb from the carpus to the ground. A splint is then positioned on the dorsal aspect of a forelimb or the plantar aspect of

TABLE 38-4

Emergency Splinting Techniques for Fractures in Large Domestic Animals

Location	Species/Age	Splint
Distal phalanx	Horses, foals Cattle, calves	No splint needed
Middle phalanx	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint to proximal metacarpal/tarsal 3 and cast material, Kimzey splint*
Proximal phalanx	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint to proximal metacarpal/tarsal 3 and cast material, Kimzey splint*
	Cattle, calves	No splint needed
Distal sesamoid (navicular)	Horses, foals	No splint needed
Proximal sesamoids	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint and cast material, Kimzey splint*
Metacarpal/tarsal 3	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint and cast material, Kimzey splint* if fracture distal
Metacarpal/tarsal 3 & 4	Cattle, calves	Bandage with dorsal (front limb) or plantar (hindlimb) splint and cast, cast
Metacarpal/tarsal 2 & 4	Horses, foals	No splint needed
Olecranon/ulna	Horses, foals	Robert Jones–type bandage with caudal splint to lock carpus in extension
Radius	Horses, foals Cattle, calves	Robert Jones–type bandage with lateral splint to withers, second caudal splint if needed
Humerus	Horses, foals Cattle, calves	No splint needed
Scapula	Horses, foals Cattle, calves	No splint needed
Tibia	Horses, foals	Robert Jones–type bandage with lateral splint to tuber coxae
Femur	Horses, foals Cattle, calves	No splint needed
Pelvis	Horses, foals Cattle, calves	No splint needed

*Leg-Saver splint, Kimzey Inc., 164 Kentucky Ave., Woodland, CA 95695 (530-662-9331; fax 530-662-9178); www.kimzeymetalproducts.com.

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a hindlimb. The toe is pointed toward the ground to align the dorsal cortices and minimize stretching of the palmar/plantar vascular and nerve structures. A second splint should be placed on the medial or lateral side of the limb if any instability is present in those directions. The splint should be secured with inelastic tape. For additional stability, several rolls of fiberglass casting tape should be placed around the entire bandage and splint structure, incorporating the hoof into the cast.

MIDLIMB FRACTURES (MIDMETACARPUS TO DISTAL RADIUS, MIDMETATARSUS TO PROXIMAL METATARSUS). A Robert Jones–type bandage should be placed on the limb from the ground to the elbow in a forelimb, or the ground to the calcaneal tuber in a hindlimb. The bandage should be less extensive in the hindlimb to facilitate splint placement. In the forelimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the elbow. In the hindlimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the calcaneal tuber. The splints are secured using inelastic tape, followed by several rolls of fiberglass casting tape around the entire structure.

UPPER LIMB FRACTURES (MIDDLE AND PROXIMAL RADIUS, TARSUS, TIBIA). A Robert Jones–type bandage should be placed on the limb from the ground and extend as far proximal as possible. In the forelimb, a splint should be placed on the lateral aspect of the limb from the ground to the withers. For increased stability, a second splint may be placed on the caudal or cranial side from the ground to the proximal forearm if necessary. Horses with olecranon fractures that disable the triceps muscle benefit from placement of a caudal splint to reestablish carpal extension. In the hindlimb, a splint should be placed on the lateral aspect from the ground to the tuber coxae. Splints placed high in this fashion will help minimize abduction of the limb.

HIGH LIMB FRACTURES (PROXIMAL TO ELBOW JOINT, FEMUR). Fractures in these locations are covered by extensive muscle, and attempts at splinting are usually unsuccessful and unhelpful to the animal. If triceps muscle function is disabled, a splint on the caudal aspect of the carpus, locking it into extension, is beneficial.

TRANSPORT. Transportation of horses with long-bone fractures can be difficult. They should be trailered in a manner that allows them to lean on dividers for support, and be tied loosely to prevent them from turning around in the trailer but still able to use their heads for balance. When possible, horses with forelimb fractures should be transported with the head facing the rear of the trailer, and those with hindlimb fractures should be transported with the head facing the front of the trailer. These positions allow the horse to control its weight most easily with the uninjured limbs during deceleration of the trailer.

Pathophysiology of Bone Healing

Healing of a fracture terminates in the return of the injured bone to its original form.[5] The process of fracture healing involves several biological steps that overlap and interact with each other. Typically, three phases are recognized: inflammatory, reparative, and remodeling.[5,6] The *inflammatory phase* occurs in the initial 2 to 3 weeks after bone fracture, and chemical mediators cause chemotaxis, migration of leukocytes, and vasodilation to the injured area. These mediators protect the injury from infection and stimulate angiogenic factors. Cytokines from platelets aid in angiogenesis and mesenchymal cell growth.[5] Granulocytes and macrophages destroy invading bacteria and stimulate cell repair through the release of growth and angiogenic factors. If the inflammatory phase is impaired, fracture healing may be compromised.[5]

The *reparative phase* overlaps with the inflammatory phase and may last up to 12 months. This phase attempts to reestablish bone union. Interfragmentary stabilization by periosteal and endosteal callus formation begins if the fractured ends are not immobilized.[6] Bony union develops as a result of endochondral and intramembranous ossification.[5,6] In the reparative phase, interfragmentary motion may greatly influence fracture healing.

The *remodeling phase* takes place both during and after the reparative phase. Osteonal remodeling allows for replacement of necrotic regions of bone. When the bone is loaded, the negatively charged concave surface will attract osteoblasts to add new bone, and the positively charged convex surface will attract osteoclasts to remove bone.[5,6] The result is the ability of a fractured bone to straighten itself by creating new bone formation on the concave surface and removing bone from the convex surface.

Repair of a fractured bone with the use of rigid internal fixation will inhibit naturally occurring callus formation and encourage bone to heal through haversian remodeling. *Haversian remodeling* requires that a fracture be rigidly fixed, have adequate reduction, and have an adequate blood supply.[5,6] Haversian remodeling then functions to revascularize necrotic bone at the fragmented ends of the fracture and bridge interfragmentary gaps. This form of remodeling begins 2 to 3 months after injury.

Fractured bones are often described as healing by primary (direct) or secondary (indirect) intention.[2,5,6] Primary bone healing only occurs with complete anatomic reduction and rigid stability. In large animal fracture repair, this is difficult to achieve because of the size of the animal and micromotion at the repair site.[2] Secondary bone healing utilizes endosteal and periosteal callus formation, and new bone formed at the fracture site develops after initial formation of fibrous tissue or fibrocartilage.[5,6]

The rate of bone healing may be decreased if blood supply is inadequate, infection is present, soft tissue damage is extensive, or stability of the bone fragments is inadequate.

Treatment and Prognosis

Treatment options for fractures in large animals include conservative therapy with stall rest and external coaptation (casts, splints), and surgical stabilization with open reduction and internal fixation. It is important to recognize incomplete and stress fractures to manage them appropriately with conservative therapy, preventing progression to a catastrophic fracture. The majority of fractures require some form of stabilization for the best chance of a successful outcome. Most horses require surgical stabilization for successful fracture repair. Ruminants are more amenable to successful fracture repair with nonsurgical options.[2]

Conservative therapy with stall rest and external coaptation may be successful in some foals and calves with complete nondisplaced fractures. Young animals have a greater and faster ability to heal bone in a reasonable amount of time, and their body weight is much less than that of a mature animal. In foals and calves, fracture configurations tend to be simpler, and the surgical implants available for repair are of a suitable strength for the animal's size. Complications in young animals include closure of a physes with fractures in these areas, infection, and angular limb deformities from overuse of the contralateral limb.

Severely comminuted fractures are more common in adult animals because of the greater force required for bone breakage. Proximal limb fractures in an adult horse often defy successful treatment because severe comminution of the bone occurs, implants are not strong enough to support the bone until it is healed, these horses are less likely to protect the limb, and laminitis formation in the contralateral limb is a common complication. Stall rest with external coaptation alone is rarely associated with a good outcome; most horses need some form of internal fixation for success. Horses are often required to be athletes, and fracture repair resulting in survival but not soundness may be unacceptable. In general, ruminants have a better prognosis for survival than horses because of their less excitable temperament, and complete soundness is often unnecessary for a successful outcome. In ruminants, external fixation may be more successful than external coaptation because it provides increased stability and costs less than internal fixation.[2] Open fractures in horses greatly decreases the prognosis for survival and may delay the ability

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TABLE 38-5

Treatment and Prognosis for Large Animal Fractures

Fracture Location	Fracture Type	Treatment	Prognosis
Distal phalanx	Articular	Medical/Surgical	Guarded
	Nonarticular	Medical	Good
Middle phalanx	Comminuted	Surgical	Guarded
Proximal phalanx	Comminuted	Surgical	Guarded
	Noncomminuted	Medical/Surgical	Good
Distal sesamoid	Fragmented	Medical/Surgical	Poor to guarded
Proximal sesamoids	Articular	Medical/Surgical	Poor to guarded
	Nonarticular	Medical/Surgical	Fair to good
Metacarpal/tarsal 3			
Lateral condyle	Nondisplaced	Surgical	Good
	Displaced	Surgical	Guarded
Medial condyle	Articular	Surgical	Guarded
Diaphyseal	Comminuted	Surgical	Guarded
Metacarpal/tarsal 3 & 4	Diaphyseal	Medical/Surgical	Guarded to good
Metacarpal/tarsal 2 & 4	Distal	Medical/Surgical	Good to excellent
	Proximal	Surgical	Guarded to good
Olecranon/ulna	Articular	Surgical	Good
	Nonarticular	Medical/Surgical	Good
Radius	Complete	Surgical	Poor
	Complete*	Surgical	Guarded to good
	Incomplete	Medical	Good
Humerus	Complete	Medical	Poor
	Complete*	Surgical	Guarded to good
Scapula	Complete	Surgical	Poor to fair
Tibia	Complete	Surgical	Poor
	Complete*	Surgical	Guarded to good
Femur	Complete	Medical	Poor
	Complete*	Surgical	Guarded to good
Pelvis	Articular	Medical	Guarded
	Nonarticular	Medical	Guarded to good

*Foals, calves, and small ruminants.

to perform internal fixation. In ruminants, open fractures are less common but also carry a poorer prognosis.

Implants used for surgical open reduction and internal fixation methods vary based on the specific bone involved, the animal's age, the strength of the bone fragments used in the repair, and the surgeon's preference. Common implants used in large animals include intramedullary interlocking nails, dynamic compression plates (DCPs), locking compression plates (LCPs), limited-contact DCPs, screws, wires, pins, and dynamic condylar screw plates. Table 38-5 lists specific treatment options and prognoses.[4]

HUMERUS. The humeral fracture is often in a spiral or long oblique configuration. In ruminant and equine species, both conservative and surgical treatments have been used. In foals, surgical repair may include the use of intramedullary interlocking nails, DCPs, or intramedullary nails. Prognosis for a closed fracture in a foal is fair to good and depends on configuration, age, and weight.[7,8] Humeral fractures in adult horses are not reparable at this time. Recent reports of horses with deltoid tuberosity or greater tubercle fractures of the humerus indicate some successful treatment results.[9,10] Conservative treatment may be successful in adult horses with nondisplaced fractures and has been used in small ruminants and foals with acceptable outcomes. Ruminants have a better prognosis in general than equine species.[2]

RADIUS. Survival rates for ruminants with radial fractures repaired by external or internal fixation have been reported as 86%.[11] Radial fractures in foals repaired with internal fixation have a good prognosis, but in adult horses the success rate is poor.[12] Animals with incomplete fractures that do not progress have a good prognosis for a full recovery.

OLECRANON. There are several different fracture configurations, and the olecranon fracture may be articular or nonarticular. These fractures are common in both young and older horses. Surgical and conservative treatments have been used with success, although internal fixation is the preferred treatment method.[13,14] Typically the fracture is repaired with a DCP or LCP applied as a tension band. The prognosis with surgical repair is good, with 75%, 81%, and 87% of horses returning to athletic use, depending on the fracture type.[13,14,15] Conservative treatment has been reported to result in a 73% return to soundness.[16]

FEMUR. Diaphyseal fractures are more common in calves, whereas proximal physeal fractures are more common in foals. Femoral fractures in calves may occur during parturition events. In young calves, these fractures have been repaired by internal fixation and femoral head and neck osteotomies with success. A recent study found calves treated surgically for femoral diaphysis fractures had fewer complications than those treated conservatively.[17] In foals, fracture repair with internal fixation gives the best chance of survival, and the use of intramedullary interlocking nails has shown positive results.[18] Femoral fractures in adult horses are not reparable at this time.

TIBIA. Tibial fractures in ruminants have been repaired using splints, external fixators, transfixation pin casts, and DCPs. Fractures repaired with external fixation in adult cattle had a 64% success rate, whereas conservative therapy yielded 44% success.[19] Internal fixation is the repair method of choice in horses. Foals have a fair to good prognosis for survival. Adult horses have a poor prognosis for survival because tibial fractures are often open, have limited blood supply, and are often severely comminuted.

METACARPUS/METATARSUS. In cattle, these fractures are common and have a good prognosis when treated with internal fixation, casts, or transfixation pin casts. Calves may incur distal physeal fractures after forced extraction during a dystocia, and these may be

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casted with good success. In horses, cannon bone fractures are frequently open because of a lack of soft tissue coverage. Treatment options include internal fixation with DCP/LCPs and screws, or transfixation pin casts. A recent study evaluating outcomes in mature horses and foals with complete diaphyseal third metacarpal/metatarsal fractures treated with internal fixation found that 62% survived, although the survival rate was much higher for foals.[20] Another study reported a 67% success rate with surgical repair.[21]

PHALANGES. In ruminants, fractures of the proximal or middle phalanx are treated with reasonable success by applying a block to the uninjured claw or by cast application. In horses, proximal and middle phalangeal fractures have been treated by internal fixation with screws and DCPs. Prognosis for survival is good, but return to athletic function depends on the degree of osteoarthritis that develops after fixation. A recent report of proximal phalanx fractures in non-racing horses found that those treated with internal fixation had a better outcome than those managed conservatively.[22] One review of proximal phalangeal fractures in racehorses reported that 61% to 75% were able to race.[23] Prognosis for comminuted middle phalangeal fractures repaired with PIP arthrodesis is 50% for forelimbs and 80% for hindlimbs.[2] Severely comminuted fractures may also be treated successfully with transfixation pin casts or the Nunamaker external skeletal fixator.[24] Fractures of the distal phalanx in horses may be successfully treated with surgical fixation, hoof casts, or modification in shoeing, depending on fracture configuration. A recent study found that 77% of horses had a successful outcome but did not find that immobilization of the hoof influenced outcome.[25]

SUMMARY. Animals identified with incomplete fractures should be treated conservatively with stall rest and should be tied to prevent them from lying down if the fracture is at risk of becoming complete (e.g., radius). Animals with stress fractures should be treated conservatively with stall rest and a careful rehabilitation program, with ongoing radiographic evaluation.

Many fractures in large animals can be repaired and allow survival of the animal. Prognosis in general is better if the animal is young and weighs 500 pounds (225 kg) or less, the fracture is closed, appropriate emergency stabilization is implemented, and prompt reduction and stabilization are performed.

Spontaneous Fractures in Ruminants

Kara Schulz

Definition and Etiology A spontaneous (or pathologic) fracture occurs when bone is weakened by underlying disease to the degree that nontraumatic forces applied to the bone result in bone failure. Commonly affected bone structures include the long bones, vertebrae, ribs, scapula, pelvis, and mandible.

Clinical Signs and Differential Diagnosis Clinical signs of lameness, postural or angular limb deformities, and swelling may be observed in the absence of historical trauma. Additional chronic fractures may be noted with careful physical examination. The primary differential diagnosis is a fracture of normal bone that is due to traumatically applied force.

Pathophysiology, Epidemiology, and Clinical Pathology In ruminants, the underlying conditions that can lead to weakening of the bone's composite structure and subsequent fracture include neoplastic bone lesions, osteomyelitis, osteodystrophy associated with rickets in young animals, osteomalacia associated with nutritional imbalances in adults, and osteoporosis associated with copper deficiency.

Both neoplastic bone lesions and osteomyelitis can lead to pathologic bone fracture from resultant decreases in bone mineral matrix. Lymphosarcoma and a variety of less commonly reported tumors such as hemangiosarcoma, liposarcoma, osteogenic sarcoma, and osteoma among others have caused spontaneous bone fractures in ruminants.[1-3] Lesions may have an osteolytic, osteoblastic, osteoporotic, or mixed roentgen sign depending on the tumor or infectious agent involved.[4] Localized bone infection can be traumatic or hematogenous in origin.[5] Reported cases include osteomyelitis of the sternum, distal sesamoid bone, and mandible, as well as osteitis of the third phalanx.[6-9] *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is the most common bacterial isolate,[5,6] although other diseases processes like actinomycosis may be involved.

Development of osteodystrophy in young ruminants and osteomalacia in adult ruminants is commonly due to nutritional deficiencies or imbalances and can occasionally lead to spontaneous fracture. Primary (simple) deficiency implies dietary lack of a nutrient, and secondary (complex) deficiency involves reduced nutrient absorption. Primary deficiencies of minerals such as calcium, phosphorus, copper, and vitamin D (1,25-dihydroxycholecalciferol) are commonly associated with bone disease, owing to their integral role in bone mineralization and collagen cross-linking. Secondary deficiencies of these minerals occur when increased consumption of minerals like iron, manganese, magnesium, zinc, sulfur, and molybdenum impede their absorption.[10]

Hypophosphatemia is a common cause of osteodystrophy in young animals and osteomalacia in adult animals. In young animals, development of rickets due to phosphorus or vitamin D deficiency can occasionally result in spontaneous bone fracture.[11] In adults, the pathogenesis of osteomalacia-associated disease is similar but also leads to osteoporosis when mature osteoid is replaced by poorly mineralized bone matrix. Clinical signs of pica, lameness, joint enlargement, poor body condition, and estrus cycle abnormalities may be noted.[12] Primary phosphorus deficiency can occur in ruminants when low levels of phosphorus are available in forage, and secondary phosphorus deficiency can result when significant imbalance exists between calcium and phosphorus concentrations in the ration.[13] Serum phosphorus levels may not adequately reflect a deficiency until severe hypophosphatemia is present and can vary based on age and lactation status, so timely diagnosis may be hampered.[13-14] Gross postmortem findings may include brittle, porous bone and enlarged chronic fracture site scars on ribs.

Primary and secondary deficiencies of copper have been reported to cause osteoporosis and fracture in ruminants.[15] Clinical signs of pica, poor body condition, and anemia are reported.[16] Molybdenosis (molybdenum-associated copper deficiency) occurs when there is a relative excess of sulfate and molybdenum in the diet or water, leading to formation of insoluble copper thiomolybdenate compounds and reduced copper absorption. Although the exact mechanism of copper-induced osteoporosis is unknown, copper is a cofactor for lysyl oxidase, which enzymatically promotes collagen cross-linking. Abnormalities in bone collagen and decreased recruitment of osteoblasts may cause the resultant osteoporosis.[17] In cattle, copper deficiency can be diagnosed through measurement of plasma copper levels (<9 μm/L) or ceruloplasmin levels (<15 IU/L).[18]

Chronic fluoride toxicity, or fluorosis (see earlier section), has been associated with spontaneous fracture in ruminants. These animals present with ill thrift, lameness, and severe dental disease due to abnormalities in tooth wear and mandibular bone, as well as generalized osteomalacia of bone and periarticular structures.[19] Pedal bone fracture has been reported with severe fluorosis.[20] Osteogenesis imperfecta in Holstein-Friesian calves and inherited rickets in Corriedale sheep are two specific conditions that have been associated with spontaneous fractures in ruminants. Genetic conditions like these usually entail abnormalities in bone collagen formation or bone matrix mineralization.[21-22]

It is important to note that this is not an all-inclusive list; other management and nutritional issues may contribute to abnormal bone composition and lead to spontaneous fracture. A detailed history, physical examination, and diagnostic work-up can help identify underlying conditions.

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Treatment and Prevention Treatment of spontaneous fractures is similar to routine fracture fixation and will likely involve some type of coaptation, immobilization, or rest depending on the structure affected and the inherent stability of the fracture and surrounding bone. Resolution of the underlying cause is essential to the success of fixation. The prognosis is dependent on the severity of the underlying condition, with an understandably guarded to grave prognosis for many of the listed conditions. However, it must be noted that many of the nutritional imbalances leading to osteodystrophy, osteomalacia, or osteoporosis-associated fractures have been successfully treated. As with many other conditions, prevention of the underlying cause is the most effective means for reducing the incidence of spontaneous fractures in ruminants.

Bucked Shins and Stress Fractures of the Metacarpus in the Horse

Justin Dominick McCormick

Definition and Etiology The third metacarpal bone can be painfully affected by bucked shins or stress fractures, also known as *dorsometacarpal disease,* and cause variable lameness in the racehorse.[1,2] Dorsometacarpal disease is a well-recognized problem in young Thoroughbred and Quarter Horse racehorses and has been described in Standardbreds as well. Bucked shins occur mainly in 2-year-olds in response to high strains sustained during the repetitive loading experienced during the first year of training. Periostitis develops over the dorsal cortex in response to stress remodeling as speed is first introduced in early training.[2] Short oblique stress fractures are the result of an imbalance between bone fatigue and failure of bone remodeling. The mid-distal dorsolateral cortex of the left third metacarpus is the most common site of pathology, but periostitis can develop anywhere along the dorsal cortex and affect the right metacarpus as well.[1,3] Stress fractures typically develop in 3-year-olds as training continues and previously developed pathology progresses.[3-5]

Clinical Signs and Differential Diagnosis Bucked shins and stress fractures occur in young horses early in training, and less commonly in older horses that have not been appropriately conditioned before racing. Bilateral forelimb involvement is most common, with the lead limb most severely affected.[2] Heat and swelling develop acutely over the dorsal metacarpus. As training continues, soft tissue thickening becomes evident several weeks after development of the initial clinical signs.[2] The degree of pain and lameness depends on the severity of the condition and is most noticeable following intense work. Lameness typically resolves after several days of rest and recurs when training resumes. Poor performance at high speeds and reluctance to train are evident as disease progresses if exercise continues at the same intensity. Radiographic changes are often subtle in horses with acute bucked shins. Microfractures secondary to cyclic fatigue may result in periosteal and endosteal reactions that are difficult to detect radiographically.[6] Thickening of the dorsomedial cortex and periosteal proliferation may be seen in chronic cases (Fig. 38-45).[2] A complete radiographic exam, including multiple oblique views to highlight the dorsal cortex, is indicated at the time of initial onset of clinical signs to determine whether fissure lines are present. Increased focal uptake of technetium-99m (^{99m}Tc) on nuclear scintigraphy in the dorsal cortex is suggestive of disease when radiographic abnormalities are inconclusive.[6]

Differential diagnoses for pain and swelling localized to the metacarpal region are traumatic or infectious in origin and include cellulitis, periostitis, osteitis, and osteomyelitis. A thorough history, complete physical exam, and close examination of the area should be performed during initial work-up to identify any evidence of external trauma or local infection in the dorsal metacarpal region. Older horses or horses not involved in race training are unlikely to develop bucked shins, so other causes of clinical signs should be investigated.



FIG. 38-45 Lateromedial radiograph of the third metacarpal bone of a horse with chronic bucked shins. Note the dorsal cortical thickening and endosteal and periosteal response.

Failure of dorsal metacarpal bone remodeling in response to strain during exercise results in stress fractures. The majority of stress fractures occur on the dorsolateral surface of the mid-diaphysis of the left third metacarpus, but bilateral fractures can occur.[7] These stress fractures are usually observed in 3-year-olds but have been reported in older horses.[2] Similar to bucked shins, lameness is variable and exacerbated with exercise. Pain may be elicited on digital palpation over a discreet area of swelling that hardens with periosteal callus formation.[2] Clinical examination is usually sufficient for diagnosis of bucked shins or stress fractures of the third metacarpus. Median and ulnar perineural anesthesia or local anesthesia of the proximal metacarpus with a ring block may be performed to confirm the source of pain.[2]

Fissures or nonspecific linear lucencies are suggestive of incomplete fractures. They are often seen radiographically in the dorsal cortex of the third metacarpus (Fig. 38-46, *A*). The most common fracture configuration courses distoproximal at a 30- to 40-degree angle from the mid-distal dorsolateral cortex. These fractures either extend 60% to 70% through the dorsal cortex or curve back to the dorsal cortex in the form of a saucer fracture.[3] The presence of marked periosteal and endosteal proliferation on radiographs strongly suggests the presence of a cortical stress fracture. Radiographic evidence of periostitis may be delayed up to 2 weeks following the onset of clinical signs.[6] Additional radiographic examination may be indicated 7 to 10 days later if stress fractures are suspected but not evident initially.[2] Multiple fractures in the same limb have been reported.[6]

Pathophysiology The effect of race training on the growth and development of the maturing metacarpal bone appears to be directly related to the development of bucked shins.[1] As the horse enters training during its 2- or 3-year-old year, the third metacarpal bone is subjected to new strains and remodels in an attempt to adapt to the bending forces experienced during repetitive loading during exercise.[8] Cyclic fatigue during high strain decreases bone stiffness. New bone is formed over the surface of the dorsal medial cortex in response to deformation of bending forces localized to that region of the third metacarpus.[8] As cyclic loading during training continues,

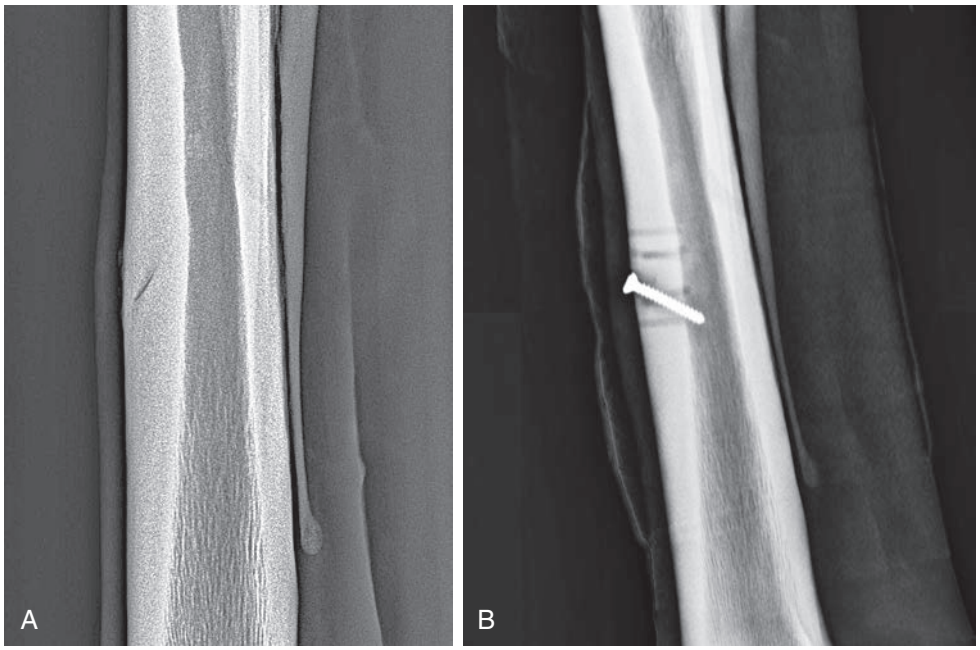


FIG. 38-46 **A,** Preoperative radiographic projection of a cortical stress fracture of the dorsolateral third metacarpal bone. **B,** Postoperative lateromedial radiographic projection of position screw placement through the fracture line, with surrounding osteostixis holes.

production of woven and lamellar bone is exhausted. Fiber-type bone is formed, which appears radiographically as periosteal proliferation.[9] As cyclic loading continues, the bone continues to lose stiffness and begins to fatigue, resulting in failure or microdamage.[2]

Incomplete stress fractures are commonly localized to the dorsolateral cortex of the third metacarpus and are observed within 1 year following the onset of dorsocortical pain.[9] Evidence suggests that cortical bone is unable to appropriately remodel during periosteal bone formation. As bucked shins develop, the dorsolateral cortex loses stiffness and becomes more vulnerable to high-stress cyclic fatigue and stress fractures.[8] The forces exerted on the limb differ during race speeds (compared to training speeds), so racing may shift stresses to areas less adapted to high-speed cyclic loading.[4]

Epidemiology The incidence of bucked shins varies with region, ranging between 30% to 90%, and is mostly seen in 2-year-old Thoroughbred racehorses during the first 6 months of training.[1] Prevalence of stress fractures is unknown, but a reported 12% of horses that buck their shins later develop stress fractures,[10] and a greater number of horses developed bucked shins and stress fractures during prolonged fast workouts while on dirt surfaces.[4,5]

Bucked shins primarily develop in the Thoroughbred, less commonly in Quarter Horses and Standardbreds.[2] Thoroughbreds are trained to race longer distances at greater speed, subjecting them to higher cyclic loading and greater risk of fatigue failure compared to other racing breeds.[10]

Treatment and Prognosis Early treatment for bucked shins is targeted at controlling pain and inflammation. The majority of cases are able to resume athletic training following 5 to 10 days of rest and antiinflammatory treatment.[2] During the rest period, the administration of NSAIDs, cold hydrotherapy, ice boots, and bandaging may help reduce inflammation and relieve pain over the dorsal metacarpus. Once clinical signs are resolved, training should be adjusted to prevent further damage from cyclic fatigue. Galloping exercise at a reduced distance with breezes (faster gallop speed but not racing speeds) every 5 to 7 days over short distances (e.g., ½ to 2 furlongs) may be reintroduced to continue to promote stress remodeling without creating microfractures in the dorsal cortex.[9] Training should be adjusted based on the horse's comfort. If pain and inflammation return, work should be decreased to reduce the number of cycles on the affected limb by limiting the horse to shorter galloping distances. As new bone is cycled, stiffness is further lost, increasing the production of periosteal new bone. Bone with an excessive amount of periosteal bone formation is considered to have lost significant stiffness, and a stop in training is recommended before catastrophic breakdown injury occurs.[9] Horses with marked periosteal bone formation on radiographs require an extended period of rest (at least 100 days) before returning to restricted training.[8] Prognosis for horses with bucked shins to return to racing is excellent if appropriate training modifications are made. Rate of recurrence is high in horses not given adequate time for rest that continue to train over long distances.

Nonsurgical management of dorsal cortical stress fractures includes confinement to stall rest and antiinflammatory therapy until there is radiographic evidence of fracture healing.[3] Horses with fractures in the distal to proximal metaphysis are able to form early callus and generally respond best to conservative management.[3] A variety of unconventional therapies have been employed over time to treat bucked shins and dorsal cortical stress fractures. Alternative treatments include topical irritants, thermocautery (pin firing), cryotherapy (freeze firing), periosteal scraping, and intralesional injection with osteogenic substances or steroids.[2] The efficacy of these treatments is debatable, and published scientific support is lacking. Regardless of treatment choice, an extended period of rest with return to a modified training schedule is required for complete resolution of disease. Extracorporeal shockwave therapy appears to provide some analgesic effects, but its effect on healing is unknown.[5,7]

Surgical management in many cases may be the best treatment option for cortical stress fractures. This is supported by the high rate of recurrence and significant number of fractures that fail to show radiographic evidence of healing following months of convalescence.[7] Surgical options include cortical drilling (i.e., osteostixis) around the fracture site, with or without intercortical screw placement across the fracture (see Fig. 38-46, *B*).[11] It is suggested that osteostixis promotes healing by facilitating exposure of intramedullary vessels to the fracture site and increases stability to the area as woven bone fills the defects.[13] Cortical screws are often placed in lag fashion; however, significant reduction of the fracture gap is

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questionable, and a positional screw appears to be adequate for stabilizing micromotion and stimulating a significant osteogenic response for healing.[11] Osteostixis does not require implant removal and may allow for an earlier return to racing,[14] but osteostixis alone may be associated with less predictable healing and recurrence of fractures.[11] Reports indicate that cortical drilling in conjunction with screw placement allows a slightly higher percentage of horses to return to racing (94%) than drilling alone (89%).[11,12] Prognosis for return to racing is good following the prescribed 3- to 4-month postoperative layoff period before returning to training. Fracture sites should be routinely examined radiographically to evaluate whether healing is adequate before resuming training; this will decrease the risk of recurrence or potential catastrophic breakdown injury.

Prevention The development of bucked shins or stress fractures of the third metacarpus in young racehorses is mainly influenced by type of training schedule and track surfaces. Long weekly galloping distances and exercise on dirt footing seem to be major risk factors for developing fatigue damage to the dorsal cortex.[5,15] Training schedules should be developed early in the horse's training to allow bone to adapt to strains similar to those experienced during racing. Early, gradual introduction of small amounts of high-speed exercise and reduction of galloping distances better replicate the strains during racing and stimulate appropriate remodeling of the third metacarpus.[15] As soon as soreness or periosteal reaction is detected over the dorsal cortex, training should be modified by decreasing the galloping distance by half and increasing the frequency of shorter high-speed workouts when pain can no longer be palpated.[1] One study reported a 33% increase in risk of developing fatigue injury to the third metacarpal bone with each additional mile galloped per week, and a 98% decrease in risk with each additional mile breezed per week.[4] Higher strains on the dorsal cortex may also be avoided by training on synthetic or grass surfaces rather than dirt.[5] Appropriate loading of the third metacarpus early in training allows the bone to remodel for racing conditions and essentially eliminates the risk of developing dorsal cortical stress fractures later in the horses career.

Equine Bone Fragility Disorder

Sarah M. Reuss

Definition Inhalation of silicates and its associated pneumoconiosis has been recognized as an important occupational disease in humans for decades. Since 1981, silicosis has also been recognized in horses with granulomatous pneumonia, pulmonary fibrosis, and silicate accumulation within pulmonary macrophages.[1] The disease is primarily seen in coastal regions of Northern California, specifically the Monterey County region. Over the years, equine practitioners have noted fractures and skeletal deformities in horses in the same geographic area. This syndrome of silicate-associated osteoporosis, also known as *equine bone fragility disorder* (BFD), was first described in the literature in 2006.[2]

Clinical Signs and Differential Diagnoses Respiratory tract and skeletal manifestations are often both seen in affected horses. There appear to be some farm and individual differences in which clinical syndrome is dominant. Respiratory system pathology was found in all horses in one retrospective, but 5 of 18 affected horses had not shown any clinical signs of their respiratory disease. When seen, respiratory signs included resting tachypnea, shallow breathing pattern, exercise intolerance, and occasionally a dry cough.[2]

Horses with equine BFD often present for chronic intermittent lameness or vague signs of generalized stiffness. One or multiple limbs may be involved, and regional anesthesia is often unsuccessful in localizing the area of pain, because it often emanates from the proximal aspects of the limbs or the axial skeleton. Neck pain and decreased ROM have also been noted with cervical facet osteoarthritis. Less commonly, horses present for acute lameness due to a pathologic fracture unrelated to exercise or trauma. Exercise intolerance may be due to a combination of respiratory compromise and orthopedic pain.

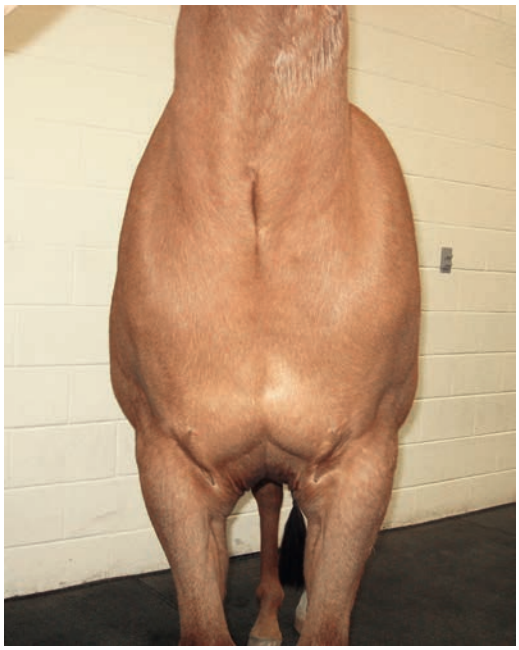


FIG. 38-47 Frontal photograph of a horse with bone fragility disorder. Note prominent bowing of left scapula.

Over time, skeletal deformities will develop, with bowing of the scapulae (Fig. 38-47) and ribs. Most horses also develop marked lordosis. As the disease progresses, horses may become severely lame owing to acute fractures without a history of trauma. Weight loss and poor hair coat are also typical.

Etiology/Pathogenesis Recent work has confirmed that the presence of osteoporosis is correlated with the presence of silicosis ($r = 0.8$; $P < 0.01$).[3] The exact mechanism by which silicosis causes osteoporosis is undetermined but might involve increased osteoclastic activity in response to chronic inflammation. No consistent abnormalities in calcium, phosphorus, parathyroid hormone, or other clinicopathologic data have been found, making other causes of metabolic bone disease less likely.[4] Silicate particles or silicate-laden macrophages disseminated to bone may also serve as a nidus for bone lesions.[3] Similarities have also been noted between equine BFD and Paget disease in people. Humans with silicosis have an increased risk of autoimmune diseases, so the skeletal lesions seen in horses may be immune-mediated as well.[5]

Silicates are common in many soils, but there is an especially high concentration of the cristobalite form in the Miocene Monterey shale soil type.[2] This formation is especially common in Monterey County but extends from Point Reyes to the Baja regions of California.[6] Although the Monterey Peninsula is the historical epicenter of this disease, affected horses have also been reported in Sonoma County, Napa County, the Sacramento Valley, and Silicon Valley.[3] The Monterey formation is also found in southwest Africa and Peru. It is unclear why this disease has not been recognized or reported in those areas. Quartz is the predominant silicate-containing mineral, but cristobalite has a less stable crystalline structure, making it more powdery and easier to inhale and reach the lower airways. Outbreaks may be seen when construction exposes the cristobalite. Onset of clinical signs may occur months to years after exposure, so affected horses may not be recognized until they have moved away from an endemic area. Horses as young as 4 years old have been affected with BFD.[4] There appears to be some individual susceptibility to disease, since not all exposed horses develop signs.

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Diagnosis Diagnosis is based on history, physical examination, and diagnostic imaging. Thoracic diagnostics to substantiate pulmonary silicosis may include radiographs, ultrasound, and bronchoalveolar lavage or transtracheal wash. Radiographic lesions with pulmonary silicosis include a mild, diffuse interstitial pattern that may progress to a structured miliary interstitial or reticulonodular pattern as the disease advances. Caudodorsal pulmonary consolidation, hilar and cranial mediastinal lymphadenopathy, and pleural effusion may also be seen.[7] Cytologic analysis of BAL or tracheal wash samples may show refractile crystalline material within alveolar macrophages.[2] Ultrasound is the least reliable thoracic diagnostic, since most of the pulmonary pathology occurs in the hilar and interstitial regions and does not extend to the pleural surface.[2]

In advanced cases with skeletal deformities, history and physical examination alone may yield a diagnosis. Nuclear scintigraphy is the most sensitive diagnostic for early disease. Increased radiopharmaceutical uptake may be seen in multiple sites, including the scapula (spine, body, neck, and supraglenoid region), ribs, sternebrae, cervical vertebrae, and pelvis (sacral tuber, ilium, ischium, and tuber coxae). The mandible and other appendicular bones (e.g., radius, metacarpus, metatarsus) may also be affected. It has been subjectively noted that severity of clinical signs is not related to the intensity or distribution of radiopharmaceutical uptake.[4] As the disease progresses, radiographic changes will become evident. These include osteoarthritis of the cervical articular facets, vertebral body lucencies, and segmental rib thickening. Pathologic fractures of the vertebrae, scapulae, ribs, pelvis, and/or maxilla with no history of trauma may also be seen. Ultrasound of the scapula, ribs, and pelvis is also diagnostic and of low risk to the horse because it does not necessitate anesthesia. Scapular spine thickening due to periosteal surface remodeling is the most frequent finding.[4] Bone biopsy can be performed and may reveal fibrosis, osteopenia, focal osteoclastic resorption, and periosteal proliferation.[3] Necropsy will reveal visible bone abnormalities like fractures, calluses, deformities, periosteal roughening, palpable firm foci throughout the lungs, and lymph node silicosis with fibrosis. Histopathologic evaluation of bone shows osteopenia, numerous resorption cavities, cement lines, and a mosaic lamellar pattern indicating abnormal osteoclast-mediated bone resorption and multiple remodeling events.[3]

Treatment Removing the horse from an endemic area will stop exposure but unfortunately not halt progression of BFD. Exercise restriction to reduce the risk of pathologic fracture should be recommended. NSAIDs do not typically provide much analgesia to affected horses. Systemic corticosteroids may provide transient relief but are contraindicated long term because they may contribute to osteoporosis. Targeted therapy with intraarticular corticosteroids may be considered for horses with cervical articular facet arthritis.

Bisphosphonates inhibit bone resorption by disrupting the function of osteoclasts, and they are commonly used to treat osteoporosis in humans. Given that this syndrome does involve abnormal osteoclast-mediated bone resorption, treatment targeting osteoclast activity might aid affected horses. Tiludronate has been used in several affected horses and seemed to provide some pain control.[5] Zoledronate is a third-generation nitrogen-containing bisphosphonate with a longer duration of action than tiludronate. Nine out of 10 horses with a diagnosis of BFD that were treated with 0.075 mg/kg of zoledronate diluted in 500 mL of isotonic solution had clinical improvement at 6 months in a prospective uncontrolled clinical trial.[8] Eight horses had improved scintigraphic findings and two had stabilization of scintigraphic abnormalities with no new sites of radiopharmaceutical uptake. No adverse effects were seen in any horses.

Prognosis Despite treatment, most horses progress to the point where euthanasia becomes necessary either because of chronic pain or acute pathologic fracture. In a recent retrospective study of 16 horses, the condition worsened over time in all horses, and 11 of the 16 were euthanized, with a median survival time of 2 years after diagnosis.[4] Although bisphosphates show some promise, a placebo-controlled trial has yet to be performed.

Temporohyoid Osteoarthropathy

Tracy E. Norman

Definition and Etiology Temporohyoid osteoarthropathy (THO) is a disease of bony proliferation at the junction of the stylohyoid and petrous temporal bones. Several etiologies have been proposed for this condition, and the true etiology is likely variable. In some cases, bony inflammation and remodeling may occur secondarily to extension of otitis media/interna or upper respiratory tract infection.[1,2] There is also evidence that many of these cases are due to primary DJD.[3] Regardless of the cause, the result is bony proliferation of the tympanic bulla, proximal stylohyoid bone, and petrous temporal bones, often resulting in arthrosis of the temporohyoid joint and subsequent fracture of the stylohyoid and petrous temporal bones. Although uncommon, these fractures can extend into the basisphenoid and basioccipital bones, resulting in meningitis and brainstem disease.[1] Pain and inflammation associated with fracture or altered mobility of the joint and impingement on surrounding nerves result in the observed clinical signs.

Clinical Signs Horses with THO may not show clinical signs, but two clinical syndromes are associated with THO. Non-neurologic signs may be chronic, and include difficulty chewing, nasal discharge, head tossing, ear rubbing, otorrhea, resentment of the bit, head shyness, and pain on manipulation of the head or ears.[1-3] Neurologic abnormalities generally include acute onset of signs of facial and vestibular nerve dysfunction, including ear droop, ptosis, muzzle deviation away from the affected side, corneal ulceration, head tilt toward the affected side, circling, ataxia, nystagmus, and collapse.[1-4] Damage to the parasympathetic portion of the facial nerve may result in reduced lacrimation.[4] Horses with neurologic deficits may also have hearing loss associated with THO.[2] Occasionally, dysphagia is observed. Rarely, seizures or sudden death may occur secondary to fractures that extend into the cranial vault.[1]

Diagnosis Pathologic alterations at the temporohyoid joint may be identified using radiography, guttural pouch endoscopy, CT, or MRI. Radiographs may show evidence of osseous proliferation at the temporohyoid joint on lateral and dorsoventral projections, but are in general found to be less sensitive at detecting abnormalities than other diagnostic modalities.[1]

Endoscopy of the guttural pouches has been shown to be sensitive in detecting early, in addition to advanced, changes at the temporohyoid joint, including soft tissue inflammation and hemorrhage, osseous proliferation, enlargement of the stylohyoid bone, and previous sites of fractures.[1] The contralateral guttural pouch should always be evaluated as well as the affected side, as some horses have bilateral disease. Because endoscopy equipment is readily available and evaluations can be performed in the conscious horse, it may be the diagnostic modality of choice.

CT and MRI may be indicated to provide additional information. CT allows exceptional visualization of bony proliferation and can reveal fractures that cannot be detected on plain radiographs because of superimposition of structures. Advancements in this technology and full understanding of the appearance of the topographical anatomy have increased the utility of this modality.[3]

MRI yields greater soft tissue detail than CT and is useful in documenting fluid accumulations in the middle and inner ear, as well as identifying inflammatory brain lesions.[1] The biggest impediment to implementing these imaging technologies is the requirement for general anesthesia and the difficulty of recovering a horse with vestibular abnormalities following the procedure.

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Treatment and Prognosis Treatment of THO may include both medical and surgical management. Medical management generally includes antiinflammatory and supportive care. If ptosis and reduced lacrimation lead to exposure keratitis and corneal ulceration, tarsorrhaphy may beneficial, and intensive medical therapy is required. If otitis is suspected, or if there is a suspected fracture into the cranial vault, the use of broad-spectrum antimicrobials with good penetration of the blood-brain barrier is indicated.

Surgical therapy for THO has been described.[1,4] Partial stylohyoidectomy has been used in some cases to reduce the forces on the ankylosed temporohyoid joint and prevent fracture of the petrous temporal bone.[1,4] This procedure risks damage to the adjacent nerves and may result in the formation of a bony union at the stylohyoidectomy site. An alternate technique is ceratohyoidectomy, which eliminates the lever arm that drives movement of and pressure on the temporohyoid joint. Ceratohyoidectomy is technically simpler to perform than partial stylohyoidectomy, avoids the complications of that procedure, and may be performed prophylactically or in cases where fracture of the petrous temporal bone has occurred.[4,5]

The prognosis for horses with THO is good to fair for a return to athletic function. Improvement in neurologic function may continue for up to 2 years. The most common neurologic deficits to persist involve the facial nerve.[1] The most common complication of THO is corneal ulceration due to poor eyelid tone and decreased lacrimation on the affected side. The majority of these horses should recover fully, but healing time may be protracted.[1]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Diseases of the Eye

ELLEN BELKNAP and ANNE J. GEMENSKY METZLER, *Consulting Editors*

Ophthalmic History and Examination

Renee T. Carter*

The clinician's approach to the ophthalmology patient should be similar to the approach taken to patients evaluated for other systemic disorders. Prior to conducting a complete ophthalmic examination, basic information as to the patient's signalment (species, breed, age, coat color, gender), use, and medical history should be obtained. A complete ophthalmic examination is then conducted in a stepwise methodical pattern to ensure all aspects of the eye are evaluated and important diagnostic steps are not overlooked.

Reasons for presentation for ophthalmic examination include:

- Abnormal appearance of one or both eyes (i.e., asymmetry or color change)
- Presence of ocular discharge
- Presence of ocular pain
- Reduced vision or blindness
- Change in the performance/behavior of the patient
- Prepurchase examination
- Follow-up of a previously diagnosed ophthalmic condition
- Examinations for inherited ocular disorders

Ophthalmic History

A series of questions regarding the clinical signs observed, the duration and clinical course of the condition, change in activity/behavior, previous eye problems, and whether other animals have been affected should be ascertained. The clinician should also obtain information on medications the owner has used to treat the eye and the animal's response to therapy. Potential causes for an ophthalmic or visual problem, including any possible relationship to neurologic or iatrogenic (e.g., drug-induced) disease, toxin exposure, or systemic illness, should be explored.

Instruments and Materials

A few basic instruments and materials facilitate an efficient and thorough examination. These include a focused light source (a Finoff transilluminator is preferred), direct ophthalmoscope with a cobalt blue filter, magnifying loupes or optivisor, and a small fixation forceps. Sterile fluorescein dye strips, tear test strips, culture swabs, physiologic saline solution (flushing solution), topical anesthetic (0.5% proparacaine), and mydriatic solution (1% tropicamide) are often also necessary. For fundic examination, a direct or Panoptic ophthalmoscope may be used or indirect ophthalmoscopy can be performed using a handheld lens and light source. To irrigate the nasolacrimal ducts, polyethylene tubing (5 French) should be available.

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Ophthalmic Examination Procedures

General Inspection

Prior to manual restraint, the animal's activities and movements in its normal environment should be observed. This provides insight into the general well-being of the patient and its visual status. The examiner should study the animal's body condition, attitude, posture, coordination, and head carriage and ability to navigate in its normal surroundings. As the animal is approached, closer inspection reveals whether facial and ocular symmetry and normal eye movements are present. Signs of ocular pain (e.g., blepharospasm, apparent photophobia, or epiphora) are noted, as well as size and position of the globes and the presence of ocular or nasal discharge, opacities, or masses.

Restraint

Adequate restraint is essential to conducting a complete ophthalmic examination in large animals. Manual restraint of small ruminants and neonates is usually adequate. For cattle, restraint in a chute with a head catch or in a stanchion with the head pulled laterally by nose tongs or a halter is ideal; restraint of a horse in stocks with a halter is recommended. Chemical restraint may be necessary in cattle, and use of a nose twitch and/or chemical restraint is often needed for horses. The animal's health and duration of the examination should be considered prior to the administration of chemical restraint. Chemical restraint may consist of a combination of injectable sedative (e.g., xylazine or detomidine for horses), with or without an injectable analgesic (e.g., butorphanol for horses). An auriculopalpebral (and occasionally frontal) nerve block using a local anesthetic agent such as 2% lidocaine facilitates examination, especially in patients with a painful ophthalmic condition. Menace responses and palpebral and pupillary light reflexes (PLRs) must be performed prior to administration of sedatives, analgesics, or local anesthetics.

Neuro-ophthalmic Assessment

An evaluation of the integrity of cranial nerves associated with normal ocular function is conducted (see Chapter 8). This includes an assessment of the following prior to sedation:

- Menace response; may not be present in neonates (use tracking or avoidance behavior)
- Palpebral reflex; complete blink response in both eyes to tactile stimuli, both on medial and lateral eyelid stimulation
- Complete direct and indirect pupillary light reflex
- Normal ocular motility when the head is moved side to side

Detailed Examination

Detailed examination of ocular structures should then be performed in a predetermined pattern (i.e., anterior to posterior).[1-3] A set pattern of examination is recommended to avoid interfering with diagnostic tests that may have to be performed (e.g., Schirmer tear test, culture). After evaluation of the animal in its normal environment, it is best

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to move the patient to an environment that is quiet and well-lit for extraocular examination and can be darkened for intraocular examination.

Standing in front of the patient, the clinician should evaluate for alterations in the normal symmetrical appearance of the eyes and periocular structures (Color Plate 39-1). Attention should be paid to lash height, pupil size and position, and globe position. If lashes are pointed downward, this may indicate enophthalmos or ptosis of the lid; if lashes are directed upward, this may indicate exophthalmos (orbital disease) or buphthalmos.

Evaluate the size, shape, and symmetry of the pupils by retroillumination using a focal light source. Evaluate both direct and consensual PLRs in a darkened environment. At this point, the examiner determines whether ocular cultures or tear measurements are desired, because these procedures must be completed before further manipulations are performed and before topical pharmacologic agents are instilled.[4] Depending on clinical signs, severity of ocular disease, and species being examined, viral, bacterial, or fungal cultures may be indicated. Sterile swabs moistened with saline and appropriate enrichment broth or transport media are applied in direct contact with the tissue surface of interest to be cultured.

Palpation of the boundaries of the orbit for irregularities, asymmetry, masses, or fractures should then be performed. The globe is then retropulsed to assess for increased resistance (indicating a space-occupying mass) and to inspect the anterior aspect of the nictitating membrane ("third eyelid"). Retropulsion is performed by gently pressing the globe back into the orbit with a finger placed over the partially closed upper eyelid. Retropulsion should not be performed if the cornea is compromised by a deep ulcer or laceration.

The eyelids are inspected for integrity, position, and movement. Each eyelid is digitally everted for inspection of the margins, meibomian gland openings, and palpebral conjunctiva. Paresis, malposition (entropion, ectropion [Color Plate 39-2]), defects, masses, inflammation (swelling, ulceration, exudate), alopecia, foreign bodies, and abnormal lashes are noted.

The nictitating membranes are examined for normal position, integrity, degree of pigmentation, and the presence of follicles or masses (Color Plate 39-3). To inspect for foreign bodies, topical anesthetic solution (0.5% proparacaine) is instilled two to three times onto the ocular surface. The nictitating membrane is then grasped and manipulated with small fixation forceps, and both sides are examined for foreign bodies. Care should be taken not to damage the cartilage of the third eyelid with toothed forceps.

Normally the conjunctiva appears moist, glistening, and semitransparent. Signs of conjunctivitis are chemosis (conjunctival edema), hyperemia, and ocular discharge. Color changes of the conjunctiva usually accompany anemia (blanched, pale) or icterus (yellow, amber). Chemosis may indicate severe hypoproteinemia. Conjunctival lesions noted include focal swellings, follicles, adhesions, or masses. The sclera underlying the bulbar conjunctiva is inspected for color, contour, swellings, masses, pigmented areas, or surface irregularities.

Lacrimal system examination entails evaluation of both secretory and excretory components. Normal secretions result in a moist, glistening ocular surface. Although not typically performed in large animals, tear test strips may be used to quantify aqueous tear secretion (see Ancillary Diagnostic Procedures). Schirmer tear testing is indicated in cases with a lackluster corneal appearance or persistent keratitis. To examine the excretory components, the upper and lower puncta and nasal openings of the nasolacrimal system are identified (Color Plate 39-4). Any overflow of tears onto the face (epiphora) is noted. Causes of increased ocular secretions (e.g., frictional irritants, foreign bodies, corneal ulcers, ocular inflammation) must be ruled out. Causes for stimulation of lacrimal secretions must be differentiated from causes of outflow occlusion, such as congenital atresia and acquired obstruction of the nasolacrimal system.

Application of fluorescein dye can detect corneal ulceration and aids in assessment of nasolacrimal system patency. Passage of dye from the nasal opening of the nasolacrimal duct within 5 minutes confirms patency (Jones test). Retrograde irrigation of the nasolacrimal duct by inserting a length of 5-French flexible tubing into the nasal punctum and flushing with saline may be necessary to differentiate insufficient drainage from excessive secretions.

The rest of the ophthalmic examination is performed in a darkened area. Using a focal light source, obtain the fundic reflex to highlight opacities in the ocular media (aqueous, lens, or vitreous). Opacities in the ocular media will obstruct the fundic reflex (Color Plate 39-5); using this reflex, the examiner may also compare symmetry of the pupils.

The cornea is then examined for irregularities and opacities. The cornea is an avascular structure that is smooth and transparent, with a moist reflective surface. Direct a focal light source across the cornea (parallel) to highlight corneal irregularities. Localization of opacities to the cornea can be conducted by using this technique or alternatively with a direct ophthalmoscope or handheld slit-lamp.

Corneal edema appears as a hazy blue corneal opacity and should be characterized as localized or diffuse (Color Plate 39-6). With severe corneal edema, bullae (vesicles) may be noted. Infectious keratitis is characterized by suppuration and necrosis. The cornea becomes more densely opaque and acquires a beige, green, or milky appearance when infiltrate is present; the margins will be indistinct and the eye painful. Corneal abscesses occur as focal areas of suppuration within the stroma underlying a nonulcerated cornea (Color Plate 39-7).

Corneal opacities may also result from focal or diffuse scarring (gray with distinct margins), areas of corneal degeneration or dystrophy (white, chalky to refractile with distinct margins), or stretching of Descemet's membrane (Haab's striae) from elevation of intraocular pressure or previous trauma (parallel lines, resemble "railroad tracks" [Color Plate 39-8]). Inflammatory products clustered on the corneal endothelium (keratic precipitates) appear as multiple beige or brown foci, usually on the ventral aspect of the corneal endothelium. This finding indicates the presence of anterior uveitis.

Intraocular examination begins with evaluation of the clarity and depth of the anterior chamber. The anterior chamber can be evaluated using a direct ophthalmoscope set on the slit-beam setting (light perpendicular to the cornea and brought close until in focus), a handheld slit-lamp, or a transilluminator directed parallel to the cornea (Color Plate 39-9). An optivisor may be needed for magnification. Opacities within the anterior chamber include inflammatory products (cells and fibrin), proteins (flare), red blood cells (hyphema), or white blood cells (hypopyon). Suspended or clustered inflammatory materials in the anterior chamber indicate anterior uveitis. Besides the presence of exudates, loss of anterior chamber transparency may result from lens luxation, vitreal prolapse, anterior synechia, or intraocular masses (neoplasia or foreign bodies). Loss of normal anterior chamber depth may result from leakage of aqueous humor, iris prolapse, iris bombé (forward bulging of the iris caused by iris-lens adhesions), or anterior lens luxation. Increased depth of the anterior chamber may be caused by a protruding cornea (keratoconus), a hypermature (resorbing) cataract, or posterior lens luxation.

The iris is inspected for altered contour, pigmentation, mobility, neovascularization, pupil size and shape, and the presence of uveal masses (including the normal granula iridica). Granula iridica (i.e., corpora nigra) are normal structures present along the pupil margin. These structures may atrophy with chronic uveitis or become cystic. Transillumination of uveal masses allows differentiation of solid structures (e.g., melanoma) from uveal cysts. In animals with lightly colored or spotted hair coats, multicolored irides should be recognized as normal variants. Although uncommon, congenital iris thinning (hypoplasia) may be noted as dark, flat, or translucent areas when transilluminated. The lens-iris interface is best evaluated when the pupil is dilated. Iris membranes, adhesions, or strands should be characterized as congenital (persistent pupillary membranes) or acquired (synechiae or remnants of iris atrophy) (Color Plate 39-10).

Pupillary openings are evaluated for size, shape, symmetry, movements, and opacities. Direct and indirect (consensual) PLRs are

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assessed. The examiner must recall that PLRs are not a test of vision (i.e., abnormal responses may be observed in visual animals, and normal reflexes may occur in nonvisual animals). Pupillary abnormalities that should be noted are inequality in size (anisocoria), abnormal movements (hippus), abnormal location (corectopia), or abnormal shape (dyscoria) (Color Plate 39-11).

Opacities of the pupil usually result from loss of lens transparency or from presence of intraocular exudates. Obscuration of the pupil space may occur with severe miosis (from acute anterior uveitis), anterior lens luxation, condensation of anterior chamber exudates, and synechiae formation (from chronic uveitis). In animals with normal PLRs, complete examination of the lens and structures posterior to the lens (i.e., vitreous and fundus) may be achieved only after dilation with a mydriatic agent such as 1% tropicamide, which usually occurs 20 to 30 minutes after instillation. Once dilated, repeat retro-illumination of the ocular media to evaluate for any opacities blocking view of the fundic reflex; fundic examination can then be performed.

Using a focused light, the lens is inspected for a smooth, transparent, convex anterior capsule and normal position (no part of the equator should be visible). When evaluating for lens opacities (cataracts), the examiner should direct the focused light through the axial part of the lens to establish the presence of a fundic reflex. Cataractous changes are observed as dark areas seen within the area of reflected light. Cataracts may be classified according to the extent to which a fundic reflex is obstructed; a *partial reflex* indicates an incomplete cataract, whereas an *absent reflex* indicates a complete cataract. If the lens profile appears distorted (wrinkled) with numerous refractile particles present, this is typically indicative of a hypermature (resorbing) cataract. Evaluate the depth of the anterior chamber and for aqueous flare by using a small focal light source directed perpendicular to the cornea. This can be performed using the small spot of light or slit-beam on a direct ophthalmoscope. Alternatively, a handheld slit-lamp may be used. The anterior chamber is the space between the cornea and iris that contains aqueous humor. Breakdown of the blood-ocular barrier (anterior uveitis) (Color Plate 39-12) will result in increased protein in the anterior chamber and can be detected as aqueous flare. The anterior chamber will appear shallow in cases with phthisis bulbi, anterior synechiae, iris bombé, or anterior lens luxation. The anterior chamber will appear deep in cases with hypermature cataracts, buphthalmia, and posteriorly luxated lenses.

Ophthalmoscopy must be used to examine the vitreous and fundus. The direct ophthalmoscope provides an upright image and high magnification, but it requires a close working distance and provides a small field of view, making it a poor screening tool. Using the direct ophthalmoscope, the vitreous should be in focus with a dioptric setting between +6 to +1, and the fundus is usually in focus between +1 and −2 diopters. Monocular indirect ophthalmoscopy (Panoptic) provides an upright image; moderate magnification and field of view are provided. Indirect ophthalmoscopy provides an inverted virtual image with a less magnified view, making it a better screening tool.

The vitreous is first examined for congenital remnants (retained hyaloid structures) and opacities, including degenerative materials or exudates. Examination of the fundus begins with identifying the optic disc (papilla) and studying its size and shape. The shape, location, and vascular pattern of the optic disc and the appearance of the fundus vary considerably among species. In ruminants the optic disc margin typically appears irregular and fluffy, indicating myelination of axons entering the optic disc. However, it tends to be horizontally elliptical or kidney shaped and located in the tapetal portion of the fundus.[5] An optic disc with extensive myelination may be elevated above the surface of the fundus (sometimes called *pseudopapilledema*). In ruminants the major retinal arterioles are large and are accompanied by venules that anastomose on the surface of the optic disc. The dorsal arteriole and venule usually intertwine as they course away from the disc over the midtapetum (Fig. 39-1). By contrast, the equine fundus is characterized by a large pink or salmon-colored

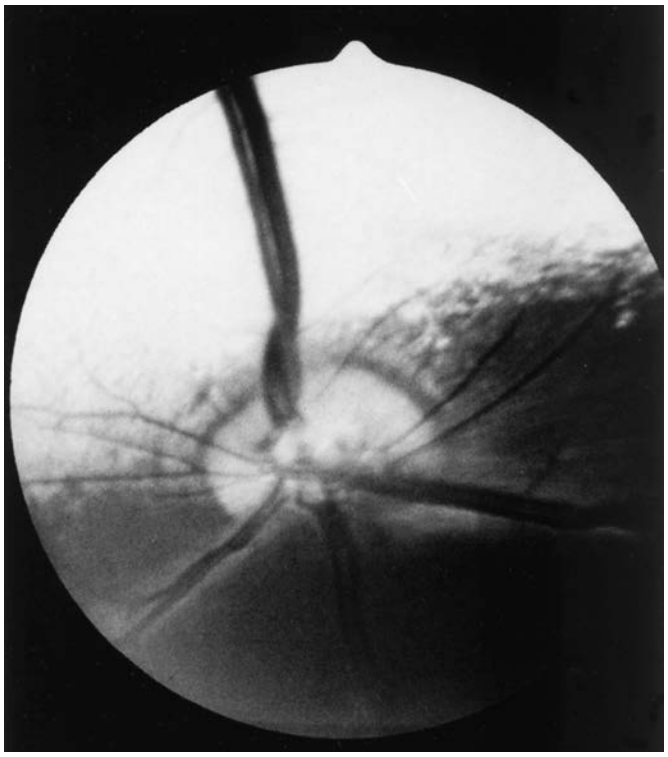


FIG. 39-1 Normal ruminant fundus characterized by a large, kidney-shaped, myelinated optic disc. Note that the large retinal arteriole and venule intertwine as they course dorsally.

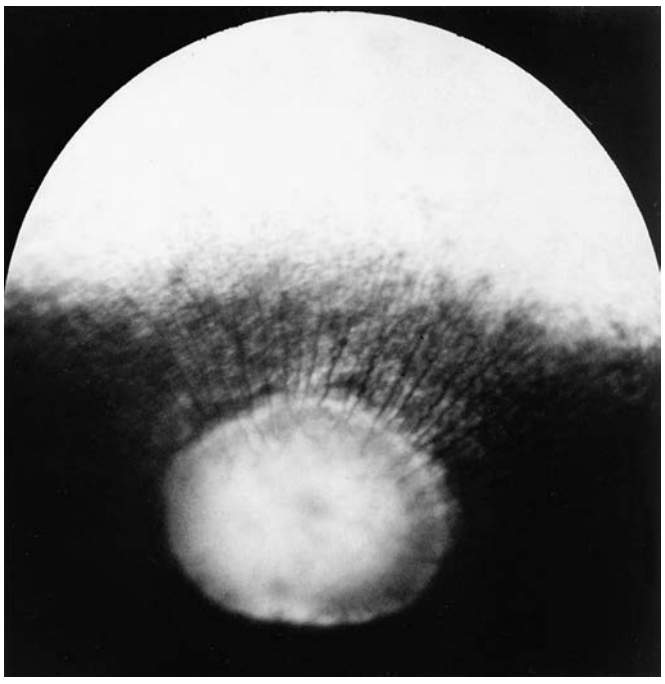


FIG. 39-2 Normal equine fundus characterized by a large, horizontally elliptical optic disc with numerous small retinal vessels entering (arterioles) and exiting (venules) the margin of the optic disc. Note that the optic disc lies in a nontapetal portion of the fundus.

horizontally elliptical or oval disc located in the nontapetum[5] (Fig. 39-2). Horses are *paurangiotic,* meaning they have vessels that only extend a short distance from the optic nerve head. The small retinal blood vessels extend radially from the margin of the disc, and no anastomotic venules are visible over the optic disc.

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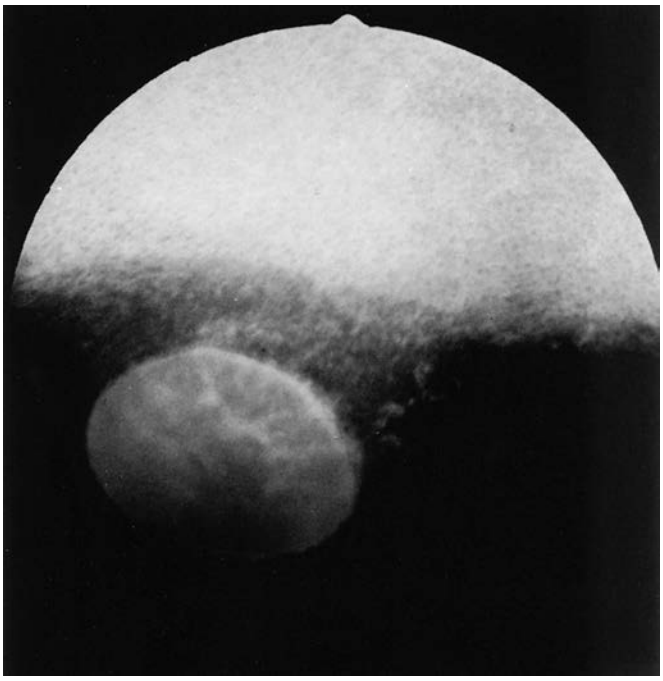


FIG. 39-3 Optic nerve atrophy (equine). Margin of disc is quite distinct because of myelin loss, which is characteristic of optic nerve atrophy. Note absence of retinal blood vessels.



FIG. 39-4 Pigmentary changes after traumatic chorioretinopathy. Irregular linear areas of hypopigmentation and hyperpigmentation are present in the tapetal fundus of a horse after ocular trauma. Pigmentary changes reflect retinal pigment epithelial disturbance from previous hemorrhage and edema. *(Courtesy Dr. K.N. Gelatt.)*

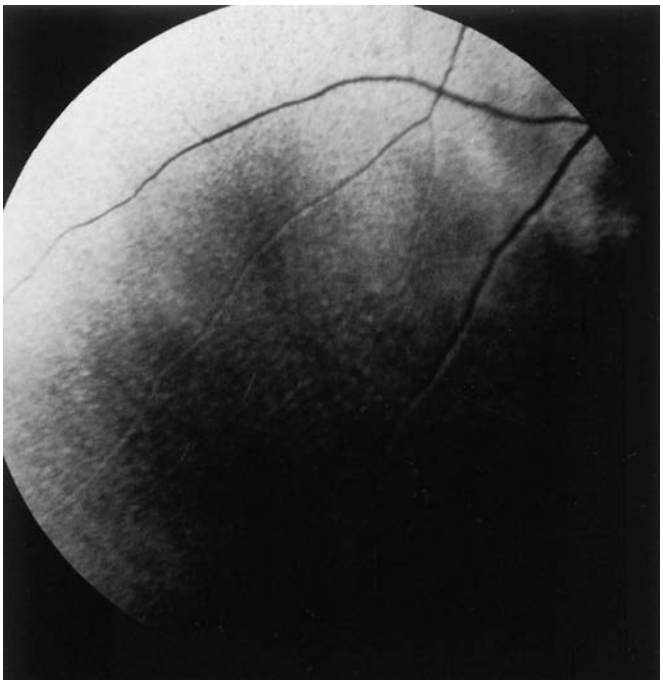


FIG. 39-5 Retinal degeneration (bovine). Peripheral retinal vessels are greatly attenuated near the tapetal-nontapetal junction. Attenuation is accompanied by hyper-reflectivity of the tapetal region. These changes are consistent with generalized retinal atrophy.

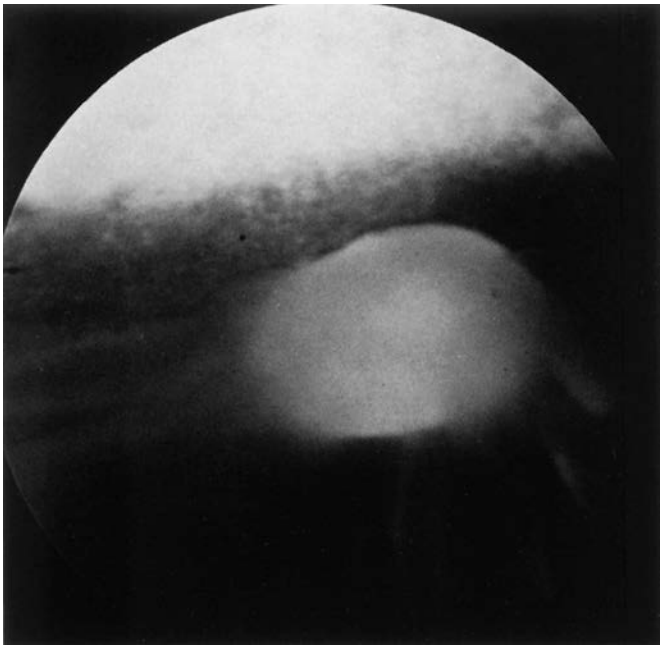


FIG. 39-6 Retinal separation (equine). Gray linear areas radiate from the optic disc into the nontapetal region of fundus. Note that the margin of the disc is quite indistinct in the affected area. Absence of retinal vessels indicates concurrent retinal degeneration.

In both ruminants and horses the fibrous tapetum is present in the dorsal two thirds of the eye and is penetrated by choroidal capillaries; thus the fundus in these species is typified by dark, stippled foci termed *stars of Winslow* (end-on capillaries). Coloration of the tapeta of large animals also varies considerably and may range from gold to bluish green. In animals with heterochromia irides, areas of the fundi may characteristically be devoid of pigmentation and may lack a tapetum. These areas may appear orange or red because of direct visualization of the choroidal vasculature.

Abnormalities of the optic disc include hypoplasia (micropapilla), elevation (papilledema), depression (cupping), degeneration (atrophy [Fig. 39-3]), and vascular changes (e.g., congestion, attenuation, hemorrhage). The tapetal fundus is evaluated for clarity, coloration, pigmentation (Fig. 39-4), and integrity of the retinal vessels (Fig. 39-5). The nontapetal fundus is evaluated for uniformity of pigmentation. Both tapetal and nontapetal areas are assessed for retinal elevations or separations (Fig. 39-6), hemorrhages, degenerations, disorganization (dysplasia), or scleral defects (colobomas).[5]

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Ancillary Diagnostic Procedures

Several additional procedures may form important supplements to the complete ophthalmic examination. Although some ancillary procedures require specialized equipment and expertise, many may be performed in general practice.

Fluorescein and rose bengal are ocular surface stains most often used as aids in diagnosing conjunctival and corneal diseases. The tip of a sterile dye strip is moistened with saline or eye-irrigating solution, and a drop of the stain is instilled onto the eye. Fluorescein is a water-soluble dye used to detect exposed corneal stroma resulting from an epithelial defect (erosion), stromal ulceration, or descemetocele and is viewed with cobalt blue light. The pattern of fluorescein staining for a descemetocele is characterized by a donut-shaped area of positive fluorescence, with the perimeter retaining stain and the center or deepest area (Descemet's membrane) not retaining stain. Fluorescein may also be used to evaluate the patency of nasolacrimal ducts, because an open duct allows the transmission of stain, which may be observed exiting the duct system at the nasal orifice (Jones test). Rose bengal is retained by devitalized surface cells and is therefore useful in detection of subtle abnormalities like hyperplastic or desquamating cells associated with ocular surface drying, herpetic infection, keratomycosis, or squamous cell carcinoma. Stain uptake appears pink when illuminated with white light.

Although tear deficiencies are uncommon in large animals, tear test strips may be beneficial to quantify aqueous tear production in selected cases. A sterile filter paper strip (40 × 5 mm with notched end) is inserted into the lower conjunctival fornix. In large animals it is sufficient to measure the amount of wetting in 30 seconds (≥20 mm is normal). Tear testing is indicated in patients with a dry, lackluster corneal surface, persistent ocular discharge, or keratitis.

Cytologic evaluation of ocular surface scrapings or intraocular aspirates may differentiate between inflammatory and neoplastic diseases or in some cases may provide a definitive diagnosis. Orbital aspirates may be diagnostic in cases of exophthalmos caused by neoplasia (e.g., lymphosarcoma). Immunofluorescent or polymerase chain reaction (PCR) testing of cytologic specimens may confirm viral (e.g., infectious bovine rhinotracheitis) or *Chlamydophila* infections.[3] Bacterial cultures taken from the ocular surface or from ocular aspirates, with subsequent antimicrobial susceptibility testing, may be necessary for definitive diagnosis and appropriate treatment of ocular infections. The diagnostic laboratory performing ocular cultures may offer suggestions on culture procedures, including preferred transport media and handling of samples. It is especially important to consult with the laboratory in advance when anticipating culturing for fungi, *Mycoplasma, Chlamydophila,* or viral agents.

Tonometry, a means of measuring the intraocular pressure (IOP), is useful in diagnosing glaucoma (elevated IOP) and uveitis (low IOP) and in assessing response to therapy for these conditions. Tonometry is indicated in cases with corneal edema, redness, lens luxation, abnormal PLR, and cases with vision loss or a history of glaucoma. Digital tonometry (gently indenting the globe through the upper eyelid) is not considered an accurate measure of IOP; Schiøtz tonometry is not applicable to large domestic species. Applanation tonometry using instrumentation such as the TonoPen provides accurate and reproducible IOP readings in large animals and is routinely performed. Additionally, use of the rebound tonometer, TonoVet, has been used successfully and can be calibrated for use in equine patients. The clinician should be aware that eyelid blocks, sedation, and head position can all impact IOP readings.

Biomicroscopy using a portable handheld slit-lamp is useful for identifying the location and nature of anterior ocular opacities. Focal irritants (e.g., ectopic cilia, small foreign bodies) and small lesions may only be visible with the magnification provided using biomicroscopy. Alternatively, use of a focal light source with magnification in the form of an otoscope or optivisor may be helpful in providing magnification.

Funduscopic examination may be performed relatively quickly and easily using the technique of indirect ophthalmoscopy. Monocular indirect ophthalmoscopy is performed using a handheld light source and a separate 20- or 14-diopter focusing lens for equine and bovine patients; a 28-diopter lens may be utilized for smaller ruminants.

Other ancillary diagnostic procedures include electroretinography (to evaluate retinal function), visual evoked potentials (to evaluate visual pathways), and imaging procedures (radiography, ultrasonography, computed tomography [CT]). Although plain skull radiographs and some contrast studies (e.g., dacryocystorhinography) may be performed in a general practice setting, the remaining procedures require techniques and equipment usually available only at referral centers.

Signs of Ocular Disease

Renee T. Carter[†]

Symptoms of ocular disease can be grouped into 5 primary categories at the time of presentation:

- Ocular or periocular asymmetry
- Ocular color change
- Ocular discharge
- Ocular pain
- Visual deficits or blindness

Patients may present with one or a combination of these clinical signs. This section provides a general description of the signs and examples of ocular diseases in which a particular sign predominates. Table 39-1 summarizes common signs of ocular disease in large animals.

Ocular or Periocular Asymmetry

Ocular or periocular asymmetry results from unilateral changes in facial soft tissue or orbital structures, orbital volume, globe size, eyelid position, or pupil size and position. Changes in symmetry often involve a reduction or increase in volume of a certain tissue. *Reduction* in tissue volume occurs with congenital hypoplasia, cicatricial shrinkage, atrophy, or dehydration. *Increase* in tissue volume may involve the whole globe (buphthalmos) or be characterized by irregular enlargement, as seen with inflammatory or neoplastic lesions involving the globe, orbit, or eyelids. Asymmetry may also result from a neurologic dysfunction. Common examples include reduced palpebral fissure size (secondary to facial nerve paralysis), strabismus, third eyelid protrusion, and anisocoria (see Chapter 8). This section describes the common signs of ocular disease. It is not the intent to describe in detail each of the diseases that may be noted; these disorders are covered in other sections of this chapter.

Change in Globe Position

Changes in globe position affect symmetry and include exophthalmos, enophthalmos, and strabismus. Forward displacement of the eye (exophthalmos) (Fig. 39-7) is often associated with a space-occupying orbital lesion (neoplasia, inflammatory, vascular, cystic) or, less often, a congenitally shallow, underdeveloped orbit. Posterior malposition of the globe (enophthalmos) may result from active globe retraction caused by pain or from loss of supporting retrobulbar soft tissues as seen in cases of muscle atrophy, loss of orbital fat, or denervation. Congenital strabismus is a developmental abnormality that results in ocular asymmetry due to deviation of normal globe position and has been reported in Jersey, Shorthorn, Holstein, and German Brown Swiss cattle.[1,2] Strabismus can occur with exophthalmos and has also been associated with systemic disorders such as

[†]Contributions to previous editions by Cecil P. Moore and David J. Maggs are acknowledged.

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TABLE 39-1

Causes of Important Ocular Signs in Large Animals

Signs/Findings	Cause(s)		
	All Species (Ruminants and Horses)	Ruminants	Horses
Red Eyes			
Surface Redness			
Hemorrhage	Trauma Clotting disorders		
Hyperemic mass	Granulation/healing corneal ulcer Ocular squamous cell carcinoma Hemangiosarcoma		*Habronema* granuloma
Diffuse Redness			
Conjunctivitis/keratitis	Entropion Foreign body Chemical irritation	*Moraxella* (IBK) *Mycoplasma* (O, C) *Chlamydia* (O) Herpesvirus (IBR) (B, C) *Branhamella* (B) Bluetongue	Fungal keratitis *Pseudomonas* *Streptococcus* Coliforms
Uveitis	Septicemia Trauma	*Mycoplasma* Malignant catarrhal fever (B)	Immune-mediated uveitis (ERU)
Glaucoma	Trauma	IBK (B)	ERU
Hemorrhage	Trauma		
Cloudy Eye (Ocular Opacities)			
Cornea	Keratitis Trauma Ulcers	Infectious keratoconjunctivitis (see causative agents above for Conjunctivitis/keratitis by genus)	
	Scars (healed ulcers) Uveitis (see under Red Eyes) Glaucoma	IBK (B)	ERU
Anterior chamber			
Exudates, blood	Trauma Uveitis (see under Red Eyes) Glaucoma	 *Mycoplasma* (C) Septicemias (B, C, O)	ERU
Lens luxation (anterior)	Trauma		ERU
Lenses (cataracts)	Trauma Congenital (see Chapters 51 and 52) Genetic Uveitis (see under Red Eyes)		ERU
Vitreous			
Exudates, blood	Trauma (hemorrhage, detached retina) Uveitis (see under Red Eyes)	Congenital hyaloid vascular remnants (B)	ERU
Lens luxation (posterior)	Trauma		ERU
Ocular Discharge			
Watery (serous)		Conjunctivitis/keratitis (see specific etiologies under Red Eyes)	
Painful eye	Ectopic or misdirected cilia Foreign body (plant awn) Entropion Uveitis (see under Red Eyes) Trauma (ulcer, uveitis) Chemical irritation		
Nonpainful eye	Nasolacrimal atresia Nasolacrimal obstruction (acute blockage)		
Thick (mucoid or mucopurulent)	Foreign body Surface tumors Dacryocystitis Chronic nasolacrimal blockage Foreign body Sinusitis Bacterial infections	Infectious keratoconjunctivitis (see causative agents under Red Eyes for Conjunctivitis/keratitis by genus)	
Hemorrhage	Trauma Foreign body Ulcerative conjunctivitis Tumor		

B, Bovine; *C,* caprine; *ERU,* equine recurrent uveitis; *IBK,* infectious bovine keratoconjunctivitis; *IBR,* infectious bovine rhinotracheitis; *O,* ovine.

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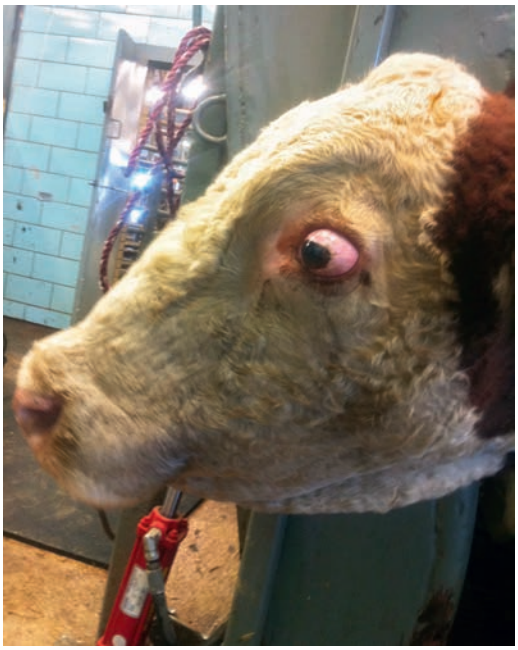


FIG. 39-7 Hereford with marked exophthalmos of the left eye that was present bilaterally.

polioencephalomalacia and listeriosis.[2] Unequal orbit volume resulting in displacement of the globe or globe malposition may also occur with traumatic orbital fractures.

Change in Globe Size

Unequal globe size can also account for ocular asymmetry. A congenitally small globe (microphthalmia) occurs as a genetic defect in cattle and horses[1,3] and has also been associated with exposure to infectious agents and teratogens. Microphthalmia is frequently accompanied by multiple ocular anomalies and may be associated with multiple organ involvement or vertebral abnormalities.[2] Acquired variations in globe size usually result from shrinkage of the globe (phthisis bulbi [Color Plate 39-13]) secondary to chronic uveitis; stretching or enlargement of the globe (megaloglobus, buphthalmos) occurs with glaucoma.

Changes in Eyelid Conformation

Asymmetry of the upper or lower eyelid may be due to entropion, ectropion, blepharitis, conjunctivitis, or facial nerve paralysis (ptosis). Entropion has been reported in Simmentals[1] but most commonly occurs secondary to microphthalmos or enophthalmos (retraction of the eye with pain, reduction in orbital volume, denervation). Trauma with secondary scar formation may result in either entropion or ectropion. Nictitating membrane (third eyelid) protrusion is frequently seen secondary to active retraction of the globe in response to ocular pain, enophthalmos caused by loss of orbital contents (dehydration, malnutrition, atrophy), presence of third eyelid masses, orbital space-occupying masses, or neurologic disorders (e.g., Horner syndrome, tetanus).

Anisocoria

Pupillary asymmetry, or anisocoria, may develop for a variety of reasons that can be grouped into (1) primary iridal lesions, including congenital iridal defects (hypoplasia, aniridia, coloboma, anterior segment dysgenesis, synechia, iris atrophy), (2) neurologic disorders (Horner syndrome, oculomotor nerve dysfunction), (3) intraocular diseases (uveitis, glaucoma, unilateral retinal lesions), (4) diseases involving the optic nerve or brainstem, and (5) previous use of pharmacologic agents like atropine that alter iris smooth muscle function.

Changes in Tissue Volume

The presence of an ocular mass may be the primary cause of ocular asymmetry. Ocular surface neoplasms are relatively common in horses and cattle. Ocular squamous cell carcinomas usually arise from nonpigmented tissues of the nictitating membrane, the lateral limbal region, or the eyelid margin (where UV light exposure is highest).[4] They may appear as irregularly raised, papillary surface masses or, less often, as smooth, vascularized lesions that invade the globe. Ulceration, exudation, and mucopurulent ocular discharge are frequent concurrent findings (see Ocular Neoplasia). Periocular sarcoids are also common in horses; their appearance is variable, ranging from flat foci of alopecia to fleshy or nodular nonulcerative lesions.[5,6] Other ocular tumors occur in large domestic animals but are relatively uncommon. Dermoids and orbital cysts are congenital masses involving the periocular tissues, eye, or orbit. Other nonneoplastic ocular masses seen in large animals include firm parasitic and foreign body granulomas and soft, fluctuant subconjunctival swelling characteristic of prolapsed periorbital fat. Ocular and orbital pseudotumors have also been described in the horse.[7]

Ocular Color Change

Changes in the color of ocular or periocular tissues or the presence of opacities in the clear ocular media (cornea, aqueous humor, lens, or vitreous) are important features of ocular disease. Such changes must be differentiated from normal congenital differences in ocular pigmentation. Developmental color dilution or absence of ocular pigmentation results in light or multicolored irides (heterochromia iridis). Examples of abnormal coloration include hyperemia of conjunctival (superficial) or episcleral (deep) blood vessels associated with ocular inflammation (see Red Eyes in Table 39-1), hemorrhage secondary to trauma or coagulopathies, pallor of the conjunctiva (which reflects severe anemia), and yellowing of the sclera and sometimes iris, indicating icterus. A change in the color of the iris may also occur with anterior uveitis.

Opacities of the ocular media may occur either as surface (corneal) or intraocular (anterior chamber, lens, or vitreous) phenomena. Brown discolorations of the cornea are the result of pigmentation, iris prolapse, embedded foreign body, or pigmented fungal plaques. Grayish scars occur from previous episodes of keratitis; infectious keratitis will present with cream- to white-colored infiltrate; corneal degeneration will appear as white deposits of lipid or mineral; vascularization occurs secondary to chronic inflammation or neoplasia; and bluish discoloration is caused by corneal edema. These color changes frequently occur in various combinations in more severe keratitis, especially those of infectious origin such as chronic keratoconjunctivitis caused by *Chlamydophila* spp., *Mycoplasma* spp., or *Moraxella bovis*. Cataracts are perhaps the most obvious cause of intraocular opacities in large animals (Color Plate 39-14). Inherited cataracts have been reported in Thoroughbreds, Quarter Horses, Morgans, and Rocky Mountain horses.[8] However, the presence of exudates within the aqueous humor or vitreous, congenital vascular remnants in the vitreous, degeneration of the vitreous, or retinal detachment may also account for intraocular opacities (see Table 39-1).

Ocular Discharge

Ocular discharge can be characterized as serous (epiphora), mucoid (catarrhal), purulent, or hemorrhagic (sanguineous). The type of discharge may assist in determining the severity and chronicity of the eye disease. Serous discharge generally indicates mild eye disease, whereas mucopurulent or hemorrhagic discharge indicates more serious disorders. A notable exception to this generalization is *equine recurrent uveitis* (ERU), which is associated with serous discharge (see Immune-Mediated Ocular Diseases). The nature of ocular discharge tends to change as the disease progresses or improves. This is most notable in inflammatory or infectious ocular diseases. Initially

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the discharge is predominantly serous, but it tends to become mucopurulent with chronicity (see Table 39-1).

Epiphora describes facial wetting and results from overflow of tears over the eyelid margin. This may result from excessive secretion of tears (e.g., painful stimulus) or from physical or functional obstruction of the nasolacrimal system. In large animals, reflex lacrimation with an associated overabundance of tears is the typical response to ocular irritation or inflammation (e.g., foreign body, lash disorders, conjunctivitis, keratitis, uveitis). When epiphora is noted, careful digital and visual examination for foreign bodies within the conjunctival fornix or under the third eyelid is indicated. Epiphora is generally one of the earliest signs of conjunctivitis, ulcerative keratitis, or anterior uveitis. In cattle with keratoconjunctivitis caused by *Moraxella bovis,* epiphora is present several days before visible corneal ulceration occurs[9] (see Infectious Bovine Keratoconjunctivitis).

Developmental defects or malformations of the nasolacrimal duct system (e.g., imperforate puncta) results in epiphora secondary to impaired outflow in neonates. In these cases, the presence of epiphora may be misinterpreted as overproduction of tears. Previously undiagnosed congenital defects may also be the cause of persistent ocular discharge in adult animals. Acquired obstructions of the nasolacrimal ducts may result from infections, foreign bodies, facial trauma, nasal tumors, or sinusitis that involve the duct system. Whether congenital or acquired, simple nonseptic obstructions are characterized by epiphora; septic occlusions result in mucopurulent discharge from the eye or nostril on the affected side. Excessive mucus production is a feature of follicular conjunctivitis, possibly as a result of the rubbing of elevated lymphoid follicles on apposing conjunctival surfaces. Lymphoid follicles are noted in subacute or chronic forms of chlamydial conjunctivitis in sheep and with *Onchocerca* larval migration in horses. Mucoid ocular discharge may be observed concurrently with epiphora in acute ocular surface infections caused by viral or chlamydial agents. Excessive tenacious mucus may also result from inadequate secretion of the aqueous component of tears (i.e., keratoconjunctivitis sicca). Although keratoconjunctivitis sicca is not diagnosed as commonly in large animals as it is in dogs, it has been reported in horses, usually as a complication of guttural pouch pathology.[10]

Purulent to mucopurulent material is characteristic when bacterial organisms are involved in the ocular disease process. Bacterial conjunctivitis occurs frequently in large domestic species and manifests as red eyes with copious mucopurulent ocular exudate. Ocular foreign bodies and surface masses (e.g., squamous cell tumors) typically have associated bacterial infections. Mucopurulent discharge in the absence of ocular inflammation suggests infection of the nasolacrimal sac (dacryocystitis) or ducts, with reflux of exudate from the lacrimal puncta.

Sanguineous or hemorrhagic discharge most often occurs after blunt or penetrating trauma to the eye (see Ocular Trauma). Foreign body penetration may damage the eyelid, conjunctiva, or globe, resulting in bleeding onto the ocular surface. Corneal ulcers may rupture and result in uveal prolapse and subsequent hemorrhage on the ocular surface. Patients with conjunctivitis or ocular surface tumors may develop ulceration resulting in bloody ocular discharge. Whenever blood is noted on the surface of the eye, it is imperative that a thorough ophthalmic examination be performed to determine the cause and evaluate integrity of the globe.

Ocular Pain

Ocular pain can be manifested as blepharospasm, epiphora, photophobia, and periocular hyperesthesia. Animals with severe ocular pain usually resist manipulation of the eyelids or any form of ocular examination by persistently jerking the head away from the examiner and by closing the eyelids tightly. In cases of persistent ocular inflammation, discomfort and pruritus may be manifested by rubbing and self-trauma to ocular or periocular structures.

Ocular pain may result from conjunctivitis, trauma, keratitis, uveitis, and glaucoma. Other causes of ocular pain include mechanical irritation from entropion, trichiasis, distichia, ectopic cilia, or foreign material.[11] Foreign bodies causing ocular irritation in large animals are typically plant materials like seeds, hay stems, straw, twigs, bark, or thorns, although particles of sand or soil can also cause severe ocular irritation. Non-embedded particulate matter is usually entrapped by mucus and washed out of the eye by reflex tearing; it typically results only in transient discomfort. By contrast, embedded foreign material (i.e., between ocular surface layers or within ocular tissues) causes persistent ocular pain.

Blindness

Visual deficits in large animals manifest in a variety of ways. Obvious signs include bumping into objects and lack of response to visual stimuli such as light or hand motions. Another sign of blindness is reliance on stationary objects (e.g., fences, railings, other animals) to maneuver within the environment. Behavioral changes include reluctance to move or to venture into unfamiliar areas, nervousness, and spooking in response to sudden noises or movements.[12] The nonvisual animal is frequently found standing isolated from the group and may experience injury by dominant individuals in the herd and suffer from weight loss.[12] Searching nystagmus is also seen in some animals with congenital blindness.

Nonvisual animals attempt to compensate for loss of vision with their other senses, which may result in an elevated head position or a head tilt. Patients may also exhibit snorting or intensive sniffing associated with nervousness, and maximum neck extension is observed. Frequently, blind animals will show exaggerated elevation of the limbs while walking. This must be differentiated from true hypermetria (see Chapter 8). Partial loss of vision may be difficult to determine, and detection depends on observing more subtle behavioral changes such as slight head cocking or tilting, difficulty maneuvering in dim light, or shying and startling from objects on one side or objects present in some specific part of the visual field. Conduction of a maze test will assist the clinician in the detection of partial vision loss. Animals may effectively compensate for congenital blindness or slow diminution of vision, particularly when they remain with other unaffected animals in a familiar environment. Visual disturbance may not be apparent until an affected animal is isolated or moved to an unfamiliar area.

There are numerous causes of blindness in large animals, including those that involve only the visual system and some that involve other nervous system tissues or are multisystemic (Box 39-1). A functional approach to blindness involves anatomically classifying the cause as one of the following:

- Cloudy ocular media (light does not reach the retina)
- Retinal detachment or retinopathy
- Optic nerve or central nervous system (CNS) disorder

Assessment of PLRs aids in localization of the lesion. Cloudy ocular media will be identified on retro-illumination. Animals with lesions involving the retina, optic nerves, optic chiasm, or optic tracts generally do not have a normal PLR, whereas those with more central ("higher") lesions involving the lateral geniculate bodies, optic radiations, or occipital (visual) cortex are likely to exhibit a normal PLR (see Chapter 8).

Ocular Trauma

Kristina R. Vygantas[‡]

Causes of Trauma

Because the eye is anatomically prominent in horses and food animals, it is prone to blunt and sharp trauma, which can range in

[‡]Contributions to previous editions by R. David Whitley and Elizabeth M. Whitley are acknowledged.

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BOX 39-1

Lesions and Diseases Causing Visual Deficits or Blindness

Obstruction of the Ocular Media*

Cornea

Scarring, edema, melanosis ("pigmentation"), inflammatory cell infiltration

Anterior Chamber

Hyphema, hypopyon, fibrin

Lens

Cataract

Vitreous

Vitreal exudation (white blood cells), vitreal hemorrhage

Retinopathies

Degenerative

Glaucoma
Retinal degeneration

Congenital

Retinal dysplasia
Microphthalmia
Retinal detachment

Inflammatory

Retinitis/chorioretinitis
Phthisis bulbi
Retinal detachment

Extraocular and Central Nervous System Disease

Congenital/Inherited

Optic nerve hypoplasia
Storage diseases (e.g., ceroid lipofuscinosis in sheep)

Inflammatory

Optic neuritis
Meningitis/encephalitis
Trauma
Neoplasia

Toxic/Nutritional

Toxic optic neuropathy (e.g., male fern)
Vitamin A deficiency (e.g., optic neuropathy/hydrocephalus)

*See Cloudy Eye (Ocular Opacities) in Table 39-1.

severity from a mild abrasion caused by a conjunctival foreign body to a severe corneal laceration with globe rupture and orbital bone fracture. Ocular injuries may result from a variety of causes, including foreign materials such as soil, sand, or stones, which may be thrown into the eye during running or by the wind; trauma from disciplinary action; scratches by vegetable matter such as hay, weed stems, tree limbs, or thorns; exposure to chemical irritants; and sudden, violent head movements during training, working, or grooming. Other sources of ocular injury include stanchions, stall or trailer latches, hooks, protruding nails, bucket handles, fencing materials, and other animals, particularly horned ruminants.

Recumbent neonates and animals with CNS disease or severe illnesses that cause depressed mentation often suffer eye injuries from abrasion by debris or bedding materials such as sand, straw, hay, or wood shavings. Such injuries may be prevented by protecting the eye from trauma through the use of a padded hood or soft mats under the head, by keeping the cornea well lubricated in dehydrated animals with reduced blinking frequency, and by administering sedation to prevent thrashing. Following ocular trauma, opportunistic or pathogenic organisms may become established in the wound bed and may cause superficial or deep corneal infections. Ocular flora native to the conjunctiva include potential pathogens that may cause severe infections.[1]

Ocular Examination in Cases of Head Trauma

The goals of examination are to determine the degree of ocular trauma and to offer a prognosis for recovery of vision and preservation of the eye. The history should elicit information as to the cause and duration of the injury, previous ocular and systemic disease or therapy, and a description of any recent sedation, anesthesia, or therapy.

Blunt or sharp facial trauma frequently results in damage to the orbit and globe, including fractures or soft tissue injuries of the orbit, corneal abrasions and edema, hyphema, traumatic uveitis, lens luxation, traumatic cataract, vitreal hemorrhage, retinal tear or detachment, corneal or scleral rupture, or proptosis. Therefore, the orbit and globe and vision should be examined as thoroughly as possible when evaluating a patient with facial trauma.

Ophthalmic examination can be performed only after adequate restraint of the head (see previous discussion). Intravenous (IV) sedation, sensory and motor nerve blocks, topical anesthesia, and the use of a halter, twitch (in horses), or nose tongs (in cattle) often are necessary for adequate examination of the traumatized eye.

Trauma to the Orbit

Orbital injuries in domestic animals frequently include fractures of the orbital rim and zygomatic arch and damage to the supraorbital process of the frontal bone.[2] Fractures of the orbit may be identified by palpation, conventional or digital radiography, CT, or magnetic resonance imaging (MRI). Contusions or lacerations of orbital soft tissues and temporary or permanent neurologic dysfunction also may be present.

Radiographic examination of the bony orbit in large animals is technically difficult and often unrewarding with conventional radiography. Standard lateral and dorsoventral views require powerful radiographic equipment for penetration of bony structures in horses and cattle.[15] Large fractures may be identified, but distinct delineation of the bony orbit is difficult because of overlying sinus and nasal structures. An oblique view of the frontal bone is often the most helpful projection.[3] This view may be taken with a portable machine because only minimal radiographic penetration of skull structures is required. Outlining the orbit and surrounding bony structures allows identification of fractures, osteomyelitis with or without bony sequestra, and soft tissue abnormalities, including swelling and radiopaque foreign bodies. If a periorbital sinus is involved in the fracture, subcutaneous emphysema may be present. The use of digital radiology may allow enhanced visualization of the bony structures of the orbit, especially when only subtle changes are present. Digital radiography systems used in conjunction with portable equipment may provide adequate detail in standard as well as oblique projections. CT and MRI are available at many referral centers. Detail of the bony and soft tissue structures is greatly enhanced by the cross-sectional views acquired by CT, as are the structures of the calvarium, sinuses, and teeth. MRI is also very beneficial in delineating soft tissue abnormalities within the orbit and sinuses.[4,5] Immediate evaluation for orbital fractures should include careful examination of the globe. In cases with substantial swelling, ice packs applied to the fracture site may reduce swelling. Systemic antiinflammatory therapy (e.g., flunixin meglumine, ketoprofen, phenylbutazone) may also be given. Systemic antibiotics should be used if sinus involvement is suspected. If the fracture fragments are only minimally displaced, surgical intervention may not be required. Surgical repair should be considered if fragment displacement or entrapment of extraocular muscles has occurred or could occur.[3,6] Trauma sufficient to cause fractures may also result in neurologic dysfunction and immobility of the eyelids.

If eyelid movement is impaired, the globe must be adequately protected and lubricated until neurologic function returns. If the globe is only minimally exposed, a sterile ophthalmic lubricant may

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be used at least three or four times daily. In more severe cases, a nictitating membrane flap or temporary partial tarsorrhaphy may be required. If neurologic dysfunction is permanent and results in significant exposure conjunctivitis or keratitis, partial or complete permanent tarsorrhaphy should be performed.[3] Enucleation with or without placement of an orbital prosthesis may be required for severely affected eyes.

Scleral rupture is another potential consequence of blunt trauma to the orbit and globe. A recent study found that the most consistent clinical sign of scleral rupture in horses is eyelid and conjunctival swelling.[7] Other clinical features of this condition are hyphema, subconjunctival hemorrhage, and a collapsed anterior chamber. Ultrasonographic findings include poorly defined scleral margins and echoic/hyperechoic material in the anterior and posterior chambers and in the vitreous.[7]

Traumatic puncture wounds of the eyelids and conjunctiva may result in orbital cellulitis and exophthalmos in food animals and horses. The onset of swelling may be sudden. Pyrexia and leukocytosis may be present. If a retrobulbar abscess occurs, temporomandibular movement causes extreme pain; the animal may have the eyes partially closed, be off feed, and stand with the neck extended. The client may observe a relatively sudden onset of exophthalmos, eyelid swelling, severe chemosis, and exposure keratitis.[3,8] Therapy should consist of systemic and topical antibiotics. Ophthalmic ointments and lubricants should be used to provide protection from desiccation of the exposed cornea and conjunctiva. With time, the cellulitis may organize into a discrete abscess that can be located by palpation or ultrasound. The wound or abscess should be débrided or drained to facilitate healing, especially if a well-organized abscess is present.

Although traumatic proptosis is uncommon, it may occur in horses and food animals. The prognosis for return of vision is guarded to poor, depending on the extent of the damage to the optic nerve and retina. If the globe is ruptured or the extraocular muscles are avulsed, the eye should be enucleated. If the extent of the damage cannot be evaluated initially, the globe should be repositioned, a temporary tarsorrhaphy performed, and the globe reevaluated after 7 to 10 days of topical therapy. Treatment should include topical broad-spectrum antibiotics and atropine. With severe fractures or serious ocular damage, consultation or referral to the appropriate specialist is advised.

Trauma to the Eyelid

Eyelid trauma is frequently accompanied by injuries to other ocular structures. Careful ocular examination should be part of the evaluation of animals with eyelid trauma. Injuries may range from swelling (blepharedema) or orbital cellulitis to extensive lacerations and avulsion. Blepharedema may be accompanied by hemorrhage and usually resolves quickly without therapy; however, recovery may be hastened by the use of ice packs and systemically administered ketoprofen or flunixin meglumine.

Horses are particularly prone to eyelid lacerations because of the prominence of the eye and their tendency toward sudden head movements when startled. Lacerations may be divided into those without eyelid margin involvement, those with eyelid margin involvement, and avulsions of part or all of an eyelid. For all types of eyelid injury, several basic principles should be followed. Lacerations should be treated promptly to avoid distortion from excessive swelling, infection, scarring, and loss of function. Lacerated or displaced tissue should not be excised. It is impossible to replace the mucocutaneous junction of the eyelid margin. If eyelid margin is sacrificed, the risk of scar formation and secondary corneal damage is high. The laceration should be thoroughly and carefully flushed with sterile saline and explored to remove all foreign material. In acute trauma, cold compresses may assist in decreasing swelling. In suturing an eyelid laceration, it is essential to preserve the eyelid margin; therefore, eyelid lacerations should be repaired with minimal débridement. In cases of avulsion of part or all of the eyelid, a variety of blepharoplastic procedures may be performed to help restore functional eyelid margin.[9-11] For a more detailed description of the principles of surgical repair of the eyelids, an ophthalmic surgical text is recommended.[9,10]

Postoperative care of all eyelid lacerations should include standard wound hygiene, application of fly repellent and topical ophthalmic antibiotics, and prevention of self-trauma. In contaminated wounds, systemic antibiotic therapy is indicated for 5 to 7 days. Tetanus prophylaxis should be administered.

Improper repair of eyelid lacerations can lead to abnormal function and secondary problems, including chronic epiphora and associated dermatitis, exposure keratitis, ulcerative keratitis, cicatricial entropion or ectropion, conjunctivitis, and pigmentary keratitis.

Trauma to the Nictitating Membrane

Lacerations involving the nictitating membrane (third eyelid) should be repaired to avoid irritation and damage to the cornea. This appears to be more important in horses than in ruminants. The margin should be realigned as precisely as possible, and the lacerated conjunctiva should be repaired with absorbable small suture material such as 5-0 to 7-0 polyglactin (Vicryl [Ethicon, Somerville, N.J.]). Topical ophthalmic antibiotics should be used 3 to 6 times daily for 7 to 10 days. The entire nictitating membrane should be excised only if it is irreparably damaged.

Trauma to the Conjunctiva

Conjunctival lacerations result in swelling (chemosis) and hemorrhage. The cornea and sclera should be examined carefully for evidence of lacerations or perforation. If the globe is excessively soft on digital palpation, the anterior chamber is shallow or flat, or hyphema or subconjunctival hemorrhage is present, a concurrent scleral laceration is probable.[7]

Chemosis and hemorrhage frequently resolve without therapy. However, if the chemosis is severe enough to cause exposure and drying of tissues, topical sterile ophthalmic lubricants or antibiotic ointments are indicated to prevent secondary irritation. Conjunctival lacerations rarely require closure unless they are extensive. Subconjunctival hemorrhage sustained during parturition is common in foals and calves and requires no therapy, although topical ocular lubricants or antibiotic ointments are often prescribed.

Trauma to the Cornea

Corneal injuries in horses and food animals include blunt compressive trauma, foreign body penetration, ulcerative keratitis, and lacerations. Corneal perforation often results in iris (or iris and ciliary body) prolapse. Therapy is dictated by the type and extent of corneal injury, the complications encountered, the intended use and economic value of the animal, and other financial considerations.

Blunt Trauma to the Cornea

Blunt trauma to the globe from lead shanks, whips, and other objects can result in corneal endothelial injury and subsequent edema. Signs of traumatic uveitis also may accompany such an injury. The corneal edema that results from blunt trauma to the globe may be focal, linear, or diffuse. Therapy for blunt trauma includes a topical hypertonic (5%) saline solution or ointment two to four times a day to decrease corneal edema. A linear keratopathy characterized by a nonedematous, deep, striate, refractile opacity in the cornea may represent a focal thinning or break in the Descemet's membrane that has resulted from blunt trauma to the cornea. This type of lesion must be distinguished from Haab's striae, which are linear breaks in the Descemet's membrane that result from elevated IOP in glaucoma.

Corneal Foreign Bodies

Plant matter embedded in the epithelium or superficial stroma is the most frequently encountered corneal foreign body. Foreign bodies

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usually are easily removed with a moistened cotton-tipped applicator or ophthalmic forceps. Sedation, motor or sensory nerve blocks, and topical anesthesia facilitate removal. Culture and sensitivity tests and cytologic examination of corneal samples are recommended before therapy is initiated. The cornea is stained with fluorescein dye to evaluate the extent of corneal ulceration. While awaiting laboratory results, medical therapy should include a topical ophthalmic antibiotic (bacitracin-neomycin-polymyxin, gentamicin, or tobramycin three or six times daily) and atropine as needed. The prognosis is guarded until the cornea heals; the eye should be reevaluated in 24 to 48 hours.

Complications of corneal foreign bodies include bacterial and fungal infection, corneal perforation, and severe corneal scars that may restrict vision. Subpalpebral lavage systems are used in severe injuries when frequent prolonged therapy is needed or when treating intractable animals.[12] Originally, the placement of the subpalpebral catheter was described in the upper lateral eyelid, although many practitioners place the lavage system in the medial aspect of the inferior eyelid, allowing the third eyelid to protect the cornea from trauma from the lavage catheter itself.[13]

Corneal Ulcers

Corneal ulcers in horses are usually initiated by trauma and should be considered contaminated by bacteria or fungi until proven otherwise. Trauma may play a lesser role in food animals, in which primary infectious etiologies are more common (see Infectious Bovine Keratoconjunctivitis). The conjunctival fornices and eyelids should be carefully examined for foreign material. Diagnosis is based on cytologic examination, culture and sensitivity testing of corneal samples, and fluorescein staining of the cornea. Material for bacterial and fungal culture is collected from the ulcer with sterile rayon-tipped swabs. Cotton swabs are less satisfactory because cotton exhibits some antimicrobial properties. The eyelid margins and skin should be avoided, and better culture results are obtained if the swab is moistened with a sterile solution (sterile water or saline) before specimen collection. The most reliable results are obtained if the swabs are placed in a transport medium at the time of collection (Port-A-Cul [Becton Dickinson, Sparks, Md.]). Immediately after collection, the swab is replaced in the tube or inoculated onto standard bacterial and fungal agar plates, or blood agar and thioglycolate broth.

Corneal scrapings for microscopic examination are collected with the use of topical anesthesia. The eyelids are retracted, and the margin of the corneal ulcer is gently rubbed with a small brush, cytology spatula, or the blunt handle end of a Bard-Parker scalpel blade until a small amount of cellular material is collected. This material is transferred to 2 to 6 clean glass slides, spread over a 1-cm (0.4-inch) area, and allowed to air-dry. One smear is stained with Diff-Quik; one with Wright-Giemsa, periodic acid–Schiff (PAS), or GMS for fungal hyphae; one with Gram stain; and possibly one with new methylene blue.

Therapy of corneal ulcers is based on the removal of the cause if it is still present, control or prevention of infection with topical antimicrobials, use of topical atropine for relief of painful ciliary body spasm and prevention of synechia, and, in horses, systemic use of nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine or phenylbutazone. The initial choice of topical antibiotic should be based on the results of cytologic evaluation and later modified if necessary, according to the results of culture and sensitivity testing. If gram-positive organisms are demonstrated on corneal cytology, topical chloramphenicol or fluoroquinolones are a good first choice of therapy.[14] If gram-negative organisms are seen, initial empirical therapy should include a topical aminoglycoside or fluoroquinolone antibiotic,[14] but since the ocular flora is primarily gram-positive, use of broad-spectrum combinations such as bacitracin-neomycin-polymixin B should be considered. If cytology demonstrates fungal hyphae, initial therapy with a topical antifungal agent should be instituted immediately. In a recent study of fungal isolates from equine ulcerative keratomycosis cases, voriconazole was shown to be the most effective antifungal drug for initial therapy.[15] Subpalpebral lavage systems greatly facilitate the delivery of topical medication to the equine eye.[12,13]

Surgical intervention should be considered in cases of deep corneal ulceration and especially when the Descemet's membrane is exposed. Surgical procedures most often used for corneal ulceration include conjunctival pedicle flap and keratoplastic procedures. Ophthalmic tissue adhesives and soft contact lenses may also be used as nonsurgical therapy for deep corneal ulcers. Perforating ulcers with iris prolapse and mixed bacterial and fungal keratitis or ulcers present greater than 2 weeks usually have a poor visual outcome.[16]

Corneal Lacerations

Corneal lacerations may be caused by sharp, protruding objects or projectiles. Corneal lacerations can occur with or without scleral laceration and, if they are nonperforating, may be treated as corneal ulcers. By contrast, perforating corneal lacerations must be repaired surgically. Preoperative preparation includes tetanus prophylaxis (horses and goats), systemic antibiotics, and sample collection for corneal culture and sensitivity. Ocular ultrasonography is very useful in determining the integrity of intraocular structures. However, care must be exercised during ocular examination, ultrasonography, and surgery and anesthesia (especially induction and recovery), because extrusion of the intraocular contents may occur if excessive pressure is exerted on the globe or if the eyelids are forced open. In some cases, complete examination of the globe should be delayed until the animal is anesthetized.

General anesthesia, adequate magnification, proper instrumentation, appropriate suture material and needles, and adequate postoperative care are necessary for successful repair of a corneal laceration. Postoperative therapy must include topical antibiotics and mydriatics/cycloplegics, along with systemic antiinflammatory agents. The prognosis for recovery of vision and preservation of the globe generally is guarded. Complications that may occur after repair of corneal lacerations include phthisis bulbi, corneal fibrosis, synechia formation, blindness, retinal detachment, cataract formation, uveitis, endophthalmitis, bacterial or mycotic keratitis, and wound dehiscence with subsequent iris prolapse.

The prognosis after surgical repair of corneal or corneoscleral lacerations is best when the animal is presented immediately with a small wound in which the cornea or sclera is sealed and the anterior chamber has re-formed. Minimal hyphema, clear intraocular media, a clearly visible fundus, and laceration length of less than 15 mm are additional findings that indicate a favorable prognosis.[16] In horses the success rate when only the cornea is involved is about 70% for recovery of vision and 90% for a cosmetically acceptable globe.[17] With corneoscleral lacerations the prognosis is much worse. In our experience, the success rate in such cases is 20% for recovery of vision and 70% for a cosmetically acceptable globe. Most phthisical globes are not considered cosmetically acceptable. Therefore, enucleation should be considered initially with severe corneoscleral lacerations, because the prognosis is poor for return of vision and guarded for preservation of the globe. Several surgical procedures have been described in horses to provide a cosmetic appearance to the globe and orbit, including placement of an intraocular silicone prosthesis.[18,19]

Trauma to the Uveal Tract

Trauma to the globe can damage the iris, ciliary body, and choroid. The resulting inflammatory response may range from very mild with rapid recovery to loss of vision and chronic discomfort. Signs of inflammation of the iris and ciliary body include blepharospasm, epiphora, miosis, aqueous flare, corneal edema, fibrin in the anterior chamber, hyphema, hypopyon, low IOP, and synechia formation. Concurrent damage to the corneal epithelium may be present and must be evaluated with fluorescein dye. Damage to the choroid may also affect the retina and lead to retinal detachment or degeneration.

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Traumatic uveitis is treated in a manner similar to uveitis of other etiologies. Therapy is directed toward dilating the pupil to prevent synechia formation, cycloplegia to prevent painful ciliary spasm, and controlling the intraocular inflammatory response. Topical atropine is instilled to maintain mydriasis and provide cycloplegia. Topical corticosteroids and prostaglandin inhibitors such as 0.1% diclofenac (Voltaren [Novartis, East Hanover, N.J.]) are used to decrease inflammation of the anterior segment.

The topical corticosteroid of choice is 1% prednisolone acetate or 0.1% dexamethasone. Subconjunctival injection of corticosteroids may also be quite beneficial in controlling inflammation. However, the use of topical and subconjunctival corticosteroids must be avoided in the presence of corneal ulceration or abrasion. Systemic medication should include flunixin meglumine, ketoprofen, phenylbutazone, or oral corticosteroids. Care must be taken to avoid secondary complications from systemic corticosteroids.

Trauma-induced hyphema usually has a good prognosis if the blood has clotted and fills less than half the anterior chamber. Stall rest, topical 1% atropine, topical corticosteroids, and systemic antiinflammatory therapy should be instituted to control the associated uveitis. If a penetrating wound is suspected, topical and systemic antibiotic therapy should be included with periodic fluorescein staining. Surgical intervention to remove large blood clots is rarely indicated because it may result in additional bleeding or may worsen the uveitis. Dilute tissue plasminogen activator (tPA; Activase [Genentech, South San Francisco, Calif.]), 50 to 75 µg, may be injected into the anterior chamber to disrupt or lyse intraocular hemorrhage and fibrin and to aid in resolution of synechiae. For maximum effectiveness, tPA should be used within 24 to 72 hours of clot formation.[20,21] Systemic tPA for use in humans is diluted for intraocular use but is expensive. However, diluting the drug and repackaging it into sterile vials that are stored at −70° C and then thawed for injection has made the cost more reasonable for veterinary use.

Chronic uveitis after ocular trauma may be associated with lens damage or the introduction of infectious or foreign agents into the eye and carries a poor prognosis. If the lens is ruptured, its surgical removal is advocated. Ocular perforation is a frequent cause of panophthalmitis in food animals and horses. Although therapy consists of systemic and topical antibiotics, as well as tetanus prophylaxis in susceptible species, panophthalmitis usually necessitates eventual enucleation.

Trauma to the Lens

Blunt or sharp trauma to the eye may damage the lens by causing lens opacity (cataract), rupturing the lens capsule, or less often may cause a shift in position (subluxation or luxation). Release of lens protein into the eye after lens capsule rupture may induce severe granulomatous uveitis. In such cases the eye should be treated vigorously for lens-induced uveitis with topical atropine and topical and systemic antiinflammatory drugs. If the globe has been penetrated, topical and systemic antibiotics are indicated. The prognosis for preservation of vision is poor. Lens removal is often required to control the inflammatory response.

Cataracts (lens opacities) associated with ocular trauma may occur acutely or develop weeks after the initial injury. The opacity may be only focal and not appreciably affect vision, or it may be complete and cause a visual deficit. If the remainder of the eye is normal, surgical removal of the cataractous lens may improve vision.[22,23] In a recent retrospective of surgical cataract removal in horses, the highest success rate was noted in the removal of traumatic cataract, as compared with cataracts of other known etiology.[23]

Trauma Involving the Vitreous

Trauma to the eye may result in hemorrhage into the vitreous or release of inflammatory products that cause vitreal degeneration. Either circumstance can result in vitreal syneresis (liquefaction), formation of vitreal traction bands, and subsequent retinal detachment. Symptomatic treatment of inflammation is generally adequate, but vitrectomy may be beneficial in the management of vitreal traction bands to prevent subsequent retinal detachment.[24]

Trauma to the Retina

Retinal tears, hemorrhage, edema, and detachment may be caused by trauma.[25] In cases of opaque ocular media, retinal separation may be diagnosed by ocular ultrasonography (Fig. 39-8). Retinal degeneration may follow ocular trauma. Retinal hemorrhage and edema should be treated with systemic corticosteroids. With current technology, surgical repair of retinal tears, lacerations, or detachments in food animals and horses may be feasible in selected cases.

Trauma to the Optic Nerve

The pathogenesis of damage to the optic nerve is not well understood. Shearing forces at the optic foramen from displacement of the brain after severe head trauma (Fig. 39-9), direct contusion or avulsion of the optic nerve, or loss of blood supply to the nerve and subarachnoid hemorrhage probably all have roles in optic nerve injury.[26] Early examination may reveal only a dilated pupil that may be partially or completely unresponsive to light. Later, changes may include optic nerve atrophy (Fig. 39-10) and peripapillary retinal pigmentation changes. Therapy with systemic antiinflammatory drugs may be of benefit, but severe damage is usually irreversible.

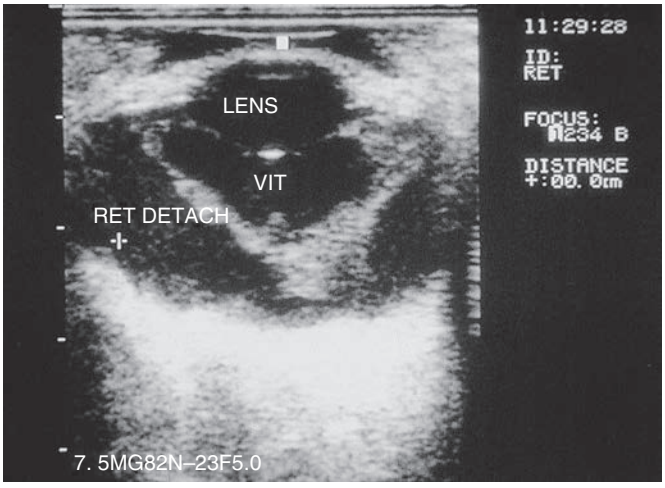


FIG. 39-8 Ocular ultrasound of a horse eye after blunt trauma to the globe. Note characteristic V-shaped retinal detachment.

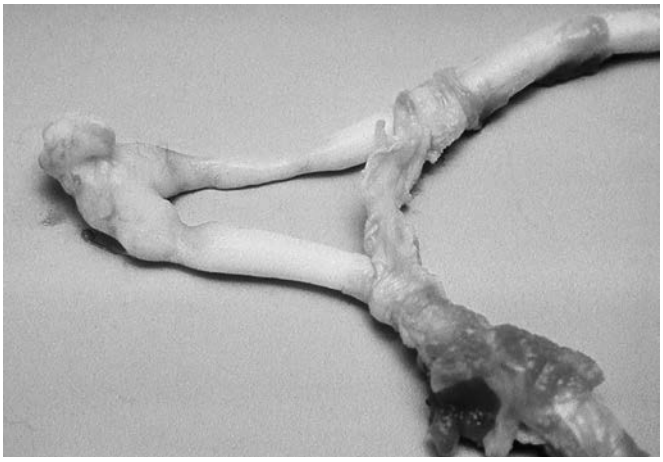


FIG. 39-9 Optic nerves and chiasm of a foal that was blind as a result of head trauma. Note the constrictions of the optic nerves caused by necrosis and degeneration. *(Courtesy Dr. C.L. Martin.)*

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FIG. 39-10 Appearance of optic nerve 3 months after head trauma in a horse. Note pale optic disc and peripapillary retinal degeneration. *(Courtesy Dr. C.L. Martin.)*

Traumatic optic nerve atrophy is usually characterized by sudden onset of unilateral or bilateral blindness, dilated fixed pupils, and a lack of menace response. In horses the traumatic episode is frequently characterized by damage to the poll from rearing over backward and striking the back of the head, from rearing up and hitting a ceiling beam, or from blunt trauma (blows) to the side or front of the face. The animal usually stands without loss of consciousness, and the injury is not considered serious by the owner at the time. Initially, blindness with a normal-appearing ocular fundus is observed.

Within 3 to 4 weeks after the trauma, examination of the fundus reveals a pale optic disc (see Fig. 39-10). Later, loss of peripapillary retinal vessels is usually evident. The optic disc often appears depressed, with increased prominence of the lamina cribrosa. Confirmation of optic nerve or optic tract lesions causing blindness may be made by the absence of a direct PLR with a normal electroretinogram. In some cases, the pathologic lesion is a rupture of the nerve axons from stretching forces produced by movement of the brain.[26] Chiasmal hemorrhage and fractures of the basisphenoid bone may be observed at necropsy. Therapy with systemic corticosteroids (dexamethasone, 2.5 to 5 mg IV or IM) and IV dimethyl sulfoxide (DMSO) has generally not been successful,[26] although the lack of response to medical therapy appears related to the severity of the injury.

A segmental optic nerve atrophy involving one to three quadrants of the optic disc occurs in horses. The appearance is characterized by pallor, loss of normal vasculature, and increased prominence of the lamina cribrosa in the affected quadrants. The etiology is unknown, but traumatic injury is suspected in most cases. Response to medical therapy is poor.

Chemical Injury

Ocular irritation caused by insecticides and disinfectants inadvertently applied to the eye is relatively common in the farm or ranch setting. Chemical burns to the cornea and adnexa may have serious consequences and may warrant a poor prognosis for salvage of the eye. Alkali burns are more severe than acid burns. Corneal burns from acids tend to be sharply demarcated and nonprogressive, whereas alkali burns cause progressive coagulation, melting, and sloughing of the corneal stroma.[3] Chemically induced melting of the cornea must be differentiated from bacterial and fungal infections. Treatment for a suspected or known chemical burn should include lavage of the affected area with copious amounts (500 to 2000 mL) of sterile saline solution. Tap water may be used by the owner until veterinary assistance is available. It may be necessary to sedate the animal. No attempt should be made to neutralize the substance, because this may cause precipitation within the cornea. The damage should then be evaluated with the aid of local nerve blocks.

Treatment should include appropriate topical antimicrobials, atropine, and a collagenase inhibitor such as autologous serum or possibly acetylcysteine (Roxane Laboratories Inc., Columbus, Ohio), which inhibits collagenases and metalloproteinases by binding calcium. The commercially available preparations contain 10% and 20% acetylcysteine and should be diluted to 5% and 10% to avoid epithelial toxicity. Acetylcysteine lasts only about 4 days once opened and should be refrigerated. Hourly application of serum or acetylcysteine may be needed. Systemic antiinflammatory drugs should be used to control secondary uveitis. Therapeutic soft contact lenses have been used to protect the corneal stroma in patients with extensive corneal ulcerations.

Thermal Injury

Facial burns secondary to barn or stable fires may damage the eyelids, conjunctiva, and corneas. Thermal injuries also may cause anterior uveitis and exfoliation of the lens capsule. Therapy for minor burns to the eyelids is directed toward keeping the injured area moist with antibiotic dressings and protecting the cornea if eyelid dysfunction occurs. Treatment for injury to the conjunctiva or cornea should include topical antibiotic and systemic antiinflammatory drugs in horses. Full-thickness eyelid burns may require grafting procedures to protect the cornea and minimize scarring. Third eyelid or conjunctival flaps may be required to protect the cornea until eyelid function returns.

Infectious Ocular Diseases

Caryn E. Plummer

This section describes the major infectious ophthalmic diseases of large animals (Table 39-2). Infectious bovine keratoconjunctivitis (IBK), or "pinkeye," the most common ocular disease of cattle, will be detailed in another section. Infectious ocular disease in large animals may be either the result of a pathogen primarily affecting the ocular tissues or an ocular manifestation of a systemic infection, wherein the ocular signs are secondary or concurrent to the systemic illness. As a general rule, surface ocular diseases are often primary in origin, whereas intraocular diseases are either primary or secondary. The first infections described in this section are those with predominantly ocular signs, followed by descriptions of ocular manifestations of systemic disease.

There are many potential ophthalmic manifestations of infectious disease in large animals. Few diseases have pathognomonic or classically distinctive signs, so the combination of signalment, ocular clinical signs, systemic clinical signs, and laboratory diagnostics are necessary to confirm a diagnosis. Clinical signs associated with conjunctivitis are nonspecific to the underlying cause and include conjunctival hyperemia and chemosis. Other clinical signs may include follicle formation (often a manifestation of chronicity) and serous to mucopurulent discharge. Differentiation of primary conjunctivitis from secondary conjunctivitis resulting from other diseases (systemic disease or intraocular disease) is very important. A thorough ophthalmic examination will help with this determination.

In cattle and small ruminants, corneal disease may be initiated by an infectious agent, but infectious corneal disease in horses most often occurs secondary to corneal trauma. It can also be a manifestation of primary ocular disease or systemic disease. Signs of keratitis include pain (blepharospasm, photophobia, epiphora), ocular

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TABLE 39-2

Major Infectious Ocular Diseases of Large Animals

Agent	Common Name/Disease	Major Sign(s)	Cattle	Sheep	Goats	Horses
Mycoplasma conjunctivae	Pinkeye	Keratoconjunctivitis		++	++	
Mycoplasma mycoides subsp. *mycoides*	Pinkeye	Keratoconjunctivitis			+	
Acholeplasma oculusi (oculi)	Pinkeye	Keratoconjunctivitis		+	+	
Chlamydia psittaci	Pinkeye	Keratoconjunctivitis		++		
Branhamella (Neisseria)	Pinkeye	Keratoconjunctivitis		+	+	
Mycoplasma agalactiae		Keratoconjunctivitis		+	+	
Mycoplasma arginini		Keratoconjunctivitis		+	+	
Listeria monocytogenes		Keratoconjunctivitis	+	+		
Bovine herpesvirus type 1 (infectious bovine rhinotracheitis)		Keratoconjunctivitis	++		+	
Colesiota (Rickettsia) conjunctivae	Pinkeye	Keratoconjunctivitis		+		
Equine viral arteritis		Keratoconjunctivitis				+
Equine herpesvirus type 2		Keratoconjunctivitis				+
Mycoplasma bovoculi		Conjunctivitis	+			
Ureaplasma spp.		Conjunctivitis	+			
Equine adenovirus		Conjunctivitis				+
Moraxella spp.		Conjunctivitis				+
Streptococcus equi	Strangles	Conjunctivitis				+
Moraxella bovis	Pinkeye	Corneal ulcer	++			
Equine herpesvirus type 1	Rhinopneumonitis	Keratitis				+
Malignant catarrhal fever		Uveitis, keratitis	+			
Neonatal septicemia		Uveitis	+	+	+	+
Mycobacterium bovis	Tuberculosis	Uveitis	+			
Salmonella spp.		Uveitis				+
Borrelia burgdorferi	Lyme disease	Uveitis				+
Leptospira interrogans		Recurrent uveitis				+
Brucella abortus		Recurrent uveitis				+
Scrapie		Retinitis		+		
Histophilus somni (formerly *Haemophilus somnus*)	Infectious thromboembolic meningoencephalitis	Retinitis	+			
Bovine viral diarrhea		Retinal dysplasia, cataracts	+			
Bluetongue		Chorioretinitis, conjunctivitis	+	+		
Toxoplasma gondii		Chorioretinitis				+
Rhodococcus (Corynebacterium) equi		Panophthalmitis				+
Bovine leukemia virus		Exophthalmos	+			
Cryptococcus neoformans		Exophthalmos				+

discharge, corneal edema, variable corneal vascularization, loss of stromal integrity (melting or keratomalacia), and secondary anterior uveitis.

Uveitis is inflammation of the uveal tract, which includes the iris, ciliary body, and choroid. Initial clinical signs may include episcleral injection, blepharospasm, photophobia, miosis, aqueous flare, hypopyon, fibrin, hyphema, and corneal edema. Intraocular inflammation can affect the entire eye and may result from direct invasion of the globe by a pathogen or as the result of a systemic inflammatory response. If untreated, uveitis can lead to permanent vision loss, cataract, secondary glaucoma, and phthisis bulbi. Some systemic infections may result in neuro-ophthalmic signs, such as facial paralysis, Horner syndrome, trigeminal neuropathies, nystagmus, strabismus, or ptosis. Others may cause retrobulbar disease or periorbital swelling.

This section deals with viral-, bacterial-, and fungal-mediated ocular disease; parasitic infections are addressed in a separate section. Many viral diseases affect the eye either directly or indirectly. Those that affect the globes may require direct ocular management. Other infections mediate disease primarily through cranial nerve neuropathy, and management is secondary. Any systemic bacterial infection has the potential to affect the eyes. Certain specific bacterial diseases (e.g., tetanus, botulism) may have their own distinctive ophthalmic signs, but most bacterial infections, especially when sepsis has developed, can be associated with nonspecific ocular inflammation. Fortunately, systemic fungal infections are not common in the immunocompetent animal, although ocular surface infections are common, especially in the horse. For more detailed information on the specific ocular conditions mentioned in this chapter, please consult an ophthalmology textbook and the recent literature.

Conjunctivitis and Keratoconjunctivitis

Mycoplasmal Keratoconjunctivitis in Goats and Sheep

Definition and Etiology *Mycoplasma conjunctivae* has been frequently isolated throughout the world from epidemics of keratoconjunctivitis, respiratory disease, and arthritis in goats and sheep.[1-4] *Mycoplasma mycoides* subsp. *mycoides* has been isolated from an epidemic of mastitis, arthritis, and keratoconjunctivitis in goats.[5] *Acholeplasma oculusi (oculi)* has been isolated from sheep and goats in epidemics of keratoconjunctivitis.[6,7] *Mycoplasma agalactiae* and *Mycoplasma arginini* have also been described as causing keratoconjunctivitis and systemic disease.[8]

Clinical Signs and Differential Diagnoses Clinical signs of mycoplasmal keratoconjunctivitis include epiphora, conjunctival hyperemia, and occasionally follicular conjunctivitis. In experimental conjunctival inoculation with *M. conjunctivae,* clinical signs began on day 2 and lasted for 5 weeks.[9] Later in the disease, keratitis with corneal neovascularization (Color Plate 39-15) and occasionally anterior uveitis can be seen.[1,10] One case of choroiditis and hyalitis has been described.[11] Signs can be seen in individuals, as well as in herd or flock outbreaks. The disease is usually unilateral but can be bilateral. Differential diagnoses include other infectious

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causes of keratoconjunctivitis, such as *Chlamydophila* spp. (sheep), *Branhamella* spp., aerobic bacteria, parasites, and infectious bovine rhinotracheitis (goats), as well as noninfectious causes such as trauma. There may be a slight variation in clinical signs experienced by sheep and goats. While both will exhibit blepharospasm, conjunctivitis, and keratitis, sheep will occasionally develop a more severe form of the disease associated with mucopurulent conjunctivitis, corneal ulceration, and uveitis with hypopyon (Color Plate 39-16). Goats do not typically ulcerate their corneas, despite the presence of severe and vision-threatening keratitis.

Clinical Pathology In conjunctival scrapings taken early in the disease, many neutrophils are seen; later, lymphocytes predominate. Plasma cells and necrotic epithelial cells are also observed.[12] Organisms can occasionally be found in epithelial cell cytoplasm in coccobacillary or varied forms.[11] Pigment granules can be mistaken for organisms.[6,12,13]

Mycoplasmal organisms can be cultured and identified from conjunctival swabs; serum antibody titers can be measured,[14,15] or PCR can be used to identify *M. conjunctivae* in conjunctival smears.[16,17] Egwu and Faull[18] describe rising serum and lacrimal antibody titers in sheep topically inoculated with *M. conjunctivae.* However, Trotter and colleagues[2] report low serum titers to *M. conjunctivae* in normal animals and no rise in titer in animals subconjunctivally inoculated with *M. conjunctivae* that subsequently developed signs of disease.

Epidemiology Mycoplasmal infections apparently are transmitted directly from animal to animal, as evidenced by herd or flock outbreaks. Subclinical carrier states exist, and *M. conjunctivae* can be cultured from nonclinical animals.[19,20] There is some evidence for vector transmission (flies) as well.[21] Animals can become reinfected, but if they do, their clinical signs are usually more mild than during the initial infection. Keratoconjunctivitis can be induced in sheep with topical inoculation of *M. conjunctivae.*[18,22,23] Clinical signs were identical to natural outbreaks and spread to uninoculated sheep. The organism can be cultured from eyes long after clinical signs abate.[9] Co-infection with other organisms may occur and result in more severe clinical signs.

Treatment and Prognosis In most animals, mycoplasmal keratoconjunctivitis associated with *M. conjunctivae* is transient. Affected animals usually recover spontaneously in 10 days, although some animals seem to have recurring episodes that last for several weeks. In a controlled clinical trial, one dose (20 mg/kg) of long-acting oxytetracycline was given to experimentally inoculated lambs. This treatment seemed to hasten the cessation of clinical signs, although the results were not analyzed statistically.[24] The treatment did not, however, eliminate the *M. conjunctivae* infection, and may promote a carrier state. Other drugs recommended for the ocular disease include topical oxytetracycline or oxytetracycline and polymyxin B.[1] Subconjunctival oxytetracycline is not currently recommended because it may cause a severe inflammatory reaction. In vitro antibiotic testing of *M. conjunctivae* shows that tylosin, oxytetracycline, streptomycin, and chlortetracycline are suitable for treatment.[25]

Prevention and Control Introduction of new animals into a herd or flock has been implicated in starting an outbreak of keratoconjunctivitis. Therefore, isolation and, if necessary, treatment of new animals are important before contact with the herd.[26-28] Transmission between species has been documented, so housing of domestic sheep and goats where they might comingle with wildlife is not recommended.[26-28] No other specific recommendations have been made for prevention and control of *M. conjunctivae.*

Bovine Mycoplasmal Conjunctivitis

Mycoplasma bovoculi and *Ureaplasma* spp. have been isolated from cattle with conjunctivitis and IBK. Inoculation of normal calves with *M. bovoculi* or *Ureaplasma* isolates produced conjunctivitis characterized by serous discharge and conjunctival hyperemia. Experimentally induced conjunctivitis ran a course of over 1 month. Cases can be confirmed by culture or PCR performed on conjunctival swabs.[29] Mycoplasmal infection may predispose the animals to development of IBK from *Moraxella bovis*[30,31] (see later IBK section). Therefore, although treatment of mycoplasmal conjunctivitis may not be warranted, it may be advisable in areas where IBK is endemic. Topical oxytetracycline ointment applied three times daily or intramuscular (IM) injection of long-acting oxytetracycline is recommended.

Other mycoplasmal organisms (e.g., *Mycoplasma arginini*) can be isolated from cows' conjunctiva but are not thought to cause the disease. *Mycoplasma bovis* was found using PCR performed on normal conjunctival samples,[29] but it was not thought to cause conjunctivitis. *Mycoplasma bovigenitalium, Mycoplasma bovirhinis,* and *M. bovoculi* were isolated from members of two cattle herds with conjunctivitis and bronchopneumonia.[32] However, when viral cultures were performed, bovine herpesvirus type 1 (BHV-1; also called infectious bovine rhinotracheitis [IBR]) was isolated in the same individuals. The mycoplasmal organisms may have contributed to the disease in these herds. In another cattle herd with an outbreak of respiratory disease, keratoconjunctivitis followed, and *M. bovis, M. bovirhinis,* and *M. bovoculi* were isolated in various combinations from affected calves.[33]

Chlamydial Keratoconjunctivitis in Sheep and Goats

Definition and Etiology Chlamydial agents have been isolated from outbreaks of keratoconjunctivitis in sheep flocks. The agent was originally described as a strain of *Chlamydia psittaci.* The agent is now called *Chlamydophila pecorum,* which can also cause abortion (see Chapter 43) and polyarthritis in lambs.[34,35]

Clinical Signs and Differential Diagnoses Early clinical signs consist of epiphora, chemosis, and conjunctival hyperemia. Later in the disease, follicle formation in the conjunctiva becomes prominent. Still later, corneal vascularization may be seen (Color Plate 39-17). Most cases are bilateral and symmetric.[36,37] In some flock outbreaks of keratoconjunctivitis, outbreaks of polyarthritis are also noted. Most lambs that develop chlamydial polyarthritis will also develop conjunctivitis.[36,37] Differentials include other infectious causes of keratoconjunctivitis, such as *Mycoplasma* and *Branhamella (Neisseria)* spp., aerobic bacteria, and parasites, as well as noninfectious causes like trauma.

Clinical Pathology Early in the disease, conjunctival smears show numerous neutrophils and some lymphocytes. Later, there are more neutrophils and fewer mononuclear cells. Cytoplasmic chlamydial inclusions are occasionally seen in up to a third of the eyes scraped and can be definitively identified by fluorescent antibody staining.[34] Conjunctival epithelial cells are often necrotic. Chlamydial organisms can be cultured from conjunctival scrapings and from blood taken from sheep with polyarthritis and conjunctivitis.[36-38] In one study, titers to chlamydial antibodies were found at 1:16 or higher in a number of the affected lambs, although titers on normal lambs were not reported.[37] PCR can also be used to identify the organism.

Epidemiology Chlamydial organisms are apparently transmitted by direct contact, as evidenced by flock outbreaks. Chlamydial organisms caused conjunctivitis in five lambs inoculated topically.[39] An uninoculated lamb housed with the five lambs also developed conjunctivitis. Lambs subsequently developed follicular conjunctivitis.[38] In another study, chlamydial organisms were injected intraarticularly, intravenously, and intramuscularly and caused polyarthritis and conjunctivitis.[38]

Treatment and Prognosis In uncomplicated cases the disease is self-limiting, and eyes are normal within 2 to 3 weeks.[37] The same treatments indicated for *Mycoplasma mycoides* subsp.

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mycoides (systemic oxytetracycline and, when possible, a topical tetracycline ophthalmic preparation) are also effective in treating chlamydial conjunctivitis/polyarthritis of sheep.

Colesiota (Rickettsia) conjunctivae Keratoconjunctivitis in Sheep

Colesiota (or *Rickettsia*) *conjunctivae* has been described as the cause of infectious keratoconjunctivitis in sheep, but documentation is sparse. The organism has not been cultured, only identified cytologically on conjunctival scrapings. Clinical signs include epiphora, conjunctival hyperemia, and corneal neovascularization.[40] Several authors have since suspected that this organism is the same as *Chlamydia psittaci* (now known as *Chlamydophila pecorum*).[41,42]

Branhamella (Neisseria) ovis Keratoconjunctivitis in Sheep and Goats

Branhamella ovis is a gram-negative diplococcus similar to *Moraxella*. This agent has been cultured from eyes of sheep and goats with keratoconjunctivitis and from normal eyes.[43-45] *B. ovis* has also been cultured from cattle with serous conjunctivitis and, rarely, keratitis.[46] Clinical signs are usually mild and include epiphora and conjunctival hyperemia. Severity of clinical signs is increased when co-infections with other organisms, such as *M. conjunctivae,* are present. Conjunctivitis but not keratitis has been experimentally induced in goats[47] and lambs,[48] and *B. ovis* could be cultured from the eyes of the lambs for up to 20 days after inoculation. Outbreaks of *B. ovis* have been successfully treated with parenteral tylosin, topical neomycin-polymyxin B, and a corticosteroid,[43] or with subconjunctival penicillin.[47]

Moraxella Conjunctivitis in Horses

Two reports have described a *Moraxella* sp. recovered from several horses in herd outbreaks of conjunctivitis, ocular discharge, and erosions of eyelid epithelium at the canthi.[49,50] The organism was similar but not identical to *M. bovis,* and the disease was reproduced experimentally in horses by instillation of the organism into the conjunctival sac. Huntington and coworkers[50] described successful treatment of the lesions with chloramphenicol ointment, whereas Hughes and Pugh[49] described the lesions as healing spontaneously.

Keratitis

Bacterial Keratitis in Horses

Definition and Etiology Bacterial keratitis occurs when a traumatic corneal ulcer becomes infected with opportunistic bacteria; no bacteria are known to *initiate* ulcers in horses. The most devastating clinical manifestations are associated with *Pseudomonas aeruginosa* and *Streptococcus equi* subsp. *zooepidemicus.*[51-59] However, any bacteria that has access to the ocular surface may colonize and complicate a corneal wound.[54,55,60]

Clinical Signs and Differential Diagnoses Whether infected or not, corneal ulcers cause signs of pain (blepharospasm, epiphora, apparent photophobia). The conjunctiva is hyperemic, and the ulcerated area of the cornea retains fluorescein stain. Acute superficial ulcers are usually not infected, and the cornea maintains its normal curvature in the ulcerated area. If a superficial ulcer is slow to heal, it should be sampled for microbial culture and sensitivity, since delayed healing may be a sign of an early or subclinical infection. A deep ulcer (resembling a divot in the corneal stroma) should always be assumed to be infected.

Other signs of corneal infection are rapid progression and white or yellowish infiltrate within the cornea (signifying influx of neutrophils and bacterial colonization within the corneal stroma). An ulcer that is rapidly becoming wider or deeper or begins to melt (corneal stroma softens or begins to dissolve) is highly suggestive of a bacterial infection (Color Plate 39-18). Many corneal ulcers are accompanied by some degree of anterior uveitis (miosis, aqueous flare, hypopyon, anterior chamber fibrin). The uveitis that occurs during a corneal infection tends to be much more severe than that which is present with sterile corneal wounds. In cases in which the initially damaged epithelium heals over microorganisms in the corneal stroma, a bacterial abscess may form.[61] Such lesions do not stain with fluorescein, and many topical antibiotics cannot reach the site of infection. Most stromal abscesses, particularly if they are located in the deep or posterior stroma, are fungal in etiology.[62-64] Fungal keratitis may exhibit similar clinical behaviors and may become secondarily infected with bacteria.

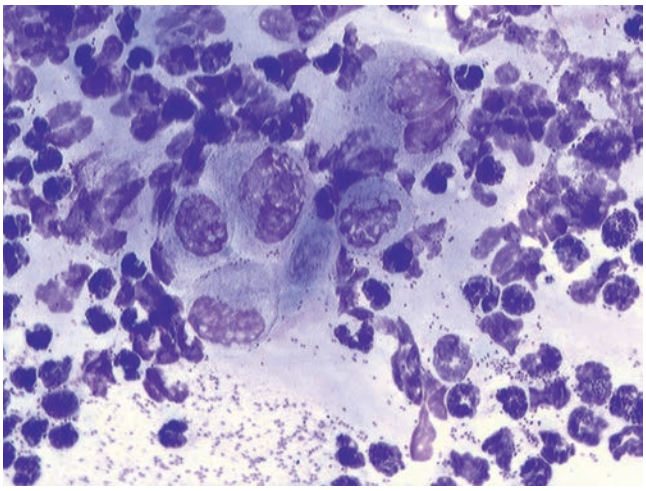


FIG. 39-11 Cytology of bacterial keratitis. Wright-Giemsa, ×100. Note corneal epithelial cells in center of field, numerous degenerate neutrophils, and intracellular and extracellular cocci and diplococci bacteria.

Clinical Pathology A diagnosis of a bacterial keratitis is made via corneal cytology and microbial culture and sensitivity (C&S). Stained scrapings may show intracellular and extracellular bacteria and neutrophils (Fig. 39-11). Bacterial morphology and Gram staining will guide the choice of empirical therapy while the results of C&S are pending. Bacterial organisms are definitively identified after culture of the ulcerated cornea. Aerobic culturing techniques are usually employed. Culturing for anaerobic organisms may be indicated if aerobic culture does not reveal an organism and the ulcer fails to respond appropriately to medical therapy. Anaerobic infections are far less common in the equine cornea than aerobic bacterial and fungal infections.[60]

Pathophysiology Bacterial keratitis is the result of pathogenic or opportunistic organisms colonizing a damaged cornea. The cornea is most likely to be damaged by mechanical trauma, but other causes such as chemical injury or corneal exposure are possible. Many different types of bacteria can be cultured from a normal eye, including *Corynebacterium, Streptococcus*, *Staphylococcus, Bacillus,* and rarely *Pseudomonas* spp. or other gram-negative bacteria.[51,53] Damage to the epithelium enables bacteria to adhere to the exposed corneal stroma and begin replicating.[57] Some bacteria such as *Pseudomonas* elaborate collagenases and other proteoglycanolytic enzymes,[58] which results in corneal destruction. Proteases and collagenases liberated by white blood cells and possibly corneal epithelial and stromal cells also contribute to this "melting" process.[65,66] In this way, what begins as a small wound to the cornea can progress to a corneal perforation within 24 to 48 hours.

Treatment and Prognosis Prognosis is guarded for any corneal ulcer that is rapidly progressing or melting. These ulcers can easily progress to corneal perforation and loss of vision or of the eye despite timely, appropriate treatment. On the other hand, with aggressive therapy many eyes with infected ulcers can be saved and vision maintained, although scarring may be present.

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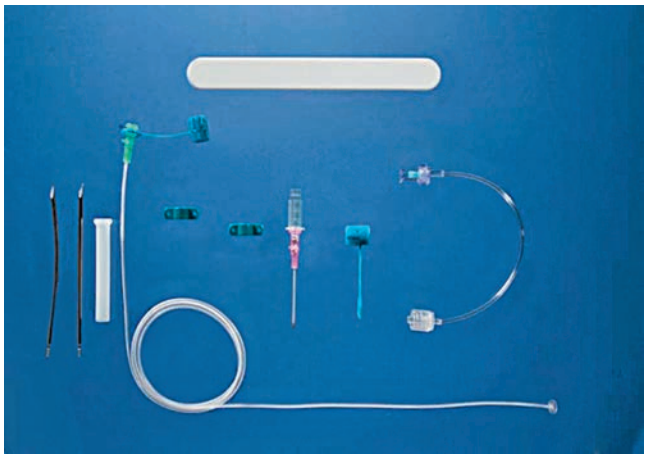


FIG. 39-12 Subpalpebral lavage kit. *(Courtesy Mila International Inc.)*

In any ulcer in which a bacterial component is suspected, C&S of the ulcer and a corneal scraping for Gram staining and cytology should be taken. The horse is restrained or sedated and an auriculopalpebral block is performed. A sample for culture should be obtained with a moistened swab before any solutions or medications are applied to the eye. Following culture, a topical anesthetic is applied to the cornea, and the ulcer margins are then scraped gently with a cytology brush, a Kimura spatula, or the blunt handle end of a scalpel blade.

In cases of equine bacterial keratitis, therapeutic goals are to eliminate the bacteria, prevent or slow melting if present, and treat the concurrent uveitis.[67-69] Because this requires very frequent applications of numerous medications to a horse with a painful and often fragile eye, a subpalpebral lavage system is usually required.

PLACEMENT OF SUBPALPEBRAL LAVAGE SYSTEM. The following equipment is necessary:

- Subpalpebral lavage (SPL) kit (MILA International [Fig. 39-12])
- White tape
- Applicator stick (tongue depressor)
- Injectable anesthetic (lidocaine, mepivicaine)
- Topical ophthalmic anesthetic (proparacaine, tetracaine)
- Monofilament nonabsorbable suture on a cutting needle

The horse should be sedated. Additional manual restraint (e.g., twitching) may be necessary depending upon the animal's temperament, degree of discomfort, and the handler's comfort and experience. The auriculopalpebral nerve is blocked over the zygomatic arch to paralyze the orbicularis oculi muscle and reduce spontaneous eyelid movement. If the SPL is to be placed in the upper eyelid, a supraorbital (frontal) block is performed to anesthetize the eyelid. This nerve is accessed at its exit from the supraorbital foramen. If the SPL is going into the lower lid, a line block is performed along the ventral orbital rim for regional anesthesia. Topical anesthetic is then applied to the eye by directing a gentle stream onto the globe and into the conjunctival fornix with a small syringe with a 25-gauge needle broken off at the hub. The eyelid and conjunctival fornices should be flushed with a dilute Betadine solution (0.5%).

Once the periocular structures are prepared, the plastic applicator stick from the kit is advanced under the eyelid and used as a guide for the needle to which the SPL tubing is attached. The needle is directed between the eyelid and the guide and then through the skin. In the upper eyelid, it should be placed as high as possible and should grab the periosteum of the orbital rim as it exits, which will help keep the lavage footplate in place and decrease the likelihood of slippage and subsequent irritation of the cornea. With placement in the lower lid, care must be taken not to inadvertently push the end of the needle onto or against the fragile globe as it is being introduced through the skin. The needle and Silastic tubing are threaded through the hole in the skin until the footplate is in direct contact with the palpebral conjunctiva. Tape is used to secure the tubing to the upper eyelid,

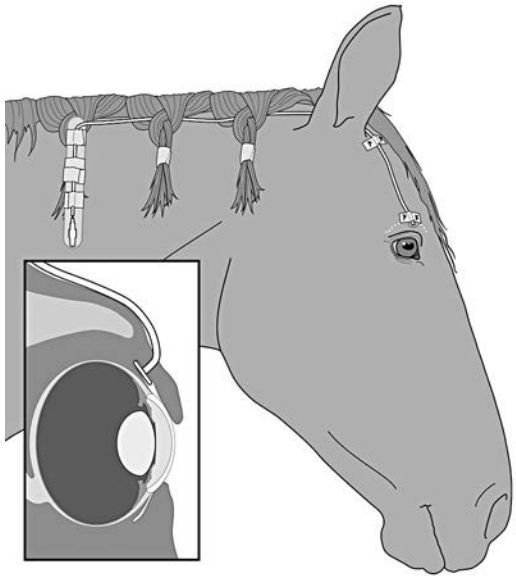


FIG. 39-13 Diagram illustrating a subpalpebral lavage system with correct positioning in superior fornix and fixation with a tape butterfly at exit site of tubing from the eyelid. Tubing is woven through braids in the mane, and injection catheter and stopcock taped to a stick applicator (tongue depressor). *(Diagram courtesy Anne Gemensky Metzler.)*

and sutures secure the tape to the skin. The tubing can be braided through the forelock and then run down the neck through several braids to keep it secure. A small catheter is directed into the distal end of the tubing, and an injection port is fixed to the end of the catheter. The catheter and tubing are taped to an applicator stick to prevent kinking. The stick is then taped to a braid of the mane (Fig. 39-13).

Poorly placed lavage tubes or tubes that slip ventrally can rapidly produce a corneal ulcer. A displaced tube footplate can also cause topical medications to leak into the subcutaneous tissues, rapidly leading to a swollen and inflamed eyelid. Therefore the tube position should be checked at least once daily by gentle dorsal traction on the exposed tubing to ensure it has not slipped into the conjunctival cul-de-sac. Excess traction will pull the footplate through the conjunctiva and into the eyelid itself. Most horses tolerate this system well, and well-maintained tubing may be kept in place for up to several months. Occasionally, horses try to rub their heads and can damage the tubing; neck cradles or protective eye cups can be used in such horses.

MEDICAL/SURGICAL APPROACHES AND GOALS. For noninfected ulcers a broad-spectrum preparation (e.g., neomycin-polymyxin-bacitracin, neomycin-polymyxin-gramicidin, chloramphenicol) is appropriate. In a cornea with rapidly developing keratitis or melting ulcer, the clinician should always suspect the presence of an infectious agent. Treatment should be started with an appropriate antibiotic, the choice of which should be based upon cytologic analysis and Gram stain, administered every 1 to 2 hours. If gram-negative organisms are observed, neomycin–polymixin B–bacitracin, aminoglycoside antibiotics (gentamicin, tobramycin), or fluoroquinolones (ciprofloxacin, ofloxacin)[70] are reasonable choices for treatment. To avoid contributing to bacterial resistance, fluoroquinolones should not be used for bacterial prophylaxis in *noninfected* ulcers. If gram-positive organisms are seen on the corneal cytology, neomycin-polymyxin-bacitracin, neomycin-polymyxin-gramicidin, chloramphenicol, levofloxacin, ticarcillin, cefazolin, penicillin, or ampicillin can be used.[59,69] Cefazolin is mixed with artificial tears to a concentration of 55 mg/mL,[64] ampicillin to 10 mg/mL,[52] and penicillin G to 100,000 U/mL. If the ulcer continues to worsen, antibiotics should be changed on the basis of the initial sensitivity results, and the cornea should be recultured because organisms can become resistant to the first antibiotic used or a secondary infection can develop. For

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resistant organisms, sensitivity testing that gives minimum inhibitory concentration (MIC) may be very useful because higher drug concentrations are more readily and safely attainable in the cornea than in the systemic circulation.

Melting of the cornea must be treated with collagenase and protease inhibitors, in addition to antimicrobial medications. Autologous serum, oxytetracycline–polymixin B, disodium EDTA (mixed with sterile water to a concentration of 0.17%), or *N*-acetylcysteine (5% to 10% in artificial tears) can be used topically for their antiprotease and anticollagenase activity, as can systemic doxycycline (10 mg/kg orally [PO] twice daily or 20 mg/kg PO once daily).[52,71] Tetanus toxoid, topical doxycycline, and ilomastat have also been applied to the diseased cornea to decrease collagen dissolution.[72]

Surgical therapy can also be used and may improve prognosis. Conjunctival pedicle grafts can be used to bring a blood supply and subconjunctival fibroblasts to deep corneal ulcers, with the goal of slowing progression and aiding stromal reconstruction[59] while still allowing medication to reach the site of the ulcer. A conjunctival graft allows observation of the cornea so that treatment can be adjusted as corneal health improves or changed if the cornea continues to deteriorate. A nictitating membrane "flap" should *not* be used in rapidly progressing or deep ulcers, because it creates a barrier to topical medications and observation of the cornea such that worsening of the ulcer goes unnoticed, reculturing cannot be performed, and appropriate changes in therapy cannot be instituted.

A corneoconjunctival transposition using autologous tissue or a corneal graft (penetrating keratoplasty) using donor cornea is an excellent treatment to repair very deep ulcers, descemetoceles, and perforations if melting has ceased and the ulcers are sterile.[63,64,73] Other substances that can be substituted for cornea are porcine small intestinal submucosa,[74] equine amniotic membrane,[75] or bovine pericardium. Placement of any graft requires microsurgical instruments, techniques, training, and experience. Highly specialized techniques, such as keratectomy with a conjunctival graft, penetrating keratoplasty, posterior lamellar keratoplasty, or deep lamellar endothelial keratoplasty, are necessary to treat stromal abscesses.[55,62,64,76-78]

The initial desired response to appropriate therapy of a malacic ulcer is simply cessation of worsening of the ulcer. That is, the ulcer does not appear to be healing or shrinking but also is not becoming larger or deeper. This suggests that bacteria have been killed and tissue destruction has halted. Epithelium will then begin to grow down the sides of the ulcer, covering the stroma or Descemet's membrane if it is exposed, and blood vessels will slowly begin growing into the cornea from the limbus. Once reepithelialization is complete, new infection with microorganisms is unlikely. If surgery has not been performed, however, the area that had been ulcerated will be (sometimes markedly) thinner than the surrounding stroma. Thickening of this area will occur by very slow reconstruction of stromal collagen by corneal fibroblasts ("keratocytes") or when corneal blood vessels fill the old ulcer bed. This can take weeks to months, and until this happens, the cornea may be susceptible to traumatic rupture.

Another goal of therapy for an infected ulcer is suppression of the trigeminal nerve–mediated anterior uveitis that is associated with any corneal irritation. Topical atropine is used for this purpose because it decreases pain associated with ciliary body muscle spasm and maintains pupil dilation, which reduces the chance of posterior synechia formation. Atropine should be applied to effect (i.e., until reduced pain or pupil dilation noted). This may be as frequently as every 6 hours initially but should be decreased and used to effect once pupillary dilation is maintained. Because topical atropine is absorbed into the systemic circulation and is associated with altered GI motility, small quantities of drug should be applied (1/8- to 1/4-inch strip of ointment or 0.05 to 0.1 mL solution), gut sounds should be assessed frequently, and the patient should be monitored for signs of colic. Systemic NSAIDs also should be used to decrease corneal and uveal inflammation. However, these drugs do slow corneal neovascularization to some extent. Topical NSAIDs (as with corticosteroids) are contraindicated in infected ulcers.[79,80] Topical corticosteroids are sometimes recommended by some to reduce corneal vascularization once epithelialization is complete. However, corneal vascularization is a critical means by which corneal stroma (and strength) is re-formed, and topical corticosteroids hasten regression of granulation tissue, suggesting that this approach is inadvisable. No evidence indicates that corticosteroid administration decreases the final size of the scar, and steroids may compromise healing and predispose to local immunosuppression, additional or persistent infection, and corneal rupture.

Fungal Keratitis in Horses

Definition and Etiology Fungal keratitis (or keratomycosis) occurs when an ulcerated cornea becomes infected with a mycotic organism. As with bacteria, no fungi are known to *initiate* corneal ulcers. The most common genera isolated in cases of equine fungal keratitis are *Aspergillus* and *Fusarium* spp., but many other species of other genera have been cultured.[81-86] Horses seem unusually susceptible to fungal keratitis compared with the other domestic species.

Clinical Signs and Differential Diagnoses Fungal keratitis is very common in the horse, particularly in certain geographic regions (i.e., southeastern United States), but has been reported all over the world. Nonspecific signs of keratomycosis might include pain (blepharospasm, photophobia, epiphora), serous to mucopurulent ocular discharge, corneal edema, variable corneal vascularization, loss of stromal integrity (melting or keratomalacia), and secondary anterior uveitis (aqueous flare, hypopyon, fibrin, miosis), which may be severe. Fungal keratitis has various numerous clinical presentations with varied clinical behaviors, ranging from superficial punctate nonulcerative keratitis forms, to necrotic plaques, to stromal lesions with keratomalacia and furrowing, to deeper stromal defects or deep stromal abscesses.[87] A superficial epithelial to subepithelial form presents with microerosions and multifocal, whitish punctate to branching subepithelial opacities that often retain rose Bengal stain.[88] This form, if treated promptly, will usually resolve without incident. However, the forms wherein overt ulceration develops are much harder to control. Superficial fungal ulcers often appear with a roughened, gritty ulcer bed and considerable edema (Color Plate 39-19). Often this form develops into a more severe presentation wherein enzymatic destruction of corneal collagen results in a furrow or groove around the margins of the lesion.[89] This furrow is a form of corneal melting and may progress rapidly and lead to corneal perforation. In other cases of keratomycosis, a plaque of tissue that is typically an accumulation of necrotic collagen, degenerating inflammatory cells, and a mat of fungal organisms forms centrally within the ulcer bed (Color Plate 39-20).[87,89] A very common manifestation of fungal infection is the formation of a white or yellow deep stromal abscess, typically accompanied by corneal vascularization and edema and moderate to severe anterior uveitis (Color Plate 39-21). Fungi have an affinity for the deep corneal stroma and Descemet's membrane, and in severe cases the organisms may invade through the cornea into the anterior chamber. Fungal involvement should be suspected in any corneal ulcer that is associated with plant or organic material, has been treated with corticosteroids, does not heal as quickly as expected, does not vascularize as expected, exhibits a gritty or pigmented surface, develops a plaque, groove, or deep stromal abscess, or if the uveitis present worsens initially when topical antifungal therapy is initiated. Vascularization is usually necessary for the resolution of fungal lesions in the cornea.

Clinical Pathology A diagnosis of superficial fungal keratitis is made when fungal hyphae or yeast are seen on cytologic analysis or cultured from corneal scrapings (Fig. 39-14). A diagnosis with deep keratitis or a stromal abscess may require a full-thickness corneal biopsy from which the fungus is identified using culture or histopathologic evaluation. Unfortunately, some diagnoses of fungal keratitis are made only after enucleation.[84] Fungal C&S is recommended, but because results are often pending for prolonged periods,

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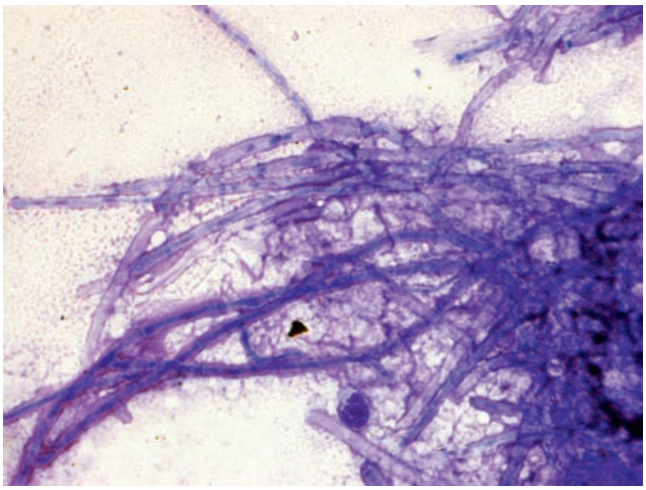


FIG. 39-14 Cytology of fungal keratitis. Diff-Quik, ×100. Note numerous basophilic septate and branching fungal hyphae. A single neutrophil serves as a reference for size of hyphae. *(Image courtesy Anne Gemensky Metzler.)*

empirical antifungal therapy is required. Recent reports have described the use of confocal microscopy in the standing horse to confirm and assess the depth of fungal keratitis.[90]

Pathophysiology Fungal hyphae do not colonize intact corneas. Damage to epithelium is necessary for pathogenic or opportunistic fungi to begin growth in the corneal stroma. This usually results from a traumatic incident that may or may not be noticed by the owner. Use of antibiotics and corticosteroids alters normal flora and decreases the normal immune response, which may encourage fungal growth. Fungi implicated in keratomycoses are usually present in the horse's environment and can be cultured from more than 90% of normal horse eyes, with *Aspergillus* spp. being the most common isolate.[81] There is one report in the literature of keratomycosis caused by *Candida albicans* secondary to disseminated candidiasis.[85]

Epidemiology This disease is sporadic, with varying seasonal distribution and worldwide incidence.[89,91]

Treatment and Prognosis Keratomycosis in any form typically requires extended medical therapy (generally >6 weeks, sometimes considerably longer), and if stromal loss is detected, early surgical intervention is advisable. Treatment consists of eliminating the fungus from the cornea and controlling secondary bacterial invasion and melting, along with reflex uveitis, as for bacterial keratitis. Subpalpebral lavage systems are usually essential for delivering these drugs. Healing is usually not complete until corneal neovascularization has reached the infected area, except when the fungus has reached Descemet's membrane; in these cases blood vessel growth does not always stop fungal growth. Medical therapy is most effective for treating superficial disease. For deep disease, surgical therapy is often necessary in combination with medical therapy. Deep lamellar and penetrating keratoplasty probably carry the best prognosis,[55,84,88,92] although superficial keratectomy with a conjunctival graft can also be used for lesions in the anterior stroma.

A number of antifungal agents are available. Miconazole, used as the undiluted IV preparation, was once the drug of choice for many ophthalmologists. Unfortunately, it is no longer available commercially in this formulation, although it can be compounded. Natamycin (Natacyn) is manufactured as an ophthalmic suspension and is the drug of choice for treating fungal keratitis in humans. However, natamycin does not penetrate intact epithelium well, and some *Fusarium* spp. may be resistant to the drug.[93,94] Fluconazole (Diflucan) is now often recommended as a replacement for miconazole. However, one study reported that fluconazole had lower in vitro activity than a number of other antifungal drugs.[94] The IV preparation is a 2 mg/mL solution, which is used undiluted as a topical preparation. Miconazole and fluconazole do penetrate intact corneal epithelium when given topically, but drug concentrations in the stroma are higher if epithelium is absent.[95] Fluconazole can also be used subconjunctivally, intracamerally, or intravitreally. Ophthalmologists may use fluconazole systemically to treat deep corneal fungal disease, because this drug does reach adequate concentrations in the aqueous humor, which may be appropriate for deep stromal or endothelial infections.[96] No toxicity studies have been performed on the horse, but anecdotal evidence does not suggest toxicities, and fluconazole has been associated with resolution of deep disease.

Compounded formulations of itraconazole/DMSO ointment have also been used for equine keratomycosis. High concentrations of itraconazole can be achieved in the corneal stroma with this preparation, even when the overlying epithelium is intact, and it has been used successfully in clinical cases.[97] In contrast to fluconazole, systemically administered itraconazole does not penetrate noninflamed equine eyes.[98]

Other drugs have been suggested as treatment for fungal keratitis. Voriconazole administered either topically in a 1% solution or systemically penetrates intact corneal epithelium and reaches therapeutic corneal concentrations; it has been found to be efficacious against the common fungal species.[99-102] Miconazole dermatologic or vaginal creams seem to work for mild superficial disease, but no clinical trials describing their efficacy and safety for ocular use have been reported. Amphotericin B has good antifungal properties but can be very irritating. It is useful for the rare cases where a yeast is the offending pathogen. In vitro research shows that silver sulfadiazine is fungicidal against isolates from equine patients with keratomycosis.[93] Unfortunately, in vitro results do not necessarily correlate with clinical results in patients with keratomycosis.[102-104] Corneal penetration of the drug, the horse's immune system, and the site and severity of the fungal infection all play important roles in drug choice.[93]

In addition to topical antifungal agents, therapy should proceed as with any ulcer, with topical antibiotics, antiprotease medications, and atropine, as well as systemic NSAIDs when indicated. Systemic NSAIDs should be used for the secondary uveitis, especially at the beginning of treatment when fungal death can exacerbate uveitis. However, NSAIDs probably slow neovascularization of the cornea, and treatment with these drugs should be decreased as the uveitis is controlled.[79]

Prognosis is guarded to poor in many cases of fungal keratitis. Usually the best possible outcome is a visual eye with some degree of residual corneal scarring. Because no evidence suggests that corticosteroids decrease the eventual size of the scar, and because they will promote the presence of residual hyphae, their use is not recommended in a healing fungal ulcer. Complications of fungal keratitis include perforation of the ulcer with loss of the eye, superinfection with bacteria, and phthisis bulbi.

Viral Keratitis in Horses

Equine herpesvirus serotype 2 (EHV-2) has been isolated from eyes in herd outbreaks of keratoconjunctivitis in horses.[105,106] Clinical signs in one outbreak included apparent photophobia, epiphora, corneal neovascularization, corneal color change, and pinpoint ulcerations; eyes healed within 2 weeks.[105] In another outbreak, conjunctivitis and multifocal superficial corneal opacities were seen; eyes healed within 2 weeks on topical idoxuridine.[106] Experimental inoculation of EHV-2 intranasally in two ponies pretreated with dexamethasone caused conjunctivitis, lymphadenopathy, and coughing.[107] Conjunctiva from both ponies was positive for virus by PCR 6 months after inoculation. EHV-2 can also be isolated from the blood of normal horses,[108] and positive PCR results can be obtained from normal eyes as well as eyes with keratoconjunctivitis, making diagnosis difficult. Miller and colleagues[109] confirmed EHV-2 by fluorescent antibody staining after isolating virus from the cornea of a Thoroughbred mare with multiple superficial punctate corneal lesions. The keratitis was successfully treated with topical 1% trifluridine ophthalmic solution.

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Acute cases will be quite painful (blepharospasm, serous epiphora), with chemosis and conjunctival hyperemia. Recurrence is common and is often associated with corneal vascularization. The superficial or punctuate lesions (epithelial, subepithelial, or anterior stromal) of EHV may or may not retain fluorescein stain. Diagnosis may be difficult, and other differential diagnoses should be considered, including fungal keratitis and immune-mediated keratitis. Therapy for EHV keratitis includes topical antiviral and NSAID therapies. Idoxuridine (0.1%) and trifluridine (0.3%) limit viral replication but do not kill the virus; frequent dosing is required (4 to 12 times daily for 3 to 5 days until the condition stabilizes, then 3 to 6 times daily thereafter). A newer antiviral, 0.5% cidofovir, is effective in cats and requires only twice-daily dosing, but its use in horses has not been reported. Topical NSAIDs such as 0.03% flurbiprofen and 0.1% diclofenac are helpful for secondary uveitis and keratitis, but they should be used with caution because they have been reported to cause recrudescence of viral keratitis in human patients. Systemic flunixin meglumine is often helpful to improve comfort. If defects in the corneal epithelium are present, the additional use of a broad-spectrum topical antibiotic agent is indicated to prevent secondary bacterial infection.

Ocular Manifestations of Systemic Disease

Neonatal Septicemia

Neonatal septicemia in calves, foals, lambs, and kids may occur in the first few weeks after birth and may arise from umbilical infection or oral intake of bacteria. Septicemia is especially common in colostrum-deprived neonates. Secondary meningitis, polyarthritis, uveitis, and chorioretinitis may develop. Ocular signs include miosis, aqueous flare with fibrin deposition in the anterior chamber, hypopyon or hyphema, and in severe cases, panophthalmitis. Many different bacteria and fungi are capable of inducing sepsis, particularly in the immune incompetent, but some of the most commonly implicated agents include *Escherichia coli, Streptococcus* spp., *Pasteurella* spp., *Salmonella* spp., *Rhodococcus equi, Corynebacterium pyogenes,* and *Klebsiella* spp. Therapy should include systemic antibacterial agents (based, when possible, on sensitivity testing) and treatment for uveitis (topical corticosteroids or NSAIDs, topical cycloplegics/mydriatics, and systemic NSAIDs). Prognosis, even for cases treated early, is guarded.[52,110-112]

Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis)

Etiology Bovine herpesvirus type 1 (BHV-1) may involve the respiratory or reproductive tracts, nervous system, or conjunctiva or may cause widespread systemic disease (see also Chapter 31). Conjunctivitis is the most common ocular manifestation of the disease, and it may occur as an isolated clinical entity or with involvement of other body systems.[113-115]

Clinical Signs and Differential Diagnoses Although conjunctivitis is frequently bilateral, it can be unilateral. Ocular discharge, initially serous and later becoming mucopurulent, is usually seen without blepharospasm. Chemosis may be severe, especially by 1 week after infection. Both the palpebral and the bulbar conjunctiva are injected, and petechial hemorrhages may occur. Multiple white plaques 0.2 to 0.5 mm in diameter may develop on the palpebral and, to a lesser extent, the bulbar conjunctival surfaces at 1 to 2 weeks after onset of clinical signs. These may coalesce later in the disease (5 to 9 days). Corneal vascularization and perilimbal edema and opacification occur in severe cases. Iridocyclitis (seen as miosis) may occasionally occur in severe cases.

Corneal changes of BHV-1 are differentiated from those of IBK (caused by *Moraxella bovis*) by their peripheral rather than central distribution and lack of corneal ulceration in BHV-1, unless BHV-1 and IBK occur concurrently in the same eye (see later IBK section). Corneal vascularization and opacification as occurs in malignant catarrhal fever are accompanied by marked signs of anterior uveitis[116] and other signs of generalized vasculitis.

Although ocular disease with BHV-1 may occur as an isolated entity, concurrent upper respiratory tract signs, including rhinitis and dyspnea, are common. Affected animals may be pyrexic, and a fall in milk yield may occur. Abortion in pregnant animals may occur following ocular manifestations of the disease.

Diagnostic Procedures BHV-1 can be recovered from infected eyes during the first 7 to 9 days of the disease but infrequently thereafter. Swabs may be taken for viral isolation in cell culture, which is probably the most reliable means of making a definitive diagnosis. Fluorescent antibody techniques may be used on conjunctival scrapings, and serology may be helpful if blood samples can be collected during the acute and convalescent stages of the disease. PCR is also being used. Histopathology to detect intranuclear inclusions is not likely to allow reliable diagnosis of the disease.[116,117]

Pathophysiology Specific strains of the virus usually cause only one form of the disease (e.g., ocular form) in a herd. Ocular infection results in lymphoid hyperplasia, visible as white plaques. On histology, these are composed of plasma cells and lymphocytes in the conjunctival stroma and subepithelial area. Mild conjunctival epithelial ulceration may occur. During the recovery phase of the disease, diphtheritic membranes secondary to conjunctival necrosis develop on the conjunctival surface.

Treatment and Prognosis Recovery from the conjunctival form of the disease is spontaneous within 10 to 20 days. In certain situations, palliative treatment may be helpful. This is achieved by cleaning the ocular discharge from the lids and applying a topical broad-spectrum antibiotic to prevent secondary bacterial infection. Treatment of the conjunctival form of the disease with topical antiherpetic agents has not been studied and would rarely be practical or cost-effective.

Prevention and Control Vaccination of susceptible animals is the most effective means to prevent and control the disease. BHV-1 vaccination programs are discussed in Chapter 48.

Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis) in Goats

Goats are susceptible to BHV-1, which in some cases may result in ocular disease, particularly keratoconjunctivitis. In one goat with ocular signs, conjunctivitis and keratitis with keratoconus were seen 5 days after the onset of severe respiratory illness. BHV-1 virus was isolated from ocular and nasal discharge.[118]

Peste des Petits Ruminants in Goats and Sheep

Peste des petits ruminants (PPR) is caused by a paramyxovirus of the *Morbillivirus* genus. This highly infectious disease affects both domestic and wild small ruminants and is characterized clinically by fever, diarrhea, depression, polypnea, conjunctivitis, lacrimation, rhinitis, erosive stomatitis, edema of eyelids, photophobia, cutaneous eruption with erythematous areas (especially noticeable in wool-free parts of the body), and axilla lesions evolving into papules.[119,120] Ocular discharge is initially serous but becomes mucopurulent as secondary bacterial infections develop, which are common. Goats tend to be more severely affected than sheep, but both can suffer very high mortality rates, especially immune-incompetent juveniles.[119,120] Also known as *pseudorinderpest,* this disease is found mainly in Africa, Asia, and the Middle East.

Scrapie in Sheep and Goats

The scrapie agent causes a degenerative CNS disease in sheep and less often in goats. Barnett and Palmer[121] described two sheep with scrapie that also had multifocal hyperreflective areas in the tapetum, histologically seen as small areas of retina raised by an accumulation of eosinophilic material between photoreceptors and retinal pigment

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epithelium. The eosinophilic material was characterized as a complex lipid. It was not shown that scrapie had caused the lesions.[121] Subsequently, using a monoclonal antibody, a goat with natural scrapie was found to have the scrapie prion protein in the retina, without any microscopic retinal lesions.[122] A sheep experimentally infected with scrapie was also found to have prion proteins in the retina,[123] as was a sheep experimentally infected with the prion responsible for bovine spongiform encephalopathy (BSE).[124] Prion proteins can also be found in the nictitating membrane,[124,125] which may permit the antemortem diagnosis of scrapie. (See Chapter 35 for more information on scrapie.)

Bluetongue in Sheep and Cattle

Bluetongue is a disease of ruminants caused by an arbovirus that is transmitted by *Culicoides* gnats. Clinical signs include fever and vasculitis that lead to oral lesions, lameness, swollen face, pulmonary edema, and death (see Chapter 32). In pregnant ewes vaccinated with modified live virus (MLV) on day 40 of gestation, fetuses developed cerebral anomalies.[126] These anomalies have also been described in clinical cases in which ewes had been vaccinated with MLV at about 5 or 6 weeks of gestation. In addition, when the fetus was vaccinated with MLV vaccine between days 50 and 75 of gestation, lesions of retinitis and choroiditis were noted that appeared centered around retinal vessels. In some eyes, inflammatory lesions produced persistent areas of retinal dysplasia.[127]

Conjunctivitis and mucopurulent ocular discharge may be seen in cattle chronically infected with bluetongue virus. Although topical antibiotics could be applied to reduce secondary bacterial infection and reduce the ocular discharge, this would rarely be necessary.[128] Systemically ill or congenitally infected animals may have anterior uveitis and corneal edema as a result of this infection.[129]

Bovine Viral Diarrhea

The causative agent of bovine viral diarrhea virus (BVDV) is in the genus *Pestivirus,* a member of family Flaviviridae that, in congenitally affected animals, causes retinal inflammation and necrosis. Cattle infected between days 75 and 150 of gestation may produce calves with cerebellar hypoplasia or ocular lesions. Calves with ocular signs may be blind, and nystagmus may be present. PLRs may or may not be absent. Other abnormalities may include microphthalmia, cataract, leukocoria (either as a result of cataract or dense white inflammatory infiltrate in the anterior vitreous), retinal hemorrhages, chorioretinitis, retinal dysplasia or folds, retinal detachment, or optic neuritis or atrophy.[130-133] The optic disc may appear atrophic, and areas of tapetal color change and hyperreflectivity may be seen, with retinal vascular attenuation. In some cases, inflammatory debris may persist in the vitreous after birth, precluding adequate fundic examination. Congenital cataracts also occur in this disease, and although the pathophysiology is unknown, they probably develop secondary to the intraocular inflammation and necrosis. Cataracts mainly involve the lens cortex.

Transplacental infection may occur when the dam is infected during pregnancy. The severity of the disease is related to fetal age at the time of intrauterine infection. Severe fetal disease and often fetal death occur in cattle infected between 50 and 100 days of gestation. Infected fetuses can also survive and become persistently infected with the virus. In these cattle, viral antigens can be found in neurons of the retina and CNS in the absence of clinical signs.[134] Ocular discharge has been reported in cases of acute or chronic cases of BVDV, although the significance of these observations is uncertain.[133,135]

Serum samples collected from affected calves before ingestion of colostrum can be submitted for serologic assessment using the serum-virus neutralization test, or virus isolation can be attempted from buffy coat cells of a whole-blood sample collected into EDTA. (See Chapter 32.)

Bovine Leukosis

Lymphosarcoma in adult cattle is usually caused by bovine leukemia virus, although noninfectious sporadic cases are reported in young animals. Lymphosarcoma is the most common orbital neoplasm in cattle and may result in unilateral or bilateral progressive exophthalmos.[136,137] If undiagnosed, exposure keratitis and chemosis develop. Intraocular involvement can occur, although it is less common than orbital neoplasia. Generalized lymphadenopathy or other signs of generalized lymphosarcoma usually accompany the orbital form. Specific serologic tests for bovine leukemia virus (BLV) will confirm the diagnosis. Enucleation or exenteration is rarely indicated because of the poor systemic prognosis for affected animals. Differential considerations for progressive exophthalmos include frontal or maxillary sinusitis or nasal or orbital neoplasia (especially squamous cell carcinoma), actinomycosis, and actinobacillosis.

Tuberculosis in Cattle

Tuberculosis caused by *Mycobacterium bovis* may cause granulomatous lesions in the eye of affected cattle. The uveal tract (iris, ciliary body, or choroid) is initially affected, with later expansion of granulomas into other ocular structures. Uveitis, keratitis, and chorioretinitis with retinal detachment are seen clinically.[138]

Malignant Catarrhal Fever

Malignant catarrhal fever (MCF) is a sporadic disease characterized by fever, lymphadenopathy, and generalized vasculitis resulting in inflammation of the mucosal membranes of the mouth, nose, and eye; the skin; and the gastrointestinal (GI) and nervous systems, with variable but usually high mortality. The African form is caused by alcelaphine herpesvirus type 1. The North American form is caused by a similar virus, ovine herpesvirus type 2.[139,140]

Various forms of the disease are described on the basis of clinical signs (see Chapter 32). Ocular involvement is seen in the acute "head and eye" form, which is the most common presentation of the disease. Ocular signs include photophobia, epiphora, episcleral injection and scleritis, severe conjunctivitis, keratitis (corneal opacification caused by edema and vascularization appearing perilimbally), anterior uveitis, and exophthalmia. Less significantly, and difficult to diagnose clinically, retinal vasculitis may develop. Bullous keratopathy may develop as a result of edema in the anterior cornea, with subsequent rupture of bullae to form painful corneal erosions.[141] The absence of central corneal ulceration distinguishes the disease from IBK, and the severity of the ocular lesions is worse than would be expected in BHV-1, BVDV mucosal disease, or bluetongue. Differentiating this disease from rinderpest could be clinically difficult in areas where both are endemic in cattle.

Serology and PCR are being used to confirm the clinical diagnosis.[142,143] The ocular lesions are those of a nonsuppurative uveitis and vasculitis. The lesions involve the conjunctiva, cornea, anterior uvea, and retinal blood vessels; the choroid is rarely involved. Serofibrinous and cellular infiltrates develop in the uvea and retina as a result of vasculitis and thrombosis. Perivascular cuffing and optic neuritis may be detected histologically.[144-146]

Prognosis for the eyes and the animal's recovery is poor.[141,147] Most importantly, in endemic areas, cattle should be kept away from sheep, which may act as a reservoir for the disease, and affected animals should be isolated.[148]

Thromboembolic Meningoencephalitis

Thromboembolic meningoencephalitis (TEME) is a fatal septicemia caused by infection with *Histophilus somni* (see Chapter 35). Calves and young adult cattle can be affected, but the disease most often occurs in feedlot cattle less than 1 year of age. The organism is capable of damaging vascular endothelial cells and activating blood clotting. Therefore, most of the ocular histologic signs are referable to thrombosis of retinal vessels.

Although conjunctivitis may be seen, the main ocular findings are in the fundus. Retinal hemorrhages and exudates may be focal or diffuse. Retinal infiltrates may elevate the retina and involve the vitreous. Retinal edema, hemorrhage and necrosis, vascular thrombosis, and infiltration of the retina and vitreous with neutrophils are seen histologically. Eosinophilic cytoid bodies (swollen axons) are seen in

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the nerve fiber layer of the retina. Retinal detachments may result from retinal edema. Later in the disease, areas of chorioretinitis result in chorioretinal scars. The anterior segment is less involved in this disease than in MCF, in which keratitis and anterior uveitis are usual.[149,150]

Leptospirosis in Horses and Cows

Leptospirosis is caused by a filamentous bacterium known as a *spirochete.* Disease is seen in most domestic animals as well as humans. Various serovars of *Leptospira interrogans sensu stricto, Leptospira kirschneri,* and *Leptospira santarosai* have been shown to affect various organs (e.g., kidneys, liver, spleen, muscles, CNS, eyes) and have been associated with abortions.[151] These organisms primarily cause a vasculitis and endotheliitis in these organs.[152]

Because leptospiral organisms cause vasculitis, it is reasonable to assume that uveitis might be present in an acute infection, and this has been reported in horses during the acute phase of leptospirosis.[153] Uveitis has also been seen experimentally in a calf during acute disease.[154] However, the role of leptospires in uveitis seen weeks to months after the acute disease remains much more controversial. Evidence for such a role is most complete in the horse, in which leptospiral uveitis and its role in equine recurrent uveitis (ERU) or "periodic ophthalmia" have been described.[153,155,156] ERU is an immune-mediated disorder that is the leading cause of blindness in horses (see section on Immune-Mediated Ocular Diseases). Although the recurrent episodes of ERU are not directly caused by reinfection with microorganisms or parasites, numerous bacterial, viral, protozoal, and parasitic organisms have been implicated in the initiation of the syndrome. Uveitis was not seen until 18 to 24 months after the acute outbreak of leptospirosis. Treatment with systemic antibiotics did not seem to affect the uveitis. In this study, serum titers to *L. interrogans* serovar *pomona* often remained high for at least 6 years.[155] In another study, uveitis was seen in 22 eyes of 18 ponies experimentally infected with serovar *pomona*. The earliest sign of uveitis was seen at 1 year after inoculation. Anterior uveitis with cataract formation and posterior synechiae were also seen, as were recurrences.[156]

Recently, leptospiral organisms have been identified using PCR[157] or by culture[157-159] in the eyes of horses with ERU. A study in California using a PCR assay for *Leptospira* showed that 30 of 55 eyes (21 of 30 horses) with ERU had detectable *Leptospira* DNA in their aqueous humor.[157] Interestingly, in other studies, treatment with systemic antibiotics did not decrease the inflammation.[159-161] In Western Europe a total of 618 vitreous and/or aqueous samples were taken from the eyes of 501 horses with either active ERU or a history of ERU. Leptospires were isolated from 199 (32.2%) of the samples. Most belonged to serogroup *grippotyphosa,* with the rest in serogroup *australis, sejroe, pomona,* or *javanica.*[158] In contrast, 36 samples of vitreous from 21 normal horses did not grow leptospires.[159] Although leptospires are involved in ERU in many horses with this syndrome, controlling or treating this disease remains a problem. The best means of symptomatic control of ERU at this time appears to be the use of ocular bioerodible cyclosporin A implants that are surgically placed within the suprachoroidal space, with the goal of controlling immune-mediated intraocular inflammation.[162] In the same study, cyclosporine was been shown to be toxic to *L. interrogans* in vitro at the same concentration that was achieved in uveal tissue with the suprachoroidal implant.[162] (See also Equine Recurrent Uveitis.)

Listeria monocytogenes in Sheep, Cattle, and Horses

Listeriosis in ruminants is manifested mainly as either an encephalitis or a septicemia in neonates, or as a reproductive problem manifested as abortions. Ocular signs with the neural form include facial nerve paralysis and ptosis, often unilateral, on the side of the central lesion; medial strabismus, often on the ipsilateral side because of involvement of the abducens nucleus; nystagmus; and amaurosis.[163] Uveitis with hypopyon has been described in chronic cases.[164]

Listeria monocytogenes has been cultured from conjunctival smears taken from sheep and cattle with keratoconjunctivitis.[165] In most of the sheep, *Branhamella (Neisseria) ovis* was also cultured. Clinical signs included conjunctival hyperemia, epiphora, photophobia, and corneal opacification. Treatment with topical chlortetracycline was curative. Walker and Morgan[166] provide a description of two experimental sheep that developed unilateral anterior uveitis. *L. monocytogenes* was cultured from the conjunctiva of each animal. Both animals recovered after treatment with parenteral ampicillin and topical antibiotics. *L. monocytogenes* has been cultured from the conjunctivae of three cows with keratitis (one with keratitis and uveitis) and from a corneal scraping of one horse with keratitis.[167] In another case report, *L. monocytogenes* was cultured from the cornea of a horse with chronic keratitis.[168] Diagnosis is usually achieved by isolation of *L. monocytogenes* from tissues at necropsy. Early treatment with broad-spectrum antibiotics may be effective in some cases.

Rabies

Rabies remains one of the most serious zoonotic diseases today.[169] It can affect any mammal, and reports of rabies disease and death have been reported in all of the large animal species of concern in this chapter.[169,170] Ophthalmic signs of rabies are usually secondary to systemic illness and neurologic impairment and may include prolapse of the nictitating membrane, strabismus, nystagmus, and vision loss.[169-173] Prevention is the best approach to disease control, since affected animals must necessarily be destroyed once affected.[174] Fortunately, preexposure vaccination is highly effective, and postexposure (before the development of clinical signs) prophylaxis (immediate vaccination against rabies, a strict isolation period of 90 days, and administration of booster vaccinations during the third and eighth weeks of the isolation period) may be effective in unvaccinated domestic animals if administered promptly.[174]

Other Bacterial Disease in Horses

Salmonella spp. cause one of the more common and serious bacterial enteritides in foals and adult horses. It is often accompanied by septicemia in foals. Anterior uveitis and hypopyon have been seen in animals with salmonellosis, and *Salmonella* spp. can sometimes be cultured from these eyes.[175]

Rhodococcus equi is a gram-positive coccobacillus that causes bronchopneumonia in young foals. One report of *R. equi* from the eye of a foal with bilateral panophthalmitis and pneumonia can be found.[176] Clinically, the foal had bilateral miosis and hypopyon. Therapy involves systemic treatment of the pneumonia and topical and/or systemic antiinflammatory treatment for the uveitis.

Strangles is a respiratory infection caused by *Streptococcus equi* subsp. *equi* that can have an accompanying ocular discharge.[177] Chorioretinal depigmentation was noted in the nontapetal fundus of several horses in one group clinically diagnosed with strangles. Because these lesions repigmented with time, it was suggested that they were caused by embolism to the choroid during bacteremia.[178] One case of panophthalmitis caused by *S. equi* in a horse has been described.[179] Ten days after a bout of strangles, this horse developed anterior uveitis that progressed to corneal stromal abscesses and panophthalmitis. *S. equi* was cultured from the eye at enucleation. *S. equi* has also been isolated from infected corneal wounds in horses without systemic signs of strangles. These cases are treated aggressively, as with any bacterial keratitis.

Brucella abortus has been suggested as a cause for ERU,[180] although serum agglutination titers for *B. abortus* in normal horses and horses with ERU are similar.[181] This organism is certainly capable of inducing intraocular inflammation, although its role in recurrence or persistence of uveitis is unknown.

A case of anterior uveitis and bilateral chorioretinitis with retinal detachments has been described in a horse from Denmark as a result of a mycobacterial infection. Acid-fast organisms were seen in both eyes as well as in numerous other organs. *Mycobacterium avium* was cultured from these organs.[182]

Other Viral Diseases In Horses

Equine adenovirus is a DNA virus that causes bronchopneumonia (type 1) or gastrointestinal signs (type 2) in foals, especially if they

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are immunodeficient. Mucopurulent nasal and ocular discharge accompanies the respiratory system disease. Histologically, swelling and necrosis of conjunctival cells with intranuclear inclusions are seen, with accumulation of neutrophils in the lumina and adventitia of uveal blood vessels.[183] Treatment of the conjunctivitis is supportive with lubricants and antiinflammatory medications.

Equine viral arteritis is a rare disease caused by an RNA virus classified as Arterividae. Most animals are subclinically infected, but ocular and nasal discharge, rash, pyrexia, rhinitis, leukopenia, edema (palpebral, periorbital, limb, or ventral), and abortions and neonatal death are seen.[184,185] Corneal opacity and apparent photophobia have also been described.[186] The virus characteristically causes a panvasculitis.

Borrelia burgdorferi, the agent of Lyme disease, has been most often described as causing polyarthritis in horses, cows, and dogs. However, one case of apparent ocular disease has been reported in a pony infected with *B. burgdorferi.*[187] Unilateral anterior and posterior uveitis was noted, and spirochetes were found in the anterior chamber. Other clinical signs included arthritis and synovitis of both carpal joints. Some discuss this agent as a potential contributor to chronic immune-mediated uveitis (ERU).

Equine herpesvirus serotype 1 (EHV-1) is a cause of rhinopneumonitis in horses. It has been cultured from cases of superficial punctate keratitis in the horse; the significance of these isolations is unknown.[188] Six foals were experimentally inoculated intranasally with EHV-1.[189] All developed typical mild signs of upper respiratory infection. One foal developed vision problems 1 month after inoculation. Bilateral chorioretinitis was diagnosed. On necropsy, chorioretinal degeneration with mononuclear cell infiltration in some areas was seen, as well as demyelination of the optic nerve and mononuclear cell infiltrate in parts of the CNS.[189] These findings are not surprising in that EHV-1 causes vasculitis and CNS disease in horses.[190] Retinal detachments and optic neuritis are possible as well. Treatment is not usually successful.

African Horse Sickness is caused by an orbivirus that is transmitted by *Culocoides* insects. It results in profound bulging of the supraorbital fossa, the soft tissue depression above the dorsal orbital rim, which is considered a hallmark of this disease.[191,192] This swelling is due to retrobulbar edema and increased vascular pressure. Chemosis and protrusion of the conjunctiva from between the palpebral fissure is often seen as well. The systemic disease is characterized by either respiratory and/or cardiac impairment and has a high rate of mortality.[191,192] Control of an outbreak in an endemic region (Africa, Middle East) involves quarantine and usually euthanasia of affected animals, vector control, and vaccination of unaffected animals.[191,192]

Equine influenza is one of the most common infectious diseases of the respiratory tract of horses. It is endemic in the equine population of the United States and throughout much of the world. This condition is highly contagious, and the virus spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Clinical signs begin abruptly and include fever, serous nasal discharge, submandibular lymphadenopathy, and a harsh, dry, nonproductive cough.[193] Ocular signs are secondary and are usually limited to conjunctivitis with serous to mucopurulent ocular discharge.[193] The severity of clinical signs depends on the degree of existing immunity, among other factors.[194] Younger animals are most susceptible, but immunity in an older horse can be overwhelmed in animals frequently exposed at shows.[193] Vaccination of at-risk individuals is recommended.

Viral encephalitis caused by either Eastern equine encephalomyelitis (EEE) virus, Western equine encephalomyelitis (WEE) virus, or Venezuelan equine encephalomyelitis (VEE) virus is borne and transmitted by mosquito vectors and often has a seasonal presentation.[195] Any and all signs attributable to cortical and thalamic lesions may be seen with these conditions. Neurologic deficits may be asymmetric, since lesions are not necessarily symmetrically distributed. Clinical signs include altered mentation, aimless wandering, head pressing, circling, inability to swallow, irregular ataxic gait, paresis and paralysis, convulsions, and death. Ophthalmic signs include vision loss, nystagmus, strabismus, mydriasis, and abnormalities of PLRs.[195] In contrast, neurologic lesions with West Nile virus (WNV) encephalomyelitis are more prevalent in the brainstem and spinal cord than the cortical and thalamic regions.[196-198] Thus, horses with WNV may present with signs of spinal cord ataxia, hyperesthesia, and muscle fasciculations as well. Ophthalmic signs may include vision loss, facial paralysis (with secondary exposure keratitis), anterior and/or posterior uveitis, and optic neuritis.[196-198] There is no specific therapy for viral encephalitis. Symptomatic support might include fluid therapy, antiinflammatory agents if indicated, and anticonvulsants if necessary. Topical lubricants for the eyes may be necessary.

Cryptococcosis, Histoplasmosis, and Aspergillosis in Horses

Cryptococcus neoformans is a pathogenic fungus that may cause systemic infection in horses and other mammals. Ocular signs are not usually reported in horses with cryptococcosis, although there is one report of a frontal sinus granuloma with a retrobulbar mass causing exophthalmos, periorbital swelling, blindness, and optic neuritis.[199-200] The frontal sinus and retrobulbar area were involved with a fungal granuloma, but the eye itself was normal. The chorioretinitis associated with *C. neoformans* seen in other species has not been described in the horse, cow, or small ruminant. *Cryptococcus albidus* has been cultured from the cornea of a horse with chronic keratitis.[201] Diagnosis is based on histopathologic evidence of fungal hyphae in tissue samples or on cytology, as well as a positive culture.

Histoplasma farciminosum, a fungal agent found mainly in Africa, is responsible for epizootic lymphangitis, a disease manifested with nodules and draining lesions of the subcutaneous lymphatic system. A conjunctival form of this disease results from deposition of the organism on the ocular mucous membranes by biting flies. Ocular signs include serous to mucopurulent discharge, blepharedema, and conjunctival papules. Disease progression leads to ulceration of the papules, which may result in secondary keratitis and/or obstruction and erosion of the lacrimal duct. Diagnosis is mainly by cytologic analysis and culture, although serologic assays are also available. Amphotericin B is the treatment of choice, and a vaccine is available for horses in endemic areas. Organisms consistent with *Histoplasma* spp. were seen on cytology of a corneal scraping taken from a horse with chronic keratitis.[202] This horse was successfully treated with topical fluconazole.

Aspergillus spp. are considered opportunistic fungi that rarely cause systemic disease in immunocompetent horses. Aspergillosis may be a cause of guttural pouch mycosis and may also occur secondary to chronic obstructive pulmonary disease.[203,204] Associated ocular signs can include Horner syndrome, facial nerve palsy, and blindness resulting from ischemic optic neuritis secondary to extension of disease.[203] These organisms are ubiquitous in the environment, and horses are frequently exposed. Treatment with systemic antifungal agents may be attempted, but the prognosis is guarded and dependent upon the underlying disease process and severity of the lesions. In contrast to the systemic form of the disease, local *Aspergillus* infections in the cornea are common (see section on Fungal Keratitis in Horses).

Infectious Bovine Keratoconjunctivitis

John A. Angelos

Infectious bovine keratoconjunctivitis (IBK), or "pinkeye," is the most common ocular disease of cattle and has been identified in cattle populations worldwide. Clinical signs include corneal ulceration, corneal edema, photophobia, blepharospasm, and lacrimation. In less severely affected animals, recovery with or without permanent corneal scarring occurs. In the most severely affected animals, corneal rupture and lens/iris prolapse may occur, causing permanent blindness. IBK is most common in calves, typically affecting one eye, although both eyes may be affected. Estimates of annual incidence of

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IBK are 5% of all beef cattle, with more than 50% of herds affected.[1] Epizootic outbreaks occur, with case-attack rates approaching 90% to 100% of yearling cattle.[2,3] Cattle of all breeds may be affected, but a higher incidence is reported in Herefords[4] and a lower incidence in Brahmans and cattle with more pigmentation at the ocular margins.[5,6]

Genetic susceptibility to IBK is now being more thoroughly investigated and may yield additional discoveries that could lead to improved methods to control this disease. Genetic investigations of cattle affected with IBK have already suggested the presence of a gene or group of genes that are associated with IBK.[7] Five SNPs on bovine chromosome 20 have also been identified that are significantly associated with IBK.[8] Recently, a relationship was reported between a specific SNP in the Toll-like receptor 4 gene and the rate of IBK infection in Angus cattle.[9]

Economic Impact

Cattle with IBK have reduced weight gain that results in economic losses to producers. A study of more than 45,000 health records of weaned calves demonstrated almost 20-pound (9-kg) lighter weaning weights in calves diagnosed with IBK versus healthy calves.[4] Postweaning 205-day weights of bulls and heifers with IBK showed losses of 36 and 40 pounds (16 and 18 kg), respectively, over unaffected herdmates.[10] In 1169 pasture-raised calves over a 4-year period, the average weight reduction was 11 pounds (5 kg) for calves with IBK in one eye and 35 pounds (15.75 kg) for calves with IBK in both eyes.[11] Economic losses from reduced weight gains along with treatment-associated expenses account for annual losses in the United States estimated at $150 million in 1976.[12] It is likely that current losses greatly exceed this estimate.

Etiology and Epidemiology

Although *Moraxella bovis* is the only organism for which Koch's postulates have been fulfilled with respect to IBK,[13] other viruses and bacteria have also been associated with the disease, including BHV-1 virus[14,15] and *Mycoplasma* spp.[16,17] These organisms may increase risk for IBK by enhancing opportunities for corneal injury[18-20] and increasing ocular and nasal discharge that may facilitate transmission of *M. bovis*. In an outbreak of IBK in young calves, *Mycoplasma bovoculi* and *Mycoplasma bovis* were isolated from affected animals, but *Moraxella bovis* was not isolated.[21] In a recent study, BHV-1 exposure as indicated by positive titer was not found to predispose calves to developing IBK in a herd where *Moraxella bovis* was present.[22]

For many years, a role for hemolytic gram-negative cocci in IBK pathogenesis has been suggested from the observations of researchers in the field. In 1966, hemolytic gram-negative cocci were isolated from calves with severe keratitis and corneal ulceration.[23] In Australia, *Neisseria* spp. were isolated in 24 of 25 outbreaks of IBK; *M. bovis* was identified in only two of these outbreaks.[24] *Neisseria (Branhamella) catarrhalis* was reported in almost 45% of IBK cases, whereas *M. bovis* was isolated from only 28% of IBK cases.[25] *Moraxella bovis* and *Neisseria* species were also cultured from normal eyes of cattle.[26,27] *Moraxella ovis* and *Neisseria ovis* were also reported from cattle in Israel with IBK.[28,29] Experimental inoculation of *N. ovis* into the eyes of calves did not cause lesions typical of IBK, despite previous corneal irradiation.[30] *Moraxella ovis* was reported in mule deer with keratoconjunctivitis, although experimental inoculation of *M. ovis* isolates into eyes of mule deer fawns did not cause IBK.[31] Recently, hemolytic and cytolytic activity from culture filtrates of *M. ovis* isolated from cattle with IBK has been described, suggesting a possible role for bacteria other than *M. bovis* in the pathogenesis of IBK.[32]

During an IBK drug efficacy trial during summer 2002 in northern California, the majority of bacterial isolates from IBK-affected calves were found to be hemolytic gram-negative cocci.[33] Genetic and biochemical characterization of these isolates subsequently identified these organisms as a novel species that was distinct from *M. bovis* and *M. ovis;* it was named *Moraxella bovoculi*.[34] It is likely that *M. bovoculi* has circulated within cattle populations for many years, and until this gram-negative coccus had been shown to be distinct from *M. ovis,* it may have been misidentified by diagnostic laboratories as *M. ovis, Branhamella ovis, M. ovis*-like, or *Branhamella ovis*-like. Recently, however, only a weak causal role for *M. bovoculi* (as well as for *M. bovis*) was reported in a study of the ocular flora that was isolated from IBK-affected calves.[35]

In addition to bacterial infection, other risk factors for IBK include flies, solar irradiation, and mechanical trauma from plant awns. *M. bovis* survives up to 3 days on the external surface[36] and 2 days in the gut[37] of face flies *(Musca autumnalis).* IBK was experimentally induced in cattle that were exposed to face flies that had fed on *M. bovis* cultures.[38] Insecticide-impregnated ear tags or back/face rubbers to reduce fly populations have proved effective in reducing IBK in cattle populations.[39] An association between solar irradiation and IBK has also been documented.[40-42] Corneas of calves exposed to ultraviolet (UV) irradiation incur corneal epithelial cell degeneration[43] that predisposes eyes to establishment of *M. bovis* and IBK. An experimental model for IBK has been developed in which calves are exposed once daily for 2 or 3 days to UV irradiation using sunlamps held 24 inches (60 cm) from the corneal surface; after the last exposure, animals are infected by instillation of *M. bovis* into the eye.[44-46] Plant awns have been associated with IBK, most likely through direct mechanical damage to the cornea that facilitates infection with *M. bovis* and subsequent development of IBK.

Only hemolytic strains of *M. bovis* are considered pathogenic. Nevertheless, nonhemolytic, nonpathogenic *M. bovis* can be isolated from normal cattle,[2,47-49] from cattle exhibiting conjunctivitis,[50] and simultaneously with hemolytic *M. bovis* from cattle with IBK.[49] Outbreaks of IBK typically occur annually during summer months, and such outbreaks may be caused in part by cattle subclinically harboring *M. bovis*.[49,51]

Pathophysiology of *Moraxella bovis*

M. bovis produces many hydrolytic enzymes that may be important in facilitating ocular injury, including C4 esterase, C8 esterase-lipase, C14 lipase, phosphoamidase, phosphatase, leucine and valine aminopeptidases, and gelatinase.[52] To date, however, only two *M. bovis* proteins have been linked to pathogenicity: pili and cytotoxin. Pilin proteins of *M. bovis* are of the *N*-methylphenylalanine type (type 4 pili[53-55]) and enable bacteria to adhere to the corneal epithelium and colonize the surface of the cornea.[56-58]

The *M. bovis* cytotoxin (cytolysin/hemolysin) is a pore-forming protein that is also considered necessary for pathogenesis. Broth supernatants of hemolytic but not nonhemolytic strains of *M. bovis* will cause lysis of bovine erythrocytes, neutrophils, lymphoma cells, and corneal epithelial cells in vitro.[59-62] The lytic activity of *M. bovis* cytotoxin occurs through calcium-dependent formation of transmembrane pores in target cell membranes.[63] Ocular lesions induced by a purified hemolytic and cytolytic fraction of *M. bovis* are identical to the ocular lesions observed in naturally occurring IBK; extracts from nonhemolytic *M. bovis,* however, do not cause corneal lesions.[64]

An association between the *M. bovis* cytotoxin and the RTX (***r***epeats in the structural ***t***o***x***in) family of bacterial exoproteins followed the discovery that *M. bovis* cytotoxin induces formation of pores in target cell membranes.[63] It was subsequently shown that an approximately 110-kilodalton protein in concentrated culture supernatants from cytolytic *M. bovis* cultures could be recognized by a monoclonal antibody to HlyA, an RTX toxin of uropathogenic *E. coli*.[65] The presence of RTX toxins has been reported in numerous animal pathogens, including *Mannheimia haemolytica,* the agent of shipping fever pleuropneumonia in cattle,[66] *Actinobacillus pleuropneumoniae,* an agent of swine pleuropneumonia,[67] *Pasteurella aerogenes,* an abortifacient in swine and other mammals,[68] and *Actinobacillus equuli,* associated with foal septicemia.[69] Enterohemorrhagic *E. coli* O157:H7 also harbors a plasmid-encoded RTX toxin.[70]

The best-characterized RTX toxin is HlyA of uropathogenic *E. coli.* The gene encoding this toxin is assigned the abbreviation *hlyA* and is contained within a four-gene operon organized 5′-C-A-B-D-3′. The product of the RTX A gene is a structural toxin that must be activated by the RTX C gene product to become hemolytic.[71-73] The activation occurs through fatty acylation of conserved lysine

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residues.[74,75] After activation, the toxin is secreted by membrane transport proteins encoded by the B and D genes and a third protein, TolC.[76,77] Regulation of transcription through the RTX operon in *E. coli* is a complex process and involves the protein RfaH and JUMP-Start DNA sequences.[78] As with *E. coli* hemolysin, the *M. bovis* cytotoxin gene *(mbxA)* is contained within an RTX operon (*mbx* operon) that encodes activation and export proteins; this operon is absent in nonhemolytic *M. bovis*.[79] The *mbx* operon defines a pathogenicity island, and acquisition/loss of *mbx* genes may explain the ability of *M. bovis* to change from the hemolytic to nonhemolytic phenotype.[80] *Moraxella bovoculi* and *M. ovis* have also been shown to encode RTX toxins that reside within classical RTX operons.[81] Near complete identity between the deduced amino acid sequences of cytotoxin genes between geographically diverse *M. bovis* isolates has been reported and demonstrates that there is a high degree of conservation in the gene encoding this important pathogenic factor.[82]

Immunity to Moraxella bovis Secretory immunoglobulin (Ig)A is the major immunoglobulin found in normal bovine lacrimal secretions.[83] During experimentally induced IBK, tear IgG1 and IgG2 concentrations increase.[84] Early studies suggested that calves with more severe IBK had higher lacrimal IgA titers to crude *M. bovis* antigen preparations than calves with less severe IBK.[85] A subsequent study identified a predominant tear IgG response to a crude whole-cell *M. bovis* antigen in calves with naturally occurring IBK and concluded that *M. bovis*–specific antibodies in lacrimal secretions did not prevent IBK in calves.[86] Enzyme-linked immunosorbent assay (ELISA) has been used to quantify nonspecific *M. bovis* antigens in tears and has revealed that IgA titers are higher than IgG titers.[87] A study on a small number of calves then suggested that both lacrimal (secretory IgA) and humoral (IgG) antibodies against *M. bovis* whole-cell antigen conferred resistance against IBK, versus a humoral IgG antibody response alone.[88] It was concluded that serum antibodies against *M. bovis* may account for a reduction in the length and severity of clinical signs associated with IBK. Unfortunately, none of these studies adequately controlled for total antibody isotypes present in serum or ocular secretions. In addition, crude *M. bovis* antigen preparations were used in these assays.

In other diseases associated with RTX toxin–producing pathogens, the protective role of immunity against RTX toxins is not well understood. In one study, a *Mannheimia haemolytica* leukotoxin subunit vaccine was not protective,[89] but calves infected with a mutant strain of *M. haemolytica* that secreted inactive leukotoxin had reduced lung lesion scores but similar clinical severity scores as calves receiving wild-type *M. haemolytica*.[90] The introduction of genes encoding the hemolysin (HlyA) into other *E. coli* strains increased virulence,[91] although an HlyA-deficient mutant was still pathogenic.[92] Pigs infected with nonhemolytic *Actinobacillus pleuropneumoniae* developed lung lesions that were similar to lesions in pigs infected with a virulent strain, and it was concluded that the hemolysin of *A. pleuropneumoniae* serotype 2 was not essential for disease.[93] However, other studies found that pigs vaccinated with *A. pleuropneumoniae* serotype 1 hemolysin were protected after challenge.[94,95] These studies underscore the fact that immunity to diseases caused by RTX toxin–producing bacteria is complex and may not depend on an antibody response to an RTX toxin alone.

Experimental Vaccination Early studies that reported reduced *M. bovis* infection rates and decreased occurrence of IBK after reexposure to *M. bovis* indicated that vaccination against IBK might prevent disease.[41] Subsequent work showed that calves vaccinated intramuscularly with live *M. bovis* had less severe IBK after challenge.[96] Formalin-killed *M. bovis* was also reported to be as effective as live cultures in preventing experimentally induced IBK[97]; under field conditions, however, a formalin-killed autogenous bacterin was not efficacious.[98] Recent studies that have examined the efficacy of autogenous *M. bovis*[99] and *M. bovoculi*[100] vaccines have reported such vaccines to be ineffective at preventing naturally occurring IBK.

In an effort to identify other candidate *M. bovis* vaccine antigens, researchers began to examine the use of component or subunit vaccines to prevent IBK. In early studies, *M. bovis* pilin antigens were found to protect calves from homologous challenge.[101] Purified *M. bovis* ribosomes were not protective.[102] Bacterin-containing pili plus corneal-degrading enzymes were protective in field trials, and protection was correlated with the corneal-degrading enzyme level in the vaccine.[103] In that study, however, the exact composition of corneal-degrading enzymes was not reported. In a later study, two commercial *M. bovis* pilus-based vaccines were not protective for calves in a heterologous challenge model.[104] Although pilin is immunogenic, there is marked antigenic diversity between different pilus types because of the presence of two structural pilin genes and variability in the amino acid composition of the pilin molecule caused by inversions within pilin genes.[57,58,105,106] Limited antigenic cross-reactivity was reported between heterologous pili,[107,108] and emergence of novel pilus types can precipitate IBK outbreaks.[109] Such antigenic variability is believed to reduce the overall efficacy of pilus-based vaccines. Nevertheless, more recent work has demonstrated conserved epitopes across different pilus types,[110,111] suggesting a possible future role for conserved pilus antigens in IBK vaccines. In Australia, the prevalence of a limited number of pilus antigens in *M. bovis* suggests that the use of vaccines containing certain broadly represented pilus types may help to reduce losses associated with IBK.[112]

Unlike pili, the *M. bovis* cytotoxin seems to be more conserved across different *M. bovis* strains. IBK-affected cattle were shown to develop systemic immune responses to cytotoxin,[113-116] and antihemolysin antibodies to one *M. bovis* strain neutralized hemolysin from 33 different strains of *M. bovis*.[116] A partly purified cytotoxin vaccine also protected calves against IBK after challenge with heterologous *M. bovis*.[113] These reports suggest a role for a cytotoxin-based vaccine to prevent IBK from multiple *M. bovis* strains, which could therefore be superior to traditional pilus-based vaccines.

Methods to partly purify the *M. bovis* cytotoxin have now been published,[117] and its efficacy in a vaccine to prevent IBK has been demonstrated.[118] The labor-intensive process of preparing native cytotoxin has also led to the investigation of recombinant *M. bovis* cytotoxin vaccines to prevent IBK. In one field trial, calves vaccinated with the recombinant carboxy terminus of *M. bovis* cytotoxin had a lower cumulative proportion of ulcerated eyes compared with saline and adjuvant control calves.[119] Along with recombinant *M. bovis* cytotoxin, other recombinant cytotoxin-based vaccines to prevent IBK have been investigated, including recombinant *M. bovis* pilin plus cytotoxin,[120] recombinant *M. bovoculi* cytotoxin,[121] and recombinant *M. bovis* pilin-cytotoxin plus recombinant *M. bovoculi* cytotoxin.[122] Although trends for reduced IBK in calves vaccinated with recombinant *M. bovis* cytotoxin suggest promise for recombinant vaccines, it is likely that inclusion of additional protective antigens in such vaccines will be necessary to increase their efficacy against IBK.

The vast majority of IBK vaccine trials have evaluated vaccines administered by a parenteral route, but mucosal routes of vaccine delivery have occasionally been investigated. In one study, aerosol vaccination of cattle with uncharacterized *M. bovis* antigens was reportedly effective against IBK.[123] Intranasal *M. bovis* pilin vaccines have recently been evaluated and were shown to stimulate pilin-specific IgA in ocular secretions. The presence of such antibodies, however, could not be correlated with prevention of *M. bovis* ocular infection or development of IBK lesions.[124]

Treatment and Prevention Although vaccination against *M. bovis* has traditionally been considered the foundation of a successful IBK prevention program, other aspects of disease prevention are also important and should not be overlooked, including minimizing risk factors for disease and optimizing trace mineral status through supplementation when necessary. To reduce fly populations, insecticide-impregnated ear tags placed on calves and topical insecticides with back and face rubbers are recommended. Clipping mature grasses before cattle are turned out may help minimize risks

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associated with direct mechanical corneal injury from plant awns. In areas where trace mineral deficiencies (especially of copper and selenium) are prevalent, attention to supplementation of these trace minerals is important.

For vaccination against IBK, commercially available *M. bovis* bacterins are available but not universally effective. With the increase in reporting of *M. bovoculi* from clinical samples following the initial report of that organism in 2007, producers and veterinarians have also sought to improve vaccination coverage by utilizing autogenous *M. bovoculi* (and/or *M. bovis*) vaccines in prevention programs. Anecdotal reports that would support or refute the use of *M. bovis* and/or *M. bovoculi* bacterins are easy to come across on discussion listserves of cattle veterinarians. To date, however, more recent studies investigating the efficacy of autogenous *M. bovis* or *M. bovoculi* vaccines to prevent IBK have reported these vaccines to be ineffective.[99,100]

Moraxella bovis is susceptible to a variety of antimicrobials, including penicillin administered subconjunctivally,[125] oxytetracycline parenterally or orally (20 mg/kg once or twice followed by 2 g/calf/day for 10 days),[126-128] florfenicol IM (two 20-mg/kg injections 48 hours apart) or subcutaneously (SC) (40 mg/kg once),[129,130] ceftiofur crystalline-free acid SC (6.6 mg ceftiofur equivalents/kg once) in the posterior aspect of the pinna,[33] and tulathromycin (2.5 mg/kg) SC.[131] The antibiotic sensitivities of 57 California *M. bovoculi* field isolates have been reported and suggest that commonly used antibiotics for the treatment of IBK associated with *M. bovis* should also be effective against *M. bovoculi*.[132]

Immune-Mediated Ocular Diseases

Kathryn L. Wotman • Mary Lassaline Utter • Mary Belle Glaze

This section describes immune-mediated ocular disease in large animals, beginning with a review of ocular immunology, followed by discussion of immune-mediated ocular diseases including immune-mediated keratitis, eosinophilic keratitis, and equine recurrent uveitis.

Except for the conjunctiva, the eye has no lymphatic drainage. Access of antigens to potentially reactive lymphoid tissue is also restricted by the avascularity of the cornea and the presence of selective blood-ocular barriers. As unlikely as immunologically mediated abnormalities might seem under these circumstances, immune-related inflammation remains a leading cause of blindness in the horse. Reports of immune-mediated ocular disease in ruminants are rare.

Ocular Immunology

The conjunctiva represents an extension of the mucosal immune system. A variety of immune cells can be found in conjunctival tissue, including intraepithelial $CD8^+$ lymphocytes and mast cells, as well as aggregates of $CD4^+$ T-helper (Th) and B lymphocytes, $CD1^+$ dendritic cells and macrophages, and within the substantia propria.[1] The conjunctiva processes ocular surface antigens with the help of regional lymph nodes. Antigen presentation is likely preceded by local tissue damage and release of inflammatory mediators that recruit inflammatory cells to the site. Under the influence of cytokines like interferon (IFN)-α, tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-12 released by local and recruited cells, tissue dendritic cells process and carry host and pathogen molecules to regional lymph nodes to activate $CD4^+$ Th cells. Stimulated lymphocytes migrate back to the conjunctiva (T cells) and lacrimal gland (B cells), where they participate in cell-mediated reactions and local production of IgA and to a lesser degree IgG, respectively.[1-3]

Because the globe itself is without lymphatic drainage, intraocular antigens must be processed at a distant site. These antigens pass into the systemic circulation, preferentially stimulating the spleen as well as the bone marrow and other distant lymphoid organs. After 5 to 7 days, sensitized lymphocytes migrate back to the eye and localize within the uvea and limbal conjunctiva. As with those on the ocular surface, these immunologically competent cells are capable of antibody production and can participate in cell-mediated reactions. Further exposure to the same antigen can provoke an anamnestic response, endowing the uveal and limbal tissues with behavior comparable to that of a regional lymph node.[4]

The intraocular immune response varies from that of a classic immune reaction, presumably to limit excessive inflammation within the eye. Anterior chamber–associated immune deviation (ACAID) is characterized by preferential stimulation of T suppressor cells that inhibit development of both $CD4^+$ and B cells necessary in delayed-type hypersensitivity reactions and production of complement-fixing isotypes of antibody, respectively.[1,5] Cells in the uvea and corneal endothelium also express Fas ligand (FasL), which limits inflammation through apoptosis of activated leukocytes entering the eye.[1]

Each of the four major types of immunologic reactions occurs within the eye.[6] Type I (immediate) hypersensitivity is usually manifested as conjunctivitis, an acute local inflammatory reaction that follows IgE-mediated release of histamine, proinflammatory cytokines and chemotactic mediators from tissue mast cells, and synthesis of cytokines, leukotrienes, prostaglandins, thromboxane, platelet-activating factor (PAF), and kinins.[7] These mediators of the IgE/mast cell inflammatory pathway increase vascular permeability, constrict smooth muscle, dilate blood vessels, and activate leukocyte chemotaxis and the complement cascade. Allergic reactions of the lids and conjunctiva undoubtedly occur in all domestic species.

Type II (cytotoxic/cytolytic) hypersensitivity is an antibody-mediated cytolytic reaction in which the antigen is a cell surface or basement membrane component. Three basic effector pathways lead to cell destruction: (1) opsonization, with increased efficiency of phagocytic destruction, (2) antibody-dependent cellular cytotoxicity, inducing the release of enzymes capable of destroying cells and digesting basement membranes, and (3) lysis of immunoglobulin-bearing cells.[8] Conjunctival damage resulting from autoantibodies directed against epithelial basement membranes is described in equine ocular pemphigoid.

Type III (immune complex) hypersensitivity may share similar effector mechanisms with those described for cytolytic reactions, but antigen locale accounts for dissimilar disease manifestations in these two pathways.[7] This immune complex reaction may explain the clinical signs of pemphigus foliaceus[9] and the intraocular inflammation observed in horses after influenza vaccination or contact with infected animals.[10] Antibody-mediated cell destruction has also been implicated in uveitis.[6]

Type IV (cell-mediated/delayed) hypersensitivity is an important factor in contact allergy of the lids and conjunctiva and may also play a role in ocular toxoplasmosis. The tissue destruction associated with herpetic keratoconjunctivitis in the horse has been attributed to a cell-mediated response.[6] Increasing evidence implicates delayed hypersensitivity in the pathogenesis of equine recurrent uveitis.[11,12] The reaction requires an initial antigen exposure that results in sensitization of antigen-specific T lymphocytes. Reintroduction of antigen induces interleukin production, with subsequent T-cell activation, proliferation, and cytokine production. Once activated by cytokines, recruited leukocytes display increased activity to many antigens.[13]

Allergic Blepharoconjunctivitis

In humans, several forms of allergic conjunctivitis are mediated by IgE, and histamine (H_2) receptors have been discovered on the human ocular surface.[14] The ubiquitous presence of H_2 receptors in domestic animals implies a similar distribution[2] and the potential for immediate hypersensitivity reactions of the eyelids and conjunctiva.

Affected animals demonstrate acute swelling of the eyelids and conjunctiva, accompanied by serous ocular discharge, mild conjunctival hyperemia, and pruritus. If the stimulus persists, multiple

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subconjunctival aggregates of lymphocytes appear as tiny semitransparent follicles within the conjunctival cul-de-sac. In contrast to bacterial conjunctivitis, crusting and purulent discharge are not typical of allergic conjunctivitis.

Diagnosis of allergic blepharoconjunctivitis is often presumptive, based only on careful and thorough elimination of all other causes of lid and conjunctival swelling. Trauma, orbital inflammation, neoplasia, mechanical irritants, conjunctival parasites, and other infectious agents (both ocular and systemic) should be considered. In support of an allergic etiology, conjunctival cytology may reveal eosinophils in response to mast cell degranulation.

The offending allergen may be difficult to identify. Insect stings and toxic plants (e.g., nettle) are possible causes, as are molds and pollens. Allergic conjunctivitis was described in 17 of 187 cows pastured adjacent to a field of blossoming cotton.[15] A group of Angus-Holstein cattle demonstrated excessive lacrimation and ocular pruritus associated with familial allergic rhinitis. Several inhaled allergens have been incriminated, including capeweed, clover, dock, lucerne, pepper tree, paspalum, wattle, ryegrass, sorrel, and fungal extracts.[16] New feeds and certain drugs (e.g., oxytetracycline, penicillin, sulfonamides) may produce generalized urticaria, with accompanying eyelid and conjunctival edema.[17] Similar findings have been reported in cattle with milk allergy. Agents directly inducing mast cell degranulation through osmotic or charge interactions include hypertonic saline, NSAIDs, thiopental, opiates, neuromuscular blocking agents, mannitol, radiocontrast agents, polymyxin B, and vancomycin.[18] Occasionally, allergic conjunctivitis may be associated with a topical medication like neomycin. Clinical signs exacerbate with continued application and diminish when the medication is discontinued.

Ocular signs subside with removal of the offending allergen, but this is often impractical. Individual animals may be treated with a topical ophthalmic corticosteroid preparation such as 0.05% dexamethasone ointment to hasten resolution of swelling and redness. An agent with antiprostaglandin activity, such as oral or parenteral flunixin meglumine (Banamine) at 0.5 mg/kg q12h, may be of benefit in the horse. Signs associated with urticaria respond to a decreasing regimen of oral prednisone or prednisolone, initiated at a dosage of 1 mg/kg once daily in the nonpregnant animal.[19] Single parenteral doses of short-acting corticosteroids, epinephrine, or antihistamines have also been used with reported success in food animals.[16]

Ocular Manifestations of Immune-Mediated Dermatoses

Pemphigus foliaceus is the most common of the autoimmune skin diseases described in horses. Lesions are often first noted on the head and lower extremities but spread to other parts of the body with time. Vesicles, bullae, pustules, erosions, and crusting are commonly noted on the skin and mucous membranes, including the eyelids and conjunctiva. Pemphigus foliaceus, bullous pemphigoid, and recently pemphigus vulgaris have been described in the horse.[21-25] Direct immunofluorescence reveals intercellular deposition of IgG and complement (C3) within the epidermis. Histopathology from biopsied lesions is reported to be more reliable, with findings of acantholytic cells with associated neutrophilic inflammation and intraepidermal and subcorneal pustules.[26] In humans, dogs, a Welsh pony stallion, and recently in the equine muzzle skin, circulating autoantibodies to epidermal transmembrane proteins desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1) have also been demonstrated, which leads to acantholysis, vesicle formation, and epidermal clefting.[20,25,27]

Ocular manifestations of pemphigus may include ulceration or crusting of the eyelids, mucoid ocular discharge, and conjunctival hyperemia with erosions. Corneal ulceration may result from mechanical trauma to affected eyelids and conjunctiva, or may be a primary manifestation of disease, as has been reported in humans with pemphigus vulgaris.[25,28] Diagnosis is based on clinical findings, cytology, histopathology, and positive immunofluorescence of affected skin. See the discussion of immune-mediated dermatologic disorders for therapeutic recommendations and prognosis.

Other immune-mediated diseases, such as systemic lupus erythematosus (SLE), occur infrequently in the horse but can affect the eyelids. In addition to skin lesions, vasculitis may be manifest by hemorrhages in mucous membranes, including the conjunctiva.[21,29]

Eosinophilic Keratoconjunctivitis

Eosinophilic keratoconjunctivitis (EK) is an inflammatory condition of the cornea and/or conjunctiva that can present as unilateral or bilateral ocular disease in the horse. The seasonality typically noted with EK, late spring to early fall, suggests an environmental etiology, but the specific cause of the disorder is unknown. As the name suggests, eosinophils on conjunctival or corneal cytology are diagnostic.[30-36] Recurrence of signs is not uncommon in subsequent years.

Clinical Signs

Clinical signs of mild to severe blepharospasm, epiphora, characteristic caseous mucoid ocular discharge, conjunctival hyperemia, and chemosis are typically noted at the onset of disease. Corneal lesions typically appear as raised white or pink corneal plaques. The plaques may be surrounded by corneal edema, with vascularization extending toward the ulcer and/or plaque from the limbus. Progression to corneal ulceration that extends from the limbus axially is often noted first in the ventromedial cornea quadrant underlying the third eyelid.

Diagnosis

Diagnosis is based on clinical signs and cytologic findings of predominantly eosinophils on corneal or conjunctival scrapings and may include segmented neutrophils, mast cells, plasma cells, and lymphocytes. Differential diagnoses include mycotic keratitis, onchocercal keratoconjunctivitis, neoplasia, foreign body granuloma, traumatic keratitis, squamous cell carcinoma, and calcific corneal degeneration.

Pathophysiology

The eosinophilic inflammation found in the cornea and conjunctival surfaces suggests a type I allergic reaction. Although the inciting allergen has yet to be elucidated, parasites such as *Onchocerca* or *Habronema* spp. are often implicated, but neither has been specifically identified in a case of EK.[37] One proposed mechanism for EK is an allergic or inflammatory response to long-term use of ivermectin as an anthelmintic, triggering the complement cascade and cellular chemotaxis in patients with ocular onchocerciasis.[31] A recent case series of a Standardbred broodmare farm with 19 affected mares described environmental management with minimal medical intervention, including specifically fly control, as a key to decreasing incidence of disease, time to resolution of disease, and lowering the number of recurring cases.[32] This suggests that an environmental allergen that may be associated with flies themselves or transferred by flies stimulates the type I allergic reaction. Similarities to vernal keratoconjunctivitis in humans suggest that eosinophil-granule major basic protein may play a significant role in the equine disease, inhibiting corneal epithelial migration and protein synthesis and promoting collagen degeneration.[38] Eosinophil-derived collagenase also has been reported to degrade type I collagen, the predominant collagen in the cornea.[30]

Treatment and Prognosis

The mainstay of treatment of EK has been topical steroids such as prednisolone acetate 1% suspension, or neomycin polymyxin B dexamethasone ophthalmic ointment in the face of an active corneal ulcer. Cyclosporine has also been used topically as an immunomodulating drug. Prophylactic topical antibacterial and antifungal treatment is often instituted at the same time. Lesions remodel with minimal corneal scarring, but mean duration of treatment in one series of patients was 64 days (range, 45 to 105 days).[31] Use of topical NSAID preparations may increase the severity of clinical signs of EK in horses because of potentiation of leukotrienes, the primary promoter of eosinophilic inflammation.[30] Medical

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management and prognosis were recently evaluated in horses diagnosed and treated in the Mid-Atlantic United States and revealed an average time to resolution of 3.7 months.[33] Treatment in some horses included use of tapering doses of systemic dexamethasone starting at a rate of 0.04 mg/kg PO for 1 day, 0.03 mg/kg for 2 days, and 0.02 mg/kg for 3 to 5 days.[33] A group of horses evaluated in the study was also treated with oral cetirizine, an H_1-antagonist that may be useful in decreasing the migration and adherence of eosinophils.[33,34] Horses treated with oral corticosteroids had a shorter time to resolution when compared to horses that were not given oral corticosteroids. Treatment with oral cetirizine did not decrease time to resolution of ocular disease, but these horses were significantly less likely during the follow-up period to have recurrence of disease (1/13 horses [8%] had recurrence with cetirizine compared to 8/14 [57%] without cetirizine).[33] Excision of the corneal plaques by superficial keratectomy appears to enhance healing, attributable to removal of the eosinophil-granule major basic protein.[30,31]

Immune-Mediated Keratitis

Nonulcerative Keratouveitis

Nonulcerative keratouveitis is an uncommon corneal disease in the horse, characterized by a pink, vascularized, and somewhat localized stromal infiltrate of predominantly lymphocytes near the limbus.[39,40] The overlying epithelium is intact, so fluorescein dye is not retained by the cornea. Accompanying anterior uveitis is typically severe and unremitting, with blepharospasm, epiphora, conjunctival hyperemia, corneal edema, miosis, aqueous flare, and hypopyon. The primary differential diagnosis is a corneal stromal abscess; other considerations include fungal keratitis, EK, onchocerciasis, and neoplasia.

The pathogenesis is presumably immune mediated, based on histopathology and response to therapy.[39] Systemic leptospirosis was incriminated etiologically in a 2-year-old Thoroughbred filly with a unilateral corneal infiltrate of lymphocytes and macrophages and a choroidal infiltrate of lymphocytes, eosinophils, and basophils that was also positive for IgG and C3.[41] Brooks and colleagues[39] speculated that autoimmunity against corneal antigens may play a role.

Before beginning therapy, it is essential to rule out stromal abscessation and fungal keratitis, in which the prescribed antiinflammatory regimen would be contraindicated. Treatment consists of a potentially lifelong regimen of a potent topical corticosteroid that will penetrate through intact corneal epithelium (1% prednisolone acetate or 0.1% dexamethasone sodium phosphate) q4-6h, 1% cyclosporine q12h, and/or an NSAID (e.g., flurbiprofen) q8h.[39,42,43] Topical 1% atropine is administered to effect to minimize ciliary spasm and limit synechiae. A systemic NSAID such as flunixin meglumine is administered q12-24h. Clinical signs typically recur if medication is discontinued. Prognosis is poor, without expectation of cure. Chronic inflammation may result in phthisis bulbi or unremitting pain that necessitates enucleation.[44]

Nonulcerative Keratitis

Chronic nonulcerative corneal opacities that vary in color and depth within the cornea without signs of overt discomfort or intraocular inflammation have been described.[45-48] In a report of 19 horses aged 5 to 11 years diagnosed with nonulcerative keratitis, 11 horses had clinical signs for more than 12 months before referral.[45] The disorder comprises three distinct clinical entities classified as superficial, midstromal, or endothelial, based on the location of the corneal pathology. *Superficial keratitis* is characterized by a superficial white to yellow infiltrate with diffuse mild to moderate vascularization. *Midstromal* lesions are typically more diffuse, with denser cellular and vascular components. A deep cellular infiltrate with mild corneal vascularization and variable degrees of diffuse corneal edema are typical of *endothelial keratitis.* Intraocular inflammation is not a feature of the disorder, regardless of lesion location. Differential diagnoses include stromal abscess, EK, bullous keratopathy, subepithelial herpes keratitis, nonulcerative keratouveitis, and the more recently described subepithelial keratomycosis (SEK). The infiltrates seen with SEK lie beneath the epithelial layers and may appear as punctate lesions or more geographic opacities that respond favorably to antifungal treatment.[46] Unlike what is typically noted in the equine eye with lesions due to fungal infections, SEK does not have significant blepharospasm or intraocular inflammation as a feature.[46]

An immune-mediated pathogenesis is theorized, based on histopathologic characteristics and response to immunosuppressive therapy. Lesion appearance and description has varied, but typically within the United States, changes are described based on depth: superficial stromal, midstromal, and endothelial. Response to treatment and prognosis vary depending on the location of the infiltrate.[47] Regardless of lesion depth, histopathology reveals a predominantly lymphocytic-plasmacytic infiltrate, with stromal fibrosis and vascularization. Three of five horses were seropositive for *Leptospira* in one study.[45] Presumably the immune system is reacting to a self-antigen or antigens of a foreign protein or infectious agent within the cornea. Even though infectious agents have not been documented in this particular disorder, immunologic cross-reaction with self-antigens (i.e., molecular mimicry) may occur, as described with leptospiral organisms or their DNA in the equine cornea.[49,50] Keratectomies from 10 horses with superficial immune-mediated keratitis (IMMK) showed a predominantly cell-mediated inflammation with cytotoxic and helper T cells being the most common cells noted.[51] Local immunoglobulin was also identified in the corneal samples, but this could not be directly associated with a systemic humoral response, leaving the role of this arm of the immune system in question as to the pathogenesis of IMMK.[51]

Owing to the frequency at which the abnormal equine cornea is afflicted with an infectious agent (bacterial, fungal, viral), diagnostic samples (cytology, culture) should be considered prior to starting therapy with immunosuppressive agents. Concurrent therapy with topical antibiotics and antifungals may be warranted. Lesions of superficial stromal keratitis can be controlled with long-term topical dexamethasone and/or cyclosporine applied q12-24h.[45,48] Tacrolimus (FK 506) is a more potent immunosuppressive agent than cyclosporine and can be used topically to aid in decreasing the activity of T cells, but its efficacy in terms of IMMK has yet to be studied.[47] Topical ophthalmic NSAIDs (e.g., diclofenac, bromfenac, flurbiprofen) may be a reasonable alternative to topical steroids, particularly for long-term use in some cases. Lesions in 4 of 11 horses treated by superficial keratectomy and conjunctival grafting resolved without the need for ongoing medication, suggesting that surgical removal of the inciting antigen in addition to a direct blood supply may stop the inflammatory process.[45] A similar chronic therapeutic regimen is used in midstromal keratitis; Matthews[48] states that topical corticosteroids are less effective than cyclosporine in the deeper stromal disorder. Keratectomy followed by a conjunctival graft was curative in one horse with midstromal IMMK.[45] Response to antiinflammatory agents varies in patients with endothelial keratitis, resulting from differences in pathogenesis. Only two of four horses were controlled with constant topical dexamethasone and cyclosporine in the Gilger report.[45] In contrast, Matthews[48] described complete resolution of endothelial keratitis with topical 1% dexamethasone applied q6h for 3 to 7 days. In general, due to the deep location within the cornea, endothelial IMMK carries a poor prognosis for response to treatment and often progresses.[47] Although retention of vision is likely in most cases of nonulcerative keratitis, long-term or even lifelong therapy is required to control the corneal disease.

Equine Recurrent Uveitis (Periodic Ophthalmia, "Moon Blindness")

Definition and Etiology Equine recurrent uveitis (ERU) is distinguished by a pattern of intraocular inflammation in which recurring episodes of acute uveitis are separated by periods of clinical quiescence. Inflammation of the iris and ciliary body (anterior uveitis or iridocyclitis) predominates in the early stages; repeated episodes

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damage the cornea, lens, vitreous, retina, and optic nerve. A more insidious form of ERU characterized by persistent low-grade inflammation occurs in the Appaloosa and Draft breeds of horse.

Equine recurrent uveitis is a leading cause of blindness in the horse and mule. Although the exact prevalence is unknown, estimates as high as 10% to 25% have been reported.[52,53] The financial impact on the equine industry is estimated at 100 to 250 million U.S. dollars annually as a result of the effects on performance and the costs of veterinary care.[54]

Despite extensive clinical research, the specific cause of ERU is still unknown. The pathogenesis is immune mediated, and characterization of T-lymphocyte populations in affected horses documents a delayed hypersensitivity reaction as the basic immunologic mechanism underlying the recurrent inflammatory episodes.[12] Identification of the triggering antigen has proved more elusive, suggesting the disease does not result from persistence of or repeated exposure to a single antigen, but rather to a variety of circulating antigens or native ocular antigens. *Leptospira interrogans* serovar *pomona* is the most frequently incriminated infectious pathogen,[53] but diversification of T-cell responses to a particular antigen or group of antigens over time may result in evolution of the immune response to encompass endogenous ocular self-antigens.[9,55]

Clinical Signs The ocular lesions observed in ERU vary depending on the severity and duration of the disease.[44,52,54,56,57] ERU can occur at any age, but the initial uveitis episode frequently occurs in horses 4 to 8 years of age. Acute episodes are painful, characterized by blepharospasm and excessive tearing. Affected eyes are often described by owners as "red" and/or "cloudy" because of changes in the conjunctiva, cornea, anterior chamber, or vitreous. Dilation of subconjunctival vessels near the limbus, termed *ciliary flush,* may intensify the generalized conjunctival hyperemia. As corneal endothelial function decreases, diffuse corneal edema gives the eye a bluish white appearance. The cornea may also exhibit peripheral circumferential vascularization, cellular precipitates on its inner (endothelial) surface, and linear stromal opacities.

Increased uveal vessel permeability causes the aqueous humor to appear cloudy after influx of plasma proteins (flare), inflammatory cells (hypopyon), erythrocytes (hyphema), or fibrin into the anterior chamber (Fig. 39-15). The iris often appears edematous and lackluster or "muddy." A change in iris color may be noted in breeds with lightly colored eyes, changing from blue to green in response to uveal edema, vascular congestion, and cellular infiltration. Prostaglandins and other inflammatory mediators cause pupillary constriction, favoring the formation of adhesions between the iris and lens (posterior synechiae) that distort the pupillary shape. Even without adhesions, the inflamed iris responds poorly to mydriatic agents. IOP is usually decreased because of diminished aqueous production by the inflamed ciliary body, but intermittent IOP elevations can occur.[58] The ciliary body can also deposit cellular exudates within the anterior vitreous, creating an opacity within the pupillary space that may be mistaken for cataract.

Active chorioretinitis causes dullness and loss of detail in affected tissues. Retinal detachment may follow choroidal exudation. Multifocal depigmented or hyperpigmented foci on either side of the optic disc are the sequelae of chorioretinitis ("chorioretinal scars"), commonly referred to as peripapillary "butterfly" lesions (Fig. 39-16).

Intraocular damage increases each time inflammation recurs. Permanent corneal opacity caused by edema results if the corneal endothelium is severely compromised. Chronic recurrent uveitis is characterized by widespread posterior synechiae, iris depigmentation or hyperpigmentation, and iris atrophy. The anterior chamber may appear shallow if aqueous trapped in the posterior chamber by extensive iris-to-lens adhesions causes the iris to balloon forward (iris bombé). Most lens changes occur weeks or months after uveitis begins. Abnormalities may range from pigment flecks on the anterior lens capsule (Fig. 39-17) to dense cataracts. Lens luxation often follows degeneration of the lens zonules and vitreous. Retinal detachment may also follow vitreous liquefaction or may result from traction by fibrous tissue bands within the vitreous. If retinal degeneration is substantial, the optic disc atrophies (Fig. 39-18). Permanent hypotony is followed by shrinkage of the globe (phthisis bulbi). Conversely, chronic uveitis may result in secondary glaucoma. The combination of these acute and chronic ocular lesions determines the degree of vision loss in the affected animal.

Equine recurrent uveitis may be accompanied by transient and variable inflammation of the pineal gland.[59-62] Similar pineal inflammation has been reported in experimentally induced recurrent uveitis in laboratory animals.

Diagnosis Not every case of uveitis in the horse qualifies as ERU. Diagnosis is based on a chronic, recurrent history of intraocular inflammation and the presence of characteristic ocular lesions. In cases where the history is unknown but recurrent disease is

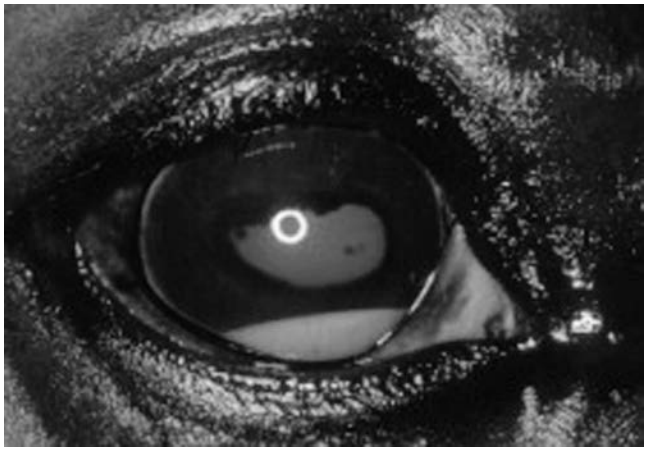


FIG. 39-15 Active uveitis characterized by hypopyon, pupillary irregularities secondary to posterior synechiae, pigment adherent to anterior lens capsule, and a dull tapetal reflection.

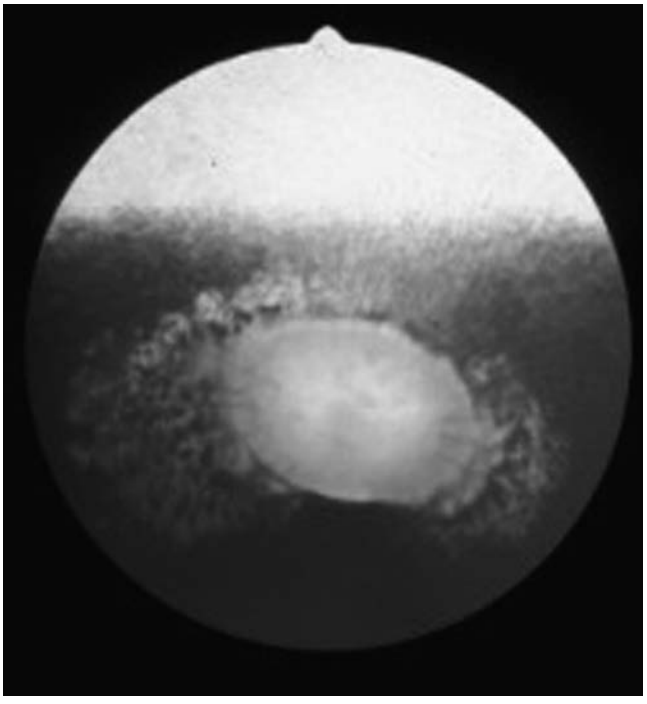


FIG. 39-16 Fundus adjacent to optic disc takes on a mottled appearance as a result of pigment migration after previous chorioretinal inflammation from recurrent uveitis. Because of the shape, such lesions are sometimes referred to as "butterfly lesions."

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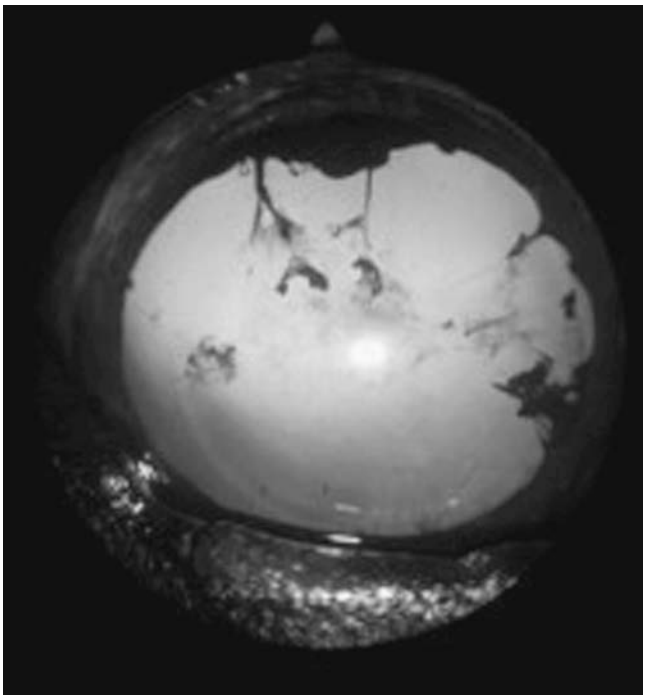


FIG. 39-17 Prior episodes of anterior uveitis are indicated by pigmented remnants on anterior lens capsule and thin adhesions of iris to lens (posterior synechiae). Pupil is pharmacologically dilated.

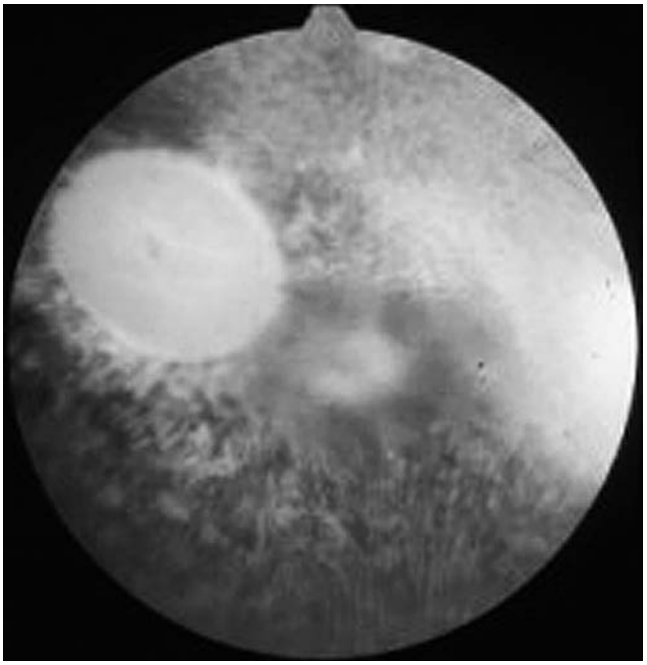


FIG. 39-18 Disc pallor and nontapetal depigmentation accompany an adjacent dark gray preretinal exudate in a horse with chronic active recurrent uveitis. This patient had poor vision.

suspected, at least several of the following indicators of previous inflammation should be observed before a presumptive diagnosis of ERU is made: corneal edema or vascularization, synechiae, iris color change, corpora nigra atrophy or "polishing," lens capsular pigmentation, cataract, lens luxation/subluxation, vitreous opacities or traction bands, retinal detachment, or peripapillary scarring.[52] Other causes of a red and painful eye that can mimic acute ERU include conjunctivitis, corneal ulceration, corneal stromal abscessation, keratouveitis, and glaucoma.

Serologic testing of paired serum samples for *Leptospira* spp. or other infectious agents incriminated as causes of equine uveitis (see Table 39-2) may contribute to a diagnosis of ERU, but negative titers neither exclude the diagnosis nor eliminate leptospirosis as a contributing factor to the disease.[63,64] Acute leptospiral infections are characterized by high-titer seroreactivity to at least one serovar by the eighth day[65]; the titer usually falls with time, but seroreactivity may persist for many years. Some authors suggest that a leptospiral titer of 1:400 or higher is of clinical importance, particularly for *L. interrogans* serovar *pomona*.[52] A higher titer in the aqueous than in the serum is indicative of intraocular antibody production and further supports a leptospiral cause for the uveitis.[66] *Onchocerca* microfilariae may be identified in conjunctival biopsies, although detection of live microfilariae does not necessarily indicate a causal relationship.[67,68] Equine leukocyte antigen (ELA) typing may help determine susceptibility to ERU.[69]

Histopathologic lesions of the ciliary body considered pathognomonic for ERU include the presence of a thick, noncellular hyaline membrane adherent to the nonpigmented epithelium (NPE) and the presence of eosinophilic linear cytoplasmic inclusion bodies within the NPE.[70,71] Clusters of lymphocytes and plasma cells also accumulate in the posterior iris, ciliary body, near the ora ciliaris retinae, within the choroid, and near the optic nerve head.[54,72] Dense bundles of fibrils coupled with necrotic cells and mononuclear inflammatory cell infiltrates characterize the changes within the vitreous.[73]

Pathophysiology

Breed has been established as a risk factor for ERU. In a 1988 retrospective study of more than 16,000 equine patients at Cornell University, researchers determined that the Appaloosa had a significantly higher risk of developing uveitis than Thoroughbreds.[74] A subsequent New York field study substantiated the breed predilection, concluding that the Appaloosa was 8.3 times more likely to develop uveitis than all other breeds combined.[53] Within the Appaloosa breed, those with overall light hair coats and focal dark spots are more likely to develop ERU than horses with a dark, basic coat pattern and a light "blanket" over the rump.[54] Trotters and warmbloods were overrepresented in a report of 130 ERU-affected horses in Germany.[75] Of 669 mares included in a serologic study of leptospirosis, significantly fewer positive titers were found in Thoroughbreds and Standardbreds.[76]

In humans, an immunogenetic predisposition to certain types of uveitis has been linked to the major histocompatibility complex (MHC), a closely aligned cluster of genes designated the HLA region (for human leukocyte antigen) located on a single chromosome.[77] Similar genetic loci occur in the horse, and the gene products are referred to as *equine leukocyte antigens* (ELAs). Products of these genes are glycoproteins found either on most nucleated cells (class I antigens) or restricted to accessory cells such as monocytes or macrophages (class II antigens). The immunoregulatory role of the MHC is especially important in discriminating self-peptides from those of nonself origin. Recent studies have shown an increased risk of uveitis linked with the MHC class I haplotype ELA-A9 in a group of German warmblood horses.[69] As proposed in studies of human HLA-associated uveitis, cross-reactivity between self-antigens and ELA cell surface peptides could explain an inadvertent immunologic attack on normal cells.[78,79]

Experimental findings in ERU patients indicate that a T cell–mediated autoimmune mechanism underlies the recurrent episodes of inflammation. T lymphocytes are the predominant cell type to infiltrate the anterior uvea,[11,72] choroid,[80] and vitreous[81] of horses with ERU, and affected horses demonstrate cell-mediated immunity to retinal autoantigens and peptides.[81-83] B lymphocytes have been reported primarily in retinas from horses seroreactive for *L. interrogans* serovar *pomona,* suggesting that *Leptospira*-associated ocular inflammation may be a distinct subset of equine uveitis.[84] Equine ciliary body epithelium may play a role in recruitment and activation of leukocytes through expression of a chemotactic cytokine (chemokine),[85] although in the normal ocular microenvironment, ciliary

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body pigment epithelium suppresses T-cell activation by direct cell contact and the action of unidentified molecular mediators.[86] Analysis of mRNA collected from horses with uveitis demonstrates elevated levels of IL-2 and IFN-γ, indicating a Th1 response in the disease process.[87] In the absence of bacteria or viruses, this Th1 response by $CD4^+$ uveal T lymphocytes suggests a delayed-type hypersensitivity (DTH) reaction to self-antigens or sequestered antigens in the uveal tract.[12,88] In contrast to the ocular T-lymphocyte population, systemic lymphocytes of ERU-affected horses do not exhibit a Th1 response.[12] The expression of a deviant MHC class II antigen on resident ocular cells (e.g., Müller, retinal pigment epithelial) suggests that aberrant immune regulation may also play a role in ERU.[11,89]

Aqueous and vitreous immunoglobulin levels have been used to characterize immunologic responses within ERU-affected eyes. Using radioimmunoassay, an early study found that aqueous levels of IgG, IgM, and IgA were 50% to 120% greater in diseased eyes than in normal controls, but that the IgG/albumin ratio suggested leakage of protein through an impaired blood-aqueous barrier rather than intraocular antibody synthesis.[90] Subsequent reports support local ocular antibody production but disagree on the dominant immunoglobulin in ERU-affected eyes. Wagner and coworkers[91] found selectively increased IgA levels in the vitreous of affected horses; Eule and colleagues[92] reported substantial IgM titers in 79.6% of intraocular samples from ERU-affected eyes. In contrast to the intraocular immunoglobulins, there are no significant differences in serum immunoglobulin concentrations between healthy and ERU-affected horses.[91,92]

Both exogenous and endogenous antigens have been proposed as stimuli for these basic immunologic responses. One theory suggests that an infectious agent such as *L. interrogans* (or another, perhaps noninfectious, exogenous antigen) causes the initial iridocyclitis. Sensitized immunocompetent cells enter the uvea during this first inflammatory episode, imparting immunologic memory that is specific for the inciting antigen. Subsequent challenge of these cells by the immunogen causes recurrence of the inflammatory reaction.[6,93] However, although some reports suggest persistent infection as the cause of ERU,[94] the premise of an infectious agent that exclusively induces and maintains ERU through a classic anamnestic response does not fully account for the disorder's clinical course and response to therapy.

The role of leptospiral infection in ERU has been studied extensively in recent years. All major serogroups of *L. interrogans* have been identified in the horse and implicated as initiating factors in ERU.[53,64,95-98] In a report of 130 ERU cases in Germany, 58.8% demonstrated positive titers to leptospirosis, an incidence 7 to 10 times higher than the control population.[75] Anti-*Leptospira* antibodies have been found in the serum, tears, aqueous humor, and vitreous of infected horses.[64,96,99-101] Wollanke and colleagues[101] reported positive serum antibody titers to *Leptospira* serovars in 25% (24/97) of normal-eyed horses and 22% (50/227) of ERU-affected horses, but only the ERU-affected animals had positive antibody titers in the vitreous.[101] Leptospiral organisms have been cultured from the aqueous and vitreous of ERU-affected horses.[63,64,98,102,103] However, in one study, *Leptospira* was not frequently detectable in fixed ocular tissues of horses affected with ERU when using traditional immunohistochemical and real-time PCR techniques.[104] In another study, there were no differences in bacterial DNA detection or in serum or aqueous humor anti-*Leptospira* antibody production between clinically normal horses, horses with ERU, and horses with ocular inflammation not associated with ERU in the southeastern United States.[105]

Horses seropositive to *L. interrogans* serovar *pomona* are reportedly 13.2 times more likely to have signs of uveitis than seronegative horses.[53] Ocular signs during the acute infection are subtle or absent, but overt ocular inflammation develops months to years later.[106-109] Risk factors for equine leptospirosis include rodent and wildlife exposure, proximity to ponds and rivers, a dense equine population on site, and increasing age.[76,110,111]

Although direct *Leptospira*-mediated injury to the eye cannot be ruled out in the pathogenesis of ERU, a growing body of evidence instead links leptospiral infection with autoimmune responses to ocular tissue components. Complement-binding anti-*Leptospira* antibodies capable of cross-reacting with equine corneal tissue and lens have been found in the tear film and aqueous humor of horses with leptospirosis.[99,100,112] These antibodies bind corneal epithelial cells, activating complement and initiating tissue damage, a mechanism replicated in tissue culture.[113] A leptospiral protein epitope that shares antigenic determinants with the equine cornea and lens has been found in bacterial homogenates,[49] and a DNA fragment of several serovars of *L. interrogans* was determined to encode a 90-kilodalton protein that cross-reacts with equine corneal proteins.[50,114] Novel leptospiral lipoproteins, identified as LruA and LruB, stimulate local intraocular IgA and IgG production and also cross-react with equine ciliary body, lens, and retina.[115] Immunohistopathologic examination has also demonstrated leptospiral cross-reactivity with iris pigment epithelium and retina from horses with ERU.[84,116] This antigenic relationship between *Leptospira* spp. and equine ocular tissues supports the concept of molecular mimicry as a contributing factor in ERU; exposure to exogenous antigens that share molecular structural sequences with equine self-antigens initiates an autoimmune response.[10]

Toxoplasmosis, brucellosis, salmonellosis, streptococcal hypersensitivity, *E. coli, Rhodococcus equi,* borreliosis,[117,118] intestinal *Strongylus,* and onchocerciasis have also been implicated as causes of ERU, with no consistency in culture or serology results in affected horses.[44,53] Viruses suspected of a role in ERU include equine influenza virus, equine herpesvirus (EHV-1, EHV-4),[119] equine arteritis virus, and possibly equine infectious anemia.[44,52,54] More recent studies on vitreous and serum samples from affected horses question the role of *Borrelia burgdorferi,* Borna disease virus, and *Toxoplasma* in ERU.[120,121]

Both humoral and cell-mediated hypersensitivities have been implicated in the lesions of ocular onchocerciasis. Immunoelectrophoretic studies have demonstrated an influx of IgG and complement (C3) into the tears of affected horses in response to larval death.[122] The resulting chemotaxis of mast cells, eosinophils, and lymphocytes perpetuates the inflammatory response and facilitates destruction of the parasite. Human patients with ocular onchocerciasis demonstrate conjunctival infiltration by $CD3^+$ T lymphocytes and increased expression of class II MHC antigens in conjunctiva and iris,[123] as well as deficiencies in suppressor T-cell function that may interfere with the normal regulation of antibody function.[124]

In addition to the role of infectious agents in the pathogenesis of ERU, autoimmunity may occur when a normally sequestered component is exposed to lymphoid cells or when the antigenicity of a component increases as a result of a structural alteration.[125] Several endogenous ocular proteins, including retinal soluble antigen (S-antigen, or S-Ag), interphotoreceptor retinoid-binding protein (IRBP), cellular retinaldehyde-binding protein (CRALBP),[126] and uveal melanin-associated proteins are known to induce uveitis in various animal models.[127-130] Clinical studies also implicate these potent autoantigens in the pathogenesis of some forms of human uveitis.[131-133] An autoimmune phenomenon in response to damaged uveal tissue has been proposed in the pathogenesis of ERU.[134] The isolation of S-antigen in the horse and the subsequent finding of anti-S antibodies in the aqueous humor and vitreous of horses with uveitis support the theory that this species is similarly capable of local production of antibodies to normally sequestered autoantigens.[81-83,135] Experimental uveitis with features similar to spontaneous ERU has also been induced in horses after injection of IRBP in complete Freund's adjuvant.[80] Autoantibodies to S-Ag and IRBP were found in 72% of vitreous specimens from horses with uveitis.[81] A more recent equine study concluded retinal S-Ag is a weaker autoantigen than IRBP; T and B cells were activated after immunization with S-Ag, but only one in five horses developed uveitis or demonstrated inflammatory cell infiltration of the uveal tract.[136] Because the retina and NPE of the ciliary body originate from neuroectoderm, it is even possible

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that ciliary body damage may release an S-like antigen or another uveitogenic substance.[137] Evidence suggests that response to S antigen is predominantly T-cell dependent.[138]

Verma and coworkers[115] proposed a link between leptospiral cross-reactivity and the release of other ocular autoantigens, based on strong IgG and IgA responses to LruA and LruB lipoproteins in uveitic eyes but not in companion sera. The early phase of ERU may involve production of non–complement-fixing antibody and non-DTH T lymphocytes specific for LruA and LruB. The antibodies and cells react with the leptospiral lipoproteins, initiating a process that ultimately liberates IRBP and other ocular autoantigens.

The concept of "epitope spreading" has been offered as an explanation for the relapsing character of ERU.[139] The theory proposes that after destruction of an initial target, the immune response spreads from the first autoantigenic determinant to others not previously recognized by the immune system.[140-141] Active uveitis subsides as regulatory cells suppress the inflammation, recurring as the immune response shifts to an epitope of the same autoantigen (intramolecular spreading) or a completely different autoantigen (intermolecular spreading). A recent 22-month study of peripheral T-cell reactions in 8 horses with spontaneous ERU demonstrated intramolecular shifts to different S-Ag–derived (6/8) or IRBP-derived (5/8) epitopes and intermolecular shifts in all horses, spreading from IRBP-derived to S-Ag–derived peptides (5/8) or vice versa (3/8).[139] A shift of the immune reaction could be correlated to new uveitic episodes in 10 of 14 relapses that occurred during the observation period. The confounding factor in this theory is the shifts in immune response observed during quiescent stages, perhaps to minor uveitogenic epitopes that fail to result in overt inflammation or as part of an unknown regulatory or protective function of these T-cell clones.

Regardless of etiology, the ocular inflammatory process may attract other reactive lymphocytes to the eye. During primary uveitis, only 10% of the ocular immunoglobulin-secreting cells are specific for the inciting antigen. The remaining cells produce antibodies against immunogens that may not have entered the eye but with which the host had previous contact. As a consequence, the eye may develop recurrent inflammation after systemic exposure to any one of multiple antigens. It is therefore conceivable that subsequent episodes of uveitis may differ etiologically, creating a perplexing clinical picture.[142]

Treatment

ACTIVE INFLAMMATION. Reduction of intraocular inflammation is the primary therapeutic objective in acute uveitis. Preservation of vision depends on successful management at this stage, when sight-threatening sequelae are minimal. If a specific cause for the uveitis is identified, it is also targeted pharmacologically. In most cases, symptomatic therapy combines corticosteroids, NSAIDs, and mydriatic/cycloplegic agents. Nonspecific suppression of T-lymphocyte activation with cyclosporine implants[143] and surgical removal of T cells and, potentially, organisms from the eye by core vitrectomy[144] are recent innovations aimed at preventing recurrence of disease.

No therapy is indicated in nonpainful eyes with lesions of chronic end-stage uveitis. Those eyes that remain painful or do not respond to therapy are candidates for enucleation or evisceration, followed by silicone prosthesis implantation in the orbit or sclera, respectively.

CORTICOSTEROIDS. The severity of the uveitis dictates the routes and frequency of corticosteroid administration. Although topical therapy is most often used, efficacy is limited by the agents' relatively short contact time with the eye. Therefore, topical corticosteroids must be applied three or four times daily, even in eyes with mild clinical signs. In more severe uveitis, topical preparations should be combined with other routes of therapy. A subpalpebral lavage system should be considered when frequent application is indicated (see under Bacterial Keratitis in Horses).

Either ophthalmic solution or ophthalmic ointment is acceptable for topical use in the horse. Prednisolone acetate 1% suspension has excellent intraocular penetration and is considered the drug of choice. Potent dexamethasone preparations, 0.1% solution or 0.05% ointment, are also effective. In general, therapy should be continued for at least 2 weeks after clinical signs have resolved. Ideally, that assessment includes an objective IOP measurement to ensure resolution of ciliary body inflammation and dysfunction.

The subconjunctival injection of a repository corticosteroid preparation is an alternative or supplement to frequent topical therapy. Triamcinolone acetonide 4% suspension is effective for 1 to 3 weeks when injected in a 0.5- to 1-mL volume (20 to 40 mg) beneath the superior bulbar conjunctiva. Subconjunctival injection of methylprednisolone acetate suspension has a comparable antiinflammatory effect but is more likely to cause granuloma formation at the injection site. Duration of effect of either drug depends on the severity of the uveitis. Non-ocular use of either drug has been linked to equine laminitis.

Intravitreal triamcinolone injection may provide a safe and effective method to control ERU. In one study evaluating the ocular distribution and toxicity of intravitreal triamcinolone, 6 horses were injected intravitreally with either 10, 20, or 40 mg of triamcinolone. There was no evidence of overt toxicity from intravitreal triamcinolone injection in normal horses, and a single intravitreal injection resulted in ocular levels of triamcinolone for 21 days. However, the risk for bacterial infection after intravitreal injection or anterior chamber aspiration in horses appears to be high.[145]

Evaluation of inflamed eyes should always include topical application of fluorescein dye to rule out ulcerative keratitis. This precaution is especially critical when considering the use of subconjunctival corticosteroids that deliver prolonged and irreversible effects. Topical and subconjunctival corticosteroids are contraindicated in the presence of corneal ulcers because they delay healing, potentiate the destructive effects of endogenous and microbial enzymes, and predispose the cornea to secondary infection.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS. Parenteral corticosteroids may be used when topical and subconjunctival agents are ineffective in controlling inflammation, but NSAIDs are usually preferred in such cases. Use of these antiprostaglandin agents counteracts an important mediator of intraocular inflammation, minimizing the role of parenteral steroids in uveitis therapy and the attendant risk of laminitis. Flunixin meglumine (Banamine) is the NSAID of choice for the eye, administered at a dose of 0.5 mg/kg IV or IM twice daily for 5 days, then 0.25 to 0.5 mg/kg PO once or twice daily. Oral phenylbutazone at 4.4 mg/kg twice daily can be used in cases of mild uveitis or in animals requiring chronic low-dose oral prophylaxis for recurrent disease. Dosage requirements for aspirin make it less practical in acute cases, but prolonged oral administration of 15 mg/kg twice daily has been used to avert relapses. Frequency of NSAID administration should be reduced as clinical response occurs, because antiprostaglandins have been linked to gastrointestinal ulceration and renal dysfunction with high doses or chronic use.

Topical ophthalmic NSAIDs are generally more costly than corticosteroids and not as potent if used alone. However, an additive antiinflammatory effect can be seen when topical NSAIDs are used in conjunction with topical corticosteroids in horses with acute or resistant uveitis. Although generally considered a safe alternative to topical corticosteroids in the presence of corneal ulceration, topical NSAIDs have been implicated in the development of melting corneal ulcers in humans. Available generic solutions include 0.03% flurbiprofen sodium and 0.1% diclofenac sodium. Dosage frequency is empirical, with intervals ranging from 6 to 12 hours.

MYDRIATIC/CYCLOPLEGIC AGENTS. A parasympatholytic mydriatic/cycloplegic agent must be used if equine uveitis is to be managed successfully. By dilating the pupil and decreasing iris-to-lens contact, the chance of posterior synechia formation—and secondary glaucoma—is reduced. An adequately dilated pupil may also

promote vision during the acute episode. Ciliary spasm is relieved, making the horse more comfortable, and the iridociliary vessels return to a more normal state of permeability, with normalization of aqueous humor constituents.

Topical application of 1% atropine solution or ointment is indicated at a frequency no more than two to four times daily until the pupil dilates. The ultimate goal is to maintain mydriasis with the least frequent application possible, keeping in mind the resistance of the inflamed iris and ciliary body to the effects of atropine. Horses on an intensive parasympatholytic regimen should be strictly monitored for signs of reduced gut motility and colic, because systemic effects occur with frequent topical atropine administration.[146] Pupillary dilation may persist for 4 weeks or more after cessation of therapy.

If mydriasis is slow or incomplete, 10% phenylephrine hydrochloride solution may be used topically in conjunction with atropine.[147] Although a study in the horse suggests that phenylephrine is ineffective when combined with a parasympatholytic agent, investigators did not rule out a possible benefit if dosage or duration of therapy was increased.[148] However, frequently applied phenylephrine has been associated with the development of corneal ulcers, corneal endothelial toxicity with secondary corneal edema, and increased uveal exudation, so response to the drug should be carefully monitored.

ANTIBIOTICS. Because current evidence suggests an immune rather than an infectious basis for recurrent uveitis, antibiotics have assumed a secondary role in ERU management. Although topical antibiotic preparations may discourage opportunistic bacteria during intensive corticosteroid therapy, few will cross the intact cornea and reach therapeutic levels in the anterior chamber or uveal tract. In horses with positive leptospiral titers in serum or ocular fluids, systemic antibacterial therapy with oral doxycycline (10 to 20 mg/kg twice daily for 4 weeks) may minimize recurrences of uveitis.[149] In eyes with mechanical disruption of the blood-aqueous barrier, administration of enrofloxacin IV at 7.5 mg/kg q24h resulted in aqueous humor concentrations greater than the reported MIC for *L. pomona,* suggesting that enrofloxacin may be a good antibiotic choice for horses with leptospirosis-associated ERU.[150]

OTHER THERAPIES. The ocular toxicity and intravitreal and subconjunctival distribution of rapamycin was evaluated in six normal horses. Rapamycin, a macrolide immunosuppressive and antiproliferative drug, was injected intravitreally (5 mg) or subconjunctivally (10 mg). There was no evidence of ocular toxicity on ophthalmic examination or histopathology. RAPA was not detected intraocularly 7 days post injection in eyes receiving subconjunctival RAPA, but was detected in the vitreous at 21 days post injection. Drug could be detected in both the aqueous and vitreous humor after intravitreal injection. However, the efficacy of intravitreal RAPA is not known.[151]

If leptospiral infection has been well documented in a group of horses with uveitis, periodic vaccination against the disease may be considered. However, although vaccination significantly increased the interval to recurrence (median, 126 days) compared with nonvaccinated controls (median, 86 days), the practice failed to slow the progression of disease in a group of 41 ERU-affected horses.[152] Currently, no commercial bacterin is approved for use in the horse.

An intracameral injection (25 µg/0.1 mL) of tPA can be used to accelerate fibrinolysis and clear hypopyon in the anterior chamber of horses with severe uveitis. However, tPA should be avoided in eyes with evidence of hemorrhage in the previous 48 hours.

The precise role of *Onchocerca* species in the pathogenesis of ERU is not yet determined, and considerable controversy exists regarding the necessity or benefit of microfilaricidal therapy in cases of ocular onchocerciasis (see later under Ocular Parasites).

Acupuncture and homeopathic remedies such as poultices of chamomile and oral methylsulfonylmethane (MSM) have been used in the treatment of ERU, but efficacy of these unconventional modalities is unknown.

Prevention of Disease Recurrence

CYCLOSPORINE. Cyclosporine A (CsA) is a noncytotoxic immunosuppressive drug that blocks transcription of IL-2 and decreases T-cell responsiveness during the initiation of inflammation.[153,154] These properties could block the nonspecific activation of T cells in recurrent episodes of ERU. With its poor inherent antiinflammatory properties, cyclosporine is likely to be more effective in preventing recurrences than treating active inflammation. Unfortunately, topical application of cyclosporine fails to achieve effective intraocular levels in horses and other species.[155] However, reports of sustained intraocular levels of CsA in ocular tissues[156,157] and resolution of clinical signs in experimental uveitis after implantation of a CsA-impregnated device into the vitreous of rabbit eyes[158] set the stage for implantation of a similar device into the anterior vitreous of horses with experimental uveitis. The CsA-containing implant significantly decreased the duration and severity of inflammation, cellular infiltration, tissue destruction, protein concentrations, and the level of transcription of proinflammatory cytokines in the experimental group.[143] The intravitreal device also prevented recurrences in 81% of horses with spontaneous ERU, but overall success was limited by complications from intraocular hemorrhage, cataract progression, and retinal detachment.[159] Because of significant risk of postoperative complications in the face of concurrent inflammation, a horse with active uveitis is not a suitable candidate for cyclosporine implantation until the inflammation is adequately controlled by conventional means.[54] Intravitreal delivery devices containing other immunosuppressive agents such as tacrolimus were also effective in suppressing inflammation after intravitreal implantation in rabbits with experimental uveitis.[160]

To minimize ocular morbidity related to implantation, ongoing studies of cyclosporine have focused on development and evaluation of a deep scleral delivery device.[161] Superficial episcleral implantation failed to achieve substantial intraocular levels of CsA or control inflammatory episodes in ERU-affected horses. Therefore, effects of a bioerodible implant infused with CsA and inserted into the suprachoroidal space beneath a partial-thickness scleral flap 1 cm posterior to the dorsolateral limbus were studied. Initial reports of the suprachoroidal device are encouraging. High concentrations of CsA were achieved in the equine ciliary body, choroid, retina, and optic nerve. In horses with severe ERU, only 15% of eyes were blind a mean of 14.2 months after implantation. In contrast, 90% of patients with severe ERU treated conventionally are blind within 1 year.[54] In vitro studies of CsA also documented a direct inhibitory effect on *Leptospira* growth at concentrations achievable within the uveal tissues after deep scleral implantation.[161]

In one retrospective study evaluating the long-term efficacy, complications, and duration of effect of suprachoroidal CsA implants in horses with equine recurrent uveitis (ERU), the long-term maintenance of vision of these horses was demonstrated. In 151 eyes of 133 horses from the United States and Europe that had CsA devices implanted with a mean and median follow-up time of 28.9 and 26.3 months (range, 13 to 85 months), at last follow-up 78.8% of eyes were considered visual.[162] The overall mean frequency of uveitis episodes after CsA implantation was 0.09 ± SD 0.08 episodes per month. Among implanted horses, the most common complications leading to vision loss at last follow-up were persistent uveitis episodes (54%), glaucoma (22%), mature cataracts (16%), and retinal detachment (6%). Persistent uveitis episodes tended to be the highest cause of vision loss in implanted horses with less than 24 months and more than 48 months of follow-up.[162]

CORE VITRECTOMY. Pars plana vitrectomy has been used to remove fibrin, inflammatory cells, and debris trapped in the vitreous and to improve vision and delay progression of clinical signs in affected horses.[144,163,164] Proponents theorize that removal of T cells or infectious organisms like *Leptospira* may reduce adverse interactions between the vitreous and the uveal tract, thereby reducing the recurrence of ERU. The technique appears more beneficial in European warmbloods with ERU than in Appaloosas with ERU in the United States. In one German study, recurrence of ERU was prevented in

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85% (29/34) of treated eyes followed for 5 months to 5 years, but 45% of horses developed significant cataract formation.[144] A study of vitrectomy performed in the United States was also complicated by postoperative cataract formation and progressive loss of vision, despite some decrease in recurrence of uveitis.[165] More recent reports of vitrectomy performed on more than 1200 eyes at the University of Munich described no further recurrences of ERU in 98% of patients.[166] Cataract formation and retinal detachment were reportedly rare in this group of animals. Investigators explained their success on the basis of improved patient selection and surgical expertise.

Prognosis The long-term prognosis for vision in horses with recurrent uveitis is poor, although statistics of actual rates of vision loss are limited. Dwyer's 11-year study of ERU-affected horses reported that 56% of the 160 study animals experienced blindness in one or both eyes.[54] Appaloosas and *Leptospira*-seropositive horses were at increased risk for blindness over the course of the study. All seropositive Appaloosas (100%) lost vision in at least one eye; 50% were completely blind. Of seronegative Appaloosas, 72% lost vision in one or both eyes, and 29% were totally blind. Seropositive horses of other breeds lost vision in one or both eyes 51% of the time, with total blindness in only 17%. Seronegative non-Appaloosas had the best prognosis, with 34% losing vision in one or both eyes and total blindness in only 6%.

Bovine-Specific Ophthalmia

A recurrent uveitis of cattle has been described and compared to that of the horse.[167,168] As with ERU, its definitive etiology is unknown, although a viral infection was originally suggested. Clinical signs include conjunctival hyperemia, corneal edema and vascularization, inflammatory cells and hemorrhage within the anterior chamber and uveal tract, and retinal and choroidal edema and hemorrhage. The disorder is uncommon and does not share the notoriety of its equine counterpart. Therapy is directed at reducing inflammation, as described for the horse.

Ocular Parasites

Anne J. Gemensky Metzler[§]

Parasites are an often overlooked cause of ocular disease in large animals. Ocular parasitic diseases can threaten vision and reduce the economic value of the animal through decreased function, decreased production, or both. The mechanisms by which parasites damage ocular tissues are extremely varied and range from direct tissue effects of aberrant parasite migration to complex immunopathologic responses to parasitic antigens. This section reviews the major ocular parasites of large animals, with reference to the ocular tissue of primary importance. Parasitic eyelid diseases are discussed in Chapter 40.

Corneal and Conjunctival Parasitism

Ocular Onchocerciasis

Ocular disease caused by *Onchocerca cervicalis* is the result of aberrant migration of noninfective microfilariae into the palpebral, conjunctival, and corneal tissues.[1] The larvae do not appear to have a predilection for ocular tissues; rather, the eye is involved as part of a generalized subcutaneous migration. Prevalence of onchocerciasis appears to vary with region of the world. One study concluded that 50% of horses with cutaneous onchocerciasis will have ocular involvement,[2] while in another study, roughly 50% of horses evaluated had dermal microfilariae, and of those, 40% had ocular abnormalities consistent with onchocerciasis.[3]

The pathogenesis of ocular onchocerciasis in horses remains unclear, but an immune-mediated inflammatory response to microfilaria has been implicated. In humans, keratoconjunctivitis and uveitis associated with local presence of *Onchocerca volvulus* microfilariae occur only after the microfilariae die. The endosymbiont *Wolbachia pipientis* bacteria are released, inducing an intense host immune response with subsequent dermal pruritus, uveitis, and often blindness.[4,5] Studies of the immunopathogenesis of *O. volvulus* in humans found that much less corneal inflammation occurred when larvae without *Wolbachia* were injected than when larvae containing *Wolbachia* organisms were injected.[6] Because *Onchocerca* microfilariae are commonly found in equine dermal and ocular tissues without evidence of inflammation, a similar mechanism may be involved in horses, but this has not been elucidated.

Ocular onchocerciasis occurs mostly in adult horses.[7] The older the host, the greater the exposure to the vector and the parasite, and presumably the greater the potential for ocular migration of microfilariae. Furthermore, increased immune sensitivity may occur with increased exposure to dead microfilariae.

Clinical Signs Conjunctivitis and keratoconjunctivitis concentrated at the temporal limbus are the most common manifestations of ocular onchocerciasis. Acutely, chemosis and hyperemia of the conjunctiva occur, accompanied by increased lacrimation and blepharospasm. Small, raised, white nodules (0.5 to 2 mm in diameter) in the limbal conjunctiva and similar-sized punctate, subepithelial corneal opacities are often present. Corneal lesions are often wedged shaped, with the base of the triangle at the limbus, and are characterized by varying degrees of superficial and deep neovascularization and cellular stromal infiltrates. Untreated, the lesions progressively enlarge, although the rate of progression and the severity of the disease vary. With chronicity, patches of depigmentation (vitiligo) occur in the perilimbal bulbar conjunctiva. Recurrent episodes of keratoconjunctivitis are common.[1]

Migration and subsequent death of microfilariae in the uveal tract result in uveal inflammation. Both the anterior and the posterior uveal tract may be involved. The clinical signs of *Onchocerca* uveitis include apparent photophobia, epiphora, miosis, aqueous flare, inflammatory cells in the anterior chamber, and globe hypotonicity. However, these signs are not specific for onchocerciasis, and other etiologies must be considered (see Table 39-2).

Chorioretinitis reportedly is a manifestation of posterior segment involvement. Active lesions are recognized ophthalmoscopically by hyporeflective areas representing chorioretinal edema and inflammatory exudates, usually observed around the optic disc in a "butterfly-shaped" pattern.[1,3] However, aqueous and vitreous opacification often precludes accurate assessment of the fundus.

Diagnosis Characteristic clinical signs are highly suggestive of *Onchocerca* keratoconjunctivitis, but definitive diagnosis requires corneal or conjunctival biopsy. Conjunctival biopsy may be collected after topical anesthesia, whereas general anesthesia is typically necessary for partial-thickness lamellar keratectomies to obtain corneal biopsies. A single 3- to 5-mm biopsy is divided into two samples. One sample is placed on a slide with physiologic saline, minced, and warmed to 37° C (98.6° F) to stimulate larvae movement and therefore enhance their detection. Slides are examined repeatedly over the next hour for migrating microfilariae. The organisms are 200 to 240 mm long and 4 to 5 mm in diameter, with a short, unsheathed tail. The other half of the biopsy specimen is placed in 10% buffered neutral formalin for histopathologic examination.

The presence of microfilariae in ocular tissue does not substantiate a diagnosis of *Onchocerca* keratoconjunctivitis unless evidence of a host inflammatory response exists. The cytologic response is usually pleomorphic, with neutrophils, lymphocytes, plasma cells, and eosinophils present. Varying degrees of neovascularization, pigmentation, lamellar disorganization, collagen degeneration, and calcification are

[§]Contributions to previous editions by Robert English and Mark Nasisse are acknowledged.

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present in the cornea. The overlying epithelium becomes thickened and keratinized.[8,9] The presence of eosinophils in corneal and conjunctival scrapings is suggestive of a parasite etiology, but *Onchocerca* microfilariae are rarely found. Definitive diagnosis of *Onchocerca* as the cause of uveitis is rarely possible.

The differential diagnosis for equine keratoconjunctivitis also includes squamous cell carcinoma, habronemiasis, and bacterial or fungal corneal stromal abscesses. Because horses with ocular *Onchocerca* have a generalized larval migration, they may also have dermatitis, especially of the ventral thorax.

Treatment In humans chronically infected with *O. volvulus,* systemic ivermectin therapy decreases ocular microfilaria burden and improves associated ocular disease. Recently, concurrent treatment with doxycycline has been found to improve efficacy of ivermectin therapy by sterilizing adult female worms through elimination of the symbiotic *Wolbachia* bacteria.[10] Furthermore, by eliminating the *Wolbachia,* the subsequent dermal and ocular inflammatory response when microfilaria die is reduced.[6,11]

In horses, microfilaricide therapy has also been associated with increased ocular inflammation. Therefore, treatment is directed at first controlling the inflammatory reaction with systemic antiinflammatory medications and then eliminating the parasite.[12] Corticosteroids have been the mainstay of this initial antiinflammatory treatment and may be given topically, subconjunctivally, or systemically, depending on the severity of the inflammation, extent of ocular and dermal involvement, and temperament of the horse. Like ivermectin, moxidectin has been found to be 100% effective in treatment of *Onchocerca* sp. microfilaria-associated dermatitis in horses, but without inducing the dermal edema seen after treatment with ivermectin.[13,14] Systemic NSAIDs or corticosteroids are indicated to treat and/or prevent severe uveitis with concurrent *Onchocerca* dermatitis and before larvicidal therapy. The antiprostaglandin activity of NSAIDs like phenylbutazone (2.2 to 4.4 mg/kg PO q12-24h) and flunixin meglumine (0.5 to 1.1 mg/kg PO, IM, or IV q12-24h) is beneficial, especially when corneal ulceration prohibits topical use of corticosteroids. Prednisolone, at an initial dose of 0.5 to 1 mg/kg PO daily for 5 to 7 days, is tapered as the inflammation decreases. Refractory cases have been treated for extended periods with 0.25 mg/kg prednisolone every other day.

When keratoconjunctivitis or uveitis is severe and/or refractory to systemic antiinflammatory treatment, topical application of corticosteroids may be indicated. However, since the corneal infiltrates associated with onchocerciasis are clinically indistinguishable from infectious organisms, extreme caution should be exercised when prescribing or administering topical or subconjunctival corticosteroids in horses. Because of superior solubility, 1% prednisolone acetate and 0.1% dexamethasone sodium phosphate are the preferred topical corticosteroid preparations. Depending on severity, lesions may be treated two to four times daily. Subconjunctival corticosteroids are also beneficial but must be used with caution if corneal ulceration exists. Therapy is tapered as the inflammation is controlled.

Elimination of the microfilariae is recommended once inflammation is controlled (see Chapter 40). Topical antibiotics are also recommended to prevent bacterial infection when corneal or conjunctival epithelial ulceration is present. With uveal involvement, topical mydriatic/cycloplegic agents such as atropine are indicated to relieve ciliary spasm and reduce the risk of posterior synechia formation.

Because systemic ivermectin or moxidectin therapy is not effective in killing adult worms, routine deworming is recommended to eliminate microfilaria and prevent maturation to adult worms.[15] Adult worms may survive in the nuchal ligament of horses for extended periods of time.[7]

Ocular Habronemiasis

Equine ocular habronemiasis occurs when larvae from *Habronema muscae, Habronema microstoma,* or *Draschia megastoma* are deposited on ocular tissues. Flies serving as intermediate hosts for *Habronema* are attracted to moist areas of the body for feeding. Periocular sites with ocular discharge, such as the conjunctiva at the medial canthus, and periocular wounds provide feeding sites. As the flies feed, *Habronema* larvae are deposited on the surface of ocular tissues, migrate into the tissues, and produce a local granulomatous hypersensitivity reaction. Equine habronemiasis occurs worldwide.

Clinical Signs Ocular lesions typically consist of raised, proliferative, nonhealing wounds present at the medial canthus or, less commonly, at other periocular sites. The lesions are friable and pruritic and bleed easily. Lesions often contain small (1 to 2 mm), yellow, caseated nodules ("sulfur granules"). Fistulous tracts and subdermal nodules may develop below the medial canthus.[16] Corneal neovascularization, edema, and ulceration can occur as a result of altered lid function and irritation to the cornea from contact with the rough, irregular surface of the lesion. Corneal involvement increases the degree of ocular pain and blepharospasm.

Habronemiasis lesions are typically seasonal, occurring in the warm summer months when the fly population increases. Certain horses appear to be predisposed to developing cutaneous and ocular habronemiasis, and recurrence may be seen in these animals each summer.

Diagnosis Demonstration of the larvae in the granulomatous lesions or fistulous tracts is diagnostic. Biopsies of the affected tissue are directly examined for *Habronema* larvae and may also be submitted for histopathologic examination. Cytologic examination of conjunctival scrapings reveals a mixed inflammatory response, with neutrophils, eosinophils, and macrophages predominating; however, *Habronema* larvae are usually not seen. The differential considerations for these lesions include squamous cell carcinoma, sarcoids, phycomycosis, onchocerciasis, foreign body reaction, eosinophilic granuloma, and exuberant granulation tissue. Identification by PCR of *Habronema* DNA in the excised tissue may support a diagnosis of habronemiasis.[17]

Treatment Until recently, routine treatment was topical, with systemic therapy reserved for severe or refractory cases. However, oral ivermectin (0.2 mg/kg) kills both adults and larvae in the stomach and has become the treatment of choice. Lesions begin to regress in 7 days and are usually healed by 1 to 5 weeks after treatment if reinfestation is prevented.[18,19] Other effective larvicides include trichlorfon, ronnel, and diethylcarbamazine (DEC).

Topical, intralesional, and systemic corticosteroids may be used to decrease the inflammatory response to the larvae, but with ivermectin larvicidal treatment, they may not be needed. Topical antibiotics are indicated, and topical corticosteroids should be avoided if corneal ulceration is present. Débridement and drainage of granulomatous areas and fistulous tracts may increase topical drug penetration, decrease inflammation, and prevent abscess formation. Fly control and prompt treatment of disorders causing ocular discharge or exposure of fresh tissue are important in preventing habronemiasis.

Ocular Thelaziasis

Thelazia spp. nematodes in the conjunctival sac of large animals are considered commensal but can cause clinical ocular disease. *Thelazia* spp. have a worldwide distribution, with *Thelazia lacrymalis* found more often in horses and *Thelazia gulosa, Thelazia rhodesii,* and *Thelazia skrjabini* found more frequently in cattle.[20] The infection rate for cattle and horses in the United States is estimated at 15% to 38%, with horses younger than 3 years of age affected more often than adult horses.[21-24] The complete life cycle of the parasite is unknown, but *Musca autumnalis* (face fly) and other *Musca* species serve as the intermediate host or vector.[25]

Clinical Signs Most horses and ruminants infested with *Thelazia* show no clinical signs. However, chronic conjunctivitis,

follicular conjunctivitis, conjunctival cysts, and superficial keratitis can occur, especially in the summer months when flies are active.[26] The disease is often mild but can progress to cause corneal neovascularization, edema, and ulceration. Dacryocystitis due to parasite migration in the nasolacrimal system occurs and is more common in cattle than horses. Migration into the lacrimal gland and its ducts is seen and theoretically may lead to keratoconjunctivitis sicca.[24,27]

Diagnosis Direct visualization of the adult *Thelazia* worms in the conjunctival sac or nasolacrimal flushings is diagnostic. The parasites are motile unless topical anesthetic is used. Adult *Thelazia* are 8 to 18 mm long and milky white, and their cuticle contains prominent transverse striations.

Treatment In cattle, both ivermectin and doramectin given systemically at 0.2 mg/kg are effective in eliminating *Thelazia.*[28,29,30] It is unclear whether ivermectin therapy is effective in eliminating *Thelazia* in horses, and efficacy of newer drugs such as doramectin or moxidectin has not been reported.[28] Alternatively, the parasites may be removed manually with saline flushes or forceps after topical anesthetic is administered, followed by topical ophthalmic organophosphate therapy.[30]

Ocular Elaeophoriasis

Elaeophoriasis, or "sore head," is a disease of sheep that is caused by the nematode *Elaeophora schneideri.* Adult *Elaeophora* organisms are found in the common carotid and internal maxillary arteries of deer, where microfilariae are produced and migrate into the capillaries of the face and head. Biting flies of the genera *Hybomitra* and *Tabanus* transmit the microfilariae to new hosts. The disease is most prevalent in the fall and winter in western parts of the United States where sheep are grazed at high altitudes. *Elaeophora* infections in deer are usually not associated with clinical signs. In small domestic ruminants, Bighorn sheep, and elk, however, the migrating microfilariae can cause a hypersensitivity reaction in facial and ocular capillaries.[31,32]

Clinical Signs Migration of *Elaeophora* microfilariae in ocular capillaries leads to local inflammation. Although the uveal tract is affected more often, sheep with elaeophoriasis may develop chronic keratoconjunctivitis evidenced by epiphora, blepharospasm, conjunctival hyperemia, chemosis, and corneal opacities. Clinical signs of anterior uveitis caused by *Elaeophora* are nonspecific and include epiphora, blepharospasm, miosis, clouding of the anterior chamber, and cataract formation. Funduscopic changes indicative of chorioretinitis and optic neuritis are common and include retinal edema, pigment changes in the tapetal and nontapetal fundus, optic disc edema, and optic disc atrophy.[31]

Diagnosis and Treatment Diagnosis depends on demonstrating the microfilariae in skin or conjunctival biopsies. Treatment of heavily parasitized animals may cause death by occlusion of the carotid arteries with *Elaeophora* adults. Drugs used in treatment include piperazine (50 mg/kg PO), diethylcarbamazine (100 mg/kg PO), and stibophen (35 mL IV). The efficacy of ivermectin to treat *Elaeophora* is unknown. Symptomatic treatment of keratitis and uveitis is indicated.

Ocular Manifestations of Nasal Bots

Larvae of the arthropod *Oestrus ovis,* the sheep botfly, can aberrantly migrate up the nasolacrimal duct and enter the conjunctival sac, causing local inflammation. Conjunctival migration is accompanied by epiphora, conjunctival hyperemia, and chemosis. Finding the larvae within the conjunctival sac is diagnostic. Treatment consists of ivermectin, moxidectin, or eprinomectin.[33-35] Visible larvae may be mechanically removed. The nasal botfly *Gedoelstia hassleri* is reported to cause conjunctival and corneal lesions in horses in South Africa.

Ocular Manifestations of Trypanosomiasis and Piroplasmosis

Many species of the protozoal blood parasite *Trypanosoma* can infect horses and ruminants, causing fever, anemia, weight loss, edema of the ventral abdomen and limbs, sudden death, and ocular signs such as conjunctival edema, hyperemia, and petechiation.[36] Sheep infected with *Trypanosoma brucei* can develop keratoconjunctivitis and panuveitis, including chorioretinitis and optic neuritis. Demonstration of the organism in blood smears is diagnostic. Quinapyramine sulfate and chloride has been effective in treating many horses, but persistent or recurrent infections have raised concern about possible drug resistance.[36,37]

Other blood protozoans, including *Babesia* and *Theileria,* can also cause conjunctival edema, petechiation, icterus, swollen eyelids, and blood-stained tears.

Uveal and Retinal Parasitism

Onchocerciasis, Elaeophoriasis, and Trypanosomiasis

Onchocerca cervicalis cause equine parasitic uveitis and chorioretinitis, and *Elaeophora ovis* and *Trypanosoma brucei* cause uveitis in sheep. Ocular manifestations of these diseases are discussed under Corneal and Conjunctival Parasitism.

Toxoplasma Iridocyclitis and Retinitis

The intracellular protozoan parasite *Toxoplasma gondii* can cause ocular disease in large animals.[38] Invasion and replication in the retina and uveal tract lead to retinitis, chorioretinitis, and anterior uveitis. The acquired form of toxoplasmosis in ruminants, however, is often not associated with clinical signs, and ocular lesions are uncommon. Toxoplasmosis is rare in horses and has not been reported in cattle.

Clinical Signs The most common ocular findings with ocular toxoplasmosis are iridocyclitis and retinitis.[38,39] Retinitis is the primary posterior segment lesion, with secondary involvement of the choroid. Retinal degeneration, clumping of pigment in the retinal pigment epithelium and choroid, and optic disc avascularity are seen ophthalmoscopically; however, these lesions are not pathognomonic for toxoplasmosis. Orbital pain and swelling may result from parasitic invasion of extraocular muscles and orbital fat.

Diagnosis and Treatment Diagnosis and treatment of toxoplasmosis is discussed in Chapter 35.

Miscellaneous Intraocular Parasites

The most common intraocular parasite in horses is *Setaria,* with *Setaria digitata* found more frequently within the eyes of horses than *Setaria equina.* Ocular infestation is presumed to result from aberrant migration of the larval stage. Although *Setaria* causes minimal inflammation in the peritoneal cavity, it can cause serious intraocular inflammation. Diagnosis is by visualizing the parasite in the aqueous humor and detecting microfilaria in the blood. Treatment involves symptomatic antiinflammatory therapy and ivermectin therapy,[40,41] but surgical removal of larva from the anterior chamber has also been reported.[42]

Other filarides found free within the anterior chamber of horses' eyes include *Dirofilaria immitis* and *Onchocerca cervicalis.*[2] Diagnosis and treatment are the same as for *Setaria.* Severe endophthalmitis resulting from intraocular infection with the free-living nematode *Halicephalobus* has been reported in a horse.[43] The ocular disease was accompanied by a fatal encephalopathy. Diagnosis was based on finding the parasite during microscopic examination of intraocular tissues.

The canine cestodes *Echinococcus granulosa* and *Echinococcus multilocularis* may form intraocular hydatid cysts in humans, but

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in horses and ruminants, subclinical orbital involvement is more common.[44] There is no medical treatment, and surgical removal is often impossible. Diagnosis is made on histopathologic examination of affected tissues.

Coenurus cerebralis, the intermediate form of *Taenia multiceps* and *Taenia serialis,* can develop in the CNS of sheep, causing a disease known as "sturdy" or "gid." Besides having abnormal gait and mentation, affected animals are often centrally blind.[45] No treatment exists, and the disease is typically fatal.

Ocular Neoplasia

Meredith L. Voyles[‖]

A wide variety of tumor types may involve the ocular or periocular tissues of food animals and horses. Except for the most common neoplasms, limited information is available regarding treatment modalities, drug dosages, overall prognosis, and prevention or control. The tendency has been to adapt information and methods used in other areas of medicine for use in large animals. Table 39-3 lists potential presenting signs and corresponding ocular neoplastic conditions or related differential diagnoses for horses, cattle, sheep, and goats. Table 39-4 categorizes ocular neoplasms that have been reported in the literature for each of these species. The greatest amount of information pertains to the horse.

Despite the variety of primary and secondary neoplasms affecting the ocular and periocular tissues, most tumors produce similar effects on the eye, with tissue distortion and loss of function being the initial concerns. Strategic therapy and management goals may vary from curative or palliative (e.g., eliminating discomfort by enucleation) for individuals to elimination of the problem (e.g., culling from the herd) for a population. Specific tumor treatment options are often similar for neoplasms involving a particular ocular region or location. When designing a management plan, however, the specific histologic tumor type is important in determining prognosis. Classification of a tumor as "benign" versus "malignant" or "localized" (e.g., equine sarcoid) versus "systemic" (e.g., lymphosarcoma) greatly influences treatment options and management approaches. The following discussion addresses the major tumors of concern in large animals and briefly surveys miscellaneous tumors that have been associated with ocular signs.

Bovine Ocular Squamous Cell Carcinoma

Definition and Etiology Bovine ocular squamous cell carcinoma (OSCC), also commonly called "cancer eye," represents the most economically important neoplasm of large animals. It is the most common tumor affecting cattle in North America, and according to estimates from federally inspected abattoirs in the United States, 12.5% of all bovine carcass condemnations were caused by OSCC.[1] The economic impact includes carcass condemnations, production losses, treatment expenditures, and management costs.

OSCC arises from the epithelial surfaces of the conjunctiva (corneoscleral junction, nictitating membrane, and palpebra) or cornea. The etiology is probably multifactorial, with genetic, environmental, and viral factors being proved or suspected.[1-3] In particular, increasing levels of solar irradiation and decreasing amounts of circumocular pigmentation are linked to an increased prevalence of OSCC.[4,5]

Clinical Signs and Differential Diagnoses The gross appearance depends not only on the anatomic tumor site (because this determines the overall interaction between epithelium and underlying connective tissue elements) but also the stage of malignancy. In general, premalignant squamous cell tumors are small, white, elevated, hyperplastic plaques or papilloma-like structures with verrucous surfaces (Fig. 39-19). In contrast, malignant tumors are more irregular, nodular, pink, erosive, and necrotic in nature (Fig. 39-20). Necrotic tumors often have a characteristic foul odor (Color Plate 39-22). Squamous cell carcinomas that invade the orbit may become massive and eventually aggressively invade bone. Often the gross appearance allows a diagnosis to be established, but at times, cytology or histology is necessary to differentiate among benign tumors, carcinoma in situ, and invasive SCC. Bovine OSCC typically involves (in decreasing order of frequency) the lateral limbus, eyelid margins (especially the lower), nictitating membrane, and medial canthal regions.[1,2] Clinical signs resulting from metastatic lesions are not common, although lymphatic tissues may become infiltrated with neoplastic cells.

Despite the characteristic appearance of lesions, differential considerations (especially in the horse) include adenocarcinoma, adenoma, angiosarcoma, basal cell tumor, conjunctival follicular hyperplasia, dermoid, fibroma, fibrosarcoma, granulation tissue, habronemic blepharoconjunctivitis, lymphosarcoma, mastocytoma, plasma cell tumors, sarcoid, and schwannoma (see Tables 39-3 and 39-4).

Pathophysiology The tumor in all species develops through a series of premalignant stages (i.e., hyperplastic plaques or epidermal plaques and papillomas) to progress over months and years to a carcinoma in situ, and finally, an invasive squamous cell carcinoma. Neoplastic lesions may arise without notable precursor stages. It is unlikely that tumors arise in the cornea unless previous vascularization has occurred.[8] Spontaneous regression of 30% to 50% of bovine precancerous lesions may occur,[1] and in rare cases, early OSCC may regress spontaneously. Tumors arising at the limbus are confounded by the dense and poorly vascularized sclera and cornea, thus hindering metastasis to extraocular sites. Nictitating membrane tumors extend to the base of the membrane and cartilage more rapidly, with spread into the orbit and surrounding bones occurring much sooner than with tumors involving the globe. Although metastasis will eventually occur, extensive extraocular spread is limited in cattle by the practice of sending most affected animals to slaughter.

Epidemiology Although OSCC has been reported in a wide variety of cattle breeds, the Hereford breed (either purebred or crossbred) is most often diagnosed with this tumor as a result of the common use of this breed as a range animal and the strong genetic trait for a white face. Thus, selective breeding for partially to fully pigmented periocular skin greatly reduces the occurrence of this tumor.[1] The tumor is more common in older cattle, with the peak age prevalence being 7 to 8 years. Exposure to increasing levels of actinic radiation raises the prevalence of bovine OSCC.[4] The prevalence of ocular squamous cell tumors, including nonmalignant tumors, involving Hereford herds in regions with abundant sunlight can range from 20% to 40%. Research performed in cattle herds suggests that a high plane of nutrition or a lower-than-normal body weight in cows for the first 2 years acts to increase the prevalence.[1] The possibility that bovine OSCC may be induced by viruses (e.g., papillomavirus) warrants further research.

Necropsy Findings Depending on the extent of involvement, gross changes are noted that involve the globe, conjunctiva and nictitating membrane, orbit, bones of the orbit, and regional cervical lymph nodes. In rare instances, metastasis to thoracic and abdominal organs can occur.

Treatment and Prognosis Numerous modalities are available, and applications depend on availability of instrumentation, location and extent of the tumor, and value and intended function of the animal. Choices include radiofrequency hyperthermia (RDM Hypertherm [RDM International, Phoenix, Ariz.]), cryonecrosis, intralesional injection of biologic response modifiers (BRMs) such as

[‖]Contributions to previous editions by Steven M. Roberts are acknowledged.

TABLE 39-3

Ocular Neoplasia and Differential Diagnoses by Species Based on Presenting Clinical Signs

Clinical Sign	Equine	Bovine	Caprine	Ovine
Ocular pain	*Habronema* blepharoconjunctivitis* Brainstem neoplasia Ocular dermoid Ocular trauma Squamous cell carcinoma* Sarcoid	Brainstem neoplasia Ocular dermoid Orbital lymphosarcoma* Sporadic bovine leukosis Squamous cell carcinoma*	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma
Exophthalmos	1 Optic nerve neuroepithelial tumor 2 Lymphosarcoma 3 Retrobulbar neoplasia	4 Enzootic adult lymphosarcoma* 5 Nasal and paranasal sinus neoplasia 6 Nonprogressive bilateral exophthalmos 7 Oral, maxillary, and mandibular neoplasia 8 Retrobulbar neoplasia 9 Sporadic bovine leucosis Squamous cell carcinoma*	Nasal and paranasal sinus neoplasia Oral, maxillary, and mandibular neophasia Squamous cell carcinoma	Adenocarcinoma of nasal cavity Nasal and paranasal sinus neoplasia Squamous cell carcinoma
Intraocular mass	Exudative optic neuritis Mastocytoma Medulloepithelioma Ocular melanoma Optic disc astrocytoma Optic nerve neuroepithelial tumor Squamous cell carcinoma Proliferative optic neuropathy Uveal or iris cyst	Ectopic lacrimal gland Ocular melanoma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma
Nictitating membrane protrusion	10 Horner syndrome 11 Ocular trauma 12 Orbital neoplasia 13 Nasal and paranasal sinus neoplasia	14 Horner syndrome 15 Lymphosarcoma 16 Ocular trauma 17 Nasal and paranasal sinus neoplasia	18 Ocular trauma 19 Nasal and paranasal sinus neoplasia	20 Ocular trauma 21 Nasal and paranasal sinus neoplasia
Nasolacrimal duct obstruction	Cutaneous squamous cell carcinoma* *Habronema* blepharoconjunctivitis 22 Nasal and paranasal sinus neoplasia	23 Nasolacrimal duct occlusion 24 Nasal and paranasal sinus neoplasia	25 Nasolacrimal duct occlusion 26 Nasal and paranasal sinus neoplasia	27 Nasolacrimal duct occlusion 28 Nasal and paranasal sinus neoplasia
Ocular discharge	29 Conjunctivitis 30 Ocular trauma 31 Lymphosarcoma 32 Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	33 Conjunctivitis 34 Ocular trauma 35 Lymphosarcoma 36 Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	37 Conjunctivitis 38 Lymphosarcoma 39 Nasal and paranasal sinus neoplasia	40 Conjunctivitis 41 Lymphosarcoma 42 Nasal and paranasal sinus neoplasia
Periorbital or eyeball mass	43 Adenocarcinoma 44 Angiosarcoma 45 Hemangioma 46 Hemangiosarcoma 47 Lipoma 48 Lymphosarcoma 49 Mastocytoma 50 Melanoma 51 Nasal and paranasal sinus neoplasia 52 Ocular dermoid 53 Reticulum cell sarcoma 54 Retrobulbar neoplasia Sarcoid* Squamous cell carcinoma* Warts	55 Ectopic lacrimal gland 56 Fibroma 57 Fibrosarcoma 58 Ocular dermoid 59 Ocular melanoma 60 Retrobulbar neoplasia 61 Squamous cell carcinoma*	62 Fibroma 63 Fibrosarcoma 64 Melanoma 65 Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma	66 Fibroma 67 Fibrosarcoma 68 Melanoma 69 Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma
Buphthalmia	70 Glaucoma 71 Ocular melanoma 72 Ocular trauma 73 Medulloepithelioma Infectious bovine keratoconjunctivitis* Ocular melanoma Ocular trauma	74 Ocular trauma 75 Ocular melanoma 76 Ocular trauma		

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TABLE 39-3

Ocular Neoplasia and Differential Diagnoses by Species Based on Presenting Clinical Signs—cont'd

Clinical Sign	Equine	Bovine	Caprine	Ovine
Corneal mass	Angiosarcoma Hemangioma Hemangiosarcoma Keratomycosis Ocular dermoid Squamous cell carcinoma*	Enzootic adult lymphosarcoma Infectious bovine keratoconjunctivitis* Interstitial keratitis Ocular dermoid Squamous cell carcinoma*	Keratomycosis Ocular dermoid Squamous cell carcinoma Fibroma	Keratomycosis Ocular dermoid Squamous cell carcinoma
Facial mass	Angiosarcoma Cutaneous habronemiasis Hemangioma Hemangiosarcoma Lymphosarcoma Mastocytoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Oral, mandibular, and maxillary neoplasia Retrobulbar neoplasia Salivary gland neoplasia Sarcoid* Schwannoma of eyelids Sialoadenitis	Enzootic adult lymphosarcoma Fibroma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Papillomatosis Retrobulbar neoplasia Sebaceous cyst Sporadic bovine leukosis Squamous cell carcinoma*	Fibrosarcoma Histiocytoma Melanoma Nasal and paranasal sinus neoplasia Papillomatosis Squamous cell carcinoma Fibroma Fibrosarcoma Lymphosarcoma Nasal and paranasal sinus neoplasia Ocular melanoma Papillomatosis Squamous cell carcinoma	

*Denotes the most prevalent and important differential diagnostic considerations.

TABLE 39-4

Ocular Neoplasms Reported in Large Animal Species

Neoplasm	Equine	Bovine	Caprine	Ovine
Adenocarcinoma	+			+
Angiosarcoma	+			
Basal cell tumor	+			
Chondroma rodens	+			
Equine sarcoid	+			
Hemangioma	+			
Lymphangioma	+			
Lymphosarcoma	+	+	+	+
Mastocytoma	+	+	+	+
Medulloepithelioma	+			
Nasal/paranasal sinus neoplasia	+			+
Ocular melanoma	+			
Optic nerve astrocytoma	+			
Optic nerve neuroepithelioma	+	+		
Papilloma	+			
Retrobulbar neoplasia	+			
Reticulum cell sarcoma	+	+	+	+
Schwannoma	+			
Squamous cell carcinoma	+	+	+	+



FIG. 39-19 Bovine ocular squamous cell carcinoma. Note the small premalignant hyperplastic plaque involving the medial limbus and the large malignant nodular mass on the lower eyelid. The large mass is becoming ulcerated and necrotic.

allogeneic OSCC extract, mycobacterial cell wall fraction (Normagen [Fort Dodge Laboratories, Fort Dodge, Iowa]), *Propionibacterium acnes* (ImmunoRegulin [ImmunoVet, Tampa, Fla.]), intralesional chemotherapy with cisplatin (Platinol [Bristol-Meyers, Wallingford, Conn.]) with or without initial debulking,[9,10] radiotherapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and surgical removal (local excision, enucleation, and exenteration with or without salivary gland and lymph node resection). Intralesional use of cisplatin (1 mg/cm^3 of tumor volume) is highly effective, but multiple injections are necessary (four times at 2- to 3-week intervals). Handling of the drug and animal after treatment must adhere to U.S. Occupational Safety and Health Administration (OSHA) guidelines,[11] and animals must not be used for food consumption. Appropriate precautions should be followed with off-label use of cytotoxic drugs. Surgical debulking with adjunctive cryonecrosis or radiofrequency hyperthermia is an effective and affordable treatment modality. Cryonecrosis is achieved with liquid nitrogen, using a probe or spray delivery system to freeze the tissues to −30° C (−22° F) twice, with complete thawing between freeze cycles. Radiofrequency hyperthermia is performed with piercing or surface probes to heat the tissues to 50° C (122° F) for 30 seconds. Multiple treatment sites are necessary for lesions larger than 0.5 cm in diameter.

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FIG. 39-20 Bovine ocular squamous cell carcinoma involving cornea and conjunctiva. Note irregular and invasive growth into cornea. The surface is rough and necrotic.

Because recurrence rates range between 30.4% and 42.4%,[3,7] owner compliance to return the animal for follow-up treatment is a significant determinant in overall survival. Financial constraints were the most common reason for cessation of treatment. Many horses that die as a consequence of OSCC are euthanized at the owner's request. The overall prognosis is determined by the degree of neoplastic involvement of normal tissue, but a guarded prognosis is warranted. If treatment is to be undertaken, intervention should begin at the earliest stages of tumor development. In animals destined for slaughter, the guidelines for condemnation of bovine carcasses affected with OSCC shown in part A of Box 39-2 should be considered.

Prevention and Control In cattle, factors such as genetics, UV light, and environmental factors (e.g., wind, dust) are known to be involved in OSCC. Ocular viral infection may also be contributory. If possible, affected animals should be culled as soon as possible because most production situations preclude environmental factor modification.

Equine Ocular Squamous Cell Carcinoma

Definition and Etiology Equine OSCC is the most prevalent equine ocular neoplasm (followed by equine sarcoid) and typically occurs in horses with nonpigmented eyelids.[3,6] The amount of perilimbal and nictitating membrane pigmentation represents another important causal factor in cattle and horses that has received little attention but should be considered on prepurchase and health examinations (see Chapters 1 and 2).

Clinical Signs and Differential Diagnoses Similar tissues are involved in horses as in cattle. These sites include palpebra (eyelids), limbus (corneoscleral junction), conjunctiva, nictitating membrane, and cornea (Color Plate 39-23). Some reports suggest that the nictitating membrane is more frequently involved than the corneoscleral junction.[3,6]

In addition to the traditional sites, horses also are affected by corneal stromal invasive SCC. The tumor in this location appears as a non-raised mass lesion that grows directly deep into the corneal stroma (Color Plate 39-24). The smooth appearance may lead to clinical underestimation of the greater underlying tumor invasion.[12,13]

Pathophysiology Horses demonstrate multiple tumor locations and local invasion in up to 50% of cases.[7,8] The tumor has high rates of local infiltration and recurrence, significantly lowered with additional therapy as described later.[14] Metastasis beyond extraocular sites is rare in horses.

BOX 39-2

Guidelines for Inspection (Antemortem and Carcass) and Disposal of Animals, Carcasses, and Parts Affected with Neoplasia

A. Epithelioma of the eye
   1. Any animal found on antemortem inspection to be affected and the eye has been destroyed or obscured by neoplastic tissue and which shows extensive infection, suppuration, and necrosis, usually accompanied by foul odor, or any affected animal with cachexia, regardless of extent, shall be condemned.
   2. Carcasses of animals with the eye or orbital region affected will be condemned if the affection has:
      a. Involved the osseous structures of the head with extensive infection, suppuration, and necrosis;
      b. Metastasized from the eye or orbital region to any lymph node (including the parotid lymph node), internal organs, muscles, skeleton, or other structure, regardless of the extent of the primary tumor; or
      c. Regardless of extent is associated with cachexia or evidence of absorption or secondary changes.
   3. Carcasses of animals affected to a lesser degree than above may be passed for human food after removal and condemnation of the head, including the tongue, provided the carcass is otherwise normal.

B. Neoplasms
   1. An individual organ or other part of a carcass affected with a neoplasm shall be condemned. If there is evidence of metastasis or that the general condition of the animal has been adversely affected by the size, position, or nature of the neoplasm, the entire carcass shall be condemned.
   2. Carcasses affected with malignant lymphoma shall be condemned.

From Code of Federal Regulations, Title 9, Chapter 3, Parts 309.6, 311.11, and 311.12 (1-1-87 edition).

Epidemiology Equine OSCC in North America demonstrates an increased prevalence with increasing longitude (°W), altitude, and mean solar irradiation.[6] Breeds with a greater risk of developing OSCC include Draft breeds, especially the Belgian (odds ratio [OR] = 21.7), Appaloosa (OR = 7.9), paint and pinto (OR = 4.5), and grade horses (OR = 3.1). Coat colors showing an increased risk include white (OR = 26.7), cremello/palomino (OR = 13.7), gray (OR = 6.7), red/white and strawberry/white (OR = 4.7), buckskin (OR = 4.4), and chestnut/sorrel (OR = 3.8).[6]

Treatment and Prognosis Surgical excision with adjunctive therapy as described in the previous section is used in horses. Most common adjunctive therapy in horses includes cryonecrosis (liquid nitrogen), radiofrequency hyperthermia, and radiation therapy (cesium-137, cobalt-60, gold-198, strontium-90, iridium). Intralesional cisplatin or carboplatin is more commonly being used as well. Recurrence rates for ocular and adnexal SCC is high (44.1%). This can be reduced to 11.9% with adjuvant radiation therapy. The anatomic site in horses with the highest recurrence rate was the limbus (corneoscleral junction) or bulbar conjunctiva.[14]

Prevention and Control Specific preventive measures have not been systematically evaluated in horses, but recommendations include reducing UV light exposure, using protective fly masks in horses (to decrease solar irradiation and environmental irritants), tattooing lightly pigmented periocular skin, and avoiding breeds thought to have an increased risk of tumor development.

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Ocular Manifestations of Lymphosarcoma

Definition and Etiology Lymphosarcoma is a fatal systemic neoplastic disease of the lymphoreticular tissue. The adult or enzootic form of bovine lymphosarcoma is likely the most devastating and common neoplasm of dairy cattle. This is a systemic disease with ocular manifestations rather than a primary ophthalmic problem. (See Chapter 37 for specific information regarding bovine lymphosarcoma and the bovine leukemia virus.) Lymphosarcoma represents the most common cause of orbital neoplasia in cattle,[15] excluding OSCC that involves the orbit by local extension. Lymphosarcoma may affect horses[16] and goats. The etiology in horses and goats is unknown.

Clinical Signs and Differential Diagnoses Clinical signs are usually associated with exophthalmos caused by orbital disease. Neoplastic lymphoid cell infiltration behind the globe results in exophthalmos, subsequent exposure keratitis, and eventual proptosis[15] (Fig. 39-21). One report has documented intraocular lymphosarcoma in a Holstein cow as the presenting sign of generalized lymphosarcoma.[17] Subtle exophthalmos is often overlooked because of the natural exophthalmic state of some dairy breeds. Typically, these animals present with a history that suggests an acute onset of exophthalmos, when actually, orbital involvement has been present for a time. Clinical signs associated with the exophthalmos and exposure keratitis include corneal edema, vascularization, ulceration, epidermalization, conjunctival hemorrhage, chemosis, and ocular discharge. These signs may develop, progress, and change quickly once corneal protection is compromised. Other physical examination findings are discussed in Chapter 37. Differential considerations for exophthalmos include orbital cellulitis, trauma, retrobulbar hemorrhage, retrobulbar soft tissue masses, chronic sinusitis, and sinus neoplasia (see Tables 39-3 and 39-4).

Clinical Pathology Definitive diagnosis is achieved by cytologic samples obtained with a spatula after topical anesthesia[1] or specimens excised for biopsy and fixed in formalin. Benign lesions typically contain superficial anucleated, keratinized squamous cells and deeper epithelial cells with enlarged nuclei and coarse chromatin clumping. Biopsies of these lesions show that the basal layer or basement membrane has not been invaded. Malignant OSCC lesions are composed of pleomorphic cells with bizarre shapes, large hyperchromatic nuclei containing large clumps of chromatin, and prominent nucleoli. On biopsy examination, invasion across the basement membrane is noted, and keratin-pearl formation or marked anaplasia is usually present.[8] In the event of regional lymphatic involvement, fine-needle aspiration or preferably a biopsy may demonstrate neoplastic infiltration.

Equine lymphosarcoma involving the eye also represents a systemic disease with ocular manifestations. Other systemic manifestations are discussed in Chapter 37. Ocular lesions include uveitis, nictitating membrane masses, chemosis and conjunctivitis, and neoplastic infiltration of the eyelids and orbit.[17] Differential considerations should include any chronic inflammatory disease, equine infectious anemia, equine piroplasmosis, and infectious causes of uveitis (see Table 39-2).



FIG. 39-21 Orbital lymphosarcoma. Diffuse orbital involvement causing exophthalmos and secondary exposure keratitis of the right eye.

Necropsy Findings As with the clinical signs, necropsy findings are variable. In cattle, orbital involvement is common, with lymphoid tumors being firmly attached to the periorbita and walls of the orbit. Extraocular muscles are frequently infiltrated with tumor cells. The globe itself is typically not involved.[8] Ocular lesions occur less often in horses than in cattle. In the horse, the globe (uveal tract) can be involved in addition to extraocular tissues. As with other systemic neoplastic diseases, multiple organ involvement is expected with lymphosarcoma.

Treatment and Prognosis This systemic disease may be treated palliatively or systemically in an attempt to achieve remission for a time. Enucleation provides palliative treatment, and chemotherapy with corticosteroids, vincristine, and L-asparaginase may induce remission. Off-label use of these cytotoxic drugs must be approached with extreme caution, and treated animals must not be used for food consumption. Most cattle with orbital lymphosarcoma either die or are euthanized in terminal stages of disease within 6 months of the original diagnosis.[15] Horses can have a much more protracted disease course, with many presenting because of chronic illness of up to 12 months' duration.[16] The overall prognosis is unfavorable, regardless of the species involved.

Prevention and Control Control of bovine lymphosarcoma depends on efforts to eradicate bovine leukemia virus, a monumental task in most cases. In other large animal species, prevention and control recommendations for lymphosarcoma are not possible until the etiology can be identified. If animals are destined for slaughter, the guidelines for condemnation of bovine carcasses affected with lymphosarcoma as shown in part B of Box 39-2 should be followed.

Ocular Manifestations of Equine Sarcoid

Definition and Etiology Equine sarcoid is a locally aggressive, nonmalignant, fibroblastic tumor of equine skin (see Chapter 40). It appears to be the most common equine neoplasm, with 14.7% of ocular and adnexal tumors in the horse being sarcoids (all involving the eyelids).[18] This neoplasm develops more frequently in sites predisposed to trauma and areas that come into contact with existing sarcoids, and it does not metastasize to internal organs.

Clinical Signs and Differential Diagnoses Sarcoids involving the eyelids are classified according to the scheme used for cutaneous lesions: verrucous, fibroblastic, mixed, or occult. Tumors of the eyelids may appear smooth and nodular, crusted and nodular, ulcerated, or pedunculated (Figs. 39-22, 23, and 24). Regardless of their appearance, the tumors are nonregressing. Periocular sarcoids are subject to trauma; thus the verrucous type frequently transforms into the fibroblastic type with surface ulceration. It is difficult to differentiate sarcoid from fibroma, fibrosarcoma, neurofibroma, neurofibrosarcoma, schwannoma, or nonneoplastic granulation tissue (see Tables 39-3 and 39-4).

Treatment and Prognosis Problematic lesions can be treated by a variety of modalities, none of which is uniformly successful. Often, multiple treatment sessions are required for tumor control. Treatment modalities include surgical excision (50% success

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FIG. 39-22 Equine sarcoid. Upper eyelid exhibits a smooth nodular mass typical of many periocular sarcoids.



FIG. 39-23 Equine sarcoid involving medial aspect of eyelid. At examination or during treatment, sarcoids may become ulcerated. This tumor became ulcerated after one injection of a *Mycobacterium* cell wall preparation but subsequently resolved.



FIG. 39-24 Multiple equine sarcoids extending from the lateral canthus into periocular tissues.

rate), cryonecrosis (30% success rate), radiofrequency hyperthermia (RDM Hypertherm), intralesional injection of BRMs (bacille Calmette-Guérin),[18] chemotherapy with intralesional cisplatin (Platinol, with or without initial debulking),[8,9] radiation therapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and chemotherapy (5-fluorouracil) combined with surgical excision. BRM therapy has not proved as successful for sarcoids located at other body sites. An available commercial *Mycobacterium* product (Normagen) can be used, but it does not demonstrate the clinical efficacy seen with previously used research preparations. If the sarcoid is static, flat, and hairless, it may be best left alone, because any trauma—surgical or otherwise—could increase the lesion's growth rate and invasiveness. Response to therapy varies on the basis of tumor location, duration, severity, and previous therapeutic measures.

Treatment of periocular sarcoid with BRMs shows particular promise but has the disadvantage of requiring a potentially long course of treatment involving a series of intralesional injections. Intratumoral use of cisplatin is highly effective (see Chapter 40). Successful treatment measures exist for equine sarcoid, and if a complete treatment protocol is followed, the prognosis is favorable. As with any neoplastic disease, at the first evidence of recurrence, the animal should be reevaluated.

Miscellaneous Tumors with Ocular Involvement

The tumors previously discussed represent the most significant ocular or periocular neoplasms of large animals. However, to the individual animal or owner, any tumor type represents a significant problem. Thus, clinicians must remember that numerous primary and secondary neoplastic processes can involve the eye and surrounding tissues. Secondary tumors may be either metastatic masses or locally invasive masses extending from sites near the eye. The greatest variety of ocular neoplastic disease has been reported in the horse (see Table 39-4).

Adnexal tumors that have been reported include adenoma, adenocarcinoma, basal cell carcinoma, fibroma, fibrosarcoma, hemangioma,[19] hemangiosarcoma,[20] lymphosarcoma, melanocytoma, melanoma, papilloma, plasma cell tumors, and schwannoma. Few reports thoroughly address treatment of these tumors.

Surgical excision of small lesions, cryosurgery, radiation therapy, intralesional cisplatin,[9,10] and medical treatment with cimetidine[21,22] have been used successfully on selected tumors. Oral cimetidine (2.5 mg/kg three times daily for an initial 3-month period) may be useful as a means of melanoma control. If lesions are progressively enlarging, cimetidine has been reportedly successful in arresting or resolving tumor lesions. This treatment is also a useful adjunct to cryonecrosis, surgical excision, or chemotherapy. The prognosis is poor for malignant ocular and periocular masses, because metastatic disease or local recurrence usually results. This is especially true with angiosarcomas[7] that involve primarily the conjunctiva but may also involve the corneoscleral junction. Limited success with angiosarcoma treatment has been achieved in a case of equine orbital lymphangiosarcoma through enucleation and chemotherapy with IV vincristine (four doses of 1.3, 1.3, 1.2, and 1 mg/m^2 of body surface area on days 0, 7, 14, and 51, respectively) and prednisone. Seven years after treatment, the horse showed no signs of recurrence. An additional case of conjunctival and nictitating membrane malignant hemangiosarcoma was treated by local excision and perioperative intratumoral cisplatin. Follow-up demonstrated tumor lysis and no recurrence after 6 months.

Any tumor involving the nasal and paranasal cavities has the potential to involve the ocular structures as the result of orbital spread. Enzootic adenocarcinoma in sheep is an example of this type of process. Although infrequently noted, exophthalmos secondary to orbital invasion of this tumor has been reported.[23] Primary orbital neoplasia in the form of a multilobular osteoma (chondroma rodens) or extra-adrenal paraganglioma has been reported in the horse[24,25] and reminds one that a space-occupying mass (neoplasia) can affect the eye by causing progressive exophthalmos.

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Neoplasia involving the CNS, diencephalon, or occipital cortex can result in a central blindness, abolished pupillary light responses, and mydriasis. Other forms of intracranial neoplasia can secondarily involve the eye as a result of cranial nerve dysfunction. For example, an intracranial schwannoma caused exposure ulcerative keratitis in a cow that presented with left facial paresis.[26]

Reports of neoplasia involving the globe, all in horses, describe the clinical, histologic, and treatment aspects of epibulbar melanocytoma,[27] intraocular melanoma,[28,29] and medulloepithelioma.[30] Optic nerve tumors have included neuroepithelial tumors and meningiomas. In the intraocular cases, the globe was rendered nonfunctional by the neoplastic process, and the involved eye was subsequently enucleated. An optic nerve neuroepithelial tumor displayed metastatic spread as a result of extension into the brain through the optic foramen, causing brain compression.[31] Although documented cases of these miscellaneous ocular neoplasms are not widespread, they must be taken into consideration as possible causes of large animal ocular neoplasia.

Other than vascular tumors, most ocular tumors do not display a severe metastatic threat. Although enucleation may be curative, histologic evaluation of excised tissues and long-term patient follow-up are necessary if accurate epidemiologic and prognostic data are to be available. Once an accurate diagnosis has been made, the clinician and owner must determine, in light of all available medical information and the proposed use of the animal, whether treatment should be curative or palliative or whether elimination of the problem from the herd should be of greater concern than care of the individual animal.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 40

Diseases of the Skin

STEPHEN D. WHITE, *Consulting Editor**

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Autoimmune Skin Disorders

Stephen D. White

Pemphigus Foliaceus

Definition and Etiology The term *pemphigus* is derived from the Greek word for "blister" and is used to describe a group of autoimmune vesiculobullous disorders characterized histologically by intraepidermal acantholysis and immunologically by intercellular deposition of immunoglobulin. Pemphigus foliaceus is the most common of this group of autoimmune diseases; in large animals it has been reported in horses,[1,2] goats,[3,4] and a donkey.[5] In small animals, pemphigus foliaceus has been putatively associated with drugs,[6] but this has not been identified in large animals. The factors precipitating the development of pemphigus foliaceus in large animals are unknown. The clinical lesions recognized in horses and goats are primarily scaling and crusting.

Pathophysiology Pemphigus foliaceus is characterized by the production of autoantibodies. In humans and dogs, these are directed against transmembrane proteins (desmoglein 1 in humans and a minority of dogs, desmocollin-1 in most dogs[6a]). The pemphigus autoantibody binds to the transmembrane protein, resulting in release or activation of one or more proteolytic enzymes. These enzymes destroy the attachments between adjoining epidermal cells. The result is *acantholysis;* the epidermal cells assume a rounded shape and separate from one another, leading to the formation of intraepidermal clefts and vesicles.[7]

Clinical Signs Pemphigus foliaceus is characterized clinically as a generalized exfoliative dermatitis (Fig. 40-1, Color Plate 40-1). Ventral or peripheral limb edema and crusts are the most common clinical signs.[1] In one study, no age, breed, or gender predilection was noted, although 80% of affected horses first exhibited signs between September and February.[1] In the horse, lesions are usually first noted on the head, limbs, or ventrum. Initial lesions also may be associated with fever, depression, or rarely urticaria. The disease usually progresses to involve the entire body over days to weeks. The primary lesion is a pustule, but these are fragile and transient lesions. Pustules rupture soon after formation, resulting in erosions, epidermal collarettes (rings of exfoliating superficial epidermis), scale, and crust. The lesions may or may not be associated with pruritus or pain.[1,2]

In the goat, pemphigus foliaceus also presents as a generalized exfoliative dermatitis. In the limited number of cases described, lesions were initially noted on the limbs, perineal region, and ventrum. The lesions consisted of crusting and scaling resulting from rupture of vesicles and bullae. Pruritus and malaise appear to be variable findings.[3]

Diagnosis Diagnosis of pemphigus foliaceus in large animals is typically based on biopsy of lesions submitted for routine histopathology. Characteristic histologic findings include intragranular to subcorneal cleft and vesicle formation associated with acantholysis. Both follicular and surface epithelia are frequently involved. Neutrophils tend to predominate in the inflammatory infiltrate, although eosinophils may also be present.[1-3] Because certain strains of *Trichophyton* species of dermatophytes may also cause acantholysis, any histology suggestive of pemphigus foliaceus must be stained for fungi.[8] Direct immunofluorescence or immunohistochemistry as an aid in the diagnosis of pemphigus foliaceus in horses and goats has also been reported but is somewhat limited to research and academic institutions.[3,7,9] Indirect immunofluorescence testing (for pemphigus antibodies in serum) is reported to be unreliable for the diagnosis of pemphigus foliaceus in horses, although this may be due to variability in the substrate used.[7,10]

Therapy Treatment is corticosteroids at immunosuppressive doses, such as prednisolone at 1 mg/kg orally (PO) every 24 hours (q24h) or dexamethasone at 0.08 to 0.1 mg/kg PO q24h, then tapering. Oral prednisolone is preferred to prednisone because some horses are unable to metabolize prednisone into the active metabolite of prednisolone.[11] Injectable gold (Solganal [Schering]) was also used successfully, but this product is no longer available. There are anecdotal reports of benefits using another gold salt, aurothiomalate (Myochrysine [Sanofi Aventis]), 1 mg/kg intramuscularly (IM) every 7 days. Gold salts take 1 to 3 months to reach effectiveness, when dosage frequency can be tapered to every 14 to 30 days. Adverse reactions of gold salts, although rare in the horse, include thrombocytopenia and glomerulonephropathy.

There are also reports of azathioprine (1 to 3 mg/kg PO q24-48h) being used for various autoimmune skin diseases in horses.[12,13] A potential side effect is thrombocytopenia because horses have low levels of the enzyme thiopurine methyltransferase (TPMT),[14] which is responsible for the metabolization of azathioprine in other species, including humans. However, the author has administered azathioprine (1 to 3 mg/kg PO for 1 month, then q48h) to 8 healthy horses with no deleterious effects.[15] Azathioprine is used as a steroid-sparing drug with corticosteroids, eventually to decrease the steroid needed. Approximate cost in a 500-kg horse for daily azathioprine is $300/month.

Goats have also been treated successfully with corticosteroids (dexamethasone, prednisolone) and aurothioglucose.[3,4,9] Dosages approximate those for the horse.

Prognosis The response to treatment in equine pemphigus foliaceus varies from patient to patient. Many horses require lifelong administration of medication to control the clinical signs; others may be gradually weaned from medication without further relapse. In one study where follow-up information was available for 13 horses, 4 were euthanized because of complications from the disease or its

*Contributions to previous editions by Anne G. Evans are acknowledged.

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FIG. 40-1 Pemphigus foliaceus in a horse; note generalized crusts.

treatment. The reported cases of caprine pemphigus foliaceus are insufficient in number to establish a reliable prognosis.

Pemphigus Vulgaris

Pemphigus vulgaris is a rare autoimmune skin disease anecdotally reported[7] in horses and recently definitively diagnosed in a Welsh pony.[16] In that report, the diagnosis was confirmed with both direct and indirect immunofluorescence and immunoprecipitation studies, the latter identifying circulating immunoglobulin (Ig)G directed against the epidermal transmembrane protein desmoglein 3, similar to the pathogenesis in humans and dogs. Clinical signs are vesicles and ulcerations seen in mucocutaneous and cutaneous areas. Initial corticosteroid treatment improved the clinical signs, but onset of laminitis necessitated a dose decrease with a recurrence of lesions and development of oral ulcers. Despite successive adjunctive treatment with azathioprine, gold salts, and dapsone, the disease progressed and the pony was euthanized. Necropsy showed additional lesions of the cardia of the stomach.[16]

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune vesiculobullous and ulcerative disorder that affects the cutaneous basement membrane zone (BMZ). It has been rarely noted in horses.[7,17] Initiating triggers for the disease in the horse are unknown.

The pathophysiology of bullous pemphigoid in horses is assumed to be similar to that described in other mammals. Complement-activating anti-BMZ antibodies bind to a glycoprotein antigen in the lamina lucida of the BMZ. In horses, this has been shown to be bullous pemphigoid antigen II (also called *collagen XVII*). Complement activation results in degranulation of mast cells and chemotaxis of neutrophils and eosinophils. Eosinophils release tissue-destructive enzymes with resultant injury to the BMZ, loss of dermoepidermal adherence, and subsequent blister formation.[7]

Equine bullous pemphigoid is characterized clinically by painful, crusted, or ulcerative lesions of the skin (face and axillae), mucous membranes, and mucocutaneous junctions. Bullae are rare.[7,16] Ulceration may involve the gastrointestinal (GI) tract. The diagnosis is based on histopathologic and, when available, immunofluorescent findings. Treatment is the same as for pemphigus foliaceus; the few cases reported have not had favorable outcomes, but the author has seen a case that initially responded well to corticosteroids.

Alopecia Areata

Alopecia areata is a disease of horses and cattle typified by areas of nonpruritic alopecia.[7,18,19] One horse has been described with severe hoof dystrophy on all four legs.[20] In one report, the median age was 9 years, with an age range from 3 to 15 years. Alopecia was the primary dermatological abnormality in all horses and most commonly affected the mane, tail and face, although any part of the body could be affected (Color Plate 40-2).[21] Histologically, a lymphocytic infiltrate surrounding the base of the hair follicle is seen, but in long-standing cases this infiltrate may not be present.[22] A mare with a T-cell lymphocytic infiltrate causing a mural folliculitis of the isthmus (central section) of the hair follicles was described.[22] Antibodies targeting the hair follicle itself have been documented.[23] Most horses regrow the hair, but this may take up to 2 to 3 years, and the disease may wax and wane, worsening most commonly in the spring and summer months.[21] Corticosteroids *may* hasten hair regrowth. Mane and tail "dystrophy" of Appaloosas and other breeds may in fact be a form of alopecia areata. Because of the circular nature of the alopecia, this disease is often mistaken for ringworm.

Hypersensitivity Disorders

Stephen D. White

Atopic Dermatitis

Definition and Etiology Atopic dermatitis can be defined as an abnormal immunologic response to environmental allergens like pollens, barn dust, and molds. It is increasingly being recognized as a cause of pruritus in horses. The disease may be seasonal or nonseasonal, depending on the allergen(s) involved. Age, breed, and gender predilections have not been extensively reported. A familial predisposition may be present.[1]

The presumed etiology is a type I (immediate) hypersensitivity response mediated by IgE. Evidence indicates that atopic horses do produce allergen-specific IgE[2,3]; the IgE is presumed to be directed against specific allergens. When that allergen is bound to two or more IgE antibodies on the surface of a mast cell, the mast cell releases granules containing various substances that cause erythema, vascular leaking, and pruritus.

Clinical Signs Pruritus, often affecting the face, distal legs, or trunk, is the most common clinical sign. Alopecia, erythema, urticaria, and papules may all be present. Urticarial lesions may be severe but nonpruritic. In one study of 54 horses with atopic dermatitis, 28 horses had urticaria, 8 had pruritus, and 18 had both.[3] Horses may have a secondary pyoderma typified by excess scaling, small epidermal collarettes, or encrusted papules *(miliary dermatitis).* Diagnosis of atopic dermatitis is based on clinical signs and exclusion of other diagnoses, especially parasite *(Culicoides)* allergy.

Diagnosis Diagnosis is based on clinical signs and exclusion of other pruritic skin disease. Confirmation to formulate allergen-specific immunotherapy (ASIT [hyposensitization]) is based on either intradermal testing (IDT) or serum allergy tests. IDT involves a series of intradermal injections of aqueous allergen extracts along with a positive (histamine) and negative (saline) control. Injections are usually performed over the lateral cervical or thoracic region, and the sites are then observed for 30 minutes to 24 to 48 hours for evidence of wheal formation. A positive reaction does not necessarily mean that the horse's clinical signs are caused by the reacting allergen, but rather that the horse has antibodies to the allergen that, on intradermal exposure, cause wheals to form. False-negative IDT reactions may occur, the most important cause of which is the use of corticosteroids, antihistamines, or phenothiazine tranquilizers before testing, especially within the previous 14 days.[3a]

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Horses with atopic dermatitis generally have a higher incidence of positive reactions than healthy horses, but the diagnosis (as in other species) cannot be solely made on the basis of the IDT or serologic test alone. Such tests should be interpreted in light of the history of the disease. For example, a horse with seasonal signs is more likely to have an allergic response to seasonal allergens (pollens in summer, barn dust in winter). This interpretation will help the clinician determine which allergens might be relevant in hyposensitization, should the owners choose that treatment.[2-6]

IDT and available serologic tests look for allergen-specific IgE in the animal's blood,[7] but their use on horses and other domestic species is not without controversy. A recent study showed no statistical difference in the efficacy of hyposensitization between horses tested with IDT and those tested with serology.[3] Preferentially, IDT and/or serologic testing are performed on horses with atopic dermatitis that have owners interested in pursuing hyposensitization. It should be remembered that in regard to food allergy, neither serologic testing nor IDT likely has any relation to reality. Clinical research is ongoing to determine the most important allergens, their testing dilutions, and effective control substances.[8,9]

Therapy Corticosteroid treatment is usually effective in the control of pruritus or urticaria due to atopic dermatitis. The usual oral medication used is prednisolone (1 mg/kg PO q24h), although dexamethasone (0.05 mg/kg PO q24h) can also be used. The injectable dexamethasone solution may be used orally, although the clinician should remember that the bioavailability is 60% to 70% of the injectable route.

Corticosteroids in horses may cause various adverse effects, including steroid hepatopathy, laminitis, and iatrogenic hyperadrenocorticism. Therefore, other modalities of treatment may be used, such as the antihistamines hydroxyzine pamoate (200 to 400 mg/500 kg PO q12h) or cetirizine (0.2 mg/kg PO q12h); doxepin, a tricyclic antidepressant with antihistaminic effects (300 to 600 mg/500 kg PO q12h); or diethylcarbamazine syrup (6 to 12 mg/kg PO q24h). Hydroxyzine, cetirizine, and doxepin may cause either drowsiness or nervousness, although these adverse effects are uncommon. Cetirizine is very expensive, and since it is the active metabolite of hydroxyzine, if the latter is ineffective in an individual horse, the cetirizine probably will be as well. Pyrilamine maleate, though often used in the horse, in fact has poor oral bioavailability.[10] Some clinicians have noted improvement when an essential fatty acid (EFA) product is added to the feed. Platinum Performance (Platinum Performance Inc., Buellton, Calif. [Dr. W. Rosenkrantz, personal communication, 2004]) has been used successfully in some atopic horses as an adjunctive treatment.

In general, hyposensitization injections for any manifestation of atopic dermatitis in the horse should be evaluated for efficacy for at least 12 months. The veterinarian should maintain consistent communication with the client to monitor the progress of treatment and encourage the owner to continue with the injections for the full year. Although most horses will need to be maintained on injections for life, if hyposensitization is successful, perhaps as high as 25% may be able to discontinue the treatment without recurrence.[3] Experience at the University of California, Davis, School of Veterinary Medicine (UCD-SVM) shows that about 65% to 70% of atopic horses improve with hyposensitization[3,11]; other researchers have reported even better results but in a noncontrolled study.[12]

Urticaria

Definition and Etiology Urticaria is characterized by transient focal swellings in the skin or mucous membranes called *wheals,* which represent localized areas of dermal edema. Angioedema is essentially identical but involves the subcutaneous tissues. The swelling of angioedema is diffuse, often involving the entire face and neck of the animal.

Urticaria is more frequently recognized in the horse than in ruminants. *Allergic urticaria* is usually caused by atopic dermatitis (environmental allergens like pollens),[1,5,6,13,] drug eruptions (especially antibiotics[14] and nonsteroidal antiinflammatory drugs [NSAIDs]), contact allergies, and food allergies (rarely).[15]

Physical urticarias are less common and involve a nonimmunologic pathogenesis. The three most important categories include mechanically induced, such as dermatographism, essentially a "pressure" urticaria; cold urticaria; and exercise-induced urticaria. Miscellaneous diseases that can cause urticaria include dermatophytosis (initial lesions),[16] pemphigus foliaceus, "stress" (sometimes seen in racehorses immediately before a race), and vasculitis (Box 40-1). Urticaria is a recognized manifestation of milk allergy in cattle.[17]

Pathophysiology The wheals result from vasodilation and transudation of fluid from capillaries and small blood vessels. Both immunologic and nonimmunologic factors can trigger release of

BOX 40-1

Possible Causes of Urticaria in Horses and Ruminants

Allergic Urticaria

Inhalants

Pollens, animal danders, mold spores, feather down, aerosols, smoke, dust, and volatile chemicals

Injectants

Drugs, diagnostic agents, vaccines, insect stings, serums, and blood

Ingestants

Drugs, various food items, beverages, and occult additive materials found in foods

Infections

Foci of bacteria, fungal, viral, and parasitic infections

Contactants

Animal products, plant materials, cosmetics, plastic, and other chemicals

Drugs

Penicillin, aspirin, quinine, sulfonamides, insulin, and many others

Milk Proteins

Milk retention (cattle)

Urticaria Caused by Urticariogenic Materials

Drugs

Cocaine, morphine, codeine, atropine, quinine, thiamin, pilocarpine, polymyxin B, D-tubocurarine, dextran, dehydrocholate sodium (Decholin), and other drugs

Foods

Certain citrus fruits, strawberries, and certain fish

Toxins

Cobra venoms, jellyfish toxin, and certain plant and insect toxins

Physical Urticaria

Dermographic (induced by blunt-scratch injury)
Heat
Cold
Light

Miscellaneous Urticaria

Erythema multiforme
Pemphigus foliaceus
Infections
Collagen vascular disease
Neoplasia
Psychogenic

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Stimulating factors	Target cells	Mediators	Urticaria
Immunologic	Tissue mast cell	Histamine	Wheals
Type I	Blood basophil	Kinine	
Type II		Products of the arachidonic acid cascade	
Type III		Acetylcholine	
Complement			
Urticariogenic materials			
Physical agents			
Idiopathic			

FIG. 40-2 Flow of pathophysiologic events in the development of urticaria.



FIG. 40-3 Acute urticaria in a horse caused by an adverse drug reaction.

mediators from mast cells and blood basophils that will ultimately produce the characteristic wheals (Fig. 40-2). The most frequently cited immunologic mechanism of urticaria is type I hypersensitivity (IgE). Non–IgE-dependent, immune-mediated urticaria may be induced by either type II (cytotoxic, involving antibody and complement) or type III (immune complex) hypersensitivity reactions. Complement-activated urticaria may involve either immunologic or nonimmunologic mechanisms and may occur through either the classic or the alternative pathway. Urticariogenic materials can induce wheal formation without involving immunologic mechanisms by being ingested, injected, or contacting the animal. Physical agents, including mechanical injury, thermal changes, and solar radiation, may induce urticaria. An example of mechanically induced urticaria is *dermatographism* (whealing after blunt scratch injury to the skin). Local or generalized exposure to heat or cold may induce urticarial lesions in certain individuals.

Clinical Signs and Differential Diagnosis Wheals range from 1 to 10 cm (0.4 to 4 inches) in diameter and tend to involve the cervical and craniolateral thorax (Fig. 40-3). The animal may or may not be pruritic. Alopecia is not usually a feature of urticaria. The most important factor in distinguishing urticaria from other nodular diseases is that the individual lesions pit with pressure. This is easily demonstrated in the early stages of wheal formation, when the lesions consist primarily of dermal edema. In the later stages, when there is cellular infiltration into the dermis, the pitting is less apparent.

Diagnosis Urticaria is usually a clinical diagnosis; the diagnostic dilemma is to determine the *cause* of the urticarial eruption. A skin biopsy not only will lend support to the clinical diagnosis of urticaria but also may show evidence of pemphigus foliaceus, dermatophytosis, or vasculitis. Initiation of ectoparasite control, IDT or serologic tests for atopic dermatitis, fungal culture, skin biopsy, and/or feed trials may all be used to determine the underlying disease.[13]

Therapy Avoiding the allergen/initiating factor or treating the underlying disease is the best therapy. When this is not possible or when the allergens cannot be identified, medical therapy should be used, as described under Atopic Dermatitis.

Milk Allergy

The principal cutaneous manifestation of milk allergy is urticaria and is usually seen in cows during the drying-off period. Increased intramammary pressure presumably causes milk proteins to gain access to the circulation, where they induce a type I hypersensitivity reaction.[18] The disorder is believed to be hereditary and familial, with cattle of the Channel Island breeds demonstrating increased susceptibility.

The urticarial reaction can be localized or generalized. Other clinical signs that may be noted include muscle tremors, respiratory distress, restlessness, ataxia, dullness, and even maniacal behavior. Diagnosis is made by observing an edematous swelling at the site of an intradermal injection of the cow's milk or the milk protein casein diluted 1:1000, in combination with the appropriate clinical signs.[18,19]

Treatment involves the use of antihistamines early in the course of the disease. Prevention requires avoiding milk retention. An affected cow is likely to suffer recurrences of milk allergy, so culling is usually recommended.

Erythema Multiforme

Erythema multiforme (EM) has been recognized clinically in the horse and in one bull (Fig. 40-4). This is an immunologic reaction in the skin, and programmed keratinocyte cell death (apoptosis) is the prominent change seen on biopsy. The keratinocytes may be killed specifically by killer lymphocytes. The many possible etiologic factors include infectious diseases, drugs, systemic disease, and neoplasia. In the horse, drugs are probably the most frequent inducers of EM, although in many cases an underlying disease is undiagnosed.[20,21] In one bull the EM may have been caused by a pyelonephritis found on necropsy.[22] Clinical lesions are characterized by macules, papules, urticarial lesions, or vesicular bullous lesions. Individual lesions may

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FIG. 40-4 Erythema multiforme in a horse.

expand peripherally, leading to formation of target-like lesions. Scaling and crusting are usually not a feature of equine EM unless the disease is characterized by erosions or ulcers. Individual lesions can persist for several days, unlike urticarial lesions. Pruritus and pain are variable but not usually seen. Lesions may occur in association with or after an infection or drug administration. The late Dr. A.A. Stannard of UCD-SVM had theorized that reticulated and hyperesthetic leukotrichia may also represent a type of EM in the horse.[21] A recent report associated EM in a horse with equid herpesvirus 5.[23] Interestingly, a similar disease, toxic epidermal necrolysis, has rarely been reported in cattle.[24]

Differential diagnoses include urticaria, amyloidosis, and other nodular papular diseases. The diagnosis is made on history, physical examination, and skin biopsies. Histologic changes are distinctive and often include a lichenoid pattern with keratinocyte apoptosis. Vesicular lesions may be present and can include more confluent areas of keratinocyte destruction with massive spongiosis and subepidermal and intraepidermal edema.

Treatment should be directed toward the underlying cause if one can be found. A drug eruption should be high on the list, and searching the history for recent drug administration is important. Although some cases of EM are self-limiting and may resolve within 1 to 3 months,[20] corticosteroid treatment as for pemphigus foliaceus may be tried. In our experience, reticulated leukotrichia does *not* resolve spontaneously and does not respond to corticosteroids.

Vasculitis

Vasculitis is a histopathologic term that implies the presence of inflammatory changes in the walls of blood vessels, and it is associated with a broad spectrum of disorders. *Cutaneous vasculitis* is recognized in horses and is most often seen as a feature of photoaggravated dermatitis, drug reactions, or purpura hemorrhagica.[25] Mules and donkeys may also be affected.[25]Affected vessels may be limited to the skin or may involve other organs, resulting in systemic disease. The cutaneous lesions are characterized by crusts, scales, edema, purpura, necrosis, and ulceration, most often affecting the legs (Fig. 40-5, Color Plate 40-3).

As a clinical entity, *photoaggravated vasculitis* seems to be more common (if poorly understood) in California and the western United States. Although previously termed *leukocytoclastic vasculitis,* the most common histologic finding is cell-poor and lymphocytic/histiocytic vasculitis.[25] It generally affects mature horses and produces lesions confined to the lower extremities that lack pigment, although pigmented legs may also be affected. Lesions are multiple and well demarcated, with the medial and lateral aspects of the pastern the most common sites. Initially, erythema, exudation, crusting, erosions, and ulcerations develop, followed by edema of the affected limb(s). Some lesions may have a "punched-out" appearance. Chronic cases may develop a rough or "warty" surface.



FIG. 40-5 Cutaneous vasculitis in a horse. **A,** Vasculitis involving forelimbs. **B,** Vasculitis involving mucous membranes of inner lip.

Pathogenesis is uncertain; an immune complex etiology has been suggested, and when lesions are restricted to nonpigmented areas this suggests a role for ultraviolet (UV) radiation. Drug reactions may be a potential cause.[21] One report also implicated *Staphylococcus intermedius.*[26]

It must be emphasized that cutaneous vasculitis can occur anywhere on the body and may become generalized.

The differential diagnosis is photosensitization, particularly that caused by contact. The diagnosis is confirmed by skin biopsy, which demonstrates vasculitis, often with vessel wall necrosis and thrombosis involving the small vessels in the superficial dermis. These changes may be difficult to demonstrate.

Treatment involves corticosteroids at relatively high doses (prednisolone at 1 mg/kg PO q12h or dexamethasone at 0.08 to 0.2 mg/kg PO q24h) for 2 weeks, then tapered over the next 4 to 6 weeks.

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Reducing UV light exposure is helpful, either by bandaging affected legs or stabling inside during daylight hours, or both. In some cases, topical corticosteroids (e.g., betamethasone valerate cream 0.1% or triamcinolone spray 0.015%) may enable the horse to be weaned off systemic corticosteroids. Pentoxifylline (8 to 10 mg/kg PO q12h) may be an effective adjunct treatment. Another alternative (but more expensive) is 0.1% tacrolimus ointment q24h (Protopic [Astellas Pharma US]). This disease recurs in approximately 25% of cases.[25] These horses are prone to secondary bacterial infections, and a month of antibiotic treatment (usually trimethoprim-sulfa) is often indicated if the horse has fever or its legs are extensively swollen.

Cutaneous vasculitis seemingly is rare in ruminants; one report in calves describes lesions on the forelegs and ear tips occurring within a month on one farm. Histology showed a fibrinous-necrotic or leukocytoclastic vasculitis. Glucocorticoid (prednisolone) therapy was effective.[27] A recent article describes systemic vasculitis (polyarteritis nodosa) in four flocks of sheep. Clinical and histologic signs involved several organ systems, including the skin.[28] Vasculitis and purpura hemorrhagica are discussed in more detail in Chapter 37.

Drug Eruption

A drug eruption is a cutaneous reaction to any agent that enters the circulation by ingestion, injection, inhalation, or percutaneous absorption. Drug eruptions may or may not be associated with systemic signs. Many drug eruptions are thought to be immunologically mediated hypersensitivity reactions, although on occasion they may occur with the initial administration of a drug and therefore without any prior sensitizing exposure, characteristic of an immunologic reaction. Drug eruptions may also occur after years of repeated asymptomatic exposure to a drug, although this is probably less common than formerly supposed. Any medication can cause a drug eruption, but the compounds most frequently incriminated include antibacterial agents (especially semisynthetic penicillins and the sulfas), phenothiazine tranquilizers, NSAIDs and antipyretics (especially phenylbutazone), local anesthetics, and anticonvulsants. In general, the more recently a drug has been given, the more likely it may be the cause of a skin disease. The clinician should try to determine a temporal association between administration of the drug and the skin disease.

Because drug eruptions can result in a wide variety of cutaneous manifestations, they must be considered in the differential diagnosis of all skin disorders. Certain clinical symptoms are more often associated with drug eruptions. Urticaria and angioedema, diffuse erythema, papular rashes, intense pruritus that is poorly responsive to corticosteroids (Fig. 40-6), sharply demarcated ulcers secondary to vasculitides, vesicular and bullous eruptions, and photosensitization should arouse clinical suspicion of a drug eruption. Typically, cutaneous lesions are noted 24 to 48 hours after drug administration, although there may be a longer lag interval. The eruption usually subsides within 24 to 48 hours after exposure ceases, although lesions may persist up to 6 months after the offending agent is eliminated.[21]

A diagnosis of drug eruption is based on clinical suspicion associated with an incriminating history of drug administration and by ruling out other possible causes. In a suspected case, all medications should be discontinued. If lifesaving medications are being administered, a chemically unrelated compound with similar pharmacologic effects should be substituted. Administration of corticosteroids may provide some relief, but drug eruptions are variably responsive to corticosteroids. Although development of a cutaneous reaction after readministration of the suspected agent would support a diagnosis of drug eruption, readministration is not advisable because it can be fatal. Future exposure to any implicated compounds and chemically related substances should be avoided.



FIG. 40-6 Drug eruption in a horse; note pruritus.

Contact Dermatitis

Definition and Etiology Contact dermatitis is recognized in both horses and ruminants and can be subdivided into irritant and allergic contact dermatitis. *Irritant contact dermatitis* occurs more often and is defined as a cutaneous reaction to an irritating concentration of an offending agent. The substance chemically damages the skin without immunologic mediation. The reaction may occur after a single contact with a strong irritant or after repeated contacts with a milder irritant. *Allergic contact dermatitis* represents a cutaneous reaction in a sensitized animal to a nonirritating concentration of the offending agent. Tissue damage is immunologically mediated by delayed-type hypersensitivity (type IV), so prior exposure is required to sensitize the skin to the material eliciting the dermatitis.[15,17] It may be difficult to differentiate between the two types of contact dermatitis, and it may not be clinically important. In our experience, the vast majority of contact dermatitis cases are iatrogenic, caused by topical products placed on the skin by veterinarians or owners.

Clinical Signs The clinical lesions associated with allergic and irritant contact dermatitis are very similar. Predisposed areas include the muzzle, extremities, and areas contacted by tack. Early lesions include erythema, edema, and vesiculation that progress to erosions, ulcerations, and crusting and ultimately to lichenification and hyperpigmentation. A gravity-induced drip pattern may be evident when the irritant is a liquid.[29]

Diagnosis A detailed history is very important—the bedding, all topical products and blankets, and other potential environmental antigens/irritants should be noted. Certain woods release various irritant oils and have been implicated when incorporated into the bedding.[30] Patch testing is possible but usually impractical. Provocative exposure is the most useful test for diagnosis of contact dermatitis, although it does not reliably distinguish between allergic and irritant contact dermatitis. It requires avoiding contact with all suspected agents for 7 to 10 days to permit clearing of the skin lesions. The patient is then reexposed to these agents on an individual basis at 7- to 10-day intervals while being observed for recurrence of the dermatitis. When a positive reaction is observed, challenge with the suspected agent should be repeated to confirm the diagnosis. The process is time-consuming, requiring owner patience and cooperation.

Therapy An animal with a suspected or confirmed diagnosis of acute or irritant contact dermatitis should be placed in an environment where there is negligible chance of exposure to agents that might have produced the dermatitis. Symptomatic treatment pending spontaneous resolution includes gently washing the affected regions with water. Pentoxifylline at the dose noted earlier for vasculitis may be helpful in horses.

Bacterial Diseases

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Dermatophilosis (Streptothricosis, Rain Scald, Lumpy Wool, Strawberry Foot Rot)

Definition and Etiology Dermatophilosis is caused by an actinomycete bacterium, *Dermatophilus congolensis.* The organism is a gram-positive, non–acid-fast, branching, filamentous, aerobic bacteria that divides longitudinally and then transversely to form parallel rows of coccoid zoospores. Dermatophilosis affects horses, cattle, sheep, and goats, as well as a wide range of other mammals.[1-4]

Three conditions must be present for *Dermatophilus* to manifest: a carrier animal, moisture, and skin abrasions. Chronically affected animals are the primary source of infection, but they become a serious source of infection only when their lesions are moistened, which results in release of zoospores, the infective stage of the organism. Mechanical transmission of the disease occurs by both biting and nonbiting flies, ticks, and possibly fomites. Because normal healthy skin is impervious to infection with *D. congolensis,* some predisposing factor that results in decreased resistance of the skin is necessary for infection to occur, especially prolonged skin wetting by rain. The organism has been isolated from the environment of affected animals. Distribution is worldwide, but frequency of occurrence of dermatophilosis varies with geographic location; areas with increased rainfall are predisposed. There is no apparent age, breed, or gender predilection.

Clinical Signs Dermatophilosis is usually seen during the fall and winter months, with the dorsal surface of the animal most often affected (Fig. 40-7, Color Plates 40-4 and 40-5). In horses, this association with the wetter months of the year has led to the term *rain scald.* Occasionally the lesions involve the lower extremities when animals are kept in wet pastures ("dew poisoning") or if horses are left in the stall while the stall is cleaned with high-pressure water hoses. In the early stages of disease, the lesions can be felt more easily than they can be seen. Thick crusts can be palpated under the hair coat. Removing the crusts and attached hair exposes a pink, moist skin surface, with both the removed hair and exposed skin assuming a paintbrush shape. The undersurface of the crusts are usually concave, with the roots of the hairs protruding. In cattle and goats, the older term *cutaneous streptothricosis* is sometimes still used. In sheep the condition is referred to as "lumpy wool" or "mycotic dermatitis" when wooled areas are affected, and "strawberry foot rot" when distal extremities are involved.

Body areas predisposed to infection include those that are most susceptible to maceration and trauma. The distal extremities, muzzle, and entire length of the dorsum are frequently the initial sites of infection. Nonpigmented skin is also reported to be more susceptible to infection. Horses develop lesions in areas rubbed by tack, and cattle often have involvement of the udder and scrotum. Goat kids may have a tendency to develop lesions on the pinnae and under the surface of the tail. Sheep may develop a form of dermatophilosis that begins as an encrusted proliferative dermatitis at the coronet region; removal of the external crusts reveals a pink-red granulation bed that resembles the surface of a strawberry. Lesions can extend from the hoof to the hock, and with loss of the crusts, ulceration occurs. Under appropriate conditions, dermatophilosis can become generalized.

Diagnosis Diagnosis is made by demonstrating the "railroad-track" cocci on impression smears. A portion of one of the crusts should be minced and mixed with a few drops of sterile water on a glass slide, Gram stained, and examined microscopically. Alternatively, bacterial culture or histopathology may be used for diagnosis, particularly in chronic cases. A thick crust composed of alternating layers of parakeratotic stratum corneum, dried serum, and degenerating neutrophils is the most characteristic change. A superficial folliculitis may be a prominent feature of the disease.[1] In Gram-stained sections, the branching filamentous organisms can be observed in the crusts and follicles.

Therapy The animal should be removed from the wet environment if possible. Careful removal of possibly painful crusts, washing with iodophors or lime sulfur, and administration of antibiotics (for horses, 22,000 units/kg procaine penicillin G IM twice daily, or 30 mg/kg trimethoprim-sulfa PO twice daily) for 7 to 10 days.[4] Long-acting oxytetracycline given as a single 20-mg/kg IM dose has been reported to be effective for bovine and ovine dermatophilosis. The crusts are important in contagion, so these should be disposed of rather than brushed to the ground. Reduced tick control has been associated with increased incidence of the disease.[5]

Folliculitis/Furunculosis and Impetigo

Definition and Etiology Bacterial *folliculitis* (superficial pyoderma) is defined as inflammation of the hair follicles secondary to a bacterial infection. *Furunculosis* is the term used to describe a follicular infection that breaks through the follicular wall ("boil"). Bacterial infection that causes subcorneal pustules but does not involve hair follicles is called *impetigo.* Folliculitis and furunculosis are often seen in horses[1,4] and goats[3] but are an uncommon problem in cattle and sheep. Impetigo is relatively common in cattle and goats.

Bacterial folliculitis is usually caused by a coagulase-positive *Staphylococcus* spp. Both *S. aureus* and *S. pseudintermedius* (formerly

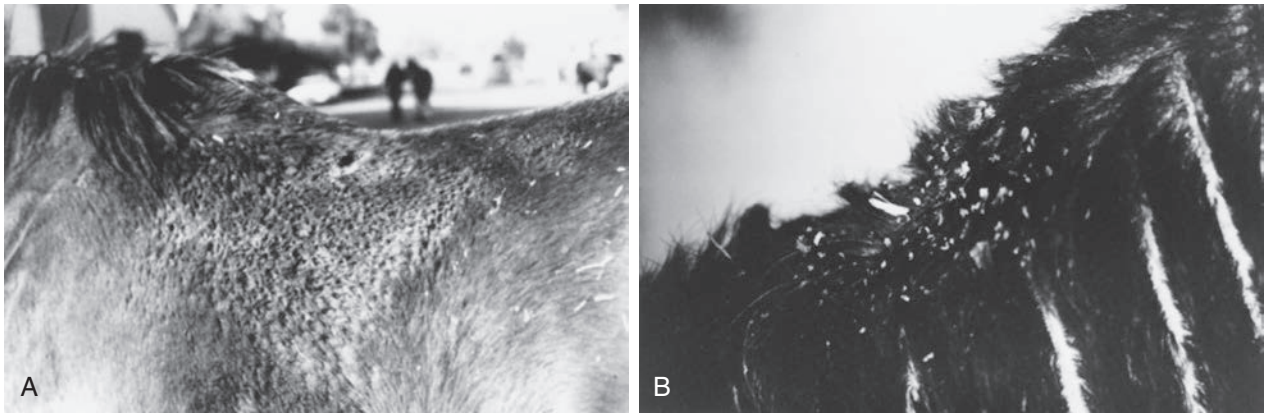


FIG. 40-7 Dermatophilosis *(Dermatophilus congolensis).* **A,** Horse with suppurative crusts and matted hair on the back. **B,** Scaling and crusting over withers and neck of a bovine.

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S. intermedius) have been isolated.[6,7] In one study in horses, *S. aureus* accounted for twice as many isolates as *S. pseudintermedius;* the same study isolated some strains of *S. hyicus* as well.[8] *Staphylococcus delphini* has also been isolated from horses on occasion. Many isolates are resistant to penicillin G.[8] Occurrence of pyoderma has been linked to poor nutrition and husbandry in some cases.[9]

Clinical Signs Clinical signs of staphylococcal pyoderma are most often crusts, usually in a circular pattern suggestive of dermatophytosis (this may be why equine pyoderma is underdiagnosed), epidermal collarettes (circular skin lesions with an exfoliative border, as seen in dogs with superficial pyoderma), or encrusted papules similar to the miliary dermatitis reaction pattern in cats.[6] These infections tend to vary in intensity of pruritus. Histology often shows folliculitis and furunculosis, but bacterial colonies are not always seen. A truncal form of bacterial folliculitis (contagious acne, contagious pustular dermatitis, Canadian horsepox) is often associated with poor grooming and trauma from tack and saddle, warm wet weather, and heavy work. It is painful and interferes with working and riding. It is usually caused by a coagulase-positive *Staphylococcus* spp. but may also be due to *Corynebacterium pseudotuberculosis*[10] (more often a cause of deep pyoderma, as discussed later). In horses, folliculitis often develops in the saddle and lumbar region, particularly in the summer. The affected area may initially be swollen and sensitive, followed by formation of follicular papules and pustules. These may become confluent or rupture, forming plaques and crusts. Deep pyoderma followed by ulceration may develop over large areas of the body, especially the neck, sides of the thorax, inner surface of the thighs, and prepuce.

A pastern bacterial infection (pastern folliculitis) is often seen. Again, the causative agent is usually a coagulase-positive *Staphylococcus* spp. As with most primary pyodermas, the mechanism by which the organism gains its foothold is unknown; it is not contagion or poor sanitary conditions. The lesions are usually limited to the posterior aspect of the pastern and fetlock regions; one or more limbs may be involved. Initial lesions consist of papules and pustules. If left untreated, they coalesce and may produce large areas of ulceration and suppuration that may be quite painful. The disease is usually not associated with systemic signs, and the general health of the horse is not affected.

A relatively uncommon nodular disease termed *botryomycosis* mimics actinomycosis or a deep fungal infection but is most often caused by *Staphylococcus* spp. in the horse. These may require surgical excision as well as long-term antibiotics.

Public Health Considerations In a 2000 study, methicillin-resistant coagulase-negative staphylococcal species were cultured from healthy horses in Japan. The authors concluded, "These organisms must be considered a potential threat to horses and veterinarians who care for them."[11] In a 2006 study from the Netherlands, methicillin-resistant coagulase-negative staphylococci were found frequently.[12] The organism was usually *Staphylococcus sciuri* rather than *Staphylococcus epidermidis,* which was found in the humans in close contact with these horses. No methicillin-resistant *S. aureus* (MRSA) was found in healthy horses.

There is little public health concern about methicillin-resistant *S. pseudintermedius* (MRSP) or *S. delphini* because clustering of equine cases does not appear to be important, and zoonotic disease potential seems to be limited.

In contrast, a single strain of MRSA was isolated from *both* humans (13%) and horses (4.7%) on horse farms in Canada and New York state.[13] In looking at horses admitted to a university teaching hospital (Ontario Veterinary College), MRSA was isolated from 120 (5.3%) of 2283 horses. Of these 120 horses, 50.8% were positive at admission, and clinical infections due to MRSA were present or developed in 14 animals. Horses colonized at admission were more likely to develop clinical MRSA infection. Administration of ceftiofur or aminoglycosides during hospitalization was the only risk factor associated with nosocomial MRSA colonization. Another strain of MRSA was isolated from a small number of horses at the Veterinary University, Vienna, Austria.[14]

Of most concern is the finding of humans reporting skin lesions after contact with a community MRSA-positive affected foal, despite short-term contact with standard protective barriers. Isolates from the foal were indistinguishable from those affecting humans.[15] In another study, MRSA was isolated from 15.6% of veterinarians or technicians in large animal practice, as opposed to only 4.4% for small animal personnel; large animal practice was the only variable statistically significantly associated with colonization of MRSA.[16] On two horse farms with endemic MRSA, active screening and strict implementation of infection control protocols resulted in a rapid decrease in number of colonized horses. The majority of horses eliminated MRSA without antimicrobial treatment.[17]

Therapy The antibiotic usually used for bacterial skin infections in the horse is oral trimethoprim-sulfamethoxazole (TMS [30 mg/kg PO q12h for 2 to 6 weeks, longer for deep infections]).[6] Interestingly, dosing intervals for intravenous (IV) administration of TMS in horses may not be appropriate for use in donkeys or mules. Donkeys eliminate the drugs rapidly compared with horses.[18] In cases of staphylococcal resistance to TMS, enrofloxacin or doxycycline may be used. Doxycycline is less expensive but associated with a higher incidence of colic. Dosage is usually 10 mg/kg PO q12h. Off-label use of oral enrofloxacin formulations for poultry, ruminants, or swine has been suggested. The formulation for poultry may be used; the dose is 7.5 mg/kg PO once daily. Use of enrofloxacin in young horses (<2 years old) should be avoided because of concerns about damage to the articular cartilage.[19] One report of use of an oral gel formulation of enrofloxacin (100 mg/mL of gel) showed good clinical efficacy for infections in several organs, but almost one third of the horses had some diarrhea, and 10% had oral lesions.[20] It was hypothesized that this latter side effect could be overcome with a tap-water rinse of the oral cavity after administration; however, we have seen oral lesions and a swollen tongue, suggestive of a contact reaction, develop in a horse receiving the oral water rinse. Interestingly, enrofloxacin binds to melanin in equine hair, although the clinical implication is unknown.[21] Ceftiofur sodium (2.2 mg/kg IM or IV q12-24h) may also be used for pyoderma in horses, although its usefulness over a long period is limited by its parenteral route. In one report of 15 horses, vancomycin was used, alone or in combination with an aminoglycoside, to treat MRSA and enterococcal infections. The average vancomycin dosage was 7.5 mg/kg IV q8h over 30 minutes. The antibiotic, alone or in combination with an aminoglycoside, was safe and effective. Because of the problems with emerging resistance, we recommended vancomycin use in horses be limited to cases where culture and susceptibility indicate effectiveness and no reasonable alternative treatment exists.[22]

For localized lesions, mupirocin ointment 2% or silver sulfadiazine cream (Silvadene) may be effective. Recently a gel with 0.4% stannous fluoride (MedEquine Gel [Dolphin International Inc., Camdenton, Mo.]) was reported as resolving bacterial skin infections in horses.[23] As shampoos, ethyl lactate (Etiderm [Virbac, Fort Worth, Tex.]) or a *tris*-EDTA/4% chlorhexidine combination (Triz-Chlor 4 [Dechra, Overland Park, Kan.]) are helpful.

Pyoderma in ruminants has not been studied as much as in horses. In goats, lesions (often pustules that progress to crusts) usually begin on the udder and spread to the abdomen, thigh, perineum, and face. Pruritus is variable. Stress from parturition is also an important predisposing factor in goats. In sheep, a generalized staphylococcal scalded skin–like disease has been reported in lambs.[24] Staphylococcal infections associated with *Psoroptes ovis* infestation have also been noted.[25,26]

In cattle, furunculosis caused by *C. pseudotuberculosis* manifests as a locally extensive, raised, raw lesion that is frequently hemorrhagic. The lesions are almost constantly covered with a serosanguineous exudate, and palpation of the lesions usually elicits a pain response. Treatment is similar to treatment of dermatophilosis,

taking into consideration culture and susceptibility results, as well as withdrawal times for food animals.

Equine Staphylococcal Cellulitis

Cellulitis is a severe deep, suppurative process in which a poorly defined area of infection tends to dissect through tissue planes. Although many organisms are capable of producing cellulitis, staphylococcal cellulitis has been recognized as a specific disease entity in Thoroughbred racehorses.[27] Coagulase-positive staphylococci have been isolated from all reported cases, and when speciated, the isolates were classified as *S. aureus.*[28] Other studies of pathogenic *Staphylococcus* spp. from horses have suggested that *S. aureus* and *S. (pseud) intermedius* are the major cutaneous pathogens,[28,29] with no significant difference in their susceptibility patterns.[28] In a retrospective study of limb cellulitis in 44 horses, coagulase-positive *Staphylococcus* spp. were cultured from 33 of 36 horses from which specimens were obtained. Horses that were febrile at admission or developed laminitis were significantly less likely to survive.[30]

The cause of staphylococcal cellulitis is uncertain. Management practices may be associated with the condition, because bathing, grooming devices, and handlers can be a source of the organism.[29]

The initial symptom is acute swelling and lameness that involves one or more limbs. Lesions progress rapidly by dissection along tissue planes. The overlying skin becomes devitalized and frequently sloughs. Accompanying systemic signs include increased rectal temperature and heart rate. Laminitis of either the affected or the contralateral limbs, osteomyelitis, and bacteremia are possible sequelae.[27] Diagnosis is based on the results of bacterial culture and biopsies for routine histopathology.

Treatment must be aggressive and initiated early in the course of the disease. Pending the results of bacterial culture and sensitivity, treatment should include broad-spectrum antibiotics like TMS. To decrease edema, promote weight bearing, and reduce the chance of laminitis, therapy should include NSAIDs, hydrotherapy, and support wraps.[27] The prognosis for complete recovery is guarded.

Equine *Corynebacterium pseudotuberculosis* Cellulitis

Solitary or multiple abscesses or nodules with many draining tracts that progress to diffuse cellulitis are often caused by *C. pseudotuberculosis;* when it affects the pectoral region, it is called "pigeon fever" in the United States. This type of deep *Corynebacterium* infection may occur where caseous lymphadenitis is common in sheep (although proximity to sheep is not a requirement), and it also may be seen seasonally when insect populations and activity are maximal. This may occur in the dry seasons, giving rise to another vernacular name, *dry land distemper,* when the process affects the inguinal region. Insect vectors seem probable, especially stable, horn, and house flies.[31] Draining nodules or abscesses are especially common in the pectoral region and occasionally affect the face, neck (Color Plate 40-6), axilla, groin, and limbs; they begin deep and enlarge, often with much edema, and rupture in 1 to 4 weeks, discharging viscid creamy pus, a major source of contamination. Abscesses most often rupture externally. Diagnosis is by clinical signs, with the infection readily identified by bacterial culture of aspirate samples from abscesses. The synergistic hemolysis inhibition test is useful for diagnosis of internal abscesses but unreliable for external abscesses.[32]

Treatment depends on location. If the abscess is in the axilla and thus painful on movement or prevents locomotion, establishing drainage is important, and antibiotics are indicated.

The antibiotics most commonly used are ceftiofur (2 to 4 mg/kg IM q12-24h), enrofloxacin (7.5 mg/kg PO or IV q24h), procaine penicillin (20 to 50,000 IU/kg/day), rifampin (3 to 5 mg/kg PO q12h), and TMS (30 mg/kg PO q12h).[32,33] Treating with TMS and rifampin concurrently can lead to a greater incidence of colitis and is to be avoided. If the decision is made to use antibiotics but drainage cannot be easily established (e.g., axillary abscess, with owner unwilling to allow veterinarian to use trocar and drain), antibiotics *must* be used for a minimum of 1 month. If the abscess is solitary and not causing pain or fever, antibiotics are usually unnecessary, but bringing the abscess to a head with hot packs or heat-inducing agents (ichthymol) is important. Once an abscess has drained, gentle cleaning with tamed iodines or chlorhexidine is indicated.

Early diagnosis and long-term antimicrobial treatment are important for a successful outcome in horses with internal *C. pseudotuberculosis* infection. Ultrasonographic imaging is an important technique for identifying specific organs affected, aiding in obtaining samples for a definitive diagnosis, and monitoring response to treatment. Pregnant mares with internal infections are at risk for fetal loss. Preexisting chronic organ disease may be associated with a poor prognosis.[34]

Digital Dermatitis (Papillomatous Digital Dermatitis, Bovine Digital Dermatitis, Foot Warts, Heel Warts, Hairy Foot Warts, Mortellaro's Disease, Strawberry Heel Warts)

Steven L. Berry

Digital dermatitis (DD) of cattle is an infectious, contagious, painful dermatitis of the digital skin of cattle. It is primarily a disease of housed dairy cattle and was first described in Italy in 1974.[1] Digital dermatitis has also been found in feedlots and pasture-based dairies. Papillomatous digital dermatitis was reported in the United States[2] and is currently thought to be a more chronic form of DD. The first documented U.S. cases of DD occurred in New York in 1980.[3] During the 1990s, reported first observations of DD increased dramatically in the United States,[4,5] and this disease is a major cause of lameness in dairy cattle in many countries.[2,6] The average cost of a case of lameness is estimated to be $378 USD, with premature culling being the highest portion of the cost.[7] It is difficult to assign costs to specific diseases, but DD is thought to incur lower costs than sole ulcers or foot rot. However, prevalence of DD can be much higher than the other lesions, so the total cost is high.

Clinical Signs Roughly 80% of DD lesions occur on the plantar aspect of the hindfoot immediately proximal to the heel bulbs and adjacent to or extending into the interdigital space.[2] Less common sites for lesions are the plantar aspect of a forefoot and the dorsal aspect of any foot.[2] Multiple lesions may exist on a single animal, even on a single foot, but lesions are confined to the digital skin and have not been reported to occur above the level of the dewclaws.[2]

The gross appearance of the lesions and predilection for hindlimbs and skin–horn junctions, especially those bordering the heel bulbs and interdigital space, distinguish this disease from other bovine dermatitides. Lesions are most often 2 to 6 cm across at their greatest dimension, circular or oval, and have clearly demarcated raised borders. Lesion borders are often surrounded by hairs that are 2 to 3 times normal length. Lesion surfaces may have filiform papillae varying in length from 1 mm to 3 cm and 0.5 to 1 mm in diameter, hence the name *hairy foot warts.* Lesions lacking the filiform papillae ("hairs") may have a granular surface. Lesions vary in color and appearance. Washed surfaces are generally very painful and either red and granular or may be composites of white-yellow, gray, brown, or black papillary areas with red granular areas interspersed. The lesions bleed easily if traumatized.[2] When DD lesions develop in the interdigital space, they frequently occur on a preexisting interdigital fibroma.

The time required for these lesions to progress to the mature ("hairy" or papillomatous) form appears to vary. Lesions slowly enlarge and become raised masses 2 to 6 cm in diameter that are red, gray, or black, and oval, spherical, or ∪ shaped.[2] Proliferative or

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papillomatous lesions are seen less often in Europe than in the United States.[6]

A foul odor may or may not be present.[8,9] This odor appears to be caused by secondary bacterial growth in the exudate covering the DD lesion. Swelling of the pastern and fetlock regions is not present in uncomplicated cases. Lameness is a herd characteristic on dairies where DD has a high prevalence but is an inconsistent finding on individual infected cattle and is not consistently related to lesion size or chronicity. If DD lesions remain untreated, the claws of feet with plantar or palmar lesions may develop a clubbed appearance because the cow prefers to bear weight on (and wear down) the toes, allowing the heels to overgrow.

Differential Diagnoses Differential diagnoses for an individual case of DD include interdigital necrobacillosis (foot rot, foul in the foot, or interdigital phlegmon), interdigital hyperplasia (corns or interdigital fibroma), interdigital dermatitis, and traumatic injury with granulation tissue. For herd problems of lameness localized to the digit, the differential diagnosis list should include DD, interdigital necrobacillosis, interdigital dermatitis, laminitis, excessive sole wear from caustic or abrasive flooring, and improper or no foot trimming. If signs of polysystemic disease exist, coronitis due to viral diseases (e.g., bovine virus diarrhea) should also be considered.

Epidemiology Once introduced into a herd, DD spreads rapidly among adult cows, often affecting the majority of adults within the first year of infection. When established in a herd, lameness is more commonly seen in first- and second-lactation cows, usually after entry into the milking string.[10-12] Lesions are typically present in a significant proportion of older cows, but lameness is commonly less than that in the younger cows. Bulls and yearling heifers can also be affected but usually comprise a small fraction of clinical cases. In California, the disease is not seasonal, but it is more severe in the winter months in Europe.[6] Freestall herds tend to be more commonly affected than stanchion (tie stall) herds. Cattle confined to pasture are rarely affected.[13] DD is almost exclusively seen in dairy cattle, with no breed predilection yet demonstrated. Eradication of the disease in endemic herds is thought to be very unlikely.

Retrospective epidemiologic studies in the United States indicated that two risk factors are significant in high-prevalence herds: (1) muddy or wet conditions and (2) purchasing replacement cattle from off premises.[4,14] Attempts to experimentally transmit the disease were successful when scrapings from active lesions were applied to feet of calves subjected to constant moisture and low oxygen tension,[15-17] conditions present on confinement dairies if manure management and hygiene are inadequate. Poor freestall or bedding area management will exacerbate the problem by forcing cows to stand in manure slurry for longer periods, not allowing their feet to dry out periodically. Other risk factors identified are the use of outside hoof trimmers and not washing hoof-trimming equipment between cows.[14]

Pathogenesis Numerous obligate anaerobic organisms have been associated with DD.[18-25] Spirochetes from the genus *Treponema* have been identified most consistently, comprise the bulk of the colonizing bacterial mat found on active lesions, and are the organism found to invade the epidermis and dermis.[23,24,26-29] These spirochetes also produce a humoral response in cows with active lesions.[30] DD lesions show gross and histologic similarities to viral papilloma, but bovine papillomavirus has not been found in lesions.[2,3,6]

Current evidence indicates that DD is multifactorial, involving environmental, microbial, host, and management factors.[2,4,11,12,14,24] Factors like rough flooring, poor drainage, accumulation of feces and urine on floors, overcrowding, and dirty, wet, or uncomfortable bedding areas have an adverse effect on digital skin health and could increase the risk of DD. The mode of transmission between cows and between herds is currently unclear. Clinically and subclinically affected cows and fomites (e.g., foot-trimming instruments, livestock trailers, farm equipment) may be sources of infection for naive herds.

A California study found that antibodies against two antigenically distinct spirochetes were increased on dairies with DD compared with DD-free dairies. Cattle with DD in a high-prevalence dairy were also much more likely to have antibodies to the spirochetes than cattle without lesions in the same dairy. There was no cross-reactivity between the two spirochetes or to other spirochetal diseases of cattle.[30] The higher prevalence of clinical disease in the younger animals in endemic herds suggests that some degree of immunity may develop in older cows. Nonetheless, chronic and recurrent cases in otherwise healthy adult cattle have been reported, and immunity to DD, if it does develop, may be incomplete or temporary. Recurrence is common in individual cows after treatment with antimicrobials.[31,32] Spontaneous regressions of lesions and resolution of lameness have also been observed but appear quite rare.

Pathologic Findings Histopathologic criteria to establish a diagnosis of DD are[2]:

- Circumscribed plaque of eroded acanthotic epidermis attended by parakeratotic papillomatous proliferation profusely colonized by spirochete-dominant bacterial flora
- Loss of stratum granulosum
- Invasion of stratum spinosum by spirochetes
- Infiltration of neutrophils, plasma cells, lymphocytes, and eosinophils in the dermis

If biopsies are performed, they should be full-thickness 4- or 6-mm punch biopsies, washed off with sterile saline, and placed in buffered formalin. Histopathology is helpful to confirm a diagnosis of DD but is not necessary because lesions have such a characteristic appearance and location.

Results of a biopsy study on treatment and recurrence of DD indicate that the clinical and histopathologic diagnoses were in agreement for active lesions before treatment.[31] Histopathology on day 28 post treatment with lincomycin or oxytetracycline, however, found a high percentage (55%) of lesions that appeared to be healed but still had microscopic evidence of infection.[31] It could not be determined whether lesions were incompletely healed or recurrent infections.

Treatment and Prevention The most common treatments for DD involve use of topical antibiotics.[2,6,8,31-34] There are currently no antibiotics labeled for treatment of DD in the United States, so adherence to off-label drug use regulations is imperative. Laws regarding use and disposal of certain chemicals, as well as where on the dairy such medications can be used, often vary among locales. Consultation with local regulatory agencies is prudent before initiation of a control program on a dairy.

The most commonly used treatments for DD are topical oxytetracycline or lincomycin used as a spray or applied with a bandage. For topical spray treatments, oxytetracycline or lincomycin are mixed with deionized or distilled water in a 2- to 4-L agricultural sprayer (25 g/L oxytetracycline, 8 g/L lincomycin) and applied directly to the heels of DD-affected cattle daily for a period of 5 to 14 days. The recurrence rate is high, so to control the disease, topical treatments will have to be repeated after 45 to 60 days on affected cattle. There have been no reported antibiotic residue violations resulting from topical application of antibiotics.[35] Parenteral antibiotics have been reported to be efficacious by U.S. and U.K. researchers[2,36] but require milk withholding. Other European researchers, however, have not found parenteral antibiotics efficacious.[6,8]

Footbaths containing 5% formalin,[6,8,37,38] lincomycin (1 to 4 g/L),[6] oxytetracycline (1 to 4 g/L),[6,37,39] copper sulfate (0.25 to 1 g/L), or zinc sulfate (20%)[37] provide effective control of the disease in infected herds. On large dairies, footbaths may be more effective at controlling DD when the disease is at a low prevalence (<10%). When the disease has a high prevalence, individual topical treatment is probably more efficacious at reducing prevalence. The efficacy of footbaths is reduced if feces and debris are allowed to accumulate in the treatment

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solution. This problem can be limited by placing two footbaths in tandem, with the first containing water or a mild detergent solution for cleaning the feet and the second containing the antiseptic solution. The footbath solution should be changed every 150 to 300 cow passages. Footbaths should be a minimum of 8 feet long and 2 to 3 feet wide, with a depth of 5 to 6 inches. The baths should be covered to limit dilution by rain and should be located in an exit alley off of the milking parlor to avoid splash contamination of the teat ends before milking. Additional footbaths can be placed in other locations to treat bulls, dry cows, and heifers. Footbath treatment frequency should be based on empirical evidence of efficacy[40] (e.g., every 1 to 7 days).

Improvement of stall, corral, and alley hygiene; provision of dry and comfortable bedding; reduction of stocking rate; and improved ventilation to allow drying of stalls and alleys may result in reduction of the incidence or severity of clinical cases. Foot-trimming equipment, mobile tilt tables, and livestock trailers should be thoroughly cleaned and disinfected to prevent potential transmission of the agent(s) of DD between dairies.

Interdigital Dermatitis

Interdigital dermatitis is a condition of acute or chronic inflammation of the interdigital skin, characterized by no to moderate lameness. Inflammation is confined to the epidermis. Diffuse epidermal erosion in the interdigital cleft may be seen in early cases. More chronic cases show hyperkeratosis, which creates a roughened appearance to the interdigital skin and dorsal and palmar commissural skin folds. A malodorous gray serous exudate may be present, and there is mild sensitivity to pressure. This condition is frequently accompanied by cracks in the heel (heel horn erosion), with potential under-running of the heel horn.[39]

Some investigators have hypothesized that interdigital dermatitis and DD are forms of the same disease complex.[41,42] *Dichelobacter nodosus* may be a primary or a contributory pathogen.[39] Interdigital dermatitis and DD share several histologic characteristics (including spirochetal involvement),[8,43] and both can be successfully treated and prevented with the same topical antibiotics or footbaths.[8] However, interdigital dermatitis can persist on dairies that practice regular foot bathing.[39] The causative organisms may survive within deep heel cracks that are not permeated by footbath solutions; hence heel cracks must be trimmed away to allow for exposure.[39]

Interdigital dermatitis differs from interdigital necrobacillosis (foot rot), in which infection extends into the dermis, leading to fissure formation, infection of deeper structures, and cellulitis of the pastern and fetlock regions.

Viral Diseases

Stephen D. White

Papillomas (Warts, Fibropapillomas)

Definition and Etiology Cutaneous papillomas or warts occur (in decreasing order of frequency) in cattle, horses, goats, and sheep.[1-4] The growths usually occur in young animals,[4] as well as on teats of mature cattle and goats and are white, tan, or gray firm, protruding masses with a dry, horny surface. They vary in size from 1 to 500 mm and may be single or multiple. Species-specific papillomaviruses (subgroup of papovavirus) are responsible for causing warts.[5-7] It is now accepted that parts of the bovine papillomavirus (BPV) genome are found in naturally occurring equine sarcoids.[8] There are at least 10 BPV strains, designated BPV-1 through BPV-10 (Table 40-1),[9] and there are probably more. At least two strains of virus are currently recognized in horses.

Clinical Signs Warts are usually small, benign growths that appear on young animals younger than age 2, persist for 3 to 12 months, and then spontaneously regress without causing clinical signs (other than a blemish). In cattle, warts on the teats, penis, or interdigital skin[10] or in the alimentary tract may produce clinical signs of pain or occlusion. Warts usually develop in the ears of young cattle after tagging or tattooing, especially if instruments are not disinfected between individuals; these are not age related. Teat warts also predispose to environmental mastitis. Occasionally, individuals with (presumed) defective cellular immunity may develop multiple extremely large warts that may result in weight loss.

In horses, warts on the face are rather common but rarely cause a significant problem (Fig. 40-8). The previously reported congenital wart in young horses has now been more properly termed a *hamartomatous lesion* (epidermal nevus) and has been shown not to be virus induced.[11]

Warts are relatively rare in goats. They occur mainly on teats and may spread throughout the herd. A 1936 report described a herd outbreak involving the head, neck, shoulders, and forelegs in milking goats.[12] Does without adequate pigmentation on the udder develop persistent mammary gland warts that may undergo transformation to become squamous cell carcinomas.[13] There are probably at least two different strains of goat papillomavirus (head/neck and mammary).

Warts are rare in sheep but may occur on the face or legs. Differential diagnosis in sheep and goats includes contagious ecthyma

TABLE 40-1

Distribution and Appearance of Bovine Warts by Type of Virus

Virus Strain	Usual Site	Appearance	Comments
BPV-1	Nose, teats, glans penis	Filamentous or frondlike	Can prevent breeding when on penis
BPV-2	Head, neck, brisket, occasionally alimentary tract	Pedunculated or broad-based mass	Most common typical warts
BPV-3	Atypical warts, head, neck, possibly interdigital*	Nonpedunculated protruding growths, delicate fronds with hair between	Persist for years
BPV-4	Alimentary tract, urinary bladder	Pedunculated mass	See Chapters 32 and 34
BPV-5	Teat	Smooth, white	Persist for years; other types may also occur on teats
BPV-6	Teat	Round and either flat or frondlike	Similar in appearance to BPV-1 when frondlike

Modified from Hunt E. 1984. Infectious skin diseases of cattle. Vet Clin North Am Large Anim Pract 6:163.

*Suspected, but BPV-3 not yet isolated from interdigital warts. Some authors speculate that interdigital warts may be caused by yet another new BPV strain.

BPV, Bovine papillomavirus.

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FIG. 40-8 Typical warts (papillomas) on the nose of a yearling horse.



FIG. 40-9 Aural plaques on inner surface of pinna of a horse's ear.

(orf), ulcerative dermatosis, dermatophilosis, and sheeppox and goatpox.

Treatment and Control Small warts can be crushed, pinched off, or surgically removed. Cryosurgery can be used on larger warts. Many regress spontaneously within a few months, even without treatment.

When show animals are involved or when animals have multiple large papillomas, tissue can be removed and made into crude autogenous vaccine (2 mL intradermally 3 times weekly) by homogenizing, grinding, freeze/thawing twice, filtering, and killing virus with 0.5% formalin. Autogenous wart vaccines are variable in their efficacy, as are commercial vaccines.[14-16] The latter rarely seem to result in effective regression of existing warts but may prevent development of new lesions if the same BPV strain is involved. Autogenous vaccines are capable of preventing new lesions caused by the same BPV strain in a herd. There is no indication that cattle vaccines have any efficacy in other species. No wart vaccines for horses, sheep, or goats are currently marketed.

Because the viruses can be directly or fomite transmitted, prevention involves isolation, preventing animals from rubbing on each other, and not sharing halters, brushes, and other equipment. Dipping of dehorning, tagging, and tattooing instruments in a viricidal solution between animals will also slow spread of the virus.

Aural Plaques

Aural plaques may be a form of viral papilloma that often affects the inner pinna (Fig. 40-9). Nonpruritic, these plaques may also occur on the genitalia and mammary glands. The color varies from pink to grayish-white. Plaques do not resolve spontaneously, as do the "classic" papillomas seen in young horses. Biopsy or "shaving off" aural papillomas may stimulate reduction or resolution of the masses, although in some horses, this may only be temporary (6 to 12 months). This has been theorized to be due to the release of "papilloma antigens" into the bloodstream during the surgical procedure, prompting an immune response against the tumor. Imiquimod (Aldara-3M, Minneapolis, Minn.), a nonsteroidal local immune response–modifier cream, has been helpful in some cases, used 3 times weekly, every other week, for 2 to 4 months.[17] Owners should wear gloves and should be forewarned that there is frequently an impressive inflammatory reaction to the cream in the initial weeks of treatment.

A papillomavirus has been demonstrated in aural plaques on electron microscopy and with immunohistochemical techniques.[18]

Pseudocowpox

Pseudocowpox is a common parapoxvirus of cattle related to the viruses of contagious ecthyma (soremouth) of sheep and goats and bovine papular stomatitis (see Chapter 32 for these diseases). All three parapoxviruses may cause nodular lesions on humans. The lesions of pseudocowpox are usually confined to the teats of cattle, and the disease is common worldwide. Cyclic waves of reinfection occur in a herd, where it causes minor teat lesions characterized initially by a small papule 2 to 3 mm in diameter, followed by crusting and circular spread of the lesion. Approximately 10 days later, the 15- to 20-mm lesion appears as a ring or horseshoe-shaped scab.[19] Lesions occasionally involve the udder, medial thighs, or scrotum. Deep ulceration is rare. There are no systemic signs of illness. The major problem associated with the teat lesions is an increased incidence of mastitis. The most important and common differential diagnoses are bovine herpes mammillitis and viral papillomas. Rare viruses involving the teat include vaccinia and cowpox.[19] Cowpox is a rare disease of cattle in Europe that causes ulcers and may also produce lesions in humans. Vesiculation is rare in pseudocowpox, in contrast to bovine herpes mammillitis, vaccinia, and cowpox.

Bovine Herpes Mammillitis (Bovine Herpesvirus, Bovine Ulcerative Mammillitis)

Bovine mammillitis teat lesions are caused by bovine herpesvirus type 2 (BHV-2), which is widely disseminated in most cattle populations.[20,21] The disease may be epidemic or endemic. The virus may also cause oral lesions, udder lesions, or generalized skin disease in cattle. The teat lesions start as swollen, tender, edematous teats. Vesicles may appear in some lesions, whereas others ulcerate almost immediately. The teats become painful, and ulcers require 3 to 10 weeks to heal.[20,21] Mastitis is increased because the scabs on the teats are laden with bacteria. Diagnosis may be confirmed by isolation of the virus, the BHV-2 serum neutralization tester, or histologic demonstration of herpesvirus particles.[20,21] Therapy consists of segregation of affected animals from the rest of the herd, and affected cows should be milked last. Milkers should wash hands between cows. In severe cases, secondary infection may be controlled by topical antibiotic creams or parenteral antibiotics, with proper residue avoidance precautions in place.

Sheeppox and Goatpox

Sheeppox and goatpox are caused by capripoxviruses.[22] Both occur in Africa, Asia, and the Middle East; goatpox also occurs in parts of Europe and the United States. The two diseases are clinically similar, although sheeppox has the most severe systemic signs of the animal pox diseases. Studies have shown that the viruses are phylogenetically distinct and can be differentiated by molecular tools.[23] The diseases affect all ages, causing pyrexia, anorexia, conjunctivitis, rhinitis, and skin lesions. Prophylaxis using attenuated vaccines is the preferred control measure because the immunity is long-lasting.[22,23] Morbidity is high. Mortality may reach 80% with sheeppox but usually is low with goatpox. Humans may develop skin lesions from goatpox.

Fungal Diseases

Stephen D. White

Dermatophytosis (Ringworm)

Dermatophytosis refers to infections of the keratinized tissues of the skin (stratum corneum layer of epidermis, hair, claws, hoof, and horns) by *Microsporum* and *Trichophyton* spp. Dermatophytosis is relatively common in the horse and in cattle, less so in goats, and rare in sheep.

Etiology and Pathogenesis The most common equine dermatophyte species isolated from horses are *Trichophyton equinum, Microsporum equinum, Trichophyton mentagrophytes,* and *Trichophyton verrucosum.*[1-3] *T. verrucosum* infections in humans caused by transmission from horses have been reported.[4] In ruminants the majority of dermatophytosis lesions are caused by *T. verrucosum* and to a lesser extent by *T. mentagrophytes.* Transmission of the disease is usually animal-to-animal by direct contact or indirectly through fomites like grooming instruments, tack, housing, fencing, or feed bunks. The incubation period may range from 1 to 6 weeks.

Several factors may influence the susceptibility of an animal to dermatophyte infection. Age is probably most important, with younger animals more susceptible to infection. The susceptibility of young animals is most likely related to lack of prior exposure/infection and thus no immunity, as well as crowding of young animals and conditions that decrease resistance to infection (e.g., poor nutrition). Environmental factors like warmth and humidity also may play a role. Calves kept indoors or exposed to foggy weather with little or no sunlight have an increased incidence.

Under normal circumstances, dermatophytes only invade fully keratinized, nonliving tissues.[1] This results in weakened hair shafts, leading to alopecia.

In many cases, dermatophytosis is theorized to be a self-limiting disease, with the duration of infection ranging from 1 to 4 months. The spontaneous regression is at least partly related to the development of immunity, of which cell-mediated immunity is the more important. The immunity that develops is probably not complete, and its duration is unknown.

Clinical Signs The lesions are often circular and usually appear first on the face or in the axillary/girth area and may spread over the trunk, rump, neck, head, and limbs (Fig. 40-10). Occasionally in the horse, dermatophytoses may be limited to the pastern region. Rarely, dermatophytes may be a cause of coronary band disease in horses. The mane and tail are rarely involved. Cattle and goats are frequently affected around the eyes and face (Fig. 40-11, Color Plate 40-7).

Lesions may be superficial or deep. Superficial infections are much more common and manifest with development of thick crusts or more generally a diffuse moth-eaten appearance with desquamation and alopecia, sometimes in a ring pattern. A small crust may form over the follicle, and the hair is lost. Occasionally the initial lesions may be urticarial, progressing to multifocal sharply demarcated areas of alopecia and scaling. The degree of pruritus varies but is usually mild or absent. Erythema is usually absent or obscured by pigmented skin. The lesions in cattle are usually characterized by excessive crusting, taking on an almost wartlike appearance.

Dermatophytosis must be considered in the differential diagnosis of any dermatoses characterized by multifocal alopecia or scaling and crusting. For a solitary lesion in horses, the occult sarcoid is the primary differential diagnosis. The two most important differential diagnoses of more extensive lesions are dermatophilosis and pemphigus foliaceus.

Diagnosis Direct microscopic examination of infected hairs is of value, but in general the most common and reliable method of diagnosing dermatophytosis is fungal culture (see Chapter 11). Broken hairs at the periphery of lesions are most satisfactory for this purpose. Large crusts should be avoided. The use of specialized indicator media is preferred. On occasion, dermatophytosis is diagnosed histopathologically. Interestingly, *Trichophyton* spp. occasionally may cause acantholysis, mimicking pemphigus foliaceus on histopathology.[5]

Therapy Although 50% captan (2 tablespoons powder in 1 gallon water) has been recommended in the past and is certainly safe for tack, its effectiveness on the animal has been questioned. Lime sulfur (LymDyp [IVX Animal Health, St. Joseph, Mo.], LymDyp DVM [Bayer, Shawnee Mission, Kan.], LimePlus dip [Dechra, Overland Park, Kan.]), 1 cup to 1 gallon of water, and bleach 1:10 with water are both effective but messy, odiferous, and staining. Shampoos containing miconazole, ketoconazole, and/or 3% to 4% chlorhexidine may be effective. In Europe and Canada, an enilconazole rinse (Imaveral [Jaansen]) approved for horses and cattle is highly effective.

Systemic treatment is occasionally needed. The efficacy and proper dose of griseofulvin in horses has not been thoroughly researched, but we have advocated and used a dosage of 100 mg/kg PO daily for 7 to 10 days on a small number of horses. Griseofulvin is a teratogen and should not be used in pregnant mares. Alternatively, 20% sodium iodide (NaI) may be given IV (250 mL/500-kg horse once or twice every 7 days) but is also contraindicated in pregnant mares because it may cause abortion.[2]

Vaccinating cattle against *T. verrucosum* has long been successful in Eastern Europe and Scandinavia. Effective control of ringworm in

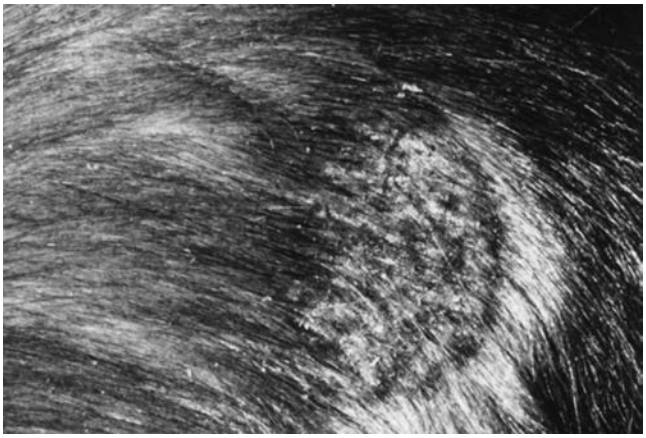


FIG. 40-10 Ringworm lesion (due to *Trichophyton* spp.) in a horse's flank area.



FIG. 40-11 Ringworm lesions (due to *Trichophyton verrucosum*) around a calf's eye.

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cattle has been achieved in regions implementing systematic vaccination.[6] Vaccination against *T. equinum* in horses may reduce the incidence of new infections and protect a high percentage (>80%) of vaccinates from infection. These data are based on results with an inactivated vaccine containing both conidia and mycelial elements.[7] In cattle, newer vaccines consisting of recombinant protein and deoxyribonucleic acid (DNA) derived from heat-shock protein 60 of *T. mentagrophytes* have shown success experimentally.[8] Such vaccines are not yet available in the United States.

Malassezia Dermatitis

The exact species of the yeast *Malassezia* growing on large animals' skin is just beginning to be investigated.[9] In one study of horses and livestock, the *Malassezia* spp. isolated were identified as *M. furfur, M. slooffiae, M. obtusa, M. globosa,* and *M. restricta.*[10] The author has examined several mares with a *Malassezia* infection between their mammary glands, which was intensely pruritic. The mares rubbed their tail and ventral abdomen. Physical examination showed a dry, greasy-to-the-touch exudate. Cytology of the exudate showed numerous yeast organisms, which were identified on culture as *Malassezia* spp. Treatment with a topical 2% miconazole/chlorhexidine shampoo was curative. The author is aware of other similar cases. However, healthy nonpruritic mares may also have large numbers of yeasts in the intramammary area.[11]

Sporotrichosis

Sporotrichosis is caused by the yeast *Sporothrix schenckii,* which is most common in vegetation. The yeast becomes pathogenic in animals as a result of its dimorphic ability to convert from a yeastlike form at tissue temperatures between 35° C and 37° C (95° F and 98.6° F) to a mycelial phase (with branching, septate hyphae) at environmental or laboratory temperatures of 25° to 30° C (77° to 86° F).[12] The disease has been reported in many species of domestic animals.

The initial lesions are nodules, which frequently ulcerate, and the disease may progress to a lymphatic-cording disease. Rarely, the fungus will eventually spread to the lungs. In a retrospective study from UCD-SVM, equines were the second most common species affected, after cats.[13] Diagnosis is made by demonstrating the organism on histopathology, immunofluorescent antibody testing on affected tissues, impression smears, and culture.[13,14] This is a zoonosis, so care should be taken in handling suspected samples.

Successful therapy with a number of different systemic iodine preparations (NaI, KI) has been reported. Organic iodides have proved to have superior efficacy to inorganic iodides in treating equine sporotrichosis, with ethylenediaminedihydroiodide (organic iodide powder [Neogen Corp., Lexington, Ky.] or EDDI 20 Gr. Dextrose base [Vedco, St. Joseph, Mo.]) being commonly used preparations. This product is in the form of a feed additive and can be mixed with a small amount of grain and administered at 1 to 2 mg/kg of the active ingredient once to twice daily for the first week, then 0.5 to 1 mg/kg once daily for the remainder of the treatment. In general, lesions will begin to regress during the first month of treatment, and therapy should be continued for *at least 1 month* beyond complete resolution of all cutaneous nodules and healing of any ulcerated lesions. Prematurely discontinuing therapy will invariably result in an unnecessary relapse of the disease. During treatment, the horse should be closely observed for any evidence of iodide toxicity (iodism), which includes excess scaling and alopecia, a serous ocular or nasal discharge, excess salivation, anorexia, depression, coughing, nervousness, or cardiovascular abnormalities. Should any of these signs develop, the treatment should be discontinued for 1 week, then resumed at three quarters the dosage at which the iodism was noted. In most cases, the treatment is subsequently well tolerated.[15] Although both itraconazole and terbinafine have been shown to be effective in vitro against the organism isolated from a horse, there is an absence of clinical reports of their use.[16] Successful management of an infected donkey with both KI and fluconazole has been reported.[13]

Histoplasmosis

Histoplasma capsulatum var. *farciminosum* ("farcy," the cause of equine epizootic lymphangitis in east Africa) infection has been reported in donkeys, where it can have considerable economic impact.[17] Cutaneous lesions resemble those seen in sporotrichosis. Treatment has not been well established but may be similar to the treatments for *Sporothrix schenckii*.

Phaeohyphomycosis

Phaeohyphomycosis is actually caused by a number of ubiquitous fungi that are either saprophytes or plant pathogens. These include *Alternaria, Dreschlera, Cladophialophora, Cladosporium, Phialophora,* and *Stemphylium* spp. The correct terminology currently depends on the histologic appearance of the organism, as follows[18]:

- *Chromomycosis:* any pigmented fungi
- *Chromoblastomycosis:* pigmented fungi, primarily yeast
- *Phaeohyphomycosis:* pigmented fungi, both hyphal elements and yeast
- *Hyalohyphomycosis:* nonpigmented fungi, mainly hyphal elements

Cutaneous lesions arise from either trauma to the skin or disseminated disease. Animals with disseminated disease probably have a deficient immune system. Similar to the other deep mycoses, these lesions present as expanding nodules and draining tracts. Diagnosis is by biopsy or occasionally cytology. Histopathology shows foamy or epithelioid macrophages, and special stains will show the organisms. Veterinarians and their staff should be careful in handling material from infected animals, because the inadvertent inoculation of these organisms can cause human infections.

Treatment has generally included surgical excision or amputation if practical. Potassium iodide, as for sporotrichosis, and (if the owners can afford it) fluconazole at 5 mg/kg may be effective.

Zygomycosis

Similar to phaeohyphomycosis, zygomycosis is caused by a number of related fungal species that are ubiquitous saprophytes. GI and respiratory tract involvement is possible. Cutaneous lesions are thought to be caused by wound penetration. The disease typically occurs in tropical and subtropical areas. The two orders of Zygomycetes that cause disease are Mucorales, including the genera *Rhizopus* and *Mucor,* and Entomophthorales, including the genera *Conidiobolus* and *Basidiobolus.* Most cutaneous reports are in horses, although ruminants may have other organ systems affected.

The skin disease is ulcerative, nodular, and generally found on the trunk and neck. Generally, only one large nodule is present. Diagnosis is by histopathology and culture; a serum agar immunoprecipitation test has been useful in diagnosing conidiobolomycosis. Surgical removal, if possible, is preferred for treatment. Medical options include the iodides (not effective against the order Mucorales) and possibly the azoles or amphotericin B.[1]

Pythiosis

Pythium insidiosum is considered to be the causative agent of *swamp cancer,* also known as *Florida horse leech, bursattee,* and *kunker.* This organism is termed a *protista* and is found in tropical and subtropical areas worldwide, although its range may be expanding; it has been recently reported in a horse in northern California.[19] The pythiosis lesion occurs most often on the limbs, abdomen, neck, and lips and consists of dense granulation tissue containing masses of yellow-gray necrotic tissue, which sometimes are calcified and often are present as cores in fistulae and are removable intact. Such masses are known as *leeches* or *kunkers.* The granuloma ulcerates and extends peripherally and may reach a very large size in a short time. The overlying and adjacent skin is destroyed by both the inflammatory reaction and the self-mutilation by the horse. Important differential diagnoses are

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systemic fungal infections, habronemiasis ("summer sore"), and neoplasia. Although most reports in large animals are in horses, cattle and sheep may also be affected.[20,21]

Histopathologic examination of affected tissue reveals pyogranulomatous inflammation directly surrounding the organism. Isolation of organisms from the lesions is necessary for further identification and study but histologic demonstration of the protozoa within tissues reacting to its presence is critical in establishing the causal relationship in an individual lesion. In obtaining culture, the kunkers are preferred to the actual tissue. For samples that cannot be processed immediately, acceptable handling techniques include storage at room temperature for up to 3 days, refrigeration for up to 5 days, shipping on cold packs, and storage in antibiotic solution, each combined with subsequent inoculation on selective media.[22] Recent advances in enzyme-linked immunosorbent assay (ELISA) or molecular techniques offer better potential for organism detection and identification.[23] Wide surgical excision combined with immunotherapy has been effective in some cases.[23,24]

Parasitic Skin Diseases

Stephen D. White

Pediculosis

Lice are obligatory ectoparasites that are generally host specific. Adults and nymphs are seldom able to live more than a few days away from their host. Large animals suffer from infestation with several species of lice that belong to the orders Mallophaga, the biting lice, and Anoplura, the sucking lice (Table 40-2).[1]

Clinical infestations are most apparent during the winter months and reflect efficient louse reproduction during the late fall and that summertime temperatures on body areas exposed to sunlight are too high for lice. Apparent carrier animals within a herd maintain populations during the "off" season and serve as a source for reinfestation of the herd during the fall.[1] The hallmark of infestation is pruritus, and many clinical changes result from self-trauma. The neck and tail are typically affected first,[2] but infestation and clinical signs may become generalized. The coat becomes dry and scaly. Patchy alopecia and crusted ulcerations result from excoriation. A heavily infested animal may become anemic. Significant hide damage occurs as a result of excoriation, and hairballs may accumulate in the GI tract from self-grooming. Reduced productivity and weight loss result from decreased feed intake associated with restlessness. Diagnosis is usually by examination; a hand lens is useful (e.g., otoscope without cone). Interestingly, when a horse is exercised and becomes warm and sweaty, the lice will climb out toward the tip of the hair and are easier to find.[3]

Several treatment approaches exist. Ivermectin at 200 µg/kg every 14 days for 2 applications is effective for sucking lice but not biting lice. Application of an appropriate topical insecticide to infested animals and to all contact animals at 2-week intervals for 2 or 3 treatments is usually curative for both types of lice. Repetition of treatment is necessary to break the louse life cycle, because eggs are not killed by insecticides and will hatch despite therapy. Effective topical agents include pyrethroids, permethrins, selenium sulfide, imidacloprid, phoxim, and fipronil.[3,4] Development of resistance is also possible.[5] Appropriate attention should be paid to withdrawal times in food animals. Cleaning of fomites like blankets, brushes, and rope halters is probably indicated, although lice do not live long off the host.

TABLE 40-2

Lice Associated with Large Domestic Animals

Host	Mallophaga (Biting)	Anoplura (Sucking)
Horse	*Bovicola (Damalinia) equi* *Werneckiella equi equi*	*Haematopinus asini*
Cattle	*Bovicola (Damalinia) bovis*	*Haematopinus eurysternus* *Haematopinus quadripertusus* *Haematopinus tuberculatus* *Linognathus vituli* *Solenopotes capillatus*
Goats	*Bovicola (Damalinia) caprae* *Bovicola (Damalinia) limbatus* *Bovicola (Damalinia) crassipes*	*Linognathus stenopsis* *Linognathus africanus* *Linognathus vituli*
Sheep	*Bovicola (Damalinia) ovis* *Bovicola (Damalinia) capre*	*Linognathus pedalis* *Linognathus ovillus* *Linognathus africanus*

Trombiculidiasis

Trombiculidiasis is caused by the larval stages of mites commonly called "harvest mites" or "chiggers." The most common species affecting large animals are *Eutrombicula alfreddugesi* (North America) and *Neotrombicula autumnalis* (Europe). The adults and nymphs are free living. The larvae feed on mammalian hosts, secreting substances in their saliva that hydrolyze the epidermis and allow extraction of tissue fluids. The individual larval stage is short, but the infestation may be ongoing with the acquisition of new larvae from the environment. In the northern hemisphere, *E. alfreddugesi* is active from late spring through early fall, whereas *N. autumnalis* is more common in the late summer to midfall. The mites may be found in wooded areas, grass, and hay.[3,6]

The clinical signs of trombiculidiasis are crusts and papules, especially on the face, neck, and extremities. Pruritus is variable.[6] Rarely, this parasite has been implicated in headshaking in horses.[7] Diagnosis may be made early in the course of infestation by careful inspection (e.g., hand lens) and finding the minute red-orange larvae in the center of a papule. The six-legged larvae have round bodies and may be identified specifically on skin scrapings or acetate tape preparations.[3] Although the larvae only remain on the animal host for several days, clinical signs may persist longer, so trombiculidiasis should be suspected even in the absence of mites in an animal with appropriate signs in the summer and fall.

The disorder is in theory self-limiting because of the short time of attachment of the parasite. However, if the pruritus is severe, corticosteroid administration is indicated.[3] Various products have been used on the horse to eliminate the larvae; 5% lime sulfur, fipronil, and permethrin are generally the safer parasiticides to use.

Mange

Mange is a general term for infestation by any mite species.

Psoroptic Mange

Psoroptic mange has been recognized in horses, cattle, sheep, and goats (and rabbits). The host specificity of *Psoroptes equi, P. ovis, P. natalensis,* and *P. cuniculi* is controversial; two reports state that the mites are all genetically homogeneous with little or no host specificity,[3,8] whereas another report documents an inability to transfer *Psoroptes ovis* to goats.[9] The mites do not affect people. Psoroptic mange is common in cattle but has been eradicated from horses and sheep in the United States; it is still a concern for sheep production in the United Kingdom and elsewhere in the world. The mites have a 2-week life cycle on their host but can live away from the host for up to 3 weeks. *Psoroptes* mites live on the surface of the epidermis and do not burrow. Symptomatic infestation tends to be more prevalent during the cooler months.

The hallmark of infestation in all species is pruritus. In cattle, crusted papular lesions are typically first apparent on the withers but then generalize, resulting in weight loss, secondary infections, and

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decreased production.[10] Horses develop papules, crusts, and alopecia most often at the base of the mane, tail, ears, and intermandibular area, with subsequent spreading to the trunk.[3] An otitis externa may be present, seemingly with *Psoroptes cuniculi*.[3] In sheep, typical lesions include papules and crusts in wooled areas, and secondary infection with *S. aureus* may occur.[11] The intense pruritus can be debilitating. Certain sheep breeds (e.g., Merino) are more susceptible to infestation than others.[9] The immune response in sheep has been extensively studied, with early innate and longer-term adaptive cutaneous immunoinflammatory responses as well as mite antigen–directed IgE being reported.[10] Goats usually have lesions restricted to the ears, although infestation and symptoms may spread to the neck and body.[12,13]

Diagnosis is based on demonstrating mites in skin scrapings and ear swabs from affected animals. Psoroptic mites are recognized by their round bodies and long, segmented pedicles.[12] Recently, serologic assays have been useful in diagnosis, especially in identifying subclinically infested animals.[14]

A number of topical insecticides have been recommended for treatment and should be applied to all affected and contact animals according to the manufacturer's guidelines. These include deltamethrin, coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[6,12,15] The contaminated environment should also be treated. Ivermectin, doramectin, and moxidectin have been used for *Psoroptes* species in large animals at 0.2 mg/kg subcutaneously (SC),[6,16,17] but treatment does not always eliminate live mites from all animals. There may be lesser efficacy when using generic formulations of ivermectin.[18] It has been recommended that *P. ovis*–infested cattle be isolated for a minimum of 14 days after treatment to prevent transmission to susceptible contact cattle.[17] *Psoroptes*-infested ears in horses should not be treated topically because of the resulting discomfort; reliance is on systemic treatment. Psoroptic mange is a reportable disease in the United States.

Chorioptic Mange

Chorioptic mange, also known as *leg mange,* is common in cattle and sheep, uncommon in goats, and seen with variable frequency in horses, depending on geographic area. Draft horses may be more susceptible than other breeds. *Chorioptes* spp. are relatively host specific and include *C. bovis, C. texanus, C. ovis, C. equi,* and *C. capre.*[6,12,19] The mites do not penetrate the epidermis[6] and do not affect humans.[17] They have a life cycle that spans 2 to 3 weeks and can live off the host for only a few days.[15]

This disease is variably pruritic, more so in ruminants than horses, and less so than infestations with *Psoroptes* or *Sarcoptes* mites. Lesions consisting of papules, erythema, scaling, crusting, ulceration, and alopecia result from self-trauma. In cattle, the lower aspects of the hindlimbs, the perineum (particularly the perianal fossa), tail, and scrotum are usually affected. Sheep typically demonstrate involvement of the lower limbs and scrotum. Goats have involvement of the lower limbs. Horses typically have lesions on the pasterns, although the ventral abdomen may become involved in severe cases. In all species, infestation can become generalized.[3,6,17]

Mites are often numerous and readily demonstrated with skin scrapings. Cattle may be asymptomatic.[17] Chorioptic mange will respond to treatments described for psoroptic mange, although ivermectin and related compounds are more effective in ruminants than horses; in horses, lime sulfur or fipronil applied once weekly for at least 1 month is recommended.[3,20-25] One study in horses showed efficacy using a single dose of moxidectin 2% oral gel (Equest [Fort Dodge Animal Health, Fort Dodge, Iowa]) at the manufacturer's recommended therapeutic dose of 0.4 mg/kg body weight.[24] Other studies have not found it to be effective in eliminating the parasite in a multi-horse situation.[26] Chorioptic mange is a reportable disease in the United States.

Sarcoptic Mange

Sarcoptic mange is an uncommon contagious disease of horses, cattle, sheep, and goats. The etiologic agent is *Sarcoptes scabiei;* several subspecies are relatively host specific but can be transmitted to humans. The mite burrows into the epidermis, where the egg is deposited, and its life cycle is complete in 10 to 17 days. Transmission is usually by direct contact, but the mite has a variable survival time off the host, so environmental and fomite transmission are possible.[3,6]

Clinical signs are all referable to the severe pruritus caused by the mite. Lesions include papules, scaling, crusting, ulceration, and alopecia. The head (especially the ears) and neck are usually the initial areas of involvement, although lesions become generalized.[3,6,15] Horses in areas frequented by infected wild foxes may have lesions affecting the legs and ventral abdomen.[3] Dairy cattle may have an associated udder cleft dermatitis.[27] Sheep tend to have initial involvement of the nonwool areas. The ears should always be scraped for mites; the mite is identified by its rounded body, terminal anus, short legs, and long unsegmented pedicles.[3,6,15]

Because mites may be present only in small numbers, negative skin scrapings do not rule out the disease. Diagnosis should be based on clinical suspicion and response to therapy.[3,6,15,28]

Topical acaricides have been recommended for treatment and are applied to all affected and contact animals at 10- to 14-day intervals for 4 to 6 treatments. These include lindane (not recommended owing to toxicity in humans), coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[3,6,15] Ivermectin 0.2 mg/kg at 2-week intervals for 2 to 4 injections (ruminants) or orally (horses) has been shown to be effective, as has injectable moxidectin and topical doramectin. The contaminated environment should also be treated. It is recommended that the state regulatory agency for livestock disease control be consulted for methods of treatment and products to use, because sarcoptic mange is a reportable disease.

Demodectic Mange

Demodectic mange is a rare disorder, although it has been recognized in all the large domestic species. The mites live in hair follicles and sebaceous and sweat glands and are host specific. They are not contagious between members of the same species, but *Demodex* spp. are presumably transmitted from mother to offspring during the first few days of life by direct contact with the dam. Little else is known regarding the life cycle of the mite.[3,6] Two species of *Demodex* are recognized in the horse.[3,28] *Demodex caballi* is a normal inhabitant of the pilosebaceous apparatus of the eyelids and muzzle and may be found in skin scrapings of these areas on horses in the absence of skin lesions. *Demodex equi* inhabits the pilosebaceous apparatus of the remainder of the body, and on horses is the species that has been associated with disease. The species found on cattle, sheep, and goats are *Demodex bovis, D. ovis,* and *D. caprae,* respectively.[3,6,15,17,]

Clinical signs are variable depending on the species affected. The disease is quite rare in horses, which may develop alopecia of the head and trunk; we have seen one case of concurrent demodicosis and chorioptic mange on the legs of a draft horse. Underlying pituitary dysfunction of the pars intermedia has been seen in some horses.[3] Pruritus and secondary pyoderma are variable. Goats and cattle usually develop nodular lesions that involve the face, shoulder, and neck.[29,30] In goats the nodular contents are white and caseous; microscopic examination for mites differentiates the lesions from *C. pseudotuberculosis.*[30] Sheep tend to develop periocular nodular lesions.

Diagnosis is based on recognizing mites with microscopic examination of skin scrapings or exudates obtained from nodular lesions. The mites are elongated and have short, stubby legs.[3,6,15]

No treatment has proved to be consistently effective in large animals, although relatively few case reports exist in the literature. Amitraz has not been successful in the treatment of caprine demodicosis.[30] Horses sprayed with 0.025% amitraz developed somnolence, depression, ataxia, muscular weakness, and progressive large intestinal impaction, suggesting that amitraz is contraindicated in equids.[31] Daily ivermectin has been suggested as a successful treatment for equine demodicosis, but dosages have not been codified. Oral

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FIG. 40-12 Severe *Culicoides* hypersensitivity in a horse, showing typical distribution of withers, shoulders, and head (not visible).

ivermectin (0.67 mg/kg once weekly for 12 weeks) and pour-on eprinomectin (0.5 mg/kg) each successfully treated one goat with generalized demodicosis.[32]

Culicoides Hypersensitivity

The females of various *Culicoides* fly species ("no-see-ums," "punkies") may feed on either the dorsal or ventral surface of the horse, affecting the mane, saddle, and rump or causing a ventral midline dermatitis in a diffuse pattern. Alopecia, papules, crusts, and erythema may all be present (Fig. 40-12). The insects induce a hypersensitivity response through salivary antigens; this condition is termed *Culicoides hypersensitivity* (Queensland itch, sweet itch) and is recognized in various areas of the world. Evidence indicates a hereditary predisposition to develop the hypersensitivity. Histopathology of lesions frequently reflects a hypersensitivity response.[33] Although many species of *Culicoides* exist, the three most commonly suspected of causing the allergic response are *C. variipennis, C. obsoletus,* and *C. nubeculosus*.

Numerous studies have attempted to define the nature of the hypersensitivity response. One study found serum antibodies to *Culicoides* salivary glands in both healthy horses exposed to *Culicoides* bites and horses with insect dermal hypersensitivity.[34] In contrast, no antibodies were detected in serum from native Icelandic horses that had not been exposed to *Culicoides.* Anti–salivary gland IgG antibodies were detected in both groups of horses, whereas IgE antibodies were only detected in clinically affected horses.[34] Another study compared two groups of affected Icelandic horses: those born in Iceland (no previous exposure to *Culicoides*) and transported to Europe, where they were then exposed to the flies, and those born in mainland Europe. The former had IgE and IgG antibodies to a greater number of the insects' salivary proteins.[35] Further investigation of immunoglobulins in relation to *Culicoides* found significantly more IgE-bearing cells in the dermis and epidermis of acute and chronic lesions than in skin biopsies from healthy horses.[36] Further evidence for a hypersensitivity response was demonstrated in a study in which intradermal injection of a *Culicoides* antigen extract induced T-lymphocyte and eosinophil accumulation in the skin of affected horses.[37] Other studies have supported the immunologic nature of this disease.[38-42]

The hallmark of disease is pruritus. Although no gender predisposition has been noted, Icelandic horses may have a higher incidence of allergic reactions to the *Culicoides* insects than other breeds. The disease is uncommon in horses younger than 1 year of age, with an onset usually between 2 and 4 years. *Culicoides* hypersensitivity may be seasonal, at least during the first few years of life, in temperate climates. Diagnosis is primarily by clinical signs. *Culicoides* antigens (commercially available in the United States by Greer, Lenoir, N.C.) seem useful in both diagnosis and treatment,[43,43a,44] but this has to be documented in large case studies.

Therapy is aimed at insect control, especially the following:

1. Stabling horses at sunrise and sunset, peak *Culicoides* feeding hours.
2. Ultrafine setting or screens placed in windows (60 squares to the square inch).
3. Fly control, especially keeping horses away from standing water and using permethrin repellents, usually 2% permethrin sprays. Frequently, sprays must be applied more often than the label recommends (i.e., daily, at least at first). We have had success using a nonpesticide herbal spray or roll-on (MedZone [VetShield & Sheen, Sun City, Ariz.]).
4. Overhead or stall fans (drafts interfere with insects' flight).
5. "Dresses" that physically obstruct the insects from reaching the skin.
6. Hyposensitization is controversial; success may vary with the presence of an adjuvant or the actual antigen used.
7. Oral prednisolone to manage the pruritus.

Ventral Midline Dermatitis of Horses

This is a reaction pattern in horses to ectoparasites, and not necessarily specific for any one arthropod. *Culicoides* hypersensitivity, *Onchocerca cervicalis* infestation, and black flies (Simuliidae) may cause generalized ventral midline dermatitis (VMD), whereas horn flies *(Haematobia irritans)* cause a focal dermatitis. Severe chorioptic mange may also involve the ventral midline. In all cases, the lesions have variable alopecia, pruritus, and crusts. Treatment is based on eliminating or repelling the causative organism.

Other Flying Insects

Stable flies *(Stomoxys calcitrans),* black flies (Simuliidae), horn flies *(Haematobia irritans),* horse flies (*Tabanus* and *Hybomitra* spp.), deer flies (*Chrysops* spp.), house flies *(Musca domestica),* face flies *(Musca autumnalis),* and mosquitos are commonly associated with irritant and allergic skin disease, as well as being vectors of many parasites (Color Plate 40-8). They must be controlled by limiting breeding areas and by repellents; 2% permethrins are often used. It is important to remember the relationship of these various flies to the environments they favor or require for breeding and when they feed, as follows:

Horse flies, deer flies	Vegetation and water	Daytime feeders
Horn flies	Cattle	Daytime feeders
Stable flies	Manure/decaying bedding	Daytime feeders
Black flies	Running water	Morning and evening
Culicoides	Standing water, manure/decaying vegetation	Twilight to dawn
Mosquitoes	Water	Dusk to 2 hours after sunset

Screwworm Infestation

Screwworm flies cause primary myiasis; the species of importance in the Americas is *Cochliomyia hominivorax (Callitroga americana).* The fly was formerly found throughout the American tropics and subtropics from the southern United States to northern Chile.[45,46] It is no longer found in the United States or Mexico as a result of state, federal, and international eradication efforts.[47]

The adult fly is about 3 times the size of a house fly, with a metallic bluish or blue-green color.[45,47] Females are attracted to fresh wounds (castration, dehorning, branding, and shearing sites), abraded body orifices, areas soiled by discharges or excretions, and navels of newborns. They lay batches of 150 to 500 white eggs on the margin of damaged tissue in rows that overlap like shingles. Eggs hatch within 24 hours, and the larvae begin to feed in a head-downward position. Larvae are obligate parasites that require living tissue as feedstuff. They cannot develop in carrion. Larval development continues for 4 to 10 days, and at the time of their maturation, they may have created a cavity 10 to 12 cm (4 to 5 inches) in diameter.[46] Mature larvae are

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about 2 cm in length, pink, pointed anteriorly and blunt posteriorly. The larvae then drop to the soil and pupate. The life cycle averages about 21 days and is favored by hot, humid weather.

Screwworms do not have a dormant stage in their life cycle and cannot overwinter in cold climates.[45] Thus the susceptible stage of development is the pupae, which will not survive soil temperatures below 15°C (59°F). The feeding larvae burrow deeply, creating a cavernous lesion characterized by liquefaction necrosis, profuse brownish exudate, and an objectionable odor. The syndrome is self-perpetuating in that wounds infested by screwworm larvae become increasingly attractive to gravid females. The end result is often death of the host as a result of secondary bacterial infection, toxemia, and fluid loss.[46]

Treatment of wounds requires clipping and cleansing, as well as destroying all larvae. Dressings containing larvicides and antiseptics should be applied. Preparations containing lindane or organophosphates have been used in an ointment or gel base. The treatment is repeated twice weekly. When large numbers of animals are affected, a 0.25% solution of coumaphos, chlorfenvinphos, or fenchlorphos may be applied to herds with a power sprayer. Calves may become ill from the spray; thus applications should be restricted to the ventral abdomen.[46] Another study showed the curative efficacy of fipronil 1% against *C. hominivorax* larvae infestation in castration wounds was 100%.[48] Even more impressive, doramectin as a prophylactic treatment was 100% effective in prevention of *C. hominivorax* infestations.[49]

Control of screwworm flies in the United States has been achieved largely through the release of sterile males, because of the single mating tendency of the female fly. The eradication program has proceeded through Mexico south to the twenty-first-degree parallel.[45] Screwworm myiasis is a reportable disease in the United States, and suspect larvae should be preserved in 70% alcohol for positive identification.[50]

Blow Fly Strike (Fleeceworms, Woolmaggots, Secondary Screwworms)

Blow flies are found throughout the western hemisphere. The species of importance include *Cochliomyia macellaria* (secondary screwworm), *Phaenicia sericata* (green bottle fly), and *Phormia regina* (black blow fly). The flies tend to be most common in the warmer regions, with the exception of *P. regina,* which is widespread throughout the cooler parts of North America and Europe.[45] Blow flies cause serious loss of sheep and wool in many countries.[47] Female flies are attracted to decaying animal matter, such as wounds infested by primary screwworms, infected sores, carcasses, and fleeces that are dampened with feces, urine, or bloody fluids.[45] They lay eggs in batches of up to 300, which hatch within hours. The larvae feed on necrotic tissue but may invade healthy tissue. Larvae develop for 3 to 5 days and, when fully mature, are white and 6 to 12 mm in length. The larvae then drop to the ground for pupation. As soil temperatures fall, larvae fail to pupate and may overwinter until the following spring. The entire life cycle is generally complete in 2 to 4 weeks under ideal conditions of warm temperatures and high humidity.[46]

Unlike primary screwworms that feed in pocket-like aggregations, secondary screwworms tend to be dispersed throughout the infested tissue. In wool infestation the larvae may remain on the skin surface, feeding on the decomposing wool, or may penetrate the skin through small abrasions. The most common site of involvement is the breech. Infested tissue attracts more ovipositing females, and thus the syndrome is perpetuated.[45] Affected sheep are restless and do not feed. They move with their heads close to the ground, bite or kick at their wounds, and continually wriggle their tails. Affected wool is moist and brown with an obvious odor. Animals may become systemically ill and die.[50]

Treatment of individual wounds is as described for screwworms. Control involves management practices that decrease the incidence of wounds or skin irritations. Sheep are often clipped below the tail and between the hindlimbs ("crutched"), where wool is likely to become saturated with urine or feces. Castration, shearing, docking, and lambing are avoided during the summer season.[45]

Cutaneous Onchocerciasis

Definition and Etiology Cutaneous onchocerciasis in horses is a common filarial dermatitis with a worldwide distribution. Its incidence in the United States has decreased dramatically since the introduction of ivermectin for routine deworming. In a report from South America, *Onchocerca cervicalis* microfilariae were detected in midventral skin biopsy samples in 215 (17.9%) of 1200 horses examined, and the adult worms were recovered from 200 (16.6%) ligamentum nuchae from the same animals.[51]

The disease is caused by the microfilaria of *O. cervicalis* and is seen primarily in adult horses.[52,53] Adults typically are found coiled in the funicular part of the ligamentum nuchae, where they produce calcified nodules. Viviparous females may live for up to 5 years and produce large numbers of microfilariae that migrate through connective tissues to the superficial layers of the dermis. Preferential areas of microfilarial localization include the ventral midline, lower eyelid, and lateral limbus of the eye.[52] The infection is transmitted by *Culicoides,* which act as an intermediate host. The larvae are ingested by the vector and undergo development into the third-stage larvae (L_3) in approximately 2 weeks. The L_3 larvae enter the animal host through lesions created by the feeding vector.[54] Many horses are infected with the parasite without demonstrating clinical disease.[52,54] A form of cutaneous onchocerciasis seen in donkeys in Africa and possibly in other nearby areas causes severe ulceration in the withers and neck region; it is the adult parasite (sometimes extractable by the handful) that causes this problem. This is possibly caused by the species *O. raillieti*.

Pathophysiology Pathogenesis is believed to involve a hypersensitivity reaction to antigens released by dying microfilariae.[52,54] This theory has support because not all infected horses demonstrate disease, neither the presence nor the severity of the dermatitis is correlated with the number of organisms present, and treatment with filaricides often causes a temporary exacerbation of clinical signs.

Clinical Signs Clinical signs occur most often in older horses and can include both ocular and cutaneous lesions.[52,54] Ocular lesions include uveitis, conjunctivitis, keratitis, and depigmentation of the lateral limbus.[55] Cutaneous lesions include diffuse or patchy alopecia, erythema, and scaling. Focal cutaneous depigmentation is common. Lesions tend to occur in regions where microfilariae are typically present in highest concentrations, such as the ventral midline, face (Fig. 40-13), base of the mane, anteromedial proximal forelimbs, and anterior pectoral region. An inflammatory, alopecic, or hyperpigmented area in the center of the forehead is highly suggestive of the disorder.[54] The dermatitis is generally reported as being nonseasonal and nonpruritic.[54,56]

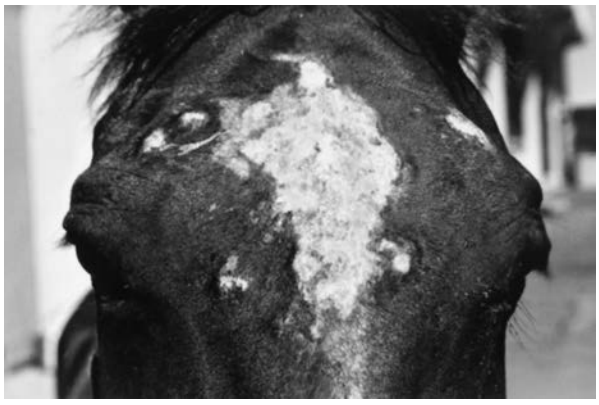


FIG. 40-13 Cutaneous onchocerciasis in a horse.

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Diagnosis and Histopathology

Because many normal horses have microfilariae without disease, the finding of microfilariae does not prove that they are the cause of the cutaneous lesions. In addition, because microfilariae tend to "nest" in the dermis, there is a tremendous difference in the number of microfilariae recovered from adjacent skin samples.[53,57] Thus, although the absence of microfilariae makes cutaneous onchocerciasis unlikely, it does not definitively exclude it as a diagnosis. Differential diagnoses should include ventral midline dermatitis caused by the horn fly *Haematobia irritans,* hypersensitivity reaction to *Culicoides,* dermatophytosis, and infestation with mange mites.

Ultimately, diagnosis should be based on history, supportive clinical findings, exclusion of other differential diagnoses, and most importantly, response to treatment.

A positive *Onchocerca* microfilarial saline preparation demonstrates slender, delicate microfilariae that are approximately 8 × 220 µm. Typical histopathologic changes include an eosinophilic and lymphocytic perivascular dermatitis, a finding that is nonspecific and common to many other equine parasitic dermatoses (see Chapter 11). Aggregations of microfilariae may be found in the superficial dermis or perifollicular region.[52,54,57]

Therapy

Ivermectin or moxidectin are the treatments of choice and are administered at 0.2 mg/kg PO.[58,59] Most horses improve within 2 to 3 weeks. Minor adverse reactions, including fever and swelling of the periorbital, facial, and ventral midline regions, may occur in up to 25% of infected horses treated with ivermectin; moxidectin did not cause posttreatment dermal reactions in one study.[59] Severe reactions may benefit from treatment with corticosteroids, but most reactions resolve within 24 to 72 hours. Because there is no effective adulticide, recurrence may be noted as soon as 2 months after therapy. Most animals remain free of clinical signs for 6 to 12 months.[56,58] Re-treatment is recommended at 4-month intervals. Interestingly, ivermectin has been reported as having both greater and lesser GI absorption in donkeys than in horses. This awaits more clarifying studies.[60]

In cattle, onchocerciasis has been caused by the microfilariae of *Onchocerca gutturosa* and *Onchocerca lienalis* and, in Africa, *Onchocerca ochengi.*[61,62] Flies of Simuliidae are the vectors. The disease causes nodules and crust on the skin, including the teats; adult worms surrounded by neutrophils were detected free in the teat canal.[63] Ivermectin and moxidectin are effective treatments.[61]

Stephanofilariasis

Cutaneous stephanofilariasis is a filarial dermatitis of cattle. The disease is caused by organisms of the genus *Stephanofilaria* and has been observed in cattle in many countries.[64,65] Within the United States the disease is most prevalent in the western and southwestern regions, where it is caused by *Stephanofilaria stilesi.*[50,55,65] Adults and microfilariae inhabit the epidermis. The parasite is transmitted by the female horn fly *(Haematobia irritans)* when it feeds on lesions on the ventral midline.[55] The microfilariae are ingested and develop to infective L_3 larvae in 2 to 3 weeks. The L_3 stage is introduced into the animal host on subsequent feedings.[65]

Clinical signs of cutaneous stephanofilariasis include a ventral midline dermatitis initially associated with a papular eruption. The scrotum may also be affected.[66] The lesions progress to nodules, alopecia, and crusted ulcers. There may be mild pruritus.[46] Diagnosis is based on history and appropriate clinical signs, excluding differential diagnosis and demonstration of the nematode. Biopsies may be taken as described for equine onchocerciasis, or the crust can be removed from an acute lesion and deep skin scrapings performed to recover the parasite. The tissues should be minced in isotonic saline and then examined microscopically. Multiple skin scrapings may be required to demonstrate the parasite. Either adults or microfilariae may be found. The adult male is about 3 mm in length and the adult female 6 mm in length.[63] Microfilariae are 50 µm in length.[63] Characteristic histopathologic findings include a perivascular dermatitis associated with an eosinophilia. Microfilariae may be noted in the dermis, and adults in epithelial-lined cysts at the base of the hair follicles, although both may be difficult to find.[63]

There is no approved treatment for stephanofilariasis, although approved topical organophosphates have been suggested.[53] Some authors have not recommended treatment, because clinical signs are relatively mild in many animals.[65] Cattle with zebu ancestry may be more resistant.[64]

Hypoderma (Warbles)

Definition and Etiology

Infestation with the larvae of *Hypoderma* spp. is a common and serious economic problem in cattle and is recognized sporadically in horses that are pastured near cattle. Occurrences have also been reported in sheep, goats, and humans.[67] Warble flies are present in the northern hemisphere between 25 and 60 degrees latitude in more than 50 countries of North America, Europe, Africa, and Asia. *Hypoderma* species are not established south of the equator.[53,67] The U.S. cattle industry loses millions of dollars annually because of cattle grubs.

Two species of *Hypoderma* parasitize cattle: *H. bovis* and *H. lineatum.* The latter prefers warmer climates and is the only *Hypoderma* sp. present in the southern United States. Each of the species occurs in the northern United States and Canada.[53] *H. lineatum* and *H. bovis* have very similar life cycles, but the stages of *H. lineatum* tend to occur 3 to 8 weeks earlier than those of *H. bovis.* Timing of the life cycle also varies with local geographic and climatic factors.[53,67]

The adult flies are beelike in appearance, covered with dense chin bristles (hair), 12 to 188 mm in length, and have nonfunctional mouthparts.[68] They have a short lifespan, only 1 week. Adult flies are active in the spring to early summer, with *H. lineatum* appearing 3 to 4 weeks before *H. bovis.* Female *H. lineatum* flies deposit eggs on the hairs of the legs or lower body, whereas *H. bovis* tends to deposit eggs on the rump or upper parts of the hindlimbs. Total egg production by a single female has been estimated to range from 500 to 800.[68] The eggs hatch in 3 to 7 days, after which the larvae penetrate the skin and begin their migration through the connective tissues. *H. lineatum* larvae migrate to the subcutaneous connective tissues of the esophageal wall, whereas *H. bovis* larvae migrate toward the spinal canal. The first-stage (L_1) larvae remain in this location for 2 to 4 months during autumn and early winter. Between January and February the larvae begin a final migration through the connective tissues to the subdermal tissue of the back of the host, where they form a breathing hole through the skin. Cysts (warbles) develop around L_1 larvae. Within the cyst the larvae undergo 2 molts over a 4- to 6-week period. The L_3 larvae (grubs) emerge from the breathing pore, fall to the ground, and pupate. Adult flies emerge from the pupae in 1 to 3 months, and emergent adults are ready to mate almost immediately.[50,68] The life cycle is complete in 1 year. Most larvae fail to reach normal size and complete their life cycle in the horse.[67,68]

Clinical Signs

CATTLE. During the spring and summer when adult flies are active, "fly worry" may be a serious problem. Cattle exhibit a stampeding behavior called "gadding" when chased by ovipositing females, even though the flies do not bite or sting. This fear reaction results in self-injury and decreased feeding and milk production.[68] Diagnosis of warble flies in goats by ELISA has been reported, but it is not known whether this is applicable to cattle.[69]

Clinical lesions are not usually observed in association with migration of L_1 larvae unless the larvae die along the migratory path.[67] Lesions that have been associated with infestation of L_1 larvae of *H. bovis* include fat necrosis and inflammation of the connective tissues surrounding the spinal canal. Secondary periostitis, osteomyelitis, and rarely paralysis or other nervous disorders may occur. Similarly, infestation with L_1 larvae of *H. lineatum* in the submucosa of the esophagus may cause inflammation and edema in the surrounding tissues. Swallowing and eructation may be hindered, resulting in bloat and subsequent respiratory failure.[67]

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Lesions most often observed with *Hypoderma* infestation are attributed to L_3 larvae. Warbles occur along the back from the shoulders to the tailhead and from the dorsal midline to a point about one third the distance down the sides. The lesions may be firm to fluctuant, raised, and painful to the touch. They measure approximately 3 cm in diameter and contain a breathing pore that usually exudes a yellowish serum. Excisional biopsy of a nodular lesion reveals the larvae within a cystlike structure that contains yellow fluid. The surrounding tissue is necrotic. Secondary infection of the cysts can result in large suppurating abscesses. The number of warbles in an infested animal may range from 1 to 300. Infestations are most serious in younger animals and become progressively less severe with age. Emergence of the grub results in healing, although carcasses retain evidence of infestation and are devalued at slaughter.[53,67] Diagnosis is usually by direct clinical examination, but immune diagnosis by the use of pooled serum and/or milk sample is also possible.[70]

HORSES. Most horses have only one or two grubs, but heavy infestation is present in rare cases. Lesions associated with L_3 larvae include small nodular swellings that develop dorsally, and frequently in the region of the withers. Most lesions have a breathing pore.[50] Differential diagnosis is most often eosinophilic granuloma (nodular collagenolytic granuloma, nodular necrobiosis), but mastocytoma, sterile nodular panniculitis, and amyloidosis should also be considered. Posterior paralysis associated with involvement of the spinal cord has been reported in both horses and cattle.[68]

The season, location of the lesion(s), and presence of a breathing pore are usually diagnostic. Larvae can be recovered by enlarging the breathing pore with a scalpel and extracting the grub.

Therapy When small numbers of cattle are affected with just a few grubs, manual removal of the grubs is possible by simply enlarging the breathing pore. This is usually the preferred treatment in horses as well if only one or two lesions are present. Care must be taken to remove the larvae in their entirety, because breaking the larvae and rupturing the cyst during removal can result in a severe systemic reaction.[53,67]

Systemic insecticides are the only means of eliminating the migrating larvae. Organophosphates or the macrocyclic lactones (doramectin, eprinomectin, ivermectin, moxidectin) have been used for this purpose and are applied on the midline of the back.[67,71] Administration of insecticides should be timed to provide treatment in early autumn after all eggs have hatched and larvae are in the early stages of their connective tissue migration. Third-stage larvae are less susceptible to insecticides, and destruction of larvae in later stages of migration increases the risk of serious secondary illness. It is advisable not to administer systemic insecticides later than 8 to 12 weeks before the anticipated first appearance of grubs along the back.[53,67] In the northern United States and Canada, treatment of cattle with systemic insecticides is not recommended from October 1 to March 1; this is when *H. bovis* larvae are located in the epidural space and *H. lineatum* larvae reside in the esophagus.[53]

Sheep Keds

The sheep ked, *Melophagus ovinus,* is a wingless fly approximately 6 to 7 mm in diameter with a ticklike appearance. Sheep keds have a worldwide distribution. They primarily parasitize sheep and occasionally goats that are kept under poor management conditions.[53,72]

The entire life cycle is spent on the host. Females live 4 to 5 months, individually laying 10 to 15 larvae that are cemented to the wool or hair. The larvae pupate in 12 hours, and the adult emerges 3 weeks later. Adults feed on blood and do not survive longer than a few days off the host. Transmission is by direct contact, and infestation is more common in the winter months.[53,54,72]

Clinical signs of infestation include pruritus with subsequent self-trauma, wool stains from the flies' fecal material, and in severely parasitized animals, anemia. Multiple firm nodules (cockles) develop as a result of repeated puncture of the skin as the keds feed.[53,54] Infestation results in economic loss from a reduction in dressed carcass weights of lambs, reduced clean dry weight of fleece, wool staining, and reduced value of sheep skins because of nodular defects.[53,72,73] Diagnosis is based on demonstration of the parasite.

Therapy involves shearing all sheep in the affected flock, followed by 2 topical applications of malathion, diazinon, or coumaphos at 14- to 21-day intervals to kill emerging adults.[53] Because the larvae are attached to the wool or hair some distance above the skin surface, many larvae and pupae are removed by shearing.[54,73] Imidacloprid has been shown to be effective in killing the parasite.[74] All new animals should be isolated and treated before introduction to prevent reinfestation. A control program includes annual treatment of the entire flock.

Cutaneous Habronemiasis (Equine Summer Sore)

Habronemiasis ("summer sore") is a granulomatous disease caused by the deposition of *Habronema microstoma, Habronema muscae,* or *Draschia megastoma* larvae by flies at the site of wounds or natural body moisture (sheath, eyes).[75,76] Adult parasites normally reside in the stomach, where they cause little tissue reaction, with the exception of *D. megastoma,* which produces gastric nodules of varying sizes near the margo plicatus. Females are viviparous, and larvae are passed in the feces, where they are then ingested by the larvae of flies acting as intermediate hosts. *H. muscae* and *D. megastoma* develop in the house fly, *Musca domestica,* and *H. microstoma* develops in the stable fly, *Stomoxys calcitrans.*[53] The L_3 larvae are then deposited around the horse's mouth and swallowed to pass to the stomach, where they mature to adults. Cutaneous lesions occur when the larvae are deposited in damaged skin or areas of natural body moisture. The larvae cannot penetrate normal healthy skin.[54] In these aberrant locations, they are unable to mature to adults, and the resulting proliferative lesions are thought to represent a hypersensitivity reaction to the dead or dying larvae. In temperate parts of the world, habronemiasis is a seasonal disease, occurring in warm, wet weather.

Arabians, gray horses, and horses with a dilute hair coat seemingly have a predilection for this disease. The medial canthus of the eye, male genitalia, nictitating membrane ("third eyelid"), and distal extremities are the most common parts of the body affected.[75] Lesions consist of ulcers and nodules. Diagnosis is based on clinical signs, history, and the presence of calcified concretions (sulfur granules) and is confirmed by biopsy. The nodular lesions may take on the gross appearance of neoplasia. Alternatively, the larvae may infest a preexisting tumor, especially squamous cell carcinoma of the male genitalia, and a biopsy is crucial for accurate diagnosis. Characteristic histopathologic findings include granulation tissue with a diffuse infiltration of eosinophils and an ulcerative epithelial surface. The granulation tissue usually contains focal areas of coagulation necrosis surrounded by a dense eosinophilic infiltrate. Cross sections of larvae can often be identified within some of the necrotic foci.[75] Rarely, larvae are found in scrapings from the lesions.[53] Larvae are not always found in the biopsy sections[75]; in these cases, if neoplasia has been ruled out, presumptive treatment for habronemiasis should be performed. A polymerase chain reaction (PCR) assay for diagnosing habronemiasis has been developed and may hold promise in the future for cases where larvae are not found on biopsy.[77]

Treatment in the past has been either corticosteroids or organophosphates, topical or systemic. Ivermectin (0.3 mg/kg PO) has been shown to be effective and is considered the treatment of choice by many clinicians. Moxidectin (0.4 mg/kg PO) may also be used. Systemic corticosteroids (e.g., prednisolone 1 mg/kg PO once daily for 10 to 14 days, then tapered over 2 weeks) or intralesional or topical corticosteroids are often used because of the hypersensitivity reaction nature of the disease process. In severe cases, surgical removal or debulking of the lesion should be considered.[76]

Habronemiasis has been seen in horses routinely given ivermectin as part of their deworming program.[76] Prompt removal and disposal of manure and soiled bedding are important to eliminate vector

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breeding habitats. Insect repellents should be applied to affected horses. Face guards (fly masks) will also prevent infection. In general, the prognosis for resolution of individual lesions is good if the therapeutic goals are achieved.

Besnoitiosis

Donkeys have a higher reported incidence than horses for infections with the protozoal parasite *Besnoitia bennetti.*[78-81] This organism is the same species that afflicts cattle and is closely related to *Besnoitia tarandi,* which afflicts reindeer *(Rangifer tarandus).*[79] The mode of transmission has not been determined. Skin lesions affect the nares, skin, and sclera. Males and younger animals may be at greater risk.[81] Diagnosis may be from histopathology, serologic testing, and PCR. Unfortunately there is no known treatment.

Bovine besnoitiosis, due to the cyst-forming organism *Besnoitia besnoiti,* is widespread in Africa, Asia, and southern Europe. Economic losses result from decrease in cattle and milk production, transient/definitive sterility of bulls, and mortality.[82] Goats are also affected by this parasite. Lesions are reported as warm and painful edema progressing to excessively folded skin, primarily on the legs, udder or scrotum, and head.[83] The mode of transmission is unknown, although arthropods, ingestion, and proximity to an infected animal have been suggested. Diagnosis is as with donkeys.[84,85]

Tumors and Cysts

Squamous Cell Carcinoma

Stephen D. White

Definition Squamous cell carcinomas (SCCs) are tumors composed of squamous epithelial cells. They occur in all domestic species and are the most common bovine ocular tumor (see Chapter 39) and the second most common tumor recognized in the horse.[1] Although their gross appearance may vary, these tumors are usually slightly raised, broad based, and white to pink and have a cobbled or cauliflower-like surface (Color Plate 40-9). SCCs frequently occur on the penis and sheath of aged stallions and geldings (see Chapter 43). They also occur on the lips, nose, eyelids, eyes, and ears of horses. SCC often accompanies cutaneous papillomas of the udder and teats in Saanen milk goats, as well as female Angora goats in South Africa. The ears, base of the horns, and prepuce may also be affected.[2] SCC is reported as being the most common cancer of the ear of sheep; an outbreak primarily affecting the eyelids in 15% to 18% of a sheep population has been reported.[3] Diagnosis is by biopsy. There is increasing evidence that SCC in horses and sheep is associated with papillomavirus infection.[4-6]

The treatment of choice is wide surgical excision.[7,8] Solar elastosis (aggregates of thick, wavy, interwoven elastic fibers mixed with areas of degenerated collagen), when seen histologically with SCC, may lend a more favorable prognosis after complete surgical removal of lesions.[9] Other treatment modalities reported as successful include cryosurgery, radiofrequency hyperthermia, and radiation therapy.[10] Another study showed topical application of 5-fluorouracil (5-FU) and intralesional cisplatin were effective in horses with SCC.[11-14] Piroxicam was successful in the long-term control of SCC with metastases in one horse.[15]

Equine Sarcoid

Alain P. Théon

Sarcoids

Epidemiology Equine sarcoid was first reported by Jackson in 1936.[1] It is the most common tumor in equidae (horses, mules, and donkeys) worldwide and accounts for more than 50% of cutaneous tumors. Sarcoids are locally aggressive, non-regressing fibroblastic tumors of the dermis and subcutis, with a variable proliferative epithelial component. This dual involvement of the epidermis and dermis is the hallmark of sarcoids and explains the multiple and evolving clinical appearance of the tumor. The epidermal component of sarcoids shares features of a benign papilloma, and the fibroblastic component is consistent with a low-grade fibrosarcoma.[2] These characteristics lead to an incorrect histologic diagnosis of fibrosarcoma or nerve sheath tumors when the surrounding skin is not included in the tissue analyzed.[3]

Despite numerous clinical reports on sarcoids, the clinical and epidemiologic data are still puzzling. Inconsistent and sometimes conflicting, they support no gender, breed, age, or genetic predispositions or any anatomic predilection.[4] The data reflect in part the frequent lack of histologic confirmation of the disease in reported studies and may represent regional or national variations of the clinical characteristics of sarcoids.

Epidemiologic evidence of a causative agent comes from the fact that age is not a risk factor. Unlike spontaneous tumors, affected horses are likely to have asynchronous or metachronous lesions,[4] and anecdotal sarcoid outbreaks have been reported.[5] Although papillomaviruses are strictly species specific, it is widely accepted that BPV types 1 and 2 are associated with the pathogenesis of sarcoid disease. BPV-1 is more commonly found in Europe[6] and BPV-2 in the western United States.[7] However, the full viral life cycle has never been demonstrated in equidae, and viral particles have never been detected in lesions. Hence, the disease is understood as the result of an abortive infection where BPV gene sequences exist episomally[8,9] or integrated in host DNA.[10] The presence of viral genetic material is apparently necessary for tumor development. BPV DNA sequences are always found in sarcoids. Equine fibroblasts can be transformed in vitro following BPV-1 infection.[11,12] Detection of sequences of early expressed genes of the viral genome (including E5, E6, E7, and occasionally E2) is consistently found in sarcoid tumors and surrounding normal cutaneous margins but not in other tumor types.[13-15] Both the epithelial and fibroblastic components of the tumor contain unique viral gene sequences that are actively transcribed.[16] However, it is not sufficient to produce the disease, and its role in the etiology of sarcoids continues to be questioned. BPV DNA sequences have been detected in healthy skins of horses not known to have ever been in contact with a source of BPV[17] and in some cases of dermatitis.[18] In addition, the presence of viral DNA sequences has also been reported in skin swabs of unaffected horses and peripheral blood mononuclear cells of horses with unrelated skin lesions (abscess, carcinoma, and hoof canker).[19,20]

Experimental transmission studies of sarcoids have been unsuccessful. Inoculation of sarcoid cell-free extract in cows does not induce warts or induce sarcoids in unaffected horses.[3] Experimental cutaneous infection with BPV induces fibropapillomas clinically similar to sarcoids, but the lesions regress spontaneously with production of neutralizing antibodies to the virus and viral DNA sequences in white blood cells.[21,22] The infection in horses is considered abortive because BPV cannot replicate in horses nor be serially passed from BPV-induced fibropapillomas.[22] An alternative theory is that an equine variant of BPV may be the cause of sarcoids.[23]

The mode of transmission of the disease is unknown and does not require contact with cows. Intradermal injection of primary sarcoid fibroblasts containing viral episomes,[21] naked full-length BPV-1 genome,[21] or transforming genes (E5 and E7)[24] does not induce sarcoids in horses and donkeys. Evidence of a transmissible infectious cell line has not been found.[25] Because only complete BPV virions can induce transformation, contamination cannot occur by casual contact with contaminated fomites or affected horses,[17] by BPV-infected insect bites,[26] or by blood samples.[20] As a result horses are considered to be nonpermissive hosts for BPV,[27] and horizontal BPV transmission remains to be documented.

The mechanisms of cellular oncogenesis are similar to those of other transforming papillomaviruses. Oncogenesis is associated with episomal or genomic integration and expression of the 3 transforming genes E5, E6, and E7. E5 is always found and expressed in

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sarcoids. E5 protein binds to and activates the platelet-derived growth factor beta receptor (PDGFβ-r),[28] which triggers several downstream effector pathways controlling cell proliferation and cell survival[28] and invasion.[29] In addition, E5 protein has been shown to inhibit equine MHC class I by reducing transcription of the MHC I heavy chain gene and blocking transport of the MHC I complex to the cell.[30] It is speculated that ELA downregulation depresses adaptive immune response and allows cells to evade immune surveillance. E6 and E7 proteins cooperate with E5 in inducing transformation. E6 and E7 proteins bind to cell cycle control gene products, the Rb and p53 proteins, respectively, preventing apoptosis and therefore enhancing survival of transformed cells.[31] In addition, E7 and E5 proteins inhibit anoikis, which provides transformed cells a survival advantage[32] and contributes to immune evasion by impairing innate immune response.[33]

The variable presence, location (episomal vs. integrated), copy numbers (viral load), and expression[12] of BPV transforming genes in tumor cells, as well as the status of host immunocompetence, may explain the variable appearance, location, and behavior (growth rate, local invasion) of sarcoids.

Preliminary genomewide association study (GWAS) analyses of genetic predisposition to develop equine sarcoid have identified regions on chromosomes 20, 23, and 25 that include genes regulating virus replication and host immune response.[34,35] Further investigations may unveil defective genes potentially responsible for the development of sarcoids that may be used for early identification of susceptible animals through genetic screening and for disease prevention through careful breeding. GWAS analyses may also provide a biological rationale for development of new targeted treatments.

Biological Behavior Sarcoids represent a wide spectrum of fibroblastic tumors ranging from indolent, apparently benign lesions to aggressive and invasive tumors. Clinically, many sarcoids initially behave as benign lesions because they are slow growing, giving the false impression that the lesion is inactive. In addition, sarcoids are frequently classified as biologically benign tumors, because they do not metastasize to distant organs, and regional lymphatic metastasis is rare and usually associated with multiple unsuccessful treatments.[36] However, the equine sarcoid is not a benign tumor, because it is a progressive disease that invades and destroys surrounding normal tissue, does not regress spontaneously, and recurs predictably after surgical mass removal.[3,31,37] Early lesions are restricted to the dermis and epidermis, but advanced lesions commonly invade the subcutis and may extend through fascia into deeper muscular structures. Considering sarcoids as benign tumors leads to inappropriate management early in the course of the disease and thus to multiple recurrences, and results in unsatisfactory cosmetic and functional outcomes as well as unnecessary expenses to control the disease.

Molecular understanding of the different pathways leading to sarcoids may explain why some lesions remain quiescent for many years and eventually undergo progressive transformation to the aggressive fibroblastic type, while some lesions arise de novo as aggressive tumors.[2,3,38] Identifying signaling cascade controlling invasiveness may provide therapeutic targets against the most aggressive sarcoids.[28,29,39]

Diagnosis Sarcoids are recognized as having different multiple clinical manifestations including occult, verrucous, and nodular clinical types (Fig. 40-14).[3] In addition, about a third of affected horses have multiple sarcoids at different clinical stages at the time of diagnosis.[4] The different clinical aspects represent stages of tumor progression and reflect the relative predominance of the dermal or epidermal component. Lesions with a predominant epidermal component include occult and verrucous sarcoids. Occult sarcoids appear as an almost circular area of alopecia with a gray scaly surface. Verrucous sarcoids may be sessile (flat variety) or pedunculated (warty variety); the skin is thickened with a dry rough surface, with partial or total alopecia. Nodular sarcoids, also called *fibroblastic sarcoids,*

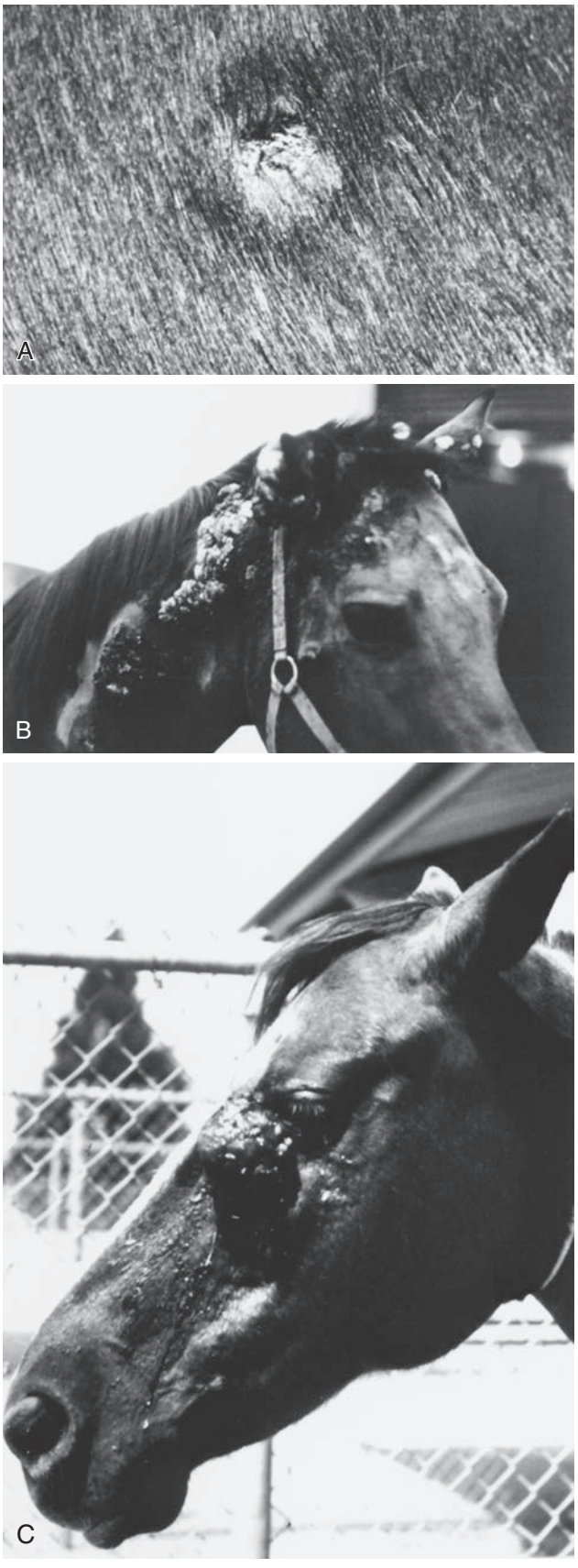


FIG. 40-14 Equine sarcoids. **A,** Small occult sarcoid. **B,** Multiple verrucous sarcoids. **C,** Fibroblastic sarcoid.

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range in appearance from a dermal/subcutaneous nodule to a large exophytic mass with a skin surface that eventually ulcerates. The nodular type is locally invasive, destroying adjacent tissues, and may ultimately infiltrate lymphatic vessels and nerve sheaths and disseminate to form regional metastases.[36] Mixed forms represent a transition from one type to another. The multiplicity of recognized clinical forms confirms the equivocal and progressive nature of the disease.

The polymorphic appearance of sarcoids and the diverse list of differentials make the clinical diagnosis of sarcoids unreliable. The diagnosis and treatment of sarcoids require a biopsy because they are often overdiagnosed clinically. In a review of 681 horses referred to the Equine Oncology Clinic at the UCD-VMTH for evaluation and treatment of clinically diagnosed sarcoids, 31% of lesions were found to be nonneoplastic dermatologic conditions.[40] After ruling out a nonneoplastic skin conditions, any clinically suspicious lesion should be biopsied.[41] As with any tumor, early recognition and treatment of a small lesion is always associated with a better prognosis. It is important to keep in mind that any large and invasive sarcoid associated with a poor prognosis was, earlier in its evolution, an apparently inactive small lesion that was not recognized or was neglected. There is no contraindication for a biopsy of a suspicious skin lesion so long as definitive and effective treatment is instituted immediately after the diagnosis is made. There should be no fear about performing a biopsy of a suspected sarcoid, because very effective treatments are available. However, a biopsy—like any trauma—can increase proliferation of a previously slow-growing tumor and may accelerate tumor progression. As a result, a biopsy should not be recommended if the owner is not willing to pursue treatment if needed, because the process of biopsy without subsequent treatment has the same effect on overall prognosis as an unsuccessful attempt at treatment.

Treatment Sarcoids are low-grade fibrosarcomas and share common features of soft tissue sarcomas. They are locally invasive and tend to infiltrate into surrounding normal tissues through and along fascial planes 2 to 4 cm from the palpable tumor mass. Treatments that are used can be broadly grouped into ablative (surgery, laser vaporization, cryotherapy, hyperthermia, and caustic ointments), cytotoxic (radiation therapy, chemotherapy), and biological (immunotherapy) modalities. Overall treatment goals are to (1) destroy all tumor cells in the gross tumor and also in the normal-appearing surrounding tissues and (2) minimize damage to healthy tissues. These goals are difficult to achieve with ablative treatment methods, because they are not selective against tumor cells. A cuff of surrounding normal tissue containing microscopic disease must be ablated to remove all tumor cells. Early complete surgical resection has a central role in the treatment of sarcoid. Alternate ablative modalities have no oncologic benefits over a well-planned conventional surgery and do not allow histopathologic evaluation of surgical margins to assess the quality of the procedure.

Topical applications of escharotics with zinc chloride–based caustic ointments (Indian Mud [Original Cream Company, Magnolia, Ark.], XXTERRA [Larson Laboratories Inc., Fort Collins, Colo.], Animex [NIES, Las Vegas, Nev.]) or 5-FU cream (Efudex 5% fluorouracil [Hoffman La Roche Inc., Nutley, N.J.]) are used empirically for treatment of sarcoids. Unfortunately, no evidence-based data have yet been published documenting treatment efficacy against histologically confirmed sarcoids. As a result, no evidence-based information on treatment protocol, efficacy, prognosis, and toxicity is available.

Because tumor size and previous unsuccessful treatment attempts are the most important prognostic factors,[37,42] early and histologically complete surgical resection is the mainstay of treatment of sarcoids.[41] Failure to eliminate the disease results in regrowth of a tumor that is histologically and biologically more aggressive and requires wider excision than the primary lesion. It is critical to submit the resected tissue specimen for histopathologic examination to determine the status of the surgical margins. As a rule, grossly or histologically incomplete resection (i.e., positive or close pathologic margins [≤5 mm]) must be followed by a re-resection if possible or by effective adjuvant treatment. For noninvasive sarcoids resected with pathologic margins greater than 5 mm, and invasive sarcoids resected with pathologic margins greater than 1 cm, the risk of recurrence is low, and no further treatment but observation at regular intervals for at least 1 year is recommended. For invasive sarcoids resected with surgical margins between 5 and 10 mm, the risk of recurrence is high, and adjuvant treatment may be recommended, particularly when tumor recurrence may be difficult to manage because of unfavorable anatomic location. Access to molecular techniques (PCR and RT-PCR) designed to detect BPV E5 or E6 in pathologic margins will help assess the risk of recurrence and determine the need for adjuvant treatment.[43,44]

Among the nonsurgical treatments, radiation therapy and intratumoral chemotherapy with a viscous-fluid slow-release formulation of cisplatin have well-documented efficacy against biopsy-confirmed sarcoids of all clinical types and in any location.[42,45,46] The selective effects of these treatments have the advantage of controlling the disease while avoiding disruption of anatomic structure and preserving function. When compared to radiation therapy, intratumoral chemotherapy with cisplatin is as effective but without long-term side effects and does not require any special license. The overall cure rate (all stages and clinical types combined) after treatment with intratumoral cisplatin therapy used alone or as adjuvant to surgery has been reported to be as high as 96%.[42] Treatment includes a series of 4 intratumoral administrations of cisplatin (≈1 mg/cm^3 of tissue) given at 2-week intervals. Widely available and inexpensive compounded crystal is formulated in a water/sesame seed oil emulsion stabilized with sorbitan monooleate (Span 80).[42] Treatments are done on an outpatient basis under sedation, and the methods of administration and safety precautions have been described.[47] Although other antineoplastic drugs[48-50] and drug formulations[37,47,49,51] for intratumoral chemotherapy have been evaluated, cisplatin in sesame seed oil emulsion remains the most effective drug.[42] Attempts at increasing (1) cisplatin uptake in tumors cells by electroporation applied under general anesthesia[52] or (2) drug exposure with cisplatin-containing biodegradable beads implanted intraoperatively[53] require anesthesia and complex procedures but have not shown any improved therapeutic benefits. Systemic chemotherapy with doxorubicin has shown preliminary evidence of efficacy for fast-growing fibroblastic sarcoids but not for indolent verrucous sarcoids.[54]

BPV-associated equine sarcoids are distinct from other equine tumors in that they express targetable viral foreign antigens, the expression of which is necessary to maintain the cancerous phenotype. While therapeutic vaccines aim to develop a strong cellular immune response to BPV antigens that are expressed in transformed cells, prophylactic vaccines aim to prevent a putative BPV infection by inducing a neutralizing antibody response. Immunotherapy has been evaluated for treatment of sarcoids. Therapeutic humoral immunization has not been found effective for treatment of affected horses. Vaccination against BPV-1 virus-like particle in sarcoid-bearing horses[24] and donkeys [55] resulted in BPV-1 neutralizing antibodies but was not therapeutically effective. Since the vaccine was immunogenic, trials of protective vaccination are under way.[56]

Therapeutic vaccines aim to control tumors by activating the patient's own cellular immune response to recognize and kill cancer cells. Nonspecific cell-mediated immunotherapy uses immune stimulatory agents that act nonspecifically to elicit both innate and adaptive immunity and results in the induction of proinflammatory cytokines, chemokines, and other immune mediators. This in turn leads to the generation of a Th1-biased cell-mediated immune response and a concomitant generation of cytotoxic effector cells against antigens in the tumor. Bacillus Calmette-Guérin (BCG) cell wall derivatives (Nomagen [Fort Dodge Laboratories, Fort Dodge, Iowa]) and imiquimod (5% imiquimod cream [Aldera-3M Pharmaceuticals, Minneapolis, Minn.]) are two nonspecific immunostimulants that have been reported for treatment of sarcoids. BCG cell wall

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derivatives administered intralesionally[57] have been shown to be effective only for periocular sarcoids.[37,58,59] The number of treatments depends on the rate of tumor regression, and the treatment schedule is dependent on normal tissue toxicity; most sarcoids require 2 to 9 treatments over several weeks.[37] Encouraging results have been reported with a biological response modifier used topically (5% imiquimod cream). The ointment is recommended for the treatment of viral warts and basal cell carcinomas in people. It is applied as a thin layer to the tumor surface 3 times a week on nonconsecutive days up to 32 weeks until resolution.[60] The reported 60% response rate suggests that topical imiquimod may be a therapeutic option for specific equine sarcoids. However, the data must be confirmed in a larger series of horses with sarcoids of all types and adequate long-term follow-up. In our experience, imiquimod has been effective only for treatment of occult sarcoids and persistent papillomas in adult horses. Treatment did not prevent progression of verrucous or fibroblastic sarcoids. In all cases, treatment was associated with severe and painful skin inflammation.

Continued expression of E5, E6, and E7 proteins by equine sarcoid tumor cells makes them excellent targets for specific immunotherapy.[23,61] Cell-mediated immunity is critical for the control of papilloma-associated tumors.[62] In people, trials with therapeutic vaccines that target the E6 and/or E7 proteins using peptide or protein-based vaccines, live vector vaccines, cell-based vaccines, and DNA vaccines have been disappointing for treatment of human papillomavirus (HPV)-associated tumors.[62] Although E5 is uniformly expressed by sarcoid tumor cells, no attempt at targeting the E5 protein has been made in veterinary medicine. The renewed interest in E5 protein as a target for therapeutic vaccine in human medicine[63] may provide a biological rationale for targeting E5-expressing sarcoid cells. Dendritic cells (DCs) are the central players in the initiation of the adaptive immune response and play a key role in the antitumor T-cell responses. A preliminary study with autologous monocyte-derived dendritic cells (MoDC) isolated from horses with sarcoids and loaded with tumor lysates showed that the treatment was safe and prevented tumor recurrence after surgery in 13 of the 21 treated horses.[64] Although the data are preliminary and must be confirmed in a larger study, they underscore the need for an increased understanding of dendritic cell biology that will lead to further development of innovative strategies to optimize vaccine-elicited T-cell antitumor immune responses.

Mastocytosis

Stephen D. White

In horses, mastocytosis (mast cell tumors, mastocytomas) occur in animals 1 to 18 years old (average, 9 years), with no breed predilection. A predilection for males has been proposed but is not always sustained.[1,2] In addition, multiple mast cell tumors resembling urticaria pigmentosa of humans may occur in newborn foals; these occur spontaneously and regress.[2,3]

Equine mastocytosis is usually solitary and occurs most often on the head and trunk, although occasionally multiple tumors may be seen.[4] Lesions are 0.5 to 20 cm in diameter, well to poorly circumscribed, firm to fluctuant, dermal or subcutaneous, and may or may not be alopecic, ulcerated, and hyperpigmented. Lesions on the legs tend to be very firm and immovable.

Histology may vary from sheets of mast cells with few eosinophils (presumably early lesions) to sections showing both sheets of mast cells with numerous eosinophils and collagen degranulation. Ultrastructural features are similar to those noted in mastocytomas of other species.[5]

Clinically, most mast cell tumors in horses do not recur after being excised (22 of 25 in one study).[5] In one anecdotal case of metastasis from a tumor on the muzzle to regional lymph nodes, the tumor and the nodes were removed, and the horse was clinically sound 3 years later. There is some debate as to whether equine mastocytomas are benign neoplasias or focal dysplasias of mast cells.

Mastocytomas are uncommon in cattle but typically occur in young calves.[6,7] One report describes a cutaneous mast cell tumor in a kid goat.[8] Although equine mastocytomas are almost always benign, mastocytosis in cattle may be malignant or benign and therefore carry a more guarded prognosis.

Melanoma

Stephen D. White

Equine Melanomas

Melanomas occur in all domestic animals, but of the large domesticated species, they are most important in the horse. Excessive exposure to sunlight has not been definitively proven to predispose horses to the development of melanoma. A disturbance in melanin metabolism associated with graying has been hypothesized to stimulate formation of new melanoblasts or to stimulate their activity, resulting in focal areas of overproduction in the dermis and epidermis, with subsequent tumor formation.[1] A higher incidence is observed in the Arabian, Lipizzaner, and Percheron breeds, probably because gray coat color occurs more often in these breeds. There is no gender predilection.

Melanocytic skin tumors of horses traditionally have been described in aging gray horses in typical locations: ventral tail, perineum, external genitalia, lip, udder, and periocular and parotid gland regions. These tumors have been the subject of several classification schemes in attempts to correlate histopathologic appearance with clinical behavior (i.e., benign or malignant). One study distinguished three basic types of melanocytic skin tumors, as discussed next.[2]

Melanocytic nevi (melanocytoma) occur in the superficial dermis or at the epidermal-dermal junction and frequently have epithelial involvement, with nests of relatively large, mildly to moderately pleomorphic cells showing variable cytoplasmic pigmentation and occasional mitoses. More than 70% of these occur in horses younger than 6 years of age and may occur in horses of any color (not just gray). Most of these tumors occurred in atypical locations. Of 28 melanocytic nevi, only one became invasive; the rest exhibited benign behavior.

Dermal melanomas are found in the deep dermis and are composed of small, homogeneous, indistinct tumor cells, either round or dendritic, with no mitoses. (If there are multiple confluent dermal melanomas, this is referred to as *dermal melanomatosis*). About 80% of these tumors are in horses older than 6 years[2] or between 5 and 15 years[3] and are much more common in gray horses. Most of these tumors occurred in typical locations. Of 14 cases available for follow-up in one study,[2] eight had malignant behavior, as demonstrated by metastases.

In another study, clinicopathologic characteristics of cutaneous melanomas occurring in 83 Camargue-type gray-skinned horses showed that the tumors occurred most frequently underneath the tail (93.9%) and at high rates in the perianal region (43.0%), lips (33.0%), and eyelids (24.0%) but rarely in the vulva (3.8%).[4] Microscopic examination indicated that these tumors were composed mostly of melanocytes and numerous melanophages, and that these cells manifested a remarkable cellular atypia. Early stages of the tumors occurred in close association with apocrine sweat glands but not at the dermal-epidermal junction.

A clinical study was conducted on 296 gray horses of the Lipizzaner breed.[5] Of the 296 horses, dermal melanomas were present in 148 horses (50%), 68 of which were older than 15 years; 51 of these were melanoma bearing. In 75.6% of cases, melanotic tumors were detected underneath the tail. None of the affected individuals had any severe clinical effect or was handicapped in performance. The authors concluded that in contrast to melanomas in solid-colored horses, characterized by early metastases, melanomas in gray horses showed less malignancy. Affected individuals often had encapsulated nodules or structures similar to human blue nevi. This finding at least

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partially reflects confusion in terminology between true malignant melanomas and dermal melanomas.

Anaplastic malignant melanomas are composed of sheets of extremely pleomorphic epithelioid cells with poor pigmentation and many mitoses. These are usually seen in horses older than age 20 and occur in horses of any color. Metastasis usually occurs first to the regional lymph nodes, then to the lungs, spleen, and liver. Hematogenous spread may also occur. Metastatic growths may be larger than the primary lesions and softer in consistency.

In regard to treatment, one study reported good success with excising dermal melanomatosis from the perineal, perianal, perirectal, or ventral tail regions.[6] In a study of three horses, cimetidine (2.5 mg/kg PO q8h) was shown to decrease the number and size of melanoma growth.[7] However, another study of 10 horses found that cimetidine had no consistent effects on either the number of tumors or the tumor surface area over the 16 weeks of treatment at 5 mg/kg PO q12h.[8] Another article noted a cure rate of 81% for melanomas treated with intratumoral injections of cisplatin.[9] A recent article reported significant tumor regression when injecting interleukin-18– and interleukin-12–encoding plasmid DNA into the tumors of horses with metastatic melanomas.[10]

Bovine Melanomas

Melanomas represented a large proportion of the cutaneous neoplasms of cattle in an older study.[11] The majority are benign, well-differentiated tumors, subcutaneous in location, and without site predilection. Dark-haired cattle are predisposed, particularly the Aberdeen Angus breed. There is no gender predilection.[11] Melanomas usually occur in young cattle and are occasionally recognized as congenital lesions.[12]

Caprine and Ovine Melanomas

Melanomas have been observed only rarely in sheep and goats.[11-14] A survey of 800,000 slaughtered goats revealed only 5 melanomas.[12] The most common site for melanomas in the goat is the perineal region,[13] although there is a case report of a malignant melanoma occurring in the coronary band region.[14] Melanomas in Angora goats histologically resemble the corresponding tumors in humans.[15]

Cutaneous Lymphosarcoma

Stephen D. White

Equine Lymphoma

Cutaneous lymphoma has occasionally been reported in horses.[1-8] Both T-cell and B-cell forms have been reported.[9,10] Lesions present as either cutaneous or subcutaneous nodules. Diagnosis is made by biopsy and, ideally, immunohistochemistry to determine cell type.[7,8] In one horse, progesterone receptors were demonstrated on the lymphoma (B) cells, and the lesions regressed after removal of an estrogen-secreting ovarian tumor.[4] This horse also had a history of partial regression of its tumor after administration of a synthetic progestin, altrenogest (0.044 mg/kg PO once daily for 10 days). Another horse demonstrated reduction in tumor size after administration of another synthetic progestagen, megestrol acetate (0.2 mg/kg PO once daily for 8 days), as well as a local injection of 20 mg betamethasone into a mass.[5] Clearly, treatment is far from standardized, but the progesterone drugs may offer a reasonable treatment modality. Lymphosarcoma is discussed in Chapter 37.

Bovine Lymphoma

Cattle occasionally are affected by cutaneous lymphoma. The presentation is multifocal intracutaneous nodules, often accompanied by alopecia. Lymphadenopathy, leukocytosis, and lymphocytosis are often present, and internal organs may be affected.[11] The juvenile form is not necessarily associated with the bovine leukemia virus (BLV) and is of T-cell origin.[12]

Ovine Lymphoma

There are rare reports of cutaneous lymphoma in sheep.[13,14]

Cysts

Stephen D. White

Cutaneous cysts are benign lesions characterized by an epithelial wall with keratinous contents. Cutaneous cysts are subdivided into several types on the basis of their histopathologic features.

Epidermal Cysts

Among large animals, epidermal cysts have been reported in horses,[1] cattle,[2] and sheep.[3] These cysts may be more properly called *follicular cysts* because the epithelial lining is probably most often derived from the follicular epithelium rather than the epidermis. The cysts can be found anywhere on the body, single or multiple, congenital or acquired, and generally range in size from 0.2 to 3 cm in diameter. The cysts are covered by intact epithelium and generally do not attach to the overlying epidermis. Microscopically, epidermal cysts consist of a wall of stratified squamous epithelium surrounding a keratin-filled lumen. Epidermal appendages are not associated with the cyst wall, a feature that distinguishes epidermal from dermoid cysts.

Epidermal cysts are thought to originate from occlusion of a hair follicle or by traumatic implantation of the epidermis. A tentative diagnosis may be made by performing fine-needle aspiration of a lesion and obtaining a fluid that is clear to brownish in color. Aspiration of the contents may temporarily decrease the size of the cyst, but it typically refills. Definitive diagnosis is made by excisional biopsy, which is curative. Epidermal cysts are benign lesions, although painful inflammatory responses and ulceration may result if the cyst is ruptured, with extrusion of contents into the adjacent dermis and subcutis.

Dermoid Cysts

Dermoid cysts are very similar clinically to epidermal cysts but are much less common. Among large animals, they have been identified in horses,[1] goats,[4] and cattle.[5] In cattle, dermoid cysts may be congenital, have been reported to be as large as 10 cm (4 inches) in diameter, and are said to develop most frequently over the cranial area of the thorax[5] and in the pharyngeal region. In horses, dermoid cysts may be single or multiple and are observed most frequently along the dorsal midline between the withers and the croup. Dermoid cysts are believed to result from displacement of embryonic cells into the subcutaneous tissue. They can be distinguished histologically from epidermal cysts by the presence of epidermal appendages within the wall of the cyst and by a lumen that often contains hair and secretions from sebaceous and sweat glands in addition to keratin. As with epidermal cysts, surgical excision is diagnostic and curative.

Dentigerous Cysts

Dentigerous cysts are a congenital defect recognized in horses and are believed to be the result of an abnormality of the first branchial cleft.[6] Clinically, a unilateral saclike swelling that contains embryonic teeth is seen at the base of the ear. The lesion may be firmly attached to the concheal cartilage or temporal bone. Dentigerous cysts tend to fistulate. Treatment consists of surgical excision.[6] Dentigerous cysts have also been reported in sheep and are suspected of being related to a nutritional deficiency of copper.[7]

Wattle Cysts

Wattle cysts are found in goats and usually are present at the base of the wattle. Nubians and Nubian crossbreeds may be predisposed to developing these cysts. The cysts are congenital, but they may not be apparent until the animal is several months old. Tentative diagnosis is based on aspiration of clear fluid, which will temporarily decrease the size of the cyst. Surgical excision is diagnostic and curative.

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Histologic examination reveals a cyst wall composed of one or two layers of cuboidal to columnar epithelial cells. The cyst cavity contains homogeneous, amorphous basophilic substances.[7]

Environmental Diseases

Stephen D. White

Frostbite

Frostbite is an uncommon injury among healthy, well-nourished animals, with all species being susceptible. It is caused by prolonged exposure to subfreezing temperatures. The length of time needed to cause frostbite depends on the ambient temperature, area of the body exposed, and health status. The areas most often affected by cold injury include the ears, tail, teats, scrotum, and distal legs.

Frozen tissue must be handled gently and thawed rapidly in warm water 38° C to 44° C (100.2° F to 111.1° F) as soon as possible after it is known that refreezing can be prevented. Tissue damage is greatly increased if thawing and subsequent refreezing occur (freeze/thaw–freeze/thaw syndrome). Tissue thawing is painful, and analgesics should be administered. Slow thawing is less painful than rapid thawing but results in much greater tissue damage. Frozen tissue should not be massaged during warming. Damaged areas are best left exposed during the healing process rather than covered with occlusive dressings, and premature débridement should be avoided because more tissue may be viable than first apparent. The animal should be given good supportive care and may have to be restrained to prevent self-mutilation. Management practices should be changed to prevent recurrence. Tissues previously damaged by freezing are more susceptible to cold injury when reexposed to subnormal temperatures.[1,2]

Photosensitization

Photosensitivity is an abnormal reaction of the skin when exposed to light. Photosensitivity in the horse is usually caused by a photodynamic agent in or on the skin that absorbs or transfers energy from light and transfers it to body cells. The activating light is generally in the ultraviolet A (UVA) range (320 to 400 nm). Melanin in the skin screens UV light, thereby limiting photosensitivity reactions to the white and light-colored areas of the body.[3]

Photodynamic agents may be drugs, topical medications, foodstuffs, contactants, or excessive phylloerythrin from liver disease. Examples of plants containing photodynamic agents follow:

Common Name	Scientific Name	Agent
St. John's wort	*Hypericum perforatum*	Hypericin
Buckwheat	*Polygonum fagopyrum*	Fagopyrin
Perennial ryegrass	*Lolium perenne*	Perloline
Whiteheads	*Sphenosciadium capitellatum*	Unknown

In addition, we have sometimes seen alfalfa or clover induce a photosensitivity reaction; these plants have been suspected to contain either an ingested or contact photodynamic agent. Additional reports describe photosensitivities apparently induced by the ingestion of gluten in horses and of cocoa shells in calves.[4,5]

As horses ingest plants containing chlorophyll, this molecule is degraded by bacteria in the intestine into the porphyrin, phylloerythrin. Some phylloerythrin is normally absorbed into the portal circulation, removed by the liver, and excreted by the bile. In liver disease the hepatic excretion of phylloerythrin is decreased, leading to excessive levels in the peripheral circulation and eventually in the skin, causing photosensitivity in about 25% of horses with liver dysfunction.[6-8] One of the more common reasons for liver disease in the United States is ingestion of the following plants containing pyrrolizidine alkaloids:

Common Name	Scientific Name
Common groundsel	*Senecio vulgaris*
Ragwort, stinking Willie	*Senecio jacobea*
Tarweed	*Amsinckia intermedia*
Rattleweed	*Crotalaria* spp.
Salvation Jane	*Echium lycopsis*

Consumption of alsike clover *(Trifolium hybridum)* may induce hepatic dysfunction (with histologic lesions distinct from those caused by pyrrolizidine alkaloids), leading to photosensitization signs (alsike clover poisoning, dew poisoning). Cases seem to be correlated to years with heavy rainfall and ingestion of the plant blossoms.[9]

Ingested plants and feed should be noted and collected for future analysis. Environmental considerations include the type of pasture (or other material) with which the animal is in contact, the amount of time the animal is exposed to sunlight, any seasonality of the condition, and any other horses involved. A seasonal incidence would tend to negate liver disease; multihorse involvement should arouse suspicion of an ingested or contact photosensitizer. A thorough history of recent drug therapy should be obtained.

Physical examination usually reveals lesions limited to the hairless, white, or lightly pigmented areas of the skin. The involved skin is erythematous, swollen, and painful. The lesions may progress to serum exudation, thickening, fissuring, and in severe cases, necrosis and sloughing (Fig. 40-15).

Therapy is related to etiology. Chronic liver disease carries a guarded prognosis. Removal of feedstuffs containing photodynamic agents, or removal of the horse from a pasture with plants containing these agents, will usually result in full recovery if the horse is also kept out of the sun for 1 to 2 weeks. Corticosteroids are helpful in controlling inflammation and pruritus. Oral prednisolone at 1 mg/kg daily for 1 week, then halving the daily dosage for a second week, is an effective regimen.

Skin Disorders of Unknown or Genetic Origin

Stephen D. White

Equine Seborrhea

Several possibly related equine skin diseases characterized by scaling and crust formation are referred to as *seborrhea.* Contrary to claims in the older literature, there is little evidence that seborrhea is related to excess sebum production by the sebaceous glands. Most types of seborrhea are probably diseases of abnormal cornification (development of the stratum corneum). Further, most cases reported as "generalized seborrhea" in the horse were probably pemphigus foliaceus, equine sarcoidosis (chronic granulomatous disease), or some other immune-mediated or autoimmune disease. Mane and tail seborrhea is typified by moderate to heavy scaling, with minimal or no pruritus. Some horses have considerable alopecia of the tail.

Cannon keratosis is a common equine skin condition. It involves the cranial surface of the rear cannon bone region and rarely the forelimbs. The lesions consist of areas of scaling and crusting with varying degrees of alopecia. There is no pruritus or other signs of inflammation. Cannon keratosis occurs in both males and mares, so there is no basis for the theory that the condition is caused by urine splatter ("stud crud").[1] In a recent report, the response to treatment with 4 topical preparations was evaluated in an 11-year-old Morgan horse mare with histologically confirmed quadrilateral cannon hyperkeratosis. Each limb was treated for 30 days, and response to treatment was evaluated both histologically and visually. A water-based emollient and 0.1% tacrolimus ointment produced encouraging clinical responses.[2]

Linear Keratosis and Linear Alopecia

Linear keratosis and linear alopecia are rare equine dermatoses of unknown cause. There is one report in a cow.[3] Lesions do not follow blood or lymphatic vessels, nerves, or dermatomes. Because both

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FIG. 40-15 Photosensitization. **A,** White blaze of a horse is selectively affected. **B,** White stocking of a horse is selectively affected. **C,** Area around eye where hair is less dense is most severely affected.

conditions coexist in some horses, it has been suggested that they are variations of the same abnormality, and we have seen one case where both histologic presentations were simultaneously present in the same clinical lesion. Both conditions have been seen in a wide variety of breeds, but Quarter Horses appear to be predisposed. Most horses develop lesions between 6 months and 5 years of age.

Linear alopecia is characterized by gradual development of annular areas of alopecia, usually in a linear, vertically oriented configuration. One or more linear areas may be present. The lesions are usually 2 to 10 mm wide by a few centimeters to over 1 m in length and occur on the neck, shoulder, and lateral thorax. Mild surface scale and crust may be present. Lesions are neither painful nor pruritic. Affected horses are typically otherwise healthy.

Linear keratosis is characterized by the gradual asymptomatic occurrence of one or more unilateral, linear, vertically oriented bands of hyperkeratotic papules that progress to marked hyperkeratosis and alopecia. We have seen one case where the lesions were confined unilaterally to the jugular furrow (Color Plate 40-10). Lesions vary from 0.25 to 3.5 cm in width by 5 to 70 cm in length and occur most often over the neck, shoulder, and lateral thorax. Lesions have also been reported to involve the legs, hip, and pectoral region. Again, affected horses are typically otherwise healthy.

These disorders are visually distinctive. Histopathologic findings in linear alopecia include early lymphocytic, infiltrative mural folliculitis and later granulomatous, infiltrative mural folliculitis. The mural infiltrate is often directed at the middle area (isthmus) of the follicle. Sebaceous glands may be involved in some cases, and complete follicular destruction and permanent alopecia are seen in severe chronic lesions. Histopathologic findings in linear keratosis include irregular to papillated epidermal hyperplasia and marked compact orthokeratotic hyperkeratosis.[4] We have seen one horse with lesions grossly diagnosed as linear keratosis, whereas the histopathology had features of both conditions.

Neither condition is known to undergo spontaneous resolution. Owners should be advised of the potential hereditary nature of these disorders. Linear alopecia has been anecdotally reported to respond to topical or systemic glucocorticoids, but recurrence is likely. Response to therapy is more likely to be seen in early lesions, when complete destruction of hair follicles has not occurred. Linear keratosis responds poorly to treatment. Topical keratolytic and keratoplastic agents, such as sulfur/salicylic acid–containing shampoos or 50% propylene glycol, can reduce the hyperkeratosis but must be continued for life. We have had some success using tacrolimus (Protopic 0.1% ointment [Astellas Pharma US]), a drug similar to cyclosporine but better absorbed through the skin, once or twice daily. Because neither condition is symptomatic, observation without treatment may be an acceptable approach. Interestingly, a report exists of a familial incidence of linear epidermal nevi in Belgian horses.[5]

Albinism

Complete and partial albinism occurs in cattle, sheep, and horses. It is a genetic defect (probably autosomal recessive) in melanin synthesis, resulting in white skin, white hair, pink eyes, and photophobia. In horses, albinism must be distinguished from *lethal white syndrome,* which is primarily a problem in Paint horses (especially, but not exclusively, in overo breedings). The defective gene has also been found in American Miniature Horses, half-Arabians, Thoroughbreds, and cropout Quarter Horses (foals born to registered Quarter Horses that have too much white to register with the AQHA).[6] The Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status (www.vgl.ucdavis.edu/service/horse/index.html).

The lethality of albinism in horses comes from the association with intestinal aganglionosis. The foals die shortly after birth. Because some white foals are not affected, euthanasia should be performed only after signs of intestinal malfunction occur. This disease is similar to Hirschsprung disease in humans and is linked to a mutation in the endothelin-B receptor gene.[7]

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Juvenile Arabian Leukoderma (Arabian Fading Syndrome, Pinky Syndrome, Hereditary Vitiligo)

Loss of melanin in the skin (depigmentation) occurs in young Arabian horses 6 months to 2 years of age (Fig. 40-16, *A*). The areas most frequently affected are periocular tissues, muzzle, genitalia, anus, perineum, inguinal region, and undersurface of the base of the tail. Depigmentation may persist, repigment, or wax and wane. The condition is probably hereditary.[1]

Vitiligo

This condition is best defined as "idiopathic depigmentation." Typically, no trauma has occurred to produce the loss of pigment, and other skin structures are not affected (i.e., no scarring or alopecia) (Fig. 40-16, *B;* Color Plate 40-11). There is no known treatment for vitiligo. The condition may be seen in any species although is perhaps best recognized in the horse.

Reticulated and Hyperesthetic Leukotrichia

Reticulated leukotrichia occurs mainly in Quarter Horses, usually as yearlings, and occasionally in other breeds. The lesions occur on the dorsal midline and consist initially of linear crusts arranged in a characteristic cross-hatch pattern (Fig. 40-17). The crusts shed, alopecia occurs, and white hair grows in permanently. There is leukotrichia without leukoderma (depigmented skin). Histologically, these lesions resemble an epidermal form of erythema multiforme, resulting in individual keratinocyte necrosis. *Hyperesthetic leukotrichia* is a similar disease both clinically and histologically, except the crusts are extremely painful to the touch. Within a few weeks, white hairs appear in the affected areas. The crusts resolve, and the pain subsides in 1 to 3 months, but the leukotrichia persists. Several cases have been linked to recent rhinopneumonitis vaccination. These diseases may rarely recur, and there is no known effective treatment.[7]

Hereditary Equine Regional Dermal Asthenia (Hyperelastosis Cutis)

Hereditary equine regional dermal asthenia (HERDA) occurs early in life in horses. Most affected horses are Quarter Horses, but registered Paint horses and Appaloosas with Quarter Horse lineage have developed this disease.[8,9] Many of the Quarter Horses are from high-quality cutting lines. Reported cases have been from North America, but the disease and its associated genetic defect have been reported from Europe and South America.[10-13] The disease (or similar condition) has also been reported in a crossbred Arabian mare, a thoroughbred gelding, a Hanoverian foal, and a Hafflinger horse.[14-17] Rarely, a similar disease has been noted in cattle, termed *dermatosporaxis;* this is caused by mutations in the procollagen I N-proteinase gene.[16,18]

The working hypothesis for HERDA in horses is a defect in the structure or healing process of the collagen fibers in the middle to deep dermis. Affected horses have less cutaneous tensile strength than healthy horses.[19] Typically, these areas are over the back and sides of the neck (Fig. 40-18). The skin in these areas may be easily torn or stretched and often develops seromas and hematomas ("blisters" filled with either serum or blood). Healing is usually adequate but often leaves unsightly scars. Diagnosis is often based on the clinical signs alone; histologic findings are sometimes subtle, but "clumped" or poorly organized collagen fibers below the level of the hair follicles may be seen. A zone of middermal to deep dermal separation has been reported in two horses and is present in some biopsy

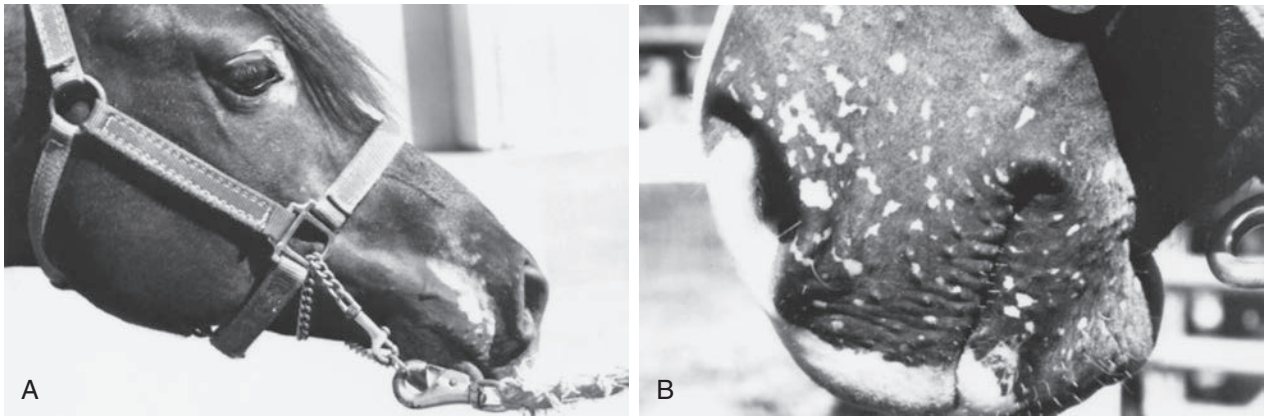


FIG. 40-16 **A,** Juvenile Arabian leukoderma. **B,** Vitiligo in a horse. *(Courtesy Dr. Anthony Stannard.)*

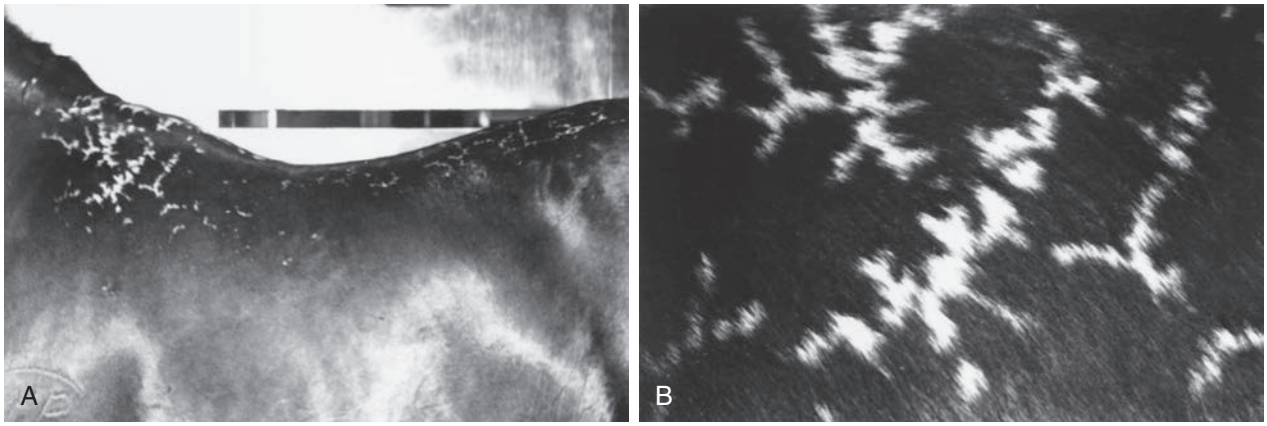


FIG. 40-17 Reticulated leukotrichia in a yearling Quarter Horse. *(Courtesy Dr. Anthony Stannard.)*

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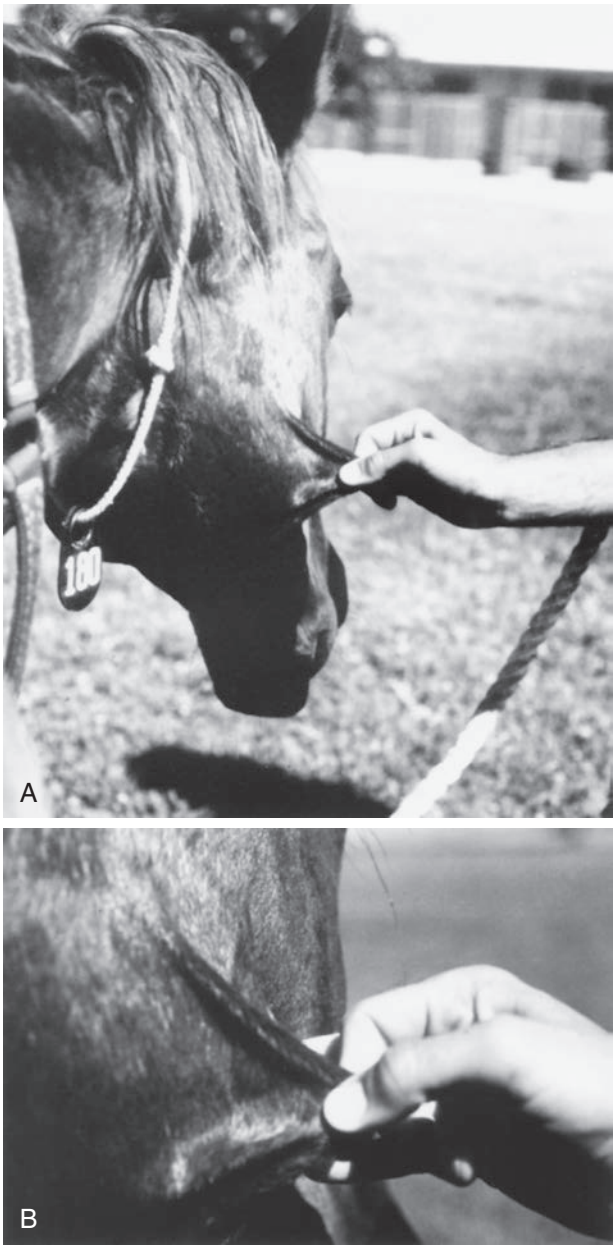


FIG. 40-18 **A,** Hereditary equine regional dermal asthenia (HERDA, hyperelastosis cutis) in a horse, showing hyperextensible skin. **B,** Close-up of A. *(Courtesy Dr. Anthony Stannard.)*

samples.[9,20] Poorly oriented collagen fibers are sometimes seen on electron microscopy. Interestingly, affected horses may have decreased corneal thickness, increased tear production, and increased incidence of corneal ulcers.[21]

This condition is almost certainly present at birth, but HERDA is often not noticed until about 2 years of age, when horses start being trained with tack and saddle, and the resulting friction and trauma induce the typical lesions.[22] As with many genetic diseases, no effective treatment or cure exists; some of these horses have been maintained as "pasture pets."

This disease follows an autosomal recessive mode of inheritance, so in order for the foal to be affected, both the sire and dam must carry the gene, and if they were bred again, there would be about a 25% chance that the next foal would also be affected.[23] Recently a genetic marker was determined for this disease.[24] The marker relates to a missense mutation in equine cyclophilin B (PPIB), which in recent work has been shown to cause a functional defect in this protein, resulting in less effective catalysis of the rate-limiting step in collagen folding.[25] The Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier or affected status (http://www.vgl.ucdavis.edu/service/horse/index.html). Both carriers and clinically affected horses with HERDA should be removed from breeding programs.

Epidermolysis Bullosa

Epidermolysis bullosa (EB) includes a number of diseases typified in humans and animals by the common finding of blister formation after minor trauma. Most forms are congenital and apparent soon after birth. In animals and humans, subsets of EB are classified by the histologic location of the blister or cleft. These subtypes (and respective cleft location) are termed *EB simplex* (basal cell layer of epidermis), *junctional EB* (intralamina lucida or basal cell layer), and *dystrophic EB* (sublamina densa).

Junctional EB has been reported in Belgian foals of both genders, in other breeds, and in a donkey.[26-29] Lesions are usually noted within 3 days of birth and include multiple asymmetric skin erosions and ulcers, often encrusted. Lesions may be especially prominent around the coronary bands (causing the hoof to crack and slough) and on the oral, anal, and genital mucosa. Histology and ultrastructural findings indicate a cleft in the intralamina lucida of the basement membrane zone. This is presumably caused by a defect in the anchoring filaments that connect the basement membrane to filaments in the superficial dermis.[27] A laminin-5 (laminin 3A32) defect has been demonstrated in Belgians and in two French draft breeds, Trait Breton and Trait Comtois; the mutation is a cytosine insertion in exon 10 of the LAMC2 gene.[30-32] Because of this knowledge, the Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status in Belgian draft horses and related breeds (www.vgl.ucdavis.edu/service/horse/index.html).

Clinical presentation and the age of the foal are highly suggestive of EB diagnosis. Histology and, ideally, electron microscopy are required to confirm the diagnosis. There is no known treatment, and affected horses as well as the sires and dams of affected horses should not be bred; the mode of inheritance is autosomal recessive.

The disease previously known as *epitheliogenesis imperfecta* in Saddlebreds is now recognized as *junctional epidermolysis bullosa.* Lesions are most common on the limbs, head, and tongue. Hooves may slough in severe cases. Clinical presentation is usually diagnostic.[33-36] In moderately to severely affected animals, the disease is fatal within a few days; the foals die of septicemia or other developmental abnormalities. Mildly affected areas may heal by scar formation.

Ruminants

Epidermolysis bullosa has been reported in cattle and sheep. The simplex form has been reported in Angus and Friesian-Jersey crossbred cattle (in the latter, a keratin 5 defect was noted), junctional EB in a Charolais calf (deficient expression of an epidermal integrin), and dystrophic EB in Brangus calves.[37-40] In sheep, dystrophic EB in the white Alpine, Assaf, Suffolk, South Dorsett Down, and black face Scottish breeds has been shown or theorized to involve mutations in the gene encoding for collagen VII.[41-44] Junctional EB has been described in German black-headed mutton sheep, with a defect traced to the formation of laminin 332, similar to the defect in the Belgian horses.[45] Clinical signs of EB in ruminants are similar to those seen in horses, with ulcers, especially around the coronary band and in the oral cavity.

Eosinophilic Granuloma (Nodular Necrobiosis, Collagenolytic Granuloma)

Eosinophilic granuloma is the most common equine nontumor nodular disease in our practice. In most cases the etiology is unknown, although a hypersensitivity reaction to insect bites has been suggested. There is no apparent age, breed, or gender predilection. The

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FIG. 40-19 Eosinophilic granuloma (nodular necrobiosis) with dermal nodules on a horse's withers. *(Courtesy Dr. Anthony Stannard.)*

disease often begins in warmer months. Lesions up to 5 cm (2 inches) in diameter may be single or multiple and most often affect the neck, withers, and back (Fig. 40-19). Skin biopsy reveals multifocal areas of abnormal-staining collagen surrounded by granulomatous inflammation containing eosinophils, lymphocytes, and histiocytes.[1] This is not thought to be caused by degeneration, but rather by degranulation of eosinophils and the coating of normal collagen fibers with the degranulated material.[46]

Development of equine eosinophilic granuloma has been noted in areas of previous injections using standard silicone-coated, stainless steel hypodermic needles.[47] The reaction may occur at sites of IV and IM injections. Lesions consist of nonpainful cool, raised papules or nodules 0.25 to 1 cm in diameter at sites of previous injection. The nodule appears 24 to 48 hours after the injection, and the subsequent eosinophilic granuloma can persist for months to years. Affected horses do not develop a lesion at the site of injection if nondisposable, noncoated needles are used. The use of the noncoated needles is recommended for any horse that develops injection-site collagenolytic granulomas.

Horses with solitary or a few lesions may be treated by surgical excision (not in the saddle area) or glucocorticoid injections under the lesions. Triamcinolone acetonide (3 to 5 mg per lesion) is effective. It has been recommended that no more than 20 mg triamcinolone acetonide be administered at once to any horse, because any more of this drug may cause laminitis.[1] Horses with multiple lesions may be treated with oral prednisolone at 1 mg/kg once daily for 2 to 3 weeks. Multiple small (<1 cm) lesions may be indicative of insect bite hypersensitivity.

Cutaneous Amyloidosis

Cutaneous amyloidosis is an uncommon nodular dermatosis of unknown etiology. There is no age, breed, or gender predilection. The condition appears to be a primary form of amyloidosis, in that concurrent inflammatory processes are not present, and amyloid (a fibrillar protein substance derived from immunoglobulins) deposition is usually restricted to the skin and occasionally the regional lymphatics, regional lymph nodes, and upper respiratory mucosa.[1,17] One case was documented as being caused by lambda light-chain deposition from an extramedullary plasmacytoma.[48] Another horse showed amyloidosis concurrent with lymphoma.[49]

Papules, nodules, and plaques on the head, neck, shoulders, thorax, or inguinal areas are firm, 0.5 to 10 cm in diameter, nonpainful, and nonpruritic. The overlying skin is normal, although it may scale or crust in severe cases (Fig. 40-20). The course of cutaneous amyloidosis is progressive and prolonged. Megestrol acetate may be an effective treatment (0.2 mg/kg PO q24h until lesions resolve). Because certain forms of primary amyloidosis in humans have a genetic basis, it may not be advisable to use affected horses for breeding until more is learned about the genetics of the equine disorder.

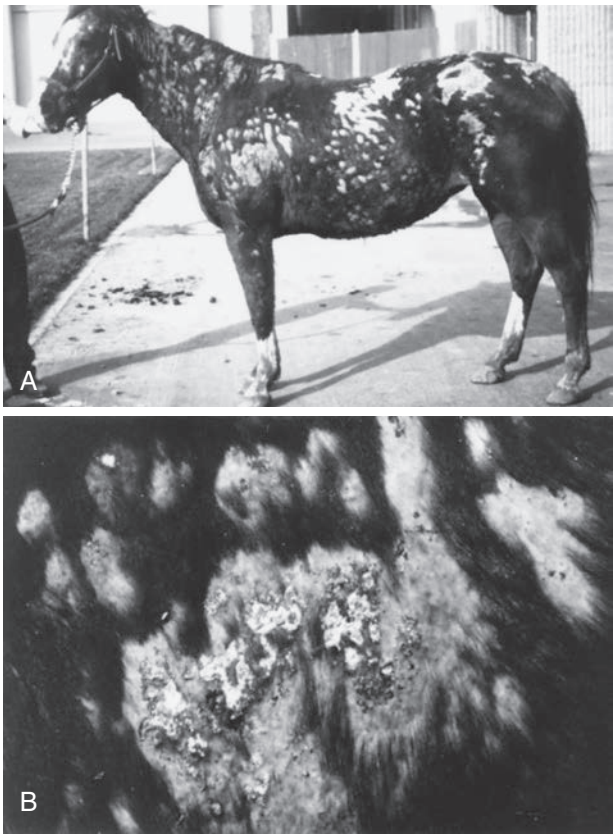


FIG. 40-20 **A,** Cutaneous amyloidosis in a horse. **B,** Close-up of skin of **A**. *(Courtesy Dr. Anthony Stannard.)*

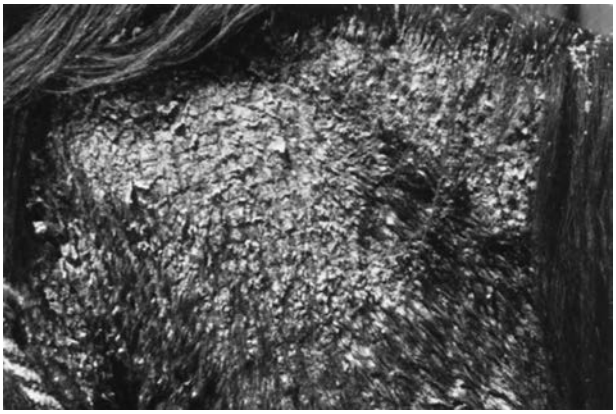


FIG. 40-21 Equine sarcoidosis (generalized granulomatous disease) in a horse. In addition to scaling and crusting skin lesions, the horse had systemic involvement. *(Courtesy Dr. Anthony Stannard.)*

Equine Sarcoidosis (Generalized Granulomatous Disease)

Equine sarcoidosis is characterized by skin lesions and usually concurrent systemic involvement. It is *not* a neoplastic disease and should *not* be confused with equine sarcoids.

The disease is infrequently encountered, and there is no known breed predilection. Geldings may be at increased risk.[50] The skin lesions typically are generalized scaling and crusting associated with varying degrees of alopecia (Fig. 40-21). Occasionally the disease is focal or multifocal in distribution. Rarely, the skin lesions consist of nodules or large tumor-like masses. The different types of skin lesions may coexist. In addition to skin lesions, the most frequent presenting complaints are weight loss, decreased appetite, and a persistent

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low-grade fever. Lung involvement is manifested by exercise intolerance, increased resting respiratory rate, and mild dyspnea.[51-53] One report showed positive titers to *Borrelia burgdorferi* in three of four horses with equine sarcoidosis,[54] another found evidence of equine herpesvirus 2,[55] and a recent report described *Mycobacterium* DNA in the liver and skin of a horse with sarcoidosis.[56] However, other investigations, using PCR, immunohistochemistry and histologic stains, were unable to demonstrate the presence of any causative organism.[49,57]

Diagnosis is by histopathology and ruling out infectious etiologies. The major histologic change is the presence of noncaseating granulomas consisting of aggregates of epithelioid cells and multinucleated giant cells. Neutrophils, lymphocytes, and plasma cells are present in small numbers. In the skin the granulomas tend to be located in the superficial portion of the dermis. Because of the small number of horses studied and the variability of clinical signs, response to therapy has not been well documented. An abstract reported that 5 of 6 horses did well and lived longer than 1 year with prednisolone treatment.[58] Another extensive review showed that some horses did well on corticosteroid therapy (usually at doses approximating those used to treat pemphigus and other autoimmune skin diseases); GI involvement was a sign of poorer prognosis.[50] Recently reported cases suggest that some horses with sarcoidosis may have localized rather than generalized skin disease, and confirm that spontaneous resolution (seemingly when the stress of working is reduced or eliminated) may occur.[58a,58b]

Chronic Progressive Lymphedema

Chronic progressive lymphedema (CPL) is the term for a condition seen in Shires, Clydesdales, Belgians, and probably other draft breeds (Color Plate 40-12). It is characterized by progressive swelling, hyperkeratosis (thickening), and fibrosis (hardening) of the skin on the lower legs. This chronic progressive disease starts at an early age, progresses throughout the life of the horse, and often ends in disfigurement and disability of the limbs. Inevitably, it leads to the horse's premature death. In the Belgian draft horse, it has reduced the average life expectancy of a stallion from 20 to only 6 years.

The pathologic changes and clinical signs closely resemble a condition known in humans as *chronic lymphedema* or *elephantiasis nostras verrucosa*. The lower leg swelling is caused by abnormal functioning of the lymphatic system in the skin, which results in chronic lymphedema (swelling), fibrosis, a compromised immune system, and subsequent secondary infections of the skin. Based on preliminary research, it appears that a similar pathogenic mechanism is involved in the disease that affects these specific draft horse breeds.

The clinical signs of this disease are highly variable. The earliest lesions are characterized by skin thickening and crusting; both are often visible only after clipping the long feathering. Secondary infections develop very easily in these horses' legs and usually consist of either chorioptic mange or bacterial infections. Both dark skin and white skin on the lower legs are equally affected. These lesions are consistent with pastern dermatitis, certainly seen in other breeds. In horses with CPL, however, these lesions do not respond well to therapy.

As the disease progresses, one or two thick skin folds and sometimes multiple small, well-demarcated ulcerations develop, predominantly in the rear of the pastern region. The ulcerations are covered with adherent crusts. Manual removal of the crusts or even movement during exercise results in bleeding. These small sores may seem to respond initially to various topical medications but often reverse course, only to progress in severity and multiply in number. Small lesions tend to coalesce into larger and more intractable (resistant to treatment) areas of skin ulceration. Over time, the lesions extend up the leg, often affecting the skin as high as the knees or hocks. These lesions are, at the very least, irritating to the horses and at times can be quite painful. Severely affected individuals often exhibit generalized swelling in all four legs.

This condition is therefore primarily a lymph system disease, and the pastern dermatitis in these draft horses is secondary to the body's inability to supply fluids properly and oxygenate the skin of the lower leg. The lymphatics break down over time, and the protein-rich fluid leaks into the tissues of the lower leg, which results in fibrosis of the tissues under the skin and thickening of the skin itself. The tissue fibrosis leads to even more blockage of fluid within the legs, inhibiting circulatory flow. This results in neovascularization, a process by which the body develops new blood vessels in a futile attempt to provide oxygen to its tissues.

Researchers suspect that a deficiency or abnormality in the connective tissue component known as *elastin* is the underlying factor and perhaps the cause of the lymphatic degeneration in these horses.[59,60] In affected animals, the lymph vessels and deep tissues of the skin do not have sufficient amounts or the proper configuration of elastin. The lack of this critical tissue element apparently instigates the progression of disease and the chronic progression of clinical signs. One report documents high levels of antielastin antibodies in affected horses.[61] A more recent report found that affected horses had increased amounts of dermal elastin in both the distal limb and neck, whereas unaffected horses of a susceptible breed had decreased amounts. These findings support an earlier hypothesis that CPL of horses is a generalized disease. Reduced efficiency of the elastic network in supporting the dermal lymphatics may explain the development of CPL.[62]

As the condition becomes more chronic, the lower leg enlargement becomes permanent, and the swelling is firm on palpation. More of the thick skin folds and large, poorly defined, firm nodules develop. The nodules may become quite large and often are described as golf ball or even baseball sized. Both skin folds and nodules first develop in the back of the pastern area. With progression, they may extend and encircle the entire lower leg. The nodules become a mechanical problem because they interfere with free movement and are frequently injured during exercise. This disease often progresses to include massive secondary infections that produce copious amounts of foul-smelling exudates, generalized illness, debilitation, and even death.[60,61]

In one report of possibly the same condition in several draft breeds, the authors found a perivascular dermatitis dominated by T lymphocytes with an increase in major histocompatibility complex (MHC) class II–positive, dendritic-like cells. Immunohistochemical labeling for cytokeratins CK5/6(4), CK10, and CK14 indicated a change in their expression pattern. This correlated with the degree of epidermal hyperplasia, indicating abnormal differentiation of keratinocytes. There was a statistically significant correlation between the severity of skin lesions and several other factors, including increasing age, increasing cannon circumference, prominence of anatomic structures (e.g., fetlock tufts of hairs, ergots, chestnuts), and bulges in the fetlock region.[63] Another more recent report, again looking at various draft breeds (Rhenish German, Schleswig, Saxon-Thuringian, and South German) identified a quantitative trait loci for CPL.[64]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 41

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Endocrine and Metabolic Diseases

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Equine Endocrine and Metabolic Disorders

Dianne McFarlane, *Consulting Editor*

Pituitary and Hypothalamus

Dianne McFarlane

Physiology of the Equine Hypothalamic-Pituitary Axis

The pituitary gland is composed of two embryologically distinct portions: an adenohypophysis, derived from invagination of the pharyngeal epithelium known as *Rathke's pouch,* and the neurohypophysis, derived from neural tissue of the hypothalamus. The adenohypophysis can be further divided into the pars distalis, pars tuberalis, and pars intermedia. The pars distalis contains five different endocrine cell types, each of which is responsible for the release of a unique hormone or set of hormones in response to hypothalamic releasing factors delivered from the median eminence via the hypothalamic-hypophyseal portal system. The pars tuberalis is a highly vascular band of cells surrounding the pituitary stalk. The pars tuberalis is rich in melatonin receptors and is believed to be involved in regulating the seasonal rhythm of reproductive hormone production.[1] The neurohypophysis or pars nervosa is a collection of nerve axons and terminals that originate in the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin and arginine vasopression (antidiuretic hormone) produced in the cell bodies of these nuclei are transported into the pars nervosa for storage and eventual release into the systemic circulation.

The pars intermedia of the horse incorporates tissue derived from both the adeno- and neurohypophysis.[2] It is composed of a single endocrine cell type, the melanotrope. Melanotropes are directly innervated by nerve terminals of the hypothalamic periventricular dopaminergic neurons. These originate in the periventricular nucleus of the hypothalamus adjacent to the third ventricle, project through the infundibulum, and terminate in the pars intermedia (Fig. 41-1).[3] These neurons release the neurotransmitter dopamine, which acts to tonically inhibit the release of hormones from adjacent melanotropes. Dopamine released from the nerve terminals interacts at dopamine (D2) receptors on the melanotropes to inhibit cell proliferation, transcription of proopiomelanocortin (POMC), and release of POMC-derived peptides.[4] Additional regulatory signals to the pars intermedia may be delivered by direct systemic arterial supply and from the hypothalamic-hypophyseal portal veins.[5] In addition to being under tonic inhibition, melanotropes are also positively regulated by thyrotropin-releasing hormone (TRH), which stimulates hormone release from melanotropes.[6] Additional regulatory molecules likely exist but at this time are poorly defined in the horse.

The primary product of the melanotrope is the hormone precursor protein POMC, which is also expressed by the corticotropes of the pars distalis. However, due to differential post-translational processing by proteases called *prohormone convertases,* each cell type secretes a different complement of POMC-derived peptides (Fig. 41-2). Due to the action of prohormone convertase I, POMC in corticotropes is primarily processed into adrenocorticotropic hormone (ACTH). ACTH circulates to the adrenal cortex, where it stimulates secretion of cortisol. Melanotropes contain active prohormone convertase I and II, and therefore POMC in the pars intermedia (PI) is cleaved into the secretory peptides, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide (CLIP). A small amount of ACTH may also be produced. Further processing of the peptides, including cleavage of C-terminal amino acids and *N*-acetylation, serves to control the activity of the final peptide product. For example, the most abundant form of β-end produced in the normal horse's pars intermedia is Ac-β-end (1-27), which lacks opioid activity. The most abundant β-end in horses with pituitary pars intermedia dysfunction (PPID) is β-end (1-31), which is an opioid agonist.[7]

The physiologic role of the pars intermedia POMC-derived peptides, α-MSH, β-end, and CLIP, has not been extensively studied in the horse. In other species, α-MSH has several diverse actions, which are mediated through interaction with one of five distinct G-protein–coupled melanocortin receptors. α-Melanocyte stimulating hormone is named such due to its ability to induce skin pigmentation in amphibians. Its role in pigmentation is through interaction with melanocortin receptor 1 (MC1R), which is predominantly expressed in skin. In horses, mutation of the *MC1R* gene is associated with the chestnut coat color.[8] In white Camarque horses the degree of coat pigmentation is directly correlated to the plasma concentration of α-MSH.[9] α-MSH is also an integral mediator in control of energy homeostasis. MC3R and MC4R are both expressed in the central nervous system (CNS), particularly in the hypothalamus, where they function in the leptin-melanocortin pathway, regulating appetite-satiety balance and fat metabolism.[10] Animals and humans lacking functional MC3R or MC4R are obese, and melanocortin receptor defects are a common monogenetic cause of obesity in humans.[11] Plasma α-MSH concentration in obese men has been reported to be higher than in lean men.[12] It has been suggested high plasma concentration in obese individuals may be an attempt to maintain

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homeostasis in individuals with a defect in MC4R. Plasma α-MSH concentration was also found to be positively correlated to obesity in horses.[13]Another function of α-MSH is as a potent antiinflammatory agent.[14] α-MSH has been demonstrated to have multiple immune-modulating effects. Its most profound effect is in regulation of cytokine response. α-MSH inhibits activation of NF-κB by lipopolysaccharide (LPS) and interferon-γ (IFN-γ). Recent data in mice have suggested that α-MSH may suppress LPS-mediated inflammation by facilitating the interaction of IRAK and IRAK-M.[15] IRAK is a kinase that functions in activation of NF-κB following TLR-4 (the receptor for bacterial LPS) stimulation.[15] IRAK-M is a negative regulator of IRAK. As a result, NF-κB activation and proinflammatory cytokine release of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are all decreased following α-MSH administration. Fever and other clinical evidence of inflammation are also reduced. In addition, α-MSH also inhibits neutrophil function, including adhesion, chemotaxis, and oxidative burst.[16-17]

β-End is a known endogenous opioid. Secretion of β-end provides analgesia and behavioral modification. It also suppresses immune responsiveness and has effects on vascular tone.[18-19] Corticotropin-like intermediate lobe peptide (CLIP, ACTH 18-34) has not been extensively studied in any species. In pancreatic islet cells in culture CLIP was shown to be a pancreatic β-cell secretagogue, stimulating the release of insulin.[20] However, when administered to rats by either intraperitoneal or intraventricular injection, ACTH but not CLIP resulted in release of insulin and decrease in blood glucose.[21]

A distinct seasonal effect on the activity of the pars intermedia of horses and ponies has been demonstrated in horses residing in tropical and temperate environments.[22-28] Plasma α-MSH concentration is considerably higher in horses and ponies in August through October, compared with samples collected in the winter, spring, and early summer. An effect of season on α-MSH concentration has been described for humans, hamsters, and sheep.[29-31] The functional importance of the seasonal cycle is unknown, but several physiologic events occur in parallel with the α-MSH cycle. In sheep, body weight, voluntary food intake, and condition all peak simultaneously with α-MSH, with seasonal maximums occurring in September. Soay sheep with surgically created hypothalamic-pituitary disconnection have an increase in circulating concentration of α-MSH and chronic increase in body weight.[30] These findings suggest that α-MSH or other POMC-derived peptides may play a role in metabolic preparation for winter in sheep. It is possible that horses and ponies have a seasonal increase in POMC-derived peptides to metabolically prepare them for a decrease in accessible food observed in the wild in winter. If so, dysregulation of this pathway might be associated with abnormalities in body weight and fat storage. Weight loss and abnormal fat distribution are two clinical signs associated with equine PPID. Development of a winter coat also begins as length of day decreases in the fall. The development of hypertrichosis in horses with PPID leads one to speculate that the naturally occurring seasonal increase in POMC-derived peptides contributes to development of winter coat growth. This has not been critically assessed in equids.

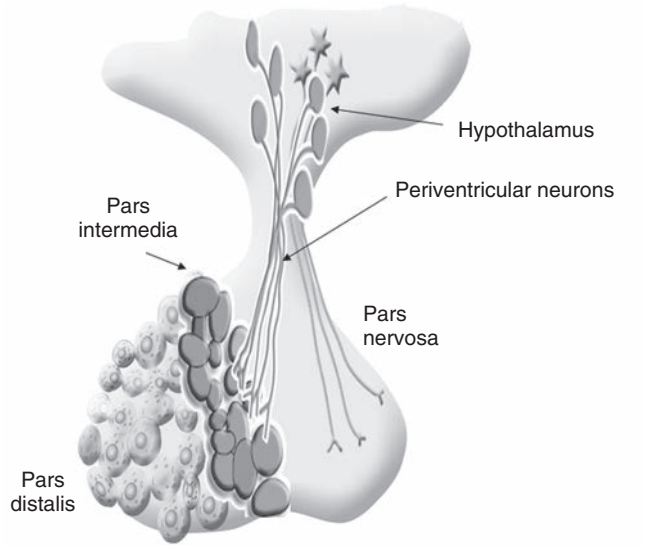


FIG. 41-1 Physiology of the equine pituitary pars intermedia. The melanotropes of the pars intermedia produce the hormone precursor protein, proopiomelanocortin (POMC), which in the pars intermedia is cleaved into the hormones, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide (CLIP). Production of POMC in the pars intermedia is under inhibitory control by dopamine released from the nerve terminals of the periventricular neurons. The cell bodies of the periventricular neurons are in the hypothalamus, adjacent to the third ventricle.

Equine Pituitary Pars Intermedia Dysfunction

Equine PPID is one of the most common diseases of horses and ponies 15 years and older.[32-34] PPID was originally termed *equine Cushing disease* because of features similar to human Cushing disease. However, in contrast to human Cushing disease, PPID affects the pituitary pars intermedia rather than the pars distalis, is typically not a neoplastic condition, and the adrenocortical contribution to the clinical syndrome is of much less importance. To avoid confusion, equine Cushing disease is now more correctly referred to as PPID.

In the past 2 decades the population of aged horses has increased dramatically. This, in conjunction with the vast amount of information available to the horse-owning public, has led to a heightened client awareness of age-associated equine health issues and a desire to promote healthy aging in their horses. As a result, diagnostic testing and treatment of horses for PPID has increased. Yet despite increased clinical recognition of this disease, much about PPID remains poorly understood.

Pathophysiology The pathologic hallmark of PPID is hypertrophy, hyperplasia, and microadenoma or macroadenoma formation in the pituitary pars intermedia with increased secretion of POMC peptides. Horses with PPID develop enlarged pituitaries that may reach five times normal weight. As the pars intermedia expands,

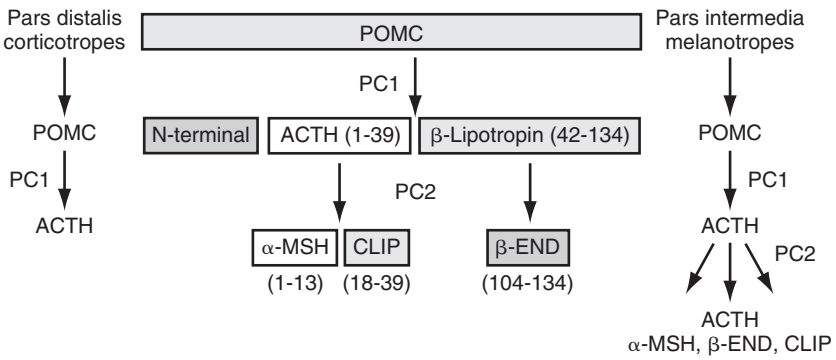


FIG. 41-2 Proopiomelanocortin (POMC) processing. POMC is cleaved by prohormone convertase I into adrenocorticotropic hormone (ACTH) in the pars distalis and into α-melanocyte stimulating hormone, β-endorphin, and corticotropin-like intermediate lobe peptide by prohormone convertase I and II in the pars intermedia. Only a small amount of ACTH is produced by the normal pars intermedia.

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it compresses the adjacent pituitary lobes and hypothalamus, often resulting in a loss of function of these tissues. In contrast, the pars intermedia remains active in horses with PPID, secreting relatively large quantities of POMC-derived peptides into the peripheral circulation. Horses with disease may have as much as a 40-fold increase in plasma concentration of pars intermedia POMC-derived peptides.[35] Clinical signs of disease likely result from a combination of increased circulating POMC peptides and loss of neuroendocrine function of adjacent tissues.

Evidence indicates loss of dopamine inhibition is critical in the pathology of PPID. Dopamine and dopamine metabolite concentrations in the pars intermedia of PPID horses are decreased eightfold compared with age-matched controls.[7] Systemic supplementation of dopamine or a dopamine agonist to horses with PPID results in a decrease in plasma concentration of POMC peptides.[35] Horses treated with the dopamine agonist pergolide show improvement in both clinical signs and biochemical abnormalities associated with disease.[36-39] Immunohistochemistry of formalin-fixed tissue showed a fivefold decrease in pituitary dopaminergic nerve terminals ($P < 0.001$) and a 50% reduction in the number of dopaminergic periventricular cell bodies ($P < 0.01$) in the hypothalamus of PPID animals.[40] Considered together, this evidence suggests a loss of functional periventricular dopaminergic neurons or "dopaminergic neurodegeneration" occurs in horses with PPID (Fig. 41-3). Loss of periventricular dopaminergic inhibition of the pars intermedia in other species results in pathologic changes similar to those of PPID. Surgical disruption of the periventricular hypophyseal dopaminergic tracts in rats results in increased expression of pars intermedia melanotropes.[4] In addition, D2 dopamine receptor knockout mice develop pars intermedia lesions similar to PPID.[41] These data suggest PPID is primarily a disease of hypothalamic origin, rather than the consequence of a spontaneously forming pituitary adenoma.

One potential cause for dopaminergic neurodegeneration is oxidative stress. Oxidative stress causes modification of cellular components including proteins, DNA, and cell membrane lipids due to excessive exposure to reactive oxygen species leading ultimately to cell death, or in the case of neurons, neurodegeneration. Dopaminergic neurons are particularly vulnerable to oxidative damage because dopamine metabolism itself produces free radicals. Horses with PPID have evidence of oxidative damage, including accumulation of pars intermedia 3-nitrotyrosine[40] and decreased plasma thiol.[42] The oxidative damage in PPID does not appear to be the result of impaired antioxidant capacity because systemic and pituitary antioxidant capacity of affected horses appears unchanged.[43]

Clinical Signs Equine PPID affects many aged equids, resulting in a variety of clinical signs including hypertrichosis (hirsutism), laminitis, muscle atrophy, fat accumulation, polydipsia, polyuria, secondary infections, lethargy, infertility, persistent lactation, sweating dysregulation, and metabolic abnormalities including hyperglycemia and hyperinsulinemia (Fig. 41-4).[44-45] The most unique clinical manifestation of PPID is an abnormally long, curly haircoat that fails to shed (previously referred to as *equine hirsutism,* although more correctly called *hypertrichosis*). Often, horse owners may report the horse sheds its winter coat slowly or incompletely in the year(s) before development of a full failure to shed. Hair may be initially retained along the legs or under the mandible (Fig. 41-5). The mechanism responsible for development of hypertrichosis in horses with PPID has not been reported. The onset of hypertrichosis in an aged horse or pony is considered essentially pathognomonic for PPID,



FIG. 41-4 Typical horse with pituitary pars intermedia dysfunction (PPID). This 22-year-old Morgan mare shows obvious hirsutism. Other clinical signs of PPID included laminitis and weight loss despite an excellent appetite.

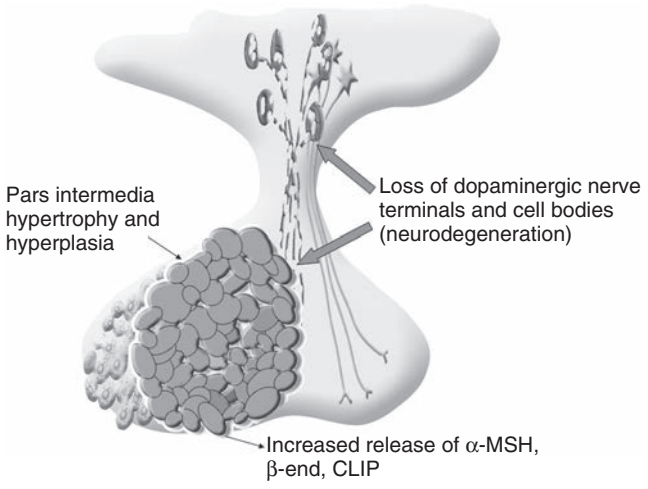


FIG. 41-3 Pathophysiology of equine pituitary pars intermedia dysfunction. Loss of functional dopaminergic periventricular neurons leads to a decrease in dopamine at the pars intermedia. This in turns results in dysinhibition of the melanotropes of the pars intermedia. The outcome is hypertrophy and hyperplasia of the pars intermedia and increased systemic release of the pars intermedia proopiomelanocortin (POMC)-derived peptides, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide (CLIP).



FIG. 41-5 Coat changes vary among horses with pituitary pars intermedia dysfunction (PPID). Retained hair along the lower limbs **(A),** under mandible **(B),** and as guard hairs and tufts along trunk **(C).**

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although the author has observed similar haircoats in severely debilitated aged animals with confirmed normal pituitary pars intermedia function.

Laminitis secondary to PPID is reported to occur in approximately 30% to 40% of diagnosed cases and can necessitate euthanasia in affected animals.[39,46-48] When adult horses with laminitis of unknown origin were examined, 30% to 70% had evidence of PPID,[49-50] suggesting PPID may be underdiagnosed, especially when laminitis is the presenting complaint and hirsutism is absent. The pathogenesis of laminitis in PPID is not currently well understood but is the subject of ongoing investigation. Historically, it has been suggested that laminitis secondary to PPID is the consequence of high circulating cortisol concentration. However, the inability to induce experimental laminitis in normal horses using corticosteroids and the absence of hypercortisolemia or adrenal hyperplasia in most horses with PPID indicates this is unlikely to be the pathogenic mechanism. More recently, a primary role for hyperinsulinemia in induction of endocrinopathic laminitis has been proposed. Several lines of evidence support this hypothesis. First, sustained administration of a high concentration of insulin or dextrose to normal horses and ponies has been shown to induce laminitis that is similar both clinically and histologically to naturally occurring endocrinopathic laminitis.[51-54] Additionally, several investigators have documented a strong association between serum insulin concentration and naturally occurring laminitis.[50,55-56]

In the author's experience weight loss due to muscle mass atrophy is the most common and possibly earliest clinical sign of PPID (Fig. 41-6). Despite weight loss, PPID horses often have a potbellied appearance and, as a consequence, owners may fail to notice the lost weight. Weight loss and muscle atrophy may result from several factors, including poor dentition, poor nutrition, heavy parasite burden, minimal exercise, and protein catabolism induced by increased cortisol activity. Histologic evidence of type 2 myofiber atrophy has been documented in muscle biopsies from horses with PPID, consistent with corticosteroid-associated muscle atrophy in other species.[57] In a small group of horses, pergolide treatment was associated with improvement in myofiber-type composition, although myofiber ratio and cross-sectional area were no different. Significant improvement in muscle mass was also observed in a large group of horses with PPID after 6 months of treatment with pergolide mesylate.[39]

Despite weight loss and muscle mass atrophy, horses with PPID often have abnormal accumulations of fat, most notably in the crest of the neck, tailbase, sheath, and superorbital fossa. This fat accumulation typically predates the weight loss and has a similar pattern as that observed in horses with equine metabolic syndrome (EMS). The similarity of the clinical signs and at-risk breeds of these two diseases has resulted in a misdiagnosis of PPID in animals that have EMS. Unlike what was previously postulated, these two conditions, PPID and EMS, are no longer considered mutually exclusive conditions. There has also been speculation that animals with EMS or sustained obesity with hyperinsulinemia may be at greater risk for developing PPID as they age. Although epidemiologic data are currently lacking to support this association, client-provided anecdotal data suggest this may warrant more critical assessment.



FIG. 41-6 Horse with pituitary pars intermedia dysfunction (PPID). The major clinical sign of disease in this horse with PPID was weight loss. Muscle mass atrophy along the dorsum, with a potbelly appearance, is characteristic of PPID.

Polydipsia and polyuria (PU/PD) occurs in some horses with PPID and is typically mild in severity.[44-48,58-59] The mechanism responsible for PU/PD may include (1) compression of the pars nervosa resulting in decreased arginine vasopressin (antidiuretic hormone) production, (2) osmotic diuresis secondary to hyperglycemia and glucosuria, or (3) cortisol induced. Cortisol is thought to cause PU/PD in other species by interfering with the secretion and/or action of arginine vasopression.[60] Evidence suggests ACTH and cortisol may inhibit the renin-angiotensin-aldosterone axis as well. The mechanism of PU/PD in horses with PPID has not been extensively examined. Glucosuria is not a common finding in horses with PPID. In one study, two PPID horses with marked hyperglycemia were found to have similar water consumption to normal horses, suggesting that osmotic diuresis is unlikely a major mechanism of PU/PD in the PPID horse.[48]

Horses with PPID have been reported to be more susceptible to infection, including endoparasitism, bacterial sinusitis, skin infections, abscesses, and respiratory infections.[44-45,58-59] The morbidity and mortality of secondary infection in equine PPID has been reported to range from 27% to 48%.[46-47,58-59] In the absence of parasite control, a heavy parasite burden is common.[61] Routine, quantitative fecal egg counts are recommended to ensure an adequate anthelmintic program. Vigilance on the part of the owner and veterinarian is important in both prevention and early recognition of infections because they may be clinically insidious. Bronchopneumonia was found at necropsy in 7 of 19 horses with PPID.[62] Bronchopneumonia should be considered in the PPID horse with fever or tachypnea and ruled out in horses with intermittent hyperhidrosis.

Diagnosis of Pituitary Pars Intermedia Dysfunction

Equine PPID is both common and life threatening; therefore early and accurate diagnosis with appropriate intervention is considered critical. Antemortem diagnosis of PPID currently relies on testing hypothalamic-pituitary-adrenal axis responsiveness or measurement of endogenous plasma concentrations of POMC-derived peptides such as ACTH. These tests have been the subject of recent evaluation, and the search for improved testing strategies is ongoing. Accepted best practices for the diagnosis of PPID have evolved significantly over the past 5 years, and further changes are likely to follow.

Currently, three antemortem diagnostic tests are most commonly used in practice settings: (1) the overnight dexamethasone suppression test (DST), (2) measurement of endogenous plasma ACTH concentration, and (3) ACTH release following thyrotropin-releasing hormone stimulation. The overnight DST was long considered the "gold standard" method of antemortem PPID diagnosis.[63] In the unaffected horse, intramuscular (IM) administration of dexamethasone decreases release of ACTH from the pars distalis, resulting in a serum cortisol concentration of less than 1 µg/dL (27.59 nmol/L) 19 hours after dexamethasone (Fig. 41-7).[63] Horses with PPID fail to suppress serum cortisol concentration due to ACTH production from the pars intermedia. Although originally this test was reported to have a sensitivity and specificity of 100%, horses included in that study were selected for having end-stage PPID, resulting in a favorable bias when assessing test performance.[64] Although highly specific for PPID, the DST has shown poor performance in identifying horses with earlier PPID. In fact, the DST was only useful in identifying horses with end-stage disease (defined as those with hypertrichosis and grossly enlarged pituitary adenomas) when a random population was assessed using necropsy as the gold standard.[64]

Measurement of endogenous concentrations of POMC-derived peptides is also useful in the diagnosis of PPID.[65] Measurement of

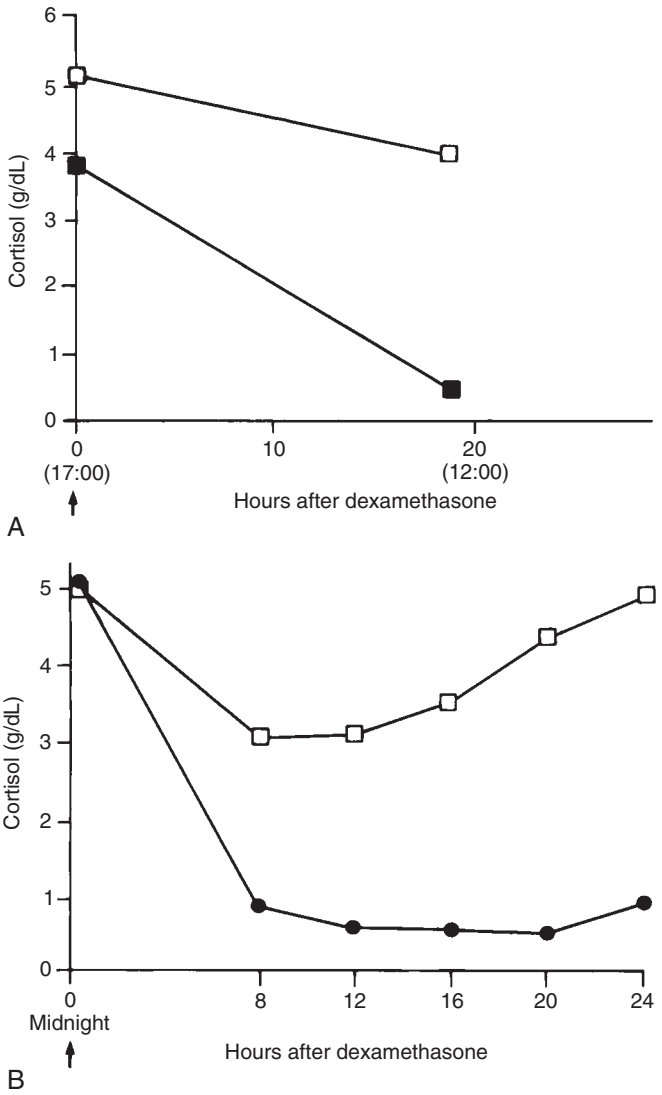


FIG. 41-7 Dexamethasone suppression test. □, Cushing; ■, control; ↑, 40 µg/kg dexamethasone intramuscularly; **A,** overnight; **B,** standard.

ACTH is perhaps the most commonly used method for diagnosis of PPID in ambulatory practice because it requires collection of only a single plasma sample and poses no risk to the patient. Difficulty in sample handling was long cited as a limitation of this test; however, more critical evaluation has found equine ACTH to be more stable in plasma than originally assumed, and as long as a plasma sample remains cooled, separation of plasma can be delayed as long as 12 hours without affecting results.[37,47] Measurement of plasma concentrations of ACTH was originally reported to have a sensitivity and specificity of approximately 80% to 90%.[47,65] However, evaluation of a larger, randomized equine population has found the test to have a sensitivity and specificity of approximately 70% and 80%, respectively.[64] α-MSH concentration, although used in research to assess pars intermedia function, is not commercially available at this time. However, in multiple studies α-MSH concentration did not perform significantly better than ACTH concentration in identification of PPID.[26,64-66]

A positive test result in an animal with clinical signs of PPID is considered strong diagnostic evidence. However, due to the poor performance of the DST and ACTH concentration at identifying early disease, it is not uncommon for a clinician to have a suspicion of PPID in a patient that has a negative diagnostic test result. When this occurs, further testing using a provocative test is indicated. Presently, the dynamic test that has been shown to most accurately identify PPID is the thyrotropin-releasing hormone (TRH) stimulation test with measurement of plasma ACTH concentration.[67-69] The TRH stimulation test was historically recommended for use in horses with a history of laminitis. The diagnosis of PPID was made by demonstrating an increase in serum cortisol concentration 30 to 90 minutes after TRH administration.[70] However, further work showed this assay to be unreliable, with false-positive tests common.[6] Recently, Beech and colleagues have shown TRH-stimulated ACTH release to be a superior diagnostic test.[67-69] TRH is known to be a physiologic releasing factor of the equine pars intermedia.[6] Measurement of plasma ACTH, rather than serum cortisol, is a more direct assessment of pars intermedia response, eliminating the influence of adrenal gland response or ACTH bioactivity. It has been demonstrated that in PPID immunoreactive plasma ACTH is not as bioactive as plasma ACTH from the healthy horse.[71-72] Therefore in horses with PPID the TRH response may be attenuated at the level of cortisol release.

Other strategies to improve the ability to diagnose PPID include combining multiple tests, such as the DST, TRH stimulation test, or plasma ACTH measurement, repeating the same or a different test several months later or testing during the fall (see later) using seasonally specific reference ranges.

Seasonal variation in both static and dynamic testing of pars intermedia function has been well documented.[22-27,73-74] Testing performed in autumn, between August and October in the northern hemisphere, yields a significantly greater hormone response or concentration than testing performed between November and July.[22-27,73-74] Initially, these findings led to the recommendation to avoid endocrine testing in autumn. However, further work has demonstrated that the difference in ACTH concentration between normal horses and those with PPID is much greater during autumn.[25] As a consequence, provided seasonally specific reference intervals are available, testing in autumn is more discriminating and therefore preferable to testing during other times of the year.

Although unlikely to be practical in most cases, advanced imaging of the pituitary using computed tomography (CT) or magnetic resonance (MR) has also been examined in a limited number of cases as a method for documenting pituitary or pars intermedia enlargement.[75-77] Accuracy of CT at estimating width, height, length, and volume of the equine pituitary gland in disarticulated heads from 25 normal horses was determined to be 81% to 93%, 58% to 71%, 88% to 99%, and 43% to 53%, respectively.[76] In a more recent study in which CT measurements were performed in a small number of live horses, accuracy was between 92% and 105%, likely due to the larger dose of contrast agent administered.[77] Despite the ability to characterize overall size of the pituitary, CT does not provide information on the internal structure of the gland, including the relative size of the pituitary lobes and the presence of microadenomas. MR imaging is the preferred diagnostic imaging modality for pituitary masses in humans, and its usefulness in characterizing the pituitaries of horses is currently being evaluated.[78]

Necropsy Findings Postmortem examination of the horse with PPID reveals a grossly enlarged pituitary due to hypertrophy and hyperplasia of the pars intermedia.[79-81] The normal horse's pituitary typically weighs between 1 and 3 g; the affected horse's pituitary may be two to five times this size. Enlargement may be due to an adenoma (>1 cm), which often contains areas of hemorrhage and necrosis. Alternatively, microadenomatous (≦1 cm) hyperplasia may be present. Melanotropes in the affected gland are pleiomorphic (polyhedral or spindle shaped) with eosinophilic, granular cytoplasm.[79-81] Cells are organized into nodules, rosettes, bundles, or follicular structures separated by fine septal tissue. Pigment deposition is common in the pars nervosa, and hemosiderin may be observed when hemorrhage is present. Other lesions include compression of the pars distalis, pars nervosa, or in the case of large tumors that outgrow the sella turcica, compression of the optic chiasm or hypothalamus. Associated lesions of other organs are also common, including those related to disease complications such

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as laminitis, intestinal parasitism, pneumonia, or sinusitis.[62] Mild enlargement of the pars intermedia is also observed in the healthy aged horse,[82] and moderate enlargement with microadenomas has been observed in clinically normal horses during the autumn.[81]

Treatment and Prognosis Treatment of PPID is aimed at improving general health and reducing the risk of disease complications such as laminitis and infections. Management practices should be optimized for care of an aged horse. Diet and feeding practices, dental and hoof care, and deworming schedule should be assessed. Feeding of a pelleted diet designed for senior horses along with strategic deworming and correction of dental abnormalities is useful in maintaining the animal's weight and improving overall general health. Body clipping the horse that fails to shed during warm weather is critical to limit excessive sweating and avoid hyperthermia. Vigilant observation for evidence of infection or laminitis followed by early intervention is important to avoid protracted illnesses.

Pharmaceutical interventions for PPID function by decreasing the concentration of circulating POMC peptides and/or cortisol, which theoretically should reduce the risk of disease complications beyond what can be achieved by management alone. Ideally, treatment should also reverse or retard the hyperplastic growth of the pars intermedia, thereby limiting compression of adjacent tissues.

The preferred drug for the treatment of PPID is pergolide, a dopamine agonist, which has been shown to improve clinical signs and diagnostic test results in treated animals.[36-39,44] An initial dose of 0.002 mg/kg orally every 24 hours has been recommended.[44] Response to drug should be assessed by both clinical improvement and normalization of diagnostic test results. If no response is observed in 4 weeks, the dose is increased by 0.002-mg/kg increments monthly until clinical signs and biochemical abnormalities normalize.[44] Complications associated with pergolide use in the horse include anorexia, colic, and diarrhea. These are typically dose dependent and often resolve spontaneously following a reduction in dose. Once an effective dose is established, endocrine testing should be repeated every 6 to 12 months to ensure hormonal control is maintained because many horses will require periodic increases in dose over time.

Cyproheptidine, a drug with antiserotoninergic, antihistaminergic, and anticholinergic activity, was one of the original drugs used to treat horses with PPID. However, several studies using objectively measurable outcomes failed to show consistent efficacy of the drug.[36-37] In addition, although historically inexpensive, the cost of cyproheptidine has increased significantly, making pergolide the more rational treatment choice. Cyproheptidine may be useful as an adjunct therapy in horses resistant to pergolide monotherapy. Cyproheptidine may be added at 0.3 to 0.5 mg/kg orally once daily to horses that show minimal response to 0.006 mg/kg or higher dose of pergolide.[44]

The prognosis of horses with PPID is not well documented. Many horses live for years following diagnosis, particularly if receiving optimized management. Anecdotal reports of PPID horses that have responded to pergolide for more than 5 years suggest long-term effective treatment is achievable. As with all diseases, early recognition, appropriate intervention, and avoidance of complications are the keys to a positive outcome.

Adrenal Glands

Kelsey A. Hart

As in other species, in the horse the paired adrenal glands lie immediately craniomedial to the kidneys. Equine adrenal glands weigh approximately 15 g each and are approximately 8 to 10 cm in length, 3 to 4 cm wide, and 1.5 cm thick, though there is much variation in adrenal size and shape among individual horses. Each gland is divided into an outer cortex that secretes corticosteroids and an inner medulla that secretes catecholamines.

The adrenal medulla functions as a neuroendocrine organ and is essentially a modified sympathetic ganglion. Preganglionic sympathetic neurons extend from the CNS and synapse directly on adrenal medullary chromaffin cells; when stimulated, these cells release catecholamines directly in the systemic circulation to produce a global sympathetic response. In the horse, the primary adrenal medullary catecholamine appears to be epinephrine, though norepinephrine and dopamine are also produced.[1] Diseases affecting the adrenal medulla are rare in horses—as in all species—though adrenal medullary neoplasms are reported.

The adrenal cortices are divided into three cellular zones: (1) the outer zona glomerulosa; (2) the middle zona fasiculata, which is the largest zone and comprises approximately 75% of the weight of the gland; and (3) the narrow inner zona reticularis. Cells in the zona glomerulosa are primarily responsible for the secretion of mineralocorticoids (e.g., aldosterone) in response to hypotension and electrolyte derangements (hyperkalemia, hyponatremia). Zona fasiculata cells synthesize and secrete glucocorticoids (e.g., cortisol, corticosterone, 11-deoxycortisol) in response to stimulation by adrenocorticotropic hormone (ACTH) after activation of the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 41-8) by physiologic or pathophysiologic stressors. The predominant circulating glucocorticoid in the horse is cortisol.[2] Cells in the zona reticularis also

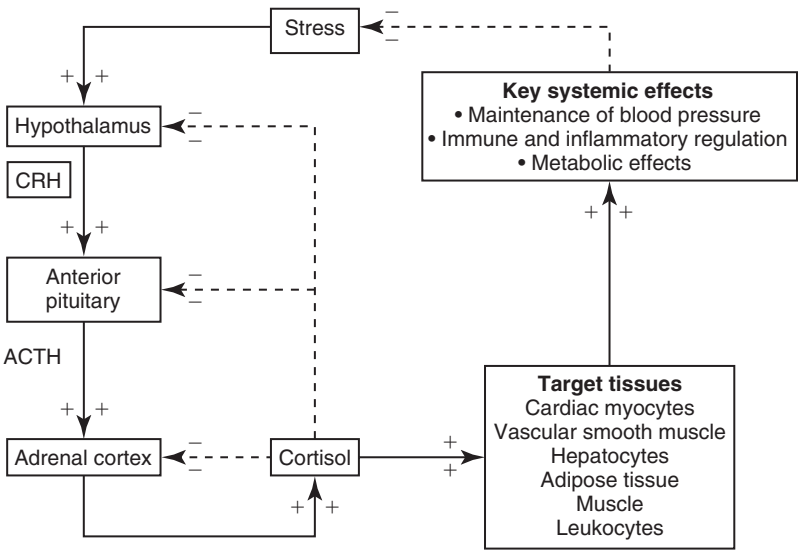


FIG. 41-8 The hypothalamic-pituitary-adrenal (HPA) axis. Stimulatory interactions are illustrated with solid arrows and + signs, and inhibitory interactions (negative feedback) are illustrated with dashed arrows and – signs. *ACTH,* Adrenocorticotropic hormone; *CRH,* corticotropic releasing hormone. *(From Hart KA, Barton MH. 2011. Adrenocortical insufficiency in horses and foals. Vet Clin North Am Equine Pract 27:19.)*

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secrete small amounts of glucocorticoids but primarily produce adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione. All corticosteroid hormones are structurally similar with a common sterol backbone and one 5-carbon and three 6-carbon rings, and they share a common synthetic pathway originating from cholesterol (see Fig. 41-8). The specific corticosteroids produced by a particular adrenocortical cell depend on which biosynthetic enzymes are expressed in that cell (see Fig. 41-8), which varies among the three functional zones.

All steroid hormones are lipophilic and thus are transported in the plasma predominantly bound to plasma proteins, including albumin and steroid-binding globulins such as cortisol-binding globulin (CBG). However, because steroid hormone receptors are located in the cytoplasm of steroid-responsive cells, it is only the free, unbound portion of circulating steroid hormones that is available to enter cells via diffusion across the plasma membrane to bind these intracellular receptors. Binding of the steroid hormone to the receptor causes conformational changes that allow dissociation of regulatory heat shock proteins, permitting the hormone-receptor complex to localize to the nucleus, bind DNA at hormone response elements (HREs), and upregulate or downregulate transcription of steroid hormone–responsive genes.

Glucocorticoids are the most abundant circulating adrenal corticosteroid hormone and play an integral role in the endocrine response to stress. The HPA axis (Fig. 41-9) is activated when physiologic, pathophysiologic, or environmental stressors activate peripheral and CNS components, whose signals are then interpreted and integrated in the hypothalamus. This stimulates hypothalamic paraventricular nuclei, resulting in the release of corticotropin-releasing hormone (CRH) into the hypothalamic-hypophyseal portal vessels. CRH then acts locally in the adjacent anterior pituitary gland to stimulate CRH receptors on the cell surface of pituitary corticotroph cells, resulting in the release of ACTH (corticotropin) into the systemic circulation.

ACTH binds cell surface receptors (melanocortin2 receptor, MC2R) on adrenocortical cells and stimulates the adrenal glands to synthesize and secrete cortisol. MC2R is a G protein–coupled transmembrane receptor that acts via adenylate cyclase to increase cyclic AMP levels, which then activate biosynthetic enzymes necessary for cortisol synthesis, including 3-β-hydroxysteroid dehydrogenase (3-β-HSD), 17-α-hydroxylase, 21-α-hydroxylase, and 11-β-hydroxylase (see Fig. 41-9). This latter enzyme, present only in glucocorticoid-producing cells, catalyzes the final step in cortisol synthesis from 11-deoxycortisol.[3]

Cortisol is not stored in adrenocortical cells, but rather is secreted into the systemic circulation immediately following ACTH-induced synthesis. In most adult mammals, including horses, approximately 90% to 95% of circulating cortisol is bound to CBG and albumin.[4-8] Many cell types are sensitive to glucocorticoids, permitting cortisol to exert diverse effects necessary for maintenance of homeostasis and stress responses in both health and disease. Essential glucocorticoid-mediated physiologic responses include maintenance of blood pressure, provision of energy to tissues, and control of an appropriate inflammatory response. The sum of cortisol's systemic effects serves to reduce the physiologic stress that initially activated the HPA axis, to ultimately restore basal HPA axis tone. In addition, cortisol itself acts via negative feedback mechanisms at hypothalamic, pituitary, and adrenal levels to further downregulate HPA axis activity. Thus

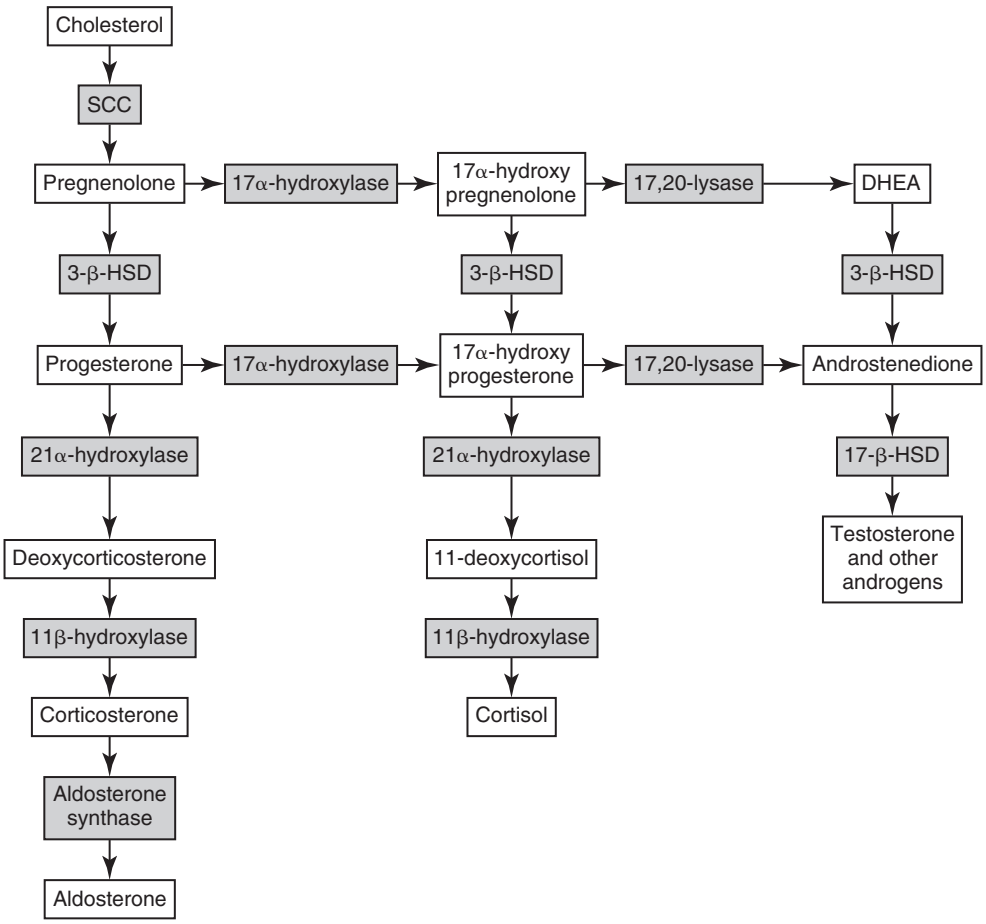


FIG. 41-9 Biosynthetic pathway for adrenal corticosteroids. The enzymes responsible for catalyzing each biotransformation are shown in the black boxes over the arrows. 3-β-HSD, 3-β-hydroxysteroid dehydrogenase; *DHEA,* dehydroepiandrosterone; *SCC,* side chain cleavage enzyme. *(From Hart KA, Barton MH. 2011. Adrenocortical insufficiency in horses and foals. Vet Clin North Am Equine Pract 27:19.)*

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with an intact HPA axis, plasma cortisol concentrations are maintained at a level appropriate for the existing degree of physiologic stress.

Cortisol secretion patterns in adult horses exhibit both ultradian (pulsatile) and circadian rhythms with peak secretion in the morning and the nadir in the evening, similar to many other species.[9-12] These ultradian and circadian rhythms are easily disrupted in horses by simple routine changes and illness.[9,13] Cortisol responses to ACTH stimulation testing in adult horses are described and suggest adult horses show a comparable dose-dependent effect of exogenous ACTH on cortisol concentrations as is described in other species.[11,14-16] In general, an approximately twofold to fivefold increase in cortisol concentration is observed within 30 to 90 minutes after intravenous (IV) administration of a 0.1- to 10-µg/kg dose of exogenous ACTH (cosyntropin) in healthy adult horses[14,16]; the magnitude of cortisol increase varies with the ACTH dose administered.

HPA axis function in the foal differs from both adult horses and other species in several key ways. Compelling evidence shows that maturation of the HPA axis occurs in the days just prior to parturition and continues during the first several weeks of life, much later than is described in other species.[17-20] Premature foals have lower serum cortisol and higher ACTH concentrations than full-term foals immediately postpartum.[20] These low baseline cortisol and concurrent high ACTH concentrations in premature foals imply that foals may have impaired adrenocortical sensitivity to ACTH, limited cortisol synthetic capacity, or both, as compared with adult horses.

Data from ACTH stimulation test responses in foals support this theory. Premature foals show a blunted cortisol response to exogenous ACTH, with only a 28% increase in plasma cortisol 30 to 60 minutes following stimulation, as compared with a 208% increase in normal term foals.[17] Evidence suggests that the fetal foal's adrenal gland may be incapable of synthesizing cortisol and some other steroid hormones until late in gestation. Fetal foals do not express substantial levels of the key steroidogenic enzymes cholesterol side chain cleavage enzyme, 17α-hydroxylase, and 3-β-HSD until just before parturition in the foal,[21,22] much later than is described in other species.[23]

Furthermore, adrenocortical function may not be fully mature at birth even in full-term foals. Though increased at birth due to the stress of parturition, by 12 to 24 hours of age, mean basal cortisol concentrations are onefold to twofold lower in healthy neonatal foals than reported mean concentrations in healthy adult horses despite comparable or higher concurrent ACTH concentrations in foals.[24-28] This apparent decreased cortisol response to endogenous ACTH in the full-term neonatal foal is supported by further evidence of limited cortisol responses to exogenous ACTH. Insulin-induced cortisol responses in foals within 12 hours of birth are less than half of the responses achieved in 7- to 14-day-old foals, [29] and healthy term neonatal foals aged 1 to 7 days are reported to have approximately half the magnitude of cortisol response to ACTH stimulation testing than adult horses.[14,25] This decreased adrenocortical responsiveness appears to persist during the first few months of life, as 12-week-old foals show significantly greater cortisol responses to a low-dose (0.1 µg/kg) ACTH stimulation test than younger foals.[30]

Finally, foals differ from adult horses in their plasma cortisol binding capacity and cortisol secretion and metabolism patterns. In foals younger than 1 week of age, 30% to 60% of circulating cortisol is free, in contrast to 5% to 10% in adult horses.[31] This is likely due to decreased CBG concentrations in foals—as has been shown in infants[32,33]—though an assay for equine CBG is not currently available. Free cortisol is preferentially excreted and metabolized over bound cortisol,[34] so it is not surprising that increased cortisol clearance rates in foals as compared with adult horses have recently been described.[12] Healthy full-term foals appear to be able to increase their daily cortisol production rate to compensate for this increased clearance, though as serum total cortisol concentration at 1 week of age remains significantly lower in foals than adult horses,[12] foals' capacity to further and appropriately increase cortisol production in severe stress may be limited. It is likely that impaired cortisol responses in neonatal foals result from multiple factors, including decreased cortisol synthetic capacity and increased cortisol clearance and possibly other as yet undefined differences in ACTH sensitivity or activity. Regardless of the cause, this evidence of fetal and neonatal HPA axis immaturity is certain to substantially affect foals' stress responses during the neonatal period.

Mineralocorticoids (e.g., aldosterone) are produced in small quantities relative to glucocorticoids but have equally important physiologic roles. Angiotensin II, via activation of the renin-angiotensin-aldosterone system by hypovolemia/hypotension or increases in plasma osmolality, and increased plasma potassium concentration are the primary stimulants of aldosterone synthesis and secretion. ACTH is also necessary for aldosterone synthesis, but ACTH administration to healthy adult horses resulted in a decrease in plasma aldosterone concentration in contrast to increases seen in other species.[35,36]

Like glucocorticoids, aldosterone circulates in the plasma bound to albumin or steroid-binding globulins and primarily acts by binding cytosolic mineralocorticoid receptors to alter transcription of genes necessary for sodium and potassium transport. Mineralocorticoid receptors are predominantly expressed in sodium-transporting epithelia in the distal renal tubules and colon, with lesser expression in the rest of the intestinal tract and the heart. Aldosterone induces transcription of an aldosterone-regulated kinase that increases activity of apical membrane sodium channels.[37] The net effect of this is increased sodium flux across epithelial cells, resulting in increased renal and intestinal sodium and water resorption and concurrent stimulation of potassium excretion via the basolateral Na^+/K^+ ATPase.[37] Mineralocorticoids are vital for appropriate fluid and electrolyte balance, and mineralocorticoid deficiency rapidly results in hyponatremia, hyperkalemia, and hypovolemia.

Reported resting and exercising plasma concentrations of aldosterone in horses have been described.[38,39] In contrast to their limited cortisol responses to appropriate stimuli, newborn foals appear to be able to mount a substantial aldosterone response to hypovolemia/hyponatremia.[40,41] In fact, one study suggested that the aldosterone response in foals appears to be exaggerated in comparison to that in adult horses and may reflect differences in tubular sensitivity to aldosterone between neonates and adults.[41] However, well-established reference ranges for plasma aldosterone concentrations in foals are not currently available.

In adult males, circulating androgens are primarily of testicular origin, but in females more than half of plasma androgens may originate from the adrenal cortices. ACTH is necessary for the synthesis and secretion of adrenal androgens, but another factor (or factors) that is not yet identified is also required for adrenal androgen synthesis.[11] Adrenal androgens are also transported in the plasma bound to albumin and CBG and act via cytosolic steroid hormone receptors to modulate gene transcription. DHEA and androstenedione can be extraglandularly metabolized to active testosterone and estrogens and play a particularly important role in early pubertal sexual development in most species. Androstenedione concentrations in adult horses are reported, and sex and age variations in adrenal androgen concentrations may be relevant but at present are poorly understood in horses and foals.[27,42] Increased adrenal androgen production is postulated to play a role in mares with estrus-related behavior problems, though this has not been definitively proven.[27]

Critical Illness-Related Corticosteroid Insufficiency

Definition and Epidemiology Critical illness–related corticosteroid insufficiency (CIRCI) has been recently described in septic foals and adult horses with colic. CIRCI (also known as relative adrenal insufficiency) is best understood in people and is defined as an insufficient cortisol response or inadequate cortisol activity for the existing degree of critical illness.[43-47] Although serum cortisol concentrations in patients with CIRCI are often increased relative to

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resting concentrations in healthy individuals, the cortisol response remains insufficient for the markedly increased demands of acute severe illness.[43,48-50] In people CIRCI is reported to occur secondary to severe illness, such as sepsis or acute respiratory distress syndrome (ARDS), severe trauma, or major surgery, and appears to affect up to 40% to 60% of adult and pediatric patients with sepsis and septic shock.[45,46,48]

In CIRCI, the cortisol insufficiency is transient and resolves if the patient survives the primary illness. However, due to the vital role the HPA axis plays in the physiologic response to the stress of illness, the occurrence of CIRCI during critical illness substantially worsens the morbidity and mortality of the primary disease. For instance, septic people with CIRCI have significantly higher incidence of multiple organ failure and decreased survival rates as compared with septic patients with appropriate HPA axis function.[44-46,49,51,52]

Current understanding of HPA axis function in critically ill horses and foals is limited; to date, CIRCI is best characterized in septic neonatal foals.[53-58] Although basal ACTH and cortisol concentrations are higher in septic foals than healthy age-matched control foals and in nonsurviving foals (as one would expect with the stress of illness), several studies have reported significantly increased ACTH-to-cortisol ratios in nonsurviving septic foals.[53,55,57] Such high ACTH-to-cortisol ratios, with high ACTH concentrations and low corresponding cortisol concentrations, suggest cortisol synthesis failure at the level of the adrenal gland may occur in the septic full-term foal.

Findings from ACTH stimulation tests in hospitalized foals also provide evidence for adrenocortical dysfunction in this population. Peak and delta cortisol (peak–basal cortisol concentration) responses to ACTH stimulation tests do not appear to differ between healthy and ill foals, but increased disease severity and poorer prognoses were associated with decreased cortisol responses to ACTH stimulation in hospitalized foals.[56,58] Specifically, nonsurviving foals had significantly lower delta cortisol responses to low-dose ACTH stimulation as compared with survivors,[58] and foals that met criteria for CIRCI (as characterized by an inadequate delta cortisol response to a high-dose ACTH stimulation test) had a significantly greater incidence of shock, multiple organ dysfunction syndrome, and nonsurvival than foals with an adequate cortisol response to ACTH.[56] When human diagnostic criteria for CIRCI[59] based on inadequate delta cortisol responses to high-dose ACTH stimulation were adapted and applied to hospitalized foals 1 week of age and younger, approximately 50% of all hospitalized foals and a subgroup of septic foals met these criteria.[56]

The incidence of CIRCI in critically ill horses has only been examined in one study to date, but findings suggest it may also occur in this population.[60] Twenty-four percent of severely ill horses had inappropriately low basal cortisol concentrations at hospital admission, and 85% of these horses had inadequate delta cortisol responses to ACTH stimulation.[60] Marked adrenal hemorrhage at necropsy was also seen in nonsurviving horses in this study.[60]

In concert, this evidence suggests that CIRCI occurs in critically ill and septic neonatal foals and in critically ill horses with comparable frequency and impact as in people with similar illnesses.

Pathophysiology

The specific pathophysiologic mechanisms leading to the development of CIRCI are poorly understood in all species and have not yet been systematically evaluated in horses or foals. A combination of factors is likely involved in the development of HPA axis dysfunction in CIRCI, including direct damage to HPA axis components from the primary disease, inhibition of cortisol production by medications used to treat the primary disease, and suppression of activity of one or more components of the HPA axis by infectious organisms or the patient's own immune and inflammatory response.[44,45] Periods of hypotension associated with hypovolemic, endotoxic, or septic shock can result in decreased adrenal perfusion and ischemic injury to the metabolically active adrenocortical cells. If this occurs for prolonged periods or to an extreme degree, the damage may be irreversible, resulting in severe adrenocortical hemorrhage and necrosis known as *Waterhouse-Friderichsen syndrome* in people[61]; similar adrenal pathology has been recently described in critically ill horses and foals.[60,62] Milder adrenal circulatory insults may result in transient injury and dysfunction. In addition, drugs like the anesthetic agent etomidate and several antimicrobial agents (e.g., ketoconazole, rifampin) can directly inhibit adrenocortical cortisol synthesis.[45,63]

It is the patient's own immune and inflammatory response, though, that appears to play the most vital role in the development of CIRCI. Bacterial components such as endotoxin, as well as host proinflammatory cytokines, all play an appropriate and important role in initiating and maintaining the HPA axis response to critical illness by directly stimulating HPA axis activity at multiple levels.[44,61,64-66] However, bacterial ligands and inflammatory cytokines may also be capable of *suppressing* HPA axis function at one or more levels, in the face of an overwhelming bacterial infection or excessive host inflammatory response. For example, inducible nitric oxide synthase-mediated death of hypothalamic neurons in cardioregulatory centers has been described in patients that died of septic shock and may play a role in HPA axis dysfunction in such patients.[67] Bacterial endotoxin has been shown to directly decrease pituitary CRH receptor gene expression in both rats and cattle.[68,69] In addition, the proinflammatory cytokine TNF-α, which is increased in sepsis, can directly impair both pituitary ACTH release and adrenocortical cortisol synthesis.[45] Finally, cholesterol availability for corticosteroid synthesis may be limited during sepsis, as several studies have shown decreased levels of plasma high-density lipoprotein (HDL) in critically ill individuals and correlated these decreased HDL levels with blunted cortisol responses to ACTH stimulation testing.[45] Interactions between the adrenal axis and the immune response in horses are not well characterized, but equine adrenocortical tissue has been shown to directly secrete IL-6, IL-10, and TNF-α in an ex vivo model,[70] and a positive association between plasma ACTH concentration and leukocyte IL-6 expression has recently been shown in septic foals.[71]

Several studies suggest that peripheral tissue cortisol resistance may develop in some critically ill patients. Specifically, impaired GR binding affinity has been documented in an ovine model of acute lung injury[72] and a rodent burn model,[73] where it was partially ameliorated when TNF-α and IL-1β were reduced by neutralizing antibodies. Furthermore, nuclear localization of cortisol-GR complexes was impaired in human leukocyte cells exposed to plasma from patients that died of acute respiratory distress syndrome.[74] Thus the complex relationship between endocrine and immune regulation of HPA axis function at multiple levels determines overall cortisol production and activity during sepsis. Any imbalance in these interactions can result in absolute or functional cortisol insufficiency and may play a critical role in the pathogenesis of CIRCI; further study of specific mechanisms resulting in CIRCI in horses and foals is needed.

Clinical Signs

The clinical presentation of CIRCI is typically vague and insidious because signs related to the primary illness usually predominate. Indeed, it is the primary illness that should prompt the clinician to consider CIRCI as a possible complicating factor, as data in people, dogs, horses, and foals suggest it is more likely in certain diseases than others.[44,45,56,60,75] Recent studies in horses suggest that CIRCI should be considered as a possible complication in any critically ill horse or foal, but particularly in septic foals and horses with evidence of a systemic inflammatory response syndrome (SIRS).[55-58,60] Clinicians should also have a high index of suspicion for cortisol insufficiency in premature foals due to the late maturation of the HPA axis and adrenal gland in foals. Human studies suggest that CIRCI also occurs in conjunction with ARDS, massive trauma, and major surgery,[44,45] so it should also not be overlooked in horses with similar diseases.

Specific manifestations of CIRCI are directly related to inadequate cortisol support for maintenance of blood pressure, nutrient metabolism, and regulation of the immune/inflammatory response. They can include one or more of the following: (1) persistent hypotension despite appropriate volume resuscitation and vasopressor support;

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(2) persistent hypoglycemia or hyperlactatemia despite glucose support and adequate perfusion; or (3) persistent signs of SIRS. Specific diagnostic criteria for SIRS in horses and foals have not been universally defined but can include tachycardia, fever or hypothermia, leukocytosis (neutrophilia), leukopenia (neutropenia), or increased band neutrophils.[76,77] Specific signs of mineralocorticoid deficiency (such as persistent hyponatremia, hypochloremia, or hyperkalemia) are not a consistent feature of CIRCI but do occasionally occur.

Diagnosis Specific diagnostic criteria for CIRCI in horses or foals are not well defined. Indeed, determination of the ideal diagnostic criteria for CIRCI in any species is inherently difficult as quantifying a universally appropriate cortisol response to variable and constantly changing disease severity in individual patients is next to impossible. Thus diagnostic criteria for CIRCI in people and infants are not universally accepted, but current recommendations include documentation of either (1) an inappropriately low basal cortisol concentration during critical illness or (2) an inadequate delta cortisol response to high-dose (supraphysiologic) ACTH stimulation testing.[59] Testing for CIRCI in people is typically done at ICU admission for patients with diseases likely complicated by CIRCI (e.g., sepsis, ARDS) or when clinical signs consistent with CIRCI such as persistent hypotension after fluid and vasopressor support are identified. Cutoff values for adequate basal and delta cortisol concentrations in illness are based on responses to environmental stress in healthy individuals.

In general, measurement of basal plasma hormone concentrations offers a rapid and safe means of assessing adrenocortical function in the critically ill horse or foal. Well-established commercial radioimmunoassays or chemiluminescent immunoassays are readily available and well validated for measurement of equine cortisol.[8,78] In foals, age-related variation in HPA axis function needs to be considered when determining cutoff values for CIRCI diagnosis.[25,30,79] Specific basal cortisol cutoff values for diagnosis in CIRCI in ill foals or horses have not been critically evaluated, but basal cortisol less than 9.9 μg/dL in foals younger than 4 hours old, less than 7.0 μg/dL in foals 12 to 24 hours old, less than 4.4 μg/dL in foals 36 to 48 hours old, less than 2.5 μg/dL in foals hours to 7 days old, and less than 9.7 μg/dL in horses have been used to diagnose CIRCI in recent reports.[56,60] However, due to the pulsatile nature of cortisol secretion, plasma concentrations can vary widely during a 24-hour period in both healthy and sick horses and foals with time of day, season, emotional state, and moment-to-moment changes in physiologic stressors.[9,12,13] Thus correct interpretation of a single random cortisol concentration in an individual animal as appropriate or not can be difficult. Further, diagnosis of CIRCI based on a low basal cortisol concentration was not correlated with increased disease severity of decreased survival in septic foals, as was diagnosis based on ACTH stimulation testing.[56]

Assessment of cortisol concentrations in conjunction with regulatory hormone (ACTH, CRH) concentrations can provide a more comprehensive picture of HPA axis function. Plasma CRH and ACTH concentrations are easily assessed in most species via commercially available immunoassays, but as the majority of CRH is secreted into the hypothalamic-hypophyseal portal vessels rather than into the systemic circulation, accurate measurement of CRH requires sophisticated sampling methodology. In addition, although in healthy individuals ACTH and cortisol concentrations are fairly closely correlated, ACTH-cortisol dissociation is not uncommon during illness in horses and foals.[13] Documentation of an increased ACTH-to-cortisol ratio might be helpful for CIRCI diagnosis, especially in foals, but due to wide variation in these parameters in individual animals,[53,55-57] specific cutoff values for appropriate ACTH-to-cortisol rations are not currently proposed for diagnosis of CIRCI in horses or foals.

Dynamic tests like the ACTH stimulation test circumvent some of these limitations with diagnosis of CIRCI based on basal hormone concentrations. Typically, in the classic "high-dose" ACTH stimulation test, serum cortisol concentration is measured just before and 30 to 90 minutes after IV or IM administration of a supraphysiologic quantity of ACTH (1 to 2 μg/kg or higher). This high-dose ACTH stimulation test produces a maximal adrenal response, so an inadequate increase in cortisol concentration in this test is used to diagnose both absolute, irreversible adrenal insufficiency (e.g., Addison disease) and transient CIRCI.[11,45,48,59]

The high-dose ACTH stimulation test, however, may be less sensitive for diagnosis of the transient, reversible HPA axis suppression that occurs in CIRCI. In some patients with CIRCI, the adrenal gland fails to produce an appropriate cortisol response to physiologic concentrations of ACTH but may still respond adequately to supraphysiologic ACTH concentrations.[50,80] A measurable cortisol response can be produced by administration of lower ACTH doses (0.01 to 0.2 μg/kg) in horses and foals,[14,16,25,30,56,81] and such "low-dose" stimulation tests could also be used to diagnose CIRCI in equine patients. Delta cortisol responses vary with foal age and dose of ACTH administered, but in general an increase from basal cortisol less than onefold to twofold 30 minutes after low-dose ACTH stimulation testing[14,16,25,30,81] and less than threefold to fourfold 90 to 120 minutes after high-dose ACTH stimulation testing[14,25,81] may be suggestive of CIRCI in horses and foals. However, one study that examined a paired low-dose/high-dose ACTH stimulation test in hospitalized foals found significant associations between increased disease severity and nonsurvival and inadequate cortisol responses to the high dose but not the low dose of ACTH.[56]

It is important to note, however, that ACTH stimulation tests only evaluate the adrenal component of the HPA axis. Therefore patients with cortisol insufficiency due to impaired HPA axis function at the hypothalamic and/or pituitary levels may produce an appropriate cortisol response to exogenous ACTH that could be falsely interpreted as intact HPA axis function. Insulin tolerance, CRH stimulation, or metyrapone tests are preferred for global assessment of the HPA axis and diagnosis of HPA axis hypofunction and have been described in foals and horses.[29,82-84] However, risks associated with severe hypoglycemia and the potential for preexisting glucose/insulin derangements in critically ill horses and foals limit the utility of insulin tolerance testing in patients with potential CIRCI, and the CRH stimulation and metyrapone tests are currently limited by expense and reagent availability, so these tests are not currently recommended for diagnosis of CIRCI in horses and foals.

Finally, some of the physiologic consequences of CIRCI may be associated with cortisol resistance in peripheral tissues rather than circulating cortisol insufficiency.[44,73,74,85] In such cases, all of the previously mentioned tests may suggest intact HPA axis function, with appropriate endogenous cortisol concentrations and normal responses to dynamic testing, despite clinical evidence of cortisol insufficiency such as persistent hypotension, metabolic derangements, or inflammatory dysregulation. Unfortunately, methodology for assessing cortisol activity at the tissue level is currently limited and is not described in horses to date.

Treatment and Prognosis Specific therapeutic protocols for management of CIRCI in horses or foals have not been critically evaluated. It is important to remember that the goal of CIRCI treatment is *physiologic* cortisol replacement because a number of studies in septic patients have demonstrated deleterious effects of high-dose (supraphysiologic) corticosteroid regimens in sepsis.[59] Thus it may be ideal to avoid more potent and longer-acting corticosteroids such as dexamethasone and prednisolone in favor of hydrocortisone (which is identical to endogenous cortisol), though these drugs are sometimes used in people with CIRCI.

At present, cortisol replacement therapy in the form of hydrocortisone at approximately 1 to 4 mg/kg/day as twice-daily to four-times-daily IV boluses in septic adult humans and infants or as a 100-mg IV bolus followed by an IV CRI of 10 mg/h in septic adult humans is recommended.[59,86] Concurrent mineralocorticoid replacement therapy with fludrocortisone appeared beneficial in one human study,[87] but its use is at present considered optional in human CIRCI

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and is typically limited to patients with evidence of persistent electrolyte derangements or lack of response to hydrocortisone alone.[59]

Specific therapeutic protocols for neonatal foals or adult horses with CIRCI are not described. In one case report, a septic foal with adrenocortical insufficiency, as evidenced by a low basal cortisol and impaired cortisol response to ACTH stimulation, demonstrated clinical improvement and eventual normalization of cortisol responses following a course of prednisolone supplementation in addition to standard therapy for sepsis.[54] Recent evidence also suggests that in healthy 2- to 6-day-old foals, a short tapering course of hydrocortisone (1.3 mg/kg/day divided every 4 hours IV) has potentially beneficial antiinflammatory effects without significantly impairing innate immune function.[88] Adjustment of daily cortisol production rates in foals based on an "illness factor"—as has been done in people to determine steroid supplementation regimens in CIRCI—suggests that a hydrocortisone dose of 1 to 4 mg/kg/day divided every 4 to 6 hours may be appropriate for foals with CIRCI.[12] However, this or other corticosteroid regimens have not been critically evaluated in septic foals or horses with CIRCI.

Other Adrenal Gland Disorders

Non-CIRCI Adrenocortical Insufficiency in Adult Horses

Classic adrenocortical insufficiency characterized by glucocorticoid and mineralocorticoid insufficiency and unrelated to critical illness is not well defined in horses or foals, and Addison disease (permanent adrenocortical insufficiency secondary to immune-mediated adrenocortical destruction) has not been reported. Transient adrenal insufficiency characterized by low basal ACTH and cortisol concentrations and impaired cortisol responses to ACTH stimulation testing has been described in one horse following abrupt cessation of long-term anabolic steroid supplementation.[89] A syndrome of adrenal exhaustion resulting in lethargy, anorexia, and poor performance is also anecdotally described in racehorses and has been attributed to adrenal insufficiency associated with long-term anabolic steroid administration or chronic stress. Horses with presumptive adrenal exhaustion are often treated with exogenous ACTH for presumed adrenocortical stimulation, though measurement of basal cortisol concentrations and ACTH stimulation testing in race and endurance horses has not provided convincing evidence for adrenal insufficiency in these equine athletes.[90,91] Decreased cortisol responses to ACTH are also described in mares with abnormal estrus-related behavior,[27] but the clinical significance of this behavior is not known.

The potential for iatrogenic adrenal insufficiency associated with HPA axis suppression by exogenous steroid administration, though, should be considered in horses on chronic glucocorticoid or anabolic steroid supplementation, and care should be taken to avoid abrupt cessation of such therapy. As described earlier, the adrenal glands appear to be a shock organ in the horse and can also undergo hypoxic or ischemic damage during bouts of endotoxemia, sepsis, and SIRS.[60,62] Thus there is the potential for protracted or permanent adrenocortical dysfunction in animals who survive critical illness, though this specific manifestation is not reported in horses or foals to date. Adrenocortical insufficiency should be considered in horses with persistent lethargy, weight loss, hyponatremia, hypochloremia, hyperkalemia, or hypoglycemia, especially if they have recently received exogenous corticosteroids or recovered from critical illness. Failure to increase serum cortisol concentration greater than or equal to 1.5- to 2-fold baseline values by 30 minutes after a low-dose ACTH stimulation test (< 0.5 µg/kg IV) or greater than 3- to 4-fold baseline values by 90 to 120 minutes after high-dose ACTH stimulation test (>1 µg/kg IV) is consistent with a diagnosis of adrenocortical insufficiency.[14,16]

Adrenal Medullary Neoplasia

Although nonfunctional adrenal medullary nodules may be an incidental finding at necropsy in the horse, functional adrenal medullary tumors (pheochromocytoma) are also reported.[92-95] Clinical signs result from increased circulating catecholamine and include excessive sweating, agitation, colic, tachycardia, mydriasis, hyperglycemia, and hypertension. Pheochromocytomas are predisposed to hemorrhage, and acute, fatal hemoperitoneum secondary to ruptured pheochromocytoma is described in horses.[92,96] Although most cases are diagnosed at necropsy, determination of urinary catecholamine levels can be used for antemortem diagnosis if an abdominal mass and appropriate clinical signs are detected.[94] In some cases, pheochromocytomas occur along with other endocrine tumors or hyperplasia in a multiple endocrine neoplasia syndrome described in people, small animals, and two equine reports.[95,96]

Hypoaldosteronism

In people, primary hypoaldosteronism is uncommon and most frequently occurs as a result of congenital defects in some component of the aldosterone biosynthetic pathway.[11] Hypoaldosteronism is also reported in renal diseases that damage the juxtaglomerular apparatus integral to function of the RAAS, and peripheral resistance to aldosterone is also reported in people.[11] Such syndromes have not been described in horses, but idiopathic hypoaldosteronism is described in an alpaca.[97] In addition, hypoaldosteronism is a documented cause of renal tubular acidosis (RTA) in people[98] and should not be overlooked as a possible contributor to RTA in horses.

Anhidrosis

Babetta Breuhaus

Description of Disease

Anhidrosis is characterized as an inability to sweat in response to appropriate stimuli. It occurs in geographic areas that experience hot, humid weather for prolonged periods of time. Clinical signs are especially likely to occur when nighttime temperatures do not fall below 70° F. Classically, anhidrosis affects horses that are not accustomed to these environmental conditions and are moved to a hot, humid area. However, partial or complete anhidrosis is also diagnosed in horses that have grown up in these same areas. It appears that horses that are worked or exercised in hot, humid conditions are more likely to develop the condition than horses that are not worked. Stress may also contribute to onset of the problem. A recent large epidemiologic study conducted in Florida concluded that Thoroughbreds and warmbloods, especially those with a family history of having developed anhidrosis, were more likely to develop the condition.[1] The study also supported earlier beliefs that horses that performed more strenuous work and horses that were not born in Florida were at increased risk for becoming anhidrotic. The prevalence of anhidrosis increased, both in terms of percent of farms that housed at least one anhidrotic individual and in terms of overall percent of affected horses, as horses lived farther south within the state.[1]

Etiology and Pathophysiology The cause of anhidrosis is unknown. Presumably, there is an abnormality in stimulation or production of sweat. Equine sweat glands produce sweat as an ultrafiltrate from plasma; water and electrolytes are secreted into sweat gland ducts, and this fluid is transported to the skin surface as sweat. Physiologic stimulation of sweating in horses is achieved by activation of α_2-adrenergic receptors, both by direct neural stimulation and from circulating catecholamines.[2-4] It is unclear at this time whether nerve fibers act directly on the sweat glands themselves, or on local capillaries, thereby altering delivery of circulating agonists.[5] Sweat glands from anhidrotic horses do not respond normally to direct stimulation, and there is histologic evidence of sweat gland atrophy.[6,7] However, it is unknown whether the observed sweat gland atrophy is the primary cause of anhidrosis or merely secondary to disuse. Histologic examination of skin from anhidrotic horses showed no

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FIG. 41-10 Horses that cannot cool by sweat production will often show dilated peripheral skin vessels.

evidence of neural disruption to the sweat glands,[7] and circulating concentrations of epinephrine are actually higher in anhidrotic horses than in horses that sweat normally,[8] suggesting that the problem is more likely caused by decreased ability of sweat glands to respond to stimulation rather than failure of the thermoregulatory system to perceive the need to sweat or failure of stimulation to sweat. Cultured epithelial cells from sweat glands of anhidrotic horses had lower transepithelial resistance compared with cells derived from sweat glands of horses that were able to sweat freely.[9] In addition, cells from anhidrotic horses failed to show a change in short circuit current (indicative of chloride secretion) in response to purinoceptor or β-adrenoceptor agonists. Most theories of pathogenesis of anhidrosis suggest that chronic stimulation to sweat in a hot, humid environment leads to downregulation and/or desensitization of α_2-adrenoreceptors. The observation that only some horses living in a given environment develop anhidrosis, as well as the recent evidence of a breed and familial predisposition to the problem, suggest a possible genetic predisposition. It seems likely that β-adrenoceptor polymorphisms exist in horses and that certain polymorphs are more susceptible to downregulation.

In addition to a neural mechanism, there may also be an endocrine component to this disease. Pregnant mares were found to be somewhat less at risk of developing anhidrosis than nonpregnant mares.[10] An association of anhidrosis with hypothyroidism most likely stems from the observation that thyroid supplementation helped anhidrotic horses racing in Hong Kong in the 1950s.[11] However, the author has not observed any improvement in anhidrotic pleasure horses supplemented with thyroid hormones, and measurement of thyroid hormones at rest and in response to TRH showed no difference between normal horses and horses with anhidrosis.[12]

Evidence in some humans indicates that acquired idiopathic anhidrosis may have an immunologic pathogenesis. Serum IgE concentration was increased in one reported case.[13] Sweat gland atrophy with infiltration by lymphocytes and mast cells, as well as IgG and C3 deposition in the basement membrane, has been described.[13,14] Steroid therapy improved the ability of one of these patients to sweat. An immune-mediated basis for anhidrosis has not been studied in the horse. Basement membrane was noted to be thickened in skin biopsies from 10 anhidrotic horses.[7] However, inflammation (i.e., infiltration with white blood cells) was noted in only one of six anhidrotic horses housed at ambient conditions.[7]

Expression of the water channel aquaporin-5 was decreased in sweat glands from anhidrotic horses compared with sweat glands from horses that sweated normally.[15] Although these results may help explain why hypohidrotic or anhidrotic horses cannot produce as much sweat as normal horses, it is not clear whether loss of these water channels is a cause or a consequence of decreased sweat gland secretory capacity.



FIG. 41-11 Salt crystals secreted in response to exercise (lunge test) in an anhidrotic horse. Following a lunge test, this horse excreted the salt crystals shown here, without a fluid component to the sweat. The author has observed this in two horses diagnosed with anhidrosis.

Clinical Signs and Differential Diagnoses

Early clinical signs of hypohidrosis include exercise intolerance, particularly in warm humid weather, and tachypnea, initially during or after exercise, and then at rest as the severity of disease increases. Owners may call their veterinarian thinking their horse has a respiratory problem. As hypohidrosis worsens or the horse becomes anhidrotic, owners realize their horse is not sweating as much as they would expect for the level of work it is performing, or it is taking longer than normal to cool out after exercise. Areas of residual sweat production often include under the mane, in the axilla or inguinal areas, and under the saddle. Dilated vessels under the skin may be noted (Fig. 41-10). A few horses exhibit extrusion of salt crystals without accompanying water (Fig. 41-11). Body temperature can increase to dangerous levels if signs are not recognized and affected horses continue to work in hot weather. The haircoat often becomes dry and thin in chronically affected horses, particularly over the face (Fig. 41-12) and cannon bones.

Clinical Pathology and Diagnostic Tests

Hypohidrosis or anhidrosis can be included in a differential diagnosis of exercise

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FIG. 41-12 Chronic anhidrosis often causes facial hair loss or thinning.



FIG. 41-13 Terbutaline intradermal sweat test. Six serial 10-fold dilutions of terbutaline are injected intradermally along the neck. Normal horses, such as the one shown here, will sweat at the injection site of all concentrations, except perhaps the most dilute (10^{-8} w/v). In the normal horse, sweating will typically begin within 5 minutes of injection. Reduction in the amount or delay in onset of sweating is diagnostic for hypohidrosis. A complete failure to sweat in response to all terbutaline injections is diagnostic for anhidrosis.

intolerance on the basis of history and clinical signs. The diagnosis can be confirmed by performing an intradermal sweat test.[6,16-19] Six serial 10-fold dilutions of an α_2-adrenergic agonist such as terbutaline (10^{-3} w/v to 10^{-8} w/v) are prepared. Each dilution (0.1 mL) is injected intradermally along the neck or the pectoral region. In normal horses, a localized area of sweat will appear at the site of injection at all concentrations, except perhaps the most dilute concentration (i.e., 10^{-8}). The amount of sweat produced at each site is proportional to the concentration of terbutaline injected (Fig. 41-13). Sweating will first be noted in normal horses within 5 minutes of injection at the higher concentrations. Onset of sweat production may be delayed and amount of sweat produced reduced in hypohidrotic horses, or hypohidrotic horses may only sweat at the higher concentrations of terbutaline. Anhidrotic horses do not sweat, even at the highest concentration.

While failure to sweat in response to intradermal terbutaline injection confirms a diagnosis of anhidrosis, horses that are hypohidrotic may continue to produce sweat, even at the lower concentrations. For these horses, a lunge test will help confirm the diagnosis. Body temperature, heart rate, and respiratory rate are recorded. The horse is then lunged at a trot for 30 minutes on a hot day. During this time, the horse is observed for evidence of sweat production. Body temperature, heart rate, and respiratory rate measurements are made immediately at the end of lunging and every 10 minutes thereafter for the next 30 minutes. While the heart rate response reflects the degree of fitness, the body temperature and respiratory rate responses correlate better to the horse's ability to cool itself. If the horse's respiratory rate is not back to what it was before the onset of lunging by 30 minutes after the end of the exercise, it is highly likely that the horse is having a problem cooling.

The most likely differential diagnoses for hypohidrosis include various respiratory diseases. In the author's experience, some hypohidrotic or anhidrotic horses also have mild airway inflammation, documented most often by increased mast cells or eosinophils in bronchoalveolar lavage fluid. It is unknown whether the two problems coexist coincidentally or if there is a mechanistic link. Either way, it is likely that airway inflammation would decrease the ability of a horse to use its respiratory system to help cool itself, and this is likely to be more critical in a horse that cannot sweat.

Treatment, Prevention, and Prognosis The only consistently successful treatment is movement of the horse to a cooler environment, although this is not always practical or feasible. Other environmental or dietary alterations may or may not be helpful. For hypohidrotic horses or horses that are having their first episode of anhidrosis, it is important to stop any workload and decrease the stress level. Concurrent disease conditions such as airway inflammation should be appropriately treated. Shade, fans, misting fans, and window air conditioners can be used to try to decrease the temperature in the horse's local environment. Applying water by hose or sponging the horse with water during the hot part of the day can take the place of sweat. Electrolyte supplementation (especially KCl) has been advocated,[17,18] and various products that appear to help some but not all horses are available commercially. One such supplement (One AC, MPCO, Phoenix, Ariz.) contains L-tyrosine, ascorbic acid, niacin, and cobalt and claims to improve sweat production by supplying precursors to dopamine synthesis. The theory is that dopamine improves skin vasodilation, resulting in increased blood flow to sweat glands during exercise. To the author's knowledge, no studies at present support or deny this claim. Other treatments that have been used with mixed success include vitamin E administration,[20,21] acupuncture, and Chinese herbs.[17,18]

Medical therapy of anhidrosis has primarily been unrewarding. Anecdotally, the α_2-adrenergic agonist clenbuterol increases sweat production in hypohidrotic horses and may be useful if used sparingly, only when weather conditions are particularly bad (i.e., extremely high heat and humidity). However, traditional recommendations are to avoid use of α_2-adrenergic agonists in hypohidrotic horses because their use may precipitate complete anhidrosis.[22] In a recent study, oral clenbuterol administration was shown to lose its beneficial effect on airway reactivity after 21 days of administration.[23] In that same study, prolonged clenbuterol administration had no effect on results of intradermal terbutaline sweat tests. However, the horses used in that study were neither hypohydrotic nor anhidrotic. The effect of prolonged clenbuterol administration on sweating or response to intradermal sweat tests in anhidrotic horses has not been reported. There is increasing evidence in human medicine that combination treatment of chronic airway disease with both α_2-adrenergic agonists and corticosteroids results in a synergistic effect, with corticosteroids helping to prevent desensitization and tolerance to α_2-adrenergic agonists and α_2-adrenergic agonists potentiating the antiinflammatory effects of the corticosteroids.[24,25] Thus combination therapy may be useful in hypohidrotic horses, but to date no controlled studies have been performed. Corticosteroid therapy may also be useful if there is an immune component to the pathogenesis of anhidrosis.

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Once a horse has had an episode of anhidrosis, there are certain measures that can be taken to try to prevent recurrence of the problem in subsequent years. Before the hot part of the year begins, start the horse on any supplements that have been helpful previously and make certain the horse is cardiovascularly fit. Also, make sure that any respiratory problems are under control before the onset of hot weather. As the hot season approaches, try to avoid procedures that might require administration of heavy doses of α_2 sedatives (e.g., xylazine, detomidine) that stimulate the horse to sweat. Plan to do these procedures during the cooler parts of the year. During hot periods, work the horse only during the cool parts of the day. Use external water sources to decrease the need for the horse to sweat.

The prognosis for hypohidrotic horses is guarded for future athletic performance in a hot environment. It is the author's opinion that the longer an anhidrotic horse has been left untreated or unmanaged, the less likely the horse will be to sweat again despite any of the treatments described earlier. However, if an underlying disease or problem can be identified and treated successfully in a horse that is just becoming hypohidrotic, the likelihood that the horse will sweat better the following season is improved.

Thyroid Disease

Babetta Breuhaus

Thyroid gland physiology and control of thyroid hormone secretion in horses is similar to other species. Thyroid hormones are important for growth, maturation of organ systems, and regulation of metabolism. They stimulate protein synthesis and catabolism, increase body heat production, and stimulate basal metabolic rate. The thyroid gland concentrates iodides from the blood and synthesizes and secretes both thyroxine (T_4) and tri-iodothyronine (T_3). Once secreted, thyroid hormones circulate both bound to proteins and unbound ("free"), with the free fractions being the active fractions. T_3 is more metabolically active than T_4, and although some T_3 is secreted by the thyroid gland along with T_4, the main source of T_3 in the body is from conversion of T_4 to T_3 in peripheral tissues.

Thyroid hormone secretion is regulated by the hypothalamus and pituitary. Thyrotropin-releasing hormone (TRH), made in the paraventricular nucleus and released from the median eminence of the hypothalamus, stimulates release of thyroid-stimulating hormone (TSH) from the anterior pituitary, which travels in the blood to the thyroid gland to stimulate release of thyroid hormones. Circulating thyroid hormones exert negative feedback on the hypothalamus and pituitary to limit further release of TRH and TSH. Neurotransmitters that play a role in thyroid hormone regulation include α-adrenergic agonists (stimulatory) and somatostatin and dopamine (inhibitory). Glucocorticoids and the cytokines TNF and IL-1β also inhibit TSH secretion.

Alterations in thyroid hormone status that have been described in horses include thyroid gland neoplasia, hyperthyroidism, and hypothyroidism. Certain drugs, diets, and physiologic or pathophysiologic states can also influence circulating thyroid hormone concentrations. Although equine thyroid dysfunction has been reviewed recently,[1] several studies of equine thyroid function and dysfunction have been performed or are in progress since that time.

Thyroid Gland Neoplasia

Thyroid gland neoplasias are not uncommon, and it is not unusual to find them as incidental findings during necropsy of older horses.[2,3] Thyroid adenomas are most common, but other reported thyroid neoplasias include carcinomas, adenocarcinomas, and C-cell tumors. Although there are also scattered case reports in the literature of horses that were found to be hypothyroid or hyperthyroid due to a thyroid tumor, most thyroid gland tumors are benign and nonfunctional. The glands enlarge physically, but usually there is no metastasis and circulating thyroid hormone concentrations remain within normal limits. As such, treatment of most thyroid gland neoplasias is unnecessary, until or unless the glands become big enough to start to interfere with swallowing or breathing. Once a thyroid gland tumor becomes enlarged enough for the owner to notice it, a reasonable approach would be to measure circulating thyroid hormones (both total and free concentrations of T_4 and T_3). Provided that circulating thyroid hormone concentrations are normal, and provided that the horse is comfortable and the tumor is not big enough to interfere with alimentary or respiratory function, surgical removal is not mandatory. The size of the gland should be monitored. If the gland starts to enlarge rapidly or if circulating thyroid hormone concentrations increase, then the gland should be removed surgically sooner, not later. After thyroidectomy, the horse will need to be treated with thyroid hormone supplementation to maintain circulating concentrations of thyroid hormones within the normal range.

Hyperthyroidism in Adult Horses

Hyperthyroidism is extremely rare in horses. There are three documented case reports in the literature, and all of these have been associated with thyroid gland neoplasias.[4-6] Circulating thyroid hormone concentrations are also sometimes temporarily increased in horses exposed to excess iodine, such as in a topical blister. Clinical signs of hyperthyroidism in horses include weight loss, tachycardia, tachypnea, hyperactive behavior, ravenous appetite, and cachexia. Diagnosis is confirmed by measurement of increased circulating concentrations of thyroid hormones. A T_3 suppression test can also be performed. Treatment of a hyperactive thyroid tumor has generally been thyroidectomy. It is recommended that biopsy and nuclear scintigraphy be performed before thyroidectomy to determine if both right and left sides of the thyroid gland are hyperplastic. If so, removal of only one side may obviate the need for postoperative thyroid hormone supplementation. It is also possible for one side of the gland to be hyperactive while the other side is normal or suppressed. In this situation, nuclear scintigraphy is important to identify which side of the gland needs to be removed. In one case report, a hyperthyroid horse was treated successfully with oral propylthiouracil.[6] The horse responded rapidly to treatment that was initiated at 8 mg/kg once daily and then maintained at the same dose every other day.

Hypothyroidism in Adult Horses

Hypothyroidism is poorly understood in the horse, and its existence is controversial. Although autoimmune thyroid disease is somewhat common in people and dogs, it has only been described in one report of histologic changes found at necropsy in a group of horses in Eastern Europe.[7] The prevalence of true hypothyroidism in adult horses is unknown but is almost certainly overestimated. Hypothyroidism has been thought to contribute to a variety of problems in the horse, including obesity, laminitis, anhidrosis, recurrent rhabdomyolysis, and poor fertility. However, proper documentation of hypothyroidism in such cases for the most part does not exist. Anecdotal reports of beneficial effects of thyroid hormone supplementation in these horses are also largely unsubstantiated. Despite this, many horses with these conditions receive thyroid hormone medication over extended periods of time, and many of them do not really need it. Besides the obvious waste of money, potential health risks associated with unnecessary thyroid hormone supplementation have only been explored minimally in horses.[8] In humans, thyrotoxicosis or oversupplementation with levothyroxine can result in decreased bone density, increased risk of atrial fibrillation, and perhaps increased risk of myocardial infarction or precipitation of congestive heart failure.[9]

Clinical signs of hypothyroidism in adult horses appear to be subtle. Traditionally, horses that gained weight easily, had cresty necks, and tended to suffer from recurrent bouts of laminitis were thought to be hypothyroid. However, in the author's experience, thyroid function tests in horses that fit this description are usually normal and it is more likely that these horses either have PPID or

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equine metabolic syndrome. In a few published case reports of horses that were documented to be hypothyroid, clinical signs were primarily lethargy, exercise intolerance, and poor haircoat.[10-12] In experiments in which horses were made hypothyroid, either by surgical removal of the thyroid glands or by administration of antithyroid drugs,[13-25] obesity and laminitis were not reported. Although resting heart rate, cardiac output, respiratory rate, and rectal temperature decreased in horses after thyroidectomy,[17] and serum concentrations of triglycerides, cholesterol, and very-low-density lipoproteins increased,[16] the changes were mild and absolute values remained within the normal reference interval for adult horses. For this reason, measurement of these values would not help identify a hypothyroid horse in the general population.

Other Alterations of Thyroid Function

Certain physiologic states, drugs, diets, and pathologic states can alter thyroid hormone synthesis, metabolism, or binding, resulting in altered serum concentrations of thyroid hormones. For example, fasting lowers circulating concentrations of thyroid hormones in many species studied, including the horse.[26] Phenylbutazone or dexamethasone administration, strenuous exercise, and diets high in energy, protein, zinc, and copper have also been shown to alter circulating concentrations of thyroid hormones in horses.[27-35]

Nonthyroidal Illness Syndrome

Nonthyroidal illness syndrome has been described in humans, dogs, and cats suffering from systemic illnesses but has not been studied extensively in horses. A preliminary report by the author suggests that nonthyroidal illness syndrome is similar in adult horses compared with other species.[36] Thyroid hormone concentrations have also been reported to be lower in sick and septic foals compared with age-matched healthy foals.[37,38] In the more recent study, thyroid hormone concentrations were inversely correlated to sepsis score, and nonsurviving septic foals had lower concentrations of total and free T_4, as well as total and free T_3, compared with surviving septic foals. In humans, milder forms of illness result in decreases in serum concentrations of T_3, with T_4 remaining within the normal range or only slightly decreased. As nonthyroidal illness becomes more severe, total T_4 decreases and eventually free T_4 also begins to decrease. The magnitude of thyroid hormone suppression has been correlated to severity of disease and to mortality.[39-41] Mechanisms by which thyroid hormones decrease during illness include decreased peripheral conversion of T_4 to T_3 by 5′-deiodinase, altered binding to serum carrier proteins, and hypothalamic-pituitary dysregulation or suppression.[41-45]

Fescue Ingestion

Tall fescue *(Festuca arundinaceae)* is a perennial grass that is grown commonly in the Southeast because it is relatively easy to establish, has a long growing season, and has good disease and drought resistance that allows it to survive hot, humid summers. A variety of reproductive problems have been described in mares consuming fescue, and these have been shown to be caused by alkaloids produced by an endophytic fungus *(Neotyphodium coenophialum)* that lives symbiotically on the fescue plant and acts as a dopamine agonist (for a review, see Evans 2002).[46] Because TSH release from the pituitary is inhibited by dopamine,[47] it has been suggested that fescue consumption could lead to secondary hypothyroidism. Fescue ingestion was proposed as the cause of lower serum TSH concentrations in mares and foals consuming endophyte-infected fescue on a farm in central Kentucky compared with mares and foals on a nearby farm grazing pastures that were mainly free of endophyte-infected fescue.[48] However, the author found no differences in baseline concentrations of thyroid hormones or TSH, or in their responses to administration of TRH, in adult, nonpregnant horses fed endophyte-infected fescue seed for 2 months.[49] It appears that dopamine acts more as an acute modulator of TSH secretion, rather than as the primary control. In humans, while acute dopamine blockade results in increased TSH secretion and increased circulating thyroid hormones, chronic administration does not cause long-term alterations in thyroid hormone status.[47] Thus it is likely that compensatory mechanisms override any dopaminergic effect of chronic fescue ingestion in the horse.

Syndromes Associated with Hypothyroidism

OBESITY. As mentioned earlier, horses that gain weight easily and have a tendency to deposit fat in the crest of the neck, over the rump and tailhead, or in the sheath have long been regarded as hypothyroid. It is now known that these horses are likely to have normal thyroid function and to be insulin resistant. Anecdotally, thyroid hormone administration to these horses usually does not result in weight loss. This is especially true if feed consumption is not restricted and if the amount of thyroid hormone supplementation is titrated to maintain serum thyroid hormone concentrations in the normal range. However, administration of levothyroxine at a dose of approximately 0.1 mg/kg/day (48 mg) for 48 weeks was associated with weight loss and increased insulin sensitivity in six healthy, euthyroid mares, despite the fact that they had access to pasture and a round bale of hay during the day and were given hay at night when they were stalled.[8,50] Although serum total T_4 concentrations increased four to five times their presupplementation concentrations, no adverse health effects were observed. Thus when used to help obese horses lose weight, the amount of thyroid hormone given needs to be enough to make the horse mildly hyperthyroid. It is preferable for feed intake to be controlled at 1.5% to 2% of the desired body weight per day, consisting of grass hay or other feed that is low in soluble carbohydrates. It is important to understand that when thyroid hormones are administered in this manner, they are being used as a pharmacologic tool and should only be given for a short period of time; lifelong administration is not indicated.

LAMINITIS. A role for decreased thyroid function in the pathogenesis of laminitis is poorly documented and remains a controversial topic. Although decreased serum thyroid hormones have been associated with some horses that experience acute laminitis, it is unlikely that decreased thyroid function alone causes laminitis. In 13 studies in which hypothyroidism was induced either by surgical removal of the thyroid glands or by administration of propylthiouracil, laminitis did not occur.[13-25] Thus any alterations in serum thyroid hormone concentrations in horses experiencing laminitis may be caused by factors associated with the episode of laminitis, rather than the cause of the laminitis itself. Such factors could include drugs used to treat laminitis (e.g., phenylbutazone), development of nonthyroidal illness syndrome, or a direct effect of factors such as endotoxin or one of the inflammatory cytokines that contribute to the onset of laminitis in some cases. In the author's experience, TRH stimulation tests performed in horses that have suffered an episode of laminitis or that have had bouts of recurrent laminitis show normal thyroid hormone responses when these tests are performed once the horse is stabilized and has been off all medications for 4 weeks.

Despite evidence of normal thyroid function in horses with laminitis, some veterinary clinicians still believe that treatment of horses with iodinated casein during an acute episode of laminitis results in improvement. These horses are often treated without prior measurement of thyroid hormones. Some are treated even when measurement shows serum thyroid hormone concentrations to be within the normal range. These horses are then often kept on thyroid hormone supplementation indefinitely. To date, no controlled studies have been performed to determine whether or not administration of thyroid hormones during acute episodes of laminitis is beneficial. However, because the action of β-adrenergic agonists on vasculature is usually vasodilatory, it is possible that thyroid hormone administration increases circulation to the foot by its ability to potentiate β-adrenergic receptor numbers and sensitivity.[51-53] Or it is also possible that thyroid hormone supplementation alters carbohydrate and fat metabolism in a way that increases insulin sensitivity.[54] Thus any beneficial effect of thyroid hormone administration in horses suffering from laminitis may be pharmacologic rather than physiologic.

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ANHIDROSIS. Anhidrosis is a condition of adult horses characterized by a decreased ability or inability to sweat in response to appropriate stimuli. The cause is unknown. Hypothyroidism has long been associated with anhidrosis, perhaps because treatment with iodinated casein was reported to help increase sweat production in anhidrotic horses in the 1950s.[55] However, the author found that baseline concentrations of thyroid hormones and TSH were normal in horses with anhidrosis.[56] Thyroid hormone responses to TRH were also normal, but TSH responses to TRH were significantly greater in anhidrotic horses than they were in horses with normal sweat production. The clinical significance of this greater TSH response to TRH in anhidrotic horses is unknown. As for laminitis, it is possible that any observed benefit of thyroid hormone supplementation is pharmacologic rather than physiologic. Because equine sweat glands are stimulated to secrete by activation of β_2-adrenergic receptors and thyroid hormones modulate adrenergic receptor function, perhaps making horses mildly hyperthyroid iatrogenically restores β-adrenergic receptor numbers or sensitivity or potentiates sweat responses to whatever neural stimulation remains.

RHABDOMYOLYSIS. A link between hypothyroidism and rhabdomyolysis was suggested by a report of muscle stiffness, poor performance, and rhabdomyolysis in four Thoroughbred and two Standardbred racehorses that had low baseline T_4 concentrations.[57] The horses improved after administration of iodinated casein. However, T_4 response to TSH was normal in these horses. A subsequent study showed normal resting concentrations of T_4 but decreased T_4 response to TRH in five horses that had suffered previous episodes of rhabdomyolysis.[58] In a study of 18 Quarter Horses with polysaccharide storage myopathy and 18 Thoroughbreds with recurrent exertional rhabdomyolysis, circulating concentrations of T_4 and T_3 were within normal range. Stimulation tests were not performed.[59] Thus a role for hypothyroidism in the pathophysiology of equine rhabdomyolysis is unclear. Because it is now known that the clinical syndrome of rhabdomyolysis is caused by more than one underlying pathophysiologic etiology, it is possible that hypothyroidism may contribute to some, but not all, cases of equine rhabdomyolysis. If hypothyroidism is suspected, thyroid function should be assessed, ideally by measuring both resting concentrations of free thyroid hormones, as well as by response to TRH or TSH. If resting concentrations of free thyroid hormones are found to be low, nonthyroidal factors should be ruled out before thyroid hormone supplementation is prescribed.

INFERTILITY IN MARES. Thyroid hormone administration to broodmares has been a fairly common practice, despite lack of evidence that the mares were actually hypothyroid in the first place or evidence that thyroid hormone supplementation improves fertility of horses. This practice presumably is an extrapolation from human medicine, where hypothyroidism in women adversely affects fertility. However, two of three fillies that had undergone thyroidectomy became pregnant without thyroid hormone supplementation[13] and two additional publications showed no association between thyroid hormone status and conception rates in mares.[60,61] The first study was performed in 329 clinically normal broodmares.[60] Resting serum T_4 concentrations were below normal in 12% of the mares, normal in 86%, and increased in 6% of the mares. There was no association between serum T_4 concentration and whether or not the mare was pregnant 15 to 16 days after ovulation. There also was no association between whether or not the mare was receiving thyroid hormone supplementation (60 were, 269 were not) and pregnancy status. In the second study, resting serum concentrations of total T_4 and T_3, as well as their responses to TRH, were measured in 79 Thoroughbred and Standardbred broodmares.[61] Resting and stimulated thyroid hormone concentrations were not different between mares that became pregnant and mares that did not become pregnant.

Although the studies referenced earlier suggest there is no association between thyroid status and fertility or infertility in the mare, it is still possible that hypothyroidism contributes to infertility in a small subset of mares and that this effect is being lost among all the other potential causes of failure to conceive. However, given that true hypothyroidism appears to be rare in the horse, this would have to be a small number of mares, certainly not the number of mares that are currently being routinely supplemented. Is there any basis then to the clinical impression held by some that thyroid hormone supplementation helps some mares get pregnant? Perhaps if there is, it is more related to obesity, insulin resistance (IR), and equine metabolic syndrome than to hypothyroidism. Women with IR and metabolic syndrome are subfertile, and there is evidence that thyroid hormone administration to normal-weight mares increases insulin sensitivity.[50,54] Thus it is possible that insulin-resistant, overweight mares are subfertile, and thyroid hormone supplementation is beneficial, not because the mares were hypothyroid in the first place, but because it improves their insulin sensitivity. At the time of this writing, no studies have been performed to examine this hypothesis.

Assessment of Thyroid Function in Adult Horses

The thyroid glands of the horse can be assessed by measuring circulating concentrations of thyroid hormones, by measuring their responses to stimulants such as TRH or TSH, by testing the ability of administration of exogenous thyroid hormone to suppress endogenous hormone, by imaging (including ultrasound, computed tomography, magnetic resonance imaging, and nuclear scintigraphy), and by biopsy.

Reference ranges for thyroid hormone concentrations in healthy adult and neonatal foals have been published.[1] Donkeys appear to have higher circulating thyroid hormone concentrations than do horses.[62] Because certain drugs and pathophysiologic states can lower serum concentrations of thyroid hormones in otherwise euthyroid horses, it is important that thyroid hormone measurement or function tests not be performed while horses are ill, are receiving certain drugs, or are on thyroid hormone supplementation. The author recommends that thyroid hormone testing be performed in horses that have not received any medications for at least 2, and preferably 4, weeks before testing. If a horse has been receiving thyroid hormone supplementation without prior documentation of hypothyroidism, the author recommends weaning the horse off supplementation and then testing thyroid function once the horse has not received any supplementation for at least 4 weeks.

Tests that are currently available for assessment of thyroid function in the horse include measurement of total and free fractions of T_4 and T_3 and response of these hormones to administration of either TRH or TSH.[27-29,58,63-66] Although results of TRH or TSH stimulation tests are thought to provide a better indication of thyroid status than single point-in-time measurements of thyroid hormone concentrations, these tests are not routinely performed by ambulatory clinicians because of the impracticality of having to take multiple blood samples over time. In addition, TRH and TSH have not always been readily available commercially for sterile, single-dose application or at times have been prohibitively expensive.

To perform a stimulation test, a control blood sample is obtained, TRH (1 mg to the average 450- to 500-kg horse) or TSH (5 IU) is given intravenously, and subsequent blood samples are obtained. Most references say that T_3 should double at 2 hours, and T_4 should double at 4 hours. The author routinely performs TRH stimulation tests and prefers to measure both T_3 and T_4 before and 1, 2, and 4 hours post TRH administration, in order to make sure the peaks are not missed. In 36 normal horses that participated in various studies conducted by the author, the mean increase in total T_4 was 2.2 times at 4 hours. However, the range was 1.3 to 3.8 times. Increases in free T_4 and free T_4 by dialysis (mean and range) were 1.7 (1.1 to 2.1) times and 1.8 (1.1 to 2.8) times at 4 hours, respectively. Increases in total and free T_3 (mean and range) were 3 (1.1 to 10.3) times and 4.2 (1 to 53) times at 2 hours, respectively. These seemingly lower thyroid hormone responses to TRH injection are in agreement with findings in a recent report of levothyroxine administration to normal horses.[67] Closer examination of the data from the author's horses revealed that, in general, the few individuals with small increases in T_4 or T_3 either

started with higher resting values or had peaks that occurred later (T_4) or earlier (T_3) than 4 or 2 hours. Individuals with lower T_4 responses in general were not the same individuals with lower T_3 responses. Thus one must be careful when interpreting results of a TRH stimulation test. Failure of T_3 to double by 2 hours or T_4 to double by 4 hours after TRH injection does not necessarily mean that the horse is hypothyroid. Individuals with high responses tended to be individuals with very low resting thyroid hormone concentrations.

If single point-in-time measurement of thyroid hormones is the only option available for evaluation of thyroid status, measurement of free fractions of thyroid hormones (alone or in conjunction with measurement of total amounts of hormone) provides more useful information than measurement of total amounts of thyroid hormones alone. Measurement of serum TSH concentrations in single samples will also likely aid diagnosis of thyroid status, once a TSH assay for the horse becomes commercially available.

During illness in humans, measurement of serum free T_4 by direct methods often underestimates values, when compared with measurements of free T_4 after dialysis or ultrafiltration.[68-72] This also appears to be the case in dogs[73] and horses.[36] Thus serum concentrations of free T_4 measured by equilibrium dialysis are more likely to reflect true thyroid status in ill horses, compared with other methods of free T_4 measurement. Measurement of fT_4D instead of fT_4 may help prevent equine clinicians from misdiagnosing ill horses as being hypothyroid.

A T_3 suppression test has been described[5,6] and may be useful to confirm hyperthyroidism. A blood sample is obtained before IM administration of 2.5 mg 3,5,3′-triiodothyro-L-thyronine (T_3) diluted in 5 mL of sterile saline, given twice daily for 7 doses (4 days). Additional blood samples are drawn 5 minutes before each dose of T_3 and then twice daily on days 5 and 7 and in the morning of day 10. In normal horses, T_4 and T_3 measurements will be within reference range in the control blood sample. Administration of exogenous T_3 should result in a 10- to 20-fold increase in T_3 concentration while T_4 gradually decreases, remaining suppressed for at least 5 days after the last dose of T_3. In hyperthyroid horses, control blood samples will have increased concentrations of T_4 and T_3. The increase in serum T_3 after T_3 administration is not as pronounced as in normal horses, but T_3 does remain increased throughout the administration period. T_4 does not suppress.

Ultrasound imaging is most likely to be performed when thyroid glands are enlarged. Ultrasound imaging can differentiate enlargement due to solid tissue versus cystic fluid. It is also useful as an aid in getting a representative biopsy sample. Nuclear scintigraphy is useful to demonstrate gland activity, which may or may not be equal in the right and left lobe.

Treatment of Hypothyroidism in Adult Horses

Management of horses that have been properly diagnosed as being hypothyroid or horses that have undergone thyroidectomy theoretically should be fairly straightforward. Serum thyroid hormone concentrations should be monitored, and dosages of thyroid hormone supplementation should be adjusted to maintain serum thyroid hormones in the normal range. This is not necessarily as simple as it sounds. T_4 is the most common form of thyroid hormone supplementation, and although T_4 administration increases serum concentrations of T_4, serum concentrations of T_3 may not change or may actually decrease if T_3 is not also given or if the horse is not truly hypothyroid. In addition, T_4 dosage recommendations have been made on the basis of thyroid hormone concentrations obtained after thyroid administration to normal horses with intact thyroid glands.[74] Thyroid hormone pharmacokinetics may be different in truly hypothyroid horses; pharmacokinetic studies in horses made hypothyroid by thyroidectomy or by administration of antithyroid drugs would be useful. Until such studies are performed, the following recommendations can be made. T_4 is available in several forms. Iodinated casein contains approximately 1% T_4 and is given at 5 to 15 g/horse/day PO.[13] The recommended starting dose of levothyroxine was 20 µg/kg horse/day PO,[74,75] but a more recent study suggested that doses as high as 50 to 100 µg/kg/day are well tolerated and may be necessary.[67] If a sensitive TSH assay becomes commercially available, dosages should be adjusted to normalize TSH.

Thyroid Function in Normal Neonatal Foals

Fetal concentrations of T_3 and cortisol are low.[76] In many species, fetal serum thyroid hormones increase just before birth and probably play a role in the rapid growth and organ system development that occur in late gestation. Normal neonatal foals have serum concentrations of thyroid hormones that are approximately 10 times adult concentrations.[37,77,78] Thyroid hormones remain high during the first week of life and then slowly decline, reaching normal adult concentrations by approximately 1 month of age. These high concentrations of thyroid hormones are thought to be important in maintaining thermogenesis, regulation of cell differentiation, and maturation of many body systems, especially the respiratory, nervous, and musculoskeletal systems. Thyroid hormones increase thermogenesis by increasing metabolic rate and, of particular relevance to the neonate, increasing heat production from brown fat.[79] Thyroid hormones also stimulate lung development and surfactant production, and these effects are potentiated by concurrent administration of glucocorticoids.[80] Skeletal growth and maturation are stimulated synergistically by thyroid hormones and growth hormone.[81] The mechanism or mechanisms by which thyroid hormones are increased in the peripartum period are unknown. One might expect the increase to be centrally driven. However, in a study by the author,[37] serum TSH concentrations were not increased in equine neonates, compared with adults, nor did they change over the first month of life, while serum thyroid hormone concentrations were declining.

Thyroid Function in Premature Foals

Premature human infants experience transient hypothyroxinemia, with serum T_4 concentrations correlated to gestational age.[82-85] In a study by the author, serum concentrations of total and free thyroid hormones and TSH, both at rest and in response to TRH, were measured in normal, healthy neonatal foals that were full term (normal foals), in premature neonatal foals (premature foals), and in full-term neonatal foals that were ill and hospitalized for conditions similar to premature foals (sick foals) to determine the possible contributions of an immature hypothalamic-pituitary axis and nonthyroidal illness to thyroid dysfunction in premature foals.[37] Normal foals did not receive any medications. Both sick and premature foals received medications routinely used to treat conditions including (but not limited to) failure of passive transfer, sepsis, and perinatal asphyxia syndrome. Blood samples were collected for measurement of baseline concentrations of thyroid hormones and TSH at predetermined ages, and TRH stimulation tests were performed in foals younger than 3 days of age. Premature foals had significantly lower serum concentrations of total and free fractions of thyroid hormones than normal foals. Baseline serum concentrations of TSH were not different, but TSH responses to TRH were exaggerated in premature foals compared with normal foals. Serum concentrations of T_3 and TSH were similar in sick term foals and premature foals, but serum concentrations of T_4 in sick term foals were intermediate between premature and normal foals. These results suggest that sick foals experience nonthyroidal illness syndrome, primarily a low T_3 state. The effect of drugs commonly used to treat ill foals on serum thyroid hormone concentrations in the premature and sick foals in this study were not examined. More profound alterations in thyroid function in premature foals, compared with sick term foals, may be caused by an immature hypothalamic-pituitary-thyroid axis. It remains to be seen whether early thyroid hormone supplementation in premature foals might improve short-term survivability and preserve long-term athletic function. Traditional thought has been that administration of thyroid hormones to patients with nonthyroidal illness syndrome is not beneficial and might even be detrimental. However, these beliefs have been challenged,[41,42] and the issue remains controversial.

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Although results are variable, treatment of premature human infants with T_4 has resulted in improved intelligence quotient (IQ) and neurologic development at 2 years of age[82,83] and may reduce the incidence of cerebral palsy in extremely preterm infants.[86] T_3 administration to human neonates with severe respiratory distress syndrome improved survival.[87] However, in a recent study, levothyroxine administration to premature infants was associated with development of late-onset refractory hypotension.[88] By increasing metabolism, levothyroxine therapy may lead to acute adrenal insufficiency.[89]

Congenital Hypothyroidism in Foals

Two syndromes of congenital hypothyroidism have been described in foals. Hypothyroid foals with visible goiters have been produced by mares ingesting either too much or too little iodine or by mares ingesting goitrogenic plants.[90-92] These foals are born weak, with poor sucking and righting reflexes, hypothermia, and developmental abnormalities of the musculoskeletal system, including tendon contracture or rupture and delayed bone development, particularly of the small cuboidal bones of the carpus and tarsus. Thyroid hormone supplementation to more severely affected foals may improve survivability, but dosage recommendations are scarce. Irvine recommends basing the dose on secretion rate.[81] For oral administration of T_4, this would equal $10 \times 0.22 \times$ kg body weight (BW) $\times 0.08 \times$ plasma T_4 (μg/L), or approximately 1 to 2.5 mg/day PO for a 1- to 3-day-old 50-kg foal. Because there is a time delay for T_4 to act, and because T_3 is more active than T_4, T_3 supplementation at one third the calculated T_4 dose may provide more benefit initially.

A second syndrome of congenital hypothyroidism has been described in foals, primarily in the western parts of the United States and Canada.[93-97] This syndrome is characterized by thyroid gland hyperplasia; increased gestational length and musculoskeletal abnormalities, including mandibular prognathia; flexural limb deformities of the front legs; ruptured digital extensor tendons; and incomplete ossification of the carpal and tarsal bones. Despite the prolonged gestation, other indicators of prematurity may be present, such as a silky haircoat. At the time of birth, baseline serum concentrations of T_4 and T_3 are usually within the normal neonatal ranges, but the response to TSH administration is decreased.[98] The cause is unknown but suspected to be a dietary deficiency or toxicity of the mare during gestation. Likely candidates include nitrate, low iodine, low selenium, or goitrogenic plant ingestion by the mare.[96,98] Because thyroid hormone concentrations are normal at the time of birth, thyroid hormone supplementation is usually not administered. Supportive care to try to prevent collapse of the carpal and tarsal bones is recommended.

Equine Metabolic Syndrome

Nicholas Frank

Definitions Equine metabolic syndrome (EMS) is a collection of endocrine and metabolic abnormalities associated with the development of laminitis in horses, ponies, and donkeys.[1] Fasting and postprandial hyperinsulinemia and IR are detected in horses with EMS and are forms of insulin dysregulation. Current research suggests that EMS has a genetic basis, with the phenotype developing when genetically predisposed animals encounter environmental factors that promote obesity and exacerbate insulin dysregulation. Although insulin dysregulation must be confirmed with blood testing, accompanying clinical signs of EMS, including generalized obesity, regional adiposity, and laminitis, are easily detectable. Other laboratory findings in horses with EMS include hypertriglyceridemia and hyperleptinemia. Clinical presentation varies among horses, with increased adiposity evident before laminitis in most animals. However, a lean EMS phenotype has also been observed and laminitis can develop in these animals before the syndrome is first recognized. Different subtypes of EMS are likely to be delineated in the future.

It is important to distinguish EMS from PPID (refer to previous section) yet recognize that both disorders can occur concurrently and influence one another. These disorders are compared in Table 41-1. If EMS is genetically determined and this underlying problem persists for the life of the horse, then PPID can develop and exacerbate glucose and insulin dysregulation.

Etiology EMS is likely to have a genetic basis and this is currently being investigated. The prevalence of EMS in specific breeds of horse has not been adequately assessed to date, but ponies, Morgans, Paso Finos, and Arabians are predisposed and other breeds are also represented. Affected horses are commonly referred to as "easy keepers" because they seem to require fewer calories to maintain body weight. Environmental factors including diet and exercise play important roles in the development of obesity and the EMS phenotype. Feeding grain to a susceptible animal is often enough to induce obesity, and the grass consumed on pasture represents a significant source of calories. Carbohydrate intake on pasture is influenced by grazing time, the area available for grazing, and the water-soluble carbohydrate (WSC) and starch content of pasture grasses. Amounts of these carbohydrates vary considerably by geographic location, climate, soil quality, and season. Equine metabolic syndrome affects adult horses and there is no reported sex predilection.

Clinical Signs and Differential Diagnoses Glucose and insulin dysregulation can only be detected through blood testing, but increased adiposity and laminitis are easily recognizable features of EMS in most cases. Many horses with EMS suffer from generalized obesity that can be assessed using the body condition score (BCS) system developed by Henneke and colleagues,[2] with obesity defined by a BCS of 7 or greater on a 1 (poor) to 9 (extremely fat) scale. A mare suffering from EMS is shown in Fig. 41-14. Regional adiposity is commonly detected in horses with EMS and can be present in the absence of generalized obesity in horses with the lean phenotype. Expansion of adipose tissues within the neck is commonly referred to as a *cresty neck,* and horses with this physical characteristic should undergo glucose and insulin testing. Mean neck circumference can be measured and recorded,[3] and a neck crest scoring system has been developed to assess horses and ponies with EMS.[4] Enlarged fat deposits may also be found close to the tailhead, within the prepuce or mammary gland region, or randomly distributed as subcutaneous masses. Abnormal fat deposits are also observed in horses with PPID and are more prominent in horses with the EMS genetic predisposition. Laminitis is sometimes the presenting complaint for horses with EMS and is detected by observing the horse's gait. Subclinical laminitis can be present in horses without the owner noticing and manifests as divergent growth rings ("founder lines") or radiographic evidence of third phalanx rotation or sinking. Lateral radiographs of the feet are recommended to fully assess horses with EMS.

Clinical Pathology Complete blood count and serum biochemical analysis results are usually unremarkable, with the exception of high-normal blood glucose concentrations in some cases and mildly increased plasma gamma glutamyl transferase (GGT) activity in obese horses and ponies. Plasma triglyceride concentrations are usually within reference range for the laboratory, although results of a recent study suggest that a lower cutoff value of 27 mg/dL can be used to screen horses for EMS.[5] Horses, ponies, and donkeys with EMS are susceptible to hyperglycemia and hypertriglyceridemia when challenged by systemic disease and hospitalization. Older horses concurrently affected by EMS and PPID may be more susceptible to this type of transient diabetes mellitus and require insulin therapy to control hyperglycemia and glucosuria.[6]

Low resting total triiodothyronine (tT_3) or total thyroxine (tT_4) concentrations are sometimes detected in horses with EMS, but the significance of this finding has been overstated in the past. It is a common misconception that obese horses suffer from

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TABLE 41-1

Comparison of Equine Metabolic Syndrome and Pituitary Pars Intermedia Dysfunction

Equine Metabolic Syndrome (EMS)	Pituitary Pars Intermedia Dysfunction (PPID)
Clinical Presentation	**Clinical Presentation**
Any mature horse Obesity and regional adiposity; prominent fat pads along the crest of the neck, above the tailhead, or in the prepuce/mammary gland; animals often described by owners as *easy keepers* A lean EMS phenotype is also recognized with regional adiposity Some affected horses appear normal but have excessive insulin responses to oral sugars Infertility or abnormal cyclicity in mares Subclinical or clinical laminitis; acute episodes occurring after exposure to pasture or feed with high sugar content Excessive insulin responses to oral sugars Commonly accompanied by insulin resistance	Begin evaluating horses at 10 years of age **Early PPID:** Subtle regional hypertrichosis and/or delayed shedding for a few weeks; duller, coarser haircoat Reduced muscle mass, shift in metabolism, poor performance **Advanced PPID:** Generalized hypertrichosis (hirsutism) Weight loss and skeletal muscle atrophy; rounded abdomen More pronounced fat deposits along the neck crest and in front of the tailhead in some cases Recurrent or chronic infections such as sinusitis, skin infection, dental disease, or hoof abscesses Reproductive abnormalities including infertility and persistent lactation Chronic laminitis in some cases
Pathophysiology	**Pathophysiology**
Not fully established Current theories focus on a genetic predisposition to insulin dysregulation; affected horses have excessive insulin responses to oral sugars Hyperinsulinemia might promote increased adiposity Obesity, lack of exercise, and PPID are modifying factors and lower insulin sensitivity, with insulin resistance exacerbating hyperinsulinemia Laminitis results from persistent hyperinsulinemia	Loss of dopaminergic inhibition leads to hyperplasia and hypertrophy within pituitary pars intermedia Excessive proopiomelanocortin (POMC) production with resulting increased α-melanocyte-stimulating hormone, adrenocorticotropin hormone, corticotropin-like intermediate peptide, and β-endorphin production
Management Goals	**Management Goals**
To reduce glucose and insulin responses to oral sugars by limiting the sugar content of the diet Limit access to pasture To induce weight loss if obese by restricting caloric intake To improve insulin sensitivity through weight loss and exercise Appropriate farrier care	Improvement in clinical signs and hormone concentrations through pergolide treatment Provision of supportive care including body clipping, appropriate farrier care, dentistry, and nutrition



FIG. 41-14 Photograph of a 7-year-old Morgan horse crossbred mare that suffers from equine metabolic syndrome.

hypothyroidism because obesity is associated with hypothyroidism in dogs and humans. However, advanced testing rarely supports a diagnosis of hypothyroidism in horses with EMS, with most animals having normal TRH stimulation test results. Low tT_3 and tT_4 concentrations in horses with EMS are more likely to reflect extrathyroidal changes in thyroid hormone metabolism or low thyroid-stimulating hormone (TSH) concentrations. Phenylbutazone is an extrathyroidal factor that significantly lowers serum tT_4 concentrations in horses because of protein binding, and this drug is commonly used to treat laminitis.[7]

Thyroid-stimulating hormone concentrations vary as the body adapts to different metabolic states,[8,9] and this might also explain why low thyroid hormone concentrations are detected in some horses with EMS. This is referred to as secondary hypothyroidism and can be confirmed by measuring TSH concentrations. Unfortunately, diagnostic laboratories do not measure TSH in equine blood at present, so it is difficult to determine the prevalence of secondary hypothyroidism. Levothyroxine supplementation is controversial in these cases because physiologic adaptation does not require treatment. In the author's opinion, levothyroxine supplementation should be reserved for horses with persistently low free thyroxine concentrations or abnormal TRH stimulation test results. Levothyroxine is also administered at higher dosages for 3 to 6 months to accelerate weight loss, and that protocol is described later.

Diagnostic Testing Morphometric measurements, including body condition score, midneck circumference, cresty neck score, height, and girth at the withers and umbilicus should be recorded. Insulin status must also be assessed, and recommendations have changed since the American College of Veterinary Internal Medicine consensus statement was published in 2010.[1] An oral sugar test (OST) has been developed and is recommended as a screening test for postprandial hyperinsulinemia.[10] Horses from high-risk breed groups and those with a dam or sire that has suffered from EMS should be screened and managed proactively to reduce the risk of laminitis.

The oral sugar test is performed by fasting the horse overnight and then administering corn syrup (Karo Light, Cordova, Tenn.) orally using 60-mL catheter-tip syringes at a dosage of 0.15 mL/kg. Blood samples are then collected 60 and 90 minutes later, and insulin concentrations are measured. Results of initial studies with the OST suggest that insulin concentrations less than 45 μU/mL at 60 and 90 minutes are detected in healthy horses, values between 45 and 60 μU/mL are equivocal, and a concentration greater than 60 μU/mL at either time point indicates postprandial hyperinsulinemia.[5,10] When the OST is performed on the farm, the owner can administer the corn syrup and arrange for the veterinarian to arrive in time to collect the blood samples. An in-feed oral glucose test (OGT) can also be performed and involves fasting the horse overnight and then feeding a small meal containing dextrose powder (1 g/kg body

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weight) mixed with water and a small quantity of chaff or low-sugar chopped forage. Blood samples are collected 60 minutes later and an insulin concentration greater than 85 μU/mL is consistent with EMS.[11] Owners sometimes express concern about administering sugars to their horse when insulin dysregulation is suspected. Complications have not been reported, but an alternative approach is to measure the fasting insulin concentration first to detect moderate or severe insulin dysregulation and then proceed to the OST to fully assess the animal if the fasting insulin concentration is normal.

Fasting insulin concentrations provide evidence of insulin dysregulation in moderately or severely affected horses. Insulin concentrations should always be interpreted within the context of the type of assay used and reference range provided by the laboratory. When insulin is measured using a radioimmunoassay, hyperinsulinemia is defined by a fasting insulin concentration of greater than 20 μU/mL. Note that some laboratories provide insulin concentrations in pmol/L, and an approximate conversion factor of 7 is used to convert units from μU/mL to pmol/L. An endocrine and metabolic panel that has been developed to evaluate horses for EMS includes fasting glucose, insulin, leptin (reference range; <4 ng/mL), and triglyceride concentrations. The reference range for fasting glucose concentrations is less than 100 mg/dL (5.6 mmol/L), and it is important to include this measurement because diabetes mellitus is occasionally diagnosed in horses.[6]

An insulin tolerance test (ITT) can be used to measure insulin sensitivity and diagnose IR, but this test does not assess pancreatic insulin secretion and this is a significant limitation. However, this test can be used to assess horses when factors such as obesity or PPID are lowering insulin sensitivity and exacerbating hyperinsulinemia. If a conservative approach is preferred to allay concerns about inducing hypoglycemia, the ITT can be performed in two steps. Alternatively, the practitioner can move directly to the second step and monitor the horse closely for clinical signs of hypoglycemia. In the first step, horses are screened by injecting soluble (regular) insulin intravenously at a dosage of 0.03 IU/kg body weight. Blood is collected at 0 and 30 minutes, and glucose concentrations are measured using a hand-held glucometer. Insulin sensitivity is normal if the concentration decreases by 50% within 30 minutes. This insulin dose is too low to confirm the diagnosis of IR, however, so a second step must be performed when results of the first test are abnormal. The second test is performed on a different day with insulin administered at a 0.1 IU/kg dosage. Horses that fail to show a 50% reduction in blood glucose concentrations over 30 minutes at the higher dosage are insulin resistant.[12] Feeding the horse immediately after the 30-minute blood sample is collected limits the duration of hypoglycemia.

The combined glucose-insulin test (CGIT) can also be used to measure insulin sensitivity. This test involves collection of a baseline blood sample, IV infusion of 150 mg/kg BW 50% dextrose solution, immediately followed by 0.10 IU/kg BW regular insulin.[13] Blood samples are collected at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes postinfusion. Glucose and insulin responses must both be assessed. Insulin resistance is defined by blood glucose concentrations remaining above baseline for 45 minutes or longer. The insulin response is assessed by measuring insulin concentrations at 0 (preinjection) and 45 minutes. Insulin concentrations greater than 20 μU/mL at baseline or greater than 100 μU/mL at 45 minutes are considered abnormal. These values reflect the amount of insulin secreted by pancreatic beta cells in response to dextrose, as well as clearance rates for exogenous and endogenous insulin. This test does not, however, allow assessment of the insulin response to incretin hormones. This is a concern if postprandial hyperinsulinemia is the first manifestation of insulin dysregulation. There is a small risk of inducing hypoglycemia when the CGIT is performed, so 60 to 120 mL of 50% dextrose solution should be administered intravenously if muscle fasciculations or profound weakness develops. Note that stress is an important cause of transient IR that can significantly affect ITT and CGIT results. Horses should remain calm before and during the procedure to avoid false-positive results.

Pathophysiology

Limited scientific evidence has been presented to date to support a genetic basis for EMS,[14] but it has long been recognized that this condition is more common in certain breeds of horse, and results of ongoing genetics research are promising. If it is assumed that some horses are genetically predisposed to EMS, then diet and exercise are two important modifying factors that affect expression of the phenotype. For example, a genetically predisposed horse that is overfed will express the EMS phenotype, whereas the same horse remains healthy when kept in a lean condition and exercised regularly. Obesity is an important factor because it induces IR, and this raises insulin concentrations. Internal fat depots might also play an important role in the pathophysiology of EMS, and the concept of internal pathologic fat must be considered. Adipose tissues secrete inflammatory cytokines as obesity progresses,[15] and adipokine production shifts, with increased leptin secretion[16] and decreased adiponectin production in obese animals.[17] Adipose tissue deposits in different regions of the body might also respond differently as obesity develops. Higher concentrations of mRNA coding for IL-1β and IL-6 have been detected in nuchal ligament adipose tissue, when compared with adipose tissues from other regions of the body in horses.[18]

Current theories regarding the pathophysiology of EMS focus on insulin dysregulation because postprandial hyperinsulinemia links EMS to the development of laminitis on pasture. Laminitis has been experimentally induced in both ponies and Standardbred horses by infusing insulin intravenously at high levels,[19,20] and increased insulin responses to simple sugars are detected in horses and ponies with EMS.[10,11] Temporal relationships among the components of EMS are poorly understood. IR refers to the failure of insulin-sensitive tissues to respond to insulin, and skeletal muscle, adipose, and liver are the primary tissues affected. In the past, it has been assumed that hyperinsulinemia results from a compensatory increase in insulin secretion in response to tissue IR.[21] Decreased insulin clearance plays a role in this process, and lower C-peptide/insulin ratios are detected in horses with EMS.[22] However, it is also conceivable that hyperinsulinemia develops first and then insulin sensitivity decreases as excessive insulin downregulates tissue responses by homologous desensitization.[23] If horses are genetically predisposed to postprandial hyperinsulinemia, then IR might develop at a later time as the condition progresses.[23] Other factors such as obesity and PPID would contribute to this process by exacerbating IR.

Altered regulation of incretin hormones might contribute to the postprandial hyperinsulinemia detected in horses with EMS. Glucagon-like peptide 1 (GLP-1) and gastrointestinal polypeptide (GIP) are secreted from the small intestine in response to ingested sugars and other nutrients, and they stimulate the insulin secretion from pancreatic beta cells.[24] Incretin hormones raise insulin concentrations and slow gastric emptying as glucose concentrations increase after feeding, and this minimizes postprandial hyperglycemia. Both incretin hormones are degraded by the enzyme dipeptidyl transferase 4 (DDP4). Postprandial hyperinsulinemia in horses with EMS might therefore reflect increased incretin hormone secretion or slowed degradation by DPP4. Accordingly, an affected horse or pony grazing on pasture grass rich in sugars and protein might experience prolonged postprandial hyperinsulinemia.

Management

Once insulin dysregulation has been diagnosed, potential modifying factors must be fully assessed before deciding on a management plan. These factors include obesity, high-sugar diets, inadequate exercise, and concurrent PPID. For example, if obesity is present, the initial focus of management should be weight loss. If PPID has developed in a horse with EMS, pergolide should be prescribed. A thorough diet history is required, and the diet of the horse must be adjusted to decrease the amount of sugars and reduce energy intake if obesity is present. Horses should be regularly exercised, and this is an integral part of weight management plans.

Weight loss can be induced in obese horses by lowering energy intake and increasing exercise. Many horses with EMS are being

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overfed, and removal of grain from the diet is sufficient to induce weight loss. Pasture access should be restricted in obese animals because horses with EMS often maintain the same body condition unless grass intake is limited. Recommended strategies for limiting grass consumption include (1) housing the obese horse with EMS with a companion in a small grass paddock that is one third to one half of an acre (equivalent to a square with 120- to 150-ft dimensions) in size or (2) application of a grazing muzzle during turnout. Other methods of limiting grass intake include short (1-hour) turnout periods, strip grazing with an electric fence, or housing in a dirt paddock.

Each patient should be individually assessed before formulating a management plan. A mildly affected horse with EMS that is obese through overfeeding will generally respond well to energy restriction and can be allowed to graze on pasture with a muzzle in place. Grazing at night or in the early morning is safer for horses with EMS, except after a hard frost when grasses rapidly accumulate sugars.[24] In contrast, a severely hyperinsulinemic horse with recurrent laminitis should be held off pasture initially and then housing conditions adjusted over time after testing is repeated. The mildly affected horse with normal insulin concentrations after weight loss can return to pasture grazing, whereas the horse that is persistently hyperinsulinemic must remain in a small grass paddock.

If removing grain from the diet and limiting pasture access does not result in weight loss, the amount of hay fed should be progressively decreased. Hay should be fed in an amount equivalent to 1.5% to 2% of current body weight (e.g., 18 to 24 lb grass hay/day for a 1200-lb horse). If the horse is not losing weight after 4 weeks, the amount fed should be lowered to 1.5% of ideal body weight (15 lb hay/day for an ideal weight of 1000 lb). An obese horse or pony that is not losing weight after an additional 4 weeks can then be lowered to 1.0% of ideal body weight in hay (10 lb/day), but this is the minimum amount recommended. A balanced vitamin/mineral supplement or ration balancer should also be provided to all horses that are on hay-only diet to maintain adequate micronutrient and protein intake.

Attention must also be paid to the sugar content of the diet, and the importance of this component of the management plan depends on the severity of insulin dysregulation. Hay containing large amounts of simple sugars and hydrolyzable starches is a significant concern for severely affected horses, and owners of these animals should analyze their hay or purchase it from suppliers who provide these reports. In contrast, the mildly affected obese horse can remain on the same hay as before, just in smaller amounts. Mild and severe insulin dysregulation has not been defined through objective research, but the author has greater concern when OST insulin concentrations exceed 100 μU/mL at 60 or 90 minutes. Commercial laboratories including Equi-Analytical Laboratories, Inc. (Ithaca, N.Y.) analyze hay samples and provide percentages for water-soluble carbohydrate (WSC) and starch, which are added together to provide the nonstructural carbohydrate (NSC) percentage. Water-soluble carbohydrates include simple sugars and fructans, whereas cellulose and lignin are structural carbohydrates. Hay containing less than 10% NSC on a dry matter basis should be selected if available. If the NSC content of the hay is above this percentage, it can be soaked in cold water for 30 to 60 minutes before feeding to lower the soluble sugar content, although results vary considerably depending on the type of hay.[25] A number of commercial products are also available as bagged hay or forage alternatives if low-NSC hay cannot be purchased. Most horse owners also prefer to feed a small amount of concentrate to encourage horses to enter their stalls and consume supplements. A measuring cup of low-sugar commercial pelleted feed can be fed twice daily to obese horses when needed.

Some horses with EMS have a lean phenotype, although regional adiposity is often present. Increased adiposity can also take the form of internal adipose tissue depots that are harder to assess. Measuring plasma or serum leptin concentrations provides insights into the biological activity of these adipose deposits.[26] When hyperleptinemia (>4 ng/mL) is detected, it reflects increased leptin production from abnormal adipocytes and/or reduced sensitivity to this hormone at the hypothalamus. Leptin is sometimes referred to as the satiety hormone. Leptin resistance may contribute to the increased appetite observed in horses and ponies with EMS.

A horse with EMS that has a lean body condition is more challenging to manage. The first question to be addressed is whether the animal is concurrently affected by PPID, so horses older than 10 years of age should undergo testing. Others with the lean EMS phenotype include horses that were obese in the past and lost weight through diet and exercise plans. The modifying factors of obesity and lack of exercise have been addressed in these animals, but insulin dysregulation persists. Diets that provide energy with fat and fiber should be selected to maintain or increase body mass, including soaked molasses-free beet pulp with added vegetable oil. Many commercial low-sugar/low-NSC pelleted feeds are available for purchase, and fat can be provided as vegetable oil (0.5 to 1 cup twice daily), rice bran, or a high-fat concentrate.

Treatment

Two medical treatments are used to manage horses with EMS and both have specific indications. Levothyroxine sodium is administered to accelerate weight loss when (1) severe insulin dysregulation is present in an obese horse that cannot be exercised because of laminitis and (2) obesity persists despite diet and exercise management. When used for the management of obesity, levothyroxine sodium is administered at a high dosage level for 3 to 6 months to induce weight loss by increasing basal metabolic rate.

Levothyroxine sodium (Thyro-L, Lloyd, Inc., Shenandoah, Iowa) lowers body weight and improves insulin sensitivity in horses[25] and can be administered by mouth or in the feed at a dosage of 0.1 mg/kg body weight once daily. One teaspoon contains 12 mg levothyroxine sodium, so a horse with body mass 450 to 500 kg receives 48 mg (4 tsp) per day at this dosage level. A higher dosage is occasionally selected if there has been no change in body condition or weight after 3 months. A dosage of 0.15 mg/kg has been used in these cases. Treatment is continued until the horse reaches ideal body condition score or until the end of the 6-month period. When treatment is discontinued, the dosage is lowered to 0.05 mg/kg (24 mg for a 500-kg horse)/day for 2 weeks and then 0.025 mg/kg (12 mg)/day for 2 weeks. Medical problems have not been associated with the administration of levothyroxine to healthy horses for 12 months,[27] although some horses can exhibit increased activity and mild hyperexcitability when treated. Pasture access must be restricted when horses are treated with levothyroxine; otherwise, effects on body mass are compensated for by increased feed intake.

Long-term administration of levothyroxine at lower dosages is controversial. Although obese horses often have low or fluctuating resting thyroid hormone concentrations, low thyroid hormone concentrations accompany many systemic conditions and are not associated with adverse health effects. There is little medical justification for thyroid hormone supplementation at lower dosages in horses with EMS, but adverse health effects have not been reported.

Metformin hydrochloride is a biguanide drug that is commonly administered to control hyperglycemia and increase tissue insulin sensitivity in people suffering from diabetes mellitus. It has also been reported to improve resting insulin concentrations and proxy measures of insulin sensitivity in horses and ponies when administered at a dosage of 15 mg/kg PO q12h.[28] However, insulin sensitivity or indices of glucose and insulin dynamics did not improve in nonobese insulin-resistant ponies in a subsequent study.[29] This discrepancy may be explained by the relatively low oral bioavailability of the drug, which is reported to be 7.1 ± 1.5% in fasted horses and 3.9 ± 1% in fed animals.[30] Although metformin has low oral bioavailability in horses, results of a recent study show that the drug acts at the level of the intestine to blunt glucose and insulin responses during oral glucose tolerance tests.[31] The current recommendation for metformin is 30 mg/kg PO q8-12h to control postprandial hyperglycemia and hyperinsulinemia in horses with EMS. Metformin should ideally be given 1 hour before the horse is fed or turned out on pasture.

Parathyroid Gland, Calcium and Phosphorus Regulation

Ramiro E. Toribio

Calcium

Calcium is the fifth most abundant element in the body, representing approximately 1.5% of the body weight. Physiologic functions such as muscle contraction, hormone secretion, enzyme activation, cell division, cell membrane stability, neuromuscular excitability, and blood coagulation are calcium dependent.[1-3] Processes that result in cell injury and death, such as free radical production, cytokine release, protease activation, vasoconstriction, and apoptosis, also require calcium.[2,3]

Calcium has structural and nonstructural functions, and it is found in three main compartments: the skeleton, soft tissues, and extracellular fluid. Approximately 99% of the total body calcium (and 80% of phosphorus) is in the skeleton as hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) in a calcium-to-phosphorus ratio of 2:1. As part of the skeleton, calcium provides support against gravity, protects vital internal organs, and houses blood-forming elements. The skeleton is also a reservoir for calcium. The nonstructural functions are related to calcium as a regulatory ion. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and in the extracellular fluid.[1-3] In blood, most calcium is in plasma as a free or ionized form (≈55%), bound to proteins (≈40%), and complexed to anions such as citrate, bicarbonate, phosphate, and lactate (≈5%) (Fig. 41-15).[1-4] In adult horses, serum ionized calcium represents 50% to 55% of the total serum calcium, while in foals ionized calcium is 43% to 56% of the total serum calcium.[2-8] Free, unbound, or ionized calcium (Ca^{2+}) is the biologically active form of calcium. Of the protein-bound calcium, approximately 80% is associated with albumin and 20% with globulins. Calcium binds to negatively charged or anionic proteins, and this affinity is pH dependent. During acidosis, increased H^+ concentrations decrease Ca^{2+} binding to anions, resulting in increased plasma Ca^{2+} concentrations. Alkalosis lowers Ca^{2+} concentrations. Hypoalbuminemia results in total hypocalcemia (pseudohypocalcemia), with Ca^{2+} concentrations remaining within the normal range.

Calcium and phosphorus requirements in horses depend on age, physiologic status, and amount of work or exercise performed (Table 41-2). Serum Ca^{2+} concentrations are not a reliable indicator of dietary calcium intake. A balanced diet for horses must have 0.15% to 1.5% of calcium and 0.15% to 0.6% of phosphorus in feed dry matter (Box 41-1). A calcium-to-phosphorus ratio less than 1:1 can have negative effects on calcium absorption and skeletal development; however, a calcium-to-phosphorus ratio as high as 6:1 for growing horses may not be detrimental if phosphorus intake is adequate.[9] Adult horses should receive approximately 40 mg of calcium/kg/day (see Table 41-2). Average horses must absorb 20 to 25 mg of calcium and 10 to 12 mg of phosphorus/kg/day to meet their needs and balance losses. Calcium and phosphate content in some

TABLE 41-2

Calcium and Phosphorus Requirements in Horses

	Percent in the Diet		Daily Intake (grams)	
	Ca	P	Ca	P
Foals (<6 mo)	0.80	0.55	33	20
Weanlings	0.60	0.45	34	25
Yearlings	0.50	0.35	31	22
2-yr-olds	0.40	0.30	25	17
Mare, late pregnancy	0.45	0.30	34	23
Mare, lactation	0.45	0.30	50	34
Mature horses	0.30	0.20	23	14

Modified from references 2 and 95-97.

BOX 41-1

Acceptable Ranges of Minerals and Vitamins in Feed of Horses[98]

Ca (%)	0.25-1.5
P (%)	0.15-0.6
Mg (%)	0.08-0.16
Vitamin D (IU/kg)	300-800

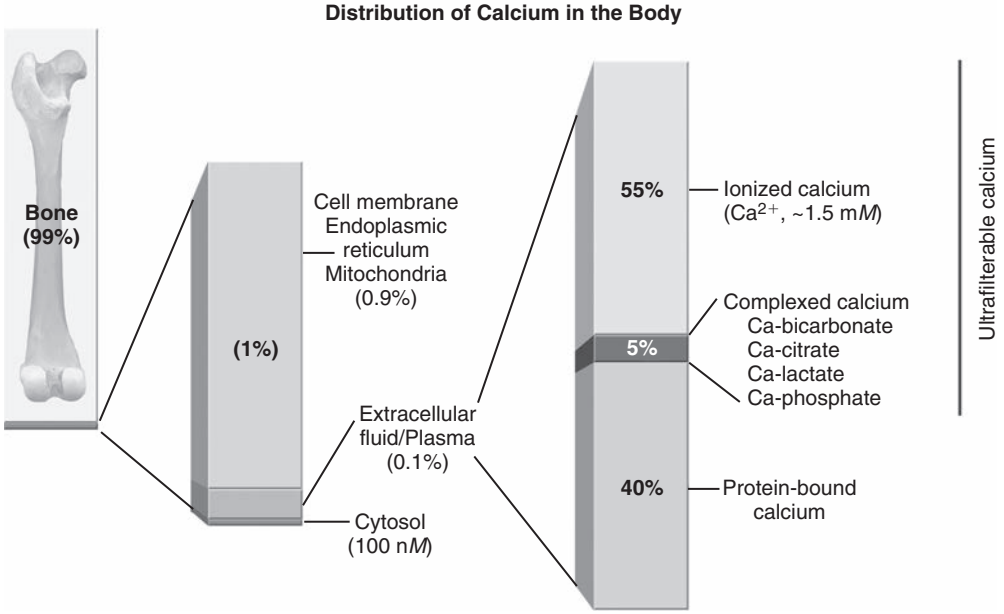


FIG. 41-15 Calcium distribution in the body. Approximately 99% of the total body calcium is in the skeleton. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and extracellular fluid. In blood, calcium exists in a free or ionized form (Ca^{2+}), bound to proteins and complexed to anions such as citrate, bicarbonate, phosphate, and lactate. In horses, serum Ca^{2+} represents 50% to 55% of the total serum calcium concentration.

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TABLE 41-3

Calcium and Phosphorus Content of Some Mineral Supplements

	Calcium (%)	Phosphorus (%)
Calcium carbonate	34	0
Dicalcium phosphate	27	21
Monocalcium phosphate	17	21
Bone meal	30	14
Monosodium phosphate	0	22
Defluorinated phosphate	32	15
Calcium gluconate 23%	2.14	0

Modified from references 2 and 95-97.

TABLE 41-4

Mineral Composition of Some Equine Feeds on a Dry Matter Basis

Source	Ca (%)	P (%)	Mg (%)
Alfalfa	1.71	0.30	0.36
Alfalfa hay	1.41	0.21	0.34
Timothy	0.40	0.26	0.16
Timothy hay	0.51	0.29	0.13
Bluegrass	0.50	0.4	0.18
Oat hay	0.32	0.25	0.29
Orchard grass	0.25	0.39	0.31
Barley	0.05	0.37	0.15
Corn	0.05	0.60	0.03
Oats	0.09	0.38	0.16
Wheat	0.05	0.42	0.14
Cottonseed meal	0.18	1.22	0.59
Linseed	0.43	0.90	0.67
Skim milk	1.36	1.09	0.13
Soybean meal	0.40	0.71	0.31
Molasses, cane	1.10	0.15	0.47
Wheat bran	0.14	1.27	0.63

Modified from NRC. 2007. Nutrient requirements, feedstuff composition, and other tables, pp 293-310. In National Research Council (U.S.), Committee on Nutrient Requirements of Horses (eds), Nutrient requirements of horses. National Academies Press, Washington, D.C.

mineral supplements and equine feeds are presented in Tables 41-3 and 41-4.

Horses have distinctive features with regard to calcium metabolism. These include high serum total and ionized calcium concentrations,[8] a poorly regulated intestinal calcium absorption (high absorption),[10] high urinary fractional excretion of calcium,[8] low serum concentrations of vitamin D metabolites,[11-14] and decreased parathyroid gland sensitivity to Ca^{2+}.[15,16]

Most calcium absorption occurs in the small intestine.[10,17] Compared with other species, horses absorb a larger proportion of the dietary calcium. Horses can absorb 50% to 75% of the calcium and less than half the phosphorus in their diet, with little effect of age.[10] Calcium absorption is inversely related to dietary calcium content. High content of phosphate (or phytate, oxalate) inhibits calcium absorption; however, high dietary calcium content has minimal effect on phosphorus absorption. Oxalates reduce calcium absorption. Some plants containing harmful amounts of oxalate are listed in Table 41-5. The dietary cation-anion balance (DCAB) affects Ca^{2+} absorption in horses; a low DCAB increases intestinal Ca^{2+} absorption, whereas a high DCAB has the opposite effect.[18] Glucocorticoids decrease intestinal absorption of calcium, decrease bone resorption, and increase urinary excretion of Ca^{2+} in horses.[19,20]

Calcium is eliminated through feces, urine, milk, sweat, and the fetus. In the kidney, approximately 60% of calcium is reabsorbed in the proximal tubules by passive mechanisms and 35% is reabsorbed in the thick ascending loop of Henle and distal tubules by active mechanisms.[21] The rest (≈5%) represents the urinary fractional excretion of calcium. Endogenous losses of calcium in horses have been estimated around 20 to 25 mg/kg/BW/day. Assuming a 50% calcium digestibility, a 500-kg horse would require 20 g of calcium to replace losses, or 40 mg/kg/day; growing and lactating horses can double these requirements. Interpretation of the urinary excretion of calcium can be difficult because horses eliminate large amounts of calcium (primarily calcium carbonate) in urine.[2,3,22]

TABLE 41-5

Plants That Contain Oxalates*

Common Name	Scientific Name
Bermudagrass	*Cynodon dactylon*
Buffel grass	*Cenchrus cilaris*
Dallis grass	*Paspalum* spp.
Elephant grass	*Panicum* spp.
Foxtail grass	*Setaria* spp.
Greasewood	*Sarcobatus vermiculatus*
Halogeton	*Halogeton glomeratus*
Kikuyu	*Pennisetum clandestinum*
Kochia, summer cypress	*Kochia scoparia*
Lamb's-quarters	*Chenopodium* spp.
Napier, mission grass	*Pennisetum* spp.
Pangola	*Digitaria decumbens*
Panic	*Panicum* spp.
Para grass	*Brachiaria* spp.
Pokeberry	*Phytolacca americana*
Purple pigeon grass	*Setaria incrassate*
Purslane	*Portulaca oleraceae*
Red-rooted pigweed	*Amaranthus* spp.
Rhubarb	*Rheum rhaponticum*
Russian thistle, tumbleweed	*Salsola* spp.
Setaria	*Setaria sphacelata*
Sorrel	*Rumex* spp.
Soursob, shamrock	*Oxalis* spp.
Sugar beet	*Beta vulgaris*

*These plants have an oxalate content higher than 0.5% of dry matter or a calcium-to-oxalate ratio of less than 0.5.

Phosphorus

In blood, phosphorus exists as organic (intracellular) and inorganic (extracellular) phosphates. Organic phosphate consists of phosphate esters (phospholipids) bound to proteins and blood cells, and it represents most of the phosphorus in circulation; however, only inorganic phosphate (PO_4) is measured. PO_4 is found as ionized phosphate (≈50%), complexed with cations (Na^+, Ca^{2+}, Mg^{2+}; ≈35%), and bound to proteins (≈15%). At pH 7.4, PO_4 exists as divalent (HPO_4^{2-}) and monovalent ($H_2PO_4^-$) anions in a 4:1 ratio. In acidosis this ratio is 1:1, and it can be as high as 9:1 during alkalosis.[23] In soft tissues, most of the phosphate is organic, intracellular, and incorporated into nucleic acids, phospholipids, and energy compounds such as ATP and creatine phosphate. Thus phosphate is important for muscle contraction; neurologic functions; enzyme activity; electrolyte transport; oxygen transport (2,3 DPG); intermediary metabolism of proteins, carbohydrates, and fats; gene transcription; and cell proliferation and differentiation. Approximately 80% of the PO_4 is in the skeleton bound to calcium as hydroxyapatite. PO_4 regulation is closely associated to Ca^{2+} homeostasis.

Phosphorus requirements depend on age, physiologic status, and amount of work or exercise performed (see Table 41-2). In horses, phosphorus absorption ranges from 30% to 55% and occurs in the small and large intestines.[17,24] High aluminum in the diet reduces phosphorus absorption. In the kidneys most of the PO_4 is reabsorbed in the proximal tubules by a Na^+-dependent mechanism, and the urinary fractional excretion of PO_4 in horses is low (<0.5%).

Chronic excess of phosphorus results in clinical signs consistent with calcium deficiency, including lameness, abnormal cartilage and bone development, fractures, and osteodystrophia fibrosa

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(nutritional secondary hyperparathyroidism). Acute renal failure and hypoparathyroidism are associated with hyperphosphatemia. Conditions that result in cell membrane fragility and lysis such as hemolysis, rhabdomyolysis, and tumor necrosis may cause hyperphosphatemia.

Hypophosphatemia occurs from inadequate intake, decreased intestinal absorption, renal waste, hyperparathyroidism, sepsis, intracellular shift, and some malignancies. Intracellular PO_4 shift is a common cause of hypophosphatemia in critically ill humans and small animals and occasionally occurs in horses with starvation, refeeding syndrome, and parenteral nutrition (hyperglycemia, hyperinsulinemia).

Chronic phosphate deficiency can be manifested as weight loss, weakness, pica (depraved appetite), lameness, and developmental orthopedic disease (DOD). Rickets, as described in other species with PO_4 or vitamin D deficiency, is not a recognized condition in foals. Serum PO_4 concentration is more indicative of dietary phosphorus intake and status than serum Ca^{2+} because PO_4 homeostasis is not as precise as that of Ca^{2+}.

Normal calcium, magnesium, phosphorus, and regulatory hormone concentrations are presented in Table 41-6. Ionized calcium concentrations are lower in foals and pregnant mares than adult horses.[5,6,22] Of interest, serum total and ionized magnesium concentrations tend to be higher in foals than adult horses.[5,6,22] Serum PO_4 concentrations and alkaline phosphatase activity are greater in foals compared with adult horses due to growth, increased intestinal absorption, bone osteoblastic activity, and bone formation.[2,6]

TABLE 41-6

Normal Serum Concentrations of Calcium, Phosphorus, Magnesium, PTH, Calcitonin, PTHrP, and Vitamin D and Urinary Fractional Excretion of Calcium (FE_{Ca}) and Phosphorus (FP) in Healthy Horses and Foals

Total calcium in horses (mg/dL)	11.1-13 (2.8-3.25 mmol/L)
Total calcium in foals (mg/dL)	11-14 (2.75-3.5 mmol/L)
Ionized calcium in horses (mg/dL)	6-7 (1.5-1.75 mmol/L)
Ionized calcium in foals (mg/dL)	5.8-6.6 (1.45-1.65 mmol/L)
Phosphorus in horses (mg/dL)	2-4.8 (0.64-1.54 mmol/L)
Phosphorus in foals (mg/dL)	4.4-8.4 (1.4-2.7 mmol/L)
Total magnesium in horses (mmol/L)	0.53-0.91 (1.27-2.2 mg/dL)
Total magnesium in foals (mmol/L)	0.56-1.11 (1.34-2.66 mg/dL)
Ionized magnesium in horses (mmol/L)	0.46-0.66 (1.10-1.58 mg/dL)
Ionized magnesium in foals (mmol/L)	0.43-0.67 (1.03-1.61 mg/dL)
PTH (pmol/L)	<4 (<40 pg/mL)
Calcitonin (pg/mL)	<40 (12 pmol/L)
PTHrP (pmol/L)*	<3 (<30 pg/mL)
FE_{Ca} (%)	2-8
FE_P (%)	0-0.5
$25(OH)D_3$	1.90 ± 0.23 ng/mL—winter[12]
	2.43 ± 0.09 ng/mL—summer[12]
	4.2 ± 0.34 ng/mL—winter[14]
	6.2 ± 0.36 ng/mL—summer[14]
$1,25(OH)_2D_3$	18.6 ± 7.3 pg/mL—winter[14]
	18.7 ± 8.0 pg/mL—summer[14]
	55.0 ± 24.0 pmol/L[11]

Data from the College of Veterinary Medicine, Ohio State University, unless otherwise noted. Foal calcium and magnesium data from recent publications.[5,6]

*Measured in ethylenediaminetetraacetic acid (EDTA) plasma.

FE_{Ca}, Urinary fractional excretion of calcium; *FE_P*, urinary fraction excretion of phosphorus; *PTH*, parathyroid hormone; *PTHrP*, parathyroid hormone–related protein.

Conversion units: Calcium (mmol/L = mg/dL × 0.25; mg/dL = mmol/L × 4); magnesium (mmol/L = mg/dL × 0.4; mg/dL = mmol/L × 2.43); phosphorus (mmol/L = mg/dL × 0.323; mg/dL = mmol/L × 3.1)

Calcium and Phosphorus Homeostasis

Extracellular ionized calcium (Ca^{2+}) concentrations are regulated by a homeostatic system that includes three hormones: parathyroid hormone (PTH), calcitonin (CT), and 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$, calcitriol); three body systems (kidney, intestine, and bone); and a calcium-sensing receptor (CaR).[2,3,22] PTH increases during hypocalcemia and hyperphosphatemia while CT increases during hypercalcemia (Fig. 41-16). Under physiologic conditions parathyroid hormone–related protein (PTHrP), which also activates the PTH-1 receptor, has little effect on Ca^{2+} homeostasis.[25] PO_4 is closely associated with Ca^{2+} homeostasis. Extracellular ionized magnesium (Mg^{2+}) has permissive effects on calcium homeostasis by facilitating PTH secretion and action.

Organs involved in PO_4 homeostasis include the intestine (absorption), kidney (excretion), and bone (storage). Extracellular PO_4 concentrations are under the control of various endocrine factors including PTH, $1,25(OH)_2D_3$, CT, insulin, and phosphatonins (FGF-23/klotho axis).[3] In healthy animals, endocrine control of intestinal absorption of PO_4 is minimal, but hormones such as $1,25(OH)_2D_3$ can increase absorption in PO_4-deficient states. PTH and the FGF-23/klotho axis are considered the main regulators of PO_4 concentrations.[26-28] The role of phosphatonins, which inhibit renal PO_4 reabsorption and $1,25(OH)_2D_3$ synthesis in a number of species,[26-29] is unknown in the horse.

PTH is secreted by the chief cells of the parathyroid gland in response to hypocalcemia and hyperphosphatemia. Parathyroid chief cells detect changes in Ca^{2+} concentrations by a calcium-sensing receptor (CaR).[16,30] Through the PTH receptor, PTH increases renal Ca^{2+} reabsorption (distal nephron), decreases renal PO_4 reabsorption (proximal tubules), stimulates renal calcitriol synthesis (proximal tubules), and stimulates osteoclastic bone resorption (see Fig. 41-16). Calcitriol ($1,25[OH]_2D_3$) increases intestinal absorption and renal reabsorption of Ca^{2+} and PO_4 and inhibits PTH synthesis and secretion.[2,3] PTH secretion is under the influence of Ca^{2+}, PO_4, and vitamin D. Biologically active intact PTH is measured with immunometric assays.

Vitamin D plays an important role in Ca^{2+} and PO_4 homeostasis and, to a lesser extent, in magnesium metabolism. Vitamin D_2

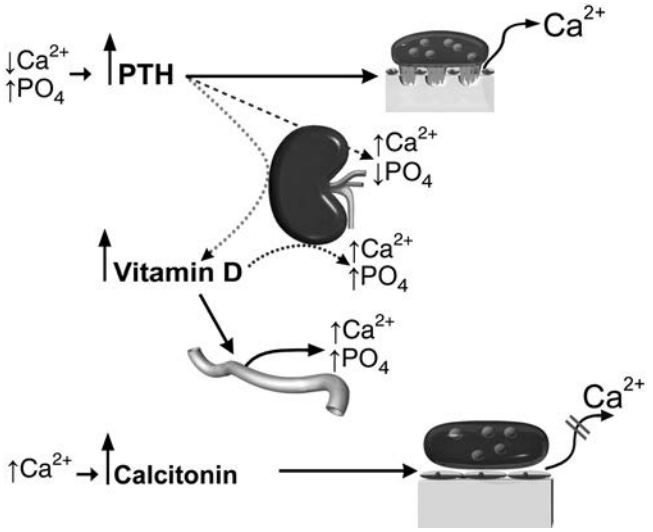


FIG. 41-16 Calcium and phosphate homeostasis. A decrease in serum Ca^{2+} or increase in serum PO_4 concentrations increases PTH secretion. PTH increases renal Ca^{2+} reabsorption and vitamin D synthesis, decreases renal PO_4 reabsorption, and increases osteoclastic bone resorption. In turn, vitamin D increases intestinal absorption and renal reabsorption of Ca^{2+} and PO_4. On the contrary, hypercalcemia decreases PTH secretion and stimulates calcitonin secretion to inhibit osteoclastic bone resorption.

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(ergocalciferol) and vitamin D_3 (cholecalciferol) are secosterols derived from photolytic cleavage of the B rings of ergosterol (plants and yeasts) and 7-dehydrocholesterol (animals), respectively. Vitamin D_3 is transported to the liver by a vitamin D–binding protein (GC-globulin), where it is hydroxylated (25α-hydroxylase) to 25-hydroxyvitamin D_3 (25[OH]D_3, calcidiol), which is then transported to the kidney to produce the active metabolite, 1,25$(OH)_2D_3$ (calcitriol), by 1α-hydroxylase. In mammalians, 25$(OH)D_3$ is the major circulating form of vitamin D. Hypocalcemia, hypophosphatemia, and PTH stimulate 1,25$(OH)_2D_3$ synthesis by inducing renal 1α-hydroxylase activity, whereas hypercalcemia, hyperphosphatemia, FGF-23, and 1,25$(OH)_2D_3$ inhibit 1α-hydroxylase.

Vitamin D stimulates intestinal absorption and renal reabsorption of Ca^{2+} and PO_4. 1,25$(OH)_2D_3$ increases the expression and activity of proteins important for transcellular Ca^{2+} transport, including epithelial Ca^{2+} channels, Ca^{2+} binding proteins (calbindin D_{9k}, calbindin D_{28k}), Na^+/Ca^{2+} exchangers, and Ca^{2+}-ATPases.[2,3,31] The effects of 1,25$(OH)_2D_3$ on intestinal absorption and renal reabsorption of PO_4 are mediated by Na^+-PO_4 cotransporters.[3] In addition, 1,25$(OH)_2D_3$ increases Mg^{2+} renal reabsorption.[32] In bone, 1,25$(OH)_2D_3$ increases bone matrix synthesis and mineralization and stimulates osteoclastic activity and bone resorption. In the parathyroid gland, 1,25$(OH)_2D_3$ inhibits chief cell proliferation, PTH synthesis, and secretion.[33] Vitamin D deficiency results in rickets in young animals and osteomalacia in adults; however, the existence of rickets in the horse is not well documented.

Calcitonin (CT) is a 32-amino-acid peptide secreted by the parafollicular cells (C cells) of the thyroid gland in response to hypercalcemia in a number of species, including the horse.[31,34] CT inhibits osteoclast function and bone resorption and decreases renal reabsorption of Ca^{2+} and PO_4 in most species.[2,3]

PTHrP is produced by almost every tissue in the body and has a broad range of functions that have little to do with Ca^{2+} homeostasis.[25] Under physiologic conditions, PTHrP functions (morphogenesis, cell differentiation) are considered to be paracrine, autocrine, and intracrine. For the most part, the endocrine functions of PTHrP are considered pathologic (humoral hypercalcemia of malignancy; HHM). HHM is a paraneoplastic syndrome that results from excessive secretion of PTHrP by some tumors. By interacting with PTH receptors, PTHrP promotes bone resorption and inhibits renal Ca^{2+} excretion, causing hypercalcemia in humans and domestic animals, including the horse.[35-40]

Organs involved in Ca^{2+} homeostasis (parathyroid gland, thyroid gland, and kidney), known as the *calcium-sensing system,* express a calcium-sensing receptor (CaR) that is activated by extracellular Ca^{2+} and, to lesser affinity, by Mg^{2+}.[30] CaR activation inhibits PTH secretion and stimulates CT secretion in various species, including the horse.[15,16,31] In the kidney, CaR regulates Ca^{2+} and Mg^{2+} reabsorption independently of PTH. Renal CaR activation inhibits the furosemide-sensitive $Na^+/K^+/2Cl^-$ cotransporter in the distal nephron, resulting in diuresis and urinary waste of Ca^{2+} and Mg^{2+}, in humans and horses.[30,41]

Calcium Disorders in the Horse

Calcium dysregulation in the horse is associated with hypocalcemic and hypercalcemic disorders. Equine pathologic conditions characterized by abnormal calcium homeostasis include hypoparathyroidism,[42-44] primary hyperparathyroidism,[45-47] nutritional secondary hyperparathyroidism,[48] renal failure,[49] humoral hypercalcemia of malignancy,[35-39] vitamin D toxicity,[50,51] exercise-induced hypocalcemia,[52,53] idiopathic hypocalcemia of foals,[54] cantharidiasis,[55] gastrointestinal disease,[22,55-59] and sepsis.[6,8,22,56,58,59] Low Mg^{2+} concentrations can contribute to calcium dysregulation.

Hypocalcemic Disorders

Conditions associated with hypocalcemia in the horse are presented in Box 41-2. Calcium deficiency can be acute or chronic. Horses with acute calcium deficiency develop clinical signs associated with neuromuscular excitability and decreased smooth muscle cell contractility (Box 41-3). A decrease in extracellular Ca^{2+} concentrations increases cell membrane Na^+ permeability. The resting membrane potential decreases, thus making muscle cells and nerve fibers more excitable. This results in spontaneous and continuous discharges, muscle fasciculations, tremors, tetany, and seizures. Tachycardia and cardiac arrhythmias may be present, although bradycardia may develop during severe hypocalcemia. Low serum Mg^{2+}

BOX 41-2

Equine Clinical Conditions in Which Hypocalcemia Has Been Reported

Acute renal failure
Bicarbonate administration
Cantharidin toxicosis (blister beetles)
Chronic renal failure
Colic
During lactation (lactation tetany)
During transport (transit tetany)
Dystocia
Endotoxemia
Endurance exercise
Enterocolitis
Furosemide administration
Heat stroke
Hypomagnesemia
Late pregnancy
Liver disease
Magnesium toxicosis
Malignant hyperthermia
Oxalate ingestion
Pancreatitis
Pleuropneumonia
Postoperative myopathy
Primary hypoparathyroidism
Retained placenta
Rhabdomyolysis
Sepsis

BOX 41-3

Clinical Signs Reported in Horses with Hypocalcemia

Anxiety
Asphyxia
Ataxia
Bruxism
Cardiac arrhythmias
Colic
Convulsions
Death
Depression
Dysphagia
Dyspnea
Excitation
Hyperhidrosis
Hypersalivation
Hyperthermia
Ileus
Laryngeal spasm
Muscle fasciculation
Seizures
Stiff gait
Synchronous diaphragmatic flutter
Tachycardia
Tachypnea
Tetany
Tremors
Trismus

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concentrations are a frequent finding in horses with hypocalcemia and can further aggravate neuromuscular excitability. Chronic calcium deficiency in general is manifested as abnormal cartilage and bone development (DOD) and lameness. When calcium deficiency is suspected, feed analysis is recommended to determine if dietary calcium and phosphorus content are adequate.

Synchronous diaphragmatic flutter (SDF), or "thumps," may occur in horses with hypocalcemia associated with gastrointestinal disease[22,55]; endurance exercise[60]; hypoparathyroidism[44,61]; idiopathic hypocalcemia[54]; tetany (lactation, transport)[62]; sepsis[22]; blister beetle toxicosis[55,63]; retained placenta[22,64,65]; and alkalosis.[2,3] SDF develops when depolarization of the right atrium stimulates action potentials in the phrenic nerve as it crosses over the heart. Clinically, these animals have a rhythmic movement on the flank from diaphragmatic contractions that are synchronous with the heartbeat.

During alkalosis there is increased Ca^{2+} binding to albumin, resulting in ionized hypocalcemia. Alkalosis also increases Mg^{2+} binding to proteins. Exercising horses may develop alkalosis from hyperventilation (respiratory alkalosis) and chloride losses in the sweat (metabolic hypochloremic alkalosis). Hypomagnesemia is common in horses with SDF and hypocalcemia.

Hypocalcemic tetany is the development of sustained skeletal muscular contractions in horses with hypocalcemia. Although hypocalcemic tetany can occur in any horse with hypocalcemia, lactating mares and horses transported for long distances are at greatest risk. Lactation tetany in mares may occur any time immediately before foaling up to the end of the lactation period. In particular, mares producing large amounts of milk and eating diets low in calcium, grazing lush pastures, or performing physical work (draft mares) are at risk. Clinical signs may include anxiety, depression, ataxia, muscle fasciculations and tremors, stiff gait, tachypnea, dyspnea, dysphagia, hypersalivation, and hyperhidrosis (see Box 41-3).[2,3]

Hypocalcemic seizures, seen in foals and adult horses, are caused by decreased CNS extracellular Ca^{2+} concentrations leading to increased neuronal excitability. Clinical signs usually improve with calcium treatment, although some animals may require repeated treatments. In general, horses and foals with refractory hypocalcemic seizures have a poor prognosis for recovery.

Ileus and *retained placenta in mares* are both believed to result in part from decreased smooth muscle tone and contractility secondary to hypocalcemia.[2,3] Although in skeletal muscle most of the Ca^{2+} required for contraction comes from the sarcoplasmic reticulum, in smooth muscle Ca^{2+} comes from the extracellular space.[2] For this reason, any condition that results in hypocalcemia can decrease smooth muscle contractility. Retained placenta in mares occurs in up to 10% of foalings,[64] and it has been associated with hypocalcemia.[64]

Hypoparathyroidism in horses is characterized by hypocalcemia, hyperphosphatemia, hypomagnesemia, and decreased serum PTH concentrations. Primary hypoparathyroidism results from decreased secretion of PTH, whereas secondary hypoparathyroidism results from magnesium depletion and sepsis. There are few documented cases of primary hypothyroidism in horses.[43,61] Hypoparathyroidism should be suspected in any horse or foal with refractory hypocalcemia. Clinical signs include ataxia, seizures, hyperexcitability, SDF, tachycardia, tachypnea, muscle fasciculations, bruxism, stiff gait, recumbency, ileus, and colic.[2,3,43,66] Laboratory findings include hypocalcemia, hyperphosphatemia, and low or normal serum intact PTH concentrations. Hypomagnesemia may be present in some horses and foals.[6,22] Secondary (functional or acquired) hypoparathyroidism per se has not been reported in the horse; however, some critically ill foals and horses with hypocalcemia have impaired parathyroid gland function,[6,8,22] which could be a form of hypoparathyroidism secondary to inflammatory cytokines and/or hypomagnesemia.

A number of critically ill foals develop a form of hypocalcemia that is refractory to calcium treatment.[54] These foals have low or normal PTH concentrations despite hypocalcemia, suggesting hypoparathyroidism. This condition has been called *neonatal idiopathic hypocalcemia*.[54] It is believed that abnormal parathyroid gland function may result from increased inflammatory cytokines.[6,54] Prognosis for survival in foals with refractory hypocalcemia is poor.

Sepsis and endotoxemia are the most common causes of hypocalcemia in equine patients admitted to veterinary hospitals.[6,8,22] Clinical observations also indicate that hypocalcemia is common in horses with severe gastrointestinal disease.[22,56,58] Hypocalcemia in septic patients often results from parathyroid gland dysfunction (insufficient PTH secretion), as well as intracellular calcium sequestration.[2,3,22] Inflammatory mediators known to be increased in horses and foals with sepsis and endotoxemia such as TNF-α, IL-1, and IL-6 have been shown to increase CaR activation and decrease PTH secretion by equine parathyroid cells.[16]

Horses under intense exercise develop electrolyte and acid-base abnormalities. *Exercise-induced hypocalcemia* may result from Ca^{2+} losses in the sweat; intracellular movement of Ca^{2+}; increased Ca^{2+} binding to albumin, lactate, phosphate, and bicarbonate during alkalosis; and parathyroid gland dysfunction.[2,3,52,53]

Oxalate toxicity causes hypocalcemia by interfering with calcium absorption; a diet consisting of 1% of oxalate or higher can reduce most intestinal calcium absorption.[67] It is important that the equine diet contains less than 0.5% of oxalate or a calcium-to-oxalate ratio over 1. Clinical signs associated with oxalate excess are those of phosphate excess, calcium deficiency, and nutritional hyperparathyroidism. Oxalates are present in several grasses and toxic plants (see Table 41-5).

Equine cantharidiasis (blister beetle toxicosis) is a condition reported in the southwestern and midwestern United States and results from the ingestion of alfalfa contaminated with beetles (*Epicauta* spp.) that produce cantharidin (cantharidic acid).[55,63] Clinical signs develop from the irritant effects of cantharidin on mucosal surfaces (gastrointestinal and urinary tracts). Cantharidin often causes acute hypocalcemia and hypomagnesemia. Thus clinical signs of severe hypocalcemia (muscle fasciculations, SDF, ataxia, dyspnea, laryngeal spasm, and cardiac arrhythmias) may be present.[55,63] It is unclear why these horses develop hypocalcemia; however, it may be a combination of severe gastrointestinal disease associated with acute renal tubular necrosis and parathyroid gland dysfunction.

Hypocalcemia and hypomagnesemia are common findings in horses with *acute renal failure*.[2,3] Reabsorption of Ca^{2+} and Mg^{2+} in the kidney is highly dependent on functional epithelial cells,[2] and these cells are susceptible to various insults (hypoxia, ischemia, and toxins).[21]

The pathogenesis of hypocalcemia in *exertional rhabdomyolysis* is unknown.[68] It is speculated that damage to muscle fibers during intense exercise results in Ca^{2+} influx and sequestration in the sarcoplasmic reticulum.

There have been anecdotal reports that racing horses receiving excessive amounts of dietary calcium supplements may develop signs of hypocalcemia during or after exercise. One can speculate that this could be the result of suppression of the mechanisms responsible for calcium homeostasis.

TREATMENT OF HYPOCALCEMIA. Calcium deficit, maintenance, losses, and sequestration should be considered when treating hypocalcemia. If parathyroid gland function is normal, minimal to no calcium supplementation may be required. Most horses with hypocalcemia do not show overt signs of hypocalcemia. Lack of therapy, however, can result in development of additional complications, in particular ileus. Horses with functional kidneys can rapidly eliminate large amounts of calcium, and hypercalcemia from excessive calcium administration is rare, particularly if the horse is receiving fluid therapy. When possible, calculate the calcium deficit on the basis of Ca^{2+} concentrations (mg/dL = mmol/L × 4). From a practical standpoint, standard formulas for electrolyte deficit can be used (multiplied by 10 because calcium is expressed as mg/dL). Total calcium can be used to estimate calcium deficit, keeping in mind that total calcium has more variability than Ca^{2+} concentration because it is dependent on plasma protein concentration. A horse can have total hypocalcemia, but serum Ca^{2+} concentrations may be within the

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normal range (pseudohypocalcemia), and calcium administration may not be necessary. It is also important to remember that 9.3% of calcium gluconate is elemental calcium, which means that a 23% solution of calcium gluconate contains 2.14% of elemental calcium, or 21.4 mg/mL. Avoid the use of injectable calcium chloride because it can cause subcutaneous irritation.

Frequent monitoring of Ca^{2+} concentration and adjustment of dosage is important. Rapid administration of calcium may result in cardiovascular complications, especially in septic horses, which may be more vulnerable to the toxic effects of calcium. In the authors' experience, horses can handle high calcium dosages. For an average-size horse with mild ionized hypocalcemia (5.0 mg/dL), the authors administer 50 mL of 23% calcium gluconate per 5 L of crystalloid fluids, at a fluid rate twice maintenance. Oral treatment with calcium salts is feasible in some horses with non–life-threatening, refractory hypocalcemia. Dicalcium phosphate and calcium carbonate (limestone, 200 to 300 g/day) can be used safely (see Table 41-3). In horses with refractory hypocalcemia, measuring Mg^{2+} concentrations is recommended.

Hypercalcemic Disorders

Hypercalcemic disorders in horses are divided into two groups: (1) parathyroid gland–dependent hypercalcemia (develops due to parathyroid gland hyperfunction) and (2) parathyroid gland–independent hypercalcemia (develops despite parathyroid gland suppression). This distinction is clinically relevant in the differential diagnosis and in the interpretation of specific diagnostic tests, including intact PTH, PTHrP, Ca^{2+}, PO_4, and vitamin D concentrations. Parathyroid gland–dependent hypercalcemia in the horse is limited to primary hyperparathyroidism, whereas parathyroid-independent hypercalcemia results from various conditions (secondary hyperparathyroidism, chronic renal failure, hypercalcemia of malignancy, hypervitaminosis D, calcinosis, and idiopathic systemic granulomatous disease).

Primary hyperparathyroidism results from an excessive and autonomous synthesis and secretion of PTH by the parathyroid gland that is not responsive to the negative feedback of Ca^{2+}. Primary hyperparathyroidism has been reported in ponies and horses[43,45-47] and results from parathyroid adenomas or parathyroid hyperplasia. The elevated PTH concentrations increase renal Ca^{2+} reabsorption, decrease PO_4 reabsorption, increase $1,25(OH)_2D_3$ synthesis, and increase bone resorption (osteodystrophia fibrosa). Laboratory findings include hypercalcemia, hypophosphatemia, hypocalciuria, and hyperphosphaturia. PTHrP concentrations are within normal limits (low or undetectable). Clinical findings include facial bone enlargement, lameness, and a poor body condition. Radiographic findings include decreased long and facial bone density, fibrous proliferation of the maxilla and mandible, and loss of the lamina dura surrounding the molars.[45] Endoscopic examination may reveal narrowing of the nasal passages.

Postmortem findings include enlargement of the maxilla and mandible, stenosis of the nasal passages, and loosening of premolars and molars. Histologic evaluation of the parathyroid gland is important to confirm the diagnosis of primary hyperparathyroidism; however, finding the parathyroid glands in the horse is a challenge due to their small size and variable location.[2,16] Although not documented in horses, in other species treatment consists of surgical removal of the affected parathyroid gland.

Secondary hyperparathyroidism is characterized by excessive secretion of PTH in response to hyperphosphatemia and hypovitaminosis D from chronic renal failure (renal secondary hyperparathyroidism) or hyperphosphatemia and/or hypocalcemia from nutritional imbalances (nutritional secondary hyperparathyroidism). *Renal secondary hyperparathyroidism* is not a well-recognized disease in the horse. Unlike humans and small animals in which chronic renal failure results in hyperphosphatemia, horses with chronic renal failure (CRF) often have hypophosphatemia. Moreover, the hypercalcemia in horses with CRF is the result of renal Ca^{2+} retention rather than increased PTH concentrations.[2,3,69] The increased Ca^{2+} concentrations in turn decrease PTH secretion; thus PTH concentrations in horses with CRF frequently are below or within the normal range.[3,42] In contrast, *nutritional secondary hyperparathyroidism* is a well-documented pathologic condition of the horse.[2]

Nutritional Secondary Hyperparathyroidism

Definition and Etiology Horses fed diets low in calcium, high in phosphorus, or with a phosphorus-to-calcium ratio of greater than or equal to 3:1 may develop nutritional secondary hyperparathyroidism, also known as bran disease, miller's disease, big head, osteodystrophia fibrosa, osteitis fibrosa, and equine osteoporosis.[2,3,48,70-73] Pastures and toxic plants with a high content of oxalates (see Table 41-5) predispose to secondary hyperparathyroidism.

Pathogenesis Excessive dietary PO_4 reduces intestinal calcium absorption and results in hyperphosphatemia. Dietary oxalates form insoluble calcium oxalate ($Ca[COO]_2$), reducing calcium absorption. Both high phosphorus and low calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion in the horse.[3,74] Hyperphosphatemia directly stimulates PTH secretion and inhibits renal $1,25(OH)_2D_3$ synthesis. Because $1,25(OH)_2D_3$ inhibits parathyroid cell proliferation, low $1,25(OH)_2D_3$ concentrations contribute to parathyroid cell hyperplasia and PTH secretion. Hyperphosphatemia also results in the formation of calcium phosphate precipitates, reducing blood Ca^{2+}, and inducing additional PTH secretion. PTH increases osteoclastic activity, bone resorption, and bone loss (Fig. 41-17).[75] There is facial bone loss with excessive accumulation of subperiosteal unmineralized connective tissue (osteodystrophia fibrosa), resulting in facial enlargement (big head) (Fig. 41-18). Because this is a condition of slow progression, the homeostatic mechanisms that regulate extracellular Ca^{2+} concentrations (PTH, vitamin D, calcitonin) in general are effective in maintaining Ca^{2+} within the normal range. These horses preserve normocalcemia at the expense of the skeletal reserves and do not develop clinical signs of acute hypocalcemia.

Clinical Signs Clinical signs result from increased bone resorption and include unthriftiness; intermittent, shifting lameness; and a stiff gait. Younger animals may develop physitis and limb deformities. There is a typical and symmetrical swelling of the facial bones; however, facial bone enlargement may not be evident in old horses (see Fig. 41-18). The facial changes and the increased bone resorption around molars and premolars may result in masticatory problems. These horses are physically weak and may be in poor body condition from the pain associated with lameness and mastication. In severe cases, teeth may become loosened and spontaneous fractures of long bones may occur. Upper airways obstruction, dyspnea, and epiphora may be present.[3,48,70-72] Soft tissue mineralization was described in a foal suspected of having nutritional secondary hyperparathyroidism.[76]

Laboratory Findings Typical laboratory changes in horses with nutritional secondary hyperparathyroidism include hyperphosphatemia, hypocalcemia or normocalcemia (hypercalcemia is unusual), and increased intact PTH concentrations, especially if the animal is eating a low-calcium or high-phosphorus diet at the time of evaluation. The urinary fractional excretion of calcium is low (hypocalciuria) while the excretion of phosphorus is increased (hyperphosphaturia). Serum alkaline phosphatase activity and collagen degradation products may be increased. Laboratory findings may be within normal limits if the animal is eating a balanced diet.

Radiologic Findings Decreased bone density is frequent; however, bone mass must be decreased by 30% before it can be detected radiographically.[3] Decreased facial bone density along with fibrous proliferation is a consistent finding. Resorption of alveolar

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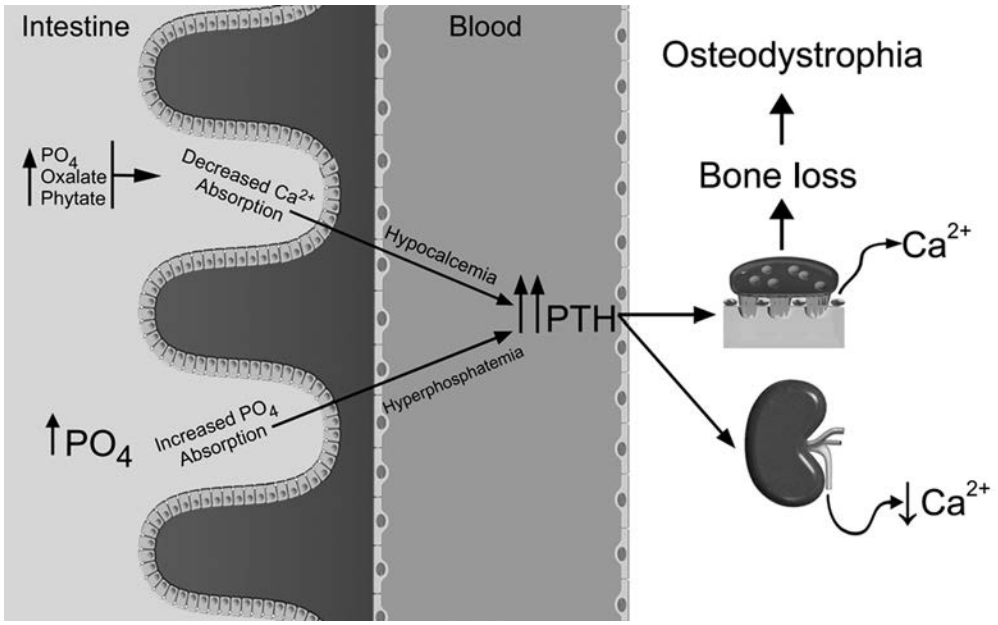


FIG. 41-17 Pathogenesis of nutritional secondary hyperparathyroidism in horses. Excessive dietary phosphorus reduces intestinal absorption of calcium and induces hyperphosphatemia. In addition, phosphate, oxalate, and phytate bind dietary calcium to reduce absorption. Both high-phosphorus and low-calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion. PTH increases osteoclastic activity and bone resorption, resulting in bone loss (osteodystrophia fibrosa).

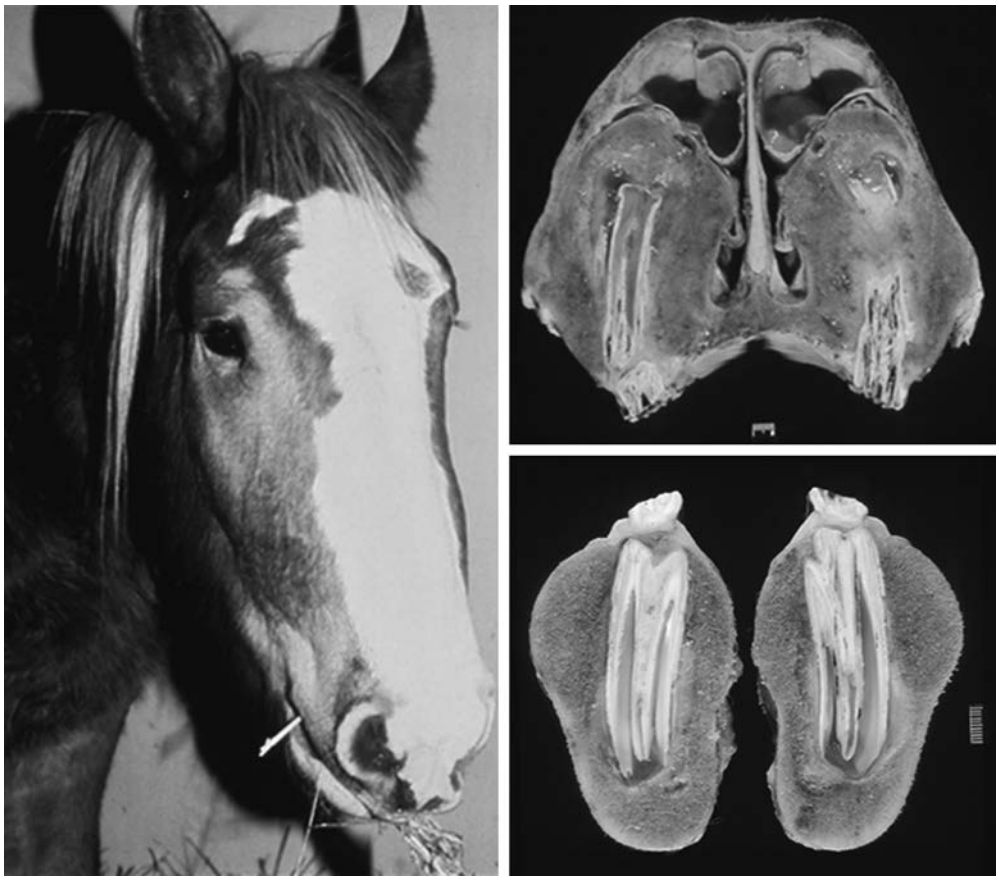


FIG. 41-18 Big head. Two-year-old Belgium horse presented to the Ohio State University Veterinary Teaching Hospital with clinical signs consistent with nutritional secondary hyperparathyroidism, including facial bone enlargement and upper respiratory noise. The horse was fed excessive amounts of grain. There was narrowing of the nasal passages, loss of bone mass, and excessive accumulation of unmineralized bone matrix (osteodystrophia fibrosa) in maxillary and mandibular bones.

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sockets and loss of the dental lamina dura may be present before other radiographic changes are present, and long bones are affected only in advanced cases.

Necropsy There is increased bone resorption, bone fragility, accumulation of fibrous tissue around facial bones, obstruction of nasal passages, and parathyroid gland hyperplasia (see Fig. 41-18).

Treatment Diet evaluation is indicated. Eliminate or reduce any grain-based diet and avoid high-containing oxalate feeds. The addition of alfalfa to the diet may be helpful. Supplementation with calcium carbonate (limestone; $CaCO_3$) or dicalcium phosphate may result in improvement.[48] Ground limestone, which contains no phosphorus, is recommended as a good source of calcium (35%). An affected animal may require a total of 100 to 300 g/day. The diet should have a calcium-to-phosphorus ratio of 3-4 : 1. Limestone may decrease feed palatability, and adding molasses should be considered. Supplementation with vitamin D has been proposed. Horses may require 9 to 12 months for complete recovery, although some bone changes may not regress. Confinement of severely affected horses is advised. The use of nonsteroidal antiinflammatory drugs may be indicated in some animals.

Hypervitaminosis D

Definition and Etiology The ingestion or administration of ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) results in disturbances of the calcium and phosphorus metabolism in horses.[50,51,77-79] Ingestion of plants containing 1,25$(OH)_2$D-like compounds results in typical clinical signs of vitamin intoxication.[77-83] The ingestion of *Solanum glaucophyllum (S. malacoxylon)* results in a condition known as "enteque seco" in Argentina and "espichamento" in Brazil.[79,80,82,83] In Hawaii, *Solanum sodomaeum,* and in the southern United States, jessamine *(Cestrum diurnum)* may cause hypervitaminosis D.[77,78,81,83] In Europe, the ingestion of golden oat *(Trisetum flavescens)* results in enzootic calcinosis.[84-86]

Pathogenesis Hypervitaminosis D increases the intestinal absorption and renal reabsorption of calcium and phosphorus. Hyperphosphatemia is the most consistent and early laboratory finding in horses with vitamin D intoxication.[50,51,76] Serum calcium concentrations may be increased or within the normal range.[50,51,76,77,80] Hypervitaminosis D results in parathyroid cell atrophy and decreased PTH secretion. In addition, hypercalcemia contributes to decreased PTH secretion, lowering bone turnover. Azotemia and hyposthenuria may be present.[50,51]

Clinical Signs Most clinical findings in horses with hypervitaminosis D are the result of hyperphosphatemia. These horses often have weight loss, poor appetite, lameness, and painful stiffness, and they are reluctant to move. Acute death from severe cardiovascular mineralization has been reported.[50,51] Polyuria and polydipsia are frequent findings. In cases with hypercalcemia, mineral deposition in the kidneys may precede mineralization elsewhere, resulting in renal failure. Lameness is probably due to calcification of ligaments and tendons.

Radiologic Findings These horses often have increased bone density, decreased size of the medullary cavity, and increased calcification of soft tissues.

Treatment Reducing dietary calcium intake and the use of calcium-binding agents such as sodium phytate has been proposed.[79] Glucocorticoids are used in humans with hypervitaminosis D because they may inhibit the vitamin D–mediated intestinal calcium absorption. In equids, glucocorticoids decrease intestinal absorption of calcium, increase urinary excretion of calcium, and decrease bone resorption.[19,20] Dexamethasone has been administered to horses with hypervitaminosis D with variable results. Drugs that suppress osteoclastic bone resorption (bisphosphonates) have not been evaluated in horses with hyperparathyroidism. The prognosis for horses with hypervitaminosis D is poor.

Necropsy Findings Postmortem examination may reveal mineralization of soft tissues. Mineralization of the endothelium of the aorta and pulmonary vessels, as well as of the endocardium, is frequent. Mineralization may be found in the kidney, liver, lymph nodes, lungs, ligaments, and tendons. Osteopetrosis of epiphyses and metaphyses may be present. Atrophy of the parathyroid gland can be severe.[81]

Hypercalcemia of Malignancy

Humoral hypercalcemia of malignancy (HHM, pseudohyperparathyroidism) is a paraneoplastic condition in which humans and animals develop hypercalcemia associated with various types of tumors. These malignancies secrete PTHrP, which interacts with PTH receptors to increase renal reabsorption of Ca^{2+} and bone resorption.[87] In horses, HHM has been associated with squamous cell carcinoma, adrenocortical carcinoma, lymphosarcoma, multiple myeloma, and ameloblastoma.[2,3] Laboratory findings include hypercalcemia, hypocalciuria, hypophosphatemia, hyperphosphaturia, normal or low PTH concentrations, and increased PTHrP concentrations. HHM should be suspected in any horse with hypercalcemia, no evidence of renal disease, and normal PTH concentrations.

Neonatal Hypercalcemia and Asphyxia

Clinical observations indicate that a number of critically ill newborn foals develop hypercalcemia associated with peripartum asphyxia. The mechanisms underlying this problem remain unknown, although it is speculated to be associated with placental insufficiency.

Idiopathic Systemic Granulomatous Disease

This is an immune disorder documented in horses and ponies (equivalent to human sarcoidosis), in which crusty skin lesions develop along the coronary bands and mucocutaneous junctions. Granuloma formation in multiple organs is the hallmark.[88-90] Some animals may develop hypercalcemia.[88] Lesion distribution may resemble those of multisystemic eosinophilic epitheliotropic disease of horses.

Calcinosis

Soft tissue calcification (liver, heart, kidney, lungs, vessels, muscle); hyperphosphatemia; and elevation of the calcium × phosphorus product were documented in horses with a number of pathologic conditions.[91] The mechanism by which these animals develop calcinosis is unclear, although it is likely that hyperphosphatemia plays a role.

Treatment of Hypercalcemia

Hypercalcemia as an equine emergency is rarely presented; however, the differential diagnosis of hypercalcemia is important for its treatment. Few disorders in the horse are associated with hypercalcemia (hyperparathyroidism, CRF, HHM, and hypervitaminosis D). Mild to moderate hypercalcemia in general is not life threatening, and treatment should be directed to the primary cause. Although unreported, parathyroidectomy will be the treatment of choice for primary hyperparathyroidism. Bisphosphonates and calcimimetics (cinacalcet) are also recommended in people with hyperparathyroidism[92,93]; however, there is no information on their use for this condition in horses. Bisphosphonates can cause renal injury in people and apparently in horses as well. In theory, calcitonin could reduce serum calcium concentrations but this effect is transient. Surgical removal of epithelial tumors can be a successful treatment for HHM. Some horses with lymphosarcoma may show improvement with

chemotherapy. Bisphosphonates and gallium nitrate have shown benefits in reducing serum calcium and bone resorption in people with HHM.[94] In severe cases of hypercalcemia that may require medical treatment, initial therapy should include the administration of 0.9% saline solution and loop diuretics. Furosemide is the diuretic of choice because inhibits the $Na^+/K^+/2Cl^-$ cotransporter in the distal tubules, increasing the urinary excretion of calcium. Thiazide diuretics are contraindicated because they stimulate calcium reabsorption. Glucocorticoid administration should be considered, in particular for horses with hypervitaminosis D.

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Bovine Metabolic Disorders

Sherrill A. Fleming, *Consulting Editor*

Ketosis of Ruminants (Acetonemia)

Sherrill A. Fleming

Definition Ketosis, a condition characterized by abnormally elevated concentration of ketone bodies in the body tissues and fluids when fatty acids are incompletely metabolized, occurs in cows and ewes during times of increased bodily mobilization of fat stores, usually just after they have given birth.[1] The ketone bodies are acetone (Ac), acetoacetic acid (AcAc), and β-hydroxybutyric acid (BHB), although BHB is technically not a ketone body but is formed from AcAc. Ketosis has been categorized as type I or type II on the basis of blood glucose and blood insulin. Type I ketosis is the classic primary or spontaneous ketosis, causing a reduction of glucose in the blood and liver (decreased glycogen) and an increased fat mobilization culminating in elevated ketone body accumulations from a negative energy balance during early lactation.[2] Type II ketosis involves high blood insulin and transient hyperglycemia secondary to overconditioning and fatty infiltration of the liver (also see Chapter 33 for discussions of fatty liver and pregnancy toxemia). Recent publications have argued that more appropriate nomenclature would be clinical and subclinical ketosis, with clinical ketosis being elevated ketone bodies accompanied by clinical signs of ketosis and subclinical ketosis being elevated ketone bodies accompanied by few clinical signs but with a higher risk of undesirable consequences (lowered milk production, associated diseases, and risk of early culling).[3] Baird and colleagues[4] stated that "a certain degree of ketosis is a natural state in the ruminant, and the ketotic animal may only represent the extreme of a normal metabolic range." Ketosis becomes a disease condition only when the absorption and production of ketone bodies exceed their use by the ruminant as an energy source, resulting in elevated blood ketones, free fatty acids (FFAs), or nonesterified fatty acids (NEFAs) and decreased blood glucose (Fig. 41-19). Any disease process occurring in early lactation that reduces feed intake may cause secondary ketosis.

Etiology Dietary carbohydrate that is presented to the liver for energy metabolism in ruminants is limited due to ruminal fermentation, but processes that require glucose peak in late gestation and early lactation. Gluconeogenesis must occur for cattle to meet these glucose demands and is provided by the volatile fatty acid, propionic acid, which is produced in the rumen or by breakdown of body proteins. Alternate sources of energy that can be used by muscles are fat-derived NEFAs and ketone bodies. Liver function is key in energy metabolism because it maintains the energy requirements of glucose, glucose precursors (propionic acid), amino acids, butyric acid, NEFAs, lactic acid, and ketone bodies during positive energy balance and negative energy balance. Failure to adjust to the rapid changes in the transition from pregnancy to lactation results in subclinical and clinical ketosis.

Ketosis is a production disease of modern agriculture. Dairy cattle have been genetically selected for high milk yield, which has resulted in elevated milk production during early lactation. This milk production exceeds the capacity of the animal to ingest sufficient feed to meet requirements for energy.[4] The input into the animal must equal or exceed the output to prevent a negative energy balance (Table

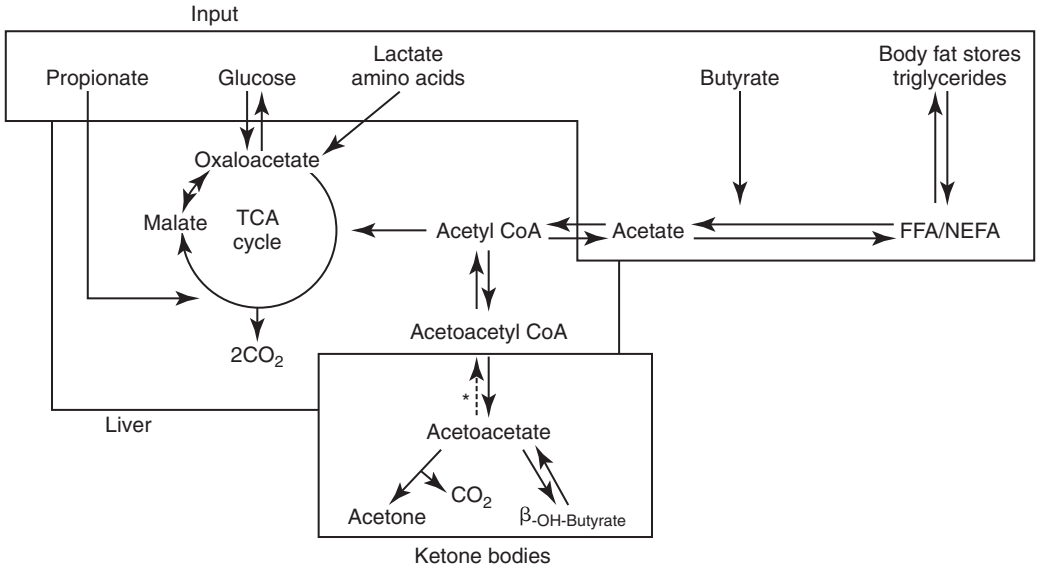


FIG. 41-19 Major pathways of energy metabolism and ketone body formation. *Reaction is negligible in liver and mammary gland but does occur in other tissues.

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TABLE 41-7

Summation of Components of Energy Balance in the Bovine

Inputs	Throughputs	Outputs
Food	Digestion	Defecation
Water	Hepatic metabolism	Urination
Respiration and O_2	Fat metabolism	CO_2
Endocrine influences	Mammary gland metabolism	Lactation
Environment and stress	Tissue metabolism (fetus)	Muscular activity Heat loss Reproduction

41-7). The high-risk time period is immediately after calving, and there appear to be individual cow differences that represent poor adaptive responses to the negative energy balance.[3]

The milk production of dairy cattle peaks by approximately 4 weeks after parturition, but the dietary intake on a dry matter basis does not peak until 7 to 8 weeks.[5] High-producing dairy cows will be in a negative energy balance for as long as 8 weeks, despite the provision of a high-quality, palatable diet. To offset the negative energy balance, the individual cow must mobilize body fat and protein stores in the form of triglycerides and amino acids for gluconeogenesis. Ketone bodies are normally produced by the liver and ruminal wall, although ruminal wall ketone production is insignificant during clinical ketosis.[6] The mammary gland indirectly contributes to ketone body production by using glucose for lactose production.[7] The liver, however, is the major source of overall ketone production during ketosis. All tissues in the normal cow can adapt to the use of ketone bodies as an alternate energy source except the liver. It must be stressed that normal, high-producing dairy cows will have some level of ketosis during the rising curve of their lactation until their energy intake balances milk production, despite the provision of good-quality feed. During this period cows lose 30 to 100 kg (65 to 220 lb).[8-11] The difficulty is in identifying and preventing the factors that move a cow from the normal level of ketone body formation into the subclinical and clinical categories.

Any disease condition that decreases dietary intake may cause secondary ketosis as a result of increased fat mobilization and ketone production. During the immediate postpartum period, cows are susceptible to many diseases that are likely to reduce their normal feed intake. Ketosis may also be secondary to the ingestion of preformed ketones in the diet (silage high in lactic or butyric acid).[6] Biogenic amines such as putrescine, tryptamine, cadaverine, and histamine contained in ketogenic silage may play a role, possibly by decreasing intake.[13,14] Cobalt deficiency has been implicated as a potential cause of ketosis.[15] There is also a high incidence of ketosis in herds affected by fluorosis.[16] Contamination of concentrates with low levels of lincomycin has been reported to cause herd outbreaks of clinical ketosis.[17] The onset of bovine somatotropin (BST) use in dairies was speculated to increase the incidence of ketosis, but this has not been demonstrated.[18,19]

Clinical Signs and Differential Diagnoses Clinical ketosis is most commonly seen as a gradual loss of appetite and decrease in milk production over several days. Loss of appetite is usually sequential, with refusal of grain, then silage, and lastly forages. As feed intake decreases, weight is lost rapidly, and milk production drops. During early lactation, reduction in milk production lags behind the reduction in energy intake. The incidence of type I ketosis tends to occur 3 to 6 weeks postpartum as milk production peaks, in contrast to type II, which is seen immediately after calving.[2] Physical findings include normal vital signs; firm, dry feces; moderate depression; and sometimes reluctance to move. Ruminal motility may be decreased if the animal has been anorectic for several days. Occasionally pica is seen. Often the odor of ketones can be detected on the breath and in the milk. Clinical signs may spontaneously disappear without treatment when equilibrium between milk yield and dietary intake is reached. Transient nervous signs such as staggering and blindness may occur for short periods of time. Displaced abomasum (particularly left displaced abomasum [LDA]), metritis, mastitis, and peritonitis (particularly traumatic reticuloperitonitis) are common primary disease entities leading to secondary ketosis. Although LDA has traditionally been thought to result in ketosis, recent work has demonstrated that elevated blood NEFAs and ketones precede LDA by 2 days and increase the risk of the condition by as much as eightfold.[20] Ketosis decreases immune responsiveness, leaving affected cows more vulnerable to concurrent infections. This is attributed to the hypoglycemia and suppressive effects of NEFAs.[20] Less common causes of secondary ketosis are subclinical hypocalcemia, mild ruminal overload and laminitis, lameness caused by sole abscesses and ulcers, pyelonephritis, and musculoskeletal injuries after calving.

In the nervous form of ketosis, there is an acute onset of bizarre neurologic signs, including circling, proprioceptive deficits, head pressing, apparent blindness, wandering, excessive grooming behavior, pica, and excessive salivation. These animals may show hyperesthesia, bellowing, moderate tremors, and tetany.[21] They may behave aggressively toward people or inanimate objects and appear ataxic when ambulating. Episodes of nervous signs last 1 to 2 hours and recur at 8- to 10-hour intervals.[8] Diseases such as listeriosis, rabies, lactation tetany, acute lead poisoning, and *Claviceps paspali* poisoning should be considered as possible differential diagnoses.

A thorough physical examination must be performed to differentiate primary from secondary ketosis. A mild fever and increased heart rate are often associated with primary diseases that are inflammatory in nature. Moderate to severe ketonuria may be seen. During the first 2 weeks after calving, cows may require treatment for concurrent diseases. If appetite does not return after standard therapy for the primary disease entity, further therapy for ketosis may be necessary. The tendency for ketosis to recur necessitates careful reassessment by repeating the physical examination to detect primary diseases causing secondary ketosis.

Subclinical ketosis is not associated with clinical signs. Physical examination parameters are within normal ranges. The diagnosis is made on the basis of screening tests during the first 2 weeks of lactation.[3]

Clinical Pathology and Laboratory Aids Ketone bodies may be detected in urine, plasma, and milk (Table 41-8).[8,22-29] The literature is reported in the International System of Units (SI units) (mmol/L) and conventional units (mg/dL), which makes interpretation difficult. The vagueness of clinical signs has made it difficult to determine precise definitions of ketone bodies in clinical ketosis. As a general guideline, animals with clinical ketosis will have blood glucose concentrations of 20 to 40 mg/dL, total blood ketones greater than 30 mg/dL, total urine ketones greater than 84 mg/dL, and total milk ketones greater than 10 mg/dL. Individuals with subclinical ketosis are those that have no clinical signs of ketosis but have low-normal blood glucose, total blood ketones of 10 to 30 mg/dL, and total milk ketones of 2 mg/dL. Recent studies have statistically determined BHB to give the best correlation for subclinical ketosis with a threshold of 1400 µmol/L (1.4 mmol/L, 14.4 mg/dL).[30] Use of cow-side BHB meters (Abbott Precision Xtra meter, Abbott Laboratories, Abbott Park, Ill.) has refined the definition of subclinical ketosis to blood BHB between 1.2 and 2.9 mmol/L and clinical ketosis to blood BHB of greater than 3 mmol/L.[3] Secondary ketosis tends to fall between the ranges for clinical and subclinical ketosis, depending on the duration of the primary disease process.[7]

Commercially available tests have changed substantially in the past few years, with greatly improved diagnostic capability. Urine ketones may give a positive result in otherwise normal cows because ketones are concentrated 2 to 20 times the blood ketone level. Ketone bodies in the milk more closely reflect ketone blood levels, making

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TABLE 41-8

Blood, Urine, and Milk Analysis in Ketosis

	Normal		Subclinical		Clinical	
	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
Blood glucose	52	(2.86)	28	1.54		
FFA	3				33	
Ac	0				15.1	0.26
AcAc	0	<0.35		0.36-1.05	4.4	>1.05, 0.5
BHB	10.7	(1.08)	>10	0-1.5	23.5	>1.5
TOTAL	3; 6.1		10-30		>30; 41; 48	5
Urine Ac	1	(0.17)			22	3.78
AcAc	3.4	(0.35)			37.3	3.80
BHB	11.7	(1.18)			25.1	2.54
TOTAL	9.54; 16.1				89; 305.77	
Milk Ac	0			0.17-0.25; 0.4	16.2	>1-2
AcAc	0				1.6	0.16
BHB	4.9	(0.49)			7.9	0.80
TOTAL	4.9		2		27.5; 37.35	

Ac, Acetone; *AcAc,* acetoacetic acid; *BHB,* β-hydroxybutyric acid; *FFA,* free fatty acid.

milk ketones a better indicator of ketosis (≈50% of blood concentration).[28,29] Of the ketone bodies, AcAc tends to be the most unstable and difficult to detect in samples. Various products that detect the Ac, AcAc, and/or BHB are available. A recent review of available tests found that two products, one detecting AcAc in urine at the "small" reading (Ketostix, Bayer, Elkhart, Ind.) and the other detecting BHB in milk (KetoTest, Sanwa Kagaku Kenkyusho, Nagoya, Japan), had acceptable sensitivity and specificity for screening herds for subclinical ketosis.[30] In a second study, Pink test liquid (www.profs-products.com, Germany) and Ketolac (Hoescht, Germany) were also found to be satisfactory for diagnosis of subclinical ketosis.[31] Blood levels of volatile fatty acids (VFAs), FFAs, and NEFAs are increased in ketosis. New test kits that are capable of assessing NEFAs on site (VDx Diagnostic Analyzer, Newburg, Wis.) have been developed. NEFA levels of greater than 0.5 mEq/L were satisfactory in detecting herd problems with subclinical ketosis.[32] Problems exist with diurnal variation in blood levels of VFAs, FFAs, and NEFAs, making timing of blood sampling difficult.[29,34-36] These tests can be used to monitor dairy herds for negative energy balance and the risk of subclinical and clinical ketosis and associated disease problems.[34] However, the current state of the art in monitoring fresh cow programs is the hand-held ketone meter (Abbott Precision Xtra System, Abbott Park, Ill.), which has immediate results, moderate cost, ease of use, and high sensitivity and specificity.[37] It is worth noting that hemolysis of blood samples will affect the accuracy of blood NEFA measurements but not BHB.[38]

The central role of the liver in energy metabolism of ruminants associates the onset of clinical ketosis with elevations of liver enzymes and abnormal liver function test results. Serum aspartate aminotransferase (AST) and sorbitol dehydrogenase (SDH) may be increased in severe cases. The degree of liver dysfunction is mild compared with that of cows with fatty liver syndrome. The sulfobromophthalein (BSP) clearance test was the classical evaluation of liver function, particularly in overconditioned cows at risk for fatty liver syndrome development (see Chapter 33) but is currently unavailable. Serum bile acid levels have had variable results and may not be useful in differentiating mild, moderate, and severe fatty infiltration of the liver, but they do correlate with severe hepatic damage.[38,39] The BSP clearance test also did not differentiate between mild and moderate fatty infiltration of the liver. Liver biopsy and determination of triglyceride or triacylglycerol (TAG) are the gold standards for accurately assessing the degree of hepatic lipidosis and are relatively simple to perform in cattle.[39]

White cell counts vary and may reflect stress or the primary disease process that the animal is experiencing. Studies vary in the reported effect of elevated ketone bodies and decreased blood glucose on lymphocyte proliferation and immunoglobulin production.[20] Serum calcium and magnesium levels may be slightly decreased in animals that are anorectic. Cortisol levels are usually within the normal range, and plasma insulin is elevated initially but depressed as the feed intake is decreased.[2]

Pathophysiology Ruminants are exquisitely programmed to use forages in the production of energy for growth, maintenance, pregnancy, and lactation. The control of energy in the ruminant is under the hormonal control of mainly insulin and glucagon. Corticosteroids, growth hormone (GH), catecholamines, hormone-sensitive lipase, and leptins have also been shown to have important roles in the fine-tuning required at the critical times of transition between late pregnancy and early lactation.[11] It is important to keep in mind that ketone bodies are an integral part of normal energy metabolism in ruminants, and it is only when the negative energy balance overwhelms the ability of the cow to use the available ketone bodies that a disease condition occurs.

Control of blood glucose in ruminants is mainly under the control of insulin, which favors cellular uptake of glucose, lipogenesis, and glycogen synthesis while decreasing lipolysis and hepatic gluconeogenesis.[40,41] Ruminants are considered to be relatively insulin resistant, but during early lactation low insulin concentrations are accompanied by high tissue insulin sensitivity.[42] Glucagon counteracts insulin by increasing lipolysis and hepatic gluconeogenesis and decreasing lipogenesis. Catecholamines modulate energy metabolism by favoring lipolysis and decreasing lipogenesis. GH levels are normally high in early lactation and inhibit lipogenesis in adipose while increasing gluconeogenesis in the liver. Adipocytes have been of increasing interest in all species because they have been shown to produce a variety of endocrine factors (leptin, resistin, IL-6, TNF-α, and adiponectin).[43-45] Leptin has potential for influencing feed intake and resistance to insulin and increasing energy expenditure and has been documented to be increased in obesity. The extent and importance of these interactions have not been completely investigated in ruminants.

In the normal lactating cow, energy is presented to the liver in the form of VFAs, bacterial protein, and a small amount of glucose and protein that escapes degradation in the rumen (Fig. 41-20).[2,8,9] The principal VFAs are acetate, propionate, and butyrate, which are produced in approximately a 70:20:10 ratio, respectively, in the rumen. Acetate is mainly used in fat synthesis, although some evidence suggests that it may be a minor glucose source by entering at the acetyl coenzyme A (CoA) level. Butyrate is condensed into acetoacetyl CoA, which can be partially oxidized to ketone bodies or transformed into acetyl CoA that can enter the tricarboxylic acid (TCA) cycle (no net gain of glucose). Propionate enters the TCA cycle

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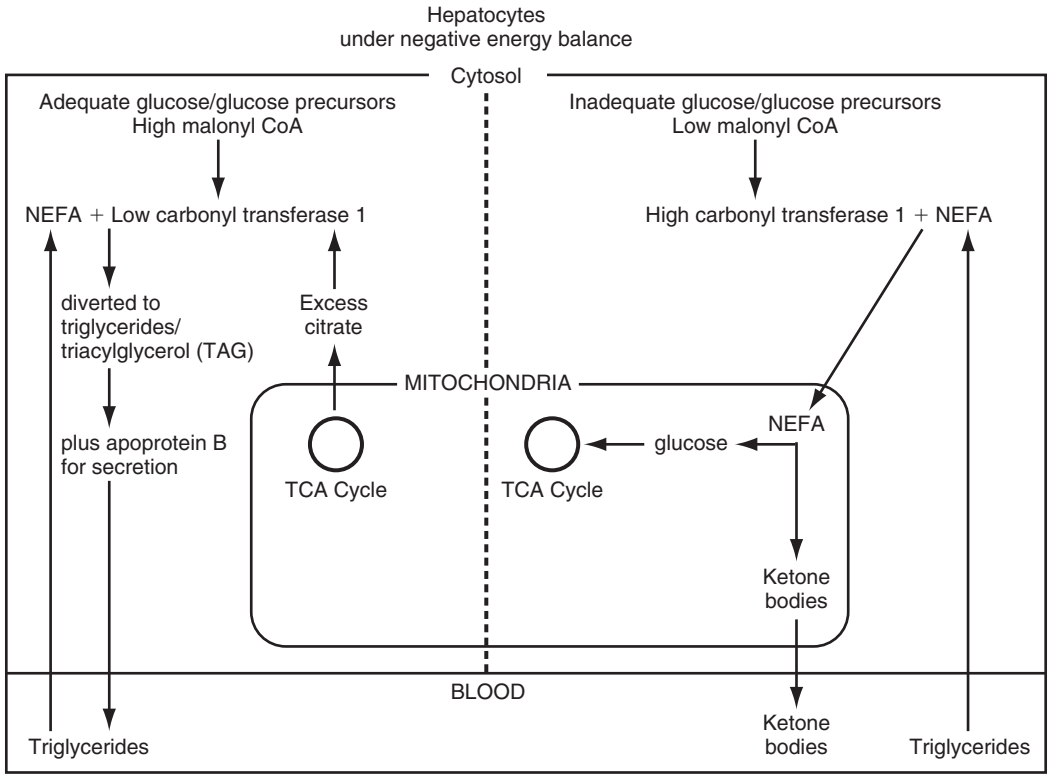


FIG. 41-20 Hepatocyte cellular metabolism under negative energy balance in the presence *(left side)* or absence *(right side)* of adequate glucose or glucose precursors.

directly at the level of succinyl CoA (equivalent to 30% to 50% of glucose production in the ruminant).[46] Therefore acetate and butyrate are ketogenic, and propionate is glycogenic (see Fig. 41-20). The normal ratio of production in the rumen is four ketogenic to one glycogenic VFA. Significant production of ketone bodies occurs in the ruminal epithelium and mammary gland, as well as in the major production site, the liver.[7,47] Ketone bodies are normally used by the TCA cycle in the heart, kidney, skeletal muscles, and mammary gland through the acetyl CoA pathway.

Efficient oxidation of acetyl CoA depends on an adequate supply of oxaloacetate, which is generated from gluconeogenic precursors, mainly propionate (from the rumen) and lactate and pyruvate (from anaerobic metabolism of glucose).[2] Skeletal muscle mass also provides amino acids for gluconeogenesis. Lactating cows preempt a large quantity of propionate and lactate for milk production in the form of lactose.[42] Supplies of oxaloacetate are reduced, slowing down the TCA cycle and the use of acetyl CoA. The backlog of acetyl CoA is diverted into the formation of ketone bodies.

Adipose tissue stores energy in the form of triglycerides, which can be mobilized to provide NEFAs that enter the TCA cycle through acetyl CoA, thus adding to the formation of ketone bodies, or are reesterified into triglycerides/triacylglyceride or TAG (see Fig. 41-19). The ruminant liver is inefficient in partitioning the increased NEFAs into triglycerides and secreting them into the circulation as lipoproteins. Apoprotein B is required to form VLDLs. Deficiency of apoprotein B will result in accumulations of TAG or fatty infiltration of the liver and abnormally elevated ketone bodies. The negative energy balance that occurs in postpartum dairy cows further reduces available carbohydrate and accelerates fat mobilization and ketone body formation. The ketone bodies in clinical ketosis are mainly produced from NEFAs in the liver, which shift in response to low carbohydrate supplies from the pathways of esterification and complete oxidation of acetyl CoA to CO_2 to partial oxidation of acetoacetyl CoA to ketone bodies.[2,41,45] The net results are ketonemia, ketonuria, ketolactia, hypoglycemia, and low levels of hepatic glycogen.

Clinical ketosis in ruminants occurs when the demand for glucose by the mammary gland or fetus exceeds the energy resources available from the diet and fat mobilization, resulting in hypoglycemia. The daily glucose requirements of a dairy cow increase above normal maintenance by 30% in late gestation and by 75% with the onset of lactation.[43] The average energy requirements of a 1000-lb lactating cow have been estimated to be 50 g of glucose per hour.[46,47] Only 10% of the glucose requirement is available in the form of glucose.

In late pregnancy and early lactation it is common for a negative energy balance to occur, which results in subclinical ketosis. Subclinical ketosis may resolve spontaneously or progress to clinical ketosis. Any additional nutritional, metabolic, or other disorder resulting in decreased feed intake will make the subclinical ketosis clinical.

Epidemiology The morbidity of clinical ketosis is extremely variable and difficult to measure. Management and nutrition are influential factors that vary widely from farm to farm and area to area. Prevalence rates (number of cases at a point in time) have been reported to be 13.1% (range 3% to 22%, depending on lactation) for clinical ketosis and 33.8% (range 31% to 41%) for subclinical ketosis.[48,49] Incidence rates (number of cases that occur in 1 year) have been reported to range from 1.87% to 13% for clinical ketosis and 7.3% to 12.1% for subclinical ketosis.[48-52] Studies using newer tests for ketone bodies have reported subclinical ketosis incidence rates of 43% and 59% using cutoff points of 1400 and 1200 µmol/L, respectively.[53] Most cases occur in the first 6 weeks after calving, with the peak incidence at 3 to 4 weeks after calving.[48,53,54]

The ability to use hand-held cow-side testing devices has allowed in-depth study, and analysis of BHB has determined that the earlier cows are detected with subclinical levels of BHB after calving and the higher the levels of BHB, the higher the risk of negative consequences. Subclinical ketosis of BHB greater than 1.2 mmol/L by 3 to 5 days in milk (DIM) were 6.1 times more likely to develop a displaced abomasum, were 4.5 times more likely to be removed from the herd, and produced 2.2 kg less milk/day for the first 30 days of lactation. Peak prevalence of subclinical ketosis occurred at 5 DIM,

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and the median time until BHB returned to less than 1.2 mmol/L was 5 days. Cows at the higher range for subclinical ketosis (BHB > 2.4 mmol/L) were 3 times more likely to develop a displaced abomasum, 50 times more likely to be removed from the herd, and were expected to produce 180 kg less milk during the first 30 days of their lactation.[3]

Breed differences have been found, as well as genetic tendencies within bull-daughter families.[5,51] The incidence of clinical ketosis increased with parity, peaking at the fifth to sixth lactation.[49,51] Cows that were diagnosed with clinical ketosis once had increased risk of ketosis at subsequent calvings.[52,53] Recurrence of ketosis in individuals may reflect digestive capacity and metabolic efficiency, as well as milk production, which are likely to have a multifactorial mode of inheritance.

Generally, clinical and subclinical cows are high producers and are overconditioned at calving.[54,55] Fat cows have been shown to have a 25% reduction in dry matter intake (DMI) and higher turnover rates of fatty acids because of more fat mobilization.[56,57] Environmental factors that affect the incidence of clinical ketosis include season (increased during midwinter), climate, stabling (increased in stabled vs. loose housing), and feeding regimen (increased with number of feedstuffs used and fewer numbers of feedings per day).[52,55,56] Diets that are less than 8% protein on a dry matter (DM) basis before calving or that have protein levels greater than 20% after calving have been associated with high incidences of herd ketosis.[58] One study reported an association of increased incidence with a high standard of management and decreased incidence if the wife, versus other family members or paid workers, assisted with chores.[59]

Thirty percent to 40% of cases are complicated by concurrent diseases such as metritis, traumatic reticuloperitonitis, and abomasal displacements.[59] These cows are classified as having secondary ketosis. A diagnosis of parturient paresis, alone or in combination with retained placenta, increased the risk of clinical ketosis.[52,55] Cows with metritis are more likely to be diagnosed as having subclinical ketosis.[48] Displaced abomasum and lameness in a previous lactation were associated with clinical ketosis.[55] One study reported that cows with elevated NEFA concentrations prepartum and elevated BHB postpartum had an increased risk of developing an LDA and ketosis.[20] Cystic ovaries, increased calving to first service interval, and increased calving to last service interval have been associated with subclinical ketosis.[48,55,56] Others reported no association between ketosis and the calving interval and number of inseminations.[3,60] Most genetic studies are based on the lactation previous to the diagnosis of ketosis and have found either no difference or a tendency toward higher production in cows with ketosis.[50,60-63] One study demonstrated a genetic correlation between milk production and ketosis using only first lactation records.[64] Subclinical ketosis was found to be associated with losses of 1 to 1.4 kg of milk per day or 4.4% to 6% of the mean daily production.[48] Other authors found an association between diagnosis and treatment of clinical ketosis, with an increase of 2.5% in production over the entire lactation.[63] A negative correlation of ketosis with culling rate indicated that high-producing cows with ketosis were less likely to be culled than low-producing cows.[52,65]

Necropsy Findings

The mortality rate from primary ketosis is extremely low. In animals that die with clinical ketosis, a fatty liver is likely to be the only pathologic finding. In secondary ketosis, lesions are associated with the primary disease condition.

Treatment and Prognosis

A recent systematic review of ketosis treatments revealed that there is a lack of well-designed studies to determine the utility of common treatment modalities for bovine ketosis.[65] In fact, only 10 studies met the criteria for inclusion. The conclusions of this review were that oral propylene glycol is the treatment of choice. Clinical ketosis that includes nervous signs may benefit from IV 50% dextrose. Butaphosphan, an organic phosphorus source and cyanocobalamin (vitamin B_{12}) show promise in treatment of ketosis but need further study. There is limited evidence that insulin therapy is useful in ketosis therapy other than refractory cases or hepatic lipidosis. The use of corticosteroids or corticosteroids in combination with insulin in ketosis therapy is not recommended at this time.

Treatment of secondary ketosis requires correction of the primary condition while ensuring the provision of an adequate diet. In ketosis secondary to the butyrate content of silage, the diet can be manipulated to eliminate or dilute the silage.[6]

Many treatments have been used for primary clinical ketosis. The goal of treatment is to limit the mobilization of fat by increasing the availability of glucose or glucose precursors and promoting uptake of glucose by cells.[66] The pathophysiologic reasoning for specific treatments of ketosis has been reviewed.[67] Traditional treatment with IV glucose, oral propylene glycol, corticosteroids, and insulin appears to clinically improve patients at least initially. In addition, many nontraditional treatments and feed supplements have shown variable success in treating and preventing ketosis.

Traditional therapy with IV injections of 100 to 500 mL of 50% glucose (dextrose) gives marked clinical improvement. A transient hyperglycemia is produced; return to preinjection levels occurs in 2 hours. Blood ketones drop immediately, clinical signs disappear, and milk production increases by 5 to 10 lb for at least one milking.[67] Nervous signs may reappear in 12 to 24 hours, and milk production drops again over 2 to 3 days. Monitoring cows treated with boluses of 50% dextrose revealed that blood glucose and insulin returned to normal within 2 hours. NEFAs and BHB levels dropped initially and returned to pretreatment levels within 12 hours. It must be noted that this study was done on normal cows, although blood BHB was consistent with subclinical ketosis.[68] This would confirm the finding of fewer relapses if the glucose injections are repeated frequently. However, the concurrent finding that serum phosphorus levels dropped as glucose and insulin were high and persisted for 12 hours post treatment suggests that hypophosphatemia is a possible outcome. Solutions containing a mixture of 25% dextrose and 25% fructose have been used in an attempt to prolong the hyperglycemic action. Ideally a continuous IV glucose infusion at 0.5 g/min should be administered until milk ketone test results are negative.[46,67] In the author's opinion a slow infusion of 20 L of 2.5% glucose (with half normal saline) over 24 hours improves the clinical response. This solution allows fast enough drip rates for ease of catheter maintenance without the danger of causing osmotic diuresis and excessive water loading, although the dextrose bolus study did not find a significant difference in urine output post treatment.[68] Urine is monitored by dipsticks for negative glucose and decreasing levels of ketone bodies several times daily. Daily monitoring of the blood glucose (once or twice daily) measures the adequacy of dextrose administration. Careful monitoring for hypoglycemia is required when intravenous glucose is discontinued. This may be impractical for field situations but is worthwhile in clinical settings with valuable individuals.

Glucose precursors may be given orally in the feed or as a drench and provide a source for gluconeogenesis. These include a propylene glycol drench at 225 g (8 oz) twice daily for 2 days, followed by 110 g (4 oz) once daily for 2 days or glycerol at 500 g twice daily for up to 10 days.[68,70-76] Propylene glycol as a drench increases the supply of glucogenic precursors (propylene, propionate, and propranolol) to the liver, which in turn decreases the glucose demand by peripheral tissues.[70] As glucose demand goes down, blood glucose rises and induces insulin release. Insulin release slows release of triglycerides from adipose tissue and thus decreases NEFAs and BHB. This effect is only seen with propylene glycol oral boluses and not with continuous exposure through inclusion in feed. Using hand-held cow-side testing for BHB to begin propylene glycol treatments to subclinical ketosis cows found that treated cows were 1.5 times as likely to resolve the subclinical ketosis, were 0.54 times less likely to develop clinical ketosis, and produced more milk than control cows on the same farm.[75] The cows were dosed once daily with 300 mL (10 oz) of propylene glycol orally until blood BHB reached less than 1200 mmol/L or 17 DIM was reached.

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Overuse of propylene glycol may have a deleterious effect on ruminal flora, decrease ruminal motility, and cause diarrhea, necessitating its discontinuation and the institution of ruminal transfaunations.[71] In one study, adding propylene glycol to the diet of postpartum cows decreased NEFA and BHB levels but did not significantly change milk production, health, or fertility and therefore was not economically beneficial.[72] Glycerol drenches at 1 to 2 L orally per cow alleviated symptoms of ketosis, but including glycerol in the transition feed did not.[73,74] Sodium propionate (125 to 250 g twice daily orally), ammonium lactate (120 g twice daily orally), and sodium lactate (360 g twice daily orally) have also been used as feed additives to provide alternate glucose sources. All of these tend to lower the butterfat test result and may cause digestive disturbances if prolonged treatment is used.[67] Glucocorticoids have been used to prolong the hyperglycemic effect by decreasing tissue uptake of glucose and reducing milk production for up to 3 days. Dexamethasone (0.04 mg/kg) and betamethasone are most commonly used. In one study a single treatment of dexamethasone (0.04 mg/kg) significantly increased blood glucose for 6 to 9 days and decreased milk production for 1 to 7 days.[76] Caution must be used because overdosing may reduce feed intake and exacerbate the condition of cows with fatty liver syndrome.[77] Anabolic steroids such as trienbolone acetate have resulted in decreases in blood levels of ketone bodies without depression of milk production but are prohibited in the United States.[78]

Low doses of long-acting insulin (200 IU of protamine zinc insulin subcutaneously [SC] once every 48 hours) have been used as an adjunct to IV glucose and glucocorticoid therapy. Use of the newer slow-release insulin (Humilin, Ultralente human insulin rDNA, Eli Lilly, Indianapolis, Ind.) at a dose of 0.14 IU/kg of body weight IM provided an insulin peak by 12 hours postinjection, with return to preinjection levels by 24 hours.[79] Blood glucose lowered by 21% at 6 to 12 hours and returned to preinjection levels within 24 hours. Pancreatic secretion of insulin is reduced in ketotic cows in response to IV infusions of glucose.[80] Insulin assists in suppressing fatty acid mobilization and increasing tissue uptake of glucose while stimulating hepatic glycolysis. IV glucose combined with insulin when administered over several days has been shown to decrease NEFAs and liver triglycerides and increase hepatic glycogen.[81]

There has been interest in using glucagon injections to stimulate gluconeogenesis and limiting lipolysis, which decreases triglyceride accumulation in the liver during early lactation. Recent studies reported glucagon had no adverse effects but had only minor effects on the lipid transport in early lactation.[82] Glucagon is not commercially available.

Lipotrophic agents such as choline (25 to 50 g daily PO), cysteamine (750 mg IV every 2 to 3 days), and L-methionine have been suggested as feed additives or treatments that increase mobilization of fat in the liver.[83-85] Choline (25 g daily) may also be given subcutaneously but should *not* be given intravenously because it acts as a neuromuscular blocker. Trials with rumen-protected choline in the periparturient dairy cow have shown that hepatic lipidosis is reduced by improved fatty acid processing with increased apolipoprotein A and very-low-density lipoprotein (VLDL) synthesis, resulting in more efficient energy balance.[86] Rumen-protected choline reduced the incidence of clinical ketosis, mastitis, and morbidity when fed before calving and in the first weeks of lactation but not when only fed before calving.[87,88]

Cobalt deficiency and therefore vitamin B_{12} deficiency have been implicated as causes of ketosis.[12] Vitamin B_{12} is an essential cofactor in the metabolism of propionate as it enters into the TCA cycle.[9] Blood and liver levels of vitamin B_{12} are reduced in the postparturient cow.[14] Vitamin B_{12} and cobalt may be added to the diet.[89] Vitamin B_{12} in combination with butaphosphan when injected at calving and repeated the second day significantly decreased the median BHB levels and the percentage of subclinical ketosis cows compared with untreated controls but only in cows starting their third lactation or higher.[90]

Supplementation of prepartum and early lactation diets with chromium decreased serum NEFAs but had no effect on milk production or milk components.[91] Decreased NEFA was greatest at 1 week postpartum. Chromium may potentiate the action of insulin and has a role in the activation of thyroid hormone. A study that combined chromium with L-methionine increased liver glycogen and dry matter intake in postpartum cows increased dry matter intake in postpartum cows but did not make significant changes in BHB or NEFAs.[92]

Nicotinic acid (niacin) and nicotinamide have been used with variable effects.[9] Nicotinamide coenzymes in mammary tissue were reduced in ketotic cows compared with normal cows.[93] The suggested dose of nicotinic acid is 6 g orally once daily for up to 10 weeks after calving. Milk production was slightly increased, and blood levels of ketone bodies and FFAs were lower in niacin-treated cows.[94] Niacin decreases blood ketones and FFAs and increases blood glucose. Niacin has also been used in combination with propylene glycol or monensin, but no significant differences were found between treatment and control groups.[95,96] Diets fed before and after calving with daily dosages of 12 g or 24 g per day of an encapsulated niacin product demonstrated a significantly lowered blood NEFA but did not change BHB levels.[97,98] It also lowered milk production and at the higher dosage reduced dry matter intake before calving. Niacin may show more promise for improving fat metabolism in hepatic lipidosis than for ketosis.

Biotin is a coenzyme in the process of gluconeogenesis and has been studied in the peripartum period.[99] Although NEFAs and hepatic lipid were lower, biotin did not decrease BHB.

Ionophores increase the ratio of propionate formation in the rumen and have been documented to decrease the incidence of clinical ketosis.[30] Monensin (Rumensin, Elanco, Greenfield, Ind.) is cleared for inclusion in feed for dry and lactating dairy cattle in the United States and is valuable as a tool for managing clinical and subclinical ketosis.

Chloral hydrate is a traditional treatment that increases the breakdown of starch in the rumen and influences the ruminal production of propionate. The initial oral dose is 30 g, followed by 7 g twice daily for several days.[67] Chloral hydrate may be particularly helpful for its sedative effects in treating cows with recurring nervous ketosis.

As in all metabolic diseases, nursing care is important. Supportive therapy may include ruminal transfaunations, provision of a variety of palatable feeds, and exercise.

Prevention and Control Because the underlying mechanism of clinical and subclinical ketosis is one of negative energy balance during the first 8 weeks of lactation, prevention and control can be addressed in three steps. The feeding and management of cows during late lactation and the dry period should promote good body condition at calving (see Chapter 9 for BCS system). Optimum intake of lactating rations at the commencement of lactation must be encouraged by introducing the ration in a stepwise fashion. The ideal ration during early lactation is highly palatable and of an appropriate energy density.[12]

A moderate amount of body fat should be available for mobilization and milk production at parturition. The body fat that is lost in early lactation must be stored in the previous late lactation by feeding to National Research Council (NRC) recommendations.[10] Body condition of the dry cow must be maintained, and fetal growth must be provided for. It is essential that cows do not become too fat before parturition.[8,54,55] There is evidence that fatty infiltration of the liver begins before parturition, particularly in individuals with fat cow syndrome.[40]

The introduction of the lactating ration should be made as smoothly as possible to encourage maximum intake and minimize digestive upsets. Feeding of the lactation ration in limited amounts may begin as early as 4 to 5 weeks before parturition so that typically 8 to 9 lb of concentrates are being fed at parturition. After calving, incremental increases of a few pounds per day are made until ad lib levels are reached (at ≈2 to 4 weeks).[8] Ensuring adequate bunk space and minimizing pen changes at the time of parturition will have a critical, positive effect on DMI immediately.[34]

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The ideal early lactation ration is highly palatable and meets NRC recommendations. It is beyond the scope of this text to outline detailed ration balancing. The key aspects are maintaining high energy density and optimum levels of fiber and protein without compromising the DMI. Calculations of the energy requirements of a lactating cow are expressed as total net energy of lactation and are obtained from NRC charts.[12] Recommendations for fiber content of the diet are based on the acid detergent fiber (ADF) and NDF. NDF is a good estimate of the bulk of a diet, and the DMI of a ration depends on the NDF (1.2% of body weight). Not all forage analysis laboratories report the NDF, but it can be approximated by dividing the total digestible nutrients by 100. Protein should be provided as both rumen degradable (soluble and nonprotein nitrogen) and rumen undegradable (bypass). Excess protein and fat should be avoided.[34] Specific instructions for formulating these ingredients into a ration are provided by multiple ration-balancing programs.[12] In contrast, a recent study found that feeding a higher forage and lower concentrate diet in the 3 weeks prepartum reduced the incidence of subclinical ketosis postpartum.[100] There was no difference in dry matter intake between the two test groups postpartum, but the high forage group did have slightly lower milk production through the first 22 weeks of lactation, which was only significantly different from days 7 to 28. Controlling energy of prepartum diets by including more forages may be useful in managing ketosis.

The diet must also be balanced in its minerals. Cobalt may be added if there is an indication of inadequate levels.[89] Encapsulated niacin is recommended as a feed additive at 12 g/head/day in early lactation rations.[98] Inclusion of chromium in peripartum diets may also be beneficial.[92]

Problems that arise from silage with high butyrate concentrations may require substitution or dilution of the affected silage with other feeds for the cows in early lactation. High-butyrate diets are often tolerated because they encourage a higher milk butterfat content.[6,69] The addition of protected fats in the form of the calcium salts of long-chain fatty acids or a high proportion of saturated long-chain fatty acids (palmitic and stearic acids) increases the energy density of the ration without reducing the fiber content.[101] These compounds are not degraded in the rumen but are digested in the abomasum and small intestine. Feeding protected fats results in increased milk production, slightly decreased DMI, and increased FFAs, as well as stabilized blood ketones and weight loss through a glucose-sparing effect. However, there is some evidence that added fat does not help in the periparturient period and may interfere with other treatments.[102] Glucogenic precursors such as propylene glycol and sodium propionate have been incorporated into early lactation rations for many years. Both of these compounds are not palatable to dairy cattle and are better reserved for treatment of individual cases of ketosis.

Subclinical and clinical ketosis should be detected and treated as early as possible to prevent deleterious effects on health and production. This may be accomplished by encouraging clients to use ketone tests routinely on milk or urine during the first 2 weeks or up to 50 to 60 days after parturition.[76] Several companies are developing commercial automated sampling systems that can routinely test milk for ketone bodies.[103-105] Cattle with positive test results should have a thorough physical examination. Use of hand-held cow-side BHB testing protocols should be considered for monitoring transition cows. Institution of supportive therapy for subclinical ketosis should include administration of oral propylene glycol until BHB levels subside. A high prevalence rate of clinical and/or subclinical ketosis would necessitate investigation of the feeding program.

Calcium, Magnesium, and Phosphorus

Jesse P. Goff

Adequate blood calcium (Ca), magnesium (Mg), and phosphorus (P) concentrations are vital to normal function of animals. Mechanisms for maintaining blood Ca, Mg, and P concentrations within normal limits perform efficiently most of the time. Occasionally, these homeostatic mechanisms fail, and metabolic diseases such as milk fever occur. Inadequate blood Ca, P, Mg, or potassium (K) concentrations (discussed later in chapter) can cause a cow to lose the ability to rise to her feet because these minerals are necessary for nerve and muscle function. Less severe disturbances in blood concentrations of these minerals can cause reduced feed intake, poor ruminal and intestinal motility, poor productivity, reduced immune function, and increased susceptibility to other metabolic and infectious disease.

Calcium

Ca is the major mineral of bone. Extracellular Ca is essential to ensure transmission of nervous tissue impulses, excitation of skeletal and cardiac muscle contraction, and blood clotting. It is also a component of milk. Intracellular Ca, although just 1/10,000 the concentration of extracellular Ca, is involved in the activity of a wide array of enzymes and serves as an important second messenger conveying information from the surface of the cell to the interior of the cell. Low extracellular Ca concentration lowers the potential difference across nerve and muscle cell membranes. The potential difference is closer to the threshold potential, making the nerves easily excitable. This can cause muscle fasciculations or even tetany. However, at the neuromuscular junction, the amount of acetylcholine released during an end plate action potential is directly related to the amount of Ca that enters the terminal end of the motor neuron, which is in turn dependent on extracellular Ca concentration. Thus hypocalcemia reduces the strength of muscle contraction, resulting in paresis. In many species (dog, cat, human, horse) the prevailing effects of hypocalcemia are on the nervous tissue, resulting in tetany. In the cow and sheep, the effects of hypocalcemia on the motor end plate predominate and failure to release acetylcholine manifests as paresis and inability to rise to their feet. Both effects of hypocalcemia are occurring at the same time in all species, but clinical symptoms differ depending on which effect of hypocalcemia predominates.

Calcium Homeostasis

The skeleton of a 600-kg cow contains approximately 8.5 kg of Ca. Blood Ca concentration in the adult cow or sheep is maintained at 8.5 to 10 mg/dL (2 to 2.5 mM) and is slightly higher in young animals (Fig. 41-21). There are just 3 g of Ca in the plasma pool of a 600-kg

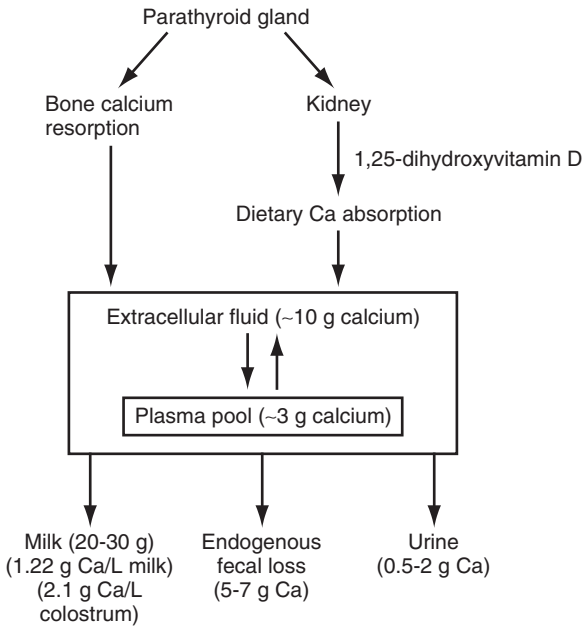


FIG. 41-21 Calcium homeostatic response of the 600-kg cow in early lactation to a decline in blood Ca concentration at the onset of lactation.

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TABLE 41-9

Diagnosing Acute and Chronic Macro-Mineral Insufficiency or Imbalance in Ruminants*

Mineral	Tissues to Use	Normal	Subclinical Deficiency	Clinical Deficiency
Calcium (acute)	Serum, plasma (mg/dL)	8.0-10.5	5.5-7.5	<5.0
Calcium (chronic)	Serum, plasma (mg/dL)	8.0-10.0	8.0-10.0	6-10.0
	Rib bone ash (% Ca)	37-39	35-37	<35
	Urine (mg/dL)	>2.0	0.5-1.5	<0.1
Phosphorus (acute)	Serum, plasma (mg/dL)	4-6	2-4	<1.2
Phosphorus (chronic)	Serum, plasma (mg/dL)	4-6	3-4	<3
	Rib bone ash (% P)	17-20	15-17	<12
Magnesium (acute)	Serum, plasma (mg/dL)	2.0-2.3		<1.1
	Vitreous humor (mg/dL)	1.9-2.5	1.5-1.85	<1.5
	Urine (mg/dL)	10-25	2-5	<0.5
	Cerebrospinal fluid (mg/dL)	2-2.5		<0.5
Magnesium (chronic)	Serum, plasma	2.0-2.3	1.6-1.9	<1.5

*The tissue needed to ascertain acute problems is intended to guide diagnosis of the initial cause of recumbency in downer cows.

cow and 8 to 9 g in the extracellular pool. Ca concentration in the blood is tightly regulated, primarily by the parathyroid gland, which responds to even a small decrease in blood Ca concentration by secreting parathormone (PTH) into the blood. First, PTH increases renal tubular reabsorption of Ca from the glomerular filtrate. Only small amounts of Ca are lost in urine (<1 to 2 g/day in the cow), so this action of PTH is sufficient to restore normal blood Ca concentration only if the Ca deficit is small. Larger Ca deficits cause prolonged secretion of PTH (hours to days), which stimulates osteoclastic resorption of bone Ca to use skeletal calcium to make up the deficit. PTH can also stimulate renal production of 1,25-dihydroxyvitamin D. The 1,25-dihydroxyvitamin D enhances Ca absorption by stimulating intestinal epithelial cells to produce Ca binding proteins and Ca pumps so that Ca within the lumen of the gut is efficiently transported across the intestinal epithelial cells into the blood. Should an animal be fed a Ca- or vitamin D–deficient diet, it will generally maintain normal blood Ca concentrations for weeks to months by resorbing bone Ca. However, this ultimately will cause bone disease such as osteoporosis and rickets (growing) or osteomalacia (adult rickets). If blood Ca concentration goes above normal, PTH secretion ceases and the thyroid gland C cells secrete calcitonin. This hormone increases Ca excretion in urine and decreases osteoclast activity so that more Ca is retained in bone.

Acute Hypocalcemia (Milk Fever) in Dairy Cows (and Goats)

Half of all dairy cows will experience subclinical hypocalcemia (<8 mg/dL) within 24 hours of calving as a result of the sudden loss of blood calcium to the mammary gland to support the onset of lactation (Table 41-9). This reduces ruminal and abomasal contractility and feed intake and raises blood nonesterified fatty acids (NEFAs), though clinically these animals appear normal. Hypocalcemia also contributes to metritis, mastitis, and retained placenta by negatively affecting uterine and teat sphincter contractility. It also has a direct effect on the ability of immune cells to respond to external stimuli because intracellular Ca store depletion interferes with Ca action as a second messenger. If blood Ca concentration continues to decline, the cow may experience ataxia and may be slightly bloated as eructation is reduced. In some cows, blood Ca will fall below 5 mg/dL (1 mM), and in a few Ca will be as low as 2 mg/dL. These cows are recumbent and unable to rise and have a condition commonly referred to as *milk fever* or *parturient paresis.* They often lie with the neck out in an S-shaped curve. Close examination of muscles in the legs and neck will reveal fasciculation of some muscle groups. Heart muscle loses contractility, so on auscultation the heartbeat is muffled. The heart rate is generally increased to compensate for the low ventricular ejection volumes. The cow loses the ability to thermoregulate and takes on the ambient temperature of its surroundings. In most cases this causes the skin, especially skin of the ears, to be cold. However, in hot climates or when the cow is recumbent in the hot sun the body temperature may be elevated well above normal. Milk fever typically occurs within a day or two of calving—usually after calving subsequent to colostrum milk-out but occasionally just before calving due to the sudden rush of calcium into the mammary gland to form colostrum.

BOX 41-4

Primary Causes of Recumbency Initiating the "Downer Cow Syndrome"

Mineral imbalances
- Hypocalcemia—plasma Ca < 5 mg/dL
- Hypomagnesemia—plasma Mg < 1.2 mg/dL
- Hypophosphatemia—plasma P < 1.5 mg/dL

Severe toxemia—moderate reduction in plasma Ca, Mg, and P
Dystocia
Pregnancy toxemia syndrome—low plasma Ca, Mg, P, and glucose
Fractures
Coxofemoral luxation
Rupture of gastrocnemius muscle
Lymphosarcoma of spinal cord

Acute hypocalcemia also occurs with many infectious conditions, such as mastitis or metritis, especially if endotoxins are elaborated. As a rule the blood Ca concentration during endotoxemia is 6 to 8 mg/dL. This form of hypocalcemia is a result of redistribution of Ca within organs caused by interleukin-1 and other proinflammatory cytokines and is not discussed further other than to note that not all hypocalcemic cows have the syndrome known as milk fever (Box 41-4).

Treatment of milk fever and hypocalcemia should be done as early as possible, especially if recumbency is present. The pressure exerted by the massive weight of the cow can cause a "crush syndrome" effect on the down side appendages in as little as 4 hours. This causes ischemia of the muscles and nerves and is followed by necrosis of these tissues, resulting in the "downer syndrome" cow.[1] The fastest way to restore normal plasma Ca concentration is to administer an IV injection of Ca salts (commonly Ca borogluconate). In general, commercial preparations for IV use supply from 8.5 to 11.5 g of Ca per 500 mL. They may also contain sources of Mg, P (often as ineffective phosphite), and glucose. The most effective IV Ca dose is approximately 2 g of Ca per 100 kg of body weight. A good rule of thumb is to administer the Ca at a rate of 1 g/min. If Ca is administered too rapidly, fatal arrhythmia of the heart and cessation during systole can occur. IV Ca treatments increase blood Ca above normal for approximately 4 hours. Ca salts can also be injected subcutaneously, but

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absorption is variable because blood flow to the periphery is often compromised. The amount of Ca that can be injected into a single subcutaneous site should be limited to 1 to 1.5 g of Ca (50 to 75 mL of most commercial preparations). Ca preparations designed for IM administration are also available (Ca levulinate or Ca lactate). Most of these preparations must be limited to 0.5 to 1 g of Ca per injection site to avoid tissue necrosis. To get an effective dose of Ca into the clinically hypocalcemic animal might therefore require 6 to 10 injections into widely separated sites. Oral Ca treatments are not recommended as treatments for clinical milk fever cases, although they can be effective aids in prevention of milk fever and help prevent relapses when administered 12 to 24 hours after IV treatment.

Etiology of Milk Fever

Dairy cows producing colostrum (containing 1.7 to 2.3 g of Ca per kilogram) or milk (containing 1.2 g of Ca per kilogram) typically secrete 20 to 30 g of Ca each day in early lactation. Put simply, hypocalcemia and milk fever occur when cattle do not obtain enough Ca from their bones and diet to replace Ca lost to milk, as well as supply the Ca needed for maintenance (10 to 12 g absorbed Ca/day). The long-accepted reason this occurs was that high dietary Ca fed to the cow before calving placed the cow in such a state of positive Ca balance that the parathyroid gland atrophied, rendering it too sluggish to adequately respond when onset of lactation placed the cow into negative Ca balance. However, in recent years it has been discovered that high dietary Ca does not have this effect, and in most cases PTH secretion is quite adequate in these animals. However, the efficacy of the secreted PTH seems to be a major issue.

Role of Metabolic Alkalosis

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia by altering the conformation of the PTH receptor, rendering the tissues less sensitive to PTH (Fig. 41-22).[2-5] Lack of PTH responsiveness by bone tissue prevents effective use of bone canaliculi fluid Ca (sometimes referred to as *osteocytic osteolysis*) and prevents activation of osteoclastic bone resorption. Failure of the kidneys to respond to PTH reduces renal reabsorption of Ca from the glomerular filtrate. More important, the kidneys fail to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Therefore enhanced intestinal absorption of dietary Ca, which normally would help restore blood Ca to normal, fails to be instituted.

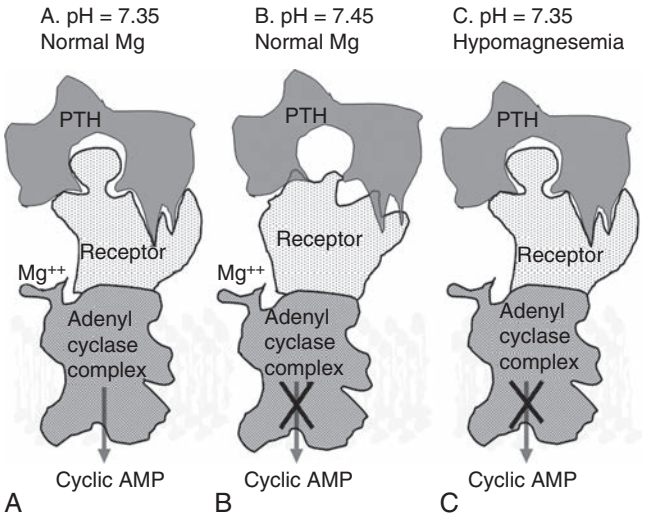


FIG. 41-22 Parathyroid hormone (PTH) affects the surface of target bone and kidney cells. **A,** Under normal conditions, PTH released in response to hypocalcemia interacts with its receptor, located on the surface of bone and kidney cells, in a lock and key fashion. This stimulates G proteins and adenylate cyclase (adenylate cyclase complex) resulting in production of cyclic AMP, which acts as a second messenger within the cytosol of target cells. This initiates mechanisms such as bone calcium (Ca) resorption and renal production of 1,25-dihydroxyvitamin D to restore blood Ca concentration to normal levels. **B,** Alkalotic conditions induced by high-potassium diets induce a change in the shape of the PTH receptor protein so that it is less able to recognize and bind PTH, resulting in failure to activate the cell by producing cyclic AMP. **C,** Mg is required for function of the adenylate cyclase complex. Hypomagnesemia reduces ability of PTH stimulated cells to produce cylic AMP, resulting in failure to activate the cell.

Metabolic alkalosis of dairy cows is caused by high-potassium diets. This is best explained by Stewart's[6] strong ion difference theory of acid-base physiology, which states that the number of moles of positively charged particles (cations) in any given solution (including body fluids) must equal the number of moles of negatively charged particles (anions) in the solution. When they do not, water must undergo a change in its dissociation equilibrium until the charges are balanced. The dissociation equilibrium of water is described as $H_2O \rightarrow H^+ + OH^-$. Often the H^+ ion attaches itself to an existing water molecule in the solution to form H_3O^+ (hydronium ion), which is also in equilibrium with water. Put into extremely simplified terms, when positively charged particles such as potassium (K^+) are added to a solution, such as the plasma, it causes a shift in the dissociation equilibrium of water. The number of positively charged H^+ cations will decrease, and the number of OH^- anions will increase to maintain the electroneutrality of the solution (the solution becomes more alkaline). Conversely, adding anions such as chloride (Cl^-) or sulfate (SO_4^{-2}) to a solution causes an increase in H^+ and a decline in OH^- to maintain electroneutrality, and the pH decreases (the solution becomes more acidic).

Diet can affect blood pH. Cations and anions enter the blood from the digestive tract, making the cation-anion difference of the diet the ultimate determinant of blood pH. The major cations present in feeds and the charges they carry are sodium (+1), potassium (+1), Ca (+2), and Mg (+2). The major anions and their charges found in feeds are chloride (−1), sulfate (−2), and phosphate (variable but assumed to be −3). Cations or anions present in the diet will alter the pH of the blood only if they are absorbed into the blood. The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood.

When formulating dairy cow late-gestation diets, the cation-anion difference of a diet is described in terms of mEq/kg or mEq/100 g of diet, using various equations involving Na, K, Ca, Mg, Cl, sulfate (S), and P, with and without adjustments for absorbability of each mineral in the diet:

Dietary Cation-Anion Difference (DCAD)

$= (Na^+ + K^+) - (Cl^- + S^{-2})$

$= (Na^+ + K^+) - (Cl^- + 0.6\ S^{-2})$

$= (0.2\ Ca^{+2} + 0.16\ Mg^{+2} + Na^+ + K^+) - (Cl^- + 0.6\ S^{-2} + 0.64\ P^{-3})$

The equations largely become an academic pursuit because several of the variables in the formulas shown are somewhat fixed constants. One strategy is to set dietary Ca at 0.85% to 1% and dietary P and Mg at 0.4%. Dietary sulfur needs to be above 0.22% to ensure adequate substrate for ruminal microbial amino acid synthesis but below 0.4% to avoid possible neurologic problems associated with sulfur toxicity. The key to milk fever prevention is to keep Na and K as close to the requirement of the cow as possible (0.1% for Na and 1% for K). Using low-K hays and straws is critical for close-up cows. Corn silage is also generally low in K and is often useful in formulating low-K diets. More savvy dairymen are also identifying low-K, high-Cl hays for close-up cows. The key to reduction of subclinical hypocalcemia is to then add chloride to the ration to counteract the effects of low levels of potassium on blood alkalinity. As a rule of thumb, the amount of dietary chloride needed to acidify the cow's blood (and urine) is approximately 0.5% less than the concentration of K in the diet. For example, if dietary K can be reduced to 1.3% of the diet, Cl would need to be roughly 0.8% to acidify the cow. This is where the nutritionist should begin the process of adding anions to the diet. For some dairies this will be adequate. When urine pH (discussed later) suggests the cows are not yet acidified, small additions of chloride can be made to the diet. In the author's experience, 75% of dairies will find the level of chloride needed is closer to 0.3% less than the % K achievable. However, balancing the diet immediately so that chloride content is 0.3% below % K will cause 25% of

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dairies to have cows that are overacidified. Overacidification will lead to inappetance, and this results in many other metabolic disorders for the transition cow. Chloride sources differ greatly in their palatability, and because achieving low dietary K can be difficult, it is prudent to use a palatable source of Cl when formulating the diet. Ammonium chloride (or ammonium sulfate) can be particularly unpalatable when included in rations with a high pH. If the total ration has a pH above 6, the ammonium cation is converted to ammonia, which is highly irritating when smelled by the cow. Prilling the Cl (and SO_4) salts can reduce the unpleasant taste of the salts. In the authors' experience, hydrochloric acid has proved the most palatable source of anions. Hydrochloric acid is extremely dangerous to handle as a liquid concentrate. Several companies now manufacture hydrochloric acid–based anion supplements that are safe to handle.

There is some disagreement about how much Ca needs to be in the anionic diet. The earliest papers describing use of anions to prevent milk fever often used calcium chloride as the anion source. These diets were often 1.2% to 1.5% Ca, and as a result many nutritionists feel high diet Ca is necessary when using anions to prevent milk fever. Recent studies[7,8] have demonstrated that there is no difference in efficacy of "anionic" diets when calcium is varied between 0.5% and 1.5% calcium. The key to the diet's efficacy in reducing hypocalcemia is whether or not it has induced a compensated metabolic acidosis before calving.

Determining urine pH of the cows provides a cheap and relatively accurate assessment of blood pH and can be a good gauge of the appropriate level of anion supplementation.[9] Urine pH on typical high-cation close-up diets is generally above 8.2. Limiting dietary cations will reduce urine pH only a small amount (pH 7.6 to 7.9). For optimal control of subclinical hypocalcemia, the average pH of the urine of Holstein cows should be between 6.2 and 6.8, which essentially requires addition of anions to the ration. In Jersey cows the average urine pH of the close-up cows has to be reduced to between 5.8 and 6.3 for effective control of hypocalcemia. The goal is to create a compensated metabolic acidosis in the cow so that the PTH receptor is best able to respond to PTH secreted at the onset of lactation. If the average urine pH is between 5.0 and 5.5, excessive anions have induced an uncompensated metabolic acidosis, and the cows will experience a decline in DMI. Urine pH can be checked 72 or more hours after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. Anion-supplemented diets are generally fed for the last 2 to 3 weeks before calving. Some farms have adopted a single diet for all dry cows and are feeding anions throughout the whole dry period. Over 4 to 5 weeks, urine pH does increase in cows fed anion diets as their bone releases more calcium to compensate. Under this scenario it is important to use cows that have been on the diet for just 2 to 3 weeks when gauging whether enough anions have been added to the diet.

Interpreting urine pH is sometimes challenging. When the average urine pH on a group (6 to 10 cows is a good sampling) of cows is above 6.8, it is relatively easy to say more anions need to be added to the diet. When the average is 6.2 to 6.8, it is again easy to see that you have achieved the goal of creating a compensated metabolic acidosis. Also, when the average urine pH is below 5.2, it is clear the animals are entering a state of uncompensated metabolic acidosis and anions should be reduced in the diet. A more difficult situation arises when some close-up cows have urine pH around 8 and some around 5.3 when fed the same diet! Overcrowding and diet sorting can be causes for variations in intake that result in this variability in urine pH. However, if they can be ruled out, experience suggests the animals are receiving too much anion supplementation. The animals with urine pH of 8 consumed diet well the day before sampling, but the acidosis induced by the excessive amount of anions caused them to go off feed for the 12 hours before sampling. The cows with urine pH around 5.3 consumed diet within the last 12 hours but may not have been the day before. Cows going "on and off feed" cause these great fluctuations in urine pH among the dry cows.

Agronomic Considerations for Producing Low Dietary Cation-Anion Difference Forages

Reducing K in the ration of the late-gestation cow can present a problem. By restricting K application to the soil, it is possible to avoid luxury consumption of K by legumes and cool season grasses. Producers should also be aware that forages take up Cl from the soil, and it is possible to find hays that are low in K and high (1% to 1.2%) in Cl.[10,11] Producers should use the lowest DCAD forage possible, not simply the lowest K forage. Forages intended for the close-up dry cow should routinely be analyzed for both K and Cl by a wet chemistry method. Near infrared determinations of forage mineral content are not currently useful.

High Dietary Phosphorus

High blood P concentrations inhibit the activity of the renal 25-hydroxyvitamin D 1α-hydroxylase enzyme.[12,13] As summarized by Jorgensen,[14] the incidence of milk fever increases when dietary P exceeds 90 g/day and little negative effect of dietary P is seen when dietary P is less than 50 g/day. Close-up dry cows need approximately 30 to 40 g of P each day.[15]

Use of Low-Calcium Prepartal Diets to Prevent Milk Fever

In late gestation the cow requires 18 to 24 g absorbed Ca from her diet each day to meet Ca requirements of maintenance and fetal growth. By feeding late-gestation cows a diet that supplies less Ca than they require, the cows can be placed into negative Ca balance. This causes a minor decline in blood Ca concentration, which stimulates PTH secretion, which in turn stimulates osteoclastic bone resorption and renal production of 1,25-dihydroxyvitamin D before calving. This increases bone Ca release and prepares the intestine to absorb Ca efficiently, should it become available. At parturition the lactational drain of Ca is more easily replaced because the cow's bone osteoclasts are already active and in high numbers, and the previous stimulation of enterocytes by 1,25-dihydroxyvitamin D allows efficient use of dietary Ca. Unfortunately, a truly low-Ca diet should supply considerably less than 20 g of absorbed Ca per day (considerably <50 g total diet Ca/day). This is difficult to actually achieve on most dairy farms. Most of the studies demonstrating a milk fever prevention benefit by using low-Ca forages to achieve diets with 50 to 70 g Ca supplied/day also decreased diet K because high calcium forages tend to be high in potassium as well. Increasing use of straw to reduce energy of prepartal diets coupled with the use of Ca binders, such as zeolite or vegetable oil, may make the low-Ca approach more practical.[16]

Physiologic Milk Fever Risk Factors

The incidence of milk fever rises as a cow ages, especially as she enters her third or greater lactation. As animals age the number of active bone cells is reduced. Heifers, which are still growing, rarely have problems with hypocalcemia. Lower numbers of active osteoblasts mean fewer cells to respond to PTH and mobilize bone Ca. In addition, as animals age the number of receptors for 1,25-dihydroxyvitamin D on target tissues declines.

The incidence of milk fever is higher in Jersey cows compared with Holstein cows. Although Jersey cow colostrum and milk Ca concentration tend to be higher than in Holsteins, this does not appear to be the only factor. Preliminary data from the author's laboratory suggest the intestine of Jersey cows possesses approximately 15% fewer receptors for 1,25-dihydroxyvitamin D than does the intestine of Holstein cows.

Preventing Milk Fever with Vitamin D

Earlier literature often recommended feeding or injecting massive doses (up to 10 million units) of vitamin D 10 to 14 days before calving to prevent milk fever. This will pharmacologically increase intestinal Ca absorption and can help prevent milk fever. Unfortunately, the dose of vitamin D that effectively prevents milk fever is

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close to the level that causes irreversible metastatic calcification of soft tissues, and therefore this strategy cannot be recommended. Lower doses may actually induce milk fever because the high levels of 25(OH)D and 1,25-dihydroxyvitamin D induced by the treatment suppress PTH secretion and directly suppress renal synthesis of endogenous 1,25-dihydroxyvitamin D.[17]

Treatment with 1,25-dihydroxyvitamin D and its analogues can be much more effective, but problems with timing of administration, withdrawal from treatment, expense, and availability have made these treatments not practical.[18,19]

Hypomagnesemia as a Cause of Hypocalcemia

Hypomagnesemia affects Ca metabolism in two ways. Moderate hypomagnesemia (<1.6 mg/dL) interferes with PTH action on tissues (see Fig. 41-19). When PTH binds its receptor on bone or kidney tissues, it normally initiates activation of adenylate cyclase and phospholipase C, resulting in production of the second messengers, cyclic adenosine monophosphate (AMP) and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C have a Mg^{++} binding site that must be occupied by a Mg ion for full activity.[20] Hypomagnesemia, from inadequate absorption of dietary Mg, is the second most common cause of milk fever in cows around the time of calving and is the most common cause of "midlactation milk fever" (down cows that respond to intravenous Ca) in dairy cows. More severe hypomagnesemia (<1.2 mg/dL) can actually inhibit PTH secretion in response to hypocalcemia. This appears to be a factor in the development of some hypomagnesemic tetany syndromes of grazing beef and dairy cattle. In these syndromes blood Mg concentration falls slowly over time until such point that PTH secretion is impaired. It is at this point that blood Ca concentration declines precipitously and clinical symptoms, such as tetany, become apparent.[21] Increasing prepartum and early lactation dietary Mg to 0.4% is among the most effective means of preventing milk fever and hypocalcemia.[22]

Oral Calcium Treatments at Calving

Ca is absorbed across the intestinal mucosa by two methods. The first method is by the active transport of Ca across intestinal cells—a process mediated by the hormone 1,25-dihydroxyvitamin D. The second method is by passive diffusion across the tight junctions that hold adjacent mucosal cells together. The concept behind oral Ca supplementation is that the cow's ability to use active transport of Ca *across* intestinal cells is inadequate to help her maintain normal blood Ca concentrations. By giving the animal large amounts of very soluble Ca, it is possible to force Ca across the intestinal tract by means of passive diffusion *between* intestinal epithelial cells. Best results are obtained with doses of Ca between 50 and 125 g. For best control of hypocalcemia, a dose is given at calving and again 24 hours later. Administering 50 g of Ca from $CaCl_2$ as a drench in 250 mL of water is roughly equivalent to administering 4 g of Ca intravenously.[23] Unfortunately, hypocalcemic cows have poor swallowing and gag reflexes, making them vulnerable to aspiration pneumonia. Aspiration of Ca solutions leads to a severe pneumonia. Ca chloride has been used in oral Ca preparations but can be very caustic. Ca propionate is less injurious to tissues and has the added benefit of supplying propionate, a gluconeogenic precursor. Toxic doses of Ca can be delivered orally; approximately 250 g of Ca in a soluble form will kill about one half of the cows as they develop a severe hypercalcemia.

Hypocalcemia in Late-Gestation Beef Cows and Ewes

For beef cows and ewes, especially those carrying twins, meeting the sudden increase in fetal skeletal demand (8 to 10 g/fetal calf/day) for Ca often presents a greater challenge to Ca homeostasis than does lactation. Estrogen, which increases dramatically in late gestation, decreases osteoclast activity. Inadequate Mg intake is also commonly a contributing factor that leads to hypocalcemia (see Hypomagnesemia as a Cause of Hypocalcemia earlier). This reduces the ability to use bone Ca reabsorption to meet fetal skeletal Ca demands. As a result, most primary hypocalcemic disorders of the beef cow and ewe occur in late gestation. They are usually prevented by increasing Ca and/or Mg in the gestation diet provided the animal is eating. Often the syndrome in beef cows and ewes is complicated by inadequate energy intake and a state of inappetence associated with the pregnancy toxemia syndrome.

Chronic Calcium Deficiencies

Nutritional Secondary Hyperparathyroidism

A deficiency of dietary Ca or vitamin D can reduce the amount of Ca that can be absorbed across the intestine into the extracellular fluids. Diets severely deficient in Ca will not supply adequate Ca to replenish Ca lost from extracellular pools. As a result, blood Ca concentration decreases and PTH secretion increases. PTH can act on the kidney to reduce urinary Ca loss and increase synthesis of 1,25-dihydroxyvitamin D to enhance intestinal Ca absorption efficiency. But if dietary Ca is very low, increasing the efficiency of intestinal Ca absorption cannot substantially increase the amount of Ca entering the extracellular pool of Ca. The only action of PTH that can improve blood Ca concentration in this situation is to enhance bone Ca resorption. The continued removal of Ca from bone without replacement results in fibrous osteodystrophy. The clinical signs of nutritional secondary hyperparathyroidism include hypertrophy of the parathyroid glands and cessation of growth in young animals. The lack of Ca available for mineralization of bone matrix causes the growth plates to be soft, weak, and swollen. The cortices of the long bones are thin, and minor or major fractures are common.

Vitamin D deficiency is rare but can also result in secondary hyperparathyroidism. Without vitamin D (from exposure to UV-b rays of sunshine or supplied in the diet), the kidneys are unable to synthesize 1,25-dihydroxyvitamin D. Therefore unless dietary Ca is greatly elevated, the reduced efficiency of dietary Ca absorption will prevent adequate Ca from entering the extracellular fluid. Again, PTH will activate bone Ca resorption mechanisms, sacrificing bone integrity as the body attempts to maintain normocalcemia.

Renal Secondary Hyperparathyroidism

Renal secondary hyperparathyroidism is a syndrome caused by renal failure and is occasionally observed in older animals. In cows, pyelonephritis can develop in late gestation through early lactation owing to poor urine flow and retrograde urine flow resulting in destruction of renal tissue. A major function of the kidneys in most species is to remove excess phosphate from the circulation. As renal function is lost, phosphate is retained and hyperphosphatemia develops. This occurs when the remaining amount of functional renal tissue is less than 25% of normal.

Hyperphosphatemia has two effects. The first effect is to reduce the ionized Ca content of the blood. This is because Ca and phosphate ions normally exist in blood at concentrations that are slightly below the levels that would cause saturation of the fluids resulting in precipitation of Ca phosphate salt from the solution. However, the greatly elevated phosphate level in the blood of renal failure patients can exceed the equilibrium of Ca and phosphate in solution, causing precipitation of Ca from the blood. More important, as phosphate builds up in the blood it has a second effect on the remaining renal tissue. It blocks the activation of the 1α-hydroxylase that catalyzes conversion of 25-dihydroxyvitamin D to 1,25-dihydroxyvitamin D within the kidney. Therefore even though PTH should stimulate the remaining functional renal tissue to produce 1,25-dihydroxyvitamin D, this action of PTH is blocked by hyperphosphatemia.

This reduces dietary Ca absorption and further depresses blood Ca concentration. This in turn stimulates increased PTH secretion, and reabsorption of bone Ca reserves again becomes a major means of maintaining normocalcemia. Fibrous osteodystrophy follows the prolonged secretion of PTH.

As bone Ca is reabsorbed, more P is also reabsorbed. However, the loss of renal function prevents PTH from having its usual

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phosphaturic effect, exacerbating the hyperphosphatemia. A vicious cycle of increasing blood P, increasing PTH, and increased bone resorption ensues. The loss of renal function can rarely be reversed.

Lactational Osteoporosis

During lactation in virtually all species there is an obligatory loss of bone mass from the skeleton. In this case the osteoclasts within a bone resorption unit reabsorb bone to a 50-micron depth if dietary Ca is adequate, or to greater depths if the animal is in severe negative Ca balance. However, osteoblast movement into the resorption cavity to replace this bone is transiently inhibited, and no new bone is deposited, leaving a small area devoid of bone—a porosity to the bone. This occurs to some extent in all females shortly after parturition, even when they are in positive Ca balance. However, the degree and duration can be magnified greatly by diets low in Ca. Once the animal has undergone the obligatory period of lactational osteoporotic bone loss (4 to 5 weeks in the cow), if the animal is in positive Ca balance, the osteoblasts migrate to the resorption cavity and replace the lost bone. Lactational osteoporosis can help the female meet the Ca demands of lactation by uncoupling bone formation from bone resorption. In high-producing dairy cows, dietary Ca intake is inadequate to meet lactational Ca demands for the first 4 to 6 weeks of lactation. These animals lose as much as 13% of their skeletal mass during this period, which is replaced in later lactation when dietary Ca intake allows the cow to enter a period of positive Ca balance.

Magnesium

Mg is a major intracellular cation serving as a cofactor for enzymatic reactions vital to every major metabolic pathway. Extracellular Mg is vital to normal nerve conduction, muscle function, and bone mineral formation. In a 600-kg cow there is approximately 0.84 g of Mg in the blood, 3 g of Mg in the extracellular fluids, 84 g of Mg inside cells, and 210 g of Mg within bone mineral. Bone is not a significant source of Mg that can be used in times of Mg deficit because bone reabsorption occurs in response to Ca homeostasis, not Mg status. Maintenance of normal plasma Mg concentration is nearly totally dependent on continuous dietary Mg absorption.

Hypomagnesemia

Hypomagnesemia generally leads to hyperexcitability, tetany, convulsion, and, too often, sudden death. Hypomagnesemia is often accompanied by and complicated by hypocalcemia. Hypomagnesemia is a common problem in ruminants.

Normal plasma Mg concentration is 1.8 to 2.4 mg/dL in cows and 2.2 to 2.8 mg/dL in sheep. The kidneys play a key role in maintaining Mg homeostasis, but only when diet Mg absorption is adequate. Dietary Mg absorbed in excess of needs will cause plasma Mg to rise above the threshold for renal reabsorption of Mg from the glomerular filtrate. The excess Mg remains in the urine. The renal threshold for Mg (plasma concentration at which all Mg filtered across the glomerulus is reabsorbed) is 1.8 mg/dL in the cow and 2.2 mg/dL in sheep. Plasma Mg concentrations below these levels indicate that dietary Mg absorption is not sufficient and little or no Mg will be detected in urine. Parathyroid hormone secretion can raise the renal threshold slightly, and this is why hypocalcemic animals generally develop hypermagnesemia if dietary Mg is adequate.

Moderate hypomagnesemia (1.1 to 1.8 mg/dL) is associated with reduced feed intake, nervousness, and reduced milk fat and total milk production. This can be a chronic problem in some dairy herds that often goes unnoticed. It can also predispose these animals to milk fever as described earlier.

Role of the Rumen in Hypomagnesemia

Mg is well absorbed from the small intestine of young calves and lambs. As the rumen and reticulum develop, these sites become the main, and perhaps the only, sites for net Mg absorption.[24] In adult ruminants the small intestine is a site of net secretion of Mg. Mg absorption from the rumen is dependent on the concentration of Mg in solution in the ruminal fluid and the integrity of the Mg transport mechanism, which is a Na-linked active transport process.[25]

The soluble concentration of Mg in ruminal fluid can be low for several reasons. Chief among these are low Mg content of forages and inadequate dietary supplementation. Mg solubility also declines sharply as ruminal pH rises above 6.5. Grazing animals tend to have higher ruminal pH because of the stimulation of salivary buffer secretion. When high-grain rations are fed, ruminal fluid pH is often below pH 6.5, increasing Mg solubility and thus availability. Forages can also contain organic compounds, such as unsaturated fatty acids, which are converted to tricarballylate, which can form insoluble Mg salts in the rumen.

High dietary K can reduce the rumen's ability to absorb Mg. High K concentration in the ruminal fluid depolarizes the apical membrane of the ruminal epithelium, reducing the electromotive potential needed to drive Mg across the ruminal wall.[25] Feeding ionophores (monensin, lasalocid) can improve activity of the Na-linked Mg transport system in the rumen, increasing Mg absorption efficiency approximately 10%.[26] Lush high-moisture pastures increase the rate of passage of material, including Mg, from the rumen so that Mg may leave the rumen before it can be absorbed.

Forages generally do not contain enough Mg to meet the needs of highly productive ruminants. Inorganic sources of Mg are generally relied on as supplements. Magnesium oxide (MgO) is widely used. It has the added advantage that it can serve as a means to alkalinize the rumen fluid, thus helping animals on high planes of nutrition avoid rumen acidosis. Unfortunately, several factors can greatly influence the bioavailability of Mg from MgO. In the process of producing MgO, magnesium carbonate ore is heated to oxidize the carbon, resulting in MgO. This process of heating the ore is known as *calcining*. Taken to completion, pure MgO is 60% Mg. Unfortunately, the heat required to achieve this purity renders the MgO insoluble and unavailable. The availability of MgO decreases rapidly above 56% Mg purity. Another factor affecting bioavailability is fineness of grind. For ruminants the MgO must be soluble in rumen fluid—and this requires the MgO to be a finely ground powder. Feedmill employees do not like the dust this creates and often opt for MgO with larger particle size, not knowing this affects bioavailability for ruminants. Using magnesium sulfate or magnesium chloride can ensure the Mg added to a diet is available, but these salts are rather unpalatable and can be difficult to handle in the feed mill. Because MgO bioavailability is variable, a rapid estimate of bioavailability can be made on the basis of the MgO's ability to neutralize acetic acid. Place 3 g MgO in a vessel, and add 40 mL of white vinegar (5% acetic acid). Shake or vortex vigorously for 15 seconds, allow to sit for 15 minutes, and determine the pH of the solution. Vinegar alone has a pH of about 2.8. The best MgO sources will bring the pH up to 7.5 to 8.3. The worst only raise the pH to about 3.5 to 4. Because pH is on a log scale, this represents up to a 10,000-fold difference in ability to neutralize the acid. It likely also reflects a similar difference in solubility at rumen pH and therefore availability for absorption.

Occurrence of Hypomagnesemic Tetany

Hypomagnesemic tetany occurs most often in beef cows, dairy cows, and ewes in early lactation grazing lush pastures high in potassium and nitrogen and low in Mg and Na. This is often referred to as *grass tetany, spring tetany, grass staggers,* or *lactation tetany.* Mg deficiency occurs most often in spring or fall when pastures are growing at maximal rates and is most common in grazing lactating ruminants because milk production removes 0.15 g of Mg from the blood for each liter of milk produced. Cool weather seems to play a factor as well, probably through its effects on plant Mg uptake, although there is some indication that the physiologic response of the cow to cool weather affects Mg status directly.

When plasma Mg levels fall below 1.1 mg/dL, twitching is sometimes seen in the muscles of the face, shoulder, and flank. As hypomagnesemia progresses, tetanic spasms of the muscles become more

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common, eventually causing the cow or ewe to stagger and fall (see Table 41-9). Clonic convulsions quickly follow, with chomping of the jaws and frothy salivation. Affected animals lie with the head arched back and the legs paddling. The heart rate can approach 150 beats/min, and the heartbeat is often audible without a stethoscope. Respiratory rate approaches 60 breaths/min, and rectal temperature can approach 40.5°C (105°F) as a result of the excessive muscular activity. The eyelids flutter, and there is usually marked nystagmus. Animals may get up after several minutes and repeat these convulsive episodes several times before they finally die. Hypomagnesemic tetany in calves is clinically similar to that in adults and is often accompanied by moderate hypocalcemia.

Ewes are generally hypocalcemic and hypomagnesemic. Affected ewes are usually in the second to fourth week of lactation and are usually suckling more than one lamb. Affected ewes are generally depressed, stand with their heads down, and are reluctant to move. As hypomagnesemia and hypocalcemia progress, the animals develop tetany and clonic convulsions just as in cattle. The clinical signs in goats are similar to those observed in cattle.

Cerebrospinal fluid (CSF) Mg concentrations below 1 mg/dL are responsible for the clonic convulsions seen in animals with hypomagnesemic tetany. Blood samples obtained during or shortly after an episode of tetany may have near-normal levels of Mg as a result of muscle damage and leakage of Mg from intracellular pools. CSF Mg concentration will remain low during tetany and can also be a reliable indicator of Mg status for up to 12 hours after death. Vitreous humor Mg concentrations below 1 mg/dL are also found in animals with tetany and can be a reliable indicator for 24 to 48 hours after death, provided that environmental temperatures have not exceeded 23°C.[27] Aqueous humor has not proved a reliable sample.

Treatment of Hypomagnesemia

Animals exhibiting hypomagnesemic tetany need immediate treatment. This will require administering 1.5 to 2.25 g of Mg intravenously in the adult cow. Most of the commercially available IV solutions used to treat milk fever supply 1.5 to 4 g of Mg, usually as the chloride, borogluconate, or hypophosphite salts of Mg. Response to therapy can be disappointing, and success is related to the interval between onset of tetany and treatment. Cows should not be stimulated to rise for at least 30 minutes after treatment, to avoid initiating tetany and convulsions. Cattle that recover do so approximately an hour after treatment, which is the time it takes CSF Mg concentration to return to normal. Many of these cows will relapse and require further treatment within 12 hours.

The rate of relapse can be reduced using orally administered Mg salts once the animal has regained good swallowing reflexes (to avoid aspiration pneumonia). Administering a slurry of 100 g of Mg oxide in water intraruminally or by drenching can be effective. This provides approximately 50 g of Mg to the animal. Adding 50 g of Ca carbonate, 100 g of dicalcium phosphate, and 50 g of sodium chloride may enhance the effectiveness of the slurry, especially if hypocalcemia and hypophosphatemia accompany the hypomagnesemia. Alternatively, 200 to 400 mL of a 50% Mg sulfate solution can be administered by drench. Mg sulfate is more available for absorption than Mg oxide. If hypomagnesemic tetany has occurred in one cow or ewe in a herd or flock, steps should be taken immediately to increase Mg intake in other members of the herd to prevent further losses. Administering an additional 10 to 15 g of Mg per pregnant cow, 20 g of Mg per lactating beef cow, and 30 g of Mg per lactating dairy cow daily, usually in a grain mix, will often prevent further hypomagnesemic tetany cases. Ewes and does can be treated with these same formulas at one eighth the dose. The problem with prevention is ensuring the extra Mg gets into the animal, especially when working with animals at pasture.

Prevention

USING OTHER TRANSPORT MECHANISMS TO ABSORB DIETARY MAGNESIUM. The active transport mechanism for Mg absorption across the ruminal wall is critical to the survival of the animal when dietary Mg concentration is less than 0.25%. Unfortunately, there are factors such as dietary K and plant tricarballylic acids, as well as several unknown factors, that prevent this pathway from functioning well. A second pathway for absorption of Mg does exist, but it operates only at high ruminal fluid Mg concentrations. At high ruminal Mg concentration the Mg will flow down its concentration gradient into the extracellular fluids of the cow. This passive transport mechanism is not subject to inhibition by K and is subject only to the concentration of Mg in solution in the rumen.[25]

The concentration of Mg in ruminal fluid required to use concentration gradient–driven passive absorption of Mg is at least 4 mMol/L. The minimum level of Mg required in the diet to use this pathway in order to prevent negative Mg balance in the face of high K levels in ruminants is approximately 0.35%.[28] Mg content of the close-up dry cow ration and the early lactation ration should be between 0.35% and 0.4% as insurance against the possibility that the active transport processes for Mg absorption are impaired.

ASSESSING MAGNESIUM STATUS AT PARTURITION. PTH causes increased renal tubular reabsorption of Mg. The kidneys excrete less Mg, increasing blood Mg in the typical milk fever cow. However, if dietary Mg is insufficient or ruminal absorption of Mg is impaired, the blood Mg concentration will be below the normal renal threshold for Mg (1.85 mg/dL in cattle) and almost no Mg will appear in the urine. The animal should be considered abnormal for Mg. Sampling the blood of several cows within 12 hours of calving is a simple, effective index of Mg status of the periparturient cows. If serum Mg concentration is not at least 2 mg/dL in 9 of 10 cows sampled, it suggests inadequate dietary Mg absorption from either lack of dietary Mg or interferences with absorption. This same test can be used in the first weeks of lactation to see if the lactating cow diet is providing adequate Mg to the animal. This can be important because hypomagnesemia may limit productivity of lactating cows, as well as contribute to hypocalcemia in the herd.

PHOSPHORUS. Traditionally, *phosphorus* in clinical medicine is abbreviated as P, although it should be understood by the reader that the biologically relevant form of phosphorus is actually inorganic phosphate, not elemental phosphorus. Phosphate (P) is a component of phospholipids, phosphoproteins, nucleic acids, and energy-transferring molecules such as ATP. P is an essential component of the acid-base buffer system. It is second only to Ca as a major component of bone mineral, with the skeleton of a 600-kg cow containing approximately 3.9 kg of P.

Phosphorus Homeostasis

Plasma P concentration is normally 4 to 8 mg/dL. Approximately 1 to 2 g of P are present in the plasma inorganic P pool, and 4 to 7 g of P in the extracellular P pool, of a 500-kg cow. Intracellular P concentration is approximately 78 mg/dL, and total body intracellular P content is approximately 155 g, with 5 to 6 g located within erythrocytes. Maintaining the extracellular P pool involves replacing P removed for bone and muscle growth, endogenous fecal loss, urinary P loss, and milk production with P absorbed from the diet or reabsorbed from bone. During late gestation, fetal skeletal development can withdraw up to 10 g of P per day from the maternal P pools. Approximately 0.3 g of P is incorporated into each kilogram of body tissue (muscle) gained during growth of the animal. Production of milk removes approximately 0.9 g of P from the extracellular pool per kilogram of milk produced. Salivary secretions remove between 30 and 90 g of P from the extracellular P pool each day. Factors affecting salivary phosphate secretion include the time spent ruminating (chewing activity) and the PTH status of the animal. PTH stimulates parotid salivary P secretion and can increase salivary phosphate concentrations twofold to threefold.[29] Salivary phosphate secretions help buffer the rumen and supply ruminal microbes with a readily available source of P necessary for cellulose digestion. Most of the salivary phosphate secreted is recovered by intestinal absorption. However,

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even on low-P diets, a minimum of 5 g of secreted P per day is not recovered and is lost to feces. Urinary P loss is usually between 2 and 12 g/day. Bones of a 600-kg cow contain approximately 4 kg of P, some of which can be withdrawn and returned to the blood during osteoclastic resorption of bone.

Ruminal microbes are able to digest phytic acid, so the phytate-bound P, the form of up to 70% of P in plants, is available for absorption in ruminants. P is primarily absorbed in the small intestine via an active transport process that is responsive to 1,25-dihydroxyvitamin D. Intestinal P absorption efficiency can, in theory, be upregulated during periods of P deficiency because renal production of 1,25-dihydroxyvitamin D can be directly stimulated by low plasma P. However, the plasma P level must reach very low levels (<1 to 2 mg/dL) to stimulate increased renal production of 1,25-dihydroxyvitamin D. Plasma P concentrations are generally well correlated with dietary P absorption. P absorbed in excess of needs is excreted in urine and saliva.

PTH, secreted during periods of Ca stress, increases renal and salivary excretion of P, which can be detrimental to maintenance of normal blood P concentrations. This is one reason that hypocalcemic animals tend to become hypophosphatemic. PTH could conceivably increase blood P concentration because it stimulates bone mineral resorption. Also, because PTH stimulates the kidney to produce 1,25-dihydroxyvitamin D, it can increase the efficiency of intestinal phosphate absorption. However, it must be remembered that PTH is secreted primarily in response to hypocalcemia, not hypophosphatemia.

Hypophosphatemia, Pregnancy Toxemia, and Downer Cows

Beef cows and ewes fed a diet marginal in P will have a chronic hypophosphatemia of 2 to 3.5 mg/dL (see Table 41-9). In late gestation, plasma P can decline precipitously as the growth of the fetus accelerates and removes substantial amounts of P from the maternal circulation. These animals often become recumbent and are unable to rise, though they appear fairly alert and will often eat feed placed in front of them. Cows and ewes carrying twins are most often affected. Plasma P concentration in these recumbent animals is often less than 1 mg/dL. The disease is often referred to as *pregnancy toxemia* and is usually complicated by concurrent hypocalcemia, hypomagnesemia, and in some cases hypoglycemia. Diets that are marginal in P are generally indicative of diets that are marginal in energy because grains are usually very good sources of P. It is unclear which abnormality or if the combination of all these abnormalities is truly responsible for causing the cow to become recumbent and a downer cow.

At the onset of lactation in the dairy cow, the production of colostrum and milk draw large amounts of P out of the extracellular P pools. This alone often causes an acute decline in plasma P levels. In addition, if the animal is also developing hypocalcemia, PTH will be secreted in large amounts, increasing urinary and salivary loss of P. In dairy cows, plasma P concentrations routinely fall below the normal range at parturition, and in cows with milk fever plasma P concentrations are often 1 to 2 mg/dL. Plasma P concentrations usually increase rapidly after treatment of the hypocalcemic cow with IV Ca solutions. This rapid recovery is caused by reduction in PTH secretion, which reduces urinary and salivary loss of P. Administration of Ca intravenously generally causes resumption of gastrointestinal motility, which allows absorption of dietary P and reabsorption of salivary P that was sequestered within the rumen.

Some dairy cows that develop acute hypophosphatemia do not spontaneously recover normal plasma P concentration following Ca administration for milk fever. This is the case in cows that are classified as *hypophosphatemic downer cows*. This syndrome often begins as milk fever, but unlike the typical milk fever cow, in these cows the plasma P continues to decrease (<1 mg/dL) despite successful treatment of the hypocalcemia. Protracted hypophosphatemia in these cows appears to be an important factor in the inability of these animals to rise to their feet. Why plasma P remains low is unclear. In some cases the inability to absorb the salivary phosphate is secondary to poor ruminal motility, but not in all cases. Excessive cortisol secretion could also drive blood P concentration down, probably by forcing extracellular P inside cells. Treatment of cows with phosphate-containing solutions can affect recovery in some animals if treated before muscle and nerve damage in the down-side limbs occurs. For oral treatment, the dose is a drench of 50 g of P supplied by 200-g monosodium phosphate. IV treatment consists of 6 g of P supplied by 23 g of monosodium phosphate dissolved in 1 L of saline. Oral treatment restores normal blood P a little more slowly than IV treatment, but the effect lasts much longer.[30] Many of the Ca-containing solutions used for milk fever treatment also contain phosphorus. Unfortunately, the phosphorus is in the form of phosphite (PO_3^{-3}) or phosphinic acid (PO_2^{-3}) rather than phosphate (PO_4^{-3}). Phosphate added to Ca-containing solutions forms an insoluble precipitate—Ca phosphite and Ca phosphinic acid remain soluble. Unfortunately, the body cannot convert phosphite or phosphinic acid to phosphate, so these forms of phosphorus are biologically inactive and useless for treating this syndrome.

The hypophosphatemic downer cow syndrome does not appear to be caused by low P diets because affected cows are often receiving diets containing more than 0.4% dietary P. Hypophosphatemic downer cows are an uncommon sequela of milk fever but can cause herd problems. It seems to be a problem of late winter and restricted to the northern tier of states and Canada. The best preventative measure seems to be to avoid development of hypocalcemia.

Chronic Phosphorus Deficiency

P deficiency is fairly common in grazing ruminants in some regions. Plant growth in arid climates or on tropical soils is often limited by poor soil P content or availability. Although P content of the immature plant may be suitable (0.3% P on a DM basis), the mature dry plants often contain less than 0.15% P, which can lead to P deficiency in ruminants forced to subsist on these forages. In arid areas of the world with inferior soil quality, infertility and poor growth affects nearly all animals. Beef animals grown in these areas may require 3 or more years to reach market weight. Brood cows often calve only every other year. In more temperate areas, P deficiency can develop in animals grazing overly mature forages or crop residues, such as corn stalks. Cows subsisting on these forages are at risk for developing P deficiency unless supplemented. Increasing awareness of the environmental problems associated with P content of animal wastes and increasing expense of P supplements may encourage producers to feed diets marginally sufficient in P. This can cause rickets in growing animals and osteomalacia in adults. Other clinical problems associated with chronic P deficiency are general and nonspecific and include an unthrifty appearance, reduced feed intake, pica, reduced rate of gain, and reduced milk production.

Sheep can, in some instances, be successfully raised on pasture that has been associated with P deficiency in cattle, suggesting that sheep are slightly more resistant to P deficiency syndromes than are cattle. This may simply reflect the higher intake per kilogram of body weight of sheep and their habit of selecting the less mature plants, which are generally higher in P.

Infertility is often observed in animals on poor pastures. Hypophosphatemia is not the cause of infertility in sheep or cattle fed these subsistence pastures. The true cause of infertility in females consuming these poor diets is the lack of energy needed to allow the animals to cycle and retain a conceptus. They also happen to have hypophosphatemia, but numerous studies have demonstrated hypophosphatemia by itself does not cause infertility. Unfortunately, the belief that marginal dietary P contributes to reproductive inefficiency has been used as justification for feeding diets that are much higher in P than is required. Wu and Satter[31] present convincing evidence that high-producing cows perform well in terms of milk production and fertility when fed diets containing just 0.39% P. Higher P diets do not improve fertility but can add to environmental problems from excessive P excretion.

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Rickets and Osteomalacia

Rickets is a disease of young, growing animals in which the cartilaginous matrix at the growth plate and the osteoid matrix formed during bone remodeling fail to mineralize. In adults (no active growth plates), the term *osteomalacia* is used to describe the failure of osteoid matrix to mineralize. Ca and phosphate ions come together in a ratio of 10 Ca ions to 6 phosphate ions at the point of mineralization of the bone cartilage or osteoid matrix. Bone ash content varies somewhat with the bone examined but is generally 57% to 62% of bone dry weight, with 36% Ca and 17% P in adult animals. Failure to supply P in the diet will result in low plasma P concentrations that will not support the mineralization process. Bone ash, as well as total bone P and Ca content, will be below normal.

Low plasma Ca concentrations (arising from dietary Ca deficiency) can also result in failure to mineralize bone matrices. Bone ash is reduced, and the bones become fragile and have large areas devoid of bone. In some areas of the bone the uncalcified matrix is present and can make some of the bone rubbery, bending without breaking. Joint surfaces are often eroded, contributing to lameness in affected animals.

In principle, Ca deficiency differs from P deficiency in that normal osteoid matrix is formed but fails to mineralize in P deficiency, leaving a bone that bends before breaking, whereas in Ca deficiency the normal osteoid is either not formed at all (osteoporosis) or replaced by fibrous tissue (osteodystrophy). In vitamin D deficiency it is common to see mixed lesions (osteomalacia or rickets, osteoporosis, and fibrous osteodystrophy) all in the same bone, though osteomalacia or rickets predominates. Vitamin D deficiency also seems to reduce secretion of type X collagen by the chondrocytes within the growth plate of growing animals, leading to rickets. Vitamin D deficiency also prevents the programmed cell death (apoptosis) of chondrocytes within the zone of provisional calcification; their death must precede blood vessel invasion of the physes and osteoblastic bone formation. In vitamin D deficiency it is common for both plasma Ca and P to be below normal levels.

Postparturient Hemoglobinuria

Intravascular hemolysis, anemia, and hemoglobinuria are occasionally reported during the first 6 weeks of lactation. Cows that have been treated for ketosis seem at greater risk for developing postparturient hemoglobinuria. Many, but not all, cows that develop this syndrome are hypophosphatemic. Severe hypophosphatemia is postulated to depress the ability of erythrocytes to produce ATP. Glyceraldehyde-3-phosphate dehydrogenase, a key enzyme in glycolysis, requires inorganic phosphate as a cofactor. Without sufficient ATP to power sodium pumps, the intracellular sodium concentration rises, the cells become more rigid, and as a result they rupture as they pass through the capillary beds. However, hypophosphatemia alone is rarely sufficient for increased red blood cell fragility. Often these cows are on diets that are also deficient in selenium, copper, and energy. In light of these observations, it is likely naive to suggest that the cause of postparturient hemolysis is hypophosphatemia alone (see Table 41-9).

Hypokalemia Syndrome in Cattle

Nicolas Sattler

According to reports available in the literature, hypokalemia syndrome in cattle can be defined as presence of flaccid paralysis, recumbency, abnormal neck position, and serum potassium concentration below 2.5 mmol/L (2.5 mEq/L).

Occurrence Hypokalemia is a frequent biochemical finding in cows presented with anorexia and gastrointestinal stasis.[1] It is often mild (between 3 and 3.5 mmol/L) and not associated with obvious clinical signs in ruminants. Hypokalemia syndrome is a rare clinical condition reported in a total of 42 animals in four studies.[2-5] Lactating dairy cows appear to be at a higher risk, but the syndrome has also been described in calves and heifers.

History Lactating dairy cows fewer than 60 DIM constitute the majority of cases in the literature. Any disease causing significant anorexia for 1 week or more, particularly infectious disease, is a risk factor.[3] Repeated administration of isoflupredone acetate is reported in most cases, for treatment of either acetonemia in lactating cows[2-4] or infectious respiratory disease in calves and heifers.[3] In one case, repeated off-label intramammary administration of isoflupredone acetate preceded hypokalemia syndrome.[5] Multiple doses of dextrose and insulin are also reported to be risk factors.[2-5] IV fluid administration for 2 days or longer without serum biochemistry follow-up has been documented in two cases of calves with severe neonatal diarrhea.[3]

In most cases recumbency caused by hypokalemia syndrome was not the initial event but rather occurred during the evolution of another disease such as acetonemia or infectious disease. Moreover, recumbency was not always the presenting complaint. Some animals first manifested anorexia, reduced fecal output, kyphosis, and reluctance to move. However, evolution to severe paresis and decubitus occurred rapidly in all these cases.

Clinical Signs In the early stages of the syndrome, absence of feces, paretic gait, kyphosis, inability to stand for a long time, and tachycardia are observed. Sometimes an abnormal neck posture is evident before recumbency. The typical case presentation of hypokalemia syndrome includes decubitus, S-shaped neck, abnormal feces and ruminal motility, abnormal appetite, and tachycardia with or without arrhythmia. Decubitus is a result of flaccid paralysis. The tail has little to no tonus and is held in an abnormal position, resistance to all manipulations is weak, and the cow is unable to raise her head. It is not rare to observe that the animal eats and drinks willingly if food and water are provided near the mouth. Abnormal appetite therefore may be partly caused by an inability to move the head to reach food and water. The neck is carried in an S-shaped and twisted fashion that differs from that of the hypocalcemic cow. The neck is never fixed in this abnormal position. When moved there is no resistance, and if the head is placed in an anatomically correct position there is an odd feeling of luxation. As soon as the head is not held, the neck resumes the abnormal S-shaped position, deviating to either direction. This neck posture may precede decubitus and persist after decubitus has resolved. Cardiac arrhythmias (Fig. 41-23) also accompany hypokalemia syndrome and may be ventricular (ventricular tachycardia, accelerated escape ventricular rhythm) or supraventricular (atrial fibrillation) in origin.

Hypokalemia syndrome is most often the consequence of a concomitant disease or treatments administered. Fever and acetonemia are the most frequently associated problems. The identification of the concomitant disease(s) is essential for accurate prognosis and treatment.

Etiology Hypokalemia may result from an imbalance of the internal or external potassium balance or both (Fig. 41-24).[1,6-9] Internal potassium balance is determined by exchanges between extracellular and intracellular compartments, whereas external balance is a result of systemic intake and losses. Currently, except for cases with documented repeated isoflupredone acetate administrations, the exact determinants causing hypokalemia syndrome in cows are not known.

At present, because of the limited data available, it is not possible to determine if hypokalemia syndrome cases are mainly a result of potassium depletion, internal imbalance, or both. The prolonged inappetence observed before hypokalemia, along with the amount and duration of potassium needed for treatment, suggests potassium depletion is significant. Serum potassium concentration is a poor indicator of the potassium status of the organism because 98% of whole body potassium is located in the intracellular compartment.[7,10] Determination of intracellular potassium concentration in

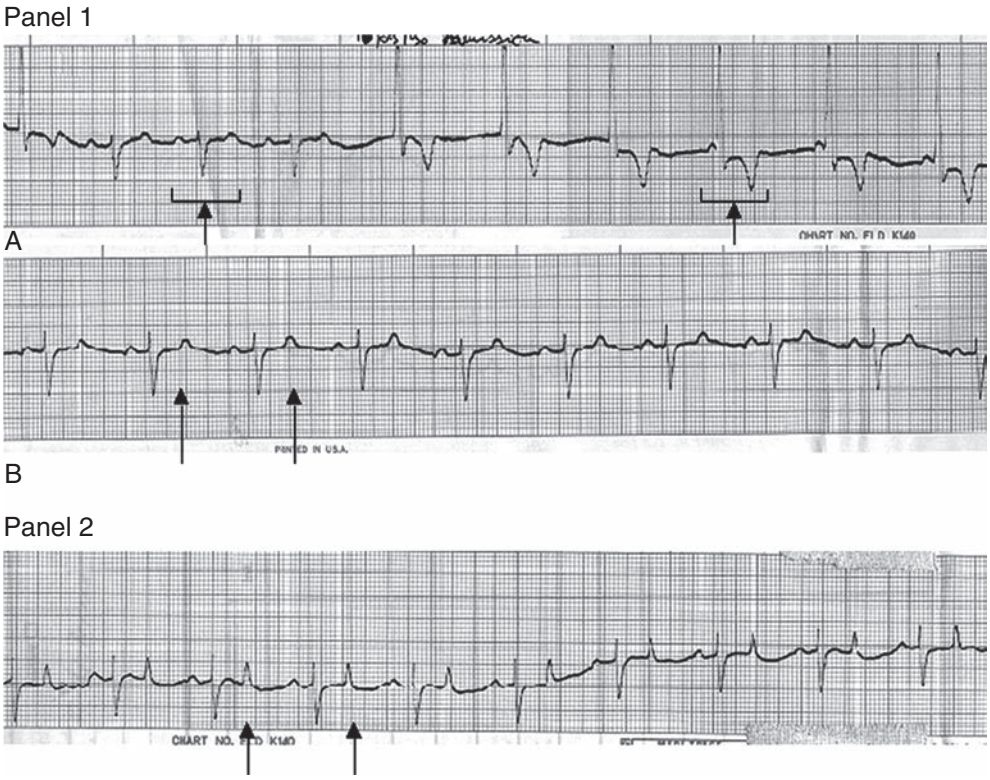


FIG. 41-23 Electrocardiograms of a cow with hypokalemia syndrome before *(Panel 1)* and after *(Panel 2)* treatment (base-apex, 25 mm/s, 1 cm = 1 mVolt). *Panel 1,* Potassium serum concentration was 2 mmol/L. **A,** Note the ventricular escape rhythm: normal heart beat and more than five ventricular QRS complexes. **B,** Note the flattened T-waves and increased intervals. *Panel 2,* Potassium serum concentration was 4 mmol/L. Note the normal T waves and intervals.

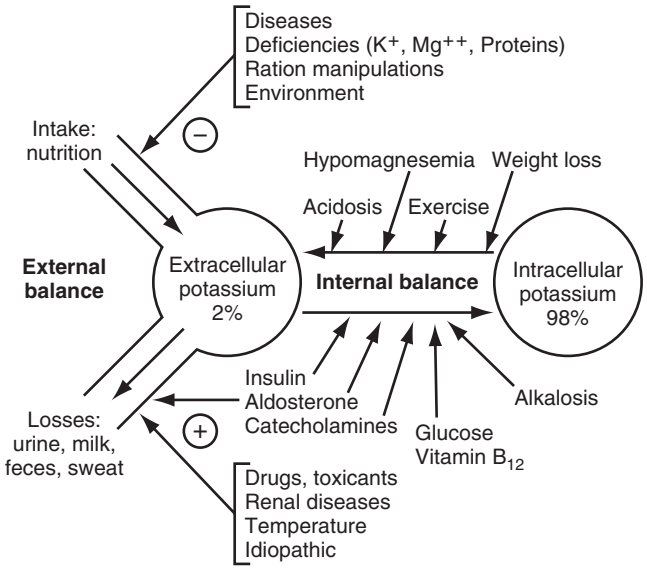


FIG. 41-24 Potassium balances and major determinants in cattle. *(Adapted from Brobst D. 1986. Review of the pathophysiology of alterations in potassium homeostasis. J Am Vet Med Assoc 188:1019.)*

erythrocytes or muscle cells could be a more accurate way to assess potassium depletion.[10,11] At present these data are not available for hypokalemia syndrome cases.

As a result of the potent mineralocorticoid activity of isoflupredone acetate, cases associated with its administration show both internal and external potassium balance abnormalities (see Fig. 41-24).[9] Repeated doses can reduce blood potassium concentration by 70%.[12] In a small experimental study ($N = 9$), the author was able to reproduce the syndrome by combining food restriction and multiple doses of isoflupredone acetate in lactating dairy cows.[13] The use of this steroid could also complicate the treatment of the hypokalemia syndrome by increasing the renal losses of potassium. On the basis of current knowledge, use of isoflupredone acetate in the anorectic, acetonemic cow that has received dextrose, with or without insulin, should be restricted to one administration at the labeled dosage. Hypokalemia syndrome has also been reported with dexamethasone administration, although it is a less potent mineralocorticoid.[3,5]

In noniatrogenic cases the relationship between protracted disease and severe hypokalemia may be explained by a decrease in potassium intake (anorexia) with increased release of catecholamines caused by stress (see Fig. 41-24). Alternatively, renal potassium adaptation[14] may be responsible for the potassium loss. Animals chronically fed a high-potassium diet are able to survive the high potassium load due to increased renal losses. These increased losses persist when potassium intake is suddenly reduced. Renal adaptation (reduction of urinary potassium excretion) takes 24 to 48 hours to occur, thus creating a potassium depletion.[14] Because of a forage-based diet, lactating dairy cows may eat more than 10 times their daily potassium requirement, causing high urinary potassium excretion.[3] Therefore these cows appear to be at risk for potassium depletion because of delayed renal adaptation when potassium intake is abruptly reduced. This model cannot explain why some cows develop the syndrome when exposed to these conditions but others do not.

Other factors known to promote significant hypokalemia, such as anomaly of the aldosterone system, diuretic (particularly furosemide) abuse, nephropathy (proximal or distal tubular renal acidosis), or severe diarrhea, have not been documented in cows with hypokalemia syndrome. Diarrhea with protracted reduced potassium intake, increased losses, and internal potassium imbalance resulting from acidosis has been associated with hypokalemia syndrome in calves.[3] Error in fluid administration causing increased urinary losses of potassium along with return to a normal internal potassium balance can further exacerbate hypokalemia in diarrheic calves.

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Pathophysiology Potassium is the most important intracellular cation.[15] The gradient between the potassium concentrations of the intracellular and extracellular compartments is the determinant of the resting cellular membrane potential and plays a role in the formation and transmission of action potentials.[16] Therefore clinical signs reported in cattle and other species with severe hypokalemia are multisystemic. Moreover, structural consequences in the myocardium[6] and the muscle cells have been reported in cattle.[2-4]

Dysrhythmia and electrocardiographic changes were present in 50% of cases in one study.[3] The arrhythmogenic electrical activity changes implicated in hypokalemia include the following: hyperpolarization of the cardiac cell resulting in spontaneous automatic activity, slow conduction caused by increased difference between resting membrane potential and threshold potential, increased action potential duration as a result of slow repolarization, depressed fast responses because of higher membrane potential when a slow repolarizing cell is stimulated, slow responses in fibers normally exhibiting fast responses, and conduction block.[17] These electrical events alone or in combination with structural changes such as necrosis can induce the atrial and ventricular arrhythmia observed.

Pathophysiology of cardiac and muscle necrosis caused by potassium depletion includes (1) ischemia caused by lack of vasodilatation during muscle cell contraction, resulting from absence of potassium release into the extracellular space, and (2) glycogen deficiency resulting from impaired glycogen synthesis.[9,18] Muscle lesions compatible with hypokalemic myopathy have not been consistently documented.[2-5] It is presently not known if the presence of hypokalemic myopathy is necessary to the occurrence of the clinical signs observed in the bovine syndrome or if it is a prognostic determinant.[2,3]

Diagnosis and Ancillary Test Results Initial presentation of hypokalemia syndrome (intestinal ileus, abnormal gait) could mimic an intestinal syndrome. History may allow distinction between these conditions. Hypokalemic syndrome often follows or is concomitant with a long disease, in contrast with the usual acute evolution of an intestinal syndrome. According to the results of a small experimental study,[13] potassium fractional urinary excretion (FE_K) could be a useful tool in the medical management of a cow suspected to be developing bovine hypokalemia syndrome. In this study, FE_K was abnormally high in the presence of severe hypokalemia 12 to 24 hours before manifestation of clinical signs. FE_K from 55% to 128% have been reported in five hypokalemia cases.[4] FE_K normal range for early lactating cattle has been reported to be 26.9% to 120%.[19]

According to the author's experience, the clinical signs of a twisted, S-shaped neck associated with flaccid paralysis as described earlier are almost pathognomonic. Other conditions that could be included in the differential diagnosis are hypocalcemia, botulism, tick paralysis, and myelopathy (cervical spinal trauma, cervical osteomyelitis, spinal neoplasia). Conditions like listeriosis, vertebral malformations, luxations, fractures, and torticollis can be associated with abnormal neck position but not flaccid paralysis and absence of pain during manipulations. Hypokalemia syndrome, even if rare, should be included in the differential diagnosis of hypocalcemia, particularly when response to calcium administration is not normal.

Confirmation of the clinical diagnosis requires serum biochemical analysis. To date, all published cases of bovine hypokalemia syndrome have been associated with serum K^+ concentrations less than 2.5 mmol/L. Aside from hypokalemia, moderately elevated AST and creatine kinase (CK) activity (median value of 171 and 1564 IU/L, respectively),[3] severe metabolic hypochloremic alkalosis (median value $[TCO_2] = 41.5$ mmol/L, $[Cl^-] = 86.9$ mmol/L),[3] and mild hyperglycemia (median [glucose] = 6.05 mmol/L or 109 mg/dL)[3] are observed in the majority of published cases. Hypophosphatemia has been observed in 25% to 40% of these cases.[2-4]

Lumbar muscle biopsy (between L2 and L5) is a way to differentiate primary hypokalemic myopathy from secondary myopathy caused by decubitus. Determination of the serum creatine kinase MB isoenzyme (CK-MB) activity could help to detect myocardium damages. Detection of myopathy in epaxial muscles and/or myocardium at necropsy is not diagnostic if potassium depletion or hypokalemia is not documented.

Some authors have suggested that electrocardiographic changes could be used to detect a potassium-depleted status, irrespective of the serum potassium concentration.[20] A method of determining both the internal and external potassium balances simultaneously in dairy cows has been presented.[11] In this study, ingested potassium, milk potassium concentration (LK), and FE_K defined the potassium external balance. Serum potassium concentration (SK) and red blood cell potassium concentration (CIEK) defined the potassium internal balance. Significant variations were detected throughout the day for CIEK, LK, and FE_K.[11] Therefore in order to monitor potassium balances over time, samples should be collected at the same time each day.

Treatment Nursing care is of primary importance to prevent complications such as mastitis or myopathy caused by prolonged decubitus, to maintain alimentation by providing food and water near the mouth, and to provide favorable conditions for the cow to get up. The animal should be kept on clean and atraumatic bedding such as pasture, sand, or accumulated litter. It must be regularly milked and turned from one side to the other at least every 8 hours. Use of a flotation tank (Aquacow Rise System, Merced, Calif., and St. Johnsbury, Vt.) is of great value once the serum potassium concentration has returned to normal range.

All other identified problems must be addressed, including dehydration, acetonemia, and infectious disease. Treatments for arrhythmias, other than potassium, were not given in the reported cases.

Specific treatment is mainly per os potassium chloride (KCl) supplementation. On the basis of published data and the author's experience, a total (per os and IV) KCl dose per day of 60 to 100 g/100 kg of body weight of cow is recommended. IV administration should be reserved for dehydrated cows because overhydration may worsen hypokalemia by increasing potassium renal losses. When KCl is given IV, the rate should not exceed 0.5 mEq of K^+/kg/hour, to avoid high risk of cardiac toxicity. Serum potassium should be monitored daily to allow adjustment of the treatment regimen. Potassium supplementation is necessary for an average of 3 to 5 days.[2-4]

The abnormal neck position can be the first and last clinical sign in the evolution of the hypokalemia syndrome. Other clinical signs usually disappear on average in 3 days, the same day potassium concentration typically returns to normal. Some degree of paresis may persist for 2 to 3 days after return to normokalemia. The author recommends continued potassium supplementation for 1 or 2 days after the return to normal clinical state and appetite. Increased renal potassium losses are promoted by the high quantity of potassium given during the treatment. In the author's experience it is important to decrease potassium supplementation slowly to avoid potassium depletion caused by delayed renal adaptation to the lower potassium diet. For example, 40 g of KCl per 100 kg of cow may be given the day after return to normokalemia, then 20 g of KCl per 100 kg of cow for 2 more days.

Because potassium depletion is a primary cause of myopathy, it is important *not* to try to raise the cow before hypokalemia has resolved. This emphasizes the importance of good nursing care and regular decubitus side changes. Once serum potassium concentration reaches the normal range, a water flotation tank is the best system to manage the recumbency.

Prognosis The survival rate was very different in the three series of cases reported: 2 of 8,[2] 7 of 17,[4] and 11 of 14.[3] The prognosis may be affected by the recumbency duration, age, concomitant disease, initial potassium depletion degree, presence and severity of hypokalemic myopathy, or treatments received.[1] The quality of the supportive care is probably a major determinant of the outcome, as for any downer cow. In the field, because of time and energy needed

from the owner, the author's experience warrants a guarded prognosis. The availability of a flotation tank appears to be a significant positive prognostic factor.[2-4]

Bovine Somatotropin

Catalina Cabrera • Aurora Villarroel • V. Michael Lane

Somatotropin, also known as *growth hormone* (GH), is a peptide hormone produced in the anterior pituitary gland of all animals and is an important endocrine factor for normal growth of all tissues[1,2] and lactation in mammals. It is released under the influence of GH-releasing factor and inhibited by somatostatin. High-producing dairy cattle have naturally elevated circulating levels of endogenous somatotropin.[3,4] The lactogenic effect of somatotropin was first discovered in 1928 after rabbits were injected with crude extracts of anterior pituitary glands,[5] and its effect in lactating dairy cows was first reported in 1937.[6] Since the 1980s, recombinant DNA manipulations allowed large-scale production of purified somatotropin.[7,8] Because the use of several synonyms of somatotropin throughout the literature can be confusing, this chapter uses *GH* to refer to natural somatotropin and *rBST* to refer to recombinant BST. It has been shown that rBST has biological activity similar to that of bovine GH.[9] Four variants of bovine GH have been reported, according to whether it has 190 or 191 amino acids (additional phenylalanine in *N*-terminal) and either valine or leucine in position 127.[10,11] The genetic determination of the amino acid present in position 127 seems to be breed specific. Homozygosity for leucine is more frequent in larger breeds such as Holstein and Brown Swiss (85% and 100%, respectively) compared with smaller breeds such as Jersey and Ayrshire (31% and 59%, respectively).[11] This variation may account for differences in milk production.

Four recombinant analogues have been developed[12,13] and differ in 0 to 9 amino acids from GH. Methionyl-rBST (leucine variant with 190 amino acids)[14] was approved for use in lactating dairy cows in the United States in November 1993[15] and is available for commercial use in more than 20 countries, including Mexico, Brazil, South Africa, South Korea, and Russia. The release of rBST for commercial use provides new opportunities and challenges for the dairy herd manager, veterinarian, and nutritionist.

Physiology of Growth Hormone

Physiologic concentrations of GH in blood are secreted in a pulsatile pattern and vary throughout the day, being lowest after midnight and highest during the day (diurnal variation) both in humans and in dairy cattle.[1,16] Baseline levels, frequency, and intensity of the secretory pulses of GH are highest during the first week of age and then decrease with age.[4,17,18] Apparently, GH levels in neonates are not influenced by colostrum intake, as evidenced by a study in which calves that received their first colostrum 24 hours after birth did not differ in serum GH levels from calves that received their first colostrum feeding at 2 hours, 6 hours, or 12 hours after birth.[19] Physiologic GH levels are heavily influenced by gonadotropin hormones; intact bulls had higher baseline levels and higher frequency and intensity of pulses of GH as compared with steers, which in turn had higher levels and pulses than heifers (intact or ovariectomized).[20] In lactating cows, GH levels are highest during the postpartum period and gradually decrease as the lactation advances and milk production decreases.[3,21-23] Blood concentrations of GH are naturally higher in high-production cows as compared with low-production cows,[4,23,24] even during the dry period.[3,21]

GH must bind to GH receptors located in specific tissues to exert its direct effects, one of which is the local secretion of somatomedins throughout many organs.[1,17,25] Of the four somatomedins identified to date, the type I insulin-like growth factor (IGF-I) is the most important.[1] IGF-I is found in serum attached to IGF binding proteins. It exerts its action when bound to IGF receptors on target tissues. The complete somatotropic axis consists of GH, GH receptors, IGF-I, IGF-I receptors, and IGF-I binding proteins. Fig. 41-25 depicts the target organs for GH action via direct effects of GH and indirect effects of IGF-I.

Overall, GH promotes increased cell size and mitosis in almost all tissues of the body that are capable of growing (directly or indirectly through the action IGF-I) and a shift in metabolism to use fat for energy in preference to carbohydrate and proteins, which are spared.[1,17] The immediate result of the increased use of fat as energy source for the body is a measurable rise in NEFA concentrations in blood.[1,17,25] Another direct effect of GH on the liver is to increase glucose synthesis.[1,17] GH stimulates the pancreas to secrete increased amounts of insulin, although a simultaneous IR that results in a diabetogenic effect is induced.[1] It has been shown in humans and rats that an increase in serum free fatty acids (FFAs) impairs the action of insulin on tissue glucose use.[26,27] The effects of GH on liver, pancreas, and adipose tissue are direct because of the presence of multiple GH receptors in these tissues.

Muscle is affected directly by GH and indirectly by IGF-I. Both GH and IGF-I act on muscle cells to increase protein synthesis and decrease protein catabolism.[1,17] The net effects of the changes in muscle and fat metabolism are to increase lean body mass.[1,17] When rBST is administered to growing cattle, it has an anabolic effect[17,28-30] similar to that of steroid hormones[29] that seems to be a result of increased feed intake rather than an increased efficiency of feed conversion.[18] GH also has an effect on bone growth through the action of IGF-I, which increases osteoblast proliferation and function.[1,17] IGF-I also mediates an enhanced response to induced infection and endotoxemia through lymphocyte blastogenesis,[31] neutrophil proliferation,[32,33] and decreased levels of TNF.[34,35]

The most obvious outward manifestation of rBST administration in the lactating cow is an increase in milk production.[6,36,37] Other manifestations include changes in body composition, both positive and negative effects on reproduction, and proliferation of immune cells. These changes are achieved through an "orchestrated control" of the metabolic functions (homeorrhesis) to support the new physiologic state of higher milk production. Table 41-10 shows the short-term and long-term effects (after homeorrhesis) of rBST administration in lactating dairy cows. The use of rBST in lactating cows increases milk production through its effect on nutrient partitioning,[25] increased rate of cell renewal in the mammary gland,[38] and support of mammary cell function.[39] Although receptors for GH in the mammary gland were recently discovered,[40,41] bovine GH does not appear to have a direct galactopoietic effect on mammary tissue.[42,43] The galactopoietic effect of rBST has been reported to be indirect, through the action of IGF-I.[44,45] IGF-I is associated with increased mammary blood flow and enhanced mammary extraction of substrates.[44,46] The heart plays a major role in nutrient partitioning by increasing contractility and output, which increases blood flow to the mammary gland.[44,47,48] These actions are responsible for a higher persistence of milk production in rBST-treated cows (Fig. 41-26). The ultimate effect is the increased use of fat as an energy source to spare glucose and acetate for mammary gland lactogenesis.[44] This avoids excessive weight gain during late lactation as measured by BCS[49,50] but can also result in weight loss when dietary energy is restricted.[51,52] The use of rBST does not cause significant changes in blood mineral levels.[45,53]

Other effects of rBST in cows include direct and indirect effects on reproductive organs. GH receptors (direct effect) are found mostly in the ovary, primarily on the corpus luteum (CL), with nearly undetectable levels on follicles.[54,55] Cows treated with rBST had heavier CLs[56] but no difference in blood progesterone levels.[56-58] Other tissues with high expression of GH receptors, although not as abundant as in the CL, included (in decreasing order) myometrium, endometrium, and oviduct.[54] In vitro exposure of endometrial cells to rBST attenuated the production of phorbol ester–induced prostaglandin (PG) $F_{2\alpha}$; on the other hand, IGF-I increased its production.[57,59] Receptors for IGF-I in the reproductive organs were expressed primarily in the myometrium and less in the endometrium, ovary, and oviduct.[54] Although follicles did not show high expression of GH or

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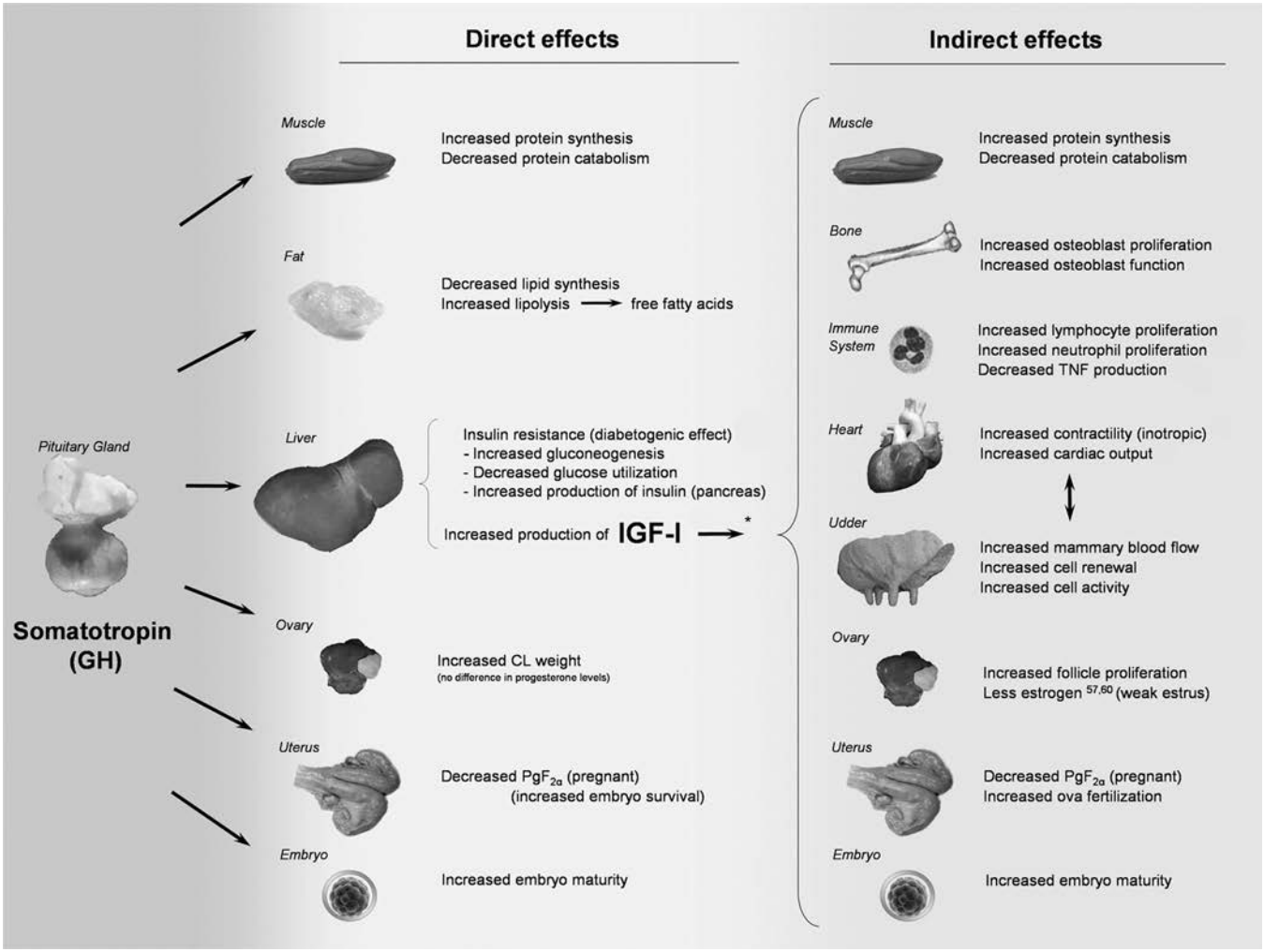


FIG. 41-25 Summary of direct and indirect effects of somatotropin in cattle. *IGF-I is produced in the liver and locally in many tissues throughout the body.

IGF-I receptors, treatment with rBST increased follicle proliferation and recruitment.[57,58] The dominant follicles were larger but contained lower levels of estrogen.[57,60] Pregnant cows had higher expression of IGF-I receptors throughout the reproductive tract compared with nonpregnant cows, especially in the myometrium.[54] The embryo has receptors for both GH and IGF-I, and both peptides increase the rate of embryo maturation.[61-63] GH is additive to IFN-τ (produced by the embryo) in its effect of attenuating uterine production of $PGF_{2\alpha}$.[59] Therefore GH may be an important factor for maternal recognition of pregnancy.

Half-life for important lactopoietic hormones is as follows[1]:

- Somatostatin: 3 minutes
- Insulin: 6 minutes
- GH: 20 minutes
- IGF-I: 20 hours

Impact of Somatotropin on Milk Production

Many studies have reported a consistent effect of increased milk production after short- and long-term administration of rBST. Most trials are not directly comparable to one another because of the use of different somatotropin analogues, dosages, lengths of study, and intervals between doses used in the studies. These experimental trials have been conducted under differing feed conditions and show similar responses in milk production to treatment with rBST in pasture-based dairy cows,[65,66] stalled cows,[67,68] and cows fed a total mixed ration (TMR).[7,69] Studies show a wide range of increase in milk production (8% to 61%) over the baseline production before rBST administration. This range reflects individual cow variation in the response to rBST, and it has been recognized since the first trial in 1937 (pituitary extract) that some cows do not respond at all.[6,70] In general, larger responses were observed at higher doses of rBST,[51,71,72] although the dose response could be characterized as a negative exponential relationship: milk response per milligram of rBST is diminished at higher doses. Larger responses have been observed when rBST was administered daily (up to 61%)[67,68,73,74] as compared with administration at 14-day intervals (up to 31%)[49,68,75,76] or 28-day intervals (up to 18%).[7,69] Most of these studies with large responses reported the short-term effects of rBST supplementation, whereas long-term trials reported milk increases ranging from 11% to 29%.[49,50,66,77] Consistently higher responses (both in kilograms and percentages) occur in adult cows as compared with first-lactation heifers.[36,49,78] Furthermore, the effect of rBST use on milk production varies according to production level before rBST administration and stage of lactation, in that lower-producing cows seem to respond better than higher-producing cows,[78-80] and late-lactation cows respond better than early-lactation cows,[49,78] both in kilograms and percentages. Although Holstein cows have a higher response to rBST treatment than Jersey cows,[69,71,79] the effective response (return on rBST investment) may be higher in Jerseys because of their higher milk solids.

In February 1994 the rBST named *sometribove* (zinc-Methionyl BST, Monsanto, St. Louis, Mo.) was first commercialized in the United States for use at a dose of 500 mg to be given once every 14 days beginning at 57 to 70 DIM and continuing until the end of lactation.[2,15] Since then, multiple studies have been reported that are now

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TABLE 41-10

Short-Term and Long-Term Effects of the Use of Subcutaneous Injections of 500 mg of rBST Every 14 Days in Lactating Dairy Cows

Target	Short-Term Effects	Long-Term Effects
Milk production	Increased, with peak on day 7-11 with a gradual decrease to baseline levels around day 14	Increased, following a typical downward trend in production as DIM increases, although with higher persistence than in untreated cows; no effect on production during the next lactation
Feed intake	No change	Increased, starting 4-10 wk after the initial treatment to provide energy for the increased milk production
Energy balance	Decreased because of increased milk production and unchanged feed intake	Normal, as feed intake accommodates to higher milk production
Milk composition	Initial increase in fat % and decrease in protein, reflecting initial negative energy balance	Normal or slightly increased protein percentage
Reproduction	Positive influence because of increase in IGF-I levels in blood	Negative influence of higher milk production and higher clearance rate of steroid hormones because of higher liver blood flow
Metabolism	Changes that reflect the state of initial negative energy balance: increased plasma levels of NEFA, insulin, and glucose	After feed intake increases to adapt to the increased milk production, metabolic indices return to normal; lower NEFA and BHB plasma levels in the next lactation
Body condition	Decrease in fat content and therefore in body weight, especially if the negative energy balance is severe	Maintenance of healthier body condition (leaner body) during late lactation than in untreated cows
Mastitis	Improved response to infection due to a proliferation of immune cells	Tendency to increase the crude incidence of mastitis, although it can be attributed to the higher risk normal for higher production
Lameness	No change	Tendency to increase the crude incidence of lameness, although it can be attributed to the higher risk normal for higher production; incidence by pounds of milk produced is decreased
Ketosis	No change	Decreased incidence of ketosis in the postpartum period that follows the lactation in which cows were treated; attributed to a leaner body composition

BHB, β-hydroxybutyric acid; *DIM,* days in milk; *NEFA,* nonesterified fatty acid.

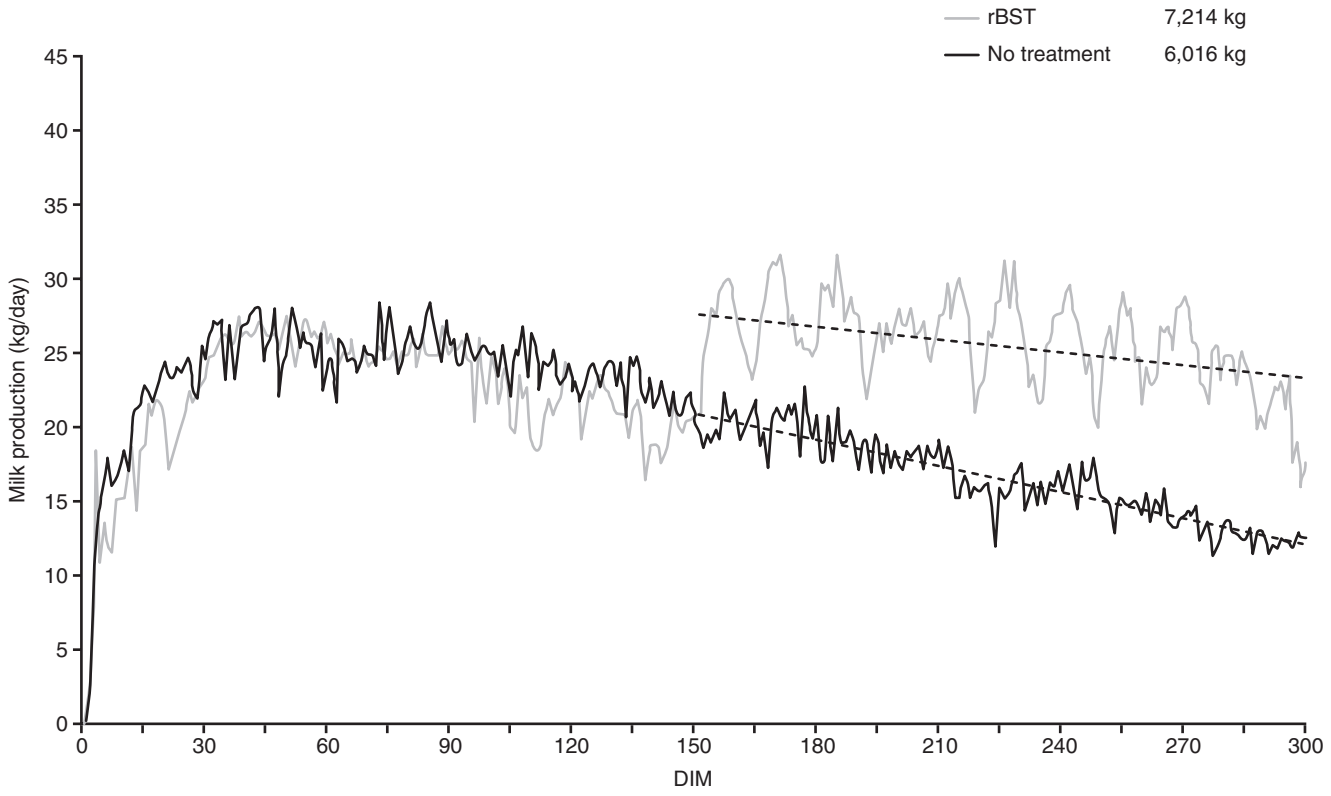


FIG. 41-26 Comparison of lactation curves of two first-lactation cows, one treated with rBST and one untreated, showing the cyclic response to rBST injection every 14 days and the improved persistence of milk production. The dips in the treated cow correspond to the administration of a new injection of rBST (every 14 days). Dashed lines represent average daily milk production. Note the variable response to different injections. *(From Lane VM, Villarroel A, unpublished data.)*

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comparable because of the uniformity of product and application. At present, Elanco markets the product under the trade name of Posilac.

Production responses were reported in 176 control herds and 164 herds using sometribove in the northeastern United States for a period of 4 years before approval and 4 years after approval.[37] In this study, cows from herds using rBST produced an average of 894 kg more milk, 27 kg more fat, and 31 kg more protein during a 305-day lactation compared with control herds. A meta-analysis of data from 28 studies using various analogs of rBST reported a production improvement of 11.3% in primiparous cows and 15.6% in multiparous cows, equivalent to 3.03 and 4.36 kg/day, respectively, over control cows.[36] In another study[49] the reported average response to sometribove in 15 U.S. herds was 4.9 kg/cow/day with a wide range among herds (2.9 to 7.6 kg/cow/day), corresponding to production increases that ranged from 11% to 31%.[37,65,68,75,76] Some trials conducted over multiple lactations have reported a lower response of cows treated in a second lactation[51,81-84]; however, all these trials used daily administration of rBST. Studies conducted using the approved 14-day interval application showed that previous treatment with rBST did not diminish milk production in subsequent lactations,[37,85] even in a study conducted over four lactations.[86]

Lactation graphs of cows responding to rBST administered at 14-day intervals show a cyclic response to treatment,[49,75,87] in which milk production started increasing on day 1 after injection, peaked on days 7 to 11, and then decreased until the next dose (see Fig. 41-26). The use of rBST does not practically alter milk components,[75,85,87] although minor changes in milk fat and protein have been observed in association with shifts in energy balance.[49,86,87] The use of rBST during late-term pregnancy in heifers can increase milk yield, improve the number of animals that resume cycling before 7 weeks, and decrease the impact of the negative energy balance.[64] Cows with higher somatic cell counts (SCCs) before treatment can be expected to have a diminished response to rBST compared with cows with lower SCCs[49] and therefore are not likely to show a positive cost benefit in favor of rBST.[88] Continuous milking (without a dry period) with rBST supplementation has been studied with the intent of reducing the incidence of mastitis and other periparturient diseases.[89] However, significant loss of milk production in the subsequent lactation occurred despite continuous rBST use. The adverse effect was more pronounced in first-lactation cows.[22,90] The reduced production was hypothesized to be due to reduced mammary epithelial cell numbers and reduced time for regeneration.[89]

Factors Limiting Response to Recombinant Bovine Somatotropin

Nutrition is the most important factor that can limit milk production response to rBST. Although short-term treatment with rBST increases milk production without increasing DMI,[73,77] long-term treatment (4 to 10 weeks) results in increased DMI to compensate for the increased production.[71,77,91] Current nutritional standards for high-producing cows[92] meet requirements for rBST-treated cows, assuming emphasis is given to consistency of the ration and feed-bunk management. If ration inconsistency leads to indigestion and "off-feed" conditions or if feed is periodically unavailable to the cow, DMI and therefore milk production will be reduced. These off-feed conditions may affect the response to rBST. McGuire and colleagues[93] found that after restriction of feed intake to lactating cows, plasma concentrations of IGF-I were markedly decreased, indicating that the stimulatory effects of rBST on lactation would not be observed in underfed cows. In this study, underfeeding of cows resulted in a marked decrease in milk production despite rBST treatment. Radcliff and colleagues[94] have shown that DMI partially controls expression of GH receptor mRNA and that cows on feed restriction had lower receptor activity for at least 1 week after ad libitum feed was restored.

Heat stress is another important factor affecting the response of milk production to rBST. Trials conducted under hot, humid conditions[65,95,96] suggest that milk production response to rBST may be more variable than that obtained under temperate conditions and that responses to higher doses may be reduced. In one trial the use of rBST was associated with reduced DMI in cows exposed to heat stress[97]; this effect was not observed in other trials.[91,98] Collier and colleagues[99] reported that acclimation to heat stress is a two-step homeorrhetic process that occurs in an acute stage of changes in secretion rate of hormones and a chronic stage of receptor population adjustments in target tissues. The time frame of acclimation is weeks rather than days. Cows treated with rBST adapt to heat stress by increasing water intake, respired vapor, and skin vapor.[95-97] These adaptations require energy and divert cardiac output away from the udder. Several studies have shown that the milk response to rBST administration is lower (up to 55%) in cows exposed to high temperatures provided with shade as opposed to shade and an evaporative cooling system.[65,98] Several studies have shown that higher rectal temperatures may be experienced in rBST-treated cows under heat stress conditions.[65,79,91,96] Although milk production was increased, the response may likely have been depressed because of energy expense toward homeostatic thermoregulation. The lower responses to rBST observed in herds in hot climate conditions may be explained in part by the effect of decreased DMI on IGF-I in plasma.[93] Dietary rations for heat-stressed cows may need reformulation for higher nutrient density to offset the reduced DMI. No negative effects have been observed during rBST use under cold conditions.[99,100]

Impact of Somatotropin on Reproduction

The aspect of rBST use most likely to result in involvement of the veterinarian is its effects on fertility. Both positive and negative effects on reproduction can accompany the positive effects of rBST on milk production. Although a study by De la Sota and colleagues[57] found that lactational status (lactating vs. nonlactating) had a greater effect on reproduction than the use of rBST, the following discussion is limited to the reproduction of lactating cows.

In general the negative effects of rBST on reproduction in lactating cows have been reported to be an increase in twinning rate and days open.[87,101,102] The increased twinning rate is likely due to better embryo survival because ovulation rate does not appear to be increased in rBST-treated cows.[62,103] There is, however, reason to suspect an increased ovulation rate on the basis of recent studies that reported increased feed intake results in higher rates of steroid metabolism in the liver.[104,105] More rapid metabolism of estradiol can result in decreased negative feedback on follicle-stimulating hormone (FSH), allowing additional follicles to undergo changes necessary to proceed to ovulation.[105] The increase in days open could be attributable to a prolonged negative energy balance associated with the increased milk production. The magnitude of the increase in days open was estimated to be 5 days in a meta-analysis performed on data from 18 studies.[102] The relative risk of nonpregnancy in rBST-treated cows during the same period as control cows was 1.38 in a meta-analysis of nine studies.[102] One explanation for nonpregnancy can be that cows treated with rBST do not show outward signs of estrus with the same intensity as untreated cows[58,106] despite an increase in plasma estradiol concentration,[107] and therefore accurate heat detection is hindered. Estrous detection rate decreased linearly with increasing dose of rBST[106] despite the finding that rBST treatment had no effect on incidence of cystic ovaries.[67,100,102,103,108]

A confounding factor in any evaluation of the effect of rBST on reproduction is the fact that rBST-treated cows maintain profitable milk production longer, and therefore these cows can be rebred, if open, at longer DIM than untreated cows. The resultant pregnancies from these breedings late in lactation will increase the average days open for the herd. On the other hand, any additional pregnancies under rBST use as a result of longer breeding windows could be considered a positive effect of the use of rBST because they would not be obtainable under the same management in untreated cows. The evidence that these two effects offset each other comes from a study that evaluated the effect of rBST use on culling in 32 herds, which showed no difference between culling rates (overall and culling because of reproductive factors) in herds that used rBST and control herds.[109] The potential negative effects of rBST on estrous behavior may favor the decision to use timed artificial insemination (TAI) programs because TAI does not rely on estrous detection to breed the cow.

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In a trial using rBST to treat cystic cows, a dose of rBST or rBST + GnRH was given 7 days before the beginning of an Ovsynch program. However, neither of these two treatments showed positive effects over controls in conception rates.[110]

Positive effects of rBST on reproduction have been elucidated in recent studies that showed first-service pregnancy rate is increased in rBST-treated cows.[111-113] This effect is due to an enhancement in oocyte maturation,[114] an increase in plasma IGF-I concentrations, increase in conceptus length, and production of antiluteolysm IFN-τ. Furthermore, there is a positive effect on endometrial preparation for implantation mediated by endometrial IGF-II mRNA.[115] This positive effect on conception is not independent of the timing of the last rBST injection.[58,111] The first-service pregnancy rate was increased in cows receiving rBST between 1 and 3 days before the first gonadotropin-releasing hormone (GnRH) injection of the Ovsynch program. In another study, pregnancy rates were increased in lactating, multiparous cows when a single dose of rBST was administered at the time of insemination.[113] Some studies have found increased conception rates in cows treated with lower doses of rBST as compared with cows treated with higher doses.[106,109,116]

Brahman-cross cows with low or moderate body condition scores treated with three doses of rBST 2 weeks apart 35 days before the breeding season had significantly higher first service conception rates.[117] Nelore cattle treated with rBST 7 days after AI failed to show either a difference in progesterone levels at day 16 or improvements in pregnancy rates.[118]

Although it is well established that rBST has positive effects on the follicle, the oocyte, the endometrium, and the conceptus, not all the studies in lactating cows show an improvement in pregnancy rate due to differences in treatment, production, reproductive management, individual cow sensitivity, or other undefined differences.[119]

In nonlactating dairy,[115] beef cows,[120] and beef heifers,[121] the failure of rBST to increase pregnancy rate can be explained by the fact that these production classes have normal IGF-I levels and do not benefit from additional concentration.

Furthermore, rBST has shown a positive effect on embryo transfer (ET) programs, both in the donor and the recipient animals.[62,122] When rBST was given at the initiation of the superovulation regimen in donor animals, two more transferable embryos were obtained—a net increase of 28% to 37%. The increased recovery of transferable embryos can be attributed to a direct effect of rBST on the superovulated ovary and an indirect effect of IGF-I. The effect on lactating recipient animals when the donor cow was not treated was to increase pregnancy rates,[62] explained by better embryo survival, because GH and IFN-τ have added effects in inhibiting uterine $PGF_{2\alpha}$ production.[59] There was no positive effect of rBST on pregnancy rate of nonlactating beef or nonlactating dairy recipients using conventional or in vitro embryos.[120] The effect of rBST on the fetus has shown some inconsistencies. In one study, calves born to rBST-treated cows had a gestation length 2 days shorter and weighed 2 kg less compared with contemporary controls,[69] whereas in another study they weighed 3 kg more than controls.[87] The effect could be dependent on energy balance (similar to the effects on milk production). In summary, rBST initially has positive effects on reproduction, but within weeks the metabolic consequence of increased milk production has a negative impact on reproduction. In herds not using rBST for increased milk production, the use of low doses of rBST could be beneficial for individual cow conception rates.

In in vitro–fertilized embryos, the use of rBST in oocyte maturation media has a beneficial effect on the oocyte's cytoplasmic maturation, developmental competence, and subsequent development to an embryo.[114]

Impact of Somatotropin on Health

Mastitis

Several studies have reported that rBST use was associated with an increase in clinical cases of mastitis.[49,102,108,123,124] In these studies no attempt was made to differentiate between contagious and environmental mastitis cases or the effect that increased milk production has on mastitis incidence. Studies on well-managed farms where contagious mastitis was being controlled reported no effect of rBST on clinical mastitis.[101,125] SCC levels in milk from rBST-treated cows are not significantly different from those in untreated cows.[37,49,75,102] If rBST supplementation is used in cows with high SCC levels, the response in milk production is lower than if rBST is used in cows with lower SCC levels.[49] The incidence of clinical mastitis in rBST-treated cows has been reported to be similar to the mastitis incidence consistent with the genetic improvement of milk yield per cow.[124,126] White and colleagues[124] suggested that mastitis should be evaluated as incidence per unit of milk produced. Cows of a given production stratum reportedly had similar mastitis incidence whether they were treated with rBST or not.[124] A meta-analysis of 11 studies found an increase in clinical mastitis cases of approximately 19.4% in the rBST-treated cows, without controlling for the increase in milk production (11% to 15.6%).[102] To further complicate interpretation of the effect of rBST, the incidence of mastitis in mid and late lactation (31 to 150 DIM and 151 to 365 DIM) depends on the incidence early in lactation (0 to 30 DIM).[127] Therefore if mastitis incidence is not measured before treatment with rBST (according to label after 57 to 70 DIM), mastitis incidence during the treatment period should be interpreted with caution. No differences in culling rates as a result of mastitis were observed in a comparison of herds that used rBST and control herds (total of 64 herds in three studies).[101,108,109] Several trials were designed to assess the effect of rBST on experimentally induced mastitis with environmental bacteria (*Streptococcus uberis*[33,128] and *Escherichia coli*[129]). Clinical signs of mastitis, milk composition changes, and bacteria counts in milk were all reduced in rBST-treated cows. Therefore overall production losses during induced mastitis episodes were lower in rBST-treated cows than in control cows, indicating a positive effect of rBST on the immune response.[31-33] Additionally, cows treated at 2-week intervals starting 21 days before the expected calving date had fewer incidences of mastitis in the first 60 DIM compared with controls.[130]

Lameness

Preapproval trials for rBST were designed as either dose titration studies or clinical trials of the effect on milk production[33]; the trials did not capture in-depth health information. A meta-analysis[102] of 18 preapproval studies that collected data on disease incidence reported negative effects of rBST on lameness and culling of adult cows (second or greater lactation). This study reported a risk ratio (RR) of 1.55 for clinical lameness and 1.36 for culling of older cows treated with rBST compared with control cows. Ruegg and colleagues,[109] however, showed no differences in culling rates (overall or because of lameness) between herds that used rBST and control herds. Another study showed that the higher risk of lameness occurred in the lactation after treatment with rBST but not during treatment.[67] In this study, however, the higher risk of lameness was attributed to management (tie-stall housing) because no changes could be found on histopathology preparations.

Metabolic Diseases

The effect of rBST on fat mobilization is a decrease in body condition score,[51,71,84] which in turn results in lower NEFA and BHB plasma levels and a lower incidence of postparturient metabolic diseases, such as ketosis and milk fever (hypocalcemia) in the subsequent lactation.[67,84] One study within the previously reported meta-analysis[102] showed a fourfold reduction in the incidence of metabolic diseases (RR = 0.25) owing to the carryover effect in the lactation after rBST treatment. Data on the incidence of other diseases commonly reported in dairy cattle were either insufficient or not collected in a consistent manner to allow objective evaluation.

In a different study, a retrospective analysis evaluating a total of 437 Holstein cows determined that supplementation with rBST with three total doses 2 weeks apart starting 21 days before the expected calving date had reduced incidence of digestive disorders and ketosis. The incidence of other postpartum diseases was no greater in the treated group.[130]

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Toxicity

Studies on the potential toxicity of high doses of rBST in dairy cattle,[73,85,131] even when administered for long periods (six times the approved dose over two consecutive lactations),[85] have shown no negative effects. The highest tested dose was 60 times the approved dose of rBST administered weekly for 4 weeks.[131] Apparent negative health effects were also not observed in the many experimental studies of rBST use.[22,49,51,75,87,108,131,132] Although cows treated with rBST tend to have lower hematocrit (packed cell volume) and hemoglobin values,[73,131,133] both remain within the normal range for dairy cattle.

Human and Food Safety

The safety of milk and meat products from rBST-treated cows is based on three tiers of biological protection:

1. Bovine GH has no activity in humans, even if injected.
2. GH and IGF-I have no oral activity and are inactivated in the gastrointestinal tract.
3. GH and IGF-I concentration in milk and meat are essentially unchanged with rBST use.

Bovine GH has been studied in depth as a potential source for therapeutic GH for hypophysectomized human patients.[134] Bovine and human GH differ in 69 of 191 amino acids in their sequences (≈36%).[10] The difference in their structure and the much lower binding affinity of bovine GH for human GH receptors (up to 3000 times)[135-137] renders bovine GH inactive in humans. Therefore contact with rBST should have no effect on people, even if injected.

The safety of consuming animal products (meat and milk) from cows treated with rBST has been extensively studied. Milk naturally contains GH and IGF-I; concentrations of both are highest during the first days of lactation[22,138-140] when milk cannot be marketed for human consumption (colostrum),[141] and decrease as lactation progresses. GH levels in milk were similar in cows treated with rBST and untreated cows and decreased by 85% to 90% when milk was heat-treated.[142] IGF-I concentration in cow milk has been reported in colostrum to be 233.8 ± 26.9 ng/mL, decreasing to 8.8 ± 1.5 ng/mL at 2 weeks postpartum.[143] Physiologic concentrations of IGF-I in cow milk vary widely according to parity and stage of lactation, ranging between 1.27 and 8.10 ng/mL in bulk tank samples.[13,138] Although treatment with rBST slightly elevates IGF-I concentration in milk,[13,144] levels remain within physiologic range. Therefore it is not possible to determine whether cows have been treated with rBST on the basis of the measurement of IGF-I and GH in milk.[144,145] Until recently, the only reliable method to determine whether cows have been treated with rBST was the measurement of GH levels in blood several times over the 14-day injection interval.[144,145] A technique has been developed to purify rBST from serum and plasma and evaluate concentration with liquid chromatography coupled with tandem mass spectrophotometry. rBST can be detected from 4 hours and 30 minutes to up to 2 weeks after administration.[146] Significant variability exists among animals that received the same dose.[147]

Levels of IGF-I in milk tended to be higher after pasteurization than in raw milk (8.2 ± 0.35 ng/mL vs. 5.6 ± 0.56 ng/mL),[138] presumably because IGF-I is released from its binding proteins. Infant formulas, which require higher pasteurization temperatures,[44] had almost undetectable levels of IGF-I (0.7 ng/mL).[138] The development of a new assay to determine rBST presence and concentration in milk and dairy products demonstrated that temperature-related procedures such as spray drying and pasteurization eliminate up to 95% of the hormone.[148]

Muscle of cows treated with rBST had levels of GH and IGF-I similar to those of untreated cows.[149] Like most ingested proteins, rBST and IGF-I are degraded by the digestive enzymes of the gastrointestinal tract, rendering them biologically inactive.[13,142,149,150] Therefore rBST has been shown to be safe and has been approved to be used with zero days' withholding of meat and milk for human consumption.[15]

Recommendations for Use of Recombinant Bovine Somatotropin

As described previously, there is overwhelming evidence that rBST has a strong galactopoietic effect and will increase average herd production when used according to label directions. When compared with other technologies developed over time to increase milk production in the dairy industry, the use of rBST and three times per day (3×) milking are the two methods that can make an immediate and significant impact on herd milk production (Table 41-11). Genetic methods[141,151-153] of improving milk production do not affect the cow on which they are applied. They will improve milk production in the female offspring once they are mature (<50% of all offspring). In contrast, methods such as cooling cows during hot

TABLE 41-11

Relative Magnitude of Increased Milk Production Obtained by the Use of Different Technologies in Dairy Cows*

Technology and Reference Category	Cost	Effect on Milk Production			Reference
		Cow	Offspring	kg/yr	
AI vs. natural service	$ Semen S/C % female calves (1—mortality)†	—	✓	367-441, 730	151, 152
ET vs. AI	$ Embryo PR % females (1—mortality)†	—	✓	372‡	153
3× milking vs. 2× milking	Labor + energy + milking hygiene products§	✓	✓	1417, 1573	154, 155
Cooling in hot weather vs. not cooling	Installation + maintenance + increased feed intake	✓	✓	769	154
rBST vs. none	$ rBST + labor + increased feed intake + facilities (if not in place) + cost of TAI program (if not in place)	✓	✓	1298, 1301	154, 155

*The reference category for each technology is provided. When comparing offspring, the reference category was the offspring of cows not exposed to the technology. Note that the effect on the cows is immediate, whereas the effect on the offspring will start approximately 3 yr later (9 mo of pregnancy plus 2 yr until calving). The effect on offspring is restricted to female offspring that survive to freshening: less than 50% of all offspring.

†Mortality of female calves from birth until they calve (2 yr of age).

‡Estimated genetic gain.

§Teat dips, towels, backflush products, and so on.

AI, Artificial insemination; *ET,* embryo transfer; *PR,* pregnancy rate; *rBST,* recombinant bovine somatotropin; *S/C,* services/conception; *TAI,* timed artificial insemination.

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TABLE 41-12

Annual Natural Resource Use and Environmental Impact of Producing 500,000 T of Cheddar Cheese from Holstein or Jersey Cows, with or without rBST[166]

Item	Holstein		Jersey	
	No rBST	rBST*	No rBST	rBST*
Milk required $\times 10^3$ t	4944	4944	3987	3987
Number of lactating cows $\times 10^3$	465.0	417.4	523.9	449.7
Total animals in the population $\times 10^3$	987.5	886.3	1079	926.2
Population body mass $\times 10^3$ t	484.6	435.0	359.6	308.6
Population maintenance energy requirement† $\times 10^6$ MJ	26,545	23,750	20,624	17,639
Population total energy requirement $\times 10^6$ MJ	50,211	47,390	43,034	40,003
Feedstuffs‡ $\times 10^3$ t	8062	7467	6470	5728
Land, ha $\times 10^3$	847.8	792.7	750.3	687.4
Water§ $\times 10^9$ L	796.8	720.5	544.8	479.3
Nitrogen excretion, t	94,894	88,017	77,660	69,626
Phosphorus excretion, t	10,550	9701	9058	8077
Manure $\times 10^3$ t	11,945	11,074	9686	8765
Methane $\times 10^3$ t	269.2	247.6	210.7	188.2
Nitrous oxide $\times 10^3$ t	1894	1806	1732	1612
Total carbon footprint§¶ $\times 10^3$ t	8104	7493	6442	5800

Modified with permission of the Author and Science Direct.[166]

*Yield response to rBST supplementation equaled 3.3 kg/day (Holstein) and 3.4 kg/day (Jersey) when corrected for calving interval and herd life.

†Refers to nutrients required for maintenance (all animals), pregnancy (dry cows), growth (heifers and adolescent bulls), and lactation (lactating cows).

‡Based on rations formulated to meet nutrient requirements using alfalfa hay, corn silage, corn grain, and soybean meal as primary ingredients.

§Adjusted for the environmental impact of rBST manufacture.

¶Total methane, nitrous oxide, and carbon dioxide emissions expressed as CO_2 equivalents.

weather,[154] milking cows 3× as opposed to 2× per day,[154,155] and using rBST improve milk production directly in the cows and their mature offspring. In fact, use of rBST can further increase milk production in herds that are already benefiting from higher production resulting from 3× milking.[154,155]

Responses to rBST are highly variable among herds; therefore individual dairymen need to determine whether the rBST response justifies the cost. Basic costs that need to be taken into account include the cost of the product plus additional labor and feed costs. Another expense to consider is the cost of implementing a TAI program (labor and drugs) to offset the negative effect of rBST on estrous expression and pregnancy rate, although TAI may have benefits independent of rBST use. Not all studies have found rBST to be significantly profitable.[156,157] The use of rBST has minimum facilities and management requirements such as a reliable restraint method (automatic headlocks, stanchions, or tie-stalls); visual identification of all cows (ear tags or freeze brands); herd management computer software; and the ability to deliver a consistent, high-quality ration, preferably a TMR.

The labeled use of rBST in the United States is 500 mg administered SC every 14 days starting at 57 to 70 DIM in dairy cows exclusively. Individual cow identification, restraint, and computerized records are important to ensure that cows are treated with rBST every 14 days. Because all cows will not show a significant improvement in milk production, individual responses may be monitored so that treatment can be limited to responsive cows. Herds that intend to profit from rBST must provide the husbandry needed to maximize DMI in the cows. Feed quality, palatability, and availability are major determinants of DMI, along with water availability, cow comfort, and heat abatement and thus will influence success of rBST usage. When cows treated with rBST become sick, they should remain on rBST because of the enhanced response to infection and endotoxemia.[31,32,34,35,128] The sick cow diet should not significantly drop in energy, or the effect of rBST (through IGF-I) on milk production and immune function will likely be reduced. Because the response to rBST in cows is greater in late lactation than in early lactation, both in kilograms and in percentage improvement, delaying the start of rBST use until later in lactation could further benefit the cows, allowing additional pregnancies to occur without a large reduction in overall response in milk production.

Potential uses of rBST, other than blanket herd use for improved milk production, include treating repeat breeder cows for improved fertility, improving fertility in embryo transfer programs (in both donor and recipient cows),[62,122] helping fat cows achieve target BCS,[49,50] preventing ketosis in the subsequent postpartum period,[67,84] and reducing or delaying culling in cows that abort and in "do-not-breed" cows. Potential uses of rBST in the future (if approved) may include production enhancement of cows during[158,159] or after lactation induction,[160] integration into programs with no dry periods,[22,161,162] and improvement in membrane integrity of bull sperm after thawing.[163] It has also been used on young stock to induce more rapid growth of lean body mass,[94,164] although some studies have shown an increase in skeletal weight but decreased carcass quality.[165] Several studies have shown that the increased production per animal will reduce the use of resources, gas emission, and environmental impact.[166] rBST also has a potential important impact in nutrient management programs to reduce manure, urine, and methane production per pound of milk[167] and milk subproduct production (Table 41-12).[166]

rBST has also been used in other species with different applications and variable responses depending on the dose and frequency. Water Buffalo heifers receiving rBST had improved oocyte quality and had a tendency to increase the number of follicles before aspiration for in vitro fertilization.[168] Sheep showed an increase in lambing rate and prolificacy when rBST was given during the estrus synchronization program,[169] and when used every 14 days during lactation it increased the milk yield by 209 mL/day after weaning.[170] Milk production in goats increased by 26.6% when given daily for 28 days.[171] It should again be noted that all uses of rBST other than to increase milk yield in dairy cows is not approved.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 42

Diseases of Muscle

STEPHANIE J. VALBERG, *Consulting Editor*

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Examination of the Muscular System

Stephanie J. Valberg

Clinical evaluation of the muscular system requires a systematic and routine method for examination. Often a veterinarian is asked to examine an animal with a history of a relatively nonspecific disease process that may be the result of muscular dysfunction. Animals with electrolyte imbalances, pleuritis, colic, chronic wasting diseases, poor performance, weakness, and a number of lameness problems may initially have signs similar to those seen with some forms of muscular dysfunction.

A thorough history of the animal or animals involved is an integral part of characterizing the muscle disorder, particularly because many disorders are intermittent in nature and triggered by certain environmental stimuli. A careful description of the animal's muscle tone, muscle mass, gait, degree of pain, exercise intolerance, and weakness while experiencing clinical signs should be obtained. In addition, the duration of illness, intermittency of clinical signs, factors precipitating clinical signs, exercise schedule, diet, current medications, vaccination history, and number of other animals affected and their familial relationships should all be recorded before the muscular system is examined.

Physical Examination

Initially the animal can be observed from all aspects at a distance while the horse is standing with forelimbs and hindlimbs exactly square. The examiner should observe the size, shape, and symmetry of all muscle groups and look for muscle fasciculations. This observation helps provide impressions about tropic changes, alterations in symmetry of particular muscle groups, and spontaneous muscle activity.

The animal can then be walked, trotted, or driven and evaluated for gait abnormalities. The symmetry of the gait and evidence of lameness, weakness, stiffness, and pain associated with movement can be noted. Gait abnormalities may result from pain, muscle weakness, muscle cramping, spasticity, decreased range of joint motion, dysfunction of motor neurons, and ataxia.

Following initial visual evaluation, muscles should be palpated to obtain an overall impression of muscle tone, consistency, sensitivity, swelling, atrophy, and heat. Firm, deep palpation of the lumbar, gluteal, and semimembranosus and semitendinosus muscles may reveal pain, cramps, or fibrosis. Comparisons between muscle groups and areas of the animal can then be made to identify atrophy or swelling. Some animals are tense and demonstrate apparent evidence of myalgia when palpation is first performed. However, given time and patience, many of these animals relax, and muscles or muscle groups that at first examination appeared to be very sensitive or hypertonic may in reality be normal. By this stage it can often be determined whether individual muscles, muscle groups, a limb or limbs, or the whole body musculature is involved. The symmetry or absence of symmetry of affected muscles or muscle groups is also important. Horses should stand perfectly square when comparing bilateral muscle groups.

Fine muscle tremors can be palpated and auscultated with a stethoscope. Concurrent signs of anxiety or pain should be noted, and the animal should be reevaluated in calm surroundings if necessary. In animals with spontaneous muscle activity, muscle groups should also be percussed with a percussion hammer. The triceps, pectoral, gluteal, and semitendinosus muscles are often easily accessed for percussion. A positive percussion sign occurs when the muscle holds a contracture for several seconds, creating a dimpled appearance below the contracted muscle (percussion myotonia) (Fig. 42-1). This occurs as the result of abnormal mechanical irritability and sustained contraction of the percussed fibers. Running a blunt instrument such as artery forceps, a needle cap, or a pen over the lumbar and gluteal muscles should illicit extension (swayback) followed by flexion (hogback) in healthy animals. Guarding against movement may reflect abnormalities in the pelvic or thoracolumbar muscles, or pain associated with the thoracolumbar spine or sacroiliac joints.

A tail pull examination while the horse is standing still and walking can be used to assess rear limb weakness. If there is evidence of weakness, differentiation between muscular and neurologic origin is ideal. This requires a detailed neurologic examination and can often be extremely difficult. In general, muscular weakness is not associated with ataxia unless it is extremely severe. Weakness is often manifested by muscle fasciculations, knuckling at the walk, frequent recumbency with difficulty rising, and shifting of weight because of an inability to fix the stifles.

If the primary abnormality identified is related to exertion, a lameness evaluation including flexion tests is often indicated as part of evaluation of the muscular system. Muscle pain may be secondary to changes in movement caused by skeletal pain. The horse should be observed at a walk or trot for any gait abnormalities and in some cases lunged for 15 minutes or ridden until clinical signs are elicited.

Clinical Pathology

Serum Enzyme Activities and Myoglobin Concentrations

Serum enzyme activities can be extremely useful in determining whether muscle cell necrosis is a predominant feature of a suspected muscle disease. Under normal conditions the serum activities of the enzymes used to assess muscle damage are low. However, leakage of the enzymes from myocytes into the bloodstream may occur if the cell membrane is disrupted through muscle cell necrosis or if the permeability of the cell membrane is increased. A number of other factors may influence the activities of enzymes within the circulation.

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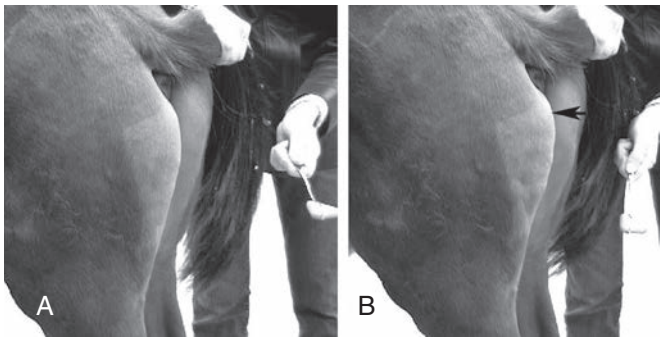


FIG. 42-1 Percussion of the semitendinosus muscle showing the muscle at rest **(A)** and an abnormal persistent firm contracture after tapping the muscle with a percussion hammer **(B)** in a horse with myotonia.

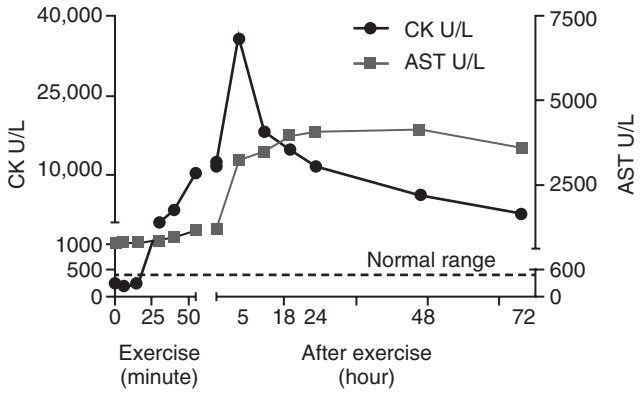


FIG. 42-2 Serum creatine kinase (CK) and aspartate transaminase (AST) activities over a 3-day period in a Standardbred trotter that developed exertional rhabdomyolysis during 55 minutes of trotting at 5 m/sec. Serum CK activity increased during exercise and peaked in the sample obtained 5 hours after exercise. Serum AST was above normal range before exercise, increased after exercise, and peaked 48 hours following exercise.

These include rate of enzyme production, alternative sources of the enzyme, rates of enzyme excretion and degradation, and alterations to the pathways involved in enzyme removal or inactivation.

Creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) activities in serum are used to assess muscle damage in large animals. Serum CK offers remarkable sensitivity as an indicator of myonecrosis and is predominantly located in skeletal and heart muscle. It is intimately involved in energy production within the cytoplasm and is readily liberated into the extracellular fluid when the muscle cell membrane is disrupted. Serum CK activity increases within hours of a muscle insult and peaks within 4 to 6 hours after injury (Fig. 42-2). Limited elevations in CK may accompany training, transport, and strenuous exercise. Elevations of CK to 400 or 500 IU/L may occur when training commences or in response to moderate exercise. Extreme fatiguing exercise (e.g., endurance rides or the cross-country phase of a 3-day event) may result in CK activities being increased to more than 1000 IU/L but usually less than 8000 IU/L. These elevations are not typically reflective of an extensive myopathy, and serum activities of CK rapidly return to baseline activities (i.e., <250 IU/L in 24 to 48 hours). Recumbent animals may also have slightly elevated CK activities that are usually less than 3000 IU/L. In contrast, more substantial elevations (from several thousand to hundreds of thousands of IU/L) in the activity of this enzyme may occur with rhabdomyolysis.

Serum AST has high activity in skeletal and cardiac muscle and also in liver, red blood cells, and other tissues. Elevations in AST are not specific for myonecrosis, and increases can be the result of hemolysis, muscle, liver, or other organ damage. Alterations in AST activity are an integral component of many serum biochemical "profiles." AST activity rises more slowly in response to myonecrosis than does CK, often peaking 24 hours after the insult (see Fig. 42-2), and the half-life of AST is much longer than that of CK. By comparing serial activities of CK and AST in animals with suspected myopathy, information concerning the progression of myonecrosis may be derived. Thus (1) elevations in CK and AST reflect relatively recent or active myonecrosis; (2) if CK remains persistently elevated, myonecrosis is likely ongoing; and (3) elevated AST activities accompanied by decreasing or normal CK activities indicate that myonecrosis is not continuing. Elevations in serum LDH activity are not specific to skeletal muscle and can occur with rhabdomyolysis, myocardial necrosis, and/or hepatic necrosis.

Under ideal conditions samples for determination of serum CK, AST, and LDH should be harvested as soon as possible because anoxia and lysis of red blood cells allows the liberation of AST and LDH. They should be kept chilled (4° C, 39° F) if not taken immediately to a laboratory for analysis within 24 hours. When a delay of more than 12 hours is anticipated, freezing of the samples is desirable.

Elevations in plasma/serum myoglobin concentrations provide an indication of recent muscle damage. Unfortunately, few laboratories can routinely measure myoglobin. Normal concentrations in resting horses have been determined by nephelometry (range 0 to 9 μg/L),[1] with measured concentrations with rhabdomyolysis ranging from 10,000 to 800,000 μg/L.[2]

Urinalysis

Urine can be obtained free catch from horses placed in stalls with fresh bedding or via catheterization. The most accurate reflection of fractional excretion of electrolytes is obtained from samples obtained without tranquilization. Urinalysis is particularly important in horses with myoglobinuria, elevations in creatinine, or suspected electrolyte imbalances. Urine specific gravity, protein content, white blood cell (WBC) count, red blood cell (RBC) count, and evaluation of cast formation should be performed to assess the potential for concurrent renal disease. A positive Hemastix test (ortho-toluidine) in the absence of hemolysis or RBCs in urine is highly suggestive of myoglobinuria. Further differentiation of myoglobin from hemoglobin is sometimes warranted and, where available, electrophoresis, nephelometry, or spectroscopy may be used. Spectroscopy does not always reliably distinguish between myoglobin and hemoglobin.

Electrolyte, mineral, and creatinine concentrations in urine and blood have been used to determine electrolyte balance in horses with muscle cramping or exertional rhabdomyolysis.[3] Problems often encountered, however, are the large fluctuations in daily electrolyte excretion that occur in the same horse and between horses, the interference of high urinary potassium concentrations with measures of sodium concentrations when an ion specific electrode is used, and the presence of calcium crystals in equine urine, which artifactually decrease the calcium and magnesium measured if urine samples are not acidified.[4] Renal fractional excretions (FEs) can be calculated using the following formula:

$$FE_x = \frac{S_{Cr} \times U_x \times 100}{U_{Cr} \times S_x}$$

where *U* is urine, *S* is serum, *x* is measured electrolyte, and *Cr* is creatinine.

If urine calcium is to be determined, acidification of urine to dissolve all calcium oxalate crystals is recommended to provide exact calcium excretion. Determination of potassium, chloride, magnesium, and phosphorus concentrations can be performed using ion-specific electrodes or by inductively coupled plasma atomic absorption.

Normal values for FE of electrolytes depend on a horse's diet. Normal values (%) for horses consuming grass, hay, and a sweet feed mix with available salt are FE_{Na} 0.04 to 0.08, FE_K 35 to 80, FE_{Cl} 0.4 to 1.2, FE_{Ca} 5.3 to 14.5, FE_P 0.05 to 4.1, and FE_{Mg} 14.2 to 21.4.[4,5]

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Exercise Testing

Evaluation of muscle disorders that are precipitated by exercise may require an exercise challenge test. Horses should be observed for evidence of exercise intolerance, as well as muscle stiffness. An exercise test should not be used in horses with overt signs of rhabdomyolysis but rather to determine if horses not currently showing clinical signs are prone to exertional rhabdomyolysis. The goal is to induce subclinical elevations in serum CK activity. Abnormal increases in CK are more likely to occur if slow trotting is performed rather than strenuous exercise.[6] Often 15 minutes of exercise at a walk and trot in unfit horses or at a constant slow trot in fit horses will elucidate subclinical elevations on CK. If signs of stiffness develop before this, exercise should be concluded. CK activities in blood samples taken immediately after exercise do not reflect the amount of exercise-induced muscle damage. For best results, blood samples for CK activity should be taken before and 4 to 6 hours after exercise. In healthy horses, 15 to 30 minutes of light exercise rarely causes more than a threefold increase in CK activity.[7,8] Elevations greater than fivefold are indicative of exertional rhabdomyolysis. Standardized treadmill exercise testing can also be used to evaluate muscle responses and measure metabolic responses to exercise.

Electromyography

Electrodiagnostic studies detect spontaneous or evoked potentials of neurogenic or myogenic origin using electrodes positioned in the muscle. Electromyography (EMG) is particularly useful to evaluate large animals with altered muscle tone. EMG of normal skeletal muscle shows a brief burst of electrical activity when the needle is inserted (insertional activity) in muscle and then quiescence, unless motor units are recruited (motor unit action potentials), or the needle is close to a motor end plate (miniature end plate potentials). Normal muscle shows little spontaneous electrical activity unless the muscles contract or the horse moves. Horses with abnormalities in the electrical conduction system of muscle, or denervation of motor units, show abnormal spontaneous electrical activity in the form of fibrillation potentials, positive sharp waves, myotonic discharges, or complex repetitive discharges.[9-12] Fibrillation potentials and positive sharp waves represent spontaneous firing of muscle fibers. Myotonic discharges are bursts of complex high-frequency potentials, whereas complex repetitive discharges are similar but have fixed amplitude and frequency. They both represent abnormal simultaneous firing of groups of muscle fibers. Motor unit action potentials can be evaluated to assess their amplitude, duration, phase, and number of phases. Myopathic changes include a decrease in duration and amplitude of motor unit action potentials.[10,12] More information about the motor unit could be provided by nerve conduction velocities (NCVs); however, the inaccessibility of motor nerves makes measurement difficult in large animals. Both EMG and NCVs are used to classify the primary disease as neuropathic or myopathic, to determine the distribution of the disease, and to provide insight into the pathophysiologic mechanisms of the disease.[9,13] Equipment costs are relatively high, and expertise is required in operation and interpretation of results. Readers are advised to consult Chapter 35 before considering the use of EMG.

Nuclear Scintigraphy

Nuclear scintigraphy is useful for identification of some forms of muscle damage, particularly an area of deep muscle damage that was not suspected on the basis of clinical examination.[14] Technetium 99 m methylene diphosphonate (MDP) is taken up in some damaged muscle in the horse and is best seen in the bone phase images (i.e., 3 hours after injection). Scintigraphy has been used in horses with a history of poor performance, with or without stiffness after exercise, to confirm a diagnosis of equine rhabdomyolysis.[15] The mechanism of MDP binding is unknown, but the release of large amounts of calcium from damaged muscle or the exposure of calcium binding sites on protein macromolecules in the damaged muscle may be responsible. Scintigraphy may be helpful in some cases involving focal damage to either proximal forelimb or hindlimb muscles.[14]

Ultrasonography

Diagnostic ultrasonography is potentially useful for identification of muscle trauma, crepitus, fibrosis, and atrophy. Muscles have a rather typical striated echogenic pattern, but this varies according to the muscle group and careful comparisons must be made between similar sites in contralateral limbs, in both transverse and longitudinal images.[14] The appearance of muscle is also sensitive to the way the animal is standing and whether the muscle is under tension, so it is important that the animal is standing squarely and bearing weight evenly. Muscle fascia appears as well-defined, relatively echodense bands.[14] Care must be taken in identifying large vessels and artifacts created by them.

In an acute injury, muscle fiber disruption is seen as relatively hypoechoic areas within muscle, with loss of the normal muscle fiber striation. The jagged edge of the margin of the torn muscle may be increased in echogenicity.[14] Tears in the muscle fascia may be identified. The defect in muscle may be filled by loculated hematoma that is hypoechoic. As the muscle repairs it becomes progressively more echogenic. Relatively hyperechoic regions may be a result of increased connective tissue or loss of muscle cell mass. Hyperechoic shadowing artifacts usually represent mineralization or gas pockets.[14]

Muscle Biopsy

Examination of muscle fibers, neuromuscular junctions, nerve branches, connective tissue, and blood vessels within a biopsy sample can provide additional information necessary to fully characterize a neuromuscular disorder.[16-18] Routine light and electron microscopic examinations, combined with histochemical evaluations, may provide insights into the particular manifestations of neuromuscular diseases and their rate of progression. A number of basic pathologic responses of muscle can be identified in paraffin-fixed sections. These include inflammatory infiltrates, muscle fiber necrosis, muscle fiber regeneration, increased number of central nuclei, variations in muscle fiber sizes and fiber shapes, vacuolar change, and proliferation of connective tissue. However, there are many pathologic alterations that cannot be detected in formalin-fixed tissue but can readily be seen in histochemical stains of fresh-frozen biopsy samples.[16-18] These include muscle fiber types and their pattern of distribution, differentiation of neurogenic atrophy from disuse atrophy or a primary myopathy, characterization of vacuolar storage material, characterization of inclusion bodies, assessment of mitochondrial density, and additional clues that may allow identification of a specific disorder or category of muscle disorders. Furthermore, formalin fixation results in artifactual cracking, fiber shrinkage, and leakage of substrates such as glycogen, which can impact proper interpretation of muscle pathology.

When considering collection of muscle biopsies, some general guidelines apply. Preferably, samples should be collected from what is considered abnormal or diseased muscle. A 6-mm-outer-diameter (Jørgen Kruuse A/S, Langeskov, Denmark) percutaneous needle biopsy technique can be used to obtain small muscle samples through a ¼-inch skin incision using a local anesthetic subcutaneously. If this technique is used, enough muscle should be obtained to form a ½-inch square sample at a minimum. These samples do not, however, tolerate shipment to an outside laboratory. The optimum biopsy for shipment of histopathology tissues to a laboratory is collected using surgical or open techniques, performed under local anesthesia. Care must be exercised to infiltrate only the subcutaneous tissues, not the muscle, with the anesthetic agent. The objective is to obtain approximately a ½-inch cube of tissue; hence a suitably long skin incision is required. Two parallel incisions ½ inch apart should be made longitudinal to the muscle fibers with a scalpel. The muscle should only be handled in one corner using forceps, and crushing should be avoided. The muscle sample is then excised by cross-secting incisions ½ inch apart, and the tissue is fixed appropriately. Routine histopathology samples can be placed in formalin; fresh samples can be placed in a watertight hard container after being wrapped in gauze lightly moistened with saline and shipped chilled to laboratories for freezing. On arrival at specialized laboratories, fresh samples for

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histochemical analysis are fixed in isopentane (methylbutane) chilled in liquid nitrogen to ensure rapid freezing and minimization of freeze artifact. Samples that potentially may be used for biochemical analysis should be immediately frozen in liquid nitrogen. Other routine histopathologic techniques may also be of diagnostic value. A special fixative may be required if such practices are to be undertaken. Samples for electron microscopy (EM) require appropriate fixation in glutaraldehyde preparations. Ideally, thin sections of muscle for EM should be clamped in vivo to maintain fibers at a resting length before they are excised. However, if pathology other than the alignment of thick and thin myofilaments is to be investigated, small muscle pieces can be excised and placed directly in appropriate EM fixative.

Responses of strips of fresh muscle to stimuli such as caffeine, halothane, and a variety of other agents can also be performed by specialized laboratories to diagnose recurrent exertional rhabdomyolysis and susceptibility to malignant hyperthermia but are not routine diagnostic procedures.[19-21]

Classification of Muscle Disorders

Stephanie J. Valberg

A muscle disorder is usually suspected in large animals because of (1) increased, decreased, or abnormal muscle tone; (2) focal or generalized muscle damage (rhabdomyolysis); (3) muscle atrophy; or (4) exercise intolerance not associated with respiratory, cardiovascular, or skeletal causes.

Altered Muscle Tone

Increased muscle tone may be neural in origin. For example, tetanus and strychnine poisoning increase muscle tone as a result of suppressed inhibition of upper motor neurons by interneurons. Increased motor neuron firing also occurs during seizures, with electrolyte imbalances and equine ear tick infestation. Visual, tactile, or auditory stimuli often precipitate painful sustained motor unit activity. Other probable neural disorders that intermittently increase muscle tone include periodic spasticity and spastic paresis in cattle, stiff horse syndrome, and "shivers" in draft and warmblood horses. Focal nerve root irritation may also result in focal muscle twitching.

Increased muscle tone can also arise from myopathic disorders. Persistently enhanced muscle tone may occur because of muscle contractures, which are characterized by fixation of myofilaments in a persistently shortened position without neural input.[22] Contractures are usually extremely painful and associated with rhabdomyolysis. Contractures occur with malignant hyperthermia and some forms of exertional myopathy. Intermittent, abnormal muscle contractions without rhabdomyolysis occur when sarcolemmal ion channels within the muscle cell membrane are dysfunctional.[23,24] Caprine myotonia congenita and equine hyperkalemic periodic paralysis are examples of diseases caused by sarcolemmal ion channel dysfunction.

Moderate weakness in horses may be caused by central spinal cord disorders. More profound weakness may arise from neuropathies affecting motor neurons (equine motor neuron disease, hypocalcemia); decreased neural input at motor end plates (botulism); marked muscle atrophy (equine motor neuron disease) or rhabdomyolysis of postural muscles; or severe electrolyte imbalances (hypokalemia). The few operative motor units fatigue easily, resulting in muscle fasciculations, shifting of weight, low head posture, difficulty prehending grain, and long periods of recumbency and difficulty rising.

Muscle Atrophy

Atrophy is defined as a reduction in muscle size, specifically a reduction in muscle fiber diameter or cross-sectional area. Atrophy may occur in response to a variety of stimuli. Denervation removes the normal low-level tonic neural stimulus that is necessary to maintain muscle fiber mass. Complete denervation of a muscle results in more than a 50% loss of muscle mass within a 2- to 3-week period.[16,25] A good example of this is "Sweeney" in horses, in which the suprascapular nerve is damaged and muscles over the scapula atrophy. Other denervating conditions such as equine motor neuron disease show a slower and more generalized progression of gross muscle atrophy. Electromyographic abnormalities following denervation are apparent within 5 days, and it may take 3 weeks for maximal changes to develop. Increased insertional activity, positive sharp waves, and bizarre high-frequency discharges and fibrillation potentials are seen in denervated muscle.[12] Pyknotic nuclear clumps and small angular slow-twitch type I and fast-twitch type II fibers with concave sides are characteristic of neurogenic atrophy in muscle biopsies. In some cases, hypertrophy of remaining motor units may occur in neurogenic atrophy and renervation is indicated by target fibers and fiber type grouping.

Muscle atrophy may also be caused by disuse, malnutrition, cachexia, corticosteroid excess, and immune-mediated myositis. Skeletal muscle is a plastic tissue, with approximately 1% to 5% of the contractile mass undergoing remodeling on a daily basis. If a negative nitrogen balance occurs, net protein withdrawal from the skeletal muscle mass begins within 48 to 72 hours. This type of atrophy is distinguished from neurogenic atrophy by a slower progression of atrophy, normal electromyographic findings, and muscle biopsies that are characterized by primarily atrophy of type II muscle fibers. The overall response of skeletal muscle is to maintain essential postural muscle groups, whereas less essential groups undergo significant reduction in muscle mass. With malnutrition, 30% to 50% of the muscle mass may be lost in the first 1 to 2 months.[25] Rapid atrophy is characteristic of immune-mediated myopathies in Quarter Horse–related breeds, which can result in the loss of 30% of muscle mass within 48 hours due to necrosis and atrophy of myofibers.[26]

Muscle Necrosis

Muscle necrosis (rhabdomyolysis) as evidenced by elevations in serum CK, LDH, and AST can be focal or generalized. Many infectious, toxic, nutritional, ischemic, and idiopathic factors result in muscle fiber necrosis. When attempting to identify an etiology, it is helpful to characterize rhabdomyolysis in horses as associated with exercise or not. Specific causes of exertional and nonexertional rhabdomyolysis are listed in Boxes 42-1 to 42-3.

Necrosis represents injury to organelles within a muscle fiber or within a segment of that fiber. Many myopathies associated with generalized rhabdomyolysis interrupt normal muscle metabolism, and cell death results from an inability to maintain homeostasis within the myofiber. Although a variety of external or internal insults may cause rhabdomyolysis, they often share a final common pathway leading to cell death.[27] Under normal conditions, considerable energy is expended by muscle cells to pump the calcium that accumulates in the sarcoplasm during contraction into the sarcoplasmic reticulum. If cell membrane function is disrupted or if the energy pathways that generate adenosine triphosphate for the calcium pump are impaired, excessive calcium may accumulate in the sarcoplasm. Although some calcium can be sequestered by the mitochondria, eventually mitochondria become overloaded and oxidative metabolism ceases; oxygen free radicals are generated; phospholipases are activated, inducing the arachidonic cascade; calcium-dependent proteases are stimulated; and complement is activated. Lipid storage disorders and antioxidant deficiencies may also cause necrosis through destruction of mitochondrial and sarcolemmal membranes. The contractile proteins within a necrotic segment are destroyed and appear homogenized with no evidence of cross-striations, and mitochondrial and sarcolemmal membranes appear disrupted. When necrosis occurs as a result of internal disruption of muscle homeostasis, the basement membrane of the cell is left intact. Macrophage infiltration and phagocytosis of necrotic debris usually occur within 16 to 48 hours of the muscle injury. Satellite cells migrate along the remaining basement membrane and form regenerative myotubes within 3 to 4 days

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BOX 42-1

Classification of Nonexertional Myopathies in Horses

Nonexertional myopathies in horses
1. Infectious
   - Viral
   - *Sarcocystis fayeri*
   - *Anaplasma phagocytophilum*
   - *Streptococcus equi*
   - *Clostridium* sp.
   - Abscesses
2. Immune mediated
   - Infarctive purpura hemorrhagica
   - Immune-mediated myositis
3. Nutritional myopathies
   - Nutritional myodegeneration
     - Selenium deficiency, vitamin E deficiency
     - Vitamin E–deficient myopathy in horses
4. Toxic myopathies
   - Feed contaminants
     - Ionophores
   - Plant toxins
     - Trematones
     - Hypoglycin A
5. Traumatic/anesthetic
   - Focal muscle strain
   - Fibrotic myopathy
   - Postanesthetic myopathy
6. Muscle cramping
   - Electrolyte disturbances
   - Hypocalcemia
   - Synchronous diaphragmatic flutter
   - Ear ticks
   - Shivers
7. Myotonia
   - Myotonia congenita
   - Myotonia dystrophica
   - Hyperkalemic periodic paralysis
8. Genetic
   - Glycogen branching enzyme deficiency
   - Polysaccharide storage myopathy type 1
   - Polysaccharide storage myopathy type 2
   - Malignant hyperthermia

BOX 42-2

Classification of Exertional Myopathies in Horses

1. Focal muscle strain
2. Sporadic exertional rhabdomyolysis
   - Dietary imbalances:
     - Vitamin E/Selenium, electrolytes
   - Exercise in excess of training
   - Exhaustion
3. Chronic exertional rhabdomyolysis
   - Polysaccharide storage myopathy type 1
   - Polysaccharide storage myopathy type 2
   - Malignant hyperthermia
   - Recurrent exertional rhabdomyolysis
   - Idiopathic exertional rhabdomyolysis

BOX 42-3

Classification of Myopathies in Food Animals

1. Infectious
   - Clostridium
   - Sarcocystis
2. Nutritional
   - Selenium, vitamin E
   - Hypokalemia
3. Toxic
   - Feed additives
     - Ionophores
   - Plants
     - Gossypol, *Cassia,* white snakeroot
   - Chemical
4. Traumatic
   - Muscle crush syndrome
5. Genetic
   - Caprine myotonia
   - Bovine pseudomyotonia
   - Porcine malignant hyperthermia
   - Bovine and ovine myophosphorylase deficiency
   - Porcine RN(–) glycogen storage disease

of injury, with mature muscle fibers developing within a month of the original damage.[16]

Muscle ischemia occurs commonly with acute trauma, the compartment syndrome in recumbent animals, downer syndrome, and vascular occlusion. Compartment syndrome often involves the triceps muscle or extensors of the hindlimb because they are often compressed in down animals or during anesthesia. Hypotension during surgery contributes to the development of this syndrome. Acute muscle infarction may occur with purpura hemorrhagica or disseminated intravascular coagulation, and on postmortem examination characteristic well-demarcated areas of hemorrhagic necrosis are evident. Muscle areas in contact with the ground in recumbent animals are most susceptible to infarctions in animals with vasculitis. Clinically, acute infarctions are an extremely painful condition that may resemble colic. Chronic occlusive diseases, such as iliac thrombosis, often allow collateral circulation to develop, thereby avoiding acute signs of ischemia at rest. Although muscle has an impressive ability to regenerate, if a disease process is severe enough to disrupt the basement membrane, muscle may be replaced by connective tissue and fat. This occurs most frequently after trauma, such as following tearing of the semimembranosus/tendinosus in horses (fibrotic myopathy) and with severe infarctions.

Disorders of Muscle Tone

Myotonic Disorders

Stephanie J. Valberg

Myotonic muscle disorders represent a heterogeneous group of diseases that share the feature of delayed relaxation of muscle after mechanical stimulation or voluntary contraction. Abnormal muscle membrane excitability appears to be the shared abnormality among myotonic disorders. The nondystrophic myotonias in large animals include myotonia congenita in horses and goats and equine hyperkalemic periodic paralysis.[28] Sarcolemmal ion channel dysfunction causes these nondystrophic myotonias. Dystrophic myotonia, a progressive disease that may also be associated with abnormalities in other body systems, has been reported in horses.[29,30] In addition, it has been noted that some horses with ear tick infestations develop percussion myotonia and painful muscle cramps.[31]

A condition that demonstrates myotonic-like signs in cattle is spastic paresis,[32,33] or Elso heel. Commonly, calves between 2 and 7 months of age are affected and have an extremely straight angle to the hock and stifle. Signs reflect a decreased capacity or inability to flex the hock because of continuous tension on the gastrocnemius muscle when standing. Involvement may be unilateral or bilateral. The Holstein-Friesian breed is most commonly affected, although other breeds have been found to suffer the disorder.[32-35] Spastic paresis may have a distinct familial pattern, but environmental exposure to toxins in utero have also been implicated as a cause.[32-34,36]

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FIG. 42-3 Normal muscle mass in an Appaloosa foal **(A)** and spontaneous myotonic dimpling of semimembranosus muscles in a foal with myotonic dystrophy **(B)**.

Clinical signs similar to spastic paresis are seen in horses with shivers, which is most commonly seen in draft horse breeds, warmbloods and warmblood crosses older than 1 year of age, and Thoroughbreds, although it may occur in light horse breeds.[37] Horses are generally taller than 16.3 hands and more often male than female. Suggested causes include genetic, traumatic, infectious, and neurologic diseases, although its exact basis is unknown. The disease primarily affects the hindlimbs and is characterized by periodic, involuntary spasms of the muscles in the pelvic region, pelvic limbs, and tail, which are exacerbated by backing or picking up the hindlimbs. The affected limb is elevated and then abducted. It may actually shake and shiver, and the tailhead usually elevates concurrently and trembles. In more severely affected animals, on backing up the hindlimb is suddenly raised, semiflexed, and abducted with the hoof held in the air for several seconds or minutes. The tail is elevated simultaneously and trembles. After a variable period of time, the spasms subside, the limb is extended, and the foot is brought slowly to the ground. There are no distinct myotonic discharges on electromyography with shivers, indicating it is not a true myotonic condition.

Myotonia

Clinical Signs Myotonia congenita in humans, horses, and goats is usually detected in the first year of life.[38-41] Affected animals commonly have conspicuously well-developed musculature and display mild to moderate pelvic limb stiffness. Gait abnormalities are usually most pronounced when exercise begins and frequently diminish as exercise continues. Bilateral bulging (dimpling) of the thigh and rump muscles is often obvious and gives the impression that the animal is well developed (Fig. 42-3). Stimulation of affected muscles, especially percussion, exacerbates the muscle dimpling below a large area of tight contraction (Fig. 42-4). Affected muscles may remain contracted for up to a minute or more with subsequent slow relaxation.[30,41] Myotonia congenita does not usually show progression of clinical signs beyond 6 to 12 months of age in horses.[30]

In goats, myotonia congenita appears to be an autosomal dominant mutation in the skeletal muscle chloride channel (CLCN1) that has incomplete penetrance.[24,40,42] Affected goats are commonly referred to as "fainting goats." Signs are usually recognizable by 6 weeks of age and vary from stiffness after rest to marked general rigidity after visual, tactile, or auditory stimulation. Clinical signs remain throughout the animal's life but are not progressive.[43] An autosomal recessive c.1775A>C mutation was identified in a New Forrest Pony with congenital myotonia. The missense mutation

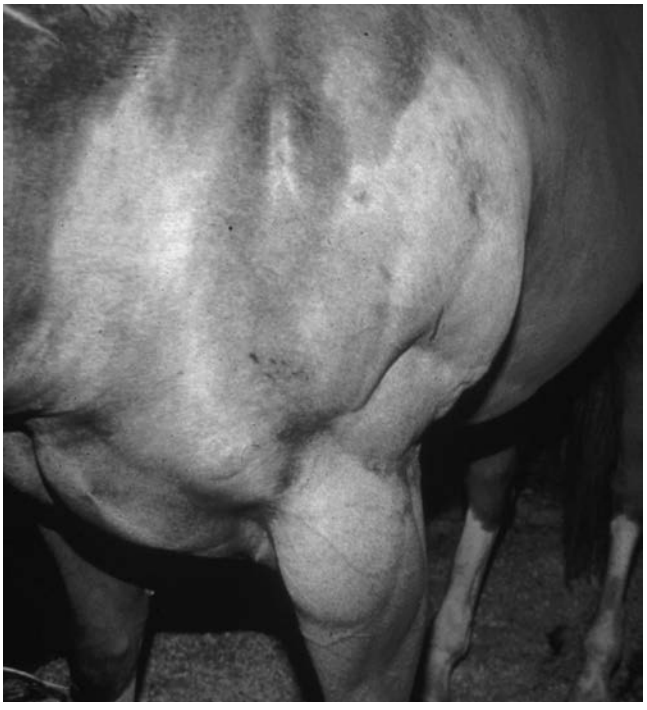


FIG. 42-4 Myotonic dimpling of the triceps in a horse with hyperkalemic periodic paralysis.

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results in a substitution of aspartic acid for alanine in codon 592 of the C-terminal cytoplasmic domain of the equine CLCN1 protein.[44]

Myotonia dystrophica appears to be a separate form of myotonia in horses.[29,30,45] Severe clinical signs of myotonia that progress to marked muscle atrophy and possibly involve a variety of organ systems have been observed in Quarter Horse, Appaloosa, and Italian-bred foals. Retinal dysplasia, lenticular opacities, and gonadal hypoplasia have been reported in one such Quarter Horse foal.[29] This condition resembles myotonia dystrophica in humans, which is caused by genetic mutations involving either the *DMPK* gene or the *ZNF9* gene.[46,47] In both cases, a short segment of deoxyribonucleic acid (DNA) is abnormally repeated many times, forming an unstable region in the gene, which alters messenger ribonucleic acid (RNA) processing. The genetic basis of myotonic dystrophy in horses is not yet known.

Diagnosis A tentative diagnosis frequently can be made on the basis of age; clinical signs (stiff gait, particularly at the onset of exercise); muscle bulging; and prolonged contractions following muscle stimulation.

Definitive diagnosis of myotonia is usually based on electromyographic examination. Affected muscle manifests pathognomonic, crescendo-decrescendo, high-frequency repetitive bursts with a characteristic "dive bomber" sound.[29,45,48] This sound is produced by the repetitive firing (after contractions) of affected muscle fibers. After a contraction diminishes, the excitability of muscle fibers is decreased and the action potentials recorded by the EMG reflect the diminution of electrical activity.[49]

Examination of muscle biopsies from foals with myotonia congenita may be normal or may demonstrate extremely variable muscle fiber dimensions up to twice those of normal age-matched controls.[41] Type I fiber hypertrophy or hypotrophy may be seen. The major changes noted with myotonic dystrophy are ringed fibers, alterations in the shape and position of myonuclei, sarcoplasmic masses, and an increase in endomysial and perimysial connective tissue.[29,30,45,50] Fiber type grouping and atrophy of both type I and type II muscle fibers may be present.

Treatment Considering that the pathophysiologic basis of myotonia in horses has not been clearly identified, recommendations for specific, effective therapy are almost impossible. In affected humans and dogs some relief of signs has been provided by drugs such as quinine, procainamide, and phenytoin. However, responses vary among patients. Phenytoin has been reported to be efficacious in two Quarter Horses with hyperkalemic periodic paralysis and myotonic dystrophy.[48]

Prognosis Prognosis appears to be variable and dependent on the severity of clinical signs. Mildly affected animals with congenital myotonia may undergo some amelioration of clinical signs with increasing age over a period of months to years. The reason(s) for this regression of signs is unknown. Other, more severely affected horses, particularly those with dystrophic myotonia, may have progression of signs, including atrophy and fibrosis or pseudohypertrophy to the point at which the animal is no longer able to move without great pain and difficulty (Fig. 42-5). Euthanasia of such animals is often warranted. Although conclusive evidence regarding the genetic basis of dystrophic myotonia in horses is still not available, owners of affected horses should be cautioned as to the possibility of this disease being heritable.



FIG. 42-5 Marked progressive atrophy of the epaxial and gluteal muscles of a horse with myotonic dystrophy.

Hyperkalemic Periodic Paralysis

Sharon Jane Spier

Equine hyperkalemic periodic paralysis (HYPP) is caused by an inherited defect in the skeletal muscle sodium channel.[28,51-54] This myopathy manifests as abnormal skeletal muscle membrane excitability leading to episodes of myotonia, or sustained muscle contraction, and paralysis. In humans, numerous muscle membrane channel defects (so-called channelopathies) have been characterized, and the molecular basis for disease is well described.[39] Other reported disorders with suspected membrane defects in horses include myotonic dystrophy and congenital myotonia.[29,41] Hyperkalemic periodic paralysis was the first equine disease attributed to a specific genetic mutation and detectable through DNA technology.[53]

Hyperkalemic periodic paralysis is an autosomal dominant trait affecting Quarter Horses, American Paint Horses, Appaloosas, and Quarter Horse crossbred animals worldwide. A "syndrome" in related horses was first recognized in the 1980s by breeders and veterinarians and first reported to be similar to HYPP in humans by Cox at the American Association of Equine Practitioners convention in 1985.[54] In December 2002, this genetic disease was publicly linked to a popular Quarter Horse sire named Impressive. This prolific sire, born in 1969, has more than 500,000 offspring registered with the AQHA (AQHA registrar, personal communication, 2012), and these offspring dominate the halter horse industry. Current estimates indicate that 1.5% of Quarter Horses and 4.5% of Paints are affected.[55] Notably, however, 58% of halter horses have the HYPP mutation.[55] Unfortunately, the gene frequency has not decreased in the past 20 years since genetic testing has been available to breeders, and controversy continues among horse breeders whose stock carry this gene (statistics from UCD Veterinary Genetics Laboratory HYPP Testing, 2006). Affected horses appear to have been preferentially selected as breeding stock due to their pronounced muscle development, and there is evidence of selection of HYPP-affected horses as superior halter horses by show judges.[56] In 1996, AQHA officially recognized HYPP as a genetic defect or undesirable trait. To increase public awareness of this genetic defect, mandatory testing for HYPP with results designated on the Registration Certificate began for foals descending from Impressive born after January 1, 1998. In response to requests from the membership, the AQHA Stud Book and Registration Committee ruled that foals born in 2007 and later testing homozygous affected for HYPP (H/H) are not eligible for registration. Breeders opposed to restrictions argue that the disease can be controlled through diet and medication and that these horses are highly successful in the show ring.[57]

Clinical Signs Clinical signs among horses carrying the same mutation range from asymptomatic to daily muscle fasciculations and weakness. In the majority of horses, intermittent clinical signs begin by 2 to 3 years of age with no apparent abnormalities between episodes.[28,52] Ingestion of diets high in potassium (>1.1%), such as those containing alfalfa hay, molasses, electrolyte supplements, and kelp-based supplements or sudden dietary changes commonly trigger episodes.[58] Fasting, anesthesia or heavy sedation, trailer rides, and

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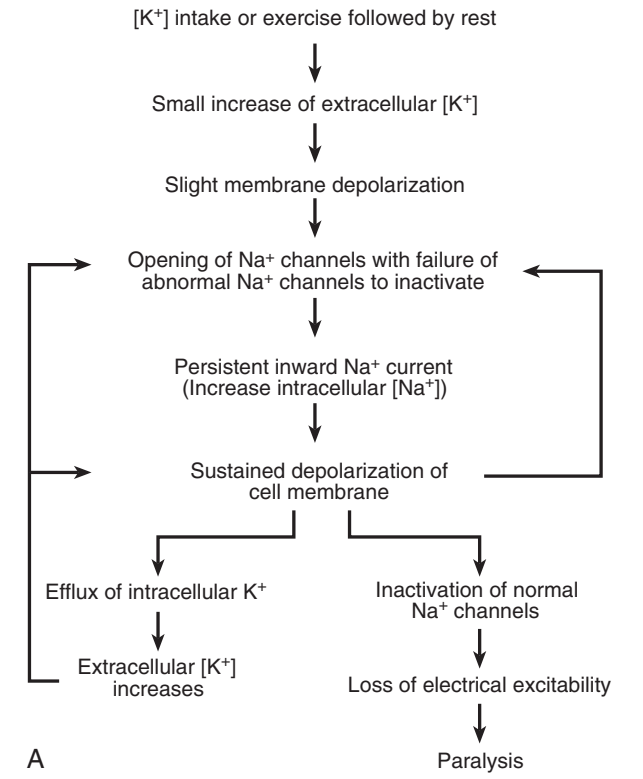


FIG. 42-6 **A,** Explanation for paralytic attacks in horses with hyperkalemic periodic paralysis (HYPP). **B,** A horse suffering from an episode of HYPP.

stress may also precipitate clinical signs; however, the onset of signs is often unpredictable without a definable cause. Other possible precipitating factors that have been noted in humans and horses are exposure to cold, fasting, pregnancy, and concurrent disease and rest following exercise. Exercise per se does not appear to stimulate clinical signs, and serum CK shows no change or only modest increases during episodic fasciculations and weakness.

In most cases, clinical episodes begin with a brief period of myotonia, with some horses showing prolapse of the third eyelid. Sweating and muscular fasciculations are observed commonly in the flanks, neck, and shoulders. The muscle fasciculations become more generalized as additional muscle groups are involved. Stimulation and attempts to move may exacerbate muscular tremors. Some horses may develop severe muscle cramping. Muscular weakness during episodes is a common characteristic of HYPP. Horses remain standing during mild attacks. In more severe attacks, clinical signs may progress to apparent weakness with swaying, staggering, dog sitting, or recumbency within a few minutes. Heart and respiratory rates may be elevated, and horses may show manifestations of stress (anxious appearance) yet remain relatively bright and alert during episodes. Affected horses usually respond to noise and painful stimuli during clinical manifestations of the disorder. Episodes last for variable periods, usually from 15 to 60 minutes. Several horses have died during acute episodes.[1] Respiratory distress occurs in some animals as a result of paralysis of upper respiratory muscles, and a tracheostomy may be necessary. In addition, young horses that are homozygous for the HYPP trait have been observed to manifest a respiratory stridor and periodically may develop obstruction of the upper respiratory tract. Horses homozygous for HYPP may present for dysphagia or respiratory distress, and endoscopic findings include pharyngeal collapse and edema, laryngopalatal dislocation, and laryngeal paralysis.[59] After the episode subsides, horses regain their feet and appear normal with no apparent or minimal gait abnormalities. Although HYPP horses appear normal between attacks, electromyographic examination of affected horses reveals abnormal fibrillation potentials, complex repetitive discharges with occasional myotonic potentials, and trains of doublets between episodes.[28,60]

Etiology

HYPP results from a point mutation that results in a phenylalanine/leucine substitution in a key part of the voltage-dependent skeletal muscle sodium channel alpha subunit.[53] In horses with HYPP, the resting membrane potential is closer to firing than in normal horses.[61] Sodium channels are normally briefly activated during the initial phase of the muscle action potential. The HYPP mutation results in a failure of a subpopulation of sodium channels to inactivate when serum potassium concentrations are increased. As a result, an excessive inward flux of sodium and outward flux of potassium ensues, resulting in persistent depolarization of muscle cells and temporary weakness (Fig. 42-6, *A* and *B*).

Diagnosis

Descent from the stallion Impressive on the sire or dam's side in a horse with episodic muscle tremors, weakness, or collapse is strongly suggestive of HYPP. Quarter Horse foals born after 1998 that are offspring of an affected parent have a statement recommending DNA testing for HYPP on the Certificate of Registration. In most cases, hyperkalemia (6 to 9 mEq/L), hemoconcentration, and mild hyponatremia occur during clinical manifestations of the disease with normal acid-base balance.[28] Serum potassium concentration returns to normal following the abatement of clinical signs. Some affected horses may have normal serum potassium concentrations during minor episodes of muscle fasciculations.[52] Differentials for hyperkalemia include delay before sample centrifugation, hemolysis, acidosis, renal failure, severe rhabdomyolysis, and high-intensity exercise.

Because veterinarians may not be present during acute episodes, the definitive test for identifying HYPP is the demonstration of the base-pair sequence substitution in the abnormal segment of the DNA encoding for the alpha subunit of the sodium channel.[53] Submission of mane or tail hair should be made to a licensed laboratory such as the Veterinary Genetics Laboratory at the University of California, Davis (www.vgl.ucdavis.edu).

Treatment

Mild exercise can sometimes abort an episode in mild cases or if horses are just beginning to exhibit clinical signs. Feeding grain or corn syrup to stimulate insulin-mediated movement of potassium across cell membranes may also be helpful. Other treatment options, which may abort an episode, include intramuscular (IM) administration of epinephrine (3 mL of 1:1000/500 kg) and administration of acetazolamide (3 mg/kg orally [PO], every 8 to 12 hours). Many horses experience spontaneous recovery from episodes of paralysis and appear normal by the time a veterinarian arrives.

In severe cases, administration of calcium gluconate (0.2 to 0.4 mL/kg of a 23% solution diluted in 1 L of 5% dextrose) will often provide immediate improvement. An increase in extracellular calcium concentration raises the muscle membrane threshold potential, which decreases membrane hyperexcitability. To reduce the serum potassium, intravenous (IV) dextrose (6 mL/kg of a 5% solution) alone or combined with sodium bicarbonate (1 to

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2 mEq/kg) can be used to enhance intracellular movement of potassium. With severe respiratory obstruction, a tracheostomy may be necessary.

Control Decreasing dietary potassium and increasing renal losses of potassium are the primary steps taken to prevent HYPP episodes. Feedstuffs to avoid include high-potassium feeds such as alfalfa hay, orchard grass hay, brome hay, soybean meal, sugar molasses, and beet molasses. Optimally, later cuts of Timothy or bermudagrass hay and grains such as oats, corn, wheat and barley, and beet pulp should be fed in small meals several times a day (Table 42-1). Regular exercise and/or frequent access to a large paddock or yard are also beneficial. Pasture works well for horses with HYPP because the high water content of pasture grass makes it unlikely that horses will consume large amounts of potassium in a short period of time. Ideally, horses with recurrent episodes of HYPP should be fed a balanced diet containing between 0.6% and 1.1% to 1.5% total potassium concentration and meals containing less than 33 g of potassium.[58,62,63] Horses will adapt to diets higher in potassium over a period of 2 weeks and will experience fewer fluctuations in potassium in blood with subsequent decreased frequency of clinical signs.[62] Because there is a wide variation in potassium concentration of forages depending on maturity and soils, it is advisable to have feeds analyzed for potassium concentrations and other nutrient requirements.[63] The tables below contain examples of feeds containing varying concentrations of potassium. Supplement with vitamin E, selenium, salt and balanced minerals where indicated to meet nutritional requirements. Commercially available complete feeds with a guaranteed K^+ content may be more convenient for some HYPP horses, especially for owners with few horses.

For horses with recurrent episodes of muscle fasciculations even with dietary alterations, acetazolamide (2 to 3 mg/kg orally, every 8 to 12 hours) or hydrochlorothiazide (0.5 to 1 mg/kg orally, every 12 hours) may be helpful. These agents exert their effects through different mechanisms; however, both cause increased renal potassium excretion. In addition, acetazolamide stabilizes blood glucose and potassium by stimulating insulin secretion. Breed registries and other associations may have restrictions on the use of these drugs during competitions as diuretics may mask prohibited substances.

TABLE 42-1

Examples of Feed Containing High, Medium, or Low Concentrations of Potassium (K^+)*

High-Potassium Feed	K^+ (%)	g K^+/lb Feed
Electrolyte supplements	30	136
Molasses	6	27
Kelp supplements	>4	>18
Alfalfa hay (90% DM)	1.4-2.4	6.4-10.9
Canary grass hay	2.6	2.6
Orchard grass hay	2.4-2.6	10.9-11.8
Soybean meal	2	9.1
Medium-Potassium Feed	**K^+ (%)**	**g K^+/lb Feed**
Fescue hay	1.7-2.1	7.7-9.5
Rice bran	1.8	8.1
Timothy hay	1.4-2.1	6.4-9.5
Coastal Bermuda hay	1.2-1.9	5.5-8.2
Kentucky bluegrass hay	1.4	6.4
Oat hay	1.4	6.4
Low-Potassium Feed	**K^+ (%)**	**g K^+/lb Feed**
Pure fats and oils	0	0
Beet pulp	0.2-0.3	0.9-1.4
Corn, oats, or barley	0.3-0.5	1.4-2.3
Pasture grass (23% DM)	0.3-0.8	1.4-3.6
Wheat	0.4	1.8
Wheat bran	1.2	5.45
Soybean hulls	1.2	5.45

*To decrease the frequency of episodes, avoid high-potassium feed; select feed that contains medium to low K^+. Feeding a balanced ration containing less than 1.5% K^+ and meals less than 33 g K^+ decreases fluctuations of blood K^+ lowering the frequency of HYPP symptoms.[12,15,16]

DM, Dry matter.

Prognosis In most cases HYPP is a manageable disorder, although recurrent bouts may occur and severe episodes can be fatal. Owners of affected horses should be strongly discouraged from breeding these animals for the long-term health of the Quarter Horse and other breeds. Because this is a dominant trait, breeding an affected horse to a normal horse results in a 50% chance of producing a foal with HYPP. All affected horses share the same mutation, regardless of whether or not owners have witnessed symptoms in their horses.[64] Affected horses are not suitable for young or inexperienced riders. Owners of affected horses should advise veterinarians of HYPP status before anesthesia or procedures requiring heavy sedation because these circumstances could precipitate an episode of paralysis.

Hypokalemic Myopathy in Dairy Cattle

Etiology Hypokalemic myopathy in dairy cattle occurs when serum potassium concentrations are below 2.5 mmol/L, producing severe signs of muscle weakness.[65-67] Ketosis, anorexia, and enhanced potassium excretion due to the administration of one or more doses of isoflupredone acetate to ketotic cows are common causes of hypokalemia. Isoflupredone acetate has both glucocorticoid and mineralocorticoid activity resulting in a decrease in mean plasma potassium concentration by 25% two days after one injection (20 mg) and 46% in cows 3 days after two injections.

Clinical Signs and Diagnosis Clinical signs of hypokalemic myopathy include severe weakness, recumbency, abnormal position of the head and neck, rumen hypomotility or atony, abnormal feces, anorexia, and tachycardia. Cardiac dysrhythmia is also common. Diagnosis is based on clinical signs combined with serum potassium of less than 2.5 mmol/L. Other common clinical chemistry abnormalities include ketosis, metabolic alkalosis, and elevated serum CK and AST activities. Muscle biopsies reveal a vacuolar myopathy.

Treatment Restoration of whole body potassium balance can be difficult, and serum potassium concentrations do not necessarily reflect muscle potassium concentrations. Recommended supplementation includes potassium chloride given intravenously (16 g/100 kg body weight) not to exceed a maximum infusion rate of 0.5 mEq/kg/h and orally (26 to 42 g/100 kg body weight) not to exceed 230 g potassium chloride orally twice daily. Early treatment should also be directed at resolving the primary cause of ketosis and anorexia, as well as providing supportive care. Survival has been reported at between 22% and 79%.

Muscle Cramping

Stephanie J. Valberg • Gary P. Carlson

Muscle cramps are a painful condition that arises from hyperactivity of motor units caused by repetitive firing of the peripheral and/or central nervous system. The origin of the cramp in most cases is believed to be the intramuscular portion of the motor nerve terminals.[22,68] Most muscle cramps are also accompanied by fasciculations in the same muscle. Muscle cramps can be induced by forceful contraction of a shortened muscle, by changes in the electrolyte composition of extracellular fluid, and by ear tick infestations in horses.[22,31] In contrast, muscle contractures are painful muscle spasms that

represent a state of muscle contracture unaccompanied by depolarization of the muscle membrane.[68] Muscle contractures occur with malignant hyperthermia and some forms of exertional myopathies and are invariably accompanied by markedly increased serum CK activity.

Dietary Electrolytes

Muscle stiffness, weakness, and occasional elevations in serum CK can occur when diets are deficient in sodium or potassium. These chronic deficiencies are rarely reflected in serum electrolyte concentration but may be detected by performing renal fractional excretions of electrolytes.[3] Sodium deficiency is particularly common in horses because forage and grain diets are low in sodium and chloride and high in potassium. Supplementation of the equine diet with salt is a necessity. Salt blocks may not be adequate in this regard, and loose salt (1 to 2 oz) added directly in the grain is often the best mechanism of supplementing horses with salt. Some horses may require higher dietary salt supplementation to maintain an adequate sodium balance. Balancing dietary electrolytes has been reported to decrease muscle cramping and serum CK activity in those horses with dietary deficiencies.[3]

Exhaustion in Endurance Horses

Muscle cramping in endurance horses occurs commonly during prolonged exercise in hot weather, particularly when the humidity is high.[69,70] Under such circumstances rectal temperatures reach as high as 41° C and horses may lose up to 15 L/h of fluids in the form of sweat that is rich in sodium, potassium, and chloride.[71,72]

Clinical Signs Affected horses demonstrate stiffness and cramping in the muscles of locomotion. Pain is a characteristic of the disorder, and affected muscle groups often undergo periodic spasms. In addition, exhausted horses are often dull, depressed, and clinically dehydrated with elevated heart and respiratory rates and persistently elevated body temperature. Common electrolyte abnormalities include a hypochloremic metabolic alkalosis with hypokalemia, hypomagnesemia, and low serum ionized calcium concentrations.[69,70,73] Synchronous diaphragmatic flutter may be seen in association with cramping.[69] Although many of the signs of muscular dysfunction are similar to those of exertional rhabdomyolysis, affected horses do not generally develop myoglobinuria.[69]

Etiology Factors contributing to cramping are dehydration, electrolyte abnormalities, and disturbances in thermoregulatory and local circulatory function. Whether this disorder is similar to heat cramps seen in human athletes is not known.

Diagnosis A variety of electrolyte abnormalities occur in affected animals.[69,73] Mild cases are distinguished by the presence of muscle cramps that subside with rest or light exercise in heat-stressed horses. In more severe cases clinical signs of dehydration and shock are often present. Horses with muscle cramping will not have marked elevations in serum CK or AST, nor will they exhibit myoglobinuria. Exhausted horses, however, may progress to develop rhabdomyolysis with marked electrolyte derangements. These horses require immediate treatment.

Treatment Under most circumstances the mild form of muscle cramping is self-limiting, and the signs abate with rest or light exercise. However, if evidence of other metabolic derangements exists, treatment for these disorders (e.g., plasma volume expansion with oral or intravenous isotonic polyionic fluids, cooling using water and fans) is frequently beneficial to the horse.[74] Because most horses with this condition are alkalotic, administration of solutions containing sodium bicarbonate is contraindicated. Dietary analysis should be performed to determine the extent of salt and electrolyte supplementation in affected horses. Daily direct addition of 2 oz of sodium chloride and 1 oz of potassium chloride to the feed is recommended for horses with recurrent cramping in addition to electrolyte supplementation before and after endurance rides.

Synchronous Diaphragmatic Flutter

Synchronous diaphragmatic flutter (SDF), also known as "thumps," usually occurs in horses suffering from derangements in fluid and electrolyte balance. Inciting causes include endurance exercise, hypocalcemia, hypoparathyroidism, digestive disturbances, and possibly the administration of medications. A characteristic clinical manifestation of the disease occurs when the diaphragm contracts in synchrony with atrial depolarization.[75-77]

Clinical Signs The classic sign of SDF is a contraction or twitch in the flank region (unilateral or bilateral) as the diaphragm contracts synchronously with the heart. In severe cases this twitch may produce an audible thumping sound. The metabolic derangements leading to SDF may also be clinically apparent in some cases. These may include signs of dehydration and volume depletion. Endurance horses suffering from SDF in association with the exhausted horse syndrome may demonstrate dehydration, inappropriate sweating responses, persistently elevated body temperature, depression, anorexia, and aperistalsis.[69,70] In some horses SDF may be a chronic, recurring problem.[75]

Etiology A variety of stimuli may result in SDF. These include prolonged exercise, particularly during hot weather; hypocalcemia resulting from lactation, transit, or stress; digestive tract dysfunction; following furosemide therapy; trauma; and primary hypoparathyroidism.[75,77] The most consistent metabolic derangement reported in horses with SDF is low serum ionized calcium concentrations usually associated with hypochloremic metabolic alkalosis.[75,76] Metabolic alkalosis may alter the ratio of free to bound calcium (increasing calcium binding to protein and decreasing ionized calcium), which possibly induces SDF.

SDF occurs in association with atrial depolarization in horses. It has been postulated that fluid, electrolyte, and acid-base derangements may disrupt the normal membrane potential of the phrenic nerve, which passes directly over the atrium, resulting in nerve discharges in response to atrial depolarization.[75,76,78]

Treatment In most cases SDF is a transient event, usually abating when the underlying cause resolves, either spontaneously or in response to treatment.[75] Most horses undergo rapid remission of signs when given calcium solutions intravenously as described later in the section Hypocalcemia in Horses. Although hypomagnesemia is often present with SDF, horses do not respond to magnesium supplementation unless calcium is administered concurrently. Response to therapy is also reflected by improved mental status, return of appetite, and gut motility.[75]

Control Electrolyte supplementation and some dietary manipulations may help reduce the incidence of SDF in some endurance horses suffering recurrent bouts. Provision of chloride, potassium, and sodium during prolonged exercise may help reduce fluid losses and the metabolic alkalosis that commonly accompanies this form of exercise and frequently occurs in association with SDF. Metabolic alkalosis decreases the amount of free calcium available. Supplementation of calcium and magnesium during endurance rides has been suggested to be helpful in horses prone to SDF.

Alternative approaches involve reduction of dietary calcium in horses prone to SDF for a few days before an endurance ride. It is postulated that this reduction in dietary calcium stimulates the endocrine homeostatic mechanisms and increases osteoclastic activity. In the short term the horse depends less on dietary calcium and is able to mobilize substantial amounts of calcium in response to the demands imposed by the exercise; calcium losses in sweat are overcome by the release of calcium from endogenous storage pools (bone).[75] Further, horses routinely fed alfalfa hay, which has a relatively high calcium concentration, may be more prone to the

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development of SDF. Limitation of this feedstuff may be indicated in chronically affected horses.

Hypocalcemia in Horses

Hypocalcemia is a relatively rare disorder in horses that has also been referred to as *lactation tetany, transport tetany, idiopathic hypocalcemia,* and *eclampsia.*

Clinical Signs Clinical signs are variable and include increased muscle tone; a stiff, stilted gait; rear limb ataxia, muscle fasciculations (especially temporal, masseter, and triceps muscles); trismus; dysphagia; salivation; anxiety; profuse sweating; tachycardia; elevated body temperature; cardiac dysrhythmias; SDF; convulsions; coma; and death.[79,80] Clinical signs may be remarkably similar to some of those seen with tetanus. This disorder may be progressive (in lactating mares in particular) over a 24- to 48-hour period, and some animals die. Clinical signs are related to the magnitude of the serum calcium concentration. Increased excitability is usually the only sign when values are below normal but above 8 mg/dL. Values of 5 to 8 mg/dL usually produce tetanic spasms and incoordination. Concentrations below 5 mg/dL usually result in recumbency and stupor.

Etiology Loss of calcium in milk, especially in mares who produce large amounts of milk, seems to predispose to this disorder.[79,80] Other factors such as heavily lactating mares grazing lush pastures, hard work or prolonged transport, and ingestion of blister beetles (cantharidin toxicosis) may precipitate attacks.

Diagnosis Clinical signs are often highly suggestive of hypocalcemia in affected horses. Historic aspects such as lactation, previous prolonged exercise, or transport may also direct the clinician to the suspected diagnosis.[79] Definitive diagnosis depends on laboratory demonstration of hypocalcemia, with total calcium concentrations as low as 4 to 6 mg/dL in some cases. In addition, a metabolic alkalosis, hypomagnesemia/hypermagnesemia, and hyperphosphatemia/hypophosphatemia have all been found in association with hypocalcemia in horses.[79] These alterations may need correction before a return to normal function is seen in some affected animals.

Treatment Although many mild cases recover without specific treatment, in others this disorder may be life-threatening. Therefore therapy is to be encouraged in most cases. Treatment involves the IV administration of calcium solutions such as 20% calcium borogluconate or those recommended for the treatment of parturient paresis in cattle.[79] Administration of these solutions at the rate of 250 to 500 mL/500 kg diluted 1:4 with saline or dextrose often results in full recovery, although in some cases it may take several days.[79] Relapses do occur. These preparations should be administered slowly in conjunction with close monitoring of the cardiovascular response. Dilution in saline or dextrose before infusion decreases the chance of cardiotoxicity. Normally there is a positive ionotropic effect in response to calcium administration.[81] However, alterations in rate or rhythm provide evidence to suspend the infusion. If no response to an initial infusion occurs, a second dose may be given 15 to 30 minutes later. Most cases respond to this form of therapy, although in some cases in which signs persist, repeated treatments may be necessary.

Ear Tick–Associated Muscle Cramping

Intermittent painful muscle cramps have been described in a small number of horses with severe *Otobius megnini* infestations.[31] Muscle cramping is not associated with exercise. These horses show intermittent signs of severe muscle cramping of pectoral, triceps, abdominal, or semitendinosus/semimembranosus muscles lasting from minutes to a few hours, with severe pain that often resembles colic. Horses may fall over when stimulated. Between muscle cramps horses appear to be normal. Percussion of triceps, pectoral, or semitendinosus muscles results in a typical myotonic cramp. Horses have elevated serum CK activities ranging from 4000 to 170,000 IU/L. Numerous ear ticks, *O. megnini,* can be identified in the external ear canal of affected horses. Without treatment for ear ticks, the spasms continue; however, local treatment of the ear ticks using pyrethrins and piperonal butoxide results in recovery within 12 to 36 hours. Acepromazine may be helpful to relieve painful cramping.

Nonexertional Rhabdomyolysis

Inflammatory Myopathies

Clostridial Myonecrosis

Steven M. Parish • Stephanie J. Valberg

Various species of clostridial organisms cause acute myonecrosis in many farm animal species. Infections are characterized by a rapid clinical course, fever, systemic toxemia, and high mortality.[82-84] Clostridial diseases are infectious but not contagious. Specific bacteria associated with clostridial myonecrosis include *Clostridium chauvoei (Clostridium welchii), Clostridium septicum, Clostridium sordelli,* and occasionally *Clostridium novyi* type B, *Clostridium perfringens* type A, and *Clostridium carnis.* Mixed infections involving several agents are common.[85] Synonyms for clostridial diseases include blackleg, malignant edema, false blackleg, gas gangrene, and gangrene. Although there may at times be distinct differences among the specific disease syndromes associated with the different clostridial agents, the pathophysiology of these diseases is similar enough to be covered under the general topic of clostridial myonecrosis.

Clinical Signs Commonly clostridial myonecrosis is rapidly progressive with the development of tremors, ataxia, dyspnea, recumbency, coma, and death within 12 to 24 hours. As such, many affected animals may be found prostrate or dead.[82,83] Mortality may approach 100%. Affected animals who are still alive are usually severely depressed, febrile (40° to 41° C, 104° to 106° F), tachypneic, anorexic, and lame. These signs are associated with a rapidly developing muscle infection and toxemia. There is usually only one primary site of infection in an affected animal. Any skeletal muscle group in the body can be involved, but most infections affect the limb or trunk muscles. Occasionally muscles such as those around the vulva, tongue, and diaphragm can be involved or the udder in a cow may be the primary site of sepsis. Areas around recent injections are common sites of myonecrosis in the horse.[84,86] Initially the skin over the area may be swollen, hot, and discolored; however, as the disease progresses, the skin over the area may become cool and insensitive with progressive sloughing. Crepitus may be detectable, indicating subcutaneous gas production. If a wound is present, malodorous serosanguineous fluid may discharge (Fig. 42-7). Aspiration of the swelling often reveals fluid with similar qualities.

Clostridial myonecrosis generally has characteristic pathologic lesions that are absent in most other conditions, making diagnosis relatively straightforward. Differential diagnoses may include other fulminant disease processes in which there is rapid debilitation or death of the animal.

Clinical Pathology Clinicopathologic data alone are seldom specific enough to confirm the presence of clostridial myonecrosis. Hematology and serum biochemical analyses usually reflect a generalized state of debilitation and toxemia (e.g., hemoconcentration and a stress/toxic leukogram may be present). Elevations in the activities of serum CK and serum AST usually occur; however, they often do not reflect the toxicity of clostridial myonecrosis. Aspirates from the affected tissues can yield diagnostic information. It is preferable to obtain tissue specimens for direct smear examination and fluorescent antibody testing, and for anaerobic bacterial culture from affected tissues.

Pathophysiology Clostridial agents are ubiquitous in the environment and can frequently be cultured from the feces, intestinal

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FIG. 42-7 Clostridial myositis in the left gluteal muscle after an injection of flunixine meglumine, which has progressed to involve the biceps femoris muscle. Fenestrations were created for débridement.

tract, and other internal organs of a variety of species.[82] Spore-forming characteristics allow these organisms to remain in the environment for long periods, but the exact mechanisms involved in the pathogenesis of clostridial myonecrosis are not fully known. Development of clostridial myonecrosis following an intramuscular injection or penetrating wound may be the result of direct spore deposition into the tissue in association with penetration. If suitable conditions prevail within the muscle, the spores undergo a conversion into the vegetative, toxin-producing form of the organism. In contrast, the pathogenesis of the disease is more difficult to explain when a wound does not exist. It is postulated that clostridial agents gain access to the body through the alimentary tract and are present in liver and muscle in the dormant spore form.[87] Subsequently, when local tissue is devitalized and conditions become appropriate for the spores to germinate, the rapid vegetative process ensues. Muscle trauma associated with injection, transporting, herding, and handling has often been incriminated as creating a suitable environment for the development of clostridial myonecrosis. The proliferation of clostridial agents in devitalized tissues is associated with the release of powerful exotoxins responsible for the local necrotizing myositis and systemic toxemia. Toxins are released by multiplying clostridia; the toxins vary, depending on the clostridial species involved. Necrotizing (lecithinase) and hemolyzing (hemolysin) toxins, as well as neuraminidase, appear to be of greatest importance. The toxins act locally and systemically to create widespread organ dysfunction. The toxins of *C. sordelli* are the most potent of all the clostridial species, and myonecrosis caused by this organism is fatal.

Epidemiology Clostridial agents are common in the environment, and susceptible animals are constantly exposed to them. Areas where previous death losses from clostridial disease have occurred may have a higher incidence or risk of disease because of increased environmental contamination. In cattle clostridial myonecrosis is generally a disease of animals between 4 and 24 months of age. However, *C. sordelli* is a more common problem in older feedlot cattle in which excessive muscle bruising may occur. Younger animals are probably protected by colostral immunity and older animals by some degree of acquired immunity. Animals on high planes of nutrition and in excellent body condition are more likely to develop the disease. Infections with *C. chauvoei* occur most commonly during the warmer seasons, with the highest incidence varying from the spring to fall, depending on when calves reach the most susceptible age group. *C. septicum, C. novyi,* and *C. perfringens* type A infections can occur at any time and are usually associated with skin wounds such as injection sites, puncture, and castration wounds. The umbilicus may be a site of invasion. Infections in the genital area can occur, usually in association with a recent dystocia.

In sheep and goats, clostridial myonecrosis is most frequently associated with wounds such as those occurring after shearing, docking, and unsanitary surgical procedures. Sheep dipped for parasites after shearing may have an increased risk if the dip becomes contaminated with clostridial spores.

Most reports of clostridial myonecrosis in horses suggest an association with puncture wounds and intramuscular injection sites.[84,86] Intramuscular administration of irritating drugs (including antihistamines, anthelmintics, phenylbutazone) may enhance the susceptibility to clostridial myonecrosis. Horses often present with or have a history of another complaint such as colic, exertional myopathy, or laminitis for which they have received injections of drugs in the preceding 48 hours.[88] Previously administered drugs (e.g., phenylbutazone) may mask the fever associated with clostridial myonecrosis, potentially confusing the diagnosis.

Necropsy Findings Swelling and autolysis are rapid in animals that have died from clostridial myonecrosis. Bloodstained fluid is often observed discharging from body orifices. Extreme swelling and crepitus may be noted over the affected body area. When acting alone, each of the clostridial agents associated with clostridial myonecrosis produces somewhat different postmortem lesions. However, it is unwise to assume that in clostridial myonecrosis only a single clostridial agent was involved, because mixed infections frequently occur.

C. chauvoei infection is characterized by engorgement of the subcutis and adjacent tissues with bloodstained fluids and gas bubbles. Cut tissue from the affected area reveals moist, dark-colored muscle in the periphery of the lesion, with lighter-colored, drier muscle with gas bubbles separating the separate bundles of muscle toward the center. Other changes include severe degeneration of parenchymatous tissues caused by the systemic toxemia. The carcass usually has a foul odor similar to that of rancid butter. This odor is a characteristic of most cases of clostridial myonecrosis. The lungs are often congested with edema, and hemorrhage and a fibrinohemorrhagic pleuritis are common. The heart may be friable and show evidence of endocardial hemorrhages, particularly on the right side. The spleen may be normal or enlarged and friable. The liver is usually pale and friable and may be autolytic and porous. Lesions are similar in sheep and cattle, except that there is usually less gas and the muscles are not as dry in affected sheep.

Similar necropsy findings are found with myonecrosis caused by *C. septicum* and *C. novyi* type B. *C. septicum* and *C. perfringens* generally occur as part of mixed wound infections in which abundant malodorous, serosanguineous fluid is found at the wound site. *C. perfringens* is common in horses.

Myonecrosis resulting from *C. sordelli* is most often associated with lesions of the neck or brisket area of cattle. Death is frequently so rapid that subcutaneous gas accumulation is rare. In addition to local myonecrosis, these animals often have massive subendocardial hemorrhages in the left ventricle of the heart and hemorrhage in the trachea, bronchi, and thymus. Extensive perirenal edema and

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hemorrhagic renal calyces and severe congestion of the lungs are common findings.

Treatment Although clostridial myonecrosis is often fatal, aggressive specific therapy combined with supportive care may be successful in individual cases. A presumptive diagnosis of clostridial disease on the basis of history and clinical signs is usually made before obtaining the results of culture and laboratory determinations such as fluorescent antibody tests. In horses, clostridial myonecrosis resulting from infections with *C. perfringens* seems to be most amenable to treatment and has the best prognosis for survival, although extensive skin sloughing over the affected area is common.[84] Antibiotic therapy, aggressive surgical débridement including fasciotomy, and supportive care are the hallmarks of successful treatment.[84] With most clostridial infections penicillin is the drug of choice. In horses, penicillin is used at a dosage of 44,000 U/kg IV every 2 to 4 hours until the animal is stable (1 to 5 days). The IV dose is then reduced to four times a day or is replaced by oral metronidazole (15 mg/kg three or four times daily). In ruminants, similar intravenous or intramuscular drug therapy is indicated. In all cases, prolonged antimicrobial therapy may be necessary.

Surgical intervention at the affected site by means of débridement or fenestration in an attempt to reduce tissue swelling, aerate the tissues, and remove necrotic tissue is considered imperative for survival in horses (see Fig. 42-7). Incisions are made through the skin and into the affected muscle to establish adequate drainage and hopefully alter the anaerobic conditions. Sufficient fenestrations should be made to establish drainage and aeration over the entire affected area.

Use of specific antitoxins is recommended when possible. However, these are often not available or not used for immediate therapy because the exact species of *Clostridium* causing the myonecrosis is not known. Cost considerations may also preclude their use. Supportive fluid therapy and use of analgesics and antiinflammatory agents for control of pain and swelling are recommended. Short-acting corticosteroids such as dexamethasone, prednisolone, or hydrocortisone may be used for initial therapy of systemic and toxic shock, but continued use is contraindicated in the face of overwhelming sepsis. If required, specific therapy should also be directed toward any other underlying problems.

Prognosis The prognosis for life in all cases of clostridial myonecrosis is guarded to poor. The disease process is often rapidly fulminant, making treatment unrewarding. However, some animals have survived because of early diagnosis, aggressive therapy, and long-term supportive care. This is particularly true in cases involving *C. perfringens* in horses. The owner should be aware from the start of treatment that extensive skin sloughing may involve most of a limb and may force euthanasia to become a consideration at a later stage.

Prevention Protection against clostridial myonecrosis is based on immunization procedures. Although clostridial agents are ubiquitous in the environment and frequently appear in the body of susceptible animals, rarely does adequate natural protection occur, although some colostral and acquired immunity may at times occur. Infection in unprotected animals usually follows a rapid, degenerative clinical course and terminates before the animal can generate an appropriate protective immune response. At present, only ruminants are commonly vaccinated against the agents responsible for clostridial myonecrosis. Vaccines used include multivalent bacterin toxoids containing antigens against two or more clostridial species, including *C. chauvoei, C. septicum, C. novyi, C. sordelli,* and *C. perfringens.* A rational program for protection usually involves vaccinating at an early age to establish immunity. Vaccination age is partly determined by other management factors, including when calves are handled for branding and castration, but 4 to 6 months of age is the usual time of initial vaccination. In areas of heavy exposure it may be necessary to vaccinate at 3 months and again at 4 months. In all clostridial species except *C. chauvoei,* two doses of vaccine are necessary to establish good protection. The duration of immunity is not long, and booster vaccinations should be administered every 6 to 8 months if protection is to be maintained. In many herds it is only necessary to vaccinate animals younger than 3 years of age (i.e., those animals that are at greatest risk), but in some high-risk herds it is necessary to maintain a vaccination program for the life of the animal.

Animals that die of clostridial diseases should be disposed of by deep burial, burning, or removal from the premises to avoid further contamination of the environment.

Rhabdomyolysis Associated with *Streptococcus equi*

Stephanie J. Valberg

Acute Rhabdomyolysis

Severe acute generalized rhabdomyolysis has been reported to occur in Quarter Horses younger than 7 years of age.[89,90] Affected horses have evidence of submandibular lymphadenopathy and/or guttural pouch empyema due to *S. equi.* Horses develop a stiff gait, which progresses rapidly to markedly firm, swollen, painful epaxial and gluteal muscles. The majority of reported cases became recumbent and unable to rise. They developed unrelenting pain necessitating euthanasia within 24 to 48 hours of hospitalization (Fig. 42-8). Hematologic abnormalities include mature neutrophilia, hyperfibrinogenemia, and marked elevations in CK (115,000 to 587,000 U/L) and AST activities (600 to 14,500 U/L). Titers to the M protein of *S. equi* are low in affected horses, unless horses are recently vaccinated for strangles. Titers to another protein called myosin binding protein have been high in a small number of horses that were tested.[89]

At postmortem examination, large pale areas of necrotic muscle are evident in hindlimb and lumbar muscles. The histopathologic lesions are characterized by severe acute myonecrosis with a degree of macrophage infiltration. Sublumbar muscles often show the most severe and chronic necrosis as indicated by greater macrophage infiltration of myofibers.

Two etiologies have been proposed. The first possibility is a toxic shock–like reaction arising from profound nonspecific T cell stimulation by streptococcal superantigens with the release of high levels of inflammatory cytokines. An alternative explanation for rhabdomyolysis may be a bacteremia with local multiplication and production of exotoxins or proteases within skeletal muscle. *S. equi* virulence factors that may account for muscle necrosis include an unidentified cytotoxic protein, several proteases, streptokinase, and streptolysin S.[91] Although *S. equi* has not been cultured in skeletal muscle from horses with rhabdomyolysis, *S. equi* bacteria have been identified in



FIG. 42-8 A horse in severe pain unable to rise due to acute rhabdomyolysis concurrent with guttural pouch empyema from *Streptococcus equi.*

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affected muscle using immunofluorescent stains for both Lancefield group C carbohydrate and *S. equi* M protein.[89] There is currently no evidence that the *S. equi* involved is an atypical genetic strain of *S. equi*.[92]

A high mortality rate has been reported in horses receiving intravenous penicillin therapy once clinical signs of strangles and myopathy were well established. It is possible that early recognition of the signs of muscle stiffness in horses with *S. equi* infections and prompt aggressive treatment may be required for a successful outcome. Although streptococcal species are exquisitely susceptible to β-lactam antibiotics, a mortality rate of 85% has been reported in human group A streptococcal myositis despite penicillin treatment.[93] An antimicrobial that inhibits protein synthesis, such as rifampin, combined with intravenous penicillin, might enhance survival rates in horses with *S. equi* rhabdomyolysis. In addition, flushing infected guttural pouches and draining abscessed lymph nodes will diminish the bacterial load. Nonsteroidal antiinflammatories and possibly high doses of short-acting corticosteroids may assist in diminishing the inflammatory response. Control of unrelenting pain is a major challenge in horses with severe rhabdomyolysis. Constant rate infusion of lidocaine, detomidine, or ketamine may provide better anxiety and pain relief than periodic injections of tranquilizers. Horses should be placed in a deeply bedded stall and moved from side to side every 4 hours if they are unable to rise. Some horses may benefit from a sling if they will bear weight on their hindlimbs when assisted to stand.

Infarctive Purpura Hemorrhagica

Stephanie J. Valberg

Infarctive purpura hemorrhagica (IPH) is a severe form of purpura with a high fatality rate. In one study prevalence of IPH was 3/53 cases of purpura.[94] Exposure to *S. equi* within 3 weeks of presentation, vaccination for *S. equi,* or a concurrent *Salmonella infantum* infection are reported as inciting causes. Titers for serum ELISA M protein may be markedly elevated.[95] The primary presenting complaint is often painful lameness with limb swelling, muscle stiffness, and/or colic. Careful physical examination reveals classic signs of PH such as petechia, oral infarctions resembling ulcers, and moderate well-demarcated limb edema; however, in addition, horses with IPH will have focal firm intramuscular swellings (Fig. 42-9). Horses with evidence of colic may have markedly decreased borborygmi and hemorrhagic gastric reflux.

Hematologic abnormalities include a leukocytosis characterized by a neutrophilia with a left shift and toxic change, hyperproteinemia, hypoalbuminemia, and marked elevations in CK (47,000 to 280,000 U/L) and AST (960 to 7000 U/L) activities.[90,95] Peritoneal fluid obtained by abdominocentesis may be normal or may have an increased total protein, nucleated, and red blood cell counts if gastrointestinal infarction is present. Ultrasonographic examination of swollen muscle reveals focal hypoechoic lesions within muscle tissue. Biopsies of abnormal muscle show diffuse acute coagulative necrosis, whereas samples from palpably normal muscle tissue show no pathologic abnormalities.

Postmortem findings of horses with IPH include infarction of the skeletal musculature (Fig. 42-10), skin, gastrointestinal tract, pancreas, and lungs, as well as *S. equi* abscessation of a lymph node. Definitive histopathologic findings include leukocytoclastic vasculitis and acute coagulative necrosis resembling infarction in numerous tissues.[95] IPH resembles Henoch-Schönlein purpura in humans, which is characterized by infarctive vasculitis of the skin, kidneys, and gastrointestinal tract due to IgA immune complex deposition. Immune complexes are present in the sera of horses with PH that appear to be primarily composed of IgM or IgA and streptococcal M protein.[96] Deposition of complement near immune complexes in vessel walls may result in cell membrane destruction, cell death, and vascular occlusion. The distinctive feature of infarctive PH in horses is the extensive infarction of skeletal muscle and consequently marked elevation in serum CK and AST activity.



FIG. 42-9 Marked swelling of the right adductor muscles of the thigh due to infarctive purpura hemorrhagica.

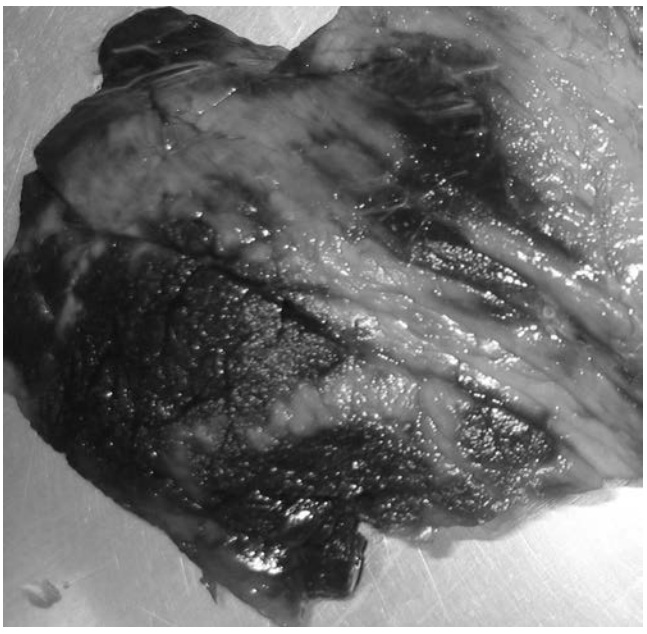


FIG. 42-10 Numerous infarctions of skeletal muscle due to infarctive purpura hemorrhagica. *(Photo courtesy Dr. Beth Davis.)*

Early recognition of signs and aggressive antibiotic and corticosteroid treatment are essential to combat the high fatality rate with IHP. Treatment of Henoch-Schönlein purpura in humans, including cases with intestinal infarctions, involves high-dose intravenous pulse therapy with methylprednisolone followed by oral corticosteroids plus immunosuppressive agents such as cyclophosphamide and

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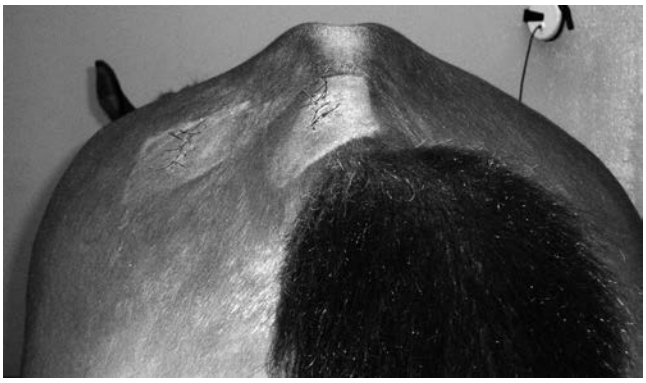


FIG. 42-11 Symmetric atrophy of the gluteal muscles with immune-mediated myositis. *(Photo courtesy Dr. Beth Davis.)*

azathioprine. One horse with infarctive PH was successfully treated with penicillin, nonsteroidal antiinflammatories, and 3 weeks of dexamethasone (0.1 to 0.07 mg/kg IM or IV) followed by a 10-week tapering course of oral prednisolone (2 mg/kg initially).[95]

Immune-Mediated Polymyositis

Stephanie J. Valberg

Immune-mediated polymyositis (IMM) has recently been reported in horses.[26,97,98] The majority of horses are of Quarter Horse bloodlines and are either 8 years of age or younger or 16 years of age or older. In approximately one third of horses with IMM, a triggering factor appears to have been exposure to *S. equi* or a respiratory disease. The most prominent clinical sign of IMM in Quarter Horses is rapid onset of muscle atrophy, particularly affecting the back and croup muscles (Fig. 42-11), accompanied by stiffness and malaise. Atrophy may progress to involve 50% of a horse's muscle mass within a week and may lead to generalized weakness. Focal symmetric atrophy of cervical muscles has been reported in a pony with IMM.

Hematologic abnormalities are relatively minor in affected horses and are usually restricted to mild to moderate elevations in serum CK and AST activity. However, in some cases serum muscle enzyme activities are normal. Muscle biopsy of epaxial and gluteal muscles show lymphocyte vasculitis, angular atrophy, lymphocyte myofiber infiltration, fiber necrosis with macrophage infiltration, and regeneration. Biopsies of semitendinosus or membranous muscles may show some evidence of atrophy and vasculitis, but significant inflammatory infiltrates may be absent in these tissues. The extent of the inflammatory infiltrates in epaxial muscles is such that a diagnosis can often be established from several formalin fixed Trucut samples.

The lymphocytic infiltrate seen in muscle samples from horses with IMM contains a high CD4:CD8 ratio with no evidence of IgG binding to myofibers.[26] The reason why specific muscle groups are affected in horses with immune-mediated polymyositis is unclear.

Horses with concurrent evidence of streptococcal infection should be treated with antibiotics. It is likely prudent to avoid intramuscular injections. Administration of corticosteroids appears to immediately improve signs of malaise and inappetence and prevented further progression of muscle atrophy. Recommended dosages are dexamethasone (0.05 mg/kg IM or IV) for 3 days, followed by prednisolone (1 mg/kg PO for 7 to 10 days) tapered by 100 mg/week over 1 month. Serum CK activity often normalizes after 7 to 10 days. Muscle mass will usually gradually recover over 2 to 3 months. Horses that are not treated with corticosteroids may develop extensive muscle atrophy, but in many cases muscle mass will gradually recover. Recurrence of atrophy in susceptible horses is common and may require reintroduction of corticosteroid therapy. Some horses develop focal residual muscle atrophy.

Virus-Associated Myopathy

Steven M. Parish

Necrosis of skeletal and cardiac muscle occurs frequently in association with some viral diseases. In most situations, viral-induced muscle damage represents a component of systemic multiple organ system involvement. For example, myocarditis occurs in association with foot-and-mouth disease, equine influenza, and equine infectious anemia. Other diseases causing myocarditis or skeletal muscle manifestations include bovine ephemeral fever, malignant catarrhal fever, bovine viral diarrhea, and bluetongue. Equine influenza A2 and equine herpes virus 1 have been reported to induce primary muscle stiffness and clinical signs resembling those seen in horses with rhabdomyolysis.[99,100] Details concerning specific clinical manifestations can be found in other sections of this text.

Sarcocystosis

Steven M. Parish • Stephanie J. Valberg

Cysts of the sporozoan parasite *Sarcocystis* are commonly seen in routine histologic sections of the heart, esophageal, and skeletal muscle of cattle, sheep, goats, and horses. More than 90% of horses older than 8 years of age have sarcocysts in their esophageal muscles. Cysts may pose no problem, but with heavy infestations multisystemic dysfunction occurs. Experimentally induced acute disease is characterized by fever, mild anemia, chronic myositis, and muscle wasting.

Epidemiology The life cycle of the parasite involves two hosts, carnivores as the definitive host and cattle or horses as the intermediate host. Three species of sarcocysts, *Sarcocystis cruzi, Sarcocystis hirsuta,* and *Sarcocystis hominis,* are known to infect cattle; Canidae, Felidae, and primates are the definitive hosts for these species. Three sarcocyst species have been described in horse muscle: *Sarcocystis bertrami, Sarcocystis equicanis,* and *Sarcocystis fayeri.* Dogs have been identified as the definitive host of these equine sarcocyst species. In sheep and goats, *Sarcocystis ovicanis* and *Sarcocystis capracanis* have been described, with Canidae as the definitive host. The most common mechanism for natural infection in cattle is by ingestion of feeds contaminated with infected carnivore feces. Feedlot workers using feed bunks as toilets may be a source of exposure for feedlot cattle.

Clinical Signs Although low-level natural infection is common in cattle, when administered experimentally, a dose of 200,000 sporocysts of *S. cruzi* is necessary to cause severe clinical disease.[101] Within 4 weeks the animal develops fever (39.4°C, 103°F), anorexia, salivation, weight loss, weakness, muscle fasciculations, severe depression, and sometimes death. Fever is the earliest sign and is biphasic relative to two periods of parasitemia, one occurring at 15 to 19 days and another at 25 to 42 days after inoculation. During the second febrile episode, affected calves frequently develop other clinical signs, particularly anemia. Extravascular hemolysis occurs, and hemorrhage into many tissues is common. The mechanisms involved in the hemolytic and hemorrhagic phases are likely to involve immune mechanisms. Mortality is greatest during this phase of the disease. Laboratory analysis may reveal elevations in serum urea nitrogen and bilirubin concentrations, sorbitol dehydrogenase, LDH, CK, and AST activities. If animals survive, these laboratory values usually return to normal in about 2 weeks. Animals surviving this phase commonly continue to be inappetent and have decreased weight gains, muscle atrophy, and hair loss on the neck, rump, and tail. These changes are mediated by alterations in a variety of pathways, the net result being a partitioning away of nutrients that are used for growth.[102] The anemia is ameliorated by a regenerative process, with normal hematologic values obtained in 1 to 2 months after clinical recovery. Similar clinical findings are seen in sheep and

goats. Abortion is common. A syndrome similar to that described in cattle has been reported in two horses with malaise, fever, and muscle atrophy.[103,104]

Diagnosis Diagnosis of sarcocystosis requires history, clinical signs, laboratory and serologic evaluation, and the demonstration of immature cysts in muscle biopsies. It is important to differentiate between the muscle cysts caused by *Sarcocystis* and those produced by toxoplasmosis because toxoplasmosis does not cause clinical disease in cattle.

Treatment and Control Specific treatment is only effective in the early stages of sarcocystosis in food animals. Experimental therapy with amprolium or the ionophore antibiotics before the second stage of parasitemia frequently prevents development of clinical sarcocystosis in cattle.[105] Successful treatment of one horse with sarcocystosis using phenylbutazone, trimethoprim-sulfa, and pyremethamine is reported.[104] Control involves preventing gross contamination of cattle and equine feeds with carnivore feces. The common use of ionophore antibiotics (e.g., growth promotants and coccidiostats) in cattle is also likely to help reduce the incidence of sarcocystosis.

Nutritional and Toxic Rhabdomyolysis

Nutritional Myodegeneration

John Maas • Stephanie J. Valberg

Definition and Etiology Nutritional myodegeneration (NMD; white muscle disease, stiff lamb disease, nutritional muscular dystrophy) is an acute myodegenerative disease of cardiac and skeletal muscle caused by a dietary deficiency of selenium or vitamin E.[106-109] This syndrome occurs in most farm animal species but is most commonly found in young, rapidly growing calves, lambs, kids, and foals, particularly those born to dams that consumed selenium-deficient diets during gestation. An in utero form of NMD may occur with affected animals showing clinical signs soon after birth. The disease has also been reported in yearling and adult cattle and occasionally adult horses. Selenium and vitamin E appear to be synergistic in preventing NMD. However, on the basis of prophylaxis and response to treatment, selenium deficiency appears to be more important.

Clinical Signs There are two distinct syndromes of NMD: a cardiac form and a skeletal form. The cardiac form is associated with acute signs of myocardial decompensation, whereas the skeletal form results in stiffness, weakness, and difficulty in ambulation.

The cardiac form of NMD usually has a sudden onset of depression, weakness, respiratory distress, rapid irregular heartbeat, severe debilitation, and often death within 24 hours. Occasionally an animal responds to therapy, but it often fails to thrive because of residual myocardial damage. Animals with predominantly cardiac signs can also manifest mild skeletal muscle problems associated with NMD. Lesions are present in the heart, diaphragm, and intercostal muscles.

The skeletal form of NMD frequently has a slower onset characterized by muscular weakness, stiffness, trembling, and recumbency with notably hard and painful muscles on palpation. Commonly affected muscle groups may include the gastrocnemius, semitendinosus, semimembranosus, and biceps femoris and muscles of the lumbar, gluteal, and neck regions. If the diaphragm and intercostal muscles are affected, the animal may show respiratory distress and evidence of increased abdominal effort when breathing. The muscles of the tongue may be involved, resulting in dysphagia. Dysphagia, especially in foals and lambs, may be the only sign. Some animals exhibit what appears to be abdominal pain with violent thrashing. Animals with skeletal NMD often respond favorably to treatment and rest. Improvement is evident after a few days, and within 3 to 5 days animals can often stand and walk.

Differentiation of NMD from other diseases causing sudden death or recumbency is important. Infectious diseases resulting in septicemia, pneumonia, and toxemia may have similar presenting signs. Acute heart failure resulting from cardiac anomalies; cardiotoxic agents such as those found in plants (oleander, cassia, yew, white snakeroot, and gossypol toxicity from cottonseed); and the ionophore antibiotics should also be considered. Other diseases causing stiffness of gait, weakness, and recumbency with no change in mental status must be differentiated from NMD. Spinal cord compression, cerebellar disease, suppurative and nonsuppurative meningitis/myelitis, polyarthritis, neurotoxins such as organophosphates, tetanus, pelvic fractures, and parasitic myositis all can cause recumbency. Clostridial myositis and traumatic injuries to muscles, long bones, and joints should be considered. Diseases characterized by abdominal pain may resemble NMD because they may also cause stiffness of gait, weakness, and recumbency.

Clinical Pathology Significantly elevated CK, AST, and LDH activities and myoglobinuria occur during the acute phase of myodegeneration. Progressively decreasing activities of CK can be used as a prognostic indicator of a reduction in the myodegenerative process. In foals, other reported abnormal laboratory findings include variable hyperkalemia, hyperphosphatemia, hyponatremia, and hypochloremia.[109] Evidence of dehydration, reflected by elevated serum protein concentrations and hemoconcentration, is common in nonambulatory animals unable to nurse or drink water.

The selenium status of an animal or members of a group can be determined by laboratory analysis of tissue biopsies and whole blood (Table 42-2). Vitamin E status in serum or plasma is satisfactory for assessing intermediate to long-term nutritional status; however, short-term supplementation or injections can confuse interpretation of circulating levels of selenium or vitamin E. Tissue biopsies and tissue specimens obtained at slaughter and necropsy provide an indication of storage and can also be used to assess herd status and success of supplementation. Whole blood selenium analysis is preferred over plasma and serum.[110] Whole blood selenium concentrations ranging from 0.07 to greater than 0.1 ppm (µg/mL) are considered normal in large animals. Normal liver concentrations of selenium are 0.9 to 1.75 µg/g of dry weight (DW), 0.9 to 3.5 µg/g DW, and 1.05 to 3.5 µg/g DW for cattle, sheep, and horses, respectively.[111] Selenium-dependent glutathione peroxidase (GSH-Px)

TABLE 42-2

Deficient, Marginal, and Normal Concentrations of Whole Blood Selenium and GSH-Px Activities in Sheep and Cattle[67,71]

Whole Blood Selenium (ppm)*	GSH-Px (U/mg Hb/min)	Category	Interpretation
0.01-0.04	0-15	Deficient	Selenium supplementation is always beneficial
0.05-0.06	15-25	Marginal	Selenium supplementation is often beneficial
>0.07	25-500	Normal	Selenium supplementation is never beneficial

**GSH-Px,* Glutathione peroxidase; *PPM,* parts per million.

GSH-Px assays are performed by different procedures in individual laboratories, and quantitative relationships between blood selenium concentrations and blood GSH-Px activities can vary. These numeric relationships are site specific, and interpretation must account for these differences.

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formed in the red cells during erythropoiesis also provides an index of body selenium status. Cross-reacting enzymes, such as glutathione reductase, are not found in erythrocytes. Adequate GSH-Px activities are greater than 30 U/mg of hemoglobin per minute in cattle, 60 to 180 U/mg of hemoglobin per minute in sheep, and 20 to 50 U/mg of hemoglobin per minute in horses. However, GSH-Px reference values are only specific to the laboratory where the analysis is performed and must be validated by comparison with blood selenium concentration. The activity of GSH-Px in red blood cells of domestic species remains constant for 4 to 6 days when maintained at 39° F (4° C); after this time significant decreases occur. The critical concentration of vitamin E (α-tocopherol) in plasma is 1.1 to 2 ppm (μg/mL) in large animals. Vitamin E deteriorates rapidly in plasma samples. Therefore plasma/serum samples for α-tocopherol analysis need to be put on ice immediately, protected from the light by wrapping in tin foil, and stored (−21° F, −70° C) if analysis is to be delayed.

Pathophysiology The effects of selenium and vitamin E deficiency have been postulated to result, at least in part, from the destruction of cell membranes and proteins leading to a loss of cellular integrity.[106,112] Selenium, which has been shown to be an essential component of at least five selenoproteins[113] (three glutathione peroxidase enzymes, a deiodinase in liver and kidney that converts T_4 to T_3, and selenoprotein-P, a plasma protein of unknown function), and vitamin E (α-tocopherol) serve as biologic antioxidants. During normal cellular metabolism highly reactive forms of oxygen (free radicals) are produced. These include hydrogen peroxide, hydroperoxides, lipoperoxides, superoxide, various hydroxy radicals, and singlet oxygen. Vitamin E is active within the cell membrane as a lipid-soluble antioxidant that scavenges free radicals that otherwise might react with unsaturated fatty acids to form lipid hydroperoxides. In contrast, GSH-Px destroys hydrogen peroxide and lipoperoxides that have already been formed and converts them to H_2O or relatively harmless alcohols. Other enzymes such as catalase and superoxide dismutase are also involved in this protective process.

Apparently important interrelationships exist among the selenium and vitamin E status of the animal, the level of polyunsaturated fatty acids (PUFAs) in the diet,[106,112] and NMD, particularly in ruminants.[106] PUFAs of dietary origin can undergo peroxidation to hydroperoxides forming toxic free radicals. During active growing periods pasture grasses and plants contain high concentrations of linolenic acid, a PUFA. Under normal conditions the rumen is thought to be important in saturating dietary unsaturated fatty acids. However, concentrations of PUFAs in the plasma often increase in calves recently turned out to pasture, possibly enhancing the chance of free radical formation and tissue damage. This indicates that the capacity of the various protective mechanisms can be overwhelmed by dietary factors such as high levels of PUFA. Not surprisingly, selenium- or vitamin E–deficient animals may be at a greatly increased risk of tissue oxidative damage when exposed to such diets. However, the potential for induction of NMD by this process should not be overemphasized because calves on a milk diet may be severely affected.

The precise interrelationships among selenium, vitamin E, other metabolic factors, and triggering mechanisms in NMD are not fully understood because many animals deficient in selenium or vitamin E have no evidence of muscle disease. In certain situations, deficiencies of both selenium and vitamin E are necessary for disease to occur. In other animals NMD can occur when a deficiency of only one of the agents is present and the other is normal in blood and tissues.

Epidemiology NMD occurs in all farm animals and is seen most commonly in young, rapidly growing calves, lambs, kids, and foals. The occurrence of NMD in very young animals usually reflects a deficiency in their dams during a substantial portion, if not all, of the gestation period. The selenium and GSH-Px values of neonatal calves tend to be similar to those of their dams.[114,115]

Marginally to severely selenium-deficient areas occur throughout a large portion of the United States and other countries of the world. Forages and grains produced in the northeastern and eastern seaboards and northwestern regions of the United States are particularly deficient because of low soil levels of selenium. Acid soils and those originating from igneous (volcanic) rock are often selenium deficient, as are those having high sulfur content or soils treated with sulfur-containing fertilizers. Sulfur inhibits selenium uptake by plants and absorption by animals. Different forages in a specific area will also vary in their selenium content. Legumes take up less selenium than do grasses. Also, forage selenium concentrations are lowest during periods of rapid growth such as in the spring and during times of highest rainfall.

Vitamin E deficiency occurs most commonly when animals are fed poor-quality hay, straw, or root crops. Grain treated with propionic acid and having high moisture content is commonly vitamin E deficient. Storage of grain crops for extended periods results in marked decreases in their vitamin E content. Calves fed milk replacers containing fish oil, linseed oil, or soybean or corn oil, all of which increase the dietary levels of unsaturated fatty acids, require increased dietary supplementation of vitamin E to avoid deficiency. In contrast, cereal grains, green growing pastures, and properly prepared hay usually have adequate vitamin E.

In young ruminants the majority of NMD cases occur in calves, 2 to 4 months of age, during the spring and summer months in association with exercise when at pasture, although congenital and perinatal cases do occur. Histologic lesions consistent with NMD have also been seen in late-term aborted fetuses.[111] These findings are suggestive of an in utero form of NMD in large animals. Yearling cattle housed during the winter, fed diets high in grain with high moisture content, and then turned out in the spring may also be affected. Lambs born in confinement and turned out to pasture at 1 to 3 weeks of age frequently develop signs of NMD. Stresses such as transport, herding, and driving can also precipitate signs of NMD. In horses, NMD generally occurs during the first year of life with most cases observed from birth to weaning.[107,116]

Necropsy Findings Bilaterally symmetric myodegeneration is a consistent finding in NMD. Skeletal muscle degeneration is characterized by pale discoloration and a dry appearance of affected muscle, white streaks in muscle bundles, calcification, and intramuscular edema (Fig. 42-12). The white streaks seen in muscle bundles represent bands of coagulation necrosis or, in chronic cases in which

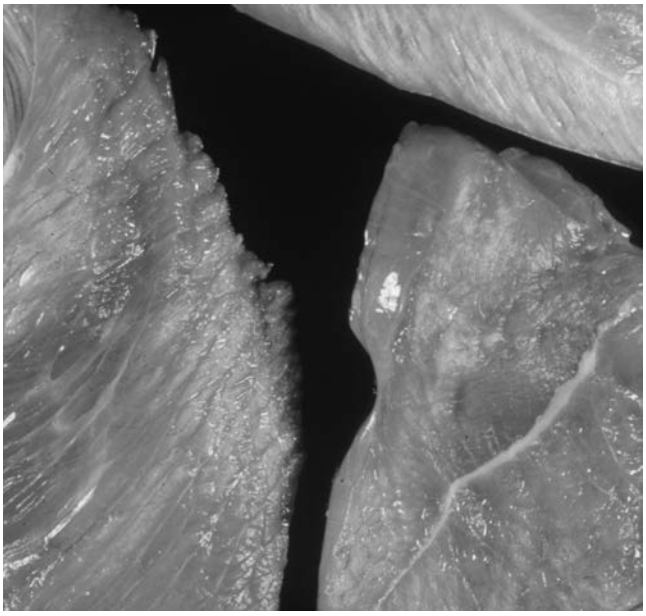


FIG. 42-12 White streaks within diffusely pale skeletal muscle due to nutritional myodegeneration.

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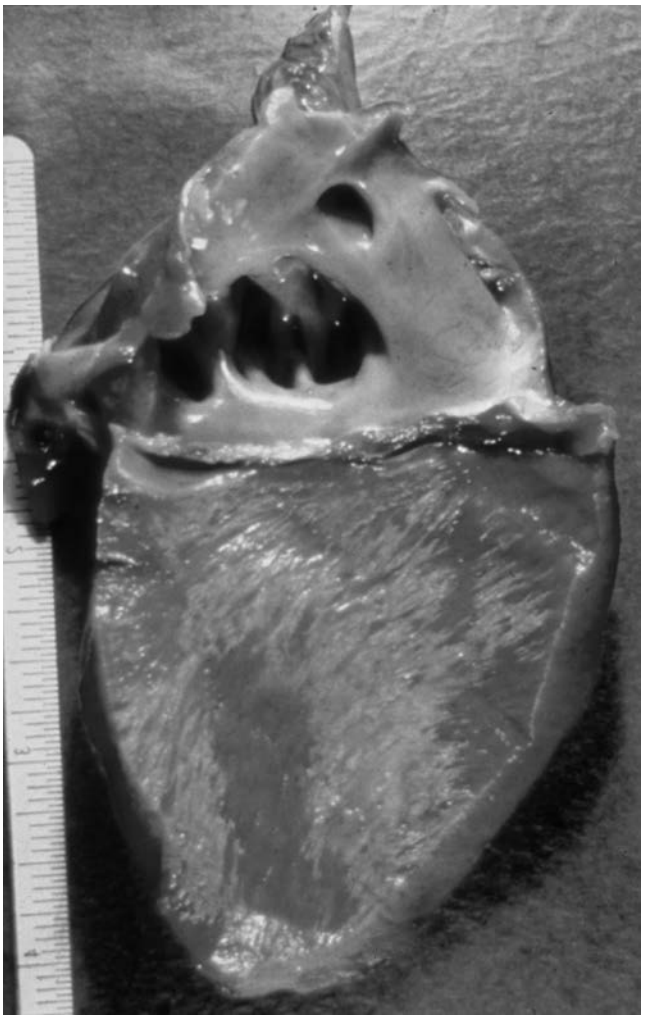


FIG. 42-13 Pale areas of muscle necrosis in the myocardium of a calf with nutritional myodegeneration.

insults may have occurred weeks before, may represent fibrosis and calcification. Affected muscle bundles are often adjacent to apparently normal or minimally affected muscle. The color of normal muscle in young calves is pale because of reduced myoglobin concentrations; therefore close inspection and histologic examination are necessary in cases of suspected NMD. Cardiac muscle undergoes changes similar to those of skeletal muscle. In calves the left ventricle and septum are most frequently involved (Fig. 42-13), but in lambs both ventricles are usually involved. Myocardial degeneration usually extends through the full thickness of the ventricular wall.

Histologically, affected muscle fibers may be hypercontracted and fragmented with some mineralization of muscle fibers and others undergoing macrophage infiltration. In yearling cattle, type I muscle cells are more frequently affected.

Treatment and Prognosis In the cardiac form of NMD myocardial damage is often extensive and incompatible with life. In contrast, the skeletal form of NMD is more generally amenable to treatment, although the prognosis for clinical recovery from the skeletal form of NMD is guarded and depends often on whether secondary complications such as respiratory disease develop. In all cases of NMD, therapy should involve specific supplementation with selenium and vitamin E and general supportive care.

Alleviation of selenium-responsive NMD requires the use of injectable selenium products. These are available with selenium concentrations varying from 1 mg of selenium per milliliter to 5 mg/mL, with all products containing 50 mg/mL (68 IU) of vitamin E as DL-α-tocopheryl acetate. The label dose for selenium is 0.055 to 0.067 mg/kg (2.5 to 3 mg/45 kg) body weight given intramuscularly or subcutaneously. Dosage of these injectable products should not be greatly increased above the label dose to prevent an inadvertent selenium toxicosis. However, when using the vitamin E/selenium combinations, the amount of vitamin E in these combination products is present as a preservative for the solution and is therefore insufficient for vitamin E supplementation. Oral supplementation is the general approach to provide additional dietary levels of vitamin E. Vitamin E can be obtained from natural or synthetic sources, which differ in bioavailability. In order for α-tocopherol acetate to be utilized in the body, the ester has to be removed and the α-tocopherol made water dispersible by the action of bile salts (micellization), which can limit α-tocopherol acetate absorption in the horse. To further enhance the bioavailability of α-tocopherol, water-dispersible formulations of vitamin E have been developed. The biopotency of these compounds in horses is much greater than synthetic vitamin E. When tested, two of the commercially available water-dispersible natural vitamin E products had a bioavailability of 5.59 (Elevate WS, Kentucky Performance Products, LLC, Versailles, Ken.) and 6.13 (Nano•E, Kentucky Equine Research, Versailles, Ken.) fold higher than synthetic vitamin E acetate (D-α-tocopheryl acetate). Recommended levels of supplementation for calves range from 15 to 60 mg of DL-α-tocopheryl acetate per kg of dry feed. For horses a daily supplement of 600 to 1800 mg of DL-α-tocopheryl acetate has been recommended.[116]

Studies with injectable selenium show that absorption and distribution occur rapidly.[117] It is thought that incorporation of selenium into heart, skeletal muscle, and other tissues may be rapid and could account for the rapid improvement in clinical signs seen in reversible cases. The discovery of four new selenoproteins may help explain these clinical observations.[113] This improvement can occur even though blood GSH-Px activity rises slowly because of the delay caused by erythropoiesis and release of red cells from the bone marrow.[117] However, platelet GSH-Px activity rises within hours and may be a more accurate reflection of changes in muscle and other tissues.

Supportive therapy may include administration of antibiotics to help combat secondary pneumonia and infected decubital lesions that are common in recumbent patients. Provision of adequate energy intake and attention to the fluid and electrolyte balance are of critical importance if recovery is to be successful.

Prevention and Control The prevention and control of NMD are achieved through supplementation of both selenium and vitamin E. Under current U.S. federal regulations, selenium can be incorporated into the total ration of ruminants and other species to a level of 0.3 parts per million (ppm). In salt/mineral mixtures formulated for free choice feeding, selenium can be incorporated at 90 ppm for sheep and 120 ppm for cattle. In certain areas or in herds, levels as high as 200 ppm selenium in salt/mineral mixtures may be necessary to maintain adequate selenium levels in the animals. Federal regulations limit the intake of supplemental selenium by sheep to 0.7 mg/head/day and by cattle to 3 mg/head/day. The use in ruminants of rumenoreticular boluses, which release a precise amount of selenium daily, has been commonplace in many countries of the world; however, under current U.S. Food and Drug Administration guidelines these products are not available in the United States. These slow-release boluses can replace supplementation by salt mixtures or by injections and are extremely valuable in extensive grazing systems. Alternatively, individual animals can be supplemented by periodic (30- to 60-day intervals) injections of selenium/vitamin E preparations to help maintain body concentrations and assist in transplacental transfer of selenium to the fetus.

Oral supplementation for horses at 1 mg of selenium per day increases blood selenium concentrations above levels known to be associated with NMD.[118] Supplementation of pregnant mares is advised in areas known to be selenium deficient; however, only limited selenium may cross the placenta.[108] Supplementation during lactation increases the levels of selenium in milk and thus provides

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a potential means of selenium supplementation in foals; however, evidence in cattle indicates that this increased level of selenium in milk may not meet nutrient requirements.

Regardless of the method of supplementation, periodic blood (or tissue) sampling of animals at risk is recommended to ensure desired levels of selenium. In high-risk areas, samples should be taken every 60 to 90 days to determine selenium status in susceptible animals and every 6 to 12 months to monitor supplementation. On the basis of these assessments, adjustments to the rate or extent of selenium supplementation may be made.

Feeding animals properly prepared and stored hay and grain or allowing them access to high-quality green forage should ensure adequate vitamin E intake.

Masseter Muscle Myodegeneration

Adult horses with selenium deficiency may be clinically normal or can present with acute clinical signs of bilateral swelling of the masseter muscles, trismus, dysphagia, and salivation.[119-121] Although postural and locomotor muscles may appear normal on clinical examination, postmortem of horses with masseter muscle myonecrosis has shown histopathologic evidence of bilateral symmetric lesions in muscles of the hind and thoracic limbs. Tachycardia and dysrhythmias may indicate the presence of myocardial damage. Accompanying clinical pathologic findings include pigmenturia, elevated serum AST and CK activity, and elevated cardiac troponin concentrations. Ultrasonography can be used to determine the extent of masseter muscle swelling or atrophy, as well as the presence of myocardial dysfunction. Prognosis is guarded, but there are individual reports of successful treatment. Important aspects of treatment include nutritional support via stomach tube, IV fluids, analgesics, IM selenium (0.055 to 0.067 mg/kg), and oral vitamin E (1000 to 5000 IU/day). Progression to bilateral muscle atrophy is common and may resolve after a period of months. Without early treatment, permanent trismus can occur due to muscular atrophy and fibrosis. Ruleouts for masseter swelling include parasites, most commonly *Trichinella spiralis, Halicephalobus* species *Haycocknema perplexum,*[122] trauma, and fibrosis due to trauma or chronic abscessation.

Vitamin E–Deficient Myopathy

Some horses with clinical signs of EMND and a deficiency in vitamin E are not diagnosed antemortem with EMND because they lack evidence of neurogenic atrophy in the sacrocaudalis dorsalis (SC) muscle. A recent study suggests that many such undiagnosed cases are the result of a specific myogenic presentation of vitamin E deficiency.[123] With vitamin E–deficient myopathy, the clinical presentation resembles EMND; however, sacrocaudalis muscle lacks evidence of neurogenic atrophy but contains an abnormal moth-eaten staining pattern of mitochondria. Muscle α-tocopherol concentrations from affected horses are low, but serum α-tocopherol concentrations are inconsistently low. This vitamin E–deficient myopathy has likely been missed previously because formalin-fixed biopsy specimens are most often evaluated for a diagnosis of EMND and mitochondrial staining is not possible with this fixative. The observed generalized weakness in the horses with abnormal mitochondrial stains could be due to a reversible manifestation of skeletal muscle mitochondrial oxidative stress associated with vitamin E deficiency. Horses can recover completely after vitamin E therapy (5000 IU/day for >3 weeks) (Fig. 42-14, *A* and *B*). Vitamin E–deficient myopathy could be an entity unto itself or a predecessor to development of EMND, but this distinction was not evaluated in the study because all horses successfully responded to vitamin E therapy, precluding a postmortem examination.



FIG. 42-14 A horse with vitamin E–deficient myopathy before **(A)** and after **(B)** 6 months of vitamin E treatment. Before vitamin E treatment, notice the marked generalized muscle atrophy and following treatment notice the normal muscle mass.

Toxic Causes of Rhabdomyolysis

Michael Murphy • Stephanie J. Valberg

Ingestion of toxic substances in feed or forage is a common cause of toxic rhabdomyolysis.

IONOPHORES. Ionophores are commonly added to feeds for their growth promotion and coccidiostat properties. Species differences in sensitivity to ionophores and the variety of ionophores on the market have led to several cases of ionophore-induced toxicosis. Rhabdomyolysis and cardiomyopathies are common sequelae to ionophore toxicosis. Experimental studies have indicated that LD50 values for monensin are 2-3, 12, 17, 26, and 21-36, for horses, sheep, pigs, goats, and cattle, respectively. Feed concentrations of 100 g/ton and 400 g/ton have been fatal to sheep and cattle, respectively.[124,125] Newborn calves dosed with 100 mg lasalocid twice daily, for cryptosporidiosis, experience muscle necrosis.[126] Other ionophores include naracin, salinomycin, and laidlomycin. Ionophores are quickly eliminated from the body after exposure.

CHEMICAL TOXINS. Several chemical agents have been associated with muscle necrosis on rare occasions. Parenteral products, insecticides, and feed contaminants have been implicated. Muscle necrosis has been reported in cattle and pigs after receiving injections of lidocaine, diazepam, digoxin, levamisole, nitroclofene, pentazocine, thiazinamium, chloramphenicol, nitroclofene, and oxytetracycline and in horses after injectable ivermectin administration. One of 70 horses poisoned with blister beetles developed muscle necrosis.[127] Animals with organophosphate toxicosis, particularly parathione, may develop muscle necrosis.[128-130] Several miniature horses

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being fed a complete feed containing tetrachlorovinphos, a feed-through fly control agent, were reported to develop chronic myonecrosis involving masseter, tongue, neck, respiratory and postural muscles, and occasionally cardiac muscle.[131] Affected horses showed signs of lethargy, dysphagia, fasciculations, tachypnea, and tachycardia. Muscle tissue showed evidence of chronic myonecrosis and lipid accumulation. Myonecrosis was attributed to acetylcholine accumulation at muscarinic and nicotinic sites producing oxidant stress. Low selenium concentrations may contribute to the toxicosis.

TOXIC PLANTS. Gossypol is of greatest significance in swine. Monogastrics, including young calves, should not ingest feed containing more than 200 ppm gossypol. Mature ruminants may tolerate 20 g of gossypol/head/day. This normally amounts to 5 to 6 lb of whole cottonseed per head per day.[124] Two common forage toxins that cause myonecrosis are *Cassia* spp. and tremetone-containing plants. *Cassia obtusifolia* (sicklepod) is prevalent in the southeastern United States, and ingestion of seeds by swine, ruminants, or horses may cause a degenerative myopathy and cardiomyopathy with evidence of myofiber atrophy, segmental necrosis, and mitochondrial disruption.[132] White snakeroot *(Eupatorium rugosum)* grows in shaded areas of the eastern and central United States, and rayless goldenrod *(Isocoma wrightii)* is common in the Southwest on open pastures. These tremetone-containing plants can cause a fatal cardiomyopathy and severe skeletal muscle degeneration in horses when ingested at 0.5% to 2% of body weight.[133,134] Other grazing livestock are likely to be affected by ingestion of these plants at 2% of body weight. Tremetone remains active in hay and in the stalks of the dead plants on pasture, so both the fresh and the dried form of the plants should be kept from livestock.[135] Microsomal activation of the toxin in the liver may be necessary for toxic effects.[133]

Seasonal Pasture Myopathy and Atypical Myopathy

Epidemiology A highly fatal acquired lipid storage myopathy of pastured horses occurs in the fall and less often the spring in Europe and central and northeastern parts of North America.[136-140] Affected horses are usually young or new to affected pastures and kept on wooded pastures for more than 12 hours a day without additional feed provided. Windy weather often precedes outbreaks.[141,142]

Clinical Signs Clinical signs develop acutely and include muscular weakness, sweating, fasciculations, stiffness, tachycardia, tachypnea, recumbency, and when urine is observed, myoglobinuria. A rapid rise in respiratory rate is usually followed by collapse and death from respiratory or cardiac failure.

Diagnosis The most notable change in serum biochemistry is a marked increase in serum CK and AST activity, which is often accompanied by hyperglycemia, lactic acidemia, and in some cases elevated serum troponin I concentrations.[143] A definitive diagnosis can be made by a pattern of accumulation of serum acylcarnitines and urine organic acids and glycine conjugates typical of a deficiency in multiple acyl CoA dehydrogenases, as well as isolation of the conjugated toxic metabolite methylenecyclopropyl acetic acid (MCPA) in blood or urine.[144-146] Serum vitamin and selenium, as well as urine tremetone, concentrations are normal. Postmortem findings include extensive necrosis in deep postural and respiratory muscles and in 50% or more of cases myocardium. Frozen sections of myocardium, intercostal, diaphragm, or deep postural muscles show marked intracellular lipid accumulation in oxidative fibers (oil red O stain).[136,139]

Pathophysiology Seeds of *Acer* species trees such as the box elder *(Acer negundo)* and the European sycamore maple *(Acer pseudoplatanus)* (Fig. 42-15) contain the toxic nonproteogenic amino acid hypoglycin A.[146] Hypoglycin A is metabolized in the liver to MCPA, and MCPA CoA irreversibly binds to multiple acyl CoA dehydrogenases, enzymes that are essential for metabolism of short- and medium-chain fatty acids and branched chain amino acids. Accumulation of fat esters can damage muscle cell membranes, and an energy deficiency also arises from an inability to metabolize fat.



FIG. 42-15 Box elder seeds that contain the toxin hypoglycin A, which causes seasonal pasture myopathy.

Treatment and Prognosis Less than 75% of horses survive.[142] Early aggressive fluid therapy, antioxidant and antiinflammatory treatment including DMSO, vitamin E, vitamin C, and nonsteroidal antiinflammatory drugs (NSAIDs) are indicated.[136] Although many older horses are asymptomatic on pastures with *Acer* species trees, young horses or new horses should not be pastured with box elder or European sycamore maple trees in the fall. Provision of additional feed or reducing grazing time during the fall may also decrease the incidence of pasture-associated myopathies.

Traumatic Rhabdomyolysis

Compartment, Downer, and Muscle Crush Syndromes of Cattle

David R. Hodgson • Stephanie J. Valberg

Muscle damage commonly accompanies the downer syndrome in large animals. The downer syndrome is discussed in greater detail in Chapters 35 and 41. Animals weakened by disorders such as hypocalcemia are more prone to tearing adductor or semitendinosus/membranosus muscles in attempts to rise.[25,147] Initial traumatic laceration of muscle leads to edema and inflammation, both of which may exacerbate local tissue degenerative changes. Additionally, the weight of a recumbent animal on dependent muscle groups creates significant increases in intramuscular pressure, resulting in decreased perfusion and ischemia of muscle and nerve. Signs of weakness and peroneal or tibial nerve paralysis most commonly accompany this type of injury. Mild elevations in serum CK can be expected in cows that are recumbent, but elevations greater than 5000 U/L usually indicate traumatic muscle damage. Treatment requires correcting the underlying cause of recumbency, fluid therapy if renal damage is evident, nonsteroidal antiinflammatories, good nursing care, adequate footing and bedding, and lifting or rolling the animal several times a day. Aquatherapy using float tanks for cattle also appears to be beneficial in relieving the pressure on muscle groups.

Postanesthetic Myoneuropathy

Postanesthetic myoneuropathy is a condition that has become much more prevalent since the advent of inhalation general anesthesia. The

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FIG. 42-16 Postanesthetic myoneuropathy showing paralysis of the right femoral and peroneal nerves.

disorder can be categorized as occurring in two forms: (1) localized myopathy-neuropathy and (2) generalized myopathy somewhat similar to malignant hyperthermia.

Localized Myoneuropathy

Clinical Signs Localized myopathy-neuropathy occurs in about 6% of horses undergoing general anesthesia.[148] It is most prevalent in muscles that are in contact with a hard surface during anesthesia or those in which arterial blood supply is compromised through positional occlusion. Commonly affected muscles include triceps, deltoid, masseter, hindlimb extensors, or, if the horse has been in dorsal recumbency, the hindlimb adductor and gluteal muscles.[149-151] Injury can also occur to nerves in these areas, resulting in temporary radial, peroneal, or femoral nerve paralysis (Fig. 42-16). Clinical signs may be apparent on recovery or may be delayed for periods of up to 30 to 60 minutes after the horse has recovered from anesthesia. Affected muscles may be swollen, hot, and painful on deep palpation, and the horse is often reluctant to bear weight on the affected limb. Myasthenia (weakness) of affected muscles is common, particularly with peripheral nerve involvement. In some horses this condition may limit the animal's ability to stand for some time following anesthesia. The loss of muscle strength, particularly when involving adductor muscles, can contribute to orthopedic injury during repeated attempts to rise. Many horses with mild to moderate muscle injury recover over a period of hours to days even if untreated.[149]

Etiology A variety of factors acting alone or in combination has been suggested to contribute to this disorder. The most important factors include duration of anesthesia, ischemia, and hypoperfusion as a result of prolonged immobility, muscle compression, systemic hypotension, and hypoxia.[149-153] There is increased lactate efflux from dependent muscles during anesthesia in horses that develop a myopathy, supporting the contention that these muscles experience compromised perfusion.[152,153] Halothane anesthesia has a greater propensity than isoflurane to compromise tissue oxygen delivery even in nondependent muscles.[151] If mean arterial pressure is allowed to fall below 70 mm Hg for several hours during inhalation anesthesia, particularly if mechanical ventilation is used, the incidence of postanesthetic myopathy increases substantially.[153,154]

Diagnosis Diagnosis is based on a history of anesthesia or prolonged recumbency, clinical signs, and possibly clinical pathology examinations. Laboratory findings include elevations in serum CK and subsequently serum AST and serum LDH activities. Elevations in CK activities of thousands to tens of thousands of IU/L are commonly demonstrated in horses with moderate forms of the myopathy.

Treatment Horses demonstrating only minor localized manifestations of the myopathy usually have an uncomplicated recovery with little or no treatment.[149] Supportive care, including the use of antiinflammatory drugs, dimethyl sulfoxide, and dantrolene sodium 2 to 4 mg/kg PO every 6 to 8 hours for up to 48 hours is often sufficient in mild to moderate cases.[155] Significant muscle atrophy may develop over the ensuing 3 to 4 weeks but will usually resolve within 2 to 3 months. Treatment of more severe cases is outlined under generalized reactions.

Control Correct positioning and judicious use of padding and water- or air-filled mattresses can reduce dependent muscle pressure up to 50%, thereby aiding in the reduction of this disorder. In addition, by elevating the upper limb during anesthesia, the pressure on the lower limbs is significantly reduced. Pulling the lower forelimb forward also markedly reduces pressure in the dependent triceps muscle. When the horse is in dorsal recumbency, padding under the shoulders and hips is absolutely imperative.

Maintaining anesthesia at the lightest plane possible for a specific surgical procedure is beneficial in prophylaxis. Similarly, if possible, maintaining systemic mean arterial blood pressure above 80 to 85 mm Hg during anesthesia is advisable. The use of ionotropic agents such as dobutamine during anesthesia has been useful in reducing the occurrence of anesthetic myopathies. Administration of dantrolene sodium (2 to 4 mg/kg PO) 1 hour before induction of anesthesia may result in a reduction in the incidence of this myopathy; however, it should be noted that decreased cardiac output can occur in conjunction with higher dantrolene doses.

Generalized Anesthetic Reactions

Clinical Signs Postanesthetic reactions involving multiple muscle groups can result in clinical signs of anxiety, hyperthermia, tachycardia, tachypnea, profuse sweating, and myoglobinuria.[150,151] Horses may not be able to rise and may struggle violently, resulting in prolonged, traumatic recoveries. In some cases a progressive increase in body temperature and muscular contractures may develop under anesthesia, and a fulminant metabolic and respiratory acidosis may be noted.[20,156,157] These animals can die within a matter of hours. In some cases, shock and pigmenturia may lead to renal failure.

Pathogenesis The generalized form of myopathy cannot be explained by the compartmental syndrome alone. Halothane and succinylcholine have been the most frequently implicated inciting agents for generalized anesthetic-induced myonecrosis in all susceptible species, including the horse.[19,156,157] There appear to be several possible explanations for generalized anesthetic reactions. In some cases, systemic hypotension and hypoxemia may create local ischemic lesions, with the pathologic changes becoming more generalized as a result of the stress of anesthesia and the sensitivity of muscle cells to anesthetic agents or muscle relaxants.[149,153] In other cases, malignant hyperthermia (MH)[19,156-158] may be responsible for clinical signs of muscle contracture, heat production, and systemic acidosis resulting from excessive calcium release by the sarcoplasmic reticulum. In swine MH is caused by a genetic mutation in the ryanodine receptor 1 *(RYR1)* gene.[159] A mutation in the same gene has been identified in Quarter Horses. Horses with this mutation may develop fatal malignant hyperthermia following halothane anesthesia.[160,161] A further possible cause of generalized anesthetic myopathies is the triggering of severe myonecrosis in horses with an underlying exertional myopathy. Horses with recurrent exertional rhabdomyolysis may be at risk for excessive release of calcium from the sarcoplasmic reticulum during halothane anesthesia, and horses with polysaccharide storage myopathy may develop rhabdomyolysis due to metabolic changes with anesthesia.[19,20,162,163]

Diagnosis Diagnosis is based on clinical signs, particularly in horses undergoing inhalation anesthesia. Routine monitoring of body temperature during anesthesia may aid in the early detection of MH. Some animals may also demonstrate metabolic and respiratory acidosis and hyperkalemia.[160] Genetic screening for MH in Quarter Horses and Paints may be warranted before elective procedures.

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Treatment Severely affected cases provide a significant therapeutic challenge. Aims of therapy should include (1) relief of pain, (2) correction of fluid and electrolyte abnormalities, (3) attempts to prevent ongoing necrosis, and (4) high-quality nursing care. Many of the same principles described for treatment of exertional rhabdomyolysis can be used for treatment of postanesthetic myoneuropathy. In severely affected recumbent horses, pain relief and sedation may help prevent struggling and progression of the myopathy.[149,150] Detomidine combined with butorphanol is effective in reducing struggling. Violent struggling only exhausts the horse and increases the potential for further injury and muscle damage. Constant rate infusions of butorphanol, opioids, or detomidine may aid in pain control where practical. Similarly, administration of nonsteroidal antiinflammatory drugs may help reduce ongoing degenerative changes in muscle. Dantrolene sodium 2 to 4 mg/kg PO every 6 to 8 hours decreases release of calcium from the sarcoplasmic reticulum, helping to break the cycle of muscle damage. Volume expansion and diuresis may prevent renal toxicity.[149]

The most common metabolic derangement with anesthetic-related myopathies is a metabolic and/or respiratory acidosis. If specific therapy for metabolic acidosis is necessary, intravenous administration of sodium bicarbonate can be used. For optimum results, doses are calculated on the basis of the results of acid-base analysis. If facilities for acid-base analysis are not available and the horse appears severely compromised, IV administration of sodium bicarbonate at a dosage of 1 to 2 mEq/kg slowly is recommended. If hyperthermia and contracture develop during anesthesia, discontinuation of anesthesia is advisable. Additional attempts to cool the animal with alcohol or cold-water baths may also be indicated. Administration of a large amount of soluble, lyophilized dantrolene sodium for intravenous administration may alleviate clinical signs in these horses. However, availability and expense of the agent in this form restrict its use. A dosage rate of 1 mg/kg IV may be appropriate, although more controlled studies are required.[149]

Good nursing care is important in severely affected horses. This involves providing well-padded areas on which horses can lie. Prevention or minimization of trauma around the eyes and appropriate care of decubital sores are important. Recumbent animals may require frequent turning to allow reperfusion of compressed muscle masses. Continued fluid therapy with polyionic fluids and possibly caloric supplementation may be indicated. The use of slings and pools to assist recumbent animals to rise has also been tried.[149] Recovery from the myopathy may occur with no apparent residual lesions. In contrast, recovery from some severe forms of the disorder may be accompanied by muscle atrophy, fibrosis, and scarring.[149]

Prevention The principles described for localized myoneuropathies apply to the prevention of generalized anesthetic-related myopathies. In addition, dantrolene sodium has been shown to reduce the incidence of MH in susceptible humans and pigs. Similar effects might be anticipated in horses. Because of limited controlled studies, the dosage rate for prevention of MH in the horse is not clearly defined. Administration at a rate of 4 mg/kg PO 1 to 2 hours before anesthesia may be beneficial in reducing the incidence of MH; however, 6 mg/kg may cause decreased cardiac output and hypotension.[155,164]

Exertional Myopathies in Horses

Local Muscle Strain

Stephanie J. Valberg

Lumbar and Gluteal Muscles

Strain of lumbar and gluteal muscles is common in jumpers, dressage, harness horses, and Thoroughbreds. Deep palpation of epaxial and gluteal muscles results in pain and dorsiflexion of the spine. Several factors may predispose horses to muscle strains, such as an inadequate warm-up, preexisting lameness, exercise to the point of fatigue, and insufficient training. Lameness can be mild, and horses usually are reluctant to engage their hindquarters during exercise. A specific gluteal syndrome has been described in which the accessory head of the middle gluteal muscle becomes acutely painful to palpation.[165] With accessory gluteal head involvement horses become progressively more lame during exercise and will refuse to continue exercise. Horses that show pain but resist dorsiflexion, ventroflexion, and lateral bending on manipulation may have a myopathy secondary to an underlying disorder of the spine or sacroiliac joint.

Adductor Muscles

The gracilis muscle can be torn in horses and cause severe pain and, occasionally, recumbency.[166,167] A careful physical examination reveals swelling of the medial thigh and pain on palpation. Ultrasonography identifies the extent of disrupted muscle fibers. Adequate rest, nonsteroidal antiinflammatory medication, and cold therapy form the basis for acute treatment. Stretches and hand walking once the initial pain has dissipated are beneficial combined with application of heat or ultrasound therapy. Exercise should be resumed gradually, preceded by an appropriate warm-up period in a long and low frame. Adequate conditioning should be ensured before starting strenuous exercise. Saddles should be checked for proper fit.

Semitendinosus and Semimembranosus Muscles

Semitendinosus and semimembranosus muscles are frequently damaged in working Quarter Horses and in chronic cases result in a fibrotic myopathy.[168-171] Tearing of the semitendinosus and sometimes the semimembranosus, biceps femoris, and gracilis muscles at the point of a tendinous insertion is usually associated with work that requires abrupt turns and sliding stops. Horses caught in ropes or fences may struggle violently enough to induce sufficient trauma, allowing subsequent development of the myopathy. In one report, 5 of 18 horses developed this condition secondary to intramuscular injections.[170] A congenital form of fibrotic myopathy has been described.[172] Affected animals are usually younger than 12 months old when clinical signs characteristic of fibrotic myopathy are first evident. Horses affected with this form of the disorder frequently have no palpable thickening of affected muscles or tendons and no history or evidence of trauma.

Affected muscles in acute cases are painful on deep palpation and may appear warm. Chronically hardened areas within the muscle may represent fibrosis and ossification. The lameness in chronic cases is usually most apparent at the walk and is characterized by an abrupt cessation of the anterior phase of the stride of the affected limb, causing the leg to jerk suddenly to the ground rather than continue its forward motion. Pain is not a feature in chronic fibrotic myopathy, and manipulative tests have little, if any, effect on the degree of dysfunction. The stride has a short anterior phase with a characteristic hoof-slapping gait. The gait reflects a mechanical hindlimb lameness that restricts normal function. Radiographs may indicate ossification of affected muscles.[170,172]

Diagnosis Serum activities of CK and AST are usually only mildly elevated. In addition to palpation, diagnosis can be confirmed by ultrasonography, thermography, or scintigraphy. Light microscopic evaluation of muscle biopsies is frequently normal in acute cases. Chronically fibrous replacement of muscle fibers is apparent.

Treatment Several surgical procedures for correction of fibrotic myopathy have been described. These involve either excision[170] or transection[169] of the fibrotic part of the muscle or tenotomy of the tibial insertion of the semimembranosus tendon.[172] Excision of the fibrotic part of the muscle and tenotomy of the tibial insertion of the semimembranosus tendon are performed under general anesthesia. Excision or transection appears to produce more postoperative complications than the tenotomy. However, according to reports, tenotomy has been reported only in a limited number of horses, and complete resolution of the gait abnormality may not

occur.[171] In a modification of the procedure described by Irwin and Howell,[169] transection of the fibrotic mass under local anesthesia in the standing horse using a bistoury knife may be effective. A Penrose drain is inserted through a second incision ventral to the first, and light exercise is resumed the day after surgery. Healing is allowed to occur by second intention.

Exertional Rhabdomyolysis

Stephanie J. Valberg

Exertional rhabdomyolysis (ER) is probably the most common muscle disorder in horses. It is a frequent cause of poor performance in a variety of breeds, including Standardbreds, Thoroughbreds, warmbloods, Arabians, Morgans, Quarter Horses, Appaloosas, and Paints. ER is a complex syndrome that likely has numerous causes. Numerous terms such as tying-up, chronic intermittent rhabdomyolysis, azoturia, Monday morning disease, paralytic myoglobinuria, and exercise-associated myositis have been used for this syndrome.

Clinical Signs

Classically, horses develop a stiff, stilted gait, with excessive sweating and a high respiratory rate during or after exercise (Fig. 42-17). Most commonly, signs are seen after only 15 to 30 minutes of light exercise. Following exercise, horses may stretch out as if to urinate, become extremely reluctant to move their hindquarters, and in severe cases show signs of colic or become recumbent. Attempts to move more severely affected animals may result in extreme pain, obvious anxiety, and possible exacerbation of the condition. Firm painful muscles may be palpated over the back and hindlimb muscles. Scintigraphic evaluation of horses with rhabdomyolysis following exercise shows symmetric damage to the gluteal, semitendinosus, and semimembranosus muscles.[15] Myoglobinuria is a classic feature of more severely affected horses. Endurance horses often show other signs of exhaustion including a rapid heart rate, dehydration, hyperthermia, synchronous diaphragmatic flutter, and collapse.[69]

Etiology

A number of factors appear to precipitate episodes of ER. Some successful athletic horses may experience one or two isolated episodes of rhabdomyolysis during their lifetime, suggesting that environmental influences play an important role in sporadic cases.[173-177] Other horses may have chronic episodes of rhabdomyolysis that compromise their ability to compete. An inherent muscle dysfunction precipitated by certain triggering factors likely contributes to rhabdomyolysis in these horses.[7,178,179] Thus ER is a description of a syndrome that has many causes. To identify the cause in individual horses, it may be helpful to initially subdivide cases into those with no intrinsic muscle abnormality (extrinsic or sporadic form) and those with a suspected intrinsic abnormality of muscle function (intrinsic or chronic form). Causes for sporadic and chronic exercise-induced muscle damage are listed in Box 42-2.



FIG. 42-17 Exertional rhabdomyolysis in a horse showing sign of pain, stiffness, sweating, and elevated respiratory rate.

Sporadic Exertional Rhabdomyolysis

Most cases of ER can be diagnosed on the basis of the animal's history and clinical signs. Confirmation of rhabdomyolysis requires determination of abnormally elevated serum CK and/or AST. Serum CK is often in the tens to hundreds of thousands of IU/L and AST in the thousands to tens of thousands. The degree of elevation in enzymes reflects the time lapse between rhabdomyolysis and obtaining a blood sample, as well as the extent of myonecrosis. Myoglobinuria is a common finding in severely affected horses. Horses with sporadic forms of ER develop rhabdomyolysis because of an extrinsic event or recurring extrinsic events that induce muscle damage with exercise. Usually a horse is presumed to have sporadic ER the first time it develops ER.[14] If ER recurs once the horse has been rested and gradually returned to exercise, then an investigation of an inherent chronic form of ER is usually pursued. Causes of sporadic ER include focal or generalized trauma to muscle, exercise performed beyond any training adaptation or performed to the point of exhaustion, and dietary imbalances that impact muscle function.

Signalment, History, and Diagnosis

Horses with sporadic ER may be of any age, breed, or sex and involved in a wide variety of athletic disciplines.[173] Sporadic ER usually occurs in horses with a history of adequate performance before onset of ER, and a familial history is absent. A diagnosis is made by history, clinical signs, and elevations of serum muscle enzymes. Once external perturbations that affect muscle function are corrected, complete resolution and a successful return to performance are expected. Resolution occurs following a reasonable period of rest, provision of a balanced diet, and a gradual introduction of a training program matched with performance demands. If over time ER recurs despite reasonable management, a diagnosis of chronic ER becomes more likely and further diagnostic testing appropriate.

Causes

OVEREXERTION. A history of an increase in work intensity without a foundation of consistent training for this level of exercise is usually the basis for suspecting a training imbalance as a cause of ER. Signs of muscle stiffness and gait changes range from mild to severe, and severity is reflected by variable elevations of serum CK activity.[14] Overexertion is a well-described cause of ER in polo horses with 81% of cases of ER attributed to overexertion and 30% of cases occurring after a day of rest.[177] The incidence of ER is as high as 9% in U.S. polo horses, with most of these horses only having one episode of ER early in the polo season.[177]

Pathologic changes are often not evident in light microscopic evaluation of muscle biopsies from individuals performing unaccustomed exercise, but electron microscopy shows significant disruption of the alignment of muscle contractile proteins within muscle fibers. In more severe cases overt segmental damage to myofibers may be apparent in muscle biopsy. Repetitive overuse of muscles, such as occurs with overtraining, may result in exercise intolerance and is associated with pathologic changes such as increased muscle fiber size variation and centrally located myonuclei in muscle biopsies.[180]

EXHAUSTION. Exhaustion occurs most commonly in endurance horses or racehorses exercising in hot, humid weather. Signs of heat exhaustion include weakness, ataxia, rapid breathing, muscle fasciculations, sweating, and in severe cases collapse. The body temperature may be elevated to 105° to 108° F. Muscles are frequently not firm on palpation, although serum CK activity can be markedly elevated and myoglobinuria may be noted.[69,70]

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DIETARY IMBALANCES. Episodes of ER may be triggered by diets with a high nonstructural carbohydrate (NSC) content and low forage content,[181,182] as well as by diets deficient in electrolytes. They may be exacerbated by inadequate selenium and vitamin E. Electrolyte balance within the body is difficult to determine accurately. One suggested means to practically assess electrolyte balance in horses is to measure urinary fractional excretion of electrolytes.[183] Measurement of urinary electrolyte excretion as an indicator of electrolyte balance is complicated because marked variation can occur from diet, exercise, and sampling technique among individuals, as well as within individuals from day to day.[4] Furthermore, the high calcium crystal concentration of alkaline equine urine requires acidification to accurately assess calcium and magnesium content.[4] The high potassium content interferes with sodium analysis using conventional ion-specific electrodes.[7] Thus although popular in the 1990s,[3,183,184] urinary fractional excretion is now rarely performed in the United States unless there is a strong suspicion that body depletion has occurred and if a laboratory can be located with gas chromatography mass spectrometry analysis of acidified urine. It is important to ensure that horses receive sodium chloride in the diet with higher concentrations needed in horses that compete in hot humid weather. Between 30 and 50 g/day combined with 15 to 25 g of "lite" salt containing potassium chloride are recommended for horses exercising in hot humid conditions and sweating extensively. The entire diet should be adequately balanced with calcium and phosphorus (ratio of 2:1 Ca-to-P is ideal).

Whole blood selenium concentrations measured in EDTA or heparin tubes are of value in assessing selenium status in animals housed in areas where soil is deficient in selenium. In cases where selenium has been administered before blood collection, glutathione peroxidase activity can be used to assess potential selenium deficiency.[185] Vitamin E concentration should be measured in serum samples kept chilled and protected from light; however, variability in serum levels can be quite large and repeat sampling is recommended if marginal levels are identified in the first sample tested. Horses with ER are infrequently deficient in selenium and vitamin E, and alone it may not be responsible for ER[186]; however, anecdotal reports suggest that in some cases supplementation may help to further prevent episodes of ER.

Treatment Treatment of ER is directed at relieving anxiety and muscle pain and replacing fluid and electrolyte losses. Tranquilizers such as acepromazine (0.04 to 0.06 mg/kg), xylazine (0.5-1.1 mg/kg IV), or detomidine (0.02 to 0.04 mg/kg) combined with butorphanol (0.01 to 0.04 mg/kg) provide excellent sedation and analgesia. For horses with extreme pain and distress, a constant rate infusion of detomidine, lidocaine, or butorphanol may provide additional pain relief. NSAIDs such as ketoprofen (2.2 mg/kg IV), phenylbutazone (2.2 to 4.4 mg/kg IV or PO), and flunixine meglumine (1.1 mg/kg IV or PO) are frequently used to relieve pain but should be used with caution on dehydrated animals. Intravenous or intragastric dimethyl sulfoxide (as a <10% solution) is used as an antioxidant, antiinflammatory, and osmotic diuretic for severely affected horses. Methyl prednisolone sodium succinate (2 to 4 mg/kg IV) has been advocated by some veterinarians in the acute stage if horses are recumbent. Muscle relaxants such as methocarbamol (5 to 22 mg/kg, IV slowly) seem to produce variable results, possibly depending on the dosage used. The administration of dantrium sodium (2 to 4 mg/kg orally) in severely affected horses may decrease muscle contractures and possibly prevent further muscle necrosis. The dose can be repeated every 4 to 6 hours if necessary. Overdosing produces muscle weakness.

Severe rhabdomyolysis can lead to renal compromise due to ischemic and combined nephrotoxic effects of myoglobinuria, dehydration, and NSAIDs. In mildly dehydrated horses, provision of free-choice electrolytes and water or administration of fluids via a nasogastric tube may be adequate. Horses with moderate to severe dehydration require IV administration of balanced polyionic electrolyte solutions. Hyperkalemia can occur with severe rhabdomyolysis, necessitating the use of isotonic sodium chloride. If hypocalcemia is present, then supplementing IV fluids (100 to 200 mL of 24% calcium borogluconate) is recommended, but serum calcium should not exceed a low normal range. Affected animals are usually alkalotic, making bicarbonate therapy inappropriate. In severely affected animals, regular monitoring of serum creatinine is advised to assess the extent of renal damage.

Following rhabdomyolysis, horses should be stall rested on a hay diet for a few days. Small paddock turnout in a quiet area for a few hours twice a day is then helpful. Horses may be hand walked at this time, but more than 5 to 10 minutes at a time may induce another episode of rhabdomyolysis. For horses with sporadic forms of tying-up, rest with regular access to a paddock should continue until serum muscle enzyme concentrations are normal. For chronic cases of tying-up, this much rest may not be appropriate. Training should be resumed gradually, and a regular exercise schedule that matches the degree of exertion to the horse's underlying state of training should be established. Endurance horses should be supplemented with electrolytes and water during an endurance ride and monitored particularly closely during hot, humid conditions.

Management Because the inciting cause is usually temporary in sporadic cases, most horses respond to a few weeks of rest, dietary adjustments, and a gradual increase in training. Regular access to a paddock once stiffness resides and weekly monitoring of serum CK activity are recommended. Horses are much more susceptible to a second episode of ER in the 2 weeks following an acute episode, and allowing horses the ability to calmly determine their own exercise through turnout often avoids exacerbating rhabdomyolysis. If that is not feasible, hand walking needs to performed with caution and limited to no more than few minutes initially. While the horse is rested, the diet can be assessed to ensure that the ration is fed in an amount recommended by the manufacturer for the corresponding level of exercise. This will ensure that the proper balance of vitamins and minerals is provided. If excessive calories are provided when fed at manufacturer's recommended levels, then the diet should be switched to a less calorie-dense vitamin/mineral balanced diet. A salt block or 30 to 50 g (1 to 3 tablespoons) of salt per day will provide the necessary additional sodium chloride, with the amount fed depending on the heat, humidity, and intensity of exercise. Once serum CK returns to normal, training can be resumed gradually. A regular exercise schedule, beginning with 20 minutes or less of exercise/day, is gradually increased to eventually match the expected amount of daily exercise to the underlying state of conditioning.

Chronic Exertional Rhabdomyolysis

Horses that have repeated episodes of ER from a young age, from the time of purchase, or when they are put back into training after a long period of rest may have an underlying intrinsic abnormality of muscle function. Many horses with intrinsic muscle defects will have repeated episodes of ER with minimal exercise even when the dietary and training recommendations for sporadic ER are followed. Five specific intrinsic causes of ER have been identified to date (see Box 42-2). Idiopathic ER represents other causes of ER that have yet to be identified. In all of these intrinsic forms of chronic ER, it appears that there are specific environmental stimuli that are necessary to trigger muscle necrosis in genetically susceptible animals. Horses cannot be cured of their susceptibility to this condition, but if the specific form of ER is identified, changes in management can be implemented in order to minimize episodes of rhabdomyolysis.

Polysaccharide Storage Myopathy

Polysaccharide storage myopathy (PSSM) was first recognized as a specific myopathy in Quarter Horse–related breeds in 1992[187]; however, there are individual cases of abnormal polysaccharide inclusion reported in equine muscle dating back to 1979.[17,188,189] The remarkable feature of the first horses reported to have PSSM was

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TABLE 42-3

Number of North American and European Horses Tested and the Percentage of Horses Testing Positive (Heterozygous and Homozygous) for the *GYS1* Mutation in Breeds Sampled Using Random Sampling and Nonrandom Sampling

Random Sampling	Breed	Number Tested	Prevalence (%)
North America (McCue et al, 2010)	Percheron	149	62
	Belgian	149	39
	Clydesdale*	132	0
	Shire	195	0.5
	Quarter Horse	335	6.6
	Paint	195	7.7
	Appaloosa	152	5.9
	Morgan	214	0.9
	Thoroughbred	96	0
	Arabian	100	0
	Norwegian Fjord	46	0
	Icelandic Pony	45	0
Nonrandom Sampling	**Breed**	**Number Tested**	**Prevalence (%)**
Europe (Baird et al, 2010)	Belgian Trekpaard	38	92
	Netherlands Trekpaard	23	74
	Comtois	88	80
	Breton	51	63
	Swedish Ardenner	29	38
	Rheinisch-Deutsches kaltblut	44	68
	Sud-Deutsches kaltblut	265	20
	Hannoverian	214	0
(Isgren et al, 2011)	Standardbred	36	0

*Both randomized and nonrandomized samples.

twofold-higher muscle glycogen concentrations than normal horses and abnormal granular amylase-resistant inclusions in histologic sections.[187] Similar biopsy findings were reported in Belgian and Percheron draft horses in 1997.[190] Since that time, many hundreds of horses of a variety of breeds have been diagnosed with PSSM.

Terminology Several acronyms are used for polysaccharide storage myopathy besides PSSM,[191] including EPSM or EPSSM (equine polysaccharide storage myopathy).[181,192] Considerable controversy existed as to whether these acronyms encompassed one muscle condition.[181,182,193] In 2008 a mutation in the glycogen synthase 1 gene *(GYS1)* was found to be highly associated with the presence of amylase-resistant polysaccharide in skeletal muscle from Quarter Horses with PSSM.[194] Genetic testing of hundreds of horses previously diagnosed with PSSM by muscle biopsy revealed that the majority of cases of PSSM characterized by amylase-resistant polysaccharide in skeletal muscle had this genetic mutation.[195] However, some cases previously diagnosed with PSSM by muscle biopsy, particularly those with excessive amylase-sensitive glycogen, did not possess the genetic mutation. This suggested that there are at least two forms of PSSM.[195,196] For clarity, the form of PSSM caused by a glycogen synthase 1 *(GYS1)* gene mutation is now termed *type 1 (PSSM1),* whereas the form of PSSM that is not caused by the *GYS1* mutation and whose origin is yet unknown is now termed *type 2 (PSSM2).*[196] PSSM1 is likely the same disorder described as "azoturia " or "Monday morning disease" in work horses in the 19th and 20th centuries.[197]

TYPE 1 POLYSACCHARIDE STORAGE MYOPATHY

Etiology Type 1 PSSM is caused by a single-base-pair mutation in the *GYS1* gene resulting in an arginine to histidine substitution at codon 309. Horses with PSSM1 have a gain of function in glycogen synthase enzyme (in basal and stimulated states) because of an autosomal dominant mutation in the *GYS1* gene encoding glycogen synthase.[194] The higher than normal activity in both basal states and when activated by insulin and glucose-6-phosphate appears to have a novel link to the regulation of energy generation in muscle fibers. A deficit in energy metabolism represented by high myofiber inosine monophosphate was demonstrated in individual muscle fibers of horses with PSSM1 after light exercise in association with high serum CK activity.[198]

Prevalence PSSM1 is estimated to have emerged approximately 1600 years ago when the great horse was being developed from European draft and light horse breeds to carry knights with heavy armor into battle.[194] The highest prevalence of PSSM1 appears to occur in draft horses derived from Continental European breeds (Table 42-3).[199] In fact, many Continental European drafts are homozygous for the dominant PSSM1 trait (90% prevalence of PSSM in Trekpaards with 40% of tested Belgian Trekpaards homozygous). North American Belgians and Percherons also have a high prevalence of PSSM1, with 36% and 54% of horses affected, respectively.[200] In contrast, the prevalence of PSSM is low in United Kingdom–derived breeds such as Shires and Clydesdales,[200] but PSSM1 is present in other U.K. horse breeds such as Irish Draught, Cob, and Connemara.[201] Numerous other breeds, more than 20 in fact, have the *GYS1* mutation responsible for PSSM1.

Prevalence estimates of PSSM1 in Quarter Horses range from 6% to 10% of the breed and 6% to 8% for Paints and Appaloosas.[55,202] The highest frequency of PSSM1 occurs in halter Quarter Horses (28% affected), and the lowest frequency is in racing Quarter Horses.[55] The *GYS1* mutation has been identified in approximately 72% of Quarter Horses diagnosed with PSSM by muscle biopsy and in 18% of warmbloods of a variety of types diagnosed with PSSM by muscle biopsy.[203] The prevalence of PSSM1 is very low to nonexistent in light horse breeds such as Arabians, Standardbreds, and Thoroughbreds (see Table 42-3).[204]

Risk Factors Some horses with PSSM1 are asymptomatic, whereas other horses routinely show stiffness with exercise.[205,206] In a family of warmbloods sired by a stallion with the *GYS1* mutation, the mutation resulted in a sevenfold higher risk of developing ER with 34% of horses with the *GYS1* mutation lacking clinical signs of PSSM1.[206] The reason for variability in clinical signs of PSSM1 probably lies in the influence of diet, exercise, other environmental factors, and other genes on the expression of the disease.[181,207,208] There is no significant temperament, body type, or gender predilection for

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PSSM1.[8] The most common trigger for clinical signs of PSSM1 is less than 20 minutes of exercise.[178,206] Clinical signs occur most commonly at a walk and trot, particularly if the horse has been rested for several days before exercise or is unfit. Diets high in NSCs also increase the risk of muscle pain and stiffness in PSSM1 horses.[207,209] About 40% of owners feel there is a seasonal incidence to the development of clinical signs, which some have attributed to quality of grass available at the time.[178,210] Although exercise is by far the most common trigger for PSSM, Quarter Horse and Paint foals and weanlings may develop rhabdomyolysis in conjunction with a systemic illness.[211]

Diagnosis

A high degree of suspicion of a diagnosis of PSSM1 arises from clinical signs and persistent elevations in serum CK and AST activities.[8,206,212] If horses have normal serum muscle enzymes at rest, an exercise test consisting of a maximum of 15 minutes lunging at a walk and trot may help to determine if subclinical ER is present.[7] Supportive evidence would include a minimum of a threefold elevation in CK activity 4 hours after exercise.

Muscle biopsy provides one means to diagnose type 1 PSSM.[18,187,213] The distinctive features of PSSM1 in muscle biopsy samples are numerous subsarcolemmal vacuoles and dense, crystalline periodic acid–Schiff (PAS)–positive, amylase-resistant inclusions (Fig. 42-18, *A* and *B*). A diagnosis can be made irrespective of diet and proximity of sampling to recent episodes of rhabdomyolysis. A false-negative diagnosis of type 1 PSSM by muscle biopsy may occur if biopsy samples are small or if horses are younger than 1 year of age.[214]

The gold standard for diagnosis of PSSM1 is genetic testing for the *GYS1* mutation performed on whole blood or hair root samples at the University of Minnesota in North America (http://www.vdl.umn.edu/ourservices/equineneuromuscular/home.html) or in Europe by Laboklin (http://www.laboklin.co.uk/laboklin/GeneticDiseases.jsp). Other laboratories are not licensed to perform this test. It is important to note that in draft horses of Continental European origin, the very high prevalence of PSSM in essence means that there is a high chance that any clinical sign could be falsely associated with the disease PSSM1.[205] Thus clinical judgment is required to determine whether the clinical signs of the animal could reasonably be associated with a myopathic process.

Clinical Signs

ACUTE. Horses usually show signs of PSSM1 at on average 5 years of age; however, this can range from 1 to 14 years of age.[178] Acute clinical signs occur when horses are calm and include tucking up of the abdomen, fasciculations in the flank, muscle stiffness, sweating, reluctance to move forward, and overt firm muscle contractures (Fig. 42-19).[178] The hindquarters are frequently affected, but back, abdomen, and forelimb muscles may also be involved. Signs of pain can last for more than 2 hours, and about 10% of cases become recumbent.[178] Less common signs of PSSM in Quarter Horses include gait abnormalities, mild colic, and muscle wasting. During an acute episode of ER, horses with PSSM1 often have markedly elevated serum CK activity of greater than 35,000 U/L and myoglobinuria may be present. Severe colic-like pain post exercise and myoglobinuric renal failure are less common presenting complaints.[8,215]

CHRONIC

Light Breeds. Chronic signs of PSSM1 in riding horses include a lack of energy when under saddle, reluctance to move forward,

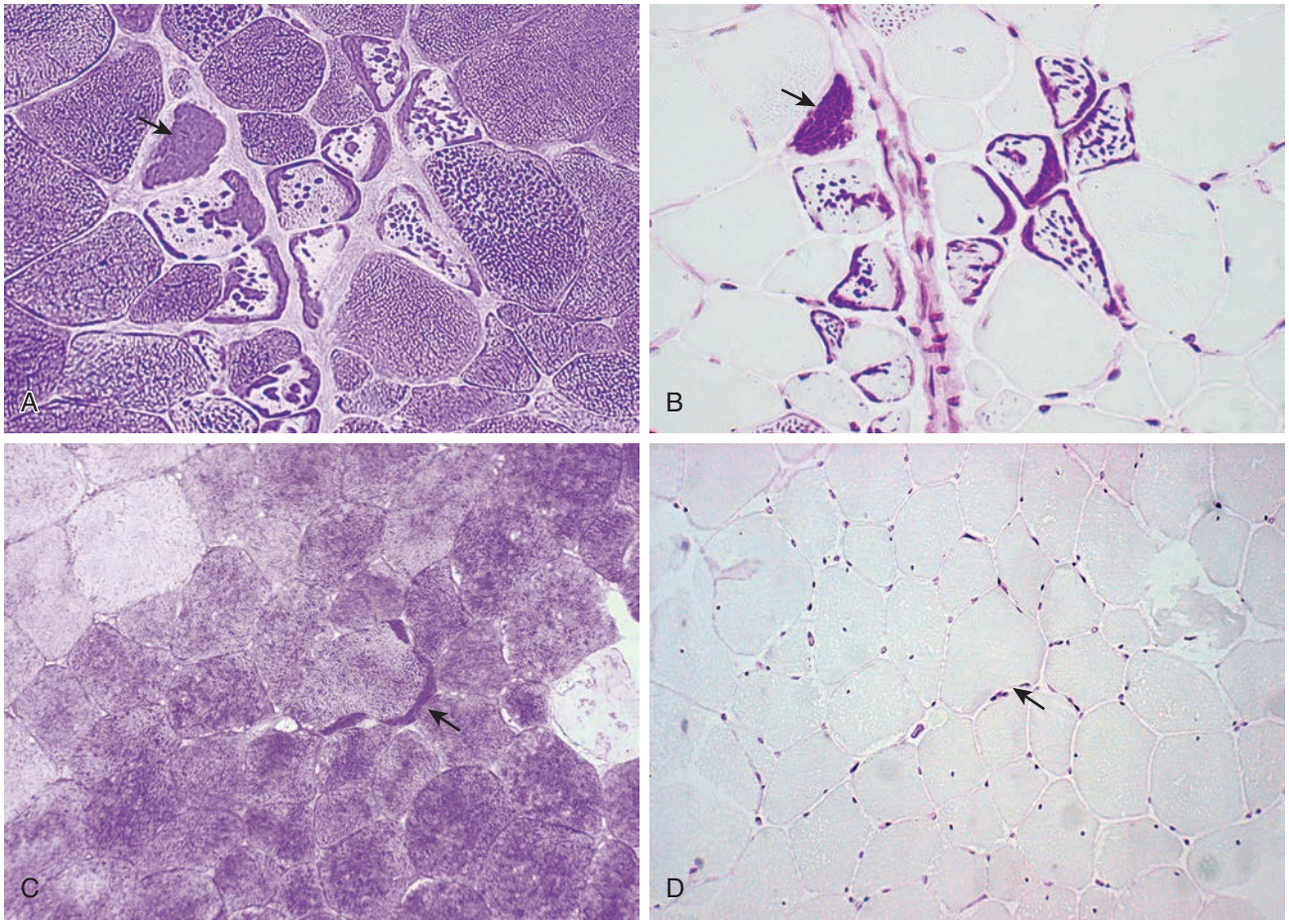


FIG. 42-18 **(A)** Consecutive sections of a gluteal biopsy from a horse with type 1 polysaccharide storage myopathy (PSSM) stained with periodic acid–Schiff (PAS) stain for glycogen and **(B)** amylase-PAS stain. *Arrows* show typical aggregates of intensely staining polysaccharide, which are resistant to amylase digestion. **(C)** PAS and **(D)** amylase-PAS stain of a gluteal biopsy from a horse with type 2 PSSM. *Arrows* show an aggregate of polysaccharide under the sarcolemma, which is sensitive to amylase digestion.

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FIG. 42-19 Typical stance of a horse with polysaccharide storage myopathy after 10 minutes of walking and trotting. Note the tucked-up abdomen and camped-out stance that were concurrent with firm muscles, fasciculations in the flank, and elevated serum CK activity.

stopping and stretching out as if to urinate (see Fig. 42-19), and a sour attitude toward exercise.[178,212] Horses may have a combination of low-grade reluctance to exercise, poor performance, and repeated episodes of ER.[216] PSSM1 may also present in dressage and show-jumpers as chronic back pain, failure to round over fences, and fasciculations or pain on palpation of lumbar muscles.[217] The range of severity of clinical signs of PSSM1 can be wide with complete incapacitation in rare cases. Serum CK activities are often elevated in unmanaged horses, even when horses are rested.[8] The median CK and AST activity for all PSSM1 Quarter Horses with muscle biopsies submitted to the University of Minnesota was 2809 and 1792 U/L, respectively.

A small number of Quarter Horses and Paints have both the *GYS1* mutation and the genetic mutation for malignant hyperthermia *(RYR1).*[208] This results in particularly severe signs of ER and a limited response to diet and exercise changes. During an episode of ER, excessively high body temperatures may develop and sudden death can occur in horses with the *RYR1* mutation. This combination occurs most often in halter and pleasure horses.

Draft Horse and Draft Crosses. The average age of draft horses diagnosed with PSSM is about 8 years of age.[205] Many draft horses with PSSM are asymptomatic. Signs of severe rhabdomyolysis and myoglobinuria may occur in horses fed high grain diets, exercised irregularly with little turnout, or put under general anesthesia.[162,205] Rhabdomyolysis can be so severe that it leads to recumbency and death.[162,215] Other signs of PSSM in draft horses include progressive weakness and muscle loss resulting in difficulty rising in horses with normal serum CK activity. Pronounced weakness is more prevalent in homozygotes for the *GYS1* mutation. Gait abnormalities, such as excessive limb flexion, fasciculations, and trembling, are also reported in draft horses. Although the condition shivers was previously attributed to PSSM, a recent study found no causal association between these two conditions.[205] The median serum CK and AST activities in draft horses from which biopsies were sent to the University of Minnesota were 459 and 537 U/L, respectively.

Pathophysiology

A high NSC diet increases the propensity to develop muscle pain with aerobic exercise in PSSM1 horses.[181,207] A potential scenario in PSSM1 horses on high NSC diets could be that nutrient switches do not fully activate enzymes such as pyruvate dehydrogenase during exercise, limiting adequate acetyl CoA for oxidative metabolism. Although acetyl CoA could also be supplied by fatty acid oxidation, PSSM horses on high NSC diets have low plasma nonesterified free fatty acid concentrations, possibly due to suppression of lipolysis by high insulin.[207] A further factor reducing fatty acid oxidation in PSSM horses on high NSC diets could be that high muscle citrate concentrations direct acetyl CoA away from the citric acid cycle toward malonyl CoA, the committed step for fatty acid synthesis.[218] In addition, accumulation of malonyl CoA causes inhibition of carnitine palmitoyltransferase, the key enzyme necessary to transport long chain fatty acids into the mitochondria for β-oxidation.[219,220] Thus PSSM horses fed high NSC diets may be unable to generate sufficient acetyl CoA from either carbohydrate or fat metabolism to fuel muscle contraction during submaximal exercise. The common occurrence of clinical signs during the first 20 minutes of exercise may be because at this stage of exercise, muscles rely heavily on glycogen/glucose for energy. Low dietary starch and fat supplementation decrease muscle citrate concentrations and increase plasma free fatty acid concentrations, which may well facilitate muscle fat metabolism in PSSM1 horses.[221]

TYPE 2 POLYSACCHARIDE STORAGE MYOPATHY. There is much less known about type 2 PSSM because, as it turns out, previous research on PSSM has largely involved horses with type 1 PSSM. Current knowledge of type 2 PSSM is based on retrospective evaluation of cases diagnosed with PSSM by muscle biopsy[212] that are now known to be free of the *GYS1* mutation and a few years of prospective clinical cases.

Prevalence

Approximately 28% of cases of PSSM diagnosed by muscle biopsy in Quarter Horses have PSSM2 because they do not have the *GYS1* mutation.[195] Type 2 PSSM seems to be common in both high-performance Quarter Horse types such as barrel racing, reining, and cutting horses, as well as pleasure and halter horses. In the United Kingdom approximately 35% of PSSM cases diagnosed by muscle biopsy have PSSM2.[201] It also occurs in Paints, Appaloosas, and Morgans. About 80% of cases of PSSM diagnosed by biopsy in warmbloods have PSSM2.[195] Breeds affected include Dutch Warmbloods (highest prevalence), Swedish Warmbloods, Selle Francais, Hanoverians, Friesians, Westphalian, Canadian Warmblood, Irish Sport Horse, Gerdlander, Hussien, and Icelandic horses. Many other light breeds have also been diagnosed with PSSM2, including Standardbreds, Thoroughbreds, and Arabians.

Pathogenesis

The cause of PSSM2 is currently unknown. Muscle glycogen concentrations are not as high as those found in type 1 PSSM, and glycogenolytic enzyme defects have not been identified in the few cases where enzymes were measured (Valberg, unpublished data). To date, the only reported abnormality in muscle ultrastructure is an increase in normal beta glycogen particles.[213] It may well be that there are a group of conditions currently captured under the term *type 2 PSSM* that have separate etiologies but share common findings of glycogen accumulation and poor performance. A heritable predisposition is suspected in Quarter Horses but yet to be proven.

Clinical Signs

ACUTE. Horses with PSSM2 do not necessarily have the same calm temperament as horses with PSSM1. In adults, acute clinical signs of rhabdomyolysis are similar between type 1 and type 2 PSSM. Muscle atrophy after rhabdomyolysis is a common complaint in Quarter Horses with PSSM2. There are more Quarter Horses younger than 1 year of age reported with PSSM2 than PSSM1, and these foals may present with an inability to rise or a stiff hindlimb gait.[196]

CHRONIC. Chronic signs of PSSM2 are often most closely related to poor performance rather than recurrent ER and elevations in serum CK activity. An undiagnosed gait abnormality, sore muscles, and drop in energy level and willingness to perform after 5 to 10 minutes of exercise are common complaints in horses with PSSM2. Warmbloods with PSSM2 may also have painful firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and slow onset of atrophy. The mean age of onset of clinical signs in warmbloods is between 8 and 11 years of age, with the median CK and AST activity being 323 and 331 U/L, respectively, according to Neuromuscular Diagnostic Laboratory records.

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Diagnosis Type 2 PSSM must be diagnosed by muscle biopsy where increased or abnormal PAS-positive material that is usually amylase sensitive is apparent, particularly in subsarcolemmal locations (see Fig. 42-18, *C* and *D*).[213] Determination of what constitutes an abnormal amount of amylase-sensitive glycogen is subjective, the specificity of the diagnosis may be low, and false-positive diagnoses may occur. Consideration should be made for state of training because highly trained horses have increased glycogen storages as a normal response to training. Further, glycogen is commonly found near capillaries in normal horses and PAS-positive sarcoplasmic masses can be found in 60% of healthy horses, so these should not be diagnostic criteria for PSSM2.[222] Formalin fixed sections show a greater deposition of subsarcolemmal glycogen and precipitation of glycogen in one area of a fiber even in healthy horses, and these should not be considered diagnostic criteria for PSSM2.[18] Other histopathologic features that may be present with PSSM2 include centrally located nuclei, subsarcolemmal vacuoles, muscle necrosis, macrophage infiltration of myofibers, regenerative fibers, and fiber atrophy.[213] Some laboratories grade polysaccharide accumulation as mild, moderate, and severe, where mild accumulation represents a category that has a higher chance of being a false-positive diagnosis. Mild PSSM cases in particular should receive a full physical examination to ensure that there are no other underlying causes for performance problems.

MANAGEMENT OF TYPE 1 AND TYPE 2 POLYSACCHARIDE STORAGE MYOPATHY. Owners need to be aware that any horse diagnosed with PSSM will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses in the most appropriate fashion to minimize clinical signs. With adherence to both diet and exercise recommendations provided in this chapter, at least 70% of horses show notable improvement in clinical signs and many return to acceptable levels of performance.[178,181,212] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function.

REST. PSSM horses that are confined for days to weeks following an episode of rhabdomyolysis often have persistently elevated serum CK activity.[214] In contrast, PSSM horses kept on pasture with little grain supplementation often show few clinical signs of rhabdomyolysis and have normal serum CK activity.[214] As a result, a common recommendation for horses with PSSM is to limit stall confinement to less than 48 hours after an episode of rhabdomyolysis and then provide turnout in paddocks of gradually increasing size. Providing horses with as much free exercise as possible on pasture appears to be beneficial in the long term. If pasture is lush, a grazing muzzle may be necessary.[216] Following an acute episode, excitable horses may require tranquilization before turnout to avoid excessive galloping. Hand walking horses initially recovering from an episode of PSSM for more than 5 to 10 minutes at a time may trigger another episode of rhabdomyolysis.

EXERCISE. The beneficial response to low-starch, fat-supplemented diets only occurs if it is instituted in conjunction with a regular incremental exercise program.[207] Regular daily exercise in PSSM horses over a 3-week period has been shown to produce a dramatic decrease in serum CK responses to exercise, whereas stall confinement often causes elevations in serum CK activity post exercise.[207,214] One common adaptation to daily training is an increase in oxidative capacity in skeletal muscle. The activity of these enzymes, however, was equally low in control Quarter Horses. Whether the beneficial effect of daily exercise on PSSM horses is a result of improved oxidative enzyme capacities or enhanced substrate flux or both has not been elucidated.

EXERCISE REGIMENS. Important principles to follow when starting exercise programs in PSSM horses include (1) provide adequate time for adaptation to a new diet before commencing exercise; (2) recognize that the duration of exercise, not the intensity, is of primary importance; (3) ensure the program is gradually introduced and consistently performed; and (4) minimize any days without some form of exercise. If horses have experienced a moderate to marked episode of rhabdomyolysis recently, 2 weeks of turnout and diet change are often beneficial before recommencing exercise. Exercise should be relaxed, and the horse should achieve a long, low frame without collection. For many horses this is most readily done in a round pen or on a lunge line but can be done under saddle if needed. Successive daily addition of 2-minute intervals of walk and trot beginning with only 4 minutes of exercise and working up to 30 minutes after 3 weeks is often recommended.[8,14] If horses had minor elevations in 4-hour postexercise CK with the 15-minute exercise test, they may begin at 15 minutes of exercise. Owners often do not recognize that walking the horse for 10 minutes or more initially can trigger muscle soreness in PSSM horses. Advancing the horse too quickly often results in an episode of rhabdomyolysis and repeated frustration for the owner. Work can usually begin under saddle after 3 weeks of ground work and can gradually be increased by adding 2-minute intervals of collection or canter to the initial relaxed warm-up period at a walk and trot. Unless a horse shows an episode of overt rhabdomyolysis during the initial first 4 weeks of exercise, reevaluating serum CK activity is not helpful for the first month. This is because it is common to have subclinical elevations in CK activity when exercise is reintroduced, and a return to normal levels often requires 4 to 6 weeks of gradual exercise.[8] Keeping horses with PSSM fit seems the best prevention against further episodes of rhabdomyolysis.

DIETS FOR POLYSACCHARIDE STORAGE MYOPATHY. The basis for designing PSSM diets is the belief that lowering the daily starch and sugar intake and increasing dietary fat content will decrease the glucose load, increase the availability of nonesterified fatty acid for muscle metabolism, and lower serum insulin concentrations.[207] Quarter Horses naturally have little lipid stored within muscle fibers. The end result would thus be decreased uptake of glucose into muscle cells, less substrate available for—and stimulation of—glycogen synthesis and normalization of substrate flux. Owners report that this type of diet improves clinical signs of muscle pain, stiffness, and exercise tolerance in draft horses, warmbloods, Quarter Horses, and other breeds.[178,181,206,212] Dietary change appears to have lesser impact on alleviating gait changes such as shivers.[212]

CALORIC BALANCE. The horse's caloric requirements at an ideal body weight are the most important considerations in designing the diet for PSSM. This is because many horses with PSSM are easy keepers and may be overweight at the time of diagnosis. Adding excessive calories in the form of fat to an obese horse may produce metabolic syndrome and is contraindicated. If necessary, caloric intake should be reduced by using a grazing muzzle during turnout, feeding hay with a low NSC content at 1% to 1.5% of body weight, providing a low-calorie ration balancer, and gradually introducing daily exercise. Rather than provide dietary fat to an overweight horse, fasting for 6 hours before exercise can be used to elevate plasma free fatty acids before exercise and alleviate any restrictions in energy metabolism in muscle.

SELECTION OF FORAGE. Quarter Horses have been shown to develop a significant increase in serum insulin concentrations in response to consuming hay with an NSC of 17%, whereas insulin concentrations are fairly stable when fed hay with 12% or 4% NSC content.[209] Because insulin stimulates the already overactive enzyme glycogen synthase in the muscle of PSSM1 horses, selecting hay with 12% or less NSC is advisable. The degree to which the NSC content of hay should be restricted below 12% NSC depends on the caloric requirements of the horse. Feeding a low NSC hay of 4% provides room to add an adequate amount of fat to the diet of easy keepers without exceeding the daily caloric requirement and inducing

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excessive weight gain. For example, a 500-kg horse on a routine of light exercise generally requires 18 MCal/day of digestible energy (DE). Fed at 2% of body weight, a 12% NSC mixed grass hay almost meets their daily caloric requirement by providing 17.4 MCal/day. Thus with a 12% NSC hay there is only room for 0.6 MCal of fat per day (72 mL of vegetable oil) in order to achieve 18 MCal of energy. In contrast, a 4% NSC Blue Grama hay would provide 13.5 MCal/day, which would allow a reasonable addition of 4.5 MCal of fat per day (538 mL of vegetable oil).

SELECTION OF FAT SOURCE. High-fat diets increase plasma free fatty acid concentrations and thus the availability of fats for oxidation in skeletal muscle.[207] Long-chain fat diets also appear to increase glycogenolytic/glycolytic and oxidative flux in PSSM1 muscle as shown by higher G-6-P, lower lactate, and higher pyruvate concentrations in muscle of PSSM1 horses fed and trained on a commercial high-fat diet (Re-Leve, Kentucky Equine Research, Versailles, Ken.) compared with sweet feed.[209] Thus one means to overcome limitations in delivery of oxidative substrates in PSSM1 horses is to provide ample long-chain fat in the diet. The major sources of dietary fat for horses are vegetable based, including vegetable oils and rice bran or animal-based fat (tallow [solid rendered fat of cattle and sheep], lard, fish oil). Vegetable oils are highly unsaturated, very digestible (90% to 100%), and very energy dense. Suitable forms include soybean, corn, safflower, canola, flaxseed, linseed, peanut, and coconut. Controlled research studies in exercising PSSM horses have shown a decrease in muscle pain and serum CK in response to the addition of corn oil[221] and also a concentrate of soybean oil and rice bran (Re-Leve).[207,221] The amount of oil added in these trials constituted at least 13% of daily digestible energy (DE). Some veterinarians have advocated as much as 25% of DE be fed in the form of fat to PSSM horses.[182] As discussed earlier, the principal consideration here should be whether this provides excessive calories and additional weight gain because feeding 13% DE as fat may well be effective in reducing muscle pain. Limited research has been performed on the form of oil to feed PSSM horses. Whether there is any direct beneficial effect on skeletal muscle of providing energy in the form of omega-3 versus omega-6 fatty acids has yet to be determined. Due to the potential additional oxidant stress of fats, vitamin E (1000 to 5000 U/day) should be fed to horses receiving high oil diets.

LOW-STARCH, HIGH-FAT CONCENTRATES. Although oils are energy dense and inexpensive, they have the disadvantages of being messy, unpalatable to some horses, prone to rancidity in warm temperatures, and difficult to feed in large amounts. As such, a number of concentrates have been developed that contain fats. The important principle to be met by such feeds is that the starch and sugar components are low enough and fat supplementation high enough to ensure that in the total diet, the calories supplied by NSC comprise no more than 10% to 15% of the daily DE and the calories supplied by fat comprise about 12% to 15% of daily DE.[207] Common fat sources used in such concentrates include, in addition to the oils mentioned earlier, stabilized rice bran or animal fats. Rice bran and its products are palatable to most horses, have a moderate NSC content approximately 25% by weight, contain approximately 20% fat by weight, as well as vitamin E, and are naturally high in phosphorus. The NSC component of rice bran can vary if the manufacturing process is not careful to exclude the white rice grain. Commercial rice bran products occur as powder or an extruded pellet and are considerably more stable in warm temperatures compared with animal fat and vegetable oils. A number of well-balanced, low-starch, high-fat commercial diets are suitable for horses with PSSM.[207] Some commercial feeds meet the recommended nutritional needs of PSSM horses in one pelleted ration. These feeds typically contain at least 10% to 15% fat by weight and less than 20% NSC by weight. Some feed companies offer similar nutritional content by blending two or more manufactured feeds or by supplementing with oils or rice bran. At present, the NSC content of equine feed products is not consistently listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers in designing an appropriate diet. There is a great deal of variation in individual tolerance to dietary starch; however, horses with more severe clinical signs of PSSM appear to require the greatest restriction in starch intake.

EXPECTATIONS. The beneficial effects of low-starch, high-fat diets require that horses are trained daily to enhance enzymes involved in fat and glucose metabolism. It is important to note that a horse diagnosed with PSSM will always have an underlying predilection for muscle soreness, and the best that can be done is to manage horses to minimize clinical signs. With adherence to both the diet and exercise recommendations, 70% to 75% of Quarter Horses and warmbloods show notable improvement in clinical signs and many return to acceptable levels of performance.[178,182,212,216] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function. PSSM horses that also have the mutation for malignant hyperthermia do not respond as well to diet and exercise recommendations and may continue to develop ER with the possibility of a fatal episode.[208]

Recurrent Exertional Rhabdomyolysis

The term *recurrent exertional rhabdomyolysis* (RER) describes a subset of ER that is believed to be due to an abnormality in the regulation of muscle contraction and relaxation.[7,19,21,223] Research into RER has primarily been performed in Thoroughbreds and, to a lesser extent, Standardbreds.[21,176,204,224] Scientific studies of RER have used a small number of horses that share common clinical signs of ER and have abnormal muscle contracture tests.[19-21] Broader epidemiologic and genetic studies have assumed that the same pathophysiologic basis for ER exists in the majority of Thoroughbreds and Standardbreds with similar clinical signs. Whether this is true or not will require more research. There are reports of some Arabians and warmbloods[212] with ER that may also suffer from RER on the basis of overlapping histories, clinical signs, muscle biopsy findings, and response to management.

Pathogenesis Rhabdomyolysis is triggered suddenly during exercise in RER horses, which results in a sharp rise in serum myoglobin and CK activity.[6] Clinically, the triggering event is often associated with excitement in a horse that already has an underlying nervous temperament.[176,204,224] Serum cortisol concentrations are higher in RER horses than normal horses before exercise and increase during an episode of ER.[225] Serum concentrations of epinephrine and norepinephrine are normal before an episode but increase dramatically in horses with marked elevations in serum CK activity.[225]

EXERCISE AND EXCITEMENT. In Standardbreds, ER commonly begins after 15 to 30 minutes of jogging at 5 m/sec, although clinical signs may not be apparent until after exercise.[6,204] In Thoroughbreds exercising on the treadmill, ER most commonly develops with intervals of walk, trot, and canter and is less common if horses are allowed to gallop.[226,227] At the racetrack, ER occurs commonly when RER horses are held back to a paced gallop.[224] During eventing, RER commonly occurs after the excitement of the steeplechase or early in the cross-country phase when horses are held to a predetermined speed. ER rarely occurs when horses are allowed to achieve maximal exercise speeds such as in racing.[176,204,224,228,229] A day or more of rest before this type of exercise results in higher serum CK activity post exercise.[204,227]

There is no basis for an association between RER and lactic acidosis.

INTRACELLULAR CALCIUM REGULATION. More recent research suggests that horses with RER may have an inherent

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abnormality in intramuscular calcium regulation that is intermittently manifested during exercise.[19,230] Basal muscle intracellular calcium concentrations in RER horses are similar to healthy horses on the basis of assays in muscle cell cultures.[230] Higher intracellular calcium concentrations have been measured in horses of unspecified breeds during an episode of ER; however, this also could be secondary to any insult that impairs energy generation or cell membrane integrity. Contracture testing has been performed in horses using surgically excised bundles of brachiocephalicus,[20] semimembranosus,[21] or external intercostal muscle.[19] Early studies by Hildebrand[20] suggested that some but not all horses with ER showed a lower threshold for caffeine- and halothane-induced muscle contractures than healthy horses. Waldron-Mease[231] and Beech[21] found that caffeine contracture thresholds were lower in semimembranosus muscle from Thoroughbreds and Standardbreds susceptible to RER versus breed-matched controls. Lentz studied intact external intercostal muscle fibers from six Thoroughbreds with RER and found a lower contracture threshold for triggering agents such as potassium, caffeine, and halothane but not 4-chloro-m-cresol compared with control horses.[19,230] An abnormality in intracellular calcium regulation was also supported by a muscle cell culture study of RER Thoroughbred horses.[230] A lower threshold for induction of myoplasmic calcium release by caffeine was found in myotube cultures from six RER Thoroughbreds compared with controls. Thus all of these studies supported an abnormality in intracellular calcium regulation in most of the Thoroughbred or Standardbred horses studied.[232] However, studies of isolated muscle membranes have not conclusively identified any specific abnormalities in intracellular calcium regulation in RER horses. Further, genetic linkage analysis using 96 horses in 4 families of Thoroughbred horses segregating for RER did not find an association linking RER with the calcium regulatory genes *RYR1* (ryanodine receptor), *SERCA* (SR ATPase), or *DHPR1* (dihydropyridine receptor).[233] Thus in spite of many detailed investigations of a small number of horses, the exact defect in regulating muscle contraction in RER horses has yet to be identified.

Prevalence and Risk Factors

Assuming that the majority of cases of ER at racetracks are due to RER, the prevalence in Thoroughbred racehorses is remarkably similar around the world with estimates ranging from 4.9% in the United States[224] to 5.4% in Australia[173] to 6.7% in the United Kingdom.[176,229] The annual incidence of ER in Standardbred racehorses in Sweden is 6.4%.[204] Exercise obviously increases the prevalence of RER in horses, and episodes are observed more frequently once horses achieve a level of fitness.[204,224]

In Standardbreds and Thoroughbreds, mares more commonly have RER than males[176,204,224]; however, no general correlation has been observed between episodes of rhabdomyolysis and stages of the estrus cycle.[234] There is an interaction between age and gender in RER Thoroughbred horses such that the proportion of affected females to males is much higher in young horses compared with older age groups.[224] Swedish Standardbreds with RER, which do not begin racing until 3 years of age, did not show the same age association with RER as Thoroughbreds.[204] Temperament has a strong effect on the expression of RER in both Standardbreds and Thoroughbreds, with nervous horses, particularly fillies, having a higher incidence of rhabdomyolysis than calm horses.[176,204,224] Young fillies are more likely to have a nervous temperament than mares or male horses. Diet also has an impact with Thoroughbred horses fed more than 2.5 kg of grain per day being more likely to show signs of RER.[226] One study also found a higher prevalence of rhabdomyolysis among Thoroughbred horses with lameness.[224] A few days of rest before exercise increases the degree of elevation on serum CK activity with the next exercise session and in practice predisposes horses to an episode of ER.[227]

Genetics

A genetic susceptibility to RER appears to exist in Thoroughbred horses where RER-afflicted Thoroughbreds may pass the trait along to 50% or more of their offspring.[179,235] A breeding trial conducted at the University of Minnesota evaluated the number of offspring of an RER horse that had a positive contracture test.[179] Results supported an autosomal dominant mode of inheritance with an equal ratio of male- and female-affected Thoroughbred offspring. Using a clinical diagnosis of RER rather than contracture test, offspring of RER-affected dams also appeared to inherit the disorder as a dominant trait with a predominance of females having clinical signs.[179] The variable penetrance of the disease, however, and other potential modifying genes make this hard to firmly evaluate. A recent genome-wide association study in U.S. Thoroughbred horses found a significant association between RER and SNP markers on equine chromosome 16.[236] The location of this association is different from that reported by a Japanese group.[237] Studies of allelic frequencies of genetic markers in Standardbred horses with RER were significantly different from healthy Standardbred horses, suggesting that there is potentially a heritable basis for this condition in this breed as well.[238] Of note is the finding that Standardbred trotters with a history of RER actually have faster racing times from a standstill start than those without a history of RER, suggesting the trait may have beneficial and deleterious effects.[204] There are also anecdotal reports of higher prevalence of RER in certain Arabian horse families. Thus although there is a familial tendency for RER, its genetic basis has not yet been defined.

Diagnosis

A presumptive diagnosis of RER is based on clinical signs of muscle pain and the presence of risk factors commonly associated with RER. Muscle histopathology is nonspecific in RER horses; either no abnormalities or evidence of centrally located nuclei in mature fibers and potentially waves of myofiber degeneration or regeneration is found.[7] There is a notable absence of abnormal amylase-resistant polysaccharide, although increased subsarcolemmal amylase-sensitive glycogen may be present.[217] The value of a muscle biopsy as a diagnostic tool in horses with suspected RER is largely confined to particularly recurrent unmanageable cases where a need arises to rule in or out other forms of ER. Serum CK and AST activities serve as the basis for detecting muscle degeneration, and they often show intermittent abnormal elevations that return to normal relatively quickly during the course of training. If CK elevations are mild, there are a number of factors to consider. Timing of the sample with regard to the onset of ER and exercise are important. Reliability is improved by obtaining blood samples at a standardized time after exercise, preferably 4 to 6 hours when CK peaks, and consistently with regard to exercise on the preceding day because serum CK activity is higher on exercise days that are preceded by a day or more of rest.[175] In addition, normal values need to be adjusted for the age and sex of horses. Two-year-old fillies generally have greater fluctuations in serum CK activity during race training than 3-year-old fillies or geldings.[175]

Management

Prevention of rhabdomyolysis in horses susceptible to RER is complex, and multiple factors need to be changed to decrease episodes. These factors include the environment, the exercise regimen, and diet. In addition, medication may be necessary at times to prevent further episodes of muscle damage.

ENVIRONMENT. Because excitement and nervousness often trigger rhabdomyolysis, stressful situations in the environment that can be modified need to be identified.[176,204,224] This may involve a change to a smaller barn with fewer horses and fewer handlers, compatible companions, and a more consistent daily routine. Many stressed RER-susceptible horses respond to a regular routine including feeding first before other horses and training first before other horses, especially if the horse becomes impatient while waiting. Other horses respond to being housed in a quiet area of the barn next to calm, companionable horses. The use of hot walkers, exercise machines, and swimming pools needs to be evaluated on an individual basis because some horses develop

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rhabdomyolysis when using this type of equipment. Horses that develop rhabdomyolysis at specific events, such as horse shows, may need to be reconditioned to decrease the stress level associated with such events or tranquilized as part of the accommodation process. Providing daily turnout with other horses seems to be beneficial for RER horses and may decrease anxiety and thereby the likelihood of rhabdomyolysis.

EXERCISE. Although a period of rest is recommended for sporadic forms of ER until serum CK normalizes, it is not recommended for horses with RER.[14] Daily exercise is important in preventing episodes of rhabdomyolysis and therefore when serum CK is less than about 3000 U/L horses are returned to regular daily exercise. Horses with more severe episodes of rhabdomyolysis may require additional time off in a paddock before gradually resuming exercise. Once back in training, some form of daily exercise is recommended. Avoiding fighting to hold racehorses to slower speeds during galloping may decrease rhabdomyolysis in RER-susceptible Thoroughbreds. Interval training and reduction of jog miles to no more than 15 minutes per session will benefit Standardbreds. For horses under saddle, a relaxed warm-up with intermittent periods of long low stretching may be of benefit and continued breaks to stretch between episodes of collection are recommended. Event horses may require training that incorporates calm exposure to speeds achieved during the steeplechase or cross-country phase, especially when used in an interval training program.

DIET. A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals are the core elements of managing RER. For RER Thoroughbreds and Standardbreds in training, the challenge is usually supplying enough calories in a highly palatable form to meet their daily energy demands. This is in part because they often require more than 30 MCal of digestible energy (DE) a day (5 kg sweet feed, 1.5% of body weight in hay), and because of their nervous temperament they may be more discriminating in their eating habits. Out of the total daily calories required by RER horses, research suggests that less than 20% DE be supplied by NSCs (starch and sugar) and at least 20% of DE be supplied by fat.[227]

Selection of Forage. Thoroughbred horses do not appear to show the same significant increase in serum insulin concentrations in response to consuming hay with an NSC of 17% as seen in Quarter Horses (Borgia L, 2010 PhD thesis, University of Minnesota). This fact combined with the high caloric requirements of racehorses may mean that it is not as important to select hay with very low NSC content in RER Thoroughbreds as it is in PSSM horses. Anecdotally, some trainers find horses with RER have more frequent episodes on alfalfa hay. The nervous disposition of some RER horses may predispose them to gastric ulcers, and thus frequent provision of hay with a moderate NSC and mixed alfalfa content may be indicated.

Low-Starch, High-Fat Concentrates. When RER Thoroughbreds are fed a moderate caloric intake (24 MCal/day) in the form of high-starch concentrates (2.5 kg of corn/oats/wheat middlings/molasses), they show little elevation in serum CK activity with exercise.[226] Most Thoroughbred racehorses, however, are fed at least 5 kg of high-starch concentrate/day at 30 MCal or more/horse/day and at this level of feeding, postexercise serum CK activity rises significantly.[224] The discovery that substitution of fat for starch in a high-calorie ration significantly reduces muscle damage in exercising RER horses was a major advance in nutritional management of RER.[227] Practically, however, it was difficult to achieve the desired caloric intake of racehorses because the maximum amount of fat that finicky Thoroughbreds will happily consume is limited often to 600 mL for vegetable oil or 5 lb/day of balanced rice bran. Management of RER horses was significantly improved when a palatable means to provide the amount of fat required by fit finicky RER Thoroughbreds was developed. A controlled trial using a specialized feed developed for RER (Re-Leve 13% fat by weight and 9% NSC) determined that NSC should be no greater than 20% of daily DE and 20% to 25% of daily DE should be provided by fat for optimal management of RER horses fed 30 MCal or more/day.[227] No beneficial effect on serum CK activity occurred when sodium bicarbonate (4.2% of the pellet) was added to a high-starch pellet feed.[227] The amount of fat in the diet of an RER horse depends on its caloric requirements. Over and above hay at 1.5% to 2% of body weight and 2.5 kg of grain, any additional calories should be supplied by fat.

The benefit of a fat diet does not appear to be a change in muscle metabolism. Muscle glycogen and lactate concentrations before and after exercise are the same in RER horses fed a low-starch, high-fat diet compared with a high starch.[239] Rather, low-starch, high-fat diets in RER horses may decrease muscle damage by assuaging anxiety and excitability, which are tightly linked to developing rhabdomyolysis is susceptible horses. High-fat, low-starch diets fed to fit RER horses produce lower glucose, insulin, and cortisol responses and lead to a calmer demeanor and lower pre-exercise heart rates.[240] Neurohormonal changes may develop in response to high serum glucose, insulin, and cortisol concentrations resulting in an anxious demeanor. Although a calm demeanor is desired during training, some racehorse trainers feeding low-starch, high-fat feeds prefer to supplement with a titrated amount of grain 3 days before a race to potentially increase liver glycogen and increase a horse's energy during the race.

Expectations. Studies in RER horses show that significant reductions or normalization of postexercise serum CK activity occurs within a week of commencing a low-starch, high-fat diet.[227] Days off training in a stall are discouraged because postexercise CK activity is higher following 2 days of rest compared with values taken when performing consecutive days of the same amount of submaximal exercise.

SUPPLEMENTS. Horses require daily dietary supplementation with sodium and chloride either in the form of loose salt (30 to 50 g/day) or a salt block. Additional electrolyte supplementation is indicated in hot, humid conditions. A myriad of supplements that are purported to decrease lactic acid buildup in skeletal muscle of RER horses are sold. These include sodium bicarbonate, B vitamins, branched chain amino acids, and dimethylglycine. Because lactic acidosis is no longer implicated as a cause for rhabdomyolysis, it is difficult to find a rationale for their use.

MEDICATIONS. Low doses of tranquilizers such as acepromazine before exercise have been used in RER horses prone to excitement.[241] A dose of 7 mg IV 20 minutes before exercise is reported to make horses more relaxed and manageable.[61] Reserpine and fluphenazine, which have a longer duration of effect, have also been used for this purpose. Horses given fluphenazine may occasionally exhibit prolonged bizarre behavior. Use of tranquilizers may only be necessary when horses are in their initial phase of training and accommodation to a new environment. Horses obviously cannot compete on these medications, and withdrawal times must be observed.

Dantrium sodium acts to decrease release of calcium from the ryanodine receptor in skeletal muscle and is used to treat malignant hyperthermia. Studies of intact equine intercostal muscle from ER horses show that dantrolene lowers already elevated myoplasmic calcium concentrations.[242] Controlled and field studies have also shown that oral dantrolene can significantly decrease signs of rhabdomyolysis in RER horses.[155,243] One study indicated that horses need to be fasted to achieve measurable blood levels of dantrolene,[155] but more recent controlled trials suggest that absorption of dantrium is superior in fed versus fasted horses (McKenzie, personal communication). Administration of 4 mg/kg of dantrium PO 1 hour before exercise to RER-susceptible horses fed high-grain diets resulted in significantly lower serum CK activity 4 hours after exercise compared with placebo.[155] A dose of 800 mg of dantrium was given to Thoroughbred horses in the United Kingdom 1 hour before exercise and

resulted in significantly lower postexercise CK activity than a placebo.[243]

Phenytoin has been reported to be effective in preventing rhabdomyolysis in horses with RER.[244] Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 µg/mL and not to exceed 12 µg/mL.[245] Drowsiness and ataxia are evidence that the dose of phenytoin is too high, and the dose should be decreased by half. Initial dosages start at 6 to 8 mg/kg orally twice a day for 3 to 5 days, and if the horse is still experiencing rhabdomyolysis but is not drowsy, the dose can be increased by 1-mg/kg increments every 3 to 4 days. Most horses require a dose of 10 to 12 mg/kg PO bid. Phenytoin is a monoaminoxidase activator and can affect dosages of other medications. Unfortunately, long-term treatment with dantrolene or phenytoin is expensive and these drugs must be withdrawn before competition.

HORMONE THERAPY. Various hormones, ranging from thyroxine to progesterone and testosterone, have been given to horses with RER. Initial studies linking low T3 and T4 concentrations in horses with ER have not been substantiated.[246,247] Some mares appear to exhibit signs of rhabdomyolysis during estrus, and it may well be of benefit in these horses to suppress estrous behavior using progesterone injections. Testosterone and anabolic steroids have been used at racetracks to prevent signs of RER, but their use is no longer permitted.

ADJUNCT THERAPIES. Massage, myofascial release, mesotherapy, stretching, aqua treadmills, and hot/cold therapy performed by experienced therapists may be of benefit in individual cases.[248-250] Their use may promote relaxation and normal muscle tension and build muscle strength.

Malignant Hyperthermia

Malignant hyperthermia (*RYR1* mutation) in Quarter Horses and Paints has also been linked to exertional rhabdomyolysis.[161,251] It is caused by an autosomal dominant mutation that exists in exon 46 of the skeletal muscle *RYR1* gene on ECA 10.

Prevalence and Risk Factors MH is a rare disorder in Quarter Horses and Paints, affecting less than 1% of the breed. Halter and pleasure horse lines have the highest prevalence. Rhabdomyolysis may be induced by exercise and anesthesia but can be extremely intermittent in nature.[251]

Clinical Signs Horses with the *RYR1* mutation may intermittently show signs of ER and high body temperatures.[96] Some MH-affected horses have died suddenly after an episode of ER. Horses with the MH mutation may also have the *GYS1* mutation associated with type 1 PSSM.[62] Such horses have more severe episodes of ER, higher serum CK activity after exercise, and a more moderated response to the diet and exercise regimens recommended for type 1 PSSM.[62]

Diagnosis Genetic testing is recommended in Quarter Horses and Paints with difficult-to-manage forms of PSSM or a family history of postanesthetic complications. Testing is available through the Veterinary Diagnostic Laboratory at the University of Minnesota (http://www.vdl.umn.edu/ourservices/equineneuromuscular/home.html) and at the University of California, Davis. Muscle biopsy is not particularly useful for diagnosing MH. Biopsies may contain mild myopathic changes including increased variation in fiber sizes, centrally located nuclei, fiber necrosis, glycogen depletion, and ring-binden fibers.

Treatment The nature of ER with horses positive for MH is so intermittent that it is hard to justify premedication with dantrolene before exercise.

Hereditary/Congenital Myopathies

Stephanie J. Valberg

Mitochondrial Myopathy

A deficiency of Complex 1, the first step in the mitochondrial respiratory chain, has been identified in a young Arabian filly that was presented for veterinary attention with clinical signs similar to ER.[252] In contrast to cases of ER, however, this horse showed no changes in serum creatine kinase following exercise. A marked lactic acidosis developed even with light exercise, and maximum oxygen consumption was drastically reduced, resulting in marked exercise intolerance. Histopathologic evaluation of muscle biopsies showed an abnormal increase in mitochondrial density, and biochemical analyses revealed a Complex 1 deficiency. The horse has shown slowly progressive signs of muscle atrophy but has otherwise remained healthy at rest.

Glycogen Branching Enzyme Deficiency

Glycogen branching enzyme deficiency (GBED) is a glycogen storage disorder causing abortion, seizures, and muscle weakness in Quarter Horse–related breeds.[253-255] It represents a separate glycogen storage disorder from PSSM. GBED is caused by a nonsense mutation in exon 1 of the *GBE1* gene at codon 102, which introduces a premature stop codon.[255] Nine percent of the breed is a carrier of this autosomal recessive mutation, and 3% of abortions are attributed to this disease in Quarter Horses.[253] The prevalence of carriers is particularly high in pleasure horses with 26% of pleasure horses carrying the *GBE1* mutation.[55] Most foals diagnosed with GBED have presented with hypothermia, weakness, and flexural deformities of all limbs at 1 day of age. Ventilatory failure may also be a presenting sign in addition to recurrent hypoglycemia and collapse. All foals have died from either euthanasia because of muscle weakness or suddenly because of apparent cardiac arrhythmia. Persistent leukopenia, intermittent hypoglycemia, and high serum CK (1000 to 15,000 U/L), AST, and γ-glutamyltransferase (GGT) activities are features of affected foals. Gross postmortem changes are not evident, and routine hematoxylin and eosin stains of tissues may be normal or show basophilic inclusions in skeletal muscle and cardiac tissues. Frozen sections of muscle, heart, and liver show a notable lack of normal PAS staining for glycogen, as well as abnormal PAS-positive globular or crystalline intracellular inclusions (Fig. 42-20). Branching enzyme activity is minimal in skeletal and cardiac muscle, as well as liver. A diagnosis is best obtained by confirming the presence of the genetic mutation

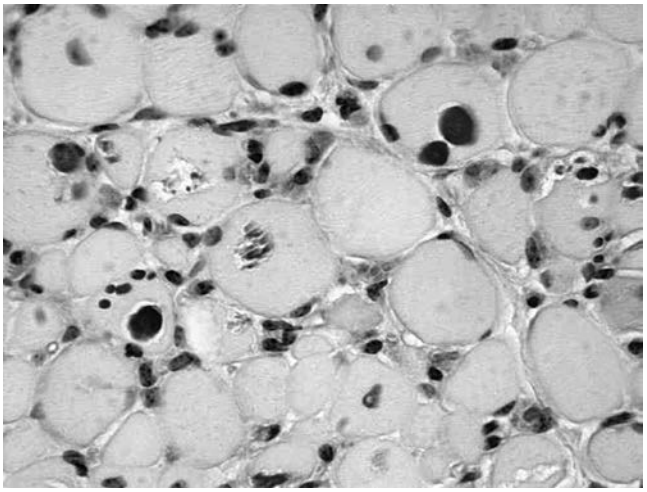


FIG. 42-20 Periodic acid–Schiff (PAS) stain of skeletal muscle from a foal with glycogen branching enzyme deficiency. Note the lack of normal diffuse magenta staining for glycogen and the presence of globular and crystalline PAS-positive inclusions.

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in tissue samples or by identifying typical PAS-positive inclusions in muscle or cardiac samples.[253-255]

Phosphorylase Deficiency in Charolais Cattle

A deficiency of the enzyme phosphorylase (McArdle disease) has been identified in Charolais cattle in the United States and New Zealand and in sheep in Australia.[256-260] Cattle show exercise intolerance and often collapse when forced to exercise. Serum CK is elevated, and severe rhabdomyolysis clinically resembling white muscle disease may be present. Screening for myophosphorylase can be performed by histochemical staining for phosphorylase activity in frozen sections of muscle biopsies. Confirmation of the autosomal recessive disease is obtained by biochemical analyses or identification of the base pair sequence defect. In Charolais a C-to-T substitution, which changes an encoded arginine (CGG) to tryptophan (TGG) at codon 489, is present and in sheep a splice-site mutation is present in intron 193. This disease should be considered as a differential diagnosis for white muscle disease in animals that are found to have normal vitamin E and selenium status.

Pseudomyotonia in Cattle

Chianini and a Dutch Improved Red and White crossbreed heifer that have a form of pseudomyotonia characterized by delayed relaxation of muscle have been identified. Clinical signs include exercise-induced muscle stiffness with normal response to muscle percussion. In contrast to myotonia, electromyography and muscle histochemistry are normal. Missense mutations have been identified in the *ATP2A1* gene encoding the sarcoplasmic reticulum SERCA1 protein.

Porcine RN(–) Glycogen Storage Disease

The RN(–) (rendement Napole) phenotype is common in Hampshire pigs. Clinically pigs appear normal; however, the 70% increase in glycogen content in skeletal muscle causes poor meat content at slaughter. It is due to an autosomal dominant mutation in the protein kinase AMP-activated gamma 3 subunit gene *(PRKAG3),* which encodes the gamma 3 isoform of AMP-activated protein kinase. The mutation affects meat quality of pigs by increasing the glycogen content of muscle.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 43

Diseases of the Reproductive System

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Female Reproductive Disorders

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Nonpathogenic Infertility

Breeding Season

Mares

The mare is a seasonally polyestrous animal, breeding during seasons of long day length. Annual breeding and nonbreeding seasons are divided by fall and spring transitional periods, which are characterized by erratic reproductive behavior and irregular estrous cycles.

Clinical Signs During the breeding season, mares ovulate every 21 days (range 19 to 22 days).[1] Estrus (5 to 7 days, but variable) is characterized by the presence of an ovarian follicle, serum progesterone level of less than 1 ng/mL, and sexual receptivity. During estrus the cervix is palpably relaxed and the uterus is edematous. One or two follicular waves occur per cycle, and preovulatory follicles are 45 to 60 mm in diameter, often with a cone-shaped appearance on ultrasonography.[2] Ovulation occurs 24 to 48 hours before the end of estrus and may be accompanied by ovarian sensitivity.[1] The ruptured follicle is replaced by a corpus luteum (CL). Diestrus (luteal phase) is predictable in length because regression of the CL, caused by release of endometrial prostaglandin $F_2\alpha$ ($PGF_2\alpha$), occurs 14 to 15 days after ovulation.[3] During diestrus and early pregnancy the cervix is tight and the uterus has increased tone. Diestrous ovulations occur and may be fertile.[4] First postpartum estrus ("foal heat") begins in the week after foaling, and ovulation occurs in most mares 7 to 15 days postpartum.

Ruminants

COWS. Cows are polyestrous, but seasonal differences in fertility may be caused by climate. The estrous cycle averages 21 days (range 17 to 25 days), and the duration of estrus averages 12 to 16 hours (range 6 to 24 hours). Cows are unique among domestic animals in that they ovulate spontaneously after the end of estrus, 24 to 30 hours after the beginning of estrus.[5]

In the absence of a bull, estrus can be detected in cows by their homosexual (bisexual) activity. Cows that stand to be mounted by another cow are in estrus (standing heat). Secondary signs that may be helpful in detecting estrus include restlessness and increased activity, vulvar hyperemia and edema, and a clear mucous discharge. Errors in heat detection are a common cause of infertility on large dairy farms.[6] The optimum time for insemination of cows is between 16 and 24 hours after the onset of estrus. Insemination of cows on the basis of standing to be mounted results in a higher pregnancy rate than if it is based on secondary signs of estrus.[7] Well-managed dairy cows with uncomplicated periparturient experiences may ovulate approximately 20 to 25 days after calving, whereas beef cows with nursing calves usually do not ovulate until 40 or more days after calving. The presence of the calf appears to be responsible for the difference in return to cyclicity.[8]

SHEEP. Coarse-wooled breeds of ewes are seasonally polyestrous during the autumn and winter (short photoperiod) in temperate climates. Ovulation can be induced in seasonally anestrous ewes by artificial simulation of day length and temperatures characteristic of autumn (reduced photoperiod and reduced ambient temperature), but the long latency period required for response to manipulation of light and temperature makes the procedure impractical. Ewes of fine-wooled breeds may be polyestrous throughout the year if adequately nourished. The estrous cycle of ewes averages 17 days (range 14 to 19 days), and the duration of estrus averages 36 hours. Ovulation occurs spontaneously 24 hours after the onset of estrus. Ewes display few, if any, signs of estrus unless a male is present. The primary signs of estrus include seeking the ram and standing for mating. Secondary signs include restlessness and rapid tail switching; vulvar edema and discharge of clear cervical mucus may be observed occasionally. Lambing ordinarily occurs during the anestrous season; therefore ewes do not return to estrus until the next breeding season.[5]

GOATS. Does in temperate climates are seasonally polyestrous from late summer until early spring (short photoperiod). Onset of the breeding season in yearling does can be advanced by exposing them to 19 hours of artificial light per day for 70 days beginning in mid to late winter. Termination of artificial light results in a relative decrease in day length and stimulation of estrus and ovulation.[5] Alternatively, the breeding season may be hastened by exposing does to 14 to 18 hours of light per day for 3 months, followed by a

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reduction to 6 hours of light per day.[7] The estrous cycle averages 21 days, and estrus lasts 18 to 36 hours. Ovulation occurs spontaneously 24 hours after the onset of estrus. An intact male or male pheromone is usually necessary for estrous detection. The primary signs of estrus are seeking the buck and standing for service. Secondary signs of estrus in does include rapid tail switching, restlessness, increased frequency of urination and vocalization, transient decrease in appetite and milk production, and edema and hyperemia of the vulva. As in sheep, parturition takes place during the anestrous season, and return to cyclicity in does is delayed until the next breeding season.[5]

CAMELIDS. South American camelids bred in North America are nonseasonal. In keeping with management decisions, they are often bred in a seasonal manner to avoid having newborn crias during the hottest or coldest months of the year. Some consider the South American camelids to be polyestrous, whereas others argue that they do not have a true estrous cycle.[9] These discrepancies arise from the fact that camelids are induced ovulators. Cyclic ovarian activity (e.g., transition from estrus to diestrus) is caused by coital activity. Unbred female camelids essentially exhibit estrous behavior continually, with perhaps short, occasional, unpredictive intervals of 1 to 2 days of decreased receptivity. Follicular waves in alpacas and llamas last around 17 days. Small follicles (<3 mm) are always present on the surface of the ovaries. After recruitment, follicles grow to approximately 5 mm in size. Dominance is established when one of the follicles reaches the size of 6 mm, and the female will show signs of receptivity to the male as long as a dominant follicle is present. The sizes of preovulatory follicles are 9 to 13 mm and 8 to 12 mm in the llama and alpaca, respectively. Females maintain fertile, dominant follicles for an average of 8 days before undergoing regression. Usually the next follicular wave has already produced the next dominant follicle before the previous preovulatory follicle begins to regress. For this reason, the female camelid usually maintains estrous behavior continually until she is mated.[9]

Cystic Follicular Degeneration

Cows

Ovarian cysts are follicle-like ovarian structures that arise because of failure of ovulation of a dominant follicle.[5,10] They are usually larger than 25 mm in diameter and persist in the absence of a CL for 10 days or more. Follicular cysts have thin walls and may be single, multiple, or multilocular structures on one or both ovaries. Partially luteinized cysts tend to be single, unilateral structures with thicker walls because of the presence of luteal tissue.

The mechanism by which ovulation fails and cysts develop is not known. Failure of ovulation may result from inadequate release of gonadotropins or ovarian dysfunction. Increased stress of conditions such as retained placenta, metritis, and hypocalcemia around the time of calving and postpartum ketosis have been associated with an increased prevalence of cystic follicular degeneration (CFD), as has a hereditary predisposition.[11] Negative energy balance in high-producing dairy cows, as well as prolonged suckling in beef cows, may inhibit lutenizing hormone release from the pituitary and subsequent failure of ovulation.[12]

Clinical Signs and Diagnosis Approximately 70% to 80% of cows affected by CFD are anestrus, whereas 20% to 30% display frequent or intense estrus (nymphomania). Cystic ovarian disease affects 10% to 30% of dairy cows. The condition is rare in commercial beef cows because of rigid culling for reproductive failure.

The physical appearance of cows with CFD depends on the duration of the condition. No changes are apparent after a short time, but in long-standing cases relaxation of the pelvic ligaments may result in prominence of the tailhead and masculine characteristics such as a crested neck.

The diagnosis of CFD is based on an accurate history and clinical examination. A history of constant or frequent estrus, short interestrous intervals, or anestrus may suggest CFD. Examination of the ovaries by palpation per rectum reveals the presence of enlarged fluid-filled structures raised above the surface of the ovary that greatly increase total ovarian size. Ovarian cysts are larger (>25 mm) than preovulatory follicles (15 to 25 mm). Differentiation between a single large cyst and several smaller cysts on the same ovary may require ultrasonographic examination, as does recognition of the presence of partially luteinized cysts (based on peripheral progesterone concentrations). Ovarian cysts appear to be dynamic structures; those that develop early in the postpartum period may regress without treatment, and a normal estrous cycle may follow, or another cystic structure may develop.

During palpation of the ovaries, several normal structures may complicate the diagnosis of CFD. Normal preovulatory follicles may approach 25 mm in diameter and have palpable characteristics similar to those of small cysts. During the follicular phase of the estrous cycle, however, the uterus responds to palpation by becoming more turgid, whereas the uterus of a cow with CFD is typically flaccid and unresponsive. In neglected cases of CFD, mucometra may develop and must be differentiated from pregnancy. During the first 5 to 7 days of the estrous cycle, the developing CL may be smooth and soft and is commonly mistaken for an ovarian cyst. More mature CLs are solid and liver-like in consistency, often feature a palpable ovulatory papilla at the apex, and are more easily differentiated from ovarian cysts. However, 10% to 20% of mature CLs may lack an ovulatory papilla, making them more easily confused with ovarian cysts. Ultrasonography is generally more accurate in identifying subtle structural differences than transrectal palpation. Salpingitis, hydrosalpinx, oophoritis, ovarian abscesses, ovarian neoplasms, and cysts of the fimbria are other causes of enlargement of the ovary and surrounding structures that must be differentiated from ovarian cysts.[13]

Histories that may erroneously suggest CFD include apparently short interestrous intervals because of inaccurate detection of estrus.[14] Oxytocin administered to stimulate milk letdown may result in short interestrous intervals and suggest CFD. The estrous cycle may be shortened by administering 100 IU of oxytocin per day on days 2 through 6[15] or on days 3 through 7 or 8.[16] Heifers treated with 100 IU of oxytocin per day returned to estrus in an average of 12.9 days versus 20.3 days in untreated controls.

Clinical Pathology Plasma progesterone concentrations are low in cows with follicular cysts. Partial luteinization may occur, and progesterone concentrations may increase over time but remain lower than those of cows with normal CLs. Estrogen concentrations in the plasma of cows with CFD are variable.

Treatment and Prognosis The goal in treating CFD is to induce luteinization of the cyst and reestablish normal estrous cycles. Several methods have been recommended.

SPONTANEOUS RECOVERY. Spontaneous recovery from CFD occurs in up to 60% of cows that develop CFD before the first ovulation after calving but in only approximately 20% of cases that develop after the first postpartum ovulation. Evaluation of therapeutic agents for CFD may be confounded by spontaneous recovery.

LUTEINIZING HORMONE. Recommended doses of human chorionic gonadotropin (hCG) range from 5000 IU either intravenously (IV) or intramuscularly (IM) to 10,000 IU IM. Of cows treated with a single dose of hCG, 65% to 80% establish a normal estrous cycle within 3 to 4 weeks; a second or third dose may be required in cows that do not respond after 3 to 4 weeks or in cases in which nymphomania persists. Anaphylaxis after repeated treatments with a larger protein hormone such as hCG can occur. Antibodies to hCG may reduce the effectiveness of sequential treatments. Therapeutic response to follicular cysts, both endocrinologically and clinically, is essentially equivalent between hCG and gonadotropin-releasing hormone (GnRH).

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GONADOTROPIN-RELEASING HORMONE. Currently the most common treatment for ovarian cysts, especially follicular cysts, is an injection of GnRH (100 µg IM). Cows responding to this treatment have an average interval to estrus of one estrous cycle or 18 to 24 days. The treatment to breeding interval can be shortened by administering GnRH at the time of diagnosis, followed by a luteolytic dose of prostaglandin 10 days to 2 weeks later. With this regimen it is not critical whether the cyst is follicular or luteal or even whether it is a misdiagnosed large, smooth CL with or without a fluid-filled central cavity. Most veterinarians agree that accurate differential diagnosis by rectal palpation among follicular cysts, luteal cysts, and some CLs can be a problem.

PROSTAGLANDIN $F_2\alpha$. Luteal-type cysts can be treated with the luteolytic activity of PGF. The advantage is the quicker return to estrus for those cows able to respond and the lower cost of PGF. Cysts that luteinize in response to GnRH regress at a time similar to that of normal CLs. Treatment with PGF may be used to reduce the interval from treatment with GnRH to estrus from 18 to 24 days to an average of 12 to 14 days by administering PGF at 9 days after GnRH. Most clinicians are only approximately 50% accurate in determining the degree of luteinization of cysts by palpation per rectum; therefore measurement of concentrations of progesterone in milk or of plasma from affected cows allows the selection of GnRH or hCG for treatment of follicular cysts and PGF for the treatment of luteinized cysts. Ultrasonography can also be used to make an accurate diagnosis.[17]

MANUAL RUPTURE. Thin-walled follicular cysts may be inadvertently ruptured during examination of the ovaries, and some practitioners may intentionally attempt cyst rupture. Recovery rates after manual rupture have rarely been studied in well-designed controlled experiments but are generally within the range reported for spontaneous recovery. Deliberate manual rupture of ovarian cysts is considered an obsolete form of treatment by some veterinary clinicians, but others routinely use the procedure—especially as an initial treatment for cysts found during the voluntary waiting period. Manual rupture of cysts may be followed by hemorrhage and adhesions between the ovary and surrounding structures. These complications appear to be much more common with use of digital pressure to enucleate CLs than with manual rupture of ovarian cysts.

Ewes and Does

Cystic ovaries appear to be more common in goats than in sheep. In one study 12% of goats had cystic ovaries when examined at a slaughterhouse.[18] The condition is often overdiagnosed by owners observing nymphomania. Treatment typically consists of administering exogenous ovulation-hastening drugs (hCG and GnRH).[19] LH surge is noted usually within 2 hours of GnRH administration. PGF may be administered 10 days later to bring the doe into heat (55 hours after PGF).

Camelids

Hemorrhagic follicles are observed in nonbred llamas and usually regress within 22 days.[20] Follicles larger than 12 mm are considered by some authors as pathologic cysts. These structures may, however, be anovulatory follicles. They may have a negative influence on the emergence of other follicular waves, but this influence seems to last for only approximately 8 days.[9,21]

Poor Nutrition

As with other species, poor body condition, depressed energy intake, and decreased vitamin and mineral intake suppress reproductive activity in ewes and does. Lowered energy balance results in poor or weak signs of estrus, depressed ovulation, abnormal cycle, and delayed puberty. Deficiencies in energy, protein, vitamins A and E, phosphorus, and many trace minerals (iodine, copper) are commonly seen. These deficiencies are most commonly associated with irregular estrous cycles.

Plant Toxicity

Ergot Alkaloids

The consumption of fescue infected with *Neotyphodium coenophialum* is associated with decreased reproductive efficiency. The ergot alkaloids have been shown to affect prolactin production in ewes and to increase the interval from introduction of the ram to conception.

Estrogen-Producing Plants

Sheep appear to be sensitive to the effects of phytoestrogens. Clinical observations include infertility, irregular and prolonged heat cycles, lowered conception rates, and early embryonic death.

Heat Stress

Fertility in lactating cows is decreased during the hot seasons of the year. Heat stress may cause decreased estrous detection, impair follicular development, disrupt function of the reproductive tract, affect oocyte competence, and lead to early embryonic death. Embryos develop resistance to heat shock as they age. Bovine morulae to blastocyst stages are unaffected by heat shock.[22]

Anestrus

Anestrus may be defined as ovarian inactivity. The causes of anestrus are multiple and include diseases of the reproductive and other systems. In addition, the problem is complicated by management factors that cause estrus to pass undetected, even though the animal's estrous cycles and estrous behavior are normal. Common causes of anestrus in mares are summarized in Table 43-1.

MARES

Puberty

The mare likely undergoes puberty between the ages of 12 and 24 months. Because the horse is not an agricultural production animal, there has been little interest in studying the onset of puberty as in other species, where hastening puberty increases production. Most mares are not bred until they are at least 3 years old, thus making prepubertal status an unlikely differential diagnosis for infertility.

Seasonal Anestrus

Clinical Signs and Diagnosis The mare is a seasonally polyestrous animal, showing anestrus during the shorter days of the year and cycling regularly during the longer days. Length of anestrus varies from one to several months, although some mares, particularly in the tropics, may cycle year round.[23] In California, Australia, and South Africa 18% to 25% of mares cycle year round.[1,24-26] Anestrous mares may be indifferent to teasing and do not show regular estrous behavior. Ovaries are small and firm on palpation, and the uterus is flaccid with a thin endometrium. The cervix has mild tone and may be indistinct. On speculum examination of the vagina, the vaginal mucosa is pale and dry, and the cervix usually appears closed but is occasionally open or may be easily opened. Mares that experience seasonal anestrus will go through a transition period in late winter and early spring, characterized by the development of waves of antral follicles that regress without ovulation because the ovulatory surge of luteinizing hormone (LH) is absent.[26] Transitional mares exhibit signs of estrus, including clitoral "winking," tail flagging, and urinating in the presence of the stallion. Eventually, increasing LH concentration coincides with a large follicle, resulting in ovulation. After the first ovulation of the season, the mare will continue to ovulate on

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TABLE 43-1

Differential Diagnosis of Anestrus in Mares

Cause	Uterus	Cervix	Ovaries	Peripheral Progesterone	Season	Other Laboratory Tests	Treatment
Pregnancy	Increased tone during early pregnancy; enlarged; positive signs of pregnancy by palpation or ultrasound	Tightly closed	Normal size during early pregnancy; out of reach of examiner in late stages	Elevated throughout pregnancy until just before term	Any season; may be more common in spring and summer	Equine chorionic gonadotropin; Cuboni test	Usually none required; therapeutic abortion if mismated
Prolonged diestrus	Normal size, increased tone and tubularity; may be similar to early pregnancy	Tightly closed	Normal size; prolonged corpus luteum is embedded within ovary	Elevated throughout prolonged lifespan (30-90 days)	Any season; may be more common in summer	Progesterone	PFF
Seasonal anestrus	Normal size; flaccid; difficult to palpate	Varies from tightly closed to open	Both are small and firm, may or may not have small follicles	Low until first corpus luteum develops	Late autumn, winter, early spring	Progesterone	Artificial lights; wait for normal breeding season
Unobserved estrus	Normal size	Characteristic cyclic changes; relaxed and open during estrus	Development of one (or more) follicles; ovulation	Elevated for ≈14 days; low for ≈7 days	Spring, summer, autumn		Improve management; tease with another stallion; sequential examinations; PGF
Pyometra	Variable enlargement	May be open, closed, or stenotic; purulent discharge may be present	Normal size, follicular development may be present	Erratic profiles; some are elevated for prolonged periods, others may have luteal regression	Any season	Endometrial cytology; bacterial culture; antibiotic sensitivity	Drain; systemic antibiotics; PGF
Undernutrition	Normal size	Varies from tightly closed to open; no cyclic changes	Bilaterally small and firm	Low	Any season	Hematology; clinical chemistry as indicated; fecal flotation	Improve nutritional status; parasite control; treat concurrent diseases
Granulosa-theca cell tumor	Normal size	Varies	One enlarged, multicystic; other small and atrophic	Low	Any season	Peripheral inhibin concentrations are elevated in ≈90% testosterone in ≈50% and AMH in >90% of mares with granulosa-theca cell tumor	Surgical removal of neoplastic ovary
Gonadal dysgenesis	Small	Varies	Small, firm, atrophic	Low	Any season	Karyotype	None

PGF, Prostaglandin F.

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successive estrous cycles. A transition period is also observed during the fall as the mare changes from a polyestrous condition to the winter anestrus. Differential diagnoses for seasonal anestrus are listed in Table 43-1.

Treatment and Prognosis As day length increases, most mares ovulate and begin regular cyclicity without treatment. Methods to advance the onset of regular ovulatory periods are discussed in the following sections.

ARTIFICIAL LIGHTING. The vernal transition can be moved but not shortened beyond its physiologic length of 6 to 8 weeks by exposure of mares to artificial light. A common artificial lighting regimen is to expose the mares to 16 hours of light and 8 hours of dark by extending the photoperiod in the evening starting in late November to initiate ovulation by February (in the northern hemisphere). Light should be added to the end of the day, or split between the beginning and end of the day, as opposed to adding light only at the beginning of the day.[26] An alternative regimen is to expose mares to 1 hour of artificial light 9.5 to 10.5 hours after the onset of darkness.[27] Use of one 200-watt incandescent bulb or two 40-watt fluorescent tubes at a height of 7 to 8 feet in a 12- by 12-ft box stall has been recommended.[28] Paddock lighting has been described.

GONADOTROPIN-RELEASING HORMONE. Treatment with GnRH or a GnRH analogue for mares in anestrus or spring transition has been shown to induce ovulation.[29-33] Twice-daily injections of a GnRH agonist induced ovulation in a majority of mares within 2 to 3 weeks.[33] Mares that are in deep anestrus (January and February, northern hemisphere) can be expected to return to anestrus after treatment.

DOPAMINE ANTAGONISTS. Domperidone and sulpiride have been reported to stimulate follicular activity and advance the first ovulation of the year in seasonally anestrous mares.[34,35] However, the efficacy of dopamine antagonists in advancing follicular growth and ovulation in anestrous mares has recently been questioned, and it has been suggested that adjustments in light and climatic conditions may influence the efficacy of the treatment.[36,37]

STEROIDS. Exogenous progestins suppress the release of LH from the anterior pituitary and may be used for estrous regulation during the vernal transition. After treatment of mares for 10 to 14 days, withdrawal of progestin may result in LH release from the pituitary and estrus beginning in 4 to 5 days, with ovulation within 10 days after cessation of treatment. Mares should be in mid to late transition and have a follicle at least 25 mm in size to respond to treatment. Progestins will not induce estrus or ovulation in anestrous mares.[38] The recommended dose of progesterone in oil is 150 to 300 mg daily by IM injection. The synthetic progestin, altrenogest, is administered orally (PO) at 0.044 mg/kg daily. Progestins may be used in combination with extended photoperiod and gonadotropins. Products that are ineffective or unavailable include repositol progesterone, melengestrol acetate, chlormadinone acetate, proligestone, medroxyprogesterone acetate, hydroxyprogesterone acetate, and norgestomet implants.

Synchronization of the first ovulation (or any ovulation during the cyclic season) can be accomplished by the administration of a combination of progesterone in oil (150 mg/day IM) and estradiol-17β (10 mg/day IM) once daily for 10 days.[39] Treatment is most effective if given after mares have been under lights for 45 to 60 days. $PGF_2\alpha$ should be given on the last day of steroid treatment. Treated mares will ovulate within 8 to 10 days after the last treatment.

GONADOTROPINS. At a dose of 2500 to 3000 IU, hCG may induce ovulation within 48 hours when administered to a mare with a follicle larger than 35 mm in diameter[40] and may reduce time to first ovulation in transitional mares, particularly when used in combination with lights and/or progesterone treatment. Ovulation response here is less predictable than that induced with hCG during the breeding season.

Crude pituitary extract has been used to induce ovulation in anestrous mares.[41] Recent data suggest that treatment of seasonally anestrous mares with recombinant equine FSH (reFSH) is effective in stimulating development of follicles and advancing the first ovulation of the year.[42] Treatment with FSH resulted in multiple ovulations but was not successful in inducing continued cyclicity.

FOLLICULAR ASPIRATION. Ultrasound-guided transvaginal follicular aspiration of follicles less than 35 mm has been shown to hasten the onset of cyclicity in transitional mares.[43] Follicular aspiration resulted in the formation of an active CL, and subsequent treatment with $PGF_2\alpha$ resulted in estrous behavior and ovulation of a dominant follicle.

Prolonged Luteal Phase and Pseudopregnancy

Mares that experience embryonic loss in the presence of endometrial cups (days 35 to 150 of gestation) are said to be *pseudopregnant* (*pseudopregnancy* may also refer to that condition in which a conceptus was lost after maternal recognition of pregnancy and before the development of endometrial cups, resulting in prolonged luteal life). In spite of the loss of the fetus and placental tissue, endometrial cups remain in place and continue to secrete equine chorionic gonadotropin (eCG) for a similar period to that in a pregnant mare, to 100 to 150 days of gestation.[44] The primary and secondary CLs occasionally regress after embryonic loss[45] but usually remain during eCG secretion, maintaining high levels of peripheral progesterone. Persistent endometrial cups throughout pregnancy and during the following breeding season have been described.[46]

Treatment and Prognosis In untreated mares, cyclic activity is often reestablished after the cessation of eCG secretion. Repeated daily injections of PGF products have been reported to cause luteal regression in pseudopregnant mares,[47] but only CLs older than 5 days respond to the treatment, which may prevent mares returning to estrus. Pregnancies have occurred in the face of high eCG,[48] but fertility of treated mares is usually low.

Lack of Behavioral Estrus (Silent Estrus)

Behavioral estrus may not be detected in otherwise normal mares as a result of inadequate estrous detection or a failure on the part of the mare to show obvious signs of estrus. The latter may occur in up to 15% of mares on well-managed farms.[49] Inadequate estrous detection may be a result of human apathy or ignorance or a result of using a low-libido or inexperienced stallion. Teasing mares as a group may make detection of estrus more difficult, especially for nervous mares, mares with foals, and mares of low social rank. Use of anabolic steroids may suppress behavioral estrus.

Clinical Signs and Diagnosis The mare fails to show estrus on adequate teasing with a stallion. Differential diagnoses are listed in Table 43-2.

Treatment and Prognosis Management should be examined to ensure a competent teasing routine. When approached by a stallion, mares in estrus stand still with ears held forward; they may elevate the tail, rhythmically evert the clitoris ("winking"), assume a squatting posture, urinate, and lean against the teasing chute toward the stallion. Mares that are in diestrus move about and hold their ears back; they may strike, kick, squeal, swish their tails, and forcefully void small amounts of urine. Experienced personnel should handle both stallion and mare. The teaser stallion should have adequate libido without being aggressive. Transrectal palpation and ultrasonography should supplement teasing. Some mares are indifferent to teasing, and records of sequential palpation must be relied on for breeding. Progesterone concentrations of less than 1 ng/mL are

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TABLE 43-2

Irregularities of the Equine Estrous Cycle: Differential Diagnosis

Etiology	Distinguishing Features
Failure to Cycle with Low Progesterone	
Winter anestrus	Season; inactive ovaries
Gonadal dysgenesis	Small, hard, inactive ovaries; karyotype; underdeveloped tubular tract; small body
Pituitary adenoma	Systemic signs; inactive ovaries
Granulosa-theca cell tumor	See prolonged or irregular behavioral estrus
Behavioral	Intimidated by stallion; recently foaled; low social rank
Failure to Cycle with High Progesterone	
Pregnancy	Presence of embryonic vesicle or fetus
Persistent CL	CL fails to regress; responds to PGF
Diestrous ovulation	CL immature at time of endogenous PGF; responds to exogenous PGF
Pseudopregnancy	Conceptus loss after maternal recognition of pregnancy; responds to exogenous PGF
Iatrogenic	History of exogenous progestin or nonsteroidal antiinflammatory drug administration
Pyometra	Uterus palpably enlarged
Short Luteal Phase	
Uterine infection	Pyometra or endometritis causing premature endogenous PGF secretion
Systemic endotoxemia	Systemic signs; endotoxin-mediated release of endogenous PGF
Iatrogenic	History of uterine manipulation, infusion, invasive procedure, or exogenous PGF
Prolonged or Irregular Behavioral Estrus	
Transitional period	Season, variable ovarian activity
Granulosa-theca cell tumor	Affected ovary large and multicystic, contralateral ovary small; elevated inhibin, AMH and/or testosterone; anestrus, nymphomaniac or stallion-like behavior
Gonadal dysgenesis	Occasionally irregular cyclicity; as above
Behavioral nymphomania	Otherwise normal mare
Normal mare	Mares in winter anestrus and pregnancy may show estrous signs

AMH, Anti-müllerian hormone; *CL,* corpus luteum; *PGF,* prostaglandin $F_{2\alpha}$.

consistent with estrus but may also occur in anestrous mares. Mares that fail to show behavioral estrus should be bred by artificial insemination (AI) (if allowed by the breed register) or appropriate restraint used for natural cover.

Behavioral Nymphomania

Abnormal estrous behavior and aggression may be demonstrated by otherwise normal mares at any stage of the estrous cycle. Cause is unknown, although exaggerated response to ovarian steroids has been proposed.[50]

Clinical Signs and Diagnosis Exaggerated signs of estrus occur, initially during estrus and then throughout the cycle. Mares may develop behavioral anomalies and become aggressive. Differential diagnoses are listed in Table 43-2. It is important to differentiate abnormal estrous behavior from unrelated behavioral problems.

Treatment and Prognosis Exogenous progestins have been used to limited effect. Short-term dexamethasone treatment (5 to 10 mg) may alleviate signs for 3 to 4 days.[50] Bilateral ovariectomy may be successful in some cases.

RUMINANTS Common causes of anestrus in cows are summarized in Table 43-3.

Unobserved or Silent Estrus

Cow

Failure of a cow to display, or a manager to observe, the signs of estrus contributes significantly to reproductive inefficiency. When the presenting history suggests anestrus (failure to have a normal estrous cycle), the clinician must determine if the cause is failure of the manager to detect estrus in normal cows or failure of the cow to cycle because of some abnormal process. In dairy herds approximately 90% of cows presented for examination because of a history of anestrus have evidence of normal cyclic ovarian changes, whereas only approximately 10% are affected by an abnormality that suspends the estrous cycle (i.e., only ≈10% are in true anestrus).

Nearly 90% of well-managed dairy cows have initiated normal-length estrous cycles by 60 days after calving, but only approximately 60% are detected correctly to be in estrus by that time.[51] Rates of estrous detection by twice-daily observation range from 50% to 73% depending on the skill of the observer.

Mounting activity and estrous behavior are reduced by hot and cold ambient temperatures and during the times of milking and feeding. More mounts are observed when cows are kept on dirt than on concrete. Estrous behavior varies with the time of day and may be an inverse reflection of extraneous activity interfering with cow behavior. In one study, 43% of cows showed heat between midnight and 6 AM; 22% between 6 AM and noon; 10% between noon and 6 PM; and 25% between 6 PM and midnight.[52]

Estrus in dairy cows averages 7 to 16 hours in length but ranges from 0.5 to 36 hours. Sixty-five percent of cows are in estrus for less than 16 hours, and 25% are in estrus for less than 8 hours.[53] The number of mounts per hour ranges from 2 to 8, and the total number of mounts during estrus ranges from 11 to 56. Total number of mounts per estrus increases with the number of cows simultaneously in estrus.

Clinical Signs and Diagnosis Dairy herds in which infertility is caused by inaccurate estrous detection are usually characterized by prolonged intervals from calving to first breeding and between services; insemination intervals of 10 to 15 days and 30 to 35 days; records of examinations that confirm cyclic ovarian changes, but in which observation of estrus is not recorded; and finding more than 15% of cows presented for pregnancy examination to be nonpregnant. Insemination during the luteal phase of the estrous cycle

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TABLE 43-3

Differential Diagnosis of Anestrus in Cows

Cause	Uterus	Ovaries	Peripheral Progesterone	Treatment
Pregnancy	Enlarged; positive signs of pregnancy	Corpus luteum in ovary ipsilateral to pregnant uterine horn	Elevated throughout	Usually none required; PGF or PGF + dexamethasone if unwanted pregnancy
Unobserved estrus	Normal; characteristic tone during estrus; postovulatory edema	Development and regression of corpora lutea and follicular waves diagnosed by sequential examinations	Elevated during diestrus and low for ≈3 days before ovulation and ≈4 days after ovulation	Improve estrous detection; estrous detection aids; synchronize estrus with PGF; teaser animals
Cystic follicular degeneration	Normal in acute cases; later flaccid mucometra may develop in chronic cases	Fluid-filled cyst(s) >25 mm in diameter; no corpora lutea; unilateral or bilateral; single or multiple cysts	Variable; low in cases of follicular cysts; slight elevation in cases of partially luteinized cysts	Spontaneous recovery; GnRH or hCG to induce luteinization of follicular cysts; PGF for partially luteinized cysts; manual rupture
Pyometra	Variable enlargement; fluid movable from horn to horn, normal-to-thick uterine wall; no positive signs of pregnancy	Corpus luteum in one ovary, frequently contralateral to larger uterine horn	Elevated throughout	PGF
Mummified fetus	Leather-like fetus within involuted uterus; no positive signs of pregnancy	Corpus luteum in ipsilateral ovary	Elevated throughout	PGF; usually slaughter, advisable for economic reasons
Undernutrition	Normal	Small; static; no cyclic changes detected on sequential examinations	Low until corpus luteum forms	Improve quality and quantity of ration
Granulosa-theca cell tumor	Normal	One ovary enlarged; other low atrophic	Low	Surgical removal of neoplastic ovary
Freemartinism	Small to nonexistent	Small to nonexistent	Low	No possible treatment
Ovarian hypoplasia	Very small to near normal	Very small to near normal; unilateral or bilateral; partial or complete	Variable; depends on degree of hypoplasia	No possible treatment

GnRH, Gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *PGF,* prostaglandin $F_{2\alpha}$.

may occur in 10% to 20% of cows and is not likely to result in conception; insemination of pregnant cows may be followed by abortion.

The diagnosis of unobserved estrus requires sequential examination of affected cows and accurate records. Other causes of anestrus are eliminated. Conditions such as CFD, pyometra, mummified fetuses, granulosa-theca cell tumors, and segmental aplasia that cause anestrus affect individual animals. Anestrus caused by undernutrition is characterized by depressed milk production and low body condition score.

Treatment and Prognosis PGF is widely used in clinical management of unobserved estrus. Mature CLs (≈day 6 through day 18 of the estrous cycle) are responsive to PGF-induced luteolysis. Estrus occurs an average of 3 days (range 2 to 5 days) after administration of PGF, depending on the follicular status of the ovaries at the time of injection. The endocrine events surrounding the controlled estrus are indistinguishable from those surrounding spontaneous estrus and ovulation. Treatment with PGF shortens the intervals from treatment to first breeding and from treatment to conception but has no effect on fertility. The benefits of PGF treatment are limited by inaccurate palpation of the temporary ovarian structures, injection during the wrong phase of the cycle, and failure of the manager to observe estrus in treated cows (timed AI can be used to overcome this problem).

Measurement of progesterone concentrations in milk samples taken on the day of breeding is useful in herds with a history of reduced fertility to confirm that cows being inseminated are not in the luteal phase of the estrous cycle. If more than an occasional cow presented for insemination has an elevated concentration of progesterone, the methods of estrous detection should be reviewed. Enzyme immunoassay kits for measuring concentrations of progesterone in milk and plasma of cows and other female animals have been described and are commercially available.

Various heat detection aids have been developed. Several use devices mounted on the tailhead to record that a cow has stood to be ridden. Pressure-sensitive devices that are glued to the tailhead and change color after sustained pressure by the weight of a mounting cow are commonly used. Similarly, pressure-sensitive devices glued to the tailhead can send a record of riding events directly to a computer. Chalk, cattle crayon marker, or paint applied to the tailhead are inexpensive aids that are rubbed off when the animal is mounted when she is in heat. These methods require daily maintenance and twice-daily evaluation to function effectively. Detection aids that measure changes in activity (pedometers), mucous conductivity, or body temperature can be used successfully. Accuracy is enhanced when measurements are related to previous estrous activity and progesterone concentrations.[54]

Prevention and Control Because unobserved estrus is primarily a problem of management, efforts to reduce time lost from delayed breeding are directed at improving efficiency of heat detection. Accurate records are required to identify cows that have not been observed in estrus by 40 days after calving. Cows not observed in estrus by 40 days after calving should be examined, and abnormalities of the reproductive organs that cause anestrus treated as indicated. The time of estrus can be predicted by palpation of the temporary ovarian structures, or estrus can be controlled with PGF. The most significant benefit of a planned herd health program is stimulation of improvements in management that decrease the interval from calving to conception as a result of improved estrous detection.

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Anestrus after insemination is frequently interpreted as a clinical sign of pregnancy. However, unobserved estrus in cows that have failed to conceive or have experienced early embryonic death (postservice anestrus) contributes significantly to increased calving intervals. Clinical management of postservice anestrus depends on diligent observation of cows 18 to 24 days after breeding and identification of nonpregnant cows as early as possible after the infertile service so that they may be reinseminated with minimum delay. Nonpregnant cows may be accurately identified by ovarian palpation or ultrasonography for absence of a mature CL, by low milk or plasma progesterone at the time of the first expected postservice estrus (≈21 days after breeding), or by palpation of the uterus per rectum before the second expected postservice estrus (30 to 42 days after breeding). Recently blood-based methods for pregnancy detection, including Pregnancy-Specific Protein B, have been validated as early as 28 days postinsemination with a sensitivity and specificity of 93.9% and 95.5%, respectively.[12]

Ewe

The breeding season of most breeds of sheep maintained at temperate latitudes is restricted to late summer, autumn, and early winter, although some breeds cycle all year long. There is almost no homosexual interaction among ewes; therefore a male must be present to stimulate display of estrus.[5]

Introduction of a ram (either intact or vasectomized) into a flock of ewes advances the breeding season. Most ewes ovulate by 3 to 6 days after introduction of rams. The induced ovulation is seldom accompanied by estrus, but the subsequent estrus approximately 17 days later is ovulatory and fertile. The "ram effect" is lost when rams are allowed to associate with ewes throughout the year.

Return to estrus after mating may be detected in a flock of ewes by fitting the ram with a brisket device that marks serviced ewes. Return of an excessive number of ewes to service after breeding alerts the owner to the possibility of infertility.

AI of ewes is rare in the United States but more popular in other countries. Detection of estrus for AI depends on use of teaser rams mingled with the ewes or led through the flock several times daily.

Doe

The breeding season of does is similar to that of ewes (i.e., it surrounds the autumnal equinox). During periods of short daylight, the normal estrous cycle of does is 20 to 21 days. Homosexual interaction among estrous does rarely occurs; so signs of estrus must be elicited by teasing. Signs of estrus may also be evoked by exposure to male pheromones by way of a "buck jar" prepared by rubbing a cloth over the scent glands caudomedial to the horns of a mature buck during the breeding season and storing the cloth in a tightly closed container. If estrus is not observed in does exposed to a mature buck or to a buck jar during the physiologic breeding season, pregnancy or pseudopregnancy might be considered as possible causes of anestrus. Severely parasitized or inadequately nourished does do not have normal estrous cycles. Deficiencies of phosphorus, iodine, and manganese have been suggested as causes of anestrus in does.

Introduction of bucks into a flock of does early in the breeding season results in initiation of estrous cycles and some degree of synchrony of estrus approximately 10 days after introduction of the bucks.[5] In contrast to ewes, however, the first ovulation after exposure to males is accompanied by estrus and fertile mating.

Camelids

Most female South American camelids, although showing signs of ovarian cyclicity as early as 5 months of age, have decreased fertility until approximately 15 months of age. A female camelid should be at least 60% of her expected adult weight before she is bred. Male camelids have a preputial attachment of the penis that is not separated until 2 to 3 years of age. Some males may actually detach as early as 15 months of age. Before this time they will show mounting behavior but will not be capable of intromission.[9]

Infertility Caused by Abnormalities of the Female Genital Organs

Abnormalities Caused by Problems with Sexual Differentiation

Sexual differentiation occurs in three stages, each stage dependent on the previous one:

1. Chromosomal (genotypic or genetic) sex is determined at fertilization in mammals by the type of sex chromosome contributed by the sperm (X or Y). In mammals, females are XX and males are XY.
2. Gonadal sex is regulated by the *Sry* (sex-determining region of the Y chromosome) gene, which produces a protein termed the *HY antigen,* as well as other sex-linked and autosomal genes downstream of *Sry.* Activation of this pathway induces testis formation in the bipotential gonads. The X-linked *Dax1* gene suppresses testis formation.
3. Phenotypic sex is regulated by substances produced in the male testes to cause regression of the female tract and formation of the male tract, or, in the absence of a testis, formation of the female tract.

Chromosomal sex is determined at fertilization. All normal mammalian oocytes contribute an X chromosome in addition to one of each representative autosomal maternal chromosome. Sperm cells contribute either an X or a Y sex chromosome in addition to one of each representative autosomal paternal chromosome. Abnormalities in chromosomal sex occur because of nondisjunctional errors during either mitosis or meiosis. Fig. 43-1 shows some examples of chromosomal sex anomalies.

Monosomy X (XO)

Monosomy X is also known as *Turner syndrome.* Owing to the lack of a Y chromosome and the consequent *Sry* gene, but the presence of the *Dax1* gene on the present X chromosome, the phenotype is female. Monosomy X is the most commonly reported chromosomal abnormality in mares.[1] Animals with this syndrome often have a history of poor performance and lack of or sporadic reproductive cyclicity. Ovaries are typically inactive, small, smooth, and firm. The uterus and cervix are usually hypoplastic. Externally the mare's genitalia may appear normal or underdeveloped.

XXY Syndrome

The genotype for XXY syndrome is part of Klinefelter syndrome. Because of the presence of a Y chromosome and the consequent *Sry* gene, affected individuals are phenotypically male, but probably owing to the presence of two copies of the *Dax1* gene on the two X chromosomes, they generally have hypoplastic genitalia and reproductive organs. It is thought that some factor (*Dax1* or some other) on the X chromosome must escape the inactivation process, which happens early in development (around day 7 or 8 in the horse). Testicular development and spermatogenesis are inhibited, resulting in small, flaccid testes and azoospermia. The testes may be retained or descended, but they are often small and soft. The penis may be normal or smaller than usual. Affected males often show normal

			Sperm					
			Normal		Abnormal			
			X	Y	XY	XX	YY	O
Eggs	Normal	X	XX	XY	XXY	XXX	XYY	XO
	Abnormal	XX	XXX	XXY	XXXY	XXXX	XXYY	XX
		O	XO	YO	XY	XX	YY	O

FIG. 43-1 Examples of chromosomal sex abnormalities.

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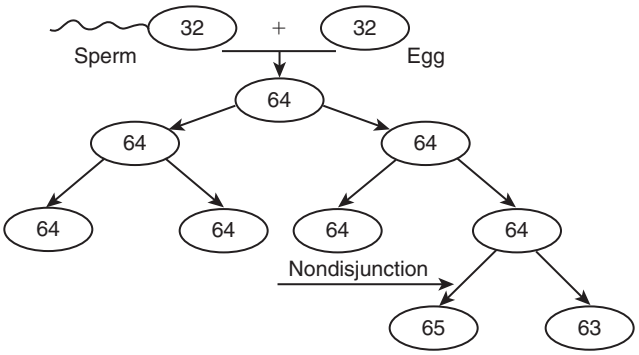


FIG. 43-2 Process of how a mosaic may occur. The haploid sperm and egg form a diploid zygote. Through the process of mitosis, diploid cells are replicated to always produce the same number of chromosomes. If, however, a chromosome pair does not separate during anaphase, called a *nondisjunction event,* cell lines that do not reflect a correct representation of the genome will be created and potentially propagated. If this happens with the sex chromosomes in the germ cell line, fertility of the individual or its offspring may be affected.

libido and sexual behavior. Low testosterone concentrations may be noted. Infertility always accompanies this syndrome. Reports have been made in numerous species, including the horse.[55,56]

XXX

More is not better. A report of an infertile mare with the 65,XXX genotype confirms this.[57] The mare had bilaterally small, inactive ovaries and a hypoplastic uterus and cervix.

MOSAICS. Mosaics are individuals that have at least two cell lines with different karyotypes arising from the same zygote (Fig. 43-2).

Phenotypes vary in accordance with the degree of mosaicism. Varying degrees of hermaphroditism and pseudohermaphroditism have been reported in many domestic species. Mosaics often have mixed gonadal dysgenesis, with an ovary and a testis, or ovotestes, owing to sex chromosome mosaic cell lines.[58,59] These are true hermaphrodites.

Chimeras

Chimeras are individuals having cell lines from two different embryonic sources. This can occur experimentally or from the natural fusion of blastocysts in utero. The possibility has been reported from a suspected double ovulation and fertilization followed by blastomere fusion in the horse (64,XX/64,XY and 63,XO/64,XY genotypes reported). Freemartinism is a common occurrence in ruminants, resulting in chimeric twins.

Freemartins

Freemartinism is a phenomenon in ruminants in which an infertile female is twin to a male. The dizygotic occurrence happens when the blastodermic vesicles of the two zygotes fuse early in development (day 18 to 20 in cattle) and share embryonic tissue. The placentas fuse (day 30 to 50 in bovines), and they share blood throughout gestation. This occurs before gonadal differentiation at day 40 to 50. Both individuals are XX/XY chimeras. The *Sry* gene of the male twin causes the freemartin gonads to develop at least partially toward the male testis. The degree of differentiation varies with each freemartin, and many freemartin gonads remain undifferentiated. The shared circulation allows testosterone and anti-müllerian hormone (AMH; discussed later) from the male twin, and possibly from the chimeric freemartin, to affect the freemartin genitalia, and so she lacks a cervix, uterus, uterine tubules, and cranial vagina. The vulva is fairly normal. The yearling freemartin fails to exhibit estrus, the udder and teats remain small, and the freemartin externally resembles a steer (only with a vulva). Diagnosis can be made by establishing a blind end to the vagina (no cranial vagina, no cervix). Of heifers born co-twin to a male, 92% will be freemartins.[60]

The male twin may develop into a fertile adult, but these individuals show a higher incidence of infertility than bulls with a 60,XY genotype. Most male twins to freemartins become steers.

Freemartinism is less common in sheep than in cattle, but it does occur. It has also been reported in goats and pigs. With increased fecundity in modern animals, the authors observe the phenomenon more often than was reported in the past. This is because ovine freemartinism is rare with twins or triplets but much more common with quadruplets or quintuplets. A notable difference between ovine and bovine freemartinism is the marked masculinity of the ovine freemartin. Gonads within the inguinal canal resemble normal prepubertal testes, and those within the abdomen resemble cryptorchid testes from rams of normal XY gonadal sex. Many ovine freemartins also have epididymides, vasa deferentia, vesicular glands, and even cremaster muscles.

Gonadal Sex

Chromosomal sex determines gonadal sex. The Y chromosome has very few genes, and all of the ones studied play a role in sex differentiation. The gene located at the sex-determining region on the Y chromosome *(Sry)* has a DNA binding domain high-mobility group (HMG) box. It produces a protein called the *HY antigen,* and its action appears to be regulated by the transcription of other genes. Their actions initiate differentiation of bipotential embryonic gonadal tissue into testicular tissue. Other genes act downstream of *Sry* to support gonadal differentiation, including *Sox9, Gata4,* and *Wt1,* and *Sf1,* which act synergistically to promote testicular differentiation. *Sox9* is a powerful promoter of testicular tissue differentiation. It is hypothesized that *Sry* upregulates *Sox9.* In the absence of the *Sry* gene, the dual copies of the *Dax1* gene on the X chromosomes suppress the formation of testicular tissue by antagonizing the *Sry* gene and the synergy between *Sf1* and *Wt1.* Another gene, *Wnt4,* has been shown to support female development, and the absence of this gene in female mice results in masculinization.[61] This evidence refutes the notion that female development is strictly a default process caused by the absence of *Sry.* Further research is elucidating other factors that actively promote the formation of ovarian tissue (e.g., *Rspo1* β-catenin signaling). Factors affecting *Sry,* or any of the other genes downstream of *Sry,* or any factors governing female development will affect phenotypic sex.

Abnormalities of Gonadal Sex: Sex Reversals

Sex reversals occur when the chromosomal sex and gonadal sex do not agree with each other. XX sex-reversed males and XY sex-reversed females are reported in many domestic species. These individuals are either XX males (testicular tissue), XY females (ovarian tissue), or true hermaphrodites (both ovarian and testicular tissue on separate gonads or the same gonad [ovotestes]). Sex reversals are relatively common in the horse and are considered to occur both sporadically and with familial inheritance.

XY SEX-REVERSED FEMALES (GONADAL DYSGENESIS). XY sex-reversed females have been reported to arise because of an absent or mutated (and nonfunctional) *Sry* gene. It is believed that the Sry chromosome is missing because of an abnormal meiotic exchange with the X chromosome. It is thought that in the sire two crossing-over events occurred between X and Y chromosomes during spermatogenesis. These animals are infertile and have a normal female appearance to their external genitalia. The ovaries and uterus tend to be hypoplastic. The gonads may, in fact, be completely undifferentiated ("streak gonads"). These animals may be true hermaphrodites (ovotestes) or XY females (only ovarian tissue).

***SRY*-POSITIVE XX SEX-REVERSED MALES.** XX sex-reversed males conversely may arise from a translocation of the *Sry* gene onto the X chromosome. These animals may be true hermaphrodites or XX males (only testicular tissue). This condition has been reported in ruminants, but not horses.

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***SRY*-NEGATIVE XX SEX-REVERSED MALES.** There are reports in horses of *Sry*-negative XX sex-reversed males.[62,63] The exact mechanism of masculinization is still uncertain. Possibilities include Y-specific sequences other than *Sry* (which would require an XY individual with an inactivated or absent *Sry* gene), XX/XY chimerism within the testicular tissue, and a mutation in an autosomal or X-linked gene farther down the cascade of genes responsible for sex determination. XX sex-reversed males may have ambiguous sexual characteristics and may be true hermaphrodites or XX males (only testicular tissue).

Goats (especially Alpine, Saanen, and Toggenburg) present another classic, common example of *Sry*-negative XX sex-reversed males. The "polled" (hornless) gene is either closely linked to an intersex locus or the polled gene itself is pleomorphic and controls both the hornless and intersex traits. This close linkage or pleomorphism is called the *polled/intersex syndrome* (PIS). A partial reason for the sex reversal is the deletion that affects a noncoding RNA (Pisrt1) and a transcription factor (FoxL2). The mechanism of testis induction has not been discovered yet. Elucidating this mechanism may be a big step in describing autosomal sex-determining factors in other species, including humans. The intersex gene is currently thought to work by mimicking the *Sry* gene and codes for the HY antigen.

The polled gene shows a dominant autosomal inheritance pattern, whereas the intersex trait shows a recessive autosomal inheritance pattern. A single dose of the P polled gene is enough to cause the polled trait, but a double dose is required to cause intersexuality in XX individuals. Therefore PP animals are hornless and infertile (if XX, fertile if XY); Pp individuals are hornless and fertile; and pp individuals are horned and fertile. Intersex individuals are always sterile and have a shortened vagina, large clitoris, bucklike head and neck, buck odor, and buck behavior. The gonads are testes or ovotestes and may be scrotal, inguinal, or abdominal. Even very masculinized intersexes with scrotal testes are azoospermic. A PP polled goat that has an XY genotype is usually initially fertile but often develops sperm granulomas later in life. The only way to avoid the intersex condition is to always breed a polled individual to a horned individual (Fig. 43-3).

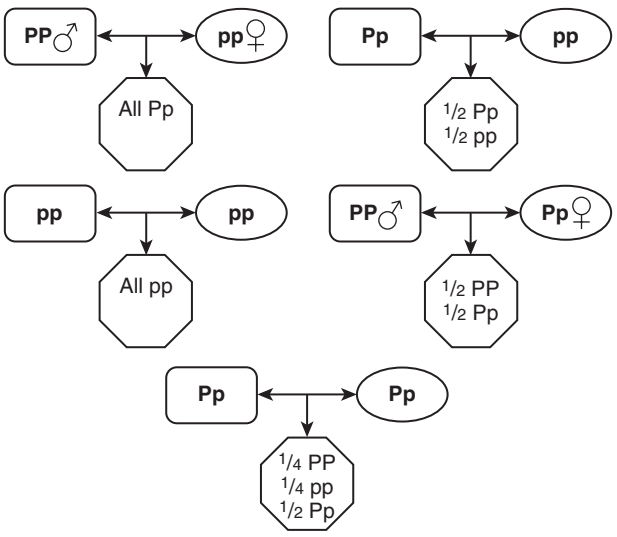


FIG. 43-3 Assuming classical Mendelian genetics, the graph illustrates expected genotypes of progeny from different breedings of polled and wild-type goats.

Phenotypic Sex

Gonadal sex determines phenotypic sex. Initially each embryo has both müllerian (paramesonephric) ducts and wolffian (mesonephric) ducts. Within testicular tissue, Sox9 triggers Sertoli cells to secrete müllerian inhibiting substance (MIS; also known as *anti-müllerian hormone* [AMH]), which initiates the irreversible regression of the paramesonephric ducts. The action of MIS or AMH is further regulated by other genes and their proteins (Sf-1, Gata factors, Wt-1, Dax-1, and FSH). Wt-1 and Sf-1 synergistically enhance AMH transcriptional activity. Gata-4 enhances AMH promoter activity by directly binding to DNA and by synergistically interacting with Sf-1.

Leydig cells secrete testosterone that is converted by 5α-reductase to dihydrotestosterone. These two steroids promote the differentiation of male genitalia. Testosterone influences the differentiation of the wolffian ducts into the internal male genitalia (vasa deferentia and epididymides), whereas dihydrotestosterone stimulates the formation of the seminal vesicles and male urethra from the urogenital sinus, and the penis from the genital tubercle. In the absence of these testicular hormones, the wolffian ducts regress and the müllerian ducts become the female internal genitalia.

In the presence of two X chromosomes, the double dose of Dax-1 has an inhibitory effect on the synergistic relationships between Sf-1 and Wt-1 and Gata-4, preventing their support of AMH production.[64] The primitive sex cords (gonadal cords) degenerate in the medulla and remain in the cortex (opposite in the horse). Subsequently there is no communication between the gonad and the mesonephros. In the absence of AMH, the müllerian ducts persist as the oviducts and fuse to form the uterus and cranial vagina. In the absence of testosterone, the wolffian ducts regress. Vestigial traces of these are located in the mesentery of the ovary, the epoophoron, the paroophoron, and Gartner ducts. The tissues that form the round ligament of the uterus are analogous to the male gubernaculum.

Abnormalities of Phenotypic Sex

Abnormalities of phenotypic sex occur when the chromosomal and gonadal sex agree (XX with ovaries or XY with testes) but the external and/or internal genitalia do not correlate or are ambiguous. Affected animals are the male and female pseudohermaphrodites. The condition can occur because of insensitivity of androgen receptors or because of any abnormality along the pathway that may affect the intervening hormones, such as the conversion of 5α-reductase to dihydrotestosterone.

TESTICULAR FEMINIZATION. Testicular feminization is reported in domestic species, including the horse.[65] Patients have external genitalia that are either female or ambiguous in appearance. The vagina may be blind-ending, or the uterus may be hypoplastic. The gonads are testicles, although they are usually abdominal or inguinal. Male behavior may be reported in horses. The problem lies in the gene for the androgen receptor, located on the X chromosome received from the dam. This X-linked recessive inheritance has been demonstrated in both humans and horses. Affected individuals are male pseudohermaphrodites; the condition has been diagnosed in multiple horse breeds. Serum testosterone is often elevated as a baseline because of loss of negative feedback, or at least in response to an hCG test.

Abnormalities of the Ovaries

MARES

Abnormally Small Ovaries

The most common causes of bilaterally small ovaries in the mare are (1) seasonal anestrus, (2) hypothalamopituitary dysfunction, (3) severe malnutrition, (4) immaturity, (5) advanced age, (6) use of anabolic steroids, and (7) gonadal dysgenesis. Clinical signs and treatment of seasonal anestrus, hypothalamopituitary dysfunction, and malnutrition are discussed elsewhere in this chapter.

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Immaturity and Advanced Age

The average age at which fillies reach puberty is 18 months, with a wide range of 10 to 24 months. Fillies younger than 2 years of age with inactive ovaries and a flaccid and relaxed reproductive tract may be too young to cycle and should be reexamined at a later time. The condition should be differentiated from gonadal dysgenesis, and karyotyping may be indicated if puberty is delayed beyond 24 months.

Older mares (>20 years) not only frequently begin cycling later in the season than younger mares[66] but also often have a longer follicular phase and, subsequently, a longer interovulatory interval.[66,67] Additionally, older mares may have elevated serum gonadotropins and fewer ovarian follicles. Some mares reach ovarian senescence when they grow older[66,68,69] and typically have small, inactive ovaries (follicles <5 mm) and a flaccid uterus and cervix. Although senescent mares may still show behavioral signs of estrus (similar to anestrous or ovariectomized mares), ovarian function is completely absent.

Oocytes collected from aged donor mares, cultured, and transferred to young recipient mares were less likely to result in pregnancy than oocytes from young donor mares.[70] Furthermore, oocytes obtained from old mares and examined using transmission electron microscopy had more morphologic abnormalities than oocytes from young mares. Results from these studies suggest that oocyte quality declines as mares age, and this factor will contribute to poor fertility in older mares.

Treatment and Prognosis No treatment is available for age-related ovarian inactivity. Because aged mares often experience a delayed seasonal onset of ovarian activity, they benefit from an artificial light regimen starting 60 to 90 days before the breeding season. GnRH has been used to stimulate follicular growth in mares with poor follicular development attributable to anestrus or transition. Several studies (reviewed by Ginther[26]) have examined the effects of GnRH administered at different doses and intervals to stimulate follicular development in mares. In general, the number of mares responding to GnRH therapy increased as the size of follicle or time of year at the onset of therapy increased.

EXOGENOUS HORMONE TREATMENT. Anabolic steroids are derivatives from androgens that have been altered to provide high anabolic activity with minimal androgenic side effects. A suppression of gonadotropin secretion has been documented when mares have been treated with these drugs.[71] Anabolic steroid administration may affect both estrous behavior and ovarian size and function. The treatment of mares with low doses of anabolic steroids can cause aggressive or stallion-like behavior, whereas high doses can inhibit ovarian activity and result in failure of follicular development and ovulation.[71] Prolonged treatment of prepubertal mares with anabolic steroids results in hypertrophy of the clitoris.[72] Ovarian inactivity in mares treated with anabolic steroids is reversible, and pituitary and ovarian function eventually return to normal in most mares after withdrawal of the treatment. Mares intended for breeding should not be treated with anabolic steroids.

Progestins are commonly given to cycling mares for the suppression of estrus or synchronization of ovulation. Mares may continue to ovulate during progestin administration, especially if treatment is started late in the luteal phase. A high incidence of persistent CL formation has been observed in mares that ovulate during progestin treatment.[73] Administration of the potent GnRH agonist deslorelin acetate (Ovuplant, Fort Dodge Animal Health, Overland Park, Kan.) to induce ovulation has been associated with delayed follicular development and a prolonged interovulatory interval.[74,75] Deslorelin acetate is effective in inducing ovulation, but treatment appears to cause a temporary downregulation of follicle stimulating hormone (FSH) secretion. The low FSH concentrations have been associated with a prolonged period of decreased follicular growth. Administration of $PGF_2\alpha$ 7 to 8 days after ovulation appears to increase the risk of delayed follicular development. It has been suggested that $PGF_2\alpha$ administration "resets" the timing of the estrous cycle during a period when limited follicular activity is present.

Treatment and Prognosis Removal of the deslorelin implant after ovulation has been detected and will decrease the incidence of prolonged interovulatory intervals.[76]

GONADAL DYSGENESIS. Chromosomal abnormalities occur in all breeds of horses. Mares are usually small and phenotypically female. The ovaries are small, firm, smooth, and inactive. The tubular tract is thin and flaccid. Endometrial hypoplasia is a common finding. Diagnosis is confirmed by physical findings and karyotype. Mares with gonadal dysgenesis are sterile, and there is no treatment.

PITUITARY PARS INTERMEDIA DYSFUNCTION. Mares with hypertrophy, hyperplasia, or adenoma formation in the pars intermedia of the pituitary (pituitary pars intermedia dysfunction [PPID]) have been reported to have abnormal estrous cycles, infertility, or both.[77,78] The mechanisms by which PPID causes reproductive abnormalities have not been determined. Potential cause(s) may be destruction of the gonadotrophs of the anterior pituitary owing to compression by the enlarged pars intermedia[79] or suppression of gonadotropin secretion owing to elevated levels of glucocorticoids or androgens produced by the adrenal cortex.[79] In support of the glucocorticoid hypothesis, administration of dexamethasone to intact mares results in reduced estrous behavior, LH concentrations, follicular growth, and incidence of ovulation.[80] In addition, administration of dexamethasone to ovariectomized mares results in suppression of pituitary LH and FSH secretion,[81] and treatment of pony mares with dexamethasone during the winter eliminates estrous behavior.[82] Many PPID horses are insulin resistant, and insulin is believed to play a role in the regulation of ovarian steroidogenesis and follicular development.[83] Obese mares with reduced insulin sensitivity have been shown to have prolonged interovulatory periods. Insulin resistance may, therefore, be one mechanism by which PPID mares exhibit abnormal ovarian function.[84] A majority of horses diagnosed with PPID are older, with the average age being approximately 20 years. Consequently the decrease in reproductive efficiency in mares with PPID may be partly a result of advanced age.

Clinical signs of PPID include hirsutism and abnormal haircoat shedding patterns, polyuria, polydipsia, and hyperhidrosis.[85] Diagnostic tests for PPID include measurements of serum glucose, insulin, adrenocorticotropic hormone (ACTH) cortisol levels, dexamethasone suppression, ACTH stimulation, and thyrotropin-releasing hormone response tests.[86] The measurement of single samples for basal cortisol or ACTH concentrations is of limited value in the diagnosis of PPID.

Treatment and Prognosis The medical management of PPID includes the administration of pergolide mesylate, a dopamine receptor agonist, at a dose of 0.5 to 2 mg every 24 hours in an adult horse. The serotonin antagonist cyproheptadine has also been used, but it may not be as efficacious as pergolide. The dose of cyproheptadine is 0.25 mg/kg every 24 hours, given once in the morning.

Abnormally Enlarged Ovaries

The most common causes of enlarged ovaries in the mare are (1) tumors, (2) anovulatory follicles, (3) ovarian hematomas, and (4) pregnancy.

Ovarian Tumors

The majority of equine ovarian tumors can be categorized as sex cord–stromal tumors (granulosa-theca cell tumors), epithelial tumors (cystadenomas), or germ cell tumors (dysgerminomas and teratomas), and mares can present with more than one tumor type.[87]

GRANULOSA-THECA CELL TUMORS. The granulosa-theca cell (GCT) tumor is the most common ovarian tumor in the mare

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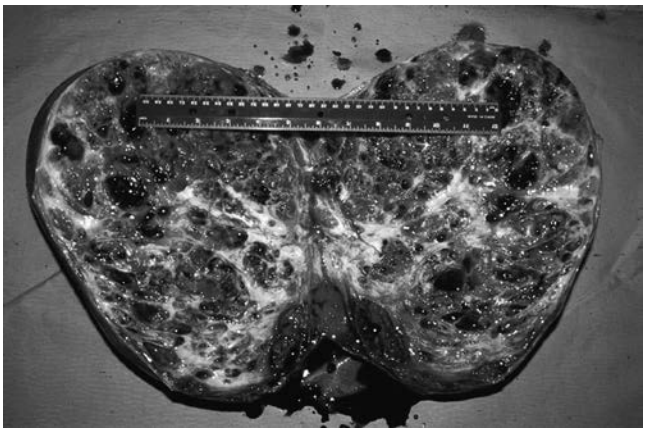


FIG. 43-4 Granulosa cell tumor removed from a mare.

(Fig. 43-4),[88] and 10% of all neoplasms in horses are GCTs. It is usually slow growing, unilateral, and benign; however, malignant tumors have been reported.[89] It occurs in mares of all ages and parity[88,90] and is occasionally found in pregnant mares.[88,91] The tumor arises from the steroidogenic cells of the follicle, resulting in abnormal secretion of inhibin and testosterone.

Clinical Signs and Diagnosis Diagnosis of GCTs is made on the basis of ultrasonographic findings, histologic evaluation, hormone profile analysis, and behavioral observations. Transrectal ultrasonographic examination of the affected ovary often reveals a multicystic or honeycombed structure, but the tumor may also occur as a solid mass or as a single large cyst. In most cases, the GCT affects only one ovary and the contralateral ovary is usually small and inactive, although mares with a GCT on one ovary and a functional contralateral ovary have been reported.[92]

Granulosa cell tumors are hormonally active, and clinical diagnostic assays for the detection of a GCT include the measurement of inhibin (α-inhibin), testosterone, progesterone, and anti-müllerian hormone (AMH).[93-97] α-Inhibin is elevated in approximately 90% of the mares with a GCT.[94,96] It has been hypothesized that inhibin produced by the GCT is responsible for inactivity of the contralateral ovary through the suppression of pituitary FSH release.[98] In contrast, earlier reports on a poor correlation between dimeric inhibin and the presence of GCT raise questions about the mechanism by which the contralateral ovary is suppressed in affected mares.[96,99] Serum testosterone in a single blood sample can be expected to be elevated (100 to 200 pg/mL) in approximately 50% to 60% of affected mares. Daily fluctuations in testosterone concentrations have been reported, and repeated samples may have to be obtained on different days in order to detect elevated testosterone.[96] Progesterone concentrations in mares with a GCT are almost always below 1 ng/mL because normal follicular development, ovulation, and CL formation do not occur. Recently, serum levels of AMH have been suggested to be a good indicator of GCTs because AMH levels in mares with GCTs were consistently higher than in normal cyclic and pregnant mares.[97] As a result of hormone secretion from the tumor, mares may show anestrus, constant estrus, irregular estrus, or stallion-like behavior. Physical changes such as an enlarged clitoris, increased muscle mass, and the development of a crested neck have been associated with GCTs, and other clinical signs such as colic, lameness, and weight loss have been observed.[88,100]

Treatment and Prognosis Treatment for GCTs is removal of the affected ovary. Surgical approaches for tumor removal include colpotomy, flank and ventral midline laparotomy, and laparoscopy. The prognoses for both life and reproductive use are good. The time from surgery to return to cyclicity varies, but most mares cycle in the year after ovariectomy.

CYSTADENOMAS. The most common tumor of the surface epithelium of the equine ovary is the cystadenoma. They are rare, benign, normally hormonally inactive tumors from the surface epithelium of the ovulation fossa. The tumor is unilateral, and the contralateral ovary is normal.

Clinical Signs and Diagnosis Mares with cystadenomas cycle normally from the opposite ovary and may even become pregnant. Rectal palpation and ultrasonography reveal the presence of one enlarged multicystic ovary, which may appear similar to a granulosa-theca cell tumor, and one normal ovary; however, final diagnosis is histologic.

Treatment and Prognosis Although cystadenomas are benign tumors and do not affect the reproductive performance of the mare, they are usually surgically removed if diagnosed. The prognoses for both life and reproductive performance are excellent.

GERM CELL TUMORS. Dysgerminomas and teratomas are rare ovarian tumors of germ cell origin. Both tumors are unilateral and hormonally inactive.

Clinical Signs and Diagnosis Both tumors make the affected ovary unilaterally enlarged and multicystic. Dysgerminomas are malignant and often metastasize to the peritoneal and thoracic cavities. Teratomas may arise from all three germinal layers, and the neoplastic ovary may contain bone, cartilage, teeth, hair, muscle, and nerves. Teratomas do not cause clinical signs, interrupt the estrous cycle, or alter the behavior of the mare. Diagnosis of dysgerminomas and teratomas is made using ultrasonography and histologic evaluation of the affected ovary.

Treatment and Prognosis Surgical removal is recommended for both dysgerminomas and teratomas. The prognosis for teratomas is usually good, but it is poor for mares diagnosed with dysgerminomas.

Anovulatory Follicles

Clinical Signs and Diagnosis Ovulation failure is a normal physiologic event for the mare during the spring and fall transition periods, but it may also occur occasionally during the physiologic breeding season. Persistent anovulatory follicles (PAFs) may be quite large (5 to 15 cm in diameter), persist for up to 2 months, and result in abnormal estrous behavior and prolonged interovulatory intervals.[101] The cause of ovulation failure is still being determined, but it has been suggested to be due to gonadotropic stimulation insufficient for ovulation,[102] reduced estrogen production by the follicle,[103] blockage of the ovulation fossa,[104] repeated use of ovulation-inducing drugs,[105] alterations of the matrix metalloproteinase system,[106] and defects in the normal ovarian pro-angiogenic activity.[107] PAFs were reported in a recent study to occur in approximately 8.2% of estrous cycles, and significantly more mares aged 16 to 20 years developed anovulatory follicles than mares aged 6 to 10 years.[108] The formation of an anovulatory follicle was preceded by development of normal endometrial folds or edema in 78.3% of these cases. Initial growth patterns of follicles destined to become anovulatory were usually normal, and the first indication of a problem was the detection of echogenic particles within the follicular fluid.[108]

PAFs may contain blood and have been termed *hemorrhagic anovulatory follicles.* The hemorrhage can be detected ultrasonically as scattered free-floating echogenic spots within the follicular fluid. The follicular fluid may form a gelatinous, hemorrhagic mass within the follicular lumen. Ultrasonographically these structures may contain echogenic fibrous bands traversing the follicular lumen (Fig. 43-5).[109] A thickening of the follicular wall may be observed in anovulatory follicles. This thickening is often associated with luteinization of the follicular wall, and 85.7% of PAFs were found to be luteal structures based on elevations in plasma progesterone concentrations.[108]

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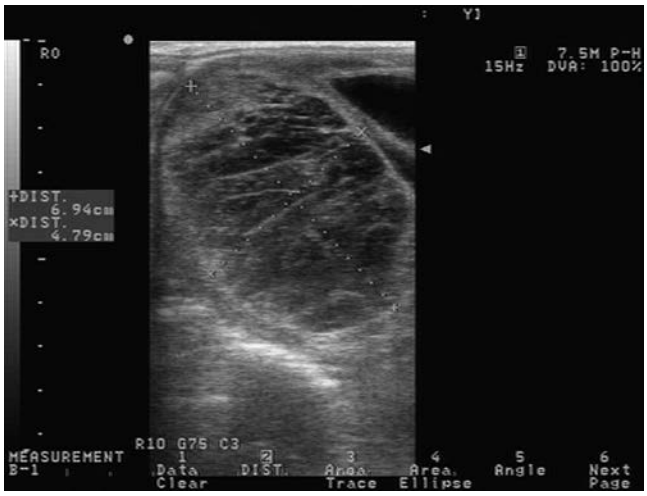


FIG. 43-5 Transrectal ultrasonographic image of a persistent anovulatory follicle in a mare.

Treatment and Prognosis Treatment with hCG or a GnRH agonist (Ovuplant) to induce ovulation or luteinization of the anovulatory follicle is generally not effective. The administration of prostaglandins may result in the destruction of the luteal cells in mares with luteinized PAFs. A majority of nonluteinized PAFs spontaneously regress in 1 to 4 weeks. Pregnancy does not usually occur if a persistent follicle eventually spontaneously ovulates or is induced to ovulate. This is likely a result of degeneration of the oocyte over time. Pregnancy obviously will not occur if the follicle becomes hemorrhagic or luteinized without ovulation.

Ovarian Hematoma

Clinical Signs and Diagnosis Hemorrhage into the follicular cavity is a normal occurrence at ovulation. Occasionally hemorrhage is severe, resulting in the formation of an ovarian hematoma that may be 10 cm in diameter or larger. Diagnosis is made using transrectal palpation and ultrasonography, and the condition presents as an enlarged ovary that is initially irregularly hypoechoic and then echogenic with organization of the hematoma. The ovulation fossa usually remains distinguishable on the affected ovary, and the contralateral ovary remains active.

Treatment and Prognosis Ovarian hematomas regress spontaneously over a period of weeks or months. The functional lifespan of the luteal tissue in a hematoma is normal, and ovarian activity is unaffected.[110] Because the affected ovary is not permanently damaged and the contralateral ovary is unaffected, the prognosis for fertility is undiminished.

Pregnancy

Multiple secondary CLs form in pregnant mares at 40 to 180 days of gestation, resulting in bilaterally enlarged ovaries that may be mistaken for ovarian pathology.

Clinical Signs and Diagnosis Ovarian enlargement is commonly bilateral. Pregnant mares may show stallion-like behavior associated with increased testosterone production from the fetus during midgestation. Pregnancy should always be considered in a mare with stallion-like behavior, elevated serum testosterone concentrations, and enlarged ovaries. Pregnancy is diagnosed by rectal palpation and ultrasonographic examination.

Persistent Corpus Luteum

The CL usually regresses 14 to 15 days after ovulation.[3] Although luteal cells appear to be sensitive to $PGF_2\alpha$ almost immediately after ovulation, complete luteolysis and return to estrus in response to endogenous or exogenous $PGF_2\alpha$ will not occur until 5 days after ovulation. Because the functional CL is lysed by $PGF_2\alpha$ from the endometrium, the CL will continue to function in the following situations.

1. In the pregnant mare the equine conceptus produces a PGF inhibitor factor, which is secreted as early as day 11 to 13 after ovulation.[26] The factor prevents PGF from being synthesized and secreted from the endometrium. This results in a prolonged luteal phase of the primary CL until the development of endometrial cups and secretion of eCG ensure the presence of functional luteal tissue in the pregnant mare.
2. Embryonic loss after the time of maternal recognition of pregnancy can result in a persistent CL for a variable period of 35 to 90 days.[111]
3. Destruction of the endometrium in infectious and inflammatory conditions such as pyometra may cause insufficient synthesis of PGF and prolonged luteal life.[112]
4. Late diestrous ovulation will result in a CL that is insufficiently mature to respond to endogenous PGF release.[1]
5. Nonsteroidal antiinflammatory drugs may inhibit endometrial PGF synthesis, resulting in a prolonged luteal phase.[113]
6. Repeated treatment with oxytocin before upregulation of oxytocin receptors occurs (before day 13) has resulted in prolonged luteal phase.[114,115]
7. Spontaneous CL persistence has been proposed as a clinical entity[79] but has not been adequately documented and is an area of controversy.[116]

TABLE 43-4

Unilaterally Large Ovary: Differential Diagnosis

Etiology	Distinguishing Features
Granulosa-theca cell tumor	Sonographically multilocular, high inhibin, AMH and/or testosterone; small contralateral ovary
Other ovarian tumor	See text
Ovarian hematoma	Ovulation fossa still palpable, cycles normally
Ovarian abscess	Large, hard ovary; sonographically echogenic
Ovarian follicle	Normal cycling mare, ovulates
Anovulatory hemorrhagic follicle	Free-floating echogenic spots

AMH, Anti-müllerian hormone.

Clinical Signs and Diagnosis A persistent CL may be suspected clinically in mares that are not expressing normal estrous behavior during the physiologic breeding season, and it must be differentiated from mares with silent heat. Diagnosis is made by transrectal ultrasonographic examination of the ovaries. The CL appears as a well-defined hyperechoic structure on the ovary. Mares with a persistent CL will have good cervical and uterine tone on palpation, and the cervix will appear tight and dry on vaginal speculum examination because of the influence of progesterone. The diagnosis may be confirmed by analysis of plasma progesterone concentrations or a clinical response to prostaglandin administration. Progesterone concentrations greater than 1 ng/mL[1] are indicative of the presence of active luteal tissue. Differential diagnoses are listed in Table 43-4.

Treatment and Prognosis After pregnancy has been ruled out with sonographic examination, luteolysis can be achieved with administration of 10 mg of the PGF product dinoprost tromethamine or similar PGF analog. The mare must be at least 5 days post ovulation to respond reliably to treatment, although administration of the drug 3 days post ovulation can be effective.[117] If the mare is

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treated with PGF in the presence of a mature diestrous follicle (≥35 mm), she may ovulate the follicle without signs of estrus in response to declining progesterone concentrations that allow LH to be secreted from the anterior pituitary. An ultrasonographic or rectal examination of ovarian follicular activity should therefore always be performed before PGF is administered to induce estrus.

Shortened Luteal Phase (Premature Luteolysis)

Premature (<15 days) luteolysis is associated with an early onset of estrus and a decrease in the interovulatory interval. The most common cause of premature luteolysis in the mare is endometritis. Inflammation of the endometrium results in an acute activation of inflammatory mediators. One of these mediators is $PGF_2\alpha$, which in addition to its inflammatory effect also may cause luteolysis and return to estrus. Consequently a mare that exhibits a shortened diestrus should be examined for endometritis. Manipulation of the reproductive tract for uterine biopsy has also been found to cause premature luteal regression.[118]

Luteal Insufficiency

Primary luteal insufficiency implies a deficiency in progesterone production. Luteal insufficiency has been suggested to be a cause of subfertility in mares.[119] Maintenance of pregnancy in some habitually aborting mares after administration of exogenous progestogens offers circumstantial evidence that progesterone insufficiency may be responsible for some cases of pregnancy loss.

Luteal insufficiency secondary to $PGF_2\alpha$ release in mares with endotoxemia has been reported[120] and should be considered in pregnant mares with gram-negative infection and/or endotoxemia-associated colic. Reports on the effect of exogenous administration of $PGF_2\alpha$ during the periovulatory period suggest that $PGF_2\alpha$ can delay the formation of a functional CL. Suboptimal concentrations of progesterone were found in mares after treatment with $PGF_2\alpha$ during the first 2 days after ovulation.[121-124] Although the CL eventually became functional and progesterone concentrations had returned to normal levels at day 14, pregnancy rates were significantly lower in treated mares.[122,123]

Clinical Signs and Diagnosis The minimum concentration of progesterone required to maintain pregnancy in the mare has been suggested to be 2 ng/mL.[120] Repeated samples are necessary to diagnose luteal insufficiency because progesterone is released episodically.

Treatment and Prognosis The most common treatment for luteal insufficiency is supplementation with the synthetic progestogen altrenogest (Regumate) at a dose of 0.044 mg/kg PO once daily. Options for duration of altrenogest supplementation include treatment until day 80 to 120 of pregnancy or greater and measurement of endogenous progesterone level of >2 ng/mL (progesterone and altrenogest do not cross-react on radioimmunoassay [RIA]) or treatment until the end of gestation. It is important to emphasize the need to monitor fetal well-being when mares are kept on progestin supplementation to maintain pregnancy. A case of fetal mummification of a 5-month-old fetus in a pregnant mare at term has been reported.[125] The mare had been maintained on altrenogest throughout gestation.

RUMINANTS

Prolonged Luteal Function

Cow

Spontaneous prolongation of luteal function in the presence of a normal, nongravid uterus does not occur in cows. But several conditions affecting the uterus do suspend the luteolytic mechanism, resulting in prolonged luteal function, persistently elevated progesterone concentrations, and anestrus. Common causes of prolonged luteal function in cows include pregnancy, pyometra, mummified fetus, and segmental aplasia, including uterus unicornis.

Clinical Signs and Diagnosis Pregnancy resulting from an unobserved or unrecorded breeding must always be considered as a possible cause of anestrus. Examination of the uterus by transrectal palpation or ultrasonography for one of the positive signs of pregnancy (fetal membrane slip, amnionic vesicle, placentomes, or fetus) must precede administration of PGF.

Pyometra is characterized by accumulation of variable amounts of mucopurulent exudate within the uterine lumen, failure of luteolysis, and subsequent anestrus. An enlarged uterus as a result of fluid accumulation and a thickened uterine wall in the absence of any positive signs of pregnancy can be used to differentiate uterine enlargement caused by pregnancy from that caused by pyometra. Fluid associated with pyometra is more viscous than fetal fluid and can be manipulated from horn to horn. Because the cervix is nearly always closed, there is generally no vaginal discharge.

Fetal mummification is occasionally encountered in dairy and beef cows and is characterized by fetal death, failure of expulsion, absorption of fetal fluids, and persistence of the CL. Cows with fetal mummification are usually presented when they do not deliver a calf at the expected time. The condition can be differentiated from pregnancy by palpation per rectum of a dried, leather-like fetus within the involuted uterus. Fetal membranes cannot be slipped, and fetal fluids and placentomes are absent.

Clinical Pathology No remarkable changes in hematology and clinical chemistry are associated with pregnancy, mummified fetus, or pyometra in cows. In all three conditions, peripheral concentrations of progesterone remain elevated above 1 ng/mL of plasma until spontaneous luteolysis occurs or the condition is treated.

Treatment and Prognosis Unwanted pregnancy is seldom encountered in dairy cows, but when cows or heifers are mated by accident or to an undesired sire, abortion may be reliably induced with PGF products (25 mg of dinoprost tromethamine [Lutalyse, Pfizer Animal Health Inc, New York, N.Y.] or 500 µg of cloprostenol [Estrumate, Mobay Corporation, Animal Health Division, Shawnee, Kan.], two injections 8 to 12 hours apart) after 7 days and before 150 days of gestation or with a combination of PGF and dexamethasone (20 mg) beyond 150 days of gestation. The PGF products are also the treatment of choice for pyometra in cows. Mummified fetuses are usually expelled 3 to 5 days after treatment with PGF. The mummy may pass through the cervix, but the vagina is likely to be dry and may not dilate sufficiently, so the mummified fetus may be retained. If the mummified fetus is not expelled by 5 days after treatment, a vaginal examination should be performed, and the mummy delivered by gentle traction if necessary. The prognosis for fertility after delivery of a mummified fetus is good, but slaughter is often recommended for economical reasons.

Ovarian Hypoplasia

Ovarian hypoplasia occurs sporadically as an autosomal recessive trait in the cow. The condition has incomplete penetrance; therefore it may be partial or complete and unilateral or bilateral. The affected gonad varies in size from a cordlike thickening in the cranial edge of the mesovarium to a bean-sized structure. The tubular genital organs remain infantile in animals with complete bilateral hypoplasia or may develop to near-normal size in heifers with unilateral or partial hypoplasia. Individuals affected with complete bilateral ovarian hypoplasia are sterile, whereas those affected by partial or unilateral hypoplasia may be subfertile. With partial hypoplasia the uterine pole of the ovary is typically affected. On direct observation by laparotomy or laparoscopy or on slaughter, the uterine pole is flat and triangular and shows converging striations. The affected part is

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devoid of follicles. Animals with partial ovarian hypoplasia can be expected to have a reduced superovulatory response to gonadotropin treatment. Heifers with abnormal karyotypes are also affected by ovarian hypoplasia. The condition should be differentiated from nonfunctional ovaries and anestrus associated with malnutrition or debilitating diseases. Treatment of ovarian hypoplasia is not successful.[126]

Freemartinism

Cow

A freemartin is a phenotypic female, born co-twin to a male, that is sterile because of arrested development of the reproductive tract. The term *freemartin* is said to have originated in England, where it referred to a heifer that was not pregnant after the summer breeding season and therefore "free" for fattening and slaughter at Martinmas, a fall festival in honor of St. Martin.[13] Freemartinism arises as a result of anastomoses between the placental circulations of twin fetuses of opposite sexes before gonadal differentiation. The ovaries of a freemartin are underdeveloped and contain seminiferous tubules. Abnormalities of the tubular genital organs vary in severity, and the structures range from cordlike bands to near-normal uterine horns. In most freemartins there is no cervix; therefore no communication exists between the uterus and vagina. The latter is a short blind pouch. Frequently, seminal vesicular glands of varying size are present.

Up to 92% of phenotypic females born co-twins to males are freemartins[60]; the history suggests a diagnosis in most cases. Singleton freemartins are possible if male and female twins are conceived and the male is lost after 30 days of gestation. Palpation per rectum of breeding-age freemartins reveals aplasia or hypoplasia of the tubular genital organs and hypoplastic ovaries. If animals too small for palpation per rectum are presented, examination of the vagina with a small glass speculum (or test tube) reveals that the vagina of a freemartin is short (6 to 7 cm in freemartins versus nearly double that length in normal heifers). A definitive diagnosis may be made by karyotyping the suspected individual; varying percentages of male cells are found in freemartins.[126] More details on freemartinism are discussed elsewhere in this chapter.

Ewe

Although freemartinism is possible in sheep, the condition is rare, despite the high incidence of multiple births. The condition can be confirmed by determination of blood cell chimerism.

Doe

Twinning is also common in goats, but vascular anastomosis is either uncommon or occurs after the critical period for sexual differentiation. Caprine freemartins comprise approximately 6% of intersexes.[5]

Intersex

Doe

Intersexes are common among Saanen, Toggenburg, and Alpine goats. The fetal testes appear to be unable to fully masculinize the duct system or external genitalia. Parts of both the mesonephric and paramesonephric ducts persist; therefore the phenotype of affected individuals may approach that of either sex. Intersexes are most frequent among polled goats, and the condition is thought to be caused by a recessive gene linked to that for polledness; however, intersexuality may rarely be seen in horned goats. Diagnosis is based on a history of abnormal sexual behavior, and identification of abnormal genital development is by physical examination. There is no satisfactory treatment, but the prevalence of the condition may be reduced by preventing mating between two polled animals.[5] More detailed information can be found elsewhere in this chapter.

Ovarian Tumors

Granulosa Cell Tumor

COW. Although rare, various ovarian neoplasms have been described in cows; granulosa cell tumors appear to be most common.[13]

Clinical Signs and Diagnosis Granulosa-theca cell tumors are characterized by unilateral ovarian enlargement, with the affected ovary being greater than 10 cm in diameter. The surface may be smooth or coarsely lobulated. Function of the contralateral ovary may be suppressed. The behavior of affected cows ranges from anestrus to nymphomania to bull-like behavior. Udder development and lactation may occur in affected heifers. Hormonal profiles, including estrogen and testosterone, may be variable among cows with granulosa cell tumors. Although inhibin has not been validated for use in cows, anti-müllerian hormone (AMH) is secreted by neoplastic granulosa cells and can be a useful diagnostic measurement.[127] Few bovine granulosa cell tumors are malignant, and they rarely metastasize. Among the other ovarian neoplasms that have been reported in cattle are dysgerminomas, interstitial cell tumors,[13] and teratomas. Causes of ovarian enlargement that must be differentiated from ovarian neoplasia include ovarian cysts, oophoritis, ovarian abscesses, and parovarian cysts.

Treatment and Prognosis The treatment for ovarian neoplasia in cattle is surgical removal of the affected ovary; however, cows may not be as fertile as mares after removal of the tumor.

EWE. Granulosa-theca cell tumors have been reported, but tumors of the genital organs of ewes appear to be rare.[13] Animals with ovarian tumors may exhibit all types of behavioral and physiologic abnormalities (nymphomania, inappropriate lactation). Diagnosis is based on ultrasonographic evaluation of ovaries per rectum or transabdominally. Treatment is ovariectomy.

DOE. Ovarian neoplasia appears to be rare in does as well. Granulosa-theca cell tumors and dysgerminomas have been reported.

Ovarian Hemorrhage

Cow

Ovulation tags develop after ovulation, resulting from blood loss associated with rupture of the follicle.[13] Fine adhesions may develop between the ovarian surface and surrounding structures. Most ovulation tags resolve spontaneously and have no effect on fertility. Severe ovarian hemorrhage may follow attempts to manually enucleate the CL. Adhesions between the ovary and its bursa interfere with their normal function. Enucleation of CLs for treatment of anestrus and pyometra has been superseded by treatment with PGF products.

Oophoritis

Cow

Inflammation of the ovary may follow traumatic manipulations, such as enucleation of CLs and attempts to drain fluid from ovarian cysts, and ascending infections from the uterus. Oophoritis may also accompany brucellosis, mycoplasmosis, and tuberculosis.

Infertility Caused by Abnormalities of the Female Tubular Genitalia

Salpingitis

Inflammation of the oviducts is characterized by macroscopic enlargement. Lesions are frequently bilateral and consist of infiltration

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by lymphocytes, plasma cells, and neutrophils, and desquamation of epithelial cells.[13]

Most cases of salpingitis follow infections of the uterus. Necrotizing and granulomatous salpingitis may follow infection by *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Mycobacterium tuberculosis,* and *Brucella abortus.* Mild inflammation of the uterine tubes that does not usually result in permanent damage accompanies uterine infection caused by *Campylobacter fetus* subsp. *venerealis* and *Tritrichomonas foetus.* Salpingitis may be a sequela to manipulations of the ovaries and uterine tubes by palpation per rectum, transvaginal ovum pickup, aggressive irrigation of an infected uterus, and inappropriate treatment with estrogenic hormones. Migrating larvae of *Strongylus edentatus* have been proposed as a possible cause of nonobstructive infundibulitis in mares, but their role is speculative.[13]

Pyosalpinx is characterized by segmental accumulation of pus within the lumen of the oviduct after mechanical blockage of either end. Pyosalpinx frequently follows severe cases of uterine infection and may be complicated by perimetritis and localized peritonitis.

Hydrosalpinx is characterized by accumulation of thin mucus within the lumen of the oviduct. Hydrosalpinx and adhesions to perisalpingial tissues are common sequelae to chronic salpingitis.

Clinical Signs and Diagnosis The usual history associated with diseases of the uterine tubes is one of infertility. Additional history may include uterine infection or traumatic therapy such as uterine irrigation, enucleation of CLs, or administration of exogenous estrogen during CL function. Salpingitis is an uncommon clinical finding in the mare. However, in one study, up to 88% of mares were found to have macroscopic lesions in the oviduct, including adhesions, fibrous bands, and parovarian cysts, which may or may not have affected fertility.[128] Accumulations of cells and debris may form intraluminal masses; however, their role in infertility has not been adequately tested.[129] The pathology of the oviduct has been reviewed.[130] Similarly, moderate lesions of uterine tube disease may escape diagnosis by physical examination in cows, but the results of abattoir studies suggest that lesions of the oviducts are not uncommon.[13] In cows, lesions involving adhesions among the ovary, ovarian bursa, oviduct, and surrounding tissues may be identified per rectum by inserting two or three fingers into the ovarian bursa and rolling the oviduct between the fingers and thumb. Easy identification of the oviduct by palpation per rectum is sometimes considered indicative of abnormalities. Diagnosis of diseases of the oviducts in ewes and does is impossible by physical examination. Although a history of infertility after one of the predisposing causes might suggest oviductal lesions, diagnosis is made by exploratory laparotomy, peritoneoscopy, or necropsy.

Lesions of the oviductal or perisalpingial tissues must be differentiated from other causes of abnormal enlargements such as ovarian neoplasia, parovarian cysts, cystic ovarian disease, and ovarian hematomas. Neoplasia of the oviducts in domestic animals is extremely rare.

Clinical Pathology Several tests that determine oviductal patency of mares[131,132] and cows[133] have been described, but neither the starch test nor the phenolsulfonphthalein dye test is reliable or consistently diagnostic. For suspected unilateral blockage,[134] each uterine horn may be catheterized individually with a Foley catheter placed at the base of the horn on different days.

Embryo Recovery Embryo recovery after either a single ovulation or superovulation is objective evidence that one or both uterine tubes are patent and functional. Improved reproductive performance of cows may follow uterine lavage; therefore embryo recovery as a diagnostic test may have therapeutic benefits as well.[135]

Treatment and Prognosis Treatment of diseases of the oviducts is not likely to be successful. Appropriate treatment for concurrent uterine infections should be instituted. A period of sexual rest may be beneficial and is indicated in valuable animals. The prognosis for reproduction in cases of bilateral obstruction of the oviducts is poor. In vitro fertilization of ova harvested from affected females is a therapeutic option. Affected females can also serve as embryo recipients.

Prevention and Control Traumatic manipulation of the ovaries, irrigation of the endometrial cavity with large volumes of fluid (>100 mL in heifers or 150 mL in cows) or irritating chemicals, and administration of estrogenic hormones to luteal phase females should be avoided.[126] Because abnormalities of the oviducts are frequently associated with uterine infections, reduction of the prevalence of uterine infections results in fewer tubal infections as well.

Uterine Abnormalities

Retained Fetal Membranes

MARES Retention of the fetal membranes beyond a period of 3 hours is an abnormal occurrence in the mare. The mare has an epitheliochorial placenta characterized by diffuse microvilli that interdigitate with endometrial crypts. After delivery, blood flow through the placental vessels is reduced. Placental microvilli shrink and disengage from endometrial crypts. The pathophysiology of the disease is poorly understood but may involve disturbances of normal prepartum endocrine events or myometrial contractility. The condition is more common after abortion, dystocia, cesarean section, and fetotomy. Partial placental retention may be localized to well-defined areas of continued placental attachment. The most common site of partial retention is the previously nongravid horn.

Equine placentas should be spread on a flat surface after expulsion and examined to ensure that the complete membrane is present. Areas of placental necrosis are common near the tips of the uterine horns, and the fragile area may be incarcerated by the rapidly contracting uterus.

Clinical Signs and Diagnosis Retained fetal membranes (RFMs) are usually visible at the vulva. However, small tags of placental tissue may remain attached to the uterus without being apparent and may be a nidus for infection, resulting in severe metritis, endotoxemia, and laminitis hours to days postpartum.

Treatment and Prognosis The severity of sequelae makes early intervention essential. Treatment should begin if fetal membranes are not passed within 3 hours of foaling. Most instances respond to vigorous early pharmacologic treatment. Occasional cases require several days of persistent treatment.

MANUAL REMOVAL. Manual removal should be avoided because trauma induces placental tearing, leaving microvilli in endometrial crypts.

OXYTOCIN. Oxytocin induces myometrial contractions, which may aid placental expulsion. Oxytocin may be administered by IV injection (5 to 20 IU every 30 to 60 minutes) or intramuscular injection (10 to 20 IU every 30 to 60 minutes), or it may be infused slowly (30 to 80 IU in 500 mL of warm saline IV over 30 to 60 minutes). Care should be taken to avoid overdosage, which may result in signs of abdominal pain and which will cause tetanic rather than orchestrated uterine contraction.

ALLANTOCHORIONIC INFUSION. If the allantochorion is intact, the allantochorionic cavity may be filled to distention with 3 to 4 gallons of warm saline or water through the cervical star.[136] The opening in the placenta is held closed until the mare exerts abdominal pressure. Oxytocin may be used in conjunction with this treatment.

UTERINE LAVAGE. If the allantochorion is not intact, uterine lavage with an isotonic saline solution will clear debris, encourage

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myometrial contractions, and may help to free the retained fragment of the fetal membrane. The isotonic saline solution may be infused into the uterus through an equine nasogastric tube (dedicated to reproductive use) manually held in place. Approximately 5 L may be placed in the uterus of a full-grown, postpartum mare at one time, but care should be taken to observe the mare for signs of discomfort and to gauge the amount of fluid felt within the uterus. During fluid infusion the operator may carefully explore the uterus manually, searching for RFM remnants. Once the uterus is relatively full of fluid, the fluid is siphoned out. Care must be taken to protect the fragile endometrium from damage incurred by the strong suction force of the siphon. The operator's hand should guard the end of the tube from direct contact with the endometrium. This process should be repeated until the effluent is clear. Uterine lavage should be performed at least once daily until 12 to 24 hours after the RFM remnants are retrieved.

ADJUNCT THERAPY. Concurrent therapy directed at controlling or minimizing common sequelae to retained placenta is often indicated.

1. *Antibacterials.* Bacterial infections are commonly associated with prolonged (>6 to 8 hours) retention of the fetal membranes. The bacterial population is frequently mixed and likely to include β-hemolytic streptococci and coliforms. In prolonged cases bacterial culture and sensitivity should be performed. Broad-spectrum antibiotics known to be effective against commonly isolated organisms are indicated. Drugs that have been recommended for systemic administration include amikacin, ampicillin, gentamicin, kanamycin, penicillin, ticarcillin (with gentamicin for *Pseudomonas* infection), and trimethoprim-sulfamethoxazole. Intrauterine administration of antibiotics and antiseptics depresses phagocytic activity of uterine neutrophils, and many chemicals irritate the endometrium. Drugs that have been suggested include those recommended for systemic administration.
2. *Antiinflammatory drugs.* Laminitis may be a sequela to metritis and is commonly associated with RFMs. Treatment with administration of antiinflammatory drugs such as phenylbutazone or flunixin meglumine is indicated to reduce the likelihood and severity of laminitis. Polymyxin B may also be indicated in cases in which preliminary signs of laminitis are noted, because of its antiinflammatory and antiendotoxic effects. Additional therapy for laminitis should be administered as indicated.
3. *Other treatments.* Caslick's surgery may be indicated in some cases of RFMs to control aspiration of air. Tetanus may complicate RFMs, and prophylaxis with tetanus antitoxin in unvaccinated animals or tetanus toxoid in previously vaccinated animals is indicated.

Some cases of RFMs are refractory to treatment, and membranes may remain firmly attached to the endometrium for several days. Aggressive attempts at manual removal should be eschewed because severe endometrial damage may follow. Persistent treatment with uterine lavage antibiotics, antiinflammatory drugs, and oxytocin is indicated until the placenta is expelled and bacterial infection of the uterus is controlled.

The prognosis for RFMs is generally good but is reduced if treatment is delayed or if retention is accompanied by infection with virulent pathogens. Sequelae to RFMs include metritis, endometrial fibrosis, invagination of a uterine horn, uterine prolapse, and laminitis.

RUMINANTS

Cow

The cotyledonary placenta of cows is usually expelled within 3 to 8 hours after calving and is considered retained if not expelled by 12 hours. RFMs are more commonly seen in dairy than in beef breeds. In dairy cattle the reported prevalence ranges from 8% to 12% after spontaneous delivery of single calves. RFMs are more likely after deliveries of male calves or twins and deliveries complicated by dystocia. Parturition after a shorter- or longer-than-normal gestation length is accompanied by an increase in the incidence of RFMs.[137]

The cause of RFMs in cattle is failure of fetal cotyledons to separate from crypts of maternal caruncles; the process of separation normally begins during the last months of pregnancy. Villi shrink after blood flow is interrupted by rupture of the umbilical vessels. Strong myometrial contractions continue during the third stage of labor, and changes in the size and shape of maternal caruncles contribute to separation of the placenta from the endometrium.[5] In addition to mechanical factors, elevated collagenase, in response to increasing relaxin and estrogen prior to parturition, promotes collagen breakdown at the cotyledon-caruncle interface.[5] A number of factors have been associated with separation failure, including induced parturition, abortion, dystocia, cesarean section, twinning, and nutritional deficiencies (selenium, vitamin E, vitamin A). The precise reasons for separation failure are unknown.[5]

Clinical Signs and Diagnosis

The majority of affected cows show no serious clinical signs other than a transient decrease in appetite and milk production. However, 20% to 25% of cows affected by RFMs develop moderate to severe metritis. The most objectionable clinical signs are the malodorous discharge and objectionable tissue hanging from the genital tract. RFMs are usually expelled by 4 to 10 days after calving when the caruncular tissue has become necrotic and is sloughed. Some affected cows show signs of endotoxemia, including depression, fever, ruminal stasis, and inappetence, as a result of RFMs.

Treatment and Prognosis

A variety of treatments have been suggested for RFMs in cows, including aggressive attempts at manual removal, myometrial stimulants, intrauterine and systemic antibiotics (alone or in combination with other approaches), and no therapy whatsoever. Because the processes that culminate in RFMs begin during late gestation, it is not unreasonable that treatment initiated at calving has little effect on the loosening process. Most treatments for RFMs are directed toward controlling the intrauterine bacterial population.

MANUAL REMOVAL. Manual removal of the placenta is indicated only when gentle traction is sufficient to withdraw the membranes in a short time. Attempts at manual removal are contraindicated if the patient shows clinical signs of septicemia. Trauma caused by manual removal inhibits phagocytosis by uterine neutrophils and predisposes to severe sequelae, including endometritis, septic metritis, peritonitis, and a delay to first ovulation.[138]

MYOMETRIAL STIMULANTS. Administration of a single dose of oxytocin does not reduce the prevalence of RFMs in cows that calve spontaneously or in cows that require assistance at delivery.[139,140] Cows with RFMs have an elevated plasma concentration of estrogen during the period of retention; therefore administration of additional estrogen for treatment of RFMs may be of questionable value.[141] Intravenous calcium solutions are indicated in cases of RFMs secondary to hypocalcemia. Because a relatively small proportion of RFMs are due to myometrial atony, myometrial stimulants may not be beneficial in many cases.[138]

PROSTAGLANDIN. In one trial, treatment with fenprostalene resulted in a shorter period of retention in treated cows, reduced the number of treatments subsequently required for metritis, and slightly reduced the intervals to first service and conception.[142] However, other researchers found that fenprostalene produced no changes in myometrial activity between days 1 and 4 after calving and concluded that uterotonic agents are unlikely to hasten placental expulsion because uterine effort is already increased in animals that have RFMs.[143] An imbalance between synthesis of PGF_2 and PGI_2 between 30 and 60 minutes after parturition has been demonstrated in cows

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affected by RFMs.[144] Prostaglandin at the time of calving does not reduce the incidence of RFMs or improve reproductive performance.[145]

ANTIBIOTICS. Intrauterine tetracycline may reduce fertility,[146] or the reproductive performance of treated cows may be as good as that of untreated herdmates.[7] Intrauterine treatment with 4 to 6 g of oxytetracycline per day until the placenta is expelled may reduce the prevalence of metritis associated with RFMs, but pyometra may develop in treated cows.[147] The placenta is released only after necrosis of the caruncles, which may be delayed by the presence of intrauterine antibiotics. Systemic antibiotics are indicated in cases of RFMs in which the cow has a fever, is off feed, or has a drop in milk production. Multiple studies have demonstrated the effects of systemic antibiotics are just as good as intrauterine antibiotics alone or a combination of systemic and intrauterine antibiotics in terms of systemic health and future fertility. Ceftiofur (2.2 mg/kg IM or subcutaneously [SC] q24h for 5 days) given to febrile cows with retained membranes has shown a beneficial effect in future reproductive parameters and may reduce the incidence of acute metritis.[138,148,149]

Cows that retain their membranes for more than 12 hours after calving are more likely to develop metritis than are cows that promptly expel the membranes. However, reproductive performance of cows that rapidly return to normal after RFMs is similar to that of their unaffected herdmates, indicating that in the absence of a secondary reproductive abnormality, RFMs have a minimum effect on future fertility.

COLLAGENASE. An alternative approach to the treatment of RFMs is the injection of collagenase into the umbilical arteries of the retained membranes.[150] This treatment is aimed directly at the lack of cotyledonary proteolysis, and although effective it is expensive and often not economically justifiable. Intrauterine infusion of collagenase is not effective. Bacterial collagenase from *Clostridium histolyticum* is used and is commercially available (Type XI, Sigma Chemical, St. Louis, Mo.). However, collagenase is not currently approved for use in food-producing animals in the United States.

Ewe and Doe

Fetal membranes are considered retained in ewes and does if not expelled within 12 hours after delivery of the last fetus. The prevalence in does is approximately 6% after spontaneous delivery but may be higher when delivery is complicated by dystocia or abortion. Selenium deficiency has been suggested as a cause.

The clinical signs of RFMs in ewes and does are usually obvious.[5] Does may ingest their placentas, complicating identification of cases of partial retention. RFMs may accompany retention of a fetus within the uterus, and does and ewes should be carefully examined.

Other tissues that may be exposed from the vulva in association with parturition are a prolapsed uterus, a prolapsed or everted urinary bladder, prolapse of some portion of the digestive tract through a uterine rupture, prolapsed rectum, prolapsed vagina, or a twin fetus.

Treatment and Prognosis Manual separation of cotyledons from caruncles is impossible in ewes and does; therefore manipulative attempts to remove the placenta are limited to gentle traction on exposed membranes at daily intervals. Treatments with intrauterine and systemic antibiotics, oxytocin (10 to 20 IU) at 12-hour intervals until the placenta is expelled, and antiinflammatory drugs have been suggested. Prophylaxis against tetanus is indicated.

Camelids

The placenta is usually passed within 1 to 2 hours of parturition. Camelid placentas resemble equine placentas (diffuse, microcotyledonary, epitheliochorial), with the exception that the left horn is almost always the pregnant horn. RFMs in camelids are most commonly seen as sequelae to dystocia or other disorders of parturition.[9] Treatment is similar to that described for the mare.

Uterine Infections

MARE

Endometritis

A failure of the uterine defense mechanisms to effectively eliminate an antigen (bacteria or spermatozoa) and inflammatory products from the uterus results in persistent endometritis, which is a major cause of reduced fertility in broodmares.[151] In the normal mare the uterus is well protected from external contamination by physical barriers consisting of the vulva, vestibule, vagina, and cervix, and any compromise of these barriers may predispose the mare to a chronic uterine infection.[152] Breeding is another source of uterine contamination. Intrauterine deposition of semen causes an inflammatory reaction resulting from bacterial contamination of the ejaculate or from spermatozoa.[153] Approximately 10% to 15% of a normal population of Thoroughbred broodmares developed persistent endometritis after breeding.[154] AI with frozen semen resulted in 16% to 25% persistent inflammation after breeding.[155,156] Natural resistance to experimentally induced bacterial contamination has been demonstrated in young mares, whereas a population of multiparous and barren mares developed persistent endometritis after bacterial contamination of the uterus.[157,158] On the basis of these studies, mares have been classified as either susceptible or resistant to persistent uterine infection.[157] Endometritis has severe effects on the fertility of affected mares. A persistent inflammation may interfere directly with the survival of an embryo or may cause premature luteolysis and embryonic loss because of increased PGF concentrations.[159]

Several classes of immunoglobulins have been isolated from the equine uterus. Although antibody-mediated uterine defense may be important for effective elimination of bacterial contaminants from the uterus in susceptible mares, concentrations of immunoglobulins in uterine secretion are similar or even elevated compared with those of resistant mares.[160-164] Polymorphonuclear neutrophils (PMNs) are the first inflammatory cells to enter an inflamed site.[165] Chemoattractive properties of uterine fluid have been described in vitro in horses, and the uterus responds quickly to an antigen with release of PMN-chemotactic mediators, which results in a rapid migration of PMNs into the uterine lumen.[166] Complement products and leukotriene B_4 (LTB_4), PGE, and PGF may all serve as chemoattractants for PMNs in the uterus.[166-170] Studies on the role of local uterine factors in PMN function suggested that an impaired phagocytosis by uterine PMNs in susceptible mares is the result of insufficient opsonization in uterine secretion rather than a primary dysfunction of the PMNs.[171]

Recent work by researchers at the University of Kentucky found that breeding, as well as a bacterial infection with *Escherichia coli,* resulted in an upregulation of both proinflammatory and modulating cytokines in the endometrium. A transient upregulation of proinflammatory cytokines was observed in resistant mares, whereas a sustained expression of proinflammatory cytokines coupled with an "unbalanced" relationship between proinflammatory and modulating cytokines was observed in susceptible mares.[172] An imbalanced cytokine expression was also observed in susceptible mares following breeding. Inflammatory modulating cytokines were expressed at a significantly lower level at 6 hours after breeding in susceptible mares when compared with resistant mares.[173]

Mechanical aspects of the uterine defense system are currently believed to be a major contributor in uterine clearance of bacteria and inflammatory products.[174-176] Through use of intrauterine inoculations of a combination of radioactive-labeled microspheres and bacteria, impaired uterine clearance was demonstrated in susceptible but not in resistant mares.[174] Studies using scintigraphic measurements of intrauterine clearance of radioactive colloids further defined a delayed physical clearance in susceptible mares.[175] Through use of electromyography (EMG) to register myometrial activity, it was observed that the impaired uterine clearance in susceptible mares was caused by reduced myometrial activity in response to the inflammation (Fig. 43-6).[176] This may be explained by an accumulation of nitric oxide (NO) in susceptible mares following breeding.[177] NO is an inflammatory mediator that causes smooth muscle relaxation. The

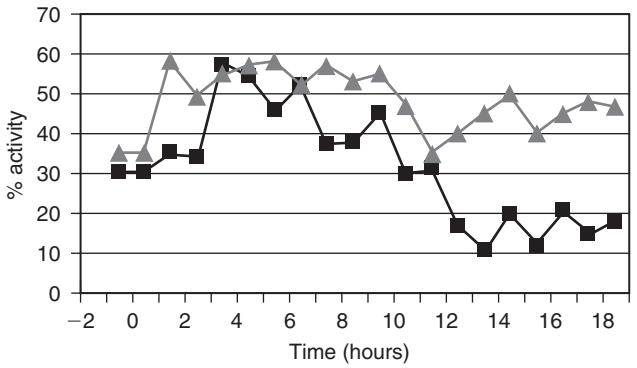


FIG. 43-6 Myoelectrical activity before and after uterine inoculation of *Streptococcus zooepidemicus* in mares susceptible (■) and resistant (▲) to persistent endometritis. Time 0 indicates time of inoculation. Susceptible mares had impaired myoelectrical activity after inoculation. *(Modified from Troedsson MH, Liu IK, Ing M, et al. 1993. Multiple site electromyography recordings of uterine activity following an intrauterine bacterial challenge in mares susceptible and resistant to chronic uterine infection. J Reprod Fertil 99:307.)*

dependent position of the mare's uterus may also interfere with effective clearance.

On the basis of pathogenesis, persistent endometritis can be divided into (1) sexually transmitted diseases (STDs), (2) persistent uterine infection, and (3) persistent breeding-induced endometritis.

SEXUALLY TRANSMITTED DISEASES. Contagious equine metritis (CEM) is an example of a true STD.[178,179] The disease is caused by *Taylorella equigenitalis,* a highly contagious and pathogenic microorganism. Although the present status of a mare's uterine defense mechanism is important for the manifestation of the disease, this bacterium is highly resistant and capable of overcoming the mare's normal disease barriers.

PERSISTENT UTERINE INFECTION. Bacteria most commonly isolated from the uterus of the mare are β-hemolytic streptococci *(Streptococcus zooepidemicus* and *Streptococcus equisimilis), E. coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.* Other aerobic bacteria isolated from the reproductive tracts of mares include α-hemolytic streptococci, *Corynebacterium* spp., *Staphylococcus* spp., *Enterobacter* spp., *Actinobacter* spp., *Proteus* spp., *Citrobacter* spp., *Candida* spp., and *Aspergillus* spp. are the organisms most commonly associated with yeast or fungal endometritis. The role of viruses, mycoplasmas, ureaplasma, and anaerobic bacteria in endometritis is poorly understood. *P. aeruginosa, K. pneumoniae,* and possibly *S. zooepidemicus* and *E. coli* can be sexually transmitted in horses, but the consequences of exposure to these microorganisms are determined by the particular strain involved and active participation of all facets of the mare's uterine defense mechanisms. In contrast to a true STD, persistent infectious endometritis is often the result of contamination of the uterus by the mare's fecal and genital flora in combination with compromised uterine defense.[180,181] It has been proposed that endometrial biofilms are responsible for chronic infectious endometritis that appear to be nonresponsive to conventional treatment.[182] A bacterial biofilm is a complex aggregation of microorganisms. They are characterized by structural heterogenicity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances, which greatly increases resistance to antibiotic therapy. The presence of biofilms has been well described in the mucosa of the mouth and the urine bladder of humans but has not yet been documented in the mare. The concept is interesting and warrants further research. An alternative explanation for persistent bacterial endometritis has been offered by Petersen and colleagues.[183] The authors suggested that bacteria can persist in the endometrial glands and the uterine wall in a dormant state. This would increase their resistance to antibiotic therapy.

PERSISTENT BREEDING-INDUCED ENDOMETRITIS. Intrauterine deposition of semen causes an inflammatory reaction resulting from spermatozoa.[184,185] The mechanism of the induced inflammation is similar to endometritis caused by bacteria, involving activation of the complement cascade.[185] The role of spermatozoa in breeding-induced endometritis implies that a transient uterine inflammation is a physiologic reaction to semen, and it appears to be a normal process by which excess sperm and bacterial contamination are eliminated from the mare's reproductive tract.[181,186] Transport of spermatozoa from the uterus to the oviduct is completed within 4 hours after breeding, and only a small portion of the ejaculated or inseminated semen reaches the oviduct.[187,188] The rapid transport of spermatozoa to the oviduct coincides with increased uterine activity.[186] Increased myometrial contraction in response to breeding is also responsible for rapid sperm elimination from the uterus through the cervix.[189] Not all excess spermatozoa are removed from the uterus through this mechanism. The remaining spermatozoa have to be eliminated by means of other uterine clearance mechanisms, such as PMN-phagocytosis of spermatozoa.[181] However, the condition may develop into a persistent inflammation in mares with impaired uterine clearance.[174,175] If sperm elimination and all physical and chemical reactions that are involved in the induced inflammation persist beyond the time when the embryo enters the uterus at 5 days after ovulation, embryonic loss will occur because of an incompatible inflammatory uterine environment. The incidence of persistent breeding-induced endometritis has been reported to be approximately 10% to 15% of a normal population of Thoroughbred broodmares and up to 25% for mares bred by AI with thawed frozen semen.[154,155]

In contrast to spermatozoa, seminal plasma has a suppressive effect on complement activation, PMN-chemotaxis, and phagocytosis.[190] A function of seminal plasma may be to act as an inflammatory inhibitor or modulator in the uterus, which may be of importance with regard to the transient nature of breeding-induced endometritis. The duration of breeding-induced uterine inflammation was shown in a study to be shorter when seminal plasma was included in an insemination dose, compared with when all seminal plasma was removed and replaced by a commercial semen extender.[191] Although the peak numbers of PMNs were the same for both groups, significantly fewer PMNs were recovered from the uterus at 24 hours compared with 6 and 12 hours after insemination when seminal plasma was included. In contrast, there was no significant difference in the number of uterine PMNs at 6, 12, and 24 hours of insemination in the absence of seminal plasma. Another function of seminal plasma in breeding-induced endometritis may be to protect spermatozoa from being phagocytosed and destroyed in an inflammatory environment. PMNs are present in the uterine lumen by 0.5 hours after breeding, but sperm transport is not completed until 3 to 4 hours later.[187,192] In addition, when mares are inseminated twice within a 24-hour period, semen from the second insemination is introduced into an inflammatory environment. This environment is detrimental to sperm motion characteristics, and motile sperm cells appear to bind to PMNs, forming large clusters of PMNs and spermatozoa. Addition of seminal plasma has been shown to reduce the binding between spermatozoa and inflammatory cells in vitro.[193] Recent data suggest that a specific protein in equine seminal plasma, CRISP-3, selectively protects viable but not dead spermatozoa from PMN-binding and phagocytosis.[194,195] Selective protection of viable spermatozoa from PMN-binding and phagocytosis increases their survival in a hostile uterine environment and ensures that a sufficient number of spermatozoa reach the oviduct for fertilization while effective sperm elimination of nonviable spermatozoa can be maintained.

Diagnostic Approach History compatible with endometritis includes infertility after breeding to a fertile stallion. Mares with severe endometritis may have shortened interestrous intervals and may show vaginal discharge. Physical and speculum examination may show anatomic defects of the vulva or cervix. Excessively easy passage of a vaginal speculum may indicate loss of integrity of the

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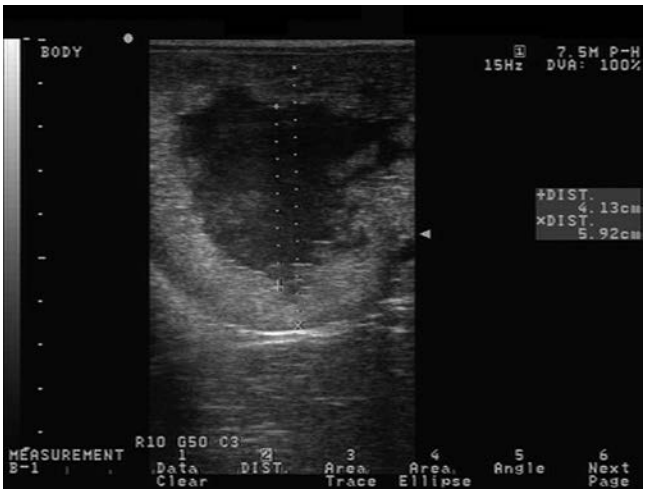


FIG. 43-7 Transrectal ultrasonographic image of uterine intraluminal fluid accumulation in a mare with endometritis.

vestibulovaginal sphincter. Discharge from the cervix and vaginal inflammation may be apparent. Transrectal palpation and ultrasonography may reveal accumulations of luminal fluid (Fig. 43-7). Diagnostically, it may be difficult to identify susceptibility to breeding-induced endometritis before breeding. Some mares have free fluid present in the uterine lumen before breeding, but most mares are not diagnosed until after they have been bred. If susceptibility to persistent breeding-induced endometritis is suspected, the mare should be monitored closely by ultrasonography per rectum at 6 to 12 hours after breeding, if possible, and at a minimum within 24 hours after breeding. If free fluid is present in the uterine lumen, the mare should be considered to have persistent mating-induced endometritis. Clearance of charcoal particles from the uterus within 48 hours of inoculation and the use of scintigraphy to measure uterine clearance have been suggested to be useful in identification of mares that are susceptible to persistent breeding-induced endometritis.[175,196] However, these methods may not be practical under field conditions.

MICROBIOLOGY. Quantitative aerobic bacterial culture of the uterine lumen is necessary to identify potential pathogens and for antibiotic sensitivity testing. Samples can be obtained using a swab, low-volume uterine lavage, or an endometrial biopsy, and they should be taken during estrus. If a uterine swab is used, the swab should be transported in a nonnutritive medium to the laboratory. Inadvertent contamination of cultures with bacteria from the lower reproductive tract is common, so the culture instrument should be guarded until it is within the uterus.[197] A false-positive bacterial sample result may be obtained as the result of contamination (even when double-guarded swabs are used), and culture results should always be interpreted together with results from endometrial cytology. Samples obtained through a vaginal speculum may decrease the risk of contamination. The use of low-volume lavage (50 to 100 mL) has been suggested to be a sensitive method to obtain an endometrial sample for culture.[198,199] It is important to use a closed system to infuse and recover fluid from the uterus in order to avoid environmental contamination when this method is used. False-negative results are frequently obtained even under optimal circumstances, and laboratory results should always be interpreted in light of clinical findings. Use of culture and histologic interpretation of an endometrial biopsy appears to be the most accurate method to diagnose persistent infectious endometritis.[200] Cultures may also be performed on endometrial biopsy samples. Culture samples for *T. equigenitalis* should be taken from the endometrium, cervix, clitoral fossa, and sinuses. Samples should be placed in Amies medium with charcoal or Steward's medium and be kept refrigerated until delivered to the laboratory.

TABLE 43-5

Endometrial Biopsy Grade and Fertility Prognosis (Kenney and Doig)

Biopsy Category	Degree of Change	Predicted Foaling Rate (%)
I	None	80-90
IIA	Mild	50-80
IIB	Moderate	10-50
III	Severe	<10

ENDOMETRIAL CYTOLOGY. PMNs migrate into the uterine lumen in response to inflammation, so endometritis is rapidly and accurately diagnosed by examination of exfoliated endometrial cells. A sample may be taken with a guarded swab, a cytology brush, or by low-volume lavage. Air-dried smears are stained with new methylene blue or modified Wright-Giemsa stain. Epithelial cells may be shed singly or in rafts. Arbitrary definitions of endometritis have been established on the basis of relative numbers of PMNs or numbers of PMNs per high-power field. Using these criteria, more than one PMN per 10 epithelial cells is consistent with endometritis. Riddle and coworkers observed that mares with more than two PMNs per 100× magnification microscopic field had significantly lower pregnancy rates than mares with two to five PMNs per 400× field.[201] Mares with more than five PMNs per 400× field had a further reduction in pregnancy per cycle. The authors also found that bacterial infection with *E. coli* was less likely to be associated with a positive cytology compared with mares infected with *S. zooepidemicus*. Presence of bacteria on a cytology slide may indicate infection but can also be the result of a contaminated slide or staining fluid. Bacteria phagocytosed by PMNs are true indicators of an infection. Endometrial cytology from normal mares may contain PMNs and spermatozoa for 24 to 36 hours after breeding. It has been suggested that eosinophils are associated with fungal endometritis and pneumovagina, but the importance of this finding is unclear. Urine crystals indicate urovagina.

ENDOMETRIAL BIOPSY. Endometrial biopsy is an accurate diagnostic and prognostic tool for endometritis. The biopsy sample should be taken during the breeding season, should be of adequate size, and should either be fixed in Bouin solution for 24 hours and then transferred to 10% formalin or immediately put in 10% formalin. Chronic endometritis is characterized by infiltration of the endometrium with mononuclear cells and deposition of layers of fibrosis around endometrial glands. Fibrosis of the endometrium is a degenerative change and is permanent. This pathology has been associated with susceptibility to persistent endometritis and delayed uterine clearance.[202,203] The severity of endometrial changes is inversely related to reproductive performance. A system to classify histologic changes has been described and is widely used[5] (Table 43-5). Special stains such as periodic acid–Schiff and Gomori's methenamine silver may be used to identify the presence of fungi in endometrial biopsies. Special staining can be used to detect degenerative vascular changes such as elastosis.

TRANSRECTAL ULTRASONOGRAPHY. The presence of free intraluminal fluid before breeding strongly suggests susceptibility to persistent endometritis.[204] Ultrasonographic examination of the uterus is helpful to assess both the quantity and quality of accumulated fluid in the uterine lumen. Normal mares may retain fluid up to 6 to 12 hours after mating. If fluid is present at 12 hours or more after breeding, the mare should be considered to have a persistent mating-induced endometritis.[205] Increased echogenicity of the fluid is associated with the presence of inflammatory cells and debris.

Hysteroscopy. Examination of the uterine lumen with an endoscope provides information about degree of inflammation in

addition to evidence of foreign bodies, transluminal adhesions, intraluminal masses, and endometrial cysts.

Treatment and Prognosis

SEXUALLY TRANSMITTED DISEASES. Mares with CEM should be treated with intrauterine infusions of antibiotics based on sensitivity tests, in combination with local treatments of the clitoral fossa and sinuses. Best results can be expected when treatment is initiated when the mare is in estrus and is combined with uterine lavage if inflammatory debris or intraluminal fluid is present. Cleansing of the vulva and the clitoris daily for 5 days with a 4% chlorhexidine or nitrofurazone ointment has been recommended.[206] Sinusectomy can also be performed.[207] Import regulations in countries free from CEM serve to prevent outbreaks of the disease. The spread of CEM on farms in endemic countries is best prevented by implementation of strict hygiene, screening of breeding stallions before the breeding season, and the use of AI, if allowed by the breed registry.

PERSISTENT UTERINE INFECTION. Treatment of mares with persistent uterine infections needs to be directed toward the underlying breakdown of the uterine defense and against the microbial agent. The first therapeutic concern should be to remove predisposing causes, such as a breakdown of external genital barriers. Persistent uterine infection frequently follows degenerative or traumatic anatomic changes and loss of integrity of the barriers of ascending infection. Therefore Caslick's surgery, repair of cervical damage and perineal lacerations, and correction of urovagina should precede specific endometrial treatment. All potential sources of contamination including intrauterine passage of diagnostic and treatment implements should be minimized. In some mares, recovery follows with sexual rest and no further treatment. Mares that are susceptible to persistent uterine infections should be bred using minimal contamination techniques to avoid bacterial contamination of the uterus.[208] Antibiotics may be administered by either local or systemic routes. Intraluminal fluid and inflammatory debris should be removed by uterine lavage before local treatment. Drugs and doses are summarized in Table 43-6. Treatment should be based on sensitivity. Mares should be treated during estrus when natural defense is maximal, and strict aseptic technique should be used. The volume of fluid used for antibiotic therapy is dependent on the size of the uterus. A total volume of 30 to 60 mL is usually sufficient. Treatment should continue daily for 4 to 6 days during the duration of estrus. Repeated contamination may indicate an unsuccessfully resolved predisposing cause. The clitoral fossa should always be considered as a primary location of bacteria grown in these cases. If culture results from the endometrium and clitoral fossa match, the clitoral fossa should be cleaned and treated locally with antibiotics. Removal of the primary microorganism may result in overgrowth of a second bacteria or fungus (superinfection). Critical studies of the efficacy of systemic antibiotics are limited, although effective levels are produced in the endometrium after systemic administration.[209] Parenteral administration may be easier, and the opportunity to introduce uterine contamination or cause uterine irritation with treatment is eliminated. Treatment of fungal infections is generally more challenging than treatment of bacterial infections. Culture and sensitivity will determine the choice of antifungal drugs (see Table 43-6). Fungal endometritis may require daily intrauterine infusions for 7 to 10 days to effectively resolve the infection. In order to avoid intrauterine infusions in the presence of high circulating concentrations of progesterone, treatment can be initiated 1 or 2 days after an injection of $PGF_2\alpha$ in diestrual mares and continued until 1 or 2 days after ovulation. A single dose of a benzoylphenyl urea (lufenuron) has been suggested to effectively treat mares with fungal endometritis.[210] Initial data from four mares were encouraging and need to be confirmed by controlled studies using larger groups of mares.

Treatment with immunostimulatory agents *(Propionibacterium acnes)* or mycobacterium cell wall extracts has been reported to improve pregnancy rates in mares with persistent endometritis, but the mechanism is not fully understood.[211] It has been suggested that mycobacterium cell wall extracts modulate endometrial cytokines in susceptible mares.[212] Other researchers did not observe a modulation of endometrial cytokines in response to treatment but found a significant effect on the clearance of uterine pathogens and fluid accumulation in infected mares that were treated with mycobacterium cell wall extract.[172] The authors did, however, see a modulation of inflammatory cytokines following treatment with dexamethasone in mares infected with *E. coli*. Other treatments that aim to stimulate the local uterine immune system include intrauterine infusion of blood plasma.[213]

Intrauterine infusions of a variety of solutions have been used to treat infectious endometritis. These include iodine, chlorhexidine, hypertonic saline, kerosene, and hydrogen peroxide. Many of these solutions are strong irritants and can cause damage to the endometrium. If povidone iodine is used for intrauterine treatment, it should

TABLE 43-6

Antibacterial Drugs Used for Intrauterine Administration for Treatment of Uterine Infections in Mares

Drug	Dose (Intrauterine Administration)	Comments
Amikacin sulfate	2 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate
Ampicillin	3 g	Gram-negative spectrum; may irritate the endometrium
Carbenicillin	2-6 g	Gram-negative spectrum; may irritate the endometrium; buffer with equal volume of 7.5% bicarbonate
Gentamicin sulfate	1-3 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate
Kanamycin sulfate	1-3 g	*Escherichia coli*, spermatocidal
Neomycin sulfate	3-4 g	Useful against sensitive *E. coli*
Potassium penicillin G	5 million U	*Streptococcus zooepidemicus*
Polymyxin B	1 million U	*Pseudomonas*
Ticarcillin	6 g	Broad spectrum
Ticarcillin/clavulanic acid	6 g/200 mg	Broad spectrum
Ceftiofur	1 g	Broad spectrum *(S. zooepidemicus)*
Antimycotics		
Nystatin	500,000 U	Dissolve in 30 mL 0.9% saline solution; daily for 7-10 days
Clotrimazole	500 mg	Suspension or cream; daily for 1 wk
Miconazole	500 mg	Effective against yeast
Amphotericin B	200-250 mg	Daily for 1 wk
Vinegar	2%	20 mL wine vinegar to 1 L 0.9% saline solution; used as uterine lavage
Lufenuron	540 mg (single dose)	Suspend in 60 mL sterile water

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be used in a dilute solution (0.05% to 0.10%) in lactated Ringer solution. The authors do not recommend routine use of these solutions in the uterus.

A 30% dimethyl sulfoxide (DMSO) solution and acetylcysteine in a 20% solution have been added to uterine lavage fluids in mares with suspected biofilms or excessive mucus in the uterus.[182] The rationale for these treatments is to break down biofilms or clear mucus by decreasing viscosity from the uterus of mares with persistent infection. Treatments should be carried out together with appropriate antibiotic therapy. Treatments have yet not been evaluated in a controlled study.

EDTA-tris has been shown to be effective in decreasing the visibility of *P. aeruginosa*.[214] EDTA is believed to increase bacteriocidal activity of antibiotics by the binding of Ca^{++} in bacterial cell walls, resulting in increased permeability to antibiotics. Tricide (Medical Molecular Therapeutics, LLC, Athens, Ga.) is commonly used in veterinary practices for this purpose. Daily uterine infusion of 300 to 500 mL followed by uterine lavage with LRS within 24 hours has been recommended. Treatments should be combined with or followed by appropriate antibiotic therapy.

PERSISTENT BREEDING-INDUCED ENDOMETRITIS. Management of mares susceptible to persistent breeding-induced endometritis should include limiting uterine exposure to semen and bacteria and assisting the uterus to physically clear contaminants and inflammatory products after breeding.[166,215,216] Preexisting uterine infections should be resolved before the mare is bred. Exposure to semen should be limited to a single breeding per cycle, if possible. This can be accomplished by closely monitoring follicular development and hormonal treatment to induce ovulation of mature follicles. Physical clearance can be assisted by the use of uterotonic drugs. Oxytocin or $PGF_2\alpha$ treatment 4 to 8 hours after breeding has been shown to aid in uterine clearance, resulting in improved pregnancy rates in susceptible mares.[124,166,204,215,217] Care must be taken with regard to the timing of $PGF_2\alpha$ treatment because $PGF_2\alpha$ can cause a delay in the formation of a functional CL when administered within 2 days after ovulation.[121-123] This was associated with pregnancy failure in two of the reports.[122,123] Large-volume uterine lavage 6 to 24 hours after breeding will also effectively assist the uterus in clearing fluid and inflammatory products.[216] Because sperm transport to the oviduct is completed within 4 hours after breeding, uterine lavage 6 to 24 hours after breeding will not have a negative effect on fertility.[187] Manual dilation of the cervix in mares with poor cervical dilation may help these mares to more effectively clear the uterus of fluid.

The use of corticosteroids in mares with excessive inflammation in response to breeding has been suggested.[218,219] The authors administered acetate 9α-prednisolone (0.1 mg/kg) twice daily during estrus, starting when a follicle greater than 35 mm was detected and ending when ovulation was confirmed,[218] or one dose of 50 mg dexamethasone at the time of breeding.[219] Preliminary results are encouraging, and further research is necessary to clarify the mechanism of action for this treatment alternative. Recent observations suggest that dexamethasone suppresses the proinflammatory cytokine IL-1β in susceptible mares at 6 hours after breeding.[220] However, no effect of treatment was observed for modulating cytokines, which previously had been suggested to differ between susceptible and resistant mares.[173] Interestingly, treatment with another immune modulator (*Mycobacterium* cell wall extract) had a similar effect on endometrial cytokine expression. More research is clearly necessary to fully understand the role of cytokines and the clinical effect of pharmaceutical modulation of cytokines after breeding of susceptible mares.

Electroacupuncture has been used clinically to increase uterine contractility in mares with delayed uterine clearance. Anecdotal reports are encouraging, and research is necessary to confirm the efficacy of this treatment alternative.

It is important for the clinician to keep in mind that a transient inflammatory response to semen is normal and required for normal fertility. Postbreeding treatments of these mares will most likely not improve fertility but may cause even further contamination and interfere with pregnancy. Only 10% to 25% of all broodmares develop a pathologic persistent form of breeding-induced endometritis.[154-156] Attention should be given to identifying and managing these mares appropriately in order to optimize reproductive efficiency.

CHRONIC DEGENERATIVE ENDOMETRITIS (ENDOMETRIOSIS). Degenerative changes of the endometrium such as periglandular fibrosis and glandular dilation are often seen in older multiparous mares. The condition is associated with susceptibility to persistent endometritis[202] and may result from repeated uterine inflammation. However, the condition has also been observed in older mares without any known history of endometritis, suggesting that degenerative fibrosis of the endometrium can be a process of aging rather than inflammation.[221] On the basis of the possibility of a noninfectious cause of the disease, it was suggested that the condition should be called *endometrosis,* rather than *degenerative endometritis*.[221] It is not clear why mares with fibrotic degenerative changes to the endometrium have an impaired physical uterine clearance mechanism. Sclerotic changes in the uterine vascular bed impair blood flow to both the endometrium and the myometrium, which may explain the effect on uterine clearance.[222]

Several treatments have been suggested for degenerative fibrosis of the endometrium, but consistent results have not been reported. Infusion of DMSO into the uterine lumen has been shown to improve fibrosis in mares with chronic degenerative endometritis[223]; however, other researchers were not able to repeat these results.[224]

Prognosis for fertility after endometritis varies with the severity of inflammation and fibrosis and the inciting cause. Prognosis should take into account the age of the mare and the level of reproductive management, in addition to the cause and likely response to treatment.

Metritis

Metritis is classically defined as inflammation of all layers of the uterine wall. Metritis occurs in the first 2 weeks after foaling and commonly follows abortion, dystocia, and RFMs. In mares, metritis is often accompanied by endotoxemia and laminitis. Transluminal adhesions between endometrial folds may follow severe metritis.

Clinical Signs and Diagnosis

Metritis is characterized by uterine accumulation of postpartum secretions, bacteria, and the products of inflammation, with discharge from the cervix and possibly the vulva. Discharge is usually fluid and red-brown and may be fetid. Systemic signs of depression accompanied by neutropenia and leukopenia are apparent with development of endotoxemia. Differential diagnoses include normal lochia and causes of profound depression in the postpartum period as a result of uterine tears and abdominal catastrophes.

Treatment and Prognosis

Treatment is directed toward removing contamination and microorganisms from the uterus while providing systemic treatment for endotoxemia. Broad-spectrum systemic antibiotics, antiinflammatory drugs, and fluid therapy are indicated. Uterine contamination may be removed by gentle intraluminal infusion of warm water or saline and siphoning off of uterine contents. Vigorous lavage should be avoided, particularly during acute systemic disease. Prognosis depends on severity of clinical signs. If metritis is diagnosed quickly and treatment is instituted, prognosis for fertility and systemic health is good. Prognosis is guarded once endotoxemia and laminitis develop.

Pyometra

Pyometra in mares is an accumulation of purulent exudate in the lumen of the uterus. Impedance to mechanical uterine outflow, such as cervical fibrosis and adhesions of cranial parts of the tract ventrally into the abdomen, often contributes to the development of pyometra. If endometrial irritation causes release of endogenous endometrial PGF, diestrus will be shortened. In some mares, endometrial destruction is so severe that PGF release is inadequate and luteal life is

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prolonged.[112] A variety of bacteria may be involved, including *E. coli, Pseudomonas* spp., and *Streptococcus* spp. Cultures may also be negative.

Clinical Signs and Diagnosis A purulent vaginal or cervical discharge may be seen. The mare may demonstrate a short diestrus, a normal interestrous interval, or a prolonged diestrus. Some mares with pyometra have mild leukopenia and normocytic-normochromic anemia, secondary to mild suppression of erythropoiesis.[112] Transrectal palpation and ultrasonography reveal a fluid-filled uterus. The uterine wall may be thin and flaccid or thick.

Treatment and Prognosis Treatment should involve correction of predisposing causes, fluid evacuation, and local antibiotic treatment. Evacuation of large amounts of fluid from the uterus may result in redistribution of fluid and circulatory shock. The mare should be monitored for signs of circulatory shock, and intravenous fluid may be administered during evacuation of large amounts of fluid from the uterus. The prognosis for life is excellent; however, the prognosis for return to normal fertility is guarded to poor because the conditions that predispose to development of pyometra in mares (cervical stenosis and adhesions) are difficult to treat and because severe endometrial destruction may develop. Endometrial biopsy should precede vigorous treatment. Hysterectomy should be considered if treatment is unsuccessful and if discharge is unacceptable or if adhesions impair athletic ability.

RUMINANTS

Bovine Uterine Infection

Deliveries complicated by dystocia or RFMs may be followed by severe bacterial infections of the uterus. The most sanitary environment possible should be provided for calving. The use of a clean pasture may be most appropriate on some farms, whereas the use of roomy, well-bedded, indoor maternity pens that are cleaned after each delivery may be appropriate on others.

Cows with abnormalities around the time of calving such as hypocalcemia, dystocia, and RFMs are more likely to develop uterine infections than are cows that calve normally. Routine treatment of cows with antibacterial drugs and chemicals has not been shown to be beneficial and in some cases has reduced fertility. Postpartum uterine infections may be prevented, or the number of such infections reduced, by strict attention to sanitation in the calving environment and during assistance with delivery, along with proper management during the dry period.[225]

Bovine uteri are normally contaminated by a wide variety of microorganisms during the puerperium. Most of the organisms are transient residents of the reproductive tract and are soon eliminated from the involuting uteri of normal cows. *A. (Actinomyces) pyogenes* can persist in the uteri of cows and act with *Fusobacterium necrophorum* and *Prevotella* (formerly *Bacteroides*) spp. to cause uterine infections. Coliforms, *P. aeruginosa,* hemolytic streptococci, and gram-positive and gram-negative anaerobic bacteria are also frequently isolated from animals with postpartum uterine disease. *A. pyogenes* and *Clostridium* spp. occasionally colonize the postpartum uterus synergistically, causing severe gangrenous metritis. Other organisms that appear to have little effect on fertility may colonize the uterus and produce penicillinase, thus influencing the selection and route of administration of drugs used to treat uterine infections.[147,226]

Clinical Signs and Diagnosis Lochia is normally expelled during the first 2 weeks after calving and may range from dark red or brown to white to clear. If uterine involution is delayed, discharge of lochia may continue until 30 days after calving. Discharge of lochia is not abnormal unless the fluid is fetid or the cow develops other abnormal clinical signs. Abnormalities of uterine involution cannot be diagnosed by palpation per rectum during the first several days after calving when both normal and abnormal uteri are out of reach and cannot be safely retracted. By 10 to 15 days after calving the entire uterus can be palpated if involution is normal. Fluid should not be palpable within the uterine lumen by 14 to 18 days after calving. Gross reduction in size and histologic repair of the endometrium are complete in dairy cows by 40 to 50 days after calving.

Postpartum metritis in cows is characterized by the presence of variable amounts of lochia within the uterine lumen that may be discerned by palpation per rectum. A vaginal discharge is usually present, but it may become obvious during palpation. Septic metritis is characterized by clinical signs of toxemia that may include fever, depression, partial or complete anorexia, and laminitis. Milk yield is depressed, and cows may be unwilling or unable to rise. Some cases may be complicated by tenesmus. Vaginitis and cervicitis may accompany metritis. Discharges associated with septic metritis vary from scanty white mucus to copious amounts of red to red-black, watery, malodorous fluid. In some cases inflammation may spread through the uterine wall and cause perimetritis and peritonitis.[227] Septic metritis in ewes and does is characterized by fever, depression, anorexia, and tenesmus.

Endometritis in cattle is usually observed between 2 and 8 weeks after calving. Discharge can range from white pus to estrual mucus. Purulent exudate may be observed only with palpation or may be found in the cranial vagina and cervical canal on examination with a speculum. The history may indicate that the cow has failed to conceive after several services but the patient is otherwise healthy.

Culture of endometrial fluid is not usually done in individual cases of bovine uterine infection but may be indicated to determine the antibiotic susceptibility of microorganisms on a particular farm or as a part of the diagnostic plan when the incidence of postpartum metritis or endometritis increases suddenly.

Endometrial biopsies are rarely used in cows but have been recommended when complete evaluation is required of the reproductive tract of cows that do not conceive or that conceive but do not complete their pregnancies.[5]

Treatment and Prognosis To be useful in treating uterine infections in cows, an antibiotic must be active against the primary uterine pathogens (*A. pyogenes* and gram-negative anaerobes), in the presence of organic debris, and in the anaerobic environment of the postpartum bovine uterus.[228] Organisms infecting the uteri of cows are usually susceptible to penicillin, but during the first month after calving, contaminating microorganisms may produce penicillinase. Therefore penicillin is not likely to be effective if given locally during the early postpartum period. By 30 days after calving, organisms that produce penicillinase are usually eliminated from the uterus and intrauterine treatment with penicillin may be beneficial. The daily intrauterine dose of penicillin required to reach the minimum inhibitory concentration of common bacteria such as *A. pyogenes* is 1×10^6 IU.[228] Oxytetracycline is active against many of the microorganisms that infect the bovine uterus, and its activity is only slightly reduced by organic debris and absence of oxygen. Intrauterine treatment with administration of 4 to 6 g of oxytetracycline per day has been recommended. Some preparations of oxytetracycline irritate the endometrium, cervix, and vagina. Intrauterine antibiotic treatment of dairy cows results in residues in their milk.[229] For example, oxytetracycline has been found in milk from 44[230] to 96[231] hours after intrauterine administration.

Penicillin by systemic administration is effective for treatment of some uterine infections in cows. Daily doses of penicillin required to reach the minimum inhibitory concentration of *A. pyogenes* are 10,000 to 20,000 IU/kg/day. Minimum inhibitory concentration of oxytetracycline for *A. pyogenes* in the uterus is usually higher than the concentration that can be achieved by systemic administration of the drug. Systemic ceftiofur (2.2 mg/kg IM or SC q24h for 5 days) achieves adequate concentrations in the uterus and is effective in treating bovine metritis.[138,148]

Treatment of septic metritis should be directed toward controlling septicemia. Large doses of broad-spectrum systemic antibiotics are

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indicated, along with fluids and other supportive therapy. Attempts to remove RFMs or irrigate the uterus are contraindicated during the acute phase of the disease. After the patient has recovered from acute septicemia, intrauterine therapy may be considered.

ANTISEPTIC CHEMICALS. A variety of antiseptic chemicals have been infused into the uterine lumen of cows in attempts to treat metritis and endometritis, but few controlled trial evaluations are available. These are attractive as a way to avoid antibiotic residues in the milk intrauterine infusion.[232] Dilute solutions of povidone-iodine (one part povidone-iodine stock solution to 10 to 20 parts saline) have been suggested as being useful in treating fungal endometritis.[50] Povidone-iodine is generally available as a 10% solution with 1% free iodine (10,000 ppm of free iodine), so a dilution of 20:1 saline-to–povidone-iodine yields a flush with 500 ppm of free iodine, which should be bactericidal.

UTERINE LAVAGE. Lavage of the uterine lumen with large volumes of warm saline (40° to 45° C [104° to 118° F]) removes accumulated fluid and debris. Uterine lavage has been used as an adjunct to antibiotic, antiseptic, and plasma treatment. Catheters designed for nonsurgical embryo recovery are suitable for uterine lavage. Saline is infused into the endometrial cavity in 0.5- to 1-L increments, allowed to reflux through the catheter, and collected for inspection. A milk hose and larger fluid volumes may be used in cattle with larger postpartum uteri, but care must be taken not to enter far into the uterus because it is friable and easily perforated. Massage or partial retraction of the uterus by palpation per rectum may be necessary to increase fluid recovery. The uterine lumen is lavaged repeatedly until the fluid returning through the catheter is no longer turbid.

PROSTAGLANDINS. In cows, repeated administration of PGF results in shortened estrous cycles and may mimic the shortened luteal phase of patients with acute endometritis. PGF therapy may be sufficient in mild cases of endometritis or may be used in combination with intrauterine or systemic therapy. In cases of chronic bovine endometritis, treatment with PGF one or two times at 10- to 14-day intervals decreased the number of days open.[233]

The prognosis in cows for recovery from endometritis is usually good if the condition does not progress to a more severe form of uterine disease. Septic metritis after dystocia or RFMs may result in permanent impairment of reproductive function, laminitis, or death of the patient in spite of aggressive therapy.

Pyometra

In dairy cows, pyometra is likely to develop in cows that ovulate before microorganisms that infect the uterus during the postpartum period are eliminated. The CL that develops after the first postpartum ovulation at approximately 15 to 18 days after calving persists, possibly because the abnormal uterine contents suspend release of PGF from the endometrium or sequester it within the uterine lumen. The uterus is brought under the influence of progesterone, which depresses phagocytic activity of uterine neutrophils and closes the cervix, allowing the bacterial infection to persist.[234] Pyometra rarely endangers the general health or life of affected cows. Postcoital pyometra may be caused by *T. foetus*.[235]

PGF is the treatment of choice for bovine pyometra. Treatment with PGF is followed in 3 to 6 days by uterine evacuation in 85% to 90% of treated cows. Response to PGF treatment may be raised with a second injection of PGF in 6 to 12 hours. After endometrial lesions are allowed to heal for 30 days, fertility is restored in most patients.

Treatment of cows with GnRH 2 weeks after calving improves fertility in some but not all situations. In herds with a high prevalence of postpartum uterine infections, treatment with GnRH may decrease fertility by inducing ovulation and CL development; thus the uterus is brought under the influence of progesterone before contaminating bacteria are removed, leading to pyometra.

Perimetritis

Perimetritis may occur in all species as a sequela to severe uterine infections, uterine rupture, penetration of the vagina during mating, traumatic insemination or obstetric procedures, and cesarean section.[126,236] Perimetritis is characterized by inflammation of the peritoneal surface of the uterus and may be accompanied by localized or diffuse peritonitis. Adhesions then develop between the uterus and other pelvic and abdominal organs.

Clinical Signs and Diagnosis

The clinical signs of perimetritis are those of peritonitis and may include fever, depression, partial or complete anorexia, stasis of the gastrointestinal tract, and evidence of abdominal pain. Abdominal pain is typified by colic in mares and by grinding the teeth (odontoprisis) in cows. In cows the condition should be differentiated from traumatic reticuloperitonitis, displacements of parts of the digestive tract, abomasal ulcers, postpartum metritis, and abdominal fat necrosis. Perimetritis in mares must be differentiated from other causes of severe abdominal pain. Antemortem diagnosis of perimetritis is difficult in sheep and goats that are presented mainly with fever, depression, anorexia, and odontoprisis.

Clinical Pathology

Cases of acute perimetritis are accompanied by leukopenia, neutropenia, and a degenerative left shift. Further evidence of peritonitis is obtained when peritoneal fluid is obtained by paracentesis and examined for its cellular and microbiologic content.

Treatment and Prognosis

The cause of perimetritis should be treated if possible. Cases of severe metritis should be treated appropriately, and uterine ruptures sutured if possible. Repair of uterine ruptures inaccessible by flank incisions may be facilitated by intentional prolapse of the uterus after administration of epinephrine, provided the tear is not too close to the cervix (see next section). Treatment with broad-spectrum systemic antibiotics is indicated. Lavage to remove peritoneal exudate has been recommended but is difficult to accomplish, especially in cows in which the rumen, abomasum, and greater omentum make ventral drainage almost impossible and in which fibrinous peritonitis with loculation of infection occurs rapidly. Other supportive treatments such as intravenous fluids and antiinflammatory drugs should be administered as indicated.

The prognosis depends on the severity of lesions. Fatalities can occur in spite of prompt treatment, and surviving animals may be infertile because of mechanical interference with gamete transport caused by adhesions between the genital organs and other pelvic and abdominal tissues. In general, the prognosis for fertility in affected animals is fair at best.

Prevention and Control

Perimetritis occurs sporadically in individual animals; therefore prevention depends on avoiding the causes. Immature females, especially heifers and fillies, should not be allowed at pasture with adult males to prevent undesired mating complicated by penetration of the vagina. Traumatic obstetric, insemination, and uterine lavage procedures must be avoided. Uterine tears that occur at parturition must be sutured immediately. Postpartum metritis must be treated promptly and appropriately before it progresses to perimetritis.

SMALL RUMINANTS

Uterine infections may follow dystocia and RFMs in sheep and goats but are not frequently a cause of infertility because lambing and kidding are followed by a period of up to 6 months of sexual rest before the next breeding season. RFMs and metritis follow abortion in ewes caused by *Listeria monocytogenes, C. fetus* subsp. *fetus,* and *Chlamydia psittaci.*

Ewes and does affected with metritis are usually treated with systemic antibiotics such as penicillin or sulfamethazine. Early and aggressive treatment is indicated.[236]

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CAMELIDS

Metritis and Endometritis

Camelids are induced ovulators, and females are usually receptive to males unless they are pregnant. Females do not, however, always have a preovulatory follicle present. Therefore it is frequently the case that females are bred at a time when they do not have a fertile follicle present. When camelids breed, the penis is inserted through the cervix and deep into the uterine horns. Unnecessary mating, or overbreeding, is the most important factor causing damage and contamination to the uterus.[237] Other major contributing factors include RFMs, rectal vaginal tears, and unsanitary obstetric manipulations.[237]

Chronic endometritis will often not cause evident clinical signs, whereas acute, postpartum endometritis may cause fever, depression, and signs of toxic shock.[237] A thick, mucoid lochial discharge is normal in the postpartum female for up to a week postpartum. Thin, watery, fetid discharge is a sign of endometritis.[237]

Transrectal ultrasonography and vaginoscopy are helpful in diagnosing endometritis and metritis. Inflamed, thickened uterine walls and hyperechoic, intraluminal fluid may be present on ultrasound examination. Vaginoscopy may reveal cervical discharge. Transrectal ultrasonography may usually be performed in llamas as in horses or cattle. In alpacas, because of smaller size, an extension probe will be necessary to facilitate transrectal ultrasonographic evaluation.

Uterine culture and cytology samples from the llama may be obtained in methods similar to those in the mare and cow. A double-guarded swab prevents environmental contamination. In the alpaca the swab should be passed through the cervix via visualization using a vaginoscope. These diagnostics should be performed during the peak follicular phase to ensure ease of passage through the open cervix and more reliable test results.[237] The most common bacteria isolated from the uteri of camelids with endometritis are *E. coli, S. zooepidemicus,* β-hemolytic streptococci, *Enterococcus,* coagulase-negative *Staphylococcus, Proteus* spp., *Enterobacter aerogenes, K. pneumoniae,* and *A. pyogenes*.[237]

Uterine biopsy can be a useful diagnostic tool for evaluation of metritis and endometritis in camelids. Endometrial biopsy samples in llamas may be obtained as in the mare. The left horn is perhaps better to target unless a particular pathology is suspected in the right horn, because camelid pregnancies almost always occur in the left horn.[237] Pathologic changes, evaluation, and prognosis are all assumed to be similar to those in the mare.[237]

Treatment for endometritis and metritis is also similar to that described for the mare. Uterine lavage with a warm, isotonic saline solution and oxytocin injection (5 to 10 IU) are the major components of treatment. Intrauterine antibiotic infusion is done after uterine lavage. The most common antibiotics used are penicillin K (1.5×10^6 U), gentamicin sulfate (200 to 300 mg), and ceftiofur sodium (250 to 500 mg).[237] Antibiotics should be diluted in sterile water or saline (saline should not be used with ceftiofur) and given once daily for 5 to 7 days. Females should be evaluated after cessation of treatment and completion of 2 weeks of sexual rest.

Prevention of endometritis often requires a "minimum contamination breeding technique."[237] This entails monitoring follicular growth via transrectal ultrasound until the follicle is of preovulatory size, breeding only once, following breeding with an injection of hCG (750 IU) or GnRH, and administering an intrauterine infusion of antibiotics 24 hours after breeding. Females should be evaluated for pregnancy 12 to 14 days after breeding.

Further preventative measures include performing prebreeding examinations on all maiden animals to avoid breeding animals that are too young or do not have follicular activity; breeding only females exhibiting strong receptive behavior (as opposed to mere submissive behavior); performing complete gynecologic examinations of all females with a history of infertility, obstetric problems, or postpartum complications; and observing strict rules of hygiene during breeding and obstetric manipulations.[237]

Pyometra

Pyometra caused by delayed uterine involution may be observed shortly after parturition. Chronic pyometra is often associated with vaginal or cervical adhesions that may be the sequelae to trauma after dystocia or aggressive obstetric manipulation.[237]

Anatomic Defects as a Cause of Uterine Infection

The most common anatomic defect associated with genital infections is pneumovagina. Other defects include urovagina and perineal lacerations. These defects should be corrected to prevent contamination with environmental and fecal organisms.

Endometrial Cysts and Lacunae

MARES Endometrial cysts and lymphatic lacunae are common degenerative changes of the endometrium that are more prevalent in mares older than 11 years of age than in younger mares.[238] Endometrial cysts can originate from endometrial glands or obstructed lymphatics. Glandular cysts are small (<10 mm) and are believed to be the result of periglandular fibrosis. Lymphatic cysts can reach several centimeters in diameter. The cause of lymphatic cysts is not fully understood, but lacunae are thought to arise after interference with normal lymph drainage from the genital tract.[5]

Clinical Signs and Diagnosis Endometrial cysts can be visualized by ultrasonography or by hysteroscopy. Cysts may mimic pregnancy when mares are examined per rectum by palpation or ultrasonography.[239]

Sequential examination reveals that size of endometrial cysts remains static, whereas amniotic vesicles enlarge. Large, discrete, fluid-filled cysts may be identified by palpation of the uterus per rectum. Smaller cysts and lacunae may be observed in endometrial biopsy sections. Uteri affected by lymphatic lacunae are enlarged and have a thicker wall than normal.

Treatment and Prognosis Endometrial cysts do not require treatment unless they are suspected to interfere with pregnancy. Endometrial cysts have been suggested to cause embryonic death and abortion if large or numerous. However, one study failed to find an association between the presence/number of cysts and fertility.[238] Obliteration of endometrial cysts using endoscopic-guided laser surgery removes the cysts permanently, but the long-term effect on fertility has not been critically evaluated. Needle aspiration, mechanical rupture of the cyst, uterine curettage, and intrauterine infusion of hypertonic saline solution have all been suggested to effectively remove endometrial cysts. However, the cysts often recur after treatment.

Uterine Prolapse

Uterine prolapse occurs when the previously gravid uterine horn becomes invaginated after delivery of the fetus(es) and protrudes from the vulva.

MARES Uterine prolapse is an uncommon sequela to normal foaling, dystocia, or RFMs in the mare. The tip of the previously gravid horn invaginates to form uterine eversion. Eversion is accompanied by pain and abdominal straining. The myometrium may contract around the ring of invaginated tissue. Transrectal palpation confirms the diagnosis, and the everted tissue may be replaced manually. Eversion may progress to complete uterine prolapse, accompanied by rapid onset of systemic signs.

Treatment and Prognosis The prolapsed uterus should be washed with clean saline and replaced manually in the standing mare

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as rapidly as possible. Replacement is aided by sedating the mare and administering epidural anesthesia. The uterus should be supported on a clean sheet held at the level of the pelvis. The uterus should be replaced, beginning with the uterine body and working gradually, replacing the tip of the horns last. Correct positioning of the uterus is important to prevent the prolapse from recurring. Replacement should be followed by treatment with broad-spectrum antibiotics, antiinflammatory drugs, and intravenous isotonic fluids. Treatment with oxytocin (10 to 20 IU IM) facilitates uterine involution. Prognosis is related to development of sequelae such as uterine tears, metritis, and endometrial damage.[240]

RUMINANTS In cows most cases of uterine prolapse occur within a few hours after calving. The condition is invariably associated with hypocalcemia, which results in lack of uterine tone and delayed cervical involution. In addition, dystocia frequently precedes uterine prolapse.

Elective uterine prolapse can be induced within 6 to 12 hours after calving by administration of epinephrine to relax the uterus for the repair of uterine tears. A 10-mL amount of epinephrine (1:1000) is diluted to 250 mL in sterile saline and administered slowly IV. After 100 mL of the solution has been given, the operator reaches through the cervix, grasps the uterine wall and caruncles, and everts the uterine horn toward the cervix. When sufficient uterine tissue has entered the cervical canal, the patient responds by straining, which assists in completion of the prolapse. Epidural anesthesia is administered to abolish further straining *after* the prolapse is complete.

Uterine prolapse in does has been associated with dystocia, hypocalcemia, and lack of exercise.[5] The predisposing factors are probably similar for ewes.

Clinical Signs and Diagnosis Clinical signs of uterine prolapse are obvious. The membranes may remain attached. Immediately after prolapse occurs the tissues are nearly normal, but within a few hours they become enlarged and edematous. The endometrium is usually contaminated with feces and bedding material. In some cases the prolapsed tissue may be lacerated or severely traumatized and may contain loops of intestines.

Clinical signs that may accompany uterine prolapse include straining, abdominal pain, restlessness, anorexia, and increased pulse and respiratory rates.[126] Parturient paresis is common in affected dairy cows. In most patients these signs are transitory, but shock may complicate some cases.

Clinical Pathology Uterine prolapse in cows is frequently accompanied by hypocalcemia and a significant increase in the packed cell volume.[241]

Treatment and Prognosis The prolapsed tissue should be protected from further damage by wrapping it in wet towels or covering it with a plastic bag. Beef cows should be restrained where they are found, to prevent trauma to the uterus or rupture of the large uterine vessels should an animal try to escape on arrival of the clinician. Treatment of hypocalcemia is usually indicated before replacement of the uterus if the cow is recumbent and semicomatose; otherwise calcium gluconate is administered after replacement. Epidural anesthesia is frequently (but not always) required.

The prolapsed tissue is washed with a mild presurgical scrub. The membranes are removed if they can be easily separated from the endometrium but are left in place if removal is difficult. Some clinicians recommend that cows stand during replacement, whereas others have found that the organ can be replaced in recumbent cows if the patient is placed on her sternum with the hind legs drawn straight out behind. The prolapse is placed between the extended limbs.[242] In fresh cases, replacement is relatively easy and is begun at the cervical pole of the organ; the dorsal and ventral parts are massaged alternately back into their normal position. After the ovarian pole has been replaced, the previously prolapsed horn must be straightened and eversion of the uterus corrected. Administration of clenbuterol is reported to relax the uterus, facilitate replacement, and reduce the need for epidural anesthesia, but its use is illegal in the United States.[243] If the patient has been neglected, accumulated fluid must be reduced by lubricating the tissue with an emollient ointment and then carefully but vigorously massaging the tissue from the ovarian pole toward the cervical pole. The hygroscopic action of sugar when applied liberally to prolapsed uteri is of limited value and vastly overrated.

Oxytocin is frequently administered to stimulate myometrial contractions after the uterus has been replaced. Metritis is a frequent sequela, and appropriate antibiotic treatment is indicated in most cases. Temporary closure of the vulva with heavy sutures after replacement is not necessary[126] but is practiced by many clinicians.[5] If replacement of the prolapsed uterus is impossible or the tissue is severely traumatized, amputation may be indicated; in this case it is important that the uterine arteries be double ligated.[244]

The prognosis varies but is generally favorable if there has been no serious damage to the uterus.[5,242] Fatalities can occur in cases complicated by shock or by rupture of large uterine vessels. The culling rate from infertility of cows with uterine prolapse is higher than that of their herdmates, and the calving interval is prolonged in affected cows. Barring hypocalcemia, the risk of uterine prolapse at a subsequent calving is no greater than for other cows in the herd.

Prevention and Control Because the condition is associated with hypocalcemia in cows, provision of a properly balanced ration before calving is indicated. Although uterine prolapse can occur after an apparently normal delivery, it is more commonly associated with dystocia and forced extraction; therefore prolapse should be anticipated, and the dam observed so that affected patients may receive prompt treatment.

CAMELIDS Uterine prolapse in camelids is usually a consequence of dystocia, RFMs, or excessive obstetric manipulation. Treatment is the same as described for other species and includes gentle, clean manipulation of the prolapsed uterus, replacing the organ starting at the cervix. Replacement is easier with early cases. Difficulty increases and prognosis decreases greatly with chronicity.[9]

Uterine Tumors

Neoplasia uncommonly affects the uterus of domestic animals. Tumors may arise from within uterine tissues or metastasize from other organs.[13] Leiomyomas are usually benign and arise from the outer smooth muscle of the uterus without need for a preparatory event. The multicentric form of lymphosarcoma may affect the uterus of cattle. Lymphosarcoma also affects does, but a predilection for the uterus is not apparent. Carcinomas, chorionepitheliomas, fibromas, fibrosarcomas, rhabdomyosarcomas, and adenosarcomas are rarely reported.

Small tumors may escape detection, whereas larger ones may be palpable per rectum in mares and cows. Leiomyomas are not necessarily associated with reproductive failure, and tumors and fetuses can coexist. Uterine walls affected by lymphosarcoma may contain discrete neoplastic nodules or be diffusely infiltrated. Tumor masses must be differentiated from normal fetuses, mummified or macerated fetuses, placentomes, abscesses, and fat necrosis.

Solitary leiomyomas thought to interfere with fertility may be removed. Other forms of uterine neoplasia are usually not treated. The prognosis is generally poor.

Segmental Defects

Segmental aplasia (white heifer disease) occurs sporadically in all breeds of cattle. In most cases the cranial parts of the genital tract (ovaries, uterine tubes, and cranial part of the uterine horns) are normal, and endometrial secretions from the parts of the uterine horns accumulate because normal drainage through the

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cervix is impeded. Various defects may be found in affected animals, ranging from nearly complete absence of tubular genital organs to an imperforate hymen that blocks secretion drainage from a normal genital tract.

Clinical Signs and Diagnosis Segmental aplasia may be associated with a history of anestrus if fluid accumulation within the uterine horns interferes with release of PGF and luteolysis. Other presenting history may involve infertility or difficulty in AI. On palpation per rectum, various degrees of aplasia may be recognized. Fluid-filled parts of the uterine horns may suggest pregnancy, from which they must be differentiated. An imperforate hymen may bulge from the vulvar cleft and may be confused with vaginal prolapse, prolapse or eversion of the urinary bladder, cystic vestibular glands, or neoplasia of the vulva or vagina.

Treatment and Prognosis The only form of segmental aplasia amenable to treatment is that in which an imperforate hymen occludes an otherwise normal tract. Incision of the hymen is followed by drainage of accumulated secretions and may allow the tract to function normally.

Paramesonephric Duct Aplasia

Aplasia of one paramesonephric duct leads to development of one uterine horn (uterus unicornis). The condition is relatively rare but does occur in cattle. Subfertility is the result of prolonged periods of anestrus caused by a persistent CL on the ovary ipsilateral to the missing uterine horn (no local luteolytic signal). The condition can be managed with exogenous PGF in the hope that ovulation will occur on the intact side. Alternatively, the unaccompanied ovary can be surgically removed.

Uterus Unicornis and Uterus Didelphis

The caudal parts of the paramesonephric ducts may not fuse properly in cattle, causing duplication of various parts of the caudal tubular tract. Abnormalities of fusion are most common in and around the cervix. The entire cervix may be duplicated; or the cervix and vagina may be normal, with the exception of the presence of a band of tissue extending dorsal to ventral across the external os of the cervix. Partial failure of fusion may involve a part of the cervix, and the affected animal may possess a single uterine body and internal cervical os, duplication of a part of the cervical canal, and a doubled external cervical os. Uterus didelphis results when the cervix and uterine body are completely duplicated. Affected cows may conceive after natural service or if artificially inseminated through the cervix and uterine horn ipsilateral to the ovary about to ovulate. Affected animals may be unable to carry a pregnancy to term because of lack of placental attachment in the nongravid horn.

Hydrometra (Pseudopregnancy in Goats)

Hydrometra occurs sporadically in goats and is characterized by accumulation of several liters of clear fluid within the uterus, abdominal distention, persistence of a CL, and subsequent anestrus.[5] It is most common in pet and dairy goats that are housed separately from males and therefore experience estrous cycles without the opportunity to conceive. Previous breeding is not necessary, but the condition may develop after mating, and does are frequently assumed to be pregnant. It can also occur after early embryonic loss in goats or sheep. The cause of hydrometra is unknown, but a deficiency in production or release of PGF from the endometrium has been postulated, as has exposure to phytoestrogens. The clinical signs of hydrometra mimic those of pregnancy. The diagnosis is suspected if the goat fails to show estrus when it cannot possibly have been bred but is in a herd where heat detection is good. Serum progesterone concentrations are elevated, and abdominal enlargement suggestive of pregnancy may occur. Results of the urinary estrone sulfate test for pregnancy are negative. Amplitude-depth ultrasound for pregnancy is positive because of fluid in the uterus. Rectal Doppler may indicate increased blood flow to the uterus, but no fetal heart sounds are heard. Real-time ultrasound reveals fluid but no fetus or caruncles in the uterus. The animal should be rechecked if fewer than 40 days have elapsed since the last possible breeding. In advanced hydrometra, large fluid-filled compartments are seen separated by undulating tissue walls, which represent the uterus coiled back on itself. The fluid is cloudy and flocculent if aspirated through the abdominal wall. Spontaneous correction is common and varies from red discharge suggestive of early abortion to expulsion of accumulated fluid approximately 150 days after an infertile mating, so-called cloudburst. No fetus or placenta is passed. Treatment of false pregnancy is with prostaglandin. The clinician needs to keep in mind that this will abort the goat if it has a true pregnancy. An initial dose of 5 to 10 mg of dinoprost (Lutalyse) or 125 to 250 μg of cloprostenol (Estrumate) is given and repeated in 12 days. Estrus and emptying of the uterus occur in 1.5 to 4 days. Oxytocin (50 IU bid for 4 days) will cause CL regression, but treatment with oxytocin is normally reserved for goats that still retain fluid in the uterus after prostaglandin therapy. The doe frequently becomes pregnant within a few days to weeks after termination of a false pregnancy if a buck is available. Sometimes hydrometra recurs. Suggestions for prevention have included selenium supplementation and breeding on the first heat of the season. The prevalence is probably increased in herds where breeding is delayed in order to obtain winter milk and in does manipulated hormonally to breed out of season. Routine pregnancy diagnosis of goats with real-time ultrasound should be advised to permit rebreeding during the same season.

Cervical Abnormality

Cervicitis

Inflammation of the cervix usually accompanies endometritis and vaginitis and is frequently secondary to trauma associated with dystocia and obstetric operations. The mucus-secreting epithelium of the cervix is more resistant to bacterial infection than is the epithelium of the uterus and vagina.

MARES The equine cervix is a straight tube made up of layered circular and longitudinal muscle. During estrus it relaxes, and the external os lies on the floor of the anterior vagina. During diestrus or pregnancy, under the influence of progesterone, the cervix is closed and the external os is elevated off the vaginal floor. Cervicitis or inflammation of the cervix may be iatrogenic or may occur secondary to trauma associated with parturition or dystocia or as an extension of vaginitis or endometritis. Endometritis and infertility follow if the cervix lacks anatomic integrity.

Clinical Signs and Diagnosis Infertility and history of an inciting cause such as urine pooling or dystocia may be the only signs of cervicitis in the mare. Cervical hyperemia and edema may be apparent on speculum examination in acute cervicitis. In more chronic injuries, direct digital examination of the cervix of the mare in diestrus may reveal transluminal adhesions or anatomic defects.

For treatment and prognosis in mares, see discussion under Ruminants later in this section.

RUMINANTS Similarly, in cows cervicitis is secondary to uterine infections and follows trauma associated with parturition and obstetric manipulations. Infection is usually caused by microorganisms normally present in the cranial vagina such as *E. coli,* streptococci, staphylococci, and *A. pyogenes*. Occasionally infection with anaerobic bacteria complicates cervicitis and results in severe toxemia.[126,245]

Cervicitis in does and ewes is uncommon but may occur secondary to vaginal and uterine infections and obstetric trauma.

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Clinical Signs and Diagnosis Examination of cows with a vaginal speculum reveals swelling and edema of the external cervical os. The mucous membrane is hyperemic and inflamed. Mucopurulent exudate may be present in the cervical canal or in the cranial vagina. Hypertrophy of the cervix is common in *Bos indicus* breeds and their crosses and may be a normal finding; therefore cervical size as detected by palpation per rectum may or may not indicate inflammation. Inflammation of the cervix without contemporary endometritis may not affect fertility. Cervicitis may occur in pregnant cows.

The clinical signs of cervicitis in does and ewes are similar to those in cattle and must be observed with a small vaginal speculum.

Treatment and Prognosis Most cases of cervicitis resolve spontaneously when coexisting endometritis and vaginitis improve. Exudate can be flushed from the cervical canal and cranial vagina with warm saline lavages, and a nonirritating antibiotic ointment applied to the affected tissue. Caustic chemicals should not be placed in contact with the cervical mucosa. Aggressive treatment with systemic antibiotics is indicated in cases complicated by infection with anaerobic bacteria.

The prognosis for most cases of simple cervicitis is fair to good. However, inflammation of the cervix in mares may progress to more severe cervical abnormalities. Cervical damage is a serious threat to future reproductive performance in mares. Anaerobic infections of the cervix may be fatal.

Prevention and Control Obstetric manipulations and operations must be temperate. When the cervix does not properly dilate during parturition, a cesarean section is preferred over forced extraction.

Cervical Lacerations

MARES Cervical lacerations are most often seen after dystocia. The condition may result in adhesions and a nonpatent cervix or in a failure to seal the uterus during diestrus or pregnancy. Cervical adhesions in combination with endometritis are a common cause of pyometra in the mare.

Clinical Signs and Diagnosis Cervical lacerations can be diagnosed by vaginoscopy and digital examination of the cervix. A digital examination of the cervix is often necessary to evaluate the degree and severity of the laceration. Evaluation of the ability of the cervix to close adequately is best performed during diestrus.

Treatment and Prognosis If cervical lacerations are diagnosed shortly after parturition, antimicrobial ointment should be applied frequently to the lesion. Early signs of adhesions should be broken down until the tissue is healed. If the laceration results in an incompetent cervix, it should be corrected surgically. Although surgical repair of cervical lacerations has resulted in restored fertility in many mares, the condition is likely to recur at the time of the next parturition. Embryo transfer should be considered if allowed by the breed registry.

Vaginal Abnormalities

Pneumovagina

MARES Pneumovagina is characterized by aspiration of air containing feces and microorganisms into the vagina. Pneumovagina is secondary to changes in perineal conformation, which include cranioventral displacement of the reproductive tract, loss of integrity of the vestibulovaginal sphincter, and loss of integrity of the vulvar labia. These changes occur more commonly in older, multiparous mares and those that have had perineal lacerations. Pneumovagina is a common antecedent to infertility.

Clinical Signs and Diagnosis In the normal mare, the anus is positioned directly dorsal to the vulva; the perineal body between the dorsal vulva and the anus is thick, muscular, and well formed; the vestibulovaginal sphincter is well formed; the vulva has a vertical alignment; 80% of the vulval labia lies below the floor of the pelvis; and the vulvar labia form a seal. Mares in which the vulva tilts horizontally at its dorsal aspect, the perineal body is thin, and the vulval labia do not form a seal are prone to pneumovagina in cases in which the anus lies rostral to the vulva. A scoring system has been developed to evaluate the perineal conformation in mares.[152] The system uses Caslick's index, which equals the distance (cm) between the dorsal commissure and the pelvic floor multiplied by the degrees of declination of the vulvar lips. Mares with Caslick's index above 150 were found to have subnormal pregnancy rates. Affected mares aspirate air on exercise or when the vulval labia are parted. Aspirated air may be noted on transrectal palpation or vaginal speculum examination. Signs of secondary changes such as vaginitis, cervicitis, or endometritis may be apparent.

Treatment and Prognosis Treatment of pneumovagina should be directed toward correcting defective perineal conformation. Cranioventral displacement of the reproductive tract in aged mares may be irreversible. Perineal confirmation in thin mares is often improved by increasing the mare's body condition. Pneumovagina is often successfully corrected by surgical closure of the dorsal vagina via Caslick's operation. Secondary changes should be treated as described elsewhere. Prognosis for correction of pneumovagina is excellent; however, prognosis for fertility depends on the extent of secondary changes.

Urovagina

MARES In normal young mares the vagina slopes craniodorsally and is largely contained within the pelvis. With aging and repeated pregnancy, the cranial vagina may slope cranioventrally and fall below the level of the pelvic floor. Under these conditions urine collects in the anterior vagina. Urine is spermicidal and the condition is often associated with subfertility.

Clinical Signs and Diagnosis In mild cases, a history of infertility may be the only indicator of urovagina. In more severe cases, urine dribbles from the vulva at rest or during exercise and may accumulate inside the hindlimbs. Speculum examination reveals a cranioventral slope of the vagina, variable inflammation of the cranial vagina and cervix, and a pool of urine in the ventral vaginal fornix. Urovagina may occur intermittently or only during estrus.

Treatment and Prognosis Surgical procedures to prevent the anterior flow of urine include urethral extension[246] and vaginoplasty.[247] Prognosis depends on the severity of secondary endometritis and the success of surgery.

Vaginitis

Vaginitis may occur as a result of ascending infection or exposure to irritants, or secondary to pneumovagina, urovagina, perineal laceration, rectovaginal fistulas, breeding, endometritis, abortion, parturition, or dystocia. Occasionally, traumatic wounds may be infected with clostridial or anaerobic organisms; however, most infection is nonspecific.

Clinical Signs and Diagnosis Signs may vary from hyperemia evident on speculum examination to mucopurulent exudation from the vulva. Severe trauma and infection may be followed by necrotic vaginitis with tenesmus, fetid discharge, elevated tail, swollen vulva, and systemic signs. Rapid formation of adhesions follows necrotic vaginitis. Metritis, RFMs, and uterine tears also may show systemic signs and vaginal discharge.

Treatment and Prognosis The inciting cause should be treated. Animals with mild vaginitis may recover spontaneously,

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whereas moderate cases require lavage with dilute antiseptic or antibiotic solutions. Fertility is unaffected in mild vaginitis without extension, and prognosis is good. Severe, necrotic vaginitis is treated with systemic antibiotics, analgesics, and antiinflammatory agents. Caslick's surgery may be necessary to prevent aspiration of air. Local application of antibiotic and steroid-impregnated ointments may help prevent adhesions. Prognosis for severe vaginitis is guarded. Vaginal stenosis and adhesions may follow vaginitis.

Prevention and Control Nonspecific vaginitis may be prevented by reducing trauma to the vagina during foaling. Clinicians should elect appropriate methods for relief of dystocia and apply extractive force to fetuses judiciously.

Infectious Pustular Vulvovaginitis

COWS Infectious pustular vulvovaginitis (IPV) affects cattle and is caused by bovine herpesvirus 1, also the cause of infectious bovine rhinotracheitis (IBR),[248] although the two strains are genetically distinct.[249] Therefore the respiratory and genital forms of the disease rarely occur concurrently, and abortions usually do not follow an outbreak of the genital form of the disease. IPV is spread by coitus and mechanical means and may affect unbred heifers. The incubation period of IPV is short (1 to 3 days), and the infection spreads rapidly through the herd, affecting 60% to 90% of the animals. IPV is not common.

Clinical Signs and Diagnosis Early in the course of the disease IPV is characterized by a mucopurulent vaginal discharge, inflammation of the vaginal and vulvar mucosa, and painful urination. Pustules develop over lymphoid follicles and progress from small (<3 mm) ulcers to coalescing erosions. The virus causes inflammation of the penis and prepuce (balanoposthitis) leading to considerable pain. Therefore animals of both sexes with IPV are reluctant to mate. The clinical signs subside in 10 to 30 days, leaving the recovered animals with transient immunity. Early in the course of IPV, lesions may be similar to those of granular vulvitis (see later section), but the lesions of IPV rapidly become more severe. Vulvovaginitis caused by *Histophilus somni* (formerly *Haemophilus somnus*) should be a differential diagnosis.

Treatment and Prognosis Treatment of IPV is usually not required, although lavage of the vagina with dilute antiseptic solutions and emollients has been recommended. Mating among infected animals should be suspended until the disease subsides. The prognosis for recovery is excellent.

Prevention and Control Vaccination against IBR is not likely to be beneficial in the face of an outbreak, but cattle may be protected if they are vaccinated before exposure. The IPV virus may survive in cryopreserved semen used for AI; therefore semen donors and semen should be free of the virus. Genital carriers may be responsible for sporadic outbreaks of IPV.

Vaginal Varicose Veins

MARES Vaginal varicose veins are common in older mares. In most cases the condition is not associated with clinical signs, but affected mares may exhibit vaginal hemorrhage. A thorough examination of the reproductive tract is necessary to determine the origin of the bleeding.

Clinical Signs and Diagnosis Clinical signs of varicose veins vary from no signs to persistent and profuse vaginal hemorrhage. Vaginoscopy or fiber endoscopy of the vagina reveals varicose veins in the vagina or the vestibulovaginal transverse fold. Vaginal hemorrhage from varicose veins should be differentiated from vaginal trauma and premature separation of the placenta in periparturient mares.

Treatment and Prognosis Most mares with vaginal varicose veins do not require treatment. Surgical ligation, treatment with phenylephrine HCl cream,[250] or laser surgery of the veins may be necessary in cases of severe bleeding. The short-term prognosis after surgery is good, but the condition often recurs.

Vestibular and Vulvar Abnormalities

Coital Exanthema

MARES Coital exanthema is caused by equine herpesvirus 3 (EHV-3) and is a venereally transmitted dermatitis of the genital region of mares and stallions.[251,252]

Clinical Signs and Diagnosis The disease is recurrent, is usually mild and transient, and affects the vulva and perineum of mares and the penis and prepuce of stallions. Lesions are initially small papules that rapidly progress to pustules and then ulcers. Lesions may rarely appear on the conjunctiva, lips, nares, and mucosa of the upper respiratory tract. Rare secondary bacterial infection and systemic signs occur. Intranuclear inclusion bodies are apparent in epithelial cells on histologic sections taken from the active edge of ulcers. Coital exanthema does not affect fertility in mares, but libido may be decreased in affected stallions because of pain during coitus.

Treatment and Prognosis Lesions usually heal spontaneously within 14 days, leaving depigmented spots. Treatment is unnecessary unless secondary bacterial infection occurs. There is no available vaccine for EHV-3. Sexual rest until the lesions are healed is recommended to prevent further spread of the disease. Prognosis is excellent.

Granular Vulvitis

COWS Granular vulvitis may occur in females of all domestic species but is most significant in cattle.[13] The disease is characterized by development of granules or papules in the vulvar mucosa accompanied by genital discharge. Infertility may or may not be a feature of the syndrome. Vulvitis may be secondary to nonspecific vaginitis.[126] *H. somni*[253] and *Mycoplasma bovigenitalium*[5] have been isolated from cattle with vulvitis, but their role in infertility is not well defined, and there may be differences in pathogenicity among strains of the organisms. *Ureaplasma diversum* has been isolated from cases of granular vulvitis in cows and ewes and may be associated with infertility when the organism is transferred into the uterus during AI.[5]

Clinical Signs and Diagnosis Granular vulvitis is characterized by the formation of raised granules or papules in the vulvar mucosa and around the clitoris with variable amounts of mucopurulent exudate. In the mild form of granular vulvitis associated with *U. diversum,* only a few granules develop and the infection has minimal effect on fertility. However, acute severe cases are characterized by hyperemia of the vulva, a profuse mucopurulent discharge, and depressed fertility. Purulent discharge during the acute phase persists for 3 to 10 days, after which the disease becomes chronic. In chronic cases the lesions are reduced in severity, and there is little or no purulent discharge. The chronic form may persist for several months, and the disease may become enzootic in some herds. The clinical signs of granular vulvitis may be similar to early signs of IPV.

Clinical Pathology Samples for microbiologic culture should be obtained from the vulva, cervicovaginal mucus, and uterus. Use of a transport medium for submission of samples to a laboratory is mandatory. The organisms may be eliminated before the samples are obtained, yielding false-negative results. Conversely, microorganisms incriminated as causing granular vulvitis may be isolated from the genital tracts of normal animals.

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Treatment and Prognosis Most cases of nonspecific vulvitis resolve spontaneously. Infertility associated with *U. diversum* infections is treated by preventing transfer of organisms to the uterus by using double-sheathed AI instruments. Natural breeding should be suspended. In addition, infusion of 1 g of tetracycline or spectinomycin in a nonirritating vehicle into the uterus 24 hours after breeding has been recommended to reduce the population of organisms that may have been transferred to the uterus. Local treatment of vulvar lesions with tetracycline or spectinomycin has also been suggested.

Prevention and Control In chronically infected herds, fertility rates may approach normal if double-sheathed AI instruments are used and affected cows are treated with appropriate antibiotics.

Ulcerative Dermatosis Genital Lesions

SMALL RUMINANTS Ulcerative dermatosis is a venereal disease of sheep caused by a parapoxvirus similar to but distinct from the virus that causes contagious ecthyma.[7,126] The disease is characterized by ulceration of the skin and mucous membranes of the vulva of ewes and penis and prepuce of rams. Lesions also occur on the lips, nares, feet, and legs. The lesions are painful, and affected animals avoid coitus. The disease subsides in 7 to 10 days.

Because of its viral cause, no specific treatment is available for ulcerative dermatosis.[7] Symptomatic treatment with local astringent and antiseptic ointments has been suggested. Morbidity of 15% to 20% is expected, although up to 60% of a flock may be affected. Mortality is low if the animals are otherwise healthy.

No vaccine is available. Males with the disease should not be used for breeding.

Abnormal Labial Approximation

MARES AND COWS The most common anatomic defect of the vulva of mares and cows is abnormal labial approximation, which leads to pneumovagina and subsequently to infertility.[50] The defect may be the result of imperfect conformation or traumatic insult to the vulva. Abnormal labial approximation is treated with Caslick's surgery or one of its modifications.

Persistent Hymen

In the developing embryo, failure of cannulation of the urogenital sinus by the mesonephric duct system results in absolute or partial occlusion of the vestibulovaginal junction. Total occlusion causes accumulation of endometrial and cervical secretions cranial to the obstruction, and occasionally the membrane may appear at the vulva. Partial occlusion may be noted only as an obstruction to breeding or during speculum examination. The membrane may be manually ruptured or incised. Prognosis is excellent.

Clitoral Hypertrophy

Clitoral hypertrophy may be a feature of intersex conditions, may occur in filly foals whose dams received progestins during pregnancy, or may follow administration of anabolic steroids.[71] Hypertrophy may persist after cessation of steroid treatment. In cows it may be associated with freemartinism.

Vulvar wattles in cattle may superficially appear similar, but the elongated epithelial structure does not involve the clitoris.

Neoplasia

Melanomas and squamous cell carcinomas (SCCs) are the most common neoplasms affecting the perineum, anus, and vulva of gray- and light-skinned horses, respectively.[254] Lesions are usually proliferative and may have surface ulceration, hemorrhage, and infection. Lesions should be differentiated from habronemiasis, granulation tissue, and sarcoids. Treatment is surgical removal. Sarcomas and melanomas may metastasize. Viral fibropapillomas are the most common tumors affecting the vulva of cattle.[13] SCCs may be seen in all species and may be more common in white-skinned animals exposed to long periods of solar radiation.[255]

Vulvar neoplasia is characterized by variable degrees of tissue proliferation. The surface of SCCs and fibropapillomas may be ulcerated, necrotic, and fly-blown. In cows squamous metaplasia of the nonpigmented skin of the vulva is frequently a precursor of squamous cell carcinoma of the vulva. Vulvar neoplasia must be differentiated from other causes of tissue proliferation, habronemiasis in mares, and ectopic mammary tissue in does.[5] Neoplasia of the vulva and vestibule is diagnosed by biopsy of the tumor.

Surgical excision is the treatment for most neoplasms of the vulva.[254] Viral fibropapillomas regress spontaneously after a period of several months. Recurrence and metastasis may occur.

Ectopic Mammary Tissue

Ectopic mammary tissue has been described in does and is characterized by swelling of the vulvar lips.[5] The abnormal enlargement begins before each parturition and persists for approximately 2 months. The condition is benign unless the tissue enlarges sufficiently to interfere with evacuation of feces or urine. Milk may be aspirated from the mammary tissue, and the condition may be confirmed by biopsy.

Abortion

MARES Information on the major causes of abortion in horses is summarized in Table 43-7.

TABLE 43-7

Major Causes of Infectious Equine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Equine herpesvirus 1 (EHV-1)	Seventh month to term	Pulmonary edema, multifocal hepatic and pulmonary necrosis, intranuclear inclusions	Histopathology, virus isolation, fluorescent antibody test, fetal serology, PCR
Equine viral arteritis (pestivirus)	5-10 mo	Myocardial arteritis	Histopathology, virus isolation, PCR, serology
Nocardioform actinomycete, *Crosiella equi, Amycolatopsis* spp.	Mid to late gestation	Characteristic placentitis located ventrally in the uterine body and at the base of the uterine horns	Culture, PCR
Streptococcus zooepidemicus	Any stage	Placentitis with or without inflammation in fetal tissues	Histopathology, culture
Mycotic abortion, *Aspergillus,* and other species	Latter half (often near term)	Placentitis, fetal bronchopneumonia	Histopathology, fungal culture
Leptospirosis	Seventh month to term	Icterus and autolysis	Culture, immunofluorescence, serology, PCR

PCR, Polymerase chain reaction.

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Noninfectious Causes

Twin Pregnancy

Despite the overall decrease in the number of twin-related abortions, twinning remains an important noninfectious cause of abortion in the mare.[256] The mare is unable to successfully support two fetuses to term and only in rare cases (<2%) is able to carry both fetuses to term and deliver without dystocia.[257] It is much more common for the mare to have a natural reduction to a singleton pregnancy during the embryonic stage or to abort the pregnancy after the fetal stage.[258,259] Some breeds more commonly than others are diagnosed with twins during the embryonic stage (e.g., Thoroughbreds have 20% to 30% double ovulations and 10% to 15% diagnosed twin pregnancies).

Clinical Signs and Diagnosis Mares should be evaluated with transrectal ultrasound 12 to 14 days after documented ovulation during a breeding cycle. The uterus should be carefully scanned from the tip of one horn to the other and along the uterine body to the cervix. Equine embryos at this stage are highly mobile within the uterus and may be located anywhere within the uterus. Increased uterine edema and fluid within the uterine lumen are often negative signs of pregnancy, but pregnancy should not be ruled out until the entire uterine tract has been scanned for the presence of embryos. After one embryo is found, the remainder of the uterus still must be visualized to ensure the absence of a twin. The embryo proper per se is not visible at this stage of pregnancy, but the embryonic vesicle is easily visualized. Care must be taken not to confuse endometrial cysts with embryos, which sometimes can look deceptively similar. It is helpful to have scanned the mare's uterus with ultrasound before breeding to document the size and location of endometrial cysts.

Treatment and Prognosis If twins are confirmed before 16 days of pregnancy, the best way to treat the mare is to manually crush one of the vesicles. This is done by visualization of the twins using transrectal ultrasound and spatially separating them from each other within the uterus. One twin is moved away from the other to the tip of a uterine horn where it is crushed manually. The remaining embryo should be evaluated 1 to 2 days later to determine its status. Manual reduction of a twin between days 16 and 20 should be performed at the base of one uterine horn because embryos are typically "fixed" at this site after day 16. Survival of the remaining embryo is greater than 90% when twin reduction is performed in this manner before day 20.[260]

It is the established practice of some veterinarians to treat mares with a nonsteroidal antiinflammatory agent (e.g., flunixin) and/or altrenogest after a twin-crush procedure. The reasoning behind this practice is that manual stimulation of the uterus may cause a release of oxytocin, signaling a prostaglandin cascade that will result in luteolysis and complete pregnancy loss. There have been no studies performed to support this theory; to the contrary, other studies have shown that the release of prostaglandin after the routine twin-crush procedure does not cause a drop in progesterone and that supplementation with antiinflammatory drugs or progesterone makes no difference in the outcome.[260,261]

Other techniques described for reduction of twins to a single embryo include transvaginal, ultrasound-guided fetal aspiration[262]; transcutaneous, ultrasound-guided fetal intracardiac injection of procaine penicillin or potassium chloride[263]; and craniocervical dislocation.[264] The success of these techniques is lower than that of manual crush, and they are performed later in gestation, after the window for manual crushing has been missed. These are all specialty techniques and are beyond the scope of this chapter.

Other Noninfectious Causes of Equine Abortion

In a survey of causes of equine abortion in the United Kingdom from 1988 to 1997, nearly 39% were caused by umbilical cord pathology.[265] Most of the cases (35%) resulted from torsion of the umbilical cord. Twisting of the umbilical cord is common in equine fetuses and often is not pathologic. A diagnosis of abortion caused by umbilical torsion should be made only if localized swelling and discoloration accompany the twisting. Congenital abnormalities may cause abortion. The most common congenital abnormality in equine fetuses is contracted tendons, accounting for 5% of abortions in a study from the United States.[256] Fetuses that implant in the uterine body instead of the base of one of the horns develop placental villous atrophy and usually abort, accounting for 2% of abortions in the same study.

Infectious Causes

Placentitis

Placentitis is the leading cause of equine late-term pregnancy loss in the United States.[256] Bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus* spp., *E. coli, Pseudomonas* spp., *Klebsiella* spp., *Staphylococcus* spp., and *Leptospira* spp. Nocardioform actinomycetes are an important cause of placentitis in central Kentucky and have recently been reported in Florida.[266-268] *Aspergillus fumigatus* and *Mucor* spp. are the most commonly diagnosed causes of mycotic abortion in mares. Fungi cause 5% to 30% of infectious equine abortions.[5]

The route of placental infection is believed to most commonly be ascending via the cervix, which results in loss of chorionic villi around the cervical star. In addition to loss of chorionic villi, additional allantochorionic lesions may include nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion. Hematogenous placentitis shows a more generalized, diffuse loss of villi.[256] Infection of the placenta results in subsequent infection of the fetus and release of proinflammatory cytokines and prostaglandins from the inflamed placenta, which ultimately leads to abortion or delivery of a premature foal.[269] The distribution of the avillous chorionic lesion classically noted in mares with ascending or hematogenous placentitis does not fit the pattern noted with nocardioform placentitis. Mares with nocardioform placentitis classically show a loss of chorionic microvilli in a focal area around the base of the uterine horns. It has been postulated that the pathogen is present or introduced in the mare at the time of breeding and settles in the ventral aspect of the uterus, where it causes the infection. This hypothesis is not proven, though it is likely that the nocardioform organisms are from the environment. Various nocardioform organisms have been reported in the soil in countries across the globe, although the pathogenicity of most of these organisms is not determined. The pathogenesis of nocardioform placentitis is still unresolved. Nocardioform organisms isolated from equine placentas include *Amycolatopsis* spp. and *Crossiella equi*.[266-268,270,271] Nocardioform placentitis often results in abortion or premature delivery.[256] Bacteria and resulting inflammation are limited to the interphase between the chorion and the endometrium. Because no bacterial invasion or signs of inflammation have been observed in the placental and fetal tissues, the abortion is likely due to nutritional deprivation resulting from separation between the chorion and endometrium. A better understanding of how nocardioform placentitis occurs is essential for the development of preventive measures for this cause of abortion.

Clinical Signs and Diagnosis Premature udder development and vaginal discharge are common signs of pending abortion caused by ascending placentitis. However, when these signs are present, the prognosis is poor even when mares are treated. Transrectal ultrasonography of the allantochorion in an area close to the cervix is useful to detect early signs of placentitis and impending abortion (Fig. 43-8).[272] Ultrasound evaluations may reveal hyperechoic fetal fluids, placental separation, increased or decreased fetal heart rates (normal range 75 ± 7 bpm[273]), and thickening of the combined thickness of the uterus and placenta (CTUP). Consistently low or high fetal heart rates are associated with fetal stress. Foals experiencing fetal distress often become bradycardic initially and then become tachycardic in the terminal phase of life.[274,275] Serial examinations should be performed to verify fetal well-being or distress. Mares

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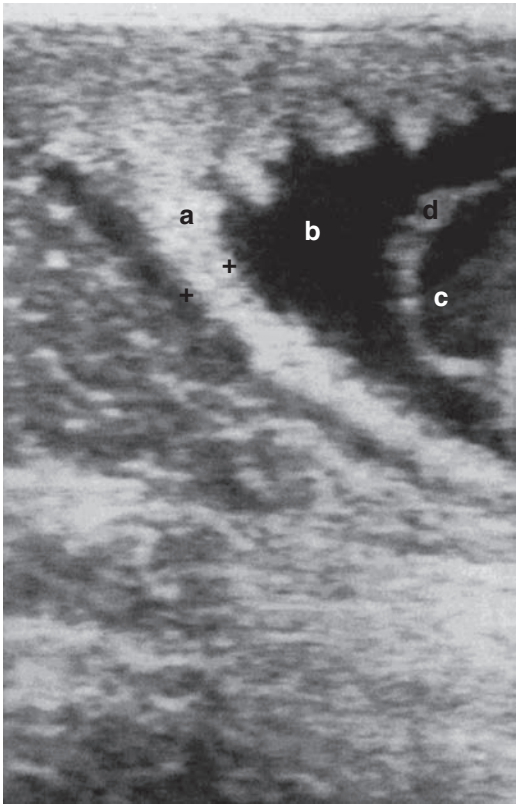


FIG. 43-8 Transrectal imaging of the combined thickness of the uterus and the placenta (CTUP). Measurements of the CTUP (distance between + and +) were recorded from the ventral part of the uterine body, close to the cervix. *a,* Placenta adjacent to the cervix; *b,* allantoic fluid; *c,* amniotic fluid; *d,* the amnion. *(Modified from Renaudin CD, Troedsson MH, Gillis CL, et al. 1997. Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare. Theriogenology, 47:559.)*

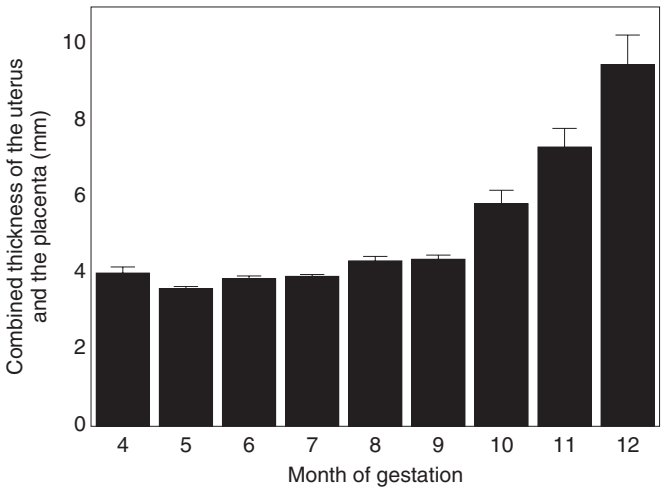


FIG. 43-9 Monthly recordings of transrectal ultrasonographic measurements of the combined thickness of the uterus and the placenta (CTUP) in normal mares from 4 months of gestation and throughout the pregnancy. Month 4 is 91 to 120 days; month 5 is 121 to 150 days; month 6 is 151 to 180 days; month 7 is 181 to 210 days; month 8 is 211 to 240 days; month 9 is 241 to 270 days; month 10 is 271 to 300 days; month 11 is 301 to 330 days; month 12 is 331 to 360 days. *(Modified from Renaudin CD, Troedsson MH, Gillis CL, et al. Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare. Theriogenology 47:559, 1997.)*

considered "at risk" for pregnancy loss are often examined on a daily basis. Fetuses experiencing distress are often evaluated several times a day. Normal measurements of CTUP have been established (Fig. 43-9).[272,276] Mares with placentitis may show increased CTUP, edema of the allantochorion, and separation from the endometrium. A

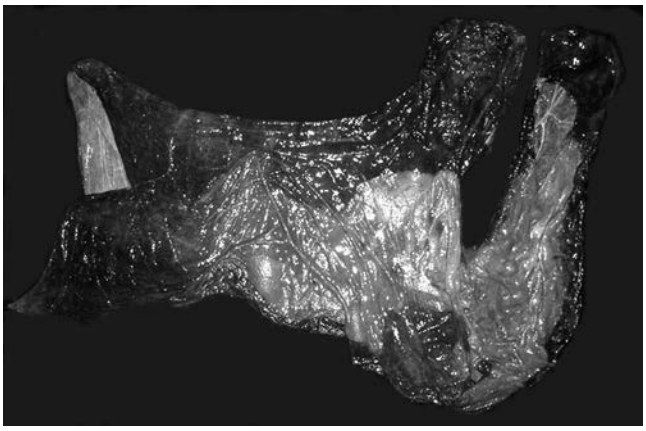


FIG. 43-10 Placenta from a mare with nocardioform placentitis. The characteristic lesions are located ventrally in the uterine body and base of the uterine horns.

5-MHz linear transducer should be used for transrectal ultrasonography. The transducer should be positioned 1 to 2 inches cranial to the cervical-placental junction and then moved laterally until a major uterine vessel is visible at the ventral aspect of the uterine body.[276] The CTUP should then be measured between the vessel and the allantoic fluid (see Fig. 43-8). It is important to obtain all CTUP measurements from the ventral aspect of the uterine body because physiologic edema of the dorsal aspect of the allantochorion has been noted in normal pregnant mares during the last month of gestation.[276] In addition, care should be exercised to be certain that the amniotic membrane is not adjacent to the allantochorion, because this may result in a falsely increased CTUP. To examine the placenta from a transabdominal approach, a 3.5-MHz sector transducer is used most frequently. All four quadrants of the placenta should be examined: right cranial, right caudal, left cranial, and left caudal. Measurements of the CTUP can be made with this technique if the fetus is not in close apposition with the uterine wall. Mares with normal pregnancies should have a minimum combined thickness of the uterus and the placenta (CTUP) of 7.1 ± 1.6 mm and a maximal CTUP of 11.5 ± 2.4 mm.[277] Pregnancies with an increased CTUP have been associated with the delivery of abnormal foals.[277] Placental separation and purulent material at the ventral aspect of the base of the gravid horn and the uterine body can be observed in mares with nocardioform placentitis. This finding can only be identified using transabdominal ultrasound.

The gross lesions of the fetus are not specific. An increased amount of fluid in the thoracic and abdominal cavities and an enlarged liver are frequently observed in aborted fetuses. Placental lesions in cases of ascending placentitis are most severe on the chorionic surface at an area from opposite the cervix ("cervical star") to the body of the placenta. The affected area is edematous, thickened, and discolored or brown with a mucoid or fibronecrotic exudate on the surface. The placenta is characteristically thickened and leathery in cases of mycotic placentitis, with lesions well demarcated from the rest of the chorionic surface. Microorganisms can be isolated from the placenta and several fetal organs, most consistently from the stomach.

Mares with nocardioform placentitis may have premature mammary development but will not have vulvar discharge, owing to the location of the infection. Placental lesions in mares infected with nocardioform actinomycetes are located ventrally in the uterine body and at the base of the uterine horns (Fig. 43-10). Affected areas are avillous, thickened, and covered by thick brown or reddish exudate. Differential diagnoses for this clinical presentation include twins and *Cellulosimicrobium cellulans* placentitis.[270]

Prevalence of fungal abortions varies greatly with region. The most common route of fungal infection is ascending via the cervix, and fungal infections may be seen with a mixed bacterial infection.

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Abortions are observed from mid to late gestation. The chorion generally shows marked evidence of placentitis with edema, thick plaques, and a thick, mucoid exudate. In rare cases, amniotic thickening may be noted. The aborted fetus is often small and emaciated owing to chronic placental insufficiency. Culture of the chorion may be diagnostic but takes time. Culture of the fetus is rarely rewarding. Impression smears of the chorion, as well as sometimes the fetal stomach, may reveal hyphae.

PROGESTERONE. The equine placenta is part of an endocrine fetal-placental interaction that synthesizes and metabolizes progestagens.[278] This endocrine function of the placenta is important for maintenance of pregnancy after the endometrial cups and the secondary corpora lutea disappear at approximately day 120 to 150 of gestation. Fetal-placental progesterone is rapidly metabolized to 5α-pregnanes. Mares with placental pathology may have increased plasma concentrations of progestagens as a result of stress to the fetal placental unit.[279,280] Unfortunately, 5α-pregnanes are not readily assayed in a commercial setting, so diagnosis of placental disease using 5α-pregnane concentrations is not possible. There is cross-reactivity between 5α-pregnanes and progesterone using some commercial radioimmunoassays for progesterone. In recent studies[280,281] using an experimental model to induce placentitis, it was found that mares that develop a chronic form of placentitis responded with increased plasma progesterone concentrations. Conversely, mares that developed acute placentitis and abortion soon after infection experienced a rapid drop in plasma progesterone concentrations. It was suggested that measurement of repeated samples of plasma progestin concentrations in mares with placentitis might be a useful method to identify mares that may abort or deliver prematurely.[280] Furthermore, sensitivity of progesterone assays can be improved when they are combined with evidence of placental thickening as detected using transrectal ultrasonography.[281]

ESTROGEN. Serum estrogen concentrations are deviated in pregnant mares between 150 and 310 days of gestation.[282] The predominant estrogens in pregnant mares are estrone, equilin, equilenin, estradiol-17β, and estradiol-17α. Douglas observed that mares aborting from placentitis had serum estrogen concentrations below those normally detected in pregnant mares.[282] The author suggested that supplementation with estradiol cyprionate (ECP) or estradiol-17β may prevent abortion in mares with placentitis. Preliminary data from the author's laboratory suggest that estradiol-17-β sulfate serum concentration drops rapidly following experimentally induced placentitis.

RELAXIN. Relaxin is produced by the equine placenta and can be detected in peripheral blood plasma from day 80 of gestation and throughout the pregnancy. The role of relaxin during pregnancy is not fully understood, but there is some evidence that placental relaxin production is compromised in mares at risk of aborting their fetuses.[283] There is currently not a commercial test available for equine relaxin.

INFLAMMATORY MARKERS FOR PLACENTITIS

Acute-Phase Proteins. Serum amyloid A (SAA) remains low throughout gestation while showing a significant increase within 12 hours of parturition and returning to baseline within 60 hours postpartum.[284] Interestingly, levels of SAA in peripheral blood have also been reported to increase in mares with placentitis.[285] However, SAA is a nonspecific marker of inflammation with significant increase observed during other sources of inflammation and even after vaccination.

In summary, no single test appears to have sufficient specificity, sensitivity, or practicality to accurately detect early subclinical cases of placentitis. A panel of diagnostic tests that accurately indicate inflammation and placental insult should be developed to allow for regular monitoring of placental health during late pregnancy.

Treatment and Prognosis Treatment efforts should be directed at combating infection, reducing inflammation, and controlling myometrial activity. Pregnant mares with clinical signs of placentitis should be treated with systemic broad-spectrum antimicrobials and antiinflammatories. Commonly used antibiotics such as penicillin G sodium or potassium (22,000 IU/kg IV q6h), gentamicin (6.6 mg/kg IV q24h), and trimethoprim-sulfadiazine (30 mg/kg PO bid) cross the placenta and reach therapeutic concentrations in both placental tissues and the allantoic fluid.[286] However, the duration of these elevated concentrations were short and below those in blood plasma. This may explain why more than 60% of mares that had been treated for placentitis still cultured positive after foaling.[287] This may explain why antibiotic treatment appears to be necessary for the remainder of gestation in mares with placentitis. Flunixin meglumine (1 mg/kg IV, PO q12h) and pentoxifylline (8.5 mg/kg PO bid) have been used to control proinflammatory cytokines associated with placentitis. Treatment with progestins has long been advocated to promote uterine quiescence in mares with uterine pathology. Presumably the antiprostaglandin effect of progestins contributes to reduced myometrial activity by interfering with upregulation of prostaglandin and oxytocin receptors.[288] Without receptor formation, gap junction formation would be inhibited and uterine contractility prevented.[289] Altrenogest at twice the recommended dose (0.088 mg/kg PO q24h) is commonly used.

Work from a large-scale clinical trial examined the efficacy of multipronged, long-term therapy for equine placentitis.[290] Investigators examined records of 477 mares over 6 years. Fifteen mares were diagnosed with placentitis. Criteria for treatment included increased thickness of the uteroplacental unit using transrectal ultrasound, placental separation, and/or vulvar discharge and udder development. The average gestational age at diagnosis was 8.6 months. Mares were treated with a combination of systemic antibiotics (trimethoprim-sulfa, ceftiofur, or penicillin and gentimicin); pentoxifylline; altrenogest; and nonsteroidal antiinflammatory agents. Mares were treated until abortion or delivery of a foal. Twelve of 15 treated mares (80%) carried their foals to term, and 11 of 15 (73%) delivered live foals. Birth weights of surviving foals from mares treated for placentitis were similar to those of foals from nonaffected mares. The benefit of this treatment strategy is supported by recent data from a controlled study on experimentally induced placentitis.[290] Data from these studies suggest that a continuation of long-term antibiotic, antiinflammatory, and progestin treatment may positively affect pregnancy outcome in mares with placentitis. This conclusion is supported from a more recent observation.[291]

Although most mares are capable of conceiving and successfully carrying a foal to term in subsequent breedings, reproductive performance may be negatively affected after ascending and hematogenous placentitis. Treatments for endometritis, such as uterine lavage and intrauterine infusions of appropriate antibiotics, should also be implemented after abortion. Most mares affected by nocardioform placentitis do not require subsequent treatment and show no signs of infertility the following breeding season.

Equine Herpesvirus 1 Abortion

The most prevalent viral cause of equine pregnancy loss is equine herpesvirus 1 (EHV-1), which causes abortion, paresis, and neonatal foal death. EHV-4 causes abortion in rare cases. The primary route of transmission of EHV-1 is via the respiratory tract. The virus invades the respiratory epithelium and establishes a leukocyte-associated viremia. EHV-1 establishes a chronic, possibly lifelong, latent infection. During the initial infection, placental endothelial cells are infected by the virus and transiently present targets to the immune system as the cells present viral particles. The virus eventually inactivates the major histocompatibility complex 1 (MHC-1) ability of the cells to present viral particles, thus evading the immune system.[292] After respiratory infection, EHV-1 causes an episode of viremia and infects the fetus via transplacental migration of virus-bearing leukocytes. Respiratory clinical signs in infected mares may be subclinical. The time between infection and abortion varies greatly

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from less than 2 weeks to several months.[293] Abortion occurs as a result of a rapid separation of the placenta, causing suffocation of the fetus.[294] Near-term fetuses may be born alive but will die within days. Aborting mares clear the virus quickly from the reproductive tract, and subsequent fertility is often not affected by the disease. Clinical signs and fetal lesions of abortion caused by EHV-1 and those caused by EHV-4 are indistinguishable from each other.[293]

As with all herpesviruses, EHV-1 establishes a latent infection that may recrudesce after stressful events, such as weaning, translocation, introduction of a new animal, or other illnesses. It is unclear whether or not a reactivation event will cause an abortion, but this is considered likely.[295] Recrudescent infections are certainly transmissible. Aborted, infected fetal materials are also highly contagious. Both of these sources may be responsible for abortion epizootics. Although epidemic abortions occur, losses may be confined to only a few mares in a herd.

Clinical Signs and Diagnosis The primary lesion of EHV-1 is necrotizing vasculitis and thrombosis resulting from lytic infection of the capillary endothelium. The fetus may become infected or remain uninfected, depending on whether or not the virus crosses the uteroplacental barrier. If transplacental fetal infection occurs late in gestation, a live, infected foal may be born but will not usually survive. Stage of pregnancy during which abortions may occur varies, but the vasculitis is most pronounced from the fifth to ninth months of gestation, and 95% of abortions occur in the last trimester of pregnancy.[296]

Abortions occur suddenly as sporadic abortions or "abortion storms" without maternal clinical signs. The aborted fetus is fresh with minimal signs of autolysis. Increased fluid in the thoracic and abdominal cavities; congestion and edema of the lungs; an enlarged liver with small (≈1 mm), necrotic, yellow-white lesions; subcutaneous edema; and icterus are commonly found gross lesions in the fetus. Samples for histopathologic diagnosis should be submitted in Bouin solution. Histologically, the most characteristic lesion consists of areas of necrosis in lymphoid tissue, liver, adrenal cortex, and the lung, with large intranuclear eosinophilic inclusion bodies. In addition, a hyperplastic necrotizing bronchiolitis is often found. Lymphoid tissues are most commonly affected (nodes, thymus, spleen, and Peyer patches). Other histopathologic lesions may include mild, multifocal, necrotizing lesions in the liver and adrenal cortex and a hyperplastic, necrotizing bronchiolitis. The placenta may be grossly normal or edematous with no specific microscopic lesions.[297]

Laboratory diagnosis of EHV-1 abortion is done by either direct demonstration of virus (virus isolation or viral antigen) or viral nucleic acid detection (polymerase chain reaction [PCR]) or indirectly through serologic evidence of recent infection. The placenta, lung, liver, spleen, and thymus should be collected aseptically in suspected cases of EHV-1 abortion for virus detection. Tissue samples for virus isolation (VI) should be kept at 4° C, not frozen at −20° C, until inoculated into cell culture. Samples that cannot be processed within a few hours after collection should be stored at −70° C. The identity of virus isolates recovered from tissue specimens must be confirmed by PCR, indirect immunofluorescent assays using EHV-1 specific antisera or monoclonal antibodies, or neutralization assays using EHV-1 specific antisera or monoclonal antibodies. Serologic tests are not considered reliable in EHV-1 diagnosis. It should be kept in mind that serum from mares that aborted may already contain peak levels of antibodies, and no increase in titers will be detectable in subsequently collected sera. Equine fetuses have been found to be capable of producing antibodies to EHV-1 at 200 days of gestation. Maternal serology is of limited diagnostic value because mares may abort several weeks after infection. The rise in serologic titer may have disappeared by the time of the abortion.

Treatment and Prognosis Studies offer conflicting results as to the efficacy of vaccinations in reducing viremia and abortions. Many studies do suggest a beneficial effect of vaccination, and the current recommendation is to vaccinate during the fifth, seventh, and ninth months of gestation.[292,296] Both killed and modified live vaccines are available. The vaccines are not fully protective, and abortion may occur in vaccinated mares. However, consistent vaccination of pregnant mares should be expected to decrease the incidence of abortion storms and sporadic abortions in a herd.

For the effectiveness of a vaccination program to be maximized, it needs to be combined with a management strategy that minimizes exposure of mares to the virus and prevents activation of a latent viral infection. All horses, young, adult, nonpregnant, and pregnant, should be vaccinated to restrict shedding of the virus. Unnecessary stress such as transportation and overcrowding should be avoided. Pregnant mares should be kept separate from other horses on the farm. Newly arrived horses should be isolated from the resident population for 3 weeks, during which time they should be monitored daily for signs of respiratory disease.

After abortion, the fetus and fetal membranes should be transported away from the area without contaminating the surrounding environment. The stall in which the mare aborted should be disinfected with a phenolic or iodinophoric compound, and the bedding should be prevented from contaminating other areas on the farm. All pregnant mares on an infected farm should remain on the farm until they have foaled. No horse should leave the farm until 3 to 4 weeks after the last abortion.

Equine Viral Arteritis

Equine viral arteritis (EVA) is caused by equine arteritis virus (EAV). The primary target of EAV is the vascular endothelial cells and macrophages. Shortly after infection EAV can be found in the macrophages and later in the lymph nodes. The virus infects circulating monocytes and becomes systemic in distribution by 3 days after the primary infection, resulting in a carrier state (important in stallions). In about a week's time after the primary infection EAV infects the blood vessel endothelium and causes enough damage by 10 days after the primary infection to cause abortion. Abortion is likely due to the effects of myometritis and vasculitis. Serum progesterone concentrations (produced exclusively by the placenta in the last half of equine pregnancy) fall to baseline levels before the abortion, because of placental hypoxia.

Although the pathophysiology is not well established, fetal death may occur by fetal anoxia secondary to compression of myometrial vessels by edema and decreased progesterone production by the placenta.[298]

History and Clinical Signs Clinical signs may be absent or highly variable and may include pyrexia, depression, anorexia, leukopenia, limb edema, stiffness of gait, rhinorrhea and epiphora, conjunctivitis, rhinitis, urticarial rash, localized or diffuse edema, and abortion. Abortion typically occurs at 3 to 10 months of gestation and follows the onset of clinical signs by several days but up to 2 months. Abortion rates in outbreaks of EVA have varied from less than 10% to 71%. Less frequently, severe respiratory distress, ataxia, mucosal papular eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema may be observed.[299] Infection is rarely fatal in adults but is more frequently fatal in neonates due to interstitial pneumonia and secondary bacterial infections. Clinical pathologic findings are variable, inconsistent, and nonspecific and include hypoxia, hypercapnia, respiratory or metabolic acidosis, lymphocytosis or lymphopenia, neutrophilia or neutropenia, thrombocytopenia, and hyperfibrinogenemia. Gross and histologic lesions differ in severity with the virulence of the particular viral strain. Edema, congestion, and hemorrhage of the subcutaneous and lymphoid tissues and viscera are the most common gross lesions. Histologic lesions may be found in the vasculature, lymphoid tissues, lungs, intestines, adrenal glands, kidneys, and skin.[299] Abortion may occur without any clinical signs in the mare, and the fetus may be fresh or autolyzed. Fetal lesions are uncommon. The infected stallions may serve as long-term carriers, and virus may be transmitted in the semen.

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Laboratory Diagnosis Laboratory diagnosis of EVA is currently based on any combination of VI, viral nucleic acid or antigen detection, and serology. The most appropriate specimens for VI from live horses include nasopharyngeal swabs or washings, conjunctival swabs, and citrated or ethylenediaminetetraacetic acid (EDTA) blood samples for separation of buffy coat cells. Placenta, fetal fluids, lung, spleen, and lymphoid tissues should be collected for VI to confirm cases of EAV-induced abortion. RT-PCR–based assays (standard and real time) have several potential advantages over the current virus isolation procedure. Serologic diagnosis of EVA is based on virus microneutralization and is standardized by the World Organization for Animal Health (still known by the French abbreviation OIE for Office International des Epizooties) and described in the OIE manual. There are no characteristic lesions of EVA infection in the fetus, although autolysis and myocardial arteritis have been reported. An avidin-biotin complex (ABC) for immunoperoxidase staining using monoclonal antibodies to individual EAV proteins has been successfully used to detect viral antigens in formalin-fixed paraffin-embedded samples, as well as in frozen tissue sections.

Epidemiology and Control Transmission may occur venereally from persistently infected stallions to mares. Reproductive performance of venereally infected mares is not affected, but contact transmission from venereally infected mares to late gestational mares may cause abortion. Major outbreaks of EVA were reported in 1953, 1984, and 2006 in the United States. With the exception of these incidents, occasional outbreaks have occurred, with abortion occurring at low incidence.[300] Mares may be isolated after infection but usually do not become carriers. A proportion of naturally infected stallions become persistently infected with EAV and shed the virus constantly in semen. Incidence of seropositive animals is higher in Standardbreds than in Thoroughbreds, and regulatory guidelines may govern the use of seropositive Thoroughbred stallions. Carrier stallions may be the reservoir for the disease between outbreaks and should be isolated and bred only to immune mares. Mares bred in this way should be isolated for 3 weeks. A modified live-virus attenuated vaccine (ARVAC, Pfizer Animal Health Inc, New York, N.Y.) is licensed for use in the United States and Canada for prevention of EAV infection in mares and stallions. A killed-virus vaccine (Artervac, Pfizer Animal Health Inc, New York, N.Y.) is licensed for use in the United Kingdom, Ireland, France, Hungary, and Denmark. Vaccination of mares up to 3 months before foaling or in the postpartum period appears to be safe. Vaccinating pregnant mares in the final 2 months of gestation is associated with an increased risk of abortion, and decisions to vaccinate in this time period must be weighed against concerns for widespread disease in naturally infected herds.[301] Control in stallions involves vaccination of seronegative stallions under the guidance of regulatory authorities.

Leptospirosis Abortion

Leptospirosis causes a number of bacterial abortions in some areas and was reported to be responsible for 2.2% of abortions in a Kentucky study.[256] The serovar responsible shows regional variability. Serovar *Leptospira pomona* has most commonly been associated with leptospirosis abortion in mares, but *Leptospira grippotyphosa, Leptospira hardjo, Leptospira bratislava,* and *Leptospira icterohemorrhagiae* have also been isolated from sporadic abortions.[302] Infected animals shed the spirochete in their urine, which contaminates groundwater and serves as a source for further infections. Many horses are seropositive for leptospires but are subclinical.

Clinical Signs and Diagnosis Clinical signs may include pyrexia, hemoglobinuria, jaundice, and abortion. Aborted chorioallantoic lesions are similar to those of other bacterial placentitis cases (nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion) but may show a diffuse pattern of distribution, indicating a hematogenous source of placental infection. Funisitis has been reported in leptospiral cases of abortion, and examination, both gross and histologic, of the umbilical cord should always be a part of every abortion investigation.[303] Serologic antibody conversion lasts for years, so serologic diagnoses are not helpful. Gross lesions are nonspecific. Diagnosis is best done by fluorescent antibody (FA) tests or Warthin-Starry (WS) silver stain of the allantochorion and umbilical cord. Demonstration of leptospirosis could aid in rapid diagnosis and have important clinical and therapeutic indications in the case of live-born, weak foals.[303]

Treatment and Control Horses may shed spirochetes in urine for up to 90 days; therefore affected animals should be isolated and treated with antibiotics. Aborting mares should be isolated, and the stalls should be disinfected. Infected mares may be treated with streptomycin (10 mg/kg twice daily), penicillin (10 to 15,000 IU/kg IM twice daily), or oxytetracycline (5 to 10 IV mg/kg) for a period of 1 week. Because *L. pomona* is the most common isolate in the United States, mares should be separated from other leptospiral hosts such as ruminants and pigs. Vaccines for cattle are not effective in horses.

Protozoal Abortion

Pregnant mares with equine monocytic ehrlichiosis (Potomac horse fever), caused by the protozoa *Neorickettsia risticii,* may abort. Abortions caused by *N. risticii* have been documented in both natural and experimental cases.[304,305] Mares were infected at 90 to 180 days of gestation and aborted at around 217 days of gestation.

Clinical Signs and Diagnosis Abortions have been observed 2 to 3 months after clinical signs of ehrlichiosis.[306] Abortions were associated with placentitis and RFMs. Fetal histologic lesions include enterocolitis, periportal hepatitis, myocarditis, and lymphoid hyperplasia with necrosis of the mesenteric lymph nodes and spleen. Recovery of the protozoan may be from fetal bone marrow, spleen, lymph node, colon, or liver.[304,305] The diagnosis can be confirmed by identifying a small number of rickettsiae by PCR assay.

Treatment and Prevention Treatment with oxytetracycline (6.6 mg/kg IV once daily) for 5 days in pregnant mares with clinical signs of ehrlichial colitis may prevent or reduce the incidence of abortion. Commercial vaccines against equine ehrlichiosis are available, but the protective effect of vaccines against abortion is unknown.

Neospora caninum is a known protozoal abortifacient in cattle. This protozoan has not been definitively shown to cause abortion in the mare, but its presence has been documented in aborted foals, suggesting the need for further investigation.[307]

Insect-Related Abortion

In the equine breeding season of 2001, central Kentucky horses experienced pregnancy losses estimated to have affected more than 3000 mares (>60% of mares on some farms[308]) and to have resulted in over $330 million in losses.[309] The syndrome was named *mare reproductive loss syndrome* (MRLS). On a much smaller scale, MRLS was documented in mare abortions in north central Florida during the 2006 breeding season. Epidemiologic studies noted abnormal weather patterns (sudden freezing in mid-April followed by unusually warm springtime temperatures) and positive correlations with the presence of black cherry trees *(Prunus serotina)* and abnormally large numbers of the eastern tent caterpillar *(Malacosoma americanum).*[310] Pregnancy loss was later linked to ingestion of the caterpillars themselves, with the toxic agent related to the larval exoskeleton.

Clinical Signs and Diagnosis Clinical signs preceding abortion and failure to maintain pregnancy are typically not observed. Both early (40 to 150 days' gestation) and late (near-term) pregnancies are affected. Hyperechoic amniotic and allantoic fluids can be noted on ultrasonographic examination, along with a dead or dying fetus (slow heart rate, <75 beats/min), which would then be expelled within several days.[311,312] Characteristic histologic lesions are noted in the placenta and umbilical cord. In many cases, endometrial cultures are positive for non-β-hemolytic streptococci and actinobacilli.

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Actinobacillus spp. identified in cases of MRLS are identical to commensal organisms found in the oral cavities and alimentary tracts of healthy horses.[313] Larval hairs (cetae) are hypothesized to migrate through the gastrointestinal system and translocate commensal organisms from the oral cavity and intestines to other sites.[310]

Treatment and Prevention Because clinical signs are absent in the mare before fetal death, treatment is not possible. Prevention is aimed at limiting exposure to *M. americanum* larvae. Applying insecticides, physically removing caterpillar nests from trees, removing black cherry trees, muzzling mares in pasture, and supplementing hay feeding in pastures to minimize grazing have all been used.

Salmonella Abortion

Salmonella abortus equi (*Salmonella abortivoequina* or "contagious abortion") was a common cause of abortion in the early 1900s but is now rare. Non-host-specific species, including *Salmonella* Typhimurium, now cause most equine *Salmonella* abortions. Abortion caused by *Salmonella* is discussed under abortions in ruminants.

Trypanosomiasis (Dourine)

The protozoan parasite *Trypanosoma equiperdum* causes a venereally transmitted genital infection that may be followed by fatal systemic dissemination in horses. Systemic illness may cause abortion. It occurs in tropical and subtropical regions and has been eradicated from North America.[13] Dourine is diagnosed by isolation of trypanosomes in uterine discharge. Exposed animals can be detected by serology (complement fixation). Control strategies require identification and treatment or euthanasia of infected animals.

Abortion Caused by Endotoxemia

Gram-negative septicemia and endotoxemia associated with intestinal disorders that alter the integrity of the mucosal barrier (e.g., intestinal obstructions, acute enteritis, colitis, grain overload) result in the release of vasoactive metabolites including PGF. Endogenous release of PGF during an episode of experimental endotoxemia has been shown to cause luteolysis and abortion during the first 2 months of pregnancy in mares.[314] The equine pregnancy is dependent on ovarian sources of progesterone for the first 80 days of gestation. After this time the fetoplacental unit takes over progesterone production, which is necessary for maintenance of the pregnancy.

Clinical Signs and Diagnosis Abortions follow a recent episode of stress induced by endotoxemic shock or gram-negative endotoxemia. Pregnancy loss at early stages of gestation may go undetected unless fetal membranes or parts are found in the stall. Abortions during later stages of the pregnancy may be observed as vaginal discharge or the detection of an expelled fetus.

Treatment and Prevention Daily administration of a progestagen (altrenogest 0.044 mg/kg PO) has been shown to effectively prevent experimental endotoxin-induced abortion.[314] If the animal is treated while the pregnancy is still CL dependent (approximately before day 80), analysis of serum progesterone concentrations after the acute episode of the disease helps in deciding if the supplementation needs to continue. Serum progesterone concentrations of less than 1 ng/mL indicate the loss of an active CL, and supplemental progestagen treatment should continue until the fetoplacental unit is known to be capable of maintaining the pregnancy. For practical reasons supplementation until day 100 is commonly recommended. Serum progesterone concentrations greater than 2 ng/mL are compatible with a functional CL, and the progestagen treatment can gradually be discontinued. Treatments with flunixin meglumine or other prostaglandin inhibitors have not been proven to effectively prevent endotoxin-induced fetal losses unless the agents are administered before clinical signs appear.

RUMINANTS Information on the major causes of abortion in cows, sheep, and goats is summarized in Tables 43-8 and 43-9.

In large commercial operations a low percentage of intermittently occurring abortions is considered acceptable; such abortions are seen as "background abortions." In beef and dairy operations 2% to 3% and 10% are considered acceptable, respectively. Abortion levels beyond these are considered abnormal and are usually investigated. When investigating bovine abortions, it is important to determine commonalities among abortion events including stage of pregnancy affected, sire used, heifers versus cows affected, dates of new arrivals to the herd, season of year, vaccination protocols, presence of dogs, and management practices among different groups. Cows and heifers on the farm presumed to be pregnant should be evaluated to detect unobserved pregnancy losses. These examinations should document apparently normal, open animals who had previously been documented as pregnant, those with mummified fetuses, and those with pyometra. If possible an entire fetus (or more than one) should be submitted for culture, serology, and histopathology. If the placenta is available, this should be submitted as well. If it is not practical to submit the entire animal and placenta, tissues including lung, stomach and contents, liver, spleen, and placenta should be collected and appropriately submitted for culture (chilled), viral isolation (frozen), and histopathology (formalin fixed).

Noninfectious Causes

Noninfectious causes of abortion in ruminants include the following:

- Heat stress
- Other stress
- Nitrate toxicity
- Malnutrition (rare)
- Pine needle toxicity
- Drug induced (corticosteroids)
- Physical

Infectious Causes

Bovine Herpesvirus 1

Bovine herpesvirus 1 causes IPV and IBR. The latter disease is the major cause of bovine viral abortion. IBR manifests as upper respiratory disease and abortion, and naive herds may experience abortion rates as high as 25% to 60% when exposed. The virus causes clinical signs in both dam and fetus. Immune dams exposed to the virus do not experience abortions. In naive animals the virus is carried in leukocytes and can become localized in placental tissues. Fetuses exposed to the virus usually die within 24 hours of placental infiltration. Although other stages of pregnancy may be affected, 5 to 6 months' gestation is the most susceptible stage. Fetal lesions include renal hemorrhagic edema; acute general necrosis in the liver, spleen, kidneys, lungs, and adrenal glands; widespread hemorrhage; petechia; epithelial destruction; and hepatic necrosis with intranuclear inclusion bodies. The amnion may be thickened without obvious signs of inflammation.

Diagnosis of IBR is by virus isolation from the placenta, identification of intranuclear inclusion bodies in fetal tissues, immunohistochemistry or serum neutralization testing. If the latter is to be used, at least two samples must be taken days apart. The first must be negative and the second positive, or the first must be positive and the second titer must show a fourfold increase. Serum testing may not be helpful because the dam may have been infected months before the abortion and the titer after the abortion may actually be falling.

Prevention of disease is by vaccination (though infection and latency may occur despite vaccination). It is recommended to vaccinate heifers at 6 months and administer a booster 3 to 4 weeks before breeding. A modified live virus is commonly used but is unsafe in pregnant cows from the third to eighth months of gestation. A killed viral vaccine is available for pregnant cow use; a modified live virus vaccine labeled for intranasal administration is also available.[315]

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TABLE 43-8

Major Causes of Bovine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bovid herpesvirus 1, IBR	Fifth to ninth months	Multifocal necrosis with intranuclear inclusions (liver, lung, spleen, kidney)	Histopathology, virus isolation, FA test of frozen fetal kidney
Bluetongue (orbivirus)	Any stage	Anomalies of skeletal and nervous systems	Pathology, virus isolation, fetal serology
BVD virus, pestivirus	Any stage	Anomalies of skeletal, nervous, cardiovascular, respiratory, or other systems	Pathology, FA test on fetal tissues, fetal serology (virus neutralization, ELISA), serologic survey in herd
EBA, foothill abortion, deltaproteobacterium	Third trimester	Lymphadenopathy, splenomegaly, hepatopathy	Pathology, PCR
Brucella abortus, brucellosis, Bang disease	Third trimester	Placentitis, fibrinous serositis, bronchopneumonia	Culture, maternal serology (card test, plate, or tube agglutination)
Campylobacter fetus subsp. *venerealis,* campylobacteriosis, vibriosis	Usually early embryonic death	Placentitis, fibrinous serositis, bronchopneumonia, hepatitis	Pathology, darkfield examination, culture (Clark media), smegma (Clark media)
Histophilus somni (formerly *Haemophilus somnus*)	Any stage	Placentitis	Histopathology, culture
Leptospira interrogans, leptospirosis	Fifth to ninth months	Icterus, edema, renal degeneration and inflammation	Fetal and maternal serology, FA in urine
Leptospira interrogans, listeriosis	Eighth or ninth month	Placentitis	Histopathology, culture
Salmonella Dublin, *Salmonella* Typhimurium	Third trimester	Placentitis	Culture
Aspergillus fumigatus, and all fungal species, mycotic abortion	Third trimester	Placentitis, bronchopneumonia, dermatitis	Histopathology, fungal culture
Sarcocystis cruzi	Third trimester	Protozoa in caruncles	Histopathology or FA of caruncles
Tritrichomonas foetus, trichomoniasis	First half	Placentitis, bronchopneumonia	Microscopic demonstration of organism, culture (Diamond media), PCR
Bovine neosporosis	Mid-gestation	Similar to those found in toxoplasma-aborted sheep fetuses	Histopathology, seroepidemiology

BVD, Bovine virus diarrhea; *EBA,* epizootic bovine abortion; *ELISA,* enzyme-linked immunosorbent assay; *FA,* fluorescent antibody; *IBR,* infectious bovine rhinotracheitis.

TABLE 43-9

Major Causes of Abortion in Sheep and Goats

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bluetongue, orbivirus	Any stage	Anomalies of skeletal or nervous systems	Pathology, IFA, serology
Border disease, pestivirus, hairy shaker disease	Any stage	Dysplasia of skeleton, CNS, and fleece	Pathology, virus isolation, serology (cross-reacts with BVD)
Coxiella burnetii, Q fever	Near term	Necrotizing placentitis	Histopathology, microscopic demonstration of rickettsiae, complement fixation, ELISA
Chlamydia psittaci, EAE	Fourth or fifth month	Necrotizing placentitis	Histopathology, microscopic demonstration of organism, fluorescent antibody on fetal tissues or cultures, paired sera
Campylobacter fetus subsp. *fetus,* vibriosis	Last 6 weeks	Placentitis, serositis, multifocal hepatic necrosis	Pathology, microscopic demonstration of organism, culture
Toxoplasma gondii, toxoplasmosis	Any stage	Necrosis and calcification in cotyledons	Pathology, demonstration of organism, serology (e.g., agglutination, ELISA)

BVD, Bovine virus diarrhea; *CNS,* central nervous system; *EAE,* enzootic abortion of ewes; *ELISA,* enzyme-linked immunosorbent assay; *IFA,* immunofluorescent antibody.

Bovine Virus Diarrhea Virus

Bovine virus diarrhea virus (BVDV) is a pestivirus that can produce early embryonic death, fetal anomalies, or abortion (see Chapter 32 for complete discussion).[315] Isolates from bovine aborted fetuses are usually noncytopathic.[316,317]

History and Clinical Signs Although fetal death is most common during the first trimester, abortion can occur at any stage of gestation.[317,318] Pathogenicity of the disease depends on gestational time of infection, the viral strain, viral biotype (cytopathic or noncytopathic), and fetal immunocompetence.[319] Often there is a history of repeat breeding and a recent episode of febrile disease in the herd before the onset of abortions.[320]

Laboratory Diagnosis Fetal loss generally occurs 10 to 27 days after exposure, with expulsion of the fetus up to 50 days later.[319] As a result the fetus is most often autolyzed, although in some cases it may be mummified or fresh. The aborted fetus may have a variety of dysplastic lesions, including cerebellar hypoplasia; cerebral malformations (hydrencephaly, porencephaly, microencephaly); cataracts; brachygnathia; arthrogryposis; alopecia; thymic hypoplasia; and intrauterine growth restriction.[5,317,320,321] Microscopic lesions

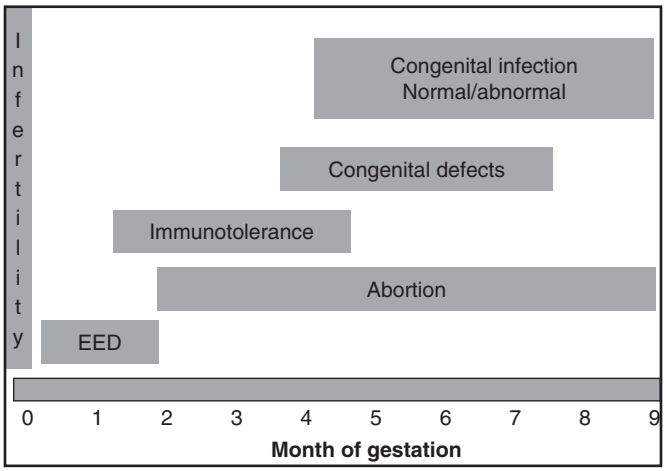


FIG. 43-11 Potential clinical reproductive outcomes after infection with bovine viral diarrhea virus. *EED,* Early embryonic death. *(From Smith KC, Blunden AS, Whitwell KE, et al. 2003. A survey of equine abortion, stillbirth and neonatal death in the UK from 1988 to 1997. Equine Vet J 35:496.)*

include a mild nonsuppurative placentitis. Nonsuppurative vasculitis may be observed in the placenta, liver, or lymph nodes.[320]

Virus isolation from fetal tissue is seldom successful, likely because of the protracted time before fetal expulsion generally occurs after infection. Viral antigen may be detected by FA test on kidney, lung, or lymph node.[320] Virus neutralization and enzyme-linked immunosorbent assay are used to detect antibodies in fetal thoracic fluid, which indicate prenatal exposure to the virus but do not necessarily incriminate BVDV as the cause of abortion. Maternal titers are seldom of diagnostic value because a rise in titer generally occurs before abortion.[5]

Pathophysiology BVDV may be shed in most body secretions. The effects of exposure to BVDV vary greatly depending on the gestational time during which exposure occurred (Fig. 43-11). In seronegative cows, exposure to BVDV at the time of breeding prevents conception.[322] Placental attachment at approximately 35 days' gestation seemingly must precede fetal infection. During the first 4 months of gestation, infection usually causes fetal death and abortion. Fetuses that survive infection with noncytopathic strains between 18 and 125 days of gestation will be persistently infected (PI), are typically seronegative at birth, and subsequently shed BVDV continuously.[319] They may develop mucosal disease later in life from superinfection with cytopathic BVD virus.[323,324] Fetuses infected at between 100 and 150 days of gestation, considered congenitally infected (CI), are at risk for the development of dysplastic lesions including teratologic defects in the brain, skin, or bronchioles. Fetuses infected after 150 days usually recover without dysplastic lesions.[317] Recent evidence, however, suggests that those fetuses born with neutralizing titers to BVDV are more likely to develop a serious illness within the first 10 months of life and less likely to conceive as heifers than those calves born without neutralizing titers to BVDV.[325,326]

Epidemiology Most cattle have serum antibodies to the virus. The abortion rate may approach 25% with new infection of a susceptible herd.[5]

Control BVDV is not fully controlled with vaccination. Herd health plans must focus on elimination of PI animals and prevention of new PI animals being introduced into the herd.

Leptospirosis

Leptospirosis is a spectrum of diseases caused by multiple serovars of *Leptospira interrogans. Leptospira* Hardjo is the major serovar associated with bovine leptospiral abortion, although isolations of *Leptospira* Pomona, *Leptospira* Canicola, *Leptospira* Icterohemorrhagiae, *Leptospira* Grippotyphosa, and *Leptospira* Szwajizak have also been reported.[5,320] Two serologically indistinguishable but genetically distinct types of serovar Hardjo have been identified: *L. interrogans* serovar Hardjo (type hardjo-prajitno), and *Leptospira borgpetersenii* serovar Hardjo (type hardjo-bovis). Serovar Hardjo type hardjo-bovis is cosmopolitan in cattle populations, whereas type hardjo-prajitno is isolated primarily from cattle in the United Kingdom.[320]

History and Clinical Signs In cattle, *Leptospira* Hardjo is associated with infertility, early embryonic death, abortions from 4 months of gestation to term, and birth of weak calves. Abortion rate is usually less than 10% but may approach 50% in some areas.[327] *Leptospira* Pomona abortion usually occurs in the last 3 months of gestation, with an abortion rate as high as 50%.[5] Clinical signs of leptospirosis in the cow may include icterus, hemoglobinuria, anemia, fever, and mastitis that is characterized by a flaccid udder and thick ropy secretions from all four quarters, but usually cows abort without clinical illness.[320] Dead or weak calves may be delivered at term.[327] Abortions caused by serovar Hardjo tend to occur sporadically rather than in storms (as may be seen with serovars Pomona or Grippotyphosa).

Laboratory Diagnosis The aborted fetus is usually autolyzed, icteric, and edematous. Histologically, renal tubular necrosis is accompanied by lymphocytic interstitial nephritis, pneumonia, and placentitis.[5,320]

Leptospires are rapidly destroyed by autolysis or freezing. Isolation from fetal liver, kidney, or brain is possible but slow and impractical. Leptospires may be isolated or demonstrated by darkfield microscopy, FA staining, or histologic techniques in fetal or placental tissues or in the urine of the aborting dam within approximately 2 weeks after abortion.[5,320]

Diagnosis is usually based on serology. A few infected fetuses develop microagglutination titers of 1:10 or more. It is difficult to distinguish among vaccinated, acutely infected, and recovered animals, but titers to *Leptospira* Pomona greater than 1:12,800 in the dam suggest leptospiral abortion. Maternal titer has usually peaked by the time of abortion. Single titers of 1:800 or more in unvaccinated animals, seroconversion, or fourfold changes in titers in paired sera indicate leptospirosis in the herd. Titers to *Leptospira* Hardjo are often less than 1:100 in affected cows and seldom exceed 1:1600.[320]

Pathophysiology Hematogenously spread leptospires colonize the gravid uterus up to 142 days after infection. Abortion occurs 1 to 6 weeks after acute disease with *Leptospira* Pomona infection and 1 to 3 months with *Leptospira* Hardjo.[5] *Leptospira* Hardjo remains in the oviducts of infected cows up to 22 days after calving.[327]

Epidemiology *Leptospira* organisms are ubiquitous and an important cause of abortion in all cattle-producing regions. *Leptospira* organisms persist in the genital tract and kidneys. The organisms localized in the kidneys of infected animals are shed in the urine and serve as a source of infection for other animals. The organisms localized in the female reproductive tract are responsible for abortions. Aborted tissues are infectious to other animals and humans and should be handled with caution.[328,329] Vaccination may be useful in endemic areas.

Treatment and Control In abortion outbreaks, pregnant cows can be vaccinated with killed bacterin and treated with oxytetracycline (antibiotic treatment can be limited to sick cows in dairy herds).[330] Aborting cows should be isolated and treated with streptomycin if they are not destined for slaughter. Aborted fetuses and placentas should be removed from the premises.[331] Preventing exposure to swine, rodents, and contaminated water lessens the opportunities for infection.[5,248] *Leptospira* Pomona usually has no permanent effect on fertility, but infection with *Leptospira* Hardjo has been associated with persistent herd infection and recurring abortions.[5]

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Herd vaccination is recommended at 6-month intervals or more frequently in areas with heavy exposure to leptospires. Vaccination programs are aimed at reducing urinary shedding of leptospires and decreasing fetal loss. However, a commercial pentavalent leptospiral vaccine (*Leptospira* serovar Hardjo type hardjo-prajitno is used for the *Leptospira* Hardjo component of U.S. Department of Agriculture [USDA]–licensed leptospiral vaccines) did not prevent renal colonization, urinary shedding, or fetal infection after conjunctival instillation of cows with serovar *Leptospira* Hardjo type hardjo-bovis (the only type of *Leptospira* Hardjo isolated from cattle in the United States).[332]

Epizootic Bovine Abortion (Foothill Abortion)

Epizootic bovine abortion (EBA) or foothill abortion is a syndrome of late abortions in cattle in the foothills bordering the central valley of California.[333] Once thought to be caused by *C. psittaci* or a spirochete-like organism, studies have demonstrated that EBA differs from chlamydial abortion.[333] After decades of research, a novel deltaproteobacterium was identified as the causative agent of EBA in 2005.[334,335]

History and Clinical Signs Late abortion or delivery of weak calves occurs in affected herds. Many fetuses in the sixth to seventh month of gestation may be aborted, especially from heifers without premunition immunity from natural exposure to the causative agent. Older native cows show no clinical signs of infection.

Laboratory Diagnosis A 3-month period is required for full development of pathologic changes in the fetus. Superficial cervical lymph nodes are enlarged up to 16 g, the spleen is enlarged up to 250 g, the thymus is slightly smaller than normal, and the liver may be enlarged and nodular.[320,333,336] Histologically there is loss of thymic cortical lymphocytes; remaining lymphocytes are enlarged and poorly differentiated. Follicular hyperplasia, histiocytosis, vasculitis, necrosis, and pyogranulomas occur in lymph nodes and spleen. Lymphohistiocytic proliferation may also occur around vessels in the liver, lung, and meninges.[320]

EBA has been diagnosed mainly by pathologic examination of the fetus along with a compatible clinical scenario. Studies have demonstrated high levels of IgG (3 mg/mL or more) in fetal blood.[320,333] This deltaproteobacterium is detectable in fetal tissues with PCR with reported sensitivity and specificity values of 88% and 100%, respectively.[334] Recent advances in real-time PCR assays are promising for diagnosis and may become the standard in the future.[337] Currently no serologic test for EBA exists.

Pathophysiology Infection is transmitted by the soft-shell tick *Ornithodoros coriaceus* (Pajaroello tick).[336,338] The disease can also be transmitted with fresh or frozen fetal tissue.[333] Transformation and proliferation of fetal lymphocytes and macrophages occur by 50 days but are not severe enough for diagnosis until 100 days after maternal exposure to the tick vector. IgG and IgM are deposited in vascular lesions, but increase in fetal serum immunoglobulin is not detectable until at least 80 days after tick exposure.[333,338] Repeated superinfection may be necessary to result in fetal death.[336] Because at least 90 days are required for development of fetal lesions, infection after 6 months' gestation is not likely to result in abortion.[5,320]

Epidemiology EBA was limited to the range of the tick vector in the foothills bordering the central valley of California; however, it has also been identified in regions of Oregon and Nevada.[333,335] Of the annual calf loss in California, 5% to 10% is attributed to EBA.[338] The prevalence of infection by the spirochete is far greater than the prevalence of abortion.[336] Abortion occurs 3 to 4 months after exposure to ticks but almost always late in gestation, regardless of the time of tick exposure.[339] Older native cows from enzootic areas usually do not abort, and introduced cows and heifers generally abort only once.[333] The abortion rate may be 30% to 80% in susceptible animals.[320,339]

Treatment and Control Chlortetracycline therapy (2 to 5 g/day in the feed) reduces the rate of abortion.[338] Currently no vaccine exists for EBA, but abortions can be controlled by exposing heifers to the tick vector before breeding or by changing from spring to fall calving,[5] which takes advantage of limiting exposure to the last trimester of gestation in some management systems. Therefore exposure of susceptible pregnant cattle to the tick only after the sixth month of pregnancy is a practical solution for ranchers using summer foothill pastures and fall calving. The tick lives in ground duff (e.g., leaves) and is not found on cattle that graze in irrigated pastures and most other areas outside of brushy foothills.

Brucella abortus Abortion

B. abortus infection (Bang disease) causes abortion in cattle and, less commonly, in sheep and goats. Horses may be infected with *B. abortus,* which has been associated with fistulous withers, but usually experience no infertility, abortion, or other clinical evidence of infection. Bovine infections are caused by eight biovars of *B. abortus,* three of which (biovars 1, 2, and 4) are recognized in the United States.[5]

History and Clinical Signs Abortion is the chief clinical sign of bovine brucellosis and usually occurs after the fifth month of gestation. Lameness, mastitis, epididymitis, and/or orchitis may be present in infected herds.[340]

Laboratory Diagnosis Autolysis frequently obscures gross lesions in the fetus, but fibrinous serositis may be apparent, and abomasal content may be discolored and flocculent. Placentitis is a consistent finding. Cotyledons are necrotic; the intercotyledonary placenta is thickened and opaque with accumulation of odorless, flocculent, yellow-brown exudate between maternal and fetal membranes. Histologically there is suppurative placentitis (and endometritis in the dam). Suppurative bronchopneumonia and lymphoreticular hyperplasia are frequent histologic findings in the fetus.

Diagnosis depends on culture of *B. abortus* from fetal lung, abomasum, or placenta or from maternal uterine or mammary secretions. Organisms and *Brucella* antigen can be detected in fetal tissues by avidin-biotin-peroxidase complex immunostaining.[341]

No serologic test is 100% accurate, but a positive card test or titer of 1:100 or more on plate or tube agglutination suggests brucellosis. False-negative serologic reactions occur in approximately 15% of infected cows, particularly just before or after parturition. False-positive reactions are a problem in cows vaccinated with strain 19. Supplemental tests such as the Rivanol test, complement fixation, and mercaptoethanol sensitivity of agglutination are used in suspect cases. Dairy herds are surveyed by the *Brucella* ring test on milk.[5] In goats, tube agglutination titers of 1:25 or more indicate infection.[340]

Pathophysiology Initial replication of *B. abortus* occurs in regional lymph nodes. Bacteremia is followed by colonization of supramammary lymph nodes, the mammary gland, and the gravid uterus. Uterine infection occurs during the second trimester.[5,342] In the placenta the bacteria appear first in phagosomes of erythrophagocytic trophoblasts. Replication occurs in the rough endoplasmic reticulum of chorioallantoic trophoblasts.[342] Preferential replication in chorioallantoic trophoblasts has been attributed to their erythritol content; however, the placentas of several laboratory rodents that lack detectable erythritol still support *B. abortus* replication.[343] The organism also occurs in fetal placental endothelial cells and capillary lumina, where it is associated with vasculitis and destruction of chorionic villi. Placental inflammation spreads along the allantochorion to involve additional cotyledons with resultant chorioallantoic ulceration, necrosis of trophoblasts, and ulcerative endometritis. Fetal death results from placental disruption and endotoxemia.[5,342] The fetus is frequently retained 1 to 3 days in utero. Numerous bacteria are expelled from the genital tract at parturition, but shedding usually stops by 3 weeks after abortion.[5]

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Epidemiology Infection with *B. abortus* occurs naturally by ingestion. Contaminated materials are infectious for humans and should be handled with caution. Infection is not easily transmitted between cattle separated by fences or roads.[344] Most calves infected at birth clear the infection, but persistent congenital infection has been documented.[345,346]

Bovine brucellosis has been nearly eradicated in the United States by test and slaughter of seropositive cattle and vaccination. However, a reservoir remains in bison and elk, especially in the greater Yellowstone area.

Treatment and Control Treatment of brucellosis is usually not effective. Combination therapy with long-acting oxytetracycline and streptomycin has been shown to reduce shedding in most cows and potentially eliminate infection in some,[347] but because of the eradication program used in many countries, infected cows are rarely treated. In the United States, infected individuals are destroyed and exposed herdmates are quarantined to the herd until slaughter or the herd is recertified as brucellosis free (U.S. Department of Agriculture, 2003).

In the past, strain 19 vaccine was used as part of the eradication program. However, vaccinated and field strain–infected cattle could not be differentiated. A newer vaccine for *B. abortus,* vaccine strain RB51, was developed to overcome the serologic problems associated with the strain 19 vaccine.[348] Animals vaccinated with RB51 lack antibodies to the *O*-polysaccharide chain and can thus be distinguished from field-infected cattle. Strain RB51 is also less abortifacient for cattle than strain 19, although vaccination of pregnant heifers may result in abortion and subsequent zoonotic exposure if obstetric assistance is necessary (Centers for Disease Control, Morbidity and Mortality Weekly Report, March 13, 1998), so the vaccine is to be administered only to young heifers before pregnancy.[348,349]

Campylobacter fetus subspecies *venerealis* Abortion

C. fetus subsp. *venerealis* is the main cause of bovine campylobacteriosis (vibriosis).[5] The organism is an obligate parasite of the bovine genital tract and is not known to cause disease in other species.[320]

History and Clinical Signs Infection with *C. fetus* subsp. *venerealis* mainly causes temporary infertility or early embryonic death, but sporadic abortions from the fourth to eighth months of gestation are possible.[320] The usual history includes a high percentage of cows exposed for the first time returning to estrus or found nonpregnant after the breeding season and cows calving late because they returned to estrus one or more times.

Laboratory Diagnosis Autolysis is usually minimal, and the lungs of the term fetus may be partially inflated. Dehydration, fibrinous serositis, and necrotizing placentitis may be apparent grossly. Histologically, bronchopneumonia and hepatitis may also be evident. Diagnosis is based on demonstration or isolation of the organism. By darkfield microscopy the bacterium appears as a curved rod with darting corkscrew motility[320] and can be differentiated from other *Campylobacter* spp. by immunohistochemistry.[315] Cows that abort may have serum antibody titers; however, they may not be diagnostic because they are not specific for *C. fetus* subsp. *venerealis.* Culture from placenta or fetal abomasal contents requires at least 72 hours. The vaginal mucus agglutination test is used to survey herds for infection.[5] Alternatively, the penis and preputial mucosa of infected bulls may be swabbed and cultured, although culture is difficult because the organism is slow growing and often overwhelmed by saprophytes.

Pathophysiology Within a week of vaginal infection the organism is established in the uterus, causing mucopurulent endometritis, which persists 3 to 4 months. Intrauterine infection either prevents conception or causes embryonic death, and infected heifers typically return to estrus by 40 days. Less commonly, abortions occur at up to 8 months of gestation.[5,320]

Epidemiology *C. fetus* subsp. *venerealis* is ubiquitous. Venereal transmission from infected bulls to virgin heifers approaches 100%. Cows with previous exposure to infected bulls develop immunity and therefore are less likely to experience infertility than heifers. The abortion rate seldom exceeds 10%.[320]

Treatment and Control Infected cows usually recover spontaneously within 5 months and resist reinfection. Recovery is hastened by intrauterine infusions of streptomycin and penicillin. Infertility may be permanent if endometritis or salpingitis is severe.[5] Heifers should be vaccinated with a bacterin before breeding. Most vaccines are administered 1 month before breeding and require a booster vaccination 2 weeks later (Vibrin, SmithKline Beecham Animal Health, Exton, Pa., and Trivib-5L, Fort Dodge Labs, Fort Dodge, Iowa). Higher than normal doses of vaccine may be necessary to clear the infection from bulls. Cows and bulls must be vaccinated annually. Exclusive use of *C. fetus* subsp. *venerealis*–negative semen via AI controls the disease by preventing transmission.

Histophilus somni Abortion

Histophilus somni (formerly *Haemophilus somnus*) has been associated with vulvitis, vaginitis, endometritis, weak calf syndrome, stillbirths, and occasional abortion in cattle.

Laboratory Diagnosis Aborted fetuses have been free of gross lesions. Necrotizing placentitis is associated with fibrinoid necrosis of placental arteries.[253] Diagnosis is based on recovery of large numbers of the organisms in relatively pure culture from placenta or fetus, histologic evidence of placentitis, and lack of other apparent causes.

Interpretation of maternal titers to *H. somni* is difficult, and it is best to take paired serum samples. Titers between 1:256 and 1:512 in nonvaccinated herds may be the result of early active or chronic infection. Titers between 1:1040 and 1:4096 indicate recent active infection. A fourfold change in titer in paired sera is the best indicator of active infection.

Pathophysiology Although *H. somni* can be isolated from the genital tract of clinically normal cows,[240] the rate of isolation is higher in cows with endometritis or cervicitis.[253] Experimentally, *H. somni* can adhere to zona pellucida–intact embryos and cause degeneration.[350] Vaginitis can be induced by inoculation with *H. somni,*[351] and abortion has been induced by intraamniotic, intravenous, or intrabronchial challenge with the organism.[352] Cervical infusion with the organism has resulted in colonization of the chorioallantois and placentitis, but calves were born alive without culturable *H. somni.*[353]

Treatment and Control Antibiotic treatment and vaccination anecdotally increase fertility in herds affected with *H. somni*–induced vulvovaginitis.[253]

Listeria monocytogenes Abortion

Listeriosis is caused by *L. monocytogenes.* Listerial abortions are of importance mainly in ruminants.

History and Clinical Signs Bovine abortions usually occur in the last 2 months of gestation.[320] Infected ewes and does typically abort in the last month.[5] Fever, depression, RFMs, or endometritis may occur,[5,320] but often the dam shows no clinical signs of infection.

Laboratory Diagnosis In less severely autolyzed fetuses, fibrinous polyserositis may be apparent. Most aborted fetuses have gray-white hepatic foci up to 2 mm in diameter. Similar foci may be visible in cotyledons; exudation occurs between cotyledons. Abomasal erosions have been reported in aborted lambs.[320] Histologically, suppurative placentitis and endometritis are consistent findings.

Listeria is readily cultured from abortuses without cold enrichment. Serovars 1 and 4b are commonly isolated from bovine fetuses;

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serovars 4b and 5 are the usual ovine isolates.[320] *Listeria* appears in impression smears as gram-positive pleomorphic coccobacilli.[320]

Pathophysiology Listerial abortion can be induced experimentally in cattle 6 to 8 days after infection and in sheep 3 to 11 days after infection. Fetuses die from placentitis and septicemia and are often retained in utero several days before expulsion.[320]

Epidemiology Listerial abortion is usually sporadic, and incidence seldom exceeds 15%.[320] Infection is most common in the winter and has been associated with feeding of silage. The elevated pH of spoiled silage enhances multiplication of the organism. Aborted tissues are infectious for humans and should be handled with care.

Treatment and Control The effect on fertility is usually transient, and aborting animals tend to resist reinfection. Tetracycline may be used in remaining pregnant animals in the herd.[5] Aborting animals should be segregated, and fetuses and placentas should be removed from the premises. The feeding of spoiled silage should be avoided.

Mycoplasma Abortion

Mycoplasmal isolations from the bovine genital tract have been mainly *M. bovigenitalium* and *Mycoplasma bovis*. *M. bovis* is probably the more important cause of abortion.[354] *Mycoplasma mycoides* subsp. *mycoides* (see Chapter 38 for complete discussion) and *Mycoplasma agalactiae* have been associated with caprine abortions.[5]

History and Clinical Signs *M. bovigenitalium* is associated with granular vulvovaginitis and less commonly with endometritis, especially in heifers. Infertility is more common than abortion. *M. bovis* causes mastitis and abortion.[354] In goats, mycoplasmal infection is associated with septicemia, arthritis, pneumonia, mastitis, and abortion.[5]

Laboratory Diagnosis Placentitis and fetal pneumonia have been associated with bovine mycoplasmal abortion.[354] Isolation of *Mycoplasma* from the genital tract, milk, placenta, or fetus indicates infection. However, mycoplasmosis should not be considered the cause of abortion unless placentitis or fetal inflammation is present and other more likely causes of abortion have been eliminated.

Pathophysiology *M. bovigenitalium* can be isolated from the vagina in up to 12% of clinically normal cows, but *M. bovis* is isolated from less than 1%. Vulvitis can be induced by inoculation with mucosal scarification with *M. bovigenitalium;* therefore venereal transmission may be the natural route of infection.[5,354] Experimental inoculation with *M. bovis* induces abortion with placentitis and fetal pneumonia.[354,355] *M. bovigenitalium* is rarely isolated from abortuses or normal fetuses.[5]

Epidemiology *Mycoplasma* spp. are ubiquitous, but mycoplasmal abortions are not commonly documented.

Treatment and Control Tetracycline or tylosin is the recommended antibiotic for mycoplasmal granular vulvovaginitis in heifers.[354]

Salmonella Abortion

A variety of *Salmonella* serotypes have been isolated from aborted fetuses of cattle, sheep, goats, and horses. A complete discussion of salmonellosis is presented elsewhere. Infection is acquired by ingestion of contaminated feed or water. Maternal septicemia is followed by localization of salmonellae in tissues, including the pregnant uterus, where placentitis and fetal septicemia occur. Salmonellosis accompanied by endotoxemia causes early pregnancy loss without colonization of the uterus because the infection and endotoxemia cause endogenous prostaglandin release. Endogenous $PGF_2\alpha$ initiates luteolysis and abortion in the first trimester (<100 days for cattle), as is the case with exogenous administration of PGF products.

History and Clinical Signs The animal may show systemic signs before abortion. Although abortion may occur at any stage of gestation, it typically occurs in the second half and is characterized by placental necrosis, edema, and hemorrhage. RFMs and fetal autolysis may occur. Abortion may be accompanied by diarrhea, fever, or vaginal discharge, particularly in the ewe, but often infection is not clinically apparent in the dam.[315,320,356,357] Fetuses also may be lost as a result of stillbirth or perinatal septicemia.

Laboratory Diagnosis The fetus is frequently autolyzed. Placentitis is usually present. Diagnosis is based on isolation of the organism and evidence of placentitis or inflammation of fetal tissues. FA techniques can identify the bacteria in impression smears or sections of placenta or fetal tissue.[320] The dam can be tested serologically for evidence of recent active infection,[356] but at present many diagnostic laboratories do not perform *Salmonella* serology.

Pathophysiology Infected adult animals are often short-term carriers and shed salmonellae in the feces or milk. True long-term asymptomatic carriers occur mainly with the host-adapted serotypes: *Salmonella* Dublin in cattle, *Salmonella abortus ovis* in sheep, and *S. abortivoequina* (or *Salmonella abortus equi*) in horses. Salmonellosis caused by *Salmonella abortus equi* has been eradicated in the United States. Occasionally, long-term carriers of other serotypes are seen; these are usually intestinal carriers and fecal shedders. Infection usually occurs by ingestion. There is no evidence of venereal transmission.[356] Maternal septicemia is followed by localization of the organism in a variety of tissues, including the pregnant uterus. The bacteria multiply in and cause necrosis of connective tissues of the cotyledon.[356] The incubation period between infection and abortion varies from approximately 1 week to 1 month.[5,357] Fetal death results from placentitis and fetal septicemia.[320,358] In most cases, maternal shedding of the organism in cattle ceases by 5 weeks after calving.[356]

In a second mechanism of *Salmonella*-induced abortion, *Salmonella* septicemia causes endotoxemia and release of endogenous PGF, which causes luteolysis and abortion. In this case the fetus and placenta are culture negative for salmonellae.

Epidemiology Bovine abortion resulting from salmonellosis is caused mainly by *Salmonella* Dublin and *Salmonella* Typhimurium. Abortion is sporadic and most common in the summer and fall.[356]

Ovine abortion is associated with *Salmonella* Typhimurium, *S.* Dublin, *Salmonella* Arizona, and *Salmonella abortus ovis*. *Salmonella abortus ovis* (which infects only sheep) is enzootic in parts of England and Europe but is not reported from the United States.[5,320] Young ewes in late gestation are most susceptible, and the abortion rate may approach 50%,[5,357] but usually only one or two ewes in a flock abort.[320]

Treatment and Control Metritis is a rare complication of salmonellosis that can be fatal.[320] Usually there is no lasting effect on fertility, but animals infected with host-adapted serotypes may become carriers and should be cultured and tested serologically and culled if positive. Salmonellosis can be controlled by hygiene and by avoiding the introduction of carrier animals. Aborting animals should be isolated; the fetus, placenta, and contaminated material should be removed from the premises. *Salmonella* spp. are infectious for humans; therefore aborted tissues should be handled with caution.

Ureaplasma Abortion

Ureaplasma is a small bacterium without cell walls; it differs from *Mycoplasma* in its ability to hydrolyze urea. *U. diversum* has been associated with granular vulvitis and abortion in cattle.

History and Clinical Signs Granular vulvitis appears as reddish nodules in the vulvar mucosa, with mucopurulent discharge in the early stages. The discharge is usually more copious and protracted than with IPV induced by herpesvirus.[5,354] Affected cows are not systemically ill.[320] The organism has been recovered from embryo

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flushing media and can adhere to the zona pellucida, resisting removal by washing. It is believed to be responsible for an 18% reduction in pregnancy rate in embryo recipients when the transfer medium contains the organism.

Laboratory Diagnosis Gross lesions include thickening of placental membranes with foci of hemorrhage and fibrinous exudate. Gross lesions are seldom apparent in the fetus. Microscopically the placenta is fibrotic, with heavy mononuclear cell infiltration, multifocal necrosis, fibrin deposition, and mineralization. Cuffs of lymphocytes surround fetal intrapulmonary airways.[320] Diagnosis is based on isolation of the organism from genital mucosa, placenta, or fetal stomach or lung and the presence of genital or fetal inflammation.

Pathophysiology *Ureaplasma* can be isolated from the genital tract of normal cows and from normal fetuses.[359] Vulvitis has been induced by inoculation of virgin heifers with *U. diversum.*[359] Uterine involvement is considered rare but may cause conception failure, early embryonic death, or abortion. Abortion presumably results from placentitis.[5] Intraamniotic inoculation of *U. diversum* caused placentitis, abortion, and fetal alveolitis in two of four experimental cows.[359] One cow delivered a weak calf at term. Experimental infection in ewes did not decrease fertility.[360]

Epidemiology Bovine infection is common, but documented abortions caused by *Ureaplasma* are rare.[354] Infertility is more common in heifers than in cows.

Treatment and Control Nonirritating tetracyclines by intrauterine infusion are recommended for treatment. Products may not be approved for intrauterine use.[5] Uterine contamination can be avoided by use of the double-rod technique of AI.[5]

Miscellaneous Bacterial Abortions

In addition to the aforementioned bacteria, other bacteria occasionally produce maternal septicemia. Many of these bacteria are ubiquitous, frequently contaminate aborted fetuses and placentas, and should not be considered the cause of abortion unless (1) they are isolated from the placenta and fetus in large numbers and relatively pure culture, (2) placentitis or fetal inflammation is evident, and (3) other more likely causes of abortion have been eliminated.[320]

In cows, most bacterial infections of the uterus result from septicemia. Miscellaneous bacterial causes of infertility and abortion include *A. pyogenes, E. coli, Bacillus* spp., *Pasteurella* spp., *Staphylococcus* spp., *Streptococcus* spp., *F. necrophorum,* and *Bacteroides melaninogenicus.*[320]

A. pyogenes, with or without accompanying anaerobes, has been associated with pyometra and abortion in cattle.[234,320] Abortions are sporadic and may occur at any stage of gestation. Clinical signs are seldom apparent in the cow. The fetus is commonly autolyzed, and placentitis is typical. Polyserositis may be evident. In fetuses aborted in the first half of gestation, 1-mm yellow foci (bacterial colonies) may be grossly apparent in the lung.[320]

In the ewe or doe, miscellaneous bacterial causes of abortion include *Staphylococcus aureus, Streptococcus* spp., *Pasteurella* spp., *E. coli, Yersinia pseudotuberculosis, Francisella tularensis, Histophilus ovis, Bacillus* spp., *A. pyogenes,* and *Corynebacterium* spp.[320,361-364]

A spirillum-like organism has been documented as a cause of ovine abortion, fetal mummification, stillbirth, and birth of weak lambs. Abortion generally occurs in the last 2 weeks of gestation. Placentitis is consistently present; many fetuses also have fibrinous peritonitis and focal hepatic necrosis that resemble that of campylobacteriosis.[365] Abortion can be reproduced experimentally by inoculation of pregnant ewes.[366] Diagnosis is based on pathologic lesions and identification of the spindloid flagellated organism by darkfield microscopy of fetal abomasal content or liver or by anaerobic culture on selective medium.[365,367]

Tritrichomonas foetus

Trichomoniasis is a venereal infection of cattle caused by the flagellated protozoan *T. foetus.*[5,235,320,368,369]

History and Clinical Signs Infertility characterized by a high percentage of cows returning to estrus or found nonpregnant after the breeding season and cows calving late plus occasional pyometras and abortions are the most common clinical signs of trichomoniasis. Pyometra in postcoital heifers or cows suggests that trichomoniasis may be the cause. Abortions generally occur in the first half of gestation at a rate of 5% to 30%.[368] The placenta may be expelled or retained.[5,320]

Laboratory Diagnosis Diagnosis in the female is made by culturing trichomonads or using PCR to detect *Tritrichomonas* from cervicovaginal mucus (≈76% sensitivity), uterine exudate, placental fluids, or fetal abomasal contents.[5,235,320,368,369] Preputial smegma collected from bulls by using a plastic pipette run against the mucosa can also be cultured for trichomonads (sensitivity 80% to 90%). Diamond medium (or modified Pastridge medium) is recommended for cultures from cows, bulls, or aborted fetuses.[369] The organism is sensitive to environmental conditions, and thus samples should be transported at ambient temperature, kept out of sunlight, not refrigerated, and delivered promptly to the diagnostic laboratory. The organisms are identified microscopically by their size (10 μm × 15 μm), the presence of three anterior flagellae and an undulating membrane, and a characteristic jerky, rolling motion.[320] PCR is often used now for identification of *T. foetus* because of its ability to differentiate *T. foetus* from contaminant, nonpathologic trichomonads. Due to the ability of *T. foetus* to degrade its DNA postmortem, improper sample handling may lead to false-negative results on both culture and PCR testing.[370]

There are no specific gross lesions in aborted fetuses. However, placentitis is a consistent microscopic lesion, and trichomonads can frequently be recognized in the placental stroma in histologic sections. Organisms may also be observed in the fetal lung in association with pyogranulomatous bronchopneumonia.[371]

Pathophysiology Trichomoniasis is transmitted venereally from infected bulls to cows or vice versa. The organisms colonize the vagina, cervix, uterus, and oviducts, yet they do not generally interfere with conception. Embryonic death frequently occurs within the first 2 months of infection,[5] followed by a 2- to 6-month period of immunity to reinfection.[235] Clearance of infection in cows commonly occurs within 95 days; infection rarely persists as long as 6 months.[368] However, infection in bulls older than 4 years of age is permanent and the main source of carryover from one breeding season to the next in beef cattle.[235]

Treatment and Control Systemic treatment of infected animals with imidazole compounds (ipronidazole, dimetridazole) is effective, but these compounds are prohibited in food animals in the United States.[372,373] Infected cows should be either culled or given at least 3 months of sexual rest. The use of AI with semen from *T. foetus*–negative bulls controls the disease once infected natural service bulls have been removed from the herd. In natural breeding situations, vaccination, use of young virgin bulls, and testing and elimination of positive bulls older than 3 years of age will allow herd owners to gain control over the incidence of trichomoniasis.

Neospora caninum Abortion

Abortion in cattle caused by *N. caninum* is relatively common and of economic importance, especially in dairy cattle. Congenital infection with limb paresis or dysfunction at birth as a result of encephalomyelitis may also occur. Canids are the definitive hosts and shed oocysts in their feces after ingestion of infected tissues from intermediate hosts (Fig. 43-12). Both the domestic dog and the coyote have been shown to transmit the oocysts in their feces.[374-376] Along with cattle,

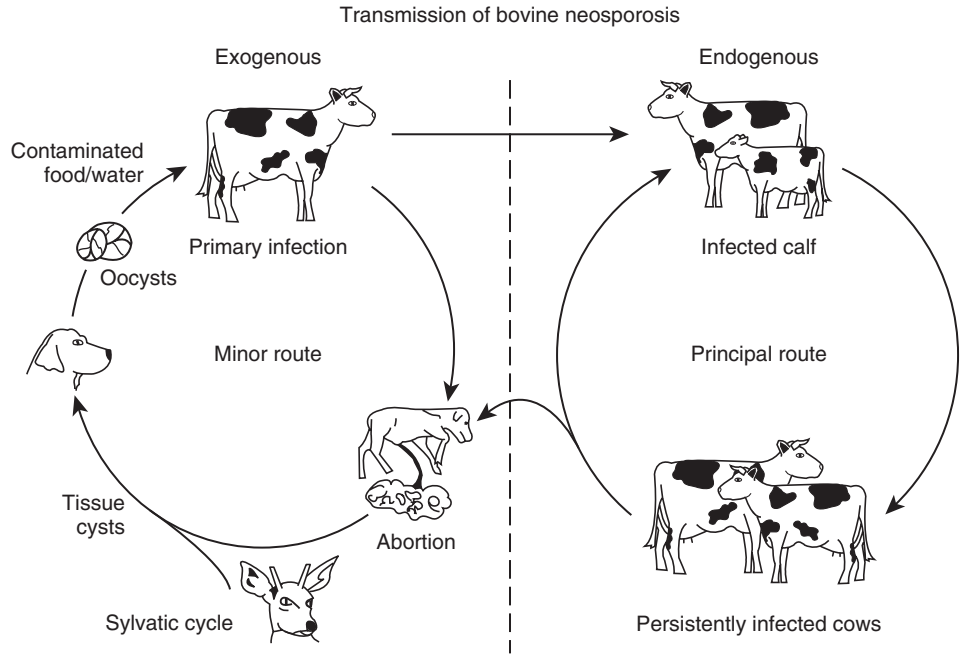


FIG. 43-12 Transmission of bovine neosporosis. Oocysts are produced by the canine definitive host, and their subsequent ingestion by a susceptible pregnant cow leads to infection of the fetus (exogenous transplacental transmission). Liveborn infected heifer calves would be expected to remain infected into adulthood, when they, in turn, may pass infection to their fetuses (endogenous transplacental transmission). Spread of *Neospora caninum* in this second way is the principal route whereby the parasite is propagated in a herd.

deer have been shown to serve as intermediate hosts.[376] The role of birds and wild rodents as intermediate hosts is suspected but has not yet been definitively demonstrated.[376] Aborted, infected fetal tissues ingested by canids will also result in massive shedding of oocysts in feces.[377] Transmission may be vertical (dam to fetus in utero) or via point-source horizontal transmission (ingestion of feed contaminated with feces containing oocysts).[378,379] Horizontal transmission from cow to cow does not occur. Bovine fetal lesions are distinctive and may include nonsuppurative encephalitis with foci of necrosis and gliosis, nonsuppurative myositis, hepatitis, and, most consistently, myocarditis.[349] Most abortions occur in the early second trimester, but they may occur throughout gestation. Diagnosis is based on characteristic lesions in aborted fetuses and seroepidemiologic study of an equal number of aborting and nonaborting herdmate cows if the proportion of seropositives is statistically higher in those that have aborted.[380] Finding one aborting cow to be seropositive does not confirm *N. caninum* as the cause, and cows that abort once because of *N. caninum* are not protected from future abortion caused by this organism. A vaccine based on whole killed tachyzoites (Neoguard1, Intervet, Millsboro, Del.) is available for *N. caninum.*

Sarcocystis Abortion

Sarcocystosis may cause abortion in cattle, sheep, and goats. Cattle are infected by *Sarcocystis cruzi,* sheep by *Sarcocystis ovicanis,* and goats by *Sarcocystis capracanis.*

History and Clinical Signs Most cattle are infected with *Sarcocystis* but do not show clinical signs of infection; however, massive or repeated infections may elicit depression, anorexia, weight loss, lameness, hair loss, emaciation, or death. Abortions occur in late gestation, usually in severely affected animals.[320,381,382]

Laboratory Diagnosis There are no specific gross lesions in the aborted fetus. Histologically protozoa may be observed in villi and small arteries of the cotyledon or (more likely) the caruncle but are seldom seen in the bovine, ovine, or caprine fetus. Parasites are more likely to be observed in the fetal brain than in other tissues.[381] Nonsuppurative inflammation may occur in the placenta or, less commonly, in fetal tissues, particularly the brain, heart, lung, liver, or kidney.[320,381,382]

FA demonstration of numerous developing protozoa in the cotyledon or caruncle is considered diagnostic. Caruncles are reported to be atrophied.[381] The protozoa can also be isolated by feeding aborted tissues to canids and recovering coccidian sporocysts from their feces.[320]

Pathophysiology The pathogenesis of abortion in sarcocystosis is unclear. Generally, numerous spores are required to induce abortion experimentally. Fetal invasion by *Sarcocystis* is rare, and abortion may result from maternal fever, anemia, or placental insufficiency.[381] Pregnant does apparently have diminished immunity to *Sarcocystis* because low doses of *S. capracanis* result in fetal death without maternal illness if given in early pregnancy.[383]

Epidemiology Ruminants are infected by consumption of canid feces that contain oocysts. *Sarcocystis* occurs in the skeletal and cardiac muscle of most cows without associated lesions or clinical evidence of illness.

Control Effective therapeutic regimens for clinically ill animals have not been developed. For the lifecycle of *Sarcocystis* to be broken, feeds should be kept free of dog or cat feces. These carnivores should not be allowed to eat aborted fetuses, placentas, or other ruminant carcasses.

Fungal Abortions

Mycotic Diseases That Cause Abortion

Fungal causes of bovine abortion include *Aspergillus, Absidia, Mucor, Rhizopus, Candida,* and *Mortierella.*[320,384,385] Mycotic abortion is uncommon in sheep and goats.[320]

History and Clinical Signs Mycotic abortions usually occur in the latter half of gestation (often near term) and seldom are associated with prodromal or postabortion clinical signs in the dam.

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Laboratory Diagnosis The most consistent lesion is placentitis with necrosis and thickening of fetal membranes. In ruminants, both cotyledons and the intercotyledonary placenta are affected. Histologically, necrotizing inflammation of the chorionic villi is associated with vasculitis and thrombosis.[320] Gross lesions may not be apparent in the fetus, but granulomatous bronchopneumonia is frequently observed histologically.[320,385-387] In bovine aspergillosis the fetus is often near term with minimum autolysis and partially inflated lungs. Emaciation and dehydration with multifocal dry, scaly skin lesions occur in approximately 25% of affected fetuses.[320] With other fungi the aborted fetus is often autolyzed, placentitis may be more severe, and skin lesions, if present, tend to be moister than those of aspergillosis.[320] The placenta is characteristically thickened and leathery. The fetus may be emaciated, and granulomatous bronchopneumonia has been observed.[386] The fungus can be isolated from the fetus and placenta or demonstrated on histologic sections with immunostaining.

Pathophysiology The route of fungal infection in the bovine uterus is thought to be hematogenous.[13]

Epidemiology Mycotic abortion generally affects only one or two animals in a herd and is more common in the winter.[320] Fungi cause 3% to 10% of bovine abortions.[388,389] *Aspergillus* accounts for up to 80% of bovine mycotic abortions; *Mucorales* account for an additional 10% to 15%.[5] *Mortierella* is a common abortifacient in Australia and New Zealand and has been associated with feeding of grass silage,[385,389] but *Mortierella* abortion is rare in the United States.

Control The only means of control of mycotic abortion is reduction of exposure to fungal agents.

DOES AND EWES
Infectious Causes

See Table 43-9.

Bluetongue Abortion

Bluetongue is an orbivirus infection that can result in embryonic death, abortion, and fetal anomalies in sheep, cattle, or other ruminants. Twenty-four serotypes of bluetongue virus have been recognized; five of these (serotypes 2, 10, 11, 13, and 17) occur in the United States (see Chapter 32 for complete discussion).[390]

Border Disease (Hairy Shaker Disease)

Border disease or hairy shaker disease is an ovine pestivirus infection that causes embryonic and fetal death; stillbirths; dysplasia of the central nervous system, skeleton, and fleece; and birth of weak lambs with low viability.

Coxiella burnetii (Q Fever)

Coxiella burnetii, a rickettsia, is the causative agent of Q fever, which can cause abortions in sheep and goats. Most infections are completely asymptomatic, and the disease is of more importance as a zoonosis than as a cause of ovine or caprine abortion.

History and Clinical Signs Late abortions or delivery of weak lambs may occur in an affected flock over a period of 2 to 4 weeks.[5,357]

Laboratory Diagnosis There are no specific gross lesions in the fetus, but the placenta is thickened with white, chalky plaques and red-brown exudate, especially in intercotyledonary areas. Histologically cotyledonary and intercotyledonary necrosis is accompanied by heavy neutrophil infiltration.[5,391] Diagnosis of Q fever abortion should be based on the presence of characteristic placental lesions with large numbers of rickettsiae and a rising maternal titer. Rickettsiae can be identified in placental impression smears stained with modified Koster stain, Stamp modified Ziehl-Neelsen stain, or Gimenez stain as pleomorphic acid-fast coccoid or filamentous organisms in trophoblasts or extracellularly. Complement fixation titers greater than 1 : 8 in the dam are considered diagnostic. Enzyme-linked immunosorbent assay is rapid and sensitive but requires species-specific peroxidase conjugate for each host species. Laboratory results must be interpreted carefully because *C. burnetii* can also be isolated from the placenta of normal animals.[5] In one survey of California dairy goats, 24% were seropositive by microagglutination.[392]

Pathophysiology *C. burnetii* infection can be transmitted by ixodid or argasid ticks or by ingestion of infected material. The organism replicates in trophoblasts and is often of low pathogenicity in sheep and goats but can result in placentitis with late abortion and shedding of large numbers of rickettsiae.[5]

Epidemiology Q fever is reported in many countries including the United States and Canada. Abortions typically occur over a 2- to 4-week period and may affect 5% to 50% of the flock.[5] The organism is also infectious for other animals including humans. Pregnant women should not handle Q fever–infected animals or tissues.

Treatment and Control Aborting does and ewes should be segregated, and abortuses and placentas removed from the premises to prevent oral transmission. Pregnant animals can be treated with tetracycline to reduce the chances of abortion. A carrier state may develop, but abortions do not usually occur in subsequent pregnancies in sheep; they may be more likely to recur in goats.[393] Inactivated vaccines (not commercially available) lessen the chances of rickettsial abortion in sheep and reduce but do not eliminate rickettsial shedding at parturition.[391]

Campylobacter fetus subspecies *fetus* Abortion

C. fetus subsp. *fetus* is one agent of ovine campylobacteriosis (vibriosis) that causes abortion in sheep and sporadic abortion in cattle and goats.[5,320,357]

History and Clinical Signs Infection of ewes causes abortion in the last 6 weeks of pregnancy, stillbirths, and birth of premature lambs. Infected ewes may have fever, diarrhea, depression, and vaginal discharge several days before parturition.[357] In cattle the infection is not associated with infertility (unlike infection with *C. fetus* subsp. *venerealis*), but sporadic abortions can occur from the fourth to eighth months of gestation.[320]

Laboratory Diagnosis *Campylobacter* causes placentitis with cotyledonary necrosis and intercotyledonary edema. The fetus is edematous and may have fibrinous polyserositis. Foci of necrosis up to 2 cm in diameter occur in the liver of approximately 40% of aborted ovine fetuses, and although not pathognomonic, suggest campylobacteriosis.[5,320] Histologic changes include suppurative necrotizing placentitis and fetal bronchopneumonia.[320] Diagnosis is based on culture (which usually requires <48 hours)[5] or on microscopic demonstration of the organism.[5]

Pathophysiology *C. fetus* subsp. *fetus* is transmitted by ingestion. The organism localizes in the gallbladder but may invade the pregnant uterus, where it replicates in chorioallantoic trophoblasts. The incubation period in the ewe varies from 7 to 25 days.[5] In the cow, dissemination of the organism to the placenta is less common.[320] In either species, localization in the placenta causes placentitis and fetal bacteremia.[320] Metritis, fetal retention, and maternal peritonitis may occur in the ewe.[5]

Epidemiology Infection with *C. fetus* subsp. *fetus* is important in sheep in the United Kingdom, the United States, and New Zealand.[5] Fetal infection is most common during the last 2 months of gestation. Outbreaks of abortion tend to occur in 4- to 5-year cycles.[5] Infection is highly contagious in confined ewes, and the abortion rate may approach 70% but is more commonly approximately 25%.[5,320,357]

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Treatment and Control Abortion outbreaks can be treated with daily intramuscular injections of procaine penicillin G (22,000 IU/kg IM) and dihydrostreptomycin (11 to 22 mg/kg SC) or with oxytetracycline in the feed (75 mg/head/day).[5] Metritis is rarely fatal in the ewe. Generally, affected ewes abort only once and therefore they may be retained as breeding stock.[320] Ovine campylobacteriosis can be controlled by the use of a killed adjuvanted bacterin at breeding and 60 to 90 days later.[5]

Campylobacter jejuni Abortion

Campylobacter jejuni is the other agent of ovine *Campylobacter (Vibrio)* abortion. *C. jejuni* is an enteric pathogen that causes enteritis and diarrhea in many species. Only in sheep is placental and fetal infection common. This organism has been associated occasionally with abortion in cattle and goats.[5,13,320,394,395]

History and Clinical Signs Ovine infection with *C. jejuni* is clinically indistinguishable from that with *C. fetus* subsp. *fetus.*

Laboratory Diagnosis Aborted fetuses are autolyzed and frequently lack specific gross lesions. Cotyledons are mottled yellow to tan, but the intercotyledonary membranes are grossly normal. Histologically necrosis occurs in chorionic villi with arteriolitis and numerous leukocytes in the lamina propria. Purulent bronchopneumonia is a common histologic finding in the fetus.[396]

C. jejuni can be distinguished from other *Campylobacter* spp. by growth at 42° C (107.3° F), resistance to cephalothin, inhibition by nalidixic acid, and the presence of heat-labile glycoprotein surface antigen 1, which does not occur in *C. fetus* subsp. *venerealis* or *C. fetus* subsp. *fetus.* Placenta or fetal tissues should be cultured on *Campylobacter* agar with incorporated cefoperazone, vancomycin, and amphotericin B (CVA medium) at 42° C (107.3° F).[395,396]

Pathophysiology Intravenous inoculation of pregnant ewes with *C. jejuni* at 114 and 123 days of pregnancy consistently induced abortion 7 to 12 days later in one study.[396]

Epidemiology and Control *C. jejuni* is ubiquitous. Certain strains have been associated with an abortion rate as high as 80%, but usually less than 20% of the animals in the flock abort.[396] Aborted tissue is infectious for humans and should be handled with caution. Treatment and control of ovine infection with *C. jejuni* are similar to those for *C. fetus* subsp. *fetus.*

Brucella melitensis Abortion

Brucella melitensis causes abortion in goats and sheep and less commonly in cattle.[5] Infection is associated with late abortion, stillbirth, or birth of weak kids or lambs.[5,340] Necropsy findings include severe placentitis and fetal serositis.[5,357] The disease is diagnosed by culture or demonstration of the organism in tissue or by maternal serology (complement fixation test).[5] Animals are infected by ingestion, and, after bacteremia, replication occurs in chorioallantoic trophoblasts.[5,342] Infection with *B. melitensis* is important in Mediterranean countries and in Central and South America but is rare in the United States.[340,357] Suspected cases should be reported to state and federal authorities. Human infection with *B. melitensis* can be severe.

Brucella ovis Abortion

Brucella ovis infects only sheep. Epididymitis in rams is the most common manifestation of infection. Ewes seldom show clinical evidence of infection; late abortions, stillbirths, and delivery of weak lambs are rare.[5,320] Fetal and placental lesions resemble those induced by *B. abortus.* Diagnosis is based on culture or on demonstration of the organism in tissue. Serology (complement fixation) can identify infected animals. However, not all ewes showing a rise in complement fixation titer at parturition deliver infected lambs. In addition, ewes can maintain elevated titers for months or years after exposure to *B. ovis.* Therefore, *B. ovis* abortion should not be diagnosed on the basis of complement fixation testing alone.[320]

Infection is thought to occur by the conjunctival route.[357] The bacterium has low virulence for the ewe but may replicate in chorioallantoic trophoblasts, resulting in placentitis and fetal bacteremia.[342] *B. ovis* infection has been reported from Europe, Africa, Australia, New Zealand, and the western United States.

Chlamydia psittaci Abortion (Enzootic Abortion of Ewes)

C. psittaci is a major cause of abortion in sheep and goats.[5,320] Ovine chlamydial abortion is called *enzootic abortion of ewes. Chlamydia* may cause abortion in cattle[320] but is not the cause of epizootic bovine (foothill) abortion.

History and Clinical Signs Chlamydiosis is best characterized in sheep and goats. Abortions or stillbirths with placentitis usually occur in the fourth to fifth months of gestation. The dam seldom shows signs of illness but may have serosanguineous vaginal discharge several days before and after parturition.[5] Other animals in the flock may be affected by arthritis or pneumonia.[397]

Laboratory Diagnosis Placentitis is the most consistent necropsy finding in chlamydial abortion. Necrosis occurs in cotyledons; the intercotyledonary placenta is thickened with accumulation of red exudate.[320,397] The fetus has no specific gross lesions.[320,397] Histologically, necrotizing placentitis is accompanied by nonsuppurative vasculitis. Nonsuppurative meningoencephalitis, necrotizing hepatitis, and proliferation of mononuclear cells in spleen and lymph nodes are other histologic findings that may occur in the fetus.[320,398]

Diagnosis of chlamydial abortion should be based on identification of the organism and the presence of typical placental lesions. Chlamydiae appear in placental impression smears stained with Giemsa, Gimenez, or modified Ziehl-Neelsen stains as 200-nm dark red spheric bodies in the cytoplasm of trophoblasts.[5,320] The organism can be positively identified by FA tests on cytologic preparations, cryostat sections of placenta or other fetal tissues, or cultures. *Chlamydia* grows in chick embryos in 1 to 6 weeks, but cell culture using mouse L cells requires only 2 to 10 days.[320]

Abortion or delivery of chlamydial-infected fetuses induces a rise in serum titer that peaks in 2 to 3 weeks.[320] Paired sera should be collected at abortion and 3 weeks later. Maternal titers greater than 1:32 generally indicate recent active infection.[399] Complement fixation is the standard serologic test for the dam; indirect immunofluorescence and enzyme-linked immunosorbent assay are also used.[400] Double immunodiffusion can be performed on fetal fluids.[320]

Pathophysiology Chlamydiae reside in the intestinal tract and are also shed from the genital tract of infected animals before and after parturition. Ingestion is the main form of transmission.[5,401] In sheep and goats, abortion occurs 4 to 8 weeks after experimental infection,[397] but the fetus is not susceptible until the last third of gestation.[5]

High maternal antibody titers do not prevent abortion or stillbirth, but experimental work suggests that cell-mediated immunity is protective.[402] Infection with small numbers of *Chlamydia* organisms seldom stimulates adequate cell-mediated immunity and consequently may be more likely to cause abortion than infection with numerous organisms.[5]

Epidemiology Chlamydial abortion has been reported from most major sheep- or goat-producing countries. *C. psittaci* also may infect other animals including human beings. Pregnant women should not handle infected animals or tissues. The abortion rate in sheep is usually approximately 5%[320] but may be up to 30% or more in goats.[5,397] Although abortions usually occur 1 to 2 months after infection in sheep, the incubation period in goats may be as short as 2 weeks.[399]

Treatment and Control Aborting does or ewes should be segregated, and abortuses and placentas should be removed from the

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premises to avoid oral transmission. Oxytetracycline therapy (80 to 450 mg/head every day in feed or water, or long-acting oxytetracycline injected subcutaneously at a dose of 20 mg/kg twice weekly until the last month of gestation)[5] reduces the number of abortions and stillbirths in sheep[402] and goats, particularly if instituted in the first half of pregnancy.[5] However, short-term treatment does not eradicate infection or prevent chlamydial shedding at parturition and should be reserved for abortion outbreaks.[403] Most ewes develop cell-mediated immunity, which eliminates the organism from the genital tract by 3 months after lambing and protects against abortion for approximately 3 years.[5,403] Does are more likely than ewes to have placental retention and metritis after abortion.[401] Killed vaccines (Animal Health Division, Shawnee, Kan.) can be used in enzootic areas 4 to 6 weeks before breeding but are not 100% effective. Experimentally avirulent live vaccines have been used with success.

Toxoplasmosis Abortion

Toxoplasma gondii is a ubiquitous protozoan that is a major abortifacient in sheep and goats but only rarely causes abortion in cattle or horses.

History and Clinical Signs Infection does not cause clinical illness in the adult but may result in embryonic death, fetal death and abortion, stillbirth, or birth of weak, nonviable lambs or kids.

Laboratory Diagnosis The most characteristic gross lesion of toxoplasmosis is the presence of white, chalky foci of necrosis and calcification up to 2 mm in diameter in cotyledons.[404,405] The intercotyledonary areas of the placenta are grossly normal. Specific gross lesions are not observed in the aborted fetus, but histologically most have nonsuppurative encephalomyelitis[405] and many also have pneumonia, myocarditis, or hepatitis. Tachyzoites may be found in placenta or other fetal tissues but are not numerous.[406,407] The tachyzoites are oval, 2 to 4 by 4 to 8 mm, with a central nucleus and appear larger in impression smears than in paraffin sections. Several serologic tests, including the modified agglutination test, indirect FA test, Sabin Feldman dye test, indirect hemagglutination test, and enzyme-linked immunosorbent assay, reliably detect toxoplasmosis in pleural or amniotic fluid or presuckling serum from nondecomposed fetuses.[320,408,409] The modified agglutination test is commercially available, safer, and more sensitive than the dye test. Fetal antibodies to *T. gondii* can be detected 35 days after infection.[404] Absence of fetal antibody does not always preclude a diagnosis of toxoplasmosis.[320] High maternal titers are not diagnostic of toxoplasmal abortion, but lack of titer eliminates toxoplasmosis as the cause for abortion.[404] The peroxidase-antiperoxidase method for detecting *Toxoplasma* antigen in fetal tissues or placenta is reliable even in autolyzed fetuses. Fetal heart, lung, brain, spinal cord, skeletal muscle, and placenta are the preferred specimens for the peroxidase-antiperoxidase method and should not be held in formalin more than 2 days before paraffin embedding.[407] *T. gondii* can be isolated by intraperitoneal inoculation of placental or fetal tissue suspensions into mice.[320]

Pathophysiology Placental infection occurs approximately 14 days after ingestion of oocysts.[407] Infection acquired before 50 days' gestation may result in embryonic death and resorption. Infection between 60 and 100 days' gestation usually causes fetal death or birth of weak lambs. Infection during the last month of gestation often has no apparent effect on the fetus.[404] In experimental infection of ewes between 6 and 14 weeks of pregnancy, abortions occurred 1 to 2 months after inoculation.[409] In natural infections, most abortions occur 1 month before parturition.[404]

Epidemiology Toxoplasmosis is a major cause of ovine abortion in many sheep-raising countries, including the United States.[405,406,410] Sheep are infected by ingestion of oocysts from feed or grass contaminated with cat feces. Most ewes are infected by 4 years of age.[411] Aborted tissues may be infectious for humans and should be handled with caution.

Control Infected ewes or does seldom abort from toxoplasmosis in subsequent pregnancies.[405] The prevalence of abortion can be reduced by avoiding contamination of feedstuffs with feline feces. Cats should not be allowed to eat placentas or carcasses that may contain tachyzoites or tissue cysts. In endemic areas, exposing replacement ewes to aborting ewes may provide immunity before breeding age.[5]

Mycoplasma Abortion

Treatment of *Mycoplasma* infection in goats is usually not recommended because treated animals may remain carriers. The infection is eliminated from the herd by testing milk and slaughtering infected animals.[355]

Leptospirosis

Serovar *Leptospira* Pomona is the major ovine isolate,[320] but *Leptospira* Bratislava and *Leptospira* Hardjo have also been isolated from sheep.[320] *Leptospira* Grippotyphosa is the major caprine isolate.[5] Leptospiral abortion is less common in sheep and goats than in cattle.

CAMELIDS The incidence of abortion in llamas and alpacas is low. Infectious causes in North America include leptospirosis, toxoplasmosis, chlamydiosis, and other nonspecific uterine infections.[237] Bovine virus diarrhea is considered an emerging disease in alpaca herds and may be responsible for some of the early pregnancy losses and abortions in some herds. Diagnostic workup for abortion in camelids is similar to that described in this chapter for other species.

Male Reproductive Disorders

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Infertility Caused by Diseases of the Penis and Prepuce

Penile Injury

STALLION

Definition and Etiology If the penis is injured while erect, it may swell rapidly and massively from vascular rupture and hemorrhage. Hemorrhage usually originates from the superficial penile vessels in the plexus external to the tunica albuginea.[1] The stallion may be kicked during mating, or hematomas may follow breeding a mare with a tightly sutured vulva or may be induced if the mare moves suddenly during mating.[2,3] Injuries can also occur during semen collection if proper techniques are not employed.

Clinical Signs and Differentials Cutaneous abrasions, lacerations, and visible hemorrhage may be present. Paraphimosis

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occurs when enlargement is sufficient to prevent retraction of the penis through the preputial ring.[1] Edema may extend to the scrotum and interfere with thermoregulation of the testes.[4] Venous thrombosis, lymphatic occlusion, excoriation, and swelling accompany chronic inflammation.[1] Hemorrhage from the corpus cavernosum penis (CCP) is uncommon. Rupture of the surrounding tunica albuginea, when healed, may develop fibrous adhesions that lead to penile deviation during erection.

Treatment and Prognosis Immediate treatment is directed toward reducing edema and inflammation, as well as controlling infection. Treatment is similar to that described for paraphimosis in a later section. Sexual rest is indicated until the lesions have healed.[5] If treatment is initiated early and paraphimosis does not occur, the prognosis for recovery is good.[1,3]

BULL

Definition and Etiology The penis of bulls is susceptible to injury during mating. The vigorous thrust that accompanies copulation predisposes the penis and prepuce to excoriations, lacerations, and bruising. Rupture of the tunica albuginea (penile hematoma or "broken penis") occurs if the penis is misdirected during copulation.[6] Penile hematomas most commonly occur in young, sexually aggressive bulls. Injuries occur when these bulls attempt to breed heifers or cows that are not receptive, when females falter or collapse under the weight of the bull, or when the bull slips because of poor footing.[2] During copulatory thrusting in which the penis is bent, the tunica albuginea ruptures on the dorsal or dorsolateral surface of the penis opposite the attachment of the retractor penis muscle. Presumably, CCP pressure rapidly increases as the functionally closed system is compressed during bending to rupture the tunica albuginea. Experiments with fresh postmortem specimens indicated that a CCP pressure of 1180 to 1720 psi was required to rupture the tunica albuginea. Tearing virtually always occurred at the site described in naturally occurring cases. Mean peak CCP pressure recorded during normal coitus (275 psi) occurs when cavernous spaces fill with a relatively small volume of blood, perhaps as little as 110 mL.[6] Blood escapes from the CCP into the surrounding tissue.[1] The size of penile hematomas may be related to the number of repeated trials made by the bull before cessation of attempts at mating. Larger hematomas restrict full retraction of the penis and result in prolapse of the prepuce from the sheath. Secondary preputial injury is common.[1]

Clinical Signs and Differentials Diagnosis of penile hematoma is made on the basis of the presence of a swelling immediately cranial to the scrotum. Initially it is soft, fluctuant, and painful, and it becomes firm as clot organization and fibrin formation progress.[2] The main differential diagnosis is extensive preputial laceration. If a distance of more than two handbreadths is present between the scrotum and the enlargement, the swelling is more likely to be a preputial laceration. Other differential diagnoses include rupture of the urethra, abdominal hernia, and chronic, fibrous adhesions. Dysuria usually does not occur in conjunction with penile hematoma. Other signs of urethral rupture or blockage, such as extensive preputial cellulitis and "water belly," elevated blood levels of urea nitrogen and creatinine, and tissue necrosis do not occur. Abscess formation of penile hematomas sometimes occurs. A soft, fluctuant center is characteristic of an abscess. Occasionally, differentiation between blood clot and abscess may be difficult. An aseptic tap can be done to determine the character of the fluid, but the risk of inducing an abscess in a sterile hematoma is great and a tap should only be used as a last diagnostic resort or just before surgery.

If penile hematoma has been present for longer than 2 weeks, fibrous adhesions may form that prevent penile extension. Adhesions are frequent sequelae to an abscess and have also been reported to occur secondary to infiltration of local anesthetics to block the dorsal nerves of the penis.[2] Another sequela is the development of venous shunts that communicate between the CCP and either peripenile vasculature or the corpus spongiosum penis.[1,7] Such vascular shunts result in rapid drainage of blood from the CCP and impotence caused by failure to achieve or maintain full erection. If the dorsal nerves of the penis are damaged, sensation of the distal penis is lost or deficient and results in failure of the bull to successfully seek out the female's vagina and/or ejaculate. Organization of the portion of the blood clot (thrombosis) within the body of the CCP may result in functional blockage of engorgement of the more distal cavernous spaces, preventing full erection.

Treatment and Prognosis Treatment of penile hematomas should be aimed at not only restoring the bull to usefulness but also preventing recurrence. Approximately 50% of bulls with hematomas that are treated conservatively (i.e., nonsurgically) are reported to return successfully to breeding.[1] Some theriogenologists feel that small hematomas (less than football size) do not require surgery.[8] However, Auburn University faculty report that surgical intervention is required to optimize chances of full recovery. Surgical correction has the advantages of (1) removing the blood clot before extensive fibrous adhesions develop; (2) permitting removal of blood clot from within the body of the CCP itself, thereby reducing the chance of blockage of cavernous filling; and (3) suturing the tunica albuginea, which should reduce the chance of recurrence of the condition after return to service and the likelihood of development of vascular shunts that will prevent complete filling of the CCP. Surgical intervention is not recommended before coagulation of the extravasated blood. Once significant fibrin formation is present, the prognosis for successful correction is greatly reduced and should only be attempted in valuable bulls.[1]

Additional recommendations before electing surgical intervention include extending the penis manually. Cases in which the penis can be extended from 6 to 8 inches or more beyond the sheath orifice, and in which penile sensation remains, carry a better prognosis.[9] If engorgement of the distal penis does not occur after careful stimulation with the electroejaculator, blockage of the CCP should be suspected and reduces the prognosis. Finally, cases with abscesses are poor risks because severe restrictive adhesions usually develop.[1]

Regardless of whether surgical or conservative intervention is selected for a penile hematoma, the bull should be treated with high levels of systemic antibiotics in an attempt to prevent abscess formation. Penicillin is a good choice because abscesses are usually caused by *A. pyogenes.* Postsurgical complications are much the same as those that may occur without surgery, but these adverse consequences are reported to occur less frequently after surgery. Bulls should not be returned to service for 2 to 3 months after treatment.[1,2]

RAM AND BUCK

Adhesions of the penis and prepuce caused by trauma are uncommon in adult small ruminants. The penis does not separate from the prepuce until puberty and cannot be extended before this time (4 to 5 months of age in bucks).[10] Most traumatic lesions of the penis or prepuce in sheep and Angora goats are from shearing injuries.[11] Blockage of the urethral process by calculi can cause necrosis and sloughing of tissue that may extend into the glans penis.[11] Fighting among horned animals may result in injury to the external genitalia including the penis. In dairy goats the intersex condition can result in congenital malformation of the penis and prepuce (hypospadius).[12]

Phimosis and Injury to the Prepuce

STALLION

Definition and Etiology Stenosis of the preputial orifice prevents extension of the penis. The defect is likely to be a sequela to an injury that results in cicatrix formation but may rarely be congenital.[1,2] Tumors (such as melanoma or squamous cell carcinoma) or *Habronema* granulomas may encroach on the preputial cavity, thereby preventing penile extension.[13]

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Clinical Signs and Differentials Acute posthitis often accompanies injuries to the prepuce or infections such as equine coital exanthema and dourine.[1,2] Edema is common with acute posthitis, particularly after trauma. Gravitational effects typically worsen the preputial edema, which may induce prolapse of the external prepuce, trapping the penis in the swollen internal prepuce with a constricting preputial ring.[1] Cicatricial scar formation may follow, narrowing the diameter of the preputial orifice. Transpreputial ultrasound examination may be of benefit in differentiating tumors or abscesses from inflammatory edema or hemorrhage. Containment of the penis within the prepuce causes preputial urine accumulation, worsening balanoposthitis and secondary bacterial infection. The extended chronic inflammation leads to cicatrix formation with phimosis.[14]

Treatment and Prognosis Preputial edema can be relieved by administration of diuretics and exercise. Application of crushed ice in plastic bags, or preputial immersion in cold water, may reduce inflammatory edema if applied soon after injury. Subsequently, emollient antibiotic preparations and hydrotherapy can be used to massage injured tissues and reduce edema. Systemic antibiotics and nonsteroidal antiinflammatory drugs are indicated to control secondary infection and inflammation. Sexual rest is indicated until the lesions have healed.[5]

A biopsy can be procured from encroaching tumors to identify cell types and improve prognostic capability.[5] Cicatricial scars can sometimes be successfully removed surgically. Once inflammation and infection are resolved with local or systemic antibiotic and antiinflammatory drug treatment, incision of the ventral aspect of the preputial orifice (preputiotomy) may be necessary to enlarge the opening sufficiently to permit penile extension.[15] Large tumors or granulomas of the prepuce can sometimes be successfully removed surgically if sufficient elastic and membranous tissue remains to permit normal penile extension and retraction.[5] The prognosis for return to breeding soundness, however, is guarded when surgery must be performed. Postsurgical adhesions may develop that result in continued phimosis or penile deviation. In cases of habronemiasis, treatment with systemic insecticides or ivermectin may be indicated to kill remaining parasitic larvae.[13] Congenital abnormalities can seldom be corrected surgically.

BULL

Definition and Etiology Trauma to the prepuce involving the elastic lamellar layers may prevent the required flexibility of the prepuce to permit penile extension. Breed predisposition to preputial injuries corresponds to genetic differences in pendulousness of the sheath and development of the muscles responsible for retraction of the prepuce. The polled gene is linked to weak or failed development of the preputial muscles, leading to habitual preputial eversion, which predisposes to injury. Brahman-blooded cattle have the added predisposition of a loose, pendulant sheath. With their tendency to partially evert the preputial membrane through the sheath orifice, they are at greater risk of damaging the prepuce accidentally than those breeds of cattle in which the sheath is held in close apposition to the abdominal wall.[1,2,16]

Inability of the bull to extend the penis most commonly follows injury to the penis and prepuce that culminates in strictures or adhesions that restrict normal penile movement.[1,2,17,18,19,20]

Other causes of phimosis include congenital anomalies such as a short penis, a short retractor penis muscle, and developmental abnormalities of the reproductive tract such as occurs in pseudohermaphrodites.[2,18]

Clinical Signs and Differentials The more common preputial injuries are contusions, abrasions, lacerations, and frostbite. When the injured prepuce can be retracted, the injury may not be suspected unless hemorrhage is noted from the sheath or the bull is observed having difficulty during breeding. Although minor injuries may spontaneously resolve, more extensive injuries commonly progress to abscess formation and fibrous stricture formation.[1,8,19,20] Extension and examination of the penis may result in further injury if the case is complicated by phimosis. In such cases an attempt to extend the penis to facilitate examination is contraindicated because forcibly stretching the prepuce will extend the laceration and spread infection to uncontaminated areas.[1]

Treatment and Prognosis Treatment of preputial injuries in the bull may be either medical or surgical. With few exceptions, such as fresh avulsive lacerations in the fornix area, surgical intervention carries a better prognosis when medical treatment is first carried out to control inflammation and infection.[19] The healing leaves more normal tissue to be identified and salvaged during surgery. In cases in which the injured prepuce is retracted into the preputial cavity, digital, speculum, or endoscopic examination can be done in an attempt to locate lesions and determine the extent and depth of tissue involvement. Systemic administration of antibiotic is necessary to reduce the incidence of abscess formation preoperatively, and antibiotic should be administered through the surgical and postsurgical periods if surgery is elected. When the injured prepuce remains prolapsed in presented bulls, the first consideration is to attempt to return the prepuce to the preputial cavity.[1,19] The exposed epithelial covering of the prepuce is easily injured and becomes quite edematous and friable because of its pendent location. Hydrotherapy for 20 to 30 minutes may be helpful in cleansing the exposed prepuce and reducing edema. After gently cleansing the prepuce and determining the degree of patency of the lumen, a protective emollient preparation is used to massage edematous swelling upward out of the prolapse.[19] Massage for 15 to 30 minutes may be required to reduce swelling sufficiently to permit the prepuce to be returned to the preputial cavity. If the prolapsed prepuce can be returned to the sheath, a retention technique should be used to prevent reprolapse. With the prepuce in place, a tube can be inserted just beyond the swollen internal portion of the prepuce to avoid urine retention. The tube is taped in place at the external preputial orifice. Tape should not extend past the proximal end of the tube or urine retention and migration into peripreputial tissue will occur. If this technique will not retain the prepuce, a purse-string suture in the skin of the sheath orifice can be used.[1] It should be tight enough to retain the prepuce but leave sufficient space for urine to pass freely. To avoid suture abscesses and stricture formation, the sheath should be clipped and prepared aseptically for suture placement and sutures should be removed as soon as swelling and inflammation subside. If the prolapsed prepuce cannot be returned to the preputial cavity, the prognosis for correction without surgery is guarded. After cleansing as described previously, a portion of stockinette is coated in ointment and applied over the prepuce. A diaper constructed from heavy canvas or burlap with straps and centrally located perforations for urine drainage is applied under the prepuce and tied up over the back to hold the prepuce gently next to the abdominal wall to decrease gravitational edema. It is changed daily until infection and swelling are controlled and the prepuce is either returned to the sheath or surgery is performed. Alternatively, the prolapsed portion of the prepuce can be wrapped in medicated gauze followed by application of a gentle but firm pressure wrap around a section of tubing. The pressure wrap is left in place temporarily to reduce edema, at which time the wrap is removed and the prepuce replaced into the sheath.[19]

Once sufficient healing has occurred, the necessity for surgery is determined by extending the penis.[1] Adhesions most commonly take the form of encircling cicatricial strictures that must be removed surgically. Guidelines suggested for predicting successful outcome of surgery include (1) a minimum of 5 cm of normal prepuce should be present on either side of the surgical site or proper unfolding may not be possible after surgery, and (2) free prepuce remaining after surgery should be at least twice the length of the free portion of the penis or the prepuce may be too short to permit full penile extension. Presurgical and postsurgical considerations, as well as surgical

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techniques used to correct phimosis, are described by Walker and Vaughan.[1]

Congenital anomalies contributing to phimosis are diagnosed on the basis of physical examination of the entire reproductive tract. Abnormal karyotypes may be helpful in determining causes. If the penis cannot be extended with the techniques described and evidence of injury or adhesions is not present, congenitally short penis or retractor penis muscles should be suspected.[2]

Accompanying history may provide information that the bull could copulate when young, but as he aged his abdomen progressively enlarged, causing the penis to be of relatively insufficient length to effect copulation.[2]

RAM AND BUCK

Phimosis is uncommon in small ruminants. It may be congenital or acquired as a result of adhesions or preputial scarring associated with trauma or balanoposthitis.[11] Acquired phimosis can be the result of ulcerative posthitis due to the presence of *Corynebacterium renale, C. pilorum,* or *C. cystitidis*. These bacteria normally inhabit the prepuce and transform urea to ammonia, which is highly irritating to the prepuce. High urine urea levels, which are noted in animals fed high-protein diets, may increase the risk of ulcerative posthitis.[21,22] This condition is diagnosed during the physical examination and/or by observing the animal during the breeding process. If phimosis is due to acute inflammation of the prepuce (posthitis), it may resolve when the preputial swelling reduces. However, the prognosis is guarded until scarring can be evaluated.

Paraphimosis

STALLION

Definition and Etiology

When injury of the penis and the laminae of the prepuce is attended by hemorrhage and edema, paraphimosis (the inability to retract the penis into the prepuce) is likely to occur.[1] Prolonged penile prolapse, caused by debility or paralysis after the use of some tranquilizers, usually culminates in extensive penile trauma.[23,24] Protracted priapism (persistent erection) can lead to penile trauma and complications similar to penile prolapse.[25] Penile paralysis and priapism are distinctly different conditions. Penile paralysis develops secondary to insufficient tone of the retractor penis muscles.[26] Motor innervation of the retractor penis muscles in stallions is believed to be solely supplied by α-adrenergic fibers. When α–adrenergic blocking drugs such as phenothiazine-derivative tranquilizers are administered, paralysis of these muscles can cause penile prolapse.[27] The prolapsed penis is flaccid and cannot be maintained in the retracted position.[1,26] Priapism is a persistent erection without sexual arousal and is initially unassociated with penile paralysis. It develops from engorgement of the CCP with blood, and although the horse may not achieve a full erection, its penis is not flaccid.[28,29] When the penis fails to detumesce, CO_2 tension in the CCP increases, resulting in increased blood viscosity and subsequent venous occlusion where collecting veins join the cavernous spaces. Edematous swelling of corporeal trabeculae further reduces venous outflow, thus increasing the likelihood of irreversible venous occlusion, fibrosis of the cavernous trabeculae, and arteriolar occlusion. Disruption of the arteriovenous supply and fibrosis of the CCP prevent subsequent erections.[5,30]

Clinical Signs and Differentials

Penile paralysis has been reported in exhausted or debilitated horses, in horses with myelitis or spinal injury, and in horses with severe injury to the penis.[1,23] Traumatic inflammatory edema often results in severe swelling of preputial membranes that prevent retraction of the penis into the prepuce. The inability to retract the penis results in further gravitationally induced edema and, as the problem worsens; edematous fluid eventually oozes through the increasingly fragile penile and preputial integument. Cellulitis develops and the integument becomes thickened, inelastic, desiccated, necrotic, and irreversibly damaged.[1,5] In cases of long-standing priapism, the distal end of the penis becomes cool to the touch and the clot may become palpable in the body of the CCP as fibrin organization occurs. The organized clot may be visible on ultrasound examination.[25]

Treatment and Prognosis

Prognosis for recovery becomes guarded to grave the more chronic the paraphimosis becomes. Principles of treatment are similar to those described for the bull. The key to success is early aggressive intervention to reduce the edema via compression so that the penis can be placed within the prepuce.[31] To maintain the penis within the prepuce, a temporary purse-string suture of heavy vetafil can be placed near the preputial orifice. Alternatively, a padded plastic bottle from which the bottom has been removed can be used to support penile hematomas.[32] After the injured penis is dressed, the bottle is placed over it and pushed back into the sheath. The bottle is held in place with straps running over the lumbar area and on either side of the scrotum up over the tailhead. Voiding of urine occurs through the bottle. The apparatus should be cleaned and replaced twice daily until the penis can be retained in the retracted position. Another effective method for maintaining the penis within the prepuce is through the use of a 2-inch outer-diameter probing made of PVC tubing that is secured to the stallion's abdomen using elasticated bandage tape.[33] If the penis cannot be returned into the prepuce, an external support for the prolapse should be applied. Prolonged penile prolapse may result in excess gravitational pull that damages smooth muscle cells, the retractor penis muscle, and the pudendal nerves[1,26]; such sequelae decrease the prognosis for recovery and return to a successful breeding career. Chronic, refractory penile prolapse results in severe balanoposthitis that may require circumcision or penile amputation. Surgical penile retraction (the Bolz technique) is described by Walker and Vaughan.[1] A simple amputation technique that can be performed in the standing horse, using a modified Vinsot procedure, has recently been described.[34]

Medical treatment of horses with priapism has generally been unsuccessful.[5,28] In cases of drug-induced priapism seen within 2 to 4 hours of occurrence, slow IV injection of 8 mg benzotropine mesylate may cause detumescence and penile retraction to occur.[35] If not seen immediately, treatment is the same as for traumatic paraphimosis. Rapid detumescence can be induced by injecting 10 mg of phenylephrine into the CCP, even in long-standing cases. However, the detumescence may only be transient. Flushing the CCP with heparinized lactated Ringer solution through 12-gauge needles to remove sludged blood has been recommended for horses with priapism of 12 to 24 hours' duration that have not responded to medical treatment.[5] If a blood clot forms in the CCP, the prognosis is poor and amputation may even be necessary. Some stallions, if severe nerve damage does not occur, may regain the ability to breed and ejaculate when assisted with placement of the penis into either the vagina of the mare or an artificial vagina. When the stallion does not regain the ability to completely retract the penis into the sheath, continued penile trauma is likely to result in damage to the sensory nerves to the glans penis. Such horses may achieve an erection but may have difficulty in both seeking the mare's vulva for intromission and ejaculating. Ultrasonography of the CCP to detect cavernosal fibrosis may be useful in assessing prognosis for recovery from priapism. Prognosis for recovery is good once penile retraction occurs, but breeding should not be permitted until healing is complete.

BULL

Definition and Etiology

Paraphimosis is less common than phimosis in the bull. Causes may be the same for both conditions, but for paraphimosis include penile tumors, parasitic invasion, traumatic or spinal disease affecting innervation of structures responsible for penile retraction, inadvertently severed retractor penis muscles, or physical trapping of the penis by a constricted prepuce after injury. Penile paralysis and paraphimosis sometimes occur as a result of spinal injury or disease and in rabies cases as well.[1,2,17-20,36]

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Clinical Signs and Differentials Persistent exposure of the penis results in congestion, inflammation, and necrosis of the penile integument.[2,17,18]

Treatment and Prognosis Management of the prepuce has been discussed. Exposed portions of the penis should be frequently cleansed and protected by a bandage soaked in oily antibiotic preparations. The prolapsed penis should be supported close to the abdomen to reduce edema. The penis should be returned to the sheath as soon as possible and mechanically restrained if necessary. If the ability to retract the penis does not return in a few days, prognosis for recovery is poor.[1]

RAM AND BUCK Paraphimosis is uncommon in small ruminants. The diagnosis is obvious, although the etiology may not be. Treatment involves the same principles as in the bull. Prognosis is guarded and correlates with the degree of injury and necrosis at the time the condition is discovered.

Urethral Injury and Urethritis

STALLION

Clinical Signs and Differentials Traumatic injuries to the urethral process are usually obvious and are characterized by hemorrhage. *Habronema* granulomas are firm and friable. Ulcers of the urethral process often become secondarily invaded with bacteria such as *Pseudomonas* spp. Parasitic lesions tend to regress during winter, but if untreated they may mineralize and result in recurrence of hemospermia during the following breeding season.[37]

Lesions can occur throughout the urethra including the pelvic urethra in the area of the ejaculatory ducts. Diagnosis is based on demonstration of the lesions by fiberoptic examination.[5] Ultrasonography and fractionation of the ejaculate may be helpful in eliminating involvement of the accessory sex glands.[38]

Urethral inflammation and lacerations may result in fibrous strictures.[39] Strictures are often painful and may separate and bleed during urination and ejaculation. Bacteriologic culture of the urethra, urine, and semen; fiberoptic examination; and histologic examination of biopsies of lesions are helpful in making a diagnosis.[1] Strictures in the distal urethra may be identified by contrast radiography of the extended penile urethra.[1,39]

Clinical signs of uroliths include dribbling of urine with chronic cystitis, dysuria and stranguria, occasional hematuria, recurrent colic, and a stilted, painful gait in the hindquarters. Penile protrusion is frequent or constant in cases of chronic, involuntary escape of urine.[1] Diagnosis is by urinalysis, revealing the characteristic crystals, red and white blood cells, and bacteria. Urethral calculi typically restrict the passage of urethral catheters. Bladder calculi may be palpated per rectum or visualized by ultrasonography.[1,37]

Treatment and Prognosis Treatment of urethral injuries involves first removing inciting factors such as a tight stallion ring. Sexual rest is indicated while palliative therapy is given. The ability to void urine should also be established. Systemic treatment with antibiotics that are eliminated in the urine may be useful as a prophylactic measure or in cases in which secondary bacterial invasion has occurred. More severe cases of urethritis may be treated locally by either infusion of oily antibiotic preparations through sterile, rubber urethral catheters passed to the area of the seminal colliculus of the pelvic urethra, or alternatively by inserting soluble suppositories through a perineal urethrostomy. After resolution of the urethritis, the urethrostomy is allowed to heal by granulation.[39] Lacerations of the proximal urethra that result in hemospermia can be treated by perineal incision into the corpus spongiosum urethra (CSU) or by perineal corpus spongiotomy where the corpus spongiosum penis (CSP) is incised, but the incision is not extended into the urethra. These surgeries are believed to prevent stretching of the urethra when engorgement of the corpus spongiosum occurs during urination or erection. Repeated stretching is thought to prevent urethral lacerations from healing.[40]

Inflammation of the urethral process may respond to local antibiotic salves. Treatment of parasitic granulomas with ivermectin speeds resolution of these cases.[13,41,42] Larger, nonresolving granulomas with mineralization may require surgical removal.[43] The skin of the urethral process should be rolled inward when sutured to the mucous membrane to prevent eversion that predisposes it to reinjury after healing. Remaining hemorrhagic or ulcerative lesions are lightly cauterized with silver nitrate.[37] More proximally located nonresolving urethral strictures, prolapsed subepithelial vessels, or ulcers can be removed surgically. Leave as much normal urethral mucosa as possible to avoid postsurgical stricture formation.[39]

Calculi lodged within the lumen of the pelvic urethra can be removed via perineal urethrostomy. Treatment for urethral calculi is described in the discussion of diseases of the urinary system, Chapter 34.

BULL

Definition and Etiology Urolithiasis is the primary problem affecting the urinary system that may interfere with normal function of the reproductive tract of the bull.[44] It is of less importance in bulls than in steers but occasionally occurs and may result in hematuria or urethral obstruction.[1,2] Urolithiasis is thoroughly discussed in Chapter 34.

Balanoposthitis

STALLION

Definition and Etiology Inflammation of the glans penis (balanitis) and prepuce (posthitis) often occur together (balanoposthitis). Traumatic injury resulting in inflammation of the penis and prepuce has been discussed. Balanoposthitis may also be caused by dourine, EHV-3 (see Equine Coital Exanthema later), miscellaneous bacteria, and parasites.[3,17,18,45,46]

Equine Coital Exanthema

Equine coital exanthema is caused by EHV-3.[47] The occurrence of neutralizing antibodies to EHV-3 primarily in horses of breeding age suggests that spread of this infection may be primarily by genital contact.[48] Typically an inapparently infected mare transmits the virus to a stallion at the time of breeding. The stallion then transmits the infection to other susceptible mares before developing clinical signs of the disease. Clinical signs in the stallion are sometimes more severe than those observed in the mare and may include systemic manifestations such as dullness, anorexia, and fever.[48] Vesicles up to 1.5 cm in diameter develop first on the penis and then on the prepuce 2 to 5 days later. The vesicles progress to circumscribed pustules with raised borders and depressed centers, which slough and ulcerate.[42,49] Scabs are seldom noted on penile lesions because they are rubbed off by extension and retraction of the penis during breeding.[49] Some affected stallions may refuse to breed mares, whereas others breed willingly, even while extensive penile lesions are present. Healing occurs in a few weeks, often leaving depigmented spots.[49]

Some immunity to the virus is acquired after infection because reinfection without recurrence of clinically apparent disease is common. It is probable that the virus remains in the genitalia in a latent form.[17] Recurrent coital exanthema usually occurs in aged broodmares but may also occur in stallions.[49] In stallions, recurrence within the same breeding season is uncommon. The relationship between viral recrudescence and recurrent coital exanthema in the equine is unknown but may mimic that which occurs in human genital herpes infections.

Diagnosis usually can be made on the basis of the characteristic clinical signs. During the acute stage, the virus can be isolated from swabs or scrapings taken from the edge of erosions, inclusions in

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lesion specimens, or confirmed by using an electron microscope to visualize typical herpesvirus particles in fluid or tissue samples. Probably the most sensitive, specific, and accurate tool for the detection of EHV-3 is by PCR. Demonstration of antibody titers in serum may be useful in establishing time of exposure to the virus.[50]

Infection with EHV-3 is self-limiting.[17] Local treatment with antibiotic ointments will not speed healing but may minimize secondary bacterial infection and soreness.[49] Care should be taken to avoid iatrogenic transmission of the infection (e.g., through contamination of sleeves, water, and examination or insemination equipment) to susceptible animals. Attending veterinarians may choose to refrain from breeding affected stallions until the lesions heal. One method that may be helpful in circumventing transmission of the infection while still breeding the stallion is to collect semen in an open-ended artificial vagina as soon as lesions are no longer painful. Collecting the semen as it directly exits the urethra reduces the chance of viral contamination from the penile and preputial lesions. It is imperative, however, to adhere to any breed registry restriction regarding AI.[5]

Bacterial Infections

STALLION

The external genitals of stallions harbor potentially pathogenic bacteria, fungi, and yeasts, yet balanoposthitis caused by bacterial agents is uncommon.[51-53] These organisms are usually considered to be surface contaminants, and the stallion is a lesionless carrier in most instances in which venereal transmission occurs.[24] Sperm motility, however, may sometimes be adversely affected by bacteria and their products in semen.[52] Offensive odors may occasionally be associated with heavy colonization of the penis and sheath with *Pseudomonas* spp. or *Proteus* spp.[2] Documentation of a bacterial infection is dependent on serial isolation of a pathogen, preferably in large numbers and relatively pure culture.[53] A single isolation of *Taylorella equigenitalis* is considered diagnostic for contagious equine metritis.[24] Samples for bacteriologic culture should be retrieved from the fossa glandis, free portion of the penile body, and folds of the external prepuce before washing the genitals of a stallion presented to an estrual mare.[53]

If there is evidence of horizontal transmission of *Pseudomonas* or *Klebsiella* to mares, or if longevity of sperm is reduced in association with these organisms, the preferred method of management is to breed mares artificially with semen mixed with an antibiotic-containing semen extender.[54] Antibiotic selection is based on trials comparing extended semen with and without antibiotic. Extenders containing antibiotics that control the offending bacteria and permit maintenance of sperm motility are then used to breed mares.[55] Bacteria are usually not recovered after 5 to 30 minutes of incubation at room temperature.[52,54,55] Penicillin G (1000 to 1500 U/mL), streptomycin sulfate (1000 to 1500 µg/mL), polymyxin B (100 to 1000 U/mL), reagent grade gentamicin sulfate (100 to 1000 µg/mL), amikacin sulfate (100 to 1000 µg/mL), and ticarcillin (100 to 1000 µg/mL) are usually the most suitable antibiotics.[5] Gentamicin sulfate and amikacin sulfate should be buffered with 8.4% sodium bicarbonate solution to adjust pH to approximately neutral before mixing with semen extender. A suitable volume of extender can be infused into a mare's uterus immediately before cover when natural service is necessary.[54]

Colonization of the external genitals with *P. aeruginosa* and *Klebsiella pneumoniae* can be treated by thoroughly washing the penis and prepuce, including the fossa glandis and diverticulum, daily with an iodine-based surgical scrub. The genitals are then rinsed with copious quantities of tap water with dilute disinfectants added (10 mL concentrated HCl per gallon of water for *Pseudomonas* colonization, or 40 mL of 5.25% sodium hypochlorite bleach per gallon of water for *Klebsiella* colonization).[56] Drying of the penis can be followed by generous application of 1% silver sulfadiazine cream. The procedure is repeated daily for 1 to 2 weeks followed by serial cultures to determine if treatment was successful.[57] The clinician should be cognizant that recolonization with these organisms may occur and that routine scrubbing and disinfection may predispose to infection of the genitals with potential pathogens by displacing commensal organisms.[51]

BULL

Balanoposthitis in the bull is caused by traumatic injury and infections. Whereas injury of the prepuce is more common, penile inflammation often accompanies the traumatic posthitis. A multitude of potentially pathogenic organisms inhabit the prepuce, and injuries predispose to infection, particularly when deeper tissues are exposed. Pain and preputial discharge may be evident. Because of the presence of the many organisms in the preputial cavity, culture to identify a specific offending organism is likely to be misleading. When injury results in infection of the penis and prepuce, sexual rest in conjunction with local antibiotic treatment is indicated. Treatment should be performed as previously outlined for the penis and prepuce until inflammation is corrected.

Balanoposthitis unassociated with trauma has been associated with infections caused by infectious bovine rhinotracheitis-infectious pustular vulvovaginitis (IBR-IPV) caused by bovine herpesvirus 1, tuberculosis, and screwworm infestation.[2,17,18,58] Acute lesions associated with IBR-IPV infections are numerous small pustules that progress to ulcers and erosions in a few days. Purulent preputial discharge is present, and lesions may become confluent. The prepuce and penis may become quite inflamed and swollen. Healing is commonly spontaneous and rapid, beginning in 1 week and usually complete in 2 weeks. Severe cases may take longer to resolve.[58] Virus is shed from the prepuce for 2 weeks or longer, during which time venereal spread is possible. Sexual rest for 6 to 8 weeks has been recommended to prevent spread and to avoid abrasions that may aggravate inflammation.[2] Enlargement of the lymphoid follicles may be present along with a seromucoid exudate for several weeks. Histologic changes include the transient appearance of eosinophilic intranuclear inclusions in degenerating epithelial cells.[17] Infusion of the preputial cavity daily may be of benefit in treatment, particularly in more severe cases. Vaccination with attenuated intranasal products has been reported as a method to prevent viral shedding into semen in bulls from AI studs.[2,59] Bulls infected with BHV-1 remain infected for life as the virus remains latent in the sacral ganglia.[60,61] Viral shedding through the ejaculate occurs intermittently. Therefore valuable serologic-positive bulls could be tested for the presence of the virus in semen. Detection of BHV-1 in semen by real-time polymerase chain reaction is more sensitive than virus culture isolation. Two straws of extended processed ejaculate are necessary to detect the presence of the virus.[60,61] Tuberculosis of the penis and sheath apparently has not been reported in this country for some time. It is characterized by enlarged, granulomatous lesions on the glans penis, prepuce, and sigmoid flexure that are prone to hemorrhage. Penile lymph glands may abscess.[2]

RAM AND BUCK

Definition and Etiology

Balanoposthitis (also called "pizzle rot," "sheath rot," and "ulcerative posthitis") commonly affects the penis and prepuce of intact and castrated male small ruminants (see also Chapter 34).[11,12,62,63] In sheep, it is important to differentiate pizzle rot from ulcerative dermatosis. Ulcerative dermatoses, caused by a parapoxvirus, also present lesions in lips and legs, as well as in the genital area (see also Chapter 32). In goats, the caprine herpesvirus produces balanoposthitis in males and vulvovaginitis in females.[64,65] It is also a cause of abortion.[66,67]

Persistent Penile Frenulum and Penile Deviations

STALLION

Definition and Etiology

Persistent frenulum is rare in the stallion. However, penile deviations can occur in older stallions, particularly those that have been subjected to semen collection through most of their breeding career. In the United States, most of the affected horses have deviations to the right. It is thought that repeated bending of the penis to the left to facilitate entry into the artificial

vagina causes damage to the corpus cavernosum penis on the right side resulting in filling defects and subsequent deviation.

Treatment and Prognosis For most affected stallions, treatment is unnecessary and the horse continues to ejaculate normally. Some stallions have such a severe deviation that attempts to collect semen results in pain and lack of ejaculation. For these stallions collecting semen on the side ipsilateral to the direction of deviation often alleviates the problem.

BULL

Definition and Etiology Phallocampsis, or deviation of the erect penis, is a relatively common condition in the bull. The most common cause of penile deviation is persistent penile frenulum.[2] Other types of penile deviations include spiral, ventral, and S-curved deviations.[1] Less commonly, preputial or penile injury may result in scar tissue formation that subsequently leads to deviation of the erect penis.[1]

When the penile frenulum persists, it remains connected to the ventral surface of the tip of the penis and the prepuce and causes the penis to bend ventrally during erection by preventing complete extension.[68] Copulatory ability is interfered with except in some of the Zebu-influenced breeds that are endowed with a plentiful prepuce.[1] Diagnosis is based on physical examination of the extended penis.

Because spiraling of the penis is thought to be a normal physiologic event that occurs in the vagina during ejaculation,[69] care should be taken in making this diagnosis. Bulls affected with penile deviations often have a history of no problems in mating cows for some time, occasionally for several breeding seasons. If such bulls have been closely observed, it may have been noted that the condition did not occur on every mating attempt, but the frequency of occurrence gradually increased until bulls might require numerous mounts to successfully intromit and breed a cow in estrus.[2] Penile deviations occur at full erection when the CCP is maximally distended with blood. Caution should be exercised in diagnosing this condition during erection stimulated by electroejaculation. Such erections are not considered to be entirely physiologic and frequently result in penile deviations in bulls that have no deviations under natural mating conditions. The spiral deviations that occur with use of the electroejaculator may be a result of tension exerted by the retractor penis muscles.[1] Diagnosis is best based on observing occurrence of the deviation frequently in natural mating situations.

The ventral or rainbow deviation of the penis is less common than the spiral deviation and is a result of the apical ligament being too thin to support the engorged, stretched distal end of the erect penis.[1] The ventral curvature may be quite pronounced, preventing affected bulls from directing and inserting the penis into the vagina of the female.

The least common of the spontaneous penile deviations is the S-shaped curvature. It primarily occurs in older bulls with an apical ligament that is short in relation to an excessively long penis.[1] Penile deviations that result from adhesions that developed from penile or preputial injury are diagnosed by physical examination.

Treatment and Prognosis Persistent penile frenulum is easily corrected by severing the persistent band. Owners of affected bulls should be advised of the probable genetic basis and therefore the undesirability of retaining such bulls for breeding.[1] Treatment of spiral and ventral deviations is surgical.[1]

Tumors of the Penis and Prepuce

STALLION

Clinical Signs and Differentials The most common neoplasm of stallion genitalia is squamous cell carcinoma (SCC). Generally, it is of low malignancy.[1,70] The tumor usually involves the glans penis but may also involve the shaft of the penis and prepuce and produce a fetid discharge.[17,18] Large tumors may ulcerate and bleed, resulting in hemospermia. Carcinomas may resemble *Habronema* granulomas, which are more common and are diagnosed by histologic examination of affected tissue.[2,5] Carcinomas are usually well differentiated and surrounded by eosinophils. Necrosis and calcification may occur, but parasite larvae are usually not present[17] unless secondary habronemiasis has occurred from flies feeding on the ulcerated tissue. Carcinomas may extend into the CCP or may metastasize to the inguinal lymph nodes or other abdominal or thoracic organs.[17] The superficial inguinal lymph nodes lie midway between the prepuce and external inguinal ring; secondary tumors in this region often grow rapidly and develop necrotic centers with purulent sinuses that must be differentiated from bastard strangles.[1]

Tumors encountered much less frequently include melanoma, papilloma, angioma, lymphosarcoma, and sarcoid. Melanoma is a common equine tumor, especially of gray horses,[13] and occasionally involves the penis and prepuce[1,2,71] (see Chapter 40). Genital papillomas are rare in stallions but may occur on the glans or shaft of the penis. The lesions appear as multiple proliferative cutaneous growths and may become friable and result in hemorrhage during erection and ejaculation.[5] The lesions are generally thought to be caused by a papillomavirus,[72] and papillomavirus antigens have been found in cutaneous and genital papillomas.[73] Angiomas and lymphosarcomas have occasionally been reported on the genitals of stallions.[3] Sarcoids may involve the skin of the prepuce or scrotum.[1,71]

Treatment and Prognosis When SCCs are relatively small and noninvasively attached to the skin, neoplasms may be successfully treated by cryosurgery or hyperthermia.[74] Hyperthermic treatment (50° C for 1 to 2 minutes) appears to be most successful for SCC when lesions are small (less than ≈2 cm). If the tumor is extensive but superficial, cryosurgery may be attempted after the tumor is debulked and hemorrhage controlled. The remaining base of the tumor is then frozen and thawed twice; healing occurs as necrotic tissue is sloughed. Successful treatment of small lesions has been reported with topical application of 5-fluorouracil.[75] If removal of tumors is unsuccessful or if neoplasia is extensive, penile amputation may be necessary.[1,76] If superficial inguinal lymph nodes are involved, euthanasia may be required.[1]

In contrast to nongenital squamous papillomas, genital forms are generally quite refractory to treatment.[5] Surgical removal and autogenous vaccine administration to treat fibropapilloma of the penis of two stallions did not effect a cure.[37]

BULL

Definition and Etiology Fibropapilloma is the only tumor that frequently invades the bovine penis or prepuce.[17,18] The tumor may be single or multiple and usually affects young bulls. The cause is thought to be a papillomavirus antigenically similar to the virus that causes cutaneous papillomatosis in cattle.[77] Frequent mounting among young bulls is thought to result in damage to epithelial surfaces of the penis and prepuce that serves as a route of entry for the virus.[1,2]

Clinical Signs Small papillomas may be discovered during routine breeding soundness evaluations, but many become larger before they are discovered. Large fibropapillomas may prevent withdrawal of the penis into the preputial cavity. Fibropapillomas are pedunculated and attached at a narrow base in early cases. The surface becomes cauliflower-like and friable; hemorrhage is easily induced.

Treatment and Prognosis Many fibropapillomas regress spontaneously within a few months. Regression may be more likely in bulls approaching 2 years of age and usually occurs within 4 months of the appearance on the penis.[77,78] Several vaccines, including autogenous preparations, have been used for treatment;

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but vaccines may be more successful for prophylaxis.[2] Frequently, surgical removal is indicated, but the fibropapillomas may recur. If only superficial attachment is present, surgical removal is easily accomplished. Catheterization of the distal urethra before surgery is helpful in identifying its location to avoid injury. If attachment has become extensive and sessile, amputation of a portion of the distal penis may be necessary.[1] Housing of young replacement bulls in individual pens, if possible, is recommended as a method to reduce the incidence of penile fibropapillomas.

Parasitic Infestations of the Penis and Prepuce

STALLION

Definition and Etiology *Habronema muscae, Habronema microstoma,* and *Draschia megastoma* larvae commonly invade the urethral process, glans penis, and preputial ring of stallions.[1,13] Other terms for this condition are "genital bursatti" and "summer sores."[17]

Clinical Signs Shallow irritations progress to irregular 1- to 3-cm granulomatous growths that may involve the entire circumference of the urethral process.[2] Lesions are friable and bleed when manipulated. Stretching of the infected urethral process during penile engorgement and ejaculation may result in hemospermia.[5] Pruritus associated with the lesions may be intense. Frequent micturition and dysuria may resemble urine spraying that accompanies accumulation of smegma in the urethral diverticulum ("bean"). Lesions subside during the colder months in northern areas but usually reappear and increase in size during subsequent warm weather.[2] Diagnosis is made by seeing yellowish granules (calcified larvae) in the lesion and by microscopic identification of larvae.[13]

Treatment and Prognosis See Chapter 40 for treatment and prognosis information.

Hemospermia

Hemospermia refers to contamination of ejaculates with blood. Stallions with overt hemorrhage into ejaculates are subfertile. Erythrocytes, rather than serum, have been implicated for the marked depression of fertility, although the precise factor(s) involved are not known.[39] A small amount of sanguineous contamination is compatible with fertility, especially if the semen is quickly diluted with a suitable extender before insemination. A disproportionate number of leukocytes to erythrocytes suggest infection of the internal genital organs. Specific causes of hemospermia include lacerations of the penis, cutaneous habronemiasis, urethritis, urethral lacerations, and infection or inflammation of the accessory genital glands,[5] which are discussed elsewhere in this chapter.

Urospermia (Urination during Ejaculation)

Definition and Etiology Urospermia is an uncommon but perplexing disorder of breeding stallions. Affected stallions generally exhibit normal libido and mating ability, but semen becomes contaminated with urine during the ejaculatory process. The problem may be incessant or unpredictably intermittent; urination can occur at any time or continuously during ejaculation. The amount of urine is up to 250 mL or more.[5]

The underlying cause(s) of urospermia is speculative. Closure of the bladder sphincter and seminal emission are controlled by the α-adrenergic sympathetic nervous system, and a disturbance in this pathway might contribute to urospermia.[79] Similarly, neuropathies that result in bladder paralysis (e.g., cauda equina neuritis or nerve damage secondary to EHV-3 or sorghum/Sudan grass poisoning) can create urinary incontinence that permits voiding during ejaculation. Most stallions with urospermia do not exhibit signs of a neurologic deficit.[5] In ruminants, urine can also contaminate semen collected by electroejaculation. To reduce this risk it is recommended to avoid water ingestion 12 to 24 hours before semen collection.

Clinical Signs and Differentials Gross contamination of ejaculated semen with urine is easily detected by its color and odor. Contamination with significant quantities of urine adversely affects sperm motility and fertilizing capacity. Elevated concentrations (relative to serum levels) of urea nitrogen or creatinine in semen document the presence of urine in the ejaculate.[5,80]

Treatment and Prognosis Treatment options for urospermia vary, can be arduous, and are often unrewarding. Delay of semen collection (or breeding) until immediately after the stallion has voided urine may be a helpful management policy. Urination can be stimulated by administration of a diuretic drug (e.g., furosemide). Stallions may also void urine when provided access to feces of another stallion. Some stallions can be trained to urinate on command. Alternatively, the bladder can be catheterized to aid evacuation of urine before breeding, but urethritis or cystitis may result from routine use of this procedure. Fractionation of ejaculates using an open-ended artificial vagina can be used alone or in combination with any of the previously mentioned measures. When an open-ended artificial vagina is used, only the first three jets of the ejaculate are collected. These jets contain a majority of the spermatozoa in the ejaculate and urination may not occur until the end of the ejaculatory process. Dilution of urine-contaminated semen in extender can restore sperm motility.[81] Semen may be centrifuged after initial dilution and the sperm pellet resuspended in extender before insemination[5]; however, centrifugation to remove urine may not provide a significant advantage to dilution in extender.[81]

Pharmacologic agents such as bethanechol chloride or flavoxate hydrochloride have been used in an attempt to correct urospermia but usually without success.[5] α-Sympathomimetic drugs have sometimes been used successfully to prevent retrograde ejaculation in men, but their use has not been critically studied in stallions.[82] Oral administration of imipramine (100 to 500 mg twice daily) has reportedly been useful for controlling urospermia in stallions, presumably by enhancing contractility of the bladder neck during emission.[79]

Infertility Caused by Diseases of the Scrotum and Testes

Scrotal Injury, Hydrocele, and Hematocele

Definition and Etiology Trauma to the scrotum can result in excoriation, lacerations, hemorrhage, and edema.[2,17] Systemic diseases such as hepatic disease and equine infectious anemia may result in scrotal edema.[2,24] Suppurative inflammation may develop as an extension of scrotal injury.[2] Adhesions often develop between the visceral and parietal tunics when inflammation, infection, or hemorrhage occurs.[18] Adhesions are usually thin fibrous strands that become thickened with time. In such cases the testis and its tunics are not freely movable within the scrotum.[17]

Hydrocele is an accumulation of serous fluid within the vaginal tunic.[18] Ascites, anasarca, or local lymphedema may contribute to hydrocele because the vaginal tunic communicates with the peritoneal cavity.[17] Accumulation of a significant volume of fluid around the testis may cause thermal degeneration and a decline in seminal quality.[83] In Texas, a seasonal hydrocele has been described in bulls submitted to breeding soundness examination during the fall and winter season.[84,85] This type of hydrocele was associated with ascites and intestinal edema and has been attributed to a hypersensitivity reaction to gastrointestinal nematodes.[85,86]

Hematocele occurs when trauma to the scrotum results in accumulation of blood within the testicular tunics.[18] Hematoceles can be primary due to a testicular trauma or secondary to hemoperitoneum.

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Scrotal damage initially accompanies hematocele. Thermal degeneration of the testes follows, and a thick fibrous capsule encompasses the testis after the blood clot organizes.[87]

Clinical Signs and Differentials Diagnosis of scrotal injury, hydrocele, and hematocele is made by physical and ultrasonic examination of the scrotum. Testes remain freely movable within the scrotum if hydrocele is present. Ultrasonographic examination reveals variable amounts of anechoic fluid present surrounding the testes and epididymides, which are easy to visualize because of their echoic nature against the fluid background. With hematocele, evidence of trauma is often present, with thickening of the scrotal skin. Blood surrounding the testis and epididymides becomes progressively more echogenic with time as the clot organizes.[5,88] Extensive edema of the scrotal fascia next to the tunica dartos may be difficult to differentiate ultrasonographically from hematocele. Abdominal paracentesis is helpful in eliminating ascites or peritonitis as causes of hydrocele. Palpation per rectum of stallions and bulls may occasionally reveal that the internal inguinal rings are enlarged, readily permitting fluid transfer into the vaginal cavity.

An aseptic tap is useful to identify the character of this fluid and must be performed with care not to contaminate or penetrate the testis or its visceral vaginal tunic.[87] A modified transudate of low cellularity is typical of fluid drained from a hydrocele.[89] Fluid usually returns after drainage unless the initiating cause is corrected.[5] Determining and treating the cause of ascites (e.g., pepsinogen levels in stomach abomasal injuries, gastrointestinal parasites in feces) could provide permanent cure of the ascites and hydrocele.[85,86]

Treatment and Prognosis Acute scrotal injury is treated with cold water or ice application to reduce edema (see earlier discussion on penile and preputial injuries). Lacerations and abrasions should be treated with topical antibiotic ointments. Systemic antiinflammatory drugs and antibiotics may reduce swelling, control infection, and prevent abscess formation.[5,87]

Scrotal thickening usually results in elevation of testicular temperature, causing degeneration and atrophy similar to that seen with experimental scrotal insulation.[90-92] Semen quality quickly deteriorates, and a rapid reduction in numbers and motility of spermatozoa occurs with a concurrent increase in morphologic abnormalities of spermatozoa.[2,17,93] If swelling and edema resolve and adhesions do not develop among the testes, tunics, and scrotum, spermatozoa may gradually reappear in the ejaculate by 1 to 2 months after injury, but 4 to 5 months may be required for testes to return to normal size and sperm production.[4] One or both testes may remain atrophic and become firm because of fibrosis and loss of tubules. If only one testis is atrophied, the normal testis may eventually hypertrophy.

If hemorrhage occurs within the scrotum or testicular tunics, the prognosis for return of testicular function is poor. In unilateral cases, surgical removal of the clot and affected testis may minimize damage and speed recovery of the remaining testis.[94,95] Hydrocele is managed by correcting the underlying cause of fluid accumulation such as peritonitis or ascites.[87] Exercise may aid in control of fluid accumulation in some horses. Some stallions and bulls with persistent minor fluid accumulations within the tunics may continue to produce sufficient normal spermatozoa.[2] Permanent testicular degeneration may result in cases with extensive fluid accumulation that are unresponsive to therapy. If the condition is unilateral, removal of the affected testis may permit the animal to remain in service.[89] Because hydrocele and associated impairment of spermatogenesis may be transient (2 to 6 months),[84] caution should be exercised in recommending castration or culling of affected animals until demonstration that the disorder is long-standing.

Scrotal Dermatitis/Abscess

The scrotal skin is delicate and vulnerable to dermatitis. Causes include nonspecific environmental contaminants, bacteria, fungi, parasites, and frostbite.* Scrotal abscesses are not uncommon in small ruminants and are due to shearing injuries and penetrating wounds.[11] Treatment is directed toward removing the affected testis. Bulls affected by frostbite should be provided a warm and dry environment.[98] Systemic and local antibiotics may be indicated. Abscesses should be drained. Thermal degeneration of the testes may follow dermatitis and may be temporary or permanent.[2] Semen quality should be evaluated at periodic intervals after skin lesions have resolved to gauge prognosis for improvement and return to fertility.

Testicular Aplasia and Hypoplasia

Definition and Etiology Complete absence (aplasia) of one or both testes is rare, and usually occurs in conjunction with anomalous development of other organs.[2,99] Testicular hypoplasia may be unilateral or bilateral and affects both scrotal and abdominal testes.[18] Testicular hypoplasia is thought to result from failure of germ cells to multiply in the gonad.[2] Causes of testicular hypoplasia may include transplacental infections and intoxications, zinc deficiency, hormonal insufficiency, impaired testicular descent, abnormal karyotype, and vascular disturbances.[11,12,17,18,93,100] Exogenous administration of hormones to prepubertal males can result in testicular hypoplasia. Testicular size of adult stallions is reduced after prolonged administration of exogenous steroids.[101-103] Scrotal circumference is diminished in bulls implanted with zeranol.[104]

Clinical Signs and Differentials Hypoplastic testes are usually smaller than normal, but they are occasionally normal in size.[17,105-107] Stallions 3 years of age should have a scrotal width greater than 8 cm.[24,108] Yearling rams with a scrotal circumference of less than 30 cm and mature rams with a scrotal circumference of less than 32 cm are not recommended for breeding.[109] The texture of affected testes varies from normal to soft in mild or moderate hypoplasia. Severely affected small testes are firm because of the relatively increased amount of stromal connective tissue.[18] History is an important component in the clinical assessment in order to differentiate hypoplasia from atrophy. If uncertain, reexamination needs to be performed. Factors that influence the scrotal circumference in ruminants are breed, age, body condition score, and season.[110] In bulls the minimum recommended scrotal circumference is 30 cm for 15 months old or younger and 34 cm for 2 years old or older by the criteria established by the Society of Theriogenology.[111] Scrotal circumference in bulls is positively correlated with the number of normal functional seminiferous tubules and is negatively correlated with pathologic seminiferous tubules in bulls.[107] In bulls the heritability for scrotal circumference is medium to high.[110,112] In addition, scrotal circumference is negatively correlated with age at puberty of the female offspring. Bulls with higher scrotal circumference will produce females that acquire puberty earlier than females produced by contemporaneous bulls with smaller scrotal circumference.[110,112]

Depending on the number of seminiferous tubules affected, ejaculates from males with testicular hypoplasia may be azoospermic or contain a low concentration of spermatozoa with numerous morphologic defects.[2] Round spermatogenic cells may also appear in ejaculates, along with giant and medusa cells.[18]

Treatment and Prognosis No successful treatment is available for severe hypoplasia. The useful breeding life of males with testicular hypoplasia may be shortened because affected bulls are thought to be predisposed to early testicular degeneration.[105] Because of the value of some individuals, particularly stallions, owners may elect to breed males with small testes. Effective management of such stallions is based on breeding a book of mares limited by the number of normal, motile spermatozoa present in ejaculates.

*References 2, 11, 13, 17, 18, 93, and 96-98.

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Cryptorchidism

Definition and Etiology Incomplete or abnormal testicular descent is thought to be a genetic abnormality.[2,12,18] The inheritance pattern in horses is thought to be dominant,[113] although studies of offspring of some cryptorchid stallions suggest that inheritance of the condition may be multifactorial.[114] The relative risk for equine cryptorchism also appears to be influenced by breed.[115] Other modes of inheritance have been suggested from studies of offspring of cryptorchid rams, bucks, and bulls. These include a recessive gene with incomplete penetrance in Angora goats,[116] a dominant gene with variable expressivity in Hereford cattle,[117] and either an autosomal recessive gene or a dominant gene with incomplete penetrance in inbred sheep.[118]

Testes originate near the kidney and migrate to the superficial inguinal rings before descending into the scrotum; the epididymis precedes the testis in descent. Retained testes are located at some point along the path of migration.[17] Ectopic testes not associated with cryptorchidism may be found under the skin of the ventral caudal abdomen or elsewhere in bulls.[1,18]

Clinical Signs and Differentials The majority of cases of cryptorchidism in stallions are unilateral.[119] Although testicular descent can occur in horses up to 2 years of age, the testes are normally descended at birth in large animals.[120] Testes are readily palpated in the scrotum of colts at 30 days of age.[2,3] Spermatogenesis is inhibited in the abdominal testis because of the elevated temperature within the abdomen. The interstitial cells remain active and secrete testosterone,[3,17,18] enabling even bilateral cryptorchids to maintain libido and copulatory activity. The descended testis may be hypertrophic[17]; unilateral cryptorchids are fertile but are not considered sound breeders.[2,121]

Deep palpation of the superficial inguinal rings may reveal the testis in the canal ("high flankers"). If the testis is not located in the inguinal canal, transrectal palpation or ultrasonography can be performed in stallions and bulls in an attempt to locate a testis or to detect the vas or epididymis entering the superficial inguinal ring, thereby providing evidence of descent into the inguinal canal.[122]

Clinical Pathology Equine cryptorchids have high basal concentrations of testosterone (usually >100 pg/mL) and respond to human chorionic gonadotropin (hCG) administration (10,000 to 12,000 IU IV) with a significant elevation of circulating testosterone within 30 to 60 minutes if testicular tissue is present. Geldings and "false rigs" (geldings with malelike behavior) have low basal concentrations of testosterone (<40 pg/mL) and do not respond to hCG stimulation. Stallion testes contain a high concentration of conjugated estrogens, and a single measurement of high plasma conjugated estrogens (>400 ng/mL) is reported to be almost as reliable in diagnosing cryptorchidism as hCG stimulation.[123,124] Recent data suggest that anti-müllerian hormone (AMH) serum concentrations may serve as a useful marker for the presence of cryptorchid testes in the horse.[124a] In some ruminants, measurement of testosterone concentrations before and after administration of hCG has also proved helpful in identifying cryptorchidism.[125]

Treatment and Prognosis Stimulation of testicular descent with repeated injections of gonadotropin-releasing hormone (GnRH), sometimes combined with hCG or acupuncture, has been attempted, but the success has not been critically evaluated. Surgical removal of the abdominal and scrotal testes is indicated.[1] Surgical placement of the retained testis into the scrotum is not considered an ethical procedure.

Testicular Degeneration

Definition and Etiology Testicular degeneration is an acquired condition with multiple etiologies.[126] Infections or traumatic orchitis may progress to permanent degeneration. Degeneration may be associated with thermal factors after elevation of body temperature by systemic infections; prolonged increase or decrease in ambient temperature; scrotal insulation from edema, dermatitis, scrotal hernias, or hemorrhage; or abnormal conformation resulting in an incompetent heat exchange system.[†] Degeneration results when testicular vasculature becomes occluded in torsion of the spermatic cord.[130] Obstruction of the proximal epididymis and malformation of the efferent tubules results in degeneration caused by pressure within the seminiferous tubules.[93] A variety of chemicals and ionizing radiation are capable of inducing testicular degeneration.[17] Administration of steroid hormones may induce testicular degeneration by inhibiting secretion of gonadotropins.[104,131] Gradual degeneration also occurs with increasing age.[132]

Clinical Signs and Differentials Diagnosis of testicular degeneration is based on physical examination and semen evaluation. Testes are typically thought to be small, but they may be normal size. The testicular consistency and elasticity of the testes is also decreased. Semen examination reveals a low concentration of spermatozoa, a decreased number of spermatozoa in the ejaculate, and a high percentage of spermatozoa with morphologic defects, sometimes with premature (round) germ cells.[1] Without a history of normal testis size and function before atrophy, differentiation from testicular hypoplasia is usually not possible.[18,24] Discrepancies between testicular size (measured by scrotal width in stallions and scrotal circumference in ruminants) and daily sperm output may indicate testicular degeneration.[104,107,133,134]

Clinical Pathology The measurement of plasma hormone concentrations may be helpful in establishing a diagnosis of testicular degeneration in large animals. However, the relationship between the concentrations of various hormones and the parameters of testicular function appears to be quite variable. Measurements of hormone concentrations in subfertile stallions have demonstrated that serum gonadotropins can be abnormally low or high.[135] Hormonal criteria for confirming testicular degeneration in stallions typically include low concentrations of testosterone, with concurrent low LH concentrations in early cases of degeneration, or with high FSH and low estradiol concentrations in cases of chronic (or irreversible) testicular degeneration.[4] Less is known concerning hormone concentrations in other large animal species with testicular dysfunction. In one study, plasma testosterone concentrations were lower in young beef bulls with testicular degeneration than in a similar group of normospermic bulls; however, patterns of secretion and plasma concentrations of LH and FSH were not significantly different between the two groups.[107] Scrotal insulation of rams resulted in an increase in plasma FSH concentrations and a decrease in plasma testosterone concentrations within 1 to 4 weeks.[136]

Testicular biopsy can confirm degeneration.[137] Excision of an amount of tissue sufficient for evaluation often results in hemorrhage, pressure degeneration, and necrosis.[2] Therefore testicular biopsy is usually undertaken only as a final recourse. However, testicular biopsy in the stallion appears to be a relatively safe procedure.[138]

Treatment and Prognosis Once testicular degeneration has occurred, treatment is usually of no benefit.[2] However, any factors that might contribute to testicular degeneration (such as febrile conditions or systemic illness) should be corrected. Treatment of injuries of the scrotum and its contents has been described previously in this chapter.

Recent findings regarding variations in serum hormone concentrations in subfertile stallions have stimulated an interest in gonadotropin replacement therapy, including the use of GnRH. Although the hypothalamic-pituitary-testicular (HPT) axis of the stallion is remarkably refractory to GnRH-induced downregulation compared with other domestic species,[139] there are few controlled studies to

[†]References 2, 3, 17, 18, 90, 98, and 127-129.

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evaluate the effectiveness of GnRH therapy. In one study, pulsatile or constant administration of GnRH for 20 weeks did not promote testicular growth or alter spermatozoa output in reproductively sound or unsound stallions.[140] In some cases, degeneration is temporary and improved semen quality is evident after 2 to 5 months. The prognosis for an animal recovering its fertility and the economic losses the client will sustain from treatment and decreased production must be considered when deciding whether treatment of testicular degeneration is warranted.

Orchitis

Definition and Etiology Orchitis is most commonly caused by infection or trauma. Bacterial infections may develop hematogenously or occasionally by retrograde movement from infected accessory sex glands.[18] Extension of infection to the testes from periorchitis or epididymitis also occurs.[93] Testicular enlargement is due to edema that accompanies the inflammatory reaction. Contusion and inflammation of the testes occur in racing stallions, particularly Standardbreds.[3] *Streptococcus zooepidemicus* is commonly isolated from infectious orchitis in stallions.[4] In bulls, infectious orchitis is caused by *B. abortus, M. tuberculosis, A. pyogenes, Nocardia farcinica,* bovine herpesvirus 1 (IBR-IPV), and other miscellaneous organisms.[2,17,18,93] Epididymo-orchitis in rams may be associated with *B. ovis* or *Actinobacillus seminis* and *Actinobacillus*-like organisms.[12]

Clinical Signs and Differentials Acutely orchitic testes are hot, swollen, and painful. The swollen testis is turgid because of restriction by the tunica albuginea. Edema of the testicular parenchyma and concurrent presence of periorchitis or epididymitis may be detectable by ultrasound examination. Increased testicular temperature, congestion, and interference with circulation lead to ischemia and infarction. Abscesses sometimes develop, occasionally culminating in purulent liquefaction of testicular parenchyma. Testicular atrophy and fibrosis follow as the condition becomes chronic.[17,18]

Acutely affected animals may refuse to mate. Ejaculates may contain numerous white blood cells. Variable mineralization of seminiferous tubules can occur as a chronic change. Decreased sperm motility and increased sperm morphologic abnormalities are evident. Standardbreds affected by acute orchitis may switch from a trot to a pace, whereas Thoroughbreds may suddenly develop a hopping gait.[2]

Treatment and Prognosis Treatment consists of scrotal cryotherapy and systemic administration of antiinflammatory drugs. Bacterial orchitis is treated with antibiotics chosen by semen culture and in vitro sensitivity. Antibiotic therapy should continue for 1 to 2 weeks beyond resolution of testicular swelling and pain.[5] Testicular atrophy and sterility are common sequelae to orchitis.[3] Changes in the testes, including precise measurements of in situ testis size, are followed by sequential ultrasound examinations or caliper measurements. Serial semen analyses over a period of several months allow the clinician to monitor response to treatment and return of testes to normal production of spermatozoa.

Prevention and Control Support devices may aid in preventing recurrence of traumatic orchitis in racehorses. With *Brucella* or *Actinobacillus* orchitis in sheep, the presence of subclinical carriers in the flock must be considered.[22,62]

Testicular Neoplasia

Definition and Etiology Primary testicular tumors are uncommon in large animals but may be slightly more frequent in older bulls than in stallions or rams. Testicular tumors originate from the interstitial (Leydig) cells, Sertoli cells, and the germinal epithelium. Testicular teratomas and lipomas of the testicular surface and lymphosarcoma also occur.[‡] Although the incidence of testicular tumors is relatively greater in retained than in scrotal testes in dogs, this predisposition has not been confirmed in large animals, perhaps because most are castrated at an early age before the time of usual onset of testicular neoplasia. Retained testes in the horse, however, are thought to be more prone to neoplasia. Teratomas in particular are found more commonly in cryptorchid than in scrotal testes, probably because they are embryonal in origin and their size prevents migration of the testis into the scrotum.[17,18]

Seminomas are the most common primary testicular tumor in the descended testes of adult stallions with the majority occurring in stallions older than 10 years of age.[17,18,144] Seminomas are not hormonally active and are usually benign, but they may be malignant and invade inguinal and abdominal tissues.[5,145] Seminomas are rare and benign in bulls and are rarely seen in aged rams, in which they are occasionally highly malignant.[17] The tumor arises from the germinal epithelium, occurs in retained and scrotal testes, and grows rapidly.[2,17]

Interstitial (Leydig) cell tumors have been reported in stallions and bulls[93] and can have a negative impact on semen quality and fertility.[146,147] Most do not produce androgenic hormones.[17] They may be single or multiple in one or both testes and are commonly 1 to 2 cm in diameter.[17]

Sertoli cell tumors are reported in horses, cattle, and sheep, but they are rare. Although metastasis is uncommon, extension of neoplastic tissue into the testicular vein and lymphatics can result in hydrocele.[17] Because of the importance of Sertoli cells in spermatogenesis, these tumors are likely to exert an adverse effect on semen quality and fertility. Tumors in newborn or young calves may be due to impaired embryogenesis.[17,143]

Teratomas are usually a benign tumor commonly found in cryptorchid testes of horses.[141,148] They are rare in other large domestic species. The tumors are often cystic and vary in diameter from 10 to 25 cm or more. Structures present in teratomas arise from all three embryonic layers and include hair, nervous tissue, salivary glands, adipose tissue, cartilage, and bone.[17,18]

Clinical Signs and Differentials Neoplastic testes are often larger than normal, with an affected scrotal testis often twice the size of the unaffected testis, especially in cases of seminoma. Abdominally located testicular tumors can be quite large. Neoplastic testes, particularly seminomas, are typically irregular and firm. Swelling may extend into the spermatic cord, and pain that interferes with breeding or is evident on palpation may be present. Ultrasonographic appearance of testicular tumors tends to be discrete, well-circumscribed hypoechoic areas within the usually homogeneous testicular parenchyma.[5,88] However, seminomas may involve so much of the testis at the time of diagnosis that differentiation between neoplastic and normal tissue can be difficult.

Swelling of the affected testis may interfere with thermoregulation of the contralateral testis, resulting in decreased sperm production. Semen examination, however, may reveal seminal parameters to be within normal limits, and fertility may be acceptable. A significant amount of normal testicular parenchyma may remain covering the tumor, and living spermatozoa may or may not be present in the epididymis on the same side.[2,17,18,149]

Treatment and Prognosis Testicular tumors should be surgically removed. Although metastasis is uncommon, early identification and removal of unilateral tumors prevents spread to other tissues. If semen quality is satisfactory in seasonal breeders, removal may be delayed until the breeding season is completed to avoid the transient decrease in semen quality associated with postsurgical swelling. If neoplasia is bilateral, surgical removal may be delayed until semen quality deteriorates sufficiently to negate the use of the animal for breeding.[5]

[‡]References 2, 17, 18, 70, 93, 131, and 141-143.

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Infertility Caused by Diseases of the Spermatic Cord

Torsion of the Spermatic Cord

Definition and Etiology Torsion of the spermatic cord occurs more commonly in stallions than in other large animals because of the horizontal position of the testes within the scrotum. Torsions may be transient or permanent and typically are of 180 to 360 degrees, but rotations may be greater.[130] Abnormal elongation of the caudal ligament of the epididymis (scrotal ligament), the proper ligament of the testis, or an excessively long mesorchium may encourage spermatic cord torsion.[130,150]

Clinical Signs and Differentials Torsion of the spermatic cord occurs in degrees that vary from those producing no pain or abnormality of semen to those involving vascular obstruction and acute colic.[3] Torsion is often a transient condition that does not interfere with testicular function or cause pain.[121] In those cases the testis is usually rotated 180 degrees or less. If torsion is of sufficient degree to result in vascular compromise, acute pain results.[2,3,150,151] Diagnosis of torsion of the spermatic cord is aided when displacement of the tail of the epididymis and scrotal ligament is evident on palpation. The head of the epididymis is normally located craniodorsal to the testis, and the tail lies caudally, where it is attached to the testis by the proper ligament. The tail of the epididymis is most readily palpable, and its location is helpful in determining the degree of rotation. Torsions of 360 degrees or greater generally cause clinical signs that must be differentiated from strangulation of herniated contents into the scrotum. The primary method used to differentiate between the two conditions is palpation per rectum of the superficial inguinal ring to identify if herniation is present.[5]

Clinical signs of vascular impairment with spermatic cord torsion include abdominal discomfort, elevated heart and respiratory rates, unilateral swelling and edema of the scrotum, and increased testicular temperature.[5] Affected testes are painful and quickly become soft and friable.[2,3,150,151]

Treatment and Prognosis Manual correction of spermatic cord torsion is sometimes possible, but recurrence is likely. To attempt manual correction, the horse is sedated and the testis is rotated in the direction opposite the torsion. Both hands are used to reposition the scrotum as the testis and its tunics are rotated.[3] Surgical correction is indicated if manual correction is not possible.[5] Nonsteroidal antiinflammatory drugs and analgesics may be administered to control pain.

The rapidity with which correction must occur is unknown; human testes may be salvageable if torsion is corrected within 6 hours. If hemorrhage or necrosis of the testis is evident, removal is indicated because the contralateral testis may become permanently damaged. The mechanism of the damage is probably immunologic, resulting from antibodies to spermatozoa liberated as a result of ischemia.[152]

Varicocele

Definition and Etiology Varicoceles are abnormally distended and tortuous veins of the pampiniform plexus.[62,129] Varicoceles are most often recognized in rams, where dilations in vessels may reach 15 cm and discourage movement and libido.[118] Data from slaughterhouse necropsies show an increased incidence of varicoceles with age, reaching approximately 2% in rams 3 years and older.[99] Varicoceles have been reported infrequently in stallions.[5]

Varicoceles may result from insufficiency of veins draining the testis or a deficiency of the fascia and connective tissue surrounding those veins that allows backflow and stasis of blood in the vessels.[17] Infertility associated with varicocele is thought to be due to disturbance of the local thermoregulatory mechanism, causing increased testicular temperature and subsequent disturbance in spermatogenesis.[5] In addition, the varicose veins could also affect the level of oxygenation and normal interchange of hormones between the arteries and veins.[83] In rams, bilateral varicoceles are more common than unilateral varicoceles.[153,154] This is in sharp contrast with men in which 70% of varicoceles are unilateral and located on the left side.[153] Concomitant atrophy of the testis is common in rams.[99] Bilateral varicoceles and atrophied testes have been reported in the ram.[154]

Clinical Signs and Differentials Diagnosis of varicocele is made by palpating the dilated tortuous veins ("bag of worms") within the spermatic cord.[2,62] Confirmation of the varicocele has been accomplished by ultrasonographic examination in stallions. Large echolucent areas in the venous plexus of the spermatic cord, sometimes with concurrent distention of the central vein of the testis, are described as the identifying features.[88] The ultrasonographic appearance of a suspected varicocele can be compared with the structures of a noninvolved contralateral testis and spermatic cord, or those of another nonaffected animal.

Thrombosis of the varicocele can occur.[2,17] The large, organizing laminated thrombi can be mistaken as *Corynebacterium pseudotuberculosis* abscesses in the scrotal fascia of rams.[17] Varicoceles might also be mistaken for sperm granulomas of the caput epididymis. Unless thrombosis has occurred, varicoceles are typically fluctuant and soft and fail to elicit pain when palpated.

Treatment and Prognosis Surgical removal of varicocele has improved semen quality and fertility of some human patients but has not been reported in large animals. Thrombosis of a varicocele necessitates unilateral castration, with transection of the spermatic cord proximal to the thrombus.[1] Castration is also recommended for rams because of potential heritability risks.[118]

Infertility Caused by Diseases of the Epididymis and Accessory Sex Glands

Epididymitis

Definition and Etiology Epididymitis is caused by infection or trauma and may occur separately but is commonly secondary to orchitis or infection of the accessory sex glands.[17,18,155] The tail of the epididymis is commonly involved, but the head and body may be affected. *Streptococcus zooepidemicus* is commonly isolated from equine epididymitis, although a number of other miscellaneous organisms including *Proteus mirabilis* have been incriminated.[2,156] In bulls, *B. abortus, A. seminis, A. pyogenes,* and other miscellaneous organisms cause epididymitis.[17,18,155] In mature rams the disease is commonly associated with *B. ovis,* whereas in ram lambs organisms from the *Actinobacillus, Haemophilus, Histophilus,* and *Corynebacterium* groups are prevalent.[62,157] Routes of infection have been postulated to be hematogenous, venereal, or ascending from genitourinary passages, similar to routes of infection proposed for orchitis.[2,17] Injuries, such as penetrating wounds, especially during shearing, could compromise the scrotal sac leading to epididymitis. All routes of infection are likely to occur to some degree, depending on the pathogen and species involved. In an interesting study performed in yearling rams, conjunctival inoculation of *B. ovis* culminated primarily in localized infections of the reproductive tract, which tended to first result in lesions of the distal tail of the epididymis.[158]

Clinical Signs and Differentials Diagnosis of epididymitis is based on detection of clinical signs that include pain when irregular swellings of the epididymis are palpated, changes in shape and texture of the organ, adhesions between the epididymis and scrotal tunics, and enlargement of the tail of the epididymis.[2,5,62] The course of epididymitis varies from acute swelling and edema to chronic abscesses, periorchitis, and fibrosis.[17,18] Granulomas may develop if

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sperm escape into surrounding tissue.[99,155,159] In rams, epididymal lesions may be palpable along the entire length. Abnormal sperm morphology (especially detached heads) and leukocytes in the ejaculate may be seen before lesions are palpable.[160]

Animals affected with the *Actinobacillus, Histophilus,* and *Haemophilus* groups of organisms may acquire an epididymo-orchitis syndrome.[62,161] Affected rams are usually younger than 1 year of age. They may be subclinical carriers or acutely ill with pyrexia, depression, pain as evidenced by an arched back, and unilateral or bilateral swelling and tenderness of the scrotal contents. If these animals recover from the acute phase, the disease may become chronic and is characterized by an enlarged, firm, and often irregular epididymis; palpable adhesions of portions of the epididymis to the testis and vaginal tunics; atrophic testes; abscess formation; and draining fistulas to the scrotal surface. Ultrasonographic examination of the epididymis may reveal dilated ducts, fluid accumulation around the tail of the epididymis, and cystic areas within the epididymis that contain purulent material.[5,88]

Clinical Pathology Inflammatory cells may be present along with abnormal sperm in the ejaculate of affected animals. Seminal leukocytes correlate positively with epididymitis lesions and correlate negatively with seminal quality.[160] Bacteriologic culture of the semen may aid in identifying infectious causes. Serologic tests for *B. ovis* and *H. ovis* are available and are helpful in determining exposure to the organisms.[62,161]

Treatment and Prognosis Infectious causes of epididymitis are treated with systemic antibiotics selected by in vitro sensitivity. The ability of the antibiotic to gain access to the epididymides must be considered. Treatment should continue for 1 to 2 weeks after inflammatory cells disappear from the semen. In unilateral cases, removal of the testis, epididymis, and spermatic cord on the affected side may salvage some valuable animals for breeding. If unilateral castration is elected, sequential postcastration examinations are indicated to ensure infection has not spread to remaining reproductive organs.[5]

Treatment of ram epididymitis is usually not recommended but might be attempted in valuable animals with minimal clinical signs. Oxytetracycline 10 mg/kg and dihydrostreptomycin 25 mg/kg IM twice daily for 7 days resolved shedding of *B. ovis.*[162]

In cases of moderate or severe bilateral epididymitis, the prognosis for recovery is poor. Obstructions and granulomas usually develop, resulting in sterility.[99] Testicular atrophy is a common sequela to epididymitis.

Seminal Vesiculitis (Vesicular Adenitis)

Definition and Etiology Inflammation of the vesicular glands is uncommon in stallions but more likely in bulls.[17,18,163-165] Bacterial infections including *B. abortus* and *P. aeruginosa* are incriminated in stallions.[3,38,166,167,168] In bulls, a variety of microorganisms have been isolated from cases of vesicular adenitis including *Actinobacillus actinoides, Aeromonas hydrophila, A. pyogenes, B. abortus, Chlamydophila psittaci, C. renale, C. pseudotuberculosis, E. coli, Histophilus somni, M. tuberculosis, Mycobacterium paratuberculosis, Mycoplasmas, Proteus mirabilis, Streptococcus, Staphylococcus, Ureaplasmas,* and *T. foetus.*[2,17,18,163,169-181] In bulls the most frequent microorganism isolated is *A. pyogenes.*

Vesicular adenitis may affect bulls of all ages but is most common in young growing bulls fed high-energy rations and housed together.[163] The prevalence may reach 20% to 30% in small groups of yearling bulls in close confinement.[165] The role of viral pathogens in outbreaks of the disease is not defined. Infections may arise by either ascending or descending routes from other areas of the urogenital tract, or hematogenously. Some bulls with vesicular adenitis submitted to necropsy presented anatomic defects at the level of the seminal colliculus, which could impair its normal opening and closing.[182] In addition, it has been suggested that spermatozoa or urine reflux into the vesicular glands could produce inflammation.[183] Frequent homosexual activity among young bulls, high nutrition, and fast growth rates may be involved in spread of the infection.[2,163]

Clinical Signs and Differentials The seminal vesicles of affected stallions may be of normal size or enlarged and painful when palpated per rectum.[166,167] Stallions may refuse to cover or may be unable to ejaculate.[3] Semen contains numerous neutrophils and blood.[38] Fertility of infected semen is reduced.[38] Bacterial pathogens are readily recovered from semen of affected stallions.[5] However, special culturing techniques are necessary to pinpoint the seminal vesicles as the site of internal genital infection (see Clinical Pathology later).[53]

Bulls affected with vesicular adenitis may be asymptomatic or exhibit nonspecific clinical signs other than deterioration of semen quality. In severe cases, pelvic inflammation and peritonitis result in pain reflected by reluctance to move, stiff gait, tense abdomen, difficulty on defecation, and refusal to mate.[2] In acute vesicular adenitis the palpation per rectum of the vesicular glands produces pain, and the examination is positive for an enlarged gland with loss of its lobulation and increased consistency. Other reproductive organs, particularly the ampullae, testes, and epididymides, may be inflamed.[163] Necropsy specimens of bulls with vesicular adenitis have shown concomitant inflammation of the prostate and bulbourethral glands (seminal vesicular syndrome)[163,184]; however, these changes cannot be detected by palpation per rectum. The vesicular glands may not be significantly increased in size during the acute phase. If inflammation becomes chronic, the glands usually enlarge, eventually losing their lobularity and becoming fibrotic.[2,17] Abscesses are often associated with *A. pyogenes* and may rupture into the rectum or urinary bladder.[2,18] Transrectal ultrasonography could be used to determine the degree and extension of the lesion in the vesicular glands.[185,186] Tubercular vesicular adenitis results in marked enlargement of the glands with caseous nodule formation. *B. abortus* causes suppuration, necrosis, and calcification of the glands.[17] Purulent exudate is present in the ejaculate, sometimes as thick clots. Neutrophils may become less evident in semen as the condition becomes chronic. The ejaculate volume could be reduced. Presence of floccules or flakes in the ejaculate can be observed, and color could vary from normal to yellow-brown. Poor sperm motility, increased morphologic defects, and an elevated pH are characteristics of semen from bulls with vesicular adenitis.[2] The levels of fructose, citric acid, and alkaline phosphatase in seminal plasma are reduced.[173,181,187] The catalase reaction is increased.[177]

Fertility of mildly affected bulls may remain satisfactory. More extensive involvement in which semen quality is markedly affected results in subfertility or infertility.[165] Semen from bulls with vesicular adenitis freezes poorly, and antibiotics used in extenders usually do not control the high numbers of bacteria present.[165,188,189]

Clinical Pathology Bacterial pathogens can be recovered from the semen of affected stallions. However, without other evidence of infection of the accessory sex glands, recovery of pathogens from the semen should be interpreted with caution because the bacteria could originate from another location. Repeated samples for culture should be obtained from the sheath, penis, fossa glandis, preejaculatory fluid, urethra (before and after ejaculation), and seminal vesicle effluent manually expressed through a sterile urethral catheter positioned at the colliculus seminalis. Prostatic fluids can be collected through a catheter by massage per rectum. The first jet of a fractionated ejaculate includes the secretions of the ampullae.[53] Alternatively, a suitable fiberoptic endoscope can be passed in the urethra to the level of the seminal colliculus and into the seminal vesicles. Purulent material may then be aspirated for culture.[5]

Vesicular secretions from bulls can be collected by extending and disinfecting the penis followed by irrigation of the distal urethra with sterile saline. A sterile catheter is then passed 30 cm into the urethra, and the accessory sex glands are massaged to stimulate their secretion. Fluid is collected into sterile containers.[190]

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Treatment and Prognosis Accessory sex gland infections are treated with antibiotics selected by culture and in vitro sensitivity. Antibiotics are administered for 2 to 4 weeks, but treatment failures may occur.[38] Negligible amounts of certain antibiotics may diffuse across mucosal cell borders into the seminal plasma.[191] Properties of antimicrobials suitable for parenteral treatment of accessory sex gland infections include high lipid solubility, a favorable pKa, and low protein binding. The antimicrobial should have a pH that is basic relative to the accessory gland fluid into which penetration is desired.[192] Vesicular and prostatic fluid have a pH of 7.3 to 7.5, whereas bulbourethral gland secretion has a pH of 8.0 to 8.2.[53,108] Antimicrobials that may prove suitable for treatment include the basic macrolides such as erythromycin, which is fat soluble and has a high pKa, and trimethoprim, which also has a high pKa and a high percentage of nonionized molecules in plasma favoring diffusion across the lipid membrane of epithelial cells.[192] Because of its antimicrobial spectrum and tissue diffusion characteristics, enrofloxacin has been found to be effective for systemic treatment of seminal vesiculitis in stallions. Treatment of stallions by lavage and instillation of antimicrobials directly into the seminal vesicles via a flexible videoendoscope can be accomplished by skilled operators. Removal of the affected gland has been performed in stallions and bulls.[166,188,189,193,194] A technique used with fair success in stallions with localized vesicular adenitis has been repeated irrigation through a catheter guided into the vesicles by endoscopy. Antibiotics are instilled into the vesicular gland lumen after each irrigation.[5] In bulls, treatment is controversial.[181-183,193,195,196] Some experts recommend antibiotic treatment, either oral or parenteral, for a minimum of 10 days.[2,195-197] In bulls, direct injection of different substances into the vesicular glands has been reported.[196-198] Administration of antibiotics, dimethyl-sulfoxide, and iodine solutions to induce gland fibrosis has been described with mixed results.[195] In young bulls with vesicular adenitis, parenteral administration of antibiotics was no different than in the "no-treatment" group,[196] which is in agreement with previous reports describing spontaneous recovery.[2,181,199] Additional measures to treat inflammation include performing repetitive semen collections, not only for monitoring the ejaculate but to evacuate the inflammatory secretions from the seminal glands as well.[181] Massage of the seminal glands per rectum has also been proposed.[2] The inclusion of nonsteroidal antiinflammatories to reduce inflammation, pain, and fibrosis has also been suggested.[181] Laser biostimulation of vesicular glands per rectum, in conjunction with antibiotics and antiinflammatories, has also been employed; however, no information about the efficacy of this treatment has been reported.[200] Seminal vesiculectomy could be used as an alternative after lack of response to medical treatment. Different techniques have been applied with variable results and complications.[187-189,193,194,201] If the bull recovers from surgery it can exhibit a decrease in seminal parameters such as motility, volume, sperm output, and seminal constituents,[187,188] which could affect the freezability of the semen.[189]

The prognosis of vesicular adenitis is difficult to determine due to the multiple etiologic organisms. Therefore the prognosis for correction of vesicular adenitis is only fair to poor. Mild cases may recover spontaneously in 2 to 3 months. In chronic cases, glands that do not abscess become fibrotic and destroyed even though purulent material does not persist in the ejaculate.[2,196] In stallions with vesicular adenitis, immediate filtration of the ejaculate in order to remove cellular debris and mixing of semen in an appropriate antibiotic-containing extender to control bacterial growth may maintain sperm motility and fertility.[55]

Blockage of the Efferent Ducts (Sperm Stasis)

Blockage of the efferent ducts between the testes and penile urethra sometimes occurs in stallions. If the condition is bilateral, azospermia results in spite of apparent ejaculation. The ampullae are frequently tense, and enlargement may be demonstrated by ultrasonography.[202-204] Massage of the ampullae per rectum followed by prolonged sexual stimulation and semen collection may result in ejaculation of a semen sample with a high concentration of spermatozoa, often present as "strings" or "plugs."[202] Large numbers of detached sperm heads, often in clumps, are commonly observed. Collection of semen on a regular schedule may aid in preventing recurrence once the blockage is relieved. Empiric treatment by blockade of β-receptors and stimulation of α-receptors has been successful in some stallions that fail to ejaculate.[205]

Sperm granulomas caused by accumulation of spermatozoa in blind efferent ducts are a common cause of infertility in the buck.[12] Granulomas have also been identified in stallions[206] and particularly in rams with sperm extravasation as a result of chronic epididymitis.[17,18]

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PART SIX

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Preventive and Therapeutic Strategies

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• CHAPTER 44

Critical Care and Fluid Therapy

K. GARY MAGDESIAN, *Consulting Editor*

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Equine Fluid Physiology

C. Langdon Fielding

Physiologic fluid compartments consist of total body water (TBW), extracellular fluid volume (ECFV), and intracellular fluid volume (ICFV). TBW is the most clearly defined compartment because it represents the total amount of water comprising an individual. Values for TBW in adult horses have been reported to range from 0.623 to 0.677 L/kg.[1-4] Values in foals are larger than adult horses and have been reported as 0.74 L/kg.[5] Acute changes in TBW in clinical patients can be detected with serial body weight measurements, but this becomes less accurate over longer periods of time.

ECFV represents the component of TBW that is not contained within the cells. This includes plasma volume, interstitial volume, and transcellular compartments (gastrointestinal tract, joint fluid, cerebrospinal fluid [CSF], body cavities, etc.). The ECFV has been measured using a number of techniques in horses; reported values in adult horses range from 0.214 ± 0.01 to 0.253 ± 0.01 L/kg.[1,6] Estimations of ECFV in foals are significantly larger, including 0.38 to 0.40 L/kg in newborn foals and 0.290 L/kg in foals 24 weeks of age.[5,7] Plasma volume has been determined to be 0.050 L/kg in healthy adult horses and 0.090 in foals at 2 days of age.[5,7]

ICFV is the volume of fluid contained within cells. It has been estimated as the difference between TBW and ECFV. Bioimpedance technology has also been used to estimate the volume of intracellular space in horses, whereas standard indicator dilution techniques cannot be easily applied to the ICFV.[1,2] Reported values for ICFV in adult horses range between 0.356 ± 0.01 and 0.458 ± 0.06 L/kg.[1,2] The ICFV of newborn foals is estimated to be 0.38 L/kg.[5]

Rapid changes in fluid balance and compartment volumes can occur during disease states, especially critical illness. The next section discusses the physiologic relationships between these fluid volumes.

Plasma and Interstitial Balance

Although both the plasma volume and interstitial volume are components of the ECFV, the plasma volume is separated from the interstitial space by blood vessel walls, with constant flow of fluid and proteins into the interstitial space. The plasma and interstitial volume, therefore, are in constant flux, and a single equation (the Starling hypothesis) describes the flow between these two spaces:

$$\text{Net capillary filtration } K_f([P_{cap} - P_{if}] - \sigma[\pi_P - \pi_{if}])$$

where K_f is the capillary filtration coefficient, being dependent on capillary surface area and hydraulic conductivity. The other five terms in the equation represent the primary determinants of fluid balance between plasma and the interstitium:

1. π_p is the colloid osmotic pressure (COP) within the capillary (capillary oncotic pressure).

   COP is determined by the concentration of plasma proteins, primarily albumin, and their ability to attract ions. Normal COP in adult horses is approximately 20 mm Hg (19 to 26 mm Hg) and in neonatal foals is 18.8 ± 1.9 (15 to 22.6) mm Hg.[8,9] Hypoproteinemia with resultant decreased oncotic pressure can occur during a variety of diseases in horses but is most often a result of loss or decreased production. Losses most commonly occur through the diseased gastrointestinal tract in large animal species (protein-losing enteropathies); losses may also occur as a result of glomerular diseases or large accumulations of protein-rich effusions within body cavities or the interstitial space. Decreased production of protein (specifically albumin) occurs in response to systemic inflammation because albumin is a negative acute-phase protein.[10] Hypoproteinemia also occurs uncommonly because of liver disease.[11] Decreases in COP are also commonly observed during intravenous fluid therapy in horses undergoing general anesthesia.[12]
2. π_{if} is the COP within the interstitium.

   Interstitial COP is more difficult to measure than plasma COP, but estimates of this number include 12 to 15 mm Hg in other species under experimental conditions.[13] Changes in total plasma protein concentration are likely to also affect the interstitial protein concentration and therefore alter both oncotic pressure components in Starling's equation. This may explain why some horses with significant hypoproteinemia do not show clinical signs of interstitial fluid accumulation (i.e., edema). That is to say, the gradient between capillary and interstitial oncotic pressure is only minimally affected when both have decreased proportionally, especially with time. It has been speculated that acute changes in plasma total protein concentration, however, may lead to edema formation more often than chronic hypoproteinemia; this is because of a relatively larger decrease in plasma protein concentration as compared with that in the interstitium with acute disease. Conversely, administration of hyperoncotic intravenous fluids (fluids with a COP greater than 20 cm H_2O) can potentially shift the balance of oncotic pressure back to the vascular space by raising plasma COP. However, the colloid molecules from these fluids must remain within the vascular space to have this effect, which may be negated by significant alterations in capillary permeability.
3. P_{cap} is the hydrostatic pressure within the capillary.

   Vascular hydrostatic pressure represents the pressure of plasma within the vessels pushing out toward the interstitium. A number of factors influence this pressure, including blood volume, vascular tone, and central venous pressure (CVP). This outward pressure on the vessel walls serves as the driving pressure for the continuous flux of fluid and protein out of the vessels into the interstitium. Pathologic increases in hydrostatic pressure can be caused by right-sided heart failure or other obstructive processes, such as venous thromboses, which can lead to edema formation. Pulmonary capillary hydrostatic pressure increases with left-sided heart failure and significant pulmonary vasoconstriction. Administration of intravenous fluids can also increase capillary hydrostatic pressure. Fluid losses resulting from diuretic administration

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and acute blood loss are examples of changes that result in decreased capillary hydrostatic pressure.

4. P_{if} is the hydrostatic pressure within the interstitium.

   The hydrostatic pressure of the interstitium varies in different tissues but often is overlooked as a significant contributor to fluid balance between the vascular and interstitial spaces. The importance of the interstitial hydrostatic pressure as it pertains to fluid balance has been reviewed by Reed and Rubin.[13,14] Degeneration of the interstitial collagen network may cause a decrease in interstitial hydrostatic pressure, resulting in a shift of fluid into the interstitium. Inflammatory cytokines have been implicated as a cause for these changes in interstitial hydrostatic pressure. Severe burn injury can also result in marked negative pressures within the interstitium, causing a draw of fluid into the interstitial space and subsequent edema formation. In the future there may be practical therapeutic options to manipulate interstitial hydrostatic pressure and alter fluid balance.

5. σ is the capillary reflection coefficient for proteins.

   Changes in capillary permeability can dramatically increase the flux of fluid and protein from the intravascular space into the interstitium.[15] If this increase in flow cannot be balanced by a corresponding increase in lymphatic return, edema results. Increased vascular permeability has been regarded as a major mechanism of edema formation; however, it may be only one component of the significant fluid shift that results from a systemic inflammatory response syndrome (SIRS). Adult horses and neonatal foals may have significant differences in interstitial composition and vascular permeability. It has also been proposed that foals have an increased capillary filtration coefficient as compared with adults.[16] These hypotheses may explain the propensity of neonatal foals to form edema relatively easily in response to overzealous fluid administration. Because of this increased risk, careful monitoring and serial assessment of the balance between plasma volume and the interstitium are warranted when treating neonatal foals with fluid therapy.

Extracellular to Intracellular Fluid Volume Relationship

There are three main determinants of net movement of fluid between the ECFV and ICFV: tonicity of the ECFV, tonicity of the ICFV, and cellular membrane permeability.

TONICITY OF THE ECFV. The tonicity (or effective osmolality) of the ECFV is estimated by the following equation[17]:

$$\text{Effective extracellular fluid osmolality} = (2 \times \text{Na}) + \frac{\text{Glucose}}{18}$$

Under normal circumstances, sodium and chloride are the primary determinants of ECFV tonicity; the equation doubles the sodium concentration rather than including the concentration of specific anions, some of which may not be easily measured. It should be noted that BUN is not included in the tonicity formula, because BUN is an ineffective osmole. Other effective osmoles can be added to the ECFV, thereby increasing tonicity and inducing a shift of water from the ICFV to the ECFV. The tonicity of the ECFV is primarily regulated by vasopressin (ADH). Administration of fluids with a tonicity greater or less than ECFV tonicity is a means to manipulate the balance of fluid between the ECFV and ICFV. This explains why hypertonic saline causes a shift of water from the ICFV to the ECFV. Recent mathematic models have been used to predict the influence of tonicity on the absolute volumes of these fluid compartments.[18] Similarly, fluid loss that has a tonicity different from the ECFV will also alter the ratio of fluid between the ECFV and the ICFV.

TONICITY OF THE ICFV. The tonicity of the ICFV is primarily determined by the intracellular concentration of potassium and its related anions. The tonicity of the ICFV and ECFV are the same at any given time point, a homeostatic mechanism meant as a safeguard to prevent acute changes in cell volume. Any imbalance in tonicity between the two fluid spaces will result in a rapid shift of fluid in order to maintain osmolar equality. The tonicity of the ICFV can be altered over time by the cells in response to changes in ECFV tonicity; an example of such a response is the production of idiogenic osmoles during hypernatremia.[19] Significant changes to ICFV tonicity during disease (resulting from damaged cell membranes) can result in accumulation of intracellular potassium, calcium, or cellular debris.

CELLULAR MEMBRANE PERMEABILITY. Cell membranes are selectively permeable to water and ions. Changes in this permeability usually do not cause large alterations in global fluid balance during healthy states. However, cell membrane damage during disease states can result in significant fluid shifts. In fact, a shift of fluid from the ECFV to the ICFV is an indicator of cellular membrane damage.

Effects of Fluid Physiology on Clinical Fluid Therapy

Specific disease states dictate individualized fluid plans. However, with intravenous therapy the administered fluid enters the vascular space. From there, the characteristics of the administered fluid will determine its movement from the vascular space into the interstitium and from the ECFV to the ICFV. Hyperoncotic or hypertonic fluids result in the greatest relative expansion of plasma volume, with a corresponding reduction in ICFV. Hypotonic fluids result in the smallest increase in ECFV but add volume to the ICFV, owing to a decrease in the tonicity of the ECFV. Estimates of the volumes of the different fluid spaces (whether based on clinical or laboratory values) before and during fluid therapy will allow for evaluation of the physiologic response in the clinical setting. The standard and universal administration of isotonic and hypo-oncotic fluids (such as lactated Ringer solution [LRS] or physiologic saline) to all patients regardless of disease condition ignores the available research and clinical insight to suggest otherwise.

General Principles for Fluid Therapy in Critical Care

K. Gary Magdesian

Current guidelines for replacement fluid therapy in human critical care emphasize the "fluid challenge" method, believed to be more effective and safer than traditional estimates of percent dehydration.[1] The author's (KGM) protocol of fluid administration in horses follows this same algorithm. Considerations for the fluid challenge technique incorporate four primary decision phases: (1) type of fluid, (2) rate and volume, (3) goals or endpoints of fluid therapy, and (4) safety limits to fluid therapy.

1. Types of fluids include crystalloids (isotonic, hypotonic, and hypertonic) and natural and synthetic colloids. There is much controversy and no consensus as to whether crystalloids or colloids are more effective or advantageous in human critical care.[1] The advantages of both fluid types are capitalized on by using them together in the treatment of some cases of hypovolemia. Otherwise, because of cost differences and lack of demonstrated benefit of colloids as compared with crystalloids in terms of mortality for fluid resuscitation in critically ill human patients, the use of colloids cannot be recommended over crystalloids.[2] Recent publications have suggested increased mortality and complication rates in humans receiving hetastarch as compared to crystalloids. See page 1374, Fluid Therapy for Diarrhea and Colitis in Horses. Table 44-1 lists the composition of several commercially available crystalloids that are used in equine practice.
2. The rate of fluid therapy for replacement (i.e., treatment of hypovolemia) is based on the "fluid challenge" principles, whereby a 30-minute bolus of 10 to 20 mL of isotonic crystalloid per kilogram is administered with subsequent reassessment of perfusion parameters.[1] This challenge method assumes that uncontrolled

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TABLE 44-1

Composition of Commercial Replacement and Maintenance Fluids

Crystalloid	Sodium (mEq/L)	Potassium	Chloride	Calcium	Magnesium	Osmolarity (mOsm/L)	Organic Salt
Replacement							
Lactated Ringer solution	130	4	109	3	0	272-273	28 lactate
Saline (0.9%)	154	0	154	0	0	308	0
Ringer solution	147-148	4	156	4.5	0	310	0
Plasma-Lyte 148	140	5	98	0	3	294	27 acetate 23 gluconate
Normosol-R	140	5	98	0	3	294	27 acetate 23 gluconate
Maintenance							
Plasma-Lyte	40	13	40	0	3	111	16
Normosol-M	40	13	40	0	3	110	16
45% NaCl + 2.5% dextrose	77	0	77	0	0	280	0
5% dextrose	0	0	0	0	0	252-253	0

hemorrhage is not present, because that would warrant hypotensive resuscitation instead. Perfusion parameters include mentation, heart rate, mucous membrane color, capillary refill time, jugular fill, extremity temperature (limbs, ears), and pulse quality. Blood or plasma lactate concentration, arterial blood pressure, urine output, and urine specific gravity are additional monitoring tools that aid in assessment for need of further fluid challenges. After the initial bolus, additional boluses—over 30 to 60 minutes depending on the degree of hypovolemia present—would be administered if perfusion parameters dictate. These are repeated until signs of shock abate, or a lack of improvement is noted with subsequent boluses, or fluid limits are reached (see later). Most animals require one to three of these boluses, and rarely are four required. Alternatively, or in addition to isotonic crystalloids, hypertonic saline (7% to 7.5%) can be administered at a rate of 4 to 5 mL/kg IV once. Plasma sodium concentration should be monitored. Colloids, because of their distribution that is limited to the central compartment, are bolused at lower volumes than isotonic crystalloids, such as 3 to 5 mL/kg for hetastarch. Up to 10 mL of hetastarch per kilogram may be administered per day, being limited by development of dose-dependent coagulopathies. If after reassessment of the perfusion parameters, additional resuscitative fluids are deemed necessary, another similar bolus is given, although each subsequent bolus is usually provided at a slightly slower rate unless the patient is markedly hypovolemic. This is repeated until signs of hypoperfusion resolve (endpoints are achieved) or safety limits are reached, at which point inotrope and/or vasopressor therapy is indicated if hypoperfusion persists.

3. The goals or endpoints of fluid therapy include both replacement and maintenance of fluid balance. *Replacement* refers to the replenishment of fluid deficits, primarily referring to those in the extracellular fluid compartment. *Maintenance fluid therapy* refers to the provision of maintenance fluid requirements to account for metabolism, insensible losses, growth, and ongoing losses. In general terms, *replacement* refers to replenishment of circulating volume and secondarily of interstitial fluid deficits; *maintenance* refers to provision of fluids after hypovolemia and dehydration have been corrected. Maintenance fluid therapy maintains both circulating volume and hydration status, including that of the intracellular compartment. In this section, replacement fluid is emphasized; the goals of replacement fluid therapy include rapid correction of hypovolemia by reversal of the signs of shock, including seven perfusion parameters: tachycardia (except in some neonatal foals), pale mucous membranes, prolonged capillary refill time, cold extremities, poor pulse quality, depressed mentation, and, in horses, reduced jugular fill. Urine production is another positive sign indicating correction of fluid deficits. Dehydration is corrected more slowly and is marked by reduced skin turgor (increased skin tent), dry mucous membranes, and dry corneal surface (reduced tear production). Additional goals of volume replacement include correction of hypotension, tachycardia, oliguria, and blood lactate.[1] A decrease in urine specific gravity (in the absence of renal failure), an increase in arterial blood pressure and CVP, and improvement in venous oxygen saturation are specific endpoints. The goals of maintenance fluid therapy are different; they are to maintain a normal degree of hydration by providing for ongoing losses, including insensible losses (respiratory, cutaneous evaporative losses) and any abnormal ongoing losses such as diarrhea. Maintenance fluid rates for horses vary with ambient temperature, use, diet, and metabolic status. In general, a reasonable starting point for maintenance fluid requirements includes 2 to 3 mL/kg/h for adult horses (possibly slightly lower if off feed) and 4 to 6 mL/kg/h for neonatal foals.[3,4]
4. The safety limits to fluid therapy are indicators of intravascular volume overload, including supranormal CVP, a decrease in arterial oxygen saturation (Pa_{O_2}), and clinical indicators of volume overload and overhydration. Once maximal CVP is achieved (10 to 12 cm H_2O in neonatal foals and 15 cm H_2O in adult horses), replacement bolus fluid therapy must stop; if continued, edema will form as systemic and capillary hydrostatic pressures increase in response to test boluses. A decrease in oxygen saturation in serial arterial blood samples, or in Sp_{O_2} measured with pulse oximetry, in a horse receiving fluid boluses may be consistent with development of pulmonary edema; this may precede development of tachypnea or frank edema in large airways/nostrils. Although no published reports address fluid overload in clinical equine patients, one experimental study evaluating hyperhydration before moderate-intensity exercise in horses suggested the development of arterial hypoxemia during exercise.[5] These animals were administered oral fluids equivalent to 6% of body weight (approximately 26 L of isotonic fluid by nasogastric tube). Hyperhydration resulted in arterial hypoxemia, suspected to be caused by pulmonary edema associated with hyperhydration, during moderate-intensity exercise.[5] Clinical indicators serving as limits to fluid therapy include visible subcutaneous edema and tachypnea; with optimal monitoring, fluid therapy will not be allowed to continue to this point. Another endpoint or limitation to fluid therapy is a lack of further improvement in perfusion parameters despite repeated fluid boluses. This would indicate that hypoperfusion is not solely due to hypovolemia and would require inotropes and/or pressor agents (e.g., dobutamine and norepinephrine, respectively). If safety limits are reached before

the goals of fluid therapy are achieved, the next step is also to turn to inotrope and vasopressor therapy.

See page 1374, Fluid Therapy for Diarrhea and Colitis in Horses.

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Critical Care and Fluid Therapy Monitoring Techniques

K. Gary Magdesian

Monitoring tools provide for advanced critical care in the large animal intensive care unit. Several of these tools are pertinent to fluid therapy and provide guidance, endpoints, and safety limits. Many of these allow for direct monitoring of fluid during administration of therapy, whereas others provide indirect information through hemodynamic data. Both of these are important to overall case management of the critically ill equine patient.

Central Venous Pressure

Central venous pressure (CVP) is the pressure within the vena cava; the term most commonly refers to that within the cranial vena cava. It is determined by blood volume as well as venous tone and cardiac contractility. With serial measurements CVP provides a limit to the administered volume of fluid. Normal CVP is approximately 2 to 12 cm H_2O (1.5 to 8.8 mm Hg) in foals and 5 to 15 cm H_2O (3.7 to 11 mm Hg) in adults.[1-4] Subnormal to negative CVP values signify hypovolemia; however, normal values do not necessarily imply euvolemia. This is because CVP is affected by compensatory responses such as venoconstriction, and is affected by cardiac contractility and intrapleural pressures among others.

CVP is easily measured in neonatal foals through the use of 20-cm central venous catheters, such as long-term single- to triple-lumen polyurethane catheters. Measurements can be obtained in adult horses with the use of 55-cm commercial CVP catheters. CVP can also be measured by passing a smaller gauge polyurethane catheter or polyethylene tubing through a 14-gauge, 5¼-inch standard intravenous catheter. CVP can be measured with a disposable water manometer (for spot readings) or using a pressure transducer for continuous waveforms. Interpretation of CVP waveforms requires knowledge of component waves and descents, including the a, c, and v waves and x and y descents. The a wave represents atrial contraction. The mean of the a wave is the appropriate point at which to measure CVP (at expiration). The c wave is associated with tricuspid valve closure and a bulging of the valve into the right atrium, and the v wave is caused by atrial filling from venous return. The x descent occurs after the a wave and represents the fall in pressure associated with atrial relaxation. The y descent occurs after the v wave, representing a drop in CVP caused by ventricular relaxation and reopening of the atrioventricular valves.

High CVP readings also occur with pericardial tamponade, pleural effusion, or pneumothorax, as well as false increases from catheter occlusion and air within the lines. For accurate and consistent serial results, a zero reference point should be selected and used for each measurement. The top of the sternal manubrium is a good reference point for the level of the pressure transducer or water manometer. The pressure transducer or water manometer can be taped to a fluid pole, providing a fixed zero point for repeated measurements in standing horses.

It should be noted that adequacy of intravascular volume cannot be guided by any one CVP level. Precision and reliability are limited by variable zero reference points, the effects of afterload and ventricular compliance, and alterations in intrathoracic pressure.[5] There is no linear relationship between intravascular volume and filling pressures, and CVP should be regarded as only an indirect estimate of volume. Serial measurements and trends over time are more useful than single numbers. CVP can be used on a clinical level for monitoring fluid therapy as follows: If the patient responds to fluid boluses without increases or with only minor increases (2 to 3 cm H_2O) in CVP, it is appropriate to continue infusions until signs of hypoperfusion are reversed.[5] Additional guidelines used in human patients are as follows: If the CVP increases to 3 to 7 cm H_2O (2 to 5 mm Hg), the infusion should be paused and perfusion reevaluated after a 10-minute wait. If the change in CVP was an increase of 7 cm H_2O (5 mm Hg) or greater after the fluid bolus, the infusion is stopped.[5] In this regard CVP is a better "upper limit" to fluid therapy rather than an actual goal to strive for, other than normalization in horses with low CVP values.

Arterial Blood Pressure

Arterial blood pressure measurements provide some insight into perfusion status, particularly when used in conjunction with clinical signs and lab work, such as blood lactate concentration. It can be measured either directly through the use of arterial catheters or indirectly with a blood pressure cuff on the tailhead. Arterial lines can be placed in the great metatarsal artery of recumbent foals and the transverse facial artery in standing adult animals for direct measurements. Indirect measurements are best performed with oscillometric blood pressure monitors that provide systolic, diastolic, and mean arterial pressure (MAP). Cuffs are provided by the manufacturer and vary in width and length with size of the patient.

Arterial blood pressure in healthy neonatal foals is highly variable and depends on breed, gestational age, and size of foal. In general, normal mean arterial blood pressure (direct) is 84.4 ± 3.7 mm Hg at 1 day of age and up to 101.3 ± 4.4 mm Hg at 14 days of age.[2] Indirect blood pressure readings in Thoroughbred foals has been reported as 144 ± 15, 74 ± 9, and 95 ± 13 mm Hg for systolic, diastolic, and mean pressures, respectively.[6] Direct blood pressure has been reported for adult horses: 126 to 168 (systolic)/85 to 116 (diastolic) with a range for the mean arterial pressure of 110 to 133 mm Hg.[7-10] Indirect blood pressure in adult horses is 111.8 ± 13.3 mm Hg for systolic pressure and 67.7 ± 13.8 mm Hg for diastolic pressure.[11]

Blood pressure values should not be regarded as the sole criteria for intervention. Rather, they should be used in conjunction with perfusion parameters, blood lactate concentration, and urine output in deciding whether there is need for further fluid administration or inotrope and vasopressor support. The exact blood pressure value that should trigger intervention in horses and foals is unknown and likely varies with the individual patient; however, end organ perfusion requires a mean arterial pressure of 60 mm Hg, thereby making that a reasonable general target.

Blood or Plasma Lactate Concentration

Blood or plasma lactate concentrations are very useful in monitoring fluid support as well as perfusion and metabolic status. Increased blood lactate concentration may be a result of hypoperfusion and reduced oxygen delivery (hypovolemia, hypotension, anemia, hypoxemia, heart failure). Other considerations for hyperlactatemia should include SIRS, sepsis, catecholamine surges, liver or renal failure, thiamine deficiency, alkalosis, hyperglycemia, exercise, seizure activity, and the action of drugs such as salicylates and theophylline.[12-15] SIRS may increase circulating lactate concentrations independent of perfusion status; inflammatory mediators and cytokines activate pyruvate dehydrogenase kinase, an inactivator of pyruvate dehydrogenase, resulting in reduced activity of the citric acid cycle. Normal lactate concentrations in horses are less than 2 mmol/L, with most horses having concentrations less than 1 mmol/L.[16-18] Neonatal foals have decremental values after birth, with reported concentrations of 4.9 ± 1.02, 2.25 ± 0.6, and 0.89 mmol/L at birth, 12 hours of age, and 24 hours of age, respectively.[18-20] In a study performed by the author, foals had values of 2.4 ± 1.0, 1.2 ± 0.3, and 1.1 ± 0.3 mmol/L at 0 to 2, 24, and 48 hours of age, respectively, compared with 0.6 ± 0.2 mmol/L in adult horses.[21]

Cardiac Output

Advanced monitoring in equine critical care includes cardiac output measurement. A number of methods of cardiac output monitoring have been described in horses, including the Fick principle, indicator dilution methods (such as lithium dilution), Doppler and volumetric

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echocardiography, pulse contour analysis, and partial carbon dioxide rebreathing. The most practical of these include lithium dilution and echocardiographic techniques.[22-26]

Lithium dilution precludes the need for placement of cardiac catheters. A small bolus of lithium chloride is injected into a peripheral vein or the cranial vena cava (via central line). Arterial blood is sampled using an arterial catheter at a constant rate and passes through a lithium electrode to generate a lithium concentration-time curve. Cardiac output is calculated from the area under the curve for lithium over time. Advantages of lithium dilution include only moderate invasiveness, good accuracy, and requirements for only small volumes of injectate. Disadvantages include the need for continuous arterial blood and limitations on repetitive measurements owing to lithium accumulation.[25-27]

Noninvasive cardiac output measurements can be made using the Bullet method through volumetric echocardiography.[24] McConachie and colleagues[24] reported that the Bullet method provided an accurate estimate of cardiac output in anesthetized foals. The Bullet method, as well as the four-chamber area-length, Simpson, and right ventricular outflow Doppler methods, had reasonable agreement with lithium dilution in adult horses.[28] For the Bullet method, cardiac output is calculated using heart rate and stroke volume (SV) as follows:

$$SV = \left(\frac{5}{6} \times LVAd \times LVLd\right) - \left(\frac{5}{6} \times LVAs \times LVLs\right)$$

where LVAd = left ventricular area in diastole (short-axis view); LVLd = left ventricular length in diastole (long-axis view); LVAs = left ventricular area in systole (short-axis view); and LVLs = left ventricular length in systole (long-axis view).

Cardiac output in healthy adult horses (400 to 500 kg) is 32 to 40 L/min.[22] Normal cardiac index, which is cardiac output expressed per unit of body weight, is 72 to 88 mL/kg/min. In the neonatal foal, cardiac output has been reported to be 7.1 ± 0.4 L/min (cardiac index = 155.3 ± 8.1 mL/kg/min) in 2-hour-old foals.[2] At 24 hours of age cardiac output was determined to be 9.0 ± 0.5 L/min (cardiac index = 197.3 ± 12.0 mL/kg/min). This increased to 15.7 ± 1.5 L/min (cardiac index = 222.1 ± 21.6 mL/kg/min) at 14 days of age.[2] A general guideline for normal cardiac index is 100 to 300 mL/kg/min in foals.[24]

Blood Glucose

Blood glucose concentration has been the focus of much study in human critical care in recent years. A number of initial studies have demonstrated improved survival and reduced complications with tight glucose control using intensive insulin therapy in critically ill humans.[29,30] Maintenance of euglycemia (80 to 110 mg/dL) resulted in reduced mortality in surgical intensive care unit patients as compared with hyperglycemia (180 to 200 mg/dL). Hyperglycemia may be associated with detrimental effects in pediatric intensive care patients as well.[31] However, after these initial studies, additional studies, including meta-analyses, did not document similar benefits and revealed some adverse events with tight glycemic control, including severe hypoglycemia.[32,33] Current guidelines therefore recommend using a glucose concentration of 180 mg/dL or less as a goal.[34] How these findings relate to critically ill horses is unknown, but prevention of hyperglycemia is likely warranted, and its effects in the equine intensive care unit require further study.

Monitoring Urine Analytes

Urine indices are useful for monitoring responses to fluid therapy. Successful production of urine output is a primary goal of fluid therapy, and measurement of urine production allows determination of "fluid balance" (input–output). Another important means of assessing the response to fluid loading is measurement of urine specific gravity and/or osmolarity. In the absence of renal failure, progressively dilute urine is a positive response to fluid administration. Horses on feed and water should be making 0.4 to 2.0 mL/kg/h urine, whereas those off feed and water will produce far less (0.13 to 0.5, up to 1 mL/kg/h depending on duration).[35,36] Horses on fluids should therefore be producing a minimum of 0.5, but optimally 1 to 2 mL/kg/h of urine.

Urinalysis should be performed, and fractional excretion of electrolytes, particularly sodium, provides information regarding tubular function and can aid in differentiation of prerenal from renal azotemia. Normal fractional excretion is less than 1% in adult horses and 0.31% ± 0.18% in neonatal foals.[37-40]

Fluid Therapy for Specific Diseases and Disorders in Horses

Fluid Therapy for Liver Dysfunction and Failure in Horses (Box 44-1)

K. Gary Magdesian

Acute liver disease may result in hypovolemia owing to lack of water intake, third space losses into the gut and peritoneal cavity, and possibly pooling of blood in the portal circulation. Portal hypertension may result in gut edema with subsequent fluid loss. Considerations of fluid therapy in cases with hepatic dysfunction include reduced metabolic capacity as well as compromised synthetic ability of the liver. Because lactate clearance primarily occurs in the liver, fluids containing lactate should be avoided. Isotonic replacement fluids, such as Normosol-R (Abbott Laboratories, North Chicago, Ill.) and Plasma-Lyte A or 148 (Baxter Healthcare Corporation, Deerfield, Ill.), and acetated Ringer solution are preferred over LRS. One millimole of acetate yields 1 mmol of bicarbonate during metabolism and is therefore alkalinizing.[1] These balanced, polyionic fluids are optimal as compared with physiologic saline (0.9% sodium chloride) because of the propensity of the latter to produce a mild hyperchloremic metabolic acidosis (HCMA), and many horses with liver dysfunction have a propensity toward acidemia anyway.[2] Hyperchloremic acidosis has potentially adverse effects, including renal afferent arterial constriction, and has negative effects on organ function, including gastrointestinal, central nervous system, and coagulation.[3,4]

Provision of dextrose, even in the face of normoglycemia, should be considered unless enteral nutrition is adequate. The addition of dextrose to fluids will minimize gluconeogenesis demands on the liver, as well as catabolism of endogenous tissues with subsequent increases in nitrogen turnover (and increased ammoniagenesis). Risk of hypoglycemia from liver dysfunction is also minimized, since patients may have insufficient liver and muscle glycogen reserves and impaired hepatic gluconeogenesis in order to maintain normal blood glucose concentrations. A dextrose supplementation rate for adult horses is 1 to 2 mg/kg/min. This equates to 3% to 6% dextrose in fluids if 1 L/h of crystalloid is administered to a 500-kg horse. The author often begins with 0.5 mg/kg/min of dextrose and gradually advances the rate of administration as the horse tolerates the dextrose (<180 mg/dL). The addition of B vitamins can be helpful for anorectic horses because they are required cofactors for oxidative metabolism. In addition many of the B vitamins are stored in the liver. Horses

BOX 44-1

Fluid Considerations for Liver Failure

1. A combination of balanced, polyionic crystalloids and colloids is optimal.
2. Acetated fluids, rather than lactated Ringer solution, should be used.
3. Colloids, particularly plasma, can be beneficial if hypoalbuminemia is present and to minimize third space accumulation of fluids.
4. Potassium supplementation (20 to 80 mEq/L) may aid in reducing hyperammonemia (<0.5 mEq/kg/h total).
5. Dextrose supplementation (1 to 2 mg/kg/min) should be provided for energy support.

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that remain anorectic for longer than 24 to 72 hours should be considered candidates for parenteral nutrition.

Horses with liver dysfunction should be monitored closely for hyperammonemia as a marker of hepatic encephalopathy. Fluids can be tailored to minimize the risks of hyperammonemia. Provision of potassium, even in the presence of normokalemia, provides for an electrolyte draw of hydrogen atoms from intracellular stores, thereby lowering pH and promoting ionization of ammonia to its less diffusible form, ammonium ion, which is not able to cross the blood-brain barrier.[5] Hypokalemia also promotes metabolic alkalosis and may compound hepatoencephalopathy owing to increased urinary losses of hydrogen ion (H^+) and increased tubular absorption of ammonia. For similar reasons, sodium bicarbonate should be used judiciously and with caution in horses with a propensity toward hepatic encephalopathy. Increases in the pH of plasma will result in conversion of ammonium ion to ammonia; this facilitates the brain uptake of ammonia with subsequent intracerebral trapping of ammonium ion.

The rate of fluid administration for horses with liver dysfunction will vary with the volume and hydration status of the individual. In general, rates should exceed maintenance requirements to account for hypoperfusion and produce diuresis of ammonium and other toxins such as conjugated (direct) bilirubin that would otherwise have been metabolized or eliminated by the liver. Volume of fluid administration should be monitored closely in horses with ascites or portal hypertension resulting from severe liver disease because of the propensity of these patients for third space fluid accumulation. Other considerations for horses with liver disease include hypoalbuminemia, hyponatremia, hypokalemia, coagulopathies, and hyperlactatemia. Monitoring CVP will aid in preventing rises in hydrostatic pressure that would contribute to transudates or ascites.

Fluid support, for "maintenance fluid therapy," can be modified in horses with preexisting ascites or edema to reduce the administered sodium load. These are hypotonic and should never be administered as a rapid bolus. Commercially available solutions with restricted sodium concentrations (maintenance crystalloids), such as Plasma-Lyte 56 or Normosol-M, can be used in foals. Because of their availability in only small volumes (1-L bags), combinations of isotonic crystalloids and sterile water or 5% dextrose in water can be used as maintenance fluids in larger patients (half isotonic fluid and half water or D_5W). If sterile water is selected, it should be allowed to mix with the isotonic fluid before entering the patient; administered alone, water could cause osmotic hemolysis. Another option in such horses is to restrict the volume of crystalloid administered through concurrent administration with colloids. Colloids expand the intravascular volume, limit the requirement for crystalloids, and may reduce the propensity of edema formation by raising oncotic pressure. However, consumptive coagulopathies would be contraindications to the administration of synthetic colloids.

Colloids are indicated in horses with significant hypoalbuminemia (<1.5 g/dL). Hetastarch can be used at a dose of up to 10 mL/kg/day unless coagulopathies are present. Liver failure may result in decreased production of clotting factors or antithrombin and can initiate disseminated intravascular coagulation (DIC). Because hetastarch can induce decreased activity of von Willebrand factor and factor VIII, as well as interfere with platelet function, it is contraindicated in horses with bleeding tendencies (after consumption of factors).[6] Plasma is an alternative colloid that has additional benefits for horses with hepatic failure. Coagulopathies associated with liver disease can be addressed through provision of exogenous antithrombin and clotting factors in plasma products. Plasma should probably not be administered to horses with serum hepatitis (Theiler disease), since this disease is poorly understood and associated with prior administration of equine-origin biologics. Recently, a flavivirus has been associated with Theiler disease.[7] Replacement of albumin is beneficial not only for oncotic pressure support, but also for drug and toxin binding and as an endogenous buffer. If hypoalbuminemia is a result of hepatic dysfunction, and not urinary or gastrointestinal losses, colloids will have a longer retention time in the circulation.

Fluid Therapy for Diarrhea and Colitis in Horses (Box 44-2)

K. Gary Magdesian

Horses with acute colitis are often presented in a state of severe SIRS with endotoxemia, hypovolemia, and malperfusion of tissues. Fluid therapy is the cornerstone of hemodynamic and therapeutic support for these horses. Not only is low circulating volume an indication for fluids, but acid-base and electrolyte derangements also warrant their use in these cases. Specifically, horses with colitis often exhibit hypovolemia, both organic and inorganic acidoses, and hyponatremia. Organic acidosis primarily is a result of hyperlactatemia, whereas inorganic acidosis is often a result of relative hyperchloremia (or hyponatremia).

Because of the poor sensitivity of physical examination in detecting hypovolemia, estimates of percent dehydration and water deficit are not very accurate.[1] A more objective means of providing fluids is through the "fluid challenge method" described in the previous sections.[1] In this protocol a bolus dose of 10 to 20 mL/kg of isotonic crystalloid is administered over approximately 30 minutes to horses with hypovolemia, with subsequent reassessment of perfusion parameters. Perfusion parameters consist of mentation, peripheral pulse quality, heart rate, mucous membrane color, capillary refill time, and extremity temperature. Lactate, arterial blood pressure, and central venous oxygen saturation are perfusion monitoring tools that should be evaluated serially in patients undergoing fluid administration and can provide endpoints to fluid therapy. Urine output is another clinical indicator of improvement in perfusion in response to fluid loading. Fluid challenge should continue as repeat boluses, albeit at progressively slower rates for each subsequent bolus, until perfusion parameters normalize or plateau in terms of improvement. No further improvement of perfusion parameters in response to boluses of fluids, with persistence of clinical indicators of hypoperfusion, suggests that inotrope or vasopressor support may be required and that further fluid therapy will not be of aid. A safety limit to fluid loading includes measurement of a high normal CVP value.

Crystalloid fluid choices for horses with colitis include replacement fluids, such as Normosol-R, LRS, and Plasma-Lyte 148 or A. Normosol-R and Plasma-Lyte 148/A are slightly advantageous over LRS from the standpoint of providing a wider strong ion difference (sodium-chloride difference). In contrast, LRS has a chloride concentration greater than that of equine plasma (109 mEq/L vs. approximately 100 mEq/L) and can compound an inorganic acidosis. Physiologic saline (0.9%) is even greater in its chloride concentration and produces a mild strong ion acidosis on administration of large volumes.[2] In addition, Normosol-R and Plasma-Lyte 148 or A contain acetate (and gluconate) rather than lactate as the alkalinizing salt. This is a significant advantage in horses with hepatic dysfunction, because the liver is the primary site of lactate metabolism whereas acetate and gluconate are metabolized by many tissues.

Colloids may be adjunctive to crystalloid therapy, particularly for horses with hypoproteinemia such as those with acute colitis. In human critical care medicine there is no consensus as to whether crystalloids or colloids provide more successful fluid resuscitation.[1]

BOX 44-2

Fluid Considerations for Horses with Diarrhea or Colitis

1. A combination of crystalloids and colloids has many benefits in horses with colitis.
2. Colloids are indicated when concurrent hypoproteinemia and hypovolemia are present.
3. Potassium, calcium, and magnesium should be supplemented as necessary.
4. Hypertonic saline has several potential benefits for horses with acute colitis, including volume expansion, immunomodulation, antiinflammatory effects, antiedema effects, and positive inotropic effects.

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A combination of both is likely optimal.[1] Colloids are particularly important for horses with hypoproteinemia, such as those with colitis. Concurrent hypovolemia and hypoproteinemia warrant administration of colloids in the resuscitative period, because the use of crystalloids alone could result in dilutional hypoproteinemia.[3]

Hypertonic saline (7% to 7.5%) is a rapid plasma volume expander that can be used in the early volume replacement period of volume resuscitation of the horse with liver failure. Hypertonic saline increases plasma volume by three to four times the volume administered. In comparison, crystalloids increase plasma volume by only 0.25 to 0.33 mL for each milliliter administered. Hypertonic saline has additional advantages beyond volume expansion, particularly for the horse with endotoxemia. These include immunomodulatory, antiinflammatory, antiedema (particularly of the endothelium and erythrocytes), and inotropic effects.[4-6] Microvasculature effects enhance microcirculatory perfusion, which is often disturbed during sepsis and endotoxemia. Reduction of endothelial and erythrocyte edema, two processes that contribute to multiple organ dysfunction during sepsis, results in reduced vascular resistance and blood viscosity.[5,6] The hypertonicity created by hypertonic saline evokes vasodilation, which also contributes to microperfusion when coupled with an increase in cardiac output caused by contractility-enhancing effects of hypertonic saline. The antiinflammatory and immunomodulatory effects include antiapoptosis, free-radical scavenging properties, inhibition of leukoactivation, and prevention of immunosuppression after sepsis.[4-6] In an experimental model of hemorrhagic shock in horses, hypertonic saline resulted in improved cardiac output, stroke volume, cardiac contractility and blood pressure as compared with isotonic saline.[7] Hypertonic saline has demonstrated attenuation of cardiovascular derangements in equine endotoxemia models as compared with isotonic saline.[8]

The dose for hypertonic saline is 4 mL/kg once, and it should be followed with isotonic crystalloids or water to replace the "borrowed" water from the intracellular space. Hypertonic saline is generally safe but should be avoided in horses with uncontrolled hemorrhage when hypotensive resuscitation is indicated. In addition, horses with marked sodium derangements should not be administered hypertonic saline. It should also be used with caution in neonatal foals.

Fluid Therapy for Sepsis (Peritonitis, Pleuritis, Pneumonia, Internal Abscess) in Horses (Box 44-3)

K. Gary Magdesian

The optimal fluid for resuscitation of patients with sepsis is unknown.[1-3] Despite this controversy, a rational approach to fluid therapy in patients with sepsis is to optimize hemodynamics (increase oxygen delivery, blood pressure, and urine output) while attempting to limit edema formation.[1,4,5] There is no evidence to support the use of either colloids or crystalloids over the other. Meta-analysis of clinical studies comparing crystalloids and colloids in human patient populations showed no outcome difference.[2,3,5-7] Regardless of the lack of consensus recommendations for fluid choices, fluid therapy is a keystone in the management of severe sepsis and septic shock. This is because septic shock is associated with both absolute and relative hypovolemia. Relative hypovolemia is the result of vasodilation and peripheral blood pooling in the face of cytokinemia. Volume repletion allows for increases in cardiac output and subsequently in systemic oxygen delivery.[6]

Fluid therapy in horses with sepsis is similar to that recommended for horses with acute enterocolitis; both conditions are examples of a state of SIRS. In fact, enterocolitis can be thought of as a form of sepsis. Sepsis incites a host of hemodynamic derangements that challenge fluid therapy. It causes myriad microperfusion abnormalities; these include hypovolemia, myocardial depression, vascular permeability derangements, vasodilation, DIC, and cellular changes resulting in abnormal membrane potential and membrane pump or channel function.[8] These pathophysiologic processes must be considered when a fluid plan for horses with sepsis is designed.

Sepsis is defined as concurrent SIRS and documented or suspected infection.[9] Many equine cases fall into this category, including horses with peritonitis, pneumonia, pleuritis, enterocolitis, meningitis, and metritis. Sepsis and SIRS are states of cytokine milieu, in which cytokines and inflammatory mediators predominate. Aside from antimicrobials, the fundamental therapy is hemodynamic support, consisting of fluid and vasopressor therapy.

Initial fluid resuscitation is centered on isotonic (or near isotonic) replacement type fluids, colloids, and hypertonic saline. Horses with sepsis often are presented with negative fluid balance resulting from both hypovolemia and dehydration. Fluid choices are the same as for horses with enterocolitis, and a combination of crystalloids and colloids may have advantages in sepsis.[4] Such a combination would address both blood volume and interstitial deficits, with colloids expanding the vascular space and crystalloids addressing both fluid spaces. Hypertonic saline may have some additional advantages during sepsis, including immunomodulatory, antiinflammatory, antiedema, vascular, and inotropic effects.[10-12] A dose of 2 to 4 mL/kg of hypertonic saline may be added to the combination of isotonic crystalloids and colloids.

Colloids are intriguing fluids for horses with sepsis. Colloids may attenuate capillary leak associated with sepsis and SIRS.[13] The exact physiology behind this colloid effect is not exactly worked out; however, theories include reduction in endotoxin-induced leukocyte-endothelial cell interactions.[14] Interactions with endothelial glycocalyx are also hypothesized in the ability of both synthetic colloids and albumin to reduce capillary leakiness.[15] However, recent meta-analyses have failed to demonstrate a benefit of colloids over crystalloids in volume replacement of the critically ill human patient.[16] Hetastarch exhibits antiinflammatory properties by reducing neutrophil adhesion and accumulation in tissues.[17] In addition, hetastarch has been suggested to be beneficial for tempering DIC in that it exerts dose-dependent effects on coagulation; however, this remains to be further studied.[18] Hetastarch lowers concentrations of von Willebrand factor and factor VIII:C and reduces platelet aggregability, which may aid during hypercoagulable states such as DIC.[18-23] Both of these properties warrant further investigation in horses with sepsis because vascular derangements and coagulopathies are quite common. It should be kept in mind, however, that bleeding may be potentiated by the administration of hetastarch to the hemorrhaging patient and hetastarch should not be administered to hypocoagulable patients.[24] It should be noted that recent research in human critical care has suggested an increase in mortality rate in patients receiving hetastarch as compared to crystalloids. In a trial comparing concentrated albumin with crystalloids in human patients, there was a trend toward improved survival with albumin in patients with sepsis.[25] Concentrated equine albumin is not currently available; however, one study showed that a human albumin product could be used safely in horses.[26]

Care should be taken to avoid overexpansion of the extracellular fluid compartment with excessive fluid administration. Horses with sepsis have a predilection for edema because of the presence of concurrent hypoalbuminemia and increased vascular permeability. Therefore, careful monitoring of fluid balance is warranted. *Fluid balance* refers to input and output of fluids, and it can be monitored

BOX 44-3

Fluid Considerations for Horses with Sepsis

1. Crystalloids are the mainstay of fluid therapy in sepsis.
2. A combination of crystalloids and colloids may have advantages in patients with sepsis when hypoproteinemia is present.
3. Fluid challenge, consisting of 10- to 20-mL/kg boluses with reassessment of perfusion parameters and monitoring tools, is a safe and effective means of determining volume to be administered.
4. Monitoring of fluid therapy increases safety, especially in patients prone to edema. Monitoring should consist of measurement of central venous pressure, arterial blood pressure, and urine output.
5. Metabolic acidosis is very common among patients with sepsis.

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with urinary collection systems. Under normal circumstances urine output should represent 50% or greater of input, with the remaining output caused by fecal and evaporative losses (skin and pulmonary). CVP is also useful in monitoring for safety limits in this group of patients; maximal normal CVP (10 cm H_2O [8.8 mm Hg] in foals; 15 cm H_2O [11 mm Hg] in adults) should not be exceeded. Serial ultrasonography and arterial blood gas analysis can be used to detect pulmonary edema from relative or absolute fluid overload, before the development of gross signs (froth, crackles, tachypnea) of edema.

Because of thrombotic risks associated with sepsis-induced coagulopathies, these patients should be instrumented with minimally thrombogenic catheters, such as long-term polyurethane catheters. Attention to asepsis and cleanliness is paramount.

In human critical care, "early goal-directed therapy" has been advocated by some clinical trials.[27] These studies have used goal-oriented therapeutic adjustments of preload, afterload, and contractility to achieve a balance between oxygen delivery and demand. Endpoints have included normalization of central venous oxygen saturation (70%), blood lactate, CVP (8 to 12 mm Hg in humans), urine output (0.5 mL/kg/h or greater), and MAP (65 mm Hg or greater in humans).[28] The therapy consisted of crystalloids and colloids for correction of CVP, vasopressors and vasodilators for MAP, and dobutamine and red blood cell transfusions for central venous oxygen saturation. Patients receiving this early goal-directed therapy received a greater volume of fluids early (first 6 hours of treatment) and less later, as compared with patients in the conventional group. The treatment group had a lower mortality rate and less severe organ dysfunction, highlighting the importance of early identification of patients with insidious or occult malperfusion, consisting of patients with global hypoxia yet stable vital signs.[27]

There has been considerable debate over what the optimal fluid choices are for human patients with sepsis: crystalloids or colloids. The ideal fluid for volume replacement remains equivocal because concrete evidence implicating one over the other is lacking.[2,29] Because of cost differences, and lack of clear benefit of one over another, crystalloids are usually favored. A current philosophy is to recognize the advantages of both fluids, with concurrent or sequential administration of both in certain types of cases. Because crystalloids distribute approximately 75% of administered volume to the interstitium, they allow for greater interstitial expansion compared with colloids. This property is advantageous when dehydration is also present, but a disadvantage when edema is a risk. In fact, crystalloid administration further dilutes total protein and albumin concentrations, thereby lowering COP and predisposing to edema. Colloids, on the other hand, are restricted to the intravascular space and therefore may be indicated in hypovolemic shock; they replace intravascular losses more rapidly than do crystalloids.[30] Colloids are associated with a plasma volume expansion between 100% and 200% of the infused volume.[31-33] In humans and anesthetized horses with colic, cardiac output is better maintained with lower volumes of fluid administration when colloids are used rather than crystalloids.[34]

Marked alterations of the reflection coefficient, as are associated with severe capillary leak and acute respiratory distress syndromes (ARDS), warrant careful consideration and monitoring of patient status when colloids are administered; because of a theoretical potential for extravascular leakage of colloids with marked endothelial alterations, patients with ARDS should be monitored closely for clinical deterioration. Despite these theoretical concerns, a more recent form of hydroxyethyl starch (130/0.4) has demonstrated protective effects in a model of acute lung injury (ALI).[35] The numbers after the colloid just mentioned (130/0.4) refer to the average molecular weight and degree of substitution of starch molecules with a hydroxyethyl group, respectively. This hydroxyethyl starch resulted in the best oxygenation and a reduced inflammatory response as compared with a modified gelatin colloid or Ringer acetate crystalloid in a rabbit model of ALI.[35] Standard hetastarch has an average molecular weight of 450 kDa and a degree of substitution of 0.7; the newer hydroxyethyl starch (Voluven; 130/0.4) has been modified to have more complete renal elimination and less tissue storage than the standard product, with fewer side effects such as coagulopathies. Recently, the FDA has approved a veterinary hydroxyethylstarch colloid for use in dogs and cats (VetStarch, Abbott Animal Health, Abbott Park, Ill.). This product also has 6% hydroxyethyl starch in a 130/0.4 formula, thereby allowing it to have lower potential complications compared with hetastarch, including coagulopathy, allergic reactions, and renal injury. It is indicated to treat and prevent hypovolemia. It would be particularly useful in the presence of concurrent hypoalbuminemia. The use of different colloids in patients with ARDS needs further study. Except for situations that may call into question the use of colloids, the concurrent use of crystalloids and colloids obviates the need for large volumes of crystalloids; this approach minimizes the risk of interstitial edema and may restore blood volume more rapidly than crystalloids alone. A "blending" of crystalloids and colloids should therefore be considered for patients with sepsis whenever colloids are not contraindicated and particularly when hypoproteinemia is present. Contraindications to synthetic colloids include known hypersensitivity, fluid overload, pulmonary edema, and renal failure (oliguric/anuric), severe hypernatremia/hyperchloremia (resulting from dilution in 0.9% saline), and intracranial bleeding.

See the previous section for glucose regulation in critically ill patients. The current goal in human patients is to maintain a blood glucose of 180 mg/dL or less.

Fluid Therapy for Renal Failure in Horses (Box 44-4)

C. Langdon Fielding • K. Gary Magdesian

Fluid therapy is the major component of treatment for renal failure in horses, regardless of cause. Renal replacement therapies have been reported in horses; however, they are not widely available, further highlighting the importance of fluid diuresis.[1-3] Peritoneal dialysis is an option to complement fluid therapy, particularly if unresponsive anuria is present.[2] Development of a fluid plan for horses with renal failure begins with classification of the disease into polyuric, anuric, or oliguric renal failure. Polyuria and anuria are self-explanatory; oliguric renal failure in this section refers to a normally hydrated animal with concurrent azotemia and urine production less than 0.5 mL/kg/h.

BOX 44-4

Fluid Considerations for Horses with Acute Renal Failure

1. Horses with acute renal failure can be polyuric, oliguric, anuric.
2. Polyuric horses should be treated with isotonic crystalloids with the goal of diuresis. A rate of administration equal to two times a maintenance rate is a reasonable starting point, but fluid balance (input and output) should be monitored. This would equate to 4 to 6 mL/kg/h as an initial starting rate, which should be tailored (increased or decreased) to perfusion parameters, urine output, patient clinical status, and monitoring tools. Balanced, polyionic commercial electrolyte solutions, such as Normosol-R or lactated Ringer solution, can be used in most cases.
3. Frequent reassessment of patient's fluid status should be done to adjust rate accordingly.
4. Physiologic (0.9%) saline is mildly acidifying because of hyperchloremia and should be avoided in patients with renal failure because hyperchloremic metabolic acidosis may reduce renal blood flow.
5. Anuric or oliguric horses should be treated promptly. Adequacy of circulating volume and blood pressure must be ensured initially. If fluid loading with isotonic replacement crystalloids and correction of hypotension does not correct the lack of urine production, then furosemide, mannitol, and dopamine can be tried. Dialysis (hemodialysis or peritoneal) can be performed if there is potential for reversible renal injury.
6. Synthetic colloids (hetastarch, dextrans) should be avoided in horses with acute renal failure.

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For both oliguric or anuric and polyuric renal failure, there are two primary considerations when beginning fluid therapy: fluid type and rate. The total amount of fluid administered is usually determined by the response to treatment and does not necessarily need to be identified at initiation of therapy.

POLYURIC RENAL FAILURE. The goal of fluid therapy in these patients is to induce diuresis, with removal of uremic toxins and maintenance of fluid, acid-base, and electrolyte balance.[4,5] The degree of renal failure that is reversible is often unknown at the onset; this is evaluated over time, particularly with response to fluid therapy. It should be noted that azotemia may not improve for up to 72 hours after initiation of fluid therapy when acute renal failure is severe. A lack of initial improvement in plasma creatinine or BUN during the first day or two of therapy should not necessarily prompt a poor prognosis or discontinuation of therapy.

The rate of fluid administration should facilitate diuresis.[5] A rate of two times maintenance fluid rate (4 to 6 mL/kg/h, where maintenance rate is 2 to 3 mL/kg/h) is a reasonable starting point; however, there is a paucity of literature to recommend evidence-based rates of fluid administration for treatment of acute renal failure or other disorders. Similar fluid rates have been suggested in small animal patients with renal failure.[5] It is unknown whether increases in the fluid rate beyond this point are beneficial. Certainly, if urine output is greater than this rate, it should be matched with fluid input.

Fluid overload is a problem in renal failure and has been reported in people.[6,7] Excessive fluid administration may result in edema and associated morbidity and mortality. Measurement of CVP can be used to monitor excessive fluid administration and has become more practical in equine patients.[8-10] Reference ranges of less than 15 cm H_2O have been reported for adult horses; values exceeding 20 cm H_2O indicate a need to decrease the rate of fluid administration to avoid development of edema.[9] The value of CVP monitoring continues to be controversial and CVP measurement should not be used as the sole means for monitoring fluid overload.[11]

A balanced isotonic crystalloid is suitable for diuresis while preventing significant electrolyte alterations.[5] Horses should be allowed free access to water whenever possible while intravenous fluids are administered. This allows for some degree of self-regulation of water balance and can provide free water for renal excretion of the large sodium load provided by isotonic crystalloids.

Hyperkalemia is a relatively common feature of acute renal failure.[12,13] This is often corrected when renal perfusion is optimized and diuresis is instituted. When hyperkalemia is present, anuria should be ruled out. Cardiac dysrhythmias can develop during hyperkalemia; potassium-free fluids (0.9% saline or isotonic sodium bicarbonate) should be administered to patients with dangerous hyperkalemia (>6 mmol/L), along with calcium, dextrose, and possibly insulin.

LRS has the benefit of containing a minor amount of free water (osmolarity 273 mOsm/L) and slightly less sodium than other fluids (130 mEq/L). A potential disadvantage, however, is that it contains more chloride (109 mEq/L) than equine plasma. Horses with renal insufficiency may be unable to excrete excess chloride provided by LRS diuresis. Mild hyperchloremia may result, causing a minor strong ion acidosis. LRS also contains potassium (4 mEq/L), which is a consideration in the hyperkalemic patient. However, studies in human renal transplant patients failed to demonstrate development of hyperkalemia as a result of LRS administration.[14]

Isotonic saline (0.9%) solution has an even higher chloride content (154 mEq/L) than LRS. In fact, neither the sodium nor the chloride concentration in this fluid is similar to those of equine plasma. Isotonic saline solution has been shown to cause hyperchloremia and a mild acidosis during prolonged administration.[15-17] This hyperchloremia may make isotonic saline a less ideal fluid for long-term management of acute renal failure. Saline does not contain potassium and therefore may be warranted in horses with hyperkalemia. However, creation of a metabolic acidosis because of hyperchloremia may also pose a risk for hyperkalemia by causing an extracellular shift of potassium; this shift occurs as a result of acute changes in blood hydrogen concentration, which occur in association with hyperchloremic metabolic acidosis.[14] The effects of saline on potassium balance in horses warrant further study. Metabolic alkalosis, caused by hypochloremia or relative hypernatremia, is an indication for saline administration.

Normosol-R and Plasma-Lyte 148 have a sodium and chloride concentration most similar to equine plasma among the commercial isotonic or nearly isotonic fluids and are excellent fluids for diuresis of acute renal failure cases. It should be noted that these contain the highest potassium concentration (5 mEq/L) of all of the commercial fluids described; however, this potassium content is unlikely to contribute to clinically significant hyperkalemia in polyuric animals because of urinary excretion of excessive potassium (possible exceptions are uroperitoneum and anuria).

Isotonic sodium bicarbonate solution can be made by mixing sterile water and sodium bicarbonate to create a solution with a sodium concentration of approximately 150 mmol/L. Isotonic sodium bicarbonate does not contain potassium or chloride and can be modified to contain an increased amount of free water as needed by lowering the sodium concentration. It exerts an alkalinizing effect by increasing strong cation (Na^+) concentrations without a corresponding increase in strong anions (i.e., strong ion alkalosis).

Blending of fluids with different compositions is also an option in order to correct or maintain electrolyte and free water balance. Over time, horses often develop a plasma electrolyte profile similar to that of the administered fluid, especially when large volumes are administered for prolonged periods; therefore, combining or changing fluids may be necessary if derangements develop. It is also clear that monitoring of electrolytes (one to four times per day) is particularly important in renal patients.

Synthetic colloids should be avoided in horses with acute kidney disease because renal injury is a known complication of administration of synthetic colloids in humans.

ANURIC OR OLIGURIC RENAL FAILURE. Anuria and oliguria should be considered emergency medical conditions; the longer the duration of little to no urine production, the lower the chances of correcting it. Urine output in healthy horses is approximately 1 mL/kg/h, but this may decrease by 80% (to 0.2 mL/kg/h) in horses deprived of water.[18,19] In humans without significant fluid deficits, a urine flow below 0.5 mL/kg/h is one criterion used to define acute renal *injury,* whereas acute renal *failure* is associated with a urine flow below 0.3 mL/kg/h.[20] Oliguric renal failure should be suspected in azotemic horses with urine production below 0.5 mL/kg/h despite the administration of intravenous fluids. Once anuria or oliguria is suspected, a methodic approach to fluid administration and monitoring should be instituted immediately because of the associated high mortality rate. A delay in instituting treatment makes reversal of anuria less likely.

Treatment of Anuria or Oliguria

1. Obtain baseline laboratory and hemodynamic parameters. These should include serum or plasma electrolyte levels, total plasma protein and blood lactate concentrations, packed cell volume, and clinical perfusion parameters. When possible, CVP, arterial blood pressure, and central venous oxygen tension should be measured as well. If possible, a body weight measurement should be obtained and recorded.
2. If CVP is not already significantly increased and there are no clinical signs of fluid overload (increased respiratory rate, peripheral edema, etc.), a fluid challenge should be initiated using 10 to 20 mL of an isotonic crystalloid per kilogram. CVP, clinical pathology, urine output, and physical examination status should be reevaluated for improvement after completion of the bolus.
3. If urine output has not significantly increased, additional fluid challenges should be given and the patient reevaluated until urine production begins or until CVP limitations are reached. A CVP

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value greater than 15 to 20 cm H_2O (>10 to 12 cm H_2O in foals) signifies an endpoint to fluid administration.

4. Arterial blood pressure should be monitored. If hypotension is present despite fluid loading, inotrope and vasopressor therapy should be considered. Dobutamine can be used as an inotrope (5 to 10 mcg/kg/min). See page 1374, Fluid Therapy for Diarrhea and Colitis in Horses.
5. Once urine flow has increased, fluids should be continued as described previously for polyuria; careful monitoring of CVP and fluid balance (measurement of serial body weight and urine output) should be done.
6. If urine flow does not begin over the next 30 to 60 minutes with fluid challenge, furosemide should be started with an initial bolus of 0.12 mg/kg intravenously (IV) followed by a constant rate infusion (CRI) of 0.12 mg/kg/h.[21] If CRIs are not possible, a bolus dose of 1 mg/kg IV can be administered instead. Furosemide may improve urine production, but there is no definitive evidence that it improves creatinine clearance or positively affects outcome in people.[22]
7. If urine production does not begin within 30 to 60 minutes of instituting furosemide therapy, a dose of mannitol should be administered (0.25 to 0.5 g/kg bolus as a 20% solution). If there is still no urine produced after an additional 30 minutes, another dose of mannitol can be administered; a total dose of 1 g/kg should not be exceeded in the anuric patient to prevent hypervolemia and edema formation. Alternatively, a CRI of mannitol (1 to 2 mg/kg/min) can be used, with a maximum dose of 1 g/kg. Plasma osmolarity should be monitored.
8. If urine output has not improved after furosemide and mannitol, the prognosis is grave without peritoneal dialysis or hemodialysis. Treatment with low-dose dopamine has been controversial in human medicine, and several large studies have failed to demonstrate a benefit.[23,24] In fact, furosemide, mannitol, and dopamine may increase urine flow but have not been shown to unequivocally improve outcome in humans with acute renal failure.[25] When dialysis is not an option for horses with anuric renal failure, dopamine can be tried in an attempt to produce urine flow (2 to 3 mcg/kg/min); its proposed action is through increasing renal perfusion with renal afferent arteriolar vasodilation.[26] Without urine flow, there is no opportunity to provide the patient with time to heal if the acute renal injury is reversible. If dopamine is successful at reversing anuria, this time can be provided.

Hyperkalemia and metabolic acid-base disorders are common in horses with anuric or oliguric renal failure.[12] As noted earlier, hyperkalemia can be associated with life-threatening dysrhythmias. Rapid initiation of diuresis and administration of sodium bicarbonate, dextrose, and insulin are therapeutic interventions for hyperkalemia. If dysrhythmias are present, calcium should be administered to raise membrane threshold potential, thereby reducing the likelihood of abnormal rhythms.

As mentioned previously, hemodialysis has been reported infrequently in horses for clinical cases of renal failure.[1] Peritoneal dialysis has been described as a cost-effective and practical approach for horses with acute renal failure.[2] More recently, continuous venovenous hemodiafiltration was performed in experimental horses for short periods (6 hours). These therapeutic options may become more commonly used in horses that do not respond to conventional fluid therapy and medical treatments of anuria described earlier.

Fluid Therapy for Horses with Vasculitis

K. Gary Magdesian

Horses with vasculitis present a unique challenge to fluid therapy in that they have increased vascular permeability and are therefore at increased risk for developing edema. Examples of such patients that may require restoration of fluid volume include horses with purpura hemorrhagica, type I hypersensitivity reactions (such as anaphylaxis or anaphylactoid reactions), and *Anaplasma phagocytophilum* infections. Often horses with systemic vasculitis have edema, particularly in the distal limbs and ventrum, in the face of concurrent hypovolemia.

Correction of hypovolemia in these horses is challenging, since increasing the extracellular fluid compartment with crystalloid fluids may compound edema and lose efficiency in terms of blood volume expansion. Such cases may benefit from colloid administration. However, depending on the degree of vasculitis and the molecular weight of the colloid, a portion of the administered colloid may also extravasate into the interstitium or third space area, thus compounding edema. Therefore, horses receiving colloid fluids should be monitored for progression of their overall status, including increasing edema in response to fluid administration.

Colloids with a molecular weight of 100 to 300 kDa and those with narrower ranges, such as pentastarch (average molecular weight of 268 kDa) and the newer (third-generation) hydroxyethyl starches (molecular weight of 130 kDa), may have reduced extravasation compared with those with smaller molecular weights and wider molecular weight ranges. One of these with a molecular weight of 130 kDa (VetStarch, Abbott Animal Health, Abbott Park, Ill.) is now available diluted in 0.9% saline for use in dogs and cats. Colloids with this size molecule may reduce endothelial-leukocyte responses and are thought to interact with the endothelial glycocalyx in reducing capillary leakiness.[1,2] Previously available commercial hetastarch solutions (such as 6% hetastarch in 0.9% saline [Teva Parental Medicines Inc., Irvine, Calif.] or 6% hetastarch in lactated electrolyte [Hextend, Hespira, Inc., Lake Forest, Ill.]) are heterogeneous in terms of particle size (range, 15 to 3400 kDa), and those molecules below 100 kDa could extravasate more readily. Hextend has an average molecular weight of 670 kDa and a molar substitution of 0.75.

The total amount of colloid administered needs to be considered, since doses above 10 mL/kg/day of hetastarch may lead to coagulopathies.[3] The safe total cumulative dose of hetastarch over time (i.e., over days) is unknown. It should be noted that recent research in human critical care has suggested an increase in mortality rate in patients receiving hetastarch as compared to crystalloids. Plasma can be administered instead; however, albumin is relatively small (68 kDa), and much of it can redistribute extravascularly because of the altered reflection coefficient.

Fluid Therapy for Horses with Hypoproteinemia

K. Gary Magdesian

Similar to horses with systemic vasculitis, those with hypoproteinemia are at increased risk for edema formation with fluid therapy, making them among the most challenging to manage. The presence of concurrent hypovolemia and hypoproteinemia is a potential indication for colloids rather than crystalloids. Administration of crystalloids alone may result in compounding of the hypoproteinemia through hemodilution.[1] With altered Starling's forces, crystalloids distribute to the extracellular fluid to a relatively greater extent than they would otherwise, because of a lack of plasma oncotic force for retention. However, colloids can also extravasate due to increased vascular permeability, and therefore colloids should not be considered the definitive fluid in such cases because they too may exacerbate edema. Currently available colloids include hetastarch, dextrans, plasma, and concentrated human albumin.[2] Because of the increased potential for side effects associated with dextrans, there is no clear indication to use them over hetastarch. Side effects of dextrans reported in horses include muscle fasciculations, swaying of the hindquarters, tachycardia, and collapse in 8 of 64 horses.[3] Potential side effects of hetastarch products include coagulopathies. Other possible side effects in humans include allergic reactions and acute kidney injury.

Numerous commercial equine plasma products are also currently available. Many include antibodies to salmonella, endotoxin, and clostridial organisms; these are unlabeled claims and are largely unstudied in terms of efficacy. Another advantage of plasma,

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especially for the hypoproteinemic horse, includes provision of albumin, antithrombin, and additional clotting factors. Because albumin has multiple functions, including as a carrier protein (drugs, toxins) and physiologic buffer, plasma cannot be entirely replaced with synthetic colloids. Concentrated albumin has been used in neonatal foals, but its use in adult horses may be limited by cost.[2] The potential side effects of human plasma products in horses are largely unknown and require further study.

In one study evaluating the response of hypoproteinemic horses with gastrointestinal disease to hetastarch, it was determined that the oncotic benefit lasted 24 hours; in contrast, hetastarch raised the oncotic pressure of healthy horses for up to 5 days.[1,4] Nevertheless, in some cases even a short-term benefit in oncotic pressure may be preferable to the further dilutional effects of crystalloids.

Fluid Therapy for Hemorrhagic Shock (Box 44-5)

K. Gary Magdesian

With the exception of prompt hemorrhage control, the key component to early trauma care is adequate fluid resuscitation. Traditionally, replacement with isotonic crystalloids of three times the volume of shed blood has been the approach in human trauma patients. Up to eight times the blood loss volume has been administered in severe shock states because isotonic crystalloids distribute throughout the extracellular fluid compartment by volume, such that only 25% of the administered volume will remain within the circulating plasma volume.

Despite its importance, high-volume resuscitation is not innocuous; ARDS has been described in patients that received massive crystalloid resuscitation after trauma.[1] Severe trauma patients enter a phase of SIRS, with some patients developing multiple organ failure and others entering a compensatory antiinflammatory response syndrome (CARS). This latter syndrome causes immune suppression and increased susceptibility to infections. Commercial LRS brands used to contain a racemic mixture of L- and D-lactate. Those solutions, along with artificial colloids, namely dextrans and some hydroxyethyl starches, had proinflammatory effects.[2] Nonracemic LRS only contains the L-lactate form and does not share in the proinflammatory effect. It appears that the D-lactate (nonmammalian form) is largely responsible for the inflammatory reaction to racemic LRS, because removing it from the solution eliminates this effect.[3] These fluids, both artificial crystalloids and colloids, can also cause neutrophil activation and upregulation of adhesion molecules.[4] Most currently available forms of LRS contain only the L-isomer form of lactate. Hypertonic saline, on the other hand, has been shown to be immunomodulatory and causes suppression of neutrophil oxidative burst activity and neutrophil-endothelial adhesions.[5-8] Hypertonic saline counteracts the inflammatory effects of dextrans when used in combination.[9] Therefore, hypertonic saline has potential advantages for early fluid resuscitation of patients with significant blood loss, after the source of hemorrhage has been controlled. This should be followed with isotonic crystalloids, perhaps acetate-containing fluids, such as Normosol-R, or physiologic saline rather than racemic LRS. Hypertonic saline should not be used in cases of uncontrolled hemorrhage. Plasma similarly does not result in inflammatory cell activation. If hetastarch is used in acute blood loss patients, hemorrhage must be controlled before its administration because of rapid volume expansion as well as dose-dependent induction of coagulopathies.[10-15]

Aggressive fluid resuscitation in the face of uncontrolled hemorrhage cannot be justified. Such fluid protocols can exacerbate bleeding as a result of increases in blood pressure, disruption of clots, and hemodilution of clotting factors. Instead, a protocol of hypotensive resuscitation should be followed when bleeding cannot be stopped directly.[16] With hypotensive resuscitation, low volumes of crystalloids or whole blood should be administered to maintain organ vitality without normalizing pressures. A goal of maintaining a MAP of 60 mm Hg will still allow end-organ perfusion while allowing for hemostasis.

BOX 44-5

Fluid Considerations for Horses with Acute Hemorrhage

1. For horses with controlled hemorrhage, a combination of hypertonic saline, colloids, and acetated isotonic crystalloids or physiologic saline can be used.
2. Because of experimental evidence of proinflammatory effects of racemic lactated Ringer solution (LRS) in severe trauma, use of this solution should be questioned in cases of severe trauma until further studies are available. Non-racemic LRS (with L-lactate) should be used when LRS is desired.
3. Hypertonic saline exhibits antiinflammatory effects and may have benefits for horses with severe trauma, especially when LRS or synthetic colloids are used for resuscitation, and after hemorrhage has been controlled.
4. For controlled hemorrhage, a volume three to four times the estimated blood loss should be administered in isotonic crystalloids.
5. For uncontrolled hemorrhage, hypotensive resuscitation should be used; small volumes of fluids are administered to maintain organ perfusion and a mean arterial pressure of 60 mm Hg until the hemorrhage can be controlled.

Fluid Therapy in Acute Neurologic Injury (Box 44-6)

Darien J. Feary

The approach to fluid therapy in horses and ruminants with acute brain or spinal cord injury is aimed at maintaining oxygen delivery and energy supply to meet the metabolic demands of the neuronal tissue, and fluid therapy is a fundamental part of preventing or minimizing secondary neuronal injury, ischemia, and irreversible damage.

The primary goals of fluid therapy for both brain and spinal cord injury follow similar principles and include prevention and/or prompt recognition and treatment of hypovolemia and hypotension, intracranial hypertension (or cerebral edema), and glucose and electrolyte abnormalities.

Although both brain and spinal cord injuries are potentially life threatening in large animals, acute brain injury is likely to be the most influenced, either negatively or positively, by the particular fluid therapy plan that is instituted. This is mainly because the cranial vault is a closed space, composed of brain (approximately 80%), blood (approximately 10%), and CSF (approximately 10%). An increase in one component has to result in a compensatory decrease in another. The presence of the blood-brain barrier, intact or not, is another important factor in the selection of the most appropriate fluid for management of acute brain injury.

The most important consideration in the management of cerebral injury is the maintenance of cerebral blood flow (CBF), which is

BOX 44-6

Fluid Guidelines for Horses with Acute Neurologic Injury

1. The clinical outcome of large animal patients with brain and spinal cord injury may be improved by the prompt recognition and treatment of systemic and central nervous system hypoperfusion.
2. Isotonic crystalloid solutions appear to be the most appropriate fluids for resuscitation in acute neurologic injury, followed by careful administration of hyperosmolar therapy with mannitol or hypertonic saline if evidence of cerebral edema is present.
3. Diligent monitoring of clinical and laboratory measures of perfusion, osmolarity, and electrolyte concentrations is important for optimizing patient care and the likelihood of recovery in these patients.

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often reduced post injury. The major determinant of CBF is cerebral perfusion pressure (CPP), which is the difference between MAP and intracranial pressure (ICP) as defined by the following equation: CPP = MAP − ICP. In the normal brain, cerebral autoregulation maintains a relatively constant CBF despite wide variations in perfusion pressure, within the range of 50 to 150 mm Hg (in humans). In the injured brain autoregulation may be impaired, often with concurrent traumatic shock and hypotension, and CBF becomes directly dependent on CPP. Therefore, it becomes critical to prevent hypotension by maintaining MAP above 80 mm Hg and to avoid increases in ICP that result from cerebral edema or hemorrhage. ICP is not routinely measured in large animal patients, limiting its use in guiding fluid therapy. However, neurologic signs suggestive of elevated ICP (e.g., obtunded mentation, mydriasis) indicate the need for specific treatment to reduce ICP, with frequent reassessment of neurologic status being important in determining response to treatment.

Fluid management in large animal patients with acute neurologic injury is essentially based on the principles and guidelines established in human medicine from extensive laboratory and clinical studies. The ideal fluid for these human patients remains controversial and is a topic of ongoing research. When presented with a large animal patient with central nervous system injury, the clinician should formulate a fluid therapy plan tailored to the individual animal, based on findings of thorough physical and neurologic examinations and assessment of laboratory data. The author (DJF) suggests the following goal-directed approach:

- Goal 1: Treat hypovolemia and hypotension with adequate fluid replacement therapy to attain a normovolemic and normotensive state.
- Goal 2: Treat signs of cerebral edema or intracranial hypertension with hyperosmolar therapy.
- Goal 3: Use fluid additives to normalize glucose and electrolyte values, and provide thiamine supplementation.

REPLACEMENT FLUID THERAPY FOR NEUROLOGIC TRAUMA CASES. Although fluid restriction historically has been advocated for patients with traumatic brain injury (TBI) under the premise that intravenous fluids increase cerebral edema formation, this practice is no longer recommended, in humans or horses, for two main reasons. First, inadequate data support the theory that fluid restriction decreases cerebral edema formation, and second, systemic hypotension has been associated with increased mortality and poor neurologic outcome in human patients with TBI.[1-3]

Therefore, prompt restoration of adequate intravascular volume with the goal of achieving and maintaining euvolemia, normal blood pressure, and tissue oxygenation should be the primary goal of fluid management in patients with neurologic injury. This is best achieved and controlled via the intravenous route in injured horses. Overhydration should be avoided, particularly in neonates, which are more susceptible to volume overload than adult horses.

Selection of the appropriate fluid for replacement therapy requires an understanding of the role of the blood-brain barrier. Because of its unique properties, the development of cerebral edema is fundamentally different from edema formation in other organs or tissues.[4] Briefly, the normal blood-brain barrier functions as a semipermeable membrane, separating the brain from the intravascular space. In the normal animal the blood-brain barrier is impermeable to large molecules (plasma proteins) but is only minimally permeable to most ions. It is freely permeable to water, however. The tonicity of the intravascular fluid, determined by its sodium concentration, influences the movement of free water across the blood-brain barrier by creating an osmotic pressure gradient between the brain interstitium and the intravascular space. In TBI the blood-brain barrier may be damaged, often producing heterogeneous regions of varying degrees of blood-brain barrier integrity and permeability. Unfortunately, demonstrating and predicting the extent of such injury in clinical patients is very difficult; the clinician often likely has to assume the presence of normal brain and functional blood-brain barrier regions for certain principles of fluid management, such as osmotherapy, to be effective.[5]

Hypotonic crystalloids, such as 5% dextrose in water or 0.45% saline solutions, are contraindicated in TBI patients. They lower plasma osmolarity and result in excess free water diffusion into the brain, with subsequent cerebral edema formation. Hypotonic fluids should be avoided for rapid volume replacement in patients with brain injury.

Isotonic crystalloids, such as 0.9% saline, LRS, and Normosol-R, create a minimal to no osmotic gradient across the blood-brain barrier, are readily available and inexpensive, and are therefore the current fluids of choice for replacement and maintenance therapy in brain and spinal cord injury patients.

Hypertonic crystalloids, such as 7.5% saline, create an osmotic gradient across the blood-brain barrier in favor of free water movement out of the brain, thereby reducing ICP. Hypertonic fluids are indicated *only after adequate provision of intravascular fluid volume* in horses with signs of elevated ICP or deteriorating neurologic status and are discussed in more detail in the following section on hyperosmolar therapy.

Colloids—such as plasma, human albumin, and the synthetic agents hetastarch, pentastarch, and dextran—exert variable oncotic pressures and are very effective for intravascular volume expansion and maintenance. The use of colloid solutions in neurologic injury is debatable, mainly because the major determinant of fluid flux across the blood-brain barrier is plasma osmolarity; because colloids contribute only a small number of particles in plasma, even large changes in plasma colloid oncotic pressure only minimally influence water movement across the normal blood-brain barrier. This is in contrast to the effectiveness of even small changes in plasma osmolarity.[6] In addition, the relatively higher cost of colloid solutions and the greater risk of development of hemostatic abnormalities and allergic reactions suggest little benefit of colloid solutions over crystalloids in cases of TBI. The exception is when they are used in combination with crystalloids for fluid volume expansion, provided that hydrostatic pressures are not increased excessively as a result of the colloid infusion.[4]

HYPEROSMOLAR THERAPY IN BRAIN AND SPINAL CORD INJURY. Hyperosmolar therapy is the pharmacologic induction of supraphysiologic serum osmolality with either hypertonic saline or mannitol and is the mainstay of medical management of patients with intracranial hypertension (ICP > 20 mm Hg) associated with TBI and intracranial haemorrhage.[7] If clinical evaluation of the equine patient with TBI suggests the patient has, or is at risk for developing, intracranial hypertension, then osmotherapy may be indicated. Clinical signs such as obtunded mentation, progressive mydriasis, or any deterioration of neurologic status may indicate increased intracranial hypertension. Hyperosmolar solutions exert their effect of reducing ICP by creating an osmotic gradient across the blood-brain barrier of at least 10 mOsm/L. It is advisable to measure plasma osmolarity in large animal patients, at least before administration of hyperosmolar solutions, to avoid excessive increases in plasma osmotic pressure. Osmotherapy should be instituted only after restoration of adequate intravascular volume and blood pressure if CPP is to be optimized.

The two most commonly used and available hyperosmolar solutions for use in large animals are mannitol (20%) and hypertonic (3% to 7.5%) saline. Both agents have been shown to be effective in lowering ICP in human TBI patients, although more recent meta-analysis of the literature suggests greater efficacy and fewer side effects with the use of hypertonic saline.[7,8]

Mannitol (20%) is a six-carbon sugar with an osmolarity of 1098 mOsm/L. The recommended dose is a 0.5- to 1.5-g/kg IV bolus administered over 20 to 30 minutes, every 6 to 8 hours. It is important to avoid rapid mannitol infusion (<5 minutes) since this can lead to transient hypotension. The ICP-reducing effects of hyperosmolar solutions are believed to be biphasic in nature. After bolus dose administration, an initial plasma-expanding effect reduces blood

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viscosity and hematocrit and improves rheologic properties of red blood cells, resulting in reduced ICP and improved CBF. After this immediate hemodynamic effect is a delayed osmotic diuretic effect resulting from the decreased reabsorption of sodium and water by the renal tubules, which also contributes to ICP reduction. Onset of effect of mannitol therapy is 15 to 30 minutes after bolus administration. Mannitol should not be administered as a continuous infusion for the purpose of treating cerebral edema, since it loses its plasma-expanding effects and increases the likelihood of development of side effects.[9]

The detrimental effects of mannitol are more likely to develop and become clinically significant with excessive or prolonged use (>2 to 3 days). Side effects include hypovolemia and hypotension caused by excessive diuresis, electrolyte disturbances (e.g., hyponatremia, hypochloremia, hypokalemia, hypocalcemia), acidosis, acute renal failure, and a rebound increase in ICP associated with reversal of the osmotic gradient, a phenomenon most likely explained by accumulation of the osmotic agent in brain tissue after movement across regions of damaged blood-brain barrier.[9] A threshold level of serum osmolarity of 320 mOsm is often used as an indicator for decrease or withdrawal of mannitol therapy. However, serum osmolarity is not a sensitive indicator of mannitol-induced renal failure, and the osmolar gap (the difference between calculated and measured serum osmolarity) is more reflective of serum mannitol accumulation. Based on this, an osmolar gap threshold of 55 mOsm/kg has been suggested for monitoring mannitol therapy in TBI.[7] There is insufficient evidence to support the dogma that mannitol is contraindicated in the presence of intracranial hemorrhage.

Hypertonic (7.5%) saline has an osmolarity of 2400 mOsm/L and, similarly to mannitol, effectively reduces ICP primarily through an immediate hemodynamic effect, followed by a delayed osmotic effect. Hypertonic saline can be administered as an intravenous bolus dose (4 mL/kg) or as a CRI. There are no clear guidelines as to the optimal concentration (3% to 23.4%) or dose of hypertonic saline in human patients with TBI. However, effective CRI dosing has been achieved in human patients using 3% hypertonic saline at 0.1 to 2.0 mL/kg/h, titrating to serum sodium concentrations of 145 to 155 mmol/L, and not exceeding serum osmolarity of 360 mOsm/L.[7] Hypertonic saline may have additional beneficial effects over mannitol in TBI because of rapid augmentation of cardiac output, contractility, and MAP with administration of smaller volumes. In addition, hypertonic saline is theoretically less likely to cross the blood-brain barrier than mannitol because the reflection coefficient of NaCl is 1 (not permeable), compared with 0.9 for mannitol (more permeable). Additional benefits of hypertonic saline on the injured brain include Na-related stabilization of cell membrane electrochemical gradients and modulation of the inflammatory response.[10]

Laboratory studies investigating the effect of hypertonic saline in resuscitation after spinal cord injury have also shown promising results, with increased spinal cord blood flow, downregulation of the inflammatory response, and attenuation of spinal cord injury.[11] Further clinical studies are needed.

Complications of hypertonic saline are uncommon and include hypernatremia and theoretical development of central pontine myelinolysis.[7] Hypokalemia can occur because of kaliuresis in response to reabsorption of large amounts of Na in the distal tubule, as well as hyperchloremic acidosis, emphasizing the importance of regular assessment of hemodynamic and plasma electrolyte and acid-base status. Coagulopathy and bleeding complications could occur as a result of dilutional effects but are of more concern in the actively bleeding patient. Risk of hypovolemia and acute renal failure are not reported for hypertonic saline in TBI, although renal insufficiency is a relative contraindication to all hyperosmolar therapy. Rebound elevations in ICP can occur with withdrawal of therapy; therefore, slow, gradual weaning of hypertonic saline infusions is recommended.[7]

Osmotherapy is likely to be most effective if initiated early (after isotonic fluid replacement) following TBI and with duration determined by response to therapy, with close observation and monitoring of neurologic status, serum electrolytes, acid-base, osmolarity, and renal function, to minimize development of side effects. Because measurement of intracranial pressure is not practical to perform routinely in equine patients with TBI at this time (it has been measured in a research setting), the efficacy of, and optimal recommendations for, hyperosmolar therapy in equine patients with TBI are unknown and based on the human medical literature.

FLUID ADDITIVES IN NEUROLOGIC INJURY

Glucose. It has been widely recognized that hyperglycemia is a common occurrence in acute brain injury in humans.[12] Hyperglycemia is believed to worsen neuronal injury and is associated with increased mortality and neurologic outcomes after TBI.[12,13] Consequently, glucose supplementation during large-volume fluid replacement should be avoided, unless the patient is hypoglycemic.

It has not been determined whether hyperglycemia after TBI is a physiologic reflection of the response and severity of injury, or if it contributes to the progression of secondary brain injury. Nevertheless, in ischemic brain tissue aerobic metabolism is impaired and excess glucose leads to lactate accumulation and intracellular acidosis via anaerobic metabolism; this can contribute to a proinflammatory and prooxidant state, thereby potentially worsening neurologic injury and increasing cell death.[7] Tight glycemic control (80 to 110 mg/dL) with the use of insulin had become commonplace for critically ill human patients worldwide. A beneficial effect of reducing blood glucose with insulin therapy in human patients with TBI has been suggested.[14] However, patients with traumatic brain injury present a more unique situation, since the brain is dependent on a constant supply of glucose for continued aerobic energy production. An increase in energy demand by the brain, such as during seizure activity, may result in metabolic crisis that contributes to secondary brain injury. Therefore, it is also crucial to avoid hypoglycemia in TBI patients. Although there are no studies in horses with TBI to enable recommendations regarding the best management of glucose to be made, recent human medical studies have shown that tight glycemic control after TBI is potentially detrimental due to increased regional glucose metabolism in the brain, leading to enhanced metabolic crisis.[15] It is currently suggested that delivery of more glucose through mild hyperglycemia (120 to 150 mg/dL) may be necessary following TBI.[15] This is more in line with the revised glucose control guidelines of maintenance of blood glucose concentrations 180 mg/dL or less in critically ill patients (not just brain injured) rather than 80 to 110 mg/dL, in order to avoid hypoglycemia.[16]

These factors should be considered in the monitoring and fluid therapy plan for any large animal with neurologic injury, particularly neonates, since they are more susceptible to hypoglycemia.

Thiamine. Thiamine (vitamin B_1) is a water-soluble B vitamin synthesized only by plants and microorganisms. Most animals have a nutritional requirement for this vitamin, although adult ruminants and horses normally can obtain adequate quantities produced by bacteria in the rumen or cecum.

Thiamine, in its active form (thiamine pyrophosphate), plays a very important role in glucose metabolism and energy production, where it functions as a required cofactor for certain enzymes (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase, transketolase) involved in glycolysis, the citric acid cycle, and the pentose phosphate pathway. Thiamine is also important in nerve and muscle function, where it plays a role in neurotransmission and excitation.

Thiamine deficiency is known to be associated with neurologic disease in humans and in ruminants (polioencephalomalacia). Determination of thiamine status of an animal requires measurement of red blood cell transketolase activity; therefore, measurement and documentation of thiamine deficiency in clinical cases is not routinely reported. Whether or not supplementation of thiamine in acute traumatic neurologic injury is indicated is not currently supported by published evidence. However, given the increased susceptibility of damaged neuronal tissue to inadequate energy production and supply, the practice of thiamine supplementation in

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neurologic injury in large animals appears justified. In addition, recent experimental investigation suggests a potential neuroprotective role of thiamine in reactive oxygen species–induced neuronal injury.[17] The author (DJF) has used a dose of 5 to 10 mg of thiamine per kilogram diluted in crystalloids. Thiamine should be protected from light.

Electrolytes. Sodium disturbances can have serious consequences in brain injury and should be corrected promptly if they are acute (<24 hours' duration). Isotonic fluid administration is appropriate in the majority of cases. Glucose and mannitol cause translocation of water into the extracellular fluid, and excessive amounts can lead to a clinically significant reduction in sodium concentration, as can free water administration with hypotonic fluids. If hyponatremia ($Na^+ < 125$ mEq/L) is believed to have been present for longer than 24 hours, slower correction (0.5 mEq/L/h) is needed to avoid development of central pontine myelinolysis.

Calcium is essential in maintaining cell membrane potentials and promoting neurotransmitter release. Excessive intracellular calcium accumulation is also well recognized as one of the most important pathways of secondary neuronal damage. During conditions of cerebral or spinal cord ischemia, inadequate energy supply in the form of adenosine triphosphate (ATP) leads to widespread neuronal depolarization and alterations in ion channel permeability, ultimately resulting in excessive intracellular calcium concentrations and cell death.

Serum total and ionized calcium concentrations are measures of extracellular calcium, and so the goal of targeting intracellular calcium homeostasis is limited to maintaining normal extracellular fluid concentrations at this time. Because of the known toxic effects of excessive calcium in neuronal injury, a conservative approach to calcium supplementation may be justified in the acute fluid management of large animal patients. In order to prevent the detrimental effects of hypocalcemia, one approach may be to avoid the addition of calcium to the intravenous fluids over the initial 24 to 48 hours unless the ionized calcium concentration is less than 1.0 mmol/L or clinical signs of hypocalcemia are present.

Magnesium is an important cofactor in many enzymatic reactions and for the regulation of sodium and potassium transport across cell membranes through activation of the Na-K ATPase pump. Magnesium is essential for central nervous system cellular energy metabolism, modulation of excitatory amino acid transmission, and calcium channel antagonism. After neurologic injury, disruptions in the blood-brain barrier may impair regulation of CSF magnesium concentrations, and hypomagnesemia is commonly recognized in human patients with brain injury.[18] Experimental and clinical evidence suggests that a depletion of CSF magnesium concentrations is associated with the risk of secondary neurologic injury.[19] Animal studies also suggest a neuroprotective effect of intravenous magnesium administration after traumatic brain injury.[20] However, studies in human patients with TBI have failed to show a consistent therapeutic effect of magnesium supplementation.[19] Although magnesium supplementation for the treatment of TBI in equine patients cannot be recommended at this time, it would seem important to monitor serum total and ionized magnesium concentrations to prevent and treat hypomagnesemia after neurologic injury. Selection of intravenous fluids containing magnesium, such as Normosol-R ($Mg^{2+} = 3$ mEq/L) may be beneficial.

Other electrolyte disturbances identified commonly in patients with neurologic injury include hypokalemia and hypophosphatemia. A combination of decreased dietary intake and increased renal loss as a result of diuretic therapy is a likely explanation. Because of the important role of potassium in establishing normal resting membrane potential and nerve conduction, among other functions, regular monitoring and intravenous fluid supplementation if serum potassium concentration decreases to less than 3.0 to 3.2 mEq/L is indicated in large animal patients with neurologic injury.

Serum phosphate concentrations are not as routinely monitored as other electrolytes in large animal patients, and so deficiency is rarely reported. Clinical signs of hypophosphatemia usually do not manifest until serum concentrations fall below 1 mg/dL in humans and animals. It is important to recognize phosphate deficiency in patients with recent neurologic injury because it can cause or contribute to altered mental status, muscle weakness, seizures, respiratory insufficiency, and ventricular dysrhythmias. Because clinical manifestations of hypophosphatemia have not been reported in horses, it is difficult to make recommendations for supplementation. I have used a dose of 0.01 mmol/kg/h of sodium phosphate when marked hypophosphatemia has been present in horses.

Fluid Therapy for Horses with Rhabdomyolysis (Box 44-7)

K. Gary Magdesian

Horses with severe rhabdomyolysis are at risk for renal failure from myoglobinuria and hypovolemia. Myoglobin causes formation of tubular casts (with resultant tubular obstruction) by precipitation with secretory proteins from the tubular cells. It is also directly toxic through release of iron and formation of free radicals. Finally, myoglobin leads to release of platelet activating factor and endothelins that lead to renal arteriolar vasoconstriction. In addition, horses and foals with severe rhabdomyolysis may develop marked electrolyte derangements from cell lysis, including hyponatremia, hypochloremia, hyperkalemia, and hyperphosphatemia.[1,2] In one study evaluating the electrolyte changes in horses with acute rhabdomyolysis, the most consistent abnormality was hypochloremia.[1] These changes have been reported in foals with rhabdomyolysis as a consequence of selenium deficiency with or without vitamin E deficiency, possibly combined with increased oxidant stress resulting from sepsis or hypoxia and reperfusion injury after parturition.[2] Three of four foals developed cardiac arrhythmias characterized by spiked T wave and decreased P wave amplitude on electrocardiographic analysis. Destruction of the major intracellular fluid compartment through extensive myonecrosis, combined with myoglobinuric renal insufficiency, produces major fluid shifts and electrolyte derangements. In this report, foals with hyperkalemia caused by rhabdomyolysis were effectively treated with mineralocorticoids, loop diuretics, and ion exchange resins to enhance elimination of potassium. Intravenous calcium, glucose, insulin, and sodium bicarbonate were also administered to help redistribute potassium back to the intracellular fluid.[2]

Metabolic acidosis is not common in horses with acute rhabdomyolysis, and alkalosis associated with hypochloremia may be more of a concern.[1] In fact, fluids with relatively higher chloride concentration as compared with horse plasma may be optimal when hypochloremia is present. These include LRS (chloride, 109 mEq/L). If LRS is used, attention should be paid to serum or plasma potassium concentrations, because LRS contains potassium chloride in the amount of 4 mEq/L of potassium (see Table 44-1). LRS might be preferable over acetate-containing fluids such as Normosol-R or Plasma-Lyte 148 in acute rhabdomyolysis cases because the liver is the primary organ of lactate metabolism, whereas the muscle tissue plays a larger

BOX 44-7

Fluid Considerations for Horses with Rhabdomyolysis

1. Horses with acute myopathies often exhibit hypochloremia and may have concurrent hyponatremia, hyperkalemia, and hyperphosphatemia, especially when the rhabdomyolysis is severe.
2. Lactated Ringer solution is a fluid with a physiologic basis for use with rhabdomyolysis.
3. Horses with acute myopathies should be administered fluids at a rate greater than maintenance requirements in order to provide for dilution and diuresis of myoglobin.

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role in metabolism of acetate. In addition, the chloride concentration of these acetated fluids is lower than that of LRS, which may be a slight disadvantage if horses have metabolic alkalosis resulting from hypochloremia. Lactate in LRS does not preclude its use in hyperlactatemic horses with muscle disorders, because hepatic metabolism of lactate occurs rapidly once plasma volume is expanded. In addition, lactate is not necessarily markedly increased in horses with rhabdomyolysis.[3]

LRS is preferred over normal saline for treatment of humans with rhabdomyolysis.[4] In a randomized blinded study of humans with rhabdomyolysis, urine and plasma pH was higher in the LRS group, whereas serum sodium and chloride concentrations were higher in the saline group.[4] Unlike the saline group, the LRS group needed little supplemental sodium bicarbonate and did not develop metabolic acidosis. Acidic urine favors formation of myoglobin-induced tubular casts and tubular obstruction. Therefore, LRS is considered by many to be the fluid of choice to maintain adequate urine flow in patients with rhabdomyolysis. One potential disadvantage of LRS in treatment of rhabdomyolysis is the presence of a low concentration (3 mEq/L) of calcium. Calcium influx plays a role in cell lysis after lipoperoxidation of muscle cells. How these data apply to adult horses, which generally have alkaline urine, requires further study. Because 0.9% saline is mildly acidifying in horses as well, it likely is not the optimal fluid choice for horses with rhabdomyolysis either. As foals often have acidic urine, LRS may be a good fluid choice for foals with rhabdomyolysis as well.

In addition to crystalloid support, sodium bicarbonate is recommended for human rhabdomyolysis only if necessary to correct a systemic metabolic acidosis.[5] Mannitol is administered to maintain urine output (300 mL/h or greater urine output in adult humans).[5]

Hereditary causes of rhabdomyolysis in horses include polysaccharide storage myopathy, glycogen branching enzyme deficiency, and recurrent exertional rhabdomyolysis (RER).[6-8] Because an alteration in muscle cell calcium regulation is a primary feature in the pathophysiology of RER, calcium supplementation of fluids administered to affected horses should be avoided.[9] Serum potassium concentrations should be monitored frequently in horses with rhabdomyolysis because of risks associated with hyperkalemia.

Because horses with acute rhabdomyolysis are at risk for renal failure, rates of fluid administration should exceed maintenance requirements to provide diuresis and dilution of urine myoglobin concentration. In adult human patients with rhabdomyolysis, the goal of urine production is greater than 300 mL/h.[5] Myoglobin is nephrotoxic directly to renal tubular epithelium, as well as indirectly causing renal arteriolar vasoconstriction and secondary hypoperfusion. Rates of fluid administration vary with individual fluid balance and renal function, but 1.5 to 2 times maintenance requirement is a reasonable starting point. The rate can be adjusted based on the rate of creatine kinase (CK) decline and resolution of myoglobinuria.

Fluid Therapy for Hyperkalemic Periodic Paralysis (Box 44-8)

K. Gary Magdesian

Hyperkalemic periodic paralysis (HYPP) is caused by a genetic defect in the sodium channel on the sarcolemma, resulting in intermittent signs of sweating, muscle fasciculations, stridor, and weakness.[1] Stressors such as anorexia, anesthesia, concurrent illness, trailering, and cold environmental temperatures can precipitate hyperkalemia and onset of clinical signs. Fluid therapy for horses with hyperkalemia should be low or free of potassium. Physiologic (0.9%) saline and isotonic sodium bicarbonate (1.3%) are both potassium-free options. Note that these two fluid types have potential effects on acid-base physiology, with saline producing a mild strong ion acidosis and sodium bicarbonate a metabolic alkalosis. Another option for horses without acid-base disturbances is to combine commercial balanced polyionic fluids, such as LRS or Normosol-R, with one of these fluids (i.e., hanging one bag of each), as long as the horse is not experiencing hyperkalemia at the time. This would dilute the potassium administered from the LRS (4 mEq/L) or Normosol (5 mEq/L) and would minimize the effects of saline or sodium bicarbonate on acid-base balance.

Horses experiencing stressors such as forced withholding of feed before surgery or being off feed because of concurrent illness should be administered fluids with dextrose and/or calcium supplementation prophylactically at a maintenance rate. These dextrose supplementations (2.5%) may minimize the development of hyperkalemia and subsequent HYPP episodes. Calcium does not decrease serum potassium concentrations but rather protects the heart from its adverse effects by raising threshold potential. Horses experiencing an active episode of hyperkalemia or showing clinical signs of HYPP should be administered 0.9% saline as the fluid choice, with the additives of calcium (0.2 to 0.5 mEq/kg of 23% calcium gluconate diluted as 50 mL 23% calcium gluconate/L or less of fluid) and dextrose (2.5% to 5% for provision of 0.5 to 2 mg of dextrose per kilogram per minute. If signs persist, a second bag with sodium bicarbonate (1 mEq/kg of bicarbonate empirically) and dextrose should be added. Calcium and sodium bicarbonate should not be administered concurrently in the same fluid administration set because of a potential for precipitation. LRS also contains calcium, and therefore sodium bicarbonate should not be added directly to it. Administration of two 5-L bags of saline to a 500-kg horse, with 2.5% to 5% dextrose, with the first bag containing calcium (250 mL of 23% calcium gluconate total) and the second containing sodium bicarbonate (1 mEq/kg of bicarbonate) given sequentially, is a reasonable approach to treating an acute episode. Some horses may not require this volume of crystalloid and can be treated with less; if less volume is desired, 4 to 6 mL of saline per kilogram can be administered. Dextrose, calcium, and sodium bicarbonate can be added to 1-L bags; the sodium bicarbonate and calcium must be kept separate from one another. In this case 5% dextrose, 0.2 mL/kg of 23% calcium gluconate (in first 1-L bag), and 5% dextrose, 0.5 mEq/kg of bicarbonate can be used (in second 1-L bag).[1]

Long-term management of horses with HYPP consists of a low-potassium diet, regular exercise, attempts to minimize stressors, and medications such as acetazolamide and phenytoin.[2] Horses undergoing chronic acetazolamide therapy could theoretically develop hyperchloremia and a tendency toward metabolic acidosis because of the effects of long-term inhibition of carbonic anhydrase. Administration of large volumes of 0.9% saline can compound hyperchloremia[3]; to minimize acidemia, it can be coadministered with isotonic sodium bicarbonate or other alkalinizing crystalloid when such horses require large volume or long-term fluid therapy devoid of or low in potassium. Phenytoin can mask the clinical signs of HYPP, even when hyperkalemia is present; it must be emphasized that phenytoin should not be the sole prophylactic medication in these horses, because hyperkalemia may be left unchecked.[2]

BOX 44-8

Fluid Guidelines for an Acute Hyperkalemic Periodic Paralysis Episode

1. 4 to 20 mL of 0.9% saline per kilogram, depending on severity and duration.
2. 2.5% to 5% dextrose.
3. 0.2 to 0.5 mEq of calcium per kilogram (0.2 to 0.5 mL of 23% calcium gluconate per kilogram total); calcium should be administered early (along with dextrose) since it is protective against arrhythmias.
4. 1 mEq of bicarbonate per kilogram in second bag along with dextrose. Note sodium bicarbonate and calcium should not be mixed in same bag.
5. For refractory cases: insulin can be added to dextrose supplementation (regular insulin, 0.005 to 0.1 unit/kg/h).

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Fluid Therapy for Competitive Endurance Horses

C. Langdon Fielding

Approximately 4% to 9% of endurance horses are eliminated from competition for metabolic reasons that include colic, rhabdomyolysis, synchronous diaphragmatic flutter, and exhaustion.[1,2] Veterinarians are responsible for the emergency treatment of horses with metabolic derangements, and fluid therapy is an essential component of the therapeutic management of critically ill endurance horses.

GENERAL APPROACH TO FLUID MANAGEMENT OF ENDURANCE HORSES. Endurance horses experience significant fluid losses during competition; even horses successfully completing rides lose approximately 5% of body weight in water.[3,4] Horses presented for treatment of metabolic problems often exhibit clinical signs of hypoperfusion. In evaluating sick endurance horses, the seven clinical perfusion parameters should be evaluated:

1. Mentation
2. Heart rate
3. Pulse quality
4. Mucous membrane color
5. Capillary refill time
6. Extremity temperature
7. Jugular fill

Urine production, when apparent, can be used as an additional perfusion parameter. In the absence of polyuric renal failure, urine output signifies renal perfusion, which is one means of assessing organ perfusion. Horses with altered mentation, persistent tachycardia (>60 bpm), poor peripheral pulse quality, pale mucous membranes, capillary refill time greater than 2 seconds, cool extremities, or lack of urine production should be considered candidates for fluid therapy. Laboratory parameters consistent with dehydration such as increased PCV, increased total protein, and increased serum creatinine have been identified in endurance horses at risk for metabolic failure.[5]

The rapid administration of large volumes of crystalloids is the basis of treatment at many ride events. Volume loading increases preload, thereby enhancing stroke volume, cardiac output, and subsequent oxygen delivery. One suggested protocol for fluid resuscitation of hypovolemic endurance horses is the fluid challenge method described earlier; this consists of a bolus dose of 20 mL of isotonic crystalloid per kilogram (10 L for an average, 500-kg horse) followed by reassessment of the seven perfusion parameters. If the parameters have not improved in response to the initial bolus, another 20-mL/kg bolus should be administered and followed by clinical reassessment. Approximately 1 hour is required to administer a 10-L bolus through a 14-gauge intravenous catheter and standard administration set; multiple catheters or those with large bores (10 gauge) can be used for more rapid administration. The majority of endurance horses requiring emergency intravenous fluid administration during competition typically require 20 to 30 L of fluids.[6,7] However, more severely affected horses may require up to 40 to 60 L of crystalloids to address hypovolemia.

Several types of intravenous crystalloids are available for administration to endurance horses. LRS and Normosol-R are balanced polyionic crystalloids commonly administered to treat hypovolemia in these horses. Specific electrolyte abnormalities may dictate the use of isotonic saline (when hypochloremic alkalosis is present) or fluid additives (potassium chloride or calcium gluconate when hypokalemia or hypocalcemia is identified, respectively). However, in one study, 0.9% sodium chloride resulted in hyperchloremia when administered to eliminated endurance horses.[6] The electrolyte and serum biochemistry profiles of endurance horses that fail to finish a race are not necessarily markedly abnormal and allow the use of commercial fluids such as LRS and Normosol R.[4] A range of electrolyte abnormalities have been identified in competing endurance horses and include hypokalemia and an increased strong ion difference (SID).[8,9] Calcium supplementation is common during fluid therapy of eliminated endurance horses. However, results of studies examining the concentration of total and ionized serum calcium in horses during endurance rides have been equivocal as to calcium status.[3,4,10] If calcium is used, it can be added to fluids through the use of calcium gluconate (1 mL of 23% calcium gluconate per kilogram at a rate of 50 mL of crystalloid per liter). Calcium supplementation is required in horses with synchronous diaphragmatic flutter and should be administered until clinical signs resolve.[11] Excessive use of calcium in endurance horses may not be warranted, since it plays a role in cell death and apoptosis, particularly with reperfusion injury; supplementation of calcium in humans with rhabdomyolysis is controversial.[12]

Endurance horses with prolonged ileus or anorexia may benefit from dextrose supplementation of fluids. A dose of 1 mg/kg/min of dextrose is well tolerated by most adult horses and is equivalent to 3% dextrose in fluids administered at a rate of 1 L/h for a 500-kg horse. Ideally, blood glucose concentrations should be monitored in horses administered dextrose to avoid hyperglycemia.

Medications commonly used in the treatment of endurance horses with metabolic derangements may affect fluid balance and should be considered in horses receiving fluid therapy. Sedatives and tranquilizers such as α_2-agonists (xylazine, detomidine, romifidine) and phenothiazines (acepromazine) have deleterious effects on cardiac output and/or blood pressure.[13,14] Drugs such as dimethyl sulfoxide (DMSO) and α_2-agonist sedatives also affect urine output and can therefore alter fluid balance.[15,16]

The following metabolic conditions are common metabolic disorders of endurance horses.

EXERTIONAL MYOPATHY. Intravenous fluid therapy is the most important feature of treatment for rhabdomyolysis. The reader is referred to the Fluid Therapy for Horses with Rhabdomyolysis section. Fluids should be administered in 10-L (20-mL/kg) boluses until urine output is achieved and the urine is grossly clear. Low doses of flunixin meglumine (0.5 mg/kg IV) are indicated for inflammation once hypovolemia is resolved and diuresis is achieved. Adequate fluid resuscitation is indicated before release of affected horses because exertional rhabdomyolysis has been associated with severe renal failure in both humans and horses.[17,18] Horses with myopathies should be monitored closely and reevaluated within 48 hours for azotemia and progress of increased muscle enzymes.

FAILURE TO RECOVERY. Horses that are eliminated from ride events because of persistent tachycardia warrant close monitoring. Such horses often require treatment at a later time. The seven clinical perfusion parameters should be evaluated thoroughly, and any animal with equivocal circulatory or hydration status should be reevaluated frequently to make sure that it is improving through voluntary eating and drinking, rather than deteriorating further. Those with clear hypovolemia or failure to improve with rest should be administered intravenous fluids as described earlier.

SYNCHRONOUS DIAPHRAGMATIC FLUTTER (THUMPS). Synchronous diaphragmatic flutter is typically associated with hypocalcemia, and concurrent metabolic alkalosis, hypochloremia, and hypokalemia are often also present and have been implicated in its development.[19] Many affected horses are otherwise stable hemodynamically and meet all the criteria for adequacy of perfusion. Despite these findings, horses with thumps often require treatment with intravenous fluids supplemented with calcium for resolution of hypocalcemia and clinical signs. Calcium gluconate can be added to 5-L bags of crystalloid (0.5 mL of 23% calcium gluconate per kilogram per 5-L bag), and fluids with dilute calcium can be administered as a bolus. Adverse effects of rapid calcium administration include bradycardia and warrant slow administration. Many mildly affected horses would likely resolve synchronous diaphragmatic flutter with oral electrolytes and/or the consumption of feed (particularly alfalfa).

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COLIC. Colic is a common problem identified in eliminated endurance horses and can result in significant mortality.[20] All horses exhibiting signs of colic should have a nasogastric tube passed as nasogastric reflux (likely resulting from ileus) is a common finding in these horses.[20] Intravenous fluids should be administered as outlined previously until the horse is no longer producing gastric reflux and the horse is passing manure regularly. Flunixin meglumine (0.5 to 1 mg/kg) can be administered intravenously once hydration is restored. Calcium gluconate can be added to 5-L bags of crystalloid (0.5 mL of 23% calcium gluconate per kilogram per 5-L bag), and fluids with dilute calcium can be administered as a bolus. Managing endurance horses with colic can be challenging because many show significant levels of pain. It is important to remember that endurance horses with colic rarely have a surgical lesion and typically respond to aggressive medical therapy.[9,20]

Fluid Therapy for Burn (Thermal) Injury in Horses (Box 44-9)

K. Gary Magdesian

Horses with severe burn injuries develop hypovolemic shock and require large volumes of balanced electrolyte replacement fluids.[1] Hypertonic saline and colloids may also be used but should be followed with isotonic crystalloids. In humans with burn injuries, the guidelines for rate of administration of isotonic fluids is 2 to 4 mL/kg for each percentage of surface area burned (Parkland formula).[2] A retrospective study found that significantly larger volumes of fluid (i.e., 5.58 mL/kg per percent total body surface area affected) were administered to patients during the first 24 hours of hospitalization than was predicted by the Parkland formula.[3] If smoke inhalation has occurred, the affected horse is at risk for pulmonary edema. In this case, fluid deficits should be corrected but not exceeded. Administration of excess crystalloids or high rates of fluids after resolution of hypovolemic shock will result in edema, which is detrimental to healing of burned tissues and potentially smoke-injured lungs. Once hydration is adequate, fluid therapy should be discontinued (if drinking) or administered at a rate necessary only to maintain hydration status. If maintenance rates of fluids are required, patients with severe burns may require more sodium than provided for by commercial maintenance fluids owing to the tremendous sodium losses through wounds.[4] In these cases, isotonic to slightly hypertonic (1.8%) crystalloids may be required.[5] Excess free water should be avoided in these patients, since it can promote intracellular tissue edema.[5]

An important component of fluid therapy of the thermal injury patient is the administration of plasma. Significant amounts of plasma proteins are lost through cutaneous burns.[4] In addition, burn patients are at risk for coagulopathies, although this has been reported to be rare.[6] Plasma transfusions are an effective source of albumin, as well as antithrombin for coagulopathies. Horses with significant burns can require large volumes of plasma in the first 2 to 3 days. A CRI of plasma can be provided when ongoing losses are present.

BOX 44-9

Fluid Guidelines for Burn Injury Patients

1. Hypertonic saline can be used in the resuscitative phase of burn patients but should be followed with isotonic crystalloids.
2. Colloids can be used in conjunction with or in place of hypertonic saline during fluid resuscitation.
3. Isotonic to slightly hypertonic (1.8%) crystalloids are often necessary because of tremendous sodium losses through burn wounds.
4. Plasma is an important component of fluid therapy in the severely burned patient because of the potential for protein loss.
5. Administration of excessive volumes of fluids should be avoided because edema is a common complication of burn injuries.

Fluid Therapy for Acute Respiratory Distress Syndrome in Horses (Box 44-10)

K. Gary Magdesian

ARDS presents a therapeutic challenge; because of altered Starling's forces (increased vascular permeability) in the pulmonary capillaries, affected horses and foals often have significant pulmonary edema, with protein-rich fluid.[1] Pulmonary capillary hydrostatic pressure becomes the main determinant of edema in these patients owing to the increased permeability of pulmonary capillaries.[2] Despite this propensity toward edema formation, horses and foals with ARDS should not be allowed to develop dehydration. Maintenance of normal blood volume and hydration status is critical to tissue oxygenation, including the diseased pulmonary tissue. The goal in therapy of ARDS patients is to reduce extravascular lung water while still maintaining hemodynamic stability and perfusion. In a human clinical trial, conservative fluid management in patients with ALI improved lung function and shortened duration of mechanical ventilation and intensive care as compared with patients managed with a liberal fluid strategy, although there was no difference in mortality.[3] The conservative management did not increase nonpulmonary organ failures.[3] It should be noted that the patients in this study were volume replete and relatively stable hemodynamically. Conservative fluid therapy therefore applies to the post-resuscitation phase of these patients, when administration in excess of physiologic needs can be detrimental.

Large swings in pulmonary vascular pressures should be avoided to minimize increases in pulmonary hydrostatic pressure. To avoid these wide fluctuations, intravenous fluids should be provided as a continuous infusion rather than as intermittent boluses.[4] The ideal type of fluid for volume replacement at the time of initial therapy of ARDS patients is unknown; however, colloids should be used judiciously owing to the theoretical risk of potentiating pulmonary edema through extravasation of colloids across the leaky pulmonary vasculature. This concern warrants further study; one study demonstrated no increase in transmicrovascular flux of radiolabeled colloids when COP was raised with albumin administration in human patients with pulmonary edema.[5] Isotonic crystalloids, administered at a modest rate and only to effect in normoproteinemic patients, and replacement of plasma proteins in hypoproteinemic patients are probably the safest fluid guidelines for these patients with the current level of understanding.

Patients with ALI or ARDS should be monitored closely for hypoproteinemia. Correction of hypoproteinemia in human patients with ALI benefits from concurrent administration of albumin.[6] Hypoproteinemic patients receiving both furosemide (as a CRI) and albumin had improved oxygenation, increased net fluid loss, and better maintenance of hemodynamic stability compared with those receiving only furosemide.[6] In addition, 50% of patients in the treatment group

BOX 44-10

Fluid Guidelines for Acute Respiratory Distress Syndrome

1. The ideal initial resuscitative fluid choice for acute respiratory distress syndrome (ARDS) patients is unknown, but crystalloids should probably be used rather than colloids because of the risk for compounding pulmonary edema as colloids leak into lungs. The exception would be the hypoproteinemic patient, in which plasma should be used to correct albumin deficits.
2. Hypovolemia and dehydration should be corrected, but excessive fluid volume should be avoided to minimize worsening of edema. A conservative long-term fluid plan is warranted.
3. Fluid balance in patients with ARDS should be assessed frequently; central venous pressure is a useful means of monitoring fluid balance to prevent large increases in capillary hydrostatic pressure.

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achieved resolution of the ALI or respiratory distress syndrome, compared with only 11% of controls. Consideration should be given to correction of hypoproteinemia in foals and horses with ARDS or ALI. An additional benefit of albumin is its antioxidant properties. Albumin can also reduce microvascular permeability and endothelial cell apoptosis.[7-9]

Monitoring of fluid therapy in these patients is especially important in order to avoid marked increases in pulmonary hydrostatic pressure. This can be accomplished through measurement of pulmonary capillary wedge pressure; however, this requires placement of an intracardiac catheter. Alternatively, CVP can be measured. This is easily performed through central lines—those placed in the cranial vena cava. In a study comparing the use of pulmonary artery catheters with that of central venous catheters in guiding treatment of ALI in humans, it was found that pulmonary catheter–guided therapy did not improve survival or organ function and was associated with more complications than central venous catheter–guided therapy.[10] The predominant catheter-related complication was development of arrhythmia. It was concluded that pulmonary catheters should not be routinely used for the management of ALI.[10]

Fluid Therapy for Horses with Metabolic Acidosis (Box 44-11)

K. Gary Magdesian

Both organic and inorganic acidoses are found in horses with critical illness. A common cause of organic acidosis in horses is lactate (lactic acidosis). Hyperlactatemia occurs with hypovolemia, sepsis, and SIRSs such as endotoxemia, marked hypoxemia, heart failure, cytopathic hypoxia, and liver failure.[1-4] Volume resuscitation can be performed with a combination of crystalloids and colloids, and possibly hypertonic saline. Acetated crystalloids (such as Normosol-R or Plasma-Lyte 148) do not contain lactate; however, even LRS (which contains sodium lactate) will correct hyperlactatemia when it is caused by hypoperfusion. Providing for hepatic perfusion will allow for clearance of the lactate previously accumulated. The exception is in liver failure, where fluids devoid of lactate should be administered because metabolism will be reduced. Other less common causes of organic (high anion gap) acidosis include ethylene glycol, salicylate toxicity, and uremic acidosis. The treatment of lactic acidosis is correction of the underlying pathogenesis. If the cause is hypoperfusion, reversal of that state should be the goal of therapy; this is accomplished through restoring blood volume, cardiac output, and finally systemic vascular resistance through the administration of fluids, dobutamine, and vasopressors, respectively. Sodium bicarbonate is therefore not a part of the routine treatment of lactic acidosis; its use in lactic acidosis is in fact controversial.[5,6] In a canine model of lactic acidosis, the administration of sodium bicarbonate actually caused a decrease in pH and bicarbonate concentration and an increase in lactate.[7] Similarly, in a model of endotoxemia in ponies, administration of sodium bicarbonate resulted in an increased blood lactate concentration.[8] Despite these controversies with sodium bicarbonate and lactic acidosis, when the pH of the patient's blood is below 7.2, administration of sodium bicarbonate until the pH reaches 7.2 is justified to prevent the detrimental effects of severe acidemia, even when the acidosis is a result of lactate. Severe acidosis can lead to life-threatening cardiovascular complications such as impaired contractility, sensitization to ventricular arrhythmias, and impaired responses to pressors.[9] Small doses of sodium bicarbonate should be administered slowly to increase the pH to 7.2, at which point increasing perfusion should be the goal.

Inorganic acidoses occur because of strong ion acidosis associated with electrolyte derangements. In horses these commonly result from hyperchloremia or hyponatremia, both of which decrease the strong ion difference. Common diseases associated with these metabolic abnormalities include enteritis, colitis, renal failure, and renal tubular acidosis (RTA). In these cases the acidosis is often caused by renal or gastrointestinal dysfunction of electrolyte homeostasis, whereas perfusion may be normal (i.e., normal plasma lactate). Chronic administration of carbonic anhydrase inhibitors, such as acetazolamide, is another cause of hyperchloremia. The fluid of choice for patients with hyperchloremic metabolic acidosis is one containing only strong cations without strong ions. Because sodium bicarbonate contains only strong cations (sodium), it is an ideal choice for patients with normal anion gap (hyperchloremic) acidosis. Sodium bicarbonate should be administered slowly to allow time for distribution and evaluation of its effects. As a fluid choice, rather than as a supplement, isotonic (1.3%) sodium bicarbonate can be used; this formulation contains 150 mEq each of sodium and bicarbonate ion per liter. Potential side effects of rapid or large-volume sodium bicarbonate therapy include hypernatremia, hypokalemia, ionized hypocalcemia, vasodilation, metabolic alkalosis (if in excess), and an increased affinity of hemoglobin for oxygen (left shift of the oxygen dissociation curve).[8]

BOX 44-11

Fluid Guidelines for Metabolic Acidosis

1. The two primary forms of metabolic acidosis in horses are organic acidosis, most often resulting from hyperlactatemia, and inorganic acidosis, often resulting from relative or absolute hyperchloremia.
2. Treatment of hyperlactatemia consists of addressing the underlying cause. In many cases, lactic acidosis is caused by hypovolemia.
3. Commercial acetated fluids, such as Normosol-R or Plasma-Lyte 148, and lactated Ringer solution are good fluid choices for hypovolemia, although volume rather than type of fluid is the most important component of treatment.
4. The use of sodium bicarbonate is controversial in lactic acidosis and may be contraindicated.
5. Sodium bicarbonate is the treatment of choice for inorganic acidosis (hyperchloremia).
6. Sodium bicarbonate can be administered as a fluid in the form of an isotonic solution.

Fluid Therapy for Heart Failure (Box 44-12)

K. Gary Magdesian

The cardiac patient represents a unique challenge to fluid therapy. Volume expansion poses significant risk to the horse with heart failure by raising venous pressures (edema risk) and potentiating sodium retention. Administration of sodium-containing fluids can lead to or compound edema and body cavity effusions. Despite these risks, patients with heart failure sometimes require fluid therapy, such as when they develop anorexia, renal failure, or diarrhea. Monitoring of CVP should be performed in these patients to aid in prevention of edema. Initial fluid therapy should consist of conservative rates, with frequent reassessment of the effects of fluids on the patient. Continuous, slow administration of fluids, rather than boluses, should be used to avoid rapid swings in CVP. Any rise in CVP should be avoided in horses with heart failure.

BOX 44-12

Fluid Guidelines for Heart Failure

1. Horses with heart failure are intolerant of significant changes in central venous pressure.
2. Fluid boluses should be avoided, and fluids should be administered at a slow, continuous rate.
3. Consideration of the amount of sodium administered should be a priority.
4. Conservative fluid rates are warranted.
5. Concurrent and careful use of diuretics may be indicated.
6. Central venous pressure should be monitored.

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The choice of fluid depends largely on concerns over sodium retention in the heart failure patient. Fluids with lower sodium content may be preferable for maintenance fluid therapy, such as maintenance fluids (0.45% NaCl/2.5% dextrose, Plasma-Lyte 56, or combinations of replacement fluids mixed with sterile water).[1] As soon as the patient is able to drink water, the intravenous fluids should be discontinued.

Because of sodium retention in heart failure, these horses are often treated with diuretics such as furosemide, which aid in minimizing edema formation.[1] A fine balance between fluid therapy and diuretics is required.

Fluid Therapy in Ruminants

Marie-Eve Fecteau

General Principles

In addition to its obvious use for correction of dehydration, fluid therapy in ruminants can be instrumental in the treatment of a variety of disorders, including sepsis, electrolyte and acid-base disturbances, gastrointestinal disease, liver disease, and renal disease. Although enteral fluid therapy is commonly used in adult cattle, parenteral fluid therapy is often regarded as impossible in field situations because of practical and/or economic reasons. In many cases of severely debilitated ruminants, targeted fluid therapy is the key treatment aiding in the recovery from a disease process. This section addresses some key principles of fluid therapy in ruminants, for both field situations and hospital setting, focusing on a variety of commonly encountered disease processes.

In adult ruminants, estimation of dehydration can be based on several factors including eyeball recession, upper eyelid skin tent, heart rate, and mucous membrane moistness (Table 44-2). Once the degree of dehydration is determined, maintenance fluid requirements, as well as ongoing losses, also need to be considered. The amount of water an adult dairy cow needs just to cover for her lactation is often underestimated. The daily water requirements of a 600-kg cow eating a corn silage–based diet in a thermoneutral environment, and milking 45 kg of milk per day, are at least 140 L of water/day.[1] Although laboratory measurements are necessary to confirm and quantify electrolyte and acid-base derangements, those derangements can be predicted on the basis of the suspected disease process. For example, cattle with abomasal volvulus typically suffer from a hypochloremic, hypokalemic, metabolic alkalosis, whereas ruminants with acute grain overload are typically acidotic and often hypocalcemic.[2] Patient-side biochemistry analyzers can be very useful during the initial evaluation of the patient and for monitoring of fluid therapy in field situations. An attempt should be made at matching fluid composition (either oral or parenteral) to the (suspected or confirmed) electrolyte and acid-base deficits of the animal. However, one should remember that the restoration of kidney function alone (by providing fluid volume) might represent the most effective step in addressing the metabolic derangements of the patient.

Oral fluids are practical and economical and can be useful in correcting mild to moderate dehydration and metabolic disturbances in ruminants. In the adult ruminant, the rumen should be viewed as a large reservoir capable of absorbing large volumes of water and electrolytes.[3] The main force for water movement across the rumen wall is the gradient of osmolality between ruminal fluid (normally isoosmotic) and blood perfusing the ruminal epithelium.[4] Studies in adult cattle have shown that net flow of water from rumen to plasma occurs whenever plasma osmolality exceeds rumen osmolality by at least 20 mOsm/kg,[5] which means that to optimize free-water absorption, rumen osmolality should be hypo-osmotic. The opposite situation is best represented during an episode of acute grain overload when the rumen osmolality quickly becomes hyperosmotic and that water is drawn to the rumen from the extravascular space, which leads to severe dehydration in those animals.[6] Therefore, the practitioner should take advantage of the ruminal capacity for water and electrolyte absorption by administrating hypo-osmotic oral electrolyte solutions to mildly to moderately dehydrated ruminants that do not suffer from preexisting abdominal distention or ileus. Enteral fluids should contain Na^+, K^+, and Ca^{2+}. Because most dehydrated adult ruminants are alkalotic, nonalkalinizing fluid formulations should be preferred.[2]

Intravenous fluids should be preferred in patients that are severely dehydrated and/or that suffer from severe metabolic disturbances or sepsis. An intravenous catheter is typically placed in a jugular vein, although the use of an auricular vein has also proved useful in adult cattle.[7] The animal should be restrained in a tie-stall or box-stall and given enough length of fluid administration set to allow him or her to lie down. Large-bore coiled intravenous fluid administration sets are useful for this purpose because they have a lesser tendency to become entangled when the animals moves around the stall. Commercially available crystalloid solutions such as LRS or 0.9% NaCl may be used, although homemade solutions can also be prepared cheaply on the farm or in a hospital setting. For example, a 0.9% NaCl solution can be prepared by adding 180 g of table salt to 20 L of filtered water using large plastic carboys. Additional recipes for homemade electrolyte solutions for cattle may be found in Table 44-3. If tap (unfiltered) water is used in the mixing of the fluids, the author recommends that the animal not be kept on those fluids for extended periods (less than 48 hours) and that parenteral antimicrobials be

TABLE 44-2

Guide to Estimation of Dehydration in Adult Ruminants

Percentage of Dehydration	Eyeball Recession	Upper Eyelid Skin Tent	Mucous Membranes
Mild (6%-7%)	Slight	Slightly prolonged (2-3 sec)	Moist
Moderate (8%-9%)	Obviously sunken	Obviously prolonged (3-6 sec)	Tacky
Severe (10%-12%)	Severely sunken into orbits	Remains tented indefinitely	Dry

Adapted from Smith GW. 2005. Supportive therapy of the toxic cow. Vet Clin North Am Food Anim 21:595.

TABLE 44-3

Homemade Electrolyte Solutions

	0.9% NaCl	Ruminant Electrolyte Solution	D_5W	0.45% NaCl + 2.5% dextrose
NaCl	180 g	140 g		90 g
KCl		25 g		
$CaCl_2$		10 g		
50% dextrose			2 L	1 L
Water	20 L	20 L	18 L	19 L

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used concurrently to minimize the risks of bacteremia and sepsis in the patient.

Response to fluid therapy should be closely monitored and adjusted as needed. Correction of electrolyte and acid-base imbalances should be based on laboratory results when available. For additional fluid therapy monitoring techniques, the reader should refer to the Critical Care and Fluid Therapy Monitoring Techniques section of this chapter.

Fluid Therapy for Specific Ruminant Diseases and Disorders

Fluid Therapy for Abomasal Disorders and Upper Gastrointestinal Obstructions

Ruminants with simple abomasal displacements that are managed promptly usually do not necessitate aggressive fluid therapy. Because simple displacements (left or right) of the abomasum do not constitute a complete gastrointestinal obstruction, they rarely cause severe electrolyte and acid-base derangements in the adult cow. In cows that appear mildly dehydrated, enteral fluids (10 to 20 L) consisting of water and electrolytes usually suffice. Older, high-producing dairy cows often have some degree of subclinical hypocalcemia, especially in the early postpartum period, and should therefore be supplemented with calcium. If present, ketosis should be treated with intravenous infusion of dextrose or oral administration of propylene glycol.

Ruminants with abomasal volvulus, abomasal impaction, or other forms of upper gastrointestinal (GI) obstructions such as intestinal volvulus or intussusception typically have more severe metabolic derangements as a result of the trapping of fluid and electrolytes within the GI compartments proximal to the obstruction. Those animals are typically moderately to severely dehydrated; and necessitate a more aggressive approach to fluid and electrolyte therapy, usually intravenously. The acid-base and electrolyte abnormalities of ruminants with upper GI obstructions typically include hypokalemia, hypochloremia, metabolic alkalosis (although reduced perfusion of peripheral tissues may lead to metabolic acidosis terminally), hypocalcemia, and prerenal azotemia.[8-9] To replenish fluid losses and improve the circulating blood volume, an initial fluid bolus of 15 to 20 L (20 to 25 mL/kg) of isotonic crystalloid solution should be administered prior to or during surgery. It is the author's opinion that the best crystalloid fluid choice for cattle with hypochloremic metabolic alkalosis is 0.9% NaCl, although other balanced crystalloid solutions such as LRS, Normosol-R, and Plasma-Lyte may also be appropriate. Following the initial bolus, fluid therapy should be continued with an additional 30 to 40 L (3 to 5 mL/kg/h) of 0.9% NaCl or another balanced crystalloid solution, supplemented with at least 20 to 40 mEq/L of potassium chloride. In metabolic alkalosis, hypokalemia may result from redistribution of potassium from the extracellular to the intracellular compartment.[10] Ruminants with severe hypokalemia may also have to be supplemented orally (10 g KCl per 100 kg BW, bid)[11] through stomach tube or in gelatin caps, especially if the intravenous fluids are supplemented with dextrose, which may cause a shift of potassium intracellularly.[12] When potassium chloride is supplemented, 1.0 g yields approximately 14 mEq. Care must be taken to never exceed 0.5 mEq/kg/h in order to avoid cardiotoxicity.[11] Multiparous cows in the postpartum period may also benefit from calcium supplementation at a rate of 25 mL/L of 23% calcium borogluconate.

Hypertonic solutions (7.2% to 7.5% NaCl), at a rate of 2 to 4 mL/kg, can also be used to rapidly expand the intravascular volume in severely dehydrated cattle.[11] Ideally, the infusion of hypertonic solution should be followed by intravenous infusion of an isosmotic crystalloid solution as stated previously. Cattle should also have access to a supply of fresh water and electrolytes, or be administered oral fluids through stomach tube if intravenous fluid administration is not possible. Oral fluid administration should be used only following surgical correction of the abomasal volvulus because a large volume of orally administered fluids may worsen abdominal distention before surgery.

Fluid Therapy for Metabolic Acidosis (Acute Rumen Acidosis and Diarrhea)

In ruminants, severe metabolic acidosis may be encountered in a variety of cases including acute grain overload (rumen acidosis) and severe enteritis with profuse diarrhea. Severe ketosis, pregnancy toxemia, and sepsis can also lead to the development of a metabolic acidosis in the affected ruminants. Fluid therapy for ruminants with severe ketosis and sepsis is discussed later in this chapter.

Animals with acute rumen acidosis are typically severely debilitated and need aggressive medical and surgical therapy. Acute ruminal acidosis is discussed in detail in Chapter 32. The rapid accumulation of lactic acid in the rumen osmotically draws water into the rumen, resulting in marked dehydration.[6] In addition, the chemical damage to the rumen mucosa allows bacterial transposition into the peritoneal cavity and portal circulation, resulting in the development of endotoxemia.[13-14] Finally, third spacing of proteins in the rumen as well as in the abdominal cavity can result in profound hypoproteinemia in the affected animals, which further compounds their precarious hemodynamic state by its negative impact on the animal's oncotic pressure. Moderate to severe hypocalcemia is also common in those cases.

Fluid therapy in calves with diarrhea is discussed in length in Chapter 20. Adult ruminants with severe enteritis and diarrhea such as those with salmonellosis may necessitate intravenous fluid therapy if they are completely anorectic, depressed, and significantly dehydrated. Oral fluids and electrolytes may be helpful in ruminants that are mildly to moderately dehydrated, but the effectiveness of those fluids may be compromised by malabsorption and ileus resulting from the enteritis. Similar to ruminants with acute rumen acidosis, cattle with acute diarrhea will suffer from varying degrees of metabolic acidosis, which is a result of the loss of bicarbonates in the diarrhea and possibly from the enteric production of D-lactate. The poor perfusion of the peripheral tissues that is sometimes seen in severe cases of hypovolemia may lead to the development of a lactic acidosis that may also contribute the overall acidosis in those patients. Also similar to ruminants with acute grain overload, ruminants with severe enteritis and diarrhea will develop a hypoproteinemia from GI losses and third spacing within the abdominal cavity. Finally, although a lesser concern in adult ruminants, sepsis caused by severe enteritis may pose an additional problem that should be addressed by the use of intravenous fluids. Intravenous fluid therapy in the face of sepsis is discussed further later in this chapter.

The goals of fluid therapy in ruminants with severe acute rumen acidosis and acute enteritis with profuse diarrhea should be (1) volume repletion, (2) correction of acid-base and electrolyte disturbances, (3) addressing the endotoxemia/sepsis, and (4) providing colloidal support. Fluids should be provided in the intravenous form, especially in the case of rumen acidosis, to avoid exacerbating the abdominal distention and because most animals suffer from severe ileus. The choice of crystalloid solution should be based on the suspected metabolic disturbances. Therefore, nonacidifying solutions such as LRS, Normosol-R, and Plasma-Lyte should be preferred over 0.9% NaCl solutions. In cases of severe acidemia (blood pH < 7.20), a sodium bicarbonate solution (1.3% to 5%) may be preferred until the blood pH is closer to normal range. The amount of sodium bicarbonate required to correct metabolic acidosis can be calculated by the following formula: $NaHCO_3$ (mmol) = BW (kg) × base deficit × 0.3. If laboratory data are not available, a clinician may choose to alternate between fluid solutions (e.g., between LRS and bicarbonate solution) in order to avoid overcorrection of the metabolic acidosis. An initial bolus of 20 to 25 mL/kg should be followed by a CRI of crystalloid fluids containing potassium (20 to 40 mEq/L) and calcium (25 mL/L of 23% solution). Fluids containing potassium and/or calcium should not be bolused in order to avoid cardiotoxicity. Care should also be taken not to fluid-overload the patient, especially small ruminants and young cattle, as excessive fluid administration

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may result in edema, including pulmonary edema. To address the hypoproteinemia and the poor oncotic pressure, colloids should be considered if finances allow. Colloids (whole blood, plasma, or hetastarch) may attenuate capillary leak associated with sepsis and will help expand the vascular space.[11] Details for collecting, harvesting, storing, and administrating whole blood and plasma are available elsewhere.[15] Hetastarch, a high-molecular-weight glucose synthetic polymer, is supplied as a 6% concentration in 0.9% NaCl, and can be administered at a rate of 5 to 20 mL/kg/h.[11] This may be more feasible in small ruminants or young cattle because the use of colloids may be cost prohibitive in a full-size cow.

Fluid Therapy for Sepsis (Toxic Mastitis, Metritis, Peritonitis)

Endotoxemic shock, which often accompanies disease processes like coliform mastitis, toxic metritis, and septic peritonitis, can lead to a marked hypovolemia necessitating aggressive fluid therapy in the affected animals. For the septic patient, expanding the effective circulatory blood volume in order to improve tissue perfusion and counteract the decreased cardiac output and hypotension is crucial. Fluid therapy in ruminants with sepsis is similar to that recommended for ruminants with severe enteritis or acute rumen acidosis (see previous section).

Oral fluids can be useful in ruminants that are mildly to moderately dehydrated; however, in animals that are severely dehydrated and that have signs of endotoxemia, intravenous fluids are preferred. If intravenous fluid therapy cannot be achieved because of practicality or costs, the combination of intravenous hypertonic saline (7.2% to 7.5%) and oral water and electrolytes should be considered. The increase in plasma osmolality results in a movement of water from the extravascular space to the intravascular space.[11] In adult ruminants, the rumen represents the major reservoir from which the animal can draw water. For this reason, the administration of intravenous hypertonic solution alone, without continuing with oral or isotonic intravenous fluids, is insufficient in addressing the hypovolemia. For a typical adult cow, 1 to 2 L of hypertonic saline (2 to 4 mL/kg)[11] intravenously is followed by the administration of approximately 20 L (5 gallons) of water orally. If intravenous fluid administration is an option, isotonic fluids should be continued at a rate of 4 to 5 mL/kg/h for a total of at least 40 to 60 L (for a typical adult cow) during the first 24 hours. Care should also be taken not to overload the patient with fluids, especially small ruminants and young cattle as excessive fluid administration may result in edema, including pulmonary edema. As discussed earlier in the metabolic acidosis section, a combination of crystalloids and colloids may also have advantages in treating patients with sepsis because colloids may attenuate capillary leak associated with sepsis.[16] In addition, some animals with severe sepsis may suffer from coagulation disorders such as DIC, and may benefit from hetastarch's dose-dependent effects on coagulation.[17]

Whether fluid resuscitation is performed orally or intravenously, calcium supplementation (25 mL/L of a 23% solution) should also be considered because hypocalcemia is often encountered in toxic cattle.[18,19] The reason for the decrease in calcium concentrations in endotoxemic cattle is not fully understood.[18,19] Ruminants that are anorectic should also be supplemented with potassium chloride (20 to 40 mEq/L). Although septic adult ruminants rarely become hypoglycemic (as opposed to neonates), dextrose supplementation (2.5% to 5%) may be beneficial in anorectic patients with concomitant ketosis and/or hepatic lipidosis. The animal's blood glucose should be monitored and kept between 80 to 110 mg/dL to avoid a hyperglycemic state.

Fluid Therapy for Negative Energy Balance Disorders (Hepatic Lipidosis/Ketosis/ Pregnancy Toxemia)

The vast majority of cattle and small ruminants with type I (primary) ketosis respond quickly to simple treatments that usually involve the administration of glucose precursors (such as propylene glycol) and/or a single administration of intravenous dextrose. However, cattle and small ruminants with severe ketosis, hepatic lipidosis, or advanced pregnancy toxemia may need a more aggressive approach of treatment to their condition, which usually involves the use of a continuous rate infusion of intravenous fluids containing dextrose. Ruminants with liver dysfunction/failure have a decreased ability to perform normal metabolic functions such as gluconeogenesis, to synthetize proteins, and to clear a variety of metabolites, including lactate.

The main goal of treatment of hepatic lipidosis, severe ketosis, and pregnancy toxemia is to limit the mobilization of fat by increasing the availability of glucose or glucose precursors and promoting uptake of glucose by the cells. It is important to note that the provision of dextrose is primordial, even in the face of normoglycemia, since it will minimize gluconeogenesis demands on the liver and prevent further production of ketone bodies. A CRI of isotonic fluids such as Normosol-R or Plasma-Lyte, containing 2.5% to 5% dextrose, is preferred over the use of 5% dextrose solutions (D_5W) because the latter contain too much free water. Because lactate clearance primarily occurs in the liver, and may be impaired in those animals, LRS should be avoided. In ruminants with suspected or confirmed metabolic acidosis, saline solutions (0.9% NaCl) should also be avoided, since they will compound the acidemia. Small ruminants with severe pregnancy toxemia may have to receive an initial bolus of fluids containing 10% to 50% dextrose to break the vicious cycle of negative energy balance. The rate of glucose administration should be around 1 to 2 mg/kg/min, which for a typical adult cow equates to about 1 L/h of a fluid solution containing 5% dextrose. The animal's blood glucose should ideally be monitored and kept between 80 to 110 mg/dL to avoid a hyperglycemic state. Insulin (total dose of 200 IU zinc protamine available from compounding pharmacies) can be used subcutaneously every 24 to 36 hours to promote glucose uptake by the peripheral tissues and inhibit lipolysis. The addition of B vitamins to the fluids may also be useful in anorectic ruminants.

Fluids should also contain potassium chloride (20 to 40 mEq/L) since most ruminants are completely anorectic and may also experience a shift of potassium intracellularly in response to dextrose administration.[12] Special caution should be taken at monitoring plasma potassium levels in cows receiving mixed glucocorticoid/mineralocorticoid drugs to aide in the treatment of hepatic lipidosis since their chronic use has been associated with the development of severe hypokalemia in cows.[20] As discussed earlier, cows with marked hypokalemia should receive oral and intravenous supplementation with potassium chloride. Calcium supplementation (25 mL/L of a 23% solution) is also important since most cows with hepatic lipidosis are in the peripartum period and may also suffer from subclinical hypocalcemia, and since clinical signs of pregnancy toxemia may resemble those of preeclampsia in small ruminants. Plasma or serum phosphorus levels should also be monitored in ruminants receiving repeated infusions of intravenous dextrose since it can cause significant drops in plasma phosphorus levels.[21,22]

Fluid Therapy for Obstructive Urolithiasis

Most ruminants with obstructive urolithiasis present with azotemia, which is usually postrenal, although prerenal azotemia from dehydration, and renal azotemia from renal damage, are possible. Metabolic disturbances typically include metabolic alkalosis, hyperkalemia, hyponatremia, and hypochloremia.[23] Hypophosphatemia is another common biochemical finding in goats presenting with acute urolithiasis.[23] If a rupture in the urinary tract is present on admission, the degree of hyperkalemia may be severe. Ruminants with urinary tract obstruction, particularly those with severe electrolyte disturbances, often need to be stabilized before surgery.

Although it may not be advised to administer large volumes of intravenous fluids prior to relieving the obstruction, most patients' hemodynamic state will benefit from a fluid bolus prior to surgery. In the very unstable patients with severe electrolyte disturbances (K^+ > 6 mmol/L), a clinician may choose to drain the urinary bladder (or the uroabdomen) prior to surgery by performing a cystocenthesis or

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by placing a self-retaining suprapubic cystic catheter (Bonnano catheter, BD, Franklin Lakes, N.J.), which can stay in place for up to 24 hours in most small ruminants and allow for urine egress from the bladder while the patient is receiving intravenous fluid therapy. It should be emphasized that the ultimate goals of preoperative fluid therapy are to improve the patient's hemodynamic state and to address its most severe electrolyte abnormalities (usually hyperkalemia) so that the patient can more safely undergo anesthesia. Also, surgery should not be delayed until the animal's azotemia is completely resolved as azotemia may persist for several days following surgery in some animals.

Much has been written about the best fluid composition to use in hyperkalemic animals. The most common recommendation is to favor fluids that do not contain potassium, such as physiologic saline, D_5W, or isotonic sodium bicarbonate solution. However, others may argue that any other type of balanced isotonic solutions such as LRS may also represent a valid option, even in the face of hyperkalemia.[24] Insulin may also be used to help correct the hyperkalemia, especially preoperatively. If insulin is used preoperatively or postoperatively, blood glucose should be monitored closely postoperatively, especially in young ruminants, since they may become hypoglycemic. Potassium plasma concentration should also be monitored closely following the combination of insulin and diuresis, since many ruminants will become hypokalemic postoperatively, especially if they remain anorexic for some time.

The fluid rate should be tailored to the patient's hydration needs, level of azotemia, and urine production. Although overhydration is rarely a concern in adult cattle with normal kidney function, small ruminants with acute renal failure should be monitored closely to avoid pulmonary edema. An initial rate of administration of 1.5 to 2 times maintenance is usually used until the azotemia is resolved.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 45

Rational Antimicrobial Therapy

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Antimicrobial Stewardship

Antimicrobial stewardship is defined as "an activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy" in order that a positive clinical outcome can be achieved with a minimum of unintentional consequences.[1,2] The dearth of new antimicrobial drug development with the advent of increasingly resistant bacteria necessitates that we use these drugs in a judicious manner that prolongs their effectiveness. Not only does inappropriate use of antimicrobial drugs result in the emergence of resistance to these drugs, they also can have such an impact on the normal microbiota that severe and sometimes fatal gastrointestinal disease can develop. Hence, veterinarians have an obligation to use these drugs in a responsible manner.

Antimicrobial therapy is the cornerstone for treatment of infectious diseases. Therapy depends on appropriate identification of the infectious agent, determination of antimicrobial susceptibility of the causative organism, and application of pharmacokinetic/pharmacodynamic principles to achieve therapeutic levels of drug at the site of infection. Additional factors such as route of administration, toxicity, cost, compliance with administration, penetration of the drug of interest to the site of infection, host factors, and development of resistance must be considered when choosing an antimicrobial drug regimen (Box 45-1). Avoiding development of resistant pathogens or commensal flora is also desirable. This chapter focuses on use of antimicrobial drugs directed toward bacterial pathogens; however, similar principles apply when choosing antifungal, antiparasitic, or antiviral therapies. The ultimate goals of antimicrobial therapy are to provide effective treatment, with the fewest adverse reactions and at the lowest cost, and to prevent development of resistance in the target organism and host microbiota. Indiscriminant or inappropriate use of antimicrobial agents leads to development of resistance in the targeted pathogen as well as the host microbiota. The consequences of resistance are many-fold, including the inability to treat certain infections, superinfections, and transfer of resistant organisms to humans.[3] As veterinarians, we have an ethical obligation to protect both animal and human health and well-being through judicious use of antimicrobial drugs. A consensus statement published by the American College of Veterinary Internal Medicine[3] provides guidance for use of antimicrobial drugs and raises important considerations for the veterinarian regarding their use.

One recommendation of this consensus statement is that the veterinarian develops standardized antimicrobial drug use guidelines for different types of cases (e.g., wounds, respiratory infections) that are appropriate for their hospital or clinical practice.[3] These authors also indicate that antimicrobial therapeutics be categorized into primary-, secondary-, and tertiary-use drugs. Primary-use drugs are older antimicrobials that have a narrower spectrum of activity (e.g., penicillin, older tetracyclines, and sulfonamides) and are used for most infections. Secondary-use drugs generally have a broader spectrum than primary-use drugs and are reserved for more serious infections or when susceptibility data indicate resistance to primary drugs. Tertiary-use drugs are those with an even further extended spectrum of activity, are effective against resistant bacteria, and are also important drugs used for human patients. These tertiary drugs should be reserved for serious infections with confirmed resistance to all primary and secondary drugs. Thus, use of higher-level drugs should be directed by antimicrobial susceptibility testing.

In addition to establishing tiers of drugs for antimicrobial use, it is important to follow a logical approach when deciding on the type of antimicrobial drug to use. This starts with establishing whether an infection is present, identification of the organism(s), determination of antimicrobial susceptibilities, and consideration of host factors. Once therapy has been initiated, assessment of the patient is essential to decisions regarding length of treatment and whether antimicrobial therapy should be altered. In addition, adjunctive therapies, such as surgical interventions should be considered.

Is There an Infection?

This is a frequently overlooked step for consideration when determining what type of antimicrobial therapy should be instituted. Too often, antibacterial drugs are used "just in case" there is an infection without proper examination for the signs of infection. A number of clinical signs and clinical laboratory findings can be evaluated that may point to the presence of an etiologic agent. The old saying that redness, swelling, and heat are cardinal signs of infection and inflammation still holds true. Certainly one frequently encountered finding is elevation of body temperature. However, inflammation for reasons other than the presence of an infectious agent may result in fever. Swelling and redness are indications of a localized infection. Development and appearance of purulent material is further evidence of infection.

Clinicopathological findings are also important supportive evidence for an infectious disease. Elevated or depressed peripheral white blood cell counts frequently accompany significant infections. In large animal species, fibrinogen elevations are observed in bacterial infections. Serum biochemistry values may also inform the decision to use antimicrobial therapy. For example, elevations in globulin may indicate production of excess immunoglobulin as seen in subacute to chronic infectious, primarily bacterial, processes. Decreases in serum albumin may develop as a negative acute phase protein in response to inflammation accompanying an invasive pathogen.[4] If possible, cytologic examination of material from the site of suspected infection should be performed. The presence of neutrophils, particularly with features of degeneration, is indicative of a septic process. Observation of infectious agents, ideally intracellularly, confirms the presence of an infection.

What Organism Is Present?

Once the presence of an infection is determined, the next step is to decide what organism might be present. Ideally, samples should be collected prior to initiating therapy so that an etiologic diagnosis can

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BOX 45-1

Considerations for Antimicrobial Choice

Agent present
Antimicrobial susceptibility of the agent
Penetration of antimicrobial drug to the site of infection
Severity of the infection
Compliance with the regimen prescribed
Route of administration
Host factors
Agent factors
Cost
Withdrawal time
Extralabel use

be made and susceptibility testing performed. In the case of a serious or life-threatening infection, therapy must be initiated prior to receipt of culture and susceptibility results. Empirical therapy often relies on clinical judgment and knowledge regarding the likely organisms present depending on the body system affected and their likely susceptibility pattern. Additional findings such as results from cytologic examination help to inform the antimicrobial choice.

Sample Selection and Transport to the Laboratory

Appropriate collection and transport of samples to the microbiological laboratory are essential to detection of the causative agent. The site of the infection should be sampled. This may seem obvious; however, a surprisingly large number of inappropriate samples are submitted to the microbiology laboratory. For example, sampling of nasal discharge is almost never the appropriate choice when faced with purulent nasal discharge. Identification of the large number of normal bacteria and interpretation of the findings are difficult when normally colonized sites are sampled. The actual source of the discharge, such as the sinus, guttural pouch, or lung should be determined and sampled directly. An exception to this rule is in the case of equine *Streptococcus equi* subsp. *equi* infections. In general, sterile sites are the best regions to sample. Lesions such as a draining tract are problematic. Frequently, they have superficial contamination of the opening of the tract that is inadvertently sampled. When possible, underlying soft tissue or bone should be collected rather than inserting a swab into the tract.

If anaerobic culture is deemed necessary, it is important that adequate volume of tissue or fluid be collected to preserve the anaerobic environment. If possible, at least a milliliter of fluid or a square centimeter of tissue should be collected. Swabs are inappropriate for anaerobic culture because air can be trapped between the fibers, leading to death of non-aerotolerant obligate anaerobes. If the sample is smaller and not taken immediately to the laboratory, it should be placed in some sort of transport media that will maintain an anaerobic environment. These anaerobic systems will maintain the presence of aerobic and facultative anaerobes as well.

Samples for microbiological culture should be transported to the laboratory as soon after collection as possible. The sample should be refrigerated if it cannot be delivered quickly, and it should be kept cool or cold but not frozen for transport to the laboratory. An exception to this rule is when anaerobic transport media (e.g., Anaerobe Systems, Morgan Hill, Calif.) is used. These vials should be maintained at room temperature.

It is best if samples are collected prior to initiation of therapy. However, if antimicrobial treatment has already been instituted, the clinician should consider withdrawing therapy for a short period of time before sampling. Between 24 and 36 hours after the last administration of drugs is advisable, and 99% of the drug should be eliminated after 7 half-lives. In seriously ill animals such as the septic foal, delaying antibiotic therapy for any amount of time to collect samples may be detrimental. In such cases, samples should be collected just prior to the next administration of drug. Some blood culture systems contain resins that bind or inactivate antimicrobial drugs and have proven to increase the ability to detect bacteria within the sample.[5]

TABLE 45-1

Gram Stain Reaction and Morphology of Commonly Encountered Large Animal Bacterial Pathogens

Gram-Positive Cocci

Streptococcus spp.
Staphylococcus spp.
Peptostreptococcus anaerobius (anaerobe)
Enterococcus spp.

Gram-Positive Rod or Filamentous

Listeria spp.
Corynebacterium spp.
Trueperella pyogenes (formerly *Arcanobacterium pyogenes*)
Actinomyces spp.
Listeria spp.

Gram-Negative Rods

Actinobacillus spp.
Mannheimia spp.
Pasteurella spp.
Haemophilus spp.
Histophilus spp.
Escherichia spp.
Klebsiella spp.
Brucella spp.
Bordetella spp.
Pseudomonas spp.
Bacteroides spp. (obligate anaerobe)
Fusobacterium spp. (obligate anaerobe)

Microscopic Examination of Sample

Initial examination of a sample provides important clues to the type of organism present. A Wright-Giemsa–type stain is frequently used to examine cytologic preparations made from samples. This staining technique can provide much information regarding the bacterial or fungal organism present. Identification of coccoid or rod-shaped bacteria along with the site of infection will often result in a differential diagnosis list of organisms to consider. An examiner with a practiced eye may be able to make an educated guess about the genera of the organism observed. A Gram stain provides additional information. Although many veterinarians do not use this stain in their clinical practice, this technique is rapid and, with a little practice, easy to perform. Identification of an organism as gram negative or positive further informs the practitioner of the likely organisms present and helps to guide empirical antimicrobial choice (Table 45-1).

What Is the Severity of the Infection?

One of the first decisions to be made when considering antimicrobial therapy is the severity of the infection. The clinician needs to decide if therapy must be initiated immediately or whether the patient can wait for results of culture and susceptibility testing before initiating therapy. Obviously, life-threatening infections require immediate and aggressive antimicrobial therapy. Infections of sites such as an equine joint may necessitate empirical therapy while awaiting the results of microbiological testing. In this case, samples should be taken for identification and susceptibility testing before initiating therapy. On the other hand, an animal with a chronic, mild, or moderate infection may wait to receive antimicrobial drugs until testing has been completed.

What Is the Likely or Confirmed Antimicrobial Susceptibility of the Organism?

In a perfect world, the clinician should have laboratory-generated antimicrobial susceptibility results to guide therapy. However, frequently therapy has to be initiated prior to receipt of culture

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and susceptibility results. Empirical therapy should be based on knowledge of the inherent resistance of suspected agents and the antimicrobial susceptibility patterns observed in the practice region. Regular generation of susceptibility data should be compiled by the microbiology laboratory and used by the practitioner in the hospital setting.

The microbiology laboratory should be proficient in antimicrobial susceptibility testing and follow guidelines established by the Clinical Laboratories Standards Institute (CLSI).[6] Quality assessment testing should be performed regularly. A number of methodologies are used to examine susceptibility to different antimicrobials. Two frequently used methods for antimicrobial susceptibility testing are disk diffusion, also known as Kirby-Bauer, and broth dilution or broth microdilution, which uses a 96-well plate.

Disk diffusion is a relatively straightforward testing methodology that can be performed with little specialized equipment. It involves creating a lawn of bacteria using a standardized amount, placing disks containing a set amount of antimicrobial drug on top of the bacterial lawn, incubating, and measuring the zone of inhibition around the disk. This zone diameter determines whether the bacterium should be considered susceptible, intermediately susceptible, or resistant to the particular drug. The advantages of this method are that it is rapid and easy to perform provided strict protocols are followed. The disadvantages are that it cannot be used for slow-growing bacteria and that it provides only an interpretation rather than information about the specific concentrations of drug that inhibits growth. Consequently, knowledge about the pharmacokinetics and pharmacodynamics of a particular drug cannot be fully used to develop a treatment regimen to deliver optimal dose of drug to the site of infection.

The broth dilution or microdilution method involves inoculation of a standard amount of bacteria into tubes or wells containing an antimicrobial drug. Most clinical laboratories utilize twofold dilutions of drug centered on the amount of drug found systemically. The plate is subsequently incubated and then the wells are examined for visible growth. The lowest concentration of drug that inhibits visible growth is called the minimum inhibitory concentration (MIC). Sometimes the wells are subcultured to a nonselective agar and then incubated, and this agar is examined for growth. The lowest concentration of drug that results in no growth is the minimum bactericidal concentration (MBC). Because of cost reasons, most clinical laboratories do not determine the MBC for each organism.

The MIC is unique for each bacterium : drug combination. The resulting MIC guides interpretation of the bacterium as susceptible, intermediately susceptible, or resistant to the particular drug. The concentration of drug at which the interpretation of testing changes from susceptible to intermediate or resistant is termed the *breakpoint*. For example, bacteria are considered susceptible to amikacin if the MIC is less than or equal to 16 μg/mL; they are deemed resistant if the MIC is greater than or equal to 64 μg/mL. If the MIC is 32 μg/mL, the isolate is considered intermediately susceptible.[6] Frequently, the clinician only needs to use the interpretation when deciding which drug to choose for therapy. However, the MIC can be used to refine therapy, through increasing the dose of drug or frequency, to optimize treatment.

Interpretation breakpoints for susceptibility testing of a bacterium as susceptible or resistant are set by the CLSI. This body bases the interpretation on three major factors: the epidemiologic breakpoint of a population of bacteria, pharmacokinetic data, and, when available, clinical outcome from treatment of animal or human patients.[7] A graph showing MICs of a population of a single species of bacteria frequently has a bimodal distribution. The trough between the two peaks is the epidemiologic breakpoint; those bacteria with higher breakpoints have acquired some sort of resistance determinant. The pharmacokinetic information used to assist with determination of the breakpoint includes the peak concentration of drug, the area under the pharmacokinetic curve, and time the drug is above a particular MIC. A simplified way to think of how these data are used is to look at a bacterium with a high MIC. It would be considered resistant because the amount of drug administered in order to exceed the MIC would be considered toxic to the animal host. Generally, the highest concentration of drug tested is near or a bit above the highest concentration of drug that can be achieved with recommended dosages.

Antimicrobial therapy should be directed to achieve levels that are above the MIC for the particular isolate. Ideally, the "best" antimicrobial drug to use depends on many factors other than the susceptibility result. Obviously, the organism should be susceptible to the drug chosen but other considerations should be included such as route of administration, penetration to the site of infection, toxicity, cost, and convenience. All of these factors being equal, the optimal choice of a drug is one in which the organism's MIC is several dilutions below the breakpoint. However, further refinement is possible when one understands the pharmacodynamic properties of the drug and bacterium.

Bactericidal and Bacteriostatic Antimicrobial Drugs

The terms *bactericidal* and *bacteriostatic* refer to the in vitro observation that a drug kills or merely inhibits growth of a particular bacterium, respectively. If one examines the relationship between the MIC and MBC, these two values are close or nearly identical for bactericidal drugs. In contrast, the MBC is several twofold concentrations above the MIC for bacteriostatic drugs. To be clear, it takes a higher drug concentration to kill bacteria with a static drug. The in vivo consequence of this relationship means that more drug must be delivered to the site of infection in order to kill the bacteria with a bacteriostatic drug. Often this is not achievable given the toxicity and pharmacokinetics of the drug. In the case of bacteriostatic drugs, the clinician must rely on the host immune responses to clear the inhibited organisms. Consequently, bactericidal drugs should be used in an immunocompromised patient. Some drugs are concentrated in areas of infection. For example, drugs undergoing renal clearance are found in high concentrations in urine. Thus, drugs that show in vitro bacteriostatic activity may achieve concentrations high enough to kill bacteria in the bladder. The converse is also true; use of a bactericidal drug at inadequate dosages or that have poor penetration to the site of infection may not achieve high enough concentrations to kill the offending organism.

Concentration and Time-Dependent Antimicrobial Drugs

Pharmacokinetic (PK) and pharmacodynamic principles can also be used to guide antimicrobial therapy. The relationship between the MIC and PK parameters such as the peak drug concentration may also determine the outcome of therapy. There are two categories of antimicrobial drugs: concentration-dependent and time-dependent drugs. This categorization is also primarily based on in vitro work but is supported by clinical data in animals and humans.[8]

Concentration-dependent drugs are those whose antimicrobial activity is best predicted by the relationship between peak drug concentration and the MIC of the organism. Drug classes that are considered concentration-dependent drugs include aminoglycosides and fluoroquinolones. The ratio between the peak drug concentration and the MIC should equal at least 8 to 10.[9] Using the example of amikacin given earlier, if the bacterium had an MIC of 2 μg/mL, the drug should be dosed to reach a peak concentration of 20 μg/mL. The time that the drug concentration is above the MIC appears to be less important for concentration-dependent drugs. Accordingly, many concentration-dependent drugs can be administered infrequently (e.g., once daily). This dosing strategy can be advantageous with certain drugs with toxicity. For example, nephrotoxicity of the aminoglycosides is best determined by trough concentrations of drug. These antimicrobials may be administered at high dosages once daily to achieve the high peak concentration, well above the MIC, while having prolonged low trough levels. Many concentration-dependent drugs have prolonged post-antibiotic effect, meaning that the effect of the drug to inhibit growth of the organism is apparent for some time after the drug is removed.

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TABLE 45-2

Antimicrobial Drugs, Classifications, Activities, Post-antibiotic Effect, and Pharmacodynamic Parameter

Drug	Activity	Bacterial Effect	Post-antibiotic Effect*	PD Parameter†
Aminoglycosides	Bactericidal	Concentration-dependent	Yes	T > MIC
β-Lactams	Bactericidal	Time-dependent	No, gram negative; yes, gram positive	T > MIC
Fluoroquinolones	Bactericidal	Concentration-dependent	Yes	AUC_{24}/MIC, Cmax/MIC
Glycopeptides (Vancomycin)	Bactericidal	Time-dependent	Yes	AUC_{24}/MIC
Macrolides	Bacteriostatic	Time-dependent	No	T > MIC
Sulfonamides	Bacteriostatic	Time-dependent	No	
Tetracyclines	Bacteriostatic	Time-dependent	Yes	AUC_{24}/MIC
Trimethoprim	Bacteriostatic (unless combined with sulfonamide)	Time-dependent	No	

Adapted from Martinez M, Toutain PL, Walker RD. 2006. The pharmacokinetic-pharmacodynamic [PK/PD] relationship of antimicrobial agents, pp 81-106. In Giguere S, Prescott JF, Baggot JD, et al (eds), Antimicrobial therapy in veterinary medicine, ed 4. Blackwell Publishing, Ames, IA.

*Yes = prolonged effect longer than 6 hours; no = less than 1 hour.

†T > MIC, time drug concentration is greater than the MIC; AUC_{24}/MIC, area under the concentration curve over 24 hours/Minimum inhibitory concentration; Cmax/MIC, Maximum concentration/Minimum inhibitory concentration.

Fluoroquinolone efficacy is best predicted by the area under the concentration curve (AUC) in relationship to the bacterial MIC. The AUC:MIC ratio should be equal to or greater than 125 for gram-negative organisms.[8-11] This ratio should be 60 or greater for gram-positive bacteria.[8] Some studies indicate that ratios that approach 250 or more be used to avoid development of resistance.[8]

Time-dependent drugs are those whose antimicrobial activity is best predicted by time that the drug concentrations are above the MIC. Many drug classes are considered time dependent, including the beta-lactam drugs and tetracyclines. These drugs should remain above the MIC for at least 50% of the time. These antimicrobial drugs generally are dosed more frequently or via continuous rate infusion for those with short half-lives.

Knowledge of the pharmacodynamic principles such as the peak drug concentration:MIC ratio or time above the MIC can guide the practitioner in appropriate dosages and frequencies for an individual drug. Monitoring of drug levels can further aid development of the therapeutic plan. Table 45-2 summarizes the pharmacodynamic parameters and activities of some example antimicrobial drugs.[12]

Where Is the Infection?

Too often the question of where the infection is located is not considered when choosing an antimicrobial drug. Penetration of the drug to the site of infection is essential for successful therapy. Remember that the MIC and interpretation of the MIC are focused on systemic (plasma) levels of drugs and rarely include the subtleties of drug penetration to various sites. Some anatomic locations are particularly difficult to enter, such as the central nervous system, ocular fluid, and bone. Abscesses are another structure that is difficult for antimicrobial drugs to penetrate; they are surrounded by a thick capsule with poor blood supply and lack of oxygen, which can limit penetration into the abscess and offer poor entry into the bacteria. The pH is generally low, which may inactivate some agents, and there is abundant protein present to bind antimicrobial drugs. A further complication is the presence of purulent debris, which can provide metabolic precursors for bacteria to bypass inhibitors of metabolism, such as trimethoprim-sulfa combination drugs. In general, lipophilic drugs will be better able to penetrate these difficult-to-reach anatomic locations. Highly polar or charged molecules have difficulty reaching these sites.

If the causative organism is found intracellularly as seen with rhodococcal pneumonia or as with *Corynebacterium pseudotuberculosis* infections, the cell membrane is an additional impediment to drug penetration. Fortunately, some drugs penetrate cells well, such as macrolides, rifampin, chloramphenicol, fluoroquinolones, and trimethoprim-sulfa combinations.

Empirical versus Definitive Therapy

Empirical therapy is used for severe infections prior to obtaining culture and susceptibility results. The choice of antimicrobial drug depends on the clinician's knowledge of the likely agents present at the site of infection and their predicted susceptibilities. Knowledge of the Gram-staining results can further guide therapy. Generally, empirical therapy is broad spectrum to cover multiple possible etiologies. Eventually, once the etiologic agent and its susceptibility have been identified, definitive therapy, using a drug(s) with a narrower spectrum, can be initiated. Definitive therapy should be directed to best result in a cure, using the narrowest spectrum of drug therapy, and have limited toxicity for the patient. The goal is to de-escalate the spectrum of activity of the drug as much as possible with definitive therapy in order to minimize the impact on commensal bacteria and development of resistance.

Combination Therapy

Many infections can be effectively treated with a single antimicrobial drug; however, in some instances, combination therapy may be chosen. Some drug combinations have been demonstrated to be synergistic based on both in vivo and in vitro studies. Synergy is seen when the ability of the combination to kill bacterial growth is greater than the mere additive effect of each drug. Drug combinations can also be indifferent, where each drug's effects are merely additive. Finally, a drug combination may be antagonistic where the drug combination effectiveness is less than the sum of the independent activities. Synergistic antimicrobial drug combinations are best used to treat resistant organisms. A common synergistic pair of antimicrobial drugs can be seen in the combination of trimethoprim with a sulfonamide. Either agent alone would be considered bacteriostatic, but since each of these drugs inhibits sequential steps in folic acid metabolism, they are considered bactericidal.

A combination of antimicrobial drugs might be chosen for empirical therapy before the agents and their susceptibilities are known in order to provide broad-spectrum therapy. The combination of a β-lactam drug with an aminoglycoside is frequently chosen as empirical therapy in equine patients. This combination is synergistic as well as broad spectrum. It is important to remember that in these cases, therapy should be reduced to a single agent or a less broad spectrum of activity as soon as testing results become available.

The presence of a polymicrobial infection is another reason why combination therapy may be used because a single agent will not be able to treat all bacteria present. For example, intraperitoneal infections are frequently caused by more than one agent. It is difficult to find a single antimicrobial drug to treat all the possible bacteria

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present such as enterics, gram-positives, and anaerobes. Individual drugs are available for use in humans that are sufficiently broad spectrum; however, many of these would be cost prohibitive in large animal patients. The clinician should be cautious, however, of isolation of multiple agents from a single site such as a wound. Superficial samples taken from these sites may have contaminating bacteria, often with highly resistant antimicrobial patterns, that are not truly part of the infectious process.

Combined antimicrobial drug therapy can be used to prevent emergence of resistant bacteria. Certainly for serious or difficult-to-treat infections such as those caused by *Pseudomonas* spp., avoiding development of resistance is important not only to the patient receiving treatment, but also to others who come in contact with it. Interestingly, the ability of combination therapy to prevent resistance seems to be important only when it results from chromosomal mutations.[13] The best illustration of this principle is in the treatment of human patients for *Mycobacterium tuberculosis,* in which combination therapy is always used to prevent development of resistance.[13]

There are some drawbacks to using combination therapy. One is the possibility of antagonism between antimicrobial drugs. Most instances of antagonism have been demonstrated in vitro, although in vivo reports have appeared.[13,14] This phenomenon has been seen between gentamicin and chloramphenicol to treat *Proteus mirabilis* infections in immunocompromised mice.[15] Use of antimicrobial drug combinations is also an increased cost to the client. Finally, there is an increased possibility of toxicity of and/or hypersensitivity reactions to the drugs when used together. Antimicrobial drug combinations that may be detrimental include penicillin with tetracyclines and chloramphenicol with erythromycin. Combination therapy should not be chosen merely to provide comfort to the clinician but rather clinicians should have specific reasons for their choice.

Drug Incompatibility

Drug incompatibility can be the result of direct incompatibility, meaning that they should not be mixed together for administration or that they should not be used together therapeutically. Table 45-3 provides information about antimicrobial drug incompatibilities.

Host Factors That Influence Antimicrobial Choice or Dosage

Age

The age of the animal may influence many aspects of antimicrobial therapy. Bioavailability of certain drugs varies with age where some drugs can be used orally in neonatal or young animals but are poorly absorbed in mature animals.[16] The drug distribution may also vary with age because young animals generally have a larger volume of distribution than adults because of their larger percentage of total body water.[17] Drug biotransformation in neonates may vary from that in adults as well.[17] Therefore, drug dosages and/or frequencies may have to be adjusted in young animals to provide adequate levels of drug at the site of infection and to minimize toxicity.

Fluoroquinolone use in young and adult animals should be considered carefully. This class of antimicrobial drug has been documented to cause cartilage damage in several species of young animals, and ciprofloxacin has been associated with tendinopathies in humans.[18-20] Of interest is the observation that fluoroquinolones are capable of having chondrotoxic effects on equine and canine chondrocytes in vitro,[21] whereas a lamb model failed to demonstrate chondrotoxicity.[22] Unfortunately, specific guidelines for safe use of fluoroquinolones in young animals are lacking. If fluoroquinolone use is necessary in young animals, it is important to limit the duration of therapy in order to minimize the chances of damage to developing cartilage. Along the same line, tetracyclines should also be avoided in young patients to avoid discoloration of enamel of developing permanent teeth.

Reproductive Status

Antimicrobial drugs may have deleterious effects on reproduction and the developing fetus. Depending on the drug, the type of placentation, and stage of gestation, some drugs are able to reach the fetus. For example, use of potentiated sulfonamides in pregnant mares has been associated with anemia, fever, and abortion.[23] Administration of pyrimethamine and trimethoprim-sulfamethoxazole to stallions has been associated with weakness and abnormal copulatory form and function.[24]

TABLE 45-3

Specific Drugs and Additives That Are Incompatible When Comixed before Administration[38,39]

Drug	pH	General Comments	Incompatibilities
Aminophylline	8-9	Not stable if pH < 8	Cephalothin Na, tetracyclines, polyionic fluid solutions, penicillin G, morphine sulfate, erythromycin gluceptate, methylprednisolone Na succinate, multiple vitamin solutions, thiamine
Ammonium chloride	4.5-6		Chlortetracycline, sulfadiazine, sulfisoxazole
Ampicillin sodium	8.5-10	Do not mix with other medication because of pH changes	
Calcium chloride	6-8.2		Cephalothin Na, chlorpheniramine, hydrocortisone or prednisolone phosphate, kanamycin sulfate, tetracyclines, sodium bicarbonate (concentration dependent)
Calcium disodium EDTA	6.5-8		Dextrose solutions, tetracyclines
Calcium gluconate	6-8.2		Cephalothin Na, tetracyclines, prednisolone phosphate, sodium bicarbonate, phenylbutazone, sulfonamides
Carbenicillin disodium	6-7		Tetracyclines, aminoglycosides
Cephalothin sodium	5.2	pH <4 or >7 Not advised; do not mix with other medication	
Cyanocobalamin (vitamin B_{12})	4-5.5		Alkaline solutions, ascorbic acid, vitamin B complex with C, vitamin K, warfarin
Dexamethasone phosphate	6.5-7		Chlorpromazine

Continued

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TABLE 45-3

Specific Drugs and Additives That Are Incompatible When Comixed before Administration[38,39]—cont'd

Drug	pH	General Comments	Incompatibilities
Ergonovine maleate	2.7-3.5		Do not mix with other medications
Erythromycin lactobionate	6.5-7.5	Do not combine with mixtures having a final pH < 5	Aminophylline, multiple vitamins, cephalothin Na, pentobarbital, sodium iodide, heparin Na, penicillin G, tetracyclines
Furosemide	8.8-9.3		Acid solutions
Gentamicin sulfate		Do not mix with other medications	
Heparin sodium	5-7.5		Sodium bicarbonate, multiple vitamins, tetracyclines, chlorpromazine or promazine, erythromycin lactobionate or gluceptate, gentamicin SO_4, hydrocortisone sodium succinate, methylprednisolone Na succinate, kanamycin SO_4, meperidine HCl, morphine SO_4, penicillin G (K^+), protamine
Hydrocortisone sodium succinate	7-8		Cephalothin Na, tetracyclines, heparin Na, kanamycin SO_4, multiple vitamins, pentobarbital Na, promazine, erythromycin, tylosin
Kanamycin sulfate	4.5	Cephalothin Na, dextrose, heparin Na, hydrocortisone Na succinate, penicillins, sulfadiazine	
Levamisole	Neomycin, phenylbutazone, sulfonamides, tetracyclines		
Lidocaine	6-7		Alkaline solutions
Magnesium sulfate	5.5-7		$NaHCO_3$, calcium-containing solutions, tetracyclines
Mannitol	4.5-7		Strongly acidic or alkaline solutions, whole blood, penicillin G
Methylprednisolone sodium succinate	7-8		Aminophylline, heparin Na, tetracyclines, vitamin B
Multiple vitamins			Aminophylline, cyanocobalamin, erythromycin lactobionate, heparin Na, hydrocortisone Na succinate, penicillin G, sodium bicarbonate, tetracyclines
Nitrofurantoin sodium	7.7-9.8		Calcium chloride, insulin, phenol, procaine
Oxytocin	2.5-4.5	Do not mix with other medications	
Penicillin G (K^+ or Na^+)	6-7	Significant inactivation if pH <5.5 or >8	Tetracyclines, acetylcysteine, multiple vitamins, vitamin B with C, lincomycin, aminophylline, pentobarbital, thiopental, cephalothin Na, erythromycin, sodium bicarbonate, sulfonamides, heparin Na, gentamicin
Pentobarbital sodium	10-10.5		Acidic solutions, cephalothin Na, erythromycin, tetracyclines, sodium bicarbonate, succinylcholine chloride
Ringer lactate solution	6-7.5		Epinephrine HCl, tetracyclines, sodium bicarbonate, sulfadiazine Na
Sodium bicarbonate	7-8		Calcium-containing solutions, magnesium sulfate, vitamin B with C, tetracyclines, penicillin G (Na or K), thiopental sodium, pentobarbital Na, streptomycin
Sodium iodide	7.5-9		Vitamin B with C
Succinylcholine chloride	3-4.5		Alkaline solutions, pentobarbital Na, thiopental Na
Sulfonamides	Basic		Acidic solutions, ammonium chloride, gentamicin SO_4, kanamycin SO_4, lincomycin HCl, methicillin, penicillin G, tetracyclines, vitamin B with C, calcium gluconate, dextrose, tylosin, procaine
Tetracyclines	1.8-2.8		Aminophylline, penicillins, magnesium or calcium salts, cephalothin Na, erythromycin, lactobionate, heparin Na, hydrocortisone Na succinate, methylprednisolone Na succinate, multiple vitamins, nitrofurantoin, novobiocin, polymyxin B, lactated Ringer or Ringer solution, sodium bicarbonate, sulfonamides, barbiturates
Thiamine (vitamin B_1)	3-4	Neutral or alkaline pH causes decomposition	Iron salts
Thiopental sodium	10-11		Acidic solutions, promazine HCl, sodium bicarbonate, succinylcholine Cl, atropine SO_4, penicillins, cephalosporins, tetracyclines, hydrocortisone Na succinate
Ticarcillin disodium	6-8		Aminoglycosides
Tylosin			Hydrocortisone, tetracycline, streptomycin, sulfonamides
Vitamin B complex	10-11		Alkaline solutions, cephalothin Na, cyanocobalamin, erythromycin lactobionate, hydrocortisone Na succinate, tetracyclines
Vitamin B complex with C	3-6.5		Aminophylline, cephalothin Na, erythromycin lactobionate

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The lactating large animal must also be considered. Many antimicrobial drugs can be found in milk and may be transferred to the lactating animal or human who consumes the milk. Some drugs reach the milk in high concentrations whereas others are found in low amounts relative to plasma. Regardless, almost all antimicrobial drugs may be found in milk. Such adulteration may make the milk unsuitable for human consumption, and appropriate withdrawal times should be adhered to before milk enters the human food chain.

Treatment of bacterial mastitis provides several challenges and is covered in more detail elsewhere in this book. Treatment should be initiated early and based on susceptibility of the particular causative agent. If individual milk culture and susceptibility testing is not feasible, then treatment should be based on historical information from the affected herd. Penetration into milk is also an important consideration when using systemic drugs to treat mastitis. Many drugs are found in much lower concentrations in milk, such as the β-lactams and sulfonamides. Others can be concentrated into milk, such as the macrolides. Because of the low concentrations found in milk for many of the drugs used in food production animals, intramammary administration is preferred, although systemic administration can also be used and is probably indicated in the systemically ill animal or when abscesses preclude delivery of the drug via the intramammary route. As for systemic administration, withdrawal times should be closely followed with intramammary infusions.

Renal and Hepatic Function

As for all drugs, metabolism of antimicrobial drugs takes place in the liver and/or kidneys and excretion follows these routes. Therefore, compromised renal or hepatic function should be considered when choosing an antimicrobial drug. Aminoglycosides are well known for their nephrotoxicity and should be avoided in cases with elevations in serum blood urea nitrogen or creatinine. If their use is still warranted despite renal dysfunction, the frequency of administration or in some cases the dose should be altered. Therapeutic monitoring of aminoglycoside levels should be performed to guide therapy. Macrolides and rifampin are metabolized and excreted via the hepatic route, and liver enzymes should be monitored for elevation during use. Knowledge of the route of excretion of active drug can be used to concentrate drugs at the site of infection. In the case of bacterial pyelonephritis or cystitis, renal excretion of many antimicrobial drugs can be used to the clinician's advantage during treatment.

Immune Status

The effectiveness of the immune response is important for successful antimicrobial therapy. Many drugs only reach bacteriostatic levels at the site of infection and thus may only inhibit growth of the offending agent. In these cases, the immune response is essential for clearing the infection. Bactericidal concentrations of drugs at the site of infection should be used in cases of immunocompromise. Immunodeficiency, whether primary or secondary, may be an indication for use of combination therapy.

Duration of Therapy

Unfortunately, there are few guidelines in veterinary medicine that direct duration of therapy. Certainly serious or deep-seated infections such as endocarditis, pyelonephritis, and osteomyelitis warrant prolonged antimicrobial administration. In human patients, such infections would be treated for 6 weeks or longer. In veterinary medicine we must frequently rely on response to therapy. Resolution of pyrexia, decreases in white blood cell count or fibrinogen, or resolution of abnormal radiographic and ultrasonographic findings are important parameters to monitor when deciding to cease therapy. In some cases, re-sampling and culture of the previously infected site may be warranted. For simple infections, treatment for a few days past resolution of clinical abnormalities and clinicopathologic findings may be adequate. For complicated infectious processes, treatment may be needed for weeks or longer after apparent cure.

Route of Administration

The route of administration will vary depending on the patient species, age, severity of the infection, bioavailability of orally administered drugs, and site of the infection. Intravenous delivery of antimicrobials is indicated for serious life-threatening infections in which high levels of drug at the site of infection are indicated. Many drugs with good oral bioavailability in small animals, such as β-lactams, cannot be administered orally in large animal patients, necessitating parenteral administration. Oral administration of antimicrobials should be used cautiously in large animal species to minimize disruption of ruminal or colonic microflora in ruminants and horses, respectively. The route of administration may also be influenced by client or patient compliance. Intramuscular administration may be difficult for some clients and patients, resulting in inadequate duration of therapy and possible development of resistance by microorganisms. Therapeutic administration of antimicrobial drugs in feed is an alternative that is easy for the client but is ineffective if the animal refuses to consume it. Guidelines for therapeutic use of antimicrobial drugs in feed can be found later in this chapter.

Monitoring of Therapy

The response to treatment should always be monitored throughout antimicrobial drug administration. It helps to guide decision making regarding duration of therapy and effectiveness of the chosen antimicrobial regimen. As mentioned previously, clinical and clinicopathological findings are useful guides to judge therapeutic success. Failure to respond to therapy could indicate that the organisms present in the infection are resistant to the chosen drug, particularly if the drug was chosen empirically. It may also indicate development of resistance during therapy or that there is poor penetration of drug to the site of the infection. Monitoring of drug levels may be indicated to determine if dosage and/or frequency is adequate in cases of treatment failure. A positive response to therapy can be an indication that antimicrobial treatment can be de-escalated in the case of broad-spectrum administration or that the patient can be switched from parenteral to oral administration.

Prophylactic and Metaphylactic Use of Antimicrobial Drugs

Antimicrobial drugs for prophylactic or metaphylactic use should be used only for cases or situations that are deemed high risk for infection and in which clinical data have demonstrated that this use is effective for preventing infection or decreasing morbidity or mortality.[3] Prophylactic use of antimicrobial drugs is therapy directed toward preventing infection in which the risks or consequences of development of an infection are great and outweigh the risks of adverse outcome from the drug used. Its most frequent application is in the surgical setting to prevent surgical site infections. The decision to use prophylactic antimicrobials depends on the type of surgery and possibility of entering nonsterile sites such as the gastrointestinal or genitourinary tract, the length of the surgical procedure, the use of surgical implants (metal or nonmetal), and the degree of tissue damage. It is important that the antimicrobial drug be present at therapeutic levels at the time of contamination in order to be effective in prevention of surgical site infections.[25] The therapy should be directed toward the pathogens likely to cause the infection. In the case of surgical site infections of large animals, these include Enterobacteriaceae, *Staphylococcus,* and *Streptococcus*.[26,27] Generally, the drug should be administered 30 to 60 minutes before the actual surgery begins.[28] If the surgery is prolonged, repeated administration of the antimicrobial drug should be performed. Perioperative administration is what is important to prevent surgical

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site infections and continued use after completion of surgery is unnecessary.[29] Therapy beyond this point will not appreciably reduce the incidence of surgical site infections and may predispose to development of resistance or superinfections and increase the likelihood of adverse reactions.[25]

Prophylactic antimicrobials should be drugs other than those used therapeutically so that treatment options remain available should an infection develop. It has been recommended that older drugs be used so that newer drugs may be used therapeutically.[30] Prophylaxis should never be used in the place of good aseptic technique and is not indicated for use to prevent infection of intravenous catheters or other similar indwelling devices. Antimicrobial use in these instances only increases the likelihood that if infection develops, it will be more likely to be resistant.

Metaphylaxis is use of antimicrobial drugs after exposure to an infectious agent but before development of clinical signs. Examination of parenteral treatment of calves at high risk for infection in the bovine respiratory disease complex prior to or upon entry into the feedlot has shown decreased morbidity and mortality.[31,32] It is important to note that metaphylactic use of antimicrobial drugs will not eliminate all infections and may have a greater impact on the severity or duration of the illness. Metaphylactic administration may not always be practical for large groups of animals, and labeling may preclude antimicrobial use in this manner.

Biosecurity and Infection Control

Establishment of effective means of infection control can help to reduce nosocomial infections and decrease the need for antimicrobial therapy. Simple measures such as frequent hand washing, isolation or segregation of animals with contagious or highly resistant organisms, and control of movement of animals can go a long way to decreasing infection rates. Infection control and hygiene plans are important for any premises where animals are managed, not just for veterinary hospitals or clinics.[3]

Microbial Factors Impacting Therapy

Resistance

A number of microbial factors may influence the success of therapy. Resistance of the agent to the chosen therapeutic is a common occurrence in therapeutic failure. Resistance can result from the inherent properties of the microbe. For example, mycoplasmas lack a cell wall and are impervious to the effects of cell wall–targeting drugs like the β-lactams. Other drugs may not be able to penetrate the bacteria as is seen in the inability of anaerobes to take up aminoglycosides. A major contribution to resistance is acquisition of resistance determinants. Resistance may result from alteration of the antimicrobial target, gaining of genes capable of degrading the drug (e.g., β-lactamases), or acquisition of genes encoding efflux pumps (tetracyclines, aminoglycosides) that pump antimicrobials out of the bacterial cell. Bacteria can develop resistance through mutation of the gene encoding the protein target of the drug (e.g., fluoroquinolones and DNA gyrase). These events are not frequent, occurring once every 10^{10} to 10^{14} cell divisions. However, the rapid multiplication rate of a large number of bacteria makes this a real possibility. These events are random and their appearance is not affected by the presence of a particular antimicrobial drug. However, if a drug is present, bacteria with the mutation will have a selective advantage and will rapidly out-compete non-resistant ones.

Alternatively, bacteria can acquire genes encoding a resistance determinant. Bacteria can obtain resistance genes through several mechanisms. Movement of plasmids, a type of extrachromosomal DNA, through conjugation between bacteria of the same or different species is a major means by which resistance develops. Other mobile DNA elements can move resistance genes between bacteria. Resistance genes are frequently associated with transposons, DNA capable of excision from host genomic DNA to plasmids and subsequent transport to other bacteria. Bacteriophages (bacterial viruses) may also move resistance genes between bacteria through a process called *transduction*. Finally, resistance genes can be taken up as naked DNA in the bacterial environment through a process known as *transformation*.

The simple act of using antimicrobial drugs will result in selection of bacteria that are resistant. Survey of gastrointestinal microbes *(Escherichia coli)* after initiation of antibiotic therapy has shown that resistance will develop in normal flora.[33-35] The most effective way to avoid resistance is to minimize use of antimicrobial drugs and, when they are used, to be sure that they are delivered to the site of infection at adequate levels to kill the bacteria.

Biofilms

Bacteria can move from existing as individual cells, also known as planktonic growth, to develop into a population that functions more as a multicellular organism known as a biofilm. The definition of a *biofilm* is "aggregated microbial cells surrounded by a polymeric self-produced matrix, which may contain host components."[36] Biofilms are notoriously difficult to treat with simple antimicrobial therapy and are known to form on a variety of surfaces including catheters, orthopedic implants, and bone. Biofilm bacteria are different from planktonic organisms in several ways. First, they are less susceptible to antimicrobial agents. Second, they persist in the animal despite a vigorous immune response. Unfortunately, often the most effective way to treat the biofilm-associated infection is to remove the infected implant or bone.

Adverse Reactions

Adverse reactions to antimicrobial drugs certainly occur although hundreds or thousands of doses may have to be given before they are observed. A recent report from Switzerland indicated that 20% of adverse reactions to drugs were to antimicrobial agents.[37] Adverse events associated with antimicrobial use can range from a hypersensitivity reaction to direct toxicity to disruptions of normal microbiota. Fortunately, antimicrobial agents are directed toward the prokaryotic structures of bacteria that generally differ to some degree from the eukaryotic equivalent of the host. Consequently they are less likely to result in direct toxicity in the patient. Some drug toxicities are predictable based on their mechanism of action or accumulation in certain cells of the host. Hypersensitivity reactions are the result of immunologic stimulation by the drug or carriers in the drug formulation. One frequently observed adverse event associated with antimicrobial use is development of severe gastrointestinal disturbances. These may be the result of changes in the gut microbiota and/or proliferation of pathogenic bacteria such as *Clostridium difficile* or *Salmonella*. Adverse reactions to antimicrobial drugs should be reported to the manufacturer and to the Food and Drug Administration Center for Veterinary Medicine. Another source of adverse reactions is drug incompatibility. Table 45-3 lists some antimicrobial drug incompatibilities.[38,39]

Adjunctive Therapy

In some infections, antimicrobial drugs alone are unable to clear the infection. In these cases, adjunctive therapy should not be overlooked. Surgical débridement of necrotic material and reestablishment of an adequate blood supply helps to remove bacteria and allow better antimicrobial penetration. Sometimes simple drainage of an abscess is all that is necessary to treat certain infections, obviating the use of antimicrobial drugs.

Topical treatment may be possible in some instances. Superficial skin infections may be treated with either topical antimicrobial drugs or antiseptics. Deep or severe infections may need both systemic and topical treatment. Most ocular infections are successfully treated topically where high drug concentrations can be delivered.

Local treatment of severe internal infections can also be used as an adjunct to systemic therapy. Intraarticular administration of antimicrobials and/or regional perfusion are frequently used to treat

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joint and bone infections. These routes deliver high levels directly to the site of the infection. Although efficacious, adjunctive therapy including débridement and lavage are important to remove the bacterial burden and inflammatory substances that may be detrimental to joint structures. In these instances, systemic administration is indicated.

Medication Use in Food-Producing Animals

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Abbreviations

AMDUCA	Animal Medicinal Drug Use Clarification Act
ANADA	Abbreviated New Animal Drug Application
ANDA	Abbreviated New Drug Application
AOAC	Association of Official Analytical Chemists
AVMA	American Veterinary Medical Association
CFR	Code of Federal Regulations
CPG	Compliance Policy Guide
CVM	Center for Veterinary Medicine
ELDU	Extralabel Drug Use
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FARAD	Food Animal Residue Avoidance & Depletion
FDA	U.S. Food and Drug Administration
FDA-CVM	U.S. Food and Drug Administration Center for Veterinary Medicine
FSIS	Food Safety and Inspection Service
GFI	Guidance for Industry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MRL	Maximum Residue Limit
MUADP	Minor Use Animal Drug Program
MUMs	Minor Use/Minor Species Animal Health Act
NADA	New Animal Drug Application
NDA	New Drug Application
NRP	National Residue Program
ONADE	Office of New Animal Drug Evaluation
PAMTA	Preservation of Antibiotics for Medical Treatment Act
US	United States
USDA	United States Department of Agriculture
VCPR	Veterinarian Client Patient Relationship
VFD	Veterinary Feed Directive
WDI	Withdrawal Interval
WDT	Withdrawal Time
WHO	World Health Organization

Medicating animals that are used to produce food for human consumption is a worldwide phenomenon. Medications can be used to increase production, treat illnesses, produce healthier animals, or prophylactically and/or metaphylactically prevent or reduce morbidity and/or mortality caused by diseases. In recent years, the potential impacts of drug residues are of increasing concern for consumers, regulators, and legislators. In order to maintain public safety, it is important for veterinarians to educate themselves and work closely with their clients to help minimize drug residues in the human food chain.

Definition of Food-Producing Animal Species

For the purposes of this chapter, a food animal is any animal for which its tissues or products from that animal have the potential to enter the human food chain. In the United States, food animals are further categorized as major or minor food animal species. The Food, Drug, and Cosmetics Act defines the major food-producing species of animals to include cattle, swine, chickens, and turkeys. The U.S. Center of Veterinary Medicine (CVM), a branch of the Food and Drug Administration (FDA), has a list of definitions for bovine, swine, and poultry species and classes, which can be found in Table 45-4.[1] Furthermore, in addition to these definitions, the Code of Federal Regulations (CFR) has defined dairy cattle to include all

TABLE 45-4

U.S. Food and Drug Administration's Definitions of Species and Classes of Major Food Animals[1]

Species	Class		Definition
Cattle	Beef Cattle (cattle intended for meat production)	Suckling Calves	Immature, pre-ruminant cattle (including *dairy breeds* intended for meat production), maintained with and dependent upon their dam for nourishment. Veal calves are not considered suckling calves.
		Pasture Cattle (stocker, feeder, slaughter, and sometimes replacement beef heifers)	Weaned cattle (including dairy breeds) maintained on pasture and receiving the majority of their diet from grazing. The term *pasture cattle* is intended to refer to cattle considered to be stockers, feeders, and/or slaughter cattle. Therefore, parenthetical reference to *stocker, feeder,* or *slaughter cattle* is typically included in labeling. *Stockers* refers to weaned calves grazing pasture to enhance growth prior to finishing and slaughter; they are usually younger, weigh less, and are of lower condition (finish) than "feeders." *Feeders* refers to weaned calves grazing pasture and of sufficient weight and maturity to be placed on high-energy rations for finishing; they are generally older, weigh more, and carry more condition (finish) than stockers. *Slaughter* refers to cattle grazing pasture and suitable for slaughter. Sex differentiation (e.g., heifers, steers, and/or bulls) should be indicated on product labeling. *Replacement beef heifers* may be added to the Pasture Cattle class if the drug has been shown to have no negative impact on reproduction in female cattle during the period from weaning until first calving, and the female cattle are intended for reproduction to produce calves intended for meat production.

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TABLE 45-4

U.S. Food and Drug Administration's Definitions of Species and Classes of Major Food Animals[1]—cont'd

Species	Class			Definition
		Cattle Fed in Confinement for Slaughter		Cattle (including dairy breeds) confined in group pens and fed a high-energy diet ad libitum until slaughter. Sex differentiation (heifers, steers, and/or bulls intended for slaughter) should be indicated on product labeling.
		Growing Cattle on Pasture or in Dry Lot (stocker and feeder)		Weaned cattle (including dairy breeds) maintained on pasture or in a dry lot, receiving the majority of their diet from forage.
		Lactating Beef Cows		Lactating beef breed female cattle nursing calves intended for meat production; their milk is not intended for human consumption.
		Non-Lactating Beef Cows		Female beef breed cattle that had previously nursed calves intended for meat production, but which are not currently producing milk.
		Replacement Beef Bulls		Intact male beef breed cattle intended for reproductive purposes.
	Veal Calves			Immature cattle (including dairy breeds) lacking a functional rumen and intended for meat production. They are recognized as a separate class from suckling calves because of their handling, housing, and proximity to slaughter.
	Dairy Cattle (cattle intended for production of milk for human food)	Lactating Dairy Cows		Female dairy breed cattle that are producing milk.
		Dry Dairy Cows		Female dairy breed cattle that had previously lactated, but which are not currently producing milk (cows between two lactations).
		Non-Lactating Dairy Cattle	Replacement Dairy Heifers	Female dairy breed cattle from weaning until first calving.
			Replacement Dairy Bulls	Intact male dairy breed cattle intended for reproductive purposes.
			Dairy Calves	Female or male dairy breed cattle being fed a ration that includes milk or liquid milk replacer and which are not intended for veal production.
Swine	Boars			Intact, sexually mature, male pigs intended for breeding purposes; generally not intended for slaughter in the United States.
	Barrows			Castrated male pigs intended for slaughter.
	Gilts			Female pigs intended for slaughter or breeding purposes; have not yet farrowed a litter.
	Replacement Gilts			Breeding female pigs that have not yet farrowed a litter; usually weigh 220 to 300 lb (100 to 135 kg).
	Sows			Female pigs that have had at least one litter.
	Nursing Pigs			Pigs from birth until weaning and still nursing.
	Starter or Nursery Pigs			Boars, barrows, and gilts from approximately 2 to 4 weeks of age and approximately 50 to 60 lb (23 to 27 kg).
	Growing Pigs			Barrows and gilts from approximately 50 to 60 lb (23 to 27 kg) to 120 to 150 lb (55 to 68 kg).
	Finishing Pigs			Barrows and gilts from approximately 120 to 150 lb (55 to 68 kg) to market weight for slaughter.
Chickens	Egg			From in ovo until hatching.
	Laying Hens (or layers)			Hens that produce eggs for human consumption.
	Chicks			Chickens from day of hatch until they are able to survive in ambient temperature (no longer brooded).
	Broiler Chickens (or fryers or frying chickens)			Meat-type chickens normally grown to a market age of 35 to 49 days and market weights between approximately 4 and 7 lb (1.80 and 3.2 kg).
	Roasters (or roasting chickens)			Meat-type chickens grown to market weights between approximately 6 and 9 lb (2.7 and 4.1 kg).
	Replacement Chickens			Chickens intended to become laying hens or breeding chickens.
	Breeding Chickens			Sexually mature male and female chickens of any type intended for the production of fertile eggs; the eggs are not intended for human consumption.
Turkeys	Egg			From in ovo until hatching.
	Laying Hens (or layers)			Hens that produce eggs for human consumption.
	Poults			Turkeys from day of hatch until they are able to survive in ambient temperature (no longer brooded).
	Growing Turkeys			Turkeys grown for meat purposes to a market age of approximately 17 (female) or 22 (male) weeks; may be further divided into heavy or light turkey strains.
	Finishing Turkeys			Turkeys intended for meat production during the last 2 to 4 weeks of growth.
	Replacement Turkeys			Turkeys intended to become laying hens or breeding turkeys.
	Breeding Turkeys			Sexually mature male or female turkeys intended to produce fertile eggs; their eggs are not intended for human food use.

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female cattle of a recognized dairy breed over 20 months of age.[2] Both dry and lactating dairy cattle would fall under this category. "Minor" food animal species are defined by exclusion, meaning that the "major" animal species have been identified and all others are considered "minor." Examples of "minor" food animal species would include goats, sheep, and cervids.

On-Label Drug Use

In food animal medicine, medications can be administered to an individual animal or a herd or flock depending on numbers of animals needing treatment, disease, and/or overall management practices. Practitioners treating food-producing animals in the United States can use FDA-approved veterinary products according to the label. Using medications according to the label directions is termed *on-label drug use,* where all of the drug label specifications (animal species and class, administration route, dose, dosing frequency/interval, indication, limitations, and withdrawal time) are fulfilled and the FDA-approved withdrawal time is observed. The FDA-approved withdrawal time (WDT) is the amount of time that must be observed after the last dose is administered and before the food product intended for human consumption can enter the human food chain. There are multiple databases where label information for FDA-approved veterinary medications is accessible and can be consulted. Table 45-5 lists a few resources.

Extralabel Drug Use and the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994

Prior to the enactment of the Animal Medicinal Drug Use Clarification Act (AMDUCA) in 1994, veterinarians could legally treat food animals with on-label medications only. Passage of AMDUCA legalized most instances of extralabel drug use (ELDU) in food animals by or on the order of veterinarians.[3] Extralabel drug uses include prescribing or administering a human or veterinary drug at a higher dose, frequency, or duration, by a different route of administration, in a different species, or for a different indication than as described on the product's label. For food animal practitioners, with this privilege comes the weighty responsibility of protecting the health of consumers of animal products. Veterinarians must meet very specific conditions before they may legally use or prescribe drugs in an extralabel fashion. Under AMDUCA, ELDU is limited to cases in which the health of the animal is threatened or when suffering or death may result from a lack of treatment. ELDU may not be used to enhance production or for non-therapeutic reproductive cycle manipulation in healthy animals and can only occur on the order of a veterinarian within the context of a veterinarian-client-patient relationship (VCPR) as described in Box 45-2. ELDU may be considered in food-producing animals only when no approved drug is available that contains the same active ingredient in the required dose, form, and concentration or when the veterinarian finds that there is no approved drug that is clinically effective for the intended use. Extralabel drug use in or on animal feed is also expressly prohibited.

AMDUCA stipulates that ELDU only applies to FDA-approved human and veterinary medications. It does not legalize the extralabel use of EPA-regulated pesticides or USDA-regulated biologics. New animal drug application (NADA) or abbreviated new animal drug application (ANADA) numbers are a good indication of whether a drug is FDA approved. The presence of a NADA or ANADA number on the product label is an indication that the veterinary drug has FDA approval. Similarly for human drugs, every approval has a unique new drug application (NDA) number for pioneer drugs or abbreviated new drug application (ANDA) number for generic drugs. Approval status of both animal and human drugs can be found on the FDA-CVM (http://www.fda.gov/AnimalVeterinary/) and FDA (http://www.fda.gov) websites, respectively.

TABLE 45-5

Useful Internet Links for Online Resources Relative to Drug Use and Drug Residues in Food Animals

Website	Description	Website Address
U.S. Drug Information		
Drugs @ FDA	FDA's searchable database of approved human drugs	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Animal Drugs @ FDA	FDA's searchable database of approved animal drugs and tolerances	http://www.accessdata.fda.gov/scripts/animaldrugsatfda/
Vetgram	FARAD's searchable drug database for food animal drugs and tolerances	http://www.farad.org/vetgram/
Bayer Animal Health	Site provides a link to the searchable U.S. compendium of veterinary products; use charts tab for summarized label information	http://bayerdvm.com/ *or* http://bayerall.naccvp.com/?m=chartindex_main&type=wt
Drugs.com	Searchable database of veterinary drugs	http://www.drugs.com/vet/
International Drug Information		
ABI's Animal Health and Production Compendium	List of international animal drug databases	http://www.cabi.org/ahpc/default.aspx?site=160&page=3207
Canadian Compendium of Veterinary Products presented by Bio Agri Mix Total Solutions	Searchable Canadian compendium of veterinary products and summarized label information	http://bam.naccvp.com/?m=chartindex_main&type=wt
Australian Pesticides and Veterinary Medicines Authority	Pubcris is a searchable database of registered pesticides and veterinary drugs	http://services.apvma.gov.au/PubcrisWebClient/welcome.do
National Office of Animal Health	UK site with searchable drug compendium of approved drugs	http://www.noahcompendium.co.uk/Compendium/Overview/
Irish Medicines Board	Searchable compendium of approved drugs in Ireland	http://www.imb.ie/
European Medicines Agency Database	Public database providing online access to information about human and veterinary medicines available to EU citizens	http://www.eudrapharm.eu/eudrapharm/

Continued

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TABLE 45-5

Useful Internet Links for Online Resources Relative to Drug Use and Drug Residues in Food Animals—cont'd

Website	Description	Website Address
USDA Foreign Agricultural Service	Veterinary drug and pesticide tolerance and MRL searchable database	http://www.fas.usda.gov/htp/MRL.asp
FAO/WHO Food Standards Codex alimentarius	Definitions of terms used in discussing veterinary drug residues in food animals	http://www.codexalimentarius.net/vetdrugs/data/reference/glossary.html
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	Description of JECFA and links to publications	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/
JECFA "Residues of some veterinary drugs in foods and animals"	Searchable database of maximum residue levels for veterinary drugs as recommended by JECFA that includes pharmacokinetic data summaries	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/
Codex alimentarius international food standards	Homepage for codex alimentarius	http://www.codexalimentarius.org/about-codex/en/
European Medicines Agency European Public MRL Assessment Report	Summary report on the established MRL and the data supporting the MRL	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_mrl_search.jsp&mid=WC0b01ac058008d7ad
U.S. Regulatory Links		
USDA/FSIS Residue Chemistry Page	Includes FSIS sampling plan (Blue Book) and results (Red Book)	http://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/chemistry/residue-chemistry
USDA Food Safety and Inspection Service (FSIS)	Homepage with contact information and links to resources	http://www.fsis.usda.gov/
FDA Center for Veterinary Medicine	Homepage with contact information and links to resources	http://www.fda.gov/AnimalVeterinary/default.htm 240-276-9300 AskCVM@fda.hhs.gov
U.S. Environmental Protection Agency (EPA)		http://www.epa.gov/
Centers for Disease Control and Prevention	CDC's Food Safety Program	http://www.cdc.gov/foodsafety/vitalsigns.html
AMDUCA and ELDU Links		
FDA-CVM Compliance Policy Guide	AMDUCA	http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ActsRulesRegulations/ucm085377.htm
AVMA: Animal Medicinal Drug Use Clarification Act (AMDUCA)	Reviews components of AMDUCA and includes list of prohibited drugs	https://www.avma.org/KB/Resources/Reference/Pages/AMDUCA.aspx
AVMA algorithm	AVMA's guide to ELDU under AMDUCA	http://www.avma.org/reference/amduca/amduca1.asp
FDA-CVM Compliance Policy Guide	Extralabel use of medicated feeds for minor species	http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/UCM074659
FARAD	U.S. site where ELDU withdrawal requests may be made online and other resources for food animal veterinarians	http://farad.org/
Canadian gFARAD	Canadian program providing information on residue avoidance	http://www.cgfarad.usask.ca/home.html
FARAD	List of restricted and prohibited drugs in food animals	http://www.farad.org/eldu/prohibit.asp
Compounding Links		
FARAD regulatory information	Details of the published law on compounding and AMDUCA	http://farad.org/amduca/amduca_law.asp
AVMA Compounding	AVMA brochure on veterinary compounding	https://ebusiness.avma.org/EBusiness50/ProductCatalog/product.aspx?ID=155
FDA-CVM Compliance Policy Guide	Compounding of Drugs for Use in Animals	http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074656.htm http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074656.htm
Society of Veterinary Hospital Pharmacists statement on compounding	Position statement on the compounding of drugs for use in animals	http://svhp.org/position-statements/
Miscellaneous Links		
National Pesticide Information Center	NPIC provides objective, science-based information about pesticides and pesticide-related topics	http://npic.orst.edu/
Minor Use Animal Drug Program (MUADP)	Searchable database for drugs approved in minor food animal species and MUMs and MUADP information	http://www.nrsp7.org/
American Association of Veterinary Laboratory Diagnosticians	Listing of AAVLD labs in the United States by state	http://www.aavld.org/accredited-labs

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BOX 45-2

Conditions Necessary for Extralabel Drug Use

1. Extralabel drug use (ELDU) is permitted only by or on the order of a veterinarian.
2. The veterinarian judges on-label treatments to be unavailable or ineffective.
3. ELDU uses only U.S. Food and Drug Administration (FDA)–approved animal and human drugs, not drugs imported from foreign countries or compounded from bulk sources. When treating food animals, approved food animal drugs should be used before approved animal drugs which should be used before approved human drugs.
4. A valid veterinarian-client-patient relationship (VCPR) exists in which the veterinarian:
   - oversees medical treatment decisions on the farm
   - is familiar with animal care through appropriate and timely visits
   - has sufficient knowledge to initiate a diagnosis
   - is available for follow-up care as needed
5. ELDU is for therapeutic or humane purposes only, not to increase production or manipulate reproductive cycles in normal animals.
6. ELDU applies only to administration to individual animals and in water, not in feed.
7. Animal identification and treatment records are sufficient to identify treated animals and their treatment history and are maintained for 2 years.
8. The veterinarian establishes an extended drug withdrawal period protective of human health supported by scientific evidence. ELDU resulting in violative or dangerous food residues is not permitted.
9. Drug labels list the name and address of the prescribing veterinarian, animals to be treated, and the drug name, disease indication, dose, frequency, duration, cautions, and withdrawal periods associated with treatment.
10. Certain extralabel uses specifically prohibited by the FDA are not used (see Box 45-4).

BOX 45-3

Conditions Necessary for Extralabel Use of Medicated Feed in Minor Species

1. Extralabel use of medicated feed is only for treatment of minor species, defined by exclusion as animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.
2. Extralabel use of medicated feed is limited to farmed or confined minor species but not unconfined wildlife.
3. Extralabel use of medicated feed is limited to situations in which the health of an animal is threatened and suffering or death may result from failure to treat.
4. There is no alternative therapeutic dosage form (besides feed) that can be practically used under legal extralabel use.
5. Only feeds formulated and labeled for use in a major species animal are used.
6. Extralabel use of medicated feed in aquaculture is limited to medicated feed products approved for use in aquatic species.
7. The medicated feed is used within 3 months of a veterinarian's written recommendation. Recommendations, feed labels, and invoices are kept for at least 1 year. Adverse reactions are reported to the U.S. Food and Drug Administration within 10 days.
8. All other Animal Medicinal Drug Use Clarification Act requirements are complied with, including a valid veterinarian-client-patient relationship, lack of label alternatives, treatment records, animal identification, and extended withdrawal times (see Box 45-2).
9. The medicated feed is used in accordance with federal, state, and local environmental regulations and approval. This is particularly important for aquaculture uses.
10. The producer has followed worker safety provisions in the approved product labeling.

When veterinary products are used in an extralabel manner, a withdrawal "interval" must be estimated based on scientific evidence and must be extended beyond the FDA-approved WDT regardless of the dose, route, or indication. This ensures that there are no illegal residues, another stipulation in AMDUCA. A residue is considered to be either the parent compound or metabolite of that parent compound that may accumulate, deposit, or otherwise be stored within the cells, tissues, organs, or edible products (e.g., milk, eggs) of an animal following its use to prevent, control, or treat animal disease or to enhance production.[4]

As stipulated by AMDUCA, veterinarians' obligations regarding extralabel drug use are listed in Box 45-2. The American Veterinary Medical Association (AVMA) has developed an algorithm that helps veterinarians determine whether the intended ELDU is legal according to AMDUCA.[5]

Veterinarians violating state or federal laws regulating the transport, sale, or use of drugs may face a variety of sanctions, including warning letters, fines, temporary or permanent revocation of license, and incarceration.

Extralabel Drug Use of Medicated Feeds in Minor Species

Even though AMDUCA prohibits the extralabel use of medications in feed, a compliance Policy Guide (CPG) 615.115 for extralabel use of medicated feeds for minor animal species does exist.[6] The AMDUCA prohibition of extralabel use of medications in feed was generated because of concerns of antibiotic resistance. AMDUCA's Section 530.11 specifically prohibits the "extralabel use of an approved new animal drug or human drug in or on an animal feed." As a matter of enforcement discretion, CVM generally has not objected to mixing a drug with an individual animal's feed, but extralabel mass medication in feed is prohibited "without limitation or exception." Veterinarians may, however, be called on to treat minor food animal species such as farmed exotic ruminants, fish, or game birds. CVM has found that for many of these species, very few approved drugs exist. In addition, CVM recognizes that some minor food animal species (such as fish and game birds) cannot be practically medicated in any way other than through the use of medicated feeds. In such situations, a veterinarian may determine that extralabel use of medicated feeds (approved for use in other species) can prevent suffering and death in these minor species.

Although AMDUCA prohibits ELDU in feed, in the previously described circumstances CVM "ordinarily will not consider regulatory action" against the veterinarian or animal producer provided that certain criteria listed in Box 45-3 are met.[6] The CVM policy being implemented in these cases is akin to that of extralabel drug use by veterinarians before the 1994 passing of AMDUCA. The drug use is still illegal, but CVM will apply regulatory discretion relative to taking enforcement action. A critical aspect of CVM's regulatory discretion in this practice is that labeled treatment alternatives are not available. The best resource to aid practitioners in determining what treatments are approved for minor food animal species is the Minor Species Drug Approval site (http://www.nrsp-7.org).

Prohibited Drugs/Drug Classes Prohibited from Extralabel Drug Use in Food Animals

Certain drugs may not be prescribed or used even under the auspices of AMDUCA.[7] Under statutory authority provided in AMDUCA, the FDA's Center for Veterinary Medicine (CVM) has prohibited approximately a dozen drugs or drug classes, making their extralabel use in food animals illegal. Other compounds not specifically listed in AMDUCA are prohibited by virtue of the fact that no approved animal or human products are commercially available. Last, extralabel use of treatments is also regulated by the Pasteurized Milk Ordinance (PMO). The extralabel use in food animals of the

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BOX 45-4

Drugs or Drug Classes Prohibited from Extralabel Drug Use*

Diethylstilbestrol (DES)
Chloramphenicol
Nitroimidazoles (including dimetridazole, metronidazole, and ipronidazole)
Sulfonamide (other than sulfadimethoxine) in adult dairy cattle†
Clenbuterol
Fluoroquinolones (e.g., enrofloxacin and danofloxacin)
Glycopeptides (e.g., vancomycin)
Nitrofurans (including nitrofurazone, furazolidone; topical use prohibited as well)
Phenylbutazone in adult dairy cattle†
Adamantane and neuraminidase inhibitors in poultry
Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys:
(i) For disease prevention purposes;
(ii) At unapproved doses, frequencies, durations, or routes of administration; or
(iii) If the drug is not approved for that species and production class.

*Extralabel use of some drugs or drug classes (not specifically addressed in the Animal Medicinal Drug Use Clarification Act) are prohibited because these drugs are not available as approved animal or human products, by U.S. Food and Drug Administration (FDA) policy or in the Pasteurized Milk Ordinance (see chapter text).
†Defined by FDA as dairy cattle (lactating or dry) older than 20 months of age.

compounds listed in Box 45-4 represents one of the FDA's highest priorities for regulatory attention. It is advised that the FDA-prohibited drug list be checked on a regular basis for updates as it is subject to change. FARAD and AVMA websites both list prohibited drugs.[8,9] Alternatively, 21CFR530, the section of the CFR pertaining to ELDU, may be accessed directly.[10]

If any of these prohibited drugs are mistakenly used in a food-producing animal, that animal and its by-products should never be allowed to enter the human food chain and ideally that animal should be isolated from other food animals.

Drugs Prohibited from Use in Food Animals:

1. Diethylstilbestrol: From the 1940s to the 1970s, U.S. physicians prescribed diethylstilbestrol (DES, a potent nonsteroidal synthetic estrogen) to pregnant women to prevent miscarriage and other reproductive diseases. In 1971 a link between in utero exposure to DES and a rare vaginal cancer (clear cell adenocarcinoma) was established. In the same year the FDA published an alert advising doctors against the use of DES during pregnancy. The U.S. Department of Agriculture (USDA) banned the use of DES in food animals in 1979.
2. Chloramphenicol: An estimated 1 in 10,000 to 50,000 people exposed to chloramphenicol will develop a non-dose-related aplastic anemia. Because of concerns that this idiosyncratic and frequently fatal complication could be triggered by residues, chloramphenicol use in food animals was prohibited in 1984. The prohibition extends to all formulations of chloramphenicol including ophthalmic ointments. Florfenicol, a synthetic member of the chloramphenicol family, lacks the p-NO2 group thought to be responsible for inducing the aplastic anemia. Florfenicol may be used extralabel in food-producing species. However, veterinarians should be aware that extralabel use of florfenicol in dairy cattle greater than 20 months of age requires extended withdrawals to allow depletion of drug residues in the liver to a level below detection by the Food Safety Inspection Service (FSIS).
3. Nitroimidazoles: Historically, dimetridazole and ipronidazole have been approved for the treatment of histomoniasis (infectious enterohepatitis, blackhead) in turkeys. Ipronidazole and the human drug metronidazole have been used off-label to eliminate the carrier state of trichomoniasis in bulls. Laboratory studies of members of this drug class demonstrated mutagenicity and carcinogenicity, leading to the prohibition of their use in food animals. Because there are no approved veterinary nitroimidazole labels, the use of any member of this drug class in food animals is illegal.
4. Nitrofurans: In the past, nitrofurazone and furazolidone were approved for a variety of protozoal and bacterial infections in poultry and swine. Topical formulations (sprays and "puffer" products) have also historically been marketed for wounds and ocular infections in livestock ("pinkeye"). Based on laboratory evidence of carcinogenicity and the absence of a reliable detection method, the FDA withdrew approval for systemic animal nitrofuran products in 1991 and prohibited all extralabel treatment (including topical use) in 2002. Because nitrofurans have no approved food animal uses, the use of any member of this drug class in food animals is illegal.
5. Clenbuterol: Marketed in the United States as an equine bronchodilator, this synthetic sympathomimetic has been used illicitly to increase weight gain and lean body mass in food animals, particularly show animals. Because muscle depletion and fat re-deposition commences after drug withdrawal, producers may be tempted to market animals with little or no withdrawal interval. Cooking temperature only minimally denatures the compound, and toxicity from residues has resulted in hundreds of emergency hospitalizations in consumers of tainted beef in Spain and Italy.[11,12]
6. Glycopeptides: Vancomycin, the only glycopeptide antibiotic available in the United States, is often the therapy of last resort for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans. Demonstration of vancomycin-resistant *Enterococcus* in the feces of poultry and swine fed the glycopeptide avoparcin led CVM in 1997 to prohibit extralabel use of glycopeptides in food animals.
7. Phenylbutazone in Adult Dairy Cattle: The use of phenylbutazone, a nonsteroidal antiinflammatory agent, in humans has been associated with a variety of adverse drug reactions including fatal blood dyscrasias. After USDA reports of a high incidence of phenylbutazone tissue residues in cull dairy cows, CVM prohibited its use in female dairy cattle older than 20 months of age. Antiinflammatory therapy for lactating dairy cattle is available as flunixin meglumine. Flunixin should be used only on-label (intravenously) because intramuscular or intravenous administration can greatly extend withdrawal times.[13]
8. Antiviral Drugs in Poultry: Concern exists that use of antiviral drugs in poultry could promote drug resistance in zoonotic pathogens, particularly avian influenza H5N1 ("bird flu"). These concerns led CVM in 2006 to prohibit extralabel use of two drug classes used in treating human influenza. Adamantanes and neuraminidase inhibitors may not be used in chickens, turkeys, and ducks. Aside from compounds specifically prohibited through AMDUCA, there are several compounds that CVM has reminded veterinarians cannot be legally obtained as finished animal or human products and therefore have no legal extralabel uses.
9. Dipyrone: At one time, approved for humans and animals, dipyrone was withdrawn from the market because of concerns of adverse events in humans associated with its use, including teratogenicity, prolonged bleeding times, and agranulocytosis.
10. Estradiol Cypionate: Before 2003, estradiol cypionate (ECP, a synthetic estrogen) was commercially marketed as reproductive therapy in food animals. ECP had not undergone a formal approval process, however, and discretionary marketing was discontinued for lack of food safety and efficacy data. Use in or compounding of ECP for food animals remains illegal.
11. Gentian Violet: Gentian violet was originally used as an additive to poultry feed as a mold inhibitor. However, the FDA has never approved the use of this product as a feed additive or as an

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animal drug, and the impact of any residues on human health is unknown. Therefore, any use in feeds constitutes extralabel use of a medicated feed and unapproved animal drug. In addition to medicated feeds, topical formulations containing gentian violet are currently being marketed. However, in 2007, the FDA issued a warning advising veterinarians of the illegal nature of using topical products containing gentian violet in food-producing animals.

12. Hormone Implants in Veal Calves: Although growth-promoting hormone implants have been marketed for ruminating cattle, these products never underwent regulatory approval for non-ruminating veal calves. Concern existed in CVM that non-ruminating calves may eliminate the hormone contained in the implants differently than ruminants. In 2005 a new warning statement was added to the label of all growth-promoting hormone implants, reminding producers and veterinarians that their use in veal calves is illegal.
13. Dimethyl Sulfoxide and Colloidal Silver: Besides AMDUCA, the Grade A PMO also directs how drugs will be used and stored on dairy farms. Dimethyl sulfoxide (DMSO) and colloidal silver may not be used in or on dairy animals and, if found during a dairy inspection, can result in "debits."

Drug Classes Prohibited from ELDU in Food Animal Species

In addition to the aforementioned specific drugs that the FDA has prohibited, there are drug classes for which some drugs may have FDA approval for use in food-producing animals, but these drug classes are prohibited any extralabel drug use. These drug classes with an ELDU prohibition include the following:

1. Cephalosporin-class antibiotics

   On April 5, 2012, in hopes of preserving their effectiveness for human populations and decreasing the likelihood of the emergence of cephalosporin-resistant strains of foodborne bacterial pathogens, the extralabel use of cephalosporins in cattle, swine, chickens, and turkeys was prohibited. This prohibition does not include (1) the extralabel use of cephapirin in food-producing animals, (2) use of a cephalosporin to treat an extralabel indication, provided that all other label directions are followed, including species, dose, route, duration, and frequency, and (3) extralabel use in minor food-producing animal species (i.e., species that do not include cattle, swine, chickens, or turkeys).
2. Sulfonamides in Adult Dairy Cattle

   The observed carcinogenicity of sulfonamides in laboratory animals, coupled with frequent finding of sulfonamide residues in milk, led to the prohibition of extralabel use of these compounds in adult dairy cattle. The FDA defines a lactating cow as any dairy cow (milking or dry) older than 20 months of age. The use of any sulfonamide in adult dairy cattle other than approved uses of sulfadimethoxine (SDM), sulfabromethazine, and sulfamethoxypyridazine is illegal. This would include use of a higher dose of SDM or using slow-release formulation SDM boluses.
3. Fluoroquinolones

   Uncertainty exists related to the magnitude and significance of human pathogen resistance resulting from antibiotic use in animals. Fluoroquinolones are mainstay treatments of antibiotic-resistant *Salmonella* and anthrax infections in humans. Concern that fluoroquinolone use in food animals was promoting human pathogen resistance prompted CVM in 1997 to prohibit extralabel use of these compounds. Any deviation from a fluoroquinolone product label (altering species use, dosage, route of administration, or disease indication) is illegal. In the case of the approved beef cattle formulation of danofloxacin, this prohibition extends to use in all non-beef-production animals, including lactating and nonlactating dairy cows, heifer replacements, bulls, and veal calves. The same applies to enrofloxacin with the exception of nonlactating dairy cattle, defined by the FDA as dairy cows less than 20 months of age, for which there is a label indication.

Considerations for Treatment of Companion Food Animal or Pack Animal Species with Prohibited Substances

The previously detailed FDA-prohibited drug and drug class list pertains to food-producing animals only and not companion species such as dogs and cats. Veterinarians occasionally treat companion animals belonging to a food-producing species (horses, llamas, pygmy goats, pot-bellied pigs). As long as these animals can be guaranteed to never enter the human food chain, CVM does not normally consider these to be food animals. However, even if they are not to be slaughtered, consideration for why the prohibition exists should be carefully examined and prudent pharmacovigilance used. Practitioners who have used a prohibited substance in a companion or pack animal that subsequently enters the food supply are subject to enforcement actions under the Food Drug and Cosmetic Act. In choosing to use a prohibited drug in a companion or pack animal, the practitioner is accepting a certain amount of liability because the ultimate fate of such treated animals is often beyond their control. Practitioners may choose to have owners sign an agreement (entered into the medical record) not to introduce the animal into the human food chain.

Compounding of Medications for Food Animals

Compounding is defined as a manipulation to produce a dosage form of a drug other than that provided for in the labeling, such as reconstitution. CVM recognizes the need for compounding within certain areas of veterinary practice, such as mixing or dilution. Because of the absence of safety, efficacy, and food safety data for compounded drugs, the potential exists for adverse reactions in treated animals or consumers of their products. In addition, if there are not sufficient scientific data upon which to estimate a withdrawal for a compounded medication, it is the responsibility of the veterinarian to ensure that the animal and any food products that result from that animal do not enter the human food chain. Under AMDUCA, it is legal for veterinarians (or pharmacists on the order of a veterinarian) to compound from U.S.-approved animal and human drugs if the conditions listed in Box 45-5 are met.[3,14]

Overall, when treating a food-producing animal, the use of compounded medications should be only a last resort because safety of the food chain should be the first priority of the veterinarian.

Antidotes Compounded from Bulk Drug

Despite the prohibition, several chemicals commonly recommended as food animal antidotes are available only through compounding from bulk drug. As described in the previous section, compounding veterinary medications from bulk drugs is illegal. However, analogous to its policy concerning ELUD in feed for minor species, CVM

BOX 45-5

Requirements for Compounding in Veterinary Practice

1. No approved animal or human drug can be used in its available dosage form and concentration.
2. Only approved animal or human drugs are used in the compounding, specifically not foreign or bulk drugs.
3. Compounding is performed by a licensed pharmacist or veterinarian in compliance with state pharmacy laws.
4. Adequate procedures are in place to ensure the safety and effectiveness of the product.
5. Withdrawal intervals are set by the veterinarian and not the pharmacist.
6. The scale of the compounding operation is commensurate with the established practice needs.
7. All other Animal Medicinal Drug Use Clarification Act requirements are met (see Box 45-2).

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will not normally consider regulatory action against veterinarians compounding certain antidotes from bulk sources if certain conditions are met, essentially the same as those listed in Boxes 45-2 and 45-5. CVM has listed chemical antidotes against which the FDA and CVM would presently not ordinarily object. These include ammonium molybdate, ammonium, tetrathiomolybdate, ferric ferrocyanide, methylene blue, picrotoxin, pilocarpine, sodium nitrite, sodium thiosulfate, and tannic acid.[6,14] This list should not be construed as containing the only drugs for which the FDA would extend regulatory discretion for compounding, and inquiries about additional compounds can directed to the FDA/CVM, Division of Compliance, at 301-827-1168. It is critical that veterinarians recognize that in toxicity cases, withdrawal periods will need to be established not only for the antidotes but also the toxicants. Some antidotes require substantially extended withdrawals, which may affect the decision to treat.[15] As a practical matter, toxicity cases are frequently resolved based on testing in state or federal laboratories. Because of these complexities, practitioners are advised to consult the diagnostic laboratories and/or FARAD when dealing with such cases in food animals.

FARAD: The Food Animal Residue Avoidance and Depletion Program

One of the regulatory requirements for legal ELDU is that the attending veterinarian recommends a scientifically based withdrawal interval recommendation before the producer can market the milk, meat, eggs, or other edible products. Commonly, the most efficient way for a food animal practitioner to meet these requirements is to consult FARAD. Veterinarians, producers, students, or regulatory personnel may obtain free consultation with specialists by contacting 1-888-US-FARAD or accessing the FARAD website at http://www.farad.org and submitting a request. Recommendations are made on a case-by-case basis depending on the individual variables of each exposure, changing tolerances or FDA withdrawal times and new information in the literature. FARAD also advises on pesticide exposure and accidental contaminations (biotoxins, heavy metals, radionuclides, unintended feeding of medicated feed).

FARAD maintains a database of all food animal products approved in the United States and more than 9000 pharmacokinetic citations describing depletion of more than 2000 chemicals in various species. FARAD collects, analyzes, and evaluates scientific data to provide withdrawal intervals when drugs are used in an extralabel manner. The FARAD website (http://www.farad.org) contains a database of approved food animal drugs searchable by drug, trade name, and species, known as Vetgram. A mobile version of Vetgram is also available on the FARAD website. Veterinarians may also find downloadable copies of published summary recommendations as well as a quick review of past recommendations there.

Published techniques for estimating a withdrawal interval (WDI) after ELDU in food animals are available.[16-18] Information that FARAD considers when estimating a WDI include:

1. General factors impacting pharmacokinetic parameters and drug residues such as conditions affecting drug absorption and elimination as well as dose, duration of treatment, and administration route.
2. Existence of an FDA-established withdrawal time. AMDUCA stipulates that a substantially extended withdrawal should be applied for any ELDU. Therefore, doses that are less than the labeled dose will still require a withdrawal that is longer than the labeled WDT.
3. Physiologic factors/compromised health conditions impacting pharmacokinetic parameters and drug elimination (e.g., dehydration, renal dysfunction, gastrointestinal disease).
4. Published pharmacokinetic parameters (i.e., time vs. concentration data, including drug residue serum, tissue, or milk data).
5. The existence of an established tolerance or maximum residue limit (MRL).
6. Analytical testing method and limits of detection.
7. Foreign drug approval data.

Testing for Drug Residues

If a practitioner or producer/owner wants to confirm that edible products (i.e., meat or milk) are at or below the tolerance, they can consider testing for drug residues. A number of commercial rapid tests exist for drug residue testing using a milk, serum, or urine matrix. Examples of some manufacturers of these tests include IDEXX Laboratories, Inc.; Charm Sciences; DSM Food Specialties; Neogen Corporation; and Silver Lake Research Corporation. Care should be taken to ensure that the test used detects residues to a level at or below the FDA-established tolerance to be certain that the food product is safe to enter the human food chain. Alternatively, samples or carcasses can be submitted to a commercial laboratory or state veterinary diagnostic laboratory for residue testing. For milk, processing plants may be willing to test.

Regulatory Monitoring of Drug Residues in Animal Products

Once products begin the process of entering the human food chain, they may undergo residue testing as part of the National Residue Program (NRP). The FSIS, the Environmental Protection Agency (EPA), and FDA cooperate to regulate animal drug residues, pesticides, environmental contaminants, and any other chemical hazards in meat or egg products. Every year, the sampling plan, known as the "Blue book," is released, which includes such details as the number of tissue or egg samples that will be tested and which chemical or drug residue it will be tested for. Results of the testing are also made publicly available on an annual basis in the "Red book."

Unchanged for many years, in July 2012, FSIS announced that scheduling of the NRP sampling plan will be changing.[19] Sample numbers per production class will be reduced because of the adoption of new analytical methods. Analysis for more chemical residues per sample will be possible, requiring fewer overall samples than in the past.

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Biosecurity and Infection Control for Large Animal Practices

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Infection control, biosecurity, biocontainment, and biosafety are essential functions at all health care operations, including veterinary practices.* All veterinarians, at some level, recognize and act to prevent adverse outcomes in patients. However, as major outbreaks of health care–associated infections (HCAI) at veterinary hospitals have become increasingly publicized,[1-12] it has become increasingly obvious that coordinated infection control practices are a critical component of delivering high-quality care at veterinary facilities, especially those with large caseloads and those that specialize in intensive care of patients. This threat is relevant to all veterinarians and all hospitals. A survey of veterinary referral hospitals at American Veterinary Medical Association (AVMA)–accredited institutions reported that 81% had recognized outbreaks of HCAI in patients within 5 years, and at least 45% had recognized more than one outbreak.[13] The two agents most commonly associated with these outbreaks were *Salmonella enterica* and methicillin-resistant *Staphylococcus aureus* (MRSA), but 12 other agents were also implicated. Fifty-eight percent of the 38 participating hospitals had to restrict admissions to protect patients and allow mitigation, and 12 of these hospitals (all were equine hospitals) were temporarily closed. Even with very limited surveillance, 51% of these same hospitals recognized significant HCAI and illness within 3 years of interviews. The agent most commonly implicated in human illnesses was *Cryptosporidium parvum*.

The standard of veterinary care is changing such that sporadic occurrences and outbreaks of HCAI may no longer be interpreted as unavoidable accidents if coordinated measures are not routinely used to minimize their likelihood. Our understanding about infection control issues in veterinary medicine has also advanced significantly during the past decade. As such, what may have passed as sufficient for infection control in veterinary practices 10 or 20 years ago may often not be sufficient today. It is also important to realize the important part that infection control and biosecurity must play in ambulatory practices and on our clients' premises. Inherently, healthy animals with lower contagious disease risks represent a smaller proportion of hospital populations than they do among populations in their home environments. However, veterinarians are obviously called upon to contact those animals most likely to be shedding contagious pathogens regardless of whether this is in hospitals or in the field. In addition, there are several examples in which patients discharged from hospitals were the likely source of viral and bacterial infections for animals in their home environments.[6,9] The magnitude of this potential hazard is perhaps best illustrated by the equine herpesvirus type 1 (EHV-1) outbreak, which occurred in association with the National Cutting Horse Association Western National Championship in Ogden, Utah, in May, 2011.[14,15] It is likely that exposure to a single horse that was shedding EHV-1 at this event resulted in over 165 horses developing clinical disease that was known or suspected to be caused by EHV-1, and at least 13 of these horses were euthanized. The outbreak spanned at least 10 western U.S. states and two Canadian provinces. Clearly the need to apply sound biosecurity and infection control practices extends well beyond the walls of veterinary hospitals.

However, it is also clear that these dramatic outbreaks are not the only circumstances in which HCAI affect patients. Lessons learned in human health care settings clearly show that endemic occurrence of HCAI typically creates a much greater overall burden in exacerbated morbidity and mortality than does the occurrence of epidemics. Unfortunately, there is insufficient information available from veterinary care settings to clearly say whether the same is true for animal patients, but there is no reason to believe that it would be different. Still, when studied systematically, the burden of disease associated with sporadic or endemic HCAI is substantial in veterinary patients. A recent publication of a multicenter study performed in five academic referral hospitals reported that nosocomial events monitored as seven different clinical syndromes were recognized during hospitalization in 19.7% (95% CI = 14.5% to 26.7%) of equine patients admitted for gastrointestinal disease at a rate of 3.9 events per 100 days of hospitalization (95% CI = 2.9 to 4.3 events per 100 hospitalization days).[16] Other studies reported in equine patients have principally focused on HCAI related to surgical site infections.[17,18] These rates are not dissimilar from rates reported for HCAI among humans in critical care settings. Thus, these notable outbreaks of HCAI and the emerging awareness of the importance of endemic occurrences should create an acute awareness that dramatically sharpens our focus on preventing all types of HCAI, including those that seem sporadic. Although the discussions in this chapter are mostly framed in the context of hospital settings, the concepts and issues apply much more broadly to ambulatory practices and animals' home premises.

*Throughout this chapter, the terms *infection control* and *biosecurity* are used interchangeably to encompass all practices related to the prevention of introduction and spread of infectious diseases in populations of animals or their human caregivers. Some authors differentiate activities by using the term *biosecurity* to specifically refer to issues related to disease introduction and differentiate this from *biocontainment,* which may focus more on control of the spread of agents after introduction. In addition, the term *biosafety* is sometimes used to specifically relate to matters pertaining to human health.

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How Much Is Enough? How Much Is Too Little?

Exposures to contagious disease threats, HCAI in patients, and zoonotic infections in care providers are undeniable risks in every veterinary practice. Because veterinarians have ethical and legal obligations to take reasonable protective actions to prevent their patients and employees from foreseeable harm associated with their actions (and inactions), it is clearly possible to not pay enough attention to infection control. The consensus opinion of veterinary infection control experts is that there is a recognizable standard of practice for infection control in veterinary medicine and appropriate effort must be given to the control and prevention of infectious disease transmission in all animal populations.[19] The implication that should be recognized is that it is possible to commit malpractice by not paying enough attention to infection control while caring for patients. There are key areas that must be addressed in all comprehensive infection control programs, including patient contact, hygiene, surveillance, communication, and education.[20] However, we cannot determine whether we are meeting an acceptable standard of care for infection control by listing the specific prevention strategies that are used, but rather we must evaluate the occurrence of HCAI in a veterinary practice along with how we respond to the identification of these HCAI. Few prevention practices for HCAI are universally considered applicable and efficacious for preventing HCAI in all settings. Rigorous attention to hand hygiene would meet these criteria, but many other common control methods such as the use of disinfectant footbaths or coveralls do not. Thus, it is not possible to judge whether a control program is sufficiently rigorous solely by evaluating procedures, protocols, and policies.

Recognition of the risks for legal liability undoubtedly give reason for pause, but a better motivation for emphasizing infection control practices should be to provide the best care possible within the scope of a practice's specialization. In order to create an environment where patient care can be optimized, it is incumbent upon veterinarians to actively manage the risk of HCAI in their patients. Achieving excellence in patient care and helping clients are undoubtedly among the highest priorities for all veterinary practices. However, the occurrence of HCAI in our patients is an ever-present hazard that interferes with our ability to deliver optimal patient care. Good infection control practices are not the only feature defining excellence in veterinary care, but it is impossible to achieve excellent patient care without appropriately controlling HCAI. The implications of suboptimal infection control may not always be readily apparent, but both sporadic/endemic infections and outbreaks can have a significant effect on patient morbidity, patient mortality, hospital economics, personnel health, personnel morale, and facility reputation. There are also liability implications for HCAI that occur in the absence of an appropriate infection control program.

Although HCAI are an undeniable hazard associated with caring for patients, and although it is possible to reduce the risk of infections through a variety of prevention strategies, it is important to note that not all HCAI are preventable using practical and cost-effective control programs. In reality, even impractical and cost-prohibitive programs would not eliminate HCAI, since there is an undefined but undeniably significant "nonpreventable" fraction of infections that will occur despite any infection control practices. To be most successful, it is important that over time administrators and personnel responsible for infection control programs strive to better understand and target prevention efforts at this preventable fraction of all HCAI.

Principles of Infection Control

In general, all comprehensive infection control programs center on four major goals:

- Decreasing the likelihood of exposure to infectious agents among patients and personnel
- Decreasing the intrinsic risks for HCAI
- Maximizing participation of personnel in infection control activities
- Optimizing the efficiency of infection control procedures and policies

These goals are achieved through five general areas of action:

- Decreasing direct and indirect patient contact
- Optimizing hygiene
- Using proven directed actions that decrease risks or are protective against HCAI, as well as actions that have a reasonable likelihood of efficacy based on biology, principles of pathogen transmission, and data from other species
- Recognizing high-risk patients and HCAI through efficient surveillance strategies
- Maximizing communication and education among all personnel

When initiating an infection control plan, it is important to take a global assessment of the contagious disease hazards in a practice, the level of risk aversion, and the resources that can be expended on infection control efforts. If a veterinary practice predominantly works in preventive health care under extensive field conditions, the contagious disease hazards may be less common and less severe than those encountered if a practice concentrates on intensive care of patients in a hospital. The specific disease hazards will also vary with the types of patients being managed (i.e., sick neonates vs. patients with acute GI disorders vs. reproduction cases, equine vs. bovine vs. camelid, etc.). Risk aversion is a concept that relates to how much a person or business is unwilling to accept or allow a negative event to occur. The inverse of risk aversion can be thought of as risk tolerance. The more risk averse a person is, the more it may be reasonable for him or her to initiate and maintain a rigorous infection control program. In contrast, a more risk-tolerant veterinarian may recognize the potential for contagious disease hazards in his or her practice but may not believe it is necessary to engage in preventive strategies that are seen as extreme. However, the risk tolerance of an individual or facility cannot be the sole deciding factor, since management decisions have impacts on patients and their owners, hospital personnel, and even animals and humans in the broader population. Thus, there is a baseline level of risk aversion that must be present. As our understanding of risks for HCAI methods for infection control advance, the bar is being raised, resulting in professional and legal risks should veterinarians fail to ensure that they are adequately pursuing infection control in their daily practices. The third component of this internal inventory is to assess the resources that will be available for infection control activities. The term *resources* in this context is intended to broadly encompass monetary resources, personnel time, and effort.

Keeping in mind this assessment of mindset and resources, the next step in developing an infection control program is to elaborate what the specific goals will be. For example, specified goals for an infection control program might include protection of hospital personnel and clients from exposure to zoonotic disease agents, creating an environment where patient care can be optimized by minimizing the risk of HCAI, optimizing education of personnel and clients regarding important infectious disease hazards, and protecting the operational capabilities of the practice. Using a comprehensive, systematic process for evaluation of disease hazards and design of control systems will then allow design of a logical control system that triages efforts to optimize efficiency. One systematic approach that the authors have used successfully is Hazard Analysis and Critical Control Points (HACCP) methodology.[21] After identifying which specific hazards (infections) are most likely to occur, as well as when and where in the systems these events might occur or be prevented, the next step is to define specific control measures. As mentioned previously, the majority of these prevention efforts are effective because they decrease the likelihood of exposing patients to infectious agents (i.e., by optimizing hygiene in the environment, personnel, or patients or by decreasing direct and indirect contact among patients). A few other prevention practices are effective because they reduce the inherent susceptibility to infection. To understand which control measures are of greatest importance and where efforts should be targeted, it is critical to consider the lifecycle and methods of

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transmission for the specific agents of concern. Among the questions that should be asked: Is the agent most likely transmitted through direct contact, or are respiratory aerosols or contaminated surfaces and fomites also important sources of exposure? Is there a subclinical carrier state associated with agent shedding or is shedding mostly restricted to clinically affected patients? Does the agent persist well in the environment and can common disinfection procedures readily inactivate organisms?

Each infectious disease may be considered individually in this evaluation process, but it is useful to remember that control measures that are effective against one agent are usually effective against others, particularly if they share common routes of transmission or have common risk factors in patients. Design of infection control programs should focus on practical actions for known problems, but it is important not to ignore the potential for newly recognized and re-emerging diseases. Infectious diseases continue to emerge internationally and many are of relevance to large animal veterinary medicine. The general strategy used in infection control protocols should be sufficiently rigorous to protect against most emerging issues, at least at a basic level. However, infection control programs should also be adequately fluid so that they can be modified to address new issues.

Another critical aspect in the practice of infection control is effective targeting of efforts. Taken to hypothetical extreme, the most rigorous infection control methods would prescribe that *every* patient be handled in complete isolation using barrier precautions verging on those used by "hazmat" personnel. Clearly this is not practical or needed in most situations, and yet, in a few rare circumstances this level of precaution can be warranted. In many more situations, some lesser level of precaution is warranted beyond that used in casual encounters with animals in their home environments. By their very nature, these extra control measures will inevitably inconvenience caregivers and clients in addition to increasing costs associated with care. These measures could also affect the quality of patient care and result in a corresponding *increase* in morbidity when taken to the extreme. The challenge is to target prevention efforts to just those patients that warrant increased concern and to use the most appropriate, albeit inconvenient, methods for controlling risks to personnel and other patients.

Another side effect of the inconvenience created by infection control efforts is that people by their very nature gravitate to the most convenient methods for daily activities. As such, the more personnel are inconvenienced through infection control efforts, the less likely they are to follow prescribed policies unless they understand and believe that procedures are needed and have value. Thus, a critical component of any effective infection control program is maximizing awareness of personnel and educating them about potential hazards and the value of established control measures. Presenting nightmarish worst-case scenarios without other objective information may be initially effective in getting people's attention, but continually using this approach as justification for infection control inevitably fails to truly motivate all or even most personnel. Establishing interactive communication regarding risks and concerns coupled with logical, objective, evidence-based presentations is clearly a better approach for convincing personnel of the need to fully participate in infection control efforts. However, this is also dependent upon engaging sufficiently in surveillance and investigation so that useful objective information will be available regarding the significance of specific disease risks in a practice.

Informed Consent and Implications for Infection Control

The principle of informed consent, as it applies to veterinarians caring for animals, implies that owners have the right to be provided with adequate information prior to treatment so that they can make appropriate decisions for their animals and themselves.[22,23] As professionals with specialized training, veterinarians can be assumed to have knowledge about the health and care of animals that goes beyond that which someone without this training will have. As such, one of the components that experts generally agree is part of the informed consent process is the disclosure of potential risks that may be associated with a veterinarian's management of his or her animals, particularly in situations in which there is greater than average risk for a particular adverse consequence.[24] As such, it is reasonable and prudent for veterinarians to routinely disclose the potential for HCAI as part of the informed consent process for all patients. This is especially true for patients with an enhanced risk of acquiring HCAI (e.g., because of required invasive procedures or because patients are immunocompromised). However, this same principle can be applied in consideration of the general risk to all patients. For example, if it is known or suspected that there is an increased risk of nosocomial infections for patients at a facility, then there is likely an ethical and legal obligation to disclose how this risk pertains to new patients *prior* to their admission. It is extremely prudent to document the informed consent process in writing with clients. Often, there is reluctance to do so based on concerns that it may deter clients, particularly when other facilities do not address the issue. However, the informed consent process can be an opportunity to educate clientele about risks (and thereby increase their overall understanding) and highlight measures taken by the facility to mitigate those risks.

Paying for Infection Control Activities

As mentioned previously, procedures used to decrease risks of HCAI inherently increase labor and material costs related to patient care. If these infection control activities are an essential part of delivering veterinary care, it is reasonable that these costs should be passed on to clients. It should not be expected that these costs should reduce profits or that they be paid by veterinarians or hospitals. Remembering that only a portion of HCAI is preventable, if veterinarians have met the expected standard of care for infection control, then it is also reasonable to assume that extra costs incurred for treating complications associated with HCAI are paid by the client. In addition, if HCAI are an expected risk related to care of any patient, veterinarians and hospitals should develop plans for management of financial issues related to these risks. It is also important to differentiate consideration for how charges might be presented to the client from how costs for infection control activities are assessed. These costs might be passed on to clients by directly accounting for each item, which is most reasonable when there are specific charges that can be attributed to a specific patient (e.g., increased nursing or materials costs associated with care of a specific patient in isolation). However, this is less applicable when costs relate to care and protection of more than one patient (e.g., costs related to cleaning and disinfection of the hospital environment). In these cases it may make more sense to compensate for costs by aggregating expenses into a general fee category related to infection control (such as a daily surcharge) or to include these costs in overhead costs that are compensated by general admission or hospitalization fees. In special circumstances, such as when it is necessary to investigate or mitigate against suspected outbreaks of infections, it is useful to have a contingency fund that has been accrued and earmarked to pay for unforeseen expenses such as mass testing or additional labor related to cleaning and disinfection. Administrators should ensure that the potential for infection control emergencies is considered and that fee schedules will allow for development of this type of reserve fund.

Environmental Hygiene

Much attention is paid to the possible role of the inanimate environment in HCAI of large animals. Contamination of the hospital environment by microorganisms is inevitable and entirely expected, and detection of microorganisms in a hospital environment does not, by itself, indicate anything of clinical relevance. A variety of factors are likely involved in the potential clinical relevance of contaminants, including the organism, numbers present, likelihood of contact with susceptible hosts, degree of susceptibility of potential hosts, environmental effects (temperature, ultraviolet exposure, humidity) and routine infection control protocols. Many microorganisms grow well on environmental surfaces, provided there is adequate moisture and

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organic debris, and may survive for very long periods. Even with relatively inhospitable conditions, many organisms persist for extended periods. If environmental pathogens are able to contact the appropriate body site of a susceptible individual in adequate numbers, disease could result. Environments where patients are housed or veterinary care is delivered can be expected to have greater numbers of environmental microorganisms than corresponding areas with lesser animal and human traffic.[25]

The relevance of environmental contamination is often difficult to determine. Even recovery of genetically indistinguishable organisms from the environment and from a patient does not confirm that exposure to an environmental reservoir was the source of infection since it can be difficult to distinguish cause versus effect. However, environmental contamination is of concern for both direct (e.g., oral inoculation from a reservoir of microorganisms in a stall) and indirect (e.g., transmission of an organism from an environmental reservoir to the hands of a care provider and then to an animal) transmission. Measures should be in used in all veterinary care environments to reduce the environmental pathogen load. This involves cleaning and disinfection of environmental sites.

Cleaning

Cleaning is defined as the removal of all visible debris[26] and is arguably the most important step in decontamination of animal environments. Even the best disinfectants will be minimally effective when used in the presence of moderate volumes of dirt and organic debris such as feces and bedding material. Dirt and debris hamper disinfection by inactivation of many chemicals, acting as a physical barrier between disinfectants and microorganisms and by providing a nutritional source for microorganisms. Not only does cleaning enhance efficacy of the disinfection process by providing optimal conditions for desired biochemical reactions, but cleaning can actually remove a majority of microorganisms so that fewer need to be killed by disinfectants. Therefore, removal of as much organic debris as possible is required for optimal disinfection. This involves manual labor, consisting of removal of all bedding and feces, and scrubbing of surfaces to remove adherent debris and biofilms. Detergents should be used to loosen organic debris, emulsify oils and fats, and remove biofilm. The disinfectant to be used must be considered when choosing a detergent because there can be interaction between chemicals in detergents and disinfectants.

Because of the effort required to clean and scrub stalls and other large areas, less labor-intensive methods are often sought. For example, cleaning with high-pressure (>120 psi) power washers is frequently used in barns and hospitals. There are theoretical advantages that seemingly justify use of high-pressure washers, especially when they are designed to dispense high-temperature water and steam. Although power washing can be quite helpful in removing organic debris, this process can also exacerbate infection control problems by aerosolizing and widely dispersing infectious agents. Further, used indiscriminately, they can even damage surfaces, which then impairs subsequent cleaning and facilitates survival of pathogens. The true risk related to the use of high-pressure washers is unclear. However, the convenience of using high-pressure systems must obviously be balanced with more intensive manual cleaning methods in order to minimize untoward consequences. Using high-pressure systems on surfaces with large amounts of gross contamination should clearly be avoided.[27] In areas likely to be contaminated with important contagious pathogens (e.g., isolation facilities), it is logical to use them minimally or at least only as a secondary cleaning process on surfaces that have been previously manually cleaned and disinfected.

Disinfection

Disinfection is the process of substantially reducing the burden of microbial contaminants on inanimate objects in order to reduce the likelihood of transmission of infectious agents. This should be contrasted with sterilization, which is the inactivation of all microbial agents on an object, and is typically only performed on materials used in invasive procedures. Disinfectants are biocidal chemicals that must be used at appropriate concentrations, allowing for adequate contact time in order to achieve the intended effect. Even with proper cleaning and selection of an appropriate disinfectant, disinfection errors can occur. It is also important to remember that microbial responses to disinfectant exposures are not uniform. There is tremendous variation in the ability of microorganisms to tolerate cleaning and disinfection. Most enveloped viruses are easy to eliminate whereas protozoal oocysts, nonenveloped viruses, and bacterial spores may be difficult or impossible to kill with surface disinfectants.[28]

For disinfection to be effective, a few key factors must be considered: the presence of organic debris, disinfectant concentration, temperature, and contact time. Organic debris inactivates disinfectants to varying degrees, emphasizing the need for careful cleaning. Most disinfectants are available as concentrates and must be diluted prior to use. Excessively dilute disinfectant solutions may have little or no effect, whereas excessively concentrated solutions can be dangerous to use in addition to being wasteful of resources. Dilution of disinfectants is an important process and must be performed by measurement, not estimation. One method to easily ensure that disinfectants are appropriately diluted is to use metered dispensing units that can be either wall mounted or attached to the end of a hose. For some disinfectants, different concentrations may be recommended for different situations. Test strips that can commonly be purchased from a variety of vendors can also be used to verify appropriate dilution and activity disinfectant solutions. This is especially important when stock solutions are prepared for use over time. Cleaning personnel must be informed of the importance of disinfectant dilution and trained in proper methods. Contact time is critical, particularly for certain disinfectants and difficult-to-kill microorganisms. If disinfectants are applied and immediately rinsed away, there is little chance that they can be effective. Most disinfectants require 10 to 30 minutes of contact time to provide maximal microbial reduction. Chemical reactions that produce disinfection are slowed in cold temperatures, which should be considered when determining the amount of contact time that is required. Disinfectants should never be combined because of the potential for inactivation and production of noxious or toxic gases.

Disinfectants

It is critical to be aware that all disinfectants do not have the same effectiveness. As with antimicrobial drugs, disinfectants have a spectrum of activity that can be highly variable between disinfectant classes (Table 46-1). Choosing the most appropriate disinfectant can be complex, involving a variety of factors including spectrum of activity, relative efficacy in the presence of organic debris, toxicity to animals and humans, potential damaging effects on certain surfaces, cost, and potential environmental effects. There is no standard disinfectant to be used in all situations in large animal facilities, although oxidizing agents such as accelerated hydrogen peroxide and peroxymonosulfate are increasing in popularity because of their broad spectrum of activity, acceptable performance in moderate amounts of organic material, relatively rapid action at room temperature, relative safety for personnel, and environmental friendliness. Other options may be appropriate in certain situations. When disinfectants with a narrower spectrum of activity are used as the primary disinfectant, protocols should be in place to use alternative products should certain situations be encountered that require a higher level of activity.

Effect of Surface Material on Cleaning and Disinfection

The material to be cleaned and disinfected can also have a tremendous impact on efficacy. Many surfaces found in large animal clinics and farms are not amenable to thorough cleaning and disinfection. These include unsealed wood surfaces, unsealed block, dirt flooring, and areas that are difficult to clean. For stalls, solid walls with a sealed surface are optimal for disinfection. This may be difficult to achieve; however, certain procedures can be performed to facilitate

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TABLE 46-1

Disinfectants Commonly Used in Veterinary Medicine*

Disinfectant	Activity in Organic Debris	Spectrum	Comments
Bleach (sodium hypochlorite)	Rapidly inactivated	Broad, including nonenveloped viruses and bacterial spores. No activity against *Cryptosporidium*.	• Used to disinfect clean environmental surfaces. • Sporicidal activity is particularly useful. • Efficacy decreases with increasing pH, with decreasing temperature, and in the presence of ammonia and nitrogen. • Varying concentrations can be used. 1:64 dilution of standard commercial (4% hypochlorite) bleach is most commonly used. Higher concentrations, up to 1:10, can be used but should be reserved for infrequent use in special situations. • Inactivated by cationic soaps/detergents and sunlight. • Chlorine gas can be produced when mixed with other chemicals. • Bleaches fabrics and is corrosive to concrete.
Quaternary ammonium	Moderate	Variable. In general, effective against gram-negative bacteria and enveloped viruses, variably effective against gram-positive bacteria, limited activity against enveloped viruses, and no activity against bacterial spores or *Cryptosporidium*.	• There are differences among different types of quaternary ammonium compounds. • Commonly used primary environmental disinfectant, although the spectrum is not necessarily optimal. • In general, low toxicity. • Inactivated by anionic detergents. • Some residual activity after drying. • Less effective in cold temperatures and low pH. • Stable in storage.
Phenols	Very good	Relatively broad spectrum, with limited activity against nonenveloped viruses and no activity against bacterial spores or *Cryptosporidium*.	• Main advantage is better activity in organic debris. • Can be irritating to skin and mucous membrane surfaces. • Reportedly toxic to cats and pigs. • Some residual activity after drying. • Noncorrosive.
Peroxygen/ accelerated hydrogen peroxide	Very good	Broad spectrum, including bacterial spores and nonenveloped viruses. Some activity against *Cryptosporidium*.	• Excellent choice for routine environmental disinfection, footbaths, and environmental fogging. • Rapid action makes them a good choice for footbaths. • Low toxicity except at high concentrations. • Environmentally friendly. • Can be corrosive to plain steel, iron, copper, brass bronze, vinyl, rubber, and concrete. • More expensive than most other disinfectant options.
Alcohols	Rapidly inactivated	Moderate to no activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Not appropriate for environmental disinfection. Can be used to disinfect certain medical and patient care items, but better options are available. • Flammable. • Minimally toxic. • Fast acting.
Chlorhexidine	Rapidly inactivated	Moderate. Limited activity against enveloped viruses. No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Not appropriate for environmental disinfection. • Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. • Minimally toxic. • Bactericidal activity on skin is more rapid than many other compounds, including iodophors. Residual effect on skin diminishes regrowth.
Povidone iodine	Rapidly inactivated	Moderate. Limited activity against enveloped viruses. No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Not appropriate for environmental disinfection. • Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. • Minimally toxic but some people can become sensitized to skin contact. • Appropriate dilution is important to maximize activity.

*It is critical to handle disinfectants and other chemicals using appropriate safety precautions. Refer to MSDS sheets for each product to obtain recommendations regarding appropriate handling and personal protective equipment that is recommended.

disinfection.[27] Cement block walls can be reasonably well sealed with at least two coats of good-quality enamel. Wood walls can be sealed using two or more coats of marine epoxy. Regular maintenance of stalls is required to seal defects that occur from kicks or chewing.

The optimal floor surface, in terms of cleaning and disinfection, is a smooth, solid, completely sealed surface. However, surfaces meeting these criteria are not all amenable to animal housing, so a compromise may be required. Finding the right balance of floor cushion, traction, durability, ease of cleaning, and cost is difficult. Regardless, certain key factors should be considered. The floor should be completely sealed so that water (and pathogens) cannot seep underneath, since this creates an obvious environmental reservoir and prevents adequate contact with disinfectants. Damaged stall matting has been cited as the likely environmental reservoir associated with serious outbreaks of HCAI.[1] If obtaining a seamless, water-impervious floor surface is not possible, floor coverings should be completely removable (i.e., rubber mats over sealed concrete floor) and must be removed regularly for disinfection. Dirt, sand, and other organic materials cannot be disinfected and are therefore unsuitable for permanent flooring in hospital stalls or other veterinary care

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facilities. If sand is required for care of orthopedic patients, plans should be made to completely remove and discard this material between every patient.

Animal Contact Items

For items that are used in patient care, disinfection processes are sometimes divided into three categories: high-, intermediate-, and low-level. High-level disinfection involves elimination of all viruses and vegetative bacteria but is not expected to inactivate bacterial spores, fungal spores, or protozoal oocysts. High-level disinfection is, in reality, difficult to attain and is uncommonly used. Intermediate disinfection involves eliminating all vegetative bacteria but not necessarily all viruses (especially nonenveloped viruses), spores, or oocysts. Low-level disinfection results in elimination of most but not all potentially pathogenic bacteria and enveloped viruses. Items requiring disinfection should be classified as to the level of disinfection required; Table 46-2 shows examples of these.

After use, all items in a patient's stall should be considered to be potentially contaminated with pathogens that the animal might be shedding. Thus, for patients suspected or known to have contagious diseases, every item in the stall should be treated as a source of infectious material and must be appropriately decontaminated or discarded. Many stall items may be difficult to disinfect, or it may not be possible to be confident in the ability to fully decontaminate them. If it is cost effective, disposal of these items is ideal. Otherwise, standard principles of cleaning and disinfection apply. It must be recognized that rough, damaged, and permeable surfaces may be very difficult to adequately disinfect. Particular attention should be paid to disinfection of surfaces that patients contact orally such as feeders and water bowls as well as surfaces likely to be contacted by hands of personnel. Appropriate decontamination of water bowls can be problematic. Ideally, the water supply should be turned off, and the bowl should be drained, cleaned, and applied with disinfectant for an appropriate time before the bowl is rinsed and the water is turned on again. Nets used to hold hay have a high likelihood of contamination and are difficult to disinfect without use of gas or plasma sterilization techniques. As such, their use should be avoided if possible.

Certain items may be at particular risk for contamination. For example, thermometers used on animals with salmonellosis are almost assuredly contaminated, and complete disinfection of digital thermometers is very difficult. It is reasonable to dedicate thermometers to individual patients and discard them when they are no longer required. An alternative is the use of disposable temperature strips, which are sometimes used in human medicine. These have not been specifically validated but are routinely used in some large animal hospitals.[29]

Twitches and muzzles have a high potential for contamination with pathogens such as *Streptococcus equi* and MRSA. Rope used for twitches is extremely difficult to disinfect, apart from removing the rope for autoclaving. Chain twitches are easier to disinfect, but many find them less desirable to use. The ideal twitch material is easy to disinfect, is atraumatic, and provides good grip on the nose. It is debatable whether the ideal material is available at this time. Twitches should be routinely disinfected, to the best of the ability considering the material. Consideration should be given to regularly changing or autoclaving rope used for twitches, and routinely decontaminating twitches with the understanding that complete disinfection may not be possible. Twitches used on animals that are known to harbor or are likely harboring nasal or upper respiratory tract pathogens should be considered contaminated and the material discarded or disinfected.

Few areas show a greater difference in approach to infection control between human and veterinary medicine than the handling of hypodermic needles after use. In human medicine, recapping of needles is strictly forbidden because of the potential for needlestick injuries and subsequent exposure to life-threatening bloodborne pathogens. In veterinary medicine, recapping of needles is very common and needlestick injuries are often not perceived to be a significant health threat to veterinary personnel. Currently, there are minimal risks to veterinary personnel in almost all situations regarding bloodborne transmission of infectious agents from large animals. However, infectious disease hazards clearly are continuing to emerge, and it is prudent to develop safe practices that minimize the potential for exposure to bloodborne pathogens that might be transmitted from domestic large animals. In addition, physical trauma from the needle and accidental inoculation of some vaccines (e.g., RB51 modified-live *Brucella abortus* vaccine), medications (e.g., hormones, cancer chemotherapeutic drugs), or bacteria can lead to serious outcomes.

TABLE 46-2

Examples of Items Requiring Different Levels of Disinfection

Level of Disinfection	Example Items
High level	Endotracheal tubes
	Tonometer tips
	Cystoscope
Intermediate level	Dental equipment
	Endoscopes
	Thermometers used on multiple patients
	Vaginal specula
Low level	Thermometers used on individual patients
	Feeding instruments
	Muzzles
	Nasogastric tubes
	Oral specula
	Stethoscopes

Hand Hygiene

Rigorous use of hand-hygiene procedures is one of the oldest recognized infection control measures, and it is perhaps the single most important infection control practice. Unfortunately, extremely poor compliance with best practices in human and veterinary hospitals as well as in the community negates much of the potential benefit. CDC guidelines suggest that health care workers in human hospitals should wash hands or use hand-sanitizing products before and after every contact with patients, as well as prior to eating, and after using the restroom. It is hard to argue that less stringent procedures are warranted in veterinary hospitals.

There are numerous indications for hand-hygiene procedures in health care settings that have been identified as part of guidelines for human medicine. As evidenced by Box 46-1, hand hygiene is needed frequently in a clinical situation, something that may be problematic in typical settings where veterinary care is provided to large animals. Maintaining optimal hand hygiene can be especially important for ambulatory clinicians and yet can also be particularly difficult to achieve because of logistical difficulties. A variety of options exist for decontaminating hands. The most common practices are hand-washing and use of waterless hand-sanitizing solutions. Both are acceptable methods in most situations, and each has individual benefits and drawbacks.

Hand-Washing

Washing with antibacterial soap has been standard method of decontaminating hands of health care workers for over a century. However, the potential benefits of this practice generally are never realized because of failure to use appropriate methods or failure to wash hands at all.[30,31] Common errors in hand-washing include inadequate duration of hand-washing, failure to use soap, use of contaminated items to dry hands, and contamination of hands immediately following hand-washing (i.e., through contact with contaminated faucets, door handles, etc.). An appropriate technique for hand-washing is outlined in Box 46-2.

The importance of the type of soap used in hand-washing is also often overlooked. Plain soaps, those without antibacterial agents,

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BOX 46-1

Indications for Hand Hygiene in Medical Practice

- When hands are visibly dirty or contaminated with proteinaceous material, blood, or other body fluids.
- Before direct contact with patients.
- Before donning sterile gloves for invasive procedures (e.g., suturing wounds).
- Before inserting an indwelling urinary catheter, peripheral vascular catheter, or other invasive device that does not require a surgical procedure.
- After contact with a patient's intact skin.
- After contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings.
- After contact with an inanimate object in the immediate vicinity of a patient.
- After removing gloves.
- Before eating and after using a restroom.

Adapted from Centers for Disease Control and Prevention. 2002. Guideline for Hand Hygiene in Health-Care Settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR 51(No. RR-16). [WWW page]. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf, accessed Apr 25, 2013.

BOX 46-2

A Recommended Technique for Hand-Washing

- Wet hands first with water and then apply an appropriate amount of disinfectant soap (as recommended by the manufacturer).
- Vigorously rub hands together for *at least* 15 seconds, covering all surfaces of the hands and fingers. Make sure to scrub fingertips and clean under fingernails.
- Rinse hands with water and dry thoroughly with a disposable paper towel. Multiple-use towels of any type are not recommended.
- Use towel to turn off the faucet (and open doors when exiting a restroom).
- Avoid using hot water because repeated exposure to hot water may increase the risk of dermatitis.

Adapted from Centers for Disease Control and Prevention. 2002. Guideline for Hand Hygiene in Health-Care Settings: Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. MMWR 51(No. RR-16). [WWW page]. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf, accessed Apr 25, 2013.

have minimal direct antibacterial activity. The main benefit of these is assistance with removal of dirt and organic debris, although efficacy data are conflicting. The use of plain soap can slightly decrease bacterial numbers on hands, but studies in human medicine have failed to demonstrate effective removal of significant pathogens from the hands of hospital personnel.[32] Also, the routine use of plain soap can at times be associated with *increases* in numbers of bacteria carried on hands if use of these products results in skin damage and irritation through drying.[33] Plain soaps are therefore not an optimal choice for routine use in medical settings, but use is certainly preferable to not washing hands in the absence of suitable alternatives (such as in field settings).

Most soaps used in hospital settings contain biocides such as triclosan or chlorhexidine. Both of these can produce greater decreases in skin contamination compared with plain soap, and both compounds have antibacterial effects that may persist after application, although the duration of activity is shorter against gram-negative organisms (especially *Pseudomonas* spp.).[31] Iodine and iodophors have been used as skin disinfectants and have a broader antibacterial spectrum. However, both (particularly iodine) can be irritating to skin and are less commonly used for routine hand-washing and skin disinfection in medical personnel. In addition, some people become sensitized to skin contact with these products.

Compliance with hand-washing protocols is often poor for a variety of reasons. The time required is a major factor, particularly in situations in which contact with a large number of patients is likely. Although hand-washing requires less than a minute to complete, if it is indicated 100 times in a day, this represents a significant amount of time cumulatively committed to this activity. Lack of convenient access to proper hand-washing facilities is also frequently a problem. If access to sinks with running water, soap, and disposable towels is not convenient (i.e., not adjacent to where animal contacts occur), it is less likely that hand-washing protocols will be rigorously followed. Regardless of the type of soap used, frequent hand-washing leads to skin irritation and damage, which compounds compliance problems by making people reluctant to wash their hands, and skin damage associated with hand-washing increases potential for colonization or transient carriage of potential pathogens.[33-36]

Nail care and jewelry can also be significant impediments to achieving optimal levels of hand hygiene.[37] Colonization with higher bacterial numbers, colonization with bacterial pathogens, and outbreaks of infectious disease have been reported in human hospitals in association with effects related to long fingernails and artificial nails.[38] Studies have shown that these hamper effective hand disinfection, and many health care facilities, particularly intensive care units, prohibit their staff from having long (¼ inch or longer) or artificial nails. The role of these factors in risks to patients in veterinary settings is unclear, but some veterinary facilities have developed similar protocols and restrictions.

Waterless Hand Sanitizers

For many years, waterless hand sanitizers have been described as an alternative to hand-washing, but in the past decade, expert opinion and evidence supporting use has evolved to where use of these products is often the primary method for hand-sanitizing in health care settings. These products are effective, inexpensive, easy to use, and easier to make widely available throughout health care settings than are hand-washing stations. Most waterless hand sanitizers use varying concentrations of alcohol (isopropanol, ethanol, n-propanol, or a combination), although a few products contain alcohol plus biocides, or biocides (e.g., triclosan and benzalkonium chloride) alone. Alcohol products are most commonly available, with concentrations ranging from 60% to 95%. Most products are available as gels or liquids, but newer products are dispensed as foams, which may increase acceptability of products. Products with alcohol concentrations greater than 95% are less effective because the presence of water is important for the bactericidal activity. Alcohols have excellent effect against gram-positive and gram-negative bacteria, but not bacterial spores or protozoal oocysts.[30,31] Antiviral effects are variable, with less reliable effects against nonenveloped viruses. Alcohol-based products have been shown to have good effect on reduction of hand contamination of health care workers and have been shown to be more effective than standard hand-washing.[39] Frequent contact with alcohol can lead to significant drying of skin, so most commercial products contain emollients, humectants, or similar skin-conditioning agents. Alcohol-impregnated towelettes are also commercially available but contain a small volume of alcohol and are no more effective for hand decontamination than washing with plain soap.[40]

One concern that is sometimes expressed about waterless hand sanitizers is their activity in the presence of organic debris. This is a particular concern in large animal practice, where the likelihood of gross contamination is high and access to hand-washing facilities is sometimes limited. However, a study of the efficacy of hand sanitizers on hand disinfection after performing physical examinations in horses reported that both alcohol and alcohol/chlorhexidine hand sanitizers were more effective for decreasing bacterial contamination than washing hands for 15 seconds with antibacterial soap.[41] This level of disinfection was noted even though the culture fluid collected off the hands was visibly dirty, indicating that there was a reasonable amount of gross contamination. Thus, waterless hand sanitizers are likely to be effective under normal large animal practice situations. When there is readily apparent contamination of the skin, however, debulking of the hands is probably required for optimal effect. It is important to remember that alcohol-containing products are

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flammable. Although very rare, fires have been associated with exposure to open flame. Common sense and ensuring that hands are rubbed together until all the alcohol has evaporated should greatly minimize any risks.

While most available products contain only alcohol as a sanitizing agent (in addition to humectants or emollients), some commercial products contain alcohol plus other biocides such as chlorhexidine. Some of these products have sufficient efficacy such that they are widely used for presurgical hand disinfection. The main advantage of using this combination of products is the residual antibacterial effect that the chlorhexidine confers. Some users complain of a sticky feel to the skin, which is one of the reasons that this combination is less commonly used for routine situations.

One of the main advantages of waterless hand sanitizers is their portability. Although it is difficult to make the water sources needed for hand-washing portable or always accessible, these products can be easily placed in ambulatory vehicles, can be carried by individual staff, and can easily be placed throughout hospitals. As such, there is a greater likelihood of obtaining compliance by facilitating access. Unfortunately, regardless of the types of products used, compliance with hand hygiene is often a major problem.[42,43] Infection control programs need to address hand-hygiene compliance through a variety of means to increase use of this critical infection control tool.

Surgical Hand Antisepsis

Scrubbing of the hands and forearms with disinfectant solutions has been a standard practice prior to surgery, but in the past decade use of scrubless or brushless protocols for hand antisepsis has become increasingly common. Recommended techniques for presurgical scrubbing vary somewhat but typically involve a systematic 2- or 3-minute scrub of all hand and forearm surfaces.[44] Other studies have demonstrated that a two-step approach, using a 1- to 2-minute surgical scrub followed by application of an alcohol-based hand sanitizer is as effective as a 5-minute surgical scrub.[45] One concern with repeated surgical scrubbing is the potential for skin irritation and subsequent increases in bacterial contamination. This has led to increasing use of brushless techniques, especially with the use of waterless hand sanitizer containing 1% chlorhexidine gluconate and 61% ethanol, which has been shown to be equal or superior to brush application of 4% chlorhexidine soap.[46] There may be some concern about the sole use of brushless techniques in situations in which there may be moderate debris contamination as could be encountered in veterinary applications. A variety of hybrid techniques have been recommended, including performing a thorough hand wash with soap or full surgical scrub at the beginning of the day followed by application of a waterless hand sanitizer product as the sole hand antisepsis technique for subsequent procedures. The main advantage of these may be elimination of alcohol-resistant bacterial spores.[47] One factor to consider, however, is that alcohol products may work better on dry hands, so hands should be allowed to thoroughly dry if hands are washed prior to application of an alcohol hand sanitizer.[47]

Barrier Protocols and Protective Attire

Barrier nursing techniques are an important infection control tool. The basic premise for their use is that placing some type of barrier between caregivers and patients prevents skin or clothing from being contaminated, whereas the contaminated outer barrier item can be discarded or left in the contaminated environment. Prevention of contamination of personnel's skin, regular clothing, personal items, and medical instruments can substantially reduce the risk of transmission of pathogens between animals, contamination of the general environment, and zoonotic transmission.

Use of Barrier Precautions

Basic barrier techniques should be used in all veterinary hospitals. Standardized, clean protective outwear should be worn over hospital-dedicated attire for any patient contact, regardless of the anticipated nature of contact or the assumed infectious disease status of the patient. The need for other barrier items varies with circumstances and is often dictated by the type of disease syndrome being managed (e.g., diarrhea or gastrointestinal disease, respiratory disease, wound infection, fever of unknown origin) as opposed to documentation of specific infections or diseases. Other factors that might indicate a need for additional barriers include farm of origin (e.g., farms with endemic *S. equi* or rotavirus infections) or a patient that is considered to have an increased risk of infection (e.g., compromised neonates). Gloves, gowns, and overboots are the most commonly used items for additional barrier protection, but masks, caps, and eye protection may also be required at times. In some facilities, overboots are not used in all areas, but personnel are required to wear footwear that can be readily disinfected. Disinfection of this footwear is required after exiting potentially contaminated areas.

Limitations to Barrier Precautions

The greatest limiting factors associated with use of barrier precautions in infection control are poor compliance and improper use. Written protocols should be developed that document practical use protocols for barrier precautions. These should specifically state when additional barriers are required; it is not possible to achieve consistent results if protocols are ambiguous or suggest too much discretionary interpretation. In addition, it is critical to educate personnel regarding the need for barrier nursing precautions and on proper application. Many human hospitals require physicians and nursing staff to undergo practical training in proper use of barrier precautions to avoid inadvertent spread of contaminants, and this type of active training may help to ensure uniform understanding and application of protocols. It is also important to regularly monitor compliance with protocols.

Protective Outerwear

Standard protective outerwear for large animal veterinary personnel should include clean coveralls, lab coats, scrubs, or other dedicated clothing (hospital uniforms). Protective outerwear should be worn for every animal contact and should be changed regularly. This includes any time outerwear becomes visibly soiled or otherwise contaminated with body fluids perceived or known to be contaminated with potential pathogens (e.g., feces, blood, nasal exudates, urine, or uterine fluid). In addition, outerwear should be changed frequently (at least daily) because gross contamination does not need to be present for pathogen contamination to have occurred. Hospital personnel should change their hospital outerwear before leaving the building to decrease the risk of transfer of infectious agents from the hospital to the community. In order to facilitate this control measure, it is optimal from an infection control perspective for veterinary practices to provide laundry services or laundry facilities. Clothing that is potentially contaminated with biohazardous material should be handled appropriately so that personnel handling laundry are aware of the hazards and how to reduce risks for exposure.

Gloves

Gloves are an important component of barrier precautions if used properly. The Centers for Disease Control and Prevention (CDC) recommends glove use by health care workers to reduce the risk of transmission of infections from patients to personnel, to prevent health care workers' skin flora from being transmitted to patients, and to reduce transient contamination of the skin on hands of personnel by microorganisms that can be transmitted from one patient to another.[48] The same concepts apply to veterinary medicine. In certain situations, glove use has been shown to be an effective means of reducing pathogen transmission in human medicine.[49] However, incorrect use can negate these effects or even be harmful. Common errors with glove use include failing to wear gloves when needed, not changing gloves after contact with infectious items, touching items (e.g., pagers, cell phones, pens, medical supplies) while wearing contaminated gloves, contamination of hands or clothing while

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removing gloves, and failing to wash hands after glove removal.[50] Although gloves are used to prevent contamination of hands, the potential for inadvertent contamination through micro-breaks in the glove surface or contamination during glove removal necessitates use of hand-washing or application of hand-sanitizing solutions in conjunction with their use.[48]

There are no widely accepted standards in veterinary medicine for when gloves must be used, apart from the use of sterile gloves during surgical procedures. Examination gloves that are clean but not sterile are often used when handling wounds or infected body sites, and for contact with animals known or suspected to be shedding contagious pathogens. Despite relatively widespread use of examination gloves in a variety of circumstances in veterinary medicine, it is quite unusual for practices to have formal protocols regarding how and when they should be used.

Gowns

Although protective gowns have traditionally been used during surgery, their use as a barrier garment when contacting high-risk patients is increasing in both human and veterinary medicine. The CDC has produced guidelines for human medicine stating that "gowns should be worn by personnel during the care of patients infected with epidemiologically important microorganisms to reduce the opportunity for transmission of pathogens from patients or items in their environment to other patients or environments."[48] In general, gowns should be worn whenever direct or indirect contact with patients or their environment may result in contamination of caregivers' clothing or skin that facilitates transmission of pathogens.

The ideal barrier gown would cover all areas of the body that might become contaminated, prevent penetration of liquids, would be of adequate strength to resist tearing and puncture under normal activities, would be comfortable to wear for long periods, would be available in appropriate sizes for all personnel, would be easy to put on and remove without contamination of regular attire, would be nonabrasive to skin, would be unlikely to startle patients, and would be of acceptable cost. Unfortunately, a product with all of these characteristics does not currently exist, and facilities must prioritize the relative importance of different gown properties. This is often difficult because neither the overall effectiveness of gowning nor the effectiveness of different gowns in veterinary situations has been adequately evaluated. The problem most likely to be encountered with barrier gowns in veterinary practice is poor resistance to liquids, especially under direct contact or pressure. In large animal practice, there is a greater likelihood of contact with relatively large volumes of fluids (e.g., with diarrheic animals) or direct contact with patient surfaces that would have moist secretions or excretions (e.g., animals with nasal discharge or large infected wounds). The types of anticipated activities may also have an impact on the required size of gown. Gowns that do not completely cover the legs and feet may be useful in some circumstances but ineffective in situations with prolonged direct contact such as with assisted neonatal nursing.

In human medicine, there are conflicting data regarding the efficacy of gowning for prevention of hospital-associated infections.[49,50] Gowns may be more effective for reducing infection of personnel. It is possible that the most significant advantage in some situations is not the protective effect of gowns or other protective outerwear, but rather the raised awareness of the potentially infectious nature of the patient, which may in turn encourage concurrent application of other important infection control practices.

Eye and Face Protection

The use of protective eyewear, including goggles and face shields, is common in human medicine during procedures that generate aerosols or airborne droplets of blood, body fluids, and secretions.[51] Use of these items is mandated in some instances by the health and safety regulations, but they are not widely used in clinical settings in veterinary medicine.[52] Face shields have the advantage that they decrease the potential for facial mucous membrane exposures in addition to ocular exposures. Inexpensive disposable face shields are commonly available and are generally quite comfortable for people with varying face shapes and sizes, and thus would seem to have great potential for use in all large animal practices. Despite the current low prevalence of bloodborne zoonotic pathogens in large animal species, it would be prudent to consider the use of some type of eye protection whenever generation of small particulates or aerosols of liquids or secretions is likely to occur, including when motorized equipment is being used for dental procedures, foot trimming, or orthopedic surgery. Situations in which eye protection should be seriously considered include examination of animals with suspected viral encephalitides. Although not studied, face protection may also help protect against zoonotic disease involving fecal-oral transmission, such as *Cryptosporidium parvum,* which has an extremely small infectious dose.

Respiratory Protection

Masks and respirators are often used to reduce the risk of respiratory and oral exposures to infectious agents, to reduce the risk of contamination of patient sites with organisms from personnel, and in some situations to prevent contamination of hands with nasal or oral microflora. Standard surgical masks may be effective against the spread of large particle droplets that are transmitted by close contact and travel only short distances (up to 3 ft) from infected patients.[53] However, the overall effectiveness of surgical masks in hospital situations has recently been questioned.[54]

Airborne transmission of zoonotic pathogens is commonly thought to be of minimal concern in most veterinary settings, and mask use is uncommon in veterinary hospitals apart from use during surgical procedures. The actual reduction in zoonotic disease risk that might be associated with the use of surgical masks during routine patient contact is unclear. However, increased awareness of risks of specific zoonotic diseases and infections in immunocompromised personnel and others with special disease risks has prompted reconsideration of recommendations regarding personal protective equipment in some circumstances. For example, although airborne transmission is not considered an important route of exposure for MRSA, the hospital personnel primarily become colonized in the nasal passages and hand-to-nose contact is frequent. Thus, mask use might prevent direct contact of hand and nose, thereby decreasing hand contamination or decreasing the risk of inoculation of the nose following contamination of the hands during animal contact. Mask use might be particularly important for prevention of MRSA exposure when working in barns containing many MRSA-positive animals and high dust burdens. This is most relevant for swine veterinarians but could include clinicians entering veal calf units in some regions. Masks capable of filtering non-oily particulate aerosols with 95% capability (N95 masks) are recommended in human medicine for dealing with airborne contagions such as the severe acute respiratory syndrome (SARS) coronavirus. Although there is currently little indication that these masks are routinely required in large animal practice, it may be reasonable to expect facilities to at least have a plan in place to implement N95 masks if required. A critical aspect of the use of N95 masks is fit-testing and training in their use, since improperly fitted or used masks may confer little or no benefit over surgical masks.

Animal Movement and Housing

Housing and movement can have a profound effect on the likelihood of exposure of patients to pathogens. Ideal facilities have no contact between inpatients and outpatients, allow for grouping and segregation of animals with different risks for contagious diseases, prevent direct contact with adjacent animals, reduce the potential for indirect exposures through contact with contaminated environments, and have adequate space so that there is time to properly disinfect all housing and handling environments between use with different animals. This, of course, is completely dependent upon early recognition and effective management of patients with higher risks of transmitting contagious diseases.

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One major problem frequently encountered in large animal facilities, particularly older facilities, is that construction and design factors often hinder infection control activities. Infection control issues were often not given high priority when designing many older facilities, so a variety of problems are often encountered. These include patient traffic flow problems, requisite mixing of inpatients and outpatients, inability to segregate different cohorts in the population, heavy traffic around important areas (e.g., surgery, isolation), inadequate stall numbers, inadequate isolation facilities, poor ventilation, improper drainage, use of materials that are difficult to clean and disinfect, design issues that hinder adequate cleaning and disinfection, etc. There are a variety of challenges with designing an optimal facility. Many measures used to enhance infection control are inherently inconvenient, and designs that optimize infection control often have a significant impact on building costs and efficient use of the facility. It can be difficult to reconcile ease of operation with the level of infectious disease risk that is desired. However, development and rigorous use of sound infection control protocols can overcome most deficits in design and construction to achieve an acceptable practice standard for minimizing HCAI.

Outpatient Areas

In general, outpatients tend to have a lower contagious disease risk, both in terms of likelihood of shedding infectious agents as well as in their susceptibility to infectious disease. However, "lower" risk does not mean "no" risk, and it is important to design holding areas that minimize contact with other animals while clinicians obtain histories and initial examinations to more clearly categorize patients relative to their contagious disease risk. Ideally, outpatients should have little or no contact with inpatient animals and minimal contact with areas visited by inpatients. However, this is often not entirely possible. For example, it is often impractical to build completely separate areas for diagnostic imaging of inpatients and outpatients. However, the general principle of separation of inpatients from outpatients should be adhered to as much as possible.

Holding stalls in admission and outpatient examination areas may need to house a large number of animals every day. As such, it is important that a sufficient number are available to allow appropriate cleaning between use, that there are established mechanisms to allow admitting clinicians to identify high-risk cases, and that this information is promptly conveyed to relevant personnel so extra precautions can be taken with that patient and the environment with which it has been in contact. Environmental precautions may range from routine cleaning and disinfection to restricting use pending high-level cleaning and disinfection, stall cultures, or patient cultures.

Inpatient Areas

Inpatients pose greater challenges than outpatients because they often have significant risk factors for infectious disease acquisition such as co-morbidity, dietary changes, antimicrobial treatment, disruption of natural defense mechanisms, surgery, and placement of invasive devices. Compromised inpatients, particularly certain patient groups (e.g., those with gastrointestinal disease), may be more likely to shed infectious agents such as *Salmonella enterica*. Thus, infection control protocols should emphasize the need to reduce the risk of transmission of infectious agents from inpatients to other hospitalized animals and hospital personnel, and to minimize risks related to contamination of the hospital environment. A variety of methods can be used to manage this risk, which needs to be balanced with levels of risk aversion and available resources to support infection control efforts.

One method of reducing the risk of disease transmission between individuals and groups (i.e., between animals in different wards or those assigned to different services) is to assign animals to different cohorts and then create physical and procedural separation among the different groups. It is important to group animals based upon known or suspected infectious disease status or infectious disease susceptibility, as well as group and separate animals with different disease syndromes (e.g., respiratory disease or gastrointestinal disease). It is also logical to group and segregate animals that are managed by different clinical services in order to decrease the probability of transmitting infectious agents through indirect contact and increase the ability to contain a cluster of infections related to one clinical service. Examples might include segregation of patients managed by surgery and medicine services to help reduce risks for transmission of different contagious agents, or managing cattle separately from other large animal patients (especially horses) to reduce risks for *Salmonella* transmission. In general, managing inpatients as smaller cohorts helps contain transmission risk, thereby decreasing the likelihood of a widespread outbreak in the entire patient population. Creating smaller cohorts of patients with different risks for contagious disease also facilitates the use of varying levels of infection control precautions for different groups.

The design of some facilities does not allow for the separation of different cohorts in different buildings or wards. When physical separation of inpatient groups (excluding isolation cases) is impossible or impractical, animals with different disease risks can still be managed differently in a common ward system. One approach is to designate areas within large wards for different cohorts. Another is to identify animals in different risk categories, applying different levels of infection control precautions, but to allow interspersing of animals from different risk categories in the same area. This is similar to the approach for patient isolation that is used in most human hospitals, but it is only effective for diseases that are not transmitted by aerosols (i.e., it is not generally effective for contagious respiratory diseases such as influenza or EHV) and where there is a reasonable ability to prevent direct (e.g., nose-to-nose contact over stall walls) or indirect (e.g., cross-contamination from stall cleaning supplies) transmission. Physical separation within a ward can be enhanced by use of chain or rope barricades to identify and minimize access to patients with elevated contagious disease risk status. A key for successful infection control using this type of system is the absolute need for prominent identification of different groups, having defined protocols for each group, and maintaining effective communication about disease status of these patients. One system that has been used is color labels to indicate infection control status. For example, colored adhesive dots can be placed on stalls or stall cards of all patients; red dots might indicate animals with a known highly contagious disease, yellow dots might indicate that animals are suspected of having an infectious disease or may have increased risk of acquiring infectious disease, and green dots might indicate that animals are considered to have an average or low risk of carrying or acquiring contagious disease agents. This type of system is easy to apply and easy to understand. In addition, more prominent signs can be used to more clearly indicate certain concerns (e.g., *Salmonella,* MRSA, rabies suspect) to all personnel. One consideration with these more specific labels, however, is whether visitors could obtain confidential and sometimes prejudicial information from visible notices.

Isolation of Highest Risk Patients

The most rigorous control of contagious disease hazards requires that transmission potential be absolutely minimized for patients suspected or known to be infected with highly contagious pathogens or pathogens associated with highly consequential diseases. In general, this means that these patients should have no direct or indirect contact with other animals or areas used in routine care of patients via personnel, fomites, aerosols, or other materials. It also means that human access to these patients and their care environment should be tightly controlled. In general, in order to achieve this level of isolation, these patients will require housing in a separate, specially designed unit.

Most isolation protocols in large animal medicine focus on a limited number of pathogens. Protocols for large animal facilities tend to focus heavily on animals clinically affected by *Salmonella enterica,* viral respiratory pathogens, and *S. equi,* and more recently on horses with neurologic disease because of the risks related to EHV-1. Whether these protocols are adequate, or excessive, for

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control of other pathogens is debatable and a broader scope is likely required in many facilities. That said, protocols that reduce the risk of transmission of one agent generally reduce the transmission potential of other agents, particularly if there are similarities regarding transmission routes or risk factors for exposure and infection.

Large animal isolation protocols need to consider a variety of issues, including indicators for isolation, cleaning and disinfection protocols, protocols regarding personnel movement and barrier precautions, protocols for patient contact and movement, manure disposal, and supply stocking. Defining methods for identifying animals that need to be isolated and establishing specific criteria for handling these animals are critical steps, and these methods must be properly communicated to all individuals associated with patient or facility care. Developing protocols for rapid identification of patients that represent a contagious disease hazard is critical to the success of any infection control program. The best isolation units are not effective if unoccupied. Specific disease and syndromic criteria for isolation should be developed to facilitate prompt isolation of appropriate individuals, typically in advance of confirmation of the presence of an infectious agent. Isolated animals should be physically separate from the rest of the hospital population at all times if at all possible. This means that isolation units should be designed so that animals will rarely if ever have to leave the unit except for those that need an emergency procedure such as surgery. Stocks, examination areas, and scales should be available. A major deficiency of many large animal isolation facilities that is recently being recognized because of concerns regarding herpesvirus myeloencephalitis resulting from EHV-1 infections is the inability to use mechanical hoists and slings to safely manage recumbent, profoundly ataxic patients. Ideally, there should be minimal contact of personnel with isolated animals and their stall environment. The ability to monitor patients in isolation using viewing windows or by remote electronic means (e.g., web cameras, closed circuit video) facilitates the ability to deliver excellent patient care while minimizing risks associated with direct contact.

These units must be strictly managed with specific predetermined protocols in order to reliably manage the risk of transmission. Isolation protocols should be comprehensive and clearly documented in writing. Proper training of all staff, particularly lay staff that may have no background in infectious diseases and infection control, is critical. Standardized protocols for management of isolation units in human health care settings have been published by the CDC.[53] However, similarly standardized guidelines have not been established for veterinary medicine, and protocols used at veterinary facilities are highly variable because they are tailored to specific operations and different facility and logistical resources. It is logical for veterinary facilities to consider guidelines that have been developed at other veterinary facilities and from human health care settings when developing their own isolation protocols.

In some situations, housing of potentially infectious animals in an isolation unit is not possible because of patient care issues or limitations in isolation space. As a result, consideration needs to be given to management of higher-risk patients within the general hospital environment. This can be done in a few different ways, including grouping of general risk groups and application of intermediate isolation techniques to cases that are considered at higher risk of being infectious but not deemed candidates for housing in an isolation unit. In-hospital isolation protocols allow for an increased level of protection but are not a replacement for a proper isolation unit and should not be used solely for clinician convenience. Protocols should be developed regarding the handling of animals, the stall, and the area around the stall. Animals that are isolated in the hospital should not leave stalls unless they are being moved for required procedures. If movement is necessary, feet should be cleaned and disinfected using appropriately diluted chlorhexidine solutions. The potential for environmental contamination can be reduced by having a person follow the animal with a bucket to collect any feces that may be passed during transit. Traffic areas should be promptly cleaned and disinfected. Protective barrier clothing such as full waterproof coveralls or full-length waterproof gown, gloves, and dedicated footwear or boot covers should be worn for any contact with the patient or its environment. The area around the stall entrance should be considered potentially contaminated and disinfected routinely (at least three to four times per day). Disinfectant footbaths or footmats used at stall doors can reduce bacterial contamination of footwear.[55,56] Attention should be paid to the pattern of water drainage from the stall and in the area. If water runs from the stall to the breezeway, or runs down the breezeway past the stall, then housing of potentially or known infectious animals in the stall may be inappropriate. Animals should not be allowed contact with neighboring animals. Barriers may be required if solid walls are not present on all sides. Specific protocols should be developed for cleaning in-hospital isolation stalls. These stalls should be cleaned last, personnel cleaning stalls must wear protective gear, and items used to clean the stall must be disinfected immediately after use.

Isolation guidelines for human medicine target the prevention of five different types of transmission: contact transmission, droplet transmission, airborne transmission, common vehicle transmission, and vectorborne transmission.[48-53]

- Contact transmission is typically the most important mode of transmission and involves transmission of infectious agents to patients by caregivers or directly between patients. In large animal medicine, this could include situations such as transfer of MRSA from a colonized person to an animal under their care, transmission of *S. equi* between horses by personnel, or direct transmission of viral respiratory pathogens between horses in adjacent stalls that can have nose-to-nose contact.
- Droplet transmission involves transmission of infectious agents in relatively large fluid droplets generated by coughing, snorting, or vocalizing. These large droplets do not remain suspended in the air for long periods nor are they transmitted long distances; therefore, special air handling is not required. An example of this is transmission of bacterial agents from a coughing horse to another horse stabled in relative proximity. An extrapolation to veterinary context might also include transmission of surface contaminants during environmental cleaning processes with water under high pressure.
- Airborne transmission involves agents that can be transmitted effectively in small particles (5 μm or smaller) that can remain suspended in air and travel greater distances. Special air handling is required to control this route of transmission. Equine influenza can be spread through a barn via the airborne route over extended distances.
- Common vehicle transmission involves infection caused by contact with contaminated items such as feed bins, muzzles, twitches, thermometers, and other medical equipment.
- Vectorborne transmission involves vectors such as mosquitoes, flies, and rodents. This may be of particular concern in some areas with reportable vectorborne diseases such as equine infectious anemia.

Surveillance

All comprehensive infection control programs should have a surveillance component because the information collected serves as sensory input to guide ongoing efforts so that they are focused and efficient. Without surveillance information, infection control programs will be guided more by emotions and opinions rather than data and evidence. Infection control programs will have much greater acceptance and utility if, in the long term, decisions are based on objective information about infection and disease occurrence at a specific hospital. Useful surveillance goals for infection control programs include developing a system to allow prompt identification of contagious disease threats, evaluating the effectiveness of infection control practices, measuring personnel compliance with infection control procedures, providing a basis for logical infection control decisions, and stimulating efficient and economical use of resources.

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Surveillance Options and Strategies

Theoretically, an optimal surveillance system would allow real-time detection of all HCAI. However, pursuing this goal would be unrealistic for reasons of practicality and would be an inefficient use of resources. Although all HCAI are important relative to patient well-being, some are more important than others. This is because the impact on patient health is much more significant for some diseases, as well as because highly contagious diseases are more likely to impact a larger number of patients. Further, regardless of whether there is a contagious etiology, HCAI that affect a large number of patients can have a tremendous impact on the cost of care and the overall burden of morbidity for patients. Focusing surveillance on these high-impact HCAI is logical as a greater proportion of these occurrences are also likely to be preventable in comparison to more sporadic problems. Further, experiences with infection control in human health care settings has shown that it is possible to be more efficient with infection control and just as effective if high-risk, high-frequency, and high-cost problems are targeted.

Determining which specific HCAI were likely preventable is a difficult and potentially contentious task. Rather than focus on individual infections, infection control efforts in human hospitals have benefited by focusing on comparing rates of infection and estimating the proportion that might be preventable by referencing some accepted standard. During the past 30 years, human hospitals have made great efforts to characterize rates of HCAI that can be expected even under the best of circumstances. By estimating rates for these "nonpreventable" infections, it has then been possible to identify hospitals with higher-than-average rates for HCAI. Because of the tremendous differences among different hospitals and among different patient populations, it has become standard to focus on more restricted, high-risk patient groups for which there is better comparability (e.g., neonatal or cardiac intensive care patients). It is also far more feasible to perform surveillance for HCAI in these high-risk patient subgroups than it is in the larger general population that has much lower risks of HCAI. Performing surveillance with standardized case definitions over time allows identification of specific risk factors, which could then be used to prospectively refine management of patients (i.e., a high-risk patient could be identified and be subjected to more aggressive control measures as a preventive strategy). Unfortunately, there is very limited information available regarding rates of disease related to HCAI that can be found at individual hospitals let alone estimation in multiple hospitals, which would be required in order to obtain inter-hospital comparisons that would be useful in identifying latent problems at specific facilities. Although making standardized comparisons between hospitals would require tremendous cooperative effort, individual facilities could make significant progress in identifying important changes in rates for HCAI if efforts were made to benchmark their infection rates over time.

When designing a formal surveillance effort to aid infection control programs, it is important to tailor efforts to a specific facility or practice. A wide variety of design possibilities are available for hospital surveillance systems, and the specific focus and methods should be carefully matched to the needs and resources of each establishment. Diseases that are the highest priority for surveillance must be specified along with standardized case definitions that will be used to identify these cases. Efforts may target disease caused by HCAI that are related to specific procedures or organ systems, or just as commonly they may target specific infectious agents of interest. For example, systems might be established to look for surgical or IV catheter site infections, methods may target surveillance for respiratory tract infections, or efforts may specifically target detection of infections with specific etiologic agents such as *Salmonella* or MRSA. It must also be determined whether clinical disease will be the outcome of interest or whether it is important to look for animals with subclinical infections. This will generally vary by disease and likely will be determined by the natural history or pathophysiology of the disease (i.e., Does shedding occur in the absence of clinical signs? Is there a chronic carrier state? What are the risk factors related to the likelihood of shedding?). Further, if clinical disease is the outcome of interest, it is important to consider whether the case definition will include some type of etiologic confirmation, or whether diagnoses will be syndromic in nature and based upon clinical signs (i.e., surgical site infections could be defined based upon recovery of a bacterial agent in the presence of clinical disease, or it could be defined solely upon the presence of a predetermined combination of clinical signs such as erythema and drainage). As discussed previously, another consideration is whether surveillance will target specific subgroups of the population or whether it will include all patients. The major benefit of targeted surveillance is that it decreases the cost and effort of data collection, but the trade-off is the inability to detect potential problems in the patients that are not being monitored. However, increasing awareness about infection control methods for common or more important diseases generally has the effect of increasing awareness and compliance with control measures that relate to other potential HCAI. It also must be determined whether surveillance will be active (i.e., patients with HCAI will be actively sought out) or whether passive surveillance (i.e., reporting is voluntary) is acceptable and appropriate. In general, active surveillance will only be used in targeted subpopulations and only to look for more common and more important diseases, and syndromic surveillance should be more heavily relied upon when the targeted population is larger or as a supplement to culture or etiologically based surveillance efforts.

Another important consideration is how data will be gathered for this effort. Significant personnel compliance is needed for active culture-based surveillance of large numbers of patients. Similarly, any type of chart review system for benchmarking expected rates of HCAI requires a significant time commitment. Surveillance efforts are greatly aided by computer-based search mechanisms, and it is strongly recommended that practices consider using electronic medical record systems to maximize the ability to perform surveillance and that medical record systems be designed to facilitate collection and recovery of infection control–related data. For example, something as simple as being able to monitor the number of febrile or leukopenic patients on a daily basis could be extremely powerful as an aid to infection control efforts. Even financial databases can be useful in surveillance efforts. For example, financial databases may be very useful for surveillance for benchmarking antimicrobial prescriptions or specific procedures, such as IV catheterization, surgeries, or submission of samples for diagnostic tests.

General, nontargeted surveillance to look for potentially pathogenic bacteria that can be found in health care environments is widely considered of no real benefit to infection control efforts. This includes sampling of surfaces in surgical theatres to catalog the different bacteria that can be found. However, there is utility in use of targeted environmental cultures where there is biological plausibility as to their relevance and when there is a plan to act on the results (and where the action differs if results are positive or negative). For example, monitoring for contamination of veterinary hospitals with *Salmonella* has been a useful adjunct to patient surveillance in comprehensive infection control programs at veterinary hospitals.[29,57,58] In addition, in some situations, such as when attempting to control ongoing outbreaks, there is no substitute for culturing the hospital environment to detect important environmental reservoirs.[1,59] Use of electrostatic household wipes has been extremely useful for sampling to detect *Salmonella* in routine surveillance as well as in the face of outbreaks.

The use of rapid and sensitive diagnostic tests is particularly important for the management of highly contagious diseases. As such, PCR and antigen detection tests, which can be much more rapid than traditional culture systems for bacteria and viruses, have become more widely used for both patient and environmental surveillance efforts. However, these tests cannot fully replace culture-based assays because analysis of microbes is essential to fully understand the epidemiologic implications for each recovery. For example, if on a single day three patients were found to be shedding

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Salmonella after use of PCR, it would not be possible to know whether these were unrelated events. In contrast, if shedding were detected using culture and the *Salmonella* isolates were then shown to be from different serogroups, this would make it unlikely that shedding was related to exposures from a single source. In some situations it may be logical to use both a rapid and culture-based assay to maximize both speed and ability to perform epidemiologic investigations. Availability of qualified laboratories, rapidity of testing, and costs will all have to be considered and balanced.

Monitoring Personnel Compliance

Success of an infection control program is absolutely dependent upon universal participation within a hospital or other animal care facility that is born from a well-developed sense of responsibility among individuals. Actively engaging all personnel in infection control programs becomes increasingly difficult as organizations become larger and more complex. Unfortunately, the most cautious actions of a majority of personnel can be for naught if even one individual neglects to take appropriate precautions under just the right (wrong) circumstances. Although it is very important for administrators to engage in surveillance to detect systematic noncompliance with policies, it is just as important to empower and expect all personnel to participate in monitoring for individual acts of noncompliance. Remembering that most noncompliance is born from a natural tendency for people to revert to the most convenient practices (that are not necessarily the most "safe" from the infection control perspective), it is important to couple surveillance efforts with education so that all personnel fully understand why they are being inconvenienced. In addition, providing useful feedback and communication about issues that arise in the hospital will help to reinforce the need for compliance. For example, monitoring and reporting of bacterial shedding or environmental contamination detected as a part of surveillance programs can help to keep hospital personnel aware of the potential hazards of reduced infection control efforts.

Measurements Related to Health and Disease

Although outcomes for individual animals may be the most important bottom line for many clinicians, it is important to remember that infection control by its very nature often has a larger population-based perspective. Thus, although diagnostic test results for an individual animal obviously have great relevance for that animal, for the population, a positive test result may not have great meaning unless it is interpreted contextually. It is therefore critical to remember that in addition to tracking numerators (e.g., numbers of infections or animals with disease caused by HCAI), some type of denominator information is needed to provide relevance over time or among different subpopulations. Some examples of relevant denominators include patient admission totals for a given period, patient-days of hospitalization, numbers of procedure events such as surgeries or catheter placements, and numbers of samples submitted for culture.

Developing a Comprehensive Surveillance Strategy

As mentioned, it is unrealistic to expect to detect all occurrences of HCAI or all animals shedding agents of interest through any hospital surveillance system. Rather, veterinarians should work toward developing strategic surveillance programs that will allow reliable estimation of rates for important events if they occur with any significant frequency, as well as rapid detection of unexpected important events. It is likely that a mix of strategies described previously will be used for the various agents and disease problems. For example, if *Salmonella enterica* shedding occurs at some low-level yet regular frequency in a hospital (e.g., 3% of all hospitalized equine patients) and is considered an important potential hazard for other patients, it is reasonable for an active surveillance program to be developed that allows detection of clinical and subclinical shedding of *Salmonella* as a patient management tool and allows detection of important trends over time so that outbreaks of HCAI could be rapidly identified and stopped. In contrast, *Clostridium difficile* or EHV-1 may not have been detected with any regularity in patients at a particular hospital or may be more difficult to actively monitor because of available testing methodologies, yet they may still be considered important because of their significance as pathogens and their potential for contagious spread. For these pathogens, it may be more reasonable to use a reliable passive surveillance strategy to call attention to patients when clinical signs or diagnostic testing indicates that these agents may be present. In addition, maintaining some level of surveillance for compliance with infection control procedures and policies is necessary to ensure that an infection control program is functioning properly.

Education and Awareness

Education of all personnel regarding infectious disease hazards to themselves, patients, and veterinary practices is essential to the long-term success of any infection control program. Successful programs are critically dependent upon all personnel knowing and following procedures and policies used for control of contagious disease transmission in a practice. Although this type of information can be acquired over time through personal experience, this is an inefficient and unreliable method for disseminating critical information.

Written Protocols

The first step to ensuring that necessary information is disseminated to all personnel is to document policies and protocols in writing. This effort is valuable for all veterinary practices but is especially critical in larger and more complex veterinary hospitals. This relatively simple step has many benefits. First, documenting procedures requires a thorough review, which by itself is beneficial. Second, documenting policies and protocols in writing imbues the infection control program with a sense of purpose and commitment. Third, documenting procedures helps to ensure consistency in application across all personnel as well as over time. As discussed, all infection control procedures are inherently inconvenient, and the natural tendency is for personnel to drift toward more convenient ways of performing activities that may not provide an adequate degree of protection against HCAI. Fourth, documenting policies demonstrates a degree of due diligence, which is useful from a legal liability standpoint relative to the occurrence of HCAI or zoonotic infections.

Once these protocols have been documented, it is important to require their use as a reference and to make a specific effort to educate personnel about the policies and procedures. A written document serves no purpose if it is not used. Veterinarians and other personnel are busy people, and the immediacy of caring for patients and clients can easily overwhelm seemingly mundane tasks such as studying written protocols. A valuable aid in this process is to have some type of training program. This does not necessarily mean formal presentations; it is valuable to organize a meeting of all personnel for the sole purpose of discussing infection control issues. Although this seems logical, training in infection control practices is not a universal occurrence even in teaching hospitals. In a survey of teaching hospitals from AVMA-accredited institutions, only 42% (16 of 38) of responding institutions reported that they required that personnel (students, technical staff, veterinarians) participate in some type of formal training program regarding infection control and biosecurity, and only 7 of these institutions provided more than a single training exposure.[13]

Training Programs

It is also important to consider the differences in training and experience among personnel. By their nature, infection control programs are dependent upon adherence to important protocols by all personnel regardless of their position description. Non-veterinarians are invaluable members of most veterinary practice teams and even personnel who might never touch patients but instead serve as receptionists or for the single specific task of cleaning are absolutely critical for the success of infection control programs. Veterinarians sometimes underappreciate how their specialized training has

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provided them a broad appreciation for basic principles of contagious disease transmission and control. Without the experiences of a veterinary education, many personnel simply do not have the same understanding of contagious diseases. Simply telling people to follow certain rules without understanding why they are necessary leads to inevitable compliance problems. Without a thorough understanding of why inconvenient infection control practices are needed, they will inevitably be discarded over time as seeming illogical. To help ensure uniformity of education among all personnel, some hospitals have developed training documents and require that new employees pass a written evaluation before they are permitted to begin work.

Another important aspect of education and awareness is to instill a need to lead by example and to empower all personnel to hold anyone else in the practice accountable for their actions. The hierarchy in authority that is often used in the delivery of patient care (e.g., veterinarians at the top of the hierarchy, personnel without formal training at the bottom) can interfere with optimal infection control. A common non sequitur related to infection control is that those with the most training can be the persons least likely to adhere to important policies. This is true in both human and veterinary medicine, as has been repeatedly shown relative to hand hygiene.[30,31] Physicians and residents have been shown, in numerous studies conducted in a variety of settings, to be significantly less likely than nurses to adhere to appropriate hand-hygiene protocols. Observations in the veterinary setting suggest that the same trends are true for hand hygiene as well as for appropriate use of barrier nursing precautions. All people pick up cues for behavioral expectations from their surroundings. If personnel who clearly understand the importance of preventive measures (physicians and veterinarians) such as hand-washing fail to routinely follow best infection control practices, there is little hope that trainees and laypersons will routinely trouble themselves to habitually use an important albeit inconvenient practice. Further, it seems that the more respected position a person holds in a practice, the more likely that individual acts of noncompliance will be influential on the actions of others. Students in teaching hospitals can watch classmates correctly follow infection control policies throughout the day and yet can be more influenced to be noncompliant by observing the single time that a senior clinician ignores a practice guideline.

One way to improve compliance and counter the influences noted previously is to use disseminated enforcement by actively encouraging all personnel to call attention to noncompliance. Once it has been determined which procedures are required for a particular situation and this has been documented, there is no reason that nontechnical staff should be any less capable than a veterinarian in determining whether a procedure has been followed correctly. It is important that this community enforcement be empowered by all in a spirit of friendly camaraderie and team building. Some hospitals have noted significant improvements in compliance using this method of enforcement and have even used competitions among "teams" with the incentive of agreeing that the loser must pay a reward to the other team (e.g., pizza lunch).

Zoonosis Awareness

One of the most important objectives for an infection control program is to protect personnel and clients from illness associated with zoonotic infections. This is another area in which veterinarians sometimes forget that not all personnel have an understanding of hazards or of how to take appropriate actions to protect themselves. Without this knowledge, personnel may take inappropriate risks or may overreact to perceived hazards in what is actually a low-risk situation. In addition to holding briefings or question-and-answer sessions, it is wise to provide a good resource text, written summaries, or URL addresses to reliable Internet resources so that personnel have tools available to help them research answers to their questions. Table 46-3 provides a brief summary of some zoonotic pathogens that might be transmitted from domestic large animals through occupational activities of veterinary personnel.

Personnel with Increased Risk of Infection

An important area without much published literature relates to risks for zoonotic infections in personnel that have an increased susceptibility to infectious diseases or those in which the consequences of clinical infection may be particularly severe. Obviously there is an overall increase in risk of infection for immunocompromised personnel, but there is very little specific information about which disease risks might be of greatest importance to this population and which personnel may be at particular risk. In addition, there are many agents that pose minimal risk to people with healthy immune systems but can pose significant infection risk to immunocompromised personnel. Individuals being treated orally with antimicrobial drugs are generally considered to have an increased risk for infections with enteropathogens, and so it is prudent that personnel being treated with antimicrobial drugs be especially attentive to protocols related to personal protection. Pregnant women have a special risk for infections that can result in fetal infections or abortion, and should therefore use practical precautions that reduce the likelihood of infection. In general, paying strict attention to good hand-hygiene protocols, routine use of gloves to reduce the likelihood of contact exposures, regular use of protective outer garments or hospital-dedicated attire, and avoiding eating and drinking around animals or in their environments should help to reduce the likelihood of exposure to potential zoonotic pathogens.

Intervention and Investigation of Outbreaks of Health Care–Associated Infections

An outbreak is defined as an increased occurrence of infections above the expected baseline (endemic) level. Outbreaks are an ever-present risk in all health care facilities, veterinary or otherwise, and outbreaks will occur, despite rigorous infection control protocols. The general principles of outbreak management are to contain the outbreak and reduce the overall impact on individual animals and the facility. It is critical to note that despite the stigma often attached to outbreaks, an outbreak of disease does not necessarily indicate poor management or malpractice. By their very nature, most veterinary hospitals will always have higher risks for the occurrence of outbreaks of infectious disease. However, making no attempt to identify HCAI, neglecting signs of a developing outbreak, or responding inappropriately to the spread of HCAI could all be construed as poor management or even malpractice. Thus, there are a number of reasons why plans for a logical, aggressive, organized, and cooperative response should be developed. Consultation with internal and external experts in epidemiology, infectious diseases, microbiology, and infection control can be useful. It is unlikely that the person involved in coordinating the outbreak response will be an expert in all areas. Consulting others does not indicate a lack of ability on the part of the response team; rather, it indicates a logical approach to a typically complex problem. It makes sense to consult with those who, through interactions at multiple facilities, have gained experience that usually cannot be obtained while concentrating on primary responsibilities as a clinician at a single institution. Ideally, these individuals are consulted early in the outbreak, and it may be prudent to develop contingency plans and contact consultants in anticipation of potential problems. The use of external consultants can be particularly useful because they can examine a situation and facility without the same degree of inherent bias that develops through experience and habit of regular daily practice in a facility.

One of the most important factors in outbreak intervention is early recognition of potential problems. Ideally, infection control programs should be designed to allow early identification of related clusters of infection or disease either through laboratory testing, clinical disease reporting, or syndromic surveillance. When an infectious animal is exposed to a susceptible population, transmission may occur. First-generation transmission—that is, transmission from the index case (directly or indirectly) to other animals—can be difficult

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Bacillus anthracis (Anthrax) • Gram-positive, spore forming, anaerobic bacterium	All species	There are three clinical forms of anthrax in humans: cutaneous, pulmonary, and gastrointestinal. Cutaneous infections manifest as skin papules and vesicles with associated cellulitis that evolve into a characteristic black eschar (scab). Pulmonary anthrax initially resembles upper respiratory infection and can evolve into severe respiratory compromise and death. The gastrointestinal form results in gastroenteritis with vomiting and dysentery.	Cutaneous transmission occurs through direct contact. Respiratory transmission occurs through inhalation of bacteria or spores. Gastrointestinal transmission results from eating undercooked contaminated meat.	Enhanced barrier precautions, including eye protection and respiratory protection using a minimum of an N95 should be used when handling affected animals or working in their environments. Blood and secretions from anthrax suspects should not be allowed to contact skin. Necropsy should not be performed on animals that have died from anthrax.
Bordetella bronchiseptica • Gram-negative bacterium	Pigs, dogs, cats, rabbits, horses	Disease is rare in humans and occurs predominantly in immunocompromised individuals, resulting in pneumonia and upper respiratory tract infections.	Respiratory infection through contact and droplet routes.	Immunocompromised individuals should avoid contact with mucous membranes and nasal discharges of susceptible animal species. Barrier precautions and adherence to good hand-hygiene protocols will reduce the risk of exposure.
Brucella melitensis, B. abortus, B. suis, and *B. canis* (Brucellosis) • Gram-negative bacterium	Cattle, sheep, goats, camelids, pigs, horses, dogs, other species	Flu-like illness, gastrointestinal signs occur frequently in adults but less often in children; irritability, insomnia, mental depression, and emotional instability sometimes develop. Recurrent fevers are the hallmark of chronic infections in addition to fatigue, arthritis, and cardiac and other complications.	Contact, droplet, or aerosol exposure to infected fetuses, placenta and placental fluids, or infected tissues; contact with contaminated fomites. Ingestion of unpasteurized milk or milk products.	Avoid contact with fluid or tissues from abortions. Use of barrier precautions including gloves, protective eyewear, and a minimum of N95 respiratory protection is recommended when performing obstetrical procedures or performing necropsies on high-risk animals.
Burkholderia mallei (Glanders and Farcy) • Gram-negative bacterium	Horses and other equid species	Flu-like symptoms, photophobia, lacrimation, diarrhea, septicemia, pneumonia, ulcerative and suppurative cellulitis, lymphadenopathy, splenic and hepatic abscesses.	Direct contact or droplet exposures to skin or mucous membranes; prolonged contact with infected animals is generally required for infection.	Enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when working with infected animals.
Campylobacter jejuni and *Campylobacter coli* • Spirochete bacterium	Cattle, sheep, goats, camelids, pigs, poultry, dogs, cats, other species	Disease varies from mild gastrointestinal distress that resolves within 24 hours to fulminating or relapsing colitis. Signs may include watery diarrhea, fever, nausea, vomiting, abdominal pain, headache, and muscle pain. Feces may contain frank blood. The acute symptoms usually diminish in 2-3 days and resolve in 7-10 days. Complications are rare but include Guillain-Barré syndrome, a disorder of the nervous system.	Fecal-oral transmission after contact with infected animals or their environments is a suspected but not well documented risk factor. Ingestion of contaminated water and food including undercooked poultry or meat, raw milk.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*—cont'd

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Clostridium difficile • Gram-positive, spore-forming, anaerobic bacterium	Pigs, horses, cattle, dogs, cats, other species	Colitis leading to fever, abdominal cramps, and diarrhea or dysentery, dehydration, and electrolyte imbalances. Rarely, severe colitis can lead to life-threatening complications such as toxic megacolon, peritonitis, and colonic perforation.	Oral-fecal exposure through contact or droplet exposure to infected animals or their environments.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.
Clostridium perfringens • Gram-positive, spore-forming, anaerobic bacterium	All species	Wound infections can result in gas gangrene with accompanying fever, swelling, and erythema of affected area, systemic signs as disease progresses. Oral exposure is associated with abdominal cramps, diarrhea, and in rare cases necrotic enteritis and septicemia.	Wound contamination through contact or droplet exposure, ingestion of food contaminated with large numbers of bacteria, potentially oral-fecal exposure through contact or droplet exposure to infected animals or their environment.	Routine use of protective outer garments or dedicated attire when working with animals or their environments. Strict adherence to good hand-hygiene protocols, and appropriate cleaning and management of wounds.
Coxiella burnetti (Q fever) • Gram-negative, spore-forming, intracellular bacterium	Primarily sheep, goats, cattle, but also camelids, horses, dog, cats, other species	Symptoms of Q fever include fever, chills, headache, fatigue, and chest pains. Pneumonia and hepatitis can occur in serious cases. In pregnant women, infections can cause premature delivery, abortion, and infection of the placenta. In people with preexisting heart valve disease, endocarditis may occur.	Contact, droplet, or aerosol exposure to urine, feces, milk, and especially fetuses and placental tissues from infected animals. Respiratory exposure to contaminated dust, occasionally ingestion of unpasteurized milk or milk products.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Caution is warranted when handling tissues or fluids of infected animals or aborted fetuses. Consider use of eye protection when performing obstetric procedures on high-risk animals. Enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when working with infected animals.
Cryptosporidium parvum (Crypto) • Apicomplexan protozoal parasite	Ruminants, pigs, horses, poultry, dogs, cats, other species	Gastrointestinal disease, including signs of abdominal pain, nausea, anorexia, and profuse watery diarrhea. Severe infections can require hospitalization for fluid therapy and electrolyte imbalances. The disease is usually self-limiting but may be chronic and debilitating in immunocompromised individuals.	Oral-fecal transmission primarily through contact with infected animals or their environments, but also through droplet exposures during cleaning.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*—cont'd

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Dermatophilus congolensis • Gram-negative, actinomycete bacterium	Cattle, sheep, goats, camelids, horses, rarely pigs, dogs, cats, other species	Pustular desquamative dermatitis.	Direct contact with lesions on affected animals.	Use gloves when handling affected animals; strict adherence to good hand-hygiene protocols.
Erysipelothrix rhusiopathiae (Erysipelas in pigs, erysipeloid in humans) • Gram-negative, facultative anaerobic bacterium	Pigs, other species	Characteristic cellulitis with raised red lesions, edema, and intense pruritus. Skin infections can progress to involve other cutaneous sites and also rarely to systemic infections with flu-like illness, septicemia, and arthritis.	Primarily via direct contact with infected animals, contamination of skin wounds. There are rare reports of transmission through ingestion of undercooked pork.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be used when working with clinically affected animals. Avoid eating or drinking near animals or their environments.
Escherichia coli O157:H7 • Gram-negative bacterium	Cattle	Fever, enteritis, diarrhea, or dysentery. In children under 5 and the elderly, infections can cause hemolytic uremic syndrome (hemolysis and kidney failure).	Oral-fecal transmission via contact or droplet exposure through exposure to cattle or their environment or through ingestion of contaminated water and food.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Francisella tularensis (Tularemia) • Gram-negative bacterium	Sheep, rabbits, cats, other species	Flu-like illness, rashes, nausea, splenomegaly, papular or ulcerative lesions at site of cutaneous exposure, lymphadenopathy and ulcerative lymphadenitis, pleuropneumonia from inhalation or hematogenous spread; ingestion is associated with enteritis, stupor, and delirium.	Contact, droplet, or aerosol exposure to tissues or secretions of infected animals, ingestion of tissues from infected animals.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments is warranted when handling tissues or fluids of infected animals or aborted fetuses. Gloves, eye protection, and a minimum of N95 respiratory protection should be used when performing obstetric procedures on high-risk animals.
Foot-and-mouth disease virus • Nonenveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, other species	Infection in humans is very rare; headache, fever, vesicular lesions on the hands or feet or in the mouth.	Contact, droplet, or aerosol exposure to infected animals.	When working with infected animals, enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.
Giardia lamblia • Flagellated protozoal parasite	Ruminants, pigs, poultry, dogs, cats, other species	Gastrointestinal disease, including signs of diarrhea, intestinal gas, stomach cramps, and nausea. A significant proportion of patients develop lactose intolerance while infected. The illness usually last 1 to 2 weeks but chronic infections can last months to years.	Oral-fecal transmission through contact with infected animals, their environments, or through ingestion of ingestion of contaminated water or food.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Hendra virus • Enveloped, single-stranded RNA virus	Horses, other species	Fever, lethargy, respiratory distress, neurologic signs including headache and disorientation.	Occupational contact with infected horses or their tissues.	Classified as a Biosafety Level 4 agent; contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*—cont'd

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Influenza virus • Enveloped, single-stranded RNA virus	Pigs, aquatic fowl; influenza viruses are generally host restricted.	Cross-species infection with influenza strains is unusual under normal circumstances, but has been rarely documented with swine and avian influenza viruses resulting in fever, malaise, upper respiratory illness, and pneumonia.	Close contact with infected pigs leading to respiratory exposure through contact, droplet, and aerosol routes.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments, or dedicated attire when working with animals or their environments. When working with infected animals, use enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.
Leptospira spp. (Lepto) • Spirochete bacterium	All mammals appear to be susceptible to at least one species of *Leptospira*.	Severity of illness varies greatly; signs include flu-like illness with fever, chills, headache, and severe myalgia. Aseptic meningitis can occur, and 5% to 10% of cases may be associated with multiple organ failure.	Skin or mucous membrane contact with urine or less commonly with blood and tissues of infected animals, ingestion in contaminated water or food.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if droplet exposure to urine is likely. Avoid eating or drinking near animals or their environments.
Listeria monocytogenes • Gram-positive bacterium	All species	Contact can result in papular lesions on hands and arms. Most commonly, flu-like illness and gastroenteritis. Less commonly, infections can result in a mononucleosis-like syndrome (glandular listeriosis) or in fetal infection, abortion, still birth, neonatal septicemia, or meningoencephalitis. Meningoencephalitis is also noted in the elderly and immunocompromised.	Immunosuppression greatly increases the risk of infection. Direct contact of skin or mucous membranes with infectious material, feces, or contaminated soil. Respiratory exposure to secretions from infected animals via droplet or aerosol routes. Oral-fecal exposures through contact, droplet, or aerosols, or ingestion of contaminated foods.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments, especially among immunocompromised people. Avoid eating or drinking near animals or their environments. Enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when performing obstetric procedures on high-risk animals or when handling aborted fetuses or tissues and fluids of infected animals.
Mycobacterium tuberculosis, M. bovis, M. avium complex • Acid-fast bacterium	All species	Signs depend on the organ system involvement. General signs of infections include anorexia, weight loss, fatigue, fever, and chills. Signs of pulmonary infection include coughing and hemoptysis. Skin lesions are characterized by ulcers, papular lesions, and suppurative lesions. Signs of other organ involvement relate to the specific system.	Inhalation and oral exposure through respiratory droplet and aerosol transmission from infected animals, oral or cutaneous exposure through contact with infected tissues or contaminated surfaces, ingestion of raw or unpasteurized milk and milk products.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if working with infected animals with clinical pulmonary disease or if performing necropsy.
Nipah virus • Enveloped, single-stranded RNA virus	Pigs, other species	Fever, neurologic signs including drowsiness, headache, disorientation and confusion, shortness of breath, and coughing.	Occupational contact with infected pigs.	Classified as a Biosafety Level 4 agent, contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*—cont'd

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Parapox viruses (Orf and bovine papular stomatitis viruses [BPSV]) • Enveloped, double-stranded DNA virus	Sheep and goats (Orf virus), cattle (BPSV)	Papular lesions at areas of contact (usually hands or arms). Lesions can be 1 cm in diameter, and surrounding tissues often become swollen and painful.	Contact with lesions on animals, scabs, or contaminated objects.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn when examining mouths of animals suspected of being infected.
Rabies virus • Enveloped, single-stranded RNA virus	All mammals	Encephalitis with accompanying behavioral and physical signs.	Bite injuries from infected animals, contact with infected animals, and contact with bats or their habitats are the most common methods of human exposure. Contact, droplet, and aerosol exposure to saliva and respiratory secretions of infected livestock is also thought to be a possible method of infection, but is not well documented.	Complete isolation of animals suspected of infection, minimizing contact with personnel. When necessary to examine or manage suspect animals, use enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, eye protection, and strict adherence to good hand-hygiene protocols. Personnel that may be exposed to rabies should be vaccinated in accordance with CDC recommendations.[60]
Rift Valley fever virus • Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, other species	Flu-like illness, photophobia, neck stiffness, and vomiting, which may progress in severe cases to one of three characteristic syndromes: eye disease, meningoencephalitis, or hemorrhagic fever. Retinal lesions are the prominent sign associated with eye disease.	Contact with blood, other body fluids, or tissues of infected animals. Accidental inoculation through sharps injuries or by inhalation of droplet or aerosols. People may also become infected by mosquitoes, or possibly from ingestion of raw milk.	Extreme caution should be taken when working with animals during epidemics. An inactivated vaccine has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure. Enhanced barrier precautions, gloves, eye protection, and a minimum of N95 respiratory protection are strongly recommended when working with high-risk animals or their tissues. Universal precautions should be taken when obtaining and processing specimens from patients. Samples should only be handled in laboratories by trained staff and processed in suitably equipped laboratories. Control of the mosquito vectors and use of personal protection are important.
Rhodococcus equi • Gram-positive facultative intracellular bacterium	Horses, also found in feces of sheep and cattle	A problem with growing recognition, infections in immunocompromised people commonly lead to life-threatening chronic, progressive, granulomatous pneumonia. In contrast, infections are very rare in immunocompetent people and are typically less severe.	Regular contact with horses is a documented risk factor for infection, presumably through oral-fecal exposure via direct contact or droplets, although there is often no documented direct exposure to horses.	Immunocompromised people working with horses should adhere to good hand-hygiene protocols and routinely use protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.

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TABLE 46-3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible through Occupational Exposures to Veterinary Personnel*—cont'd

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Ringworm (*Microsporum* and *Trichophyton* spp.) • Fungi	Cattle, horses, dogs, cats	Characteristic circular, well-circumscribed, red lesions that are pruritic. In immunocompetent people, infection is limited to the keratinized layers of the skin and hairs. However, in immunocompromised people, infections may extend to deep tissues or become systemic.	Direct contact with lesions on affected animals or with objects that have contacted affected areas.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn whenever working with animals known to have dermatophytosis.
Salmonella enterica • Gram-negative bacterium	All species	Flu-like illness, gastroenteric disease, diarrhea or dysentery, septicemia.	Oral-fecal transmission through contact with infected animals, their environments, contaminated items, or through ingestion of contaminated water or food.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with animals or their environments. Enhanced barrier nursing precautions are needed when working with clinically affected animals. Avoid eating or drinking near animals or their environments.
Staphylococcus aureus (methicillin resistant, MRSA) • Gram-positive bacterium	Horses, pigs, dogs, cats, other species	*Staphylococcus aureus* commonly colonizes the anterior nares and other sites without causing clinical signs. Infections most commonly involve skin and soft tissues, either as a primary infection or by infecting cuts or other skin injuries, including sites of intravenous injection or catheterization. Infections of the respiratory tract and urinary tract are also noted. The risk of infection may be increased in immunocompromised people. Skin infections most commonly result in swollen, painful, erythematous lesions that can often be purulent.	Direct contact with colonized or affected animals; droplet or aerosol exposure to discharge from infected sites.	Strict adherence to good hand-hygiene protocols, and routine use of protective outer garments or dedicated attire when working with horses or pigs. Enhanced barrier nursing precautions and gloves should be required when working with animals known to be colonized or infected. Cuts and abrasions should be kept bandaged and disinfected regularly.
Vesicular stomatitis virus • Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, horses, other species	Infections in humans are very rare, and typically result in flu-like symptoms. Less commonly, oral vesicles and cervical lymphadenopathy can be noted.	Mucosol exposure via direct, droplet, or aerosol exposures with clinically infected animals.	Enhanced barrier nursing precautions and gloves can be used when working with animals known to be colonized or infected. Eye protection and N95 respiratory protection may also be warranted when examining or treating lesions.

*This is not a complete list of all zoonotic diseases; less common diseases and those with vector-borne or solely foodborne routes of transmission are not included.

to detect, particularly in situations when the index case is infectious prior to developing clinical disease. The most important control aspect related to the first generation of cases is prompt identification so that an outbreak can be recognized early enough to implement measures to reduce the risk of further transmission to a second generation of cases. Often, outbreaks are not identified or addressed until multiple generations of transmission have occurred, thereby increasing the overall morbidity and mortality and complicating the response.

General principles of outbreak response include identification of the infectious agent, identification of infectious animals, identification of animals that have likely been exposed, determination of the mode of transmission, and prevention of further transmission by means such as isolation, implementation of barrier precautions, active surveillance, environmental surveillance, increased environmental disinfection, restriction of animal and personnel movement, and under extreme conditions minimizing new exposures through restricting admission of new patients.

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While useful, initial intervention measures do not require definitive identification of the etiologic agent. In the absence of a confirmed etiology (i.e., diarrhea cluster of unknown cause), outbreak intervention can still be performed using general infection control practices combined with knowledge of appropriate response to the most likely causes. General principles such as isolation of infected/affected animals and their direct contacts, use of barrier precautions, close attention to personal hygiene, restriction of animal and human movement, regular examination of animals and careful attention to cleaning and disinfection are important measures that are useful for most types of infectious disease outbreaks. Indeed, these measures alone will often constitute the full response after an etiologic agent is identified.

Identification of animals likely to be shedding the agent responsible for the outbreak is critical. Definitive confirmation is not required, and a syndromic response is often better. For example, in the midst of a *Salmonella* outbreak, it is wise to consider all animals with diarrhea, depression, or fever as likely to be infected and shedding bacteria even if culture results have been negative. The same would be true for horses that develop fevers when others suspected of having herpesvirus myeloencephalitis or influenza are hospitalized in the same facility. This will result in some misclassification, but erring on the side of being overly sensitive in identifying infectious animals is the more appropriate response when trying to halt the spread of disease. The main problem with this type of response is imposing excessive strain on available resources (e.g., isolation stalls, personnel time) because of excessive misclassification.

Identification of potentially exposed animals is also critical. Depending on the pathophysiology of disease, these animals may or may not require segregation or isolation. For some pathogens, clinical disease precedes development of the infectious state, so exposed animals can be monitored and isolated if required. For example, horses exposed to *S. equi* consistently develop fever prior to shedding the organism,[61] so close monitoring of body temperature of exposed animals and prompt isolation of animals developing fever may be sufficient to prevent propagation of an outbreak. For many pathogens, screening of all potentially exposed animals can be useful. In particular, the use of rapid screening techniques that can provide a turnaround time of a few hours (e.g., antigen detection test for equine influenza, *S. equi* PCR) can be very useful. However, testing strategies should also include some use of culture so that whole organisms will be available to aid epidemiologic investigations and must be based on good understanding of the pathophysiology of disease (e.g., when shedding typically occurs). Widespread screening of hospitalized animals will often be required to determine the extent of the outbreak and facilitate removal of infectious animals from the population. Therefore, if imposed as a response to suspected spread of HCAI, it is essential that screening not be an elective procedure. As such, it is prudent for facilities to have previously considered how costs for diagnostic testing will be distributed in the event of suspected HCAI. Surveillance for shedding of specific contagious agents at the time of admission can facilitate prevention of outbreaks as well as intervention responses. In situations in which recently exposed animals do not necessarily develop consistent overt clinical signs or in which rapid diagnostic testing is not available, it may be necessary to segregate all potentially exposed animals, either in an isolation unit or in the main hospital.

Determination of the likely mode(s) of transmission is also required for initiation of an effective response. This is usually relatively clear based upon the identity of the known or suspected pathogen. However, in general, all agents of concern for HCAI will spread through contact and common vehicle transmission, and thus controlling all methods of contact exposure to patients will be critical in response to suspected outbreaks. Although droplet transmission might be most important for respiratory agents, practicalities of cleaning hospital environments for large animals usually necessitates use of large volumes of water, which can also create hazards related to droplet transmission. As such, the potential for droplet transmission should also be tightly controlled in response to suspected outbreaks. Generally, only highly contagious viral respiratory agents pose a hazard through airborne transmission. However, in situations in which routes of transmission are not clear, it is prudent to assume the worst and manage the outbreak as if the pathogen is highly transmissible by multiple routes until proven otherwise.

Prevention of further transmission is obviously one of the most important goals of outbreak response. A variety of factors need to be considered to achieve this. In addition to identification of infectious animals, measures need to be established to prevent direct and indirect contact of these animals with other animals and the general hospital environment. Isolation and the use of barrier precautions can achieve this. The response to implemented infection control measures should be monitored closely to determine their adequacy, with an understanding that there is an inherent lag time from implementation of measures to control of the outbreak that is proportional to the incubation period for infectious diseases.

At times, partial or complete closure of the facility may be useful or necessary. Restricting new admissions decreases the number of newly susceptible individuals that might promote propagation of an outbreak. Further, if new infections appear to be occurring despite implementation of best control efforts, it is important to consider whether it is prudent or ethical to continue admitting new patients. It is also critical to consider the tremendous burden that can be necessitated by the need to deal with infection control measures and the possible effects on patient care. During outbreaks, stall space, particularly isolation space, may become limited, and decreasing the number of admissions facilitates depopulation of the facility for proper cleaning and disinfection. Clinical personnel are often overworked during outbreaks because of the number of ill animals, and excessive workload can contribute to breaches in protocols. Although there may be reluctance among some people to restrict hospital admissions because of potential negative impacts related to public relations and finances, early, short-term closure of a facility to stem a small but developing outbreak is much better than a subsequent longer closure in response to a larger outbreak with more affected animals. A key component of facility closure is proper communication to staff and the public, emphasizing the proactive approach that is being taken to protect patients and clients and to prevent a major problem from developing. Regardless of whether it is deemed necessary to restrict admission of new patients, as described previously, whenever outbreaks of HCAI are suspected, it is critical to consider whether standard informed consent procedures suitably convey the risks associated with hospitalization to clients.

If environmental contamination is suspected of being widespread, complete depopulation of a ward or even the entire hospital may be necessary to allow for thorough cleaning and disinfection. The availability of multiple wards can facilitate this process as individual problem wards can be closed and disinfected while allowing the hospital to remain functioning. Assuming sensitive culture or other antigen detection methods are available, post-disinfection environmental screening may be indicated for certain pathogens (e.g., *Salmonella enterica*) prior to reopening.

Although vaccination is often perceived as being a cornerstone of infection control, the indications and limitations of vaccination must be considered. No vaccine confers 100% protection, and vaccination should never be used as a replacement for good infection control practices. A more appropriate perspective is that vaccination is principally useful when more useful infection control methods have failed.

Requiring vaccination prior to hospital admission is an area that has received limited commentary in large animal practices. Although vaccination requirements are difficult to enforce in animals admitted for emergency procedures, it may be reasonable for facilities to consider encouraging or requiring vaccination against relevant pathogens prior to admission for elective procedures. For example, requiring vaccination prior to admission for influenza in horses or BVD in pregnant cattle or alpacas could decrease the risk of infection and transmission in hospitals. Problems that might be encountered with such an approach include the lack of relevant efficacy data for

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many vaccines, potential concerns regarding adverse effects with some vaccines, difficulty ensuring compliance, and competitive issues if all competing practices do not have the same standards.

Vaccination may be a useful intervention measure during some outbreaks, but it is important to note that efficacy of vaccines typically has not been evaluated in this specific situation. It is important to remember that there are three possible outcomes associated with any intervention: it may help, it may have no effect, or it may be harmful. For vaccination during an outbreak to be helpful in control efforts, the vaccine must be given to susceptible animals prior to exposure, must initiate a protective response before natural exposure, and must not be harmful when administered to animals that are incubating disease. These criteria are often difficult or impossible to meet in the midst of an outbreak. The greatest potential use for vaccination during an outbreak is likely intranasal influenza vaccination, since this type of vaccine can provide a rapid and effective immune response and is not contraindicated in exposed animals.

Infection Control Issues Related to Specific Pathogens

Although all contagious diseases have the potential to be important hazards for the health of individual patients, there is more empirical evidence regarding the importance of some diseases. Further, while safeguarding the health of veterinary personnel must be a priority for all veterinary practices, some zoonotic diseases have been shown to be of greater concern. Information is listed as follows, regarding control of diseases of particular importance as hazards for HCAI and zoonotic disease.

Salmonella

Salmonella enterica is the agent most commonly reported in association with outbreaks of HCAI and closure of large animal hospitals. In a survey of teaching hospitals from AVMA-accredited institutions, 20 of 38 (65%) participating institutions reported identifying epidemics of *Salmonella*-associated HCAI during the previous 5 years.[13] Seventeen of these hospitals restricted admissions in order to facilitate management of the outbreaks, and 11 reported closing completely to admissions as a control measure. *Salmonella enterica* is recognized as a pathogen around the world, and HCAI have been identified in many countries. However, the average risk among large animal patients varies tremendously among species, production practices, and even geographically within a country. In North America, the general risk of shedding is very low among animals raised in the northernmost regions and can be very high in warmer latitudes. All species are susceptible to infection, but large, intensively managed populations generally often have the highest prevalence of shedding, and the likelihood of shedding in patients while hospitalized is greatly influenced by the prevalence of infection in animals at home premises. Cattle and swine from large populations often have a higher likelihood of shedding compared with horses, camelids, and small ruminants. Given these factors that are associated with variability in infection rates, it is prudent for large animal hospitals to objectively assess the risk of shedding among their patient population in order to appropriately adjust the rigor of surveillance and control efforts.

A notable number of patients shed *Salmonella* without evidence of associated illness, but infected patients are significantly more likely to shed if they show signs of gastrointestinal illness or are systemically ill. Numbers of organisms shed per gram of feces are generally much greater in clinically affected animals. Animals known or suspected to be infected with *Salmonella* should be managed in isolation with strict barrier precautions and hand-hygiene protocols. Shedding tends to be more commonly detected in the summer and fall and may also be generally more common in warmer climates. Whereas outbreaks of HCAI are usually detected in association with the spread of clinical disease, subclinical infections can be more common than clinical infections during outbreaks. Zoonotic infections in veterinary personnel have been commonly detected in association with outbreaks of HCAI. There is apparent variability among strains in regard to virulence, infectivity, and ability to persist in the environment, and this strain variability may be a very important determining factor regarding outbreaks of HCAI. Environmental contamination near infected patients is the rule rather than the exception, and active surveillance has shown that contamination can become disseminated to quite distant areas of the hospital from only a single infected patient. In one study, a total of 12% of 452 environmental samples collected over 10 weeks in a nonepidemic period using electrostatic household wipes were positive for *Salmonella*.[57] Experience has shown that environmental contamination is even greater during outbreaks. In nonepidemic situations, there tends to be great variability in phenotypic markers (serogroup, serotype, and antimicrobial susceptibility) among isolates recovered from patients over time, which often makes it possible to differentiate isolates in epidemiologic investigations. In other situations, especially when certain strains are circulating actively in the region of a hospital, use of genetic analysis may be necessary in order to differentiate strains of *Salmonella* for purposes of epidemiologic investigations. Methods used in diagnostic laboratories for culture and molecular diagnostics are highly variable, which can significantly impact reliability of assays. As such, veterinarians should seek out laboratories that are known to have optimized laboratory methods for use in diagnostic situations. Polymerase chain reaction assays for *Salmonella* are available commercially at a number of laboratories. However, because of the importance of phenotypic and genotypic comparisons of isolates for epidemiologic investigations conducted as part of prevention and control efforts, PCR assays are not recommended for regular use in surveillance programs without parallel analysis using culture. Active surveillance programs are commonly used in large hospitals as a management tool to detect clinical and subclinical infections in large animal patients. In addition, environmental surveillance is sometimes used as adjunct to detect environmental contamination. All common disinfectants are effective against *Salmonella* organisms under optimal conditions. However, its common association with fecal material, other organic matter, and dirt requires careful adherence to good cleaning (physical disruption of surface matter using detergents) and disinfection procedures in order to minimize the likelihood of environmental persistence. Mitigation in response to outbreaks of HCAI requires thorough decontamination of all environmental surfaces, which may only be possible after closure to new admissions, although disinfectant misting may be a useful alternative in some situations.[62]

Clostridium difficile

Although less commonly implicated in outbreaks of diarrheic disease than *Salmonella enterica, C. difficile* can be an important pathogen in horses. Despite the documented risk for health care–associated transmission within human hospitals, this does not seem to be common among equine patients. *Clostridium difficile* should be considered as a differential diagnosis in horses with diarrhea and duodenitis-proximal jejunitis. Standard infection control methods used for salmonellosis should be adequate to control transmission of *C. difficile,* with the exception of disinfection. Because *C. difficile* is a spore-forming bacterium, disinfection can be difficult. Clostridial spores are highly resistant to environmental degradation and most disinfectants that kill *Salmonella* are ineffective against bacterial spores, with the exception of bleach (hypochlorite solutions) and accelerated stabilized peroxide. Peroxygen disinfectants may also be effective under optimal circumstances. An additional, albeit unsubstantiated, concern is the potential for zoonotic transmission of *C. difficile* from horses or cattle to humans. The strains of *C. difficile* isolated from animals are often indistinguishable from those that cause disease in humans. Therefore, animals infected with *C. difficile* should be considered as potential sources of zoonotic infections in humans.

Cryptosporidium parvum

Animals of all ages in a variety of host species have been shown to shed *C. parvum* oocysts, but the shedding prevalence is much greater in young animals, and the primary infection control hazard involves

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shedding by diarrheic neonates, especially calves. This is because of the extraordinary numbers of oocysts shed by affected young animals, the small infectious dose, and the hardiness of organisms. Affected calves can shed more than 10^7 oocysts per gram of feces during peak shedding, whereas humans and other animals can be clinically infected with fewer than 100 oocysts, although there does appear to be some difference among individuals as well as among strains. To further complicate control, oocysts are profoundly resistant to all disinfectants that can be regularly used in hospitals. Research has shown there are different lineages of *C. parvum* that relate to host range; genotype 1 appears to only infect humans whereas genotype 2 (sometimes called *bovine genotype*) infects a wide variety of other species including domestic large animals and humans. Cryptosporidiosis is an important zoonotic disease hazard in veterinary personnel, and there are a number of documented outbreaks involving animal caretakers. *Cryptosporidium* is considered to be a relatively common nonviral cause of self-limiting diarrhea in immunocompetent persons, particularly children. Clinical disease can be severe and even life threatening in immunocompromised persons. Diarrheic neonates can be easily and inexpensively screened using direct microscopic examination of fecal smears prepared with acid-fast stains. Regardless, it is very prudent to house diarrheic neonates in isolation and handle with strict barrier precautions and hand-hygiene protocols. Personnel cleaning these housing areas should avoid using high-pressure water to minimize the risk of aerosol and droplet exposure. This is complicated by the inherent resistance of coccidian parasites to all disinfectants, which necessitates the reliance upon vigorous scrubbing with soap and rinsing with copious amounts of water in decontamination efforts. The likelihood of inadvertent oral exposures while cleaning can be reduced by using face shields or disposable masks along with gloves and fastidious attention to hand hygiene.

Equine Rotavirus

Although outbreaks of rotavirus are fairly common on breeding farms, outbreaks in veterinary clinics are rare. Equine rotavirus is of most concern in facilities with a large neonatal caseload. Rotavirus may be shed in the feces of affected foals, clinically normal foals, and adult horses. Thus, prevention of exposure is difficult. However, it is likely that clinically affected foals are the most common source of infection, through direct contact or common vehicle exposure. As a result, isolation of affected animals and the use of barrier precautions are the most important infection control measures. With the exception of disinfectants, protocols directed at control of *Salmonella enterica* should be adequate for rotavirus control. Little specific information is available regarding the relative effectiveness of different disinfectants on equine rotavirus. However, as a nonenveloped virus, equine rotavirus should be expected to be resistant to environmental degradation and many disinfectants commonly used in veterinary medicine. The use of phenolics has been recommended because of their better activity in the presence of organic debris, but evidence of efficacy is lacking and toxicity is a concern. Oxidizing agents probably have similar to superior effectiveness and may be preferable because they have a much lower potential for toxicity.

Bovine Viral Diarrhea Virus and Border Disease Virus

The closely related members of the genus *Pestivirus* are not commonly considered disease hazards caused by HCAI, but this may be more because of a lack of detection than the lack of occurrence. The main infection control hazard is related to exposure of susceptible pregnant cattle, sheep, goats, or camelids to persistently infected (PI) animals, which continuously shed large amounts of virus. The long period between infection of pregnant females and the birth of affected offspring complicates the ability to make relevant observations about the origin and frequency of HCAI. As such, it may be important to encourage or require vaccination of valuable pregnant cattle or alpacas prior to admission. In addition, animals known or suspected to be PI should be managed in isolation with barrier precautions to minimize transmission. This includes neonates showing signs of congenital infection. Increased infection control precautions should also be used with animals from herds with a recent history of disease related to these viruses. Direct contact with PI animals is an efficient method of transmission, but limited research shows that calves can be infected through contact with contaminated stalls and through droplet or aerosol exposure over a distance of at least 1.5 m.[63] Appropriate use of cleaning and disinfection methods should readily decontaminate the environment, and all common disinfectants are effective against these viruses under optimal conditions.

Strangles (*Streptococcus equi equi*)

An important aspect of *S. equi* control is identification and management of subclinically infected animals. Syndromic guidelines for isolation upon admission (i.e., isolation when patients are admitted from farms with a recent history of clinical *S. equi* infections, or isolation of horses with fever of unknown origin or unexplained nasal discharge) can help in managing potentially infectious horses so that they can be isolated pending the results of screening. The ubiquitous nature of *S. equi* and the possibility that essentially any hospitalized horse could be a subclinical carrier means that there is an ever-present, if low, likelihood of *S. equi* introduction into the hospital environment. Experience suggests that routine universal screening of horses admitted to veterinary hospitals is not necessary to control HCAI caused by *S. equi*. However, screening and isolation of horses from farms with endemic *S. equi* would be a reasonable control strategy. Standard infection control measures, including preventing direct contact of hospitalized animals, optimizing hand hygiene, using appropriate cleaning, and disinfection, should be useful for reducing the risk of *S. equi* transmission should a colonized horse be admitted. Prompt examination and isolation of horses developing fever of unknown origin during hospitalization can indicate which horses should be removed from the general population before the onset of bacterial shedding. Vaccination in the face of an outbreak with vaccines that are currently available is not recommended because of a lack of proven efficacy and concerns regarding development of purpura hemorrhagica. There is also no evidence of a need to require vaccination of elective cases prior to hospital admission. *S. equi* is susceptible to all common disinfectants, when used properly.

Equine Influenza

Influenza is one of the most contagious diseases affecting horses. Immunity is transient and horses can be repeatedly affected during their lifetime. There is no carrier state, and maintenance in a population is dependent upon transmission from one acutely infected horse to another. In horse populations aggregated at racetracks, shows, or other venues, attack rates can reach 15% to 30%.[64] The incubation period from exposure to onset of clinical signs is typically about 2 to 4 days, which commonly coincides with the onset of virus shedding, although viral shedding can sometimes start before the onset of clinical signs. Horses are often febrile and obtunded at the onset of disease. Paroxysmal coughing is a classical sign of influenza infection that develops in some horses as disease progresses. Because of its contagious nature, identification of multiple acutely febrile horses can be an early indication that influenza virus is spreading in the population. Rapid identification and confirmation of animals shedding virus allows initiation of efforts to minimize contagious spread. Antigen detection assays are commercially available and very useful for rapid confirmatory testing (e.g., Directigen Flu A, BD Diagnostic Systems, Sparks, Md.). However, this assay has limited sensitivity; virus shedding was detected in only approximately 30% of clinically affected horses during outbreaks using this assay, so tests should be performed on multiple clinically affected horses and interpreted in the aggregate for the population.[65] Negative test results for individual samples should be interpreted with caution because of the consequences associated with not using appropriate control measures during an outbreak of a highly contagious disease. PCR tests are available and may be more sensitive than antigen detection assays, but published validations of these assays are generally unavailable.

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Influenza virus can be transmitted through aerosol, droplet, and contact transmission and can easily be transmitted over several feet in respiratory aerosols generated by coughing horses. As such, horses confirmed to be infected should be managed in complete isolation with full barrier precautions, paying strict attention to hand-hygiene protocols. Influenza virus can survive on surfaces at most for a few days in a cool, moist environment. As an enveloped virus, influenza is susceptible to damage from extreme environmental conditions and is readily inactivated by all common disinfectants if they are properly applied. Whereas clinically affected animals are the most likely to shed large amounts of virus, in nonaffected horses sampled during large outbreaks, seroconversion and virus shedding can be found in about 30% and 5% of the exposed populations, respectively.[64,65] As such, it is prudent to increase infection control precautions for all exposed but apparently unaffected horses in order to minimize risks of transmission. Early vaccination of all horses with intranasal vaccine may be of value in abbreviating the course of an epidemic. If new admissions are allowed when there is an elevated risk of influenza virus infection, horses should be required to be recently vaccinated prior to admission with vaccines having proven efficacy (preferably a minimum of 2 weeks prior to admission). Regardless of vaccination history, it is unwise to admit very young or immunocompromised horses when there is an increased risk of infection with influenza virus. Influenza virus is susceptible to all common disinfectants, when used properly.

Equine Herpesviruses

Equine herpesvirus types 1-5 are ubiquitous in horse populations and are highly contagious. EHV-1 and EHV-4 are the most widely recognized as important causes of outbreaks of disease in horses, and HCAI have been noted for both agents. EHV-4 infections are associated with contagious respiratory disease that principally affects horses under 3 years of age. EHV-1 infections are associated with respiratory disease, neurologic disease, peracute pulmonary vasculitis, abortion, and neonatal mortality in congenitally infected foals. The potential for contagious spread of herpesvirus myeloencephalitis was dramatically highlighted in 2011 when infections among horses at a horse show in Ogden, Utah, resulted in subsequent spread to documented clinical infections in 180 horses (29% with neurologic disease) on 63 premises located in 14 states and Canadian provinces, and subsequent euthanasia/death of 14 horses.[14,15] Documented spread of infections within hospitals as well as at home premises of previously hospitalized horses further highlight risks for HCAI with EHV-1.[8-10] Immunity is relatively short lived, and infections likely occur throughout the life of horses. Many, if not most, of these infections are undetected or occur with only mild clinical signs. The most common clinical sequel of infection is mild respiratory disease during the first 2 years of life. More infrequently, EHV-1 infections can result in more severe complications such as abortions in pregnant mares or paralysis. All EHV-1 and EHV-4 infections originate in the respiratory tract, but epidemiologic evidence suggests that contact and droplet transmission among horses in relative proximity is much more common than aerosol transmission over greater distances. Fever is commonly the initial clinical sign exhibited by infected horses, and identification of multiple acutely febrile patients can be an early indication of nosocomial spread of equine herpesvirus in the population. Most horses can be shown to be latently infected with EHV-1 and EHV-4 by the time they reach adulthood, and subsequently any hospitalized horse might serve as a source of infection for other patients by recrudescing virus in response to stresses of disease, hospitalization, and transport. However, clinical experience suggests that EHV-associated HCAI most commonly originate from clinically affected horses. As such, rapid identification of animals suspected of being infected, isolation of affected horses with complete segregation of materials used in their care, and use of barrier precautions with appropriate hand-hygiene protocols are generally effective for minimizing risks for HCAI. All horses exhibiting ascending weakness, paresis, or paralysis should be suspected of EHV-1 infection and managed in isolation until the animal can be proven to have stopped shedding or another diagnosis is confirmed. Herpesvirus infection should also be promptly ruled out in horses with upper respiratory disease or fever of unknown origin. Use of PCR testing as an adjunct to thorough clinical investigation is often extremely useful for this purpose. Herpesviruses are enveloped viruses and routine cleaning and disinfection procedures should be adequate for decontamination of surfaces, assuming appropriate protocols are followed. PCR testing of nasal secretions is the most useful assay for rapid confirmatory testing. Serial testing of horses is useful for establishing that shedding has stopped because field data and study involving experimental infection have shown that shedding can be intermittent and negative results for individual tests must be interpreted with caution.[10] Although many laboratories offering PCR testing now provide information about the ORF30 genotype (D vs. N or sometimes labeled as "neurotropic" and "non-neurotropic" genotypes), both genotypes can cause neurologic disease, both genotypes of virus are contagious, and both genotypes can cause epidemics of disease. As such, this information should not affect the level of caution that is taken with infected or exposed horses.[66] Without adjunctive testing, infected horses should be quarantined for a minimum of 28 days after cessation of disease. Using serial testing as a confirmatory adjunct, this quarantine period might be shortened to 14 days after cessation of disease.[9,66] Field data from one outbreak suggest that about 60% of horses can be shedding virus at the onset of clinical disease irrespective of the severity of clinical signs, and shedding can persist for 10 to 14 days after disease onset.[10]

EHV-3 is less commonly considered as a problem regarding HCAI, but it has been noted to be spread through contact with contaminated materials during reproductive procedures as well as between horses during coitus. As such, it is a notable hazard for practices that specialize in reproductive services. EHV-3 causes coital exanthema, a pustular disease affecting the vulva and vagina of mares and the penis and prepuce of stallions. Appropriate cleaning and disinfection of materials used in reproductive examinations, avoiding use of examination sleeves and gloves with multiple horses, and rigorous adherence to sound infection control precautions for breeding populations should control the spread of EHV-3. The prevalence of latent EHV-3 infections is not well documented. Recently, evidence association between respiratory disease in young horses and EHV-2 or EHV-5 infection has been published,[67] but the significance of these agents in the occurrence of HCAI is unknown.

Enveloped viruses, including all herpesviruses, are susceptible to all common disinfectants, when used properly.

Methicillin-Resistant *Staphylococcus aureus*

MRSA is emerging as an important veterinary and zoonotic pathogen. In large animals, MRSA infections have been most commonly identified in horses and pigs. Transmission of MRSA between these species and attending personnel can occur, and MRSA colonization and infection appear to be an emerging occupational risk associated with large animal veterinary practice. Transmission of MRSA is thought to mainly occur through direct or indirect contact between infected or colonized people or horses, and hospitalized horses. Aerosol transmission from MRSA-contaminated dust is a concern in intensive indoor housing situations, particularly swine barns. The potential for droplet and airborne transmission in less intensive situations is unknown and may be limited. The largest problem related to HCAI with MRSA in large animals has been associated with the infection and colonization of equine patients. Infections are principally noted at surgical sites and wounds, whereas colonization predominantly occurs in the nasal passages, although gastrointestinal colonization has also been noted. If not identified by active surveillance, colonized horses can be silent yet prolific reservoirs for infection of humans and horses. Prevention of MRSA transmission requires careful attention to practices that prevent contact and common vehicle transmission, including use of good hand-hygiene practices, restriction of horse contacts and isolation of infected or colonized animals, and use of specific measures aimed at identifying carriers. All colonized or infected horses should be treated as

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infectious, housed in isolation and handled with strict attention to contact barrier precautions. Screening by culture of nasal swabs collected at the time of admission can help control MRSA in areas where it is endemic in the community or the horse population; however, the need for routine screening varies depending on the facility, the MRSA prevalence in the patient population, and other factors. Although colonized personnel can be a source of infection of patients, staff screening is fraught with complex issues (e.g., privacy, occupational health) and is difficult to justify in the absence of an ongoing outbreak that is uncontrolled with improvement in routine infection control practices. Various studies have demonstrated high rates of MRSA carriage among equine veterinary personnel, so it is reasonable to assume that all equine facilities regularly have one or more colonized staff. For this reason, good attention to standard hygiene and infection control practices is critical. *Staphylococcus aureus* is susceptible to most disinfectants, if used properly.

Coxiella burnetti

Coxiella burnetti is the causative agent associated with Q-fever. Although most infections in humans are subclinical, personnel who contact livestock have a greater risk of infection and disease that can be severe and even fatal in a small portion of cases. It is also highly infectious, has a low infective dose, and can be transmitted through contact as well as by droplet and airborne routes. *Coxiella burnetti* can be found in a variety of animal species, but zoonotic transmission is most commonly associated with periparturient ruminants (especially small ruminants) and aborted fetuses. Serum antibody tests, antigen detection assays, and PCR can be used to identify infected animals, but the sensitivity of these assays has been questioned. Because of the potential significance of clinical infections in humans, all attending personnel should be appropriately aware of the zoonotic potential and risks associated with Q-fever. The risk of serious clinical consequences should be noted in particular by pregnant women and people with valvular heart disease or who are immunosuppressed. Medical histories for individuals and flocks should be considered to determine if there is an indication that *C. burnetti* may be a greater than average risk. Infection control measures that could be used to minimize hazards to people with a high risk of clinical infection include isolating periparturient small ruminants, paying strict attention to hand-hygiene protocols, and use of respiratory protection and barrier nursing precautions when handling potentially infected animals. Particular care should be taken during parturition and when handling aborted fetuses and newborn small ruminants. For animals known to be infected, care should be used when cleaning and disinfecting stalls or other housing environments, and contaminated bedding and other materials should be handled cautiously. *Coxiella burnetti* is susceptible to most disinfectants, if used properly.

Antimicrobial Resistance and Drug Use

While antimicrobials are undoubtedly required for proper management of a significant percentage of hospitalized large animals, it is reasonable to consider whether antimicrobial resistance and antimicrobial drug use impacts the occurrence or the ability to control HCAI. The first relates to outbreaks of HCAI with bacteria that are resistant to multiple antimicrobial drugs. These outbreaks are not extremely common but are a noted occurrence in human and veterinary hospitals and often occur in association with care in specific hospital units such as a critical care or surgery facility. Agents frequently identified in association with these outbreaks include enteric organisms such as *Escherichia coli* and enterococci, commensal opportunists such as *S. aureus,* as well as *Pseudomonas* and other bacteria. Significant research into these organisms has identified specific strains and even specific genes that are commonly identified in association with agents responsible for these outbreaks (e.g., MRSA, vancomycin-resistant enterococci [VRE], and extended spectrum β-lactamase–producing Enterobacteriaceae). The role that antimicrobial use in specific patients or even in specific hospitals has in promoting the occurrence of outbreaks of HCAI is not always conclusive. However, some experimental evidence does show that treatment with a specific antimicrobial drug is associated with an increased propensity for shedding of bacteria that are resistant to analogous drugs,[68] and the presence of multiple resistance genes can result in co-selection of resistance for multiple drugs following use of a single antimicrobial. Thus, common use of a particular drug within a hospital could apply selective pressure that more generally promotes colonization with resistant bacteria,[69] or it could enable or promote the survival of specific bacterial strains capable of causing epidemics of HCAI (e.g., VRE and MRSA). These concerns are supported by specific documentation that antimicrobial drug exposure can be associated with increased likelihood of shedding of enteropathogens[70,71] and multidrug-resistant pathogens.[72] In addition, antimicrobial drug exposure is a recognized risk factor for colitis in horses, which can be one of the most important infection control concerns in large animal facilities. Thus, efforts to reduce antimicrobial use and ensure logical (prudent) use can be beneficial to the individual patient and other hospitalized animals, in addition to the more abstract concerns about pressure toward emergence of antimicrobial resistance.[68] Surveillance aimed at benchmarking the use of antimicrobial drugs over time or to monitor use for specific conditions or in specific circumstances (e.g., outside of regular hours) may be useful for guiding policy decisions, but it is not useful for identifying specific occurrences of imprudent use. Of greatest importance is education so that all individuals with prescribing power understand the issues and the reasons for careful antimicrobial use. Measures such as developing selection algorithms for patients with specific types of disease and restricting the use of certain drug classes (e.g., glycopeptides) used by some facilities may decrease the likelihood of some occurrences of HCAI.[29]

Management of Donor Animals

It is increasingly common to use animals owned by hospitals or veterinary personnel as donors for blood and ingesta (e.g., rumen fluid) transfer to patients. Animals used for this purpose should be known to have a very low risk of contagious diseases, should be housed away from hospitalized patients, should be clinically healthy at the time of specimen recovery, and should be screened periodically for diseases that could be transmitted by use of transfer products. Diseases of concern that might be transferred by blood products from ruminants include bovine leukemia virus, bovine viral diarrhea and border disease viruses, and anaplasmosis; similarly, horses should be screened for equine infectious anemia infection. Ingesta donors should be screened for Johne's disease *(Mycobacterium avium paratuberculosis)* and *Salmonella enterica*.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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Prevention, Detection, and Response to Transboundary (Foreign) Animal Diseases

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Perhaps a private veterinary practitioner's most critical responsibility is his or her role as the nation's front line for detection and defense against exotic and transboundary animal diseases (TADs). These are important, transmissible livestock diseases that are presently absent from the United States. If introduced, they would cause significant adverse economic or national animal, public, or environmental health consequences. Although many of these disease threats are known, new or "emerging" diseases may also impact the United States and affect human, animal, or ecosystem well-being. The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS) has primary responsibility for addressing foreign and emerging diseases of livestock and poultry, and works closely with state animal health officials (SAHOs), private veterinary professionals, and the livestock industry to monitor for and to detect, control, eradicate, or mitigate the impacts of TADs on the livestock industries and the public. Box 47-1 shows a list of the diseases successfully eradicated from the United States. The *Code of Federal Regulations* (CFR), Title 9, part 53[1] details the federal government's list of reportable diseases of livestock and poultry and its policies and procedures for the diagnosis, appraisal, euthanasia, and disinfection of livestock and poultry infected with these diseases. The list specifically includes foot-and-mouth disease (FMD), rinderpest, contagious pleuropneumonia, exotic Newcastle disease (END), highly pathogenic avian influenza (HPAI), and "any other communicable disease of livestock or poultry that in the opinion of the Secretary constitutes an emergency and threatens the livestock or poultry of the United States."[1] In addition to the federal reportable disease list, many states require the reporting of additional specific disease conditions beyond those named in the Code of Federal Regulations (CFR). Additional diseases specified by states may include diseases of public health importance, such as equine encephalomyelitis, or other endemic diseases of industry concern, such as bovine trichomoniasis. Licensed, practicing veterinarians are responsible for maintaining a familiarity with the federal reportable disease list as well as those of the states in which they practice. The reportable disease list for each state can be obtained through the office of the state veterinarian. States may also have their own more specific policies and procedures for the diagnosis, appraisal, euthanasia, and disinfection of livestock and poultry infected with such reportable diseases. Box 47-2 lists some reportable diseases of horses.

The World Organization for Animal Health, Office of International Epizootics (OIE)[2] is an international organization, representing more than 167 member countries, that seeks to provide leadership and guidelines to ensure transparency and solidarity in the management of the global animal disease situation. The OIE publishes health standards for international trade in animals and animal products as well as criteria for the validation and certification of diagnostic assays. Policies and procedures that the federal government implements to manage the intrusion of TADs into the United States are often aligned with the OIE health standards and guidelines to help ensure the most rapid and efficient recovery of U.S. exports. Another equally important function of the OIE is to provide an early warning system to enable countries to have rapid situational awareness and to act quickly to protect themselves when outbreaks of OIE-reportable diseases are confirmed in member countries. More than 130 animal diseases are reportable to the OIE. It is important to remember that some of the domestic diseases that are present in the United States, such as bluetongue, are reportable to the OIE and have implications on U.S. trade with countries that are free of those diseases.

To protect the long-term overall health and viability of U.S. animal agriculture, any incursion of a TAD must be rapidly identified and controlled. In the United States, ideally control of an outbreak of a TAD leads to the complete eradication of the disease and return to pre-outbreak disease status. These TAD eradication efforts present significant short-term costs to affected industries as well as the government and the public. In some cases these effects become long term, lasting for years, and industries may never fully recover. Most TAD incursions have a significant economic cost associated with disease control and the eradication efforts. The costs associated with TAD control include the direct costs of disease control as well as the potential loss of foreign trade and the indirect costs to the affected industries that result from the implemented control measures, such as livestock movement restrictions and biosecurity. Direct costs to the government include personnel costs, indemnity costs (cost to buy diseased animals from producers for destruction), and the cost of necessary supplies and equipment for euthanasia, carcass management, and disinfection. In addition to these direct control costs, one of the most immediate consequences of a TAD occurrence in the United States would be the loss of export markets and disruption of normal industry business continuity in the United States. The indirect costs to the affected livestock sectors and other affected industries that would result from the disruption of the normal business continuity are likely to be the most significant economic costs. One example of an indirect cost or loss associated with disease control may be the reduction or loss of income for a dairyman who is no longer able to ship his raw milk across state lines to his customary milk processor. For all TADs, early detection and rapid application of situational awareness to assess the extent of the outbreak, followed by efficient implementation of necessary controls to minimize further spread, will minimize the overall impact of the outbreak on the

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BOX 47-1

Years When Foreign Animal Diseases Were Eradicated from the United States

1892—Contagious bovine pleuropneumonia
1929—Foot-and-mouth disease
1929—Fowl plague
1934—Glanders
1942—Dourine
1943—Texas cattle fever
1959—Vesicular exanthema
1959—Screwworm (southeastern United States)
1966—Screwworm (southwestern United States)
1971—Venezuelan equine encephalitis
1973—Sheep scabies
1974—Exotic Newcastle disease
1978—Classical swine fever
1985—Highly pathogenic avian influenza
1999—*Brucella melitensis*
2003—Exotic Newcastle disease
2004—Highly pathogenic avian influenza
2006—Bovine spongiform encephalopathy
2008—Turkey rhinotracheitis
2010—Rabbit hemorrhagic disease

BOX 47-2

Reportable Diseases of Horses*

African horse sickness
Contagious equine metritis
Dourine
Equine infectious anemia
Equine viral arteritis
Glanders (*Burkholderia mallei*)
Hendra virus
Japanese encephalitis
Piroplasmosis
Venezuelan equine encephalomyelitis
Vesicular stomatitis virus

*This list will vary by state.

BOX 47-3

U.S. Department of Agriculture (USDA) Accreditation Requirements

- Graduate from an AVMA-accredited school.
- Complete an initial accreditation training and attend a core orientation program.
- Complete a state-specific orientation.
- Submit accreditation application to the appropriate USDA Veterinary Services office.
- Be licensed and accredited in each state in which you plan to perform official work.

BOX 47-4

Standards for Accredited Veterinarians (9 Code of Federal Regulations, 161.3)

- Immediately report program diseases.
- Know current regulations.
- Perform activities according to regulations.
- Accurately complete all forms.
- Personally inspect all animals.
- Properly identify reactors.
- Maintain proper biosecurity.
- Use regulated materials according to the regulations.
- Maintain security of official tags, forms, and certificates.

affected producers, the affected industries, and the U.S. economy as a whole.

The risk of a TAD incursion into the United States today is much greater than it has been in the past, for two main reasons. First, there has been a rapid expansion of international trade and travel. With a greater volume of people, animals, and animal products entering the United States on a daily basis, the opportunity for a TAD to be unintentionally introduced is much higher than it has been in the past. Second, in the wake of the terrorist attacks in the United States on September 11, 2001, there is heightened awareness and concern about the possibility of agroterrorism, or the deliberate introduction of a biologic agent targeting livestock for the purposes of inflicting economic damage and societal instability in the United States. Whether a TAD is intentionally or unintentionally introduced, the detection of the first case as soon as possible is critical to minimizing the overall impact of the resulting outbreak.

Private veterinary professionals need to be familiar with the clinical signs associated with TADs, especially those that can be easily confused with clinical signs of domestic or endemic diseases. When veterinary professionals are concerned about the possibility of a TAD in clients' animals, they need to contact a federal or state animal health official, who will consult with them on the history of the herd or flock and then may examine the affected animals and take and submit necessary samples for testing at no expense to the producer or veterinarian. Testing will be prioritized by disease and level of concern after understanding the history and clinical status of the livestock of concern. Both the livestock producer and private veterinarian should be contacted with regular updates as test results become available. Several hundreds of investigations such as these occur annually in the United States, and fortunately most lead to the determination that a TAD is not involved. It is the TAD that goes undetected or unreported for some time because of lack of vigilance or reluctance to report that will cause major economic harm to the livestock industry and the nation. Veterinary practitioners should not be concerned about reporting a suspected TAD and having it turn out to be a domestic disease problem, since it is important that the animal disease emergency response system be tested regularly to ensure that it is as efficient and effective as possible. Most importantly, the impact of a delay in detection of a true TAD could be catastrophic.

U.S. Department of Agriculture National Veterinary Accreditation Program[3]

The USDA established the national veterinary accreditation program in 1907 to provide a mechanism to enable private veterinary practitioners to work on behalf of the federal government to certify animals for certain types of interstate and international movement and to assist in controlling damaging animal diseases. The current mission of the National Veterinary Accreditation Program (NVAP) is to ensure the health of the nation's livestock and animal population and to protect public health and well-being. NVAP's goal is to maintain the effective cooperation and use of private veterinary practitioners for regulatory work in a manner that is consistent with international trade requirements and enables the safeguarding of animal health. APHIS VS administers the NVAP. Participation in NVAP is voluntary and is not mandated by the federal government. Box 47-3 provides a list of the requirements for a veterinarian wishing to become accredited by the USDA. Accredited veterinarians participating in NVAP must carry out their duties according to the Standards for Accredited Veterinarian Duties described in CFR Title 9, Part 161. Box 47-4 lists the standards for accredited veterinarians. USDA veterinary accreditation is specific to a given state, so one needs to contact the USDA APHIS VS office in the state where he or she is practicing to obtain accreditation in that specific state. One

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BOX 47-5

Clinical Signs or Observations That Indicate a Foreign Animal Disease Should Be Considered

- Vesicles in oral cavity or around coronary bands
- Central nervous system signs
- Mucosal diseases
- Hemorrhagic septicemias
- Larvae in wounds
- Unusual (ornate) ticks
- High morbidity or mortality
- Unusual or unexplained illness or symptoms

BOX 47-6

Diseases of Cattle That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease*

Foot-and-mouth disease
Vesicular stomatitis
Rinderpest
Bovine viral diarrhea (BVD)
Malignant catarrhal fever
Bovine herpes mammillitis
Bovine papular stomatitis
Pseudocowpox
Infectious bovine rhinotracheitis

*Reportable diseases are highlighted in bold.

BOX 47-7

Diseases of Small Ruminants That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease*

Foot-and-mouth disease
Vesicular stomatitis
Malignant catarrhal fever
Peste des petits ruminants
Bluetongue—certain serotypes
Contagious ecthyma (ORF)
Epizootic hemorrhagic disease (EHD)

*Reportable diseases are highlighted in bold.

requirement of USDA VS for accredited veterinarians is reporting of all suspected TADs to state or federal animal health officials for evaluation and any necessary testing. Box 47-5 lists some of the clinical signs that should alert a private veterinarian that a TAD should be considered.

Accredited veterinarians are the backbone of U.S. regulatory programs for livestock and poultry diseases in the United States. The responsibilities of an accredited veterinarian are extraordinary. In fact, the United States depends extensively on accredited veterinarians for many official functions (e.g., inspecting, testing, and certifying animals trade). Livestock producers who ship animals domestically or export animals internationally rely on the expertise of accredited veterinarians to help ensure that exported animals meet the requirements of the receiving location and will not introduce diseases into the receiving state or country. The accreditation program has served the animal industry well for many years and remains integral to its continued growth. There are currently more than 60,000 active accredited veterinarians in the national database, and these accredited veterinarians are instrumental in providing national capability to perform competent health certifications and to maintain extensive disease surveillance and monitoring. Today, more than 80% of all U.S. veterinarians are accredited and work cooperatively with federal and state animal health officials in NVAP.

The accreditation process has changed dramatically over the years. In the 1980s and early 1990s, veterinarians were required to pass a written examination, but currently accreditation requires completion of an initial accreditation training and then attendance at a core orientation program in addition to meeting the other requirements listed in Box 47-4. In 2006, APHIS proposed two different categories or levels of accreditation. Category I includes all animals except food and fiber species, horses, birds, farm-raised aquatic animals, all other livestock species, and zoo animals that can transmit exotic animal diseases to livestock. Category II is for all animals. At the same time APHIS published a proposal to amend the regulations in the Federal Register, which added requirements for supplemental training and renewal of accreditation for both categories every 3 years. Details of the renewal process can be found at the USDA APHIS VS accreditation website (http://www.aphis.usda.gov).[3]

Overview of Foreign Animal Disease Investigation and Response

Protecting the nation's livestock and poultry industries, and therefore a large segment of the U.S. agricultural economy from TADs, involves four basic principles or phases of emergency management: prevention, preparedness, response, and recovery. To be effectively executed, these phases require preplanning, cooperation, and communication among individuals, groups, and organizations at the local, state, regional, and national levels. Livestock and poultry owners; veterinarians in private clinical practice; industry groups; federal, state, and local governments; universities; veterinary diagnostic laboratories; and the consideration of public opinion and perception must all be included in emergency response preparation and planning. A response to a TAD outbreak will be carried out in accordance with the guidelines established by the National Response Plan (NRP) and using the National Incident Management System (NIMS) and the incident Command System (ICS). Veterinarians who are interested in participating in either TAD emergency response or animal disaster response efforts, either as temporary employees or volunteers, must be familiar with these systems before an event occurs, in order to be effectively integrated into the response effort. There are both online and classroom-based training programs offered by federal, state, and local emergency response agencies to provide basic ICS training and certification. The Federal Emergency Management Agency (FEMA) offers several Web-based, self-paced courses.[4]

Although the details of the clinical signs and epidemiology of the TADs themselves are discussed in detail in other sections of this book, many additional references and resources are available to practicing veterinarians to help them keep apprised of the clinical presentation and importance of these diseases as well as to whom to report suspected cases. Two excellent references for disease-specific information are *Foreign Animal Diseases: "The Gray Book,"* revised in 2008[5] (available at http://www.usaha.org/Portals/6/Publications/FAD.pdf), and the website of the Center for Food Security and Public Health of Iowa State University,[6] http://www.cfsph.iastate.edu.

Prevention and Preparedness

Early recognition of a TAD may be difficult because many domestic diseases seen by veterinarians on a more routine basis have clinical signs or presentations similar to those of a TAD (e.g., foot-and-mouth disease [FMD]) and because some TADs may have mild clinical signs that could allow it to spread undetected for a period of time (e.g., low pathogenic form of classical swine fever [CSF]). Examples of both domestic and transboundary vesicular or ulcerative diseases, which may be difficult to distinguish clinically in cattle, are presented in Box 47-6. A similar list for small ruminants is provided in Box 47-7. The increased likelihood and severe consequences of an introduction of a TAD into the United States requires private

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veterinarians to be continually vigilant for unusual emerging animal health conditions or situations. To be best prepared to identify these uncommon disease conditions, veterinary practitioners must understand how they may manifest and what clinical signs they may possess. Participation in continuing education programs aimed at increasing awareness of the clinical signs and presentations of TADs can facilitate this necessary awareness. Education and awareness should also be extended to livestock producers and their employees who will likely be the first individuals to recognize an unusual problem in the herd or flock they work daily.

An important component of the prevention programs for TAD incursions in the United States is the implementation by APHIS VS of policies and procedures related to the importation of live animal species or products into the United States. These import rules vary by animal and product, as well as by country of origin. APHIS VS monitors the OIE reports of the world animal health status and continually updates these importation requirements accordingly. These requirements may dictate the quarantine and possible testing of specified animal species for specific periods before animals are allowed to enter the United States. As of 2012, there were three animal import centers, located in New York, Miami, and Los Angeles, through which animals could enter the country legally. Illegal importation of such animals and animal products via other channels poses a significant risk to U.S. agriculture. APHIS port veterinarians are responsible for the examination of the animals, their identification, and evaluation of health certificates and permits for accuracy at the importation stations. If the requirements are not met or the animals are found to be diseased, the animals are refused entry. Once it has been determined that an animal is healthy, all the test results are negative, and all the requirements have been met, then the animal can be released to its owner and the state of destination is notified of the animal's movement into that state.

Detection

Although historically, border controls and import procedures have been largely effective in keeping TADs out of the United States, there is always the possibility that a TAD could appear in the United States by either unintentional or intentional means. The responsibility for rapidly detecting, confirming, and effectively responding to incursions of TADs is primarily that of APHIS VS in cooperation with livestock and poultry owners, veterinarians in private clinical practice, and state animal health officials. An additional challenge for early detection of TADs is that very few ongoing active surveillance programs exist that routinely test for TADs in targeted, high-risk livestock populations or in conjunction with screening for clinically indistinguishable domestic diseases in state or regional animal diagnostic laboratories. Because many of the TADs can mimic domestic diseases, a TAD may not be properly identified for some time if the condition is believed to be a domestic disease problem and if it is investigated with only that limited differential in mind. Even a single day's delay in identifying a TAD can result in significantly greater disease spread or economic impact owing to the large amount of livestock movement that occurs in the United States on a daily basis. Prompt reporting, investigation, and diagnosis can prevent a TAD from spreading further, can reduce the overall economic impact of the event, and can reduce the likelihood that the disease may become endemic in a wildlife or arthropod reservoir.

The most likely person to initially suspect a TAD is the producer or private veterinarian called by the producer to investigate an unusual disease condition. It is critical that any time a TAD is suspected, it is reported to state or federal animal health officials for expedited investigation and testing as necessary. The state animal health official, usually the "state veterinarian," and federal veterinarians working for USDA APHIS VS routinely work to increase awareness of such conditions and reporting information among the state's private veterinarians and livestock producers. These activities require the support and assistance of state and university veterinary diagnostic laboratories, the Cooperative Extension Service, state and federal meat and poultry inspection services, universities, animal scientists, market operators, livestock and poultry producers, and private veterinarians.

For TAD outbreaks to be detected quickly, any suspicious signs or situations indicative of a TAD must be promptly reported to a state veterinarian, a USDA VS federal veterinarian, or both so that a TAD can be confirmed or ruled out. Private veterinarians are knowledgeable regarding the occurrence of various domestic animal diseases in their practice area and the history of such diseases on their clients' farms and ranches. This type of historical information and a herd's vaccination and animal movement history are critical to assessing the likelihood of a suspected TAD. Working with the herd veterinarian and the producer, the investigating state or federal, specially trained, foreign animal disease diagnostician (FADD) will use the herd history and clinical investigation to assess the likelihood that the situation involves a TAD and to determine the appropriate sample(s) to collect, the method of sample delivery, and what precautions must be taken at the site while test results are pending. Samples are submitted to the National Veterinary Services Laboratories (NVSL) in Ames, Iowa, or to the Foreign Animal Disease Diagnostic Laboratory (FADDL) at Plum Island, New York, to confirm the presence or absence of a TAD. On the basis of initial TAD investigation findings, often before the laboratory has completed testing of the samples, state and federal officials in the affected state may take action to quarantine affected animals at the site of the suspected case, increase surveillance in the area, and initiate steps to gather further information to assess the situation and characterize and control the outbreak if necessary.

An improvement to TAD testing options in the United States at laboratories who are members of the National Animal Health Laboratory Network (NAHLN) is that under USDA directive 580.4, select laboratories have been trained and proficiency-tested to run tests for TADs, with the permission of the NVSL director, the state animal health official, the USDA area veterinarian in charge and USDA VS may run designated tests in parallel with NVSL or FADDL. When approved, this parallel testing process can provide more timely "preliminary" results, which may facilitate local decision making. At present assays for FMD, CSF, HPAI, and END have been successfully transitioned to some NAHLN laboratories for use in national surveillance programs.

Other diagnostic tools that may be available in the near future include deeply multiplexed nucleic acid, antibody, or protein assays that could allow the simultaneous screening for many disease agents (domestic and TADs) in one reaction at a reduced cost per agent. Although these types of assays are still undergoing development and validation in the veterinary community, similar assays are in use as part of the BioWatch program, a human biothreat agent surveillance system operated by the Centers for Disease Control and Prevention in Atlanta, Georgia. Once validated and accepted as useful components of national TAD surveillance programs, such assays could become useful components of targeted surveillance programs in the United States.

Response, Management, and Control

A TAD response will be conducted according to the guidelines set forth in the NRP. This response plan incorporates best practices and procedures from various emergency management disciplines and integrates them into a unified structure that forms the basis of how the federal government coordinates with state, tribal, and local governments and the private sector during all national response incidents, including animal disease outbreaks. Under the NRP, the USDA is the lead agency coordinating the protection of agriculture and natural resources. All national responses are conducted in accordance with NIMS, which established a national emergency response framework to allow local, state, tribal, and federal agencies to more efficiently and quickly work together in an emergency. The NIMS uses the ICS to organize the response. The ICS is designed to be expandable and to meet the needs associated with incidents of all

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sizes, to allow individuals from a variety of agencies to meld more efficiently into a common management structure, to be cost-effective by reducing duplication of effort, and to provide needed logistic, administrative, and operational staff. There are five main management functions in the ICS: incident command, operations, planning, logistics, and finance and administration. Most veterinarians work in the operations or planning sections during a TAD response. The operations section is where the bulk of the tactical field work is conducted, such as diagnosis, surveillance, and depopulation.

Once a TAD has been confirmed by the USDA, the notification and coordination process for all involved parties begins. This includes federal, state, international, local, industrial, and public stakeholders. Conference calls, electronic notification, and press conferences may be used to communicate key messages. In addition, if agroterrorism is suspected, the Federal Bureau of Investigation and the Department of Homeland Security will be involved in the response efforts. If a zoonotic disease is suspected, the state and federal public health departments will also become involved. Federal officials will notify the OIE of the situation so that the international communities will be made aware of the change in the nation's animal health status. Throughout the response, the goal will be to maintain accurate, timely communications regarding the status and progress of the eradication efforts.

Once the diagnosis of the initial case is confirmed, there is still much information to be gathered to determine the true magnitude and extent of the situation. The species affected, history of the diseased herd or flock (including recent animal movements), and stage of disease in the affected animals will provide valuable information regarding the likely extent of disease. Outbreaks can be large or small, simple or complex, and localized or widespread. Timely development of situational awareness will be critical for mobilizing the necessary resources to effectively respond to the situation.

Tactical measures or procedures used to control an outbreak may include quarantine and/or animal movement restrictions; biosecurity; epidemiologic investigations; surveillance for disease in surrounding areas; vaccination, euthanasia, or treatment of affected animals; carcass disposal; disinfection; vector control; and education campaigns. The exact approach to control will vary by disease, affected region, and extent of the outbreak. In many cases federal and state veterinarian resources will be sufficient to respond to and control the situation quickly. However, if the outbreak is large or widespread, it may require the use of additional personnel resources.

When APHIS VS requires temporary personnel to assist with disease eradication, it uses the National Animal Health Emergency Response Corps (NAHERC),[7] a roster of preregistered private veterinarians and animal health technicians, to assist with the control efforts. Private veterinarians may be enlisted to examine herds or flocks for clinical disease, vaccinate animals, collect laboratory samples, perform necropsies, collect epidemiologic data, and euthanize infected animals. During the United Kingdom's (UK) 2001 FMD epidemic, many private veterinarians found that their practices had little business because their clients stopped using routine services as a precaution to reduce the chances that their farms would become infected. In other situations, veterinarians found that their clients' farms were lost (eliminated) as a result of disease control efforts. In many cases these private veterinarians joined the UK FMD task force as temporary veterinary inspectors (TVIs) working on behalf of the British government to assist in the control of the epidemic. Veterinarians in the United States who may be interested in registering for NAHERC should contact their state USDA APHIS VS office or go to the NAHERC website for details (http://www.aphis.usda.gov/animal_health/emergency_management/naherc.shtml).

Recovery

The goal of a recovery process is to return the nation to a status equal to or better than what existed before a TAD outbreak. Full recovery can be a long and arduous process. Recovery activities include payment for animals and materials destroyed for disease control purposes, successful decontamination, clean-up and restocking of affected premises, renegotiation and reestablishment of international trading status, and government and industry's reassurance to the consumers and the public that the outbreak has been managed successfully. The OIE's international animal health code sets the minimum standards that guide when a country may recover its disease-free status. The OIE standards, which are a key component to the resumption of international trade, serve to reassure the international community that trading with a previously affected country is now safe.

The ultimate cost of an outbreak for a country, its producers, affected industries, and the public can be quite high. Many of the costs beyond those to the directly affected industries can be significant yet difficult to quantify.

The Future of Foreign Animal Disease Detection and Response

A comprehensive review of the national framework for addressing animal diseases was conducted by a committee assembled by the National Academies and published in 2005.[8] The committee's findings and recommendations support the compelling need for significant changes to create a new future for animal health in the United States. Some of the key findings included the need for new tools for detection, diagnosis, and risk analysis and the expansion of the NAHLN's capabilities for both routine and emergency diagnostics. The committee called for the colleges of veterinary medicine to lead an effort to develop a national animal health education plan to educate and train individuals from all sectors in disease prevention and early detection and to recruit veterinary students into careers in public health, food systems, biomedical research, diagnostic laboratory investigation, pathology, epidemiology, ecosystem health, and food-animal practice. Since animal health has broad implications, ranging from the health of individual animals and the well-being of human communities to issues of global security and the adequacy of the global food supply, there is significant need to plan carefully for the future. The committee concluded that given the changing nature of the risks to animal health in this country, it is unlikely that the current philosophy on how to protect animal health will be adequate in the future.

Extraordinary changes including continued globalization will continue to present new threats to U.S. agriculture and necessitate the continued vigilance of the veterinary and agricultural communities. Although state and federal governments are working to provide more targeted, active surveillance programs, private veterinary practitioners, who on a daily basis provide health care to the national herd, will remain the core of the nation's early warning system for TAD surveillance. Therefore, their awareness of TADs and willingness to serve in the critical role of being part of the nation's early warning system for TADs will continue to be a cornerstone of national defense against the intrusion and the devastating impact of such diseases.

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Other Valuable Foreign Animal Disease-Related Web Resources

Plum Island Animal Disease Center. [WWW page]. http://www.ars.usda.gov/Main/docs.htm?docid=3833, accessed Sept 15, 2013.

National Biosecurity Resource Center for Animal Health Emergencies National Biosecurity Resource Center for Animal Health Emergencies. [WWW page]. http://www.biosecuritycenter.org, accessed Dec 19, 2013. (Includes a reference library and information on cleaning and disinfection, personal protective equipment, carcass disposal, and reportable diseases.)



• CHAPTER 48

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Use of Biologics in the Prevention of Infectious Diseases

W. DAVID WILSON, NICOLA PUSTERLA, PAUL J. PLUMMER, and VICTOR S. CORTESE, *Consulting Editors*

Current Concepts in Equine Vaccination and Infectious Disease Control

W. David Wilson and Nicola Pusterla, *Consulting Editors*

General Considerations

Programs for controlling infectious diseases are important components of management practices directed toward maximizing the health, productivity, and performance of horses.[1] Infectious disease in an individual horse or outbreaks of infection in a group occurs when horses experience challenge with an infectious agent at a dose sufficient to overcome resistance acquired through previous natural exposure to the disease or through vaccination. For this reason, programs for controlling infectious diseases should have the following three goals:

1. To reduce exposure to infectious agents in the horses' environment
2. To minimize factors which diminish resistance
3. To enhance resistance through the use of vaccines (vaccination alone cannot be expected to prevent disease; management practices must reduce challenge with infectious pathogens)

The incidence of infectious disease in horse populations tends to rise with an increased number and stocking density of susceptible horses at a facility, with movement of horses on and off the facility, and with favorable external environmental and management influences. Other factors that influence the risk of acquiring infection and developing disease include the age, type, breed, gender, and use of the animals; geographic, climatic, and other environmental factors; facilities' layout and management practices; and history of exposure to or vaccination against individual diseases.

The conditions on breeding farms, in performance and show horse barns, and at racetracks are ideal for introduction and transmission of infectious diseases, particularly those of the respiratory tract. On breeding farms, the introduction and commingling of horses of various ages and origins and the high proportion of young susceptible horses and pregnant mares create a situation that poses special problems and demonstrates some important considerations in the practice of disease control. The risk of acquiring infection can be reduced by maintaining distinct groups by age and function. Resident mares and foals should be kept separate from weanlings, yearlings, horses in training, and visiting mares. Visiting mares and other horses entering the farm should have a negative test result for equine infectious anemia (EIA), either by ELISA or the Coggins AGID test, and should be appropriately vaccinated and dewormed before arrival. They should be received and maintained in barns and paddocks separate from the resident farm population. Preferably, a specific group of caretakers should attend to incoming horses, and footbaths, separate equipment, and a clean change of coveralls and boots should be used.

New arrivals should be quarantined for 30 days and monitored for signs of contagious disease. The rectal temperature should be recorded at least once daily, and any prophylactic procedures not done before arrival should be performed. Foaling mares being sent to a distant breeding farm for breeding should be transported 6 to 8 weeks before foaling; this permits timely exposure to resident pathogens at the destination farm, which allows the mare's immune system to mount a response and concentrate antibodies in the colostrum to improve passive protection of the foal. Mares being shipped short distances for breeding can be transported during estrus and returned to the farm on the same day to reduce the risk of the foal acquiring infection.

Regardless of the type of equine facility, any horse that becomes ill with a possibly contagious disease should be isolated, preferably in an air space separate from the remainder of the herd, for at least 10 days beyond complete abatement of clinical signs. Separate equipment should be used, and if a separate group of caretakers is unavailable for these animals, workers should always complete their work with healthy horses before handling sick horses. Caretakers should wash their hands and boots thoroughly between horses and wear different outer clothing or coveralls. Stalls that have housed sick horses should be cleaned thoroughly, disinfected, allowed to dry, and left empty as long as possible. This approach is particularly important in dealing with organisms such as *Streptococcus equi* that can survive in a protected moist environment for several weeks.[2]

In most equine enterprises, vaccination is important to the overall management program for controlling infectious diseases. No "standard" vaccination program can be recommended for all horses; each situation must be evaluated individually by weighing the risk of acquiring infection and the medical and economic consequences of infection against the cost and expected efficacy of the product or products being considered for inclusion in the program, and their potential for inducing adverse reactions. Cost should include expenses incurred and money lost during the time the horses are out of competition, labor and medication expenses if the animals develop clinical disease and require treatment, and the expenses in time, labor, and vaccines required for proper immunization. The client's expectations should be realistic, and the veterinarian should explain the following points carefully:

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- Vaccination minimizes the risk of infection but does not prevent disease in all circumstances.
- The primary series of vaccines and booster doses should be administered appropriately before likely exposure.
- Horses in a population are not all protected equally nor for an equal duration after vaccination.
- Whenever possible, all horses in a herd should be vaccinated on the same schedule; this simplifies record keeping, minimizes replication and transmission of infectious agents in the herd, and optimizes herd immunity by protecting those animals that responded poorly to vaccination.

A properly administered licensed product should not be assumed to provide absolute effective protection during any given field epidemic. Copies of the vaccination and health maintenance records should accompany each horse leaving the facility for sales, training, or breeding. Similarly, owners of equine facilities should establish prerequisites for vaccination of all horses entering the facility and request that copies of the vaccination records accompany those horses.

Client expectations and the goals of disease control programs vary considerably. In performance horses, the goal generally is to minimize time spent out of training and thereby maximize earning potential. In this case, an enforced period of rest owing to infectious disease has much more profound economic consequences than a similar recommendation for a barren broodmare or backyard horse. On the other hand, many owners of backyard horses diligently vaccinate against even low-risk diseases, despite the expense involved, to keep their horses healthy.

Only federally licensed vaccines should be used, and strict attention must be paid to the manufacturer's recommendations for storage, handling, and routes of administration to maximize the product's efficacy and safety. However, research or clinical experience may support alternate protocols for vaccination that will improve the vaccine's efficacy without increasing adverse effects. The length of time necessary to induce a protective immune response should be considered in relation to expected exposure. When inactivated (killed) vaccines are administered by intramuscular (IM) injection, for example, optimal protection is generally not achieved until 2 to 3 weeks after completion of the primary series, or 1 or more weeks after administration of a booster dose. Inactivated vaccines administered IM generally induce a greater serologic response when an initial series of 3 doses is given rather than the 2-dose series recommended by most vaccine manufacturers. Whereas a 3- to 4-week interval between the first and second doses of vaccine is generally appropriate, a longer interval of 3 to 5 months between the second and third doses appears to optimize priming of the immune system and protection.

The primary role of authorities charged with licensing vaccines in North America has traditionally been to ensure vaccine purity and safety, with less emphasis placed on documentation of efficacy.[3-5] Consequently, little published information was available in the past documenting the efficacy of most vaccines licensed in North America. The situation has improved substantially in recent years, to the extent that published efficacy data are available for almost all equine vaccines licensed in North America since 1999. Field experience and some experimental evidence suggest that the efficacy of vaccines directed against different diseases varies considerably and that efficacy also varies among the vaccines from different manufacturers directed against the same disease.[6-8]

Vaccination is unlikely to confer protection more durable than that produced by recovery from natural disease, especially when the route of vaccination (usually IM) is different from the route of natural infection; this is because vaccines frequently do not evoke the full array of protective immune responses induced by natural infection.[9,10] For example, the efficacy and durability of protection induced by parenteral vaccines against respiratory tract pathogens are frequently questioned.[4,5,10] In part this reflects the fact that parenterally administered vaccines are generally poor inducers of the local mucosal immune responses that are important for effective protection against infection of the respiratory tract.[4,9,10] In addition, immunity achieved after natural infection with some respiratory tract pathogens is short lived.

Considerations for Use of Vaccines in Broodmares

The primary goals of vaccination programs for broodmares are (1) prevention of diseases that pose a risk to the mare or her fetus, and (2) maximizing the level of colostral antibodies that will be passively absorbed by the neonatal foal after nursing, thus providing it with protection against diseases that pose a risk during the first few months of life. Additional considerations in selecting vaccines for use in pregnant mares include (3) safety to the mare and fetus, (4) the potential for interference between multiple vaccines administered simultaneously, and (5) the influence of pregnancy on vaccine responses.

PROTECTING THE MARE AGAINST DISEASES THAT POSE A RISK TO THE MARE OR HER FETUS. Broodmares are at risk of exposure to the same diseases as performance and pleasure horses, so they should be regularly vaccinated against all core and specific risk-based diseases according to published recommendations. The high horse traffic and high concentration of foals and young horses that typify many breeding farms contribute to a high risk of exposure to contagious respiratory diseases, including equine herpesvirus (EHV)-4, EHV-1, influenza, and strangles. Inclusion of influenza in vaccination protocols for broodmares is routinely recommended, and addition of EHV-4 and strangles vaccines is frequently recommended when conditions of significant risk are anticipated. Vaccination of mares against equine viral arteritis (EVA) before breeding may be indicated when they are to be bred to a known or suspected EVA carrier stallion, either by natural cover or by artificial insemination. Whereas protection of the broodmare, fetus, or herdmates against the abortifacient effects of EHV-1 or EVA is the primary goal underlying inclusion of these antigens in vaccination protocols for broodmares, the goal of protecting the foal features at least as prominently in the rationale for vaccinating mares against tetanus, West Nile virus (WNV), eastern equine encephalitis (EEE), western equine encephalitis (WEE), rabies, influenza, EHV-4, and strangles. Inclusion of rotavirus and botulism vaccines in protocols for pregnant mares is directed almost exclusively at protecting the young foal against these diseases.

MAXIMIZING MATERNALLY DERIVED ANTIBODY TRANSFER. Maintaining consistent broodmare vaccination protocols, which typically include administration of booster doses of vaccines during the last 2 months of gestation, will not only protect the mare but also maximize the likelihood that a uniformly high level of maternally derived antibody (MDA) transfer and passive protection will be achieved within the foal crop. This is particularly important for diseases that pose a risk to the foal during the first few weeks of life. Whereas intranasally administered vaccines may afford good protection to the mare, they are typically less effective than parenterally administered inactivated vaccines in stimulating high levels of circulating immunoglobulin (Ig)G, the isotype that is passively transferred to the foal in highest concentration. Parenterally administered vaccines are preferred over intranasally administered vaccines for vaccination of mares during late gestation.

VACCINE SAFETY IN BROODMARES. Consideration of vaccine safety in broodmares must take into account risks to the pregnancy and safety to the fetus. Potential adverse effects of vaccines on pregnancy are difficult to document even when large numbers of mares are used, unless obvious problems occur. Because fetal organogenesis occurs early in gestation, and this period is also characterized by substantial embryonic loss, even in normal mares it is sound practice to avoid administering vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail. Few vaccines carry specific label recommendations for use in pregnant mares and little published data exists to specifically document the safety of equine vaccines during pregnancy. Licensed vaccines that carry label

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recommendations for use in pregnant mares include two inactivated EHV-1 vaccines (Pneumabort-K+1b [Zoetis] and Prodigy [Merck Animal Health]) marketed for use in pregnant mares as an aid in prevention of EHV-1 abortion, the Calvenza line of inactivated influenza (Calvenza-03 EIV [equine influenza virus]), EHV-1 (Calvenza EHV), and influenza/EHV-1 combination (Calvenza-03 EIV/EHV) vaccines from Boehringer Ingelheim, one inactivated Potomac horse fever vaccine (Equine Potomavac [Merial]), and one vaccine licensed for prevention of type B botulism in foals (BotVaxB [Neogen]). One conditionally licensed vaccine (Equine Rotavirus Vaccine [Zoetis]) for prevention of rotavirus infection in foals is labeled for use in pregnant mares. While not specifically labeled for administration during pregnancy, widespread use in practice over many years has failed to document that any of the inactivated vaccines currently marketed for use in horses pose an unacceptable risk to pregnant mares. Therefore, pregnant mares are routinely vaccinated with inactivated vaccines directed against tetanus, EEE, WEE, WNV, influenza, EHV-4, strangles and, to a lesser extent, Potomac horse fever (PHF), rabies, and Venezuelan equine encephalitis (VEE). Similarly, adverse impacts on pregnancy have not been documented for modified live intranasally administered strangles (Pinnacle I.N. [Zoetis]) and influenza (Flu-Avert [Merck Animal Health]) vaccines or the modified live parenterally administered EHV-1 vaccine (Rhinomune [Boehringer Ingelheim]). Safety of the recombinant WNV and influenza vaccines (Recombitek [Merial]) should not be a significant concern because the modified live canarypox vector lacks the ability to infect mammalian cells. In addition, the equivalent canarypox-vectored influenza vaccine (ProteqFlu [Merial]) marketed in the United Kingdom is labeled for use during pregnancy. Although the *Flavivirus* chimera WNV vaccine (PreveNile [Merck Animal Health]) was not specifically labeled for use during pregnancy while it was on the market, more than 300 pregnant mares were vaccinated during safety trials for licensing, without apparent adverse effects on the conceptus. In contrast, modified live virus (MLV) VEE vaccines and live anthrax spore vaccines should not be used in pregnant mares. Protection of mares against the potential abortigenic effects of EVA infection is best accomplished by completing the primary immunization series before the mare enters the broodmare band and by administering subsequent boosters during the open period before rebreeding.[11]

The practice of booster vaccinating mares against multiple diseases to maximize colostral transfer of antibodies to the foal results in the typical broodmare receiving multiple doses of many vaccine antigens and adjuvants during her lifetime. In addition to stimulating high levels of antibody against a range of antigens, this practice may also predispose these mares to a higher rate of local and systemic adverse reactions, an issue that not only warrants further investigation but may force horse owners and veterinarians to carefully consider strategies for revaccination.

POTENTIAL INTERFERENCE BETWEEN MULTIPLE ANTIGENS ADMINISTERED CONCURRENTLY. The possibility that "competition" between multiple antigens will compromise the response to some or all of the administered antigens should be considered. When administration of multiple vaccines late in gestation is indicated, it is good practice to administer no more than 4 antigens at one time and to allow an interval of 3 to 4 weeks between administering different vaccines.

INFLUENCE OF PREGNANCY ON VACCINE RESPONSES. It is widely assumed that pregnant mares are fully capable of mounting appropriate cellular and humoral immune responses to vaccines, but this issue has received little research attention. Mares that have been primed before breeding appear to mount appropriate anamnestic responses to vaccines, but preliminary data suggest that the humoral response to primary vaccination with several inactivated vaccines, including West Nile Virus and rabies, may be downregulated during gestation, resulting in failure of some vaccinated mares to passively transfer specific antibodies to the foal via colostrum.

Vaccination of Foals and Influence of Maternal Antibodies on Vaccine Responses

Maternally derived antibodies (MDAs) and perhaps other immune effectors (e.g., lymphocytes) that are concentrated in colostrum and are passively transferred to the foal play a crucial role in defense against pathogens encountered during the first few months of life while endogenous immune function continues to mature. Passive transfer of MDAs should therefore be exploited in immunization programs for foals by consistently administering booster doses of selected vaccines to mares 4 to 8 weeks before foaling and by ensuring that foals ingest adequate amounts of high-quality colostrum within 24 hours of birth. Besides passively protecting the foal, MDAs may also exert a profound inhibitory effect on the active immune response of the foal to antigens, including those contained in vaccines. This phenomenon is known as *maternal antibody interference*.

Several studies reported during the 1990s brought this issue into focus by demonstrating that foals younger than 6 months of age consistently failed to mount serologic responses to inactivated influenza vaccines.[12-18] Of potentially greater concern was the finding that a high proportion of foals vaccinated under the cover of MDAs not only failed to seroconvert in response to the recommended primary series of two or three doses of influenza vaccine, but many also failed to respond to multiple additional doses administered during the next year, suggesting induction of a potentially detrimental immunotolerance-like phenomenon.[15,16,19] Our studies confirmed an apparent lack of response of foals to multiple doses of inactivated influenza vaccines when the hemagglutination inhibition (HI) test was used to detect serologic responses, but responses were detected when the same samples were assayed using sensitive isotype-specific enzyme-linked immunosorbent assay (ELISA). Rather than representing true tolerance, it appears MDAs may cause misdirection of the immune response away from the more important virus neutralizing IgGa and IgGb subisotypes in favor of the less effective IgG(T) sub-isotype of IgG.[12] Subsequent studies in which titers of total rather than antigen-specific IgG subisotypes were determined documented that the age-related increase in concentrations of IgGb lagged significantly behind increases in concentrations of other isotypes and remained below adult levels beyond 6 months of age.[20]

Maternal antibody interference has now been documented to be a significant issue for many other antigens, including tetanus, EEE, WEE, EHV types 1 and 4, contained in vaccines administered to foals.[12,21-25] Even low levels of antibody below those detectable by many routine serologic tests and below those thought to be protective can completely block the serologic response to some vaccines, resulting in a potentially prolonged period of susceptibility before the foal is capable of responding appropriately to vaccines.[24] These findings also indicate that it is not typically feasible to serologically test samples from foals to predict whether they will respond to particular vaccines. We now recommend that primary immunization with most vaccines containing inactivated antigens should be delayed until foals are 6 months of age or older, and with the exception of rabies vaccine, three doses of vaccine should be included in the primary series rather the two doses routinely recommended by vaccine manufacturers. Typically, the third dose stimulates a serologic response of greater magnitude and durability than two doses and may also contribute to a higher "set-point" for the response to subsequent booster doses.[12,24,26,27] In contrast to the results cited, maternal antibodies do not appear to exert a marked inhibitory effect on the immune response of foals to the inactivated, live recombinant, live chimera, or DNA West Nile virus vaccines, thereby permitting antibody-positive foals as young as 3 months of age to be immunized successfully.[26,28,29] Similarly, the canarypox-vectored recombinant influenza vaccine has been shown to efficiently prime foals in the presence of MDA.[30]

Study results should be interpreted with caution because only humoral responses are typically assessed in MDA interference studies, and infectious challenge is not performed to confirm that lack of serologic response equates to lack of protection. Lack of a serologic response may correlate well with lack of protection for some

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diseases and some vaccines, whereas for others this may not be the case. In contrast, the presence of a serologic response may not correlate well with protection, as is frequently the case for respiratory tract pathogens. Because many commercially available vaccines are inactivated, adjuvanted, and administered by IM injection, they have limited potential to stimulate cellular and mucosal responses, so serologic responses induced by these vaccines likely correlate well with their potential to induce protection. In turn, MDA interference with serologic responses to inactivated vaccines likely equates to failure to induce protection. In contrast, failure to detect a serologic response to a modified live, vectored, DNA, or mucosally administered vaccine may not equate to lack of protection, because vaccines of these types induce a broader array of systemic and local responses that may not be affected by MDAs.

If MDA interference were not an issue, the approach to vaccination of foals would be greatly simplified because primary vaccination against all of the important diseases could be completed before MDAs had declined to non-protective levels. In effect, the "window of susceptibility" would be eliminated. In reality, an attainable goal is to maximize the beneficial effects of MDAs while minimizing their negative impact on primary immunization. To best meet this goal it is necessary to decide which one (or both) of the following is the primary focus: (1) to protect the foal and weanling against specific high-risk infectious diseases that affect this age group and have the potential to cause significant disease, either directly or by predisposing to other secondary infections, or (2) to initiate primary immunization to protect against disease later in life.

Assessing risk takes into account both the likelihood the foal will become infected and the risk of serious sequelae or death if the horse does become infected and develop disease. If the disease affects the foal early in life, such as is the case with rotavirus (RV) infection, there is usually insufficient time to induce a protective immune response by actively immunizing the foal. Under these circumstances, the approach should be to maximize the degree of protection passively transferred from the dam via colostrum. Other diseases like rabies can affect horses of all ages, but the risk of acquiring infection is generally low.

Diseases of Moderate to High Risk to Young Foals but Low Risk to Adults

Diseases of moderate to high risk to young foals but low risk to adults include RV infection (on certain breeding farms in certain years) and, in geographic areas such as Kentucky and some other Eastern states, type B botulism. For these diseases, the following approach is appropriate:

- Booster-vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Introduce management practices to reduce exposure to the infectious agent.
- Vaccinate the foal if risk continues beyond the first few months of life.

Diseases of Moderate to High Risk for Weanlings and Older Horses but Lower Risk to Young Foals Born to Vaccinated Mares

Diseases of moderate to high risk for weanlings and older horses but lower risk to young foals born to vaccinated mares include EHV-4, EHV-1, strangles, influenza, tetanus, EEE, and WNV infection. For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in *most* foals. When several vaccine types are available for a particular disease, the vaccine that is least subject to MDA interference should be used. Introduce management practices to reduce exposure to the infectious agent while primary vaccination is being completed.
- If a two-dose primary series is recommended for adult horses, use three or more doses of vaccine in the primary series to improve the chances that foals that do not respond to earlier doses will respond to additional doses administered later.

Diseases of Low Risk to Foals

Diseases of low risk to foals in most circumstances include rabies, PHF, WEE, and EVA. For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling if the disease is a significant risk to adult horses and a vaccine shown to be safe for use in pregnant mares is available. If the available vaccines are not considered safe for use in pregnant mares, administer boosters before breeding.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in *any* foal (typically 9 months to 1 year of age)

Adverse Reactions to Vaccines

Though uncommon, the possibility always exists for adverse reactions (including anaphylaxis) associated with vaccine administration, so vaccines should be administered by or under the direct supervision of a veterinarian. Adverse reactions should be reported to the vaccine's manufacturer and the U.S. Department of Agriculture (USDA) (1-800-752-6255) or the U.S. Pharmacopeia (USP) Veterinary Practitioners Reporting Program (forms may be obtained or reports submitted by calling the USP at 1-800-487-7776). Anaphylaxis constitutes a life-threatening emergency requiring prompt treatment with epinephrine (0.01 to 0.02 mg/kg; equivalent to 5 to 10 mL of a 1:1000 dilution IM for a 450-kg horse). Repeated doses of epinephrine can be administered at 15-minute intervals if necessary. It has recently been shown that horses vaccinated with viral vaccines can develop IgE responses to non-target antigens, including bovine serum albumin (BSA), suggesting that subsequent administration of another viral vaccine containing the same component could elicit an adverse response, including anaphylaxis.[31]

Local irritant tissue reactions occur more frequently, particularly when polyvalent combination vaccines and injectable strangles vaccines are used. These reactions usually are self-limiting, but resolution can be promoted by parenteral or oral (PO) administration of nonsteroidal antiinflammatory drugs (NSAIDs), topical application of warm compresses or the cutaneously absorbed NSAID diclofenac (Surpass [IDEXX Pharmaceuticals, Greensboro, N.C.]), and gentle exercise. Significant reactions in the neck muscles may make the horse reluctant to lower or raise its head; feed and water buckets should be positioned accordingly. Occurrence of externally visible local reactions can be reduced by administration of the vaccine deep in the semimembranosus and semitendinosus muscles of the hindleg rather than in the neck, and by allowing the horse to exercise after vaccination. Horses that repeatedly react to polyvalent vaccines may benefit from NSAID administration before vaccination, administration of the individual antigenic components separately in different sites, use of a different brand of vaccine, use of a vaccine that can be administered by a route other than IM, or use of a vaccine that contains a different adjuvant or no adjuvant at all.

Some horses develop transient self-limiting systemic signs that may include fever, anorexia, lethargy, colic, diarrhea, tachycardia, and congested mucous membranes after IM administration of vaccines. Systemic signs are perhaps more common with certain vaccines but can be associated with any vaccine.[32,33] In addition, inactivated Immune Stimulating Complex (ISCOM) and live recombinant vectored tetanus and influenza combination vaccines have been shown to elicit a prominent acute phase inflammatory response of several days' duration in vaccinated horses.[34] A similar response likely occurs with other vaccines. It is therefore inadvisable to give horses any injectable vaccine within 2 weeks before a show, performance event, sale, or prolonged transportation. It may also be beneficial to minimize environmental dust when vaccinating horses known to have allergic airway disease or hypersensitivity.[32]

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TABLE 48-1

Types of Equine Vaccines Licensed in the United States

	Dead Vaccines		Live Vaccines		
Disease	Inactivated	Subunit	Modified-Live	Recombinant	DNA Vaccine
Tetanus		X			
Western equine encephalitis (WEE)	X				
Eastern equine encephalitis (EEE)	X				
Venezuelan equine encephalitis (VEE)	X				
West Nile	X			X, X (chimera)	X
Equine influenza	X		X	X	
Equine herpesvirus 1	X		X		
Equine herpesvirus 4	X				
Strangles		X	X		
Equine viral arteritis			X		
Rabies	X				
Potomac horse fever (equine neorickettsiosis)	X				
Botulism		X			
Rotavirus (conditional license)	X				
Equine rhinitis A virus (conditional license)	X				

If unacceptable reactions occur repeatedly, the need for continued annual or more frequent revaccination against individual antigens should be carefully reevaluated, taking into account risk of disease balanced against the risk of an adverse reaction. Many horses that experience adverse reactions have received many doses of many vaccine antigens, repeated over many years. In this situation, the vaccination protocol should be "pared down" so only the most essential antigens are administered and the maximum possible interval between boosters is employed. For diseases like rabies and tetanus for which resistance can reasonably be correlated with circulating antibody titer, one possible approach to define the maximum or optimal interval between booster doses would be to measure the antibody titer. Unfortunately, this approach is currently limited by the paucity of laboratories that offer this type of testing on a routine basis, inexpensively, and with a short turnaround time. Introduction of commercially available ELISA testing for antibodies to the SeM protein of *Streptococcus equi* subsp. *equi* (Equine Biodiagnostics-IDEXX, Lexington, Ky.) and neutralizing antibody testing for WNV virus (Cornell University, Colorado State University, the University of Florida, and the USDA Animal and Plant Health Inspection Service [APHIS] National Veterinary Services Laboratory) in recent years has made it possible to refine vaccination protocols for these diseases in horses that experience adverse reactions to vaccination. Testing for rabies antibodies is available through Kansas State University, and testing for antibodies to other pathogens may be available through state diagnostic laboratories.

Available Vaccines and the Concept of Core and Non-Core Vaccines

Fully licensed vaccines are now available in North America as aids to the prevention of tetanus, viral encephalomyelitis (EEE, WEE, VEE), WNV infection, influenza, EHV-1 and EHV-4 infection, strangles, rabies, EVA, PHF, and type B botulism. In addition, conditionally licensed vaccines are available to immunize horses against rotavirus and equine rhinitis A virus (ERAV). Tetanus, rabies, and viral encephalomyelitis caused by EEE, WEE, and WNV pose a threat to horses in all geographic areas and are therefore considered to be core diseases against which all horses in North America should be vaccinated. The abortigenic potential of EHV-1 warrants inclusion of this disease in the core for all pregnant broodmares. Although influenza is not routinely included as a core disease, vaccination against this highly contagious respiratory tract infection is strongly recommended for all horses likely to be co-located with horses from other facilities during transportation or at sales, shows, trail rides, races, or other events. The remaining diseases for which vaccines are available are considered "non-core" or "risk based." Indications for use of vaccines against these diseases will be discussed in relevant sections that follow later in this chapter. Table 48-1 details the types of vaccines licensed for use in horses in the United States. Tables 48-2 through 48-4 provide general guidelines for use of the most frequently indicated equine vaccines in foals, weanlings, yearlings, and adult horses under various management conditions and in various geographic locations.

Vaccination Recommendations for Specific Diseases

Tetanus

All horses are at risk for developing tetanus, an often fatal disease caused by a potent neurotoxin elaborated by the anaerobic spore-forming bacterium *Clostridium tetani*. Infection of tissues typically occurs via puncture wounds (particularly those involving the foot or muscle), open lacerations, surgical incisions, exposed tissues like the umbilicus of foals, and the reproductive tract of the postpartum mare (especially in the event of trauma or retained placenta). *C. tetani* is present in the intestinal tract and feces of horses, other animals, and human beings, and spores are abundant as well as ubiquitous in soil. Spores of *C. tetani* survive in the environment for many years, resulting in an ever-present risk of exposure of horses and people on equine facilities. Because tetanus is expensive to treat and has a high mortality rate, all horses should be actively immunized using tetanus toxoid as part of the core vaccination program. Active immunization reduces the need to administer tetanus antitoxin, the use of which is associated with risk of inducing potentially fatal serum hepatitis.

Protection against tetanus is mediated by circulating antibodies; toxin binding inhibition (ToBi) antibody titers of greater than 0.2 IU/mL are considered to be protective in the horse.[27,35] The many available vaccines are formalin-inactivated, adjuvanted toxoids that are inexpensive, safe, and potent antigens that induce an excellent serologic response and solid long-lasting immunity when administered according to manufacturer recommendations. Primary immunization involves administration of 2 doses of toxoid at 3- to 6-week intervals. Titers of specific antibody increase to protective levels within 14 days after administration of the second dose in the primary series and, in adult horses, persist at detectable levels for 12 months or longer, depending on the adjuvant system used in the vaccine.[27,35-37] A recent study documented substantial differences between currently licensed combination tetanus-encephalomyelitis vaccines with regard to the magnitude of the vaccine-induced tetanus specific IgGb and IgG(T) antibody responses.[8] The vaccine containing a Carbopol adjuvant induced substantially higher antibody titers

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TABLE 48-2

Guidelines for Vaccination of Adult Horses, Excluding Broodmares, Against Core and Non-Core (Risk-Based) Diseases

Disease/ Vaccine	Adult Horses (>1 Year of Age) Previously Vaccinated Against Disease Indicated	Adult Horses (>1 Year of Age) Not Previously Vaccinated Against Disease Indicated or Lacking a Vaccination History	Comments
Core Diseases*			
Tetanus (toxoid)	Toxoid: annual revaccination	Toxoid: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate annually.	Booster at time of penetrating injury or surgery if last dose was administered > 6 months previously
Eastern and Western equine encephalomyelitis (EEE, WEE)	Inactivated: annual revaccination in spring, prior to onset of vector season	Inactivated: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate annually prior to onset of next vector season.	Consider a 6-month revaccination interval for horses residing in endemic areas with a prolonged vector season (e.g., southeastern states).
West Nile virus (WNV)	Inactivated vaccine or live recombinant canarypox-vectored vaccine: annual revaccination in spring, prior to onset of vector season	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate annually prior to onset of next vector season. Inactivated *Flavivirus* chimera vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually prior to onset of next vector season. Live *Flavivirus* chimera vaccine: 1-dose primary series Revaccinate annually prior to onset of next vector season.	When using an inactivated product or live recombinant product, consider a 6-month revaccination interval for: • Horses residing in endemic areas with a prolonged vector season • Juvenile horses (<5 years of age) • Geriatric horses (>15 years of age) • Immunocompromised horses For naive horses being imported into an endemic area during vector season, preferred approach is to complete primary vaccination series prior to importation. If this approach is not feasible, protect horses from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (canarypox-vectored or live *Flavivirus* chimera) that have most rapid onset of immunity.
Rabies	Inactivated: annual revaccination	Inactivated: 1-dose primary series Annual revaccination	Booster vaccination induces persistently elevated levels of anti-rabies antibody.
Non-Core (Risk-Based) Vaccines†			
Anthrax (rarely indicated)	Live spore vaccine: annual revaccination	Live spore vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Annual revaccination	Use only in endemic areas or in the face of an outbreak. Antimicrobial drugs must not be given concurrently with this vaccine. Administer subcutaneously in neck. Use caution during storage, handling, and administration. Consult a physician immediately if human exposure to anthrax vaccine occurs by accidental injection, ingestion, or otherwise through conjunctivae or broken skin.
Botulism	Toxoid: annual revaccination	Toxoid: 3-dose primary series; second dose 4 weeks after first dose; third dose 4 weeks after second dose Annual revaccination	
Equine herpesvirus (EHV)	Inactivated or modified live: semiannual (6-month interval) to annual revaccination (see comments)	Inactivated or modified live: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 4-6 weeks after second dose	A 6-month revaccination interval is recommended for: • Horses < 5 years of age • Horses on breeding farms or in contact with pregnant mares • Horses housed at facilities with frequent equine movement on and off the premises • Performance or show horses at high risk

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TABLE 48-2

Guidelines for Vaccination of Adult Horses, Excluding Broodmares, Against Core and Non-Core (Risk-Based) Diseases—cont'd

Disease/ Vaccine	Adult Horses (>1 Year of Age) Previously Vaccinated Against Disease Indicated	Adult Horses (>1 Year of Age) Not Previously Vaccinated Against Disease Indicated or Lacking a Vaccination History	Comments
Equine influenza	Modified live cold-adapted intranasal, inactivated, or live canarypox-vectored recombinant vaccine: semiannual for horses with ongoing risk of exposure Annual for horses at low risk for exposure	Modified live cold-adapted intranasal vaccine: 1-dose primary series Revaccinate semiannually to annually. Inactivated vaccines: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 3-6 months after second dose Revaccinate semiannually to annually. Live canarypox-vectored recombinant: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate semiannually to annually.	
Equine viral arteritis (EVA)	Modified live virus vaccine: annual revaccination. Stallions and teasers: vaccinate 3-4 weeks before start of breeding season. Mares: vaccinate when open.	Modified live virus vaccine: 1-dose primary series (see comments)	Prior to initial vaccination, intact males and any horses potentially intended for export should undergo serologic testing and be confirmed negative for antibodies to EAV. Samples for testing should be collected shortly before, or preferably at, the time of vaccination. All first-time vaccinated stallions should be isolated for 3 weeks after vaccination before being used for breeding.
Potomac horse fever (PHF)	Inactivated vaccines: semiannual to annual revaccination	Inactivated vaccines: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate semiannually to annually.	Because protection following vaccination is incomplete and short lived, a revaccination interval of 3-4 months has been advocated in endemic areas when disease risk is high. However, strategic revaccination to maximize immunity prior to expected peak challenge in summer and fall is the preferred approach if vaccination is elected as an adjunct to strategic environmental control measures.
Rotavirus	Not applicable	Not applicable	
Strangles	Inactivated M-protein subunit or modified live intranasal vaccines: semiannual to annual revaccination	Inactivated M-protein subunit vaccines: 2- to 3-dose series; second dose 2-4 weeks after first dose; third dose (when recommended by manufacturer) 2-4 weeks after the second dose. Revaccinate semiannually. Modified live intranasal vaccine: 2-dose primary series administered IN; second dose 3-4 weeks after first dose Revaccinate semiannually to annually.	Vaccination is not recommended as a strategy in outbreak mitigation, but vaccination may be warranted on farms with endemic strangles, with the understanding that the risk of adverse vaccine reactions is higher in exposed horses.

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*Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

†Non-core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

than those containing either saponin or squaline combined with surfactants.[8] Revaccination once annually is recommended.

No published challenge studies are available to document the speed of onset or duration of protection induced by tetanus toxoid preparations currently licensed in North America. Conclusions regarding their efficacy are therefore based on the serologic response obtained in horses and laboratory animals and on field experience. However, a challenge study conducted in Europe almost 60 years ago found that horses were resistant to challenge 8 days after receiving a single injection of tetanus toxoid, before antibody could be detected in their serum.[38] A second study demonstrated that a series of 3 doses of tetanus toxoid induced protection lasting for at least 8 years, and perhaps for life, even when antibodies could no longer be detected.[35] A recent study in Europe documented that protective levels of antibody (>0.2 IU/mL as measured by tetanus toxin-binding ELISA) persist for at least 18 months after revaccination of horses previously primed with a 2-dose series of a tetanus toxoid/influenza ISCOM vaccine.[39] In contrast, tetanus has been documented in vaccinated horses in North America,[40] although survival was strongly associated

Text continued on p. 1448

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TABLE 48-3

Guidelines for Vaccination of Broodmares Against Core and Non-Core (Risk-Based) Diseases

Disease/Vaccine	Previously Vaccinated Broodmares	Broodmares Not Previously Vaccinated or Lacking a Vaccination History	Comments
Core Diseases*			
Tetanus	Toxoid: annual revaccination 4-6 weeks prepartum	2-dose primary series; second dose 4-6 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose.	Booster at time of penetrating injury or surgery if last dose was administered more than 6 months previously
Eastern and Western equine encephalomyelitis (EEE, WEE)	Annual, 4-6 weeks prepartum	2-dose primary series; second dose 4 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose.	Consider a 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season (e.g., southeastern states).
West Nile virus (WNV)	Annual, 4-6 weeks prepartum	It is preferable to vaccinate naive mares when open. When risk is high, initiate primary series as follows: Inactivated vaccine or live recombinant canarypox-vectored vaccine: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose. Inactivated *Flavivirus* chimera vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually, prior to onset of the next vector season. Live *Flavivirus* chimera vaccine: 1-dose primary series Revaccinate 4-6 weeks prepartum, depending on timing of first dose.	When using an inactivated product or live recombinant product, consider a 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season. For naive mares being imported into an endemic area during the vector season, preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (canarypox-vectored or live *Flavivirus* chimera) that have the most rapid onset of immunity.
Rabies	Annual, prior to breeding OR 4-6 weeks prepartum	1-dose primary series Annual revaccination prior to breeding OR 4-6 weeks prepartum	Because booster vaccination induces persistently elevated levels of anti-rabies antibody. This vaccine may be given post foaling, but prior to breeding, to reduce the number of vaccines given to mares prepartum.
Equine herpesvirus (EHV)	3-dose series with product labeled for prevention of EHV-1 abortion Administer during fifth, seventh, and ninth months of gestation.	3-dose series with product labeled for prevention of EHV-1 abortion Administer during the fifth, seventh, and ninth months of gestation.	
Non-Core (Risk-Based) Vaccines†			
Anthrax	Not recommended for use during gestation	Not recommended for use during gestation	
Botulism	Annual, 4-6 weeks prepartum.	3-dose series: first dose during eighth month of gestation; second dose 4 weeks after first dose; third dose 4 weeks after the second dose	
Equine influenza	Inactivated vaccines: semiannual, with one dose administered 4-6 weeks prepartum Canarypox-vectored vaccine: semiannual, with one dose administered 4-6 weeks prepartum	Inactivated vaccine: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 4-6 weeks prepartum Canarypox-vectored vaccine: 2-dose primary series; second dose 4-6 weeks after first dose but no later than 4 weeks prepartum	The MLV intranasal influenza vaccine can be used to protect pregnant mares against influenza, but its use for prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody. Administration of an inactivated or canarypox-vectored vaccine for the pre-foaling booster is the preferred approach.
Equine viral arteritis (EVA)	Administration during pregnancy is not recommended unless risk of exposure is high.	Administration during pregnancy is not recommended unless risk of exposure is high.	Mares potentially intended for export should undergo serologic testing immediately prior to initial vaccination and be confirmed negative for antibodies to EAV.

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TABLE 48-3

Guidelines for Vaccination of Broodmares Against Core and Non-Core (Risk-Based) Diseases—cont'd

Disease/Vaccine	Previously Vaccinated Broodmares	Broodmares Not Previously Vaccinated or Lacking a Vaccination History	Comments
Potomac horse fever (PHF)	Semiannual, with one dose administered 4-6 weeks prepartum	2-dose primary series: first dose: 8-10 weeks prepartum; second dose 4-6 weeks prepartum	Strategic environmental control measures are important for effective control.
Rotavirus	3-dose series: first dose at 8 months' gestation; second dose 4 weeks after first dose; third dose 4 weeks after second dose	3-dose series: first dose at 8 months' gestation; second dose 4 weeks after first dose; third dose 4 weeks after second dose	Check serum concentration of immunoglobulin in foal to verify adequate passive transfer.
Strangles	Inactivated M-protein subunit vaccines: semiannual, with one dose given 4-6 weeks prepartum	Inactivated M-protein subunit vaccines: 3-dose primary series; second dose 2-4 weeks after the first dose; third dose 4-6 weeks prepartum	The MLV intranasal strangles vaccine can be used to protect pregnant mares, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody. Administration of an inactivated M-protein vaccine for the pre-foaling booster is the preferred approach.

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*Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

†Non-core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

TABLE 48-4

Guidelines for Vaccination of Foals, Weanlings, and Yearlings Against Core and Non-Core (Risk-Based) Diseases

Disease/Vaccine	Foals and Weanlings (<12 Months of Age) of Mares Vaccinated during Prepartum Period Against Disease Indicated	Foals and Weanlings (<12 Months of Age) of Mares Not Vaccinated during Prepartum Period	Yearlings	Comments
Core Diseases*				
Tetanus (toxoid)	Toxoid: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-5 months after second dose (i.e., 10-12 months of age)	Toxoid: 3-dose primary series; first dose at 1-4 months of age; second dose 4-6 weeks after the first dose; third dose 3-5 months after second dose	Annual	
Eastern and Western equine encephalomyelitis (EEE, WEE)	Inactivated vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age, prior to onset of next vector season	Inactivated vaccine: 3-dose primary series; first dose at 3-4 months of age; second dose 4 weeks after first dose; third dose 4-8 weeks after second dose (shorter interval applies to foals receiving their primary series during mosquito season)	Annual in spring, prior to onset of vector season	Month of birth and geographic location influence risk of exposure to insect vectors at specific foal ages. Scheduling of primary immunization series may be amended by administration of EEE/WEE vaccines to foals at an earlier age if vectors are present. In the southeastern United States where vectors are present year-round, an additional dose should be added to primary series, beginning at 2-3 months of age. Fourth dose in the primary series should be administered at 10-12 months of age.

Continued

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TABLE 48-4

Guidelines for Vaccination of Foals, Weanlings, and Yearlings Against Core and Non-Core (Risk-Based) Diseases—cont'd

Disease/ Vaccine	Foals and Weanlings (<12 Months of Age) of Mares Vaccinated during Prepartum Period Against Disease Indicated	Foals and Weanlings (<12 Months of Age) of Mares Not Vaccinated during Prepartum Period	Yearlings	Comments
West Nile virus (WNV)	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age, prior to onset of next vector season	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 3-dose primary series; first dose at 3-4 months of age; second dose 4 weeks after first dose; third dose 4-8 weeks after second dose (shorter interval applies to foals receiving their primary series during mosquito season)	Annual in spring, prior to onset of vector season	Month of birth and geographic location influence risk of exposure to insect vectors at specific foal ages. Scheduling of primary immunization series may be amended by administration of WNV vaccines to foals at an earlier age if vectors are present. In the southeastern United States where vectors are present year-round, primary vaccination series should be initiated at 3 months of age.
	Live *Flavivirus* chimera vaccine: 2-dose primary series; first dose at 5-6 months of age; second dose at 10-12 months of age, prior to onset of next vector season	Live *Flavivirus* chimera vaccine: 2-dose primary series; first dose at 5-6 months of age; second dose at 10-12 months of age prior to onset of next vector season		There are no published data regarding use of the live *Flavivirus* chimera product in foals <5 months of age. If administered to foals <5 months of age, the recommended schedule for primary vaccination should be completed by administration of a dose of vaccine at 5 months of age or older.
Rabies	2-dose primary series: first dose at 6 months of age; second dose 4-6 weeks after first dose; next dose at 10-12 months of age	1- or 2-dose primary series: first dose at 3-4 months of age; second dose 4-6 weeks after first dose (not necessary if dam is seronegative); next dose at 10-12 months of age	Annual	For foals of mares with an unknown vaccination history, either follow approach outlined for foals of vaccinated mares, or determine serologic status of foal (or mare) and use results to classify foal as either being from a vaccinated or unvaccinated mare.
Non-Core (Risk-Based) Vaccines[†]				
Anthrax (rarely indicated)	Not applicable because vaccination of pregnant mares is not recommended	No age-specific guidelines are available for this vaccine. Manufacturer's recommendation is for primary series of 2 doses administered subcutaneously (in the neck) at a 2-3–week interval.	Annual, in spring	Anthrax vaccination is rarely indicated—only in focal endemic areas. Antimicrobial drugs must not be given concurrently with this vaccine. Exercise caution during storage, handling, and administration of this live bacterial product. Consult a physician immediately should accidental human exposure (via mucous membranes, conjunctivae, or broken skin) occur.
Botulism (type B toxoid)	3-dose primary series: first dose as early as 2-3 months of age; second dose 4 weeks after first dose; third dose 4 weeks after second dose	3-dose primary series: first dose as early as 1-3 months of age; second dose 4 weeks after first dose; third dose 4 weeks after second dose	Annual	Limited information suggests that maternal antibody does not interfere with vaccination, so foals at high risk may be vaccinated as early as 2 weeks of age.
Equine herpesvirus (EHV)	Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-5 months after second dose (i.e., 10-12 months of age)	Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-4 months after second dose (i.e., 10-12 months of age)	Semiannual (6-month interval)	The benefit of intensive vaccination programs directed against EHV-1 and EHV-4 in foals and young horses is not clearly defined because, despite frequent vaccination, infection and disease continue to occur. It is difficult to induce active immunity before weanlings experience field challenge.

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TABLE 48-4

Guidelines for Vaccination of Foals, Weanlings, and Yearlings Against Core and Non-Core (Risk-Based) Diseases—cont'd

Disease/ Vaccine	Foals and Weanlings (<12 Months of Age) of Mares Vaccinated during Prepartum Period Against Disease Indicated	Foals and Weanlings (<12 Months of Age) of Mares Not Vaccinated during Prepartum Period	Yearlings	Comments
Equine influenza	Inactivated vaccine: 3-dose primary series; first dose at 6-7 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age	Inactivated vaccine: 3-dose primary series; first dose at 6-7 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age	Semiannual (6-month interval)	An unusually high risk of exposure may warrant vaccination of younger foals. Because potentially interfering maternal anti-influenza antibody is likely to be present, a complete primary vaccination series should be given after 6 months of age.
	Live canarypox-vectored recombinant vaccine: 3-dose primary series: first dose at 5-6 months of age; second dose 5 weeks after first dose; third dose at 10-12 months of age	Live canarypox-vectored recombinant vaccine: 3-dose primary series; first dose at 5-6 months of age; second dose 5 weeks after first dose; third dose at 10-12 months of age	Semiannual (6-month interval)	
	Modified live cold-adapted intranasal vaccine: 1-dose primary series: first dose at 11 months of age If vaccination earlier than 11 months is elected, use a 2-dose primary series: first dose at 6-10 months of age; second dose at 11-12 months of age	Modified live cold-adapted intranasal vaccine: 1-dose primary series: first dose at 11 months of age If vaccination earlier than 11 months is elected, use a 2-dose primary series: first dose at 6-10 months of age second dose at 11-12 months of age	Semiannual (6-month interval)	The modified live intranasal vaccine is licensed for administration to horses 11 months of age or older with a label recommendation of 1 dose for primary immunization. If vaccine is given before 11 months of age, a second dose should be administered at 11 months or older.
Equine viral arteritis (EVA)	Colt (male) foals: single dose at 6-12 months of age (see comments)	Colt (male) foals: single dose at 6-12 months of age (see comments)	Annual for colts intended for use as breeding stallions	Prior to initial vaccination, colt (male) foals should undergo serologic testing and be confirmed negative for antibodies to EAV. Maternally derived anti-EAV colostral antibodies can persist in foal for up to 6 months, so testing and vaccination should not be performed prior to 6 months of age. Keep colts isolated for 3 weeks after vaccination.
Potomac horse fever (PHF)	3-dose primary series: first dose at 5-6 months of age; second dose 3-4 weeks after first dose; third dose at 10-12 months of age	3-dose primary series: first dose at 5-6 months of age; second dose 3-4 weeks after first dose; third dose at 10-12 months of age	Semiannual to annual	If warranted by risk, vaccine may be administered to younger foals, in which case additional doses should be administered at 4-week intervals until foal is 6 months of age.
Rotavirus	Not recommended in foals	Not recommended in foals	Not applicable	
Strangles	Inactivated M-protein subunit vaccines: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 4-6 weeks after second dose	Inactivated M-protein subunit vaccines: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after the first dose; third dose 4-6 weeks after second dose	Semiannual	Vaccination is not routinely recommended as a strategy in outbreak mitigation but may be warranted on farms with endemic strangles, with the understanding that risk of adverse vaccine reactions is higher in exposed horses.
	Modified live intranasal vaccine: 3-dose primary series; first dose at 6-9 months of age; second dose 3-4 weeks after first dose; third dose at 11-12 months of age	Modified live intranasal vaccine: 3-dose primary series; first dose at 6-9 months of age; second dose 3-4 weeks after first dose; third dose at 11-12 months of age	Semiannual	If warranted by risk, the modified live vaccine (MLV) may be safely administered to foals as young as 6 weeks of age. However, vaccine efficacy in this age group has not been determined. If the MLV product is administered to foals < 6 months of age, administration of third dose of vaccine should be timed 2-4 weeks prior to weaning if possible.

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*Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

†Non-core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

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with previous vaccination. Thus it would not be prudent to recommend extension of the annual interval for revaccination with tetanus toxoid products available in North America, pending publication of data documenting duration of immunity (DOI). Vaccinated horses that sustain a wound or undergo surgery more than 6 months after receiving their previous tetanus booster should be revaccinated with tetanus toxoid immediately at the time of injury or surgery.

Annual revaccination of pregnant mares should be completed 4 to 8 weeks before foaling to protect the mare if she sustains foaling-induced trauma or retained placenta and to enhance concentrations of specific immunoglobulins in colostrum. Colostrum-derived antibodies significantly interfere with the immune response of foals vaccinated with tetanus toxoid until they are about 6 months old.[12,36]

Primary vaccination of foals that have received appropriate transfer of colostral antibodies from a vaccinated mare should include 3 doses of tetanus toxoid beginning at age 6 months or older. Optimally, the interval between the first 2 doses of vaccine should be approximately 4 weeks, and the interval between the second and third doses should be 3 to 5 months. The 3-dose primary series is recommended for foals, because a high proportion of foals fail to seroconvert in response to 2 doses of tetanus toxoid regardless of whether maternal antibodies are detectable at administration of the first dose.[12,36] For foals born to non-immune mares, this initial 3-dose series can start at 1 to 4 months of age.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of 1 vial of antitoxin (1500 IU) to nonvaccinated horses induces immediate passive protection that lasts not more than 3 weeks.[36] More prolonged protection may be accomplished with higher doses. In addition to the use of high doses of tetanus antitoxin to treat tetanus, indications frequently cited include administration to newborn foals born to unvaccinated mares and to unvaccinated horses that sustain an injury. In these cases the concurrent administration of tetanus antitoxin and tetanus toxoid at different sites using separate syringes has been advocated, followed by administration of additional doses of toxoid at 4- to 6-week intervals to complete the primary series.[41] Because a small but significant number of horses experience serum sickness and fatal hepatic failure (serum hepatitis) several weeks after receiving tetanus antitoxin,[42,43] a preferred approach to the unvaccinated horse that sustains a puncture or deep laceration is to thoroughly clean and débride the wound, initiate active immunization by administering tetanus toxoid, and institute a course of antimicrobial treatment with penicillin or alternate antimicrobial that is active against *C. tetani*.

Equine Encephalomyelitis (Sleeping Sickness)

The equine encephalomyelitis viruses (EEE, WEE, and VEE) belong to the *Alphavirus* genus of the family Togaviridae. They are transmitted by mosquitoes (and infrequently by other bloodsucking insects) to horses from wild birds or rodents that serve as natural reservoirs for these viruses. Risk of exposure and geographic distribution of the encephalomyelitis viruses vary by season and from year to year with changes in distribution of insect vectors and wildlife reservoirs. The distribution of EEE has historically been restricted to the eastern, southeastern, and some southern states, with recent northward encroachment. WEE has caused minimal disease in horses in North America during the past 3 decades, but the virus continues to be detected in mosquitoes and birds throughout the western states. In the past, outbreaks of WEE have been recorded in the western and midwestern states, with sporadic cases in the northeastern and southeastern United States. Because EEE, WEE, or both are endemic in most areas of North America, vaccination against these diseases should be part of the core vaccination program for all horses. VEE is a reportable foreign animal disease. Epidemics of VEE occur when the virus undergoes genetic change and develops greater virulence for avian and mammalian hosts. These viral variants are able to multiply to high levels in the horse, and then the horse becomes a reservoir for infection in these outbreaks. VEE occurs in South and Central America but has not been diagnosed in the United States or Mexico for many years; routine vaccination of horses in these regions against VEE is not recommended at this time unless transportation to endemic areas is planned.

Available vaccines are formalin inactivated, adjuvanted, bivalent or trivalent, whole-virus products containing EEE, WEE, and VEE, typically in combination products containing other antigens such as tetanus, influenza, WNV, or EHV. Although correlates for protection against EEE, WEE, and VEE are not well established, circulating antibodies are assumed to be important because infection is acquired by vascular injection (mosquito bites), and current inactivated vaccines appear to have good efficacy.[44,45] A study evaluating the serologic response of horses to commercial encephalomyelitis-tetanus combination vaccines showed that the EEE neutralizing antibody responses to Encevac T (Merck Animal Health, Carbopol adjuvant) and Equiloid Innovator (Zoetis, squaline and surfactant adjuvant) were of greater magnitude and persistence than responses to Cephalovac EWT (Boehringer Ingelheim, saponin adjuvant).[8] However, no comparative randomized challenge studies have been performed using these vaccines to document whether differences in serologic responses equate to differences in efficacy. Early testing of bivalent (EEE/WEE) vaccines was performed by intracranial challenge with either EEE or WEE; the formalin inactivated preparations demonstrated 100% protection.

Primary immunization of unvaccinated adult horses is accomplished by administering 2 doses of inactivated vaccine 3 to 6 weeks apart. In areas where EEE is not a threat and mosquito vectors are active for less than 6 months of the year, annual revaccination in the spring, before the peak insect vector season, is recommended. In areas like the Gulf States where EEE is endemic and mosquitoes are active virtually year-round, many veterinarians prefer to revaccinate horses semiannually to ensure more uniform protection throughout the year. Inactivated encephalomyelitis vaccines are considered safe for use during pregnancy, so booster vaccination of pregnant mares 4 to 8 weeks before foaling is routinely recommended to enhance colostral concentrations of specific immunoglobulins. Neutralizing antibodies to WEE and EEE are transferred passively to foals through colostrum and decline with an estimated half-life of 33 and 20 days, respectively. MDAs appear to confer protection and are detectable in the serum of many foals from vaccinated mares for at least 3 months and up to 7 months, depending on the post-nursing titer.[23,46-48]

Several studies have shown that MDAs exert a profound inhibitory effect on the ability of foals to mount serologic responses to inactivated bivalent WEE/EEE vaccines, which likely accounts for some of the reported cases of vaccine failure and resultant clinical EEE in vaccinated horses, particularly those younger than 2 years of age.[19,23,24,46,47] Studies have shown that 3-month-old foals born to immune mares consistently failed to mount a serologic response to 2 doses of inactivated bivalent WEE/EEE vaccine, and the majority had not responded even after administration of a third dose.[24,26] Whereas many 6-month-old foals failed to seroconvert after administration of 2 doses of vaccine, most responded following administration of a third dose.[24] Based on these data, inclusion of a third dose in the primary series, 2 to 5 months after administration of the second dose, is strongly recommended for primary immunization of foals and yearlings.

WEE has a lower mortality rate than EEE, and prevalence of WEE in many western states is sufficiently low that the risk of foals acquiring infection during their first year of life is also low. Therefore, primary vaccination of foals of vaccinated mares in areas where mosquitoes die off in the winter and the risk of infection is low is best completed when foals are 5 to 6 months of age or older in order to minimize the potential for MDA interference. Because foals born in the late spring and summer months are still less than 6 months of age by the time the mosquito season comes to an end in many regions, primary vaccination of these foals can be delayed until the spring of the yearling year. In contrast, EEE is a highly fatal disease that poses a significant risk to foals during their first year of life, particularly in the Gulf States where competent vectors are present year-round.[19,47,49] Most veterinarians in these regions recommend commencing

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primary vaccination of foals at 3 to 4 months of age using a 3-dose primary series, followed by a fourth dose before the onset of the next mosquito season and semiannual boosters thereafter to maximize the chances of overcoming the inhibitory effects of MDAs and inducing protection.[47]

West Nile Virus

Only a few years after West Nile virus infection was first diagnosed in horses in the northeastern United States in 1999, it had spread across the entire North American continent and is now considered endemic in all mainland areas of North America and Mexico, where it has become an important consideration in the differential diagnosis of horses presenting with signs of neurologic disease. Since 1999, the disease has been confirmed in more than 25,000 U.S. horses, about 35% of which have died or been euthanized. Roughly 40% of horses that survive acute illness caused by WNV exhibit residual effects (e.g., gait and behavioral abnormalities) 6 months post diagnosis.[50]

WNV, a member of the family Flaviviridae, is transmitted by mosquitoes and infrequently by other bloodsucking insects to horses, human beings, and a number of other mammals from avian hosts, which serve as natural reservoirs for these viruses. Horses and humans are considered to be "dead-end" hosts of WNV and therefore do not contribute to the transmission cycle. The virus is not directly contagious from horse to horse or from horse to human. Similarly, indirect transmission via mosquitoes from infected horses is highly unlikely because horses do not experience a significant level of viremia.[51] Risk of infection and death appears to increase with increasing age, but the disease has been confirmed in foals as young as 3 weeks of age. Although cases have been seen virtually year-round in the southeastern United States, the risk of acquiring infection is highest during those months in which mosquito activity peaks, typically July, August, September, and October in most areas of North America. WNV infection is a core disease against which all horses residing in the continental United States and Canada should be vaccinated.

As of April 2013, six WNV vaccines (West Nile-Innovator [Zoetis], Recombitek Equine rWNV vaccine [Merial], Equi-Nile [Merck Animal Health], Vetera WNV Vaccine [Boehringer Ingelheim], PreveNile [Merck Animal Health], and West Nile-Innovator DNA [Zoetis]) are licensed for use in horses in North America. All six vaccines have met USDA requirements for safety in tests, each involving more than 640 horses. West Nile-Innovator is an inactivated whole-virus vaccine that contains a metabolizable oil adjuvant.[52] This vaccine is available as either a monovalent (single component) or as several multicomponent vaccines containing other encephalitis virus antigens (EEE, WEE, VEE) and tetanus. Recombitek Equine rWNV vaccine is a Carbopol-adjuvanted canarypox-vectored recombinant modified live vaccine,[53-55] which is also available as a multicomponent containing inactivated EEE, WEE, and tetanus antigens. PreveNile is a nonadjuvanted chimeric yellow fever 17D-vectored vaccine.[56-59] This vaccine was voluntarily withdrawn from the market in May of 2010 after an unacceptably high number of adverse reactions were reported and has not yet been reintroduced. Merck Animal Health has since produced and tested an inactivated version of this chimera vaccine, which was released in 2011 as a single-component vaccine (Equi-Nile), as well as several multicomponent vaccines that also contain EEE, WEE, tetanus, EHV-1, EHV-4, and influenza antigens (Encevac + WNV; Encevac T + WNV and Prestige V + WNV). Similarly, the Vetera line of vaccines from Boehringer Ingelheim includes both single and multicomponent (up to 8 components) versions containing an inactivated WNV antigen. West Nile-Innovator DNA is a plasmid DNA vaccine with a metabolizable oil adjuvant.[28] It appears that Zoetis is not currently marketing this vaccine.

Needle and mosquito challenge models have shown that West Nile-Innovator, Recombitek, and West Nile-Innovator DNA all significantly reduce the magnitude of viremia in experimentally infected vaccinated horses compared to nonvaccinated control horses for as long as 12 months after primary vaccination with 2 doses of vaccine.[28,52,53] Although viremia was reliably induced in nonvaccinated control horses in these challenge models, clinical disease was not. Therefore, these vaccines are labeled as aids to the prevention of viremia due to WNV infection. In contrast, an intrathecal challenge model that reliably induced severe clinical disease was used to test the efficacy of PreveNile in studies for licensure.[57] In this model, a single dose of PreveNile prevented clinical disease as well as viremia in 4- to 6-month-old horses challenged 1 year after vaccination; therefore, PreveNile was labeled for protection against viremia and as an aid in the prevention of disease and encephalitis caused by WNV.[57] Subsequently, Recombitek was shown to induce a high level of clinical protection when tested using this rigorous intrathecal challenge model in a placebo-controlled study in which horses were challenged 14 days after completion of a 2-dose vaccination series.[54] The comparative efficacy of West Nile-Innovator, Recombitek, and PreveNile has now been tested in a randomized blinded, placebo-controlled intrathecal challenge study in which groups of 5 or 6 horses 6 months of age or older were challenged intrathecally 28 days after completion of the 2-dose (West Nile-Innovator and Recombitek) or 1-dose (PreveNile) primary vaccination series.[60] In this study, all 6 unvaccinated control horses developed grave neurologic signs post challenge, whereas all vaccinated horses survived and none developed detectable viremia. Clinical disease was prevented in 100% of PreveNile-vaccinated horses, 80% of Recombitek-vaccinated horses, and 33% of Innovator-vaccinated horses.[60] These findings support the results of field studies that provide clear evidence that when used according to manufacturer recommendations, all available licensed WNV vaccines reduce the risk of disease and death after natural challenge, although clinical disease may not be fully prevented with all vaccines.[61-65]

Directions for primary immunization using inactivated whole virus, inactivated *Flavivirus* chimera, and recombinant vaccines include administration of 2 doses of vaccine 3 to 6 weeks apart (consult the specific label). Optimal protection cannot be expected until 2 weeks after administration of the second dose, although Recombitek has been shown to induce significant protection as early as 26 days after administration of the first dose when tested in both the mosquito challenge and intrathecal challenge models.[54,55] Primary immunization with PreveNile requires 1 dose. A challenge study in yearlings showed that 83% (5 of 6) were protected when challenged intrathecally 10 days after vaccination with 1 dose, indicating that onset of immunity is rapid.[57] Rapid onset of immunity is an important feature when faced with the challenge of protecting naive horses that are being introduced into an endemic area, as is the case when horses from Europe and other non-endemic countries are imported into North America.

Vaccine manufacturers recommend revaccination of previously vaccinated horses on an annual basis, or more frequently when local conditions are conducive to a prolonged period of potential exposure to infected mosquito vectors. Annual revaccination is best completed in the spring (late February through early April), before the onset of the insect vector season. In areas like the southeastern states where the mosquito season is prolonged, revaccination twice annually, once in the spring and again in the late summer or early fall (late July through early September) has been advocated in the past to maximize protection, although the rationale for semiannual vaccination against WNV has not been tested in controlled studies.

None of the licensed vaccines currently marketed in the United States carry label recommendations for administration to pregnant mares, so mares are best vaccinated before breeding whenever possible. It is well recognized, however, that pregnant mares are at risk of acquiring infection from infected mosquitoes. Consequently, it has become accepted practice by many veterinarians to administer vaccines to pregnant mares on the reasonable assumption that the risk of adverse consequences of WNV infection far exceeds the reported adverse effects of use of vaccines in pregnant mares. Thousands of doses of West Nile-Innovator vaccine have been administered safely to pregnant mares, and a published study failed to document vaccine-associated adverse effects in a large population of pregnant mares.[66] Although the Recombitek vaccine is a live vectored vaccine, the

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canarypox vector is incapable of replication in mammals and does not induce a viremia that could infect a fetus. In addition, a canarypox-vectored influenza vaccine available in Europe is licensed for use in horses during pregnancy, so the vectored WNV vaccine is unlikely to be associated with an increased risk of adverse effects in pregnant mares. As with other vaccines, it is sound practice to avoid administering West Nile vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail.

Booster vaccination of previously primed pregnant mares 4 to 8 weeks before foaling appears to induce a strong anamnestic serologic response that provides their foals with passive colostral protection lasting at least 3 to 4 months.[26] In contrast, a significant proportion of naive pregnant mares failed to seroconvert when the primary series of WNV-Innovator vaccine was administered during the second half of gestation, perhaps reflecting pregnancy-associated downregulation of Th2 responses.[26] This observation adds further justification to the recommendation that when inactivated West Nile-Innovator vaccine is used, the primary series is best completed before breeding. In a similar study, pregnancy did not appear to suppress the response of mares to primary immunization with Recombitek (Wilson WD and colleagues, unpublished observations, 2007).

In contrast to findings with many other vaccines in the foals of immune mares, MDAs do not block the response of foals as young as 3 months of age to vaccination with the inactivated West Nile Innovator vaccine or the recombinant, chimera, or DNA WNV vaccines.[26,29] Although this finding is somewhat surprising for the inactivated vaccine, it might reasonably have been expected for the other vaccines because the vector systems accomplish transfection of cells and expression of the major E-peptide and M-peptide antigens of WNV on the surface of antigen presenting cells (APCs) in association with major histocompatibility complex (MHC) class I and class II antigens. These peptide antigens are therefore not free in the tissues and circulation to be neutralized by MDAs. The impact of MDAs on the recently marketed inactivated whole virus (Vetera WNV Vaccine [Boehringer Ingelheim]) and inactivated chimera vaccines (Equi-Nile [Merck Animal Health]) is not known.

Primary vaccination of foals from properly vaccinated mares can be started by administration of the first dose of either an inactivated or recombinant vaccine as early as 3 to 6 months of age (consult the specific product label), followed by a second dose approximately 3 to 6 weeks later, then a third dose 3 to 5 months after the second dose. This third dose increases the likelihood that foals with high MDA levels that may have attenuated the response to the first dose of vaccine will become primed and protected. Even in foals that have no maternally derived WNV antibodies after nursing, the third dose of inactivated vaccine in the primary series induces significantly higher and more persistent levels of antibody than two doses. A booster should be administered during the spring of the yearling year, after which the recommendations for vaccination of adult horses should be followed. Primary vaccination of foals from unvaccinated unexposed mares should commence at 3 months of age or younger (as early as 1 month of age), depending on month of birth and seasonal level of activity of mosquito vectors in the area. The three-dose primary vaccination protocol previously outlined should be followed. Revaccination should be performed before the onset of the next mosquito season.

The influence of MDAs on the response of foals to PreveNile was recently evaluated in 3-month-old and 5-month-old foals vaccinated with a single dose. Although significant titer responses were not observed post vaccination, sensitization of cell-mediated responses was accomplished, as evidenced by significant increases in expression of granzyme B, interleukin (IL)-2, perforin, and transforming growth factor (TGF)-β, and non-significant increases in interferon (IFN)-γ expression in WNV-stimulated PBMC from foals vaccinated at 5 months of age.[29] Similar, although non-significant, trends were seen in 3-month-old foals.[29] When available, PreveNile was labeled for administration of a single priming dose to foals 5 months of age or older, primarily because 5 months was the minimum age of foals used in challenge trials for licensure. Results of the above cited study suggest that foals younger than 5 months of age could be immunized successfully with PreveNile. Regardless, a second dose of vaccine should be administered before the onset of the next mosquito season. Preliminary data suggest that the plasmid West Nile-Innovator DNA vaccine is able to circumvent the potentially interfering effects of MDA, but the vaccine was labeled for use in horses 8 months of age or older.[28]

As with EEE, horses that have recovered from clinical WNV infection will likely be protected for the reminder of their lives and should not need to be revaccinated unless changes in their immune status, as might occur with prolonged corticosteroid administration, alter their susceptibility to infection.[67]

It is remarkable that in little more than 10 years after WNV disease was first encountered in the Americas, six vaccines with documented efficacy based on challenge studies were licensed for the benefit of horses, including three that apply the most modern technologies available for either animals or humans at the time.

Rabies

Rabies is an infrequently encountered neurologic disease of equids resulting from inoculation of the rabies virus through the bite of infected (rabid) wildlife. Wildlife species that serve as the natural reservoirs for rabies virus differ among regions of North America but include raccoons, foxes, skunks, and bats. Horses most often sustain bites on their muzzle, face, or lower limbs. The rabies virus then migrates via nerves to the brain where it initiates rapidly progressive encephalitis. Even though the incidence of rabies in horses is low, the disease is invariably fatal and has considerable public health significance. All horses kept in areas where rabies is endemic in the wildlife population are at risk and should be vaccinated as part of the core vaccination program. Therefore, vaccination of horses against rabies is recommended by, or under the direct supervision of, a veterinarian using one of the three inactivated tissue culture–derived products currently licensed for use in horses (Rabvac3 [Boehringer Ingelheim], RM Imrab3 [Merial], and EquiRab [Merck Animal Health]). These vaccines are potent immunogens that induce strong serologic responses that peak within 28 days after IM administration of a single dose.

Although correlates for protection against infection with rabies virus in horses are not well defined, it is logical to assume that protection correlates with titers of circulating antibody. In humans, post-vaccination antibody titers are used to predict protection. In dogs, however, postvaccination serologic test results were not found to be completely predictive of resistance to challenge exposure during tests performed with certain inactivated vaccines.[68] Challenge studies demonstrating efficacy are required for licensing of all rabies vaccines, including those labeled for use in equids in the United States. The challenge studies are conducted by the vaccine manufacturers as outlined in the Code of Federal Regulations (CFR) from the USDA. These studies indicate a DOI of 12 months and a minimum of 80% of vaccinated animals must be resistant to severe challenge with rabies virus. A DOI of 14 months was documented in a placebo-controlled challenge study in which 4-month-old foals were vaccinated with 1 dose of EquiRab and challenged by masseter injection of virulent rabies virus 14 months later (see product data sheet).

For primary immunization, label directions on inactivated rabies vaccines licensed for use in horses suggest administration of 1 dose to horses aged 3 months or older followed by a second dose 1 year later. Thereafter, annual revaccination is recommended. Although none of the licensed vaccines carries a specific label approval for use in pregnant mares, it is important to acknowledge that only a limited number of equine vaccines are specifically licensed for use in pregnant mares, and veterinarians do administer inactivated rabies vaccines to pregnant mares. Alternatively, veterinarians may recommend that mares be vaccinated against rabies before breeding in order to reduce the number and type of vaccines given in the period before foaling. Because rabies antibodies persist in serum for a prolonged period, foals born to mares that are revaccinated while open acquire substantial titers of rabies antibody after ingesting colostrum.

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Documentation of rabies in supposedly vaccinated horses, most of which were younger than age 2, brought into question the efficacy of label recommendations for primary vaccination of foals against rabies.[69] Recent studies in our laboratory have shown that the serologic response of most 3-month-old foals from antibody-positive mares is completely blocked, even when a 2-dose primary vaccination series is used. Although the response to the first dose of vaccine is typically blocked in 6-month-old foals from antibody-positive mares, these foals appear to seroconvert after administration of a second dose 4 weeks later. Primary vaccination of foals from vaccinated mares should therefore be delayed until they are 6 months of age or older and should include 2 doses of inactivated vaccine administered approximately 4 to 6 weeks apart, followed by a third dose at 1 year of age. For foals of mares known not to be vaccinated against rabies, the primary vaccination series can be started according to manufacturers' recommendations as early as 3 months of age and may comprise only 1 dose, followed by a second dose at 1 year of age. For foals from mares of unknown vaccinal history, either of the two following options is rational and can be used: (1) Assume the mare to be antibody positive, and follow the above recommendation for foals from mares known to be vaccinated against rabies, starting at 6 months of age. (2) Document the serum antibody status of the foal by testing serum collected from the foal at 24 hours of age or older or from the dam during the periparturient period, and determine which of the approaches to follow based on the presence or absence of rabies antibodies.

Equine Influenza

Infection of the respiratory tract of horses with the orthomyxovirus influenza A/equine/2 (H3N8) remains one of the most common causes of rapidly spreading outbreaks of respiratory disease. The influenza A/equine/1 subtype (H7N7) has not been recognized as a cause of clinical disease for many years and is likely extinct in nature. Influenza is endemic in the equine populations of the United States and much of the world. Evidence of influenza infection has never been documented in resident horses in New Zealand and Iceland. Whereas outbreaks of influenza have previously been reported in Singapore, Japan, South Africa, and Australia, rigorous control measures have apparently been successful in eliminating the virus from these countries. Rapid national and international transportation of horses facilitates spread of the virus. Concentrating young horses at racetracks, training facilities, boarding stables, breeding farms, shows, or similar athletic events increases the risk of infection, as does a low serum concentration of specific antibody.[70] Older horses are generally less susceptible to infection but may become ill when partial protection is overwhelmed by exposure to horses excreting large amounts of virus. Explosive outbreaks occur at intervals of several years when immunity of the equine population wanes and sufficient antigenic drift has occurred to generate a new viral strain. In contrast to herpesviruses, EIV is not maintained in asymptomatic carrier horses and does not circulate constantly, even within large groups of horses. Rather, the disease is introduced sporadically by a symptomatic or an asymptomatic infected horse. This epidemiologic finding and rapid elimination of the virus by the equine immune response suggest that infection can be avoided by preventing entry of the virus into an equine population (e.g., quarantine of newly arriving horses for at least 14 days) and appropriate vaccination.[71]

EIV is highly contagious and spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Contaminated buckets, grooming or feeding equipment, tack, and transport vehicles may serve as fomites, because the virus can survive for hours on such objects. Severity of clinical signs of influenza, which include nasal discharge, fever, lethargy, anorexia, cough, and myalgia, depends on the degree of existing immunity and other factors. Infected horses shed virus for up to 10 days in their nasal secretions. Inactivated vaccines do not induce sterile immunity, so recently vaccinated horses can become infected, shed virus, and contribute to interepidemic persistence of infection within the equine population and propagation of infection during outbreaks.[6]

Immunity to the same (homologous) strain of H3N8 virus after natural infection persists for more than a year and involves both local and systemic humoral and cellular mechanisms These include induction of large amounts of virus-specific neutralizing IgG and secretory IgA antibody in nasal secretions, high levels of circulating IgG antibodies, and genetically restricted antigen-specific cytotoxic T lymphocytes (CTLs) that kill infected cells.[72-76] Memory CTLs can be detected in peripheral blood for at least 6 months after infection, and solid immunity persists even when circulating antibody titers have declined to low or undetectable levels.[73,74,77,78] Similarly, protection induced by the licensed modified live intranasal influenza vaccine (Flu-Avert I.N. [Merck Animal Health]) is presumably mediated through induction of local immune responses in the respiratory tract, because this vaccine does not typically induce high levels of circulating antibody.[7,79] With the exception of ISCOM vaccines, inactivated vaccines administered by IM injection have limited potential to induce CTL or nasal secretory IgA responses, and induce only low levels of neutralizing antibody in nasal secretions.[72,78,80,81] The degree of protection induced by inactivated influenza vaccines is highly correlated with postvaccination titers of circulating antibody, predominantly of the IgGa and IgGb subisotypes, as measured by HI or single radial hemolysis (SRH) tests.[70,82-84] SRH levels of 100 mm^2 or greater are considered to be at least partially protective, but levels above 140 mm^2 are required for successful prevention of disease.[82] The partial protection induced by inactivated vaccines is of limited duration (up to about 7 months, depending on the vaccine) and is manifested as a reduction in clinical signs and attenuation of viral shedding in horses exposed to infection.[71,72]

The magnitude of the serologic response to inactivated influenza vaccines depends on many factors, the most important of which are the quality and quantity (mass) of the viral antigen and choice of the adjuvant.[82,85,86] Carboxypolymer-based compounds (carbomer, Carbopol) and ISCOMs are contained in some of the most efficacious inactivated influenza vaccines, whereas some commonly used adjuvants (e.g., alum) have been associated with induction of a nonproductive immune response.[72,85] History of previous vaccination or infection, interval since the last dose of vaccine, antibody titer at the time of vaccination, age, maternal antibody status, and relatedness of the vaccine strain to circulating field strains of influenza virus are other important determinants of efficacy, at least for inactivated influenza vaccines.[84,87,88]

Antigenic drift of the A/equine/2 subtype has resulted from point mutations in the genes encoding the amino acid sequences of the hemagglutinin (H) and neuraminidase (N) glycoprotein antigens on the surface of the virus. The result is emergence of viral strains representing two antigenic lineages, American and Eurasian, of the H3N8 virus. Further antigenic drift within each lineage has generated variants that, as with the prototypical strain A/equine 2/Miami 63, are named according to the location and year in which they were first isolated. The American lineage further evolved during the 1990s into Kentucky, Florida, and South American sublineages.[89] For the Florida sublineage, two clades have been identified: clade I represented by Ohio 03 and South Africa 03, and clade II represented by Richmond 07. According to the OIE surveillance panel, clade I representatives of the Florida sublineage are present in North America, Europe, South Africa, and Japan; clade II representatives are present in Europe, India, and China.[89]

Antigenic drift, by generating antigenically heterologous viruses, reduces the degree and duration of protection conferred by previous infection or vaccination because of the specificity of immunoglobulins, and it allows horses with high titers to become infected and develop clinical signs of disease if the vaccine strain is not closely related to the drifted infectious field strain.[90] Although antigenic drift of EIV is slower than that of human influenza viruses, it is recommended that inactivated equine influenza vaccines include viral antigens from isolates obtained within the most recent 5 years. An expert surveillance panel meets annually to recommend strains that should be included in influenza vaccines in subsequent years (www.equiflunet.org.uk). In the past, federal U.S. regulations made

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updating of equine influenza vaccines through inclusion of recently isolated strains so costly and time-consuming that vaccines typically lagged more than the recommended 5 years behind the antigenic drift of field viruses, resulting in suboptimal protection. Recent changes in vaccine licensing regulations should make more frequent updating of equine influenza vaccines feasible. Even though Flu-Avert I.N. contains only a 1991 H3N8 strain of North American lineage, it has been shown to be protective against challenge with Eurasian strains and recently isolated North American strains.

The short-lived immunity after vaccination with inactivated equine influenza vaccines was the impetus for past recommendations for frequent revaccination, at intervals as short as 2 months. However, too short an interval may compromise efficacy because an optimal anamnestic response to influenza vaccination is inhibited in horses with a high antibody titer.[91] An additional consideration that potentially limits the efficacy of influenza vaccines is the phenomenon termed *original antigenic sin*, whereby horses exposed to a drifted field A/equine/2 virus will mount an anamnestic immune response directed more strongly against the strain with which they were vaccinated initially than against the drifted field virus.[86]

A considerable amount of published efficacy data based on both challenge studies and field epidemiology studies has been available for many years in Europe to support the use of influenza vaccines. In contrast, information regarding the efficacy of influenza vaccines marketed in North America has remained sparse until recently. Furthermore, studies conducted in North America during the late 1990s showed that the inactivated influenza vaccines in use at the time failed to provide much benefit in terms of reducing the risk of infection and clinical disease during field outbreaks.[6,70] Serologic testing performed during these and other studies indicated that vaccine failure was caused by failure of the influenza vaccines in use at the time to induce protective antibody titers.[6,70,92]

Fortunately, vaccine manufacturers in North America have responded to the challenge of producing more efficacious equine influenza vaccines during the past 15 years by incorporating more relevant recent viral strains, increasing antigenic mass of relevant strains, eliminating the seemingly irrelevant H7N7 strain, modifying adjuvant systems, and introducing novel technologies. An important advance occurred in 1999 when Heska Corporation marketed an attenuated live cold-adapted influenza vaccine (Flu-Avert I.N. [Merck Animal Health]) for intranasal administration. This vaccine, which contains a Kentucky/1991 strain of North American lineage, was found to be highly efficacious in blinded controlled challenge studies conducted 5 weeks, 6 months, and 1 year after administration of a single dose to naive horses.[7] Subsequently, Flu-Avert I.N. was shown to cross protect against European H3N8 strains, as well as against North American strains isolated during the late 1990s and early 2000s, and to induce a rapid onset of protection within 7 days of administration of a single dose to naive horses.[79,93] Although horses challenged 1 year after administration of a single dose showed a significant but only partial reduction in severity of clinical signs and virus shedding, a more marked reduction in clinical signs and viral shedding was found when the challenge was performed 6 months after vaccination.[7] Based on these results, revaccination at 6-month intervals is recommended. Field experience indicates that this regimen induces solid clinical protection after natural challenge. Currently, Flu-Avert I.N. is licensed for use in non-pregnant horses 11 months of age or older, primarily because this was the youngest age of the horses used in the challenge studies for licensing. Horses may shed small amounts of vaccinal virus for several days after vaccination with Flu-Avert I.N., but the amount of virus shed is so low that in-contact horses will not generally become infected or immunized with vaccinal virus shed by recently vaccinated horses, and the likelihood of reversion to virulence is extremely low.[94]

In recent years, several vaccine manufacturers in North America have updated their inactivated vaccines and demonstrated efficacy in challenge studies. Inactivated influenza vaccines containing one or more relevant H3N8 strains are currently marketed by Boehringer Ingelheim (Calvenza EIV), Zoetis (Fluvac Innovator), and Merck Animal Health (Prestige II). Each of these vaccines contains at least one American-type and one Eurasian-type strain of EIV. These companies also market a large number of multicomponent combination vaccines that contain the same inactivated influenza antigens as in their single-component products but also contain tetanus, WEE and EEE virus, EHV, or WNV antigens.

A study in which naive 9-month-old horses were challenged by aerosol with a recent influenza H3N8 strain (KY/99) 16 weeks after the last dose of a 3-dose vaccination series (0, 4, and 16 weeks) documented that Calvenza EIV and two EIV/EHV combination vaccines (Prestige II and Fluvac EHV-4/1) reduced clinical signs and viral shedding in vaccinated horses compared with nonvaccinated control horses.[96] The group vaccinated with Calvenza EIV developed significantly higher serum antibody titers after vaccination and experienced less fever, nasal discharge, and viral shedding than horses vaccinated with either Prestige II or Fluvac EHV-4/1. Based on these findings, the authors concluded that Calvenza EIV, a vaccine developed, formulated, and efficacy-tested according to European Union guidelines, was the most effective inactivated influenza vaccine available in North America at that time. This vaccine is adjuvanted with Carbopol and contains the KY/95 and Ohio 03 North American strains and the Newmarket 93 Eurasian H3N8 strains. The initial two doses of this vaccine are administered IM; subsequent doses may be administered IM or intranasally. It is proposed, but not proved, that administration of booster doses by the intranasal route may provide a stronger local mucosal immune response. This vaccine is licensed for use in horses older than 6 months of age, including pregnant mares. Prestige II currently contains the KY/93 and KY/2002 North American strains and the Newmarket 93 Eurasian H3N8 strains. The metabolizable oil (MetaStim) adjuvanted Fluvac vaccine evaluated in the above challenge study contained the KY/92 strain of H3N8 virus. This strain has since been replaced with a KY/97 strain and the product is now named Fluvac Innovator. Although OIE has recommended that it is no longer necessary to include Eurasian H3N8 strains in vaccines, Fluvac Innovator is the only equine influenza vaccine in North America that does not contain a Eurasian strain.

In 2006, Merial was granted a North American license to market an injectable canarypox-vectored recombinant equine influenza vaccine that has been used with success in Europe for several years. This vaccine, Recombitek Equine Influenza Virus vaccine, has been shown to induce strong protection in challenge studies and has the potential to positively impact influenza prevention in North America.[95] The vaccine incorporates the HA gene from the Ohio 03 and Newmarket 93 H3N8 strains into the same vector delivery platform as the efficacious WNV virus vaccine (Recombitek) and contains a carbomer polymer adjuvant in the diluent.[95] Consequently, this vaccine invokes a broad array of humoral and cellular immune responses. Challenge studies document onset of protection as soon as 2 weeks after completion of a 2-dose primary series and persistence of solid protection for at least 5 months. Administration of a booster dose at 5 months induced a strong anamnestic response that provided solid protection persisting for at least 12 months.[96] This vectored influenza vaccine can circumvent the inhibitory effect of maternal antibodies, an issue that significantly impacts primary immunization of foals using inactivated influenza vaccines.[30] Recombitek Equine Influenza Virus vaccine is licensed for vaccination of healthy horses as young as 5 months of age.

VACCINATION PROTOCOLS FOR INFLUENZA. Influenza should be considered a core vaccine on all facilities that are not totally closed so as to preclude contact with "outside" horses from other locations. As with other diseases, the full benefit of vaccination against influenza can be realized only if the primary vaccination series is completed, or booster doses of vaccine administered, several weeks before anticipated exposure. The following 5 issues should be considered when planning an influenza vaccination program: (1) primary vaccination of adult horses, (2) routine revaccination, (3) vaccination of pregnant mares, (4) primary vaccination of foals, and (5) vaccination in an outbreak.

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Primary Vaccination of Adult Horses

The following are options for primary vaccination of adult horses that have not previously been vaccinated:

- Flu-Avert: administer a single dose intranasally. A second dose administered 3 months later may be beneficial, particularly for horses vaccinated at younger than age 11 months.
- Inactivated IM-administered vaccines: administer 2 doses 3 to 6 weeks apart according to label directions. Although not specifically recommended by some manufacturers, administration of a third dose of vaccine 3 to 5 months after the second dose is indicated because it significantly enhances the magnitude of the primary response and duration of persistence of antibodies at protective levels.
- Recombitek Equine Influenza Virus vaccine: administer 2 doses 4 to 6 weeks apart, and revaccinate 5 months later.

Routine Revaccination

Improvements in injectable vaccines and introduction of new vaccine types during the past 15 years has extended the duration of clinical protection achievable through vaccination. A routine revaccination interval of 6 months appears to be appropriate for most of the influenza vaccines currently marketed in North America. This routine protocol should be customized by adjusting timing of boosters or inclusion of an additional booster to achieve maximum protection during periods when the risk of exposure is high. For example, strategic revaccination 1 month before being placed at high risk of exposure, such as at a show or sale or being transferred to a training or boarding facility, is justified to maximize protection.

Vaccination of Pregnant Mares

For the mare to produce colostrum that contains a high level of antibodies against equine influenza, she should be revaccinated 4 to 8 weeks before foaling with a vaccine that stimulates a robust serologic response. Although the intranasally administered Flu-Avert I.N. vaccine induces good protection, it does not routinely stimulate high levels of circulating antibody, at least when used for primary immunization. An inactivated injectable vaccine is therefore recommended for pre-foaling booster vaccination of pregnant mares at this time.[26]

Vaccination of Foals

The antibody status of a mare at the time of foaling is the main determinant of the postnursing circulating antibody titer in her foal and therefore has a profound impact on the ability of the foal or weanling to respond to influenza vaccines administered during the first year of life. Foals born to seronegative nonvaccinated mares respond appropriately to influenza vaccines, so primary vaccination can commence at 3 months of age or younger if significant risk of exposure to influenza exists. In contrast, maternal antibodies have been shown to completely block the serologic response of foals to a primary immunization series comprising 2 or more doses of inactivated influenza vaccines when the first dose is administered at 6 months of age or younger.[12-18,24] Interference from MDA may persist until 9 months of age or beyond for foals with high antibody titers post nursing.[12-18,24,26] Studies in Newmarket, United Kingdom, have shown that influenza virus infection is rare in Thoroughbred yearlings before they enter training, suggesting that the risk of influenza is low in horses younger than age 1 year born to mares in herds that are well vaccinated.[88,97,98] There appears to be little justification to vaccinate young foals from vaccinated mares against influenza, as was recommended in the past.[48,99,100]

The intranasal modified live vaccine (Flu-Avert I.N.) is licensed for vaccination of horses 11 months of age or older. Whereas this vaccine has been shown to be safe in foals as young as 2 months of age,[101] published data regarding the potential for MDAs to interfere with the response are lacking. Unpublished observations suggest that MDA interferes with the response of foals between 3 and 6 months of age, whereas foals with maternal antibody vaccinated at 7 months of age were protected against virulent challenge (Holland and Chambers, personal communication). Pending publication of well-controlled studies, it is recommended that if the first dose of Flu-Avert I.N. vaccine is administered before 11 months of age, a second dose should be administered at 11 months of age or older.[102]

The European-licensed live canarypox-vectored recombinant influenza is labeled for use in pregnant mares and foals as young as 4 months.[78] The North American–licensed Recombitek Equine Influenza Virus vaccine has been shown to be safe in foals as young as 4 months, but the minimum age recommended for vaccination of foals from immunized dams is 5 months. The recombinant vaccine has been shown to efficiently prime foals aged 10 to 20 weeks that had detectable MDA at the time of vaccination.[30] These foals showed clear evidence of an anamnestic antibody response when a secondary vaccination with the same vaccine was performed. The canarypox-vectored recombinant influenza vaccine therefore offers a unique opportunity to overcome the limitations of early life vaccination in the face of maternally derived immunity in foals.[30] If the foal experiences failure of passive transfer of maternal antibodies, or if the mare is seronegative for influenza, the manufacturer recommends commencing vaccination at 4 months of age and including an additional dose in the primary series.

Vaccination in an Outbreak

Definitive diagnosis of equine influenza infection should be pursued during outbreaks of suspected viral respiratory disease, because specific measures can then be instituted to contain spread of the disease. Rapid (same-day) diagnosis of influenza can be accomplished using the highly sensitive and specific polymerase chain reaction (PCR) or antigen-capture ELISA tests. In addition, virus isolation should be pursued during outbreaks to characterize new isolates and assess efficacy of current vaccines. The decision to vaccinate in an outbreak is dependent on many factors, the most important of which are the age, vaccination status, and size of the population of horses at risk; the elapsed time since onset of the outbreak; the rapidity with which a diagnosis can be confirmed; the layout of the physical facilities; and availability of personnel. Outbreaks of influenza at racetracks and similar large facilities typically take 1 month or more to spread through the entire population. Therefore, sufficient time exists to enhance immune protection of many at-risk horses while implementing other management strategies to minimize disease spread.[93] It is prudent to booster-vaccinate those horses that have been on a regular influenza vaccination program but have not been revaccinated within the previous 3 months. It is also important to induce protection as quickly as possible in horses that have not previously been vaccinated. Of the vaccines currently available, Flu-Avert I.N. induces protection most rapidly, within 7 days of administration of a single intranasal dose. This is currently the product of choice for vaccination of naive horses and those of unknown vaccination status in the face of an outbreak.[93] Adverse effects have not been reported when Flu-Avert I.N. is administered to horses that are incubating infection, although vaccination of horses that are already clinically ill is not recommended. Alternatively, an accelerated vaccination schedule using the canarypox-vectored vaccine with a primary intervaccination interval of 14 days and booster at 105 days has been shown to quickly confer long-lasting protective antibody levels.[103] All 14 vaccinates demonstrated high SRH antibody titers 14 days following V2, thereby achieving 100% herd immunity to homologous viral challenge. Rapid induction of high levels of acquired herd immunity is critical in containing an outbreak of such a highly contagious pathogen as EIV.[103] In addition to reducing clinical and economic impacts, early vaccination clearly played an important role, together with biosecurity measures and movement restrictions, in containing the 2007 equine influenza outbreak in Australia, as well as ultimate eradication of the disease from that country.[104]

FUTURE INFLUENZA VACCINES. A recombinant modified vaccinia Ankara (rMVA) vector that delivers genetic material encoding for relevant hemagglutinin (H) antigens of an H3N8 influenza virus has been developed.[105,106] The rMVA system is designed to focus the

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CTL response on the recombinant antigen and was initially tested in a prime-boost strategy in which the priming dose consisted of a DNA plasmid encoding for expression of the H antigen. The intent of this DNA prime-rMVA boost regimen was to invoke both cellular and humoral immune responses involved in protection.[106] A subsequent study showed that the rMVA system was capable of inducing virus-specific lymphoproliferative and IFN-γ messenger ribonucleic acid (mRNA) responses; antigen-specific IgGa, IgGb, and IgA antibodies; and protection from challenge, both with and without a priming dose of the DNA vaccine.[105] These data indicate that vaccination of horses with rMVA alone or as part of a prime-boost regimen is an effective means of inducing protective immunity to influenza virus infection.[105] Considerable research has been performed to document the efficacy of the DNA vaccine used in the above studies against equine influenza. However, the delivery system used (multiple sublingual, conjunctival, and subcutaneous [SC] injections delivered with a gene gun under general anesthesia) is impractical for use in the field.[105,107] Recent licensing of a naked plasmid DNA vaccine that can be conveniently administered to horses by IM injection to prevent WNV infection clearly documents the potential for development of a DNA vaccine to prevent influenza in horses in the future. Additionally, a DNA vaccine expressing the hemagglutinin protein of H3N8 influenza virus was recently shown to protect ponies against challenge when administered subdermally using a needle-free delivery system.[108]

Equine Herpesvirus (Rhinopneumonitis)

The respiratory tract is the primary route of infection for both EHV-1 and EHV-4, both of which cause respiratory tract disease that varies in severity from subclinical to severe and is characterized by fever, lethargy, anorexia, nasal discharge, and cough.[109] Seroepidemiologic studies indicate that the vast majority of foals become infected with EHV-1 and EHV-4 during the first year of life, but the clinical disease syndromes resulting from these infections are not always well defined, perhaps reflecting the modulating effect of MDAs.[110-112] Recurrent or recrudescent clinically apparent infections are seen in weanlings, yearlings, and young horses entering training, especially when horses from different sources are commingled.[109,113] In contrast, surveillance studies involving racehorses document that seroconversion to both EHV-1 and EHV-4 occurs sporadically during the course of a racing season, but these seroconversions are often not clearly associated with outbreaks of respiratory disease that follow an epidemiologic pattern consistent with an infectious agent.[114,115] EHV-1 and EHV-4 are spread by direct and indirect (fomite) contact with nasal secretions, by aerosolized secretions from infected horses, and in the case of EHV-1, by aborted fetuses, fetal fluids, and placentae associated with abortions. Management practices are therefore of primary importance for control of clinical disease caused by equine herpesviruses.

Viremia occurs frequently after infection with EHV-1, potentially leading to paralytic neurologic disease (equine herpes myeloencephalopathy [EHM]) secondary to vasculitis of the spinal cord and brain, abortion of virus-infected fetuses, or birth of infected nonviable foals. In contrast, manifestations of infection with EHV-4 (rhinopneumonitis) are generally confined to the respiratory tract because EHV-4 does not typically infect endothelial cells or produce a cell-associated viremia.[116] As with herpesvirus infections in other species, horses typically fail to clear primary infections with either EHV-1 or EHV-4, the result being that most horses in the population remain latently infected with both viruses.[109,112,117] Latently infected horses do not show clinical signs but may experience recrudescence of infection with or without clinical signs, an increase in antibody titer, and shedding of the virus when stressed. Consequently, many horses have detectable levels of SN antibody to both EHV-1 and EHV-4 in their serum.[109,112,117] These features of the epidemiology of herpesvirus infections seriously compromise efforts to control these diseases and explain why outbreaks of EHV-1 or EHV-4 can occur in closed populations of horses. Whereas most mature horses have developed some immunity to EHV-1 and EHV-4 through repeated natural exposure and do not typically show respiratory signs when they become reinfected, horses do not appear to become resistant to the abortigenic or neurologic forms of infection with EHV-1 even after repeated exposure.[118] In fact, previously exposed mature horses are more likely than juvenile horses to develop the neurologic form of the disease.[119,120]

The genetic basis underlying the apparent increased likelihood that some EHV-1 isolates will cause EHM appears to involve a single point mutation in the DNA polymerase *(DNApol)* gene.[121] This mutation results in the presence of either aspartic acid (D) or an asparagine (N) residue at position 752. More than 80% of EHV-1 isolates associated with EHM are of the D_{752} form, whereas less than 20% are of the N_{752} form.[121] Isolates of the D_{752} form have been designated "neuropathogenic strains" in recent publications, lay articles, and laboratory PCR result reports, whereas N_{752} isolates have been designated as "wild-type," "abortigenic," or "non-neuropathogenic." The latter terminology is unfortunate because both the D_{752} and N_{752} isolates are capable of inducing all syndromes (i.e., respiratory disease, abortion, neonatal death, and EHM).

Correlates for protection against EHV-1 and EHV-4 infection have been investigated extensively but are not yet fully defined. Infection with EHV-1 induces a strong humoral response, but protection from reinfection is short lived and is not achieved until the horse has experienced multiple infections with homotypic virus.[109,116] No clear relationship exists between protection from EHV-1 or EHV-4 infection and concentrations of circulating antibody induced by vaccination or infection, but clinical manifestations of disease and the duration and amount of virus shedding from the nasopharynx are reduced in animals with high levels of circulating neutralizing antibody.[116,122-126] Mucosal immunity and cell-mediated responses likely play a role at least as important as circulating neutralizing antibodies in protection against EHV-1 infection,[127] because the presence of MHC class 1–restricted CTL precursors in peripheral blood is correlated with protection.[116] Because EHV-4 replication is largely confined to epithelial cells of the upper respiratory tract, mucosal immunity is likely important in protection.[116]

Currently available vaccines include inactivated vaccines containing only EHV-1 or both EHV-1 and EHV-4, and one MLV EHV-1 (Rhinomune [Boehringer Ingelheim]). Several inactivated products are licensed only for protection against respiratory disease; currently, all contain a low antigen load. Two inactivated products (Pneumabort-K + 1b [Zoetis] and Prodigy [Merck Animal Health]) that contain a high antigen load are licensed for protection against both abortion and respiratory disease. Performance of the killed low-antigen-load respiratory vaccines is variable, with some vaccines outperforming others. Performance of the killed high-antigen-load abortion/respiratory vaccines is superior, resulting in higher antibody responses and some evidence of cellular responses to vaccination. This factor may provide good reason to choose the high-antigen-load abortion/respiratory vaccines when the slightly higher cost is not a decision factor. Alternatively, the Calvenza EIV/EHV (Boehringer Ingelheim) respiratory vaccine induces high titers of VN antibody comparable to those induced by the high-antigen-load abortion/respiratory vaccines.[8] The MLV EHV-1 vaccine (Rhinomune [Boehringer Ingelheim]) has been shown to induce a level of clinical protection and reduction in viral shedding of similar magnitude to that provided by an inactivated high-antigen-load vaccine (Pneumabort-K + 1b) and of greater magnitude than is provided by one of the killed low-antigen-load respiratory vaccines.[128] Whereas vaccination with either EHV-1 or EHV-4 can provide partial protection against the heterologous strain, vaccines containing EHV-1 may be superior in this regard.

The principal indication for use of equine herpesvirus vaccines is prevention of EHV-1-induced abortion in pregnant mares, and reduction of signs and spread of respiratory tract disease (rhinopneumonitis) in foals, weanlings, yearlings, and young performance and show horses that are at high risk of exposure. Many horses do produce postvaccinal antibodies against EHV, but the presence of those antibodies does not ensure complete protection. Consistent vaccination appears to reduce the frequency and severity of herpesvirus-induced

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disease. Although convincing evidence is lacking, field experience suggests that whereas the incidence of sporadic EHV-1–induced abortion in individual mares has not changed, the incidence of abortion storms caused by EHV-1 has declined significantly since the introduction and widespread use of EHV-1 vaccines in the United States.[117,118] Outbreaks of abortion and associated perinatal foal death, however, do continue to occur on occasion in herds of vaccinated mares.

Of the vaccines currently licensed for use in pregnant mares in North America, only inactivated monovalent EHV-1 vaccines (Pneumabort-K + 1b and Prodigy) containing abortigenic strains of EHV-1 carry a label claim for preventing abortion, whereas at least one bivalent EHV-1/4 vaccine is licensed for prevention of abortion in Europe (Duvaxyn EHV-1/4 [Intervet]). One of the vaccines available in North America, Pneumabort-K + 1b, incorporates both the 1p and 1b subtypes of EHV-1 to reflect the documented increase in the proportion of EHV-1 abortions caused by the 1b subtype that occurred during the 1980s as compared to earlier years.[129] Pregnant mares should be vaccinated during the fifth, seventh, and ninth months of gestation. Some veterinarians also recommend a dose during the third month of gestation. Similarly, vaccination of mares with an inactivated EHV-1/4 vaccine at the time of breeding and again 4 to 6 weeks before foaling is commonly practiced to enhance concentrations of colostral immunoglobulin for transfer to the foal. However, no published reports document the effectiveness of this approach in raising titers of specific antibody in mares that have already been vaccinated against EHV-1 3 times during the previous 5 months. Vaccination of barren mares and stallions with either a bivalent EHV-1/4 vaccine or a monovalent EHV-1 vaccine before the start of the breeding season and thereafter at 6-month intervals is recommended, with the goal of increasing herd immunity in an attempt to reduce viral shedding and challenge to pregnant mares on breeding farms.[117]

An MLV EHV-1 vaccine (Rhinomune) has been used as an aid in prevention of EHV-1 abortion by some practitioners for many years,[130] even though this vaccine is not currently labeled for this use. Several recent developments have created renewed interest in the potential for use of MLV vaccines to protect horses against manifestations of EHV-1 and EHV-4 infection. Sequencing of the EHV-1 genome has made it possible to document the nature of the mutation encoding for attenuation, mediated through truncation of the gp2 glycoprotein of the KyA strain.[131] Similar studies may soon yield information regarding the mutation underlying attenuation of the RAC-H strain from which Rhinomune was derived.

Because currently available inactivated vaccines do not block infection with equine herpesviruses, the most we can hope for when using inactivated vaccines is reduction of severity of clinical signs and attenuation of virus shedding to help protect herdmates. Challenge studies in weanlings aged 5 to 8 months have clearly demonstrated the efficacy of an inactivated whole virus EHV-1/4 vaccine in reducing clinical manifestations and virus shedding induced by virulent EHV-1 challenge administered 2 weeks after completion of the 2-dose primary series.[125] Efficacy was clearly correlated with vaccine-induced antibody levels at the time of challenge in this study.[125]

Specific antibodies against both EHV-1 and EHV-4 are passed in colostrum.[22,25,132-134] Field studies with EHV-1 MLVs indicate that colostral antibodies exert a profound inhibitory effect on serologic responses to vaccination up to at least 5 months of age.[21,135,136] However, a cytotoxic cellular immune response to both EHV-1 and EHV-4 was induced in a substantial percentage of foals vaccinated with an EHV-1 MLV in the presence of maternal antibody, even though humoral responses were often absent.[137] It is uncertain whether these responses would provide protection against natural challenge. Recent studies with two different commercially available inactivated bivalent EHV-1/4 vaccines and one inactivated EHV-4/influenza vaccine have shown that the majority of foals from EHV-vaccinated mares do not mount a detectable neutralizing antibody response to vaccines administered at 3 and 4 months of age, even when 3 doses are administered in the primary series.[22,24,25] An increased proportion of foals responded when vaccinated with a 3-dose series starting at 5 or 6 months of age, but a substantial number still failed to seroconvert.[24,25] Some foals with low or undetectable levels of SN antibody at the time of vaccination failed to mount a serologic response, suggesting that low levels of antibody, below the lower limit of detection of the SN test based on EHV-1 antigen, are capable of inhibiting the serologic response to inactivated EHV-1/4 vaccines.[25] The failure of a large proportion of foals younger than 6 months of age to mount serologic responses to inactivated EHV-1/4 vaccines and the influence of antibody titer at the time of vaccination on failure to respond has been confirmed using sensitive gD and gG ELISAs in studies on commercial stud farms in Australia.[138] In parallel studies, these researchers concluded that mares were the source of infection for foals, and intensive use of inactivated EHV-1/4 vaccines on breeding farms in Australia had a minimal impact on the infection rate of young foals and weanlings with EHV-1 and EHV-4.[110,112,139]

Considering the uncertainty regarding the role of EHV-1 and EHV-4 as causes of clinically important respiratory disease, the lack of published data regarding the efficacy of available vaccines in preventing infection and establishment of latency, and results of a recent study documenting the poor serologic responses of naive horses to a number of killed low-antigen-load EHV respiratory vaccines currently marketed in North America,[8] there appears to be little rationale to support the common practice of frequent revaccination of foals, weanlings, yearlings, and young performance horses against EHV-1 and EHV-4.[5] Furthermore, an obvious dilemma in designing a vaccination strategy to prevent EHV-1 and EHV-4 infection in foals and weanlings is that if primary immunization is delayed until 6 months of age or older to reduce the likelihood of MDA interference, foals are likely to encounter field infection before the 3-dose primary series can be completed. It is therefore unreasonable to expect a high degree of efficacy for vaccination programs designed to protect foals and weanlings against EHV infection using available vaccines. Despite these uncertainties, many practitioners elect to vaccinate against both EHV-1 and EHV-4. Under these circumstances, a reasonable compromise would be to start foal vaccination at 4 to 6 months of age using 2 doses of an inactivated bivalent vaccine or an EHV-1 MLV administered 3 to 4 weeks apart, followed by administration of a third dose 2 to 5 months later. Revaccination at 4- to 6-month intervals, thereafter using either an inactivated bivalent vaccine or a modified live EHV-1 vaccine, appears appropriate for yearlings and young performance or show horses that experience contact with other horses. Frequent vaccination of non-pregnant mature horses (except those on breeding farms) with EHV vaccines is generally not indicated.

Available vaccines make no labeled claim to prevent EHM, and there is no evidence that current vaccines can prevent EHM in the field. Frequent revaccination of mature horses to help prevent EHM is not justified in most circumstances because EHM is a relatively rare disease from a population standpoint, and most mature horses have previously been infected with EHV-1 and are latent carriers. Currently available vaccines do not reliably block infection, development of viremia, or establishment of latency, and EHM has been observed in horses vaccinated against EHV-1 regularly at 3- to 5-month intervals with inactivated or modified live vaccines.[119,120,140,141]

Based on the presumed similar pathogenic mechanism between EHV-1 abortion and neurologic disease,[142,143] parallels likely exist in terms of the requirement for immunologic protection. The control of cell-associated viremia is thought to be critical for preventing EHV-1 abortion and, presumably, neurologic disease. Therefore, the goal of any vaccination program aimed at the prevention of EHV-1 abortion or neurologic disease is to stimulate those immune responses that can reduce or eliminate cell-associated viremia. Two recent studies have investigated the protective effect of commercially available killed and MLV vaccines against experimental challenge with neurotropic EHV-1 strains 24 or 29 days after completion of a 3-dose vaccination series.[122,123] A significant reduction in the level of viremia

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was noted in ponies challenged after vaccination with either Calvenza or Pneumabort-K + 1b, both of which are inactivated vaccines.[122,123] Reduction in viremia post challenge was not observed in ponies vaccinated with another inactivated vaccine (Prodigy) or the MLV vaccine (Rhinomune).

A challenge study performed almost 30 years ago to test the efficacy of Pneumabort-K + 1b in preventing abortion and a recent study to test the efficacy of Rhinomune against challenge with a "neuropathogenic" strain of EHV-1 provided some evidence that these vaccines may have a place in control of outbreaks of EHM.[126,128] Interestingly, the Army 183 EHV-1 strain used as the challenge virus in the Pneumabort-K + 1b efficacy study has now been shown to carry the D_{752} mutation, as has the Findlay 03 strain used in the Rhinomune study. However, the low numbers of horses used in these studies, the failure of either vaccine to prevent infection or significantly reduce the level of viremia, the lack of statistical significance of results pertaining to prevention of neurologic signs, and the well-known difficulties encountered in accomplishing a consistent and reproducible challenge model for neurologic EHV-1 infection justify caution in interpretation.

The significant reduction in viral shedding observed in vaccinated horses provides reasonable justification for booster vaccination of nonexposed horses at risk for infection to reduce viral shedding in the event they do become exposed to EHV-1. By enhancing herd immunity, it is hoped that the level of infectious virus circulating in the at-risk population will be reduced, and in turn the risk that individual horses in the population will develop disease may be reduced.[140] This approach also relies on the assumption that the immune system of most mature horses has already been "primed" by prior exposure to EHV-1 antigens through field infection or vaccination and can therefore be "boosted" within 7 to 10 days of administration of a single dose of vaccine. Although the validity of this approach has not been critically evaluated for prevention of EHV-1 neurologic disease, its implementation seems rational when faced with one or more horses with confirmed clinical EHV-1 infection (any form) at a particular facility. Whereas booster vaccination of horses likely to have already been exposed is not recommended, it is rational to booster vaccinate nonexposed horses, as well as those that must enter the premises, if they have not been vaccinated against EHV-1 during the previous 90 days. Use of the Rhinomune MLV or one of the inactivated EHV-1 vaccines known to stimulate high circulating titers of neutralizing antibody appears justified for this purpose. Horse owners must develop an understanding of the concept of boosting herd immunity to help protect the group of horses rather than focusing on the as yet unattainable expectation that the veterinarian can reliably protect an individual horse from developing potentially fatal EHM by administering one of the vaccines currently marketed as aids to prevention of clinical manifestations of EHV-1 infection. Ultimately, enforcement of strict biosecurity measures and hygiene practices are likely to be more effective than widespread vaccination in reducing the risk of acquiring infection.

FUTURE VACCINATION STRATEGIES TO PREVENT HERPESVIRUS INFECTION. To be completely effective in blocking primary infection and establishing a lifelong carrier state with EHV-1 and EHV-4, future vaccination strategies should be directed at inducing a strong mucosal immune response in the upper respiratory tract during the first few weeks of life, at a time when high levels of maternal antibodies are present. Promising progress toward this goal was reported by Patel and colleagues,[144] who documented that intranasal administration of a single dose of temperature-sensitive modified live EHV-1 vaccine to maternal antibody-positive foals aged 1.4 to 3.5 months afforded partial but significant protection against febrile respiratory disease, viremia, and virus shedding after intranasal challenge with virulent EHV-1 performed 8 weeks after vaccination. This vaccine has also been shown to provide significant protection against abortion in challenge studies, and because it is capable of preventing the development of viremia, shows potential to prevent EHM.[127,145] Recent studies with vaccinia and canarypox-vectored recombinant vaccines and DNA vaccines have generated promising results, but more research will be needed to identify the immunodominant protective antigens of EHV-1 and their interaction with the equine immune system before these approaches will be applicable for use in the field.[146-150]

The recent Third International Havemeyer Workshop on Equine Herpesvirus Type 1 highlighted the need to improve vaccines, with MLV being identified as the vaccine type most likely to be successful in inducing a protective immune response.[151] The identified goals of future vaccine candidates will be to stimulate both humoral and cell-mediated immunity, be able to differentiate infected from vaccinated animals (DIVA), provide minimal gaps in immunity, induce a rapid onset and long-lasting immunity, be effective in the presence of maternally derived antibody to prevent infection early life, provide a wide clinical and virologic cross-protection, be safe and effective against the development of EHM, suppress reactivation of latent EHV-1 infection, and be safe when used in the face of an outbreak.[151]

Streptococcus equi subsp. *equi* Infection (Strangles)

Strangles is a highly contagious disease caused by the bacterium *Streptococcus equi* subsp. *equi (S. equi)*. Strangles primarily affects young horses (weanlings and yearlings), although horses of any age can become infected if not protected by previous exposure to the organism or by vaccination. The organism is transmitted by direct contact with infected horses or subclinical carriers, or indirectly by contact with water troughs, feed bunks, pastures, stalls, trailers, tack, or grooming equipment contaminated with nasal discharge or pus draining from lymph nodes of infected horses. The organism survives for several weeks in the environment, particularly in aquatic locations and when protected from exposure to sunlight and disinfectants, and can be a source of infection for new additions to the herd. Because *S. equi* is a clonal organism, there is minimal antigenic variation between different isolates even though isolates vary in their pathogenicity.

Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer,[152] indicating that induction of durable protection through vaccination is biologically feasible if the protective antigens can be identified and presented in an appropriate manner.[153] Although the basis for acquired resistance to strangles is not completely understood, the finding that recovered horses rapidly clear intranasally inoculated *S. equi* despite not making circulating antibody to its surface proteins indicates that to be highly effective a strangles vaccine must stimulate local nasopharyngeal tonsillar immune clearance responses and that serum antibody is of lesser importance.[154] This conclusion is further supported by the finding that ponies with high levels of circulating antibody to multiple unique surface-exposed and secreted proteins after systemic vaccination remained susceptible to challenge with *S. equi*.[154] The cell wall M protein of *S. equi* (Se-M) is recognized in the acquired immune response to *S. equi* infection, a response that involves both production of local antibodies in the nasopharynx and circulating opsonophagocytic antibodies.[155-157] The predominant opsonophagocytic antibodies are of the IgGb subisotype but also include IgGa and IgA, whereas IgGb and later mucosal IgA predominate in nasopharyngeal secretions.[156,158]

Strangles vaccines licensed and marketed for use in North America include one inactivated adjuvanted M-protein cell wall extract (Strepvax II [Boehringer Ingelheim]) and one attenuated live vaccine (Pinnacle I.N. [Zoetis]) derived from a nonencapsulated mutant of *S. equi* for intranasal administration.[159] Infection of horses with *S. equi* continues to cause troublesome outbreaks of strangles throughout North America, despite the availability and widespread use of these vaccines, indicating that their efficacy is suboptimal.[160] M-protein vaccines induce a good opsonophagocytic antibody response in serum but a minimal mucosal IgA response, which likely accounts for the incomplete protection observed when they are used in the field.[156,161] However, data do exist to document that vaccination using injectable SeM vaccines reduces the attack rate and

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severity of strangles in herds with endemic infection.[161-163] The live intranasal vaccine has been shown to induce a relevant mucosal immune response and partial or complete protection but may do so without inducing a strong serologic response.[160,164] Because vaccinal organisms in the intranasal vaccine must reach the inductive sites for immunity in the pharyngeal and lingual tonsils, accurate vaccine delivery is critical to vaccine efficacy.

Vaccination against *S. equi* is not routinely recommended for pleasure or performance horses kept in low-risk situations, but it is a consideration for horses that are resident on or being transported to premises like breeding farms where strangles is a persistent endemic problem or where a high risk of exposure is anticipated. The bacterial MLV is generally preferred over the inactivated injectable vaccine for primary vaccination of foals and weanlings and for routine use in older horses at high risk for infection. On breeding farms, efforts should be concentrated on preventing infection of foals and weanlings by booster-vaccinating broodmares 4 to 6 weeks before foaling to maximize colostral content of antibodies. Whereas the intranasal vaccine has been shown to be safe for use in mares at all stages of pregnancy and can be used in mares in the face of an outbreak, it does not reliably stimulate high levels of circulating antibody. For this reason, the IM-administered inactivated SeM product is preferred for pre-foaling booster immunization of mares. Antibodies of the IgG and IgA class recognizing the SeM are passively transferred to the foal through colostrum and are also present in the milk of immune mares.[165] Antibodies of predominantly the IgGb isotype are absorbed from colostrum and redistribute to the nasopharyngeal mucosa.[158] These IgGb antibodies, along with the SeM-specific IgA antibodies that are present in milk and passively coat the pharyngeal mucosa of nursing foals, provide protection to most nursing foals up to the time of weaning.[157,158,165] Resistance of nursing foals to strangles during the first few months of life appears to be mediated by IgGb antibodies in nasal secretions and milk and not by IgA.[165] Serologic (ELISA) responses to M-protein vaccines are poor in foals, most likely owing to the inhibitory effect of maternal antibodies.

Whereas the intranasal MLV may be less susceptible than the inactivated extract vaccines to MDA interference, this issue has not been investigated, and the manufacturer does not recommend administration of this vaccine to horses younger than 9 months of age. Considering that on farms where strangles is endemic, foals often become infected around the time of weaning (age 4 to 8 months), it is difficult to protect them if vaccination is delayed until age 9 months. A reasonable compromise on breeding farms where the risk of strangles infection is high and mares are on a regular vaccination program would be to begin primary vaccination of foals using the intranasal live vaccine as early as 4 months of age. The recommended 2-dose primary series administered 2 to 3 weeks apart should be followed by a third dose 3 to 4 months later and boosters at 6- to 12-month intervals thereafter, depending on risk of infection. The intranasal vaccine has been administered to foals as young as 5 or 6 weeks of age during outbreaks. If a vaccine is used in this manner, a third dose of the vaccine should be administered 2 to 4 weeks before the foal is weaned to optimize protection during this high-risk period. Although there are few reports of adverse effects attributable to use of the intranasal strangles vaccine in young foals, the inability of foals to mount an adequate mucosal IgA response during the first month of life and the potential for interference by maternal antibodies suggests that foals are unlikely to fully benefit from intranasal strangles vaccine administered before 4 months of age. When an inactivated M-protein vaccine is used for primary vaccination of foals, it is recommended that the initial series begin at 4 to 6 months of age, using 3 doses administered at 4- to 6-week intervals, followed by semiannual boosters for as long as high-risk conditions prevail.

Strangles vaccines should be administered only to healthy nonfebrile horses free of nasal discharge and should not be administered to those that are known to have had recent direct exposure to clinically ill animals.[153] However, outbreaks of strangles generally persist for several months to more than 1 year, particularly on breeding farms where each foal crop adds new susceptible animals to the population. Thus, strangles vaccines are frequently administered in the face of an outbreak as an adjunct to management practices designed to bring outbreaks under control, and it is not always possible to accurately determine the exposure status of each horse. Under these circumstances, the likelihood of preventing strangles is greatest for horses that have not yet been exposed and can be kept isolated from infected horses until 2 weeks after the vaccination protocol can be completed. Horses that have been vaccinated previously will generate a response more rapidly than naive horses. Similarly, the intranasal MLV is preferred over inactivated vaccines for immunization of naive horses in an outbreak because it is likely to generate a protective immune response more rapidly.

Injectable strangles vaccines tend to cause local reactions at the site of injection more often than other equine vaccines. Injection in the gluteal muscles is not recommended because gravitational drainage along fascial planes can prove troublesome in the event an abscess develops at the injection site. In addition, purpura hemorrhagica, a serious and sometimes life-threatening systemic immune complex (Arthus-type) vasculitis manifested as edema with or without petechial hemorrhages on mucosal surfaces, has been observed with low frequency in the weeks after administration of strangles vaccines. Inactivated extract vaccines are implicated more often than the intranasal MLV, but all strangles vaccines have the potential to induce purpura hemorrhagica. The antigen present in immune complexes is SeM, along with antibodies of the IgA class. Because a high serum IgG titer against *S. equi* appears to be associated with an increased risk of developing purpura, routine testing for specific IgG antibodies using a commercially available ELISA test has been recommended as a means of preventing vaccine-associated purpura hemorrhagica.[160] Horses with titers of 1:1600 or greater in the SeM ELISA and those known to have had strangles during the previous year should not be vaccinated.[160] A recent study investigated the factors associated with likelihood of horses having a high serum *S. equi* SeM-specific antibody titer.[166] This study indicated that older horses, horses other than Thoroughbreds and warmbloods, and horses that had been vaccinated with an attenuated live intranasal *S. equi* vaccine between 1 and 3 years previously had an increased likelihood of having a serum SeM-specific antibody titer of 1600 or higher. Recommendations of when to vaccinate horses after an *S. equi* outbreak largely depend on how long horses maintain a serum SeM-specific antibody titer of 1600 or higher, which can range from 9 to 27 months. Therefore, the recommendation is to wait 2 years after an outbreak before vaccinating horses against *S. equi* and to test for *S. equi* SeM-specific antibody titer 12 to 24 months following the outbreak.[167]

The bacterial modified live vaccine for intranasal administration will cause injection site abscesses if inadvertently injected IM. To avoid inadvertent contamination of other vaccines, syringes, and needles, it is advisable and considered good practice to administer all parenteral vaccines before handling and administering the intranasal strangles modified live vaccine. Other reported adverse responses after administration of the intranasal modified live vaccine include nasal discharge, submandibular or retropharyngeal lymphadenopathy with or without abscessation, limb edema, internal abscesses (bastard strangles), and purpura hemorrhagica. The overall frequency of adverse events is low but appears to be higher than reported to the manufacturer (4.8 per 10,000 doses). The majority of reported adverse events, including the development of nasal discharge, lymph node abscesses, and purpura hemorrhagica, occurs in horses on farms with endemic or epidemic strangles, so it is often uncertain whether the adverse event was caused by the vaccine or by a wild strain of *S. equi*.

RECENT DEVELOPMENTS IN STRANGLES VACCINES. The non-specifically attenuated Pinnacle strain of *S. equi* was produced by chemical mutagenesis to induce random mutations throughout the bacterial genome.[157,168] Because the point mutations responsible for attenuation have not been specifically defined, the potential exists for back mutation and reversion to full virulence.[168] In contrast, the

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live attenuated vaccine strain TW 928 contained in a strangles vaccine (Equilis StrepE [Intervet]) formerly licensed in Europe was stably attenuated by targeted deletion of the *aroA* gene.[169] This allowed development of a companion PCR test that was used in molecular epidemiologic studies to determine whether strangles in vaccinated horses was caused by the vaccine or by wild-type strains.[170] Although this development proves that targeted gene deletion is a promising route for generating stable candidate mutants for inclusion in future vaccines, the high residual virulence, unconventional route of administration (submucosal in the upper lip), and short duration of immunity induced by Equilis StrepE limited its use to the extent that the vaccine was recently withdrawn from the market.

The incomplete protection afforded by bacterins and SeM extracts administered parenterally or by attenuated live vaccines administered intranasally or submucosally, as well as the undesirable side effects associated with some of these products, has prompted research to investigate other potential vaccine antigens and vaccination strategies. Promising results have recently been achieved in challenge studies involving horses vaccinated IM and intranasally with combinations of up to seven recombinant antigens including EAG (a protein that binds α_2-macroglobulin, albumin, and IgG), CNE (a collagen-binding protein), SclC (a collagen-like protein), and two IgG endopeptidases, IdeE and IdeE2.[171,172]

Equine Neorickettsiosis (Potomac Horse Fever)

Equine neorickettsiosis, also known as *Potomac horse fever* (PHF), is caused by *Neorickettsia risticii* (formerly *Ehrlichia risticii*). Originally described in 1979 as a sporadic disease affecting horses residing in the northeastern United States near the Potomac River, the disease has since occurred in horses in 43 U.S. states, three Canadian provinces (Nova Scotia, Ontario, Alberta), South America (Uruguay, Brazil), Europe (The Netherlands, France), and India. The disease does not appear to be directly contagious, and it now appears that accidental ingestion of aquatic insects harboring metacercaria infected with *N. risticii* is at least one mode of transmission.[173] PHF is seasonal, occurring between late spring and early fall in temperate areas, with most cases in July, August, and September at the onset of hot weather. The disease may sporadically affect individual horses or cause outbreaks involving multiple horses. Foals appear to be at low risk for the disease. If PHF has been confirmed on a farm or in a particular geographic area, cases will likely occur in future years. Documentation of the involvement of operculate freshwater snails and aquatic insects like caddis flies and mayflies in the life cycle of *N. risticii* has permitted formulation of focused control measures directed at minimizing exposure of horses to the habitats occupied by these species during the summer and fall months when disease risk is highest in endemic areas.[173] Risk reduction is best accomplished by turning off barn lights at night, covering hay or storing it indoors, preventing horses from drinking at natural water sources like ponds or streams, and staying informed about local hatches of aquatic insects.[174]

Recovery after natural infection with *N. risticii* induces a strong antibody response and durable protection from reinfection lasting 20 months or longer. However, the presence of antibodies does not necessarily correlate with protection, and cell-mediated responses likely play a crucial role.[175] A β-propiolactone inactivated host cell-free *N. risticii* vaccine protects mice against homologous challenge.[176] Only one inactivated PHF vaccine for IM administration (Equine Potomavac [Merial]) is licensed and available for use in horses as an aid in prevention of PHF. The high rate of serious complications and mortality associated with this disease has been considered adequate justification for vaccinating horses residing in or traveling to endemic areas. In a series of studies in which ponies were challenged IV with *N. risticii* approximately 4 weeks after completion of the 2-dose primary vaccination series using a formalin-inactivated aluminum hydroxide–adjuvanted vaccine (PHF-Vax [Schering-Plough]) that is no longer marketed, Ristic's group (1988) reported that 78% of experimentally infected ponies were protected against all clinical manifestations of disease except fever, and 33% were protected against all signs including fever.[177] A published non-controlled field study involving the same vaccine documented induction of serologic responses in most vaccinated horses and a substantial reduction in disease prevalence, morbidity, and mortality compared with data collected in a previous year when horses were not vaccinated.[175,178]

In contrast to the results of the studies cited, an epidemiologic investigation involving a large number of horses failed to demonstrate any clinical or economic benefit from annual vaccination with currently available vaccines in New York State.[179,180] Failure of a substantial number of individual horses to mount an immune response to inactivated PHF vaccines, heterogeneity of *N. risticii* isolates, the presence of only one *N. risticii* strain in vaccines, and much more rapid waning of immunity after vaccination than after natural infection likely account for the observed failure of vaccines to provide protection against field infection.[175,181] Despite the lack of documented efficacy of approved vaccines to prevent infection in the field setting, many practitioners who work in endemic areas believe that severity of disease is attenuated and mortality is reduced in vaccinated horses when vaccines are administered at 4- to 6-month intervals, with administration of one booster timed to precede the anticipated period of peak challenge.

If vaccination is elected, a primary series of 2 doses should be administered 3 to 4 weeks apart. The manufacturer recommends revaccination at 6- to 12-month intervals, but some veterinarians encourage a shorter revaccination interval. Because the disease has a distinct seasonal pattern, revaccination in the late spring, about 1 month before the first cases are expected, followed by a second dose 4 months later, appears to be a reasonable approach for strategic immunization to maximize the chances of protection during the period of peak challenge. The available vaccine is licensed for use in stallions and pregnant mares and can be administered to gestating mares 4 to 8 weeks before foaling to maximize passive transfer of specific antibodies to foals through colostrum. Whereas about 67% of foals from antibody-positive mares were antibody negative by 12 weeks of age, antibody was detectable in 33% of foals up to 5 months of age. On the basis of these findings, the low risk of clinical disease in young foals, and the apparent susceptibility to infection of 2 foals vaccinated earlier than 12 weeks of age, primary vaccination of foals from antibody-positive dams should begin with a 2-dose primary series starting at age 5 months or older, followed by administration of 1 subsequent booster dose 8 to 12 weeks later.[178] However, the efficacy of this recommended regimen requires further study. If the primary series of 2 vaccinations is initiated before age 5 months, additional doses should be administered at monthly intervals up to 5 months of age to maximize the likelihood that an immunologic response is achieved. Vaccination of foals in endemic areas is further complicated by the distinct seasonal incidence of disease in July, August, and September, a time when most foals are between 2 and 6 months old and may be subject to maternal antibody interference with vaccination.

Botulism

Botulism is a neuromuscular paralytic disorder caused by one of eight distinct neurotoxins (A, B, Ca, Cb, D, E, F, G) produced by *Clostridium botulinum,* a soilborne, spore-forming, saprophytic, anaerobic, gram-positive bacterium.[182] Botulinum toxins are among the most potent biological toxins known and act by blocking transmission of impulses at motor end plates, resulting in weakness progressing to paralysis, inability to swallow, and frequently death. Of the seven serogroups (A through G) of *C. botulinum,* types A, B, C, and D have been reported to cause disease in horses, with types B and C responsible for most cases.[182] Three forms of botulism—toxicoinfectious botulism (shaker foal syndrome), forage poisoning, and wound botulism—have been observed in horses. *Forage poisoning* results from ingestion of preformed toxin produced by decaying plant material or animal carcasses present in feed, whereas *wound botulism* results from vegetation of spores of *C. botulinum* and subsequent production of toxin in contaminated wounds. *Shaker foal syndrome,* almost all cases of which are caused by *C. botulinum* type

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B, results from toxin produced by vegetation of ingested spores in the intestinal tract. This syndrome is a significant problem in foals between the ages of 2 weeks and 8 months in Kentucky and the Mid-Atlantic seaboard states and occurs sporadically in other areas.[183-185] Toxicoinfection with *C. botulinum* type C is currently being investigated as a cause of equine grass sickness, a largely fatal pasture-associated dysautonomia mainly affecting horses in Great Britain, continental Europe, and Australia, with reports of isolated U.S. cases.

A toxoid vaccine (BotVax-B [Neogen Corporation, Tampa, Fla.]) directed against *C. botulinum* type B is licensed for use in horses in the United States. Its primary indication is prevention of shaker foal syndrome via colostral transfer of antibodies induced by vaccination of the mare. For primary vaccination, mares should be vaccinated during gestation with a series of 3 doses administered 4 weeks apart, scheduled so the last dose will be administered 4 to 6 weeks before foaling to enhance concentrations of specific immunoglobulin in colostrum (i.e., months 8, 9, and 10 of gestation). Subsequently, mares should be revaccinated annually with a single dose 4 to 6 weeks prior to foaling. A similar type B toxoid is available to protect foals in endemic areas in Australia.[186]

Passively derived colostral antibodies appear to protect most foals for 8 to 12 weeks, although foals from properly vaccinated dams can present with botulism.[184-186] Insufficient production of specific antibody by the dam in response to the vaccination, failure of passive transfer of specific immunity to botulinum toxin, overwhelming toxin production, and loss of passive immunity by the time exposure to the toxin occurs may be reasons for vaccine failure. The clinician should be aware of the status of MDA transfer of each foal.

Maternal antibodies do not appear to interfere with the response of foals to primary immunization against botulism,[187] so a primary series of 3 doses of vaccine administered 4 weeks apart can be started when foals in endemic areas are 2 to 3 months of age or older. Other horses can be immunized using a primary series of 3 doses of vaccine administered at 4-week intervals, followed by annual revaccination. No licensed vaccines are available at present for preventing botulism due to *C. botulinum* type C or other subtypes, and because cross-protection between the B and C subtypes does not occur, routine vaccination against *C. botulinum* type C is not currently practiced. A type C toxoid approved for use in mink was administered to horses under special license to protect them during an outbreak of forage poisoning caused by contaminated alfalfa cubes in southern California in 1989. The C-terminal part of the heavy chains of botulinum neurotoxin types C and D (HcBoNT/C and D) have been expressed in *Escherichia coli* and have been shown to effectively immunize horses when administered as recombinant mono- or bivalent vaccines.[188,189] These vaccines are not yet licensed.

Horses and foals with clinical botulism may be treated with botulinum antitoxin administered IV. Antitoxin is not effective against toxin that has been translocated to motor end plates, so clinical signs may progress for 12 to 24 hours after administration of the antitoxin or until all internalized toxin has attached to motor end plates. The dose of botulinum type B antitoxin recommended for treating a foal is 30,000 IU and for an adult is 70,000 IU. Foals of unvaccinated mares born in or being moved to endemic areas may benefit from transfusion with plasma from a vaccinated horse or from administration of *C. botulinum* type B antitoxin. The efficacy of these practices warrants further study. Vaccination with type B toxoid as described earlier is an alternative to passive immunization.

Equine Viral Arteritis

Equine viral arteritis (EVA) is a contagious disease of equids caused by equine arteritis virus (EAV), an RNA virus found in the horse populations of many countries. EAV is the prototype virus in the family Arteriviridae of the genus *Arterivirus,* order Nidovirales. Although all horse breeds appear to be equally susceptible to EAV, the prevalence of infection, as determined by seroconversion, is much higher in some breeds (notably Standardbreds and warmbloods) than in others. Despite the high seroprevalence of infection in Standardbreds, clinical disease is rarely observed in this breed, indicating that subclinical infection is common.[11,190] Conversely, Thoroughbreds and most other breeds have a low seroprevalence of infection but are more likely to show fulminant clinical signs when they become infected. Most primary EAV infections are subclinical or asymptomatic. Clinical signs, if they occur, typically develop 3 to 7 days post infection and vary in severity, both within and between outbreaks, but may include some or all of the following: fever, anorexia, depression, localized or generalized urticaria, supraorbital or periorbital edema, conjunctivitis, lacrimation, serous or mucoid nasal discharge, and dependent edema involving the limbs, prepuce, scrotum, mammary glands, or ventrum. EAV is of special concern because abortion is a frequent sequel to infection in the unprotected pregnant mare. EAV can also cause life-threatening pneumonia or pneumoenteritis in young foals, and infection of the post-pubertal colt or stallion may establish a long-term carrier state.[11,191] Transmission most frequently occurs through direct or aerosol contact with virus-infective respiratory secretions, leading to widespread dissemination of the virus among susceptible horses in close proximity. Indirect transmission, though less significant, can occur through contact with virus-contaminated fomites. Venereal transmission from infected carrier stallions to mares via semen during natural breeding or artificial insemination with fresh, chilled, or frozen semen can play a significant role in introduction and spread of infection on or between breeding farms or other equine facilities. The virus can persist in the reproductive tract of stallions for many years and possibly result in lifelong infection.

Historically, large-scale outbreaks of EVA have been relatively infrequent. However, the number of confirmed occurrences appears to be increasing, likely because of increased global movement of horses, increased accessibility of carrier stallions, and increased utilization of shipped cooled or frozen virus-infected semen. Outbreaks can be associated with serious economic consequences, as clearly exemplified by the 2006 multistate outbreak in Quarter Horses that was propagated by widespread shipment of semen from the index cases, two inapparently infected carrier stallions in New Mexico. Because the carrier stallion is widely accepted as the natural reservoir of EAV and the source of diversity among naturally occurring strains of the virus, identifying these individuals through serologic testing followed by PCR testing or virus isolation from semen forms the cornerstone of eradication measures. Vaccination also constitutes an important means of controlling spread and minimizing the consequences of infection.

A modified live vaccine based on an attenuated strain of EVA virus was developed by researchers in Kentucky in 1969.[192] This vaccine (Arvac [Zoetis]) was first used extensively in the field during the 1984 outbreak of EVA in Kentucky and proved safe and effective in bringing the outbreak under control.[11] This vaccine was developed further and licensed for use in North America. Vaccination of stallions, non-pregnant mares, and prepubertal colts has been shown to be a safe and effective means of controlling EVA. Strategic use of the MLV has formed the cornerstone of a highly successful program to control EVA in the Kentucky Thoroughbred breeding population for many years.[11] Indications for vaccination against EVA are to:

- Protect stallions against infection and subsequent development of the carrier state
- Immunize seronegative mares before being bred with EAV-infective semen
- Curtail outbreaks in nonbreeding populations. Vaccination in the face of an EVA outbreak in concentrated populations of performance horses at racetracks has been successful in controlling horizontal disease dissemination within 7 to 10 days.

Primary immunization with the modified live vaccine involves IM administration of a single dose, with a booster administered annually thereafter. Virus-neutralizing antibodies are induced within 5 to 8 days after vaccination and persist for at least 2 years.[11,193] Revaccination induces high VN antibody titers that persist for several breeding seasons.[194] Although the current modified live vaccine is highly attenuated and has been shown to be safe and effective in stallions and non-pregnant mares, a small proportion of first-time vaccinated

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horses develop mild febrile reactions and transient lymphopenia after vaccination, and vaccine virus may be isolated sporadically from the nasopharynx and buffy coat for 7 days (occasionally up to 32 days) after vaccination.[11,193,195,196] Vaccinated stallions do not shed vaccine virus in either semen or urine.[194]

Primary vaccination provides sustained clinical protection against EVA but does not prevent reinfection and subsequent limited replication and shedding of field strains of virus.[197] However, the frequency, duration, and amount of viral shedding via the respiratory tract are significantly reduced in vaccinates. Vaccinated mares may transiently shed field virus after being bred to carrier stallions, so isolation of these individuals for 21 days after breeding is recommended.[11]

Annual revaccination of breeding stallions 28 days before the start of breeding season is highly recommended as a means of preventing establishment of the carrier state.[11] Annual revaccination of mares being bred to carrier stallions should occur at least 21 days before breeding. The modified live vaccine is not recommended for use in pregnant mares, especially during the last 2 months of gestation, or in foals younger than 6 weeks of age, except in emergency situations when there is a high risk of exposure. Apparent fetal infection with the modified live vaccine strain after vaccination of pregnant mares has been documented in rare instances.[193,198] A recently published study in which 73 pregnant mares were vaccinated during mid- to late gestation concluded that it is safe to vaccinate healthy pregnant mares up to 3 months before foaling and during the immediate postpartum period. Vaccinating mares during the last 2 months of gestation was associated with an increased risk of abortion.[199] The authors concluded that when faced with substantial risk of natural exposure to EAV, the risk associated with vaccination must be weighed against the much greater risk of widespread abortions in unprotected populations of pregnant mares.[199]

Foals born to seropositive mares become seropositive after ingesting colostrum. MDAs decay with a mean half-life of approximately 32 days, with the result that foals become seronegative between 2 and 7 months of age.[200,201] Maternal antibodies are unlikely to interfere with the response to vaccine administered at 7 months of age or older.[200] However, when foals younger than 6 months are vaccinated during conditions of high risk, they should be revaccinated after age 6 months. Establishment of the carrier state appears to depend on the high levels of androgens circulating in intact stallions and can be prevented by vaccinating colts, preferably before puberty and before they are used for breeding.[11] Vaccination of prepubertal colts at age 6 to 12 months is therefore central to effective control of the spread of EAV infection and should be strongly encouraged in breeds like Standardbreds and warmbloods in which EVA is prevalent and on facilities where risk of infection is high. Persistent infection has never been documented in a stallion properly vaccinated with the licensed modified live vaccine prior to exposure.[11]

REGULATORY AND EXPORTATION CONSIDERATIONS WITH VACCINATION AGAINST EVA. Horses vaccinated with the MLV can be expected to become seropositive for life. Titers resulting from vaccination cannot be distinguished from titers resulting from natural infection, so vaccination may complicate testing of horses for export. When planning a vaccination program against EVA, it is important to consult with state and/or federal animal health officials to ensure that any such program is in compliance with the state's control program for EVA if one exists. It is strongly recommended that before vaccination, all first-time male vaccinates be tested and confirmed negative for antibodies to EAV by a USDA-approved laboratory (http://www.aphis.usda.gov/cvbapps/Labs.jsp). Mares intended for export should be similarly tested. In instances where there is uncertainty or concern over whether vaccination against EVA could prevent export of a horse to a particular country, it is advisable to consult the federal area veterinarian (http://www.aphis.usda.gov/vs/area_offices.htm#CO) in charge in the state to determine the specific import requirements of that country. Several countries bar entry of any equid that is serologically positive for antibodies to EAV, regardless of vaccination history. Countries that do accept EVA vaccinated horses typically require stallions or colts to have a certified vaccination history and confirmation of prevaccination negative serologic status.

FUTURE DIRECTIONS. Development and marketing of a marker vaccine that not only affords protection but also allows vaccinated horses to be distinguished serologically from inapparently infected carriers would greatly facilitate control and even eradication of EAV from horse populations. Several new-generation EAV vaccines that potentially meet these criteria have been developed in recent years. These include an MLV DIVA vaccine with a deletion in the GP5 ectodomain,[202,203] a DNA vaccine that incorporates open reading frames (ORFs) 2b, 5, and 7,[204,205] and a subunit EAV vaccine using recombinant replicon particles derived from a vaccine strain of VEE virus that includes genes encoding both major envelope proteins (GP5 and M) of EAV.[206,207]

Rotaviral Diarrhea

Equine rotavirus, a non-enveloped icosahedral RNA virus possessing a genome comprising 11 segments of dsRNA, is one of the most important causes of infectious diarrhea in foals during the first few weeks of life and often causes outbreaks involving the majority of the foal crop on individual farms.[208-210] Older foals and adult horses are more resistant to infection. Equine RV is transmitted via fecal-oral contamination and causes diarrhea by damaging the tips of villi in the small intestine, resulting in cellular destruction, maldigestion, malabsorption, and diarrhea. The genus *Rotavirus* is one of five genera of the family Reoviridae and is divided into 7 serogroups (A through G) based on differences in the inner capsid protein, VP6.[210,211] All equine rotavirus isolates to date are in group A, which is further subdivided using neutralizing antibodies to the VP4 and VP7 outer capsid proteins into P (protease-sensitive, VP4-positive) and G (glycoprotein, VP7-positive) serotypes, respectively.[211] Five P serotypes (P1, P6, P7, P12, and P18) and eight G serotypes (G1, G3, G5, G8, G10, G13, G14, G16) have been identified and characterized in horses.[212-214] Molecular genome analysis strongly suggests that the vast majority of the currently circulating equine group A rotavirus strains are highly conserved, with only limited genetic diversity.[215] Most are of the P12 and G3 serotype and include 2 subtypes (A and B).[216]

An inactivated rotavirus A vaccine (Equine Rotavirus Vaccine [Zoetis]) containing the P12, G3 serotype (H2 strain) in a metabolizable oil-in-water emulsion is conditionally licensed in the United States and is indicated for administration to pregnant mares in endemic areas as an aid for preventing diarrhea in their foals caused by infection with RVs of serogroup A. Foal vaccination is not indicated; no data suggest that vaccinating the newborn foal with inactivated rotavirus A vaccine has any benefit in preventing or reducing infection severity. Label recommendations call for a 3-dose vaccine series to be administered to mares during each pregnancy at 8, 9, and 10 months' gestation. This protocol has been shown to induce significant increases in serum concentrations of neutralizing antibody in vaccinated mares and in antibody concentrations of the IgG (but not IgA) subclass in colostrum and milk of vaccinated mares.[217,218] It is essential that the newborn foal receive an adequate amount of good-quality colostrum so it absorbs sufficient anti-RV antibodies. After nursing from vaccinated mares, the concentration of passively derived RV-specific antibody of the IgG subclass in the serum of foals up to 90 days of age is significantly higher than that measured in serum of foals born to unvaccinated mares.[217,218] A field study showed this vaccine to be safe when administered to pregnant mares and provided circumstantial evidence of at least partial efficacy. An approximately twofold higher incidence of rotaviral diarrhea was found in foals from unvaccinated mares compared to those from vaccinated mares, although this difference did not prove to be statistically significant.[217] Similarly, a controlled field study in Argentina in which an inactivated aluminum hydroxide–adjuvanted vaccine containing the SA11 (G3P2), H2 (G3P12), and Lincoln (G6P1) strains was administered to 100 mares at 60 days before foaling and again

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30 days later, demonstrated a substantial reduction in the incidence and severity of rotaviral disease in foals from vaccinated mares compared with foals from unvaccinated mares.[219] As MDA titers wane at about 60 days of age, foals may develop rotaviral diarrhea, but the severity of diarrhea is generally milder and of shorter duration than in foals that become infected during the first 30 days of life.

Challenge studies involving two inactivated RV vaccines administered in a similar manner to pregnant mares in Japan showed that their foals were not completely protected against infection but had a substantial reduction in severity of clinical signs after challenge.[214] The major correlate for protection against rotaviral infection appears to be mucosal immunity, predominantly mucosal IgA, in the gastrointestinal tract. Studies of the immunoglobulin isotype responses of mares after parenteral vaccination with inactivated RV vaccines, and of antibodies passively transferred to their foals via colostrum, indicate that this approach is unlikely to provide foals with intestinal mucosal protection in the form of IgA.[218] Consequently, it is not surprising that current protocols do not provide complete protection. In addition, because the conditionally licensed vaccine available in the United States contains only the G3 serotype of the A serogroup, it cannot be expected to protect against infection with all field strains.

Equine Rhinitis A Virus

Two rhinitis viruses, equine rhinitis A virus (formerly known as *equine rhinovirus 1,* genus *Aphthovirus,* family Picornaviridae) and equine rhinitis B virus (formerly known as *equine rhinovirus 2,* genus *Erbovirus,* family Picornaviridae), have been identified in horses.[220-225] Seroprevalence studies confirm that both viruses are active in horse populations worldwide, with prevalence ranging from 20% to 90%, depending on the age group and use of the horses sampled.[221,222,226] The rhinitis viruses have been largely overlooked as potential causes of clinically apparent respiratory disease for many years, but recently investigated outbreaks of contagious respiratory disease, as well as challenge studies, suggest that ERAV and ERBV may indeed be important pathogens of horses, causing both lower and upper respiratory tract disease.[223,225,226] Clinical manifestations include pyrexia, nasal discharge, cough, lethargy, anorexia, pharyngitis, and submandibular lymphadenopathy.[223,225] It has also been suggested that ERAV may play a causative role in inflammatory airway disease.[226] A unique feature of ERAV is persistent shedding in urine but only transient shedding in nasal secretions after respiratory tract infection.[220]

An inactivated ERAV vaccine (Equine Rhinitis A Vaccine [Boehringer Ingelheim]) was granted a conditional license in late 2012; efficacy and potency tests are in progress. The vaccine is labeled for vaccination of healthy horses 4 months of age or older. The manufacturer recommends a primary vaccination series of three 1-mL doses administered IM at 3- to 4-week intervals, followed by revaccination annually or prior to anticipated exposure. Pending publication of more data regarding vaccine efficacy, as well as the role of ERAV as a cause of respiratory disease, these authors are unable to provide recommendations regarding use of this vaccine.

Anthrax

Anthrax is a serious and rapidly fatal septicemic disease caused by proliferation and spread of the vegetative form of *Bacillus anthracis* in the body. *B. anthracis* is acquired through ingestion, inhalation, or skin penetration through contamination of wounds by soilborne spores of the organism. Anthrax is encountered only in limited geographic areas where moist alkaline soils, particularly those with high organic content, favor survival, germination, and sporulation of the organism. Vaccination is indicated only for horses pastured in endemic areas.

The only vaccine currently licensed for vaccination of livestock, including horses, contains viable live Sterne's strain 34F2 nonencapsulated spores in saponin (Anthrax Spore Vaccine [Colorado Serum Company, Denver, Colo.]). A primary series consisting of 2 doses of that vaccine should be administered SC 2 to 3 weeks apart, followed by annual revaccination. Mild to moderate swelling at the injection site is common, and adverse systemic reactions may occur occasionally, particularly in young and miniature horses. Little objective information is available regarding use of this vaccine in horses, but clinical evidence suggests that it provides protection. Vaccination of pregnant mares is not recommended.[227] Because it is a live bacterial product, appropriate caution should be used during storage, handling, and administration of the vaccine to prevent accidental inoculation of people and maintain vaccine potency. Concurrent administration of antimicrobial drugs effective against *B. anthracis* is contraindicated if the vaccine is to function as intended.

Ovine and Caprine Vaccination Programs

Amanda J. Kreuder • Paul J. Plummer

Factors Affecting Vaccine Availability, Choice, and Usage

Labeled vaccines for several important diseases of sheep and goats are currently available for use in the United States, but the small market share for small ruminant vaccines has negatively affected the funding available for vaccine research and development compared to other domestic species. As a consequence of low funding and difficulties in recouping development costs, vaccines currently being produced for small ruminants in the United States, except one modified live vaccine for bluetongue virus, are either killed bacterin products or virulent live products. These products are more basic to develop and cheaper to produce and market. Modified live products typically require increased costs related to development and production and thus are not widely available for small ruminant–specific diseases. A current list of vaccine targets available for labeled use in sheep and goats in the United States is presented in Table 48-5, and example vaccination schedules for sheep (Table 48-6) and goats (Table 48-7) are also provided. All vaccines must pass basic efficacy and safety testing by the USDA Center for Biologics; however, for the majority of vaccines currently marketed, there is an overall lack of field-based comparative vaccine efficacy data available for the practitioner's use to determine which vaccines to select. Because the value of individual animals in flocks may be low and the cost associated with vaccination for certain diseases high, a cost/benefit analysis should be performed prior to developing a vaccine program for a particular herd. This analysis should include not only the cost of the vaccine itself but also the high cost of labor associated with administration, as compared to the anticipated risk of infection of the herd and direct costs associated with the disease.

Most available vaccines are bacterins, so avoiding maternal antibody interference and ensuring timely booster administration are key concepts for developing effective vaccine programs. Similar to other food animal species, proper vaccine administration and adherence to meat quality assurance are important. Vaccines should be administered SC whenever possible, either in the neck or behind the shoulder in the axillary region. Confusion over vaccine reactions that can lead to swellings that resemble lymph nodes infected with *Corynebacterium pseudotuberculosis* should be kept in mind when choosing a vaccination location. Compared to sheep, goats are known to exhibit more severe vaccine reactions. If vaccines labeled for other species are to be used off label in goats, it is recommended that a small number of animals be vaccinated first to observe for reactions prior to vaccinating the entire flock.

Clostridial Vaccines

The only vaccine currently recommended for routine use in all small ruminants is yearly administration of a *Clostridium perfringens* C and D plus tetanus toxoid. Vaccination or protection via passive immunity (colostrum or antitoxin administration) is particularly important prior to common husbandry tasks like tail docking and castration (tetanus), as well as introduction to high-grain diets (*C. perfringens* type D). Ideally, all ewes and does should receive a booster

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TABLE 48-5

Antigens and Antisera Currently Licensed in the United States for Sheep and Goats

Type of Infectious Agent	Disease or Organism	Labeled Species
Bacterial antigens	Enzootic abortion of ewes[a] (*Chlamydophila abortus,* formerly *Chlamydia psittaci)*	Sheep
	Vibriosis[a,e] (*Campylobacter fetus* ssp. *fetus, C. jejuni)*	Sheep
	Tetanus[a] (*Clostridium tetani)*	Sheep, goats[d]
	Clostridial enterotoxemia[a] (*Clostridium perfringens* types C and D)	Sheep, goats[d]
	Additional clostridial diseases (blackleg, malignant edema)[a] (*Clostridium chauvoei, C. novyi, C. septicum, C. haemolyticum, C. sordellii)*	Sheep, goats[d]
	Anthrax[a] (*Bacillus anthracis)*	Sheep, goats
	Caseous lymphadenitis[a,e] (*Corynebacterium pseudotuberculosis)*	Sheep, goats[d]
	Ram epididymitis[a] (*Brucella ovis)*	Sheep
	Pasteurellosis[a] (*Mannheimia haemolytica, Pasteurella multocida)*	Sheep, goats
	Coliform mastitis[a,e] (*Escherichia coli)*	Goats
Bacterial antitoxins	Tetanus antitoxin (*Clostridium tetani* toxin)	Sheep, goats[d]
	C. perfringens antitoxin (targets a combination of *C. perfringens* toxins B, C, and D)	Sheep, goats[d]
	E. coli antitoxin (targets K99 strain)	Sheep
Viral antigens	Rabies[a] (*Lyssavirus,* family Rhabdoviridae)	Sheep
	Bluetongue[b] (type 10) (*Orbivirus,* family Reoviridae)	Sheep, goats
	Contagious ecthyma (sore mouth, orf)[c] (*Parapoxvirus,* family Poxviridae)	Sheep, goats

Information taken from North American Compendium of Veterinary Products.

a, Killed or inactivated vaccine; *b*, modified live vaccine; *c*, virulent live vaccine; *d*, not all available products labeled for use in goats; *e*, some or all products conditionally licensed.

vaccination 3 to 4 weeks prior to parturition; previous research in sheep indicates that passive immunity acquired from properly immunized ewes confers protection for up to 12 weeks in lambs.[1] Current recommendations for vaccination include an initial series of 2 doses 3 to 4 weeks apart, followed by yearly boosters. Appropriate timing of the booster in the first series of immunizations is essential in the formation of an adequate immune response for the remainder of the animal's life. When to initiate the first series of vaccinations is a topic of debate because there is little evidence-based literature on which to form a decision. The following guidelines are used by the authors in clinical practice. Lambs and kids from vaccinated dams with no evidence or suspicion of failure of passive transfer (FPT) may be vaccinated starting at 8 to 12 weeks of age. In animals born to unvaccinated dams or those with suspected FPT we recommend earlier use of the initial dose; these animals should be vaccinated starting at 1 to 3 weeks of age, with a booster in 3 to 4 weeks and consideration for an additional booster 1 month later. It is relatively common for producers to vaccinate ewes/does prior to parturition and then still initiate the vaccination of kids/lambs at 1 to 2 weeks of age. In such cases the practitioner should discuss the implications of passive maternal immunity on the immune response elicited by the kid/lamb, and should consider either additional boosters (after the period of maternal antibody wane) or delaying initiation of the vaccines. In cases of puncture wounds or injury, a tetanus booster should be administered if it has been longer than 6 months since the last vaccination. An additional booster may also be given to animals entering a feedlot or to those on a high-grain ration year-round (e.g., dairy animals) to aid in prevention of enterotoxemia.

Multiple combination commercial products are available, including *C. perfringens* C/D only, stand-alone tetanus toxoid, and 7-way or 8-way clostridial combination products. There is little evidence that vaccination with multivalent clostridial products is beneficial, but these may frequently be chosen to decrease cost. If multivalent clostridial vaccines are selected, care should be taken to ensure the vaccine contains a tetanus toxoid; in some vaccines, *C. sordellii* may be substituted in place of *C. tetani*.

Rabies Vaccines

Highly efficacious vaccines for the rabies virus are commercially available for sheep in the United States. Vaccination for rabies is recommended in endemic areas, especially in animals with increased human exposure, such as pets, show animals, and petting zoo exhibits. Vaccination of valuable animals is also recommended. Despite the availability of highly effective vaccines, administration to all small ruminants is not routinely recommended, owing to the high cost associated with vaccination. In addition, unlike rabies vaccination in cats and dogs, previous vaccination of small ruminants does not necessarily constitute protection in regard to quarantine versus destruction of exposed animals. None of the currently available vaccines are labeled for goats, but they are considered relatively safe to use in this species in similar instances as with sheep. Initial vaccination after 3 months of age, followed by yearly revaccination is recommended; following the initial yearly booster, vaccination frequency can be decreased to every 3 years in some cases, depending on vaccine label.

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TABLE 48-6

Ewe and Lamb Vaccination Schedule for North America

Type of Vaccine		Timing of Vaccination					
		Ewes				Lambs	
Recommendation	Antigen	Prebreeding	Breeding	Prelambing	Lambing	Post Lambing	Weaning
Required	Clostridial enterotoxemia Tetanus			Yearly booster in all ewes 1 month prior to lambing		*Vaccinated ewe and no FPT*: first vaccine at 8-12 weeks; booster 3-4 weeks later *Unvaccinated ewe or FPT*: first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	May booster vaccine at this time, especially in high-risk animals
Optional, depending on farm history	Rabies	Yearly booster; some vaccines may only require revaccination every 3 years following initial series.					Initial vaccination after 3 months
	Vibriosis	Initial 2-dose series followed by annual booster (exact timing different based on vaccine chosen)					
	Enzootic abortion	Initial 2-dose series followed by annual booster					
	Caseous lymphadenitis	Yearly booster					Initial 2-dose series
	Contagious ecthyma					Scarification and administration of vaccine to naive animals in endemic herds	
	Bluetongue	Annual vaccination at least 3 weeks prior to breeding					Initial vaccination after 3 months
	Pasteurellosis	Yearly booster					Initial 2-dose series
Not recommended for routine use	Anthrax Ram epididymitis						

FPT, Failure of passive transfer.

Foot Rot Vaccines

Commercial bacterin vaccines labeled for foot rot in sheep and targeting 10 strains of *Dichelobacter nodosus* and *Fusobacterium necrophorum* were once available in the United States. These vaccines are no longer commercially available in the United States, but the *D. nodosus* vaccine may be imported with USDA approval on a case-by-case basis. Localized vaccine reactions were common in both sheep and goats, and vaccine efficacy on a large scale has long been debated. Available evidence suggests that antigenic competition may reduce the effectiveness of simultaneous vaccination against multiple serogroups of *D. nodosus*.[2,3]

Current research performed in regions other than North America suggests newer approaches to vaccination for this disease may be more beneficial. In areas or flocks where only one or two strains may be present, targeted use of monovalent or bivalent autogenous vaccines in combination with culling of non-responders may be of benefit in eradicating the disease.[4-6] However, it is considered uncommon for only one or two strains to be present; instead, multistrain infections are thought to more commonly occur.[7] Use of multiple bivalent autogenous vaccines with sequential administration staggered every 3 months may help avoid antigenic competition while allowing for prolonged protection against multiple serotypes.[8] Development of a "universal" vaccine through comparative genomics, transcriptional profiling, and serologic screening for potential candidate antigens has also shown promising results.[9] When these newer technologies will be commercially available in the United States remains to be seen. Given the difficulties and limited availability of vaccines for foot rot, veterinary practitioners are encouraged to consider alternate management strategies that include antibiotic therapy and potentially footbaths.

Reproductive Disorder Vaccines

Commercial vaccines are currently available for sheep only to aid in control of some of the important infectious abortion diseases and contagious epididymitis in the United States. Again, many of these vaccines lack comparative or published field efficacy data, so blanket recommendations for use cannot be made. For additional information on vaccination strategies in reproductive diseases, two excellent reviews have recently been written with a more in-depth discussion of each of the following diseases.[10,11]

An inactivated *Brucella ovis* vaccine is available in the United States for use in rams to aid in prevention of epididymitis, but it is not recommended for routine use. Inactivated vaccines are not believed to confer protective immunity to this organism but are known to interfere with serologic testing to detect carrier animals. In countries where *Brucella melitensis* is present, the Rev-1 live mutant

TABLE 48-7

Doe and Kid Vaccination Schedule for North America

Type of Vaccine		Timing of Vaccination					
		Does				Kids	
Recommendation	Antigen	Prebreeding	Breeding	Prekidding	Kidding	Post Kidding	Weaning
Required	Clostridial enterotoxemia Tetanus			Yearly booster in all ewes 1 month prior to lambing		*Vaccinated doe and no FPT*: first vaccine at 8-12 weeks; booster 3-4 weeks later *Unvaccinated doe or FPT*: first vaccine at 1-3 weeks; booster twice at 3-4 weeks and 6-8 weeks later	May booster vaccine at this time, especially in high-risk animals
Optional depending on farm history	Rabies*	Yearly booster, some vaccines may only require revaccination every 3 years following initial series					Initial vaccination after 3 months
	Contagious ecthyma					Scarification and administration of vaccine to naive animals in endemic herds	
	Caseous lymphadenitis	Yearly booster					Initial 2-dose series
	Enzootic abortion*	Initial 2-dose series followed by annual booster					
	Bluetongue		Annual vaccination at least 3 weeks prior to breeding				Initial vaccination after 3 months
	Pasteurellosis	Yearly booster					Initial 2-dose series
	Coliform mastitis			2-3 doses pre- and post kidding			
Not recommended for routine use	Anthrax						

*Constitutes off-label use of vaccine in this species.

FPT, Failure of passive transfer.

vaccine may be useful in controlling both diseases; however, in *B. melitensis*–free countries like the United States and Canada, its use is prohibited.

There are currently two commercially available bivalent bacterin vaccines for abortion due to *Campylobacter fetus* subsp. *fetus* and *C. jejuni* in the United States. In general, there is minimal cross-protection between these organisms, and sheep appear to be much more susceptible than goats to abortions caused by these agents. Recommendations for use on farms with diagnosed abortions due to *Campylobacter* spp. include an initial series of 2 doses in ewe lambs, followed by administration of an annual booster; exact timing varies based on the vaccine chosen. Recently a new tetracycline-resistant strain of *C. jejuni* (IA 3902) has emerged in the United States and is now thought to be the leading cause of *Campylobacter*-associated abortion.[12] Studies in guinea pig abortion models suggest that vaccination with certain commercial vaccines may be more beneficial than others in providing cross-protection to prevent abortion associated with this IA 3902 strain.[13] Following an abortion storm, herd immunity may initially be high, and in future breeding seasons the extent of disease may be limited to naive animals. Over time, immunity may wane, and infections may reoccur.

Chlamydophila abortus (formerly *Chlamydia psittaci*) is a common cause of abortion in both sheep and goats worldwide. Following abortion, ewes and does will develop immunity to future abortion but will often continue to shed the organism and infect other naive animals. Currently, only an inactivated culture vaccine (bacterin) is available in North America for use in sheep. Some producers have used this vaccine in goats, and it appears to be generally safe in this species. Vaccination with this type of vaccine will not prevent shedding of the organism but may decrease the rate of abortions. Vaccine efficacy is unpredictable, owing to variation in the amount of antigen present and loss of antigenicity following in vitro culture during vaccine production. Strain variation from farm to farm may also play a role in perceived vaccine failures. An attenuated live vaccine is available in other countries and is thought to be more efficacious in preventing abortion as well as shedding but is not without drawbacks. Live attenuated *C. abortus* organisms can be infective to humans handling the vaccine, and the vaccine strain has recently been

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identified in aborted placentas in the United Kingdom.[14] Newer vaccine technologies such as DNA vaccines or bacteriophage-delivered DNA may eventually offer a solution to the problems identified with current vaccine strategies.[15,16]

Vaccines for other important reproductive diseases like Q fever *(Coxiella burnetii)* and toxoplasmosis *(Toxoplasma gondii)* are not available in the United States even though they remain important causes of abortion in sheep and goats. A phase I inactivated *C. burnetii* vaccine is commonly used in many areas of Europe, with observed reductions in shedding and decreased abortion rates. This vaccine is currently part of the mandatory vaccination program in The Netherlands.[17] This vaccine is neither marketed nor approved for importation into the United States at present by the USDA. A modified live toxoplasmosis vaccine consisting of freeze-dried tachyzoites is available in Europe and New Zealand; it provides excellent long-term immunity. Both of these vaccines are potentially zoonotic and therefore must be handled carefully. Licensing of the *C. burnetii* vaccine has been considered in North America but may be hindered by licensing cost and market size. A vaccine for toxoplasmosis is not likely to become available in the United States in the near future, owing to the small market compared to overseas.

Caseous Lymphadenitis Vaccines

Vaccination for *Corynebacterium pseudotuberculosis* has been attempted with a number of different vaccine modalities; all currently marketed products in the United States are bacterin-toxoids sold as either separate or combination products. Experimental trials have demonstrated a decrease in the occurrence of both internal and external abscesses following inoculation in vaccinated animals.[18] Based on these and other data, the vaccine may have a place in some herds to decrease disease prevalence. While a large amount of research into vaccines has been done overseas,[19,20] little other U.S. vaccine research for this disease has been done. The available vaccines will not prevent all animals from developing abscesses, and animals must be vaccinated prior to exposure. Vaccine reactions (lameness, lethargy, depression) may occur and can be significant. Despite frequent use in goats, the fully licensed vaccine is not labeled for use in this species and may result in severe injection site reactions that can lead to decreased milk production and poor appetite. Recently a new conditionally licensed vaccine specific for goats has come on the market. At this writing, very little data are available regarding its clinical use. It is not approved for use in all states, so practitioners should consult their state veterinarian or the manufacturer for more information. Initial vaccination requires a 2-dose series 4 weeks apart, with annual revaccination required. Producers must be aware that vaccination will lead to a positive result on serologic testing.

Contagious Ecthyma Vaccines

Virulent live virus vaccines are available in the United States and labeled for use in both sheep and goats to decrease the severity of disease caused by contagious ecthyma virus (soremouth, orf). Use of these vaccines should be limited to herds where endemic disease is present or in outbreak situations where the disease has been newly introduced to the farm. Use of the vaccine on a farm without previous evidence of infection will result in contamination of the farm with live virulent vaccine virus. The goal of vaccination is to induce mild disease while creating immunity to future exposure. An area free of wool or hair is selected (axilla, flank, inner thigh) and a 1-in^2 area is scarified with a provided instrument, followed by application of vaccine. Development of a scab in the region of scarification is indication of successful vaccination. The vaccine is a virulent live virus, so care should be taken with administration; it poses a zoonotic risk of infection. Vaccination failures are known to occur, and it has been suggested that the increased occurrence of vaccine failures, particularly in goats, may be due to strain variation between sheep and goat isolates. Efforts are under way to develop goat-specific vaccine strains.[21]

Respiratory Vaccines

Despite the long list of bacterial and viral organisms thought to play a role in respiratory disease in small ruminants, the only available labeled vaccines in the United States are combination killed bacterins of *Mannheimia haemolytica* and *Pasteurella multocida*. Most vaccine strains are derived from bovine isolates; small ruminant strains, particularly for *M. haemolytica,* are not the same as those found in bovine cases.[22] Cross-reactivity among strains is variable, so the efficacy of these vaccines in small ruminants is inconsistent. In addition, many previously reported cases of *P. multocida* may instead have been caused by the newly classified *Bibersteinia trehalosi* (formerly *P. multocida* type T). If disease is truly caused by *P. multocida,* the vaccines may have some efficacy, but if *B. trehalosi* is the causative agent, none of the available vaccines are believed to offer significant protection to disease caused by this organism. There are currently no labeled vaccines for viral agents of respiratory disease in small ruminants, and there are no published studies evaluating the safety and efficacy of the use of bovine vaccines in these species.

Other Vaccines

An MLV vaccine is available for bluetongue virus in the United States, but it is thought to be of limited efficacy in the field because it contains only one of the six serotypes known to circulate in North America. Cross-protection among serotypes is thought to be very limited, so vaccination will only offer protection against the vaccine strain (serotype 10). The vaccine is known to cause fetal malformations in pregnant ewes and has the potential to be transmitted to unvaccinated animals during vector season.

A conditionally approved (California only) endotoxin vaccine is labeled for use in milking goats to decrease the severity of toxic mastitis caused by *E. coli*. In other areas of the country, some of the endotoxin vaccines commonly administered in dairy cattle are used off label in milking goat herds. Because of the low incidence of toxic mastitis in this species, routine use is not recommended. If these vaccines are used, administration will not prevent infection but will decrease disease severity.

Bovine Vaccines and Herd Vaccination Programs

Victor S. Cortese, *Consulting Editor*

With the increasing size of today's cattle operations and the extensive movement of cattle, disease exposure continues to occur at a high rate. These exposures often put pressure on the efficacy of the vaccines used and may give field experience as to how well they can protect cattle. The wide diversity in uses of cattle and management practices makes a single vaccination protocol impossible for all cattle production systems. Today it is even more important to scientifically choose a vaccine or design a vaccination program based on good information. When designing programs, several variables must be considered[1]:

- The presence and degree of challenge of the particular diseases on the farm or ranch (Boxes 48-1 and 48-2)
- Management practices on the facility that support or hinder vaccination programs
- The times or ages when disease problems occur and whether the diseases are associated with any stressors
- The immune system components necessary to afford protection against various diseases
- Some basic immunologic concepts
- The information available on products being considered and the source and quality of the information
- Required vaccines for a particular use of the animal (e.g., 4-H shows)

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BOX 48-1

Bovine Vaccines Seldom Needed on Most U.S. Ranches and Farms*

Anthrax vaccine
Clostridium septicum (malignant edema) bacterins
Leptospira grippotyphosa bacterins
Leptospira icterohaemorrhagiae bacterins
Leptospira canicola bacterins
Clostridium botulinum toxoids
Clostridium novyi bacterins
Rabies vaccine
Tetanus toxoids
Erysipelas bacterins
Clostridium sordellii (malignant edema) bacterins

*These vaccines also are not cost-effective.

BOX 48-2

Bovine Vaccines for Ranch- and Farm-Specific (Soilborne) Diseases

Blackleg bacterins
Clostridium haemolyticum (redwater) bacterins
Anthrax vaccine
Clostridium novyi (infectious necrotic hepatitis) bacterins

BOX 48-3

Vaccines Recommended for Use in Adult Beef Cows

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii var. *hardjo*
Leptospira pomona bacterins
Campylobacteriosis bacterins*

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine
Anaplasmosis vaccine (inactivated)
Rotavirus-coronavirus (calf scours) vaccine (inactivated)
Fusobacterium necrophorum (foot rot) bacterin
Escherichia coli bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Clostridium perfringens type C (enterotoxemia) toxoids
Anthrax vaccine
Clostridium novyi bacterins

*Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, and/or "bull-proof" perimeter fencing).

BOX 48-4

Vaccines Recommended for Use in Adult Beef Bulls

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Campylobacteriosis bacterins*

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine
Anaplasmosis vaccine (inactivated)
Leptospira pomona bacterins
Fusobacterium necrophorum (foot rot) bacterin
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Clostridium novyi bacterins

*Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, and/or "bull-proof" perimeter fencing).

Challenge

The level of disease challenge and the degree of protection continually fluctuate. Biological variability makes the degree of protection different in every vaccinated animal. The same is true for the level of exposure to a pathogen. Overwhelming challenge can override immunity and lead to disease even in well-vaccinated animals.[2]

Timing of Disease

On many farms, certain diseases occur at consistent times. Timing may give some insight into stresses that occur in the management of the cattle. Correcting these stresses can have a positive impact on vaccination and lessen animals' susceptibility to disease. This type of history is also helpful in determining the timing of vaccinations, a concept that is often underused in veterinary medicine. Knowing when a problem historically has occurred allows vaccinations to be scheduled when they will induce maximum immune responses in preparation for expected challenges.

Assessing Vaccine Efficacy

The efficacy of a vaccine can be extremely difficult for the practitioner to assess. Traditionally, serologic data showing pre- and post-vaccination titers has been equated with protection. For many diseases, however, the correlation is poor between the antibody measured and the protection generated by the vaccine in the animal.[3] Recently a study comparing BVDV protection showed an inverse relationship between antibody levels and the ability of the vaccines to prevent development of persistently infected calves.[4] Cell-mediated immune function tests have been added to show a more complete stimulation of the immune response after vaccination.[5] Although these tests provide more information about the vaccine, they still do not answer the basic question of how well a vaccine truly protects. This question can be answered only by well-designed challenge studies. There are many examples of well-designed studies involving both viral[6,7] and bacterial[8,9] agents. To assess a challenge study, the following information is needed:

1. Trial design, including animal characteristics
2. Statistical analysis of the results
3. Determination of whether statistical differences are biologically important
4. Route of administration of the challenge
5. Characteristics of the challenge organism
6. Consistency of the challenge model with the desired protection sought (e.g., respiratory vs. reproductive protection)
7. Method of clinical score assignment
8. Level of disease seen in the control unvaccinated cattle
9. Publication of the results in a peer-reviewed article

Unfortunately, the challenge model is not well established for many diseases. Field trials are even harder to assess but are valuable for judging the effectiveness (i.e., efficacy in a particular situation) and efficiency (i.e., cost-effectiveness) of a vaccine[10] (Boxes 48-3 to 48-12; also see Boxes 48-1 and 48-2). Several good references on field trial analysis are available.[11,12] Recently the Center for Veterinary Biologics (CVB) began giving vaccines different labels depending on the strength of the efficacy data submitted to them in the licensing trials.

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BOX 48-5

Vaccines Recommended for Use in Beef Calves*

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Brucellosis vaccine†

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Moraxella bovis (pinkeye) bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Anaplasmosis vaccine† (modified live)
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Fusobacterium necrophorum (foot rot) bacterin
Clostridium novyi bacterins
Mannheimia haemolytica vaccines (new)

*Under 12 months of age.
†Heifer replacements only.
‡Heifer and bull replacements only.

BOX 48-6

Vaccines Recommended for Use in Stocker Cattle

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Mannheimia haemolytica vaccines (new)
Leptospira pomona bacterins

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Moraxella bovis (pinkeye) bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Fusobacterium necrophorum (foot rot) bacterin
Clostridium novyi bacterins

BOX 48-7

Vaccines Recommended for Use in Beef Replacement Heifers

Vaccines Highly Recommended for Use in All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Campylobacteriosis bacterins*

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Tritrichomonas foetus vaccine
Anaplasmosis vaccine (modified live)
Rotavirus-coronavirus vaccine (inactivated)
Escherichia coli bacterins
Fusobacterium necrophorum (foot rot) bacterin
Moraxella bovis (pinkeye) bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Clostridium perfringens type C toxoids
Anthrax vaccine
Clostridium novyi bacterins

*Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, or "bull-proof" perimeter fencing).

BOX 48-8

Vaccines Recommended for Routine Administration to Cattle Entering Feedlots

Essential Vaccines

Infectious bovine rhinotracheitis (IBR) vaccine (modified live)
Bovine virus diarrhea (BVD) vaccine (modified live)
Bovine respiratory syncytial virus (BRSV)

Highly Recommended Vaccines

Mannheimia haemolytica vaccine*
Leptospira pomona bacterins

Vaccine That May Be Needed in Some Groups of Cattle in a Feedlot

Clostridium haemolyticum (redwater) bacterins

Vaccines Necessary Only in Specific "Problem" Feedlots

Blackleg bacterins
Bovine respiratory syncytial virus (BRSV) vaccines
Fusobacterium necrophorum (foot rot) bacterin

*Some commercial modified live cytopathic virus BVD vaccines trigger severe fatal BVD in cattle that are chronically infected with noncytopathic strains of BVD virus and immunologically tolerant as a result of prenatal infection.

Cattle Vaccines

Bovine vaccines tailored for use against 8 viral diseases, more than 28 bacterial pathogens, and 1 protozoal disease (trichomoniasis) are currently federally licensed in the United States (Table 48-8). These vaccines have been designed to aid in preventing a myriad of diseases in cattle, including reproductive, respiratory, generalized septicemic, and toxic (endotoxic and exotoxic) diseases. The vaccines have demonstrated some degree of protection against the pathogen for which they were designed, but they may not have proved protective against all the various syndromes known to be caused by a specific infectious agent. The challenge models for each pathogen and the release requirements for each vaccine are monitored by the Veterinary Biologics division of the USDA's Animal and Plant Health Inspection Service (USDA/APHIS) and can be found in Book 9 of the Code of Federal Regulations.

During gestation the bovine reproductive system, with its multilayered placenta, leaves the fetus in a naive environment susceptible to infection. Abortions may be due to infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug. It is therefore difficult to achieve protection against reproductive diseases. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta. Only a few currently licensed vaccines have proved protective against the reproductive forms of various diseases, and the duration of immunity they afford has not been established.

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BOX 48-9

Vaccines Recommended for Use in Adult Dairy Cows

Vaccines Highly Recommended for Use in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV)
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins

Vaccine Highly Recommended for Cows in Specific Infected Herds

Core endotoxin vaccines

Vaccines Highly Recommended for Dairy Cows Grazing in Specific Endemic Areas

Clostridium haemolyticum bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Escherichia coli (calf scours) bacterins
Rotavirus-coronavirus (calf scours) vaccine (inactivated)
Fusobacterium necrophorum (foot rot) bacterin
Clostridium septicum (malignant edema) bacterins
Clostridium sordellii (malignant edema) bacterins

BOX 48-10

Vaccines Recommended for Use in Adult Dairy Bulls

Vaccines Highly Recommended for Bulls in All Commercial Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Campylobacteriosis bacterins*

Vaccines Highly Recommended for Bulls Grazing in Specific Endemic Areas

Anaplasmosis vaccine (inactivated)
Clostridium haemolyticum (*Clostridium novyi* type D, redwater) bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful in Specific Herds or Geographic Locations

Leptospira pomona bacterins
Fusobacterium necrophorum (foot rot) bacterin

*Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, or "bull-proof" perimeter fencing).

Each manufacturer's development and production of cattle vaccines is different, so the composition of vaccines varies substantially among manufacturers. Outlines of production are proprietary for each manufacturer, but some information can be found in technical and marketing materials. For example, some viral vaccines are grown on bovine-derived kidney cell lines, and others are grown on porcine-derived kidney cells. Some vaccines are grown only on calf serum, whereas others are grown on both calf and fetal calf serum. Variability is seen in the strain or strains chosen for the vaccine, number of growth cycle passages chosen for attenuation, growth medium, and number of viral or bacterial particles in the vaccine.

BOX 48-11

Vaccines Recommended for Use in Dairy Calves*

Vaccines Highly Recommended for Calves in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Brucellosis vaccine

Vaccines Highly Recommended for Calves Grazing in Specific Endemic Areas

Blackleg bacterins
Clostridium haemolyticum bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccine Highly Recommended for Calves in Herds with Adult Cows Grazing in Specific Endemic Areas

Anaplasmosis vaccine (modified live)

Vaccines That May Be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Mannheimia haemolytica vaccines (new)
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Moraxella bovis (pinkeye) bacterins
Fusobacterium necrophorum (foot rot) bacterin

*Up to 12 months of age.

BOX 48-12

Vaccines Recommended for Use in Yearling Replacement Dairy Heifers

Vaccines Highly Recommended for Use in Heifers in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins

Vaccines Highly Recommended for Dairy Heifers Grazing in Specific Endemic Areas

Blackleg bacterins
Anaplasmosis vaccine (Anavac* or Anaplaz)
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful for Controlling Specific Disease Problems in Individual Groups of Dairy Heifers

Fusobacterium necrophorum (foot rot) bacterin
Moraxella bovis (pinkeye) bacterins

Vaccines Administered to Springing Heifers That May Be Useful for Controlling Specific Disease Problems in Specific Dairy Herds

Gram-negative core antigen (coliform mastitis) vaccines
Escherichia coli (calf scours) bacterins
Rotavirus-coronavirus (calf scours) vaccine (inactivated)
Clostridium septicum (malignant edema) bacterins
Clostridium sordellii (malignant edema) bacterins

*Anavac (BioLOGIC Laboratories, Davis, Calif. 95616) is the preferred vaccine for use in dairy herds where adult cows are grazing in an endemic area.

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TABLE 48-8

Antigens Available in Currently Licensed* Cattle Vaccines

Antigen Type	Common Name of Disease or Vaccine	Pathogen
Virus	BRSV	Bovine respiratory syncytial virus
	Rednose	Bovine herpesvirus type 1, infectious bovine rhinotracheitis virus (IBRV)
	BVD-MD	Bovine virus diarrhea virus (types 1 and 2)–mucosal disease
	PI-3	Parainfluenza type 3 virus
	Rabies	*Lyssavirus* spp.
	Warts	Bovine papillomavirus, bovine rotavirus, bovine coronavirus
Bacteria	Anthrax	*Bacillus anthracis*
	Bangs	*Brucella abortus*
	Vibriosis	*Campylobacter fetus* subsp. *veneralis*
	Blackleg	*Clostridium chauvoei*
	Redwater disease (bacillary hemoglobinuria)	*Clostridium haemolyticum*
	Black disease	*Clostridium novyi*
	Enterotoxemia	*Clostridium perfringens* type C
	Foot rot	*Fusobacterium necrophorum*
	Heel warts	*Treponema bacteria*
	Haemophilis, TEME	*Histophilus somni*
	Hemorrhagic bowel syndrome	*Clostridium perfringens* type A
	Overeating	*Clostridium perfringens* type D
	Malignant edema	*Clostridium septicum, Clostridium sordellii*
	Mycoplasma pneumonia and mastitis	*Mycoplasma bovis*
	Tetanus	*Clostridium tetani*
	Endotoxin vaccines	J5 *Escherichia coli*
		R mutant *Salmonella* vaccine
	Coliform scours	*E. coli* K99 and non-K99
	Food safety	*E. coli* O157 (SRP-conditionally licensed)
	Foot rot	*Fusobacterium necrophorum*
	Pinkeye	*Moraxella bovis*
	Leptospirosis	*Leptospira borgpetersenii* serovar *hardjobovis*
		Leptospira interrogans serovar *hardjobovis*
		Leptospira interrogans serovar *cannicola*
		Leptospira interrogans serovar *icterohaemorrhagiae*
		Leptospira interrogans serovar *grippotyphosa*
		Leptospira pomona
	Johne's disease	*Mycobacterium avium* subsp. *paratuberculosis*
	Salmonella	*Salmonella* Dublin, *Salmonella* Typhimurium
		Salmonella sideophore vaccines (SRP-conditionally licensed)
	Shipping fever	*Mannheimia haemolytica (Pasteurella haemolytica)*
		Pasteurella multocida
	Endotoxin vaccines	R *Salmonella*, J5 *E. coli*
	"Staph" mastitis	*Staphylococcus aureus*
Rickettsiae/protozoa	"Trich"	*Tritrichomonas foetus*
	Anaplasmosis	*Anaplasma marginale* (not federally licensed)

Modified from Bayley AJ. 1999. Compendium of veterinary products, ed 5. Iowa State Press, Iowa City, IA.

*Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

Three types of vaccines represent the basic technologies currently available in cattle viral and bacterial vaccines[2,13-17]:

1. *Modified live (attenuated) vaccines* contain living bacterial or viral organisms. These organisms usually are collected from a field disease case and then grown in abnormal host cells (viruses) or media (bacteria) to change or attenuate the pathogen. Each completed replication cycle is known as a *passage,* and the changed pathogen then is administered back to the animal to determine if it is still virulent. After several passages the pathogen begins to lose virulence factors because it cannot cause "disease" in the unnatural host cells. Once the pathogen can no longer cause "disease" in the target species, it is tested to see if it can confer protection. The final vaccine is usually passed a number of times beyond the passage where virulence disappears in order to reduce the risk of reversion to a virulent pathogen. These vaccines require good quality control to reduce the risk of a contaminant entering the vaccine.
2. *Inactivated (killed) vaccines* are easier to develop because virulence after growth is not a problem. The same pathogen is isolated from a disease outbreak. The pathogen is grown and then chemically or physically killed. The inactivation is usually achieved either by adding a chemical to the pathogen or by using ultraviolet rays. The major concern with inactivation is the potential loss of important epitopes. An adjuvant is normally added to inactivated vaccines to heighten the immune response. The vaccine is then tested for efficacy.
3. *Genetically engineered vaccines* have been genetically altered, usually through a mutation. This mutation may be induced by several different methods, but the resulting bacterium or virus has different properties that may alter virulence or growth characteristics. Most of these vaccines are modified live mutants (e.g., temperature-sensitive viral vaccines or streptomycin-dependent *Mannheimia/Pasteurella* vaccines), but inactivated marker vaccines are also genetically engineered. These vaccines have been engineered to delete a gene and cause an immune response deficient in antibodies to a certain epitope; this allows diagnostic methods to distinguish between vaccine and natural exposure responses (e.g., gene-deleted infectious bovine rhinotracheitis [IBR] vaccines).

Once its efficacy has been established, the vaccine is put through a series of experiments to determine the minimum dose required to

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achieve adequate protection, called the *minimum immunizing dose* (MID). The vaccine will contain more than the MID to ensure that it contains at least the MID at the expiration date found on the label. In effect, a vaccine's efficacy is not determined by the final product used by the veterinarian but at a reduced level of immunogens from the amount contained in the final vaccine.

Autogenous Vaccines

In addition to the vaccines licensed by the USDA, several companies will make autogenous vaccines for use by veterinarians and cattle owners. These vaccines do not fall under any particular USDA/APHIS guidelines and are usually derived from cultures (e.g., viral or bacterial) isolated from specimens submitted by the particular farm. Such vaccines can be used only on that particular facility and cannot be sold for use on other farms. These vaccines are not tested for efficacy or safety, and the components found in the vaccines may vary from batch to batch; this adds some element of risk when they are used. Nevertheless, this type of vaccine may be an option to consider when federally licensed vaccines are unavailable for a specific farm problem.

Maternal Antibody Interference Revisited

It is an accepted belief that maternal antibodies can block immune responses from vaccination. This belief has been based on a procedure of vaccination followed by a titer evaluation in the vaccinates. Many studies have shown that vaccinated animals may not display increased antibody levels if high levels of maternal antibody to that antigen are present. However, recent studies have shown that both B-cell memory responses and cell-mediated responses can be stimulated despite high maternal antibody for the same antigens.[18-20] Seropositive calves vaccinated at a young age with modified live (MLV) bovine herpesvirus type 1 (BHV-1), parainfluenza type 3 (PI-3), and/or bovine respiratory syncytial virus (BRSV) vaccines have shown higher antibody responses on revaccination than control calves vaccinated only at the second date. These young vaccinates typically do not show increased antibody responses after the initial vaccination in the presence of high maternal antibody. Cell-mediated immune responses, as indicated by antigen-specific T-cell blastogenesis, have been demonstrated in the face of high maternal antibody levels[21] when attenuated BRSV and BHV-1 vaccines were used. Similar responses have been reported in laboratory animals as well.[22-24] One study also demonstrated higher levels of protection at challenge if calves were vaccinated with a modified live BRSV vaccine.[20] It is clear from these studies that maternal antibody interference with vaccines is not as absolute as once thought. The animal's immune status, the specific antigen, and the presentation of that antigen should be considered when designing vaccination programs in which maternal antibody may be a factor.

Impact of Stress

Stress affects the immune system of all cattle, as can a number of other factors. The release of corticosteroid that occurs during the birthing process has a dramatic impact on the newborn's immune system. Newborns also have a higher number of suppressor T cells than adults.[2] These factors and others dramatically diminish systemic immune responses for the first week of life.[25] Other stresses should be avoided at vaccination time to maintain the integrity of the immune system. Procedures like castration, dehorning, weaning, and movement have to be considered as stressors in cattle, and all have the potential to temporarily diminish immune system functioning.[26-28]

Systemic vaccinations should be avoided during high-stress times because of these diminished responses and because vaccination at such times may even have undesired effects.

Booster Importance

It is important to follow the label directions for administering vaccines. Many inactivated vaccines and some modified live BRSV vaccines require a booster before protection is complete. The first time an inactivated vaccine is administered, the primary response occurs. This response is not very strong, is fairly short-lived, and is predominantly composed of IgM antibodies (Fig. 48-1). The response seen after a booster vaccination is called the *secondary* or *anamnestic response.* This response is much stronger, of longer duration, and is primarily composed of IgG antibodies.[2,12] If the booster is given too early, the anamnestic response does not occur, and if too much time elapses before the booster is given, it acts as an initial dose, not as a booster.

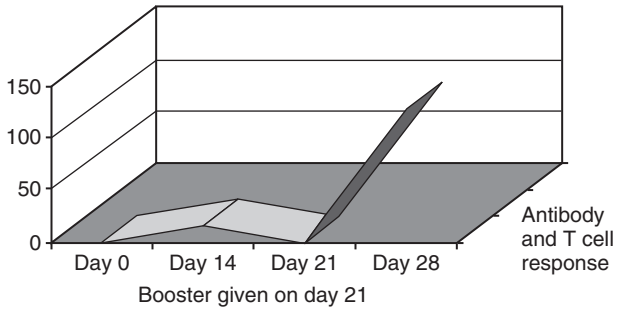


FIG. 48-1 Anamnestic response seen after booster dose is administered to vaccinates.

With most MLV vaccines (except for some BRSV vaccines), the primary vaccination also stimulates the secondary response without the necessity of a booster, because the virus or bacterium is replicating in the animal.

Adverse Reactions

Adverse reactions are a risk with any vaccination and can be categorized as one of the following two primary types of hypersensitivities[2,4,29-34]:

1. *Type I (immediate) hypersensitivity* is mediated by IgE stimulation and release of granules from basophils and mast cells. This reaction is seen within minutes of vaccination and often begins with shaking or sweating. Most of these animals respond to IV injection of epinephrine. Every vaccine can occasionally elicit an anaphylactic reaction. Cattle should always be kept under observation for at least 30 minutes after administration of a vaccine. Epinephrine should be administered at a dosage of 1 mL of 1:1000 solution per 50 kg of body weight, preferably by IV injection, at the first sign of weakness, staggering, or dyspnea. With most vaccines, anaphylactic reactions occur no more often than 1 case per 5000 to 10,000 doses administered. The rate of occurrence may be much higher after administration of *Salmonella, E. coli,* and some *Moraxella bovis* bacterins, which may have high levels of endotoxin.
2. *Type III (immune complex) hypersensitivity* is mediated by attachment of an antibody-antigen complex to complement and the ensuing activation of the complement cascade. The resultant reaction may occur locally or systemically. The reaction may be delayed, as the complexes form and the cascade begins, or subsequent, as products begin to exert their effects. The signs are similar to those of an immediate hypersensitivity reaction, and the treatment is administration of epinephrine.

One of the more common reactions seen in dairy cattle has been associated with the endotoxin and other bacterial components found in most gram-negative vaccines.[32-35] Currently, there are no requirements for monitoring or reporting the amount of endotoxin found in cattle vaccines, and the level of endotoxin may vary dramatically between vaccines and between serials of the same vaccine. Furthermore, the potency of endotoxin varies among different gram-negative bacteria. This type of reaction is seen primarily in Holsteins because of a genetic predisposition and may be seen after administration of any gram-negative bacterin. The signs vary depending on the farm's or the individual's sensitivity to gram-negative bacterial components. The number or potency of the gram-negative fractions in

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vaccinations administered simultaneously are also instrumental in causing these reactions. As a general rule, no more than two gram-negative vaccines should be administered to dairy cattle on the same day because of the possibility of adverse reactions, which may include anorexia and transient decreases in milk production, early embryonic death, abortion, and gram-negative bacterial shock (endotoxic shock), which requires treatment with flunixin or ketoprofen, steroids, antihistamines, and fluids.

Site reactions are common sequelae to many vaccines. These granulomas are usually caused by overreaction to the adjuvants, but they may also be directly aimed at the antigen or antigens. This has been a major focus of beef quality programs and has generated a push to have all vaccines labeled and to have them administered SC to avoid damaging the muscle.

Read the Labels

The vaccine label is a wealth of information that is approved by the CVB/APHIS. The CVB evaluates the supportive efficacy data supplied by the vaccine manufacturer and decides whether the vaccine can be licensed or not. They also determine what type of efficacy claim can appear on the vaccine labels and in advertising. Included are dosage, route of administration, precautions, timing, indications, storage information, withdrawal period, and shelf life. As found in Veterinary Services Memorandum 800.202 (June 2002), the CVB also does some preliminary rating of vaccine efficacy by granting one of five level of protection statements (in order of highest efficacy to lowest): Prevention of infection, Prevention of disease, Aid in the prevention of infection, Aid in disease control, Other miscellaneous claims. The label can be a good starting point for comparing vaccines.

Summary

Designing a vaccination program requires a good history of the individual farm and a basic understanding of the immune system. Vaccines that should be considered for routine or optional use in various classes of pastured beef cattle, feedlot cattle, and dairy cattle are listed in Boxes 44-3 to 44-12. The vaccines chosen should be supported by good, solid efficacy studies (and by effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch (see Table 44-8). Management decisions may be made that do not maximize the potential of the product chosen, and realistic expectations of all products should be well explained to the producer before the vaccines are administered. The owner should be involved in the vaccine decision-making process, and all information on the product should be shared.

Establishing good baseline immunity of replacement heifers and the foundation vaccination program can have dramatic effects on the health and profitability of the herd, so such programs must be well planned.

Bovine Respiratory Disease Vaccines

Bovine Herpesvirus Type 1 Vaccines

Robert W. Fulton

In 2012 more than 100 vaccines against BHV-1 were available in the United States for use in cattle.[1] These vaccines were either monovalent or in combination with other viral and/or bacterial immunogens. Vaccination protocols for beef and dairy cattle in the United States routinely incorporate use of one or more vaccines against BHV-1. These vaccines are classified into five types: (1) MLV vaccines for parenteral administration (IM and/or SC); (2) MLV intranasally administered vaccines; (3) chemically altered, live virus, temperature-sensitive vaccine for parenteral use; (4) inactivated viral (killed [KV]) vaccines for parenteral use; and (5) a combination of parenteral MLV and inactivated viral vaccine. These vaccines may be single-component (monovalent) vaccines (e.g., BHV-1 alone) or may contain several immunogens, including various combinations of bovine viral diarrhea viruses (BVDV) types 1 and 2; bovine parainfluenza type 3 (PI-3) virus, bovine respiratory syncytial virus (BRSV), *Leptospira* spp., *Histophilus somni, Mannheimia haemolytica, Pasteurella multocida,* and/or *Campylobacter* spp.[1] BHV-1 vaccines in the United States are principally derived from the Cooper/Colorado 1 strain, and in some cases the temperature-sensitive mutant RLB106.[1] The characteristics of the BHV-1 vaccines are described below.

BHV-1 MLV parenteral vaccines induce both B-cell (humoral) and T-cell (cell-mediated) active immune responses in vaccinated animals.[2,3] Calves born to dams with circulating BHV-1 antibodies may absorb the colostrally derived maternal antibodies to BHV-1 and other viruses.[4] The mean half-life of viral antibodies to BHV-1 in calves receiving maternal immunity was 21.2 days.[4] Potentially, calves receiving passive immunity to BHV-1 may have reduced response to BHV-1.[5] Calves seronegative to BHV-1 were given BHV-1 neutralizing antibody IM and subsequently given MLV BHV-1 intranasally. The passive BHV-1 immunity via BHV Ig reduced the efficacy of the MLV BHV-1.[5] The passively administered BHV-1 antibodies protected against viral shedding in viral challenged calves.[5]

MODIFIED LIVE VIRUS PARENTERAL VACCINES. The MLV parenteral vaccines were the initial vaccines licensed for use in cattle for protection against BHV-1.[6] Vaccines are attenuated by multiple passages in cell culture and often retain their ability to replicate in a susceptible animal, possibly causing a viremia. MLV parenteral vaccines are relatively inexpensive, offer a convenient route of administration, and stimulate a rapid onset of immunity (i.e., within 3 to 5 days of administration).[7-12] In general, one dose given to a susceptible animal stimulates protective immunity, which varies in duration depending on the clinical form of the disease challenge.[3,12] Duration-of-immunity studies are important to determine length of protection after initial vaccination. Calves receiving a combination MLV vaccine with BHV-1 were protected for at least 126 days after vaccination, as measured by protection against infection.[13] Licensure of BHV-1 vaccines in the United States requires efficacy studies using a standard challenge with the BHV-1 USDA Cooper strain. In addition, administration of a combination modified live BHV-1 vaccine yielded protection against virulent field strains of BHV-1.[14] The MLV parenteral vaccines may cross the placenta and infect the fetus, causing abortion.[15] Most MLV BHV-1 parenteral vaccines are not approved for use in pregnant heifers/cows or nursing calves.[1] In recent years, companies have received label claim approval for BHV-1 and BVDV MLV vaccine use in pregnant cows, providing they were initially vaccinated with that line of vaccines prior to breeding and within 12 months thereafter, and to nursing calves, provided their dams were vaccinated within 12 months as described above.[1,16] The impact of MLV BHV-1 and concurrent *M. haemolytica* vaccines have potential negative interactions. Administration of MLV vaccine containing BHV-1 and PI3V in combination with *M. haemolytica* vaccine reduced the efficacy of the *M. haemolytica* vaccine in preventing respiratory disease morbidity, respiratory disease mortality, and fibrinous pneumonia mortality and reduced the antibody response to *M. haemolytica* leukotoxin in a feedlot study.[17] In another study, coadministration of MLV BHV-1 and *M. haemolytica* immunogen interfered with the serum antibody response to *M. haemolytica* leukotoxin.[18,19] However, this interference was not seen when two intranasal vaccines containing the TS IBR were used concurrently.[20]

MODIFIED LIVE VIRUS INTRANASAL VACCINES. MLV intranasal vaccines can generally be divided into two types based on the attenuation process: (1) those modified by passage in a cell culture[19,21] and (2) those modified by treatment such that they become "temperature sensitive"[22] (i.e., they do not replicate at internal body temperature). MLV intranasal vaccines stimulate protection in susceptible animals with only one dose, in contrast to the chemically altered MLV parenteral vaccines. The label directions for some but not all

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MLV intranasal vaccines may indicate that they can be safely used in pregnant cattle.[1] These vaccines induce a rapid onset of protection (within 3 days of administration), possibly through interferon in the nasal secretions.[19] One benefit of the MLV intranasal vaccines is that they stimulate immunity at the upper respiratory tract, the portal of entry of the virus. Another benefit is their potential to immunize calves that are already seropositive because of maternal (humoral) antibodies passively transferred through colostrum.[23] Animals vaccinated with the MLV intranasal vaccines may transiently shed vaccine virus in nasal secretions and therefore might infect susceptible contact animals.[24]

CHEMICALLY ALTERED LIVE VIRUS VACCINES. The chemically altered BHV-1 vaccine strain was modified by nitrous acid treatment, which caused changes in the viral genome that resulted in a strain (RLB 106) that is temperature sensitive (TS), meaning it has limited replication at internal body temperature.[25] Presumably because of the limited viral replication, the vaccine requires two doses to stimulate immunity. Because it is temperature sensitive, the vaccine can be used in pregnant cattle.[1,25,26] This TS vaccine protected calves against respiratory disease after challenge and protected challenged pregnant cattle against abortion and stillbirth.[25] In one study, heifers received two doses of the vaccine and were challenged with BHV-1 7 months later (at 6 months' gestation). These heifers showed a significant reduction in the number of abortions and stillbirths compared with controls.[26]

INACTIVATED VIRAL VACCINES. Inactivated viral vaccines are prepared by chemical inactivation of virus grown in cell culture. An adjuvant is added to the inactivated strain to help stimulate an immune response. Inactivated BHV-1 vaccines require 2 doses (14 to 28 days apart) when used for the initial vaccination of susceptible cattle. Inactivated vaccines were once thought to induce a shorter duration of immunity against viruses than MLV vaccines and did not confer protection against mucosal infections. Experiments have shown inactivated BHV-1 vaccine protected calves against BHV-1 in a respiratory disease study and also protected pregnant cattle against BHV-1–induced abortions.[27,28,29] Controlled studies should be performed to determine the duration of immunity induced by inactivated BHV-1 vaccines and MLV vaccines, both for respiratory disease and fetal infections. A disadvantage of inactivated vaccines is that the onset of protection may not be as rapid as with MLV parenteral or MLV intranasal vaccines. An advantage of the inactivated vaccines is that they can be used in pregnant cows and nursing calves.

Use of Vaccines to Prevent and Control Bovine Herpesvirus Type 1 Diseases

Many vaccines are available for preventing and controlling the different forms of BHV-1 disease, and each vaccine has certain characteristics that should be considered when designing a vaccination program. Each vaccine also has both benefits and limitations. Probably more important is the management of the cattle.

PREGNANT ANIMALS OR ANIMALS NEARING BREEDING SEASON. MLV parenteral vaccines may infect the fetus if pregnant susceptible heifers or cows are vaccinated. Abortions have been reported subsequent to vaccination with MLV parenteral vaccines.[15] The MLV vaccine virus may also result in corpus luteum infection or disease.[30,31] Experimental studies have indicated a reduced conception rate in susceptible cattle that received an MLV parenteral vaccine 3 to 4 days before or 14 days after breeding.[30,31] It has been reported that pregnant cattle raised in contact with calves recently vaccinated with MLV parenteral vaccines had a greater incidence of BHV-1 abortion than those that did not have contact with vaccinates.[32] Consequently, the labels of MLV parenteral vaccines have usually stated that the vaccine should not be used in calves nursing pregnant cows. Recent studies have shown that calves given an MLV parenteral vaccine did not shed virus in their nasal secretions, nor did contact animals become infected with the vaccine virus.[33,34,35] Several companies have received label claim approval for the MLV vaccine containing BHV-1 and BVDV for pregnant cows, provided the cows had received the same line of vaccines with the MLV BHV-1 and BVDV prior to breeding and within 12 months thereafter.[1] Likewise, that vaccine could be used in nursing calves of cows previously vaccinated with that line of vaccines within 12 months.[1] Another concern is that the MLV vaccine virus may recrudesce, with resulting shedding of virus in cattle either stressed or receiving corticosteroids.[36] Realistically, concern about transmission of BHV-1 to animals in contact with those receiving MLV parenteral vaccines would be negligible if the contact animals were properly immunized and immune to BHV-1.

Until the vaccine labels on many MLV parenteral vaccines are changed, MLV intranasal vaccines or the inactivated or chemically altered live virus vaccines are usually recommended for pregnant cattle or those near breeding. The exceptions are the approved vaccines cited.[1] Vaccine recommendations should be weighed, with the benefits of vaccination as a guide and especially with the realization that properly vaccinated cattle are better protected when exposed to either field (virulent) or vaccine strains shed by vaccinated animals.

RAPID ONSET OF IMMUNITY. Cattle that are susceptible and likely to be exposed to BHV-1 should receive either an MLV parenteral vaccine or an MLV intranasal vaccine; both types induce immunity within 3 days of the initial dose. Rapid onset of immunity is desirable in situations like stocker calf and feedlot operations, in which calves are transported long distances to pastures or feedlots, stressing the animals and making them more susceptible to infection. Such calves also are exposed to infection with BHV-1 from contact cattle in the markets. The drawback to inactivated vaccines is that two doses are required to obtain good immunity.

DURATION OF IMMUNITY. Controlled studies on the duration of immunity are limited. A degree of protection against challenge existed at 6 to 9 months after vaccination with an MLV intranasal vaccine or an inactivated vaccine.[37,38] A parenteral BHV-1 MLV vaccine provided protection up to 126 days after vaccination.[13] Challenge studies for licensure are usually performed on calves within days of vaccination at the time of peak immunity. Also, the challenge may be for only one form of disease, usually the respiratory type. Such challenges may detect only protection against a severe form of the respiratory disease. Other manifestations of BHV-1 disease (e.g., abortions, neonatal disease, genital disease [male and female], conjunctivitis) occur, yet little or no data are available about vaccine efficacy against these other forms of disease. In one case, the genital form of BHV-1 disease (infectious pustular vulvovaginitis) occurred in heifers that had received an MLV parenteral vaccine 5 months earlier.[39] Given the lack of duration-of-immunity studies for BHV-1 vaccines and the cost of vaccines, breeding animals are usually vaccinated at least annually. In some feedyard situations, the animals may be revaccinated during the feeding period. It is industry practice that feedlot cattle receive a monovalent BHV-1 or multivalent viral combination MLV parenteral vaccine at reimplant time approximately 100 days after arrival. There have been field reports of BHV-1 respiratory disease (IBR) in feedlot cattle a few months after entry/processing, at which time they received MLV vaccines containing BHV-1.[40]

VACCINATION OF CALVES WITH MATERNAL ANTIBODY. The possibility exists that maternal BHV-1 antibodies acquired by the calf through ingestion and absorption of colostrum may interfere with vaccination. The level of these serum BHV-1 antibodies in the calf depends on the amount in the colostrum, amount absorbed, and half-life of the particular antibody (for BHV-1, 21.2 days).[4] Some calves receive no BHV-1 antibodies through colostrum, or they may lose them within 1 month. Some calves, however, may have serum BHV-1 antibodies for up to 6 months after birth.[36]

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Vaccination recommendations for neonatal calves include use of multiple doses of an MLV parenteral, an inactivated, or a chemically altered live virus vaccine or administration of an MLV intranasal vaccine. Maternal antibodies may block parenterally administered MLVs or inactivated vaccine, but the MLV intranasal vaccine may induce BHV-1 humoral and cell-mediated immunity.[23,41] Calves are often revaccinated at age 6 to 8 months regardless of their prior vaccination history.

ADVANCES IN VACCINES. Molecular techniques of biotechnology have been applied to the study of vaccines and the response to vaccination (vaccinology). These advances are especially noted for herpesviruses, including BHV-1. In addition to conventional vaccines manufactured via propagation of MLV and inactivated BHV-1 strains, current and future technologies offer opportunities for other vaccines.[42,43] These include subunit vaccines with a portion of the virus, deletion mutants with specific viral genomic fragments deleted, live vectored strains, DNA vaccines using plasmids, and plant-based vaccines. DNA vaccine comprising combinations of plasmids encoding for genes along with immunostimulatory CpG motifs have been evaluated for safety and efficacy in vaccinated cattle.[44] Use of deletion mutant BHV-1 vaccines as marker vaccines along with diagnostic tests for the deleted glycoprotein genes may permit identification of vaccinates under control programs.[45,46] Recently needle-free delivery of vaccines has been developed and implemented.[42] By high-pressure gas delivery, vaccines may penetrate the skin and be administered intradermally, SC, or IM.[42] Such delivery is designed to minimize damage resulting from IM injections. Two studies compared needle-free IM injection of multivalent MLV vaccine containing BHV-1 with conventional SC injection via syringe in dairy calves and feedlot cattle. In both studies, antibody titers to BHV-1 were higher at day 21 post vaccination in cattle vaccinated using the needle-free system than in those vaccinated using conventional needle injection.[47,48]

Vaccination Programs

The best possible vaccine provides protective immunity in the host against infection (viral replication) when challenged, protects the animal against all forms of disease (including multiple organ and systemic forms), and provides lifelong mucosal and systemic immunity. Ideally the vaccine recommendations would incorporate the results of field trials that are carefully designed to show the efficacy of the vaccine against a pathogen. Unfortunately, little information is available, as can be seen by a review of the literature, for evaluating the field efficacy of the respiratory disease vaccines.[49] The summary of results was mixed for BHV-1 vaccines and for other respiratory viral and bacterial vaccines. However, vaccines evaluated under field conditions may have included cattle already incubating the virulent infectious agent at the time of vaccination or animals that had been stressed and were unable to mount an effective immune response. Animals receiving vaccines prior to commingling and feedlot entry developed immunity that provided protection against respiratory disease, resulting in less morbidity, mortality, and treatment costs and often resulted in greater economic return to the producer.[50,51]

Veterinarians must make recommendations based on (1) experimental studies of vaccination followed by challenge under controlled laboratory conditions apart from the field conditions of normal cattle management and (2) clinical experience with vaccines. Data from challenge studies are often under the control of universities, the federal government, or a biologic manufacturer and may not be published. Government licensure studies require efficacy and safety evaluations, but these studies may not be available in scientific publications for review by those making recommendations. For these reasons, the veterinarian may not have access to all the data needed to make a good decision on vaccines.

The veterinarian's dilemma is confounded by other factors. First, licensure may be granted for vaccination efficacy that demonstrated protection against one form of disease, such as respiratory type. However, the virus may be just as important a pathogen of other organs, such as the developing fetus, as is the case with BHV-1. Second, information about the duration of immunity induced by each BHV-1 viral vaccine commercially available is unavailable or limited. Licensure studies may use challenge of vaccinated animals within 2 to 4 weeks of initial vaccination, yet cattle may be in feedyards (months) or breeding herds (years) after vaccination. Third, vaccines may induce a strong parenteral immunity, yet the surface mucosal defenses at the portal of entry may still be susceptible to infection even in presumably well-vaccinated animals. Thus it is entirely possible that natural infections could still occur in vaccinated animals. Ecologically, this point is reinforced because viruses, for which there are good immunization products, are still circulating in cattle populations after years of vaccination.

The veterinarian must therefore weigh both the benefits provided by vaccines and their limitations. This probably is best done by focusing on the real economic effects of certain disease manifestations, including morbidity, mortality, and treatment and prevention costs. Historically this approach has been applied to two important forms of BHV-1 disease: the respiratory form, singularly or in combination with pneumonic bacterial diseases, and the fetal disease (abortions). As a result, most vaccine regimens focus on preventing respiratory disease in both young and adult animals and on protecting the pregnant breeding herd of cows and heifers against abortions. Another fact to be considered is that many vaccines contain multiple viral or bacterial components (or both), some of which may require multiple doses for effective immunization, whereas others may require only one dose.

GUIDELINES

Calves. Calves may be vaccinated at weaning or 30 days before weaning. Calves vaccinated before age 6 months should be revaccinated because the earlier vaccination may have been blocked by maternal antibodies. The MLV parenteral and intranasal vaccines require only one dose in susceptible calves, whereas the chemically altered live virus or inactivated vaccines require two doses. Although the labels for most MLV parenteral vaccines state that the vaccine should not be used if the calf is nursing a pregnant cow, the likelihood of infection of the pregnant cow may be minimal, especially if she is already immune. Yet as described above, MLV parenteral vaccines are available for use in pregnant cows and nursing calves.

Breeding Cows and Heifers. Yearling heifers (12 to 14 months of age) should be vaccinated at least 1 month before breeding. Any of the vaccines may be used, but if two doses are required, the second dose should be given at least 1 month before breeding.

Pregnant cows may be vaccinated with a vaccine that has a label description warranting such use; these include MLV intranasal vaccines, chemically altered live virus vaccines, inactivated vaccines, and approved MLV parenteral vaccines. Generally one dose is used, primarily because of management considerations. However, following the vaccine label recommendations for number of doses and safety for pregnant cow use is important. Administering booster doses of BHV-1 vaccines may have two conflicting outcomes as a result of booster dose stimulation of an increase in colostral BHV-1 antibodies transferred to the newborn calf in the colostrum: (1) it may be beneficial to the calf to have increased BHV-1 serum antibodies for protection against BHV-1 disease, or (2) the calf may have longer duration of BHV-1 antibodies, which may block BHV-1 immunization. There are no published multiyear duration-of-immunity studies in vaccinated cattle challenged with virulent BHV-1. Because of the relatively low cost of BHV-1 vaccines and the need to vaccinate against other pathogens, many breeding cows are given a BHV-1 vaccine annually.

Stocker and Feeder Cattle. Cattle to be shipped to forage pasture after weaning (wheat pasture or native grass) or to feedyards should be vaccinated 2 to 3 weeks before shipment. However, management practices and marketing may only permit vaccination at initial collection point, market site, or stocker/feedlot delivery. Any of the major types of BHV-1 vaccines may be used, but those that require only one dose have two advantages: rapid onset of immunity and less handling required (1 dose vs. 2).

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Cattle presented for purchase immediately before shipment, with no known vaccination history, pose a challenge. Presumably healthy cattle may be candidates for the one-dose MLV parenteral or MLV intranasal vaccines, because these calves may benefit from rapid induction of immunity. Cattle already infected with BHV-1 may not be protected by vaccination.

Cattle entering the feedyard usually receive either the MLV parenteral or MLV intranasal vaccine, particularly for rapid onset of immunity.[52] Cattle are routinely revaccinated while in the feedyard in some operations to ensure protection against BHV-1 disease throughout the feeding period.[41]

Breeding Services. Veterinarians should consult the breeding bull center for vaccination requirements for bulls, especially relating to collection and export shipment of semen for artificial insemination (AI). MLV intranasal vaccines have been used in AI bulls, because these vaccines are less likely to cause latent infections than MLV parenteral vaccines.[53,54] As mentioned previously, MLV parenteral vaccines cause latent infections that may recrudesce with stress or administration of corticosteroids, which means the virus would be present in semen.[36,52]

Bovine Virus Diarrhea Virus Vaccines

Victor S. Cortese

Our knowledge of the different vaccines' ability to protect against infection with BVDV is rapidly increasing. Currently, three kinds of BVDV vaccines are available: MLV vaccines, temperature-sensitive vaccines (available only in Europe), and inactivated virus vaccines (Table 48-9). MLV BVDV vaccines have demonstrated advantages over the newer inactivated vaccines. Most of these advantages are common to all MLV vaccines[1,2]: (1) MLV vaccines are less expensive, (2) postvaccination anaphylactic reactions occur less often than after administration of some inactivated vaccines, (3) immunity is achieved more rapidly after administration of a single dose (within 7 to 10 days), (4) MLV vaccines produce much higher levels of serum neutralizing antibodies,[3] (5) immunity lasts longer,[4-6] (6) MLV vaccines are effective against a broader spectrum of viral strains,[3] and (7) MLV BVDV vaccines are better able to protect the developing fetus from infection.[7]

On the other hand, MLV BVDV vaccines have certain disadvantages compared with inactivated BVDV vaccines: (1) some MLV vaccines can produce mild immunosuppression for brief periods after administration,[5] (2) some have been associated with what is usually a rather low incidence of a highly fatal disease syndrome, postvaccinal mucosal disease[8,9] (see later), and (3) until recently, MLV vaccines were not ordinarily recommended for routine use in pregnant cattle.

Studies have shown that the duration of cross-neutralizing antibodies stimulated by inactivated BVDV vaccines depends on the antigenic similarity between the vaccine strain and the wild-type virus to which the cow is exposed.[10,11] If there are few common proteins, the ability to neutralize can be as short as 4 months; if there are many common antigenic sites, neutralization may last a year. MLV BVDV vaccines stimulate cross-neutralizing antibodies that can still be detected 18 months after vaccination.[3] This longer duration was further demonstrated by a modified live BVDV vaccine receiving a USDA label containing a 1-year duration of immunity against the birth of both type 1 and type 2 persistently infected calves.[12]

Recent studies have demonstrated the ability of both modified live[13,14] and inactivated type 1 vaccines[15] to provide protection against

TABLE 48-9

Currently Licensed Vaccines for Bovine Virus Diarrhea Virus

Product	Company	Type of Vaccine	BVDV†	BVD Type 1 Strain	BVD Type 2 Strain
Arsenal	Novartis	MLV	M	1b–GL760–nCP	
Bovi-Shield GOLD FP*	Zoetis	MLV	M	1a–NADL–CP	2–53637–CP
Breed-BackTM FP	Boehringer	MLV	M	1a–Singer–CP	2–296–CP
CattleMaster	Zoetis	Hybrid (TS-IBR & PI3, Killed BVD)	K	1a–5960–CP 1a–6309–nCP	
CattleMaster GOLD	Zoetis	Hybrid (TS-IBR & PI3, Killed BVD)	K	1a–5960–CP	2–53637–CP
Elite	Boehringer	Killed	K	1a–Singer–CP	
Express*	Boehringer	MLV	M	1a–Singer–CP	2–296–CP
Herdvac	Zoetis	MLV	M	1a–NADL–CP	
Jencine	Merck	MLV	M	1b–WRL–nCP	
Master Guard	Intervet/AgriLabs	Hybrid (Killed IBR, BVD)	K	1a–C24V–CP	2–125C–CP
PregGuard GOLD FP 10*	Zoetis	MLV	M	1a–NADL–CP	2–53637–CP
Prism	Boehringer	Hybrid (Killed BVD)	K	1a–NADL–CP	2–5912–CP
Pyramid 4 Pyramid 8 Pyramid 9	Boehringer	MLV	M	1a–Singer–CP	
Pyramid 5, Pyramid 10*	Boehringer	MLV	M	1a–Singer–CP	2–5912–CP
Reliant	Merial	Hybrid (Killed BRSV)	M	1a–NADL–CP	
Reliant Plus	Merial	Hybrid (Killed BRSV)	M‡	1a–Singer–CP	
Respishield	Merial	Killed	K	1a–Singer–CP	
Resvac 4/Somubac	Zoetis	MLV	M	1a–NADL–CP	
Surround	Novartis	Killed	K	1a–Singer–CP 1b–NY–NCP	
Titanium	AgriLabs	MLV	M	1a–C24V–CP	2–296–CP
Triangle+Type II BVD	Boehringer Ingelheim Vetmedica	Killed	K	1a–Singer–CP	2–5912–CP
Vira Shield 61	Novartis	Killed	K	1a–KY22–CP 1b–????–nCP	2–TN131–nCP
Vista	Merck	MLV	M	1a–Singer–CP	2a–125A–CP

*MLV Licensed for use in pregnant cattle when used according to label.

†M = modified live BVDV component(s); K = killed BVDV component(s).

‡Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

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type 2 BVDV strains, although the protection afforded by the MLV vaccine was more complete. The USDA/APHIS has established a licensing protocol for BVDV vaccines to obtain a type 2 BVDV protection claim. Most of the vaccines licensed against both BVDV type 1 and type 2 contain BVDV type 1 and type 2 isolates. The question of current vaccines' ability to cross-protect against BVDV type 1b strains has been raised,[16] and further studies are needed to determine the level of protection afforded by current vaccine strains.

Vaccination and Mucosal Disease

Mucosal disease (MD) is seen when an animal that is persistently infected is exposed to another closely related cytopathic strain of BVDV. Also, theoretically a noncytopathic BVDV strain can mutate spontaneously into a cytopathic strain, resulting in MD without any subsequent exposure. High stress and immunodepression may be involved in this mutation.[17,18]

A major concern with the MLV vaccines is whether they can cause MD.[10,19,20] For MD to occur, the cytopathic strain in the MLV vaccine must be closely related to the noncytopathic strain in the persistently infected animal. With the degree of attenuation of MLV vaccines today, an animal must be nutritionally deficient or severely stressed, or both, to face an increased likelihood of developing MD from the vaccine. This suggests that a specific set of circumstances is required and that MD caused by vaccination, when it occurs, is rare.

Bovine Virus Diarrhea Virus Vaccines and Reproductive Control

Control of BVDV centers on prevention of persistent infection and elimination of persistently infected cattle; this means identifying and removing persistently infected animals and continued vaccination to prevent persistent infection are necessary for effective control. Persistent infections occur through in utero infection of the fetus (up to roughly 125 days' gestation) with a noncytopathic strain of BVDV.[3,17] Although the mechanism of transplacental transfer of BVDV is unknown, small amounts of virus in the dam's bloodstream appear to be sufficient to produce these immunotolerant cattle. Protection of the dam may or may not correlate with protection of the fetus from subsequent persistent infection if viremia of the dam occurs. To break the cycle of in utero infection and persistent infection, it is essential that vaccination provide fetal protection.

Several studies have been performed to assess the ability of vaccines to protect the fetus against either natural or artificial challenge. Results of these studies showed that most inactivated vaccines failed to provide much fetal protection,[7,10,21-26] except for one experimental vaccine, which is reported to give a high level of fetal protection. With the experimental vaccine, inability to isolate the virus from offspring of vaccinated animals indicated good protection.[27] However, the challenge of controls resulted in only about a 50% rate of persistent infection. Only one inactivated vaccine has demonstrated a high level of fetal protection and was given the appropriate label by the USDA (see Table 48-8). Other published reports demonstrated that MLV BVDV vaccines were more effective at protecting the fetus[7,28-30] and that inclusion of a type 2 vaccine broadened the strains against which vaccinates were protected.[31] To date, vaccines licensed in the United States have not been required to provide fetal protection. However, label indications are being granted by the USDA to vaccines that demonstrated the ability to prevent development of persistently infected calves. Several vaccines have achieved this label claim (see Table 48-8).

Bovine Virus Diarrhea Virus Vaccination Programs

Because BVDV infections can cause severe death loss and immunosuppression, all herds of cattle should be vaccinated against BVDV. Although it was once thought that BVDV vaccines would not immunize calves that were passively immune to BVDV,[32,33] recent studies have shown that immunization can occur with certain inactivated vaccines[34] and with MLV vaccines (when the passive antibody titer against BVDV is 1:64 or below).[13,35] When required, BVDV vaccines can be administered to young calves, with the possibility of gaining some degree of protection. In most calves the maternal antibodies against BVDV drop below the 1:64 level by 5 to 6 months of age. If an early BVDV problem does not exist, waiting to administer the first BVDV vaccine until at least 6 months of age increases the number of animals that respond to vaccination.

Among cows given MLV BVDV vaccines in the last trimester of pregnancy, 86% of the calves from seronegative cows[36] and some calves (0[36] to 52%[37]) from seropositive dams were actively immune at birth. In addition, the calves' level of passive immunity to BVDV was enhanced, in that seronegative cows seroconverted and serum antibody titers were boostered in 52% of the seropositive cows. The rate of occurrence of BVD in neonatal calves was reduced.[38] Administration of an MLV BVDV vaccine to seronegative cows after day 118 of gestation did not result in adverse effects.[38,39] However, vaccination with an MLV noncytopathic virus vaccine before day 118 resulted in fetal resorption, abortion, congenital defects, and the birth of undersized, weak, persistently infected calves. Several authors have recommended vaccination of cows with an MLV BVDV vaccine during the last trimester of pregnancy.[22] Three MLV BVDV vaccines are now labeled for use in pregnant animals. To ensure the safety of these vaccination schedules, label directions must be adhered to.

It is important to consider the epidemiologic nonresponse rate to any vaccine when designing a BVDV vaccination program. Therefore, even though MLV BVDV vaccines do not require a booster dose, a second dose may be advised to stimulate protection in animals that did not respond to the initial vaccination. BVDV vaccination programs should include the following features:

1. A virus isolation and cull program should be instituted, along with a vaccination program that includes administration of at least one dose of an MLV BVDV vaccine to all replacement animals.
2. Vaccination with killed vaccines should be increased to 2 or 3 times a year, or an MLV BVDV vaccine should be given to open cows 3 weeks before breeding or turning in the bull.
3. The vaccines used should have been proved to stimulate protection against BVDV type 1 and type 2.

Bovine Respiratory Syncytial Virus Vaccines

John A. Ellis

Bovine respiratory syncytial virus (BRSV) is a pneumovirus in the paramyxovirus family that endemically infects cattle populations worldwide. Although the virus can cause disease in all ages of cattle, it primarily clinically affects calves in recurrent seasonal outbreaks.[1-3] Resulting respiratory disease is characterized by pyrexia, coughing, and tachypnea, which can progress rapidly to severe expiratory dyspnea.[2,4] BRSV is also considered one of the viral agents that predisposes animals to secondary bacterial infections in the bovine respiratory disease (BRD) complex; however, secondary infections are often absent in fatal BRSV-associated respiratory disease.[5,6] Subclinical BRSV infection or mild respiratory disease due to BRSV infection in dairy cattle may have a negative impact on milk production.[7]

Parenteral Vaccines

MLV and inactivated parenteral BRSV vaccines have been commercially available since the 1980s. Most of these vaccines are formulated in combination with other viral respiratory pathogens, including PI-3, BHV-1, and BVDV. The efficacy of commercial MLV nonadjuvanted and adjuvanted combination BRSV vaccines in conferring

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significant disease-sparing subsequent to experimental infection with a virulent field isolate has been demonstrated.[8] Most vaccinated calves shed virus, but the peak virus titer was suppressed compared with unvaccinated controls. Viral clearance was coincident with the simultaneous appearance of mucosal antibody, cytotoxic T cells in the lungs, and anamnestic or primary serum antibody responses. In contrast, virus clearance in unvaccinated calves was coincident with the appearance of BRSV-specific cytotoxic cells before mucosal antibody was detected.[8]

The efficacy of parenterally delivered MLV vaccines in calves with MDAs, the most relevant candidates for vaccination in the field, remains controversial and unresolved. In studies conducted in the 1980s, administration of attenuated BRSV by the IM route to passively immune calves reportedly did not elicit mucosal memory IgA or serum antibody responses or even prime for such responses,[9] but T-cell responses have been demonstrated after parenteral vaccination in passively immune calves.[10] Whether these responses correlate to a protective cell-mediated memory response when maternal antibodies decline has not been determined. The ability of modified live BRSV vaccines to prime for protective immunity in the context of MDAs is likely to vary with the concentration of MDA, the antigenic mass of the vaccine, and/or vaccine formulation.[11]

Investigations using the same challenge model in BRSV-seronegative calves as used to demonstrate the efficacy of MLV vaccines have shown a similar disease-sparing efficacy of some combination of inactivated vaccines containing BRSV formulated with different adjuvants.[12,13] Clinical protection was associated with serum concentrations of BRSV-specific IgG as determined by ELISA,[12,13] and in one case[12] the presence of IFN-γ–secreting BRSV-specific $CD4^+$ T lymphocytes in the blood of vaccinated calves. There are conflicting data concerning the ability of commercial inactivated BRSV vaccines to override maternal antibodies and stimulate protective responses after parenteral immunization, which may be related to the vaccine formulation and adjuvant.[14,15] Relevant to the importance of vaccine formulation in affecting efficacy in the context of MDAs, recent studies have demonstrated clinical protection following experimental challenge of seropositive calves that were vaccinated with BRSV antigens that were adjuvanted Quil A,[16] either together with anhydrogel or in immune-stimulating complexes (ISCOMs).[17]

Most experimental studies concerning the efficacy of commercial BRSV vaccines are consistent with previous field trials, demonstrating the safety and efficacy of parenterally administered vaccines.[18,19] In addition, one study suggested the usefulness of combination vaccines in reducing the impact of subclinical BRSV infections.[12]

Protection against BRSV infection and disease is associated at least in part with an IgA response,[1-3] but serum IgG acquired from either passive or active immunization can significantly reduce the severity of clinical respiratory disease that results from BRSV infection. Several studies have reported that the incidence and severity of disease in calves were inversely related to the maternal antibody titers.[19-21] In the case of herd immunity, passive antibodies were detectable in 50% of the calves for 3 months after birth and were present in some calves until 7 months of age.[22] Therefore administration of BRSV vaccines to cows in late gestation to booster colostral antibody titers is a rational strategy to deal with BRSV-induced respiratory disease in young calves (1 to 3 months of age) in problem herds, without having to be concerned about the immunizing potential of particular parenteral vaccines in young seropositive calves.

Intranasal Vaccines

Because BRSV is an endemic infection in most cow herds, most young calves will have BRSV-specific maternal antibodies unless there is failure of passive transfer. Given the endemic nature of BRSV, many calves are likely exposed to BRSV early in life and will contract BRSV-associated respiratory disease if their passive protection is poor or has waned. These biological factors, together with the mixed results (to date) with parenteral administration of BRSV vaccines to young seropositive calves, has stimulated interest in intranasal vaccines for BRSV. Combination intranasal vaccines containing ML BRSV are commercially available in North America and Europe. Conceptually, it was demonstrated in the late 1980s that intranasal inoculation of tissue culture–attenuated BRSV to passively immune calves primed for mucosal memory and an anamnestic IgA response subsequent to challenge.[23] Subsequent studies with culture-attenuated BRSV confirmed this phenomenon.[24] It was also demonstrated that parenteral combination MLV vaccines containing BRSV can be efficacious if administered intranasally.[25,26] Single intranasal administration of these vaccines to young calves primed for protective responses to subsequent experimental challenge. In one of these studies,[25] results demonstrated that effective priming was achieved in BRSV-seropositive calves, confirming the previous observations with experimental single-component BRSV vaccines.[24,26] Subsequent studies have further demonstrated the efficacy of combination MLV vaccines containing BRSV in young seronegative calves[27,28] and to a lesser extent in seropositive calves.[27] As with parenteral vaccines, available data indicate that the efficacy of intranasal vaccines in the context of MDAs is not an all-or-none phenomenon and is likely somewhat dependent on the concentration of MDAs at the time of vaccination and probably factors related to vaccine formulation.[27] Currently, there is little information about the duration of the protective response after vaccination. It has been shown that cattle can be experimentally reinfected by 35 days after initial infection with virulent BRSV even in the presence of circulating antibody.[3] Consistent with this, available data indicate that the duration of effective clinical immunity after a single intranasal dose of ML BRSV to neonatal calves may be less than 4 months.[27] A major focus of current research is determining the appropriate dose, antigenic form, route of administration, and interval to use to most effectively boost neonatal priming by intranasal vaccination.

Adverse Reactions to Bovine Respiratory Syncytial Virus Vaccines

A major factor hampering development of a vaccine for human respiratory syncytial virus (HRSV) is the dramatic HRSV vaccine failure in the 1960s, in which vaccination with a formalin-inactivated (FI), alum-adjuvanted HRSV predisposed children to more severe disease after subsequent HRSV infection.[29] Although this same disease-enhancing phenomenon has been demonstrated in some studies of experimental FI-BRSV vaccines in cattle,[30,31] it is unlikely that modern manufacturing practices would use formalin inactivation for BRSV or other viral vaccines. Nevertheless, there are documented cases of apparent enhancement of BRSV-associated respiratory disease in cattle that received either inactivated or MLV vaccine in the field, indicating that some commercial vaccine formulations may stimulate potentially pathogenic immune responses in some cattle.[32,33] The immunologic mechanisms responsible for vaccine-associated disease enhancement are not completely understood. The current hypothesis is that some BRSV vaccines, notably FI-BRSV, mainly prime T helper cell (Th)2-like responses involving eosinophil influx into the lung and production of high concentrations of BRSV-specific IgE.[30,31] Several studies have consistently documented a disparity in the type of antibody responses induced in cattle by MLV and inactivated BRSV vaccines.[30-36] Parenterally administered MLV BRSV vaccines generally stimulate moderate to high concentrations of VN antibody in the serum, whereas inactivated vaccines stimulate high concentrations of partially neutralizing or non-neutralizing antibody. The data are conflicting concerning the prophylactic or disease-enhancing properties of these different types of vaccine-induced antibody responses.[30,34] Alternatively, as was suggested in the case of disease enhancement after parenteral administration of a combination MLV BRSV vaccine,[32] the timing between vaccination and infection could be a critical factor. This may be related to the stage of the immune response—specifically, a predominance of BRSV-specific IgM at the time of infection may somehow predispose to enhanced disease. Collectively, evidence from numerous studies with commercially

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available BRSV vaccines indicate that some combination of cell-mediated and antibody-mediated immunity can be involved in disease sparing in BRSV-infected cattle. Available data suggest that the dichotomization of RSV-specific Th cell responses into Th1 (protective) versus Th2 (potentially pathogenic)[37] is an oversimplification of a complex biology. As the epidemiology of BRSV-associated respiratory disease in the field indicates, disease caused by reinfection is usually less severe than that after the initial infection.[1-3] These observations indicate that most cattle do not develop clinically significant allergic (IgE) response to BRSV from naturally acquired infections, or to most BRSV vaccines, in the vast majority of cases. Nevertheless, given the history of adverse reaction to RSV vaccines in humans and, to a lesser extent, cattle, care should be taken in making assumptions about the efficacy and safety of BRSV vaccines without supporting data.

Parainfluenza Type 3 Virus Vaccines

John A. Ellis

Parainfluenza virus type 3 (PI-3V) is a ubiquitous paramyxovirus in cattle populations worldwide.[1] In uncomplicated experimental PI-3V infections, clinical signs of coughing, tachypnea, and fever have been observed from 4 to 12 days after infection.[1] Although the virus was originally detected in calves with respiratory disease (often in the absence of other agents), has been used to experimentally reproduce respiratory disease, and exposure to the virus has been detected by seroconversion in animals with BRD complex, its importance as a pathogen is currently somewhat controversial.[1,2] Consequently, very little primary research has been conducted on this virus in the past 2 decades. Generally PI-3V is viewed as a potentiating agent in mixed infections, predisposing the animal to bacterial pneumonia by altering bacterial clearance in the upper and lower airways and by infecting both respiratory epithelia and alveolar macrophages.[1]

Five types of PI-3V vaccines are commercially available: (1) MLV IM vaccines, (2) MLV temperature-sensitive IM vaccines, (3) MLV intranasal vaccines, (4) MLV temperature-sensitive intranasal vaccines, and (5) inactivated virus vaccines. All PI-3V vaccines available in North America are combined with at least a BHV-1 vaccine. A single-antigen MLV PI-3V intranasal vaccine that was available in Europe had demonstrated efficacy in a challenge model that produced severe disease that was typical of that reported in the original descriptions of the virus.[1,3] Generally, the challenge models previously and currently used result in minimal if any clinical disease, making it difficult to assess the clinical immunity induced by PI-3V vaccines.[4,5] In most vaccine efficacy studies, the use of attenuated challenge results in minimal disease. This probably contributes to the impression that PI-3V is not a significant pathogen. The latter assumption was also commonly made about BRSV before more robust challenge models were developed and used.[1]

Opinions are divided as to the relative importance of mucosal versus systemic immune responses in achieving protection from PI-3V–associated respiratory disease and, by extension, the comparative efficacy of intranasal and IM vaccines. Some comparative studies[6,7] reported that intranasal vaccination resulted in better protection against experimental challenge; others[8] were unable to demonstrate any advantage to the use of one vaccine or route of administration over the other. A notable exception, however, was young calves with maternal antibodies, in which intranasal administration was thought to produce a more effective immune response. Passive antibodies may persist in calves until 8 months of age and may interfere with active immunization.[9] Consequently, calves vaccinated parenterally before 6 months of age should be revaccinated after reaching 8 or 9 months of age.[9]

Although not experimentally documented, as in the case of BRSV, it is likely that given the similar biology of PI-3V infection, a mucosal (IgA) response is necessary to prevent PI-3V infection, but that passively (maternal) or actively acquired serum IgG is likely to mediate significant sparing of clinical disease subsequent to infection. The cell-mediated (cytotoxic T cell) response in the clearance of PI-3V is a poorly documented but probably important effector mechanism stimulated by MLV vaccines, as is the case with BRSV.[1]

There is debate about the overall utility and economic benefit of using PI-3V (and BRSV) vaccines in the field.[10,11] Much of the uncertainty is undoubtedly related to the difficulties involved in determining the relative importance of a particular agent in a multifactorial disease process such as BRD complex. Few studies[1,11] address the economic impact of subclinical paramyxovirus infections in cattle. No recent studies (in the past 5 years) directly address the economic impact of inclusion of PI-3V in combination vaccines. There are conflicting data from studies conducted under commercial feedlot conditions as to the economic benefit of including PI-3V in a vaccination program.[12-14] One study found no decrease in morbidity or mortality when 2 versus 1 dose of a combination viral vaccine containing PI-3V was used in a feedlot environment.[15] A limitation of these studies and such studies in general is the difficulty in obtaining, or failure to attempt to obtain, specific etiologic diagnoses, making it difficult to determine whether an immune response against one or more antigens was responsible for any disease sparing.

Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and *Bibersteinia trehalosi*

Jared D. Taylor • Anthony W. Confer

Mannheimia haemolytica Vaccines

M. haemolytica serotype 1 (formerly *Pasteurella haemolytica* A1) is the organism responsible for the clinical signs and lesions of severe bovine fibrinous pleuropneumonia (shipping fever).[1,2] The bacterium is a gram-negative commensal of the bovine upper respiratory tract, and its presence in the nasopharynx is not predictive of impending disease.[3,4] It is hypothesized that immunosuppression due to stress or viral infection permits the bacterium to proliferate, evade clearance by normal protective mechanisms, and establish infection within the lungs. Once lung colonization is established, it stimulates a series of pathologic events leading to acute severe fibrinopurulent inflammation and necrosis. The bacterium was renamed *Mannheimia haemolytica* owing to substantial genomic differences between it and other members of the *Pasteurella* genus; however, commercial vaccines may still refer to it by its previous name, *Pasteurella haemolytica*.[5]

Immunity to *Mannheimia haemolytica*

Twelve serotypes of *M. haemolytica* occur (A1, A2, A5, A6, A7, A8, A9, A12, A13, A14, A16, and A17), and only partial cross-serotypic protection is seen following vaccination.[6] Serotypes A1, A2, and A6 are the most prevalent.[7-9] Because *M. haemolytica* is strictly an extracellular organism, humoral immunity is far more important to controlling infection than cell-mediated immunity. There is substantial evidence that cattle entering a feedlot with preexisting serum antibody titers to *M. haemolytica* have less respiratory disease and fewer deaths than those without serum antibodies.[10,11] Maternal antibodies to *M. haemolytica* and *P. multocida* can be found in both dairy and beef cattle but decline to undetectable levels between 30 and 90 days of age.[12] Natural exposure to the nasal flora causes most calves to subsequently and spontaneously develop antibodies to these bacteria.[12] Unfortunately, this antibody response is typically short lived, and calves seem to become susceptible following decline in antibody levels. Antibody responses following natural exposure target numerous cellular components and secreted products. Those with the most potential for stimulating immunity include capsular polysaccharide, lipopolysaccharide (LPS), outer membrane proteins (OMPs), iron-regulated OMPs, a secreted leukotoxin (LKT), a serotype-specific antigen, and several other secreted

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enzymes including neuraminidase, a sialoglycoprotease, and bovine immunoglobulin-specific proteases.[13,14] The central dogma of *M. haemolytica* vaccination is that immunity to the organism requires stimulation of antibodies that neutralize LKT and antibodies that bind to surface antigens, allowing for complement-mediated killing and/or phagocytosis of the bacterium.[15] There is no agreement as to what are the most important surface antigens, but OMPs and iron-regulated OMPs are the major candidates based on many in vitro and in vivo studies.[16-20] Capsular polysaccharide is theoretically an important surface antigen because it is the first surface molecule encountered by cellular and humoral components of the immune system, and its presence enhances *M. haemolytica* resistance to phagocytosis and complement-mediated killing.[21] However, antibody responses to *M. haemolytica* capsular polysaccharide do not always correlate with resistance, and vaccination with purified capsular polysaccharide failed to protect against challenge.[22,23] LPS is also a surface antigen, but antibodies to *M. haemolytica* LPS failed to correlate with resistance to experimental challenge, and passive antibodies to *M. haemolytica* LPS were not protective in experimentally challenged calves.[24,25]

Use of *Mannheimia haemolytica* Vaccines in Beef Calves

Several studies have examined how rapidly various commercial *M. haemolytica* vaccines induce antibody response and how long after vaccination antibodies remain detectable. Antibody responses quickly reach their maximum (typically within 14 days after vaccination) and abruptly wane (significantly lower by day 28, and sometimes returning to baseline by day 42).[26,28] Revaccination an extended period after initial vaccination (140 days in one case) may stimulate rapid anamnestic responses,[27] but it is unclear whether this suggests efficacy in protecting against disease.

When designing a vaccination program for prevention of bovine respiratory disease, four questions should be addressed:

1. Should calves be vaccinated for *M. haemolytica?*
2. What type of *M. haemolytica* vaccine should be used?
3. How many doses of *M. haemolytica* vaccine should be given?
4. When should the vaccination be given?

We will attempt to provide a basis for answering some of these, but the clinician ultimately must make decisions in consideration of the type of operation (cow-calf, stocker, dairy, or feedlot), management practices, interpretation of published literature, consultations with colleagues, and personal experience.

SHOULD *MANNHEIMIA HAEMOLYTICA* VACCINE BE USED?

This may be the most difficult question for the practitioner to answer. Vaccine efficacy has been primarily demonstrated with experimental models of pneumonia using one of several challenge methods, including direct *M. haemolytica* challenge via intratracheal, intrabronchial, or transthoracic routes or using a combination viral (usually BHV-1) and *M. haemolytica* challenge.[13] The majority of published reports examining vaccination efficacy through experimental challenge have used experimental vaccines, not commercial ones. There are few published reports of efficacy of individual commercial vaccines against experimental *M. haemolytica* challenge, but published studies have generally supported the efficacy of commercial vaccines, although not in all cases.[29-31]

Clinical studies examining field efficacy of vaccines are abundant and frustratingly inconsistent. Numerous studies have found a protective factor from vaccinating.[32-36] Similar numbers of studies found vaccination to be ineffective or inconclusive.[37-39] Perino and Hunsaker[40] reviewed 10 published studies of several commercial live and subunit *M. haemolytica* vaccines with respect to their efficacies in field studies of feedlot cattle. Their report concluded that commercial *M. haemolytica* vaccines available at the time did not consistently reduce morbidity or mortality or increase weight gains. Of those studies, five showed positive outcomes based on reduced morbidity, mortality, or increased weight gain, whereas five studies demonstrated no positive outcome. Three of those studies demonstrating positive outcomes involved the same *M. haemolytica* bacterin toxoid given at arrival in the feedlot; however, two clinical trials with the same vaccine showed no significant differences when given at arrival and/or 3 weeks before shipment. A more recent rigorous review of *M. haemolytica* vaccines trials using feedlot cattle found that conclusions remain conflicting at times. However, their meta-analysis determined vaccination against *M. haemolytica* offers a modest reduction in morbidity but not in mortality.[41]

When examining vaccine efficacy in field trials, it is relevant to note that diagnosis and treatment in such studies is based upon undifferentiated BRD rather than disease solely due to *M. haemolytica.* Although *M. haemolytica* is the predominant bacterial isolate associated with BRD, it is not the sole pathogen. To conclude that *M. haemolytica* vaccine is efficacious in reducing BRD, a study would require a high power (large number of cattle enrolled), a relatively high incidence of BRD, and a large proportion of that disease attributable to *M. haemolytica.* This may play a role in the lack of definitive evidence of vaccine efficacy. Given these considerations, if a clinician chooses to recommend vaccination, questions 2 to 4 posed earlier must be addressed.

WHAT TYPE OF *MANNHEIMIA HAEMOLYTICA* VACCINE SHOULD BE USED?

Numerous commercially available bovine biologics contain *M. haemolytica* antigens.[42] *M. haemolytica* vaccines are often in combination with viral vaccines, *H. somni* or *P. multocida* bacterins, and occasionally *Clostridium* spp. biologics. Despite the various licensed *M. haemolytica* biologics available, formulations of *M. haemolytica* vaccines fall into one of 9 categories, 7 of which are non-living vaccines. These are described by their manufacturers as follows: (1) bacterin with aluminum hydroxide adjuvant, (2) bacterin with water-in-oil adjuvant, (3) outer membrane extract, (4) bacterin-toxoid (leukotoxin toxoid), (5) toxoid cell–associated antigen, (6) adjuvanted toxoid (culture supernatant), (7) recently introduced recombinant leukotoxin-extracted OMP vaccine, (8) autogenous (herd-specific) bacterins produced from isolates submitted by practicing veterinarians, and (9) live streptomycin-dependent mutant. The latter vaccine is the only currently licensed live *M. haemolytica* biologic. In the past, several live *M. haemolytica* vaccines were commercially available and showed potential efficacy. However, untoward side effects like severe local and systemic reactions often occurred after vaccination. Studies have occasionally compared commercially available vaccine products under field conditions.[43-44] Unfortunately, they often are supported by industry funding (creating a potential conflict of interest) and typically do not include a negative control group, so the significance and validity of findings from these studies are unclear.

Most studies comparing commercial vaccines have relied upon antibody titers (typically to LKT and/or whole bacterial cell preparations) as the outcome of interest. Although antibodies appear important to protection, it is unclear what antigens are most important, what titer is sufficient for protection, or if a higher titer is always better. Therefore, conclusions from those studies are difficult to interpret. Direct comparisons of two or more commercial *M. haemolytica* vaccines against experimental challenge have rarely been published. In one such comparison between a commercial *M. haemolytica* bacterin toxoid and the live streptomycin-dependent mutant vaccines, the bacterin-toxoid elicited the greatest serologic responses and significantly reduced lung lesions after experimental challenge.[31] Calves receiving the live mutant vaccine had lesions that were not significantly lower than for control cattle. Demonstration of protection against experimental challenge, however, may not necessarily indicate that the vaccine will be efficacious against natural disease under field conditions.

HOW MANY DOSES OF *MANNHEIMIA HAEMOLYTICA* VACCINE SHOULD BE GIVEN?

Although many of the currently available *M. haemolytica* biologics are licensed for only one injection, manufacturers recommend a booster if possible. Of course, administration of two doses of *M. haemolytica* vaccine is not practical for most

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cow-calf operations. Shewen[45] demonstrated that one of the reasons one dose of *M. haemolytica* vaccine often stimulates adequate antibody response is that most cattle carry *M. haemolytica* in their nasopharynx and have a primed immune system that can produce a rapid anamnestic response to vaccination. However, as already noted, it is unclear whether this suggests continued efficacy in protecting against disease.

WHEN SHOULD *MANNHEIMIA HAEMOLYTICA* VACCINE BE GIVEN? Given the short persistence of elevated titers following vaccination, administering *M. haemolytica* vaccine at the appropriate time becomes critical.[46-48] Manufacturers of *M. haemolytica* biologics usually recommend vaccination between 15 and 21 days prior to "weaning, shipping, or exposure."[42] If vaccination was more than 2 to 3 weeks prior to the time of greatest risk, a booster should be given prior to shipment. This protocol is incompatible with routine management of most cow-calf operations, making it difficult to recommend vaccination as a standard practice in this segment of the industry. Further adding to the challenge of identifying an optimal time for vaccination is the possibility that concurrent administration of MLV vaccines may interfere with response to *M. haemolytica* vaccination. Cortese et al[28] examined serologic response to vaccination with four commercially available *M. haemolytica* vaccines in calves naive to BHV-1 and *M. haemolytica*. When the vaccines were given concurrent with an MLV product, the antibody response against LKT was consistently lower than when the *M. haemolytica* product was administered alone. It is unclear whether this would impact the efficacy of the vaccines in reducing disease, although previous work with an experimental vaccine suggests it could.[49] A similar effect on titers was not seen with intranasal administration of MLV vaccine, although only one product was examined in this study.[50] Concurrent vaccination with intranasal MLV and *M. haemolytica* vaccines resulted in an initial titer equivalent to that produced by the *M. haemolytica* vaccine alone. Moreover, a robust anamnestic response occurred when a booster of the *M. haemolytica* vaccine was given 90 days later in conjunction with a parenteral MLV. Thus, it appears that some of the negative effect of concurrent MLV vaccination may be muted if calves are not naive for BHV-1 and/or other viral agents.

Vaccination of cattle against pneumonic pasteurellosis upon arrival at the feedlot is somewhat controversial for numerous reasons. Most importantly, it may not allow enough time for development of solid protection prior to the period of highest morbidity.[51] Secondly, if cattle were vaccinated 2 to 3 weeks prior to shipment and had an appropriate immunologic response, antibody titers may be adequate, making revaccination not cost-effective. Finally, vaccination with an MLV vaccine at arrival is nearly universal, which may interfere with response to the *M. haemolytica* vaccine if the calves have not previously been vaccinated or exposed to respiratory viruses.[28] Vaccination history is rarely known for cattle entering a feedlot, so it may be impossible to make an informed decision regarding these considerations. Nonetheless, vaccination with an *M. haemolytica* product upon feedlot entry is often practiced.[46-48] Results in several field trials indicate that this practice can potentially afford some protection against shipping fever during the first 14 days in the feedlot.[46] Selective use of *M. haemolytica* vaccines has also been advocated. Some feedlots designate cattle as high risk and low risk for respiratory disease. Managers may be more willing to vaccinate low-risk cattle because high-risk cattle are either sick upon arrival or can break with disease soon after entry into the feedlot.[47] Therefore, vaccination of high-risk cattle would not have time to stimulate immunity. However, low-risk cattle are less likely to break with disease soon after entry into the feedlot, and when they are vaccinated there is often adequate time for immunity to develop before a respiratory outbreak occurs.[47] While this is arguably rational, research to support or refute its effectiveness is lacking. As stated earlier, a meta-analysis of vaccination for *M. haemolytica* in feedlot cattle found a modest reduction in morbidity (relative risk [RR] 0.93; 95% confidence interval [CI], 0.89-0.98) but no significant reduction in mortality (RR 0.75; 95% CI, 0.56-1.04).

In summary, there is some evidence that use of *M. haemolytica* vaccination can be beneficial, but *M. haemolytica* vaccination is not warranted or appropriate in all situations. It would likely provide the most benefit when employed by cow-calf producers, but doing so correctly would require administration at an appropriate time (2 to 3 weeks prior to shipping). It would also be preferable to not concurrently perform MLV vaccination unless an intranasal product is used or the MLV is a booster of previous administration. Whether this additional cost and effort is justified is questionable, since weaning for at least 40 days seems more important than vaccination in reducing disease.[52] For stocker/backgrounder and feedlot operations, use of *M. haemolytica* may offer less benefit and is particularly questionable in lightweight high-risk calves. These calves are likely to develop disease before vaccination could produce an immune response, and the endotoxin burden may have negative effects, including decreased feed intake. Usage may be justified in backgrounded or yearling cattle that are more likely to respond to vaccination prior to the period of greatest risk for disease.

Use of *Mannheimia haemolytica* Vaccination in Dairy and Veal Calves

Management differences between dairy and beef calves could be expected to impact disease incidence and severity as well as immune status in these two classes of cattle. In addition, evidence suggests that purebred Holstein calves may not respond immunologically as well as beef or Holstein crossbred cattle,[53] so it would seem prudent to consider this population separately. Unfortunately, studies of *M. haemolytica* vaccination in dairy and veal calves have been published less frequently than those in beef calves. In general, vaccination of young dairy calves has failed to produce significant antibody responses.[54,55] This is probably due to interference by colostral antibodies. As passive immunity wanes, calves develop anti–*M. haemolytica* antibodies as a result of natural exposure.[55] In terms of protection against natural disease, vaccinated calves had incidences of respiratory disease similar to unvaccinated controls.[56,57] In another study, an *M. haemolytica* bacterin toxoid was found to be less effective than a commercial streptomycin-dependent mutant *M. haemolytica* and *P. multocida* vaccine in reducing respiratory disease in veal calves.[58] Failure of *M. haemolytica* vaccines to provide protection in dairy and veal calves could be because *P. multocida* is usually the most common isolate from dairy calf pneumonia.

Vaccination for *Pasteurella multocida*

P. multocida, particularly serogroup A serotype 3 isolates, is the second most common bacterial species associated with pneumonia in beef cattle and the most common bacterium isolated from pneumonia in dairy calves.[2] Although *M. haemolytica* has traditionally been the major pathogenic bacterium associated with shipping fever, some studies have suggested that the incidence of *P. multocida* in BRD has increased in beef cattle.[1,48]

The antigenic makeup of non-living *P. multocida* vaccines presently available are proprietary and are described in the *Compendium of Veterinary Products* as bacterial extracts, cell-associated antigens, soluble antigens, and/or bacterins. Conventional formalin-inactivated, whole-cell, aluminum hydroxide–adsorbed bacterins have been the industry standard and are not considered highly efficacious.[42] A commercial live streptomycin-dependent mutant *P. multocida* and *M. haemolytica* vaccine is available. Its efficacy against *P. multocida* is not well documented in the literature.

The immune mechanisms involved in resistance to *P. multocida* lung infections in cattle are poorly understood. Antibodies are presumed to be important in protecting against disease, and serum antibody levels have been correlated with severity of lesions following challenge[59,60] as well as decreased risk of natural disease.[10] However, there are few peer-reviewed studies examining efficacy of vaccination in field conditions, and those that have been published suffer from severe shortcomings (typically sponsored by a manufacturer and

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often lacking a nonvaccinated control group). A meta-analysis[41] reported three trials of vaccination of feedlot cattle with products containing *P. multocida* along with *M. haemolytica*. Results of these trials were not examined separately, but instead were combined with results of studies examining only *M. haemolytica*. Nonetheless, the reported results are not compelling (one reduced BRD, one increased BRD, and one trial showed no effect). Little work has been done regarding commercial *P. multocida* vaccines in dairy calves, despite the prevalence of *P. multocida* in respiratory disease in that population. In the one trial identified, a combined *M. haemolytica–P. multocida* vaccine was no better than control.[56] There is more published work related to vaccines against *P. multocida* serogroups B and E, which cause hemorrhagic septicemia in cattle and water buffalo,[61] but those have limited or no relevance to BRD.

Studies suggest that *P. multocida* OMPs or iron-regulated OMPs could be important immunogens for protecting cattle against pneumonia, and vaccination of calves with outer membrane preparations substantially enhanced resistance against experimental challenge.[13,62,63] Although the *P. multocida* toxin, which is produced primarily by serogroup D isolates, is an important virulence factor and immunogen for *P. multocida* in atrophic rhinitis of swine, there is no evidence this toxin is important in pneumonia of cattle, nor would it be beneficial to include the toxin in a cattle vaccine.[13]

In summary, significantly less is known about the immunogenicity and vaccinology of *P. multocida* than for *M. haemolytica*. Products currently available are generally unrefined and have limited evidence of efficacy. As such, it is difficult to make recommendations regarding their use. It seems reasonable to presume these products will work no better than *M. haemolytica* vaccines and suffer from many of the same challenges, so their usefulness (if any) is likely restricted to vaccination at least several weeks prior to maximum risk. Vaccination of lightweight high-risk calves is probably of limited benefit and should be avoided owing to the potential impact of endotoxin contained within vaccine preparations. Inadequate information exists to comment on potential usefulness of *P. multocida* vaccination in dairy and veal calves.

Vaccination for *Histophilus somni* (formerly *Haemophilus somnus*)

Histophilus somni (formerly *Haemophilus somnus*) is the cause of thrombotic meningoencephalitis (TME), septicemia, and reproductive disorders in cattle. It is also the third most common bacterial isolate from beef cattle pneumonia in most epidemiologic surveys.[1,2] Cases of *H. somni*–induced pneumonia are often associated with concurrent myocardial necrosis. Potential immunogens have been experimentally studied in *H. somni* and consist of lipo-oligosaccharide (LOS),[64] several OMPs (including immunoglobulin-binding proteins that bind the Fc receptor of bovine immunoglobulin and are associated with serum resistance of pathogenic strains),[65,66] and iron-regulated OMPs.[67] As in most gram-negative bacteria, *H. somni* LOS is a dominant antigen that stimulates an antibody response to the polysaccharide moiety following natural or experimental exposure. Interestingly, *H. somni* LOS has been demonstrated to exhibit phase variation in its epitopes (i.e., antigenic drift), thus allowing the bacterium to escape the immune response.[64] Currently, there is no evidence those anti-LOS antibodies are protective.[68] Likewise, several OMPs and iron-regulated OMPs have been shown to be immunogenic in cattle. The major *H. somni* OMP is weakly immunogenic and shows strain antigenic variability.[69] Their role in stimulating immunity is unknown. Recent studies have demonstrated that immunoglobulin-binding protein A (IbpA) not only binds immunoglobulins but is cytotoxic for bovine alveolar type II epithelium.[70] In addition, vaccination of calves with recombinant subunits of IbpA enhanced resistance against experimental intrabronchial *H. somni* challenge.[71]

Several approved *H. somni* biologics are available, often in combination with respiratory viruses or other bacterial pathogens (*Clostridium* spp.). Currently licensed *H. somni* biologics are formalin-killed bacterins with aluminum hydroxide as adjuvant. Efficacy of *H. somni* bacterins has been generally favorable in stimulating protection against experimental pneumonia, against IV and intracisternal *H. somni* challenge as a model of TME, and against natural TME. Overall, vaccine-induced immunity has been best against experimental and natural TME.[41,51,72,73] Using an experimental challenge model of *H. somni*–induced pneumonia, significant protection was afforded calves vaccinated twice with *H. somni* bacterin.[74] Resistance correlated with a high serum antibody response to the bacterium. One study demonstrated a reduced risk for respiratory disease in cattle that had high antibody titers to *H. somni* upon arrival in a feedlot.[75] Therefore, the potential would appear to exist for stimulating resistance to *H. somni*–associated pneumonia. Unfortunately, commercial *H. somni* vaccines can stimulate IgE antibodies and thus potentially increase the risk for type I hypersensitivity.[76]

Under field conditions, commercial *H. somni* bacterins have had limited success in inducing protection against respiratory disease.[40] In the three trials reviewed by Perino and Hunsaker, *H. somni* vaccination resulted in reduced treatment rate,[77] an increased rate of cattle being treated for respiratory disease,[78] and no significant difference from unvaccinated controls.[79] In a more recent study, partial reduction in feedlot respiratory disease was associated with vaccinating for *H. somni,* whereas a significant reduction in respiratory disease was associated with *H. somni* vaccine in combination with *M. haemolytica* or *M. haemolytica* vaccine alone.[80] Ribble et al[81] demonstrated reduced steer mortality following *H. somni* vaccination, but not heifer mortality. A meta-analysis demonstrated no benefit associated with *H. somni* vaccines in beef cattle,[41] but the authors acknowledged that the very few published trials offered little power to find a benefit if it existed.

Vaccination for *Bibersteinia trehalosi*

B. trehalosi was originally classified as *Pasteurella haemolytica* biotype T and consists of four serotypes (T3, T4, T10, and T15).[6,82] In 2007, Blackall et al proposed the new classification of the bacterium using phenotypic and molecular characteristics of 43 European isolates, 14 of which were from cattle, and 9 of those were isolated from lung (the authors did not indicate whether those isolates were from pneumonic lungs). Traditionally, *B. trehalosi* has been associated with diseases of sheep, primarily septicemia in domestic sheep and fatal pneumonia in Bighorn sheep.[83] In recent years, *B. trehalosi* has been isolated from bovine pneumonia, and there is concern among cattlemen, dairymen, and veterinarians that the bacterium is an emerging pathogen.[84] *B. trehalosi* was isolated sporadically from bovine pneumonia as early as 1971, with occasional subsequent descriptions of isolations.[85-89] Much of the currently available information about *B. trehalosi* prevalence in bovine pneumonia is anecdotal and not well documented in the scientific literature. What little data are documented, however, indicate a low prevalence of the bacterium. The Veterinary Laboratories Agency (VLA) laboratories in the United Kingdom have documented 65 isolates of *B. trehalosi* from bovine pneumonia cases since four initial cases were recorded in 2003.[90] Isolations ranged from 0 (2005) to 22 (2009), with over two thirds of the isolates occurring in the past 3 years. Isolates have been from both beef and dairy cattle, and all ages have been affected. In 72% of the cases, *B. trehalosi* was isolated in combination with one or more other bacterial or viral respiratory pathogens. From 2007 to 2009, *B. trehalosi* was isolated from 20 to 45 cases of respiratory disease in dairy cattle annually.[84] That report also documented multiple cases of respiratory disease in two dairies and one beef cattle operation.

Little is known about immunity against *B. trehalosi,* and commercial vaccines are not currently available. There is only about 35% homology between the genomes of *B. trehalosi* and *M. haemolytica*.[91] Some *B. trehalosi* strains are hemolytic and produce leukotoxin that is antigenically related to *M. haemolytica* leukotoxin and can be neutralized by anti–*M. haemolytica* leukotoxin antibodies.[45] However,

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only about 15% of the bovine isolates have been reported to produce leukotoxin.[82] Other potential antigens (e.g., OMPs) appear to be substantially different from those of *M. haemolytica*.[92] Therefore, vaccination of cattle with an *M. haemolytica* vaccine that stimulates antileukotoxin antibodies may provide some level of immunity against leukotoxin-positive *B. trehalosi* strains, but that immunity would likely be inadequate for complete protection.

Bovine Reproductive Disease Vaccines

Victor S. Cortese • Carole A. Bolin

As discussed earlier, cows have a multilayered placenta that leaves the fetus susceptible to infection. Infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug all may cause abortion. Reproductive disease is therefore the most difficult disorder to achieve protection against. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta.

Reproductive diseases and protection against them through vaccination are areas of active research. With current research, a vaccination program can be designed to help control reproductive diseases, but there is little or no research on the efficacy of many vaccines currently used to prevent reproductive disease. Given that the causes of reproductive failure are so numerous (infectious agents account for only a small percentage), vaccination to prevent infectious reproductive losses many not appear to be effective. This is often because diagnostic testing has not been attempted or has not determined the cause of reproductive inefficiencies. A vaccination program may be inappropriately instituted when the cause is not infectious, or the current program may unfairly be deemed ineffective. Use of viral vaccines to help prevent reproductive diseases was discussed earlier in the chapter.

Brucella abortus Vaccine

Brucella vaccination has best shown the effectiveness of vaccination in controlling a reproductive disease. Successful control and even eradication of *Brucella abortus* in many areas of North America are a testament to the ability of a program involving testing, culling, and vaccination to control a reproductive disease with zoonotic consequences; vaccination with either strain 19 or strain RB51 *Brucella* has proved to be effective. However, many herd owners have stopped vaccinating against this disease as states have been declared *Brucella* free.

Abortions caused by *B. abortus* are usually seen after 5 months' gestation. Retained placentae and subsequent metritis usually follow. The abortion is due to severe placentitis. *Brucella* infections have also been associated with a decrease in conception rates and an increase in services per conception. A higher number of dead and weak calves has also been demonstrated in infected herds. Orchitis, seminal vesiculitis, or both may characterize infections in bulls.

Only heifer calves can be vaccinated for brucellosis. Both of the two licensed *B. abortus* vaccines are modified live bacterins, and vaccination of bulls may lead to orchitis.[1] Legal use of the vaccines is usually confined to heifer calves 4 to 12 months of age, because vaccination of older animals with the strain 19 vaccine may lead to false-positive results on routine *Brucella* screening tests. Because the strain 19 vaccine may cause septicemia, clinical illness, and occasionally death,[2] sick, unhealthy, or stressed cattle should not be vaccinated. The RB51 strain vaccine is an O antigen–deficient mutant of the *B. abortus* strain 2308. The RB51 vaccine has three primary advantages:

1. Antibodies induced by this vaccine do not react with the serologic tests routinely done to diagnose *Brucella* infections.
2. The vaccine can be used in adult cattle at a lower dosage under special circumstances and with USDA permission.
3. The vaccine tends to cause less post-vaccination fever and stress than the traditional strain 19 vaccines.

The long-term immunity conferred by *Brucella* vaccination is the cell-mediated type.[3,4] Calfhood vaccination does not prevent a herd of cattle from becoming infected with *B. abortus,* but it does largely prevent abortions and protects 65% to 75% of the cattle in the herd from infection while infected reactors are identified and slaughtered.[5] For these reasons, in addition to vaccination, a control program should include testing and culling of all animals that test positive.

Leptospira Bacterins

Leptospirosis occurs worldwide and is caused by infection with the spirochete *Leptospira*. The pathogenic leptospires were formerly classified as members of the species *Leptospira interrogans;* the genus has recently been reorganized, and pathogenic leptospires are now identified in 7 species of *Leptospira*.[6] As part of this reclassification, the serovar names have remained the same, but some of the common leptospiral pathogens of cattle have different species names than before. The key changes for this discussion include (1) *L. interrogans* serovar *grippotyphosa* is now *L. kirschneri* serovar *grippotyphosa,* and (2) the two types of serovar *hardjo* have been formally split into two species, serovar *hardjo* type *hardjobovis* (found in the United States and much of the world) is now *L. borgpetersenii* serovar *hardjo,* and the less common serovar *hardjo* type *hardjoprajitno* (found primarily in the United Kingdom) is now *L. interrogans* serovar *hardjo.*

Although traditionally associated with abortions, infection with various serovars of *Leptospira* are associated with a variety of clinical signs, including severe systemic disease (most often in young animals), decreased milk production, birth of weak calves, and infertility. In addition, infected cattle are known to present a risk of zoonotic transmission of the infection to humans. Many different serovars of *Leptospira* have been shown to cause reproductive failure and abortions in cattle. Of these serovars, *hardjo, pomona,* and *grippotyphosa*[7-10] are more common, with serovars *canicola, icterohaemorrhagiae,* and *bratislava* occasionally implicated. The epidemiology of infection of cattle with these serovars differs with cattle serving as the reservoir or maintenance host for serovar *hardjo* and as an incidental host for the other serovars. In general, maintenance host infections are associated with a high prevalence of infection, a poor immune response, and long-term infection and shedding, whereas incidental host infections are characterized by low overall prevalence of infection with epidemics recognized, a vigorous immune response, and short-term infection and shedding. These differences in the epidemiology of leptospirosis caused by different serovars of *Leptospira* require different strategies for prevention.

Leptospirosis can cause abortion storms in which a high number of cattle may abort within a short period. There may also be an increased number of stillbirths and births of premature and weak calves during these periods.[11] Although serovars *pomona* and *grippotyphosa* tend to cause abortions in the last trimester of pregnancy, serovar *hardjo* can cause abortions at any stage of pregnancy. Abortions are usually due to fetal infection and subsequent fetal death, although placentitis may also occur. Serovar *hardjo* can also colonize the oviducts and uterus,[8,2-13] diminishing fertility. After an initial serovar *hardjo* infection, cattle may remain infected and shed the spirochete for long periods,[14-15] whereas infection and shedding of the other serovars is relatively brief.

Current bacterins generally contain combinations of leptospiral serovar *pomona, grippotyphosa, canicola, icterohaemorrhagiae,* and either *L. interrogans* serovar *hardjo* type *hardjoprajitno* or *L. borgpetersenii* serovar *hardjo* type *hardjobovis.* A monovalent *L. borgpetersenii* serovar *hardjo* type *hardjobovis* vaccine is also available. There has been considerable debate in recent years regarding the efficacy of leptospiral bacterins for cattle. The bacterins have label claims that indicate they are to be used as an "aid in the prevention

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of disease." These bacterins should therefore be expected to decrease the severity of clinical signs, including abortion, associated with infection. In general, the evidence supports such claims for serovars for which cattle are an incidental host (i.e., serovars *pomona, grippotyphosa, canicola,* and *icterohaemorrhagiae*). Protection mediated by bacterins for these serovars is thought to occur because of induction of antibodies directed against the LPS on the surface of the *Leptospira*.[16] However, vaccination does not always prevent infection and leptospiruria caused by serovar *pomona*.[17-19]

The efficacy of bacterins for prevention of infection, leptospiruria, and clinical signs associated with serovar *hardjo* infection is significantly more controversial. Evidence that the efficacy of traditional serovar *hardjo* vaccines is less than optimal includes induction of a relatively poor antibody response in vaccinated animals, the common presence of *hardjo* infection in herds despite routine vaccination, and experimental trials that did not demonstrate protection afforded by these traditional vaccines for prevention of infection, colonization of the renal or genital tract, or transplacental infection upon challenge with *L. borgpetersenii* serovar *hardjo* type *hardjobovis*.[20-22] In these studies, cattle were not protected from infection despite the induction of antibody directed against serovar *hardjo* LPS. Further investigation and evaluation of other serovar *hardjo* bacterins has led to a hypothesis that cell-mediated immunity may play a role in protective immunity against serovar *hardjo* in cattle.[23-27] Newer serovar *hardjo* bacterins have been introduced in monovalent and polyvalent formats, and there is evidence these bacterins provide significant protection of cattle against infection, tissue colonization, shedding, and transplacental infection.[23,28,29] Other new bacterins for serovar *hardjo* are also entering the marketplace, but as of this writing, extensive data regarding the performance of these products for reproductive protection are unavailable in the literature.

Some *Leptospira* bacterins are labeled as single initial dose products, but a booster dose is recommended approximately 1 month after the first dose.[18] *Leptospira* bacterins must be administered by IM or SC injection. Although some manufacturers specify revaccination at 12-month intervals, this duration of immunity has been questioned, and more frequent revaccination is often necessary to control *Leptospira* abortions.[19-21] A 1-year duration of immunity has been documented for two of the newer serovar *hardjo* bacterins, but this duration has not been documented for other *hardjo* vaccines or for the other serovars, making vaccination every 6 months a reasonable recommendation in many circumstances. Nevertheless, because leptospiral abortions are uncommon during the first half of pregnancy, it may be possible to use an annual vaccination schedule (serovar *hardjo* excepted) in seasonally calving herds like beef herds. Cattle in such herds can be vaccinated when they are 2 to 4 months pregnant, usually at the time pregnancy is diagnosed, and protected through the remainder of the pregnancy with a single annual dose.[19]

Prevention of leptospirosis caused by serovar *hardjo* requires a somewhat different approach. Pre-breeding vaccination of heifers that is effective in managing reproductive sequelae of other types of leptospirosis may be too late to prevent the consequences of serovar *hardjo* infection. Heifers exposed very early in life may remain infected well into the time of breeding. Therefore, efforts to control serovar *hardjo* infection should be targeted at preventing the initial infection and is best done by vaccinating young stock well before the time when they are mixed with older animals. In addition, bulls can carry serovar *hardjo* and transmit the infection quite readily during breeding.[29] Therefore, bulls should be fully included in efforts to control serovar *hardjo* infection by vaccination.

Bovine Genital Campylobacteriosis Vaccines

Originally classified as *Vibrio, Campylobacter fetus* subsp. *veneralis* causes a venereal infection of cattle. The bacteria are introduced during natural breeding by infected bulls or by artificial insemination (AI) with infected semen. Bulls are usually infected by breeding with infected cows, but contact with infected bedding may also be a cause. Older bulls (>4 years of age) are more likely to be infected. After deposition in the vagina, the bacteria rapidly colonize the vagina and cervix, and in 25% of these cows are found in the oviducts. The organism can persist for months after infection of these sites. It has been shown that fertility never returns to normal in some infected animals, and some may be permanently sterile because of the damage caused by salpingitis.

Vaccination with *Campylobacter* vaccines has been shown to be effective in protecting heifers even when vaginal cultures test positive for the bacteria.[30] It appears that the uterus is very resistant to the bacteria after vaccination. Studies have demonstrated improved breeding efficiency in vaccinated herds.[30] Vaccination of bulls with oil-adjuvant vaccines not only prevents infection of bulls for up to 1 year[31] but also aids in prevention of mechanical transfer of organisms during natural service.[32] Vaccination with two doses has been shown to be effective at clearing infections from carrier bulls.[33,34]

Vaccination

Use of *C. fetus* bacterins is recommended in all breeding herds that use bulls, even if only on selected cows. In heifer herds using virgin bulls or in 100% AI-bred herds, vaccination against *Vibrio* organisms is not necessary.

Several different *C. fetus* vaccines are available, including oil-adjuvanted and aluminum hydroxide–adsorbed types. Oil-adjuvant *C. fetus* bacterins have proved to be more effective[35] and provide longer lasting protection after a single dose.[36] Unfortunately, oil-adjuvant vaccines cause localized granuloma formation and fibrosis at the site of injection. This may cause visible blemishes, which may be objectionable in registered stock or show cattle. Administration no earlier than 4 months before the breeding season is preferred.[36] When aluminum hydroxide–adsorbed *C. fetus* bacterins are used, a priming dose should be administered at least 6 weeks before the immunizing (booster) dose, and the booster should be administered 10 days before the beginning of the breeding season.[37] After administration of an aluminum hydroxide–adsorbed bacterin, serum antibody concentrations peak rapidly and decline precipitously, falling to susceptible levels by 4 weeks after 1 dose or 11 weeks after 2 doses.[39] Some aluminum hydroxide–adsorbed bacterins do not require an initial booster.

Campylobacteriosis (vibriosis) is most effectively controlled when all breeding-age animals, including bulls, are included in the vaccination program.[32] Vibrin (Zoetis) is the only *C. fetus* bacterin available in the United States that has been evaluated in bulls.[30] Two 5-mL doses are administered to breeding bulls at 4-week intervals beginning 8 weeks before the start of the breeding season.[30] In subsequent years, a single booster dose is administered 4 weeks before the start of the breeding season.[33] This dosage is 2.5 times that recommended for vaccination of cows.

Bovine Trichomoniasis Vaccines

Bovine trichomoniasis is a venereal infection of cattle caused by the protozoal agent *Tritrichomonas foetus.* Early in the course of the disease, abortions with pyometra may be seen in 5% of infected cows; these abortions occur early in gestation.[38] However, infertility is the most common sign, with long interservice intervals.[39,40] Early embryonic death is followed by a period of conception failure. Some natural resistance develops after infection, but carrier cows may be an important component of the epidemiology of this disease. In rare cases, uterine destruction may leave a cow sterile after an infection.[41]

The efficacy of *Tritrichomonas* vaccines is questionable,[42-45] but the vaccines do appear to reduce actual reproductive losses.[46] Heifers, cows, and breeding bulls should be vaccinated twice at 2- to 4-week intervals, the second dose given 4 weeks before the beginning of the breeding season[46]; SC administration is recommended. In subsequent years a single annual booster vaccination should be given 4 weeks before the beginning of the breeding season.

In a problem herd, trichomoniasis vaccination must be coupled with other control measures like culturing, culling, and treatment to effectively control the disease.

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Neonatal Calf Enteric Disease Vaccines

Gerald E. Duhamel

Neonatal calf enteric diseases (NCEDs) can have a devastating impact on the profitability of beef cow-calf and dairy operations. In addition to mortality, medical, and labor costs, NCED can significantly reduce body weight of beef calves at weaning and performance of replacement dairy heifers.[1]

Several well-characterized infectious causes of NCED have been described.[2] Some of the more common infectious agents are group A RVs, coronavirus (CV), enterotoxigenic *E. coli,* salmonellae, and *Cryptosporidium* spp.[3-9] Sporadic outbreaks of necrohemorrhagic enteritis affecting 3- to 10-day-old calves have been associated with infection with *C. perfringens* type C.[10] Other less well-characterized viruses (group B RV, calicivirus, torovirus, astrovirus), bacteria (enterotoxigenic *Bacteroides fragilis,* attaching-effacing enteropathogenic and enterohemorrhagic *E. coli, Enterococcus durans*), and protozoans *(Giardia duodenalis)* have also been associated with NCED.

Because of the continuous calving and constant introduction of replacement heifers on dairy farms and the continuous flow of susceptible calves on veal calf operations, infections caused by more than one agent should be suspected in these types of operations.[3-9,11-13] In addition to different infectious agents, mixed infections with different groups and serotypes or genotypes of viruses and bacteria can also occur. Consequently the severity, duration, and spread of clinical disease associated with complicated infections are usually greater than with a single agent, and control may be more challenging. When scours occurs in a herd that has been vaccinated against enteric diseases, possible contributing factors should be considered, including concurrent infection with pathogens not present in the vaccine (e.g., *Cryptosporidium* spp., salmonellae, nongroup A RVs, other pathogens), suboptimal management of colostrum feeding, and poor control of environmental contamination. Under these conditions, strategic improvement in husbandry practices might be sufficient to reduce the infectious threshold for NCED and obtain the full benefit of pathogen-specific vaccination. In any situation, thorough laboratory diagnostic investigation is essential to correctly identify the primary cause of NCED and any other possible contributing factors and to serve as a basis for appropriate control strategies for present and future calf crops.[14]

Management practices and risk factors associated with development of NCED are sufficiently different between dairy and beef herds that control measures can be tailored according to the type of production. For example, in dairy herds, high turnover of older cows and continuous introduction of replacement heifers pose a higher risk of introducing new enteric disease pathogens in a susceptible population than in closed beef herds. Similarly, continuous calving and proximity of susceptible calves on dairy farms create an ideal environment for recirculation of enteric disease agents back into the adult population. This in turn may increase and broaden herd immunity such that the efficacy of a vaccine in these herds might be enhanced, partly because of the booster effect vaccine can have on preexisting immunity. Beef cattle herds, in contrast, are generally relatively closed, and a susceptible calf population is present only for a relatively short period annually during the calving season. Introduction of new pathogens or new strains of enteric disease agents, particularly during the calving season, can have a devastating effect because of the potential for exposure of a high number of susceptible animals over a relatively short period of time. Conversely, after an outbreak, herd immunity might be more stable and the occurrence of NCED might be reduced during the following calving seasons.

Under both types of production systems, vaccination for NCED is rarely successful without reasonably good management programs aimed at providing adequate intake of high-quality colostrum and minimizing environmental contamination through effective sanitation. General herd health management steps that can affect the success of a vaccination program for NCED should include a calving cow-calf care plan aimed at minimizing exposure of newborn calves to infectious agents that can overwhelm innate or passively acquired immunity. This is accomplished by careful monitoring of colostrum intake, eliminating all potential means of NCED transmission, and by reducing the load and duration of exposure to pathogens present in the calving environment. The following are eight simple recommendations to accomplish these goals:

1. Establish a sound biosecurity program, including purchase of replacement animals only from reputable sources and a complete ban on the introduction of foster calves, which pose a high risk of introducing new NCED agents.
2. Provide adequate protein and energy feed, including proper concentrations of vitamin and micronutrients (e.g., copper and selenium) and abundant clean drinking water throughout gestation and calving. This can ensure heifers and cows have acceptable body condition scores at calving, produce an adequate volume of high-quality colostrum and milk, and their calves are healthy and vigorous at birth, with a fully developed and functional immune systems.[15]
3. Avoid crowding, and keep the calving area and equipment clean, dry, and protected from the elements, particularly winter wind. Provide sufficient bedding in calving pens so calves are not born in a wet, manure-contaminated environment. Separate feeding and bedding grounds should be available in the calving area. Similarly, to minimize infectious disease transmission, separate equipment for feeding and manure handling should be used.
4. Limit the spread of infectious disease agents from younger, more susceptible and potentially shedding pairs to the main herd by segregating first-calf heifer pairs from the mature cow herd during the calving season until the youngest calf is at least 4 weeks old. Because of potential problems associated with nursing in first-calf heifers, newborn calves in this group should be monitored closely for colostrum intake and early detection of failure of passive transfer so rapid intervention can be implemented.[15-17] Because first-calf heifers are at a competitive disadvantage with mature cows, segregation of pregnant first-calf heifers also ensures free access to feed and water at all times.
5. Ensure that each calf ingests roughly 10% of its body weight (at least 4 L [1 gallon]) of colostrum divided into half as soon as possible and preferably within the first 2 to 3 hours of birth, then the rest 4 to 6 hours later, but always before the calf is 24 hours old. Consider heat-treating colostrum at 60° C for 60 minutes to reduce total coliform count and thus reduce the risk of illness (including scours) as a function of improved passive transfer of maternal immunity.[18] In dairy herds, do not rely on the calf nursing the dam for adequate colostrum intake; instead routinely use nipple/bottle or bucket feeding and esophageal tubing. If a calf is unable to suckle or is at risk for failure of passive transfer of maternal immunity, force-feed fresh or freshly thawed frozen colostrum from the calf's dam or from a mature cow in the same herd or a neighboring herd.
6. Thoroughly scrub and disinfect all equipment with detergent and bleach, and let them completely dry between uses for feeding colostrum and treating sick calves. This includes such items as nipple bottles, esophageal tubes, buckets, balling guns, and calf carts.
7. Move cow-calf pairs away from the calving area as soon as possible after birth in dairy herds. In beef herds, segregate calves by age by scheduled movement of dams that have not calved to new calving pastures—the so-called Sandhills Calving System (http://vetext.unl.edu/stories/200703050.shtml).
8. Develop a calf-care program including rapid identification and isolation protocols for scouring calves from healthy calves in dairy herds, or sick cow-calf pairs from healthy pairs in beef herds, to minimize environmental build-up of infectious agents.[15]

Giving calves a healthy start maximizes their genetic production potential while reducing the costs and labor associated with treating sick animals.

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Rotavirus and Coronavirus Vaccines

RVs and CVs are ubiquitous in the cattle population; most adult cattle have VN serum antibodies.[19-23] RV infections are widespread in both dairy and beef cow-calf production systems, whereas infection with CV most often occurs as sporadic outbreaks of severe diarrhea in beef cow-calf herds or chronic low-grade diarrhea in dairy and veal calf operations. In addition to causing NCED, CV has been associated with winter dysentery in adult cattle[24] and respiratory tract infections in calves[25] and as a contributing infectious cause of BRD complex in feedlot cattle.[26] Fecal shedding of RV and CV is common among adult cattle,[27-30] providing an immediate source of viral challenge for naive newborn calves and allowing persistence of these agents at the herd level.

Although only one type of CV is known to cause NCED,[31] different subtypes of CVs can be identified on the basis of minor genomic and antigenic differences.[31-35] On a herd basis, however, affected calves can display a range of clinical signs from enteric only to mixed enteric and respiratory signs. A molecular epidemiologic investigation based on comparative analyses of a gene encoding a major structural protein of bovine CV revealed (1) identical CV strains in different animals from the same herd and from paired nasal and fecal samples from the same animals, suggesting herd outbreaks are associated with a single strain circulating among susceptible cattle, (2) identical CV strains in affected cattle from different herds in the same region, suggesting transmission between herds, and (3) different CV strains in cattle affected during different outbreaks occurring over several years in the same herd, suggesting herd outbreaks are associated with the introduction of new strains in a recovered herd.[36]

Currently, RVs are classified into at least seven distinct groups, A through G.[37] Although RVs that belong to groups A, B, and C have been found to naturally infect cattle,[30,37-41] group A RVs are by far the most prevalent group.[39,41] Members of group A RVs are further classified according to antigenic and genetic differences in their outer protein layer, composed of viral protein 7 (VP7) or G (for glycoprotein) and spikes of protease-activated attachment protein VP4 or P (for protease sensitive).[42-44] Because both of these proteins are involved in neutralization of infectivity in vitro and protection in vivo,[45-47] and multiple types of each protein can segregate independently in progeny virus, resulting in wide variations in the relative frequency of individual type and G/P combinations according to geographic location, individual farm, and calf, consideration of the G/P configuration of RVs is critical to development of an effective vaccination program for prevention of NCED.

Although a good correlation has been found between the antigenicity of the G proteins and their corresponding gene sequences, a similar relationship has not been found for the P proteins. Nevertheless, the binary G/P serotyping of group A RVs classification has largely been replaced with a G/P genotyping system based on nucleotide sequence of the corresponding genes.[48] Globally, 27 different G genotypes (G1 to G27) and 35 P genotypes (P1 to P35) have been described among group A RVs infecting animals and humans.[48] Although at least 8 distinct G types (G1, G2, G3, G6, G8, G10, G11, and untypeable) can infect cattle in the United States,[49,50] G6 appears to be the most widespread, while G8 and G10 account for lower percentages of infections.[23,50-55] Similarly, RVs with any of four P types (P1, P5, P11, and untypeable) are known to infect cattle in the United States, with P5 the most prevalent.[50,53,56]

The genome of RVs is composed of 11 gene segments that can be exchanged among RV strains when animals are infected by more than one virus differing in G/P types at the same time.[43] Therefore, mixed infections produce progeny RV with a genetic makeup derived from either parental strain by a mechanism called *gene reassortment.* Because the G and P proteins are independently involved in generation of specific VN antibodies, reassortment of the genes encoding these proteins during mixed infections can generate new progeny viruses that can evade what once was a protective immune response.[55] Genetic reassortment is a well-characterized mechanism of immune evasion that allows persistence of RVs in susceptible populations but can also promote interspecies transmission.[57] Some RV strains appear to be host specific; however, zoonotic spread of bovine RVs to humans is increasingly recognized.[57-60] In the case of bovine group A RVs, the potential for emergence of virus strains carrying any of 36 possible antigenic configurations (4 Ps × 8 Gs = 32 potential types) underscores the limitation of vaccination programs and also the importance of sound management practices designed to minimize exposure by limiting environmental contamination.

Vaccination Programs

Two approaches are widely used in an attempt to protect calves against RV and CV infection and diarrhea. The most common approach involves passive protection of the suckling neonate by transfer of high levels of specific VN colostral antibodies induced by parenteral vaccination of the pregnant dam.[21,61-69] The mechanism of passive protection with this approach is due to the continuing presence of an amount of specific VN antibodies in the intestinal lumen sufficient to neutralize infectious virus before infection of the intestinal villous enterocytes.[19,66,70-74] The continuous presence of VN antibodies in the gut lumen may also reduce the severity of the disease if infection has already developed. In addition, some of the VN colostral antibodies that are absorbed into the bloodstream are secreted onto mucous membranes and may provide local immunity later in life.[75] However, colostral transfer of immunity is less efficient in ruminants than in other species; high concentrations of maternal antibodies are present for less than 3 days postpartum, and these concentrations often fall below protective levels within 1 week of parturition.*

A delicate balance exists between passive protection afforded by lactogenic immunity and development of the calf's own innate and adaptive local immunity to RV and CV. Because most calves' level of resistance to the adverse clinical effects of RV and CV infection increases with age, disease caused by these agents can be controlled under certain circumstances by continuous hand-feeding of fresh, frozen, or fermented colostrum from vaccinated cows throughout the first 3 to 4 weeks of life.† The goal with this approach is to allow development of subclinical infection while the milk VN antibody concentration is partially protective.[63,74,79] Conversely, lactogenic immunity might interfere with development of adaptive immunity, or some calves might not be exposed to RV and CV infection until after milk antibody concentrations have fallen below protective levels, leaving the calf fully susceptible to infection.[61,63,80]

An RV and CV vaccine for parenteral administration to pregnant cows (Calf-Guard [Zoetis]) first became commercially available in 1979. This vaccine contained a single live attenuated G6:P1 strain of group A RV. However, because VN antibody concentrations in the colostrum and milk of vaccinated cows were low,[21,22,63,81] this product was later replaced by a formulation containing inactivated RV and CV, and current formulations of this vaccine contain G6 and G10 strains of group A RV (ScourGuard 4KC [Zoetis]). Meanwhile, an inactivated RV and CV vaccine (Scour Bos 9 [Novartis Animal Health U.S. Inc., Larchwood, Iowa]) containing three strains of group A RV was licensed for use in pregnant cattle in the United States. A third inactivated RV and CV vaccine (Guardian [Intervet Inc., Merck Animal Health, Omaha, Neb.]) containing two strains of group A RV and two strains of CV has since been licensed for SC administration in pregnant cattle in the United States.

Vaccination of pregnant cows with inactivated RV and CV vaccine can raise the level of VN antibodies in the colostrum.[21,61-70,82] Although there are reports of successful protection of calves against NCED by parenteral vaccination of pregnant cows with RV and CV,‡ negative results have also been reported. Failure of this vaccination strategy is generally attributed to failure of passive transfer of colostral antibodies to the calf or overwhelming virus challenge. An alternative

*References 19, 61, 64, 67, 73, 74, and 76.
†References 63, 64, 68, 69, 73, 77, and 78.
‡References 62-64, 66, 68, 69, 78, 79, and 82-89.

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explanation might be that the serotypic specificity of the passively transferred maternal antibodies may affect the protective efficacy of the RV vaccine.[91]

Information on protective immunity against infection of calves with group A RVs having the same or a different G/P serotype configuration as the vaccine strain is incomplete.[51,82,92-96] Although immunity to RV appears to be G/P serotype specific with some strains,[51,82,92,95] there is some indication that immunity directed against certain strains can neutralize in vitro[51,96] and protect challenge-exposed calves in vivo[51,95] against RV strains with different G/P configurations. Also, parenteral vaccination of seropositive cows with a single strain of RV can elicit serum VN antibodies to a broad spectrum of RV serotypes and genotypes, suggesting that this strategy may provide a means of enhancing passive protection against a range of potential RV serotype and genotype challenges.[83,93,95] However, a difference in the P protein between the vaccine RV and the infecting RV was suggested as the basis for failure of the inactivated monovalent RV and CV vaccine in beef cow-calf herds.[97,98]

Although antigenic and genotypic variation has been documented among bovine CVs,[31-35] reduced protection of nursing calves after challenge with a strain of bovine CV different from the vaccine strain has not been demonstrated. Consequently, addition of more than one strain of bovine CV in certain vaccines might not be justified at this time.

Another approach for preventing NCED caused by RV and CV involves oral vaccination of calves with an MLV vaccine (Calf-Guard) that contains an attenuated G6:P1 strain of group A RV.[99-109] The mechanism of disease prevention with this vaccine is unknown, but interference with infection by virulent virus, followed by development of secretory IgM and IgA and/or CMI in the intestinal mucosa, have been proposed.[80,102] To achieve adequate protection, the manufacturers recommend that the vaccine be given immediately after birth, before the calf has nursed. This regimen might be applicable to calves whose dams have not been vaccinated. However, because the colostrum of most heifers and cows contains some level of VN antibodies arising from natural exposure,[§] administration of colostrum should be delayed for several hours after vaccination to avoid inactivation of the vaccine virus. Under commercial conditions, it is nearly impossible to administer vaccine within minutes of birth or to effectively regulate colostrum intake in relation to the time of vaccination. Therefore, infection before vaccination, neutralization of the vaccine virus by colostral antibodies, and overwhelming challenge with infectious virus shed by unvaccinated diseased calves might explain a lack of efficacy with this approach.[64,104-107] This is evident from the data obtained in vaccine efficacy evaluation studies in which only a portion of the calves on a farm or a ranch are vaccinated in double-blind or odd/even–day vaccination trials.[76,108,109] When all calves are either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality rates from NCED are significantly reduced by this vaccination strategy,[70,99-101,108,109] but the design and statistical validity of the latter kinds of trials have been questioned.[90,105]

Although not recommended by the manufacturer, the oral attenuated vaccine has been administered to calves with unknown immune status that were raised as veal calves or replacements in heifer development operations.[6] Under these circumstances, vaccination might provide active immunity and protection against potential virus challenge when calves from several different sources are commingled.

Rotavirus and Coronavirus Vaccination Products

ScourGuard 4KC

ScourGuard 4KC consists of inactivated bovine G6 and G10 strains of group A RV and a bovine CV strain combined with K99 *E. coli* bacterin and *C. perfringens* type C toxoid. For first-calf heifers and mature cows that have not previously been vaccinated, a two-dose series of vaccine should be administered by IM injection 3 weeks apart, starting 6 to 9 weeks pre-calving. The second dose should be given 3 to 6 weeks before the expected calving date. A single annual booster dose should be administered 3 to 6 weeks before each subsequent calving.

Scour Bos 9

Scour Bos 9 consists of inactivated bovine group A RV strains G6, G8, and G10 and a CV strain combined with bacterins from four *E. coli* K99 serotypes and *C. perfringens* type C toxoid. The first vaccine should be administered by IM injection into the neck of pregnant cows and heifers 8 to 16 weeks before the expected calving date, with a booster dose of Scour Bos RV and CV vaccine 4 weeks prior to the expected calving. Only one annual dose at 8 to 10 weeks before calving is required thereafter.

Guardian

Guardian consists of inactivated bovine group A RV G6 and G10 strains together with type 1 and type 3 bovine CV strains combined with enriched K99 pili from *E. coli* and type C and D toxoids of *C. perfringens*. The vaccine should be administered by SC injection of pregnant cows and heifers up to 12 weeks before the expected calving date. A booster dose of vaccine must be given approximately 3 to 6 weeks later during the first year. One annual dose administered up to 5 to 7 weeks before calving is required thereafter.

Calf-Guard

Calf-Guard is a modified live bovine G6 strain of group A RV and bovine CV recommended for oral vaccination of newborn calves. The vaccine should be administered immediately after birth, before the calf has nursed. As indicated earlier, interference by maternal antibodies may limit the efficacy of the vaccine, so vaccination of calves older than 1 day may be ineffective.

Bacterial Scours Vaccines

Gerald E. Duhamel • Victor S. Cortese

Enterotoxigenic *Escherichia coli* (Calf Scours) Bacterins

Neonatal calf diarrhea associated with enterotoxigenic *E. coli* (ETEC) usually occurs within the first 72 hours of life. The majority of calf scour cases are caused by ETEC that produces the F5 (K99) fimbrial adhesin that mediates adherence to specific receptors located on the brush border of small intestinal villous enterocytes, resisting normal peristaltic clearance mechanisms and thus promoting bacterial infection.[1-3] Adherent ETEC produces enterotoxins that stimulate water and electrolyte loss into the intestinal lumen, leading to dehydration and electrolyte imbalance that can be fatal. These ETEC strains may also express other types of fimbriae, including F41 and F1 (type 1), sometimes in combinations by the same strain of ETEC.[1,4] Intestinal colonization and villous attachment by strains of ETEC expressing adhesive fimbriae can be prevented by vaccination of the dam with a bacterin that contains a single fimbrial antigen in common with the challenge strain.[1,4] However, disease may occasionally be caused by ETEC expressing fimbrial antigens different from the most common, $F5^+$; therefore typing of *E. coli* isolates obtained from diarrheic calves can assist with proper selection of an ETEC fimbriae-based vaccination program.[5,6]

Because calf scours associated with ETEC strains occurs so early in life, there is not enough time for a newborn calf to mount a protective immune response through vaccination. Therefore, control of ETEC-induced calf scours is aimed at (1) limiting calf exposure to bacterial pathogens, (2) vaccinating dams to provide high levels of fimbriae-specific colostral antibodies (i.e., usually against the F5

[§]References 19, 21-23, 61-69, 73, 77, 81, 82, 86, 88, 90, 94, and 103.

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antigen), and (3) providing adequate volume of colostrum as soon as possible after birth to prevent bacterial colonization of the calf intestinal tract.[3] Pregnant cows are vaccinated in late gestation to ensure high concentrations of anti-F5 colostral antibodies. When colostrum from vaccinated cows is fed to newborn calves, the antibodies prevent bacteria expressing fimbrial adhesin from binding to specific host cell receptors located on the brush border of small intestinal villous enterocytes, mostly in the jejunum and ileum.[1,8] Unbound ETEC bacteria are passed into the feces by intestinal peristalsis and thus prevented from colonizing the small intestine and causing disease. By 72 to 96 hours of age, calves are highly resistant to ETEC infection and will rarely show clinical signs of diarrhea.[1,9] Thus, feeding calves colostrum with a high concentration of antibodies against F5 fimbrial antigen, even though restricted to the first day of life, is often sufficient to prevent severe diarrheal disease.[4] Passive circulating serum antibodies that are absorbed into the bloodstream from the intestinal tract are thought to play little or no role in protective immunity against neonatal enteric disease caused by ETEC.[1] However, for maximum efficacy of ETEC vaccine programs, a concurrent well-managed colostrum program should be in place.

Nearly all strains of ETEC that have been isolated from neonatal calves have F5 fimbriae. Currently there is no evidence that a bacterin with multiple types of fimbrial antigens is more effective than products with only F5, so long as the vaccine and the challenge strains share a common fimbrial antigen.[1] However, vaccines with multiple fimbrial antigens are more likely to have at least one of the antigens found on the challenge ETEC strain. Besides non-F5 ETEC strains potentially causing calf scours, a lack of efficacy of fimbriae-based ETEC vaccines may be due to *E. coli* belonging to pathotypes other than ETEC, including attaching and effacing *E. coli* (EPEC) and Shiga toxin–producing *E. coli* (STEC), which cause hemorrhagic enteritis in 1- to 6-week-old calves. Given that EPEC and STEC strains do not produce fimbrial adhesins, fimbriae-based ETEC bacterins will not protect against these strains.[6,7] Unfortunately, commercially available vaccines for prevention of calf scours associated with EPEC and STEC are not currently available.

Escherichia coli Vaccination Programs

The general recommendations for use of fimbriae-based ETEC vaccine (bacterin) are summarized in Table 48-10. ETEC bacterins are offered as single-antigen vaccines and in combination with other antigens designed to protect against other diseases in addition to ETEC infection. Oil-adjuvant ETEC bacterins are administered by IM injection in a single dose 2 weeks to 6 months before calving, and administration is repeated annually.[10] Non–oil-adjuvant ETEC bacterins are recommended for IM or SC injection in 2 doses administered at a 2- to 4-week interval, with the second dose given 3 to 6 weeks before calving. In subsequent years a single booster dose should be administered 3 to 6 weeks before calving. ETEC bacterins do not protect calves that do not ingest adequate amounts of colostrum soon after birth. Also, because this protection is based on passive immunity, high challenge levels may overwhelm the limited amount of antibodies present in the lumen of the calf's small intestine. This is consistent with the higher prevalence and severity of clinical ETEC infections in the close confinement of large numbers of replacement dairy heifers than in less intensive cow-calf beef operations. Environmental control of bacterial contamination is paramount to effective calf scour management.

Salmonella Vaccines

Salmonellosis is due to infection by various pathogenic *Salmonella enterica* serotypes (see Chapter 32). Disease severity varies according to serotypes and strain-specific virulence determinants but is also based on the number of infective organisms, route of entry, and host natural and acquired resistance mechanisms. Bovine salmonellosis is caused predominantly by *S. enterica* serotypes Typhimurium (*S.* Typhimurium) and Dublin (*S.* Dublin), and although both serotypes can cause enteritis, clinical disease associated with each serotype is different.[11] With disease caused by *S.* Typhimurium, a ubiquitous group B *Salmonella* serotype is most often associated with enteritis resulting in diarrhea in young calves. The host-restricted serotype group D *S.* Dublin most often causes systemic infections that may result in asymptomatic shedding or in abortion in pregnant cows. Consequently, commercially available *Salmonella* vaccines contain single or combinations of *S.* Typhimurium and Dublin. Because *Salmonella* serotype Newport and other group C *Salmonella* have increased in prevalence, serotyping of *Salmonella* is critical to implementing an effective vaccination program. All currently licensed products are formalin-inactivated, whole-cell, aluminum hydroxide–absorbed bacterins, except for a genetically altered stable nonreverting aromatic dependent (*aroA* mutant) modified live *S.* Dublin vaccine (Entervene-D [Boehringer Ingelheim Vetmedica Inc., St. Joseph, Mo.]) and a siderophore receptor protein (SRP)-based vaccine (SRP *S.* Newport Vaccine, Conditional USDA License [Zoetis, Florham Park, N.J.]) One *S.* Typhimurium and three *E. coli* mutant lipopolysaccharide (LPS) core antigen vaccines can provide protection from morbidity and mortality associated with salmonellosis.

A modified live and genetically altered (via deletion of *aroA*) *S.* Dublin vaccine marketed for parenteral use is effective in 2-week-old calves against challenge with *S.* Dublin but also provides cross-protection to challenge with *S.* Typhimurium.[12,13] As with many gram-negative bacterial vaccines, adverse reactions to this vaccine have been reported. Anecdotal reports of effective oral use in calves younger than age 2 weeks indicate that this route may help avoid some adverse reactions associated with injection of an endotoxin-containing product. Killed *Salmonella* bacterins can produce measurable serum antibody responses to bacterial proteins in calves and adult cattle. However, calves vaccinated with a killed bacterin are unable to produce anti-LPS antibodies until age 12 weeks,[14] and optimum responsiveness does not occur until age 1 year.[15] Most controlled studies in which calves were vaccinated with a killed *Salmonella* bacterin and orally challenged have reported a lack of protection.[16-18] One small study that reported good protection after vaccination of 3- to 6-week-old calves with 2 doses of killed bacterin used IM challenge.[19] Another study in 6-month-old cattle found that a single intradermal dose of heat-killed *S.* Dublin protected against IV challenge.[20] Vaccination of cattle 3 months of age or older with 2 doses of killed *Salmonella* bacterins is likely to be useful for preventing salmonellosis. Although little has been published on the efficacy of a conditionally USDA-licensed SRP *S.* Newport vaccine, the clinical impression is that it is safe and effective at reducing fecal shedding of *Salmonella* but also capable of controlling disease caused by different serotypes of *Salmonella.*

Vaccination of adult cows, with passive transfer of antibody to calves through colostrum, is frequently used in dairies to control salmonellosis in neonates. Controlled trials evaluating passive protection have produced mixed results, with some indicating a lack of protection[18,21] and others demonstrating some protection in very young calves (5 days old).[22] Vaccination of dry cows may be useful for control of salmonellosis in calves younger than 3 weeks of age but is minimally effective for controlling salmonellosis in calves older than 3 or 4 weeks. There are anecdotal reports of protection against salmonellosis by repeated vaccination of young calves with an *S.* Typhimurium mutant LPS core antigen vaccine (ENDOVAC [IMMVAC Inc., Columbia, Mo.]). A J-5 *E. coli* Rc-mutant LPS core antigen–based bacterin (J-VAC [Merial Ltd., Athens, Ga.], J-5 [Zoetis, Florham Park, N.J.], and Hygieia [Biological Laboratories, Woodland, Calif.]) improved survival and reduced morbidity rate from naturally occurring bacterial infections in dairy calves vaccinated at 3 and 17 days of age.[23]

Gram-Negative Mutant Lipopolysaccharide Core Antigen Bacterins

All genera and species of gram-negative bacteria share a common set of LPS core antigens that are present within the inner layers of the bacterial cell wall.[24] Endotoxin from gram-negative bacteria is

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TABLE 48-10

Currently Licensed* *Escherichia coli* Bacterin-Toxoids, *Salmonella* Bacterins, and Core Endotoxoid Vaccines

Antigens	Vaccine	Vaccination Regimen	Manufacturer
Escherichia coli			
K99	Pili Shield	1 dose 2 weeks before calving	Grand Laboratories (Larchwood, IA)
K99, K88, F41, 987P	Prosystem 3	*Year 1:* 2 doses 5 weeks and 2 weeks before calving *Subsequent years:* 1 dose 2 weeks before calving	Intervet (Millsboro, DE)
K99	ScourGuard 3(K)	*Year 1:* 2 doses 5 weeks and 2 weeks before calving *Subsequent years:* 1 dose 3 weeks before calving	Zoetis (Florham Park, NJ)
K99, K88, F41, 987P	*E. coli* Bac	*Year 1:* 2 doses 5 weeks and 2 weeks before calving	AgriLabs (St. Joseph, MO)
?	Piliguard *E. coli*	1 dose 2 weeks before calving 1 dose 3 weeks to 6 months before calving	Schering-Plough Animal Health (Union, NJ)
Salmonella			
Salmonella Typhimurium	PolyBac B Somnus	2 doses 2 weeks apart	Texas Vet Lab (San Angelo, TX)
	Bo-Bac 2X	2 doses 2-4 weeks apart	Boehringer Ingelheim (St. Joseph, MO)
Salmonella Dublin and *S.* Typhimurium	Salmo-Shield TD	2 doses 2-4 weeks apart	Novartis, Grand Laboratories (Larchwood, IA)
	SDT-Guard	2 doses 2-4 weeks apart	Boehringer Ingelheim (St. Joseph, MO)
	Salmonella Dublin/ Typhimurium Bacterin	2 doses 2-4 weeks apart	Colorado Serum Company (Denver, CO)
Salmonella Dublin	*Salmonella* Dublin Modified Live Entervene-d	2 doses 2 weeks apart; start at age 2 weeks or older	Boehringer Ingelheim Vetmedica (St. Joseph, MO)
Salmonella			
Subunit Vaccine			
Siderophore *Salmonella* vaccine (conditional USDA license)	SRP	2 doses 2-4 weeks apart	Agrilabs (St. Joseph, MO) Intervet (Millsboro, DE)
Core Antigens			
Re *Salmonella* Typhimurium mutant (endotoxin core)	Endovac-Bovi	*Year 1:* 2 doses 5 weeks and 2 weeks before calving *Subsequent years:* 1 dose 2 weeks before calving	Immvac (Columbia, MO)
J5 *E. coli* mutant endotoxin core	JVac	*Year 1:* 3 doses 5 weeks and 2 weeks before calving *Subsequent years:* 2 doses	Merial (Iselin, NJ)
	J-5	*Year 1:* 2 doses 5 weeks and 2 weeks before calving *Subsequent years:* 1 dose 2 weeks before calving	Zoetis (Florham Park, NJ)

*Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, as of 2007.

thought to play an important role in producing clinical signs, biochemical and hematologic alterations, and lesions associated with a wide variety of bovine diseases caused by gram-negative bacteria,[24] including salmonellosis and coliform mastitis, variously caused by *E. coli, Klebsiella* spp., *Enterobacter aerogenes,* and *Serratia* spp. Vaccines based on *S.* Typhimurium or *E. coli* with mutated LPS core antigen are designed to provide broad protection against related gram-negative infections by reducing the severity of clinical signs associated with sepsis and endotoxemia.

General Considerations

Gram-negative mutant LPS core antigen oil-adjuvant vaccines are currently marketed. Three use a J-5 Rc-mutant strain of *E. coli* that lacks the serotype-specific O-chain LPS components that ordinarily prevent deeper cell wall antigens from eliciting adaptive host immune response and production of antibodies against gram-negative core antigens.[24] Another commercial vaccine uses an Re-mutant strain of *Salmonella* Typhimurium.

Theoretically, gram-negative mutant LPS core antigen vaccines are expected to reduce the severity of disease but not the rate of occurrence of infection. In four different clinical trials, however, the incidence of clinical coliform mastitis in dairy cows was reduced by 69%, 72%, 80%, and 82%, respectively, by vaccination with a J-5 *E. coli* vaccine.[25-27] Data are consistent with the hypothesis that antibodies induced against gram-negative LPS core antigens assist in either the control of bacterial infection, neutralization of bacterial endotoxin, or a combination of both. In the trial where clinical coliform mastitis was reduced by 82%, however, vaccination did not reduce the incidence of subclinical intramammary coliform infections that were present at the time of calving.[27]

Vaccination Programs

Recommendations for use of bacterins to prevent disease associated with salmonellosis are summarized in Table 48-11. Cows should not receive other vaccines containing gram-negative organisms (*Pasteurella, Salmonella, Brucella, Campylobacter [Vibrio], H. somnus, E. coli,*

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TABLE 48-11

Currently Licensed Vaccines for Prevention of Calf Scour Associated with F5 (K99) Enterotoxigenic *Escherichia coli* Infection and Disease Associated with *Salmonella enterica*

Antigen	Vaccine Name	Vaccination Regimen	Manufacturer
***Escherichia coli* F5 (K99) Vaccines**			
F5 (K99 [bacterin])	Bovine Pili Shield	*Year 1:* 1 dose 12 months to 8 weeks before calving *Subsequent years:* 1 dose before calving	Novartis Animal Health (Larchwood, IA)
F5 (K99 [cell-free extract])	Guardian	*Year 1:* 2 doses up to 12 weeks and approximately 3-6 weeks before calving *Subsequent years:* 1 dose up to 5-7 weeks before calving	Intervet Inc./Merck Animal Health (Omaha, NE)
F5 (K99 [bacterin])	ScourGuard 4KC	*Year 1:* 2 doses 6-9 weeks and 3-6 weeks before calving *Subsequent years:* 1 dose 3-6 weeks before calving	Zoetis (Florham Park, NJ)
F5 (K99) (4 strains [bacterin])	Scour Bos 9	*Year 1:* 2 doses 8-16 weeks and 4 weeks before calving *Subsequent years:* 1 dose up to 10 weeks before calving	Novartis Animal Health (Larchwood, IA)
***Salmonella* Vaccines**			
Salmonella enterica serotype Typhimurium (bacterin-toxoid)	Super Poly-Bac B Somnus	2 doses 2 weeks apart	Texas Vet Lab (San Angelo, TX)
S. enterica Dublin/ Typhimurium (bacterin)	*S.* Dublin-Typhimurium bacterin	*Adults:* 2 doses 2-3 weeks apart before placement on feed, and pregnant cows 4-6 weeks before calving *Newborn calves > 7 days of age:* 2 doses 2-3 weeks apart	Colorado Serum Company (Denver, CO)
S. enterica Dublin/ Typhimurium (bacterin)	SDT-Guard	*Adults:* 2 doses 2-4 weeks apart	Boehringer Ingelheim Vetmedica, Inc. (St. Joseph, MO)
S. enterica Newport (siderophore receptor protein [SRP]; conditional USDA license	*Salmonella* Newport Bacterial Extract	6-month-old and older: 2 doses 2-4 weeks apart	Zoetis (Florham Park, NJ)
S. enterica serotype Dublin (modified live)	EnterVene-D	*2 weeks of age and older:* 2 doses 12-16 days apart	Boehringer Ingelheim Vetmedica, Inc. (St. Joseph, MO)
***Salmonella/Escherichia coli* mutant LPS core antigen vaccines**			
S. enterica serotype Typhimurium (bacterin-toxoid)	ENDOVAC-Dairy	*Cows during dry period and heifers during third trimester of pregnancy:* 2 doses 2-3 weeks apart *Subsequent years:* 1 dose	IMMVAC Inc. (Columbia, MO)
	ENDOVAC-Beef	*Year 1:* 2 doses 2-3 weeks apart *Subsequent years:* 1 dose	
J-5 *E. coli*	J-VAC (bacterin-toxoid)	*Year 1:* 2 doses 2-4 weeks apart *Subsequent years:* 2 doses 2-4 weeks apart *Pregnant cows:* 2 doses starting at 7 months of gestation or at dry off and 1-3 weeks before calving	Merial LTD (Athens, GA)
	ENVIRACOR J-5 (bacterin)	*Cows or heifers:* 3 doses starting at 7 and 8 months of gestation and 2 weeks after calving	Zoetis (Florham Park, NJ)
	Escherichia coli Bacterin	3 doses 4-6 weeks apart	Hygieia Biological Laboratories (Woodland, CA)

or *M. bovis* bacterins) within 5 days of vaccination with J-5 *E. coli* bacterin.

A J-5 *E. coli* bacterin has also successfully reduced morbidity and mortality in experimental *S.* Typhimurium infection in calves.[28] However, because of the short half-life of passively acquired antibodies stimulated by mutant LPS core antigen vaccines,[29] vaccination of dry cows is unlikely to be an effective control measure for salmonellosis in calves except when calves are exposed to and infected with *Salmonella* in the first week or two after birth. Salmonellosis in dairy calves often occurs after 2 weeks of age. However, when vaccinated at age 3 and 10 days with an oil-adjuvant J-5 *E. coli* bacterin, calves do develop strong antibody responses by age 17 days; this strong antibody response occurs even in the presence of passively acquired antibodies to LPS core antigens.[30] Consequently, a combined program in which both dry cows and neonatal calves are immunized against LPS core antigens might be a useful approach for reducing the severity of salmonellosis in neonatal dairy calves.

Clostridial Vaccines

J. Glenn Songer

Clostridial enteric disease may be mild (e.g., *C. difficile* and *C. perfringens* type A infection in neonatal pigs) or catastrophic (e.g., *C. perfringens* type C infection in neonates), producing acute and frequently fatal disease. Infections of internal organs and soft tissues are, on the other hand, uniformly serious and, in the absence of prior vaccination or very aggressive therapy, nearly always fatal. In either case, pathogenesis is most often mediated by toxic proteins.[1] Prevention is based on immunoprophylactic amelioration of the effects of these molecules. Unfortunately, the ready availability of inexpensive, efficacious bacterins, toxoids, and bacterin-toxoids has not eliminated clostridial infections, mainly because these immunoprophylactic products are sometimes used poorly or not at all. Duration of immunity (DOI) is poor. Accurate diagnosis remains an important component in management of clostridial diseases.[2,3]

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Immunization against clostridial diseases can be complicated by the development of site reactions, leading to trimming at slaughter.[4] These problems are exacerbated by the multivalent nature of many modern vaccines and have stimulated the biologics industry to seek a new paradigm for preparation and delivery of vaccines. Approaches have included concentration of the antigen into smaller doses and use of alternate adjuvants. Recombinant proteins delivered by conventional means, application of slow-release media, in vivo expression from attenuated bacterial delivery systems, and production in vivo by replicon particles from alpha viruses will likely be a major focus of effort.

In a recent study, transdermal vaccination resulted in bovine serum antibody titers similar to those resulting from SC vaccination, and injection site reactions were significantly smaller. Thus transdermal vaccination may be effective for raising protective immunity against clostridial diseases in cattle while minimizing local reactions.[5]

Clostridium chauvoei (Blackleg) Bacterins

Blackleg is frequently diagnosed despite long-term availability of generally effective bacterins. The most common route of exposure in cattle is likely ingestion, and dormant spores seeded to skeletal muscle germinate when muscle damage provides appropriate conditions. Signs in affected animals include fever, anorexia, depression, and lameness, with extensive dry and emphysematous to edematous, hemorrhagic, and necrotic lesions. In diagnosis, differentiation between blackleg and malignant edema is important.

Vaccination against blackleg is universally advocated, especially in cattle younger than 2 years. Dogma holds that protection arises from the immune response to a heat-labile soluble antigen, but *C. chauvoei* produces alpha toxin and several other toxic factors that may be equally important targets.[6,7] Recommendations for immunization are summarized in Table 48-12.

TABLE 48-12

General Considerations for Use of Clostridial Seven-Way and Eight-Way Bacterin-Toxoids*

Protection, by Species	Coverage Designation*	
	Seven-Way	Eight-Way
Clostridium chauvoei	x	x
Clostridium septicum	x	x
Clostridium novyi B	x	x
Clostridium sordellii	x	x
Clostridium perfringens type C	x	x
Clostridium perfringens type D	x	x
Clostridium perfringens type B†	x	x
Clostridium haemolyticum (novyi type D)	x	
Dose (mL)	2-5	5
Recommended boosters	After 2-4 weeks for *C. sordellii* and *C. perfringens* C and D; after 5-6 months for *C. novyi* type B and *C. haemolyticum*. Calves initially vaccinated at <3 months of age should be revaccinated at 4-6 months (or at weaning).	
Comment	No use <21 days preslaughter	

*Note that many combinations are available commercially, including some that also contain immunogens against nonclostridial diseases. Some of these combinations also include tetanus toxoid.

†No currently licensed product is produced by use of cultures of *C. perfringens* type B, but protection against type B infection is implied by the inclusion of toxoid prepared against type C (beta toxin) and type D (epsilon toxin) strains.

Clostridium septicum (Malignant Edema) Bacterins

Malignant edema, the typical wound infection caused by *C. septicum*,[8] usually follows direct contamination of a traumatic wound, including genital tract infections after mismanaged deliveries. Infection spreads along fascial planes, and lesions that are initially warm and pitting become crepitant and cold. Death commonly occurs in less than 24 hours. "Braxy" is a form of *C. septicum* enteric infection that occurs most commonly in calves.[9] Diagnosis is often by use of a fluorescent antibody test.[10]

Cattle are protected by a single immunizing dose of *C. septicum* bacterin, but annual booster vaccination is recommended in areas with a substantial incidence of the disease[11] (see Table 48-9). Vaccines elicit antibody responses to both somatic and toxin antigens, and recent findings suggest a central role for *C. septicum* alpha toxin.[12,13]

Clostridium novyi Types A and B (Bighead and Infectious Necrotic Hepatitis) Bacterins

Clostridium haemolyticum (*Clostridium novyi* type D) (Bacillary Hemoglobinuria) Bacterins

C. novyi toxigenic types A and B cause myonecrosis in humans (gas gangrene) and domestic animals (bighead of sheep), as well as infectious necrotic hepatitis (black disease) of sheep and cattle.[14] The hallmark lesion is edema that results from vascular damage caused by alpha toxin. Dormant spores in Kupffer cells germinate when liver injury provides appropriate conditions. Type C strains are nontoxigenic and therefore nonpathogenic.[15]

Redwater is caused by *C. haemolyticum* (*C. novyi* type D). Beta toxin, a homolog of *C. perfringens* alpha toxin (CPA), mediates the pathogenesis, usually in well-nourished animals at least 1 year of age. Tissue damage caused by migrating liver flukes allows germination of dormant spores in Kupffer cells. Vegetative growth yields a local lesion that is often quite small (golf-ball size is not uncommon), and dissemination of beta toxin via the bloodstream results in intravascular hemolysis, hemorrhage, and hemoglobinuria.[16,17] When urine takes on the color of port wine, about 50% of the red cells have lysed, and death ultimately results from anoxia. A vaccination program is essential for herds pastured in endemic areas. When light exposure to fluke metacercariae is expected, a single annual dose of bacterin-toxoid should be administered to all cattle older than age 6 months, before they are pastured in the spring. With heavy exposure to flukes, a booster dose should be administered in season. The prominent roles of alpha and beta toxins suggest they may find use in second-generation vaccines.

Clostridium botulinum (Botulism) and *Clostridium tetani* (Tetanus) Toxoids

Botulism is caused by *C. botulinum* neurotoxins, which block acetylcholine release from cholinergic nerve endings.[18,19] Cattle in the United States are most commonly affected by type C. Direct contamination of feeds by the organism sometimes leads to intoxication, but it is more commonly associated with an animal carcass in the feed. Clinical signs include incoordination, flaccid paralysis, and difficulty in swallowing; respiratory paralysis causes eventual death.[20,21]

Toxoids of botulinum toxins can be employed for immunoprophylaxis, but vaccination is usually practiced only in populations at immediate risk, such as beef cattle grazed on phosphorus-deficient range land.[22] Vaccination is not practiced in the United States. Feeding of poultry litter poses a similar problem, in that it may contain animal remains, but this practice has now been suspended in the United States.

Spores of *C. tetani* are found in soil, and animal hosts are usually infected in association with some traumatic event. Spores introduced to tissue under proper conditions of anaerobiosis germinate and produce tetanus neurotoxin.[23] Tetanus can develop in postparturient

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dairy cows and in calves after castration by the elastrator method.[24] Toxin moves retrograde, binding to presynaptic axonal terminals and resulting in muscular tremor and increased stimulus response; continued motor neuron hyperactivity causes sustained tetanic spasms in the innervated muscles and then permanent rigidity. Death is due to respiratory failure.

Acquired resistance to tetanus is based on circulating antitoxin, and widespread vaccination with toxoid in populations at risk has dramatically lessened the impact of tetanus on animal production. Neonatal passive immunity acquired from the dam is followed by active immunization with toxoid after 2 to 3 months. Boosters are commonly recommended at 1- to 5-year intervals. Passive immunotherapy is intended to neutralize preformed toxin, although it is much more effective when used prophylactically than therapeutically. Universal vaccination is not usually recommended as a cost-effective means for control of tetanus.

Clostridium perfringens Toxoids

C. perfringens causes various diseases in domestic animals, and those of greatest importance affect the gastrointestinal tract[25] (Table 48-13) (see ruminant section of Chapter 32). Type B disease is extraordinarily rare in the United States. Pathogenesis can be explained by additive or synergistic effects of beta and epsilon toxins. Type C strains multiply rapidly in the neonatal gut, and in this trypsin-poor environment, beta toxin accumulates and produces local hemorrhage and necrosis, as well as systemic effects.[26] Type D strains fill vacant intestinal niches, often those opened by sudden dietary changes. Epsilon toxin monomers bind to enterocytes and interact with other monomers to produce a pore. The toxin facilitates its own uptake and, in circulation, damages the central nervous system and other systems distant from the gut.[27] Type E causes hemorrhagic enteritis in calves, and its virulence is apparently based on the action of iota toxin.[28]

Type A infections are somewhat enigmatic. Long accepted as causes of lamb enterotoxemia,[29] poultry necrotic enteritis, and canine and equine enteritis, they are increasingly found to be causes of enteritis in piglets and calves. Little is known about the pathogenesis of some type A enteric infections, but our understanding of poultry necrotic enteritis has increased dramatically, and we can easily reproduce disease in chicks and piglets. Experimental reproduction remains challenging, but type A strains are commonly found in natural cases of tympany, abomasitis, and abomasal hemorrhage and ulceration in calves.[30,31]

Some say routine vaccination against type C enterotoxemia is required only in herds where the disease has been documented, but in our experience, vaccination of all dams prior to farrowing or calving is recommended. Immunity is provided to piglets or calves via immune colostrum. Initial immunization should be followed by a booster after 3 to 4 weeks, with the second dose (and subsequent boosters pre-farrowing or pre-calving) administered approximately 2 to 3 weeks before parturition. Type D enterotoxemia occurs sufficiently infrequently in cattle that vaccination may not be cost-effective. No commercial products are licensed in the United States for use against infections by strains of types A and E, and production of autogenous toxoids or bacterin toxoids has become quite common; anecdotal evidence suggests remarkable efficacy in some cases. Similar products have been produced from strains of type E. These should be used with the awareness that unlike beta and epsilon toxin concentrations in commercial products, toxin concentrations in autogenous toxoids may not be optimal.

TABLE 48-13

Diseases of Cattle Caused by *Clostridium perfringens*

Clostridium perfringens Type	Diseases in Domestic Animals	Major Toxins
A	Myonecrosis, enterotoxemia, abomasitis, possible sudden death	Alpha
B	Neonatal hemorrhagic enteritis	Alpha, beta, epsilon
C	Neonatal hemorrhagic or necrotic enterotoxemia	Alpha, beta
D	Enterotoxemia	Alpha, epsilon
E	Enterotoxemia	Alpha, iota

Clostridium sordellii Bacterins

C. sordellii is commonly found in feces of domestic animals, as well as in the soil, and is sometimes a cause of fatal myositis, liver disease, and sudden death in cattle. Subendocardial hemorrhage and edema in the subcutaneous tissues and along fascial planes of muscles are common. The organism produces numerous toxic or putatively toxic substances, foremost of which are toxins that resemble toxins A and B of *Clostridium difficile*.[32] Immunization is achieved by administration of multiway bacterin-toxoids (see Table 48-10).

Miscellaneous Bovine Rickettsial, Bacterial, and Viral Disease Vaccines

Derek A. Mosier

A number of bovine vaccines are available for anaplasmosis, infectious bovine keratoconjunctivitis, staphylococcal mastitis, anthrax, interdigital necrobacillosis (foot rot), papillomatous digital dermatitis (foot warts), rabies, and fibropapillomas. These are discussed individually next and summarized in Table 48-14.

Anaplasmosis

Anaplasmosis is a vectorborne or mechanically transmitted disease caused by the rickettsia *Anaplasma marginale*.[1,2] The disease occurs worldwide and is most prevalent in tropical and semitropical areas. Anaplasmosis is the only major tickborne disease of cattle in North America, being enzootic in the southeastern and some midwestern and western states and sporadic in the northern states and Canada.[1,2,3] In enzootic areas with adequate numbers of arthropod vectors, most adult cattle become naturally immune through repeated exposure. Maternal antibodies protect calves until they also become subclinically infected and develop immunity. Disease is more severe in older cattle than in calves, and nonimmune older cattle are particularly at risk when they are moved into an endemic area.[1,4] Susceptibility to disease occurs when there is a lack of arthropod vectors to maintain natural infection and immunity or when a nonimmune adult is introduced into an enzootic area. In these situations or when vector or environmental conditions suggest an increased risk of disease, vaccination can be beneficial.

No widely marketed commercial vaccines against anaplasmosis were available as of 2012 in North America. A killed vaccine (Anaplasmosis Vaccine, University Products LLC, Baton Rouge, La.) is available in some states, including Arkansas, California, Florida, Indiana, Illinois, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nevada, Oklahoma, Oregon, Tennessee, Texas, Wisconsin, and Puerto Rico. The vaccine consists of an emulsion of concentrated inactivated *A. marginale* antigens and adjuvant suspended in 10% oil, similar to the last widely available commercial vaccine that was discontinued in 1999 (Plazvax [Schering-Plough Animal Health]). The killed vaccine is not USDA licensed, but it is USDA approved for use as an experimental vaccine. The vaccine has reportedly been used successfully in cows at all stages of pregnancy without an episode of neonatal isoerythrolysis. In endemic areas the vaccine is recommended for use just before the onset of the vector season. Vaccine-induced immunity does not generally occur until 2 weeks after

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administration of the second dose of an initial series or 2 weeks after a booster dose in previously immunized cattle.[5,6] Vaccination does not prevent infection or clinical disease and does not eliminate *A. marginale* from a herd, but it does reduce the severity and incidence of disease.[1,6] Inactivated vaccines could be used in conjunction with oxytetracycline in the face of outbreaks to provide both temporary and more prolonged protection.

A sheep-passaged modified live vaccine (Anavac [PHL Associates, Davis, Calif.]) has been used in California and Latin America.[7] Because this vaccine causes mild clinical disease, it has limited use for vaccination of mature susceptible cattle.[1,7] If the vaccine is administered to cattle older than 2 years of age, anemia, severe clinical disease, and death may occur, especially in bulls and heavily lactating cows.[7] The vaccine is recommended for use in healthy cattle between age 1 month and 2 years and is most commonly administered to 7- to 24-month-old cattle in herds in endemic areas. Concurrent use of certain antibiotics or other live or MLV vaccines is contraindicated.

A live vaccine (Frozen Anaplasmosis [Tick-borne gallsickness] vaccine for cattle [Onderstepoort Biological Products, Onderstepoort, South Africa]) composed of *A. marginale* subsp. *centrale,* a less pathogenic species or subspecies of *A. marginale,* is used in some countries including Africa, Australia, Israel, and Latin America but not in North America.[6,8,9] This vaccine consists of standardized and frozen red blood cells from splenectomized cattle that were infected with *A. marginale* subsp. *centrale.* The vaccine is recommended for use in 4- to 9-month-old cattle; older cattle have an increased risk of severe vaccine-induced disease. The vaccine produces mild disease but protects against subsequent severe disease caused by *A. marginale.* Immunity is considered long term or possibly for life if subsequent natural exposure occurs to ensure development of durable immunity.

Immunity to *A. marginale* is proposed to involve humoral responses to a variety of major surface proteins and enhanced macrophage phagocytosis and killing, both mediated by IFN-γ–producing $CD4^+$ T lymphocytes.[1,10,11] Inadequate protection from vaccines during field use can result from antigenic variability of the organism, geographic differences in the organism that result in a lack of cross-reactivity between *A. marginale* strains, and weak immune responses to protective *A. marginale* antigens.[1,4,12-14] Purified native, recombinant, and tick culture–derived *A. marginale* immunogens and DNA vaccines are being investigated for possible commercial use in the future.[6,9,12,13,15-17]

Infectious Bovine Keratoconjunctivitis

The most common infectious agent associated with infectious bovine keratoconjunctivitis (IBK) is *Moraxella bovis.*[1] Vaccination is most effective when done before fly season in herds with a history of problems. Certain breeds (e.g., Herefords, Hereford crosses) are particularly susceptible and may benefit from vaccination.[1,2] Commercial vaccines used to help prevent the disease consist of inactivated cultures of various strains of *M. bovis.*[3] Some products recommend 2 doses given 3 weeks apart for initial vaccination, beginning as early as 3 weeks of age to no earlier than 5 months of age. Other products recommend a single dose administered 3 to 6 weeks before the predicted onset of the disease season, with annual vaccination thereafter. *M. bovis* bacterins are also available in combination with 7-way clostridial bacterin-toxoids.[4] Although multivalent *M. bovis* bacterins can provide some protection in field use, efficacy varies depending on the *M. bovis* strains present in the bacterin and those responsible for disease.[1,5-7] Seven different disease-producing serogroups of *M. bovis* are recognized based on differences in pili, and there is variable cross-reactivity between serogroups.[3] Pilin gene rearrangements and pilin-type switching can allow *M. bovis* to switch from expression of one type of pilus antigen to another, making it difficult to predict what serogroup(s) may be necessary for protection.[2,3,6] Monovalent bacterins are generally ineffective in field use, and multivalent bacterins provide neither consistent nor reliable protection.[3,5-7] Vaccines must incorporate pili from all major serogroups or conserved immunogenic portions of all serogroups to provide optimum protection.[3,6,7] Experimental recombinant vaccines containing cloned pili of various serogroups have demonstrated some promise for future vaccines.[5,6] Another immunogen considered important for protection is *M. bovis* B-hemolytic corneotoxic and leukotoxic cytotoxin.[1-3] Experimental vaccines containing hemolytic cytotoxin preparations alone or in combination with pilus antigens have shown some efficacy in experimental trials.[1,3,8-10] Other potential immunogens include iron-regulated OMPs, proteases, fibrinolysins, and phospholipases.[1-3] Vaccine-induced protection is correlated predominantly with a suitable lacrimal immune response (predominantly IgA but also IgM and IgG) and not with serum antibody levels to *M. bovis* antigens.[1-3] Therefore an antigen delivery system that enhances lacrimal and mucosal immunity is an important feature of an effective vaccine.[11] The presence of other agents contributing to IBK (e.g., *Moraxella [Branhamella] ovis, Mycoplasma bovoculi,* or BHV-1) should also be considered when there is poor *M. bovis* vaccine efficacy.[12] Autogenous *M. bovis* or *M. bovis* plus *M. bovoculi* vaccines have not been consistently effective against the disease.[1,13,14] Use of MLV vaccines for IBR is contraindicated in the presence of an outbreak of IBK because it may exacerbate the IBK.[1]

Staphylococcal Mastitis

Staphylococcus aureus is considered one of the most important causative agents of bovine mastitis.[1] Vaccination against *S. aureus* may be beneficial in dairy herds that have an existing mastitis problem,[1,2] but vaccination in well-managed dairy herds with a low level of staphylococcal mastitis may not provide much economic benefit.[2] Staphylococcal bacterins contain conserved antigens or antigens from multiple strains or serotypes of *S. aureus.*[3-5] The typical recommended vaccination protocol is 2 doses given 2 weeks apart, followed by revaccination at 6-month intervals. Vaccination can start at 6 months of age, and one of the semiannual doses should be given 3 to 4 weeks before calving. Vaccination with *S. aureus* bacterins does not generally eliminate disease but can substantially reduce clinical mastitis and the incidence of subclinical and chronic staphylococcal infection.[1,2,5,6] Vaccination may be more effective in heifers because of their initial lower basal immunity compared with older cows.[6] The benefits of immunity induced early in life include the abilities to clear the organism and resist chronic infection on initial natural exposure. Vaccination during the dry period may be more effective than vaccination during lactation. In some but not all studies, vaccination has reduced somatic cell counts in milk.[5,6] Vaccination in combination with antimicrobial therapy has been successfully used to eliminate chronic staphylococcal mastitis.[7]

In considering the use of staphylococcal vaccines, the prevalence of various pathogens that can cause mastitis must be considered. For mastitis caused by *S. aureus,* differences between the *S. aureus* strains in vaccines and the strains specifically responsible for the disease may diminish vaccine efficacy.[1,4,8] Both long-standing bacterins and some newer-technology vaccines have achieved positive results.[1,9] Experimental trials suggest that more effective vaccines may be derived by stimulating immune responses to combinations of *S. aureus* capsular polysaccharide.[10] A vaccine based on technologies used for human staphylococcal vaccines that incorporates capsular polysaccharide from the three *S. aureus* serotypes most commonly associated with mastitis stimulated immunologic parameters necessary for protection.[11] Other vaccines have utilized highly conserved membrane proteins, iron-regulated proteins, a staphylococcal superantigen conserved by many mastitis strains, and DNA vaccines directed against adhesin proteins in attempts to achieve the "universal" *S. aureus* vaccine.[5,12-14]

In herds where other pathogens are a major cause of mastitis, *S. aureus* vaccines may be of minimal benefit.[2] Other important causes of bovine mastitis include *Streptococcus* spp. (e.g., *Streptococcus uberis, Streptococcus dysgalactiae,* and *Streptococcus agalactiae*) and coliform bacteria (e.g., *E. coli*). Recombinant vaccines containing *S. aureus* and *S. agalactiae* have shown some promise in experimental

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TABLE 48-14

Recommendations for Use of Some Bovine Disease Vaccines: *Anaplasma*, *Moraxella*, *Staphylococcus*, Anthrax, *Fusobacterium necrophorum*, Papillomatous Digital Dermatitis, Rabies, and Papillomas

	Pathogen								
Characteristic	***Anaplasma marginale*[1]**	***Anaplasma marginale*[2]**	***Moraxella bovis*[3-8]**	***Staphylococcus* Species[9]**	***Bacillus anthracis*[10]**	***Fusobacterium necrophorum*[11-12]**	**Papillomatous Digital Dermatitis[13]**	**Rabies Virus[14-16]**	**Bovine Papilloma Virus[17-18]**
Passive antibodies protective			Yes	NA	?	NA	NA	Yes	Yes
Duration of colostral immunity (months)			4-6	NA	?	NA	NA	4-10	3
Type of vaccine	Modified live	Inactivated	Bacterin	Bacterin	Sterne nonencapsulated avirulent spore	Bacterin	Bacterin	Inactivated virus	Inactivated wart tissue extract
Immunizes in the presence of passive immunity	No		No	NA	7	NA	NA	No	—
Earliest recommended age for initial vaccination (months)	1-4[a]		1[a]-5	6	Any	6	12	3	Any[a]
Site of administration	IM	SC	IM[6,7] or SC	IM	SC	IM or SC	SC	IM	SC
Doses required for protection	1	2	1[b]-2[c]	2	1-2	2	3	1	2
Interval between priming and immunizing doses (weeks)	NA	3-4	3	2	2-3	3-4	3-4	NA	3-5
Interval from first dose to protection (days)	42	35	21[b]-42[c]	28	8	35	?	?	14-30
Duration of vaccinal immunity (months)	Lifelong	12	<9	5-6	12	?	<6	>12	6
Recommended booster interval (months)	NA	12	12	5-6[d]	12[f]	12	4-6	12	6
Contraindications	Do not use in cattle over 2 years of age or in the last 4 months of pregnancy; do not administer tetracyclines	—	—	—	Avoid simultaneous administration of antimicrobials; do not use in sick animals	—	—	—	—
Side effects	Illness, anemia, abortion, death	Anaphylaxis	Anaphylaxis	Anaphylaxis	Mild illness, fever, decreased milk production	Anaphylaxis	Anaphylaxis	Anaphylaxis	Anaphylaxis

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Withdrawal time (days before slaughter)	—	60	21, 60[6,7]	21[e]	42	21	28	21	21

[1]Anavac, PHL Associates, Davis, CA.
[2]Anaplasmosis Vaccine, University Products LLC, Baton Rouge, LA.
[3]I-Site, AgriLaboratories, St. Joseph, MO.
[4]Maxi/Guard Pinkeye bacterin, Addison Biological Laboratory, Fayette, MO.
[5]Ocu-Guard MB and Alpha-7 MB, Boehringer Ingelheim, St. Joseph, MO.
[6]Piliguard Pinkeye-1 Trivalent and Piliguard Pinkeye + 7, Merck Animal Health, Summit, NJ.
[7]Pinkeye Shield XT4, Novartis Animal Health, Larchwood, IA.
[8]Vision 7 20/20 with Spur, Intervet Inc., Merck Animal Health, Summit, NJ.
[9]Lysigin, Boehringer Ingelheim Vetmedica, St. Joseph, MO.
[10]Anthrax Spore Vaccine, Colorado Serum Co., Denver, CO.
[11]Volar, Intervet, Millsboro, DE 19966.
[12]Fusogard, Novartis Animal Vaccines, Larchwood, IA.
[13]Serpens species bacterin, Hygieia Biological Laboratories, Woodland, CA.
[14]Defensor 3, Zoetis, Florham Park, NJ.
[15]Rabdomun, Schering-Plough Animal Health, Union, NJ.
[16]Imrab 3 and Imrab Large Animal, Merial, Duluth, GA.
[17]Wart vaccine, AgriLaboratories, St. Joseph, MO.
[18]Wart vaccine, Colorado Serum Co., Denver, CO.
[a]Calves vaccinated before the age at which passive immunity no longer exists should be revaccinated on reaching that age.
[b]Oil-adjuvant vaccines.
[c]Aluminum hydroxide-adjuvant vaccines.
[d]Give booster 3 to 6 weeks before calving.
[e]No milk withdrawal required.
[f]Booster can be given sooner in heavily contaminated areas.
?, Unknown; *IM,* intramuscular administration; *NA,* not applicable; *SC,* subcutaneous administration.

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models.[15] Experimental vaccines composed of bacterial proteins derived from *S. uberis* and *S. dysgalactiae* reduced somatic cell counts compared with controls after challenge.[16,17] *E. coli* J5 vaccines have also been used to successfully reduce the severity of mastitis (reviewed elsewhere in this section).

Anthrax

Anthrax is an acute, highly fatal disease caused by *Bacillus anthracis.*[1] Vaccination has proven to be an effective means of controlling the disease in endemic areas and in the face of outbreaks.[1-3] Bovine anthrax vaccines are derived from the live toxigenic, nonencapsulated spore vaccine developed by Sterne and consist of spores suspended in a diluent containing saponin and glycerin.[1] Annual vaccination of livestock in areas of endemic anthrax is recommended 4 weeks before outbreaks are expected, typically in the spring to provide protection during the summer months.[1] A single dose generally provides adequate immunity for about a year, but a second dose given 2 to 4 weeks after the first is sometimes recommended. Cattle should not be vaccinated within 42 days of slaughter. Antibiotics should not be administered within 7 days of vaccination to avoid interference with in vivo growth of the vaccine organism. Outbreaks can occur sporadically but often occur in areas with a history of flooding followed by drought.[4,5] Vaccination in the face of an outbreak does not protect all cattle, but the spread of infection and the number of new cases generally declines within 10 days.[3,5] Localized subcutaneous edema can develop at the injection site within 24 hours; it may last for several days and is sometimes severe.[2] Since the intentional release of *B. anthracis* via the mail system in 2001, there has been increased interest in technologies for the development of an efficacious long-acting human vaccine for anthrax.[2,6-8] Some of these technologies could hold promise to reduce some of the localized side effects of the current bovine vaccine,[9] but it is unlikely a new bovine vaccine will match the safety, efficacy, and cost-effectiveness of the Sterne strain vaccine in the foreseeable future. All anthrax outbreaks should be reported to local regulatory and public health officials, and appropriate guidelines for vaccination should be followed, including quarantine and vaccination of all susceptible livestock on affected and surrounding premises.

Interdigital Necrobacillosis (Foot Rot)

Interdigital necrobacillosis (foot rot) in cattle results from interdigital infection with *Fusobacterium necrophorum,* with lesser contributions from *Porphyromonas levii* (previously classified as a subspecies of *Prevotella [Bacterioides] melaninogenica*) and sometimes *Dichelobacter (Bacterioides) nodosus* (the most common cause of foot rot in sheep) and other bacteria.[1-3] Commercial *F. necrophorum* bacterins to aid in the prevention of foot rot (and hepatic necrobacillosis) are available for use in cattle. Recommendations for initial vaccination are two doses given 3 to 4 weeks apart, followed by annual revaccination. Vaccination is also recommended when endemic conditions exist or when exposure is imminent. The efficacy of *F. necrophorum* vaccines is unclear because hepatic abscesses are sometimes the study focus, but some benefit for foot rot has been demonstrated in experimental studies and field trials.[4] Vaccination is especially recommended in herds with a high incidence of disease. Protective immunity most closely correlates with the level of antileukotoxin antibodies.[5] In experimental models, truncated recombinant leukotoxin proteins provide protection and presumably would have some benefit against interdigital *F. necrophorum* infection.[6,7] Most foot rot infections involve single rather than multiple strains of *F. necrophorum,* so a vaccine that targets the specific strain involved should be effective.[8]

Papillomatous Digital Dermatitis (Foot Warts)

Papillomatous digital dermatitis, or foot warts, can be a serious problem in dairy cattle.[1] The disease is characterized by ulcerative to proliferative digital lesions that most often occur in replacement heifers and younger cows after introduction into a milking herd.[1,2] Risk is greatest in larger dairy breeds in herds of greater than 500 head. *Treponema* spp. are most commonly isolated from lesions and are considered the most important cause of foot warts. A wide variety of *Treponema* are incriminated, including *T. phagedensis, T. denticola, T. vincentii/T. medium,* and *T. pedis.*[3-5] No virus was seen in biopsies from multiple warts from dairy cattle in two herds.[6] Several bacterial species have also been isolated from lesions, including *Fusobacterium necrophorum, Serpens* spp., and *Porphyromonas levii.*[7,8] However, the precise combinations of these agents necessary to produce disease remain unclear. Commercial bacterins are available for use as preventives and/or aids to treatment and consist of killed cultures of *Serpens* spp. or *Treponema* spp. organisms. Recommendations are for 3 doses administered SC at 3- to 4-week intervals, followed by revaccination every 4 to 6 months. Company field trials report reduced onset of new infections and sometimes more rapid resolution of existing infections in vaccinated cattle. However, some trials failed to show significant improvement in vaccinated cows compared with unvaccinated ones.[8,9] The requirement for frequent boosters and the high recurrence rates of natural infection suggest that immunity to the disease is short lived or weak.[2]

Rabies

Rabies is a highly fatal zoonotic neurologic disease caused by a rhabdovirus.[1] Bovine rabies in North America is generally uncommon, and routine vaccination of cattle is not recommended in most situations.[2] However, vaccination may be a consideration in rural areas of Latin America, where vampire bats are important sylvatic vectors, or Africa, where exposure to infected dogs is a major cause of bovine rabies.[3,4] In endemic areas, vaccination of valuable cattle or herds may be a reasonable precautionary measure. This is particularly true in situations where cattle are in frequent contact with human beings, in order to reduce the anxiety of animal workers and minimize the likelihood of human exposure. Currently licensed rabies vaccines for cattle contain inactivated cell culture–derived virus.[5] The recommended regimen is initial vaccination at 3 months of age followed by annual vaccination thereafter. Because the duration of protective neutralizing antibody levels after initial vaccination can vary, some experts have suggested that a second booster dose be given either 1 month after initial vaccination or at 6 months of age.[6] Subsequent annual revaccination induces strong anamnestic responses that persist for 1 year or longer.[6] In Latin America, modified live vaccines are sometimes used but do not stimulate the same level of immunity as inactivated virus vaccines. A Capripoxvirus vector expressing rabies virus glycoprotein has shown promise in providing long-term protection against rabies (and lumpy skin disease) and may be a cost-effective mechanism for rabies control in cattle in some developing countries.[7,8]

Fibropapillomas (Warts)

Fibropapillomas (warts) are manifested in a variety of forms and locations, each caused by one of over 13 different types of bovine papillomaviruses (BPV).[1,2] Lesions associated with papillomaviruses can occur in the epidermis of the head, face, neck, and legs (BPV-1 and BPV-22), upper alimentary and urinary tracts (BPV-4), teats and udder (BPV-1, BPV-3, BPV-5, and BPV-6), and genital epithelium (BPV-1).[1,2] Immunity after infection or vaccination is virus type specific and is induced by viral structural proteins.[1] Therefore, the efficacy of both autogenous and commercial vaccines depends on which viral antigens are incorporated into the vaccine and which virus type is responsible for the disease. Vaccines containing BPV-1 and BPV-2 are generally effective for prevention, with some reports that BPV-2 also aids in regression of existing lesions.[1,3] Vaccines are usually ineffective for treatment or prevention of disease caused by BPV-3 and BPV-5.[3] Vaccination with structural capsid proteins of BPV-4 generally induces long-lasting immunity and is effective in preventing

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papillomas caused by BPV-4.[1] However, in immunocompromised cattle (e.g., those ingesting braken fern), papillomas may spread and can progress to squamous cell carcinoma.[2,4] Interpreting the response to vaccination against fibropapilloma can be complicated by spontaneous regression of some lesions. Lesions associated with BPV-1, BPV-2, and BPV-4 usually regress spontaneously within 1 to 12 months, whereas lesions caused by BPV-3 and BPV-5 do not normally regress spontaneously.[2,3]

Commercial vaccines consist of inactivated virus-laden tissue extracts derived from bovine papillomas.[5] The recommended regimen is an initial dose divided and given in at least 2 different sites, followed by a second dose in 3 to 5 weeks. Vaccination should continue for at least 1 year after elimination of disease from the herd. Autogenous vaccines can be made by homogenization and inactivation (0.3% formalin) of excised wart tissue, followed by dilution of the homogenate in physiologic saline and filtration through gauze. Three 1- to 5-mL intradermal injections given at 1-week intervals are recommended. Because autogenous vaccines generally contain the virus type associated with the disease, these often provide favorable results for both regression and prevention.[6] Vaccination is most commonly used with valuable animals destined for competitive shows or overseas sale.[3] Recombinant or native BPV proteins derived from multiple virus types have shown promise in experimental studies and could form the basis for a vaccine that protects against all BPV types.[7]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 49

Parasite Control Programs

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The traditional approach to parasite control programs has focused on using the appropriate anthelmintic at appropriate intervals. Parasitic disease in domestic animals is assumed to be the result of not dosing the animals often enough with anthelmintics. Scant consideration has been paid to the interaction of the parasite with the host and the environment because of the reliance on anthelmintics. These drugs have been placed directly into the hands of the livestock owner because the expertise of a veterinarian did not seem necessary in the control of parasites. However, reports of resistance to anthelmintics and emergence of new manifestations of parasitism are surfacing throughout the world. It has become increasingly apparent over the past 20 years that this approach to parasite control is no longer sustainable.

Secondary to the notion that parasitism is under control is the decrease in research to develop new anthelmintics. Currently there is little in pharmacologic development other than variations on the current anthelmintics. Research programs in parasitology of domestic animals are facing funding reductions as research priorities are shifted to other diseases. As producers and owners struggle to deal with the realities of anthelmintic resistance, veterinary medicine must reassess traditional approaches to parasite control programs. Veterinarians will need to reeducate themselves away from the traditional tools of deworming, anthelmintic rotation, and pasture rotation. Integrated management strategies incorporating selective use of anthelmintic agents, enhancement of host immunity to parasitic infection, and grazing/environmental management have become increasingly important in the design of sustainable parasite control programs.

The impact of parasitic infection varies widely with geographic area and management system. General guidelines may be suggested for parasitic control, but it is inadvisable to adhere to any rigid anthelmintic schedules or even management recommendations. The best parasite control programs are those designed with the goals of the producer in mind, as well as the costs and returns of treatment. Other factors that must be considered include the animal's environment, climatic variations, and geographic location. Although many producers and owners would like a "cookbook" approach to parasite control, these are rarely effective across the various management conditions. It is unfortunate that an epidemiologically and economically sound parasite control program designed for animals in one geographic area may be neither efficient nor effective in another location.

The most important concept in the design of sound parasite control programs is the interaction of the parasite with the host and the environment. An understanding of the life cycle and epidemiology will suggest the most effective methods for parasite control. In this chapter parasite factors, host factors, and environmental factors affecting transmission and disease expression are discussed for each major class of parasites in each host species (horses, cattle, small ruminants). The methods of monitoring parasite infections and anthelmintic resistance are presented in detail. The classes of anthelmintics and their modes of action are discussed and, finally, coccidiosis in cattle and small ruminants is summarized at the end of the chapter.

Equine Parasitic Disease

Martin Krarup Nielsen

The changed approaches being promoted for control of equine gastrointestinal helminths are based on a number of scientific concepts outlined in the following section. The recommendations given today are based on experts' best knowledge of parasite and host biology, as well as mechanisms of anthelmintic resistance. As time passes, some of these recommendations are likely to change as new information is generated. In essence, the traditional strategies used for equine parasite control were based on the best scientific evidence available at the time, and the recommendations now given are merely a response to the experiences gathered over the past decades. The concepts underlying the modern approaches for equine parasite control are presented in the following.

Anthelmintic Resistance

Anthelmintic resistance can be defined as "the loss of treatment efficacy of a given anthelmintic formulation that used to have efficacy against the same parasite species and stage in the same host animal, at the same dosage, and by the same route of administration." This sentence implies several things: (1) If a drug formulation never had efficacy against the parasite and stage in question, then veterinarians are not facing resistance. (2) In case of nonlabeled usage of anthelmintics, veterinarians cannot make any conclusions regarding resistance because they have no information about the expected level of efficacy. (3) Horses are always infected with several different species of parasites at the same time, and resistance often occurs in some, but not all, of these species. (4) The expected level of efficacy needs to be defined for each parasite species for each drug in order evaluate the possible presence of resistant parasites.

The current levels of anthelmintic resistance in equine parasites are presented in Table 49-1. Generally speaking, resistance has been widely documented in cyathostomins (small strongyles) and *Parascaris equorum*. It is worth noticing that as a general pattern, the resistance profiles are almost completely complementary between the two parasite categories. The drugs that seem to still work well against *P. equorum* often have no or little efficacy against cyathostomins and vice versa. However, levels of anthelmintic resistance are constantly developing and this pattern may therefore be shifting. Recent work has documented signs of emerging ivermectin and moxidectin resistance in cyathostomins,[1-4] and total drug failure is a realistic possibility in this parasite group. No new anthelmintic formulations

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TABLE 49-1

Current Levels of Resistance by Major Nematode Parasites to the Three Anthelmintic Classes in Managed Horse Herds

Drug Class	Cyathostomins	Large Strongyles	*Parascaris equorum*
Benzimidazoles	Widespread	None	Early indications
Pyrimidines	Common	None	Early indications
Macrolide lactones	Early indications	None	Widespread

BOX 49-1

Fecal Egg Count Reduction Test (FECRT) for Equidae

The FECRT evaluates the efficacy of an anthelmintic drug on the basis of its ability to reduce the fecal egg output after treatment. Fecal egg counts (FECs) are performed just before (or at the time of) and 14 days after treatment. The fecal egg count reduction (FECR) is calculated for each individual horse according to the formula:

$$\%\,\mathrm{FECR} = \left(\frac{FEC_{pre} - FEC_{post}}{FEC_{post}}\right) \times 100\%$$

It is recommended to use an egg-counting technique with a detection limit of fewer than 25 eggs per gram (EPG). Use the same technique consistently. Include horses with the highest possible pretreatment egg counts, and never use horses with counts below 200 EPG.

The FECRT should be established on the farm level by calculating the FECR for a number of individual horses and then calculating the average FECR for the treated group. It is recommended to include at least 5 to 10 horses on each farm if possible.

Suggested cutoff values for resistance depend on the drug tested and the number of horses investigated, but the following cutoff values are recommended as general guidelines for strongyle and ascarid nematodes:

Benzimidazoles:	95%
Pyrantel:	90%
Ivermectin:	95%
Moxidectin:	95%

If the farm average FECR falls below these values, anthelmintic resistance should be suspected. However, it is important to rule out other causes of decreased efficacy, such as misdosing and inadequate storage. One must also consider how many horses were tested and how high the starting FECs were. Due to inherent variability in the measurement of FEC when performing FECRT, interpretation of the data can sometimes be difficult when results fall into the borderline zones. In such cases, it is recommended to repeat the FECRT.

There are currently no available methods for diagnosis of anthelmintic resistance in equine tapeworms.

with new modes of action are expected to be introduced to the equine market in the foreseeable future.

The only available method for evaluating anthelmintic efficacy in horses is the fecal egg count reduction test (FECRT). This method is outlined in Box 49-1 along with some suggested cutoff values for determining anthelmintic resistance.

Egg Reappearance Period

Egg reappearance periods (ERPs) are defined as the period of time from anthelmintic treatment until parasite eggs are found in the feces again. Although ERPs could potentially be established for a number of different parasite categories, they are most often referred to for strongyle (i.e., cyathostomin) parasites. The ERPs were initially defined for each anthelmintic class to help identify the optimum interval between anthelmintic treatments, and this was the basis for launching the so-called interval dose program in the 1960s.[5]

TABLE 49-2

Prepatent Periods of Some Important Equine Parasites

Species	Prepatent Period	References
Cyathostomins	2-3 mo*	113
Parascaris equorum	2½-3 mo	114
Anoplocephala perfoliata	1½-4 mo	115
Strongylus edentates	11-12 mo	115
Strongylus equinus		115
Strongylus vulgaris	6-7 mo	112

*Encysted larval stages can remain dormant for years.

Nowadays, ERPs are used for an entirely different purpose. It has been observed that the first sign of developing anthelmintic resistance to a given drug is often a gradual shortening of the ERP until reduced efficacies can finally be found with the FECRT. The most prominent example of this is the observed ERPs of ivermectin and moxidectin against cyathostomin parasites. Initially, ERPs were reported to be at least 8 and 12 to 16 weeks for ivermectin and moxidectin, respectively,[6-8] but recent publications reported egg reappearance at around weeks 4 to 5 for both drugs.[1, 4] Two necropsy-based studies have suggested that these observations were due to survival of luminal yet premature stages of cyathostomin larvae.[2,3]

Prepatent Period

Prepatent periods (PPPs) should not be confused with the egg reappearance periods defined earlier. While the latter defines a response to anthelmintic treatment, the PPPs are defined in the absence of anthelmintic intervention. The PPP for any given parasite is defined as the time elapsed from the uptake of the infective stage of the parasite until it reaches patency and starts shedding eggs to be detected in the feces. Thus the PPP represents the duration of the parasitic part of the life cycle. Table 49-2 presents PPPs for some of the most important equine helminth parasites. It should be noted that although the PPPs for cyathostomin parasites are generally relatively short, they can undergo arrested development for up to several years, which thereby dramatically lengthens the PPP. [9]

Information about PPPs can be taken into account for identifying optimal times for routine collection of fecal samples and anthelmintic intervention.

Parasite Distributions

Regardless of parasite and host species, distributions of parasites among their hosts always seem to follow the same pattern. Hosts of similar age and breed and kept under identical management grazing the same pasture can have widely different parasite burdens. Parasites never follow a symmetric normal distribution but are rather said to be overdispersed.[10] Technically speaking, this means that the variance is larger than the mean, but in practical terms this has been translated to the so-called 20/80 rule.[11] This refers to the observation that about 20% of the host animals harbor approximately 80% of the parasites. Similarly, about 20% of horses are shedding 80% of the total strongyle egg output. This phenomenon is most pronounced in adult horses, where a large majority is shedding low numbers of strongyle eggs and

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very few individuals can be observed with very high counts. This pattern has been found to be consistent in individual horses over time, and the tendency is particularly strong among horses with 0 or low strongyle egg counts.[12-14] Taken together, these observations have become the foundation for the selective therapy principle covered later in this chapter.

Parasite Refugia

The term "parasite refugia" has become generally accepted as perhaps the most important factor affecting the rate of development of anthelmintic resistance in large animal parasites.[15] Parasites in refugia are the parts of any given parasite population (including all stages, both internal and external) that are not exposed to the anthelmintic drug at the time of treatment. It can be said that these parasite stages in a way "escaped" the drug and can be viewed as refugees, hence the terminology. Logically, all stages on pasture, such as eggs and preinfective larvae, are always in refugia. In addition, animals left untreated can be viewed as contributing to the refugia, and some parasitologists therefore distinguish between "pasture refugia" and "animal refugia." Finally, some anthelmintic formulations have no efficacy against some parasite stages within the horse, and these can be regarded as part of the refugia as well. Examples of this include pyrantel formulations, which have no efficacy against parasite stages present outside the gastrointestinal lumen, and ivermectin, which has no documented efficacy against encysted cyathostomin larvae.

The parasites in refugia are hypothesized to play a role in diluting out resistant parasites whenever the animals are dewormed. A simplistic explanation of this concept is the larger the refugia, the more the dilution of resistant parasites, and the slower the development of resistance. In a theoretic example, consider a horse herd that is dewormed with a drug that has efficacy against all parasitic stages of the parasites, and the treatments are carried out at a time of the year when no eggs or larvae are present on pasture. This would represent a scenario with no parasite refugia. Because no anthelmintic treatment is 100% efficacious, there will always be a few parasites surviving and passing their genes on to the next generation. In a situation with low or even no refugia, all eggs being passed in the feces after deworming will be progeny of resistant parasites mating in the intestinal tract. However, if some of the horses in the herd were left untreated and/or treatments were carried out under circumstances with eggs and larvae present on pasture, then the few resistant worms surviving treatment would be diluted out by the many nonresistant worms, eggs, and larvae, and the progression of resistance in the parasite population would be much slower.

The role of parasite refugia in the development of anthelmintic resistance was initially shown in a sheep study,[16] and recent work with a combination of computer simulations and field studies with ruminants has provided solid evidence behind the concept.[17-19] There have been no such studies performed in horses, so this understanding of parasite refugia is mainly extrapolated from the work performed with ruminants.

Important Parasites Infecting Horses

Over the past five decades the emphasis has shifted several times in terms of which parasites are considered the major targets of the control programs. When the first modern paste dewormers were introduced in the 1960s, the large strongyle *Strongylus vulgaris* was considered the most important threat to equine health and was therefore identified as the main target for the interval dose program.[5] As time went on and new anthelmintic drug classes were introduced, this parasite went from being virtually present in all horses to becoming rare.[20-21] At the same time, cyathostomins were recognized as major pathogens and were identified as the primary target of parasite control programs.[22] More recently, the tapeworm *Anoplocephala perfoliata* has been associated with an increased risk of specific colic types.[23] In addition, *Parascaris equorum* is identified as the major parasitic pathogen in foals.[24-25] These are the four major parasite pathogens, but others can play a role as well. Less important but widely occurring parasites include *Strongyloides westeri, Oxyuris equi,* and the bot larvae of *Gastrophilus* spp. Finally, the insect-borne nematodes *Thelazia* spp., *Habronema* spp., *Draschia* spp., and *Setaria* spp. can occur at significant levels in certain habitats and are included in this chapter.

Parascaris equorum

The equine roundworm has gained status as perhaps the most significant parasitic threat to equine health in managed horse populations. The major reason for this shift of emphasis is the high levels of ivermectin and moxidectin resistance observed worldwide (see Table 49-1). *P. equorum* is the primary parasite in foals until about the time of weaning. At the age of approximately 6 to 12 months, most horses clear infection with this parasite and the strongyles become the predominating parasite group instead. Equine ascarids are ubiquitous in foaling operations, although prevalence differences can be observed between individual farms.[26-27] Patent infection is not uncommon in adult horses, particularly broodmares that are highly exposed to infection.

The life cycle is classic ascarid. Eggs are perceived to be highly resilient to environmental influences and can allegedly survive in the environment for several years. Work with eggs of the pig roundworm *Ascaris suum* has substantiated this, but little work has been done with *P. equorum* eggs. The infective stage is the embryonated egg, which hatches in the stomach and small intestine of the horse. Larvae then penetrate the mucosal lining and migrate the classical hepatotracheal route. Passing through the lungs has been associated with airway symptoms in young foals,[28] but the major pathogenic role is played in the small intestine. Here, the parasites compete with their hosts for nutrients, which can result in ill-thrift, weight loss, rough hair coat, and pot-bellied appearance.[25,28] The major clinical impact is associated with verminous small intestinal impactions.[24] As with any type of small intestinal impaction, the prognosis for full recovery is guarded and surgery is often required to relieve the condition. In severe cases, the small intestinal walls will rupture and foals will have to be euthanized. Rather ironically, anthelmintic treatment has been shown to be a significant risk factor for this condition.[24] The instant paralysis elicited by most dewormers can cause the worms to aggregate in the lower parts of the jejunum and ileum. Benzimidazole-type drugs are not acting through paralysis of the worms and appear to be less associated with this condition. Given the fact that these drugs have maintained efficacy against roundworms, they appear to be a good first choice for this parasite in most instances.

Cyathostomins

Historically, this group is also referred to as *small strongyles*. It consists of 50 different species belonging to 14 different genera.[29] However, some of these species and genera have been described infecting other equids than horses, such as donkeys and zebras. Horses are always infected by multiple species, and currently there is limited knowledge about the pathogenic role of individual cyathostomin species. Cyathostomins are truly ubiquitous, and all grazing horses are exposed to infection.

The cyathostomins all follow the same basic strongyle life cycle. Strongyle eggs are passed in the feces, where they will hatch, and larvae will develop through the first (L_1) and second (L_2) stage until they finally reach the third infective stage (L_3). Hatching and subsequent larval development is highly temperature dependent. At temperatures below 6° C, eggs do not hatch but remain viable. Hatching and larval development occur at increasing rates up to about 40° C. At temperatures above this level, eggs and larvae quickly die out. Optimal conditions for development of eggs and larvae are in the temperature range of 25-33° C, where the L_3 is reached within 3 to 4 days. In comparison, this will take several weeks at around 10° C. When molting from L_2 to L_3, the larvae retain their L_2 cuticle on the outside of the new sheath. This makes the L_3 particularly resistant to environmental influences such as desiccation and freezing. Thus, for this stage, the widespread notion of the "killing frost" is a myth. In addition, intact fecal balls provide excellent protection for larvae,

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enabling them to further withstand desiccation and freezing temperatures well.[30] Due to the double-layered cuticle, the L_3 cannot uptake feed and thus lives on carbohydrates and lipids stored in its cells. The more active these larvae are, the shorter they live. Because larval activity is highly temperature dependent, it can be deduced that the higher the temperature, the shorter the survival. Dry conditions as achieved with freezing or desiccation limit larval movement and therefore facilitate their survival. However, repeated cycles of alternation between frost and thaw have a deleterious effect on most free-living stages of strongyles, although this can be mitigated by snow cover, which tends to stabilize temperatures right at the freezing point, which is optimal for survival of eggs and L_3s.[30]

Inside the horse, the L_3s exsheath in the stomach and subsequently reach the colon and cecum. Here, they enter the glands of Lieberkühn and penetrate cells at the base. From here, some species appear to penetrate deeper into the submucosa, while others remain in the mucosa. A fibrous capsule is formed around each larva, and a fluid-filled cyst is formed. Larvae can remain encysted for several years,[9] but encystment appears to be a strategy for the parasites to make it through the winter, where conditions on pasture are unfavorable for parasite transmission. Interestingly, in warmer climates, encystment appears to occur over the hot summers. Horses can harbor several hundred thousand encysted cyathostomin larvae without showing any sign of discomfort. The major clinical consequences are associated with the process of excystment, where the L_4 penetrate their cysts and migrate the short distance back to the intestinal lumen. This causes a small local inflammatory reaction around the vacated cyst. In rare cases, synchronous emergence of large numbers of larvae from their cysts can cause a severe generalized acute typhlocolitis, termed *larval cyathostominosis.*[22] This is characterized by profuse watery diarrhea and pronounced dehydration, as well as protein loss and ventral edema. This acute condition is associated with a case fatality rate of 50%.[22] Identified risk factors for larval cyathostominosis include horses aged 1 to 4 years, anthelmintic treatment within 14 days prior, and late fall, winter, or early spring in temperate climates.[31] The luminal worm burden appears to elicit some sort of a repressive signal, which prevents the encysted stages from resuming development. If the luminal burden is removed by anthelmintic treatment, the repressive signal disappears abruptly and a synchronous emergence is triggered. Treatment of acute larval cyathostominosis involves intensive fluid therapy, which can be combined with antiinflammatory drugs and antibiotics. The anthelmintic drug of choice is a single dose of moxidectin (400 µg/kg orally [PO]) because of its efficacy against encysted larvae. The 5-day elevated dose of fenbendazole (10 mg/kg PO) is also labeled for treatment of encysted cyathostomins, but the wide occurrence of fenbendazole resistance in cyathostomins makes that regimen unlikely to have maintained full efficacy once resistance has been documented to the single dose.[4,32]

Chronic cases of larval cyathostominosis also occur. These are typically characterized by weight loss and loose feces or intermittent diarrhea, often over an extended period of time. Plasma protein and albumin levels can be lowered, and ventral abdominal edema can be observed. Horses usually recover, although it may take time for them to regain full body condition.

Tapeworms

Three species of tapeworm infect horses: *Anoplocephala perfoliata, Anoplocephala magna,* and *Anoplocephaloides* (s. *Paranoplocephala*) *mamillana.* Of these, *A. perfoliata* is by far the most common, and it is the only species that has been associated with clinical disease. Being a cestode, the life cycle involves intermediate hosts, which are oribatid mites that feed on the organic material present in the feces. During this process, the mites can ingest tapeworm eggs present in the feces. Inside the mite, eggs develop to infective cysticercoids over a period of approximately 2 to 4 months. Horses inadvertently ingest these mites during grazing. In the gastrointestinal tract, the cysticercoids are liberated from the mites and the scolexes attach to the mucosal lining around the ileocecal valve in the cecum.

Prevalences of *A. perfoliata* have been reported to vary widely between farms and regions, often ranging from 20% to 80% of horses.[33] Prevalence appears to be habitat dependent, and it is likely associated with conditions favoring survival of the oribatid mites. However, the most significant factor appears to be access to pasture. The longer the time spent on pasture, the higher the tapeworm exposure seems to become.[34] Horses younger than 2 and older than 15 years of age have been reported to have significantly larger *Anoplocephala* burdens than horses in between these ages.[35] Although this could be explained by the assumed incomplete levels of immunity in these age groups, it is equally likely that they simply spend more time on pasture. Tapeworm burdens appear to accumulate through the grazing season to reach their highest in the fall and winter.[36-41]

Tapeworm infection has been associated with certain types of colic in the horse. Numerous case studies have illustrated an association of *A. perfoliata* and ileocecal intussusceptions, which are sometimes complicated by intestinal rupture.[42-43] One epidemiologic study identified *A. perfoliata* as significantly associated with ileal impactions and spasmodic colic.[23] A Canadian study attempted to reproduce these findings but was unable to find any associations between tapeworms and colic.[34] Taken together, these studies indicate that tapeworms may play a role in the development of colic, but this is largely confounded by the multifactorial nature of colics and regional differences in climate and management.

Two anthelmintics are labeled for treatment of equine tapeworms: praziquantel and pyrantel pamoate. Praziquantel is a sole tapeworm drug that has no efficacy against nematodes. For this reason, it is most often formulated in combination with ivermectin or moxidectin, although it exists in a stand-alone formulation for horses in Europe.[36] Pyrantel, on the other hand, is widely acting against luminal stages of nematodes and cestodes. At the dosage labeled for nematode treatment (6.6 mg/kg PO), the efficacy of pyrantel pamoate is greater than 80% against *A. perfoliata*.[44] A double dosage of pyrantel pamoate (13.2 mg/kg) is labeled for tapeworm treatment, and the efficacy of this has been found to be greater than 95%.[45]

Strongylins (Large Strongyles)

The strongylin group comprises the three *Strongylus* species: *S. vulgaris, S. edentatus,* and *S. equinus,* as well as *Triodontophorus* spp., *Craterostomum acuticaudatum,* and *Oesophagodontus robustus.* As mentioned earlier in this chapter, large strongyles have generally become rare in managed equine establishments. The most common of these species is probably *Triodontophorus* spp., but the *Strongylus* species, particularly *S. vulgaris,* are considered the most pathogenic of helminths infecting the horse.

The development of the external stages of the strongylins is virtually identical to what has already been described for the cyathostomins. Inside the horse, larval migrations are widely different. The three *Strongylus* species all have PPPs of 6 months and above, and they spend several months migrating in various tissues and organs of the horse. Major pathologic lesions have been ascribed to these migrations, whereas the adult worms are found to do little harm to their hosts. The lesions caused by migrating stages of *S. vulgaris* are classic in equine parasitology and well described.[46-49] Third-stage larvae (L_3) invade the mucosa of the small intestine, cecum, and colon. They then molt to L_4 before they enter local arterioles. Inside these, they migrate beneath the endothelium toward the root of the cranial mesenteric artery, leaving characteristic fibrous tracts to be seen on the intimal surface. Upon reaching their destination about 14 days post infection, they enter the lumen of the vessel and remain there, embedded in thrombus masses. Here, they grow in size and molt to L_5, while causing a pronounced verminous endarteritis with roughened intima, fibrosis of arterial walls, and increased diameter of the vessels. After about 4 months, the L_5s are transported by the bloodstream to the walls of the ventral colon and cecum, where pus-filled nodules are formed around them in the submucosa. These nodules eventually open into the intestinal lumen, and the young adult worms emerge. After another 6 weeks, the worms become sexually mature and start shedding eggs. Although the lesions are

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pronounced, they are relatively rarely accompanied by disease. A classical syndrome of thromboembolic colic, in which thrombi detach from the arteritis lesions and are carried distally until they reach a terminal branch sufficiently small to become occluded, has been described.[46] This causes ischemia and infarction of intestinal segments, which is painful to the horse.

Larvae of *S. edentatus* migrate via the portal system to the liver, where they molt to the fourth stage within the parenchyma. They migrate within the liver and then migrate subperitoneally and retroperitoneally via the hepatorenal ligament to the adipose tissue in the abdominal walls. Larvae can also be found located in the perirenal fat tissue. Here, larvae eventually molt to L_5 and migrate back to the intestinal walls. Described lesions include a filamentous peritonitis, especially around the liver and diaphragm, as well as hemorrhagic and inflammatory lesions in the abdominal wall.[50] The third *Strongylus* species, *S. equinus,* is probably the rarest, at least in managed horses in the northern hemisphere, where it is hardly encountered at all. As opposed to *S. edentatus,* it migrates within the peritoneal cavity and passes through the pancreas, where it can cause significant damage.[51] Despite their obvious pathologic impact, neither *S. edentatus* nor *S. equinus* have been associated with defined clinical syndromes.

None of the strongylins has been reported resistant to any of the anthelmintic drug formulations available. Treatment efficacies against *S. edentatus* appear to be more variable than in the other species,[52] but this seems to always have been the case and can thus not be concluded to be resistance.

Other Parasites

Other parasites frequently infect equines but are generally considered of lower importance. For completion, they are briefly covered in the following.

Strongyloides westeri, or the equine threadworm, parasitizes the small intestine of suckling foals. This parasite is remarkable because it can maintain a full life cycle outside its host, and only female worms seem to infect the foals. Infection occurs via three possible routes: skin penetration by third-stage larvae, ingestion of these larvae from the environment, or lactogenic transmission from the mare.[53] Infection usually occurs within the first weeks of life, and infected foals are usually asymptomatic. However, one study reported an association between diarrhea and high *Strongyloides* egg counts (>2000 EPG),[54] and another study described a "frenzy" syndrome in foals exposed to apparent percutaneous penetration of L_3 from the environment.[55] Because of *S. westeri,* it has become a widely used practice to deworm mares at or just before foaling. As a result, the prevalence of this parasite has been reduced to low levels in managed horse populations.[56]

Oxyuris equi, the equine pinworm, is widely prevalent, but eggs are rarely encountered in fecal samples because they are laid outside the digestive tract. Adult worms live in the descending colon and rectum. The female worm protrudes from the anus and deposits her eggs in patches on the perianal skin. When these egg patches dry up, they become itchy to the horse, and they begin rubbing their tails against various objects. This serves as an excellent means to spread eggs in the environment. The infective stage is the embryonated egg, which is inadvertently ingested from the contaminated environment. Besides the tail rubbing, *O. equi* does not cause disease or discomfort to the horse, and there is no justification for routinely targeting this parasite in the parasite control program. Recent observations made by veterinary practitioners have led to speculations whether populations of *O. equi* have developed resistance to ivermectin,[57] but this has not been verified in research studies.

Gasterophilus spp. are the widely occurring botflies, whose larval stages overwinter in the intestinal tract and then pass in the feces during the spring. They then pupate in the loose soil for a couple of months until the adult flies emerge. The two most common species are *G. intestinalis* and *G. nasalis*. Eggs are glued onto the haircoat, and larvae make their way into the oral cavity by either crawling on the skin *(G. nasalis)* or when the horse grooms itself or another herd member *(G. intestinalis)*. In the mouth, the larvae spend several weeks burrowing into the tongue and subsequently spending time in the interdental spaces before reaching the stomach.[58] In the stomach, *G. intestinalis* attaches to the mucosal lining by the margo plicatus, whereas *G. nasalis* can be found in the gastric fundus and the duodenum. Characteristic lesions have been described at the attachment site,[59] but these have not been consistently associated with disease. With the emergence of equine dentistry over the past decades, the lesions in the oral cavity are gaining more attention. It remains possible that *Gasterophilus* spp. can cause oral discomfort, but this has not been substantiated in research studies.

The equine eye worm, *Thelazia lacrymalis,* is transmitted by muscid flies and can be found within the conjunctival sac of horses, where it generally appears to do little or no harm to the eye. However, abscess formation and inflammation of the lacrimal glands have been described.[60] Prevalence rates have been reported in the range of 20% to 42% in managed horses.[61-62]

The group of stomach worms comprises *Habronema* spp., *Draschia* spp., and *Trichostrongylus axei. Habronema* and *Draschia* spp. have similar life cycles. Like *Thelazia* spp., they are both transmitted by muscid flies. The flies acquire the infective larvae while feeding on the feces. Horses get infected by accidentally ingesting infected flies. Here, the larvae eventually reach the stomach, where *Habronema* larvae apparently cause no gross lesions, while adult specimens of *Draschia* spp. can be found embedded in large tumor-like fibrous masses around the margo plicatus.[63] Common to both these species is that the larvae can be deposited by the flies in or near wounds or mucocutaneous junctions. For the parasite, this represents a dead-end pathway, from which the life cycle cannot be completed.[64-65] When larvae are deposited in this manner, they cause a condition usually referred to as *cutaneous habronemiasis/draschiasis* or *summer sores.* This is characterized by persistent, eosinophilic granulomatous lesions with eosinophilia and fibrosis. A rare, pulmonary form of habronemiasis has been described as well.[66] Anthelmintic resistance has not yet been reported in *Habronema* or *Draschia* spp., but several veterinary practitioners from subtropical and tropical regions report that skin lesions consistent with cutaneous habronemiasis do not resolve on treatment with a macrocyclic lactone (ivermectin or moxidectin). The prevalence of *Draschia* spp., on the other hand, seems to have decreased dramatically after the introduction of ivermectin.[67] *Trichostrongylus axei* possesses the rare capacity of infecting both ruminants and monogastrics such as pigs and horses. The external part of the life cycle is similar to that of the strongyle parasites described in this chapter. Inside the horse, it develops within the gastric glands, where it can cause hypertrophy of the mucosa.[68] In horses, *T. axei* has not been found to affect pH or levels of plasma pepsinogen.[69] The parasite is a rare finding in horses, but prevalence has been found to increase when horses are co-grazed with sheep.[70-71]

Setaria and *Onchocerca* spp. are filarial nematodes infecting horses. Infective L_3 larvae are transmitted by blood-sucking arthropods feeding on the horses. The larvae then migrate to their predilection site, which is the connective tissues (*Onchocerca* spp.), and the abdominal cavity *(Setaria equina)*. Here, they develop into adult worms, which then release microfilariae into the bloodstream. These microfilariae, in turn, will enter the blood-feeding arthropods, and the cycle is complete. The intermediate hosts for *Onchocerca* spp. are biting midges (*Culicoides* spp.) and black flies (*Simulium* spp.), whereas it is mosquitoes for *Setaria equina*. The latter parasite is regarded as nonpathogenic, while *Onchocerca* spp. has been associated with pronounced skin reactions. Microfilariae of *Onchocerca cervicalis* tend to congregate in certain regions of the body, including the ventral midline and face, where they are ingested when *Culicoides* feed in these regions.[72] This results in a verminous dermatitis characterized by intense pruritus.[73] Lesions can be effectively treated with macrocyclic lactones.[74] However, there is no known therapy to eliminate adult *O. cervicalis* from the connective tissue around the ligamentum nuchae of horses. Therefore, infected horses will need periodic retreatment with ivermectin or moxidectin to prevent or

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control recurrence of clinical signs.[75-77] Treatment of the skin-dwelling microfilariae has been associated with an inflammatory reaction to the dying parasites,[78] which can be confused with the widely occurring *Culicoides* hypersensitivity (summer eczema, sweet itch).

Adult *Parafilaria multipapillosa* is another filarial nematode that occurs in subcutaneous and intermuscular connective tissue of horses outside North America. Nodules form in the overlying skin and may rupture and bleed or leak tissue fluids. This condition is often referred to as "summer bleeding,"[79] not to be confused by the "summer sores" described with cutaneous habronemiasis/draschiasis. First-stage larvae are present in the exudate from bleeding lesions and are ingested by feeding horn flies *(Haematobia irritans)*. Larvae develop to the infective third stage within the fly and are transferred to horses when flies feed on lachrymal secretions or skin wounds. The larvae then migrate in the subcutaneous tissues and develop to the adult stage within a year. Eggs and microfilariae can readily be identified in smears taken from lesion exudates.[80] Little is known about anthelmintic efficacy, but lesions have been observed to recur after treatment with macrocyclic lactones.

The equine lungworm, *Dictyocaulus arnfieldi,* will be covered in the lungworm section in this chapter.

Halicephalobus gingivalis is a free-living nematode belonging to the order Rhabditida. It is widely present in the soil and humus but possesses a capacity to also invade living tissues. Infection appears to occur through soil-contaminated wounds or nasal mucosal membranes with apparent predilection in the head region,[81-84] but penile infection has also been described.[85] Inside the host, the nematode reproduces tremendously and the larvae invade deeper into the tissues. Larvae appear to have a special affinity for the central nervous system (CNS) and the kidneys.[83] Lesions are multifocal, eosinophilic, and pyogranulomatous. Once the CNS is affected, symptoms often slowly progress into a grave state. Symptoms include blindness, ataxia, loss of proprioception, head pressing, coma, recumbency, and death.[83,86-87] Treatment options are limited. Surgical debulking can be combined with repeated high oral doses of fenbendazole (50 mg/kg) or ivermectin 0.55 mg/kg),[88] but the overwhelming majority of published cases had a fatal outcome. Similarly, *Halicephalobus* spp. infection has been reported to be extremely rare but fatal in humans.[89-91]

Diagnostics

The cornerstone of diagnostics in equine parasitology remains the fecal egg counting methods. Before these are discussed, it should be emphasized that egg counts can be performed for at least three purposes: (1) evaluation of anthelmintic efficacy with the fecal egg count reduction test (see Box 49-1); (2) identification of low, medium, and high strongyle egg shedders for a targeted treatment approach; (3) for diagnosing parasite infection in clinical cases. When discussing the usefulness of fecal egg counts, it is important that this largely depends on the purpose. In other words, fecal egg counts are not equally useful for all three purposes.

Numerous techniques exist with various names such as Stoll,[92] Wisconsin,[93] or McMaster,[94] but they are all based on the same simple principle. A flotation medium is usually constructed with some sugar or chemical salt solution to have a specific density higher than most parasite eggs but lower than the fecal matter. Examples of components used in flotation media include glucose, sucrose, $NaNO_3$, NaCl, $MgSO_4$, and HgCl. Frequently used media are saturated glucose-NaCl and Sheather's sugar solution, which are relatively cheap and easy to compose. The numerous different egg counting techniques and the even more modifications of these can appear confusing, but in reality there are only three factors to consider when the choice of method must be made: (1) the detection limit of the technique; (2) the level of variability associated with the technique; and (3) the equipment requirements and time consumption in the laboratory.

The choice of detection limit will depend on the purpose with the egg count. If FECRTs are performed, it is crucial to be able to detect low egg counts in the posttreatment samples to possibly discover early signs of reduced anthelmintic efficacy. A crude McMaster, which is performed by many practice laboratories, usually comes with a detection limit of 25 or 50 EPG, which makes it unsuitable for the FECRT unless the pretreatment levels are high. However, the egg counting methods with lower detection limits are generally more laborious and often include a centrifugation step, so the choice of egg counting technique is always a tradeoff between detection limit and ease of use. For identification of high strongyle shedders for a targeted treatment approach, the detection limit is not important and McMaster methods can be used.

Egg counting methods are generally associated with high levels of variability, and it has once been estimated that every egg count generated by the McMaster technique should be interpreted with a ±50% margin of error.[95] In other words, an egg count of 400 eggs per gram (EPG) really represents the range of 200 to 600. This variability is important when interpreting the FECRT; if only one egg count is performed before and after treatment, each of these will represent one data point out of a distribution. With the chance variability both before and possibly also after treatment, there is room for high levels of variability in the FECRT. This is the reason why the FECRT always has to be performed by averaging values across several horses on each farm. Performing two or three repeated egg counts and averaging these greatly reduces this variability.

The most thorough work with validating various flotation media for detection of a large array of parasite eggs has been performed with the FLOTAC egg counting technique, which is an advanced modification of the McMaster technique.[96] By using large flotation chambers, the FLOTAC can be adjusted to perform with a detection limit of 1 EPG. Although this can also be achieved by a more traditional technique such as the Wisconsin, the FLOTAC has been shown to have much less variability.[96]

Until recently, there were no published studies evaluating egg counts as a diagnostic test for horses. From the database generated over 50 years of equine parasitology research at University of Kentucky, fecal egg counts were related to total intestinal worm counts in close to 700 horses.[97] Results indicated a high positive predictive value, indicating that an egg count–positive horse is likely to also harbor worms in the intestine. However, the negative predictive value was low, emphasizing that 0 EPG does not necessarily indicate 0 worms. Further, there were no direct linear correlations between strongyle and ascarid egg counts and the corresponding intestinal worm burdens. Thus, higher egg counts do not necessarily equal larger worm burdens. However, strongyle egg counts in the range of 100 to 500 EPG did correspond to significantly smaller strongyle burdens than egg counts above this level.[97] Taken together, this information illustrates that fecal egg counts can be used to qualitatively detect presence of strongyle or ascarid burdens, but there are considerable limitations to these techniques as clinical diagnostic tools. Further, it should be borne in mind that much of the parasitic disease observed in horses is caused by migrating or encysted larvae that are not shedding any eggs. Detecting eggs in the feces cannot be used to estimate the probable presence of larval burdens. Also, strongyle eggs are practically ubiquitous in equine fecal samples, and their mere presence cannot be used to suggest parasitic disease. In foals and weanlings, egg counts can be useful for determining whether parasite burdens are dominated by strongyles or ascarids, which is crucial information for selecting the right anthelmintic (see Table 49-1).

Another weakness of strongyle fecal egg counts is that up to 50 strongyle species infecting horses have been described,[29] and it is not possible to morphologically distinguish between their eggs. Larval cultures can be performed to differentiate large and small strongyles and for species-specific detection of the three *Strongylus* species.[98-99] In a retrospective validation, larval cultures were found to have high positive and moderate negative predictive values with no direct linear correlation between larval counts and worm counts.[97] Thus, larval cultures should be interpreted with the same caution as egg counts. A pragmatic approach has been to pool feces from several horses into one pool, but this cannot be recommended because diagnostic

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sensitivity is greatly lost with this approach and the negative predictive values are likely to be much lower.

Diagnosing tapeworm infection is a particular challenge despite the availability of several different techniques. Anoplocephalid eggs may show up on routine egg counts from time to time, but validation studies have shown that diagnostic sensitivities are low. The reason for this is believed to be the uneven distribution of tapeworm eggs in the feces. Eggs are released in clumps often retained within a tapeworm segment, which then disintegrates on its way through the cecum and colon. The eggs remain in their clumps, and egg counting methods examining just a few grams of feces can easily miss detecting these eggs. A modified egg counting technique that analyzes 40 g of feces has been found to have a diagnostic sensitivity and specificity of 0.61 and 0.98, respectively.[100] However, this was based on detection of cestode burdens comprising only a single worm. If the threshold were adjusted to detect 20 or more tapeworms, the sensitivity improved to about 90%.[100-101] Thus, the tapeworm infections most likely to not being detected with this method are small burdens unlikely to cause clinical disease. The group led by Proudman developed a serologic (ELISA) assay for detection of specific antibodies against *A. perfoliata*.[102] This assay has been found useful for evaluating the level of tapeworm exposure on the herd level. OD values correlate positively with the worm burden, and the assay can be helpful for generating information to help balance the level of tapeworm-directed treatments on each farm. It should be emphasized that this assay is not useful for diagnosis on the individual level. Antibody levels are too variable, horses remain titer positive for months after tapeworm treatment,[103] and one recent study suggests cross-reactivity with the less common *A. magna*.[104] In the United States, the diagnostic laboratory at the University of Tennessee, College of Veterinary Medicine offers a modified version of the *Anoplocephala* ELISA, but no information is available on the performance of this test. There are currently no available methods for diagnosis of anthelmintic resistance in equine tapeworms.

Integrated Parasite Control

It is often said that a "one-size-fits-all" parasite control program does not exist. There is no simple chart to just hang on the wall in the horse barn and then have all horses follow the same guidelines. To the frustration of many horse owners, farm managers, and veterinary practitioners, it is much less straightforward to identify what to do. This section outlines elements to incorporate in a modern evidence-based equine parasite control program.

The most important evidence to incorporate on each farm is the efficacy of the anthelmintic drugs that are used. Although Table 49-1 can be used to predict the drugs more likely to still have efficacy on a particular farm, the only way to really know is to evaluate the efficacy with the FECRT as described in Box 49-1. Ideally, all drugs used should be tested on every farm each year. Regardless of the deworming program incorporated, it is highly necessary to know the efficacy of the drugs used. Veterinary practitioners giving recommendations regarding the choice of anthelmintic should realize that these cannot be given without knowing the efficacy on the given farm. For ivermectin and moxidectin, the efficacies measured on day 14 post treatment should still be 100% in the large majority of instances, but the ERP may be shortened considerably on some farms. Thus, it may be a pragmatic solution to perform the posttreatment egg counts in week 4 or 5 to evaluate whether there is evidence of a shortened ERP. A shorter ERP should not necessarily discourage people from using the drug because there may not be valid alternatives, but it provides useful information about the level of parasite control achieved by using these drugs.

Egg counts can also be employed for two other purposes. In foals, they can readily tell whether parasite burdens are predominantly *P. equorum* or strongyles. This is crucial information because the drugs that are likely to work against *P. equorum* would not have efficacy against strongyles on many farms, and vice versa. In adult horses, a few repeated egg counts over time can be used to identify horses that are consistently shedding low, moderate, and high egg numbers.[11,105,106] This can then be used in a targeted selective approach, where the consistent high shedders can receive more anthelmintic treatment, and horses consistently shedding low numbers can receive less treatment. Simulations have shown that treating all horses shedding 200 strongyle EPG or above with a drug with a 99.9% efficacy yields an overall reduction of the strongyle egg shedding of 94%.[11] But when using 200 EPG as a treatment threshold, only about 50% of adult horses will need treatment, so with just half as many treatments close to the same overall egg count reduction can be reached. This selective approach, which increases parasite refugia and slows down the development of anthelmintic resistance, is widely implemented in some countries.

Recent studies have illustrated that in a system basing all anthelmintic treatments on fecal egg counts, some horses will not be dewormed for years.[107] This gives room for the large strongyle species, particularly *S. vulgaris,* to reemerge, which has been documented in Denmark.[107-108] Here, about 80% of farms using selective therapy had at least one horse infected with *S. vulgaris,* which was twice as much as in farms not using selective therapy. Although none of the horses showed clinical signs of disease, the pathogenic potential of *S. vulgaris* does suggest that horse populations would benefit from a basic foundation of anthelmintic treatments applied to all horses. Given the long life cycles and no apparent development of resistance in large strongyle species, just one or two yearly treatments with ivermectin or moxidectin would effectively reduce the occurrence. Further treatments beyond this basic foundation should be directed at high strongyle shedders in a selective approach as described earlier.

Tapeworms need to be considered in every parasite control program. They should be assumed to be present under most circumstances, although large regional differences in prevalence can occur.[33] As indicated in the previous section, the serum ELISA could be useful for generating information about the level of tapeworm exposure in a given herd. If OD values are consistently high (i.e., many horses above the level of 1 to 2), or if confirmed clinical cases have occurred, a more aggressive treatment approach can be taken. But in most cases, annual treatments in the fall appear to be of greatest benefit to minimize burdens and prevent the development of gravid forms that will otherwise contaminate pastures in the coming season. With an ivermectin/praziquantel combination formulation, this could easily be incorporated into the basic treatment foundation described earlier.

It has been a widely used strategy to regularly rotate between anthelmintic drugs when deworming horses. The theoretic basis for this strategy makes good intuitive sense; parasites carrying genes that enable them to survive treatment with one drug can be killed by applying another drug with a different mode of action. Unfortunately, there is no evidence to support this hypothesis. In fact, one equine study clearly suggested that rotating drugs with each treatment did not appear to slow development of resistance.[109] Computer modeling studies with ruminant parasitology data have convincingly shown that rotating drugs does not prevent accumulation of resistant genetic alleles and therefore does not slow down the development of resistance.[110-111] Besides, rotation would only make sense if there were several anthelmintic drugs available to which no resistance had already developed. When considering the information presented in Table 49-1, it is clear that there are only three drug classes to choose from. Thus, it will be difficult to find many horse farms without resistance already developed to one or maybe even two of them. Further, when rotation is carried out blindly without testing the efficacy of all the drugs used, the alternation between drugs may very well mask resistance, so it takes longer for it to be discovered. In summary, drug rotation does not appear to prevent or reduce the development of resistance and may create a false sense of security for the horse owner, who believes a solid strategy is in place.

Foals and young horses require specific consideration with regard to parasite control because they are the most susceptible to infection, often shed the highest egg numbers, and are more at risk for parasitic disease than their older counterparts. As a rough guideline, most

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foals should require approximately four anthelmintic treatments during their first 15 months of life. Higher treatment intensity can be justified in cases of high infection pressure or documented clinical problems in the herd. Fewer than four treatments would be considered inadequate unless low parasite transmission levels or absence of *P. equorum* can be consistently documented.

The major helminth pathogen in foals younger than 6 months of age is *Parascaris equorum*. Treatments targeting this parasite should be timed around the age of 2.5 to 3 months, when the first worms will have reached the intestine and started shedding eggs. Considering the increased risk of impactions from paralytic anthelmintics, benzimidazoles may be the best choice at this time. If this treatment is delayed just a couple of months, the worms will have grown much larger and increased in numbers, posing an increased threat of verminous impaction. A second deworming treatment should be targeted around or preferably just before the time of weaning. This is a stressful period for the foal, and large parasite burdens are undesired at this time. At weaning, the main parasitic threat is still likely to be *P. equorum,* but strongyle parasites may start to play a role as well. Therefore, fecal egg counts yield useful information about the presence of ascarids and strongyles and help guide the veterinarian to select the right anthelmintic.

Benzimidazoles are unlikely to be effective against cyathostomins on many farms, so other drug classes should be considered. Similarly, ivermectin has lost efficacy against *P. equorum* across the world. Again, it is crucial to routinely evaluate the efficacy of the anthelmintics chosen with the FECRT. A third treatment should be considered for the yearlings during the subsequent spring. This should coincide with the fecal testing and treatments that are carried out for adult horses on many farms. In areas with defined grazing seasons, a fourth treatment should be considered about midway through the grazing season. Yearlings are considerably more susceptible to parasitic infection than older horses, and leaving them untreated for an entire grazing season of 5 to 6 months' duration puts them at risk of acquiring large parasite burdens.

Gastrointestinal Nematode Infections in Cattle

Lora Rickard Ballweber

Cattle are hosts to numerous species of gastrointestinal nematodes (GINs) that, together, cause parasitic gastroenteritis (PGE).[1-3] Within the strongyle-type nematodes, *Ostertagia ostertagi* and species of *Cooperia* have been the most prevalent parasites across the United States, followed by species of *Haemonchus, Trichostrongylus,* and *Oesophagostomum*. Other species within the genera *Nematodirus* and *Trichuris* complete the GIN population in the United States. The various nematodes do differ somewhat with respect to their site of infection and pathologic effects, but their general life cycle patterns are quite similar.

Life Cycle Adult female nematodes produce eggs that are passed out of the host with the feces. Under optimal conditions in the external environment, first-stage larvae (L_1) can develop and hatch from eggs within 24 hours. L_1 grow and develop to second-stage larvae (L_2), which in turn grow and develop into third-stage larvae (L_3). In general, the third stage is the infective larval stage. After ingestion, L_3 develop into fourth-stage larvae (L_4), which then develop into immature adults. Sexually mature adult nematodes develop within 2 to 4 weeks after ingestion of the L_3 unless arrested development occurs. The life cycle of *Nematodirus* is the same except that development to infective L_3 occurs within the egg before hatching. For *Trichuris,* development to the infective L_1 occurs within the egg, which does not hatch until ingested by the animal. Approximately 8 weeks are required before sexually mature *Trichuris* are present.[1,3]

Climate and management of pastures and animals are among the numerous factors that influence the level and extent of parasitism. Although temperature is considered to be the driving force behind larval development, larval development can proceed only in the presence of adequate moisture. Larvae of all stages can be killed by extremely low temperatures, desiccation, and/or exposure to direct sunlight. Larval development and transmission tend to occur in predictable seasonal patterns based in part on regional climatic differences.[1-4] In the southern United States, infective L_3 persist longest when conditions are cool and wet (October to May) but die off quickly during the summer after rain-induced liberation from the fecal pat.[5,6] Nematodes acquired by grazing cattle during the summer months come from eggs recently deposited on pasture. In the northern United States, infective L_3 may be on pasture year-round. Significant numbers of *Cooperia* and *Nematodirus* may be acquired for up to 12 months after deposition of eggs on pasture, with acquisition of fewer numbers for up to 24 months. Acquisition of low levels of *Ostertagia* can occur for at least 14 months after deposition of eggs. In subtropical climates, seasonality may be much less marked and pasture infectivity may follow the rainfall pattern. In arid climates, large numbers of larvae may be present on the pasture whenever local conditions permit lush grass growth.[2,7-9]

Not only can larvae survive on pasture, but some species can arrest development within the host. This usually occurs when adverse environmental conditions would decrease larval survival in the external environment. Best known for this phenomenon is *O. ostertagi.* In northern temperate climates, pasture larval populations peak in the summer and early fall, and L_4 tend to overwinter in the host, resuming development in the spring. In warmer climates with hot, dry summers, the highest numbers of infective larvae may be found in the late spring to early summer, and L_4 tend to oversummer in the host, resuming development in the fall.[2,10,11]

Pathophysiology Of all the cattle nematodes, *O. ostertagi* has long been considered to be the most pathogenic nematode in temperate regions. The pathophysiology of ostertagiasis centers on the development of larvae within the gastric glands of the abomasum. As the larvae develop within the lumen of the glands, hyperplasia and intense eosinophilic infiltration occur. Mucosal glandular cells lose their differentiation, and cell junctions are weakened. Albumin is lost into the lumen. Parietal cells cease to function, causing a decrease in HCl production. The change in pH stimulates overproduction of gastrin, which initiates cell proliferation and hyperplasia. Alkalinity also decreases the bacteriostatic activity of the abomasum. When the pH exceeds 5, the conversion of pepsinogen to pepsin is inhibited. As a result, pepsinogen is released into the blood through permeable cell junctions. Initially, cellular changes occur within the parasitized glands, but as the glands distend due to nematode growth, the changes encompass the surrounding, nonparasitized glands as well. Widespread hyperplasia creates the typical "Moroccan leather" appearance of the abomasum. In experimental models, *Ostertagia* infection in calves is also associated with elevated peripheral eosinophil counts and decreased lymphocyte counts.[3,4,12]

Populations at Risk Although infections with some GINs readily induce immune responses that limit future populations of nematodes within the gut, cattle remain susceptible to *O. ostertagi* for many months. Protective immunity is usually not evident without prolonged exposure and may not occur until the animals are 2 years of age or older.[4] Consequently, clinical type I ostertagiasis occurs primarily in young cattle (up to ≈18 months of age) during their first grazing season (primary exposure), with type II disease present in older animals (2 to 4 years of age). Adult cattle, after the second grazing season, rarely show signs of nematode infection or require anthelmintic treatment. Although mature cattle ingest infective larvae, fewer larvae establish infections, so parasite numbers and the magnitude of fecal egg shedding are generally decreased. Most preventive and treatment strategies therefore are directed at young grazing stock, primarily beef calves and dairy replacement heifers.

Clinical Manifestations In young animals, GINs may simply cause poor growth and ill thrift, or they may cause serious

clinical illness and even death. Inappetence, a common feature of PGE, contributes to reductions in weight gain, growth, and, possibly, onset of puberty.

The synchronous development and maturation of inhibited larval *O. ostertagi* can result in severe clinical disease, called *type II ostertagiasis*. Usually seen in cattle months after their first grazing season on contaminated pastures, it is characterized by intermittent profuse watery diarrhea accompanied by thirst, anorexia, ill thrift, and hypoproteinemia. Fever, anemia, and submandibular edema may also be present. Conversely, type I ostertagiasis results from the rapid acquisition of large numbers of larvae that complete development to the adult stage within the usual 3-week time frame. The primary physiologic change is appetite suppression. Although the underlying mechanism for the two types is the same, the seasonal occurrence of each type varies in accordance with the epidemiologic patterns of the area.[1,3]

For both types I and II ostertagiasis, reduced feed intake and diarrhea has a negative effect on animal weight; however, leakage of endogenous protein into the gastrointestinal tract has greater impact on the loss of production. The need to replace these proteins (e.g., albumin, immunoglobulins) occurs at the expense of muscle proteins and fat deposition.[3]

Compounding the effects of *O. ostertagi* are the other GINs. Larval and adult *Haemonchus* parasites are blood feeders, capable of producing anemia. *Trichostrongylus axei* produces local and systemic changes similar to those produced by *O. ostertagi,* resulting in similar clinical signs. *Cooperia* species can induce tissue changes resulting in fluid, electrolyte, and protein losses and reduced feed intake. Infection with *Oesophagostomum radiatum* produces structural and functional changes including anemia, hypoproteinemia, diarrhea, anorexia, and weight loss.[1,3,13,14]

Control of Gastrointestinal Nematodes

ANTHELMINTICS. Anthelmintics and their doses used in cattle are given in Table 49-3. Given the higher stocking rates today versus 20 years ago and the concomitant reduction in alternative control practices, maintaining acceptable levels of animal production in the face of GINs relies heavily on the use of these compounds.[15,16] Animals benefit from the removal of the parasites, as well as by preventing immediate reestablishment of infections by those compounds with persistent activity. Macrocyclic lactones and benzimidazoles are, currently, the most popular compounds in use. Levamisole and morantel tartrate are less commonly used, and availability in some areas is limited. Drug withdrawal times must always be considered and the manufacturers' recommendations followed.

Historically, anthelmintic resistance by GINs has been far less of a problem in cattle than in sheep or goats. Unfortunately, this situation has changed. Anthelmintic-resistant nematodes of cattle have been confirmed in the United States and elsewhere, with resistance reported in all classes of compounds currently available.[4,16-20] Species of *Cooperia,* which are the dose-limiting parasites for the macrocyclic lactones, are most commonly associated with these reports; however, resistant species of *Ostertagia, Haemonchus,* and *Trichostrongylus* have also been documented.[15-18] Regrettably, producer concerns regarding anthelmintic resistance remains secondary to the production benefits gained by their use.[21] And, even where anthelmintic resistance is identified as a problem for the beef cattle industry, preventive steps taken actually contribute to the selection for anthelmintic resistance alleles.[22] Such strict reliance on anthelmintics without regard for good pasture parasite management will lead to more rapid selection of nematodes with resistance alleles.

Producer concerns may also be influenced by the fact it is species of *Cooperia* that are most commonly associated with anthelmintic resistance, and these species are considered to be of minor pathogenic importance. Thus, resistance in *Cooperia* would be a less severe problem than resistance in the highly pathogenic *O. ostertagi.* Recently, though, negative production effects associated with *Cooperia punctata* have been demonstrated,[23] as has an increased pathogenicity in an isolate of macrocyclic lactone-resistant *Cooperia oncophora* compared with a susceptible wild-type isolate.[19]

TABLE 49-3

Efficacy of Various Anthelmintics against Gastrointestinal Nematodes in Ruminants

Drug	Dose (mg/kg)* Sheep†	Dose (mg/kg)* Cattle	Adults	Hypobiotic Larvae
Benzimidazoles				
Albendazole	5-7.5	10	+	+
Febantel	5	7.5-10	+	±
Fenbendazole	5	5-10	+	±
Mebendazole	15-20		+	±
Netobimin	7.5	7.5	+	+
Oxfendazole	5	7.5	+	+
Oxibendazole	15	15	+	±
Ricobendazole	5		+	–
Levamisole and Morantel				
Levamisole	5-7.55	5-7.5‡	+	–
Morantel	5-12.5	10	+	–
Pyrantel	25		+	–
Macrocyclic Lactones				
Ivermectin	0.2	0.2§	+	+
Doramectin	0.2	0.2§	+	+
Eprinomectin		0.5‖	+	+
Moxidectin	0.2	0.2§	+	+
Other Drugs				
Closantel	5-10		+¶	–
Nitroxynil	10		+¶	–

*All doses are for oral administration unless otherwise indicated.

†Goats must be given a higher dose for equal efficacy.

‡10 mg/kg for topical administration.

§0.2 mg/kg for oral, subcutaneous, or intramuscular administration; 0.5 mg/kg topically as a pour-on.

‖Available only for topical administration at 0.5 mg/kg; not recommended for sheep.

¶Effective against *Haemonchus contortus* only.

+, Highly effective; ±, moderately effective or effective according to some authors; –, ineffective.

Note: Administration of some of these products may constitute extralabel use in sheep and goats; follow manufacturers' guidelines for meat and milk withdrawal in cattle.

Simultaneous administration of anthelmintics with a similar spectrum of activity but different mechanisms of action and of resistance has been suggested as a means of prolonging the effective life of available compounds. Computer simulation models and field data in sheep (and others) indicate that use of combination anthelmintic products along with deliberately increasing prevalence of unselected genotypes (refugia) will slow the development of anthelmintic resistance. However, once efficacy of the constituent compounds becomes less than 70%, their value in slowing anthelmintic resistance is lost.[24,25] Although combination anthelmintic products are available elsewhere in the world, they are not currently allowed licensure in the United States. This rule may change in the future.

Treatment Intervals. The choice of drug and treatment interval should be formulated for an individual herd or farm, as part of an overall GIN control program. Factors to consider include the geographic location, time of year, and grazing management.[26] There are several options for preventing clinical disease and maximizing gains in first-season grazing calves using strategic anthelmintic treatments. It should be noted, however, that these recommendations reflect the practices currently in use and assume anthelmintic resistance is not an issue on the farm in question. Recommendations are based on the calendar in the northern hemisphere, and not all products are available in every country.

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- Prophylactic anthelmintic use. (1) Two or three treatments between turnout and midsummer to minimize the number of eggs deposited on pasture. For calves turned out in early May, two treatments 3 and 6 weeks later are used. For calves turned out in April, three treatments at 3-week intervals are recommended. If using parenteral or pour-on macrocyclic lactones, the interval is extended to 5 (ivermectin) or 8 (doramectin, eprinomectin, moxidectin) weeks due to the residual activity against ingested larvae.[3,20] (2) Use of an intraruminal bolus at turnout or weaning. These provide either the sustained release of anthelmintic drugs or pulse release of therapeutic doses of anthelmintic at 3-week intervals. This strategy may be most cost-effective on farms where pasture infectivity is high. However, evidence suggests that young cattle protected with these products are more susceptible to infection in their second year at grass.[3]
- "Dose-and-move" strategy. This strategy consists of treating calves with a single dose of anthelmintic, then moving them to a "safe" pasture (risk of infection is low) just before the anticipated peak in pasture infectivity (e.g., early to midsummer in temperate climates). This strategy minimizes the number of anthelmintic treatments during the grazing season. However, it is effective only on farms where such pastures are available. Furthermore, any residual nematodes left behind will likely possess resistant genes; therefore contamination of the "safe" pasture will be with resistant nematodes. This must be taken into account when planning for the future use of the pasture (see later). Also, sufficient numbers of overwintering L_3 *O. ostertagi* may be present in the spring in some years, resulting in heavy infections and clinical disease.
- Targeted strategic treatment. This strategy relies on the selective use of anthelmintics by targeting individual animals within a herd rather than whole-herd treatments. Promoted for sheep and horses, this strategy has not been embraced by the beef cattle industry. However, a recent investigation of dairy cows indicates that selective treatment strategies can compete economically with whole-herd treatment strategies.[27]

Integrating effective pasture management can reduce the number of anthelmintic treatments necessary[28]; however, there currently is no realistic alternative to the continued use of available compounds in intensive production systems. Therefore it is imperative that the efficacy of these compounds be maintained for as long as possible. Recommendations designed to promote this in beef cattle include the following: (1) do not treat second-year (unless not previously pastured) or adult cattle to maintain a population of unexposed nematodes (refugia) on the farm; (2) do not graze first-year calves on the same pasture each year (avoids exposure to larvae produced from resistant nematodes); and (3) do not use the same family of anthelmintic year after year in calves.[29]

Adult Cattle. In general, the cattle most at risk for clinical disease and production losses are beef calves and dairy replacement heifers in their first season at pasture.[2] Development of immunity should protect the animals during their subsequent grazing seasons. Treatment of adult beef cattle is generally unnecessary, unless immunity is inadequate or pasture infectivity is exceptionally high. Anthelmintic treatment may be warranted in first-calf heifers and newly acquired cows that may not have been pastured as heifers. In some situations it may be beneficial to treat beef cows after spring calving. Despite these recommendations, a recent survey showed that approximately 86% of U.S. beef cow/calf producers routinely treat their cows one or more times per year.[22] Benefits of treating adult dairy cattle depend on a variety of factors including grazing management options and levels of GINs.[27]

OTHER STRATEGIES. Alternate grazing of cattle and sheep is promoted as an effective control measure. Ideally, a 3-year rotation of cattle, sheep, and crops is used. Few GINs cross-infect cattle and sheep. Adding this to the infective L_3 lifespan on pasture of less than 1 year, this scheme could provide good control of bovine ostertagiasis. Annual rotation of beef cattle and sheep in marginal areas has been reported to provide adequate parasite control.[3] However, in areas where *Haemonchus* is prevalent or where *Haemonchus contortus* cycles in cattle,[15,17] co-grazing these two species may be dangerous.[3] Rotational grazing of calves with adult cattle has been shown to be an effective control practice.[2,3]

Vaccination for the control of *O. ostertagi* has been an ongoing area of research for many years with mixed results.[30,31] Given that it has taken more than 20 years for development of a commercially viable vaccine against *H. contortus,* which is only beginning testing for licensure, it is unlikely a viable *O. ostertagi* vaccine will come to market within the near future.

EVALUATION OF CONTROL PROGRAMS. Success of control programs is based on the producer's expectations. Because most control programs are based on anthelmintic use, the response to treatment is the criteria by which control programs are currently evaluated.[15,22] As long as animal production meets producer expectations, the control program is considered to be a success. Fecal egg counts are most useful as a tool to evaluate pasture contamination and assess treatment efficacy; however, most U.S. producers do not have this done. In fact, most cow/calf producers do not even involve a veterinarian in the diagnosis or treatment of PGE.[22]

Lack of expected response to anthelmintic treatment may be the first indication of program failure in the form of a resistance problem.[15,17] However, inappropriate administration or underdosing of the anthelmintic may also be responsible, and determining the root cause of the treatment failure is vital for future control efforts. Detection of anthelmintic resistance currently depends on the fecal egg count reduction test (FECRT). This test only detects clinical resistance or when less than an expected response to treatment occurs. This usually occurs only when the frequency of resistant alleles in the population reaches 25%.[32] The FECRT estimates anthelmintic efficacy by comparing pretreatment and posttreatment fecal egg counts. Fecal samples are collected immediately before or at the time of treatment and then 10 to 14 days later. Although guidelines for using FECRT in cattle were proposed in 1992, they lack detail, particularly in interpretation of data.[19,33] A recent comparison of FECRT with controlled efficacy studies showed FECRT results to be reliable for detecting ivermectin-resistant *C. oncophora* and *O. ostertagi* and moxidectin-resistant *O. ostertagi*. However, due to reduced fecundity of moxidectin-resistant female *C. oncophora,* FECRT results were equivocal, with day 7 results showing efficacy but day 14 results indicating resistance.[34] Thus, for cattle, waiting the full 14 days before collection of the second sample is vitally important.[1,4] Because cattle tend to have lower fecal egg counts than sheep, use of appropriate flotation techniques capable of handling low fecal egg counts is important.[35]

Clinical Management

DIAGNOSIS. Antemortem diagnosis of ostertagiasis in young animals is primarily based on clinical signs of inappetance, weight loss, and diarrhea at a time of the year that is consistent with the parasite's epidemiology.[3] In temperate areas, type I disease usually occurs in fall, with type II in the late spring. Grazing history is important because clinical disease can develop in older animals with no prior grazing. Affected farms usually also have a history of previous outbreaks. Plasma pepsinogen levels are useful in animals up to 2 years old; however, the test is less reliable in older cattle.[3]

The most reliable method for diagnosis of ostertagiasis or PGE is necropsy. The "Moroccan leather" abomasal lesion is pathognomonic for *Ostertagia*. For PGE, casual examination of the lumen of the gastrointestinal tract is unlikely to find any of the strongyle-type nematodes because the worms are small and easily overlooked and close inspection is necessary to find these nematodes. Adult *Nematodirus* are larger and may be more readily seen, but alone they are unlikely to be the case of PGE. Nodules associated with larval *Oesophagostomum* can be found in the wall of the lower small intestine, as well as the upper large intestine, and adults can be found in the contents of the large intestine. *Trichuris* will be embedded within the cecum; removing the contents is necessary in order to see them.

Abomasal wall digestion techniques can be used to identify the presence of larval *Ostertagia*.[1-4]

TREATMENT. Animals with type I ostertagiasis can be expected to respond well to treatment with the standard dose of any of the current anthelmintics. Animals should also be moved to a less contaminated pasture. Because any parasites not removed by proper administration of the drug will have resistance alleles, tactical treatment, rather than whole-herd treatment, may be beneficial in keeping the population of resistant nematodes low.

Successful treatment of animals with type II ostertagiasis requires compounds that are effective against arrested larvae, as well as the developing larvae and adults. Only the modern benzimidazoles and macrocyclic lactones are effective at standard doses. Even though the larvae may be killed, the damage to the abomasal mucosa may limit complete recovery. Animals with profound hypoproteinemia and dehydration respond poorly compared with those showing only mild diarrhea and slight hypoalbuminemia. Severely affected animals may need supportive treatment to survive. Recovered animals often fail to thrive.

Gastrointestinal Nematode Infections in Sheep and Goats

Sherrill A. Fleming

Gastrointestinal nematode infections (GINs) in sheep and goats are responsible for severe clinical syndromes and profound production losses. Young animals, periparturient ewes and does, and animals on substandard planes of nutrition are most susceptible to outbreaks of parasitic disease. The GIN of small ruminants include *Haemonchus contortus, Teladorsagia circumcincta* (formerly *Ostertagia*), *Trichostrongylus axei, Nematodirus* spp., and *Cooperia* spp.[1] The proportions of each of these nematodes in small ruminant populations vary according to geographic location. *H. contortus* is usually the most significant pathogen in wet, temperate climates. *T. circumcincta* may be the predominant infection in northern or arid climates. *H. contortus* and *T. circumcinta* represent the majority of parasite burdens seen in small ruminants, with *H. contortus* being present in highest numbers. Anthelmintic resistance is present in all these parasites, but the prevalence is highest for *H. contortus,* making it the most economically important GIN of sheep and goats.[2]

The problem of anthelmintic resistance in GINs of small ruminants has been reported in South Africa, Australia, New Zealand, Malaysia, Spain, France, Denmark, United Kingdom, Brazil, and the United States.[2-6] In the United States resistance has been documented to all classes of anthelmintics.[4,5] Recently resistance to two and three classes of anthelmintic was found on 14 out of 15 farms and 6 out of 18 farms, respectively, in a survey of 18 goat flocks in Georgia and South Carolina.[6] The first report of total anthelmintic failure was made on a meat goat farm in Arkansas in 2005.[7] It is no longer acceptable to plan parasite control programs solely on the basis of the use of anthelmintics. Veterinarians and producers must customize programs to control exposure to infection and reduce the use of anthelmintics. A thorough knowledge of the biology of GIN is necessary to plan effective control programs.

Life Cycle[7,8]

The life cycle of GIN is direct and consists of a host phase and a free-living phase. Worms mate in the host and females lay eggs that pass in the feces. Eggs hatch and develop to infective larvae while remaining in the fecal mass. Infective larvae then move from the fecal mass onto the surrounding forage, where they can be consumed during grazing, thus completing the cycle. The time from ingestion of infective larvae to egg-laying adults, the prepatent period, is about 3 weeks. The time for development from egg to infective larvae can be as short as 4 to 10 days (especially during the summer months); therefore transmission (reinfection) and continual pasture contamination can be rapid. During the colder months development is delayed and may take 1 to 2 months to reach the infective larvae stage, so pasture contamination and reinfection are minimized. The infective larvae have a protective sheath making them relatively resistant to adverse environmental conditions and they can survive for months, thus extending transmission potential. As long as the temperature and moisture conditions remain favorable, development and survival continues; conditions that are too hot, too cold, and/or too dry threaten parasite survival.

Epizootiology[7,8]

The life cycle of a GIN has four phases:

PHASE 1—SYMBIOTIC/PARASITIC PHASE. Phase 1 is the interaction between host and parasite. During this phase, the parasite has to develop and survive in the host. After ingestion, infective larvae lose their protective sheath and invade the mucosa of the abomasum, small intestine, or large intestine depending on the GIN species involved. While in the mucosa, larvae develop to the next larval stage and then return to the surface of the gut mucosa, where they become adult worms. The major host defense mechanism is immunity. When an infectious agent enters the body, the immune system reacts to mobilize various components (antibodies, killer cells, etc.) to inhibit or kill the invaders. These components act on larval stages in the mucosa and the adults in the lumen. The strength of the immune response depends on the age of the host, nutritional status, and concurrent stressors. The immune system matures with age, leaving young animals relatively more susceptible to infection and older animals more resistant. As a result, young animals usually harbor the highest GIN populations and suffer the most severe consequences while adult animals harbor lower infection levels. Under poor nutrition and/or stressful conditions, the immune system is compromised and cannot respond adequately regardless of the age of the animal.

The prepatent period of most worms is about 3 weeks, but this period can be extended for worms that have the capability to enter a period of delayed development called *hypobiosis.* This occurs during the season of the year when the environmental conditions are unfavorable for development and survival of the free-living larval stages. Depending on the worm and the environment, this happens either during summer or winter.

PHASE 2—CONTAMINATION PHASE. Phase 2 results from eggs passed in the feces. The magnitude of this phase is affected by stocking rate, age of the animals, season of the year, and hypobiosis. The higher the stocking rate, the more feces are deposited on the grazing area, thus more eggs, and vice versa. More eggs are also passed from young versus older animals. Most worms have a definite seasonality resulting in higher egg production and deposition during different times of the year. Of particular note is the periparturient rise (PPR) in fecal egg count (FEC). This occurs at or around parturition and extends through most of the lactation period. Because parturition and lactation are stressful conditions, the dam's immune system is compromised. This allows the existing female worms to increase the number of eggs deposited in the feces. If a worm species undergoes hypobiosis, the development time to the adult stage is extended. This will result in fewer adult worms over time and fewer eggs deposited in feces. However, when these hypobiotic larvae resume development, massive numbers become mature adults over a short period of time and the resultant egg production and deposition in the feces can be high.

PHASE 3—FREE-LIVING PHASE. Phase 3 involves larval development and survival, which depend on prevailing environmental and nutritional conditions. Initially, development and survival from egg to first-stage (L_1) then to L_2 and finally to L_3 or infective larvae occurs within the fecal mass. L_1 and L_2 are unprotected and require oxygen and energy (feeding on nutrients and microorganisms) to grow. The L_3 are enclosed in a protective sheath and do not feed. Temperatures conducive for normal development and survival are between 65° F and 85° F. With lower or higher temperatures, development and survival are reduced. Moisture is also crucial for development and

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survival. Because the initial development and survival occur within the fecal mass, moisture is usually adequate to allow development to the infective larvae; however, if the fecal mass dries out quickly, due to high temperatures and/or physical disruption of the fecal mass, the L_1 and L_2 are susceptible to desiccation and will die. Generally, L_3 can survive very low temperatures, but sustained temperatures above 95° F are usually lethal. When infective larvae migrate out of the fecal mass, they are relatively resistant to environmental conditions encountered due to their protective sheath. Temperature is usually the only factor that may adversely affect L_3. The moisture conditions at ground level under forage cover are usually adequate for L_3 to move around and survive. Because they do not feed, length of survival depends on how fast they use energy reserves. The hotter it is, the faster they move and use up energy stores, which decreases survival. Eventually, infective larvae move up and down the forage when there is a moisture medium (i.e., advancing and receding dew). Rain also provides a moisture medium for larval movement on forage. For the most part, infective larvae do not move much past 30 to 50 cm from the fecal mass or 5 to 6 cm up the forage. Therefore, the lower the animals graze and the closer to the fecal mass, the greater the consumption of L_3.

PHASE 4—INFECTION PHASE. Phase 4 occurs when available L_3 are consumed during grazing. This phase is affected by stocking rate in two ways. If the same (phase 2) animals remain on the same pasture, the stocking rate determines how many eggs initially contaminated the pasture and, consequently, how many L_3 will be available to consume. If the initial contaminating animals are removed and replaced by new animals, the new stocking rate will determine the level of exposure each animal has to infective larvae during grazing (i.e., the higher the stocking rate, the more chance of exposure and vice versa). It is well known that grazing animals usually do not graze close to fecal masses, so the greater the distance between masses, the less the exposure. Eventually fecal masses disintegrate, forage grows well with the fertilization, and animals will graze over the area where exposure can be high. Natural sources of water, such as streams, ponds, or lakes, provide moisture along the banks, where forage can grow readily. When animals congregate to drink and consume the attractive forage, defecation in these areas usually leads to increased contamination and eventually more L_3. Essentially a high stocking rate has been artificially created in a relatively small area. The same can be said for areas where supplements, especially hay, are fed if conditions are right for development and survival of the free-living stages. Once L_3 are consumed, phase 1 is repeated.

Pathophysiology of Gastrointestinal Nematode Parasites

The damage done by *H. contortus* is the result of the blood sucking by L_4 and adult parasites. The pathogenesis of *Teladorsagia* in sheep is similar to that described for *Ostertagia* in cattle and is a result of destruction of abomasal mucosa. *T. axei* causes abomasitis, whereas *Trichostrongylus colubriformis* penetrates beneath the intestinal mucosa and causes blood loss and enteritis.

Clinical Signs of Gastrointestinal Nematode Parasites

Most animals acquire mixed infections of nematodes. Clinical signs may therefore reflect the effects of more than one species of parasite. There appears to be some synergism between *T. circumcincta* and *T. colubriformis,* which makes the effect of the combined infection more severe than that of either alone. Although mixed infections with GINs are assumed, the actual population of parasites in small ruminants will vary depending on the geographic location. In general, the majority of clinical illnesses results from *H. contortus* infections. Most parasitic infections in small ruminants are associated with altered gut function, anorexia, ill thrift, weight loss, and hypoproteinemia. Diarrhea is a variable sign. Animals may die suddenly without overt clinical signs or may exhibit chronic wasting. Clinical signs of *H. contortus* infection can vary from peracute to chronic and result from decreased nutrient utilization and anemia/hypoproteinemia. The most common signs are failure to thrive, weight loss, and decreased appetite. Weakness, bottle jaw, pale mucous membranes, poor capillary refill time, and possibly diarrhea develop with more severe or long-term infections. Following sudden exposure to large numbers of L_3, animals can die acutely, even before the infection is patent. Other diseases such as pneumonia and heat stress may result secondarily.

Anemic Crisis/Patient Management

The anemia created by *H. contortus* is due to blood consumed by the parasite and is usually chronic. Parasitized patients present with lethargy and weight loss and often have hematocrits less than 10%, yet many are still capable of rising and walking. Addressing the anemia by blood transfusion must be weighed carefully against stress to the patient caused by restraint, jugular catheterization, and blood administration, as well as by the hemolysis of these same cells several days later. Obviously, in life-threatening circumstances (the patient that is unable to stand), administration of whole blood can be critical. In the noncrisis situation (patient rising and/or eating), treatment with an effective anthelmintic should eliminate the parasite and halt blood loss. Because *H. contortus* consumes blood, the affected animal actually loses substrates essential to erythrocyte production (iron, cobalt, copper). Providing supplemental iron and B-complex vitamins should speed reversal of the anemia. Assuming blood loss has been halted, a 1- to 1.5-point rise in the hematocrit per day is expected when the bone marrow is maximally stimulated. In most parasitized patients, a rise of one half this value is a more realistic expectation.[9]

If blood is to be given, it is essential to be certain that the donor has a normal packed cell volume. Blood collected from animals in the same environment may be as anemic as the patient, but the individual is more capable of dealing with the anemia. In lambs weighing less than 45 kg, 1 unit of whole blood (≈450 mL) is often sufficient to survive a crisis, provided *H. contortus* has been controlled.

Populations at Risk

Young animals are most susceptible to infection and clinical manifestations of disease. Lambs and kids may become heavily infected with parasites and shed large numbers of nematode eggs. In sheep, some degree of immunity develops as the animal approaches 1 year of age. Adult animals typically have complete immunity against *Nematodirus* and variable resistance to *Trichostrongylus* spp. Some immunity to *Haemonchus* and *Teladorsagia* spp. develops with age; compared with lambs or kids, adults are more resistant to infection with these species. However, even mature animals may succumb to parasitic infection when malnourished or challenged with heavily contaminated pasture. A periparturient rise in fecal egg production is seen in ewes and does.

Goats are more susceptible to gastrointestinal nematode infections than are sheep. The difference lies in part in the host's immunologic responses to nematode antigens. Goats prefer to browse on brush and trees and only graze grass when forced to by management. Under natural conditions, goats would have a low level of exposure to infective larvae and this may explain their lower level of natural immunity compared with sheep.[10,11]

Refugia

Biologically, refugia refers to isolated populations of once widespread animal or plant or in this case, parasite species. Most parasitologists now consider levels of refugia as the single most important factor contributing to selection for anthelmintic-resistant parasites.[12,13] Worms in refugia provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. For many years parasitologists and veterinarians have recommended that all animals on a premise should be treated with an anthelmintic at the same time. However, this strategy has proven problematic, and a selective approach is now recommended. Only those animals in danger of severe parasitism should actually receive medication. This selective approach is highly compatible with host-parasite dynamics because 20% to 30% of animals harbor about 80% of the parasites.[14] Animals with low worm burdens are an important source of refugia, are not in danger of the negative effects of parasitism, and should not be treated.

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Management of Gastrointestinal Nematodes in Small Ruminants The traditional approaches of deworming often, rotating class of anthelmintics, and moving to clean pastures have only served to develop anthelmintic resistance to all classes of drugs and disseminate these resistant parasites over a wide area. It is obvious that drastic changes in the management of GIN in sheep and goats are long overdue.

FAMACHA OR SMART DRENCHING METHOD.[15] In order to maintain adequate levels of refugia, it is necessary to leave a portion of the herd or flock untreated. FAMACHA is a selective approach that targets the portion of the herd or flock with high worm burdens, including those animals that are poorly resilient to worm infections.[16] This approach will successfully control parasites in the entire group while significantly reducing drug costs and delaying the development of anthelmintic resistance. The use of this system is not without risk because individuals are not routinely treated with anthelmintics. Failure to observe animals closely for clinical signs may result in the death of some individuals. It is necessary to know which anthelmintics are effective before beginning this system. The differences among farms in overall quality of management, stocking rates, breeds of animals, preexisting levels and spectrum of anthelmintic resistance, presence of nematode species other than *H. contortus,* and production targets need to be considered before implementing FAMACHA on individual farms.

FAMACHA is a novel system developed in South Africa for identifying sheep that are anemic, and it has been extended to use in goats.[17] In this method the ocular mucous membranes of sheep and goats are categorized by comparison with a laminated color chart bearing pictures of sheep conjunctivae classified into five categories ranging from red (A/1; normal) to practically white (E/5; severe anemia). Because anemia is the primary pathologic effect from infection with *H. contortus,* this system can be an effective tool for identifying animals that require treatment (but only for *H. contortus*). FAMACHA has been tested extensively and validated in both sheep and goats in South Africa and in the southern United States.[18,19] In all studies, the numbers of false negatives were low, suggesting that when using FAMACHA according to recommended guidelines, death from anemia would be rare.

On the basis of the results of recent studies in the United States and numerous studies performed in South Africa, guidelines for using FAMACHA have been developed, and it is suggested that these guidelines be read in their entirety before FAMACHA is practiced.[16] Individual animals are scored 1 to 5 by comparing their mucous membrane color with a laminated chart. It is recommended that treatment is withheld until animals score a 4 or 5 as long as animals are in good body condition and good overall general health, are examined frequently (e.g., every 2 weeks), and good husbandry is used to identify animals in need of treatment (e.g., unthrifty, anorexic, lagging behind, bottle jaw) between FAMACHA examinations. Using this approach, the number of anthelmintic treatments administered will be reduced greatly, resulting in significantly diminished selection pressure for resistance and therefore a reduction in drug costs. Due to the increased handling of animals, labor costs will be increased. *Only adult animals should be managed with this system.* Lambs and kids have comparatively small blood volumes, poor immunity, and poor resilience and can progress rapidly from moderate to severe anemia. This precaution should also be extended to ewes and does during the periparturient and early lactation period because these animals have decreased immunity to GINs.[15,20-22] These and other animals that may be stressed by disease or in poor body condition should always be treated if scored as 3. Alternatively, in the northern parts of the country where *H. contortus* is an important problem but resistance prevalence is much lower, it may be reasonable to be more liberal when making treatment decisions (i.e., treat all 3, 4, and 5). Many more treatments are given when all scores of 3 and higher are dewormed, but a significant number of animals will remain untreated to supply refugia. These refugia combined with a relatively short transmission/treatment period are likely to produce a slow evolution of resistance, but the more intensive treatment protocols will improve animal productivity.

On farms where low to moderate levels of resistance have been diagnosed to one or more drugs (60% to 90% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less effective" drugs either singly or in combination on all animals scored as 3. There is evidence that using dewormers with different modes of action in combination have greater efficacy and do not cause a more rapid development of resistance.[23] Using drugs that are less effective in this group is unlikely to lead to clinical problems because the few 3 scores that are moderately anemic and in need of treatment should receive a sufficient reprieve from infection until the next FAMACHA examination, and the majority of the 3 scores that are not anemic do not need to be treated. This strategy will help preserve the efficacy of the drugs that are still fully effective by saving them only for the 4 and 5 categories and will also help to decrease egg contamination of pastures.

Training of producers is critical in the use of this method. It is the responsibility of veterinarians and other animal health professionals to ensure that standards of training are maintained by using the "Train the Trainer" seminars through the American Consortium of Small Ruminant Parasite Control (ACSRPC, formerly Southern Consortium or SCSRPC) at www.acsrpc.org. When using FAMACHA, it is extremely important that efficacy of anthelmintics is known because animals are not treated until they become anemic. Treating anemic animals with a drug that has moderate to poor efficacy due to worm resistance may result in animal deaths. Other important precautions for using FAMACHA include but are not limited to (1) the card is an aid in the control of *Haemonchus* spp. only; (2) the system should be used by producers only where technical assistance is available from a veterinarian or other animal health professional; (3) other management-based worm control practices must be maintained; (4) smart drenching principles should be used; (5) paleness or reddening of the conjunctivae may have other causes; (6) animals should always be scored with the help of the chart, not from memory; (7) animals are examined at least every 2 to 3 weeks at the beginning of the expected period of *Haemonchus* spp. challenge in climates where a seasonal incidence of infection occurs, and during critical periods weekly examinations may be necessary; (8) the card is protected from light when not in use and replaced after 1 year of use.[4,24]

Maintaining records of treatments that are included with the FAMACHA kits gives the owner the ability to rate the genetic merits of individuals on the premises. Host resistance to infection with *H. contortus* measured on the basis of FEC and PCV is a moderately heritable trait, and it has been demonstrated that the same animals tend to exhibit the highest FEC and lowest PCV on each occasion they are measured.[25-27] Importantly, data from recent investigations examining the heritability of resistance and resilience of Merino sheep to infection with *H. contortus* indicate a high heritability for the clinical estimates of FAMACHA scores.[18] Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance and/or resilience of the herd or flock to *H. contortus*.

FIVE-POINT CHECK.[28] Because FAMACHA is based on anemia and focuses on parasitism by *H. contortus,* a combined system that could identify problems with a variety of other potentially pathologic parasites is in the early stages of development. This is the Five-Point Check that includes checking for nasal discharge, submandibular edema, back body condition scoring, and fecal staining of perineum in addition to ocular membrane color. Anthelmintic recommendations were made on the basis of the points that had poor scores. Pilot studies showed good acceptance and usefulness of this system, but further studies need to be completed to determine the efficacy and economy of this approach.

GRAZING STRATEGIES. The goal of pasture management is to provide safe pastures for grazing by reducing the exposure of

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susceptible hosts to infective larvae.[29,30] A safe pasture is one that has had no sheep or goats grazed on it for 6 months during cool/cold weather or 3 months during hot, dry weather. Weaning sheep and goats at 2 months of age and rotating them through pastures ahead of the adults while forage is longer will minimize the exposure of susceptible animals to infective larvae. Pastures should be subdivided into smaller lots to allow longer rest periods between grazings. Pastures that are overgrown provide a good environment for larval survival because ultraviolet light and dry conditions are effective in killing larvae. Keeping pastures clipped will also assist in weed and parasite control and improve forage quality. Short-duration grazing carries pasture rotation to a level that maximizes forage production and harvesting by controlled animal grazing. It is management intensive but can be effective in controlling parasite burdens. Tilling and reseeding heavily contaminated pastures will convert them to safe pastures and provides an opportunity to improve the forage quality. Taking a cutting of hay from a pasture assists in reduction of infective larvae, but one report indicates GINs and tapeworms developing in "worm-free" lambs after feeding hay from heavily infected pastures. During the most dangerous part of the grazing season, it may be necessary to dry lot the flock and feed hay and grain from elevated feeders.

Stocking rate is an important consideration in parasite control because it affects the exposure to infective larvae and the contamination of the pasture. It is impossible to make a general recommendation on stocking rate because this will vary according to the type of pasture, time of year, current weather conditions, and type of animal being grazed. Thumb rules include five to seven goats or five sheep being the equivalent of one cow and suggest five to seven goats/acre. Goats prefer to browse brush and trees, whereas sheep prefer to graze near the ground. Pasture management must include monitoring the condition of herbage to ensure that overgrazing does not occur and to maintain a productive pasture.

In the early spring or at the onset of the rainy season, reduced pasture contamination is the most important aspect of control. The ewe or doe in the periparturient relaxation of resistance, even if she has the genetic capacity for resistance, will be a source of eggs for the environment. Strategic deworming to remove arrested or recently emerged larvae before they contaminate the pasture will have a great impact on pasture contamination. Treatment 2 weeks after a rain that removes recently acquired worms before they can begin passing eggs will also decrease pasture contamination. Providing sufficient dietary protein is vital during the periparturient period and during rapid growth so that animals will tolerate the worm burden better, as well as increase resistance to infection.[31-33] A strong link between nutrition and parasitism has been illustrated between protein intake and resistance to GIN infection. The most dramatic has been the abolishment of the periparturient egg rise in lambing ewes by providing protein at 130% of requirements. Immunity is closely related to protein repletion. GINs increase the demand for amino acids by the sheep. Lambs will voluntarily select a higher protein diet when infected with GINs compared with uninfected lambs. There is conflicting documentation that sheep will decrease feed intake when initially infected with GIN. Some authors hypothesize that the decrease in intake may be due to stimulation of the immune system or that the host is becoming selective in its diet.

Pastures may be used for hay cropping and grazed during the last half of the grazing season to effectively reduce GIN challenge. When plants high in condensed tannins are grazed, incoming larvae are adversely affected and these plants provide bypass protein for the host.[34-36] There is growing evidence in work from New Zealand and Europe that grazing or feeding of plants containing condensed tannins (CTs) can reduce FEC, larval development in feces, and adult worm numbers in the abomasum and small intestine. Preliminary tests with *Sericea lespedeza* (SL, *Lespedeza cuneata*), a perennial warm-season legume, have shown positive effects of reduced FEC in grazing goats, and in sheep and goats in confinement when the forage was fed as hay. In addition, an effect on reducing worm burden has also been reported. *S. lespedeza* is unfortunately considered to be an invasive exotic in the United States. Similar results have been observed using quebracho extract for small intestinal worms, but not abomasal worms. In addition to its potential use in controlling worms, SL is a useful crop for limited resource producers in the southern United States. It is adapted to hot, dry climatic conditions and acid, infertile soils unsuitable for crop production or growth of high-input forages, such as alfalfa. It can be overseeded on existing pasture or grown in pure stands for grazing or hay. In addition to hay, SL is being evaluated in the form of meal, pellets and cubes to be fed as a supplement to grazing animals, or as a deworming method under temporary short-term confinement. The physical structure of some plants may challenge larvae to ascend vegetation or may provide protection from adverse pasture conditions. If animals are allowed to browse, their chances of acquiring larvae diminish as the distance from the ground increases. Most infective larvae are found within 2 inches (50 mm) of the soil surface.

Alternate or co-grazing with other species of livestock may harvest *Haemonchus* larvae from the pasture. Small ruminants can graze after cattle, and this is considered to be a safe pasture, assuming adequate parasite control in the cattle. For the most part, each livestock species harbors its own parasite fauna with the exception of overlap between sheep and goats. Only *T. axei,* a minor abomasal worm, is found in all livestock species. In general, the *Haemonchus* in sheep and goats do not do well in cattle and vice versa. However, some populations of *H. contortus* may thrive in calves. If practical, cattle and small ruminants can be grazed together where each consumes the parasites of the other, which reduces available infective larvae for the preferred host species.

Anthelmintic administration should be coordinated with the weather. During hot, dry weather, there will be little or no exposure to L_3. As soon as there is significant rainfall (0.5 to 1 inch), larvae exposure goes up exponentially as previously inactive larvae become active and new larvae are hatched. Producers should be trained to plan deworming within 3 weeks of significant rain after a dry spell. Similar strategies can be used during cool weather. Once ambient temperatures drop below 50° F, the flock can be dewormed and no further treatments are necessary until temperatures become favorable to larval development and activity.

ALTERNATIVE THERAPIES

1. **Copper oxide wire particles (COWPs)** have been marketed for years as a supplement for livestock being managed in copper-deficient areas.[37] COWPs come in adult cattle, calf, and ewe boluses (25, 12.5, and 4 g, respectively). Only the cattle boluses are available in the United States. Due to potential toxicity in sheep, only one dose per year is recommended. It is also well known that copper has some anthelmintic activity against abomasal worms but not other gastrointestinal worms. That makes COWP a narrow-spectrum product. But in view of anthelmintic resistance by *H. contortus,* recent work has revisited the possibility of using COWP to specifically target *H. contortus*. Such work has shown that as little as a gram or less and 2 g may remove substantial numbers of *H. contortus* in lambs and ewes, respectively. Similar work in goats has not been tested adequately to establish what is needed, but similar doses may be appropriate. As mentioned, copper must be used cautiously in sheep because toxicity can develop due to liver accumulation. Toxicity may not be an issue in goats because they have been reported as not being as sensitive to excess copper intake. Thus, higher doses and/or more treatments during haemonchosis season may be useful in goats.
2. **Other nutritional considerations** include phosphorus, cobalt, and molybdenum.[38] Supplementation with phosphorus has been shown to prevent worm establishment. Cobalt deficiency has also been associated with reduced immunity to GINs. The addition of molybdenum at 6 to 10 mg/day decreased worm burdens in lambs. This effect was not attributable to the expected copper deficiency. Molybdenum may have a role in increasing jejunal mast cells and blood eosinophil numbers.
3. **Nematode-trapping fungi** included in feed or supplements have demonstrated potential for biological control of the free-living

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stages of GIN parasites under experimental and natural conditions.[39-41] These fungi naturally inhabit soil throughout the world where they feed on a variety of free-living soil nematodes. These fungi capture nematodes by producing sticky traps on their growing hyphae. Of the various fungi tested, *Duddingtonia flagrans* possesses the greatest potential for survival in the gastrointestinal tract of ruminants. After passing through the gastrointestinal tract, spores germinate and looped hyphae trap the developing larval stages in the fecal environment. This technology has been applied successfully under field conditions and is an environmentally safe biological approach for control of worms under sustainable, forage-based feeding systems. The major drawback is that the fungal spores must be fed daily. Daily feeding, which ensures that all animals consume an equivalent amount of feed, is necessary. For adequate control of larvae during the transmission season, spores must be fed for a minimum of 60 days. This can be expensive and time consuming. A bolus prototype that would allow a single administration where spores would then be slowly released over a 60-day period is being developed. This product is not available in the United States at this time.

4. **Vaccines** have been explored for management of the negative consequences of parasitism.[42-44] Successful vaccines have been developed for lungworms in cattle and tapeworms in sheep. The most promising vaccine for small ruminant worms has been what is called a "hidden gut" antigen and specifically targets *H. contortus*. This antigen is derived from the gut of the worm and, when administered to the animal, antibodies are produced. When the worm ingests blood during feeding, it also ingests these antibodies. The antibodies then attack the target gut cells of the worm and disrupt the worm's ability to process the nutrients necessary to maintain proper growth and maintenance, thus killing the worms. This vaccine has been tested successfully in sheep under experimental conditions but has had limited success under field conditions. Vaccines for other worms that do not feed on blood have focused on using antigens found in worm secretory and excretory products. Protection has been quite variable, and marketing of such products has not been pursued.
5. **Genetic improvement in resistance** to nematode infection is most likely based on inheritance of genes that play a primary role in expression of host immunity.[45-47] Based on survival of the fittest management conditions, several breeds around the globe are known to be relatively resistant to infection. Such breeds include Scottish Blackface, Red Maasai, Romanov, St. Croix, Barbados Blackbelly, and the Gulf Coast Native. Katahdin sheep have been considered as being more parasite resistant, but studies to document this are few and not conclusive. Using such breeds exclusively or in crossbreeding programs would certainly lead to improved resistance to worm infection, but some level of production might be sacrificed. Selection of more resistant stock can be accelerated by identifying sires that produce relatively resistant offspring. Computer programs have been used in New Zealand and Australia to rank sire genetics on the basis of resistance to GIN infections, but change takes up to 8 to 10 years. Heritabilities for FEC, a common measurement for assessing parasite burden, range from 0.22 to 0.40, which is relatively high. Thus, selection for resistance using a measurement such as FEC has been moderately successful.

ANTHELMINTIC USE. Anthelmintics have deliberately been left to the end of this section because drugs cannot be considered to be the most important aspect of a parasite control program. Guidelines for drug dosages are contained in Table 49-3. At this time, only oral administration of anthelmintics is recommended in small ruminants. In general, goats require 1.5 to 2 times the dosages of sheep, with the exception of levamisole, due to more rapid gastrointestinal transit times. It is critical that producers accurately assess weights of individual animals and dose appropriately. If an approximate dose is going to be used in all animals, that dose should be for the lightest animal in the group.

The challenge of anthelmintic resistance is life threatening in small ruminants. There is no point in repeatedly deworming with expensive drugs, if that drug is no longer effective. See the following section on Monitoring Parasite Control programs for information on detecting anthelmintic resistance. On farms where low to moderate levels of resistance have been diagnosed to one or more drugs (60% to 95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less effective" drugs either singly or in combination. Drugs in the benzimidazole family may be effective if multiple-day dosing regimens are used.

Lungworm Infection in Large Animals

Lora Rickard Ballweber

Traditionally, lungworms are those nematode parasites that reside in the lung as adults. In domestic ruminant and equine species, most clinical cases of lungworm involve the genus *Dictyocaulus.* Species of *Dictyocaulus* tend to be host specific with *Dictyocaulus viviparus, Dictyocaulus filaria,* and *Dictyocaulus arnfieldi* found in the bronchi of cattle, small ruminants, and equids (horses, ponies, donkeys), respectively. Sheep and goats may also be infected with *Protostrongylus rufescens* and *Muellerius capillaris*.[1-2] This section focuses on *Dictyocaulus* infection, with a brief discussion of other lungworm parasites found in small ruminants.

Because verminous pneumonia requires specific treatment, it is important to distinguish it from diseases caused by other infectious agents. Often the role of lungworm in the cause of respiratory disease is obscured by a parasite-induced hypersensitivity response or by superimposed secondary bacterial infections.

Life Cycle The life cycle of *D. viviparus* is direct, with no intermediate host involved. Adults produce embryonated eggs that hatch shortly after oviposition. L_1 migrate up the trachea and are passed in the feces, where they develop to L_2 and infective L_3 within a week under optimal environmental conditions. After the L_3 are ingested, they exsheath within the abomasum and migrate through the wall of the intestine to the mesenteric lymph nodes, where they molt to the L_4. The L_4 then migrate through the lymphatics and bloodstream to the lungs, arriving as early as 7 days after infection. L_4 may then develop to sexually mature adult worms, or they may arrest development as late L_4 or molt to immature adults and arrest. Arrested development can prolong the normal prepatent period from 3 to 4 weeks to approximately 5 months.[1-2]

Most problems with cattle lungworms in North America occur in areas of moist climates where larvae on pasture are protected from desiccation and larval dispersal away from the fecal pat onto herbage is facilitated. Under favorable conditions, infective L_3 can survive on pasture for as long as 11 months.[1] These larvae plus the larvae produced from carrier animals harboring small numbers of adults or adults developing from arrested larvae can result in high levels of contamination on spring pastures. In subtropical climates, larvae are virtually absent during the hot summers; larval contamination of the pasture peaks in the autumn as a result of carrier animals.[2]

The life cycle of *D. filaria* is similar to that of *D. viviparus* including the ability of the larvae to arrest development. The prepatent period is approximately 26 days, with peak larval output occurring 39 to 57 days post infection. As with *D. viviparus, D. filaria* is more prevalent in moist climates and larvae can survive on pasture throughout the winter. Spring pastures contaminated with overwintering larvae and larvae produced from adults developing from arrested larvae in carrier animals are sources of infection for susceptible lambs or kids.[1-2]

The life cycle of *D. arnfieldi* is similar to that of other species of *Dictyocaulus* except that larvated eggs are passed in the feces with the L_1 hatching almost immediately thereafter. The prepatent period is 2 to 3 months.[2-4]

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Unlike species of *Dictyocaulus, M. capillaris* and *P. rufescens* have indirect life cycles that involve molluscan intermediate hosts. Adults, occurring in the parenchyma *(M. capillaris)* or small bronchioles *(P. rufescens),* produce eggs that develop and hatch. L_1 are passed with the feces; once on pasture, larvae invade the foot of a susceptible species of snail or slug and develop to infective L_3. Sheep and goats become infected when ingesting the mollusk while grazing. The larvae penetrate the intestine and migrate to the lung in much the same manner as *Dictyocaulus.* Early L_4, developing L_4, and adult *M. capillaris* become embedded in fibrous nodules within the parenchyma. *Protostrongylus* larvae mature in the alveoli and enter the bronchioles as adults. The prepatent period for both species is 5 to 6 weeks, although arrested development may prolong the prepatent period of *M. capillaris.* Patency for both species is very long (>2 years).[2-4]

Pathophysiology Clinical bovine dictyocaulosis is characterized by bronchitis and pneumonia. The disease process is divided into four phases: penetration, prepatent, patent, and postpatent. In the penetration phase (days 1 to ≈7), no clinical sign or significant respiratory pathology occurs as the larvae migrate to the lungs. The prepatent phase (days 7-8 to 25) starts with the arrival of larvae in the alveoli and ends with immature adults in the bronchi. An eosinophilic infiltrate blocks bronchioles; excess mucus production and alveolar collapse occur. Respiratory failure as a result of severe interstitial emphysema and pulmonary edema can result in death of heavily infected animals beginning about day 15 onwards. The patent phase (days 25 to 55-60) is associated with egg-laying adults in the bronchi and trachea. Bronchial and tracheal epithelial damage occurs, air passages are blocked by exudate, and consolidation of lobules results from aspiration of eggs and L_1 into bronchioles and alveoli. Bronchitis, tracheitis, and pneumonia follow. The postpatent phase (days 61 to 90) is normally the recovery phase and is associated with the expulsion of adult nematodes. Clinical signs begin to diminish; however, peribronchial fibrosis and epithelialization of alveoli may remain. A frequently fatal syndrome, called *postpatent parasitic bronchitis,* can occur in about 25% of heavily infected animals during the postpatent phase. This syndrome is characterized by proliferation of type 2 pneumocytes in the alveoli, impaired gas exchange at the alveolar surface, interstitial emphysema, and pulmonary edema and is thought to result from the aspiration of dead and dying worm material into the alveoli. Fatal secondary bacterial infections, resulting from weakened pulmonary defenses, may also occur.[1-2]

Goats tend to be more susceptible to infection with *D. filaria* and more severely affected than sheep, although individual susceptibility to infections does occur. Heavy infections in both species produce bronchitis, pulmonary edema, atelectasis, and emphysema, although death is uncommon. As with *D. viviparus,* secondary bacterial infections can occur.[1]

The characteristic lesions of dictyocaulosis in horses and donkeys are similar. Pathologic changes include discrete circular areas of overinflation (not emphysema) surrounding affected bronchi primarily in the caudal lung lobes. Histologically these areas contain a small bronchus packed with nematodes. The small airways are often occluded with exudate. Adult worms may also be found in the main bronchi surrounded by small amounts of mucus with little cellular reaction; however, if L_1 are present, they are surrounded by an intense mucopurulent reaction. In horses, in addition to these types of lesions, many immature nematodes are present in smaller bronchi, accompanied by bronchial epithelial hyperplasia with large amounts of mucus and pus. Many areas of alveolar hemorrhage and edema are also present.[2-4]

Pathologic changes caused by *P. rufescens* result from occlusion of small bronchioles by mature worms, resulting in clogging of lesser branches with eggs, larvae, and cellular debris. Other changes include desquamation of alveolar and bronchial epithelium and cellular infiltration and proliferation of connective tissue. The results are small areas of lobular pneumonia that appear as gray to yellowish conical lesions whose base is on the surface of the lung. In sheep and goats infected with *M. capillaris,* distinct subpleural nodules containing adults and L_1 are common. However, infections in both hosts may be more diffuse with interstitial pneumonia, bronchopneumonia, or fibrinous pleuritis. Secondary bacterial infections can also occur.[1-2,5]

Populations at Risk Clinical dictyocaulosis occurs most frequently in pastured calves, lambs, and kids in the first grazing season. Clinical disease is also reported in adult cattle either as a result of primary exposure as adults, exposure of a previously immune animal whose immunity has waned due to lack of premunition, or exposure of an immune animal to a massive challenge of infective larvae *(reinfection syndrome).*[1-2, 6-8] Although dairy or dairy-cross calves are most frequently affected, beef calves are also susceptible to *D. viviparus.*[2,9-10] Many infections with either *M. capillaris* or *P. rufescens* are subclinical; however, goats do appear to be affected clinically more often than sheep with *M. capillaris.*[1-2]

Immunity to *D. viviparus* occurs after first exposure and can develop before the end of the first grazing season. However, it is variable in both degree and duration. Exposed cattle may be immune for 7 to 12 months after infection. In subsequent infections most larvae are either killed before reaching the lung or are inhibited from maturing into adults. Usually the immunity developed during the first grazing season is boosted by exposure in subsequent years and prevents manifestations of disease. However, without reexposure to infective larvae or vaccination, immunity wanes and disease can occur in adult cattle.[1-2,8]

Occasionally, outbreaks of acute lungworm disease are seen in adult cattle on pasture whose immunity is overwhelmed by exposure to large numbers of larvae. This condition is called the *reinfection syndrome.* Although most ingested larvae are killed or fail to mature, some reach the lung and incite an acute, immune-mediated reaction.[2]

Both sheep and goats develop a strong immunity to *D. filaria.* Thus disease is more common in young animals. As with cattle, the strength and duration of immunity depend on the level of and number of reexposures, as well as the length of time between exposures.[1] Although not common, cattle can be infected with *D. filaria.* Patent infections do not establish but clinical disease may occur.[1,11]

Individual horse/pony susceptibility to infection with *D. arnfieldi* is evident, with infections occurring during any time in the life of the animal. Patent infections can establish in foals (<5 months old) without accompanying clinical signs. Patent infections are rarely established in older animals, where clinical disease is more common. Donkeys apparently do not develop an immunity to infection, with larval excretion increasing with age.[2-4]

Although immunity to *M. capillaris* appears to be incomplete (adult nematodes can live for up to 4.5 years), responses to subsequent exposures do limit the numbers of adults that develop and the numbers of larvae shed in the feces. However, reexposure may be cumulative, resulting in older animals harboring larger numbers of worms.[1]

Clinical Manifestations Clinical disease ("husk") caused by *D. viviparus* in cattle can occur within 1 or 2 weeks of the introduction of susceptible animals onto contaminated pasture. However, disease most often occurs 2 to 4 months into the grazing season. Severity of disease depends on the number of larvae ingested, the animal's level of immunity, and the number of larvae reaching the lungs. Within an affected group, differing degrees of clinical severity will occur. Coughing, dyspnea, and loss of condition are typical. Slight increases in respiratory rate may progress to severe tachypnea and dyspnea characterized by the classic "air-hunger" position of head and neck extended with open-mouth breathing. Auscultation of the lungs reveals vesicular murmurs and bronchial tones that progress to moist rales as fluid accumulates. Emphysema may occur with crackling noises heard on auscultation. Mild pyrexia may be present. Milk production is usually depressed in adult dairy cattle.

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Morbidity rates are high, with most animals gradually recovering. Secondary bacterial infections can lead to recurrence of clinical signs during the postpatent phase leading to acute interstitial pneumonia.[1-2,7] Acute dictyocaulosis in calves, resulting from a massive primary infection, can occur during the prepatent period with sudden onset of severe dyspnea followed by death within 24 to 48 hours.[2] Reinfection syndrome in adult cattle shows frequent coughing and slight tachypnea and, for dairy cattle, a sudden drop in milk production starting approximately 2 weeks after exposure to heavily contaminated pastures. Deaths rarely occur.[2]

Coughing and unthriftiness are the usual signs of infections with *D. filaria*. In severe cases, dyspnea, tachypnea, and nasal discharge can occur. Death is uncommon.[1-2]

In horses, lungworm infection may or may not cause clinical signs. When present, the typical syndrome is similar to chronic obstructive pulmonary disease and includes persistent coughing, nasal discharge, and increased respiratory rate; death is uncommon. Donkeys tend to remain asymptomatic, although hyperpnea and harsh lung sounds may be present on close examination.[2,4]

Infections with *M. capillaris* are generally asymptomatic; however, impaired pulmonary gas exchange, reduced weights and breeding performance, and increased mortality have been reported.[1,12-13]

Control of Lungworm Infection

Control of dictyocaulosis in cattle has depended on vaccination and/or prophylactic use of anthelmintics, whereas management strategies designed to decrease exposure to infective larvae are more common recommendations for sheep and goats. These strategies include provision of dry pastures to decrease larval development and survival; grazing of older, clinically immune animals that shed larvae away from susceptible lambs and kids; and grazing lambs on pastures that have not been grazed by adults during the previous year. Treating or culling infected adults can also help reduce pasture contamination. For cattle, leaving contaminated pastures ungrazed for at least 6 weeks during the summer in temperate regions can reduce pasture infectivity because larvae will not survive the dessication. Young, susceptible stock may be given a prophylactic treatment in midspring or early summer to prevent or limit clinical disease. Housed animals, in particular 1- to 2-year-olds with subclinical but potentially patent infections, should be treated before being turned out to pasture in the spring. All early clinical cases should be treated in an effort to limit disease severity and decrease pasture contamination.[1-2,14-15]

Control of lungworms in horses/ponies depends on control in donkeys. Co-grazing with donkeys should not occur. If it does, donkeys should be monitored for L_1 and treated to reduce larval output and pasture contamination. Limiting contact with intermediate hosts and provision of mollusk-free housing will decrease infections with parasites that require these intermediate hosts. Treatment of animals before the start of the grazing season has also been suggested to reduce infection levels in the intermediate hosts.[1-2]

ANTHELMINTICS. Several anthelmintics are effective against lungworms (Table 49-4).[1,3-4,16-19] The macrocyclic lactones are particularly effective against both adult and developing L_4 stages and have prolonged residual activity that prevents appearance of larvae in the feces for at least 60 days.[20-21] Concerns that such highly efficacious anthelmintics would prevent induction of immunity in first-season grazing animals by killing ingested larvae, before they can penetrate the intestine and thus stimulate an immune response, appear to be largely unfounded. The immune response may be attenuated, but exposed animals still develop some degree of immunity to lungworm infection despite prophylactic treatment with these drugs.[22-26] The exception to this may be sustained-release intraruminal devices containing either ivermectin, levamisole, or a benzimidazole. Although their use can prevent clinical disease for several weeks or months during the grazing season,[26-31] some studies have shown that use of these delivery systems impaired the development of immunity in treated calves.[26,30] Other studies, however, showed that treated calves can develop immunity during the grazing season.[32]

TABLE 49-4

Drugs Used to Control Lungworm

Drug	Dose*
Macrocyclic Lactones	
Cattle: ivermectin, abamectin, doramectin, eprinomectin, moxidectin	0.2 mg/kg PO, 0.5 mg/kg topical
Sheep: moxidectin, ivermectin	0.2 mg/kg PO, SC
Goats: ivermectin	0.2-0.3 mg/kg PO, SC
Equids: ivermectin, moxidectin; eprinomectin	0.2 mg/kg, 0.4 mg/kg PO; 0.5 mg/kg topical
Others	
Albendazole	7.5-10 mg/kg PO (O, C, B)
Fenbendazole	7.5 mg/kg PO (O); 15-30 mg/kg PO (C); 5 mg/kg PO (B)
Mebendazole	15-20 mg/kg PO (O, C)
Oxfendazole	4.5 (B), 7.5-10 mg/kg PO (O, C)

*Dose depends on the product and species; follow manufacturers' recommendations; multiple treatments may be warranted depending on host species; sheep and goats should be dewormed by mouth; be aware some recommendations constitute off-label use.

B, Bovine; *C,* caprine; *IM,* intramuscularly; *O,* ovine; *PO,* by mouth; *SC,* subcutaneously.

Regardless, vaccination of treated animals before their second grazing season may be advisable.[2, 8]

VACCINES. An effective vaccine has been developed against *D. viviparus* in cattle and is available in the United Kingdom and parts of western Europe. Two doses of live, irradiated larvae are administered by mouth 4 weeks apart. The larvae migrate to mesenteric lymph nodes and provoke an immune response but die before they reach the lung. Management considerations associated with use of the vaccine include the following: (1) calves must be at least 2 months old; (2) vaccinated calves should not be placed on pasture for at least 2 weeks after the second dose; (3) vaccinated calves must not be exposed to heavily infected pastures, nor should they be mixed with animals showing signs of lungworm disease or with unvaccinated calves; (4) animals should not be treated with an anthelmintic during vaccination or the larvae in the vaccine will be killed; (5) immunity is not long-lasting, so animals must continue to be exposed to low levels of infective larvae to maintain immunity; and (6) the vaccine has a short shelf life and is relatively expensive. Farms with contaminated grazing areas and a history of lungworm disease benefit most from vaccination.[8,14,33]

Evaluation of Preventive Programs

The efficacy of preventive programs is best assessed by evaluating the number of susceptible animals that demonstrate signs of infection. Because total eradication of the parasite is difficult[16] and low numbers of parasites produce minimal problems and maintain immunity, a useful goal is the control of clinical signs and achievement of production parameters.

Clinical Management

DIAGNOSIS. Presumptive diagnosis of clinical lungworm infection is based on clinical presentation, farm history, seasonal prevalence, and response to treatment.[1-2,4] Verminous pneumonia may mimic respiratory diseases caused by other agents that require specific treatment. Although definitive diagnosis is difficult, it is important.

To document the presence of lungworm infection, it is necessary to demonstrate larvae or adult worms. In cattle and small ruminants, the presence of L_1 in fresh feces indicates lungworm infection.[1,14,34] The Baermann technique is the technique of choice for detection of L_1 in feces and is considered to be very sensitive for the diagnosis

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of patent primary bovine lungworm infections beginning about 3.5 weeks after infection, provided a sufficient number of animals are sampled.[34] Antibody detection tests have also been developed and are commercially available for use in cattle. Evaluation of their application for testing bulk milk tank samples indicates these tests appear to be most useful in diagnosing suspected dictyocaulosis in moderate to severe outbreaks. In mild outbreaks where just a few animals are coughing or on farms where prevalence is low (<20%), examination of serum and/or feces from individual animals is preferred.[35-36]

Although examining donkeys co-grazing with horses has been the standard recommendation for the antemortem diagnosis of *D. arnfieldi,*[4] diagnosis of lungworm infection in horses is often presumptive and usually based on resolution of clinical signs after treatment.[2-3]

Transtracheal wash may demonstrate a large number of eosinophils, which is supportive of verminous pneumonia, and eggs or larvae are occasionally seen with patent infections. This procedure can also help rule out bacterial pneumonia. Finding nematodes at necropsy is definitive. Adult *Dictyocaulus* are usually found in the bronchi or bronchioles, whereas adult *P. rufescens* tend to be in the bronchioles and adult *M. capillaris* are found in subpleural nodules on the dorsal aspect of the diaphragmatic lobes. Nematodes and the eggs may also be found in histologic section of the lung.

TREATMENT. Animals that are only coughing and/or tachypneic usually have small numbers of *D. viviparus,* and their treatment should result in a rapid recovery. For animals that are dyspneic and anorexic with or without a fever, lung damage is likely severe and anthelmintic treatment is unlikely to result in complete recovery. In some animals, anthelmintic treatment worsens the signs, and some heavily infected animals die. In severely affected individuals, hydration status should be monitored, particularly if the animal is not drinking. Antihistamines and antibiotics may also be included in the therapeutic regimen. Goats infected with *M. capillaris* may need multiple treatments.[2,8,14]

Evaluation of Parasite Control Programs

Sherrill A. Fleming

The efficacy of a given parasite control program should not be assumed; it should be assessed on a regular basis. The routine performance of quantitative tests for parasite burdens allows veterinarians to identify the development of anthelmintic resistance. Although fecal flotation is useful in identifying the presence of parasites, the use of the McMaster technique allows an estimation of the numbers of parasites. Both procedures are relatively simple and can easily be performed in the practice setting. Other specialized laboratory procedures are also discussed. Once resistance has been documented, it is important to identify the species involved through larval identification.

FEC and FEC Reduction Tests[1-5] (Box 49-2)

Determining numbers of nematode eggs in feces is the simplest and least invasive way to evaluate a parasite control program. Fecal examination may be of limited value in an individual animal because animals dying of parasitic infection may have no eggs in the feces, whereas animals with high FECs may be clinically normal. Nevertheless, FECs can provide information on the level of infection present in an individual animal, particularly when egg counts are repeated over the course of 2 to 3 weeks. Herd average FECs are more useful and provide an accurate reflection of the degree of environmental contamination and rate of infection. Pretreatment and posttreatment FECs can also be used to establish the efficacy of an anthelmintic in a particular group of animals. A quantitative McMaster or Stolley technique, rather than simple flotation, is crucial for accurate monitoring.

It is suggested that guidelines published by the World Association for the Advancement of Veterinary Parasitology (WAAVP) be used to perform and evaluate data from an FECRT test, applying practical modifications to fit the situation on the farm.[2] Briefly, groups of 15 animals that have not been treated within the past 8 weeks are randomly allocated to treatment groups, and FECs are performed using a modified McMaster technique 10 to 14 days after treatment. An untreated control group must be included. If fewer than 12 to 15 animals per group are available, then treatment groups should be balanced by performing a pretreatment FEC. Animals are then stratified by FEC from highest to lowest, blocked by number of treatment groups, and then within each block randomly assigned to treatment. Alternatively, where *Haemonchus* is the primary parasite, animals may be scored using the FAMACHA method as they come through the chute, blocked by FAMACHA score, and then randomly assigned to treatment within blocks. This approach is a bit more complicated but will result in groups that are balanced, which will result in a more accurate test. Calculations are performed using the following formula:

$$\text{FECR\%} = 100 \times \left(1 - \frac{X_{t_2}}{X_{t_1}} \frac{X_{c_1}}{X_{c_2}}\right)$$

where X_c and X_t are the geometric mean or arithmetic mean EPG for control (c) and treated (t) groups before (1) and after (2) treatments, respectively.[5] Software is available for free that performs all calculations and gives data interpretation.[6,7] If the RESO calculator is used, the assignment of resistance status is based on both percent reduction and the 95% confidence intervals. If the RESO calculator is not used, the following guidelines can be applied: reductions of greater than 98% indicate high efficacy, reductions of 90% to 98% indicate efficacy, reductions of 80% to 89% indicate moderate efficacy, and reductions of <80% indicate insufficient efficacy. FECRT yields reliable data only if FECs are sufficiently high to properly measure a reduction from treatment. If the control group's mean FECs are below 150 epg, then objective assessment of resistance will not be reliable. Group mean FECs of less than 150 epg can be common in adult sheep; therefore when FECRT is performed on a sheep farm it is preferable to use weaned lambs if available. With goats, low FECs are usually not a problem.

Larval Identification

Ideally, if there is less than a 90% egg count reduction, the eggs should be hatched and the larvae species identified. In the majority of cases these will be *H. contortus,* but other species, especially *Trichostrongylus* species, readily develop resistance as well. One can sometimes be fooled into an improper interpretation of egg count reduction results if mixed species are present and only one is resistant.

Egg Hatch Assays and Larval Development Tests[1]

Eggs from feces are incubated with concentrations of the anthelmintic to be tested and the eggs hatched. A dose-response curve is generated (DrenchRite test from Horizon Technology, Sydney, Australia).[1] The advantage of this test is that a single fecal sample can be tested for all available classes of anthelmintics simultaneously. The cost of this test has recently increased and may discourage owners from pursuing this diagnostic. However, when compared with the cost of using anthelmintics that are ineffective, it is easy to justify the use of this test. It is important to read instructions for submitting this test and scheduling a testing date before the samples are collected.

Larval Culture

Larval cultures can be used to distinguish between large and small strongyles in horses and to identify the various nematode species in ruminants. Most parasitology laboratories can perform this examination. It requires submission of 200 to 400 g of fresh feces. Pooled samples from several herd members are often used.

Pasture Larval Counts[8]

Counts of parasitic larvae on herbage are useful to indicate the level of exposure experienced by the grazing animal. This examination is

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BOX 49-2

Modified McMaster Technique (Fecal Egg Count)

This is one method for performing a McMaster fecal egg count. Similar protocols are used routinely in many laboratories, so you may see a slightly different procedure recommended elsewhere. The important point is to use the same procedure each time.

The first step is to collect freshly passed feces uncontaminated by soil or bedding. The best way is to wear a rubber glove and extract feces directly from the rectum. Alternatively, feces can be picked up off the ground if done soon after deposition. The collection container should be labeled with the identification of the animal and the date of collection. Fresh samples work best, but accurate results can be obtained if the sample is refrigerated during the interim. If samples are not refrigerated, the eggs will hatch within 12 to 24 hours. Once hatched, eggs cannot be counted.

Materials

Compound microscope
Scale
Saturated sodium chloride (table salt)
50-mL centrifuge tube, with screw cap and marked with milliliter increments
Pipette (1-mL syringe or eye dropper works well)
McMaster egg counting slide (Chalex Corporation, Issaquah, Wash.)
Paper towels
A fresh fecal sample, refrigerated until tested

Procedure

1. Weigh out 2 g of feces into a 50-mL centrifuge tube and fill to 30-mL line with salt solution. It is recommended to purchase a small scale and weigh feces, but if you do not have a scale you can still get a close estimation by putting 28 mL of salt solution into a 50-mL centrifuge tube first and then adding feces until a volume of 30 mL is achieved.
2. Pour off approximately 25 mL of the salt solution into another small container, keeping feces in the tube (use tongue depressor).
3. Soak feces for a few minutes and mix (soft feces) or break up (fecal pellets) with tongue depressor.
4. Add back approximately one half of the salt solution and mix well, breaking up any remaining feces as well as possible.
5. Add back the remaining salt solution and screw the cap back onto the tube.
6. Shake tube vigorously for approximately 1 minute to disrupt any remaining feces as much as possible.
7. Set tube aside for a few minutes to let bubbles dissipate.
8. Wet McMaster chamber with water and dry top and bottom on paper towels.
9. Rock (do not shake) tube several times to thoroughly mix solution without causing large air bubbles to form.
10. Immediately pipette (using 1-mL syringe or eye dropper) a sample of the suspension and fill both sides of counting chamber. Work quickly. If it takes more than a few seconds to load the first chamber, mix the fecal solution again and refill pipette before loading the second chamber.
11. Let the sample stand for 1 to 2 minutes to allow eggs to float.
12. Count all eggs inside of grid areas (more than one half of eggs should be inside grid) using low-power (10×) objective. Focus on the top layer, which contains small air bubbles (small black circles; if numerous large air bubbles are visible, remove the fluid and refill).
13. Count only trichostrongyle and strongyle eggs (oval shaped, approximately 80 to 90 microns long). Do not count *Strongyloides* species (oval, ≈50 microns long), tapeworm eggs (triangular or D shaped), or coccidia (various sizes). Note the presence of other species, but count only the trichostrongyle and strongyle eggs.
14. Once filled, the chambers can sit for no longer than 60 minutes before counting without causing problems. After 60 minutes, drying and crystal formation may begin.
15. Total egg count (both chambers) × 50 = epg (eggs per gram).

Notes

This is a dilution technique, and theoretically this ratio of feces to flotation solution will not detect infections with fewer than 50 eggs per gram of feces (one egg seen on slide), so it is not accurate for samples with low numbers of eggs. On a practical level this is not important because from a clinical standpoint, slight differences in results when egg counts are low do not matter.

Fairly soon after counting is complete, thoroughly rinse out the McMaster chamber with warm running water. Doing so will keep the chamber clean and ready to be used again. If fecal solution dries in the chamber, do not soak in soapy water for long periods because this will cause the chamber to become cloudy. If the chamber gets dirty, soak for only a few minutes in water containing dish soap and then rinse completely with tap water.

somewhat tedious but can be performed by many university laboratories. A 2-kg sample of forage is gathered for submission to the laboratory. The grass is sampled by walking a V pattern across the acreage and stopping every three paces to sample grass. The samples are subsequently washed and passed through screening to isolate and identify larvae.

Necropsy Evaluation

The nature and magnitude of parasitic infections can be established by necropsy examination. Gross examination and an estimate of adult worm population in the gut lumen are often sufficient. Many worms detach from the mucosa as the carcass cools; however, the damage done by the parasites can be seen on gross or histologic examination. Occasionally it is necessary to use digestion techniques or histologic examination to document the presence of hypobiotic larvae.

Anthelmintic Use[1]

Sherrill A. Fleming

An anthelmintic is defined as an agent that acts to destroy or expel parasitic intestinal helminths. Anthelmintic drugs are used to treat animals that are suffering the adverse effects of a parasitic burden. They may also be used to prevent and minimize the economic losses associated with parasitic infection. Anthelmintics may be used on individual animals or a group of animals.

Drug Action

To use an anthelmintic properly, it is necessary to consider its mode of action, spectrum of activity, and duration of effect. The pharmacodynamics of an anthelmintic is specific for each species that is treated. Efficacy for a given drug may be defined as its ability to kill adult or larval parasites, suppress parasitic egg production, or promote the expulsion of worms from the gastrointestinal tract.

The emergence of drug-resistant strains of nematodes has necessitated the use of each class of anthelmintic to be customized to the premise where it will be used. Package inserts should be regarded as guidelines rather than gospel. Please refer to the sections on Anthelmintic Drugs and the Evaluation of Parasite Control Programs for particulars on anthelmintic performance. Readers should refer to the sections on horses, cattle, and small ruminants for more specific recommendations.

Anthelmintic Drugs (see Table 49-4)[1,2]

Avermectins and Milbemycins

The avermectins and milbemycins are macrocyclic lactones. They act by increasing the permeability of parasite cell membranes to

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chloride ions, which results in nonspastic paralysis and death of the parasite. These drugs may also act by potentiating presynaptic release of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, although this theory has been challenged.

These products have a high level and broad spectrum of activity against adult and larval nematodes. They are also effective against various ectoparasites such as mites, lice, ticks, bots, and cattle grubs; however, they are ineffective against flukes and tapeworms. These drugs suppress nematode egg production for longer than other anthelmintics. Because of its long duration of effect, moxidectin suppresses fecal egg counts and protects against reinfection for longer than ivermectin. Concern has been expressed about the environmental impact of these long-acting anthelmintics in grazing animals.

Several products have been developed for use in animals. The avermectins include ivermectin, abamectin, doramectin, and eprinomectin. The milbemycins include nemadectin and moxidectin. Oral (drench, sustained-release intraruminal device), topical (pour-on), and injectable formulations are available, depending on the drug. Ivermectin is safe to use during pregnancy, but currently it is not approved for use in lactating dairy animals or females of breeding age. Similarly, doramectin and moxidectin are not approved for use in female dairy cattle of breeding age. Eprinomectin is unique in that it has no withholding period for milk or meat, so there are no restrictions on its use in cattle. At labeled doses, moxidectin is a safe drug; however, accidental overdosage has caused neurologic signs in foals and miniature horses.

A new product that maintains extended therapeutic levels in cattle has recently been released. This product is designed to have a shortened subtherapeutic period that should lessen the selection for resistant nematodes. However, it will not help with parasites that are already resistant to this class of anthelmintic.

Benzimidazoles

The benzimidazoles (BZDs) comprise a large class of anthelmintics that interfere with parasitic carbohydrate metabolism by inhibiting the enzyme fumarate reductase. Many BZDs have been developed and marketed. They include albendazole, fenbendazole, mebendazole, oxfendazole, oxibendazole, parbendazole, ricobendazole, thiabendazole, triclabendazole, and the probenzimidazole drugs febantel and netobimin.

BZDs are widely used in horses and ruminants. In general they exhibit a high degree of safety and a broad spectrum of activity against gastrointestinal nematodes (GINs) and lungworms. Some members of this class (e.g., albendazole) are also active against liver flukes and certain cestodes in ruminants. Albendazole and netobimin can cause teratogenicity and embryo toxicity in sheep when given during early pregnancy. Fenbendazole, oxfendazole, and oxibendazole are considered to be safe for use in pregnant animals.

Resistance to BZDs has been documented in certain equine, ovine, and caprine parasites (see species-specific sections). In general a strain of parasite resistant to one BZD drug quickly develops resistant to other BZDs or pro-BZDs, a phenomenon known as *side resistance*.

Levamisole

Levamisole acts by causing neuromuscular depolarization and paralysis of the parasite. It has been widely used in ruminants to treat GINs and lungworm infections. However, levamisole resistance has become a problem in many areas. Levamisole is the only anthelmintic that has shown resistant parasites reverting to sensitivity if not used for several years. Recurrence of resistance will develop fairly rapidly with reuse of levamisole.

The dose of levamisole should be calculated carefully because toxic doses are only one to two times therapeutic doses. Signs of toxicity may mimic those of organophosphate (OP) toxicity, including muscle fasciculations around the lips and eyelids, hypersalivation, spastic movements, depression, and diarrhea. In ruminants, muzzle foam may develop after oral administration of the drug but usually disappears within a few hours after administration. In horses, transitory excitement has been seen after treatment. Levamisole is not recommended for use as an anthelmintic in horses. Concurrent administration of morantel, pyrantel, diethylcarbamazine, or OPs could enhance the toxic effects of levamisole.

Morantel and Pyrantel

The tetrahydropyrimidines morantel and pyrantel are cholinergic agonists that exert their anthelmintic effect by depolarizing neuromuscular junctions and causing irreversible paralysis of susceptible parasites. Morantel is slower in its onset of action but much more potent than pyrantel. These products are effective against many species of adult nematodes but do not appear to be active against larval stages. Pyrantel is also effective against tapeworms in horses when given at twice the recommended dose. The margin of safety is relatively wide, and there is no contraindication to use with other cholinergic drugs. However, it is recommended that morantel and pyrantel not be used concurrently and that neither be given with levamisole. Piperazine antagonizes the effects of morantel and pyrantel, so it should not be used with either of these drugs. Resistance to morantel and pyrantel has been documented in strains of *H. contortus* and in some cyathostomes (equine small strongyles).

Organophosphates

OPs block neurotransmission by inhibiting acetylcholinesterase. Various formulations of OP drugs are available for treating gastrointestinal nematodiasis. Commonly used OPs include haloxon, coumaphos, trichlorfon, and dichlorvos. Toxicity occurs with these products in a dose-related manner, so dosages should be calculated with care. In addition, the potential danger to humans administering these products should not be overlooked. Atropine is recommended in cases of overdose in livestock.

Phenothiazine

The mode of action of phenothiazine (PTH) has not been clarified; it is thought to interfere with anaerobic metabolism of nematodes. The various formulations of PTH differ in purity and particle size. The purified product (99% PTH) with small particle size (2 μm) is the most effective.

Although PTH is effective against a wide spectrum of GINs, resistant strains of parasites have emerged in several species. The drug is synergistic with piperazine; combinations of these drugs have effective activity against PTH-resistant nematodes. PTH used in combination with piperazine can be administered at a much lower dose.

PTH toxicity has been reported. Toxic reactions include corneal inflammation, abortion, ataxia, hemolytic anemia, photosensitization, and nephrotoxicity. The drug should not be administered to debilitated or anemic animals or to animals in the last month of pregnancy.

Piperazine

Piperazine salts block neuromuscular transmission, resulting in paralysis of susceptible GINs. The worms are then passively removed from the gastrointestinal tract by intestinal peristalsis. Piperazines have low toxicity and are safe in young or pregnant animals. However, their spectrum of activity is limited, in practical terms, to ascarids. Piperazine must be used with caution in horses heavily infested with ascarids because the paralyzed ascarids can cause an impaction that may culminate in bowel rupture. Diethylcarbamazine is a piperazine derivative that has been used to control lungworm infection in sheep and cattle.

Praziquantel

Praziquantel is a cesticidal drug that causes spastic paralysis, decreased glucose uptake, and disruption of the tapeworm's tegument. Although not approved for this use, praziquantel is effective for treating tapeworm infestation in horses. It has also been used to control various cestodes in small ruminants.

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Monepantel

Monepantel is a new amino-acetonitrile compound that has a unique mode of paralyzing nematodes and is intended to be used as an oral drench. This product has been released for use in New Zealand but is not available in the United States at this time. The responsible use of this drug to prevent or slow the development of resistance to this anthelmintic is crucial.

Coccidiosis in Food Animals

Lora Rickard Ballweber

Coccidiosis causes serious economic losses in a variety of food animal species. Regular infections with a mixture of species generally occur throughout the life of the animal. Infections tend to be asymptomatic and self-limiting unless management or other factors allow the abnormal concentration of oocysts in the environment or when host defenses are compromised. Kids are especially susceptible to coccidiosis and may develop chronic diarrhea as a consequence. In many production operations, coccidiosis is an annual event.

Life Cycle Coccidiosis in ruminants is caused by intracellular parasites of the genus *Eimeria.* They are strictly host specific, developing within cells at species-specific sites along the intestinal tract. The life cycle is complex, involving both sexual and asexual phases within the same host. Unsporulated oocysts are passed in the feces and subsequently sporulate (1 to 4 days under ideal conditions) in the environment to become infective. The sporulated oocysts are ingested by the host with contaminated food or water. Digestive enzymes activate the sporozoites within the oocysts, which excyst in the intestine and enter intestinal cells. The asexual phase of development, in which two or more cycles of merogony occurs, is then initiated. Asexual fission results in the production of merozoites. Mature meronts rupture (along with the host cell), releasing merozoites, which enter other cells and repeat the cycle or progress to the sexual phase of development (gamegony). In this phase, merozoites enter new cells and produce macrogametes and microgametes. Microgametes are released by cellular rupture and fertilize a macrogamete to form a zygote. A cyst wall then forms around the zygote, resulting in the next generation of oocysts. Once again the host cell ruptures, releasing oocysts into the lumen of the intestine, where they are then passed with the feces. The prepatent period is generally 1 to 4 weeks, depending on the particular species of *Eimeria.*[1-3]

Pathophysiology Most intestinal *Eimeria* develop exclusively in the intestinal epithelial cells, although a few exceptions (e.g., *Eimeria bovis*) do exist. As a result of the developmental cycle, infected host cells are destroyed. However, the degree of damage depends on the species of *Eimeria* involved, the site of infection (see later), the number of oocysts ingested, and various host factors including age, physical condition, and premunition.[1-3] If the number of oocysts ingested is low, nonimmune healthy animals may tolerate infection and show no signs of disease. However, if nonimmune animals ingest many oocysts, widespread rupture and exfoliation of intestinal cells alter gut function, allowing loss of blood, fluid, albumin, and electrolytes into the gut. Secondary bacterial invasion can also occur. Sections of sloughed intestinal mucosa and fibrin casts may be seen in the feces, which may be blood tinged.

The most pathogenic species of ruminant coccidia are those that destroy the cells of the large intestinal mucosa (*E. bovis* and *E. zuernii* in cattle; *E. crandallis* and *E. ovinoidalis* in sheep; *E. ninakohlyakimovae* and *E. caprina* in goats) or involve deeper layers of the lower small intestine (*E. christenseni* in goats). Because the ruminant small intestine is very long, providing many host epithelial cells, enormous parasite replication can occur with minimal damage. If nutrient absorption is compromised, the large intestine can compensate to a certain extent. Conversely, the rate of cell turnover in the large intestine is much lower than that in the small, it is much shorter in length, and other regions of the gut cannot compensate for its impaired function.[3]

A condition called nervous coccidiosis has been described, primarily in weaned beef cattle.[4-8] The pathophysiology of this manifestation has never been definitively established, and conflicting theories have been proposed, including copper imbalance, plasma electrolyte imbalances, a neurotoxin, and a combination of stressors in which coccidia are only one factor.[2,4,7,8]

Populations at Risk Infections with mixtures of pathogenic and nonpathogenic species of *Eimeria* occur throughout the life of most ruminants and usually do not cause clinical signs because species-specific immunity is acquired quickly and maintained by continuous reinfection. The net effect of the immune response is a reduction in clinical signs and a decrease in oocyst production.[1,3] Therefore, adults help maintain the parasite but are not usually the source of heavy environmental contamination; rather, nonimmune animals, whose infections result in excretion of massive numbers of oocysts, are primarily responsible.[1-3] Clinical coccidiosis is therefore a disease of young, nonimmune animals that ingest large numbers of sporulated oocysts from heavily contaminated environments. Conditions favoring coccidiosis include overcrowding, housing multiple age groups together, and pens that are not cleaned regularly.[3,9] Thus coccidiosis is a disease of management. Although stress, such as from shipping, weaning, dietary changes, and/or adverse weather, appears to facilitate outbreaks, the mechanisms are not fully understood.[1-3,10]

Even though reported in range animals, coccidiosis is chiefly a disease of confinement. Clinical disease usually occurs in cattle 3 weeks to 6 months of age. In dairy cattle, coccidiosis is most common in calves when they are taken from hutches into group calf pens or mini–free-stall barns. In beef cattle the disease is most prevalent in feedlot calves. In sheep, disease is usually limited to lambs younger than 6 months old. Coccidiosis is most common in intensively reared lambs, although suckling lambs on pasture in constant use at high stocking rates are also at risk. Young kids appear particularly susceptible to coccidiosis, with clinical disease especially prevalent 2 to 3 weeks after weaning.[11] Occasionally, adult animals develop coccidiosis either from impaired cellular immunity or when stressed (moved into a new herd, prolonged travel, extreme weather conditions).[2,3]

Clinical Manifestations The destruction of epithelial cells and subsequent loss of blood, albumin, fluid, and electrolytes typically cause a profuse, sometimes bloody, diarrhea. Despite the blood loss, anemia is not usually apparent. Death is usually from dehydration. Light to moderate infections in cattle may cause watery feces, poor condition, and reduced weight gain. Severe infections cause projectile, bloody diarrhea with mucus, rectal tenesmus, inappetence, dehydration, and weight loss. Clinical signs last approximately 1 week. In lambs, clinical signs are similar to those of cattle except blood and tenesmus do not usually occur. In kids, clinical signs include pasty, watery diarrhea and dehydration.[11] Sudden death can occur in both lambs and kids, but the case fatality rate is usually low in most outbreaks. After recovery from the disease the gut does not return to normal function for several weeks, and concurrent appetite suppression leads to poor growth and/or stunting.[1]

Cattle considered to have nervous coccidiosis exhibit muscle tremors, hyperesthesia, nystagmus, and seizures. Interictal periods are normal or near normal. The mortality rate is high.[2,5,6]

Control of Coccidiosis

The presence of coccidiosis depends on the prevalence of oocysts in the environment. The level of infection is directly related to the level of fecal contamination. Houses and pens used for sequential groups of young animals often become highly contaminated and serve as the source of infection for subsequent groups. Therefore minimizing exposure of susceptible animals to infective oocysts depends on

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TABLE 49-5

Drugs Used for Treatment and Prevention of Coccidiosis in Ruminants

Drug	Treatment*	Prevention*
Amprolium	10 mg/kg bwt for 5 days (B) 25-40 mg/kg bwt for 5 days (O, C) 65 mg/kg bwt once (O, C)	5 mg/kg bwt for 21 days (B) 50 mg/kg bwt for 21 days (O)
Decoquinate		0.5 mg/kg bwt for 28-30 days
Diclazuril		1 mg/kg bwt once; a second dose can be given 14 days later
Lasalocid		1 mg/kg bwt continuously (B) 25-400 mg/ton feed, continuously (B, C) 80 mg/kg milk replacer (neonatal calves) Free choice in salt at 0.75% total salt mixture
Monensin	2 mg/kg bwt for 20 days (O)	1 mg/kg bwt for 28 days 10-20 ppm in feed, continuously 16-33 g/ton of feed, continuously
Nitrofurazone	15 mg/kg bwt for 5-7 days In feed at 0.04% or in water at 0.0133% for 7 days	33 mg/kg bwt for 14 days In feed at 0.04% for 21 days
Salinomycin		10 ppm in feed (O)
Sulfadimethoxine		50 mg/kg bwt for 5 days (O)
Sulfamethazine	247 mg/kg day 1, 123 mg/kg days 2-5 140 mg/kg bwt for 3 days 140 mg/kg bwt once, then 70 mg/kg bwt for 5-7 days	35 mg/kg bwt for 15 days (B) 25 mg/kg bwt for 7 days (O) 55 g/ton of feed (C)
Sulfaquinoxaline	10-20 mg/kg bwt for 5-7 days	
Toltrazuril	20 mg/kg bwt	20 mg/kg bwt once, timing depends on production system

*Oral administration; dose or regimen may vary among references.

B, Bovine; *bwt,* body weight; *C,* caprine; *O,* ovine.

Note: Coccidiostats used in poultry feeds may be toxic to ruminants.

management techniques that focus either on sanitation to avoid the buildup of environmental contamination or the elimination of environmental conditions conducive to oocyst survival or both.[2,3,9] Decreased stocking rates, proper manure disposal, elevated feed bunks, and routine cleaning of water troughs will help reduce contamination and exposure to oocysts. Sunlight and low humidity will kill oocysts, as does disinfection with formaldehyde, ammonia, or methylbromide; however, proper cleaning is a prerequisite for efficient disinfection.[1-3,9] Reduction of average barn temperature to 15° C and of humidity to a maximum of 80% was shown to decrease clinical coccidiosis.[1] Prophylactic use of coccidiostats is inevitable if conditions of animal husbandry cannot or do not improve.

DRUGS. The various drugs that have been used to prevent or treat coccidiosis in ruminants are listed in Table 49-5.[12-16] These drugs are most often administered in the feed or water. Therapeutic anticoccidials are used in acute outbreaks; particularly useful here in calves are the benzene acetonitrile compounds (diclazuril, toltazuril).[2] Scouring calves should be removed from the group, and supportive therapy, including electrolytes, glucose, and antidiarrheals, may help improve survival.[1,3,11]

Often outbreaks of coccidiosis can be predicted on the basis of farm history. Thus to prevent losses from coccidiosis, it is best to use drugs prophylactically or metaphylactically rather than therapeutically. Administration of coccidiostats during this time does not completely prevent infections but prevents clinical disease without interfering with the production of protective immunity.[1,2]

OTHER STRATEGIES FOR MINIMIZING CLINICAL INFECTIONS. No vaccine for ruminant coccidiosis exists. Immunization of calves with a "trickle dose" of oocysts before turnout onto infected pasture attenuates the effects of natural challenge[17] but is not commonly used. Use of growth implants containing estradiol and progesterone can attenuate the effects of high oocyst challenge in dairy calves but is not used for this purpose.[18] It has been reported that oocysts of *Eimeria alabamensis* may survive the hay-making process,[19] and hay from infected pastures should not be used to feed susceptible calve. However, whether all species of *Eimeria* can survive the hay-making process or how common survival is with various types of hay production is unknown.

Evaluation of Preventive Programs

Evaluation of any coccidiosis prevention plan is based on the presence and/or extent of clinical disease. Herds/flocks that require preventive strategies do so because they usually have a history of prior disease. Program efficacy, therefore, is evaluated on the basis of a decrease in prevalence of clinically ill animals.

Clinical Management

DIAGNOSIS. Diagnosis is based on history, which may include a stressful event, thorough knowledge of the herd management, and clinical signs of severe diarrhea (usually young animals). Postmortem findings of inflammation, hyperemia, and thickening of the cecum with masses of gamonts and oocysts in mucosal scrapings will be confirmatory. Because pathogenicity varies by species, fecal oocysts counts are not helpful *if the respective species are not identified.* Due to the short life cycle, oocyst counts are highest in early patency and drop quickly after about 1 week. Thus fecal samples should be collected when diarrhea first starts. Any standard fecal flotation method can be used to find oocysts.[1,3,11]

TREATMENT. Drugs used in the treatment of coccidiosis are listed in Table 49-5. Supportive therapy, when indicated, is primarily directed at replacing fluid losses and supporting the animal until the gut epithelium regenerates.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 50

Nutrition of the Sick Animal

MERI STRATTON-PHELPS, *Consulting Editor*
RAYMOND W. SWEENEY

The influence of nutrition on the recuperation of veterinary patients is often overlooked, although the effects of nutritional status on recuperative ability are well known. Many patients are in a state of protein calorie malnutrition when first presented to the clinician. Early intervention with supplemental calories, protein, and other essential nutrients provides the patient with the dietary resources needed to optimize immune function, promote wound healing, and improve the recovery of the animal.

Multiple research studies have demonstrated that the immune response of an animal is directly related to the nutritional state of the animal.[1-4] A deficiency of calories, protein, minerals, or vitamins alters the production of inflammatory cytokines, adversely affects leukocyte function, and decreases host resistance to bacterial infections.[1,2] Clinical studies in hospitalized horses have demonstrated an improved recovery after gastrointestinal surgery in patients supplemented with intravenous nutrition.[5]

Different forms of diet therapy may be used, depending on the clinical condition of the animal and the ability of the animal to tolerate different types of supplemental nutrition. Enteral nutrition (EN) is the preferred method of nutrition support because it provides nutrients directly to enterocytes in a physiologically normal manner. EN can be provided to large animal patients that have a functional gastrointestinal tract and can tolerate placement of a nasogastric (NG) or esophageal feeding tube. Intravenous nutrition can be provided by adding dextrose to a patient's intravenous fluids to provide energy, or supplemental nutrients can be administered in a parenteral nutrition (PN) formulation. PN may be the only suitable long-term (longer than 4 days) nutrition support choice for animals that cannot tolerate placement of an NG tube, that do not have a functional gastrointestinal tract, or that are recumbent.

Assessment of Nutritional Status

Before initiation of dietary therapy, the large animal patient must be examined to determine its nutritional needs. Animals may be anorectic owing to systemic disease, or they may be dysphagic owing to a mechanical (foreign body, abscess, poor dentition) or neurologic (botulism, tetanus, viral encephalitis) disease. Assessment of the nutritional status of the patient should include a measurement of the body weight (BW) and body condition score (BCS) of the animal. BW measurements should be taken at the time that the large animal patient is presented to the clinician and as frequently as possible during hospitalization. If a scale is not available, estimations of BW can be made with a weight tape or by using length and girth measurements (see Chapter 9). The BCS also helps in the evaluation of the nutritional status of the patient. The BCS system enables the clinician to subjectively assess the endogenous protein and lipid stores in a large animal patient. A list of BCS descriptions for different species is provided in Chapter 9. Changes in weight or BCS are often easily overlooked in day-to-day observations of the patient if a concerted effort is not made to detect them. Palpation of the animal (ribs, dorsal vertebral processes) is necessary in sheep with a heavy fleece, camelids with long fiber, and horses with a thick winter hair coat. Animals with a low BCS (1 to 3 of 9; 1 to 1.5 of 5) have minimal protein and lipid stores and are at greater risk for developing protein calorie malnutrition after a period of anorexia. Large animal patients with a high BCS (7 to 9 of 9; 3.5 to 5 of 5) that are anorectic may have an increased risk for developing complications (hyperlipemia, hepatic lipidosis) from abnormal lipid metabolism. A clinician should initiate dietary therapy in a large animal patient that loses 3% to 5% of its initial BW or whose BCS diminishes by 1 grade or more.

Biochemical tests provide another method to evaluate the nutritional status of the large animal patient. Endogenous protein catabolism is a normal physiologic response to anorexia in animals. To date, few biochemical tests are available to assess protein malnutrition in large animals. Although anemia and hypoproteinemia (hypoalbuminemia) are occasionally seen in cases of malnutrition, they are not specific and frequently are associated with another primary disease process such as parasitism or protein-losing enteropathy. Severe protein malnutrition can result in abnormally low serum urea nitrogen (SUN) concentrations in horses and ruminants. Liver disease also decreases the formation of urea nitrogen and must be ruled out when evaluating the animal. Protein malnutrition can result in an increase in the urinary excretion of 3-methylhistidine, a myofibril amino acid that is not metabolized. Measurement of this metabolite in the future may be a useful tool to monitor protein catabolism in large animal patients.[6]

Underfed horses develop a mild hyperbilirubinemia (unconjugated) that, although not directly related to nutritional status, is readily reversed when food intake resumes.[7,8] Animals that are in negative energy balance rely on endogenous stores of lipid as an energy source. Serum non-esterified fatty acids (NEFAs) and/or triglycerides are expected to rise in these animals. Once nutritional support or refeeding is initiated, these lipid metabolites usually decrease. Pathogenic elevations in serum triglyceride (greater than 500 mg/dL) develop in some equine patients that are anorectic and that have a high daily energy requirement (lactation, pregnancy), but hypertriglyceridemia can also occur in patients with insulin resistance, renal failure, obesity, and in predisposed breeds (miniature horses, ponies). Ketone bodies have a glucose-sparing effect in the body and are normally produced from fatty acids and amino acids in animals that are in negative energy balance. Ketonuria develops after the excess production of ketones and can be used to indirectly monitor the severity of caloric malnutrition in ruminants. Hypoglycemia is a common complication in large animal neonates that are malnourished but is an uncommon finding in adults. Both adult and neonatal large animals may develop glucose intolerance and hyperglycemia during periods of systemic illness and may require

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treatment with a diet that will not exacerbate the hyperglycemia. Electrolyte and mineral derangements including hypocalcemia, hypomagnesemia, hyponatremia, hypochloremia, hypophosphatemia, and hypokalemia may develop in inappetent, systemically ill large animals or during the refeeding process.[9,10] Chronically malnourished animals must be closely monitored, and biochemical signs of the refeeding syndrome should be managed with appropriate electrolyte supplementation.

Nutrient Requirements of Large Animals during Clinical Illness

Although it is generally accepted that sick animals have increased nutritional requirements, these requirements have not been quantified for specific disease conditions. Therapeutic nutrition is designed to provide adequate caloric intake during a period of hypophagia. Both overfeeding and undernutrition should be avoided when nutritional support is offered.[11] Currently, the best estimation of energy and protein requirements for hypophagic horses and ruminants is calculated from the animal's BW (see Chapter 9) or they can be determined from the National Research Council (NRC) tables.[12] For adult horses, the resting digestible energy (DE) requirement is calculated as DE_{rest} (Mcal) = 0.975 + 0.021 BW (kg), and maintenance crude protein (CP) requirement is calculated as CP (g) = 1.26 BW (kg).[12] For a 450-kg horse, these would equate to a 10.4-Mcal resting energy requirement and a 567-g crude protein requirement. The ideal BW should be used for calculating the energy requirement of an obese animal. Protein requirements can be calculated using an obese animal's current BW as long as protein restriction is not required based on the patient's clinical disease. Indirect calorimetry provides the best estimation of a patient's resting energy requirements, but currently is only available for critically ill neonatal foals who have an estimated resting energy expenditure of 40 to 50 kcal/kg BW/day.[13,14] Older foals can be fed between 70 and 100 kcal/kg BW/day. Dietary protein for foals ranges between 2 and 5 g protein/kg BW/day. For calves, the resting energy requirement is approximated as DE (Mcal) = 0.07 BW (kg) and digestible protein as DP (g) = 3.5 BW (kg), which would equate to 3.50 Mcal (3500 kcal) and 175 g of protein for a 50-kg calf. These calculated values represent starting points for formulating dietary therapy, and adjustment based on clinical response or specific medical conditions may be necessary.

Vitamin and mineral requirements, also available from NRC tables, can usually be met if an enteral diet is formulated with commercial complete feed pellets or pelleted hay. Parenteral solutions can be supplemented with vitamins and minerals. Although B-vitamin deficiencies do not occur naturally in horses and cattle, supplementation may be beneficial in large animals with gastrointestinal diseases that result in the disruption of the normal tract flora that produce B vitamins.

Oral Supplementation

The animal's feed intake should be monitored during treatment. If the animal is losing condition despite consuming all feed offered, more or higher-quality feed should be provided. If the animal's appetite is poor, the patient should be offered a variety of highly palatable feeds, including fresh grass, dried forages, and complete commercial feed pellets. Although sweet feeds are palatable, they contain a high concentration of soluble carbohydrates (sugar, starch) and their use should be limited to a top dressing of other feeds. Ruminants in particular may consume small quantities of fresh feed if it is offered frequently, whereas if the same quantity is offered in one feeding, it may be ignored after a few bites. Many dairy cows can be coaxed into eating hay if it is placed in the back of the pharynx by the clinician, and oropharyngeal stimulation may result in increased voluntary feed consumption. Fresh silage and dried brewer's grain frequently appeal to the hypophagic cow. Many sick horses and ruminants benefit from grazing if grass is available.

A hospital feeding chart should be created to facilitate monitoring of the feed consumed by a hospitalized patient. Use of an inexpensive farm scale is the most accurate way to measure the amount of feed offered to a patient. Feed that is not consumed within a few hours should be weighed and discarded to prevent the accumulation of stale, and possibly fermented, malodorous feed. If the animal does not voluntarily consume enough feed to meet 75% of its resting energy requirements or 75% of its maintenance protein requirements, or if the animal loses weight or condition, dietary therapy with a liquid diet by intragastric administration should be considered. Dysphagic animals can also be managed with a tube-fed liquid diet as the sole source of nutrition.

Liquid Diets for Horses

Adult Horses

Enteral feeding (EF) with a liquid diet should be used in horses that require nutritional support to maintain their energy and protein intake during a short period (2 to 14 days) of partial or complete anorexia. Horses that are good candidates for EF do not have gastrointestinal ileus or gastric reflux and are able to tolerate an indwelling NG tube, repeated intubation, or an esophagostomy tube. Horses fed using EF should be standing. Diet choice will depend on product availability and nutrient requirements. Energy, protein, vitamin, and mineral requirements should be calculated for each equine patient to ensure that the appropriate concentration of nutrients is administered. Enteral diets may be administered to provide partial or complete nutrient supplementation to an adult horse.

TYPES OF ENTERAL DIETS. Liquid diets may be classified into four categories: (1) commercial equine enteral diets, (2) complete feed blender diets consisting of liquefied or finely ground whole food suspended in water, (3) composition diets containing highly digestible whole protein (usually casein or soy), fat, and carbohydrate, and (4) commercially available liquid enteral diets sold for human use. Because of the large variety of equine enteral diet options, human formulations are the least desirable choice for EF and should only be used when other diet options are not available.

Commercial equine enteral diets offer a convenient option for managing a horse that requires supplemental EN. WellSolve Well-Gel (Purina Mills, LLC, St. Louis, Mo.) and Enteral Immunonutrition Formula (Platinum Performance, Inc., Buellton, Calif.) are two diets currently available for use. Both diets are mixed with water and can be administered through a small-diameter nasogastric tube. These diets can also be fed orally while a horse is being transitioned to a regular ration. Diets should be introduced gradually and fed in multiple small meals throughout the day.

Blenderized equine commercial complete feeds or hay pellets are inexpensive ($5 to $10/day), and the ingredients are usually available at most veterinary hospitals or barns. Most products contain 14% to 25% crude fiber (dry matter [DM]) and vary in energy density from 2.6 to 3.1 Mcal/kg of diet. A list of commercial feeds that can be fed as a liquid enteral diet is provided in Table 50-1. Feeds with less than 18% non-structural carbohydrates (NSC) are preferred. Between 3.4 and 6.0 kg of diet per day is required to meet the resting energy requirements of a 450-kg horse. In some equine patients, protein supplementation may be required. If tolerated, a small volume of oil (113 to 227 mL) can also be added to increase the energy density of the diet. If a plain hay pellet is used, vitamin and mineral supplementation should be considered. This type of a diet may be prepared either by grinding one quarter to one third of the daily requirement of dry pellets in a blender and suspending the blended product in water or by soaking the pellets in water before blending to create a slurry. Each meal should be made fresh. The total amount of water that is added to the preparation should be recorded and added to the daily fluid administration log for the patient. The total daily volume of the diet should be divided into three to six meals and fed throughout the day. If only partial supplementation is required,

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TABLE 50-1

Equine Feeds Suitable for Use in a Liquid Enteral Diet

Feed	Digestible Energy (kcal/kg)	Crude Protein (%)	Crude Fat (%)	Crude Fiber (%)	Non-Structural Carbohydrate (NSC) (%)	Ethanol Soluble Carbohydrate (ESC) (%)	Starch (%)
Equine Senior* (Purina Mills)	2695	14.0	4.0	13.0	20	8	9
Strategy Healthy Edge* (Purina Mills)	2860	12.5	8.0	18.0	18	5	12
Senior* (LMF)	2341	14.0	4.0	20.0		5.9	22
Senior* (Triple Crown)	3401	14.0	10.0	17.0	11.7	5.3	6.4
Low Starch* (Triple Crown)	3142	13.0	6.0	18.0	13.5	3.1	10.4
Alfalfa pellets†	2190	16.7	2.3	24.7	9.3	7.0	2.1
Grass pellets†	2050	13.1	2.6	22.1	12.1	6.8	3.3
Oat hay pellets†	1790	7.74	2.1	26.2	20.1	9.9	4.4

*As fed, manufacturer analysis.

†As fed, average values, Equi-Analytical Laboratories, 2013.

TABLE 50-2

Suggested Feeding Regimen for a Liquid Diet for a 450-kg Adult Horse[15*]

Ingredient	Day 1	2	3	4	5	6	7
Water (L)	21	21	21	21	21	21	21
Dextrose (g)	300	400	500	600	800	800	900
Dehydrated cottage cheese (g)†	300	450	600	750	900	900	900
Alfalfa meal (g)	2000	2000	2000	2000	2000	2000	2000
Electrolyte mix (g)‡	230	230	230	230	230	230	230

*Ration divided into three to four equal feedings daily.

†May substitute edible acid casein, 80 mesh, American Casein Company, Burlington, NJ.

‡Electrolyte mix ingredients: NaCl, 10 g; $NaHCO_3$, 15 g; KCl, 75 g; K_2HPO_4, 60 g; $CaCl_2 2H_2O$, 45 g; MgO, 25 g.

or if a horse is being managed in a field setting, a smaller volume can be administered twice a day. A gradual introduction to feeding a blenderized diet is important.

An ingredient-based composition diet can be designed by combining finely ground forage to provide structural carbohydrates with a concentrated source of protein. One such diet (Table 50-2) composed primarily of dehydrated cottage cheese, dextrose, and alfalfa meal requires considerable preparation by the clinician.[15] Oil (113 to 227 mL) can be added as an energy source if the horse is not hyperlipemic. The omega-3 and omega-6 content of the oil should be considered when formulating a ration to provide for the nutritional management of inflammation. Any enteral diet that contains a high concentration of oil, dextrose, or NSC should be avoided. Structural carbohydrates should comprise 50% to 75% of the diet DM. The approximate cost for complete supplementation with the homemade equine diet is $40 to $50/day for a 450-kg horse. As indicated in Table 50-2, the homemade diet is introduced gradually over a period of 7 days.

Vital HN and Osmolite HN (Ross Products Division, Abbott Laboratories, Columbus, Ohio) are human liquid enteral diets that have historically been administered to adult horses.[16,17] These diets were used before better options for EF were developed for horses, and now should only be used if no other enteral diet options are available. Abbott Laboratories produces a variety of human liquid enteral products, including formulations that contain oat and soy fiber. All human formulas contain a high percentage of calories from simple sugars and starch (greater than 50%) and should be used with caution in any horse that has laminitis or that is intolerant of soluble carbohydrates. A partial list of formulas that can be administered to adult horses is provided in Table 50-3. These products are designed for administration through a small-diameter tube and are an option for horses that can only tolerate an 18-French feeding tube (Mila NG18100, Mila International, Erlanger, Ken.). Most products contain approximately 1 kcal/mL and 4.1 to 4.2 g of protein/100 kcal. Almost 10.5 L of a human enteral product would be required to meet the stall resting energy requirement of 10.4 Mcal for a 450-kg horse, at a cost ranging from $80 to $200/day. The protein content (approximately 450 g) in 10.5 L of Osmolite or Vital HN will not meet the protein requirement of 567 g for a 450-kg horse, and supplemental protein (casein, lactalbumin, whey, soy) may need to be added to the formulation to ensure adequate protein intake. The nutrient composition and ingredient list of a human formulation should be evaluated to ensure that the horse is receiving the most appropriate product. Diets that contain a high (greater than 15%) proportion of calories as fat are contraindicated in horses with hyperlipemia and hepatic lipidosis. Any commercial human product should be fed starting at approximately 25% of the horse's resting energy requirement, with the volume gradually increased over 4 to 7 days to the target quantity.

ENTERAL DIET ADMINISTRATION. All liquid enteral diets should be gradually introduced over 3 to 7 days. The consistency of any formulation can be adjusted by blending the ingredients with water to ensure that the formulation can be delivered through the NG tube that has been selected for administration. Larger diameter NG tubes (>0.65-cm inner diameter) must be used when fiber is included in the diet. The diet should be tested using the NG tube before the tube is placed in the animal to ensure that the tube will not be clogged with the feed. The total daily enteral diet volume should be divided into three to six feedings per day and should be administered slowly enough to ensure that feed does not reflux around the NG tube. No more than 6 to 8 L of total fluid volume should be administered at one time. This volume must be appropriately lowered when treating a pony or miniature horse. Before feeding, the amount of residual fluid in the stomach should be checked. Horses with less than 2 L can be fed the meal, but if the volume of gastric fluid is greater than 2 L, the feeding should be

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TABLE 50-3

Human Liquid Enteral Products*

Product	Caloric Density (kcal/mL)	% Calories Protein	% Calories Fat	% Calories Carbohydrate	Carbohydrate Source
Osmolite	1.06	16.7	29.0	54.3	Corn maltodextrin, corn syrup solids
Osmolite 1.2 Cal	1.20	18.5	29.0	52.5	Corn maltodextrin
Vital HN	1.00	16.7	9.5	73.8	Corn maltodextrin, sucrose
Promote	1.00	25.0	23.0	52.0	Corn maltodextrin, sucrose
Promote with Fiber	1.00	25.0	25.0	50.0	Corn maltodextrin, sucrose, oat fiber, soy fiber
Jevity 1.5 Cal	1.50	17.0	29.4	53.6	Corn maltodextrin, corn syrup solids, fructo-oligosaccharides, soy fiber, oat fiber

*Abbott Nutrition, Abbott Laboratories, North Chicago, Ill.

delayed for 2 hours. Horses with persistent gastric reflux should not be fed enterally, and instead the clinician should consider treatment with PN. After the diet has been administered, the tube should be flushed with at least 500 mL of water before the tube is capped. Excessive distention of the stomach must be avoided. If the NG tube will remain in place between feedings, a muzzle may be used to prevent the horse from removing the tube. During treatment, horses should be offered palatable feeds to encourage a transition to voluntary food consumption. The equine patient can gradually be weaned from EF once it is consuming 75% of its DE_{rest} on a daily basis.

Horses treated with EF should be monitored with a regular physical examination and blood work (PCV, TP, serum electrolytes, glucose and serum triglyceride). Adjustments in the nutrient composition of the enteral diet can be made based on the horse's response to the diet. Liquid enteral diets may result in a mild, self-limiting diarrhea when fed as the sole source of nutrition, possibly because of lack of dietary fiber or because of fermentation of the highly soluble ingredients in the large colon.[15,16,18] This may be ameliorated by addition of a fiber source such as alfalfa meal. Horses that develop diarrhea should be evaluated to ensure the diarrhea is not associated with an infectious agent. Probiotic therapy can be considered as an adjunct therapy during EF.

Foals

Mare's milk is the ideal supplemental diet for orphan or critically ill foals. Healthy neonatal foals with normal gastrointestinal tract motility can initially be fed a volume of milk sufficient to meet 10% of BW (100 mL/kg BW) each day. Critically ill neonatal foals may need to be started at a lower volume (5% to 7.5% BW) for the first few days of nutritional therapy to ensure dietary tolerance. The volume should be incrementally increased until the foal is consuming 20% of its BW (200 mL/kg/day). If indigestion occurs despite a slow introduction to the milk replacer, both the frequency and volume of feeding should be decreased until the indigestion resolves. Neonatal foals should be offered milk every 2 hours as long as the feedings are tolerated and should be encouraged to nurse from their dams once they develop a strong suckle reflex. Foals that are 4 weeks of age or older can be fed every 3 to 4 hours, with a decreased frequency of feeding as the foal ages. A small-diameter NG feeding tube can be used for milk supplementation until the foal can nurse voluntarily. Foals have minimal endogenous energy stores and require supplemental nutrients within 6 to 12 hours of losing the ability to nurse. Any foal that cannot tolerate enteral feedings should be placed on PN to ensure that its dietary requirements are met.

If mare's milk is not available, foals can be fed 20% of their BW per day using a commercial foal milk replacer (Mare's Match [Land O' Lakes, Arden Hills, Minn.], Mare's Milk Plus [Mars Horsecare US Inc., Dalton, Ohio], or Foal Lac [Pet Ag, Hampshire, Ill.]). More information on milk replacers and colostrum supplements and substitutes can be found in Chapter 21. If a foal milk replacer is not available, goat's milk can be fed as a short-term substitute but is not recommended for long-term use because the nutrient profile is different from that of mare's milk and can result in constipation. Because indigestion often occurs when using milk substitutes in foals, dietary changes should be instituted gradually over a period of 1 to 2 days at a minimum.

Orphan foals should be fed from a pan or bucket because it forces the foal to actively ingest and swallow the milk and also decreases behavioral complications that can develop when an orphan foal is bottle-fed. Foals that are not ready to transition to bucket or pan feeding can be fed from a bottle. If a foal will be bottle-fed, the nipple should be checked to ensure that milk does not freely flow from the nipple. Improper use of a bottle can result in aspiration pneumonia if the foal does not have a normal swallow response.

Liquid Diets for Ruminants

In most cases the most practical and least expensive way to force-feed ruminants is the blender-type or slurry diet. Hypophagic adult cattle may be force-fed a suspension of alfalfa meal and dried brewer's grain (3 to 5 kg each in 20 L of water) two or three times daily. If a ruminal fistula is necessary (e.g., tetanus), the diet may be directed into the rumen. Presumably similar preparations would be suitable for sheep and goats, although published reports are scarce. Administration of ruminal liquor obtained from a healthy donor cow provides a good source of microflora as well as volatile fatty acids as an energy source in hypophagic cows.[19] Calves can be fed cow's milk or a high-quality commercial milk replacer. For more on milk replacers and colostrum substitutes, see Chapter 21.

Intravenous Nutrition

Intravenous Dextrose

The simplest and least expensive form of intravenous feeding is the supplementation of intravenous crystalloid fluids with dextrose. This represents a short-term solution for boosting caloric intake when a rapid return to normal feed consumption is anticipated. Dextrose can be added to make a final solution with a concentration that ranges from 2.5% to 10%. If the fluids are infused at a rate to meet maintenance fluid requirements (2.2 mL/kg/h), the patient's renal threshold of glucose (10 mmol/L or 180 mg/dL for adult horses; 12 mmol/L or 216 mg/dL for foals) will usually not be exceeded. The energy provided may be calculated based on 3.4 kcal/g of dextrose. A 450-kg horse treated with fluids supplemented with 2.5% dextrose and infused at a maintenance rate of 1 L/h (24 L/day) will receive 2040 kcal from the dextrose (close to 20% of the patient's DE_{rest}). Although protein is not provided with the dextrose therapy, the supplemental energy will blunt the catabolism of endogenous lipid and protein stores. Dextrose-supplemented fluids can be administered as the sole source of nutrition for 24 to 72 hours. Patients treated with dextrose should have their blood glucose monitored closely. An animal that develops hyperglycemia with a 5% dextrose solution may require treatment with a 2.5% dextrose solution. If complications with glucose regulation persist at this low dextrose concentration, alternative methods of nutritional supplementation

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should be initiated. If an equine patient on intravenous dextrose therapy is unable to consume more than 75% of its resting energy requirement and/or more than 75% of its maintenance protein requirement, supplemental nutrition should be administered.

Parenteral Nutrition

PN is a means of providing more complete intravenous nutritional support to animals that do not have a functional digestive tract or animals that cannot tolerate placement of an NG tube. Because of the greater expense (approximately $100/day for foals and $450/day for adult horses), the need for special infusion supplies, and the risk of complications when compared with enteral feeding, PN should be reserved for cases in which bowel rest is necessary. Possible indications for PN include postoperative feeding after gastrointestinal surgery, nonsurgical intestinal obstruction or ileus (proximal jejunitis, botulism), dietary supplementation in a laterally recumbent patient, neonatal diarrhea in cases in which oral feeding exacerbates the diarrhea, gastrointestinal intolerance in premature neonates, and hypoxic ischemic gastrointestinal syndrome. Because EN provides nutrients directly to the enterocytes and promotes both intestinal barrier function and immune system function, a small volume of a liquid enteral diet should be administered whenever possible in a patient receiving PN.

PN formulations are composed of dextrose and lipids as an energy source, and amino acids as a protein and nitrogen source. Compatible vitamin and mineral supplements can be added to the PN formulation. A variety of PN mixtures can be designed to meet the nutritional requirements of a clinically ill large animal patient. Sufficient calories in the PN solution must be provided in the form of carbohydrates and lipids to promote the incorporation of amino acids into protein instead of the catabolism of amino acids for energy. Glucose provides 3.4 kcal/g, amino acids provide 4 kcal/g, and lipids provide 11 kcal/g; amino acids include 0.16 g of nitrogen per gram. The ideal calorie-to-nitrogen ratio for adult horses is extrapolated from data calculated for critically ill humans, in whom the ideal ratio is 120:1 to 150:1 for healthy individuals, and 80:1 to 90:1 for acutely ill humans.[20] Animals with systemic inflammatory diseases or severe protein loss and large animal patients recovering from major surgery will probably benefit from a therapeutic enteral or parenteral diet that has a calorie-to-nitrogen ratio between 80 and 100, as long as protein supplementation is not contraindicated in the patient. Although PN solutions can be formulated with dextrose alone as the energy source, the addition of lipids provides many advantages. Because of the larger size of the molecule and higher energy density on a per-gram basis, replacement of dextrose with lipid lowers the PN osmolarity and/or infusion volume required to meet the energy needs of the patient and reduces the hyperglycemic effect of PN administration. The lipid content of the PN solution is usually targeted as approximately 50% but no more than 80% of the nonprotein calories in the formulation. Animals with hypertriglyceridemia (>500 mg/dL) or hepatic lipidosis that require PN should be treated with a formulation that is restricted in lipid, or that is lipid-free, whereas the concentration of dextrose or the PN administration rate should be restricted in animals with hyperglycemia. If long-term administration (longer than 5 days) is expected, calcium (200 mg/kg/day), phosphorus (110 mg/kg/day), and other micronutrient supplementation of the PN solution should be considered. Commercial multiple vitamin (e.g., INFUVITE, Baxter Healthcare Corporation, Deerfield, Ill.) and trace mineral (e.g., Multitrace5, American Regent, Shirley, N.Y.) supplements are available for addition to the PN mixture but may add as much as $20/day to the cost of the formulation.

All parenteral solutions must be mixed aseptically. A laminar flow hood should be used to prepare the formulation, but if this equipment is not available, the solution can be mixed in a clean room with low traffic such as a surgical instrument preparation room. Alternative options for PN compounding include human hospitals, human parenteral compounding companies, and the commercial compounding pharmacy CAPS (Central Admixture Pharmacy Services; http://www.capspharmacy.com). The formulation can be made in a 2- or 3-L all-in-one infusion bag (Vital Mix, Vygon Corporation, Lansdale, Penn.) in a sterile glass container, or in a sterilized carboy. Single-use infusion containers are preferred. Guidelines for PN compounding are listed in Box 50-1.

BOX 50-1

Instructions for Compounding a Parenteral Nutrition Solution

1. Compound the solution in a laminar flow hood, if available. Use a clean room in the hospital if a laminar flow hood is not available.
2. Clean the preparation area well, using alcohol as a final preparation on the counter.
3. Wear a gown, mask, and sterile gloves when compounding the parenteral nutrition (PN) solution.
4. Wipe off all injection sites and infusion ports with alcohol before connecting the infusion lines.
5. Use a new transfer set for each PN ingredient.
6. Add the dextrose and amino acid solution to the compounding bag or container. Mix gently.
7. Add the lipid solution *after* the dextrose and amino acid solutions have been mixed together.
8. Gently swirl the solution to mix the ingredients.
9. Add any vitamin or mineral supplements to the solution *after* the macronutrients (dextrose, amino acid, lipid) have been added. Ensure that there are no incompatibilities with the supplemental additives.
10. The PN formulation can be stored in the refrigerator for 24 hours, followed by 24 hours of storage at room temperature. Shield the solution from sunlight.

Parenteral solutions should be administered through a dedicated line in a large-diameter or central vessel (jugular, vena cava) to reduce complications from phlebitis but can be administered in a peripheral vein (lateral thoracic, cephalic) if the osmolarity of the solution is less than 900 mOsm/L. A multilumen polyurethane catheter (Arrow International Inc., Reading, Penn.) is ideal for PN infusion because one port can be reserved exclusively for PN infusion whereas the other port(s) can be used for blood sampling and medication or fluid infusion. In many settings, when this is not feasible, dual infusion ports can be added to a single-lumen Arrow catheter. Patient medications may not be compatible with the PN solutions and should be given through a separate line. If a separate line is not available, the PN line should be flushed with saline before and after administration of the medication. Potential drug incompatibilities should be discussed with a pharmacist. Electrolyte abnormalities should be managed by supplementation in a separate bag of crystalloid fluids. This allows a rapid adjustment in electrolyte therapy if the patient's condition changes without discarding the costly PN solution.

Administration of the PN solution should begin at 25% to 33% of the total infusion rate, and if the patient tolerates the PN, the rate should be gradually increased to the full rate over 12 to 36 hours. Patients will still benefit from PN at a partial infusion rate, and clinicians should not dismiss PN use if cost or metabolic intolerance necessitates provision of less than a full rate and PN formula volume. A fluid administration pump facilitates a constant rate of infusion and is an essential component of PN delivery. During PN therapy the patient should be monitored for hyperglycemia, hypertriglyceridemia, and serum electrolyte abnormalities. Hyperglycemia and hypertriglyceridemia should be managed first by reducing the rate of infusion and then by lowering the concentration of dextrose or lipid in the PN solution. If hyperglycemia is persistent, treatment with subcutaneous insulin zinc suspension (0.15 IU/kg, q12h) or regular insulin as a continuous rate infusion (0.005 to 0.01 U/kg/h) may improve glucose use and permit increased caloric intake without further hyperglycemia.[21] Similarly, heparin (40 IU/kg q12h) may be administered for a short period if hyperlipemia persists and if heparin therapy is safe for the patient. At the conclusion of therapy, PN should be gradually discontinued over 18 to 36 hours. Enteral feeding should resume as soon as possible.

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Patient Information

1. Initial body weight (kg) _____ kg
2. Stall resting energy requirement: DE_{rest} (kcal/day) = 975 + 21 (BW in kg) _____ kcal
3. Maintenance energy requirement: DE_{maint} (kcal/day) = 33.3 (BW in kg) _____ kcal
4. Protein requirements: Crude protein (grams/day) = 1.26 (BW in kg) _____ g
5. Fluid requirements for maintenance: 60 mL/kg/day _____ mL

Parenteral Nutrition Formulation

6. Total kcal required/day (estimate between **2** and **3** calculated above) _____ kcal
7. Calculate volume of 10% amino acids required to meet protein requirement (from **4**)
   Protein (grams) x 1 mL/0.1 grams protein for a 10% amino acid solution _____ mL
8. Calorie contribution from 10% amino acid solution (from **7**)
   4 kcal/g protein x grams of protein in solution _____ kcal
9. Total kcal required/day (from **6**) minus total kcal provided by AA (from **8**) _____ kcal

**The caloric contribution from protein can be omitted from the following calculations, if desired.*

10. Determine amount of lipid required to meet 20-70% of the remaining energy requirements:
    10% lipid solution contains 1 kcal/mL, 20% lipid solution contains 2 kcal/mL
    Ex: If providing 50% of remaining energy requirements with 10% lipid:
    (kcal (from **9**) x 0.5) x 1 mL/1 kcal (substitute 0.5 mL/1 kcal if using 20% lipid) _____ mL

11. Calculate remaining energy requirements to be provided by 50% dextrose:
    Ex: Providing 50% of calories with dextrose: (kcal (from **9**) x 0.5) x 1 mL/1.7 kcal _____ mL

12. Add 1-2 mL of B vitamin complex/L _____ mL
13. Add up to 5 mL of trace minerals/day _____ mL
14. Determine the total volume of the PN solution (**7 + 10 + 11 + 12 + 13**) _____ mL
15. Determine the rate of PN infusion for a 24-hour period: mL (from **14**)/24 _____ mL/hour
16. Calculate the calorie:nitrogen ratio for the PN solution:
    Total kcal from PN solution (from **6**)/(total g of protein/6.25) _____
17. Calculate osmolarity of the solution:
    10% Amino acid _____ mL (from **7**) x 0.840 mOsm/mL = _____ mOsm
    10% Lipid _____ mL (from **10**) x 0.276 mOsm/mL = _____ mOsm
    50% Dextrose _____ mL (from **11**) x 2.550 mOsm/mL = _____ mOsm
    \+ _____ Total mL + _____ Total mOsm
    PN solution mOsm/L = Total mOsm/Total mL x 1000mL/L _____ mOsm/L

**An 8.5% amino acid solution with electrolytes contains 0.85 g protein/mL and 1.045-1.444 mOsm/mL.*

FIG. 50-1 Parenteral nutrition worksheet for adult horses. *PN,* Parenteral nutrition.

Parenteral Nutrition in Horses

Adult Horses

The stall resting digestible energy (DE_{rest}) and maintenance protein requirements, calculated as shown earlier, should be used as guidelines when formulating a PN solution for an adult horse. Although the exact energy requirements during a clinical illness have not been determined for the equine species, provision of enough nutrients to meet the stall resting requirements should provide the adult horse with sufficient energy to blunt the catabolic effect of anorexia and illness without the risk of hyperalimentation. Horses with a limited medical budget can be managed with a PN solution that provides a portion (33% to 66%) of the DE_{rest} energy.

The preferred way to formulate a PN solution is first to meet the calculated protein requirements of the horse with the amino acid solution and then to meet the remaining energy requirements with a combination of dextrose and lipid calories. A formula with approximately 50% of nonprotein calories as lipid and 50% as dextrose can be used for an initial formulation. The final composition of the lipid and dextrose in the PN solution can be altered to manage patients with hyperglycemia or hypertriglyceridemia. An example of a worksheet used to facilitate calculations for PN formulation for an adult horse is shown in Fig. 50-1. Alternatively, the clinician can calculate the daily requirements of dextrose, amino acids, and lipids on a dose per BW basis. The formula listed in Table 50-4 provides 2.8, 1.3, and 0.8 g of dextrose, amino acids, and lipids, respectively, per kilogram per day, providing the resting stall DE and maintenance protein requirements with a calorie:nitrogen ratio of 108:1, with 48% of nonprotein calories as lipid and an osmolarity of 1026 mOsm/L. Approximate cost is $450/day not including administration sets. If the clinician is willing to forgo the benefits of lipid inclusion, the lipid component in Table 50-4 can be replaced with an additional 2.8 g/kg/day of dextrose, at a savings of nearly $200/day.

Commercially pre-prepared formulas that contain varying concentrations of amino acid and dextrose (e.g., Clinimix, 5% amino acid in 25% dextrose [Baxter Healthcare Corporation, Deerfield, Ill.]) serve as a convenient alternative to PN therapy because the formulations do not require special preparation. Clinicians can also add 50% dextrose (1.7 kcal/mL) and an amino acid solution (0.35 kcal/mL for a 10% amino acid mixture) to a bag of crystalloid fluids to provide energy and amino acids in a formulation that is less costly than a full PN solution. The final osmolarity of any PN formulation ideally

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TABLE 50-4

Parenteral Nutrition Formulation for Adult Horses

Ingredient	Dosage Rate	Volume per Day (450-kg horse)
50% Dextrose	2.8 g/kg/day	2500 mL
10% Amino acids*	1.3 g/kg/day	6000 mL
10% Lipid†	0.8 g/kg/day	3500 mL

Begin administration at 0.3 mL/kg/h and gradually increase to target of 1.1 mL/kg/h (12 L/day for a 450-kg horse).

*Available as FreAmine III, B. Braun Medical Inc., Bethlehem, Penn., and Travasol, Baxter Healthcare Corporation, Deerfield, Ill.

†Available as Liposyn III, Hospira, Inc., Lake Forest, Ill.; 20% and 30% formulations available as Intralipid, Baxter Healthcare Corporation, Deerfield, Ill.

TABLE 50-5

Parenteral Nutrition Formulation for Foals (50 kg)

Ingredient	Dosage Rate	Volume/Day (50-kg Foal)
50% Dextrose	8.7 g/kg/day	870 mL
10% Amino acids	3.0 g/kg/day	1500 mL
10% Lipid	1 g/kg/day	500 mL

Formula provides 0.87 kcal/mL. Begin administration at 0.7 mL/kg/h and gradually increase to target of 2.4 mL/kg/h (2870 mL/day for a 50-kg foal).

should be less than 1200 mOsm/L for administration in a jugular vein and 600 to 900 mOsm/L if administered in a peripheral vein.

Foals

The nutrient density of a foal PN recipe should be evaluated before the formula is blended. Many older formulas may provide excess calories, which could be detrimental, especially in a critically ill neonate. The initial target energy intake for a critically ill neonatal foal is 40 to 50 kcal/kg/day. Hypertriglyceridemia (greater than 200 mg/dL) has been associated with higher mortality in neonatal foals.[22] To limit complications, lipid calories should comprise less than 50% of the non-protein calories in a PN formulation. A conservative lipid dose is 1 g lipid/kg BW/day. The PN formula in Table 50-5 is designed to provide 8.7, 3.0, and 1 g of dextrose, amino acid, and lipid, respectively, per kilogram BW per day, a total energy of 50 kcal/kg BW/day, a calorie : nitrogen ratio of 104 : 1, and an osmolarity of 1260 mOsm/L. The PN formulation contains 21% calories from protein, 20% calories from lipid, and 59% calories from dextrose with lipid comprising 25% of the nonprotein calories. If the foal tolerates the full infusion rate, additional calories can be added from all ingredients, to achieve a recipe that provides 70 to 100 kcal/kg BW/day. An anabolic state can be achieved solely with PN therapy, but because enteral feeding is the desired goal, EN or oral milk consumption should begin as soon as possible. Changes in the rate of infusion and in the PN formulation should be made to prevent hyperglycemia, but insulin can be administered if necessary to maintain blood glucose in a normal range.

Parenteral Nutrition in Ruminants

Because of cost, use of PN is usually limited to calves, and little information exists on the use of PN in the adult bovine or the ovine and caprine species. The most common indication for the use of PN in calves is diarrhea, particularly in chronic cases accompanied by weight loss.[23] In such cases, if sufficient milk is fed to meet the calf's nutritional needs, the diarrhea is exacerbated, and PN allows the quantity of milk to be reduced without compromising the nutritional status of the patient. The PN regimen provided for foals in Table 50-5 would also be suitable for calves. However, because amino acids and lipids are the most expensive components of PN, a modified formula based on a 10 : 2 : 1 glucose : amino acid : lipid ratio has been used with success.[23] For a 50-kg calf, this would result in administration of 1 L of 50% dextrose, 1 L of 10% amino acids, and 500 mL of 10% lipids daily, at an approximate cost of $60 per day. Eliminating the lipid emulsion from the formula is an acceptable alternative that will reduce the cost by approximately 15%. A multiple B-vitamin product may be added to the formula (approximately 1 mL of supplement per liter of PN), but trace minerals are not usually necessary for the short-term administration that is most common in calves.

Catheter-related complications are rare in calves, and a central venous catheter, although preferred, is not required. The author (RWS) has had success with 16-gauge, 3¼-inch, Teflon-coated, over-the-needle catheters available from several distributors. These are placed in the jugular vein, sutured or glued to the overlying skin, and left in place for up to 10 days if no signs of phlebitis or sepsis occur.

Special Diets

Numerous diseases require specific alterations in the macronutrient and micronutrient balance in the therapeutic ration because of metabolic disturbances that accompany these conditions. Recommendations are discussed in the individual chapters dealing with these diseases and include alterations in dietary protein for hepatic disease and restrictions in the protein and calcium content of the diet for horses with chronic renal failure. A nutritionist can develop therapeutic enteral and parenteral formulations to meet the unique nutritional requirements of individual patients.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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PART SEVEN

Congenital, Hereditary, Immunologic, and Toxic Disorders

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• CHAPTER 51

Genetic Disorders

ANGELA M. HUGHES and KARI J. EKENSTEDT, *Consulting Editors*

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Inherited diseases and congenital defects are structural or functional abnormalities that may or may not be obvious at birth. There are a wide range of possible defects, from a single structural change (e.g., leg length) to the involvement of multiple organs or systems (e.g., storage diseases, chromosomal abnormalities), depending on the type and extent of toxic exposure during gestation or genetic mutation. It is important to identify animals with genetic or congenital disorders because of the economic and emotional impact on clients, but many disorders can be difficult to recognize and trace, particularly if they lead to embryonic or fetal death, abortion, dysmaturity, premature birth, or full-term stillbirth.

It is important to remember that not all congenital defects are genetic in origin and making the distinction between conditions caused by an environmental factor and a genetic cause will help clients make appropriate changes to prevent the disorder in the future. To determine the cause of a disorder, it is vital that each case be examined thoroughly. Each case should be subjected to a full, careful description of the disorder, including a complete necropsy. The environment and management conditions should be investigated for potential causative agents, and all available genetic information for the affected animal(s) and unaffected herdmates should be collected, including sex, birth date, and breed. Environmental teratogens affecting large animals include toxic plants, drugs, viruses, and physical agents (e.g., hyperthermia, irradiation). Although it may be difficult to identify inciting teratogens, analysis of affected herds will reveal patterns that follow seasonal or management changes or stressful events.

This chapter focuses on the essential genetic information that veterinarians require to inform their clients about genetic diseases and how to find information on diseases and traits with a genetic component.

Genetic Information

The basic blueprint for life in most organisms, the genetic material, is deoxyribonucleic acid (DNA). DNA is composed of two strands of *nucleotides:* adenine (A), thymine (T), guanine (G), and cytosine (C). These nucleotides, or bases, align to form complementary pairings such that A always pairs with T and G always pairs with C. These strands can be completely separated and replicated in preparation for cellular division. Alternatively, they can be partially separated temporarily, transcribed into ribonucleic acid (RNA), and translated into functional proteins.

The DNA sequence of a mammalian genome is divided into autosomes and a pair of sex chromosomes, X and Y. Each chromosome contains a variety of genes as well as "filler" DNA that does not code for proteins, but may determine where and to what degree each gene is expressed. Genes on each chromosome code for the various structural and enzymatic proteins required for life. One set of chromosomes, and thus one set of genes, is inherited from each parent. As a result, a mammal generally has two copies, or alleles, of any given gene. Simple traits or diseases involving these genes can be inherited in dominant or recessive patterns and involve the autosomes or sex chromosomes. Unfortunately, not all traits or inherited diseases are simple; many involve multiple genes and interactions between genes and the environment, which can make it difficult to diagnose and understand a complex disease or trait.

Recessive Inheritance

Traits or diseases with a recessive mode of inheritance require two affected alleles of the gene to express that trait or disease. These conditions can be *autosomal,* involving genes on the autosomes, or *sex-linked,* caused by genes on either the X or Y chromosome. Generally, autosomal recessive traits or diseases are caused by loss-of-function mutations in which the gene product has decreased ability or no ability to perform its original function. When an animal inherits the affected allele from both parents, it is *homozygous* for the gene and is unable to make functional copies of that specific protein. *Heterozygous* individuals inherit only one copy of the affected allele and they have a "backup" copy of the normal or wild-type allele to provide the functional protein. These heterozygous individuals are carriers of the trait or disease allele and can produce affected offspring if bred to another heterozygous or homozygous affected individual.

The hallmarks of autosomal recessive traits include that all offspring of two affected parents are affected and that approximately equal numbers of males and females are affected. Unaffected carrier parents can produce affected offspring, and thus the trait or disease can skip generations. In addition, mating an affected individual to a noncarrier (homozygous normal) produces all offspring that appear normal but carry the affected allele. Breeding two carrier individuals results in approximately 25% normal, 50% carrier, and 25% affected offspring.

An example of an autosomal recessive trait is spider lamb syndrome, or hereditary chondrodysplasia. Lambs affected with this syndrome display several skeletal abnormalities, including disproportionately long "spider" legs, curvature of the spine, facial deformities, rib and sternum deformities, lack of body fat, and muscular atrophy. The causative mutation is a single base-pair substitution, from a T to an A, altering a highly conserved amino acid in the fibroblast growth factor receptor 3 (FGFR-3) gene. This prevents the receptor from functioning to limit endochondral ossification and thus bone growth.[1]

Dominant Inheritance

Traits or diseases with a dominant mode of inheritance only require one affected allele to express the trait or disease, also known as the affected *phenotype,* and there is no distinguishable difference in the affected phenotype of a heterozygote and homozygote. Again, the genes that are responsible for these traits or diseases can be on the

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autosomes or sex chromosomes. Dominant traits or diseases may be caused by gain-of-function mutations that enable the mutant protein to have an altered structure or function. Alternatively, a single, functional copy of a gene may not be enough to achieve normal levels of function ("haploinsufficient"), resulting in the need for two normal copies of the gene to achieve a normal phenotype.

The main feature of an autosomal dominant trait or disorder is that affected individuals must have at least one affected parent (unless it is a new mutation), and thus the disorder does not skip generations. There is no sex bias with an autosomal dominant trait, and approximately half the offspring of a heterozygous affected individual bred to a normal individual will be affected. Breeding two heterozygous affected individuals will result in 75% affected (one third of which are homozygous and two thirds of which are heterozygous) and 25% normal offspring.

An example of an autosomal dominant disease is myotonia in goats. When startled or making sudden, forceful movements, these goats can develop severe, acute muscle stiffness causing immobility and sometimes falling over, resulting in descriptions such as "fainting," "nervous," "stiff-legged," or "epileptic" goats. A single nucleotide change, from a G to a C, was identified that substituted a proline amino acid for a conserved alanine in a chloride channel in the muscle fibers. This alteration in the chloride channel causes a diminished channel-open probability at voltages near the resting membrane potential of skeletal muscle, resulting in decreased chloride conductance and a significantly decreased electrical threshold for firing action potentials. Ultimately, this altered chloride channel allows conduction of repetitive impulses that result in sustained muscle fiber contraction and stiffness.[2]

Co-dominant Inheritance

The co-dominant (or semi-dominant) pattern of inheritance is distinguished by the fact that homozygotes can be differentiated from heterozygotes based on clinical features. A well-known example of a co-dominant disease is hyperkalemic periodic paralysis (HYPP) in Quarter Horses. In HYPP the voltage-gated sodium channels in the muscle fibers have a mutation that increases sodium permeability across the skeletal muscle cell membrane. This causes increased muscle mass, but also drooling, prolapse of the nictitating membrane ("third eyelid"), respiratory stridor, and weakness. Homozygous HYPP horses experience more frequent and severe clinical signs of disease than heterozygous horses.[3] Thus, it is important to counsel breeders to avoid producing homozygous affected horses by not mating two heterozygous horses, since approximately 25% of their offspring would be expected to be homozygous affected and 50% would be heterozygous, while only 25% would be homozygous normal. Breeding a heterozygous horse to an unaffected horse will also result in approximately 50% of the offspring being heterozygous with no possibility of producing a homozygous affected foal.

Sex-Linked Traits

Sex-linked traits and diseases involve genes located on either the X or the Y chromosome. Males have only one copy each of the X and Y chromosomes, so they are *hemizygous*. As a result, males are particularly susceptible to sex-linked conditions because if they have a mutant allele for one of the genes on either of the sex chromosomes, they lack a "backup" copy of the normal allele and will express the affected phenotype. Females generally are less likely to demonstrate sex-linked recessive traits or diseases because they have two copies of the X chromosome. However, because of random X inactivation in each cell during fetal development, some females may express an affected phenotype. To achieve this, the X inactivation must be skewed such that the unaffected chromosome is inactivated more often than the X chromosome carrying the affected allele. In rare cases in which the inactivation is significantly skewed, females may be mildly to severely affected, depending on the level of expression for the affected chromosome.

Key characteristics of X-linked recessive traits are that the trait appears with much greater frequency in males than females, half the sons of carrier females will be affected, half the daughters of carrier females will be carriers, and all of the daughters of affected males will be carriers. Hemophilia A, characterized by a strong tendency to bleed resulting from mutations in the clotting factor VIII gene on the X chromosome, is an example of an X-linked recessive disorder.

X-linked dominant traits are characterized by the following: affected offspring must have at least one affected parent, the disorder does not skip generations, and an affected male mated to normal females will transmit the mutation to all his daughters but not to his sons.

Very few Y-linked diseases are recognized in any mammalian species because of the small number of genes on the Y chromosome. In addition, the majority of the genes contained on the Y chromosome are involved in male fertility; thus, mutations in these genes generally render the animal sterile, resulting in no transmission of the mutations to future generations.

Polygenic Traits

In addition to the single-gene traits and diseases, numerous conditions are the result of two or more genes and may also involve genetic and environmental interactions. Some of these polygenic traits are economically important, such as milk quality and yield in dairy cows. For milk quality, a large number of genes may be contributing a small portion to the overall milk production of an animal.[4] In beef cattle, at least eight genes have been significantly associated with stature, and thus the physiology of growth.[5]

Now that most of our major large animal species have had their genomes sequenced, cattle and sheep livestock associations and producers are increasingly using whole-genome approaches for genetic evaluation, in an effort to tackle polygenic traits, as well as overall genetic value. For example, dairy cattle geneticists are now using single nucleotide polymorphism (SNP) markers spanning the entire genome, combined with progeny test data, in order to predict genetic merit for polygenic traits for any animal. This can be done prior to the animal's producing any offspring. The swine industry is also rapidly moving toward use of genome-wide data; however, much of these data are proprietary to specific corporations, so they may be difficult to access.

Teasing out the details of a complex polygenic system, such as assigning a specific gene and a measure of its contribution to a polygenic trait like milk production, is difficult; however, research is ongoing to identify the exact genes involved and the role each gene plays for many economically important traits and diseases. It is anticipated that our understanding of polygenic traits in large animals will increase sharply in the next few years.

Penetrance and Expressivity

For many simple traits, there is an obvious difference between the two phenotypes that can be translated to the alleles involved, or *genotype,* with 100% certainty. A good example of this is albinism, which is considered to be 100% penetrant, with *penetrance* defined as the percentage of individuals within a given genotype who actually show the phenotype associated with that genotype. Influences such as modifying genes or environmental interactions can alter the expression of certain genes such that the exact genotype is not expressed in the outward phenotype. Alternatively, the function of a gene may be subtle, making it difficult to measure distinctions adequately between genotypes. Genotypes that may not be expressed in every individual are considered to be "incompletely penetrant."

Another measure of genetic expression is the concept of *expressivity*. Modifier genes and environmental influences can affect the degree to which a genotype is expressed. For example, "variable expressivity" may be involved in pigment intensity when two individuals have the same genotype at the gene responsible for red pigmentation, but one has clearly darker red hairs than the other.

Incomplete penetrance and variable expressivity can greatly complicate analysis of genetic traits and diseases. These factors can also make breeding decisions more difficult because it may not be possible to classify an animal's genotype based solely on a phenotype. In these

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more ambiguous cases, genetic testing will play a vital role in the unequivocal determination of genotypes, allowing appropriate and informed breeding decisions.

Chromosomal Abnormalities

Occasionally, problems arise during mitosis, meiosis, or fertilization, resulting in chromosomal, or *karyotype,* abnormalities such as a chromosome missing from a pair *(monosomy)* or an extra chromosome *(trisomy).* Many karyotypic abnormalities have been identified in all large animal species, but not every chromosomal abnormality has been associated with an overt disease phenotype.[6,7] Some examples of common chromosomal abnormalities include the absence of an X chromosome, called *XO Turner syndrome,* which results in female infertility. An additional X chromosome in XXY Klinefelter syndrome causes underdeveloped males with underdeveloped male sexual behavior. In addition to abnormal numbers of sex chromosomes, rare trisomies of autosomal chromosomes have been observed in mammals; however, monosomies of autosomes are generally not compatible with life in mammals. An additional chromosomal abnormality can occur when two chromosomes unite into a single large chromosome, called a *Robertsonian translocation,* leading to reduced reproductive capacity in some species and early embryonic death in cattle. Because of possible chromosomal abnormalities, several countries have instituted mandatory karyotype examination of some breeding cattle. In addition, clinicians should consider karyotyping any animal that presents for reduced fertility or has multiple abnormalities.

Breeding Schemes

As a result of numerous advances in the field of genetics, the genetic causes of many diseases and traits are known and can be tested before using an animal in a breeding program. As research continues, more DNA-based tests are expected; however, clients may be interested in testing for a disease or trait that does not yet have a known genetic cause. For these situations, sires can be tested using breeding trials, as described in Table 51-1. For example, if a sire is bred to carrier females for a disease of concern, he would have to produce 10 normal offspring to ascertain that he is not a carrier with 95% confidence, 16 normal offspring to have 99% confidence, and 24 normal offspring to have 99.9% confidence that he is not a carrier for the disease of concern. The time required to complete test mating can be significantly shortened using superovulated affected females, insemination, and embryo transfer (two per recipient) followed by early cesarean section at 60 days and examination of the offspring for the genetic defect(s) of concern.

It has historically been common practice for artificial insemination (AI) studs to conduct such test matings for recessive genetic diseases. However, now that many of the deleterious mutations are known, genetic testing, rather than test mating, is the current preferred approach. As mentioned previously, the dairy and beef cattle, swine, and sheep industries are aggressively pursuing whole-genome genetic testing, often in combination with offspring data. Test matings are thus largely relegated to the arena of historical interest, although there may be unique situations or other species in which a test mating may still be a legitimate approach.

Positive and Negative Selection

Breeders can improve their breeding stock by selecting for or against specific traits and diseases. These processes are known as *positive* and *negative selection,* respectively. A breeder may choose to breed an animal because it has desirable genes or qualities (positive selection). Alternatively, they may choose not to breed an animal that has been shown, either through genetic or breeding tests, to carry an undesirable trait or disease (negative selection). Ultimately, both scenarios will achieve the goal of improved breeding stock.

Recommendations for Breeding Programs

When a genetic disease has been identified, it is recommended that parentage be verified by DNA analysis and the extended pedigree be confirmed. In addition, a pathologist should make appropriate examinations of tissues for an accurate diagnosis, and a certified statement detailing the condition should be written by a veterinarian or other third-party witness. The final decision with regard to the status of a particular animal should be withheld until all reasonable doubt has been removed; for bulls, this is usually at least two thoroughly documented cases or a positive genetic test, if available. The AI organization and breed registry should be informed of the status of each animal because disease information is important in future breeding decisions. Many AI organizations list any undesirable recessive alleles in their advertising, and some also remove carrier animals from service.

Depending on the value of the animal in question, a breeder may choose to remove the animal from the breeding program at the first sign of a potential genetic problem. In these cases, documentation of the abnormal conditions should still be conducted for completeness and for comparison with other cases that may be found in the future.

Caution should be exercised before drastic changes are made in breeding populations. Inbreeding and extreme narrowing of the gene pool, such as by excessive use of a small number of sires, are results that should be avoided. Maintaining diversity in the herd and overall breeding population is important in order to avoid inbreeding depression and the increase of recessive diseases. In some industries, such as swine, where crossbreeding is very common, this is less of a concern. In other industries, such as dairy, producers are increasing their utilization of cross-breeding over and above the historical standard. Most commercial AI studs and/or breed association mating programs in the dairy industry are now designed with an option to limit inbreeding, typically accomplished with simple pedigree analysis; however, the producer must choose to apply that option. Breed associations may eventually need to intervene by actively soliciting and providing incentives for outbred animals. Producers, as well as the commercial stud owners, must carefully balance the short-term gains that may come from inbreeding with the long-term consequences of the overall narrowing of the gene pool.

TABLE 51-1

Test Mating Schemes to Examine Males for Genetic Traits or Diseases at Various Confidence Levels

	Normal Offspring Needed to Reach Probability Level of:		
Females Used for Test Matings	**0.05**	**0.01**	**0.001**
Affected*	5	7	10
Normal carriers*	10	16	24
Sire's daughters†	22	35	52

*Tests for only one trait.

†Tests for all undesirable recessive traits.

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BOX 51-1

Recommended Websites for Large Animal Genetics

OMIA—Online Mendelian Inheritance in Animals: horse, cattle, sheep, goat, pig, various other species
http://omia.angis.org.au/

United States Department of Agriculture, Agriculture Research Service, Animal Improvement Programs Laboratory: dairy cattle, dairy goat
http://aipl.arsusda.gov/

Veterinary Genetics Laboratory at the University of California, Davis: horse, cattle, sheep, goat, pig, various other species
http://www.vgl.ucdavis.edu/services/index.php

Obtaining Genetic Information

Because of the ever-increasing wealth of genetic information, the most complete and current information can be found using online resources. It is recommended that clinicians use websites produced by reputable institutions to obtain the most accurate and referenced information available (Box 51-1).

Alternatively, clinicians are encouraged to contact the Veterinary Genetics services available at many veterinary schools if they are unable to locate the information they require.

References

The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 52

Genetic Tests for Large Animals

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Genetic testing based on deoxyribonucleic acid (DNA) involves the analysis of an animal's DNA to determine the individual's genotype for an inherited disorder, trait, or anonymous marker. Genetic testing can be used for positive or negative selection in a population, depending on whether it is being used to identify a disease (negative) or a trait (positive). Genetic testing can also be used for permanent individual identification and parentage determination. Many breed registries require parentage verification to ensure the accuracy of their pedigrees.

Using genetic testing results for selection requires an understanding of the mode of inheritance of the disease or trait. Most often, a genetic test will be performed for a recessive disorder to determine if an animal is a carrier. Carriers are asymptomatic but have the potential to produce diseased progeny. Because they have no outward manifestation of disease, a genetic test is extremely valuable for managing their breeding appropriately. Carrier animals can be bred to noncarriers if needed to retain valuable characteristics while not producing diseased offspring. In the case of positive selection for a trait of interest, carrier animals may have higher breeding values because they can produce a trait if bred to other carriers or to animals with the trait. Genetic tests may also be used for dominant disorders if the disease/trait has a late age of onset or if it is inherited in a co-dominant manner. DNA testing for traits that are controlled by more than one locus (polygenic) may also be used for selection for economically important traits. In these cases, one particular genotype may confer a slight advantage over another and therefore, in a large population, can have a significant effect on production. Box 52-1 defines key genetic terms; see also Chapter 51.

Individual Identification and Parentage Testing

Researchers use genetic markers distributed along all the chromosomes as tools to identify regions associated with diseases or traits. The markers are composed of small nucleotide repeats and are called *microsatellite* markers or *short tandem repeats* (STRs). These markers have a feature that makes them extremely useful to geneticists; the markers have been chosen to be "polymorphic" (show differences) between individuals. In other words, individual animals will have different lengths of the nucleotide repeats for each of these markers. The high level of polymorphism of this type of marker makes them useful for "mapping" (identifying the chromosomal location of diseases and traits).

The microsatellite markers are assayed by polymerase chain reaction (PCR) amplification using fluorescent-labeled primers. Primers are short (20 base pairs), single-strand lengths of DNA that are complementary to a specific region of the genome. PCR is the amplification of a section of DNA contained between two primers designed to complement the unique sequence flanking the STR. The PCR products are then resolved by electrophoresis based on their length. Figure 52-1 shows a single microsatellite marker in three different animals. This marker is polymorphic and would be a useful marker for individual identification or parentage. Because the markers show differences between individuals, a collection of these markers can be used as a form of identification of an animal. High statistical significance can be obtained with as few as 10 markers, depending on the species and breed. The DNA type of an animal will not change over its lifetime and can therefore be used as a form of permanent identification.

Many purebred registries require parentage verification for registration purposes. To accomplish parentage verification, a DNA sample must be available from both parents as well as the offspring. DNA samples are taken in the form of hair, blood, or buccal swabs (depending on the species and registry) and submitted at the time registration is requested. Each animal inherits one copy of each marker from its sire and one copy from its dam, so the markers can also be used to verify parentage. The most useful marker has a high polymorphism rate because that type of marker will be most likely to show differences not only between the sire and the dam, but also between the two copies (alleles) of the marker. A set of polymorphic markers (10 to 20) is used to verify parentage to ensure a high probability that the parentage is correct. Table 52-1 shows the allele sizes for a set of markers in a parentage case. For marker *A* the offspring inherited a 122 and a 126 allele. The 122 came from its dam, so the 126 came from the sire. Because sire 1 does not have a 126 allele, it has been excluded. In this example, sire 1 is excluded as the sire of the offspring, and sire 2 is verified on the basis of the results for all three markers.

Genome Maps

Early attempts to construct whole-genome maps of large animal species were based on two technologies that had been used to construct the first human genome maps: somatic cell genetics and in situ hybridization. This technology involved using labeled complementary DNA or RNA strands (i.e., probes) to localize a specific DNA or RNA sequence in somatic cells. Initial mapped markers were generally genes, or gene products, highly conserved across mammalian genomes. These markers, defined as syntenic (genes on the same chromosome but not necessarily linked) and cytogenic locations, were determined through sequences hybridizing specific DNA probes. Therefore, the first "genome maps" were defined as synteny groups: genes on the same chromosome defined by gene products that segregated in hybrid somatic cell lines. Synteny groups were developed for cattle, horses, and sheep. The next stage of mapping required the use of highly polymorphic markers, including microsatellites, within families of animals to create linkage maps. Collaborative efforts between researchers interested in large animal genomics were required to create these linkage maps for cattle, horses, sheep, and goats (Table 52-2). Radiation hybrid (RH) maps, which used x-ray breakage of chromosomes to determine the distances between DNA markers, followed. These RH maps allowed for the incorporation of genetic (i.e., linkage) and physical maps. The first RH maps

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BOX 52-1

Definitions of Genetic Terms

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome.
Base pairs: Two bases that form a "rung of the DNA ladder." A DNA nucleotide is made of a molecule of sugar, a molecule of phosphoric acid, and a molecule called a "base." The bases are the "letters" that spell out the genetic code. In DNA the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively.
Genotype: Genetic makeup, either at a single locus or at all loci.
Genome-wide association study: A study that uses genome-wide markers, typically microsatellites or single nucleotide polymorphisms (SNPs) to determine an association between a phenotype and region of a particular chromosome.
Linked: Association of genes and markers that lie near each other on a chromosome; linked genes and markers tend to be inherited together.
Locus: Place on a chromosome where a specific gene is located; a type of "address" for the gene.
Marker: Segment of DNA with an identifiable physical location on a chromosome, the inheritance of which can be followed. A marker can be a gene or some section of DNA with no known function. Also known as a *genetic marker.*
Microsatellite: Repetitive stretches of short sequences of DNA used as genetic markers to track inheritance in families.
Phenotype: Observable traits or characteristics of an animal (e.g., coat color, weight, presence or absence of a disease).
Radiation hybrid mapping: A technique for mapping mammalian chromosomes that uses x-ray breakage of chromosomes to determine distance between DNA markers and their respective order on the chromosome.
Recombination: Genetic transmission process by which the combinations of alleles observed at different loci in two parental individuals become shuffled in offspring individuals.
Single nucleotide polymorphism (SNP): Differences in a single base pair of DNA (A,C,T,G) often used as genetic markers for linkage and association studies.
Splicing: Ribonucleic acid splicing removes introns and joins exons in a primary transcript.

involved only specific chromosomes, but later generations included whole genome RH and comparative maps. The isolation of bacterial artificial chromosome (BAC) clones for a large assortment of loci in the various large animal species was instrumental in facilitating chromosomal locations for these loci. In the horse, a complete physical BAC contig map of the entire genome was developed.

Whole genome sequencing and genome assembly of large animal species was completed in the early 2000s (horse, September 2007; cow, October 2011; sheep, August 2012; goat, December 2012). In the horse, a Thoroughbred mare (Twilight) was selected for sequencing because of her low heterozygosity rate (1/1380 base pairs). In 2010, a Quarter Horse mare underwent whole genome sequencing and was aligned to Twilight.[1] In cattle, a single partially inbred Hereford cow was selected to contribute 6x whole-genome shotgun (WGS) reads and another 1.5x came from individual animals of the Holstein, Angus, Jersey, Limousin, Brahman, and Norwegian Red breeds for detection of single nucleotide polymorphisms (SNPs). Following sequencing of each species, over 20,000 protein-coding genes were annotated on the sequences by virtue of previously sequenced cDNAs as well as by prediction software that compare known genome sequences in other species with newly sequenced genomes. These annotated genome databases are publicly available (see Table 52-2).

With the advent of whole genome sequencing and assemblies, there has been a rapid expansion in the number of SNPs discovered in the genomes of large animal species. SNPs are now considered the next generation of markers to conduct breed diversity and to map disease-causing traits. The availability of such a tool as an SNP-chip facilitates rapid mapping of diseases to specific chromosomal regions and analysis of candidate genes. SNP arrays are currently available on many large animal species (see Table 52-2) and are currently being used in mapping studies of various complex disorders. Haplotype structures are being identified across species with targeted resequencing and, most recently, whole genome next-generation sequencing, of animals from different breeds.

In addition to genomic mapping, functional genomic tools have become more readily available and affordable to researchers. Expression arrays have been designed in the horse, cow, and sheep (see Table 52-2). Most recently, sequencing of the transcriptome, through technologies such as RNA sequencing (RNA-seq), has allowed researchers to evaluate gene expression differences among tissues and between animals of different disease states.

Identifying Genetic Mutations

Initial genetic mutations in large animal species were discovered through the use of comparative genomics. Genes involved in a specific disease were targeted because of equivalent diseases in other species, namely humans. In the horse (Table 52-3), the genetic mutations for many diseases that have genetic tests currently available, including hyperkalemic periodic paralysis (HYPP)[2] and severe combined immunodeficiency (SCID),[3] were uncovered by evaluating candidate genes that had been associated with similar diseases in humans. With the sequencing and annotation of whole genome maps, other diseases were discovered through whole genome linkage mapping (hereditary equine regional dermal asthenia [HERDA][4]), genome-wide association studies with microsatellites (type I polysaccharide storage myopathy [PSSM][5]) and genome-wide association studies using SNP array technology (Lavender foal syndrome[6]).

A similar theme is evident in cattle. Initial genetic mutations were discovered based on sequencing of candidate genes known to cause similar disease in humans (bovine leukocyte adhesion deficiency [BLAD][7]). Later studies used microsatellite markers and performed linkage analysis (complex vertebral malformation[8]) and, most recently, the use of SNP-based genome-wide association studies has identified recessive defects (congenital muscular dystony types 1 and 2[9]). At the time of publication, there are 90 genetic tests available in cattle (Table 52-4). It is worth noting that the majority of genetic tests currently available are for diseases/traits that are inherited as autosomal recessive traits. With the current technologies available through SNP-association mapping and next-generation sequencing, we should expect to further our understanding of polygenic traits and diseases.

Disease Testing

Clinicians can use DNA testing in disease diagnosis or to determine an animal's potential for producing diseased progeny. Generally, disease diagnosis is based on clinical signs and other diagnostic tests, but occasionally DNA testing is used, in particular for later-onset diseases or diseases for which diagnosis by traditional methods is difficult or invasive. To offer a genetic test, the gene responsible must be known. Ideally, the actual mutation that causes the disease has been identified. Rather than knowing the exact gene or mutation, only a region of a chromosome may have been implicated in a particular disease. DNA tests can be divided into two categories: mutation tests and linked-marker or haplotype tests. *Mutation* tests are based on an actual mutation that causes disease, whereas the *linked-marker* or *haplotype* test is based on the region of the chromosome that is known to cause disease, but not necessarily the actual mutation. Usually, haplotype tests are offered instead of a mutation test because the mutation has not yet been identified.

Mutations that cause disease appear in many different forms. A change of a single base pair from one base to another can cause a disease either by changing an amino acid ("missense" mutation), truncating the amino acid chain ("nonsense" mutation), or altering expression or proper splicing. For example, missense mutations have

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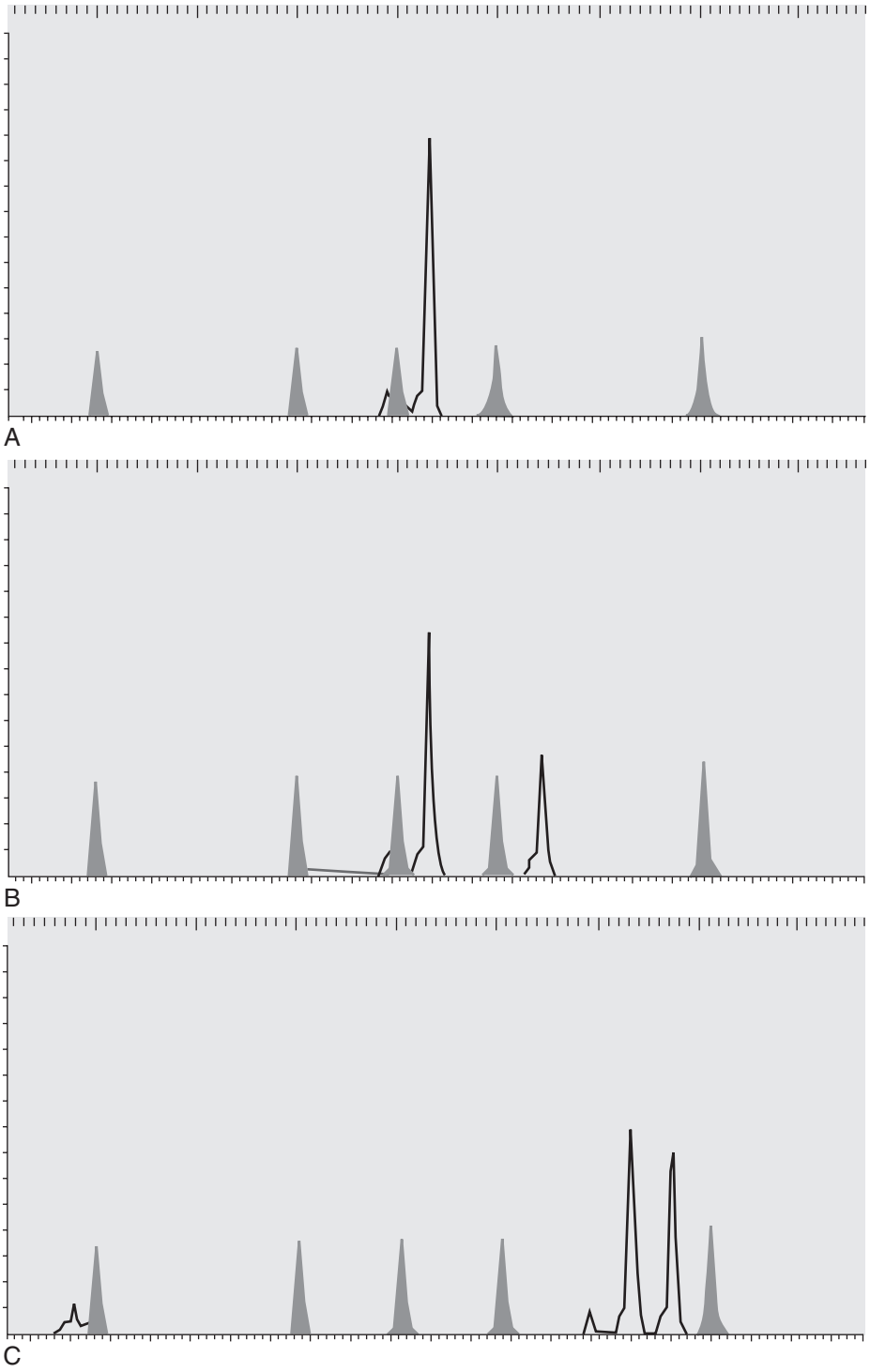


FIG. 52-1 Microsatellite markers are visualized after polymerase chain reaction (PCR) by running the fluorescent-labeled PCR product *(shown in black)* through capillary electrophoresis, which separates the products based on size relative to an internal size standard *(shown in gray).* Each panel **(A, B,** and **C)** shows the results for a different animal. Size (base pairs of DNA) is resolved along the *x* axis, and the *y* axis shows the fluorescence intensity.

been shown to cause lethal white foal syndrome in the American Paint horse.[10-12] Insertions or deletions of a single base pair (bp) can cause mutations in the coding sequence by altering the translational frame, which ultimately causes protein truncation. An 11-bp deletion in the myostatin gene causes a frameshift mutation and protein truncation in Belgian blue and Peidmontese cattle with the double-muscle phenotype.[13-15] Large deletions or insertions that remove hundreds and thousands of base pairs can also cause disease. For example, the polled intersexuality mutation in goats is caused by an 11.7-kilobase deletion that removes a regulatory element that controls the expression of two genes.[16] This endless array of possible changes in the DNA that result in disease makes each individual DNA-based genetic test different.

The basis for DNA testing is PCR. Primers can be designed specifically to amplify either the disease-causing allele or the normal allele. Alternatively, the PCR product can be digested with a restriction enzyme that cleaves the DNA at a particular sequence of bases. A restriction enzyme is chosen that shows a different cleavage pattern between the mutant and the normal version of the PCR product. Direct sequencing of a section of DNA can also be used to determine the animal's genotype. Many different methods are available to assay changes in DNA that lead to disease. Each company that offers a test may choose a different type of assay for the same mutation.

If the exact mutation that causes the disease has not been discovered, a linked-marker test can be used. A "linked marker" is a microsatellite marker similar to those previously described for individual

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TABLE 52-1

Parentage Verification Using Microsatellite Markers

Individuals	Allele Sizes for Four Markers			
	A	B	C	D
Dam	122/124	110	131/133	80/82
Offspring	122/126	110/112	133	82/86
Sire 1	128	112/114	131	84
Sire 2	126	112/114	131	86/90

TABLE 52-2

Map Status and Genomic Resource for Large Animal Species

	Horse	Cattle	Sheep	Goat
Chromosome (2n)	64	60	54	60
Linkage map	Yes	Yes	Yes	Yes
Cytogenic map	Yes	Yes	Yes	Yes
RH map	Yes	Yes	Yes	No
Whole genome sequencing	6x*	7x†	3x‡	12X§
SNP-chip available	Yes: 76,000 SNPs‖	Yes: 778,000 SNPs‖	Yes: over 50,000 SNPs‖	Yes: over 50,000 SNPs
Expression array available	Yes¶	Yes#	Yes¶	No

*September 2007 2.0 draft assembly *Equus caballus,* available from http://www.ncbi.nlm.nih.gov/genome/145.

†October 2011 4.6.1 draft assembly *Bos tauru,* available from http://www.ncbi.nlm.nih.gov/genome/82.

‡February 2010 1.0 draft assembly *Ovis aries,* available from http://www.ncbi.nlm.nih.gov/genome/83.

§December 2012 1.0 draft assembly *Capra hircus,* available from http://www.ncbi.nlm.nih.gov/genome/10731.

‖Illumina, Inc., San Diego, Calif.

¶Agilent Technologies, Inc., Wilmington, Del.

#Affymetrix, Inc., Santa Clara, Calif.

TABLE 52-3

Genetic Tests for Horses

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Androgen insensitivity syndrome (AIS)	AR	X-linked recessive	18
Cerebellar abiotrophy (CA)	TOE1/MUTYH	Autosomal recessive	19
Hereditary regional dermal asthenia (HERDA)	PPIB	Autosomal recessive	4
Junctional epidermolysis bullosa (JEB)	LAMA3	Autosomal recessive	20
Junctional epidermolysis bullosa (JEB)	LAMC2	Autosomal recessive	21
Foal immunodeficiency syndrome (Immunodeficiency of Fell ponies)	SLC5A3	Autosomal recessive	22
Gaitedness	DMRT3	Multifactorial	23
Glycogen storage disease IV (Glycogen branching enzyme deficiency)	GBE1	Autosomal recessive	24
Lavender foal syndrome (LFS)	MYO5A	Autosomal recessive	6
Malignant hyperthermia (MH)	RYR1	Autosomal dominant	25
Megacolon (Ileocolonic aganglionosis or lethal white foal syndrome)	EDNRB3	Autosomal semi-dominant	10-12
Multiple ocular defects	PMEL17	Autosomal semi-dominant	26
Myotonia	CLCN1	Autosomal recessive	27
Night blindness, congenital stationary	TRPM1	Autosomal recessive	28
Ovotesticular disorder of sexual development	SRY	Y-linked	29
Periodic paralysis II (hyperkalemic periodic paralysis; HYPP)	SCN4A	Autosomal semi-dominant	2
Polysaccharide storage myopathy type I (PSSM I)	GYS1	Autosomal dominant	5
Severe combined immunodeficiency (SCID)	DNAPKcs	Autosomal recessive	3
Thrombasthenia (Glanzmann thrombasthenia)	ITGA2B	Autosomal recessive	30, 31

TABLE 52-4

Genetic Tests for Cattle

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Disease			
Abortion/Stillbirth	MIMT1	Maternally imprinted	32
Abortion	APAF1	Autosomal recessive lethal	33
	GART	Autosomal recessive lethal	34
	CWC15	Autosomal recessive lethal	35
	SHBG	Autosomal recessive lethal	34
	SLC37A2	Autosomal recessive lethal	34

Continued

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TABLE 52-4

Genetic Tests for Cattle—cont'd

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Acrodermatitis enteropathica (bovine hereditary zinc deficiency or lethal trait A46)	SLC39A4	Autosomal recessive	36
Anhidrotic ectodermal dysplasia	EDA	X-linked recessive	37
Arachnomelia (spider limbs)	MOCS1	Autosomal recessive	38
	SUOX	Autosomal recessive	39
Axonopathy (Demetz syndrome)	MFN2	Autosomal recessive	40
Beta-lactoglobulin, aberrant low expression	PAEP	Autosomal	41
Brachyspina	FANCI	Autosomal recessive	42
Cardiomyopathy and woolly haircoat syndrome	PPP1R13L	Autosomal recessive	43
Cardiomyopathy, dilated	OPA3	Autosomal recessive	44
Chediak-Higashi syndrome	LYST	Autosomal recessive	45
Chondrodysplasia	EVC2	Autosomal	46
Citrullinemia	ASS1	Recessive	47
Complex vertebral malformation	SLC35A3	Autosomal recessive	8
Congenital muscular dystonia 1	ATP2A1	Autosomal recessive	9
Congenital muscular dystonia 2	SCL6A5	Autosomal recessive	9
Deficiency of uridine monophosphate synthase (DUMPS)	UMPS	Autosomal recessive	48
Dominant white with bilateral deafness	MITF	Autosomal dominant	49
Dwarfism, Angus	PRKG2	Autosomal recessive	50
Dwarfism, Dexter	ACAN	Autosomal recessive lethal	51
Dwarfism, growth-hormone deficiency	GH1	Autosomal recessive	52
Ehlers-Danlos syndrome, Holstein variant	EPYC	Autosomal recessive	53
Ehlers-Danlos syndrome, type VII (Dermatosparaxis)	ADAMTS2	Autosomal	54
Epidermolysis bullosa	KRT5	Autosomal dominant	55
Epidermolysis bullosa, dystrophic	COL7A1	Autosomal recessive	56
Factor XI deficiency	F11	Autosomal recessive	57
Forelimb-girdle muscle anomaly	GFRA1	Autosomal recessive	58
Glycogen storage disease II (Pompe disease)	GAA	Recessive	59
Glycogen storage disease V	PYGM	Autosomal recessive	60
Goiter, familial	TG	Autosomal	61
Hemophilia A	F8	X-linked	62
Hypotrichosis	HEPHL1	Autosomal recessive	63
Ichthyosis congenita	ABCA12	Autosomal recessive	9
Lethal multi-organ developmental dysplasia	KDM2B	Autosomal recessive	64
Leukocyte adhesion deficiency, type I	ITGB2	Autosomal recessive	7
Mannosidosis			
Alpha	MAN2B1	Autosomal recessive	65
Beta	MANBA	Autosomal recessive	66
Maple syrup urine disease	BCKDHA	Autosomal recessive	67
Marfan syndrome	FBN1	Autosomal dominant	68
Mucopolysaccharidosis IIIB	NAGLU	Autosomal recessive	69
Multiple ocular defects	WFDC1	Autosomal recessive	70
Muscular hypertrophy (double muscling)	MSTN	Autosomal recessive	13-15
Myasthenic syndrome, congenital	CHRNE	Autosomal	71
Myoclonus	GLRA1	Autosomal recessive	72
Myopathy of the diaphragmatic muscles	HSPA1A	Autosomal recessive	73
Neuronal ceroid lipofuscinosis 5	CLN5	Autosomal recessive	74
Osteopetrosis	SLC4A2	Autosomal recessive	75
Ovotesticular disorder of sexual development	SRY	Y-linked	76
Polled and multisystemic syndrome	ZEB2	Autosomal dominant	77
Protoporphyria	FECH	Autosomal	78
Pseudomyotonia, congenital	ATP2A1	Autosomal recessive	79
Renal dysplasia	CLDN16	Autosomal recessive	80
Scurs, type 2	TWIST1	Autosomal dominant	81
Spherocytosis	SLC4A1	Autosomal incompletely dominant	82
Spinal dysmyelination	SPAST	Autosomal recessive	83
Spinal muscular atrophy	KDSR	Autosomal recessive	84
Syndactyly	LRP4	Autosomal recessive	85, 86
Tail, crooked	MRC2	Autosomal recessive	87
Thrombopathia	RASGRP2	Unknown	88
Trimethylaminuria	FMO3	Autosomal recessive	89
Yellow fat	BCO2	Unknown	90
Trait			
Milk yield and composition	GHR	Polygenic	91
	DGAT1	Polygenic	92
	Leptin	Polygenic	93, 94
Meat tenderness	Calpastatin	Polygenic	95, 96
	μ-Calpain	Polygenic	97, 98

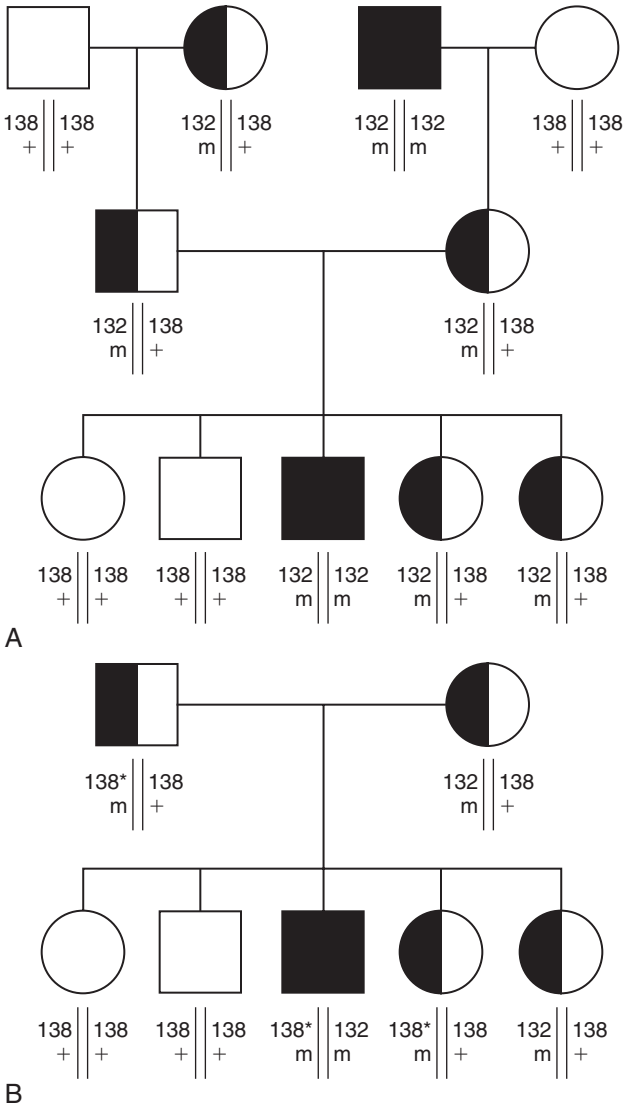


FIG. 52-2 In this pedigree, *squares* are males and *circles* are females. *Filled symbols* represent affected individuals, *half-filled symbols* represent carriers, and *open symbols* represent normal animals. The allele sizes for a marker linked to the disease locus are given below each symbol. For clarity, the genotype at the disease locus is also written below each symbol as *m* for the mutant allele and + for the normal allele. Panels **A** and **B** are two different families. The *asterisk* marks the allele in different linkage phase in family *B*.

identification and parentage analysis. The marker is "linked" along the chromosome to the disease gene. It can be used as a proxy for the actual mutation; the associated error rate can be decreased by using a set of markers that flank the gene causing the disease. When a set of markers is used, the test is called a "haplotype" test. Because the test does not directly test for the mutation, an error is still possible. Figure 52-2 shows a pedigree that is segregating a disease allele and a marker. In panel *A* the disease allele is in linkage phase with the marker allele 132. In this family the 132 allele is correlated to the disease locus. Panel *B* shows a family in which the linkage phase is different. In this family the sire has a 138 allele associated with the disease allele. Therefore, his affected son would be called a "carrier" and one of his daughters that is a carrier would be called "normal" based on this linked marker. Linked markers can be used in families with affected individuals to test for the presence or absence of the disease allele in other family members. The problem arises when a linked-marker test is used to test individual animals. The linkage phase is assumed based on research done in one family but may not be true for every animal in the breed.

BOX 52-2

Laboratories Offering Genetic Testing for Large Animal Species

Animal Genetic Testing and Research Laboratory
Department of Veterinary Science
Gluck Equine Research Center
University of Kentucky
Lexington, KY 40546
(859) 218-1212
www.ca.uky.edu/gluck
(Horse)

Animal Health Diagnostic Center
Cornell University College of Veterinary Medicine
P.O. Box 5786
Ithaca, NY 14852-5786
(607) 253-3935
http://ahdc.vet.cornell.edu/test/
(Horse)

Maxxam Analytics
335 Laird Road, Unit 2
Guelph, Ontario N 1 H 6J3 Canada
(519) 836-2400
www.maxxam.ca
(Horse)

MetaMorphix, Inc.
1756 Picasso Avenue
Davis, CA 95618
(800) 311-8808 Ext. 3016
Email: cattlecustomerservice@mmigenomics.com
www.metamorphixinc.com
(Cattle)

Zoetis (formerly Pfizer Animal Health)
100 Campus Drive
Florham Park, NJ 07932
1-888-Zoetis1
https://online.zoetis.com/US/en/Pages/US.aspx
(Cattle)

Veterinary Diagnostic Laboratory
University of Minnesota
1333 Gortner Avenue
St. Paul, MN 55108-1098
(612) 625-8787
http://www.vdl.umn.edu/
(Horse)

Veterinary Genetics Laboratory
University of California, Davis
PO Box 1102
Davis, CA 95617-1102
(530) 752-2211
http://www.vgl.ucdavis.edu/
(Cattle, horse, sheep, goat)

There are limits to all genetic testing. In mutation tests the specific mutation being assayed is the only factor being evaluated. An animal may have a different mutation in that gene or a mutation in a different gene that causes the same phenotype (phenocopy). It is therefore correct to state that an animal has been "DNA tested negative" for this specific mutation rather than "DNA tested clear" of the disease. Linked-marker tests have these same sources of error, as well as additional sources. Recombination events between the markers and the disease gene can lead to false-positive and false-negative results. The use of multiple markers that flank the gene of interest (haplotype test) can increase the probability that a recombination event will be identified. If one is identified, the laboratory will know that the test

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TABLE 52-5

Genetic Tests for Sheep

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Achromatopsia-2	CNGA3	Autosomal recessive	99
Chondrodysplasia (spider lamb)	FGFR3	Autosomal recessive	100
Chondrodysplasia, Texel	SLC13A1	Autosomal recessive	101
Ehlers-Danlos syndrome, type VII (Dermatosparaxis)	ADAMTS2	Autosomal recessive	102
Epidermolysis bullosa, junctionalis, LAMC2	LAMC2	Autosomal recessive	103
Fecundity Booroola	BMPR1B	Autosomal semi-dominant	104-106
Cambridge	BMP15, GDF9	Multifactorial	107
Embrapa	GDF9	Autosomal	108
Hanna	BMP15	X-linked	109
Iceland (Thoka)	GDF9	Autosomal	110
Inverdale	BMP15	X-linked	109
Small tail Han	ESR1	Autosomal	111
Gangliosidosis, GM1	GLB1	Autosomal recessive	112
Gangliosidosis, GM2, type 1	HEXA	Autosomal recessive	113
Gaucher disease, type I	GBA	Autosomal recessive	114
Glycogen storage disease V	PYGM	Autosomal recessive	115
Hemophilia A	F8	X-linked	116
Hypophosphatemic rickets	DMP1	Autosomal recessive	117
Hypotrichosis	HR	Autosomal recessive	118
Microphthalmia	PITX3	Autosomal recessive	119
Motor neuron disease, lower	AGTPBP1	Autosomal recessive	120
Muscular hypertrophy (double muscling)			
Callipyge	DLK1	Polar overdominant	121
Texel	MSTN	Autosomal	122
Neuronal ceroid lipofuscinosis			
10	CTSD	Autosomal recessive	123
5	CLN5	Autosomal recessive	124
6	CLN6	Autosomal recessive	125
Porphyria cutanea tarda	UROD	Autosomal recessive	126
Spongiform encephalopathy (scrapie susceptibility)	PRNP	Autosomal recessive	127
Waardenburg syndrome, type 4A	ETBR	Autosomal recessive	128
Yellow fat	BCO2	Autosomal recessive	129

TABLE 52-6

Genetic Tests for Goats

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Casein, alpha-S1, reduced concentration	CSN1S1	Autosomal	130
Casein, alpha-S2, null allele	CSN1S2	Autosomal recessive	131
Casein, beta, null allele	CSN2	Autosomal	132
Goiter, familial	TG	Autosomal recessive	133
Horns/Polled	PISRT1, FOXL2	Autosomal	16, 134
Mannosidosis, beta	MANBA	Autosomal recessive	135
Mucopolysaccharidosis IIID	GNS	Autosomal recessive	136
Myotonia	CLCN1	Autosomal dominant	137

is not valid in this individual. The second source of error with either a linked-marker or a haplotype test occurs when there is an ancestral recombination event that changes the linkage phase of the alleles. The result is that the laboratory would interpret an animal's genotype at the disease locus incorrectly, based on the linked markers.

No association or committee evaluates quality control of DNA tests that are available in animals. Most tests are published in the scientific literature, not as tests, but as articles describing the discovery of the mutation. Because some cases involve patent issues, some tests are offered before publication. Much of the research done to identify the mutations involved in the tests is performed at universities and funded by granting agencies that have both financial and intellectual interest in patenting the tests. Companies then license the rights to offer the tests. A list of licensed testing labs is included in Box 52-2. Veterinarians should contact the laboratories to inquire about available genetic tests for large animal species because laboratories are licensed to run only particular tests.

Tables 52-3 through 52-6 list available genetic tests for traits and diseases other than coat color in horses, cattle, sheep, and goats, respectively. Only tests published in peer-reviewed journals are listed. Additional tests available in cattle for various forms of the milk proteins also are not listed in Table 52-4. The breeds of cattle are not listed because rapid changes in testing mean that tests are always being validated for new breeds. It is therefore recommended that a search be performed for the availability of a test for a particular breed each time the need arises. Coat color genetic tests are listed in Table 52-7, with each particular species in which the genetic mutation has been identified referenced.

The diseases or traits that are tested can be divided into two categories: those that have straightforward Mendelian inheritance patterns (recessive, dominant, and sex-linked) and those that are more complicated because many genes are involved with conferring the phenotype (polygenic). *Quantitative trait loci* (QTL) are the genes that contribute to a polygenic disease. In cattle, a vast number of QTL

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TABLE 52-7

Genetic Tests for Coat Color

Coat Color	Gene	Species	Reference
Agouti	ASIP	Horse	138
		Cow	139
		Sheep	140
Appaloosa	TRPM1	Horse	28
Brown (Dun)	TYRP1	Cow	141
		Sheep	142
Champagne	SLC36A1	Horse	143
Cream dilution	SLC45A2	Horse	144
Dilution	PMEL	Cow	145
Dominant white	KIT	Horse	146
		Cow	147
Extension	MC1R	Horse	148
		Cow	149
		Sheep	150
		Goat	151
Gray	STX17	Horse	152
Macchiato	MITF	Horse	153
Roan	KITLG	Cow	154
Silver	PMEL17	Horse	155
White spotting	MITF	Horse	153
		Cow	147
	PAX3	Horse	153

have been placed in specific regions of chromosome for quantitative traits such as dairy form, milk production, and fertility.[17] Selection for these traits can be done with DNA testing (see Table 52-4). Because so many different QTL exist, however, selection can be challenging, and trade-offs need to be made.

Genetic testing relies on advances made in the field of genomics. Veterinarians and owners are fortunate that large animal species were chosen as economically important species for whole-genome sequencing. With the tools currently available, the number of disease- or trait-based tests available in the future will markedly increase.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 53

Immunologic Disorders

LAIS R. COSTA and GEORGE M. BARRINGTON, *Consulting Editors*

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Equine Immunologic Disorders

Lais R. Costa*

Complex defense mechanisms have developed to protect the host from outside challenges, particularly against the pathogenic effects of microorganisms. Diseases, especially infectious diseases, can result from failure of the host's normal defense mechanisms, as well as from overwhelming challenge from the outside. When animals are plagued by repeated or chronic infections, the clinician should always determine whether host factors are involved. On the other hand, the defense mechanisms might lead to exaggerated responses and result in immune-mediated injury of tissues and organs. The analysis of immunologic disorders, including immunodeficiency diseases, immunosuppression, and immune-mediated injury, depends on an understanding of the normal immune response.

Overview of Immunologic Disorders in Horses

Lais R. Costa*

Normal Immune Response in Horses

The immune response results from an intricate network of innate mechanisms of resistance and complex adaptive immune mechanisms. Cells and soluble factors of the innate branch of the immune system interact with cells of the adaptive (clonal) branch of the immune system by promoting chemotactic stimuli for leukocyte trafficking, providing co-stimulatory signals and antigen presentation. The adaptive immune mechanisms confer specific, anamnestic response following the initial encounter with an antigen or pathogen. The adaptive immune response is largely mediated by cells of the lymphocytic lineage that are capable of distinction of antigenic determinants or epitopes that are *self* from those that are *nonself,* providing constant surveillance to identify and eliminate cells and organisms recognized as foreign. The cellular and molecular mechanisms involved in the immune response of horses have been recently reviewed in detail.[1]

The innate immune mechanisms are the first line of defense and do not require previous exposure to the pathogen, allowing time for development of antigen-specific acquired immune response. Innate defense mechanisms are ever ready or induced immediately. They include soluble mediators, cells, and cell-associated molecules that lead to inflammatory reactions and effector mechanisms to eliminate the offending organism. Inflammatory reaction leads to increased blood flow, increased vascular permeability, and leukocyte migration and activation. Table 53-1 depicts some of the important soluble mediators of the innate immune mechanisms. Complement activation following association of factor C3b to microbial molecules (alternative pathway), to mannose-binding lectin (lectin pathway), or following specific immunologic recognition by antibodies (classical pathway) leads to a cascade of sequential proteolytic cleavages capable of remarkable amplification. Complement activation results in opsonization by factor C3b; release of soluble factors C3a and C5a, which increase vascular permeability and exert chemoattraction of leukocytes; and finally the formation of lytic multiprotein complex, the membrane attack complex (MAC) that lyses the cell or microorganism.

The diverse cellular components of the innate immune system include granulocytes (neutrophils, eosinophils, and basophils); macrophages; dendritic cells (DCs); mast cells; and natural killer (NK) cells. All these cells play critical roles in both innate and adaptive immune responses. Macrophages and neutrophils are capable of phagocytosis and destruction of the offending pathogen by oxidative burst. Neutrophils are quick responders specialized in killing invading organisms, particularly extracellular pathogens. They are the first effector cells to act on an invader, whereas macrophages compose the second line of defense and are particularly effective at dealing with intracellular pathogens. Macrophages originate from monocytes and become specialized phagocytic cells resident in various tissues; for instance, microglial cells in the brain, histiocytes in connective tissue, Kupffer cells in the liver, alveolar macrophages in alveoli of lungs, pulmonary intravascular macrophages in capillaries of lungs, and osteoclasts in bones. Macrophages have diverse functions in addition to phagocytic and antimicrobial functions, including secretion of cytokines that lead to amplification of the inflammatory response, stimulation of lymphocytes, modulation and even suppression of the immune response, and antigen processing and presentation. Subpopulations of macrophages exert specific immunologic functions. Macrophages along with DCs are the principal antigen-processing cells. Antigen processing and presentation in the context of major histocompatibility complex (MHC)-class II is a critical function linking the cells of the innate immune system and those of the adaptive immune system. Dendritic cells encompass a heterogeneous population of immune cells, originating either from myeloid or lymphoid precursors. Myeloid DCs, follicular DCs, and Langerhans cells comprise the population called *DC1 cells,* which originate from monocytes, and therefore are derived from myeloid precursors. They are the main antigen presenters, whereas plasmacytoid DCs, referred to as *DC2 cells,* are specialized in secreting type I interferon (IFN; i.e., IFN-α and IFN-β) during viral infections. Type I interferons activate lymphocytes and NK cells.

NK cells recognize cells under stress, including infected or tumor cells expressing antigenic epitopes that are recognized as foreign. NK cells are important in mediating antibody-dependent cell-mediated cytotoxicity (ADCC). γδ T cells comprise a heterogeneous population of T cells expressing γδ T-cell receptors (TCRs), and exert a wide

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TABLE 53-1

Examples of Soluble Mediators of the Innate Immune System and Their Main Function

Categories of Mediators	Example of Soluble Mediators	Function
Acute phase proteins	C-reactive protein	Opsonization, complement activation
	Cerulloplasmin	Iron sequester (limiting nutrients required by microorganisms)
	Ferritin	
	Fibrinogen	Hemostasis
	Serum amyloid A	Leukocyte recruitment and activation
	C3, C4	Factors of complement, involved in activation
Protease systems	Complement	Mediate inflammation, opsonization and membrane attack complex formation
	Kinins	Mediate inflammation
	Clotting and fibrinolysis proteins	Hemostasis
Host defense peptides	Equine β-defensin, equine neutrophil antimicrobial peptide, equine cathelicidins	Antimicrobial (bacteriostatic and bacteriocidal) actions
Type I interferons (IFNs)	IFN-α, IFN-β	Antiviral glycoproteins mainly produced by macrophages, dendritic cells, and fibroblasts
Biogenic amines	Histamine, serotonin	Vascular smooth muscle relaxation (vasodilation) and endothelial cell contraction (leakage of plasma into tissues)
Chemokines	IL-8, MCP-1	Chemoattractants for cells of both innate and adaptive branches of the immune system
Proinflammatory cytokines	IL-1, IL-6, TNF-α	Mediate a variety of cellular responses such as chemotaxis of leukocytes, activation of leukocytes (including T and B cells), upregulation of iNOS and COX-2, and induction of fever
Prostanoids	Prostaglandins, leukotrienes, prostacyclins	Mediate and modulate acute inflammation

range of immune functions from response to heat-shock proteins, cytokine production, and antigen processing and presentation to promoting delayed hypersensitivity. NK cells and γδ T cells are lymphoid cells considered as the interface between innate and adaptive immunity. Lymphokine-activated killer (LAK) cells comprise a subset of cytotoxic effector cells with a wide target cell spectrum. LAK cells are distinct from T cells and NK cells.[2]

Cells of the innate immune system, including neutrophils, cells of the mononuclear phagocytic system, DCs, mast cells, NK cells, and a subset of γδ T cells, are capable of recognizing pathogen incursions by pattern recognition receptors (PRRs). The ligands for PRRs are collectively called *pathogen-associated molecular patterns* (PAMPs) and include toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD), and nucleotide-binding domain leucine-rich repeat containing protein (NLR).[3] In addition, the innate immune system detects markers of endogenous cell-damage, called *danger-associated molecular patterns* (DAMPs).[3,4]

The antigen-specific or adaptive immune response involves two major populations of lymphocytes, T cells (expressing αβ-TCR) and B cells (Fig. 53-1). Classically, T cells are associated with cell-mediated immune responses that confer protection against fungal, protozoal, intracellular bacterial, and viral infections. B cells are associated with humoral immunity, which provides defense against toxins, extracellular bacterial infections, parasites, and certain viral infections. T cells originate from stem cells, which probably develop in the fetal liver. These cells must undergo a maturation process in the thymus before becoming fully functional. T cells comprise about 70% to 80% of peripheral blood lymphocytes of horses and populate the periarteriolar regions of the spleen and the paracortical regions of lymph nodes. As with T cells, B cells originate from stem cells in the fetal liver. The site of B-cell maturation varies with species and includes several different organs, such as the bursa of Fabricius in birds and the bone marrow and certain Peyer patches in mammals. Of peripheral blood lymphocytes of horses, 15% to 30% are B cells. B cells populate germinal centers of the spleen and lymph nodes.[5,6]

T lymphocytes are important in regulating the adaptive immune response, both the humoral and cellular immune responses. T lymphocytes are characterized as helper T (Th) cells, cytotoxic T (Tc) cells, and regulatory T (Treg) cells based on their primary function. T cells might be differentiated on the basis of cell surface antigens, with most Th cells expressing the CD4 surface receptor and most Tc cells expressing CD8 surface receptor.[7,8] $CD4^+$ T lymphocytes recognize antigens in the context of MHC-class II expressed on the surface of antigen-presenting cells, and $CD8^+$ T lymphocytes recognize antigens in the context of MHC-class I. Further work has shown that the function of these cells is complex and that the pattern of cytokine expression is important in regulation of the immune response. On the basis of their profile of cytokine expression, $CD4^+$ cells have been further subdivided into distinct subsets (e.g., Th1, Th2, and recently identified Th17 cells) (Fig. 53-2). Although there is some species variation, Th1 cells generally produce IFN-γ and interleukin-2 (IL-2) and are involved primarily in the generation of cell-mediated immune responses, whereas Th2 cells produce IL-4, IL-5, and IL-13 and are involved in humoral responses. Th17 cells produce IL-17, IL-21, and IL-22 and are important in clearing extracellular pathogens during host defense reactions that are not efficiently cleared by Th1- and Th2-type immunity.[9,10] Protection from disease or development of lesions can be associated with the particular type of Th-cell response, and the clinical relevance of this is currently being investigated in a number of equine diseases.

The second major class of lymphocytes is B lymphocytes, which produce immunoglobulins (Igs) and are the precursors of plasma cells. There are several classes or isotypes of Igs. They are classified according to their heavy chain: IgG (γ heavy chain), IgM (μ heavy chain), IgA (α heavy chain), IgE (ε heavy chain), and IgD (δ heavy chain). Originally, four subisotypes of IgG were identified in the horse on the basis of their immune functions and properties, IgGa, IgGb, IgGc, and IgG(T). Recently, seven IgG heavy chain constant region genes were identified, and the IgG subisotypes were reassigned.[11,12] The original subisotype IgGa includes new subisotype IgG1, the original subisotype IgGb includes IgG4, and the original subisotype IgGc includes new subisotype IgG6. The formerly called IgG(T) includes two subisotypes, IgG3 and IgG5. The characteristics and immunologic functions of the equine Ig isotypes and subisotypes are summarized in Table 53-2.[11-15] Furthermore, B cells function as important antigen-presenting cells by processing and presenting antigens in the context of MHC-class II. In addition to antigen recognition by surface Igs, B cells also recognize TLR ligands.[3] A less appreciated function of subsets of B cells is the production of cytokines.[13] Subsets of B cells have recently been recognized as regulators of the immune responses during inflammation and autoimmunity.[16,17]

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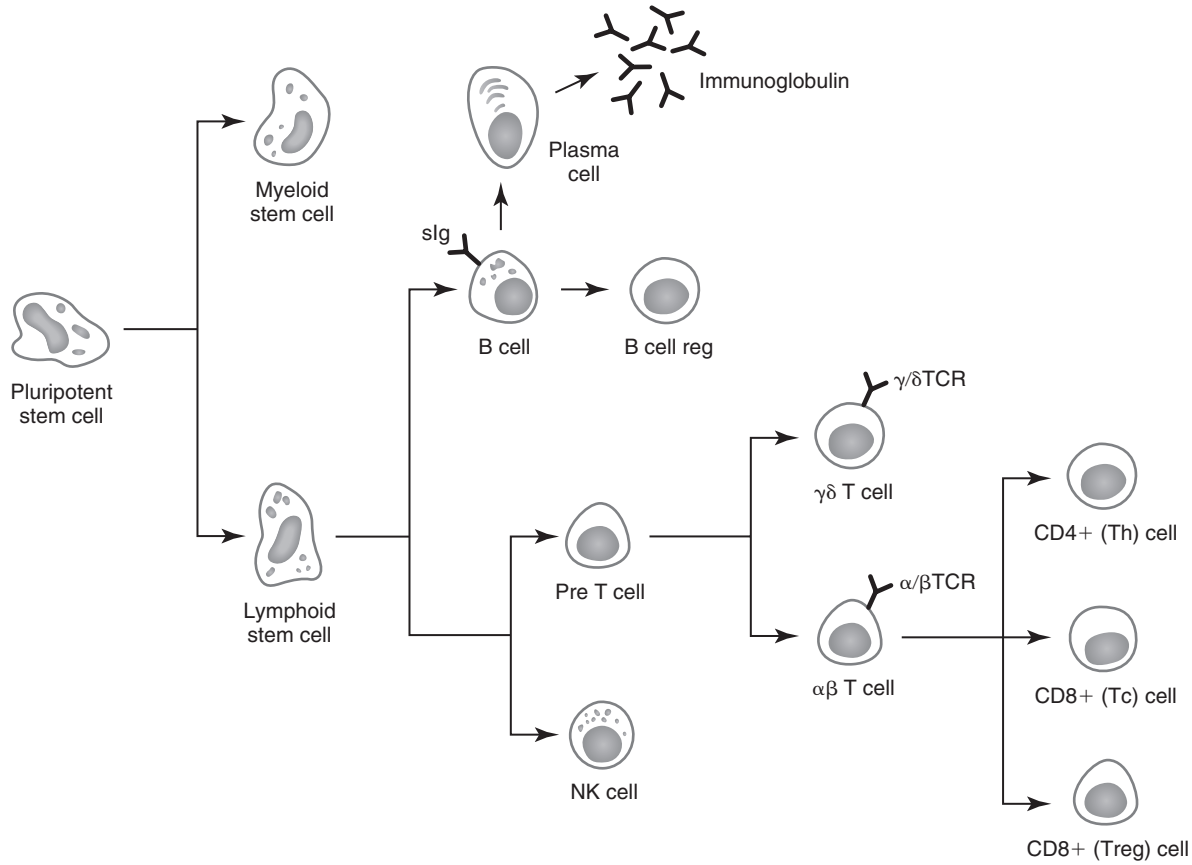
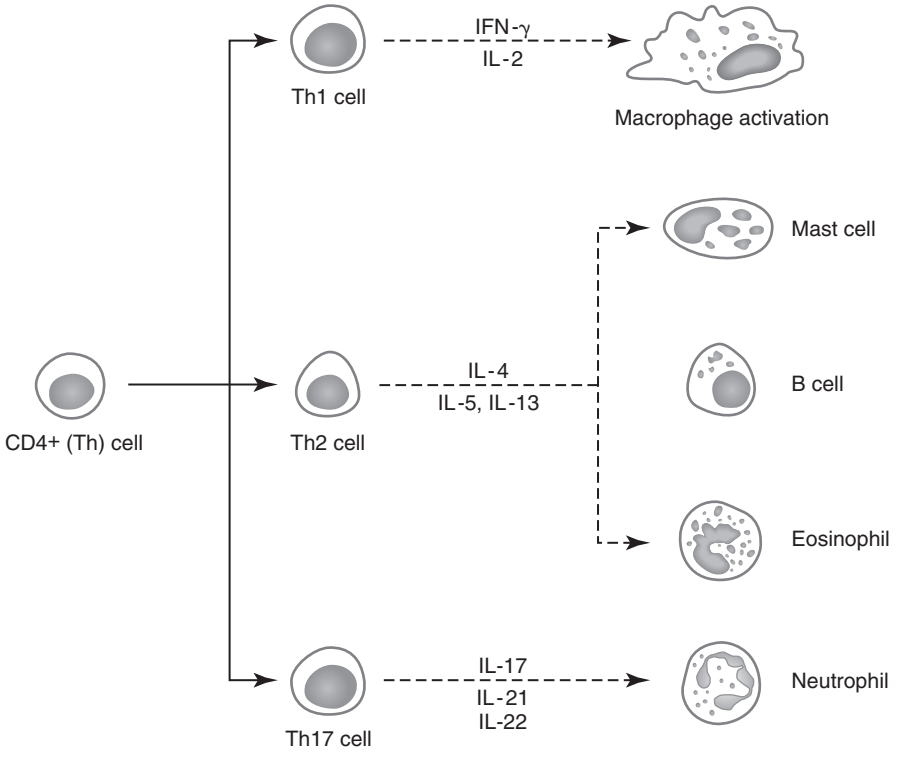


FIG. 53-1 Ontogeny of the cellular components of the adaptive immune response. Failure at any site of maturation process can manifest as immunodeficiency.

FIG. 53-2 $CD4^+$ Th cells can be divided in subsets of T-helper cells on the basis of their cytokine profile. Preliminary data suggest that the pathogenesis of certain diseases is associated with a particular type of Th response.



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TABLE 53-2

Characteristics and Immunologic Functions of Equine Immunoglobulin (Ig) Isotypes and Subisotypes[11-15]

Ig Isotype	Ig Delta	Ig Mu	Ig Gamma					Ig Alpha	Igε
Original Ig designation	IgD	IgM	IgG	Subisotype IgGa	Subisotype IgG(T)	Subisotype IgGb	Subisotype IgGc	IgA	IgE
New IgG subisotype designation				IgG1	IgG3 IgG5	IgG4	IgG6		
Special characteristics	Surface receptor of naive B cells	Surface receptor in naive and activated memory B cells; pentamer in serum and body secretions	Main Ig isotype in plasma/serum; IgG main functions are opsonization and neutralization; different subisotypes are most effective in different immune functions					Most abundant Ig isotype in body secretions (dimer, joined by J chain); monomeric form in serum	Small amount in serum; mostly found bound to receptors on surface of mast cells and basophils
Agglutination	No	+++	+	+	+	+	+	No	No
Precipitation	No	+++	+	+	+	+	+	No	No
Opsonization	No	+++	+++	+++	+++	+++	+++	No	No
Neutralization	No	+++	+++	+++	+++	+++	+++	+++	No
Complement fixation	No	Classical pathway	Classical pathway	+++	–	+++	–	Alternative pathway	No
ADCC	No	No	Yes	+++	–	+++	–	No	No
Immunity to parasites	No	No	Yes	–	+++	–	+++	No	Yes
Abundance of Ig isotypes									
In serum	NA	+		++	++	++++++	+	+	+
In tears	NA	+		++	+	–	–	+++++	–
In colostrum	NA	+		++++++	++++	+++++++	+	++	+
In milk	NA	–		++	++	+++	+	++	–

ADCC, Antibody-dependent cellular cytotoxicity; *NA,* not applicable.

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Factors Associated with Inadequate Immune Response

Numerous factors influence adequacy of the immune response of an individual animal to potential environmental pathogens. Important factors to consider in the horse are age, genetic predisposition, general fitness, training, the level of stress associated with exercise, state of health, including nutritional status, and the presence of concurrent diseases. Moreover, increased concentrations of corticosteroids can result in varying degrees of immunosuppression. The increase in endogenous corticosteroids may be associated with stress or disease. The most common condition in horses associated with increased endogenous corticosteroids is pituitary pars intermedia dysfunction (PPID). In addition, corticosteroid treatment is the most common iatrogenic cause of immunosuppression. Regardless if endogenously produced or exogenous in origin, increased concentrations of corticosteroids may exacerbate preexisting infectious diseases or decrease resistance to environmental pathogens.[18,19] Corticosteroids have a number of effects on the immune system, many of which are dose dependent. The effects of corticosteroids on the immune system are discussed later in "Drug-Induced Immunosuppression".

It is well recognized that nutritional status has a major impact on immune function, and nutritional deprivation produces impairment of immune response. Collectively called *nutritionally acquired immunodeficiency syndrome* (NAIDS), these immunologic dysfunctions include protein-calorie malnutrition and deficiencies of single nutrients. Protein-calorie malnutrition and deficiencies of single nutrients that assist in nucleic acid metabolism lead to dysfunction of the adaptive immune response, especially the T-cell functions, and result in atrophy of lymphoid tissues.[20] In these individuals, the cell-mediated immunity and humoral response to T cell–dependent antigens are subnormal. Deficiency of single nutrients can impair production of key proteins by lymphocytes and phagocytic cells.[20] Inadequate nutritional status may result from (1) increased and unmet nutritional requirement, including during growth, pregnancy, lactation, aging, and intense work, (2) disease state associated with altered nutrient intake such as conditions leading to hypophagia or anorexia, and (3) disease state associated with altered absorption of nutrients.[21] Young animals are more likely to develop NAIDS, followed by geriatric patients, contributing to the greater risk of infections in both age groups.

Age has been shown to affect immune function in multiple species. Altered immune function has been identified in both ends of the age spectrum, in foals and older horses. Foals are immunocompetent at birth, but their immune system is naive, therefore they rely on the transfer of maternal immunity through the colostrum for immunologic protection. Newborn foals have practically no circulating Igs of their own; however, they normally receive maternal transfer of colostral antibodies, especially IgG.[22-25] As the foals age, the maternal antibody levels decline and no longer provide comprehensive protection, but at the same time they might interfere with the foals' ability to mount an immune response. The immune response of foals differs from those of adults.[22-25] Phagocytocytic ability of neutrophils (when autologous serum is used as opsonin) is impaired until 3 weeks of age.[26] Killing capacity of neutrophil is reduced in neonates but gradually improves, reaching levels similar to adults by 3 months of age.[26] Oxidative burst activity and phagocytosis by peripheral blood leukocytes (only if adult serum is used as opsonin) and LAK cell activity do not differ significantly between foals from birth to 6 months of age and adult horses.[27] Total circulating lymphocyte counts at birth are similar to those of adult horses and increase linearly 2.5-fold from birth to 18 months of age.[25,27,28] This increase in circulating lymphocyte counts results principally from an increase in B cells and $CD4^+$ T cells.[25,27-29] Age-dependent changes in humoral immune response from birth to 6 months of age include the gradual increase in the numbers of peripheral blood B cells and in circulating IgM above those found in adult horses, concomitant with decline of maternal Ig levels.[25] Proliferative response of peripheral lymphocytes to mitogenic stimulation is slightly reduced at birth but rapidly increases.[27] The expression of MHC-class II on the surface of peripheral blood mononuclear cells is low in neonatal foals and gradually increases.[27] The vulnerability of foals between 2 and 4 months of age to respiratory tract infections, particularly the pathogens *Rhodococcus equi* and *Pneumocystic jiroveci* (formerly *Pneumocystis carinii*), was thought to reflect a general cellular immune-deficient state that is uncovered by the decline in protective maternal antibodies.[22,28,30] Studies evaluating cytokine production by lymphocytes of foals from birth to 6 months of age have yielded conflicting results. Mitogen stimulation of lymphocytes from newborn foals was shown to evoke a limited production of IFN-γ due to a diminished ability to express the IFN-γ gene, associated with hypermethylation of the promoter of the IFN-γ gene.[24,31] This ability was shown to increase steadily, reaching adult levels within the first year of life, suggesting that foals have an inherent inability to mount a Th1 immune response, which may contribute to their susceptibility to intracellular pathogens. Further studies showed that the number of IFN-γ and IL-4 producing cells vary with the type of mitogen used.[31] Regardless of the mitogen, the number of IFN-γ producing cells was equally low in foals younger than a week of age and at 3 to 4 months of age, compared with adult horses.[32] The number of IL-4 producing cells was low in foals younger than a week of age and even lower at 3 to 4 months of age.[32] Expression of IFN-γ, IL-4, and IL-10 by mitogen-stimulated lymphocytes from foals at 36 hours and 5 days was minimal and gradually increased by 6 and 12 weeks of age, although it remained inferior to that of adult horses.[33] Antigen-specific stimulation with *R. equi* of peripheral lymphocytes from foals during the first 3 weeks of life (i.e., days 1, 3, 7, 10, 15, and 20) induced expression of IFN-γ and IL-4 that was lowest at day 1 and gradually increased.[34] Immunization of neonates with a killed adjuvanted vaccine invoked a modest induction of vaccine-specific humoral and lymphoproliferative immune responses.[35] Both humoral and lymphoproliferative responses improved by 3 months of age, but their magnitude was far less than that of adult horses.[35] On the other side of the age spectrum, aging has been associated with an increased susceptibility to infection.[36,37] Immunosenescence is discussed in detail later in this chapter.

Exercise represents not only an increased nutritional requirement but also a physiologic stress that can significantly alter the immune response.[38,39] However, defining the precise effects of exercise on the equine immune system and susceptibility to disease has been difficult because of the complexity of the immune system; host factors (e.g., age, level of fitness); and the variable nature of exercise.[36,38,39] In general, it appears that exercise may have both positive and negative effects on the immune response.[36,38-44] Suppressive effects, such as a decline in the ratio of $CD4^+$:$CD8^+$ T cells, decreased lymphoproliferative responses, and suppression of the innate immune system, have been associated with strenuous high-intensity exercise, prolonged exhaustive exercise, or overtraining. In contrast, moderate exercise tends to have beneficial effects on the host defense mechanisms. Data in horses directly linking exercise-induced immunosuppression and increased susceptibility to infectious disease are limited. However, the potential immunosuppressive effects of exercise need to be recognized. In one study, unconditioned ponies vaccinated with a killed influenza vaccine and subjected to 5 days of strenuous exercise had an increased susceptibility to clinical influenza after challenge exposure compared with rested ponies.[45] However, ponies with exercise-induced immunosuppression responded to the administration of an intranasal modified-live equine influenza vaccine and were protected from challenge.[46] In a study of influenza infection in trained horses, moderate exercise led to increased signs of clinical disease, but the duration of disease was unaffected.[47]

Immunologic Disorders Resulting from Compromised or Deficient Immune Responses

Increased susceptibility to infections, either because of recurrence, chronicity, or severity of infectious illness beyond what is considered "normal," raises the suspicion of inadequate immune response. Inadequacy of the immune response due to deficiency of the innate, humoral, or cell-mediated immunity, or any combination of these,

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predisposes animals to infections that might culminate with their death. Pathogens most often associated with immunodeficiencies in horses include infections by *P. jiroveci, Candida* spp., *Aspergillus* spp., adenovirus, *Cryptosporidium,* and *R. equi* in adult horses.

General clinical features associated with immunodeficiencies include the following[5,21,48,49]: (1) onset of infections during the first 6 weeks of life, (2) repeated infections that respond poorly to standard therapy, (3) increased susceptibility to organisms with low pathogenicity, (4) infection with organisms rarely observed in immunocompetent individuals, (5) systemic illness after administration of attenuated live vaccines, (6) failure to respond to vaccination, and (7) persistent marked abnormalities in leukocyte numbers.

Immunodeficiency Disorders Characterized by Defects of Components of the Adaptive Immune Response

Immunodeficiencies of the adaptive immune response can be classified according to (1) the site of defect in the host defense system and (2) whether the mechanism is primary or secondary.[5,21,48,49] In primary disorders there is an inherent abnormality in the immune system that has a proven or suspected genetic basis, whereas in secondary disorders the host's initially normal ability to respond immunologically is altered. Both primary and secondary immunodeficiencies can affect various components of the immune system, and by careful dissection of the immune response, the site of the defect can often be identified. Some drugs, toxicities, neoplasia, and microbial infections lead to immunosuppression.[5,21,49] Immunosuppression associated with drugs, leukoproliferative and autoimmune conditions, and infectious processes are discussed later in this chapter. Table 53-3 depicts salient characteristics of immunodeficiency disorders of the horse. Table 53-4 lists some case reports of impaired or inadequate immune response in foals that do not fit any of the well-described immunodeficiency disorders.

Immunodeficiencies Characterized by Defects of Components of the Innate Immune Response

Inherited disorders of the innate immune system such as lethal trait A46, Chédiak-Higashi syndrome, and leukocyte adhesion deficiency have not been identified in horses. Pelger-Huët anomaly, an inherited disorder of neutrophils, occurs in horses. Heritability of Pelger-Huët anomaly has been recently described in Arabian horses.[50,51] Pelger-Huët neutrophils are characterized by reduced numbers of nuclear segmentation into lobes. They often resemble band forms, appearing mostly as bilobed dumbbell-shaped nuclei. Immunophenotyping of Pelger-Huët neutrophils of horses revealed normal expression of myeloid-specific markers and adhesion molecules, and evaluation of phagocytosis and oxidative burst via flow cytometry revealed normal neutrophil function.[51] Similar to the condition in other species, the functions of Pelger-Huët neutrophils are virtually normal, and the neutrophil survival is not affected. However, their inflexible nuclei restrict their ability to emigrate from blood vessels. Nonetheless, no clinical signs of immunodeficiency are observed and this morphologic anomaly represents an incidental finding during the evaluation of blood smears.

Inherited forms of complement dysfunction or factor deficiency have not been reported in the horse. However, depletion of complement C3 component associated with chronic infections, such as equine infectious anemia, has been reported. Moreover, the foal is born with low serum complement activity, and colostrum is not a significant source of complement. Therefore foals are transiently deficient in serum opsonic capacity and rely on their own production of complement after birth. In sepsis, complement C3 components are rapidly consumed, which delays the physiologic age-dependent increase otherwise observed in healthy foals.[52]

Immunologic Disorders Leading to Immune-Mediated Injury

Inappropriate or exaggerated immunologic responses can directly injure bodily tissues. The clinical manifestation of immune-mediated injury depends on the nature and site(s) of tissue injury. Immune-mediated tissue injury can be from humoral or cell-mediated immune responses, or a combination of both. Immune-mediated tissue/organ damage, often referred to as *hypersensitivity,* has been classified according to the nature of the immunologic pathway involved. Comprehensive reviews of these disorders in the horse may be found elsewhere.[1,53-56] Table 53-5 summarizes disorders caused by immune-mediated injury in the horse.

IgE-mediated hypersensitivity reactions, often referred to as *immediate* or *type I hypersensitivity,* consist of responses to antigens mediated by antibodies of the IgE isotype.[1,53-55] These reactions typically occur within 15 minutes from the time of reexposure to the triggering factor, unless the triggering antigen requires metabolic processing. Binding of the antigen (often referred to as *allergen*) to the IgE molecules bound to the surface of mast cells via high-affinity IgE receptors (FcεRI) leads to degranulation of mast cells and release of mediators such as histamine, serotonin, leukotrienes, prostaglandins, various chemokines, and cytokines. These mediators, broadly classified as to their ability to cause vasodilation, edema, smooth muscle contraction, and chemotaxis, are responsible for inflammation, which may be localized or systemic. Of clinical significance is that localized reactions may propagate to systemic reactions. The classic example of systemic IgE-mediated hypersensitivity is anaphylaxis. In horses anaphylaxis may be manifested as dyspnea, tachypnea, coughing, sweating, hypotension, and abdominal pain because the respiratory and gastrointestinal tracts are the shock organs in horses.

Immune complex–mediated hypersensitivity reactions are also referred to as *cytotoxic hypersensitivity.* They include reactions to cell-associated antigenic epitopes, or type II hypersensitivity, and reactions to soluble antigens, or type III hypersensitivity.[1,53-55] Immune complex–mediated hypersensitivity reactions to cell-associated antigenic epitopes or soluble antigens are mediated mostly by antibodies of the IgM or IgG isotypes. Some conditions are mediated by IgA isotypes. Immune complex formation activates complement and results in the deposition of C3b and iC3b. Complement deposition enhances destruction of antigen-bearing cells by formation of the MAC and by opsonization, which enhances phagocyte-mediated destruction. In addition, Igs also mark the cell target for ADCC by NK cells. Beyond cell destruction that is mediated by complement and ADCC, activation of C5a potently recruits neutrophils that release proteolytic enzymes (including acid phosphatases, acid hydrolytic enzymes, cathepsins, elastase, collagenase) and oxidative agents. Enzymatic and oxidative damage mediated by neutrophils and other chemoattracted cells leads to further tissue destruction. The binding of Ig molecules to antigenic epitopes on cells that are fixed in a tissue or on tissue structural elements, such as basement membrane, results in damage to the respective tissue. For instance, antibodies to pemphigus antigens of the keratinocyte desmosome are responsible for the immune complex–mediated damage that results in acantholysis, blistering, and desquamation in pemphigus complex.[56] If the antigen-bearing cell is circulating, as is the case in neonatal isoerythrolysis, the cell may be destroyed in circulation but more typically is removed by the mononuclear phagocytic system. Examples of hypersensitivity to antigenic epitopes on circulating cells include alloimmune reactions (e.g., neonatal isoerythrolysis, neonatal alloimmune thrombocytopenia, neonatal allogeneic neutropenia) and drug hypersensitivities (e.g., penicillin-induced hemolytic anemia). In the case of soluble antigens that are not cell associated, Ig binding results in Ag-Ab complexes that deposit in a variety of vascular beds, including lymph nodes, kidneys, joints, and skin. Tissue in the vicinity of the precipitated Ag-Ab complexes is damaged by the ensuing immune reaction. An important condition characterized by hypersensitivity reaction to soluble antigens in horses is purpura hemorrhagica.

Delayed hypersensitivity reactions, also referred to as *type IV hypersensitivity,* consist of exaggerated cell-mediated immune responses. Once sensitization has occurred, the reaction becomes evident within 24 to 48 hours from the time of reexposure to the

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TABLE 53-3

Features of Immunodeficiency Disorders of Horses

Disease Category	Age of Onset*	Breed	Peripheral Lymphocyte Count	B-Cell Count	IgM Concentration	Other Ig Concentrations	Lymphocyte Proliferation to Mitogens	Response to ID PHA	Response to Vx	Comments
SCID	1-3 mo	Arab, Appaloosa, Arab cross, Caspian†	Severe absolute lymphopenia (<1000/μL)	Low	None	Incapable of producing any Ig (evident when maternal Abs wane)	Absent	Absent	Absent	SCID-genetic testing available
Foal immunodeficiency syndrome	3-5 wk	Fell Pony, Dale Pony	Normal at birth, then progressive lymphopenia	Low	None	Incapable of producing any Ig (evident when maternal Abs wane)	Normal to PHA, ConA, PWM	NR	NR	Severe progressive nonregenerative anemia FIS-genetic testing available
X-linked agammaglobulinemia	2-6 mo	THB, STB, QH	Normal	None	None	Incapable of producing any Ig (evident when maternal Abs wane)	Normal to PHA, PWM; variable to ConA	Normal	Absent	No genetic testing available
Selective IgM deficiency	2-24 mo	Arab, QH, THB, STB, Paso Fino	Normal	Normal	None	Capable of producing Igs of other isotypes (IgG & IgA)	Normal to PHA, ConA, PWM	Normal	Normal	No specific testing available
Transient hypogammaglobulinemia	2-6 mo	Arab, THB	Normal	Normal	Persistently low (detectable)	Persistently low (delayed onset of Ig synthesis for variable period of time)	Normal	Normal	Delayed	No specific testing available
Failure of passive transfer of maternal immunity	Neonate (0-3 wk)	Any	Normal	Normal	Low	IgG < 800 mg/dL	Normal	Normal	Normal	IgG semi-quantitation (precipitation, latex agglutination, or ELISA) and IgG TIA
Common variable immunodeficiency	2-23 yrs (average 10 yrs)	THB, QH, WB, pony, Arab, Paint	Normal or low	Low	Undetectable	Low IgG of all subisotypes; IgA gradually declines over time	Normal to lower than normal response to PHA, ConA, PWM	NR	Poor, especially to toxoid	No specific testing available

*Onset of signs varies with the degree of transfer of maternal antibodies. Onset of signs listed in this table is in face of adequate colostral transfer of maternal immunity.

†Report of Caspian foal with clinical and postmortem findings of SCID but negative for SCID genetic testing.

Abs, Antibodies; *ConA,* concavalin A; *NR,* not reported; *PHA,* phytohemagglutinin; *PWM,* pokeweed mitogen; *QH,* Quarter Horse; *SCID,* severe combined immunodeficiency; *STB,* Standardbred; *THB,* Thoroughbred; *TIA,* turbidimetric immunoassay; *WMB,* warmblood.

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TABLE 53-4

Reports of Impaired or Inadequate Immune Response in Foals

Description	Age of Onset	Breed	Peripheral Lymphocyte Count	Peripheral T & B Cells	IgM, IgG, IgG(T), and IgA Concentrations	Lymphocyte Proliferation to Mitogens	Comments
Unusual selective Ig deficiency	4 mo	Arab	Normal	NR	IgM, IgG(T), and IgA not detectable; IgG normal	Normal response to PHA, ConA, minimal to LPS	Single case report[57]
Selective IgG deficiency	3 mo	Arab/QH cross	Normal	NR	IgG low to absent; IgM, IgM, IgG(T) normal	NR	Single case report[58]
Immune impairment associated with candidiasis and foals	4 mo	QH, ASB, Arab	Low	1 out of 3 had low B-cell counts	IgM, IgG low; IgG(T) and IgA not measured	Decreased response to PHA, ConA, PWM	Report of 8 foals with various immune impairments; 3 had similar immunologic findings[59]
CD4 and CD8 T lymphopenia	4 mo	Paint	Normal	Low $CD4^+$ and $CD8^+$ T cells	IgM normal; IgG low; IgG(T) and IgA not measured	NR	Single case report[60]

ASB, American Saddlebred; *ConA,* concavalin A; *LPS,* lipopolysaccharide; *NR,* not reported; *PHA,* phytohemagglutinin; *PWM,* pokeweed mitogen; *QH,* Quarter Horse.

TABLE 53-5

Immune-Mediated Conditions and the Immune Mechanism Mediating Tissue Injury in the Horse

Organ/Tissue	Condition	Proposed Immunologic Mechanism Mediating Injury
Systemic	Systemic anaphylaxis	Abs of IgE bound to mast cell surface via high affinity FcεRI lead to degranulation and release of vasoactive and inflammatory mediators.
	Systemic lupus erythematosus (SLE)	Autoantibodies against nuclear structures, including nucleic acids and ribonucleoproteins, mediate tissue injury. Antinuclear Abs, or ANA, combine with Ags and deposit in basement membranes of skin, glomeruli, synovial membranes, and lymph nodes.
	Multisystemic eosinophilic epitheliotropic disease (MEED)	Chronic IgE-mediated hypersensitivity reaction against undefined Ag(s) characterized by eosinophilic infiltrate in multiple tissues/organs: GI tract (leading to malabsorption and enteric protein loss), GI-associated lymph nodes, liver, pancreas (resulting in maldigestion), and skin.
	Serum sickness	Generalized hypersensitivity reaction resulting from formation of large quantities of circulating immune complexes to exogenous Ags and deposition in disseminated vascular beds, leading to systemic disease.
Respiratory system	Recurrent airway obstruction (RAO)	Hypersensitivity to inhaled organic dusts characterized by neutrophilic infiltrate. Two proposed mechanisms: (1) increased expression of IL-4 and IL-5, with development of allergen-specific enhanced Th2 response, and (2) increased expression of IFN-γ, suggesting a Th1 response.
	Hypersensitivity pneumonitis	Lymphocytic/plasmacytic bronchiolitis and lymphocytic interstitial pneumonia, sometimes accompanied by granuloma formation and fibrosis, associated with inhalation of organic antigens such as chicken dust and fungi.
Renal system	Glomerulonephritis	Hypersensitivity reaction resulting from deposit of circulating immune complexes in glomerular vascular endothelium leading to (1) acute glomerulopathy, and (2) proliferative glomerulonephritis associated with activation of complement, vasculitis, influx of inflammatory cells, and proliferation of mesangial and endothelial cells.
Nervous system	Polyneuritis equi (PNE)	Progressive, insidious radiculoneuritis characterized by granulomatous inflammation of the nerve roots, hemorrhages, demyelination, axonal degeneration, and fibrosis. Inflammatory infiltrate of the perineurium consists of lymphocytes (including T cells and B cells), plasma cells, macrophages and giant cells, eosinophils, and neutrophils. Cases of PNE present antibodies to P2 myelin.
Hematopoietic and hemolymphatic systems	Autoimmune hemolytic anemia	As a primary disorder, antibodies directed against autologous RBC Ags activate complement, resulting in rapid destruction of RBCs or removal by phagocytic cells from the mononuclear phagocyte system.
	Neonatal isoerythrolysis	Alloantibodies of maternal origin (absorbed from colostrum) recognize Ags on the foal RBC that are inherited from the sire but absent in the mare. Igs mediates RBC damage and destruction. Alloantibodies are directed against RBCs' surface glycoproteins or glycolipids, known as *alloantigens.*
	Drug-induced immune-mediated hemolytic anemia	Three mechanisms: (1) drug (e.g., penicillin, sulfonamides, phenylbutazone) binds to RBC surface glycoproteins, is recognized as foreign and eliminated; (2) drug and Ab combine, resulting in direct activation of complement with RBCs destroyed as bystanders; (3) drug modifies RBC membranes such that Abs are passively adsorbed and the RBC is removed by phagocytic cells in the mononuclear phagocyte system.

Continued

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TABLE 53-5

Immune-Mediated Conditions and the Immune Mechanism Mediating Tissue Injury in the Horse—cont'd

Organ/Tissue	Condition	Proposed Immunologic Mechanism Mediating Injury
	Neonatal alloimmune thrombocytopenia	Alloantibodies of maternal origin (absorbed from colostrum) recognize Ags on the neonate's (horse or mule) platelets. Ig-mediated damage and destruction ensue.
	Immune-mediated thrombocytopenia	Primary autoimmune disorder, in which Igs are directed at autologous platelet Ags, or secondary to infectious disease (e.g., equine infectious anemia) or lymphoma with foreign Ags precipitating on the platelets. Ags are recognized by Igs, and Ig-mediated damage and destruction ensue.
	Neonatal allogeneic immune-mediated neutropenia	Binding of alloantibodies of maternal origin (absorbed from colostrum) leads to destruction of foal's neutrophils.
	Hypersensitivity vasculitis	Immune-mediated vasculopathy resulting from deposit of immune complexes (type III hypersensitivity) in walls of small vessels (venules and arterioles) leading to neutrophil-induced damage of endothelial cells. Although most commonly the vasculitides are neutrophilic (leukocytoclastic), they may be eosinophilic, lymphocytic, or mixed. Generally lesions involve the skin, typically in dependent and nonpigmented areas.
	Equine purpura hemorrhagica (EPH)	Hypersensitivity vasculitis, most commonly after *Streptococcus equi* infection or vaccination, resulting from deposit of immune complexes, of the IgA isotype, in walls of small vessels (venules and arterioles). Commonly manifested as cutaneous and mucosal involvement, but when severe, EPH leads to extensive edema and hemorrhages of dermis, subcutaneous tissue, skeletal muscles, lungs, kidney, spleen, and intestinal wall.
Eye	Equine recurrent uveitis (ERU)	Immune-mediated ocular disease characterized by recurrent-remitting episodes of intraocular inflammation, mediated by an autoaggressive Th1 response directed against several retinal proteins, leading to destruction of intraocular structures.
	Immune-mediated keratopathy (IMK)	Primary, nonulcerative, noninfectious keratitis (progressive or chronic) characterized by mild to moderate cellular infiltrate (predominantly lymphocytes and plasma cells), corneal vascularization, and corneal edema.
Skin	Pemphigus complex	Includes pemphigus foliaceus and vulgaris; autoimmune vesiculobullous disorders of the skin or mucous membranes due to Abs to components of keratinocyte desmosome leading to release of proteolytic enzymes into extracellular space and acantholysis.
	Bullous pemphigoid	Autoimmune vesiculobullous and ulcerative disorder of the skin and oral mucosa due to antibodies to glycoprotein Ag (bullous pemphigoid Ag II, or collagen XVII) in the lamina lucida of the cutaneous basement membrane (BM). Antibody binding leads to complement activation, chemotaxis of neutrophils and eosinophils, and release of enzymes and oxidants that injure the BM.
	Cutaneous (discoid) lupus erythematosus	Autoantibodies against nuclear structures combine with Ags and attach to keratinocytes, leading to ADCC. Injured keratinocytes release IL-2, resulting in lymphohistiocytic infiltrate. Lesions may be induced or exacerbated by UV light.
	Erythema multiforme	Immunologic reaction leading to apoptosis of keratinocytes and resulting in formation of macules, papules, urticarial lesions, or vesicular bullous lesions.
	Hypersensitivity to insect bite	Salivary Ags are introduced by bites from *Culicoides* spp., or possibly *Simulium* spp., *Stomoxys calcitrans*, and *Haematobia irritans*, triggering two immunologic mechanisms: (1) an IgE-mediated hypersensitivity; or (2) a cell-mediated hypersensitivity reaction associated with Th2 lymphocyte response and nonspecific eosinophilic activation. Sensitized animals, upon reexposure to allergen, experience release of inflammatory mediators, leading to pruritus.
	Feed-related allergies	Hypersensitivity reactions mediated by IgE, immunocomplexes, or cellular responses to feedstuff (including malt, beet pulp, buckwheat, wheat, alfalfa, red or white clover, barley, bran, and oats).
	Atopic dermatitis	Genetically predisposed inflammatory and allergic skin reaction mediated by allergen-specific IgE, leading to degranulation of mast cells and release of inflammatory mediators that cause erythema, vascular leakage, and pruritus.
	Allergic urticaria	Hypersensitivity reaction mediated by 1 of 3 mechanisms: (1) IgE, (2) cytotoxic, or (3) immune complexes, leading to activation of tissue mast cells or blood basophils and resulting in release of mediators such as histamine, kinines, and prostanoids, culminating with formation of wheals.
	Allergic contact dermatitis	Cutaneous delayed-type hypersensitivity reaction to a nonirritant agent to which the horse had been previously sensitized.
	Neonatal ulcerative dermatitis, thrombocytopenia, and neutropenia	Multifocal ulcerative skin disease of neonatal foals associated with profound thrombocytopenia and mild neutropenia suspected to be caused by alloantibodies of maternal origin (absorbed from colostrum). Immunologically mediated damage and destruction ensue.
Muscle	Immune-mediated myositis	Rapid onset of muscle atrophy associated with mononuclear infiltrate of macrophages and lymphocytes (mostly $CD4^+$ cells, lesser $CD8^+$ cells, and clusters of B cells) and no evidence of IgG deposition.
Synovial	Immune-mediated polysinovitis/ polyarthritis	Nonerosive polyarthritis and effusion of other synovial sheaths, such as tendons and bursae, with deposition of immune complexes and mild lymphocytic/plasmacytic infiltrate of synovial tissue: (1) associated with remote infectious processes (e.g., *Rhodococcus equi* pneumonia); or (2) without concurrent infectious process.

Ab, Antibody; *ADCC,* antibody-dependent cellular cytotoxicity; *Ag,* antigen; *Ig,* immunoglobulin; *RBCs,* red blood cells; *UV,* ultraviolet.

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triggering agent. Initial exposure leads to development of antigen-specific memory T cells that remain dormant until reexposure to the antigen. Following reexposure, APCs capture and process the antigen to present it to T cells in the context of MHC. This interaction results in IL-1 production by APC, as well as production of IL-2 and clonal expansion of the antigen-specific T cell of the Th1 phenotype, culminating with the production of large amounts of Th1 cytokines (IFN-γ, macrophage inhibitory factor, TNF-α, and TNF-β). This cascade of cytokines recruits nonspecific circulating leukocytes, including monocytes, segmented neutrophils, and lymphocytes to infiltrate the site. Following infiltration, which is responsible for the hallmark sign of induration in type IV hypersensitivity reactions, these chemoattracted cells also produce inflammatory mediators and cytokines that amplify the reaction. Examples of delayed-type hypersensitivity in horses include insect-bite hypersensitivity, contact dermatitis often to heavy metals and aniline dyes found in tack, bedding, soaps, and blankets.[1,53-55]

Evaluation of Immunologic Response in Horses

Lais R. Costa[†]

Assessment of immune response encompasses in vivo, in vitro, and ex vivo measurements of immune function and can be divided into three categories: (1) assays for characterizing the adequacy of the immune response when an immunodeficiency or immunosuppression is suspected (e.g., assays to assess humoral, cellular, and innate immune responses); (2) assays for identifying inappropriate or exaggerated immunologic responses when immune-mediated injury is suspected (e.g., antinuclear antibody titer, assay for platelet surface–associated IgG, isotype-specific antibodies coating erythrocytes); and (3) assays of immunologic recognition of pathogens (e.g., antibody titer to specific antigens or pathogens) and protection against infectious agents.[1-4] The aspects of immune response evaluation discussed in this section include only assays for characterizing the adequacy of the immune response when immunodeficiency or immunosuppression is suspected. Assays for identifying inappropriate immunologic responses when immune-mediated condition is suspected are discussed elsewhere.[2-4] Assays of immunologic recognition of pathogens and protection against infectious agents are discussed in this book under body systems or found elsewhere.[3,4]

Characterizing the Adequacy of the Immune Response

Assessment of the adequacy of a patient's immune response is warranted when there is an increased recurrence, severity, or chronicity of infectious illness above and beyond what is considered normal, especially if the possibility of enhanced virulence of the pathogen involved has been ruled out. Because immunodeficiency disorders are uncommon, they should only be considered after more common causes of recurrent infection have been excluded. It is important to remember that inadequate immune response may occur in association with malnutrition, neoplasia (especially leukoproliferative disorders), autoimmune diseases, immunosuppressive therapy, and the presence of underlying diseases such as PPID. In addition, immunosuppression and immune evasion mediated by the infectious agent itself should be considered. Therefore the diagnostic plan should include evaluation of the patient's immune response, as well as ruling out conditions that may account for the inadequate immune response of the patient.

In foals, adequate transfer of maternal immunity can transiently mask the onset of signs resulting from immunodeficiency. Therefore immunodeficiency in foals with adequate passive transfer of maternal immunity may not be recognized early in life. Moreover, increased susceptibility to infections is often accompanied by failure to thrive and poor growth. Weight and height should be compared with breed-appropriate age standards, in order to recognize abnormal growth patterns.

A list of assays to assess and characterize the adequacy of adaptive (humoral and cell-mediated) and innate immune responses is depicted in Table 53-6. In horses, only a limited number of assays to evaluate immune response are available from a practical standpoint, and most are crude indicators of immune response and therefore detect only severe deviations from normal. Nevertheless, a number of immunodeficiency syndromes have been characterized in horses. Moreover, the clinician may be able to characterize the patient's immunosuppressive state. Reagent development for characterization of the equine immune response is evolving, and the large animal clinician is encouraged to search for up-to-date information on assays for equine immunology. Information can be found at the following websites: (1) available tests—http://www.vet.k-state.edu/depts/dmp/service/immunology/index.htm and http://www.vet.cornell.edu/labs/EquineImmuno/testOverview.cfm and (2) equine immunology reagents, including monoclonal antibodies to cell surface molecules, equine cytokine reagents and receptors, and cloned equine cytokines and chemokines—http://www.umass.edu/vetimm/equine/index.html and http://www.ca.uky.edu/gluck/HorohovDW_EIR.asp.

Failure of Passive Transfer of Maternal Immunity

Debra C. Sellon • Melissa T. Hines • Jill R. Johnson

Definition and Etiology Normal foals are immunocompetent at birth (i.e., they are capable of mounting an immune response). However, they are immunologically naive in that they have had no exposure to foreign antigens and have therefore not yet mounted any type of protective immune response or accumulated significant levels of immunoglobulins. Although foals are capable of producing antibodies, they are essentially devoid of immunoglobulin at birth, with the exception of small amounts of IgM normally produced in utero. Because they are "starting from scratch," foals are indeed more susceptible to infectious agents during the early neonatal period. Foals begin mounting immune responses and producing their own immunoglobulins immediately on exposure to antigens after birth, and immunoglobulins produced by the foal are detectable within 1 to 2 weeks of life and reach significant levels by 2 months.

Immunologic protection of the newborn foal relies on the transfer of maternal immunity through the colostrum. Under normal circumstances, temporary protection against infection for the first 1 to 2 months of life is provided to the foal in the form of passively transferred antibodies, from the dam (Fig. 53-3; Table 53-7). Because of the diffuse epitheliochorial nature of the equine placenta, no transplacental transfer of immunoglobulins occurs in horses. Instead, ingestion and absorption of immunoglobulin-rich colostrum are the sole means of passive transfer in foals. In a properly functioning system, maternal antibodies wane as levels of autologous antibodies increase, and thus the neonate is never left totally unprotected (Fig. 53-4; Table 53-8).

Failure of the foal to ingest or absorb sufficient quantities of colostrum, primarily as defined by absorption of IgG, is termed *failure of passive transfer* (FPT). *Complete* FPT is defined as a foal with a serum IgG concentration of less than 400 mg/dL at 24 hours of age. *Partial* FPT is defined as a foal with a serum IgG concentration of 400 to 800 mg/dL at 24 hours of age. The reported incidence of complete or partial FPT in foals varies from 3% to 37.8%.[1-8] Risk factors for FPT include month of foaling, adverse health events for mare or foal in the periparturient period, age of the dam, and colostral immunoglobulin content. Low total immunoglobulin content in colostrum is associated with breed (e.g., Standardbred), age of dam (e.g., older mares), and low total solar radiation (i.e., shorter days).[2,7,9]

[†]Contributions to previous editions by Jill R. Johnson, Melissa T. Hines, and Debra C. Sellon are acknowledged.

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TABLE 53-6

List of Assays to Assess and Characterize the Adequacy of Immune Response in Horses

Test	Description	Purpose	Comments
Complete blood count (CBC)[3,5]	Standard hemogram including evaluation of cell morphology.	Identify abnormalities in number and morphologic changes of lymphocytes, monocytes, neutrophils, and eosinophils.	Part of the initial assessment as the minimum database of any patient. Equine CBC can be performed by most clinical pathology laboratories.
Immunophenotyping of peripheral lymphocytes[3,4,6-14]	Enumeration of specific subsets of lymphocytes using fluorescent antibodies to cell surface markers and flow cytometry (FCM).	Determination of circulating lymphocyte types: B cells ($CD19^+$ like, $CD20^+$, $CD21^+$, $sIgM^+$), T cells ($CD2^+$, $CD3^+$, $CD5^+$), $CD4^+$ T cells, and $CD8^+$ T cells, and determination of CD4:CD8 ratio.	In normal horses, about 20% of circulating lymphocytes are B cells, about 62% are $CD4^+$ T cells, and 18% $CD8^+$ T cells. Normal CD4:CD8 ratio is 3.5 ± 1.0. Peripheral blood lymphocyte phenotyping is offered at the Animal Heath Diagnostic Center—Cornell University, and at the Clinical Immunology Laboratory—Kansas State University.
Immunophenotyping of lymphocyte types and subsets in tissues[10,11]	Immunohistochemistry using antibodies to specific cell markers in order to sort out different lymphocyte types and subsets.	Determination of B cells ($sIgM^+$), T cells ($CD3^+$), $CD4^+$ T cells ($CD4^+$), and $CD8^+$ T cells ($CD8^+$) in lymphoid tissue specimens (such as lymph node, spleen, and bone marrow).	Enumeration of cell types in tissue samples may be done in formalin-fixed (with limitations), fresh, or frozen samples; the proper preparation of sample must be confirmed with the pathology laboratory performing the procedure.
Immunophenotyping of lymphocyte types and subsets in body fluids[10,11]	Immunohistochemistry or FCM using labeled antibodies to specific cell markers in order to sort out different lymphocyte types and subsets.	Determination of B cells ($sIgM^+$), T cells ($CD3^+$), $CD4^+$ T cells ($CD4^+$), and $CD8^+$ T cells ($CD8^+$) in samples from CSF, pleural fluid, peritoneal fluid, bone marrow, and lymph node aspirates.	Enumeration of cell types in body fluids and aspirates using immunocytochemistry is offered at the Animal Heath Diagnostic Center—Cornell University; FCM is offered at the Clinical Immunology Laboratory—Kansas State University.
Histologic evaluation of lymph node[10,11,14]	Histochemistry and immunohistochemistry with specific antibodies to B-cell markers.	Lack of germinal centers and decrease or absence of expression of B-cell markers are indicative of B-cell deficiency.	Offered at most diagnostic laboratories and at the Animal Health Diagnostic Center—Cornell University.
Serum protein electrophoresis[3,4]	Separation of serum proteins by gel electrophoresis.	To quantitate γ-globulins, which are primarily Igs, and determine if they are monoclonal or polyclonal.	In horses with repeated infections, serum Ig levels are likely to be high and polyclonal in nature. Monoclonal hypergammaglobulinemia is evidence of lymphocyte malignancy. Low levels of γ-globulins are supportive of Ig deficiency. Assay is offered at most clinical pathology laboratories.
Semiquantitation of immunoglobulins (Igs)[3,15-18]	(1) Precipitation of Igs using serial concentrations of specific salts (e.g., zinc sulfate or sodium sulfite precipitation, glutaraldehyde coagulation). (2) Species-specific tests based on antigen-antibody reactions, either latex bead agglutination or enzyme-linked immunosorbent assay (ELISA).	Semiquantitative tests are quick and easy to perform and therefore useful for some conditions, such as failure of transfer of passive immunity after colostrum ingestion and plasma transfusion.	Commercial tests based on these principles are available: (1) zinc sulfate precipitation: Equi-Z test kit, VMRD, Inc.; (2) glutaraldehyde coagulation: GammaCheck E, Plasvacc USA; (3) latex bead agglutination: Foalchek, Centaur, Inc.; (3) ELISA: equine IgG ELISA, GenWay Biotech, Inc.; Horse IgG ELISA kit, Immunology Consultants Laboratory, Inc.; SNAP-Foal IgG Test, IDEXX Laboratories, Inc. Precipitation of Igs can be used in several species, although the test may work better in some species than others. ELISAs are species specific. Specificity and sensitivity vary among tests, and scientific literature should be consulted.

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TABLE 53-6

List of Assays to Assess and Characterize the Adequacy of Immune Response in Horses—cont'd

Test	Description	Purpose	Comments
Radial immunodiffusion (RID) for quantitation of Igs [3,15-18]	RID quantitates Igs of specific isotypes using a precipitation reaction to species-specific, isotype-specific immunoglobulin (where the precipitation area is proportional to the concentration of Ig).	Accurate method for quantitating specific classes of Igs (e.g., IgG, IgM, IgA). RID requires incubation for 18-24 hr. Not recommended for evaluation of foals for failure of transfer of passive immunity after colostrum ingestion because of long turnaround time.	RID kits for many Ig isotypes of domestic animals are available commercially. Although test reagents are for a single species, some cross-reactivity exists among species but must be standardized and calibrated accordingly. RID kits for equine Ig isotypes are commercially available: RID for Equine IgG (Plasvacc USA); RID Test Kit (Kent Laboratories USA); Horse IgG Test (IDBiotech France). RID for IgG and IgM is performed at several veterinary clinical immunology laboratories. Specificity and sensitivity varies among tests and scientific literature should be consulted. RID kit for equine IgA is not currently available.
IgG turbidimetric immunoassay (TIA)[19]	TIA is based on the principles of immunologic agglutination and light scattering of the agglutination products. The automated TIA is performed on a chemistry analyzer.	Accurate method for quantitating equine IgG, with good correlation with RID but shorter turnaround time. TIA can be used to evaluate foals for failure of transfer of passive immunity after colostrum ingestion.	TIA is a quantitative test with high sensitivity and specificity. Kits for equine IgG TIA are commercially available: Midland Bioproducts Corporation, for use on Roche Cobas Mira chemistry analyzers and Hitachi 704 automatic analyzers; Equine IgG serum/plasma test kit from HAR-VET for use with DVM Rapid Test Instruments. TIA for equine IgG is offered in veterinary diagnostic laboratories (e.g., Animal Health Diagnostic Center—Cornell University).
Measurement of specific antibody responses pre vaccination and post vaccination[10,11]	Paired serum samples pre vaccination and 15 to 20 days post vaccination are tested to measure Ag-specific Ab response.	To determine B-cell function by evoking an anamnestic response to a protein Ag.	Serum tetanus toxoid Ab titers pre vaccination and post vaccination are offered at the Equine Clinical Immunology Laboratory—Cornell University.
Peripheral blood phagocytic functions of opsonization capacity, phagocytosis, and oxidative burst[20-26]	Peripheral blood leukocytes are incubated simultaneously with oxidative sensitive dye dihydrorhodamine (DHR), and inactivated *Staphylococcus aureus* labeled with red fluorescent dye propidium iodide (PI), opsonized with pooled or autologous serum (heat-inactivated serum or no serum used as controls). Oxidation of DHR generates green-fluorescent rhodamine 123 (rho). Two-color FCM analysis is performed for rho and PI, for oxidative burst and phagocytosis, respectively.	To evaluate functions of the innate immune response: opsonization by serum complement components and Igs, phagocytosis by neutrophils and monocytes, and oxidative burst by neutrophils.	The opsonization capacity and phagocytosis are generally performed for research purposes. The oxidative burst activity in peripheral blood neutrophils is offered upon special request at the Equine Clinical Immunology Laboratory—Cornell University.
Intradermal (ID) skin testing with the plant lectin phytohemagglutinin (PHA)[27]	Measure the thickness of a skin fold before injection, then inject ID 50-µg of PHA dissolved in 0.5 mL of phosphate-buffered saline (PBS), and at a different site 10 cm (4 inches) away, 0.5 mL of PBS is injected as control. After 24 hr the skin thickness of both injection sites is measured.	PHA, unlike other compounds such as dinitrochlorobenzene, is capable of eliciting a delayed-type hypersensitivity response without requirement of prior sensitization. Increase in skin thickness should be greater than 0.6 mm; otherwise there is a defect in cell-mediated immunity.	The ID testing with PHA might yield false results; therefore confirmation with in vitro assay of lymphocyte blastogenesis assay is recommended.

Continued

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TABLE 53-6

List of Assays to Assess and Characterize the Adequacy of Immune Response in Horses—cont'd

Test	Description	Purpose	Comments
Lymphocyte proliferation (blastogenesis) assay[11-14]	Lymphocytes are harvested from peripheral blood sample, incubated with serial concentrations of various mitogens, and labeled nucleotide. Incorporation of radiolabeled isotope into newly synthesized DNA is measured. Alternatively, proliferation analysis is evaluated using fluorescent-label and measured via FCM.	In vitro lymphocyte blastogenesis with pokeweed mitogen (PWM) requires both B- and T-cell function for normal responses, whereas in blastogenesis with PHA, concavalin A indicates primarily T-cell function.	No longer routinely offered. Generally performed for research purpose or academic interest by immunology laboratories (e.g., the Equine Clinical Immunology Laboratory—Cornell University).
Equine cytokine 5-plex assay[28]	Detects soluble equine IL-4, IL-10, IL-17, IFN-γ, and IFN-α in biological samples using paired monoclonal Abs specific for each cytokine and fluorescent bead/microspheres that are color coded.	Detects the concentration of each cytokine as pg/mL of biological sample in order to identify typical T-cell and antiviral cytokines in biological samples from horses.	Offered at the Animal Heath Diagnostic Center—Cornell University (see http://ahdc.vet.cornell.edu/docs/Equine_Cytokine_5plex_assay.pdf)
SCID genetic testing[29]	Collect a sample from a convenient source of DNA: (1) swab of the inside of the mouth with a mucosal brush and submit the brush containing mucosal cells, (2) blood sample in EDTA or ACD anticoagulant, or (3) pulled mane or tail hair, place in a clean bag, and submit to DNA testing.	A DNA-based carrier test for the genetic mutation affecting the DNA-dependent protein kinase (DNA-PK) located in chromosome 9.	Offered by VetGen, Ann Arbor, MI (see www.vetgen.com; http://www.vetgen.com/equine-scid-service.html)
Foal immunodeficiency syndrome genetic testing[30]	Collect a sample (pulled mane or tail hair), place in a clean bag, and submit to DNA testing.	A DNA-based carrier test for genetic defect affecting the sodium/myo-inositol cotransporter gene *(SLC5A3)* located in chromosome 26.	Offered at the Animal Health Trust, Newmarket, UK (see http://www.aht.org.uk/cms-display/genetics_fis.html)

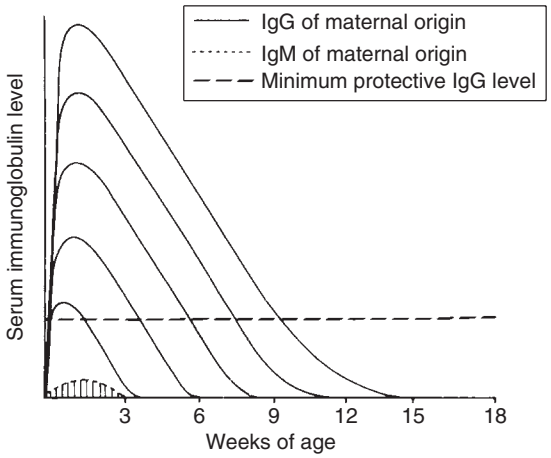


FIG. 53-3 The duration of protection provided by maternal immunoglobulins varies with the isotype of immunoglobulin and the quantity ingested during the first 24 hours of life.

Immunoglobulins are not produced locally in the mammary gland but rather are selectively concentrated from the mare's sera into colostrum in response to hormonal changes that occur in the last 2 weeks of pregnancy. The predominant immunoglobulin isotype in equine colostrum is IgG, followed by IgA and smaller quantities of IgM.[10] The reported amount of total IgG in equine colostrum is quite variable among different studies (see Table 53-7), but overall a good quality colostrum should contain 2500 to 5000 mg/dL. The reported amounts of IgA often range between 500 to 1500 mg/dL, whereas IgM generally range between 100 to 350 mg/dL. At birth the neonate has specialized enterocytes in the gastrointestinal (GI) tract that can absorb large molecules such as immunoglobulins intact by pinocytosis.[11] Absorbed proteins pass through the intercellular spaces and lacteals into the systemic circulation via the lymph. The window of gut absorptive capacity for immunoglobulins is narrow, lasting from birth until about 18 to 24 hours. Maximal absorptive efficiency occurs immediately after birth, declining to only 22% efficiency at 3 hours after birth and less than 1% by 20 hours.[12,13] The decline in immunoglobulin absorption is accompanied by transient proteinuria that peaks at 6 to 12 hours of age and declines by 24 to 36 hours of age. This proteinuria most likely reflects absorption and excretion of low-molecular-weight milk proteins.[13]

Diminished immunoglobulin absorption over the first 12 to 24 hours of life is the result of shedding of specialized enterocytes capable of pinocytosis and replacement by more mature cells that are incapable of absorbing immunoglobulins.[12,14] It has been hypothesized that delayed ingestion of macromolecules may prolong the duration of intestinal permeability to immunoglobulins. In one study, however, the type of fluid administered to foals before the ingestion of colostrum did not influence subsequent IgG absorption, suggesting that the process of gut closure is not mediated by a finite capacity for the uptake of macromolecules.[15]

The half-life for maternal antibodies in the foal's circulation varies between 20 and 30 days.[16-18] Concentrations decline as a result of normal protein catabolism, gradual dilution associated with an increasing plasma volume as the foal grows, and transfer of functional antibody into the GI tract. Most maternal antibodies are present in only negligible concentrations by 6 months of age, although antibodies to some infectious agents have been detected for up to 12 months after birth. As passive antibody concentrations decline, endogenous antibody production begins. There is a nadir in serum immunoglobulin concentrations in colostrum-fed foals at approximately 1 to 2 months of age, followed by gradually increasing concentrations until adult levels are reached at 5 to 10 months.[19,20] Serum

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TABLE 53-7

Immunoglobulin Concentration (mg/dL) in Equine Colostrum, Milk, and Normal Serum*

Sample	Breed	Total IgG	IgM	IgA
Colostrum	STB[3]	2700-15,000	50-200	10-2050
	QH[62]	21,000-32,000	ND	600-1200
Milk	QH[62]	30-75	ND	50-90
Newborn presuckle	Arabian[61]	1-10	5-15	ND
	QH[62]	0-30	ND	ND
1 day of age	STB[3]	300-3500	5-65	16-100
	QH[62]	3300-4500	ND	26-64
	Mixed[63]	1300-1900	ND	45-65
1 wk of age	QH[62]	2500-4000	ND	6-36
1 mo of age	QH[62]	1250-2300	ND	2-10
	Mixed[63]	900-1450	ND	30-50
2 mo of age	QH[62]	1450-3100	ND	0-28
3-5 mo of age	Mixed[63]	1000-1700	ND	30-50
4 mo of age	Mixed[61]	250-950	40-90	ND
10-15 mo of age	Arabian/THB[61]	1500	50	ND
Adult horses	THB, QH[64]	1500-2400	70-150	ND
	Mixed[62]	1400-3200	ND	10-70
Adult ponies	Shetland[61]	1000-1700	110-140	ND
	Welsh[62]	1600-2750	ND	ND

*Low and high values were calculated from mean and standard deviation reported.

ND, Not determined; *QH,* Quarter Horse; *STB,* Standardbred; *THB,* Thoroughbred.

TABLE 53-8

Approximate Half-Life (in Days) of Immunoglobulin Classes in Large Animals

Species	IgG	IgM	IgA	$IgG_{(T)}$ (currently called IgG_{3+5})
Equine	11.5-23	4-5	NA	20
Bovine	G1: 17 G2: 22	2.8	4.8	—
Sheep	G1: 14.5 G2: 10.6	1.8	4.1	—
Goat	G1: 13.2-17.2	NA	NA	—

From Perryman L. 1988. Department of Veterinary Microbiology and Pathology, Washington State University, Pullman, WA. Personal communication.

NA, Not available.

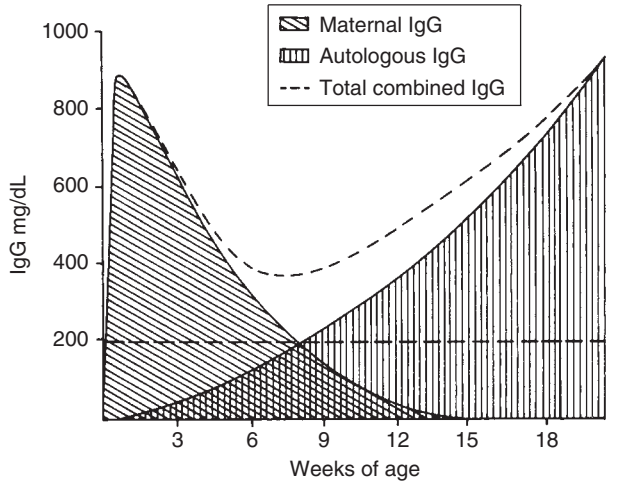


FIG. 53-4 Maternal immunoglobulin wanes, whereas the production of autologous immunoglobulin increases during the first several months of life. The combined total amount of immunoglobulin ideally remains above the level considered minimum for maintenance of good health.

immunoglobulin concentrations are similar in colostrum-fed and colostrum-deprived foals by 3 to 4 months of age.

In addition to antibody, other colostral factors may be important for optimal immune protection of foals. For example, colostrum influences cell-mediated immunity and activates granulocytes. Colostrum contains many constituents of innate immunity and immunomodulating agents, such as cytokines,[21] growth factors,[22] hormones,[22] enzymes,[23] lymphocytes, macrophages, neutrophils, and epithelial cells.[21] The cellular components of colostrum are likely to play an especially important role in local gastrointestinal immunity in the neonatal foal. Maternal cells are found in a variety of blood and tissues in the neonate after absorption of colostrum, suggesting that these cells may also play a role in systemic immunity.[21]

In foals, FPT may occur because of ingestion of poor-quality colostrum with a low immunoglobulin content, failure to ingest a sufficient quantity of colostrum, or failure to absorb colostral immunoglobulins from the GI tract.[24] Colostrum may have an insufficient quantity of immunoglobulin because of prelactation (lactation before parturition), premature foaling, a defect in the mare's ability to concentrate immunoglobulin in the colostrum, ingestion of endophyte-contaminated fescue grass or hay, or other factors. Premature lactation is most commonly associated with twin pregnancies, placentitis, and premature placental separation but occasionally occurs without any concurrent uterine, placental, or fetal pathology. Mares most likely to produce colostrum with low immunoglobulin content are those older than 15 years of age, those that foal early in the year, and Standardbred mares.[2,7,9] Insufficient colostral immunoglobulin concentration has also been associated with ingestion of endophyte-contaminated fescue grass or hay.[25,26]

Foals that are orphaned or rejected at birth, too weak to stand, or unable or lack the desire to suckle are unlikely to ingest sufficient colostrum to prevent FPT. Malabsorption is occasionally incriminated as a cause of FPT in foals that are observed to suckle adequate quantities of good-quality colostrum. This most often happens in premature or dysmature foals, possibly as a result of immature GI function, but may also occur in otherwise healthy and vigorous full-term foals.[27] Glucocorticoids enhance the maturation of small-intestinal epithelial cells and thus their loss of absorptive capacity, leading to speculation that endogenous corticosteroids released secondary to stress at parturition may impair immunoglobulin absorption in foals.[28,29] However, administration of adrenocorticotropic

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hormone (ACTH) failed to affect absorption in experimental foals, and stress has not been a consistent historic finding in foals with FPT caused by presumptive impaired immunoglobulin absorption.[5,30]

Clinical Signs and Differential Diagnoses The association between FPT and infection has been investigated in numerous studies.[1,2,4,7,8] Although the results have varied somewhat, FPT is generally considered a risk factor for infectious disease. By itself, FPT produces no clinical signs of disease and cannot be detected by physical examination. Clinical presentations that strongly suggest an underlying problem with FPT include onset of bacterial infections within the first 2 weeks of life, particularly septicemia, septic arthritis, pneumonia, and enteritis. Other immunodeficiencies or simply exposure to potent pathogens cannot be ruled out solely on the basis of the time of onset; however, even with other forms of immunodeficiency, clinical signs of infection usually do not show up for several weeks if passive transfer is adequate.

Clinical Pathology FPT is diagnosed by the demonstration of low serum concentrations of IgG in the foal as early as 6 to 12 hours after birth and probably for as long as several weeks after birth (see Table 53-7). The level of IgG considered adequate for protection against infectious disease is poorly defined and probably varies considerably with the environment. A serum IgG concentration greater than 800 mg/dL is considered adequate for most foals. However, levels of 400 mg/dL may be sufficient in healthy foals housed in clean environments. In contrast, an IgG concentration of 400 to 800 mg/dL in a foal at high risk for sepsis because of its environment or other factors indicates the need for treatment. Importantly, these figures only address *total* immunoglobulin content and not specific antibody titers, which also play a critical role in determining resistance to particular pathogens.

In healthy foals that nurse within 2 hours of birth, serum IgG concentrations become detectable at approximately 6 hours of age and peak at approximately 18 hours. Routine determination of serum IgG concentrations in apparently healthy foals is usually recommended at 18 to 24 hours of age. Foals considered to be at high risk for FPT and sepsis may be assessed as early as 6 to 12 hours of age.[31,32]

Methods available for IgG quantitation include single radial immunodiffusion, zinc sulfate turbidity, latex agglutination, glutaraldehyde coagulation, turbidimetric immunoassay, and enzyme-linked immunosorbent assay.[31,33-38] Selection of an appropriate screening test for a specific farm or foaling environment should be made after considering overall accuracy, time necessary to perform the test, simplicity of the testing procedure, technical skills and knowledge of the attending personnel, and cost. Single radial immunodiffusion is considered the most quantitatively accurate diagnostic test of those widely available to practitioners. However, this test is more expensive than some other screening tests, and results are not available for at least 24 hours, making it impractical when an at-risk foal needs rapid diagnosis and treatment. Total serum protein is not a reliable indicator of FPT in foals (unlike calves) because of the wide variation in total serum protein in cases of adequate transfer.[38] Many veterinarians prefer to use commercial kits based on enzyme-linked immunosorbent assay or glutaraldehyde coagulation technology for stall-side screening of foals.[39,40] Both types of tests have high sensitivity and negative predictive value. False-negative and false-positive results tend to be more common when attempting to accurately identify foals with partial FPT with an IgG concentration of 400 to 800 mg/dL.

No consistent changes in the hemogram and biochemical panel are seen in foals with FPT; however, a range of abnormalities related to secondary infection (e.g., neutrophilia, neutropenia), hyperfibrinogenemia, and hypoglycemia may be present. The presence and severity of these changes depend on the organisms and systems involved.

Necropsy Findings No specific necropsy findings are indicative of FPT. Necropsy findings reflect the site and severity of secondary infectious problems that have developed. Lymphoid tissue is normally developed, unless secondary infections have caused lymphoid necrosis or atrophy.

Treatment and Prognosis Treatment of FPT depends on the degree of FPT, the environment in which the foal is exposed, the foal's age at diagnosis, and the presence of secondary infectious problems. Treatment is aimed at minimizing exposure to pathogens, supplying immunoglobulins, and managing secondary infections, if present.

If FPT can be anticipated within hours of birth because of premature lactation, low specific gravity colostrum, or a weak or orphaned foal, treatment can include the provision of an alternative source of colostrum or antibody orally. Foals with complete colostrum deprivation require approximately 1.5 g IgG/kg body weight to achieve a peak serum IgG concentration of more than 800 mg/dL. In a 45-kg foal, administration of 1 to 3 L of colostrum with a specific gravity greater than 1.060, divided into multiple hourly feedings over the first 6 to 8 hours of life, is desirable. Mares that donate colostrum for feeding should be healthy, checked for blood type, negative for anti–red blood cell (RBC) alloantibodies (especially anti-A and anti-Q), and appropriately vaccinated during the last 4 to 6 weeks of gestation.

If equine donor colostrum is not available, bovine colostrum, a commercial colostrum substitute, or equine plasma may be administered orally to the foal.[41-48] Because bovine colostrum is often more readily available than equine colostrum, it may be substituted in emergency situations when equine colostrum is not available. Bovine colostrum is relatively well absorbed in the foal, but bovine immunoglobulins have a much shorter half-life in foals and do not contain antibodies specifically directed against equine pathogens. It is certainly better than no colostrum and, on the basis of a small experimental study, may be used without creating adverse reactions.[8,43-45] Approximately 2 to 4 L should be administered orally; many foals develop transient mild diarrhea.

Concentrated equine serum products such as Seramune Oral (Sera, Inc., Shawnee Mission, Kan.) are available for use in foals with FPT.[49] In one study, however, it failed to increase serum IgG concentrations in colostrum-deprived foals to adequate levels, probably because of the relatively low total IgG dose administered.[48] If the product contains 25 to 30 g of IgG per 300-mL bottle, approximately three bottles may be required to increase the serum IgG concentration of a 45-kg colostrum-deprived foal to greater than 400 mg/dL.[48]

If no other sources of immunoglobulin are available for a foal, oral administration of equine plasma or serum may be considered. This is an expensive source of oral immunoglobulin, however, and approximately 2 to 4 L are required to treat a colostrum-deprived 45-kg foal.

If the foal is older than 6 hours of age, the absorption of colostral antibody is significantly decreased, although a locally protective effect of the colostrum may still be present in the intestinal tract. If the foal is older than 12 hours of age, it is unlikely that sufficient colostrum will be absorbed; therefore immunoglobulin levels should be rechecked at 24 hours and intravenous (IV) plasma transfusion given, if indicated by persistently low serum immunoglobulin levels.

Some animals with FPT, particularly partial FPT, do well without treatment if they are systemically healthy, are not heavily exposed to pathogens, and have no preexisting infections. FPT itself is not necessarily fatal. If plasma transfusions are not administered, owners should be made aware of the risks, and these foals should be maintained in an environment with minimal exposure to potential pathogens. Foals with other risk factors for septicemia (e.g., prematurity, dysmaturity, placentitis) should receive IV plasma transfusions if they have blood IgG concentrations of less than 800 mg/dL at 12 to 24 hours of age.

If the decision is made to supplement plasma parenterally, equine plasma for transfusions can be collected and processed locally, or obtained commercially. Available sources of commercial

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equine plasma include Plasmune (formerly Foalimmune) and HiGamm-Equi (Lake Immunogenics, Inc., Ontario, NY); Equi-Plas and Polymune (Plasvacc USA, Inc., Templeton, Calif.); and Immuno-Glo Normal Equine Plasma (Mg Biologics, Inc., Ames, IA).[60] Commercial sources are convenient, save time, have been screened for anti-RBC antibody, are free of diseases such as equine infectious anemia, and originate from animals with known immunoglobulin levels. The major disadvantage is that plasma may not contain antibodies specific for the pathogens from the particular environment to which the foal is exposed.

Use of a local donor has the potential benefit of providing antibodies specific to the environmental pathogens to which the foal has been exposed. If a local donor is to be selected, several criteria should be met. First, the horse should be healthy, and results of agar gel immunodiffusion for equine infectious anemia should be negative. Second, no anti-RBC antibody should be detectable in the horse's serum. The donor's plasma should be screened for lysins and agglutinins by a blood-typing laboratory against a panel of cells representing all known blood groups. If plasma evaluated in this way is not available, the presence of anti-RBC antibody in donor plasma can be crudely evaluated with a minor crossmatch for agglutination using donor plasma and recipient blood cells. Lytic antibodies require an external source of complement for activity in vitro and may not be detected using this test.

Ideally, a third criterion is selection of a horse that is negative for blood group factors Aa and Qa. Even though there are dozens of blood group factors, Aa and Qa have been associated with the great majority of cases of neonatal isoerythrolysis (NI).[50-52] If plasma is collected and separated by sedimentation, it is inevitable that some RBC contamination be present. If Aa-positive (Aa+) RBCs are given to an animal that is Aa negative (Aa–) or if Qa+ RBCs are given to an animal that is Qa–, the recipients could become sensitized to these antigens. This sensitization would probably not have any immediate consequences for the recipient foal because the foal's cells would not be affected by the antibodies, but it has potentially sensitized any Aa– and Qa– females for production of an NI foal later (see section on allogeneic incompatibilities). To avoid these potential complications, the ideal donor should be Aa– and Qa– and possess no anti-RBC antibody in its serum. It is desirable to have identified this type of donor to avoid the need for immediate crossmatching in every case of plasma transfusion.

The volume of plasma needed to correct the measured IgG deficit in a foal can theoretically be calculated on the basis of the blood volume of the foal and the concentration of IgG in the foal's serum and in the donor plasma; however, these calculations do not reliably predict the actual levels of IgG achieved after transfusion.[31,53] A 20-mL volume of plasma per kilogram of body weight administered intravenously in general only raises serum IgG levels 200 to 300 mg/dL, and often two to three times this amount is necessary to bring serum IgG levels into the range considered minimum for protection (e.g., 400 to 800 mg/dL).[31,54] If the foal is already clinically ill, additional plasma will often be required to raise IgG levels an equivalent amount.[31,37] In a newborn foal (estimated 50 kg) with complete FPT, between 2 and 4 L of plasma is frequently necessary.

Plasma should be administered through an IV catheter placed aseptically in one jugular vein. Frozen plasma is thawed and warmed slowly to room temperature in a warm water bath. Microwave thawing or thawing with high temperatures is not recommended because this may denature important plasma proteins. An appropriate in-line blood filter should be used for IV administration of any blood product to remove fibrin clumps and other debris. Initial infusion rates should be slow (0.5 mL/kg over 10 to 20 minutes) to monitor for adverse reactions. Muscle fasciculations, piloerection, increased heart or respiratory rate, fever, respiratory distress, abdominal pain, blanching of mucous membranes, and collapse are indicative of transfusion reactions. In the absence of these or other adverse effects, the remainder of the transfusion may be administered at rates up to 40 mL/kg/h. Slower infusion rates are recommended for foals that are systemically ill. If other IV fluid therapy is being administered concurrently, slower infusion rates are also indicated to diminish the likelihood of inadvertent fluid overload.

Serum IgG concentrations in the foal should be rechecked 12 to 24 hours after plasma transfusion to confirm that the desired increase has been achieved. The delay from transfusion to IgG assessment is necessary to allow for distribution of immunoglobulin into extravascular spaces. Healthy foals transfused with plasma at 1 day of age experienced a 30% decrease in serum IgG concentrations by 7 days of age.[55] This decline might be even more dramatic in septic foals with increased vascular permeability, increased catabolism, and increased demand for utilization in immune responses.

Although several equine serum-derived products are marketed for IV administration in the treatment of foals with FPT, these products have been associated with significant adverse reactions in some foals. Administration of high-quality equine plasma is preferred for treatment of foals with FPT.

Prevention and Control Evaluation of colostral immunoglobulin content has proved to be valuable in predicting the occurrence of FPT and assessing the neonate's risk for FPT.[31,56] Colostrum with high immunoglobulin concentration tends to be sticky, yellow, and thick, but these subjective criteria are unreliable in assessing colostral quality. The quantity of immunoglobulin in colostrum may be more accurately estimated by single radial immunodiffusion (RID), refractometry, glutaraldehyde coagulation, or specific gravity.[55] Because 18 hours are required to read the results of RID, it is more practical in a field situation to assess specific gravity with a refractometer, glutaraldehyde coagulation test, or colostrometer. Sugar refractometry using a handheld Brix 0% to 50% sugar refractometer is a simple and cost-efficient stall-side screening test for assessing colostral quality.[57,58] A Brix reading of 20% to 30% correlates with adequate colostral quality; a reading greater than 30% indicates good-quality colostrum.[59] A commercial kit based on glutaraldehyde coagulation of immunoglobulins is the Gamma-Check-C (Veterinary Dynamics, San Luis Obispo, Calif.). Using a colostrometer such as the Equine Colostrometer (Lane Manufacturing Company, Denver, Colo.), colostral specific gravity should be a minimum of 1.060, corresponding to an IgG concentration of greater than 3000 mg/dL; levels of 6000 mg/dL or higher are desirable. Approximately 75% of foals that ingest colostrum with a specific gravity less than 1.060 will have serum IgG concentrations less than 400 mg/dL; when colostral specific gravity is greater than 1.060, foals usually attain serum IgG concentrations above 500 mg/dL.[56]

Some of the causes of FPT can be alleviated or recognized for early intervention by careful management. These include identification of mares that drip colostrum before parturition, attendance at foaling to ensure that foals suckle within several hours of birth or are supplemented artificially with colostrum, and screening of high-risk foals with doubtful nursing histories. Routine screening of foals at 18 to 24 hours of age allows early identification of FPT and potentially allows for therapy before the onset of infections. Although signs of septicemia secondary to FPT are often first observed on days 3 to 4 of life, a bacteremia may already be present at 24 hours of age or earlier.[56,59]

A colostrum bank can be established by collecting small amounts of colostrum from lactating mares (e.g., 200 to 250 mL) within the first 3 to 6 hours after foaling. This is only about 10% of the total colostrum produced by the average mare in the first 20 hours after parturition and therefore does not adversely affect the foal suckling the donor mare. Although the volumes are quite variable, mares produce about 300 mL of colostrum per hour and about 5 L during the first 18 hours. Colostrum can be stored frozen for at least 1 year at standard freezer temperatures, approximately −20° C (−4° F). Although frozen immunoglobulins are stable for much longer, the overall quality of the colostrum may deteriorate. Ideally, banked colostrum should be screened for the presence of anti-RBC antibodies as advised for plasma. Colostrum typically has low titers of agglutinins, which are probably not of significance unless they present a dilution of 1/8 or greater.

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Severe Combined Immunodeficiency

Melissa T. Hines • Debra C. Sellon • Jill R. Johnson

Definition and Etiology Severe combined immunodeficiency (SCID) is a group of disorders in which both T- and B-cell functions are absent.[1-4] SCID has been recognized in several species, including humans, mice, dogs, and horses.[2-8] In horses, the condition primarily affects Arabians and part Arabians, although sporadic cases have been described in other breeds, such as Caspians and Appaloosas.[2,3,9,10] Affected foals are highly vulnerable to infections as a result of a stem cell defect that prevents maturation of T and B cells and leads to a complete inability to produce antigen-specific immune responses. In horses of Arabian breeding, the condition is transmitted as an autosomal recessive trait.[11]

Clinical Signs and Differential Diagnoses Foals clinically affected with SCID are typically normal at birth, but the absence of both specific humoral and cellular immunity renders them susceptible to infections once colostral protection wanes.[2,3] Typically, affected foals will develop infectious diseases between birth and 2 months of age and die before 5 months of age. The age of onset of infectious disease depends to some degree on the adequacy of passive transfer of maternal immunity and the degree of environmental challenge by organisms. Infections in affected individuals can be caused by a variety of bacterial, viral, parasitic, and fungal agents, some of which rarely affect animals that are not immunocompromised.[2,12-17] Many body systems may be involved, but pneumonia is particularly common. *P. jiroveci* (formerly called *P. carinii*) pneumonia and adenoviral pneumonia are often found in SCID foals as compared with other foals. Differential diagnoses include other immunodeficiencies in foals.

Foals of Arabian breeding that show clinical manifestations of SCID are homozygous for the defective SCID gene. Carriers of the gene are asymptomatic but can be detected by production of an affected offspring or genetic testing.[18,19] Recently, a correlation between heterozygosity for the SCID allele and the development of sarcoids has been demonstrated, suggesting that the gene may play a role in tumor suppression.[6]

Clinical Pathology A consistent finding on the hemogram is an absolute lymphopenia, which is less than 1000 lymphocytes/μL and often much lower.[20,21] Depending on the neutrophil response, the total white blood cell count may be low, normal, or elevated, making it essential that the absolute number of lymphocytes be determined. Infected and other compromised foals, as well as some normal foals, may have low lymphocyte counts during the first few days of life; therefore persistent lymphopenia should be established before considering a diagnosis of SCID.[22]

Concentrations of autologous serum immunoglobulin are low in foals affected with SCID.[20,23-25] The presence of colostral antibody may mask these low levels of autologous immunoglobulin and therefore the degree of colostral transfer and the age of the foal should be considered when interpreting the serum immunoglobulin values (see Table 53-7). In normal foals, IgM is produced in utero, and thus some IgM should be present in presuckle serum.[26] Although not pathognomonic, the absence of IgM in presuckle serum is a feature of SCID. Also, due to the relatively low concentrations of IgM in colostrum and the short half-life of IgM (see Table 53-8), maternally derived IgM is generally absent from the circulation by about 3 weeks of age. Thus the absence of serum IgM after 3 weeks of age, although also not pathognomonic, is consistent with SCID.

Foals affected with SCID do not respond to intradermal PHA by increasing skin thickness as do normal foals, nor do they respond to delayed-type hypersensitivity (DTH) stimulators, such as dinitrochlorobenzene.[27] In vitro tests such as blastogenesis are depressed with all mitogens.[20,21,24] The definitive diagnosis of SCID in foals of Arabian breeding is based on demonstrating that the foal is homozygous for the defective SCID gene.[18,28] Blood or cheek swabs may be submitted to VetGen (for complete address in Ann Arbor, Mich., visit www.vetgen.com) for deoxyribonucleic acid (DNA) testing to determine if a horse is clear, heterozygous, or homozygous for the gene defect. Before the advent of genetic testing, the criteria required to confirm a diagnosis of SCID included (1) persistent lymphopenia (<1000/μL), (2) absence of serum IgM in presuckle samples or samples collected after 3 weeks of age, and (3) thymic hypoplasia and characteristic histopathologic changes in lymphoid tissue.[25,29] These criteria were used to diagnose SCID in a Caspian filly with pneumonia that was negative for the defective gene of Arabians.[9] This suggests that a different mutation could be involved in some cases of SCID.

Pathophysiology Foals of Arabian breeding with SCID have a mutation in the gene encoding the catalytic subunit of DNA-dependent protein kinase (DNA-PK) and thus lack activity of this enzyme.[4,7,28,30,31] The mutation results in a five-base-pair deletion in the gene on equine chromosome 9. This results in a frameshift and a 967 amino acid deletion from DNA-PK, making the protein unstable. Without functional DNA-PK, lymphocyte precursors are unable to complete gene rearrangement events that lead to the expression of antigen-specific receptors on lymphocyte surfaces, namely T-cell receptor and immunoglobulin. As a result, there is an absence of mature, functional T and B lymphocytes. IFN-γ (EqIFN-γ), which is primarily produced by lymphocytes, is deficient.[32]

Neutrophils, monocytes, and NK cells appear to be fully functional and complement concentrations are normal.[2,33,34] Although these nonspecific protective mechanisms appear to be intact, the absence of both cell-mediated and antibody-mediated immunity leaves the foal vulnerable to even innocuous infectious agents.

Epidemiology SCID has been reported in Arabians in the United States, Canada, Australia, Morocco, and Great Britain.[2,3,35-37] It is believed that the trait originated in a horse in Great Britain and was subsequently imported into other countries. The distribution of this disease provides a significant example of the *founder effect* in population genetics.

The prevalence of SCID at one time was estimated to be 2% to 3% of Arabian foals born in the United States.[38] From this, it was predicted that the numbers of SCID carriers at that time could be as high as 25% of the U.S. Arabian horse population. The number of carriers appears to have decreased. Studies of Arabian horses in 1998 and 2002 found the frequency of SCID gene carriers to be approximately 8%, leading to the prediction that 0.18% of Arabian foals would be affected with SCID, assuming a random breeding population.[6,36]

Necropsy Findings Lymphoid tissues should be evaluated both grossly and histologically in cases of suspected immunodeficiencies. In SCID the thymus is small and has a fatty appearance on gross examination.[24,29,39] Because the thymus may be difficult to identify, mediastinal tissue often must be collected "blindly" for subsequent histologic evaluation and identification of thymic remnants. Histologically, the thymus is largely replaced with adipose tissue, with only islands of lymphoid cells and partially formed Hassall corpuscles present.

The spleen and lymph nodes may not be significantly abnormal on gross examination, but they generally have microscopic abnormalities, including an absence of germinal centers and periarteriolar lymphocytic sheaths in the spleen, as well as an absence of germinal centers with scarcity of lymphocytes in other areas of lymph nodes (Fig. 53-5, *A*).

Foals with SCID typically have evidence of infectious disease on necropsy, with bronchopneumonia being particularly common (see Fig. 53-5, *B*). Infectious lesions in other systems are also frequently found, including colitis and hepatitis.

Treatment and Prognosis Affected foals invariably die by about 5 months of age, despite intensive conventional therapy (e.g., antimicrobials, plasma, isolation).[40] There is no practical method of curing affected foals at this time. Successful bone marrow transplants

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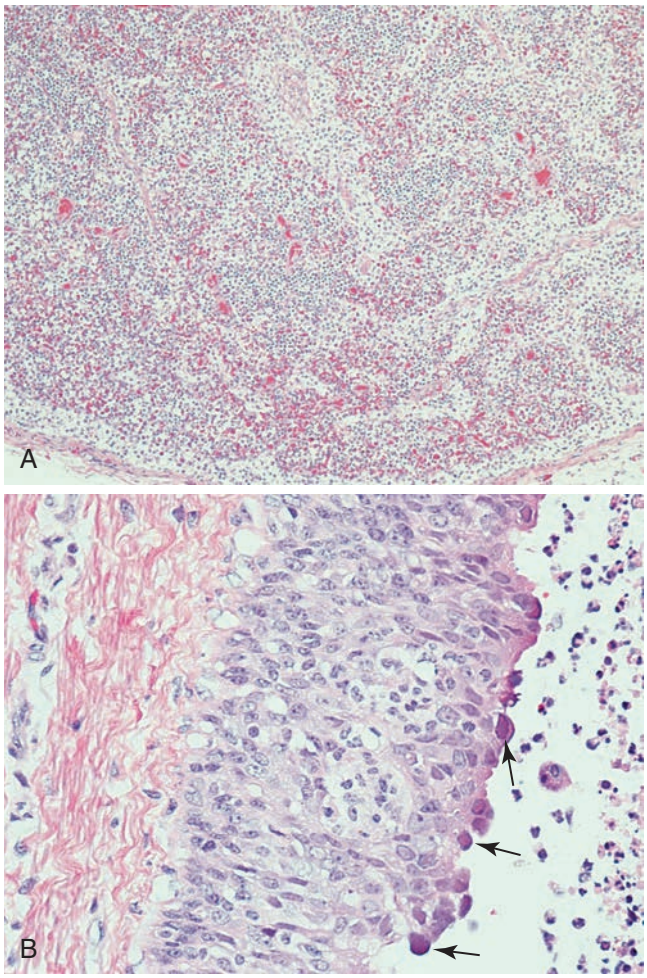


FIG. 53-5 Tissue from an Arabian foal with SCID. The foal presented at 1 month of age for evaluation of persistent pneumonia. **A,** 200× mediastinal lymph node with extensive lymphoid atrophy. The node is poorly populated with lymphocytes that fail to form lymphoid follicles, and active germinal centers are lacking. The node is predominantly composed of loosely scattered resorbed mononuclear cells and edema. **B,** 400× tracheal epithelium with adenovirus inclusion *(black arrows),* epithelial hyperplasia, and suppurative tracheitis. *(Photos courtesy Sushan Han.)*

have been performed between histocompatible full siblings in a research setting, but this option remains impractical.[41-43]

Prevention and Control SCID in horses of Arabian breeding is an autosomal recessive trait, and therefore production of an affected foal identifies both sire and dam as carriers of the SCID gene.[11] Mating of two carriers is expected to result in one in four foals affected with SCID, one in four completely normal and not a carrier, and two in four asymptomatic carriers of the SCID trait. Mating of a carrier and a normal (noncarrier) does not produce any affected foals, but half the offspring would be expected to be carriers.

The disease can be controlled in horses of Arabian breeding by avoiding the production of affected foals, which has been simplified now that carriers can be identified by genetic testing. Mares and stallions intended for breeding should be tested to determine whether they are free or heterozygous for the defective SCID gene. Under no circumstances should two heterozygotes be mated to each other. If an owner decides to continue breeding a heterozygote, the breeding partner should be confirmed homozygous normal. All foals from such matings should be tested to determine if they are clear of or heterozygous for the defective gene (50:50 probability). Homozygous normal foals may be selected for future breeding purposes, whereas heterozygous foals should be used for nonreproductive purposes.

Selective IgM Deficiency

Melissa T. Hines • Debra C. Sellon • Jill R. Johnson

Definition and Etiology Selective IgM deficiency is an immunologic disorder characterized by absent or decreased serum IgM levels with normal or elevated levels of other immunoglobulin classes. Three presentations of the disorder have been described in horses.[1-5] The most common involves foals that have severe infectious pneumonia, arthritis, or enteritis, resulting in death before 10 months of age. The second involves foals with a history of repeated episodes of infections that respond to antimicrobial therapy but recur when treatment is stopped. These foals tend to do poorly and are stunted, although they may survive for 1 to 2 years. The third involves older horses that are usually 2 to 5 years of age at initial diagnosis. These horses do not necessarily have problems with recurrent infections, but about half ultimately have lymphosarcoma.[5] Selective IgM deficiency has been most frequently reported in Arabians and American Quarter Horses, although it affects other breeds as well.

It is unclear whether the IgM deficiencies reported in foals are primary or secondary. The levels of IgM present before the onset of infections have not been measured. The occurrence of multiple cases within groups of related horses suggests a genetic basis. However, to date, breeding trials have been inconclusive with regard to the heritability of this condition. In people, both primary and secondary selective IgM deficiencies occur.[6-8] Secondary cases in human patients are often associated with neoplasia, immunologic diseases such as Wiskott-Aldrich syndrome, and gluten-sensitive enteropathies.

Clinical Signs and Differential Diagnoses Foals with selective IgM deficiency tend to have frequent respiratory infections, and *Klebsiella* is commonly isolated. Other infections, such as enteritis and septic arthritis, have also been reported. The age of onset of clinical signs may be slightly later than in foals with SCID and certainly later than in foals with FPT.

Older horses with IgM deficiency should be carefully evaluated for lymphoid neoplasia. The clinical signs and hematologic features of lymphoma in horses are often nonspecific (see Chapter 37). Although the signs can vary with the tumor location, weight loss, lethargy, edema, and pyrexia are common. Lymphadenopathy may be present. On blood work, affected horses are often anemic. Frank leukemia is uncommon. Although not a consistent finding, hypercalcemia of malignancy has been reported.

Clinical Pathology Selective IgM deficiency is defined by a persistently low or absent serum IgM, whereas other classes of immunoglobulin are normal or elevated for age. IgM levels are more than two standard deviations below the age-specific mean (see Table 53-7). Because IgM levels may transiently decrease, especially in critically ill foals, it is advisable to document that IgM levels are persistently low rather than to base a diagnosis on a single sample. Lymphocyte counts and other in vitro immunologic tests, such as lymphocyte proliferation to mitogens (including PHA, Con A, PWM, and LPS), are generally normal, and these features serve to differentiate selective IgM deficiency from other immunodeficiency conditions.[1,3,9] However, in one horse with selective IgM deficiency, lymphocytes failed to respond to the B-cell mitogen LPS, whereas responses to the T-cell mitogens ConA and PHA were normal.[4] The hemogram and biochemical profile may reflect infection or inflammation, depending on the underlying infectious process (e.g., neutrophilia, hyperfibrinogenemia, anemia) and the organ system involved, but no diagnostically specific changes occur.

Pathophysiology Whether IgM is low because of decreased production, hypercatabolism, or loss is not known. In one case with lymphosarcoma, suppressor activity was identified in the neoplastic cells, suggesting that the low IgM may be a result of suppression of B-cell function by neoplastic cells.[5,9]

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Necropsy Findings Lymphoid tissue in affected foals is grossly and histologically normal. Other findings reflect secondary infections. Pneumonia is frequently present and is often caused by *Klebsiella* infection.

Treatment and Prognosis Selective IgM deficiency has an unfavorable long-term prognosis. Most horses eventually succumb to infection despite appropriate antimicrobial therapy. However, the outcome of these cases seems less certain than with SCID foals, and a rare case recovers. Plasma therapy may provide some benefit, but because only small amounts of IgM are present in plasma and the half-life of transfused IgM is short, the effects are transient. No concentrated IgM preparations are commercially available for parenteral use. If persistently low IgM levels can be documented, a poor to grave prognosis can be expected.

Prevention and Control Some cases of selective IgM deficiency might be hereditary, and therefore it may be advisable to avoid repeating matings that produced an affected offspring. However, no firm recommendations can be made.

X-Linked Agammaglobulinemia

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Definition and Etiology Agammaglobulinemia is a rare primary immunodeficiency disorder of horses characterized by complete B-cell dysfunction with an intact cell-mediated response. The disorder has been described in Thoroughbreds, Quarter Horses, and Standardbreds.[1-4] Thus far it has only been reported in males, suggesting the possibility of an X-linked disorder. The first report of an immunodeficiency in any species was agammaglobulinemia in a young boy, and the disorder has been shown to be inherited as an X-linked trait in people.[5,6]

Clinical Signs and Differential Diagnoses Clinical signs typically begin around 2 to 6 months of age and reflect the infections that develop. Pneumonia and septic arthritis, as well as dermatitis and enteritis, have been reported. Infections often respond poorly to therapy. The differential diagnosis list should include transient hypogammaglobulinemia and common variable immunodeficiency (CVID).

Clinical Pathology Total peripheral blood lymphocyte counts are within the normal range, but there is a lack of circulating B cells with normal numbers of T cells. Changes on routine laboratory evaluation are nonspecific and may reflect chronic infection. Depending on the response to infection, neutrophil counts may be normal, low, or high.

Serum levels of IgM, IgA, and all subisotypes of IgG are persistently low or absent. Depending on the age at evaluation, the assessment of antibody levels may be complicated by the presence of maternal antibody. Considering the half-life of IgG being longer than IgM, serial sampling will demonstrate a decline in antibody concentrations, with IgM and IgA typically decreasing first, followed by a decrease in all subisotypes of IgG. In some foals, low levels of immunoglobulin may persist, possibly due to either a prolonged catabolism of antibody or some residual B-cell activity, which has been identified in human patients with X-linked agammaglobulinemia.[1-5]

Horses affected with agammaglobulinemia do not produce specific antibody in response to immunization regardless of the antigen. Cell-mediated responses are essentially normal, including lymphocyte proliferation in response to T-cell mitogens (PHA and PWM) and DTH skin testing by intradermal (ID) injection of PHA. In contrast, lymphocyte proliferation and DTH skin testing by ID injection of ConA is blunted, but the reason for this response to ConA remains unclear.[4] Total hemolytic complement activity is also normal.

Pathophysiology The molecular basis of agammaglobulinemia in horses is unknown, but a defect at the stem cell level that blocks early B-cell differentiation is suspected because all classes of immunoglobulin are affected. In human patients a mutation in *Btk,* a gene encoding tyrosine kinase, accounts for the disease.[7,8] Assessment of the *Btk* gene in horses may help in understanding this disorder.

Necropsy Findings Gross and histologic changes in the lymph nodes, spleen, and thymus have been observed in horses with agammaglobulinemia.[1-4] Lymph nodes are small and microscopically they are devoid of germinal centers and follicles. Grossly, the spleen may be small and contracted and microscopically it lacks germinal centers, periarteriolar lymphocytic sheaths, and plasma cells. The thymus may be small and difficult to locate, making it necessary to blindly sample tissue from the mediastinal region in some cases. Histologically, the thymus does not show recognizable epithelial structure and lacks defined nodules. Why cell-mediated functions are normal while the architecture of the thymus is so abnormal remains unexplained.

Treatment and Prognosis In the absence of production of autologous antibody, affected horses develop recurrent infections. Although antimicrobial therapy and administration of plasma may temporarily control infections, the long-term prognosis is poor.

Horses with agammaglobulinemia illustrate that T cells make a significant contribution to immunity along with B cells. Horses with defects in both B- and T-cell functions (e.g., SCID) seldom survive to 5 months of age, whereas horses with a pure B-cell defect such as agammaglobulinemia may survive between 1 and 2 years. Agammaglobulinemia with a lack of circulating B cells was identified in a Pinto gelding that did not exhibit recurrent pyogenic infections until 3 years of age.[9] It is not certain whether this horse had agammaglobulinemia or a form of common variable immunodeficiency. Although it could not be established whether the immunodeficiency was primary or secondary, an underlying disease process was not identified.

Transient Hypogammaglobulinemia

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Definition and Etiology Transient hypogammaglobulinemia is a rare disorder characterized by the delayed onset of immunoglobulin synthesis by the neonate.[1-4] Foals normally produce some IgM in utero and begin to produce significant amounts of immunoglobulins after birth following exposure to environmental antigens (see Fig. 53-4). Assuming adequate passive transfer, maternal antibody fills the void from birth until the foal has produced sufficient autologous antibody for protection (e.g., first 2 months). For unknown reasons, in transient hypogammaglobulinemia the onset of endogenous antibody production is delayed for as long as 3 to 5 months. As maternal immunoglobulins wane, the amount of endogenous antibody is transiently insufficient to be protective, making the foal highly susceptible to infections.

The disorder has been described in an Arabian foal and a Thoroughbred foal, but the low number of reported cases may not accurately reflect the prevalence. To make a diagnosis, serial samples may be required to document that autologous immunoglobulin is not increasing sufficiently as maternal immunoglobulin declines. Many cases that are not followed this closely probably occur.

Clinical Signs and Differential Diagnoses Clinical signs occur when passively acquired antibodies are catabolized to nonprotective levels. As with other immunoglobulin deficiencies, signs consistent with the acquired infections are seen in affected foals. The differential diagnosis list should include FPT and, if the affected animal is male, X-linked agammaglobulinemia.

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Clinical Pathology The cardinal feature is low immunoglobulin levels.[1,2] At approximately 2 to 4 months of age maternal antibody will have waned, but normal foals will have produced significant quantities of endogenous antibodies. In foals with transient hypogammaglobulinemia the concentrations of immunoglobulins, particularly all subisotypes of IgG, are substantially below the means when age-matched. Affected foals have normal cell-mediated responses in vitro and in vivo and appear to be able to respond to immunization to some antigens. Normal numbers of B and T lymphocytes are present in blood and lymph nodes. However, some foals may present CD4 T-cell lymphopenia and low CD4:CD8 ratio distribution (<2).[5] In addition, the age-dependent increase in the expression of MHC class II molecule on lymphocytes, but not on monocytes, is delayed.[5]

Differentiation between FPT and transient hypogammaglobulinemia is based on the age of the patient at evaluation. Transient hypogammaglobulinemia must be differentiated from agammaglobulinemia. Both disorders have normal lymphocyte counts and normal responses to PHA skin testing and show waning levels of maternal IgG and IgG(T) if followed serially. However, transient hypogammaglobulinemia cases usually have low but detectable levels of IgM and IgA, whereas agammaglobulinemia cases usually have no detectable levels of these immunoglobulins. Differentiation between the two may require serial sampling to show that immunoglobulin production does ultimately increase in the patient with transient hypogammaglobulinemia. Moreover, B lymphocyte count is absent in cases of agammaglobulinemia and normal in cases of transient hypogammaglobulinemia.

Pathophysiology The cause of this delayed development of the humoral immune response is currently unknown. A proposed mechanism is inadequate lymphoid tissue milieu to support B cell differentiation.[5] A syndrome of transient hypoglobulinemia of infancy has been described in children and is characterized by recurrent infections and one or more reduced serum immunoglobulin levels.[6-7] The pathophysiology of this disorder is also not completely understood.

Necropsy Findings No specific gross or microscopic lymphoid changes have been associated with transient hypogammaglobulinemia. Necropsy findings would reflect the secondary infectious processes that have affected the foal.

Treatment and Prognosis The goal of therapy is to minimize infections until the foal's immune system begins to function adequately. Treatment should include antimicrobial therapy and plasma transfusions. With appropriate support the prognosis is good, as the hypogammaglobulinemia resolves with time.

Foal Immunodeficiency Syndrome

M. Julia B. Felippe

Definition and Etiology Foal immunodeficiency syndrome (FIS), previously known as *Fell Pony syndrome* and also referred to as "anemia, immunodeficiency, and peripheral ganglionopathy," is an inheritable and fatal condition characterized by profound anemia and septicemia, the latter due to a primary immunodeficiency. A genomewide study identified a mutation in the gene *SLC5A3* on chromosome ECA26 associated with the syndrome.[1] The mechanistic implications of this mutation have not been fully resolved, and a causal relationship between the SLC5A3 mutation and FIS requires further studies to date. The presence of other mutations in that genomic region has not been ruled out as responsible for the phenotype of the immunodeficiency syndrome.

Clinical Findings/Clinical Signs and Differential Diagnoses FIS-affected foals are born apparently healthy but rapidly fail to thrive. The fatal illness becomes clinically apparent in foals within 1 month, and death occurs generally by 3 months of life due to a primary, profound, nonregenerative anemia and B cell lymphopenia, with increased susceptibility to opportunistic infections and septicemia.

The foals present with weight loss and dullness, pale mucous membranes, and signs of infection, including diarrhea and pneumonia.[2,3,4] Enterocolitis, bronchopneumonia, pancreatitis, and glossal hyperkeratosis are often caused by opportunistic infections (e.g., *Escherichia coli, Cryptosporidium* spp., adenovirus). The severe, progressive anemia results from lack of erythrocyte production in the bone marrow (nonregenerative), and it is not associated with hemorrhage or hemolysis.[2,3,5]

Clinical Pathology At birth, blood work may be normal, with normal or borderline low erythrocyte counts and hemoglobin values and normal distribution of neutrophils and lymphocytes.[5] When infections are present, abnormalities in the leukogram, including regenerative neutropenia or neutrophilia, toxic changes in neutrophils, and lymphopenia, may be present, and values vary depending on the type and phase of infection. Thrombocytes are often present in the blood in normal values unless disseminated intravascular coagulopathy secondary to septicemia is present.

Severe normocytic or macrocytic anemia develops rapidly. On the basis of bone marrow cytology, FIS-affected foals may be born with erythroid precursors but rapidly evolve to erythrocyte hypoplasia. At birth, hemoglobin and hematocrit values may be measured in the low end of the normal reference range, and peripheral blood B cell distribution may be equivalent to that of healthy unaffected foals. In a few weeks, profound anemia and B-cell lymphopenia develop. In time, cytologic evaluation of the marrow reveals differentiating myeloid precursors, megakaryocytes, and/or paucity of hematopoietic precursors. When present, proerythroblasts have been described to be binucleate.[4]

Immunologic Findings Absolute lymphopenia in FIS-affected foals likely reflects poor lymphocyte development in primary and secondary lymphoid tissues, as well as failure of lymphocyte population expansion with age.[6,7] B-cell distribution in blood may be within normal or low-normal values at birth but rapidly declines in the first few weeks of life.[5,8] Although $CD4^+$ and $CD8^+$ T-cell distribution has been reported normal in affected foals, T-cell dysfunction is suggested by the small thymus and opportunistic infections with cryptosporidia and adenovirus.[7,9] The expression of major histocompatibility complex class II (MHC class II) molecule in peripheral blood lymphocytes may be decreased and/or fail to increase with age in FIS-affected foals when compared with healthy foals, also supporting abnormal lymphocyte development.[10] Nevertheless, when stimulated in vitro, the peripheral blood lymphocytes of affected foals respond normally to mitogens PHA, Con A, and PWM.[4,7]

Although the B lymphopenia limits the ability of FIS-affected foals to produce immunoglobulins, serum IgG concentrations are often normal when clinical signs are detected due to the presence of circulating colostrum-derived antibodies during the time of diagnosis.[2,3,4,11] Nevertheless, serum IgM concentrations (a parameter not confounded by maternally derived antibodies at this age) are low in affected foals and strongly suggest impaired primary humoral immune response in FIS-affected foals.[5,11,12] FIS-affected foals develop septicemia despite normal (colostrum-derived) serum IgG concentrations, suggesting a broad lymphocytic dysfunction.[4,5]

The distribution and function of neutrophils have been reported normal, with the presence of bands and normal oxidative burst activity.[4]

Pathophysiology Bone marrow cytologic studies performed prospectively in affected foals immediately after birth and before clinical signs become evident in later age revealed evidence of initial erythroid hyperplasia with dysplasia, followed by a rapid and progressive hypoplasia and aplasia, as well as marked anemia.[5] In

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addition, a concomitant mild myeloid dysplasia could be observed, which questions the involvement of further types of cells.

The presence of erythrocytes and B cells in peripheral blood at birth suggests a limited hematopoiesis during fetal life. Nevertheless, this cell production is not sustained after birth, leading to a marked and progressive B lymphopenia and anemia in the perinatal phase, clinical signs, and death. B lymphocytes and erythrocytes are the most severely affected cell populations in FIS, and both undergo critical developmental stages in the bone marrow. The condition may be caused by independent or common genetic abnormalities that affect both cell lines. Most early B-cell differentiation essential genes and genes associated with erythropoiesis are expressed in the affected foals, and a potential common hematopoietic genetic defect is still under investigation.

Epidemiology Foal immunodeficiency syndrome is a genetic and inheritable fatal immunodeficiency condition that occurs in male and female young foals of the Fell and Dales breeds and, potentially, other breeds that include common ancestors.[13,14]

The Fell Pony breed experienced loss of genetic diversity due to the small numbers of animals and overuse of prominent stallions, which likely led to the spread of the genetic defect. Pedigree analysis of the Fell Pony breed suggests that FIS may have an autosomal recessive inheritance. Carriers are phenotypically normal. FIS was initially described in the United Kingdom and subsequently in Fell Pony foals of the United States, Czech Republic, and Netherlands.[2,4,15,16]

Necropsy Findings In the postmortem, abnormal gross findings include generalized tissue pallor, thymic hypoplasia, and inflammation and lymphadenopathy associated with infections of many organs (e.g., necrotizing enteritis, pyogranulomatous bronchopneumonia, pancreatitis, myocarditis). The medullary cavities of bones often do not contain marrow but instead pale, tan, fatty tissue, a striking finding in early age. Histopathology reveals severe erythroid hypoplasia, with small numbers or absent late erythroid precursors in the bone marrow, and high myeloid-to-erythroid ratio (ranging from 16 to 32:1, compared with the normal myeloid-to-erythroid ratio of 0.5 to 1.5:1).

Despite lymphadenopathy, there is severe lymphocytic hypoplasia and lack of secondary lymphoid follicles in the lymphoid organs; in addition, plasma cells are absent. Immunohistochemical staining detects no B lymphocytes in the bone marrow and rare or few B cells in the lymph nodes and spleen, dispersed in the tissues without forming germinal centers. In addition, peripheral ganglionopathy characterized by neuronal chromatolysis involving trigeminal, cranial mesenteric, and dorsal root ganglia has been reported.[2]

Treatment and Prognosis FIS is a fatal disease, and foals die or are submitted to euthanasia soon after the initial clinical signs. Management of infections and septicemia may be temporarily possible with antibiotic therapy; however, the combination of infectious organisms, commonly viruses and bacteria, prevents a sustained protection. The severe, progressive anemia is a major challenge for treatment.

Prevention and Control A DNA-based carrier test was developed by the Animal Health Trust (Newmarket, United Kingdom).[1,14] The genetic test offers powerful herd management planning to avoid the mating of two carriers with the genetic defect and, consequently, decrease the incidence of FIS, a fatal disease to date.

Common Variable Immunodeficiency

M. Julia B. Felippe

Definition and Etiology Common variable immunodeficiency (CVID) in the horse is a rare late-onset clinically relevant immunologic disorder of inadequate antibody production due to impaired B-cell differentiation in the bone marrow and consequent B-cell depletion from lymphoid tissues and blood. The cause of impaired B-cell development in the bone marrow is under investigation, and a primary or secondary cause has not been resolved.

Clinical Findings/Clinical Signs and Differential Diagnoses Most patients are reported to have had a healthy life until the signs of disease manifest as late-onset recurrent bacterial infections and fevers, hypogammaglobulinemia or agammaglobulinemia, progressive B-cell lymphopenia or depletion, and poor response to protein vaccination (e.g., tetanus toxoid).[1] Most common clinical signs include recurrent pneumonia, sinusitis, meningitis and/or neurologic disorders, abnormal gait (ataxia), peritonitis, gingivitis, hepatitis, diarrhea, susceptibility to gastrointestinal parasites, uveitis, conjunctivitis, and/or skin abscesses.[2,3,4] Meningitis may clinically present with marked depression, alternated by periods of normal appetite. Weight loss and/or muscle atrophy are common.

The humoral feature of this immunodeficiency predisposes to infections and disease caused by encapsulated bacteria, which requires opsonization with both antibody and complement for effective phagocytosis and bacterial killing. Therefore common pathogens involved in infections are *Staphylococcus* spp., *Streptococcus* spp., *Actinobacillus* spp., and *Klebsiella* spp. Occasionally fungal infections, such as *Aspergillus* spp., *Bipolaris* spp., *Pneumocystis jiroveci* (former *P. carinii*), or *Rhodococcus equi* infection have been diagnosed in a small number of CVID-affected horses that were treated with glucocorticoids or presented with a concomitant $CD4^+$ T-cell lymphopenia.[1,5]

A differential diagnosis is lymphoma because some forms of this type of cancer may alter lymphocyte distribution and function, including B-cell lymphopenia and hypogammaglobulinemia. If the disease manifests before the yearling phase, differential diagnoses would include transitory hypogammaglobulinemia of the young and X-linked agammaglobulinemia.

Clinical Pathology During bacterial infection, blood work reveals leukocytosis with neutrophilia, often mature, although a left shift and toxic changes may be present. Transient lymphopenia (<1200 cells/μL) is common. During the period when infections respond to antibiotic therapy, both neutrophil and lymphocyte counts may be within normal reference values.

Hyperfibrinogenemia is present accordingly to active infections. An important feature is the presence of low-normal or low globulin levels despite severe bacterial infections and hyperfibrinogenemia; the hypoglobulinemia results from the hypogammaglobulinemia. Abnormal liver enzymes may also be measured when there is septicemia.[3]

In the case of meningitis, spinal fluid analysis reveals increased protein values and pleocytosis, often with nondegenerate neutrophils, lymphocytes, and monocytes.[3] Blood culture has not been routinely performed in these patients but has resulted in bacterial growth in some cases; culture of spinal fluid may or may not result in bacterial growth.

Immunologic Findings Peripheral blood lymphocyte immunophenotyping reveals persistent, severe B-cell lymphopenia (<2%) in all patients. A relative increase in the percentage of circulating $CD8^+$ T cells and occasionally in $CD4^+$ T cells has been observed in most patients. The parameter that definitively indicates a humoral dysfunction is serum IgG concentration, which is markedly low (<800 mg/dL) in all affected horses. Serum IgM concentrations are markedly reduced (<25 mg/dL) in all patients, suggesting the inability to elaborate primary immune response. Serum IgA concentrations are often within low normal values (≈60 mg/dL) in early diagnosis in most patients despite severely low serum IgM and IgG concentrations, but levels reduce with progression of clinical disease, severity of clinical condition, and proximity to euthanasia. Affected horses do not respond to tetanus toxoid vaccination with an increase

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in serum antibody titers, and prevaccination values are often low or undetectable.

Lymphocyte proliferation assays reveal normal or subnormal responses to PWM, PHA, and Con A mitogens.[1] Upon stimulation with mitogens, the expression of IFN-γ and CD40-ligand in isolated lymphocytes of affected horses is comparable with control healthy horses, suggesting normal T-cell function and capacity for co-stimulation of B cells, which is required for B-cell differentiation and antibody production.

Besides the B-cell lymphopenia, a small number of CVID-affected horses may also present a concomitant $CD4^+$ T-cell lymphopenia, leading to a low CD4:CD8 ratio (<2). In these cases, infection with intracellular organisms that require cellular immunity may be observed, characterizing a clinical relevance for this finding.

The in vitro phagocytosis and oxidative burst activity are normal and often increased in these patients, reflecting in vivo activation.

Pathophysiology By the time of clinical diagnosis of CVID in horses, B cells are markedly rare in primary and secondary lymphoid tissues, leading to peripheral blood B-cell lymphopenia or depletion.[3,6] It is likely that B-cell production was sustained in the affected patients for a period of time before the diagnosis of CVID, and secondary lymphoid tissues were then populated with B cells, including memory cell development; however, a late-onset event impairs B-cell development in the bone marrow, and the continuous population of peripheral tissues could not be sustained.[7] B cells must be continuously generated over an individual's lifetime from hematopoietic stem cells in the bone marrow to maintain adequate population and humoral function in the lymphoid tissues.

B-cell differentiation and development is regulated by a network of transcription factors and demethylation of dinucleotides at promoter sites.[8] In the bone marrow of affected horses, the expression of key early B-cell commitment genes, including *E2A* and *PAX5,* is significantly decreased in comparison with healthy horses; in addition, *PAX5* downstream target genes are also significantly reduced in CVID-affected horses, including *CD19, IGHM,* and *IGHD*.[9] Immunohistochemical studies confirm the absence of PAX5-BSAP protein in the bone marrow of affected horses. Through a hierarchical dependence, *PAX5* directly promotes the expression of B lymphoid–specific genes while it represses the transcription of non–B lineage genes.[10] Hence, CVID in horses may be caused by impairment of B-cell development in the bone marrow at the transition between pre-pro-B cells and pro-B cells; current studies investigate epigenetic mechanisms that lead to gene silencing during the B-cell differentiation stage.

Epidemiology Affected patients are unrelated adult horses and ponies (average age 10 years, range 2 to 23 years) of both sexes and many different breeds (e.g., Thoroughbred, Quarter Horse, Arabian, Warmblood, Paint) living in distinct parts of the United States.[1] Cases elsewhere in the world have not been reported but are possible; their identification may be limited by the lack of knowledge of differential diagnosis for immunodeficiency diseases and availability of immunologic testing for the horse.

By the time the diagnosis of CVID is obtained, several months of recurrent infections and fevers may have been observed. The recurrent character of clinical signs is the most important factor that triggers the suspicion of an underlying immunodeficiency. Affected horses have been euthanized due to financial reasons or poor quality of life either soon after the diagnosis or after years of antimicrobial management.

Necropsy Findings Necropsy findings include organ lesions according to the infectious processes. In addition, histopathology confirms the lack of germinal cells, which affects the lymph node typical cortical-paracortical distribution and the primary and secondary follicles in the cortex.[1,3] In general, lymph nodes are small. In addition, there is absence of plasma cells in various lymphoid and mucosal tissues. Immunohistochemical analysis may identify occasional positive B cells dispersed or in small groups in the lymph nodes but absent B cells in the bone marrow and spleen (Fig. 53-6).

Treatment and Prognosis The majority of affected horses are subjected to euthanasia due to severe pneumonia, meningitis, and/or septicemia. When affordable, a few horses have been managed for 1 to 5 years on continuous or intermittent antibiotic and immunoglobulin therapies. Commercial equine plasma is the current available source of immunoglobulin for clinical use, and its low concentration prevents it from being a cost-effective treatment. Immunoglobulin replacement therapy in human patients is possible due to the availability of IgG concentrate products, which improves quality of life. Hematopoietic stem cell transplantation has been attempted in a horse with common variable immunodeficiency but no replacement of B-cell population, and function has been successful to date; the costs involved with the procedure discourage clinical application. When the mechanism of disease becomes revealed, gene therapy may be a more feasible treatment if appropriate.

Prevention and Control Current studies investigate the possibility of epigenetic mechanisms that lead to the impaired B-cell differentiation in the bone marrow. Epigenetic regulation can be affected by environmental or infectious elements, yet to date, common factors have not been identified in the horse patients. Therefore at this time, prevention and control measures are not known.

Drug-Induced Immunosuppression

M. Julia B. Felippe

Immunosuppressive therapy is required when an immune response causes excessive damage to tissues or autoimmunity develops. On the basis of their primary mechanism of action, immunosuppressants may be classified as inhibitors of gene expression or transcription (e.g., glucocorticoids); inhibitors of nucleotide synthesis (e.g., azathioprine); inhibitors of calcineurin phosphatase (e.g., cyclosporine, tacrolimus, rapamycin) and kinase (e.g., leflunomide); alkylating agents (e.g., cyclophosphamide, chlorambucil); and monoclonal antibodies (e.g., against T-cell receptor, IL-2R).[1-4] In the horse, only a few of these drugs have been studied and are used clinically.

Autoimmunity results from the production of self-reactive antibodies and/or T lymphocytes. The potential mechanisms involved include lack of central negative selection of autoreactive cells; molecular mimicry of microbes and self-epitopes; or the development of new epitopes on self-proteins secondary to tissue injury caused by viruses, bacterial exotoxins, chemicals, or tumors.

The type of mechanism involved in autoimmunity (e.g., antibody-mediated and/or cellular-mediated) may require immunosuppressive therapy with corresponding cellular metabolism targets. In addition, the combination of drugs may increase the success and decrease the necessary course of immunosuppressive therapy; nevertheless, this approach has been empirical in large animals and still lacks scientific evidence. Although the goal for immunosuppressive therapy is to decrease tissue damage caused by exacerbated immune response, systemic susceptibility to infections, particularly to fungal and viral organisms, is a risk in patients under therapy.[5,6]

Glucocorticoids are potent immunosuppressant drugs.[7] The lipophilic glucocorticoids pass freely through cell membranes and bind to a cytosolic glucocorticoid receptor (GR).[8,9] This interaction allows the GR transcription factor to translocate into the nucleus, bind to glucocorticoid-responsive elements, and regulate gene transcription that promotes or represses synthesis of cytokines, chemokines, inflammatory enzymes, and adhesion molecules. Frequently used glucocorticoids in horses include hydrocortisone, dexamethasone, prednisolone, methylprednisolone, isoflupredone, triamcinolone, beclomethasone, and fluticasone. Oral prednisolone has better bioavailability than prednisone in the horse.[10] In general, therapeutic doses are high and frequent in the initial phase of treatment, and dosage is subsequently tailored to the clinical condition.

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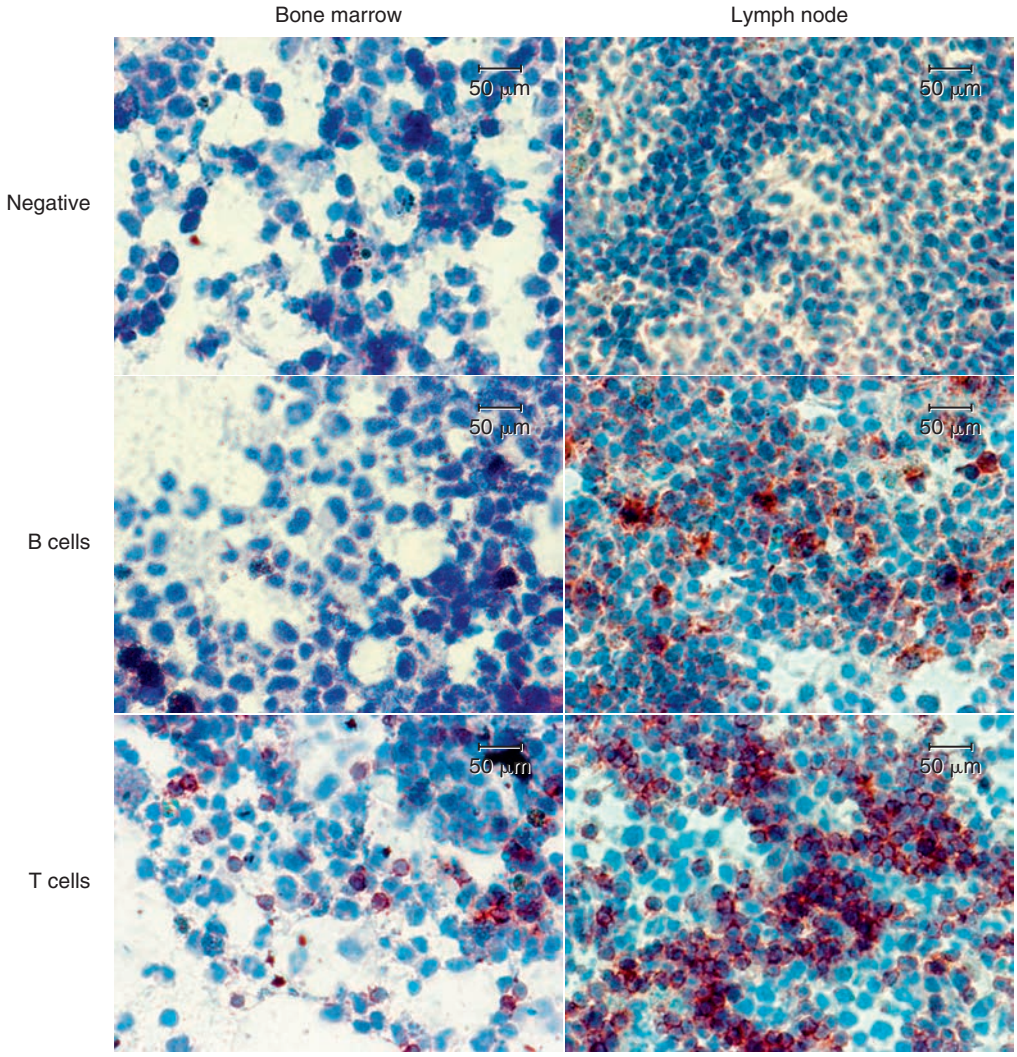


FIG. 53-6 Immunohistochemical analysis of bone marrow and lymph node microsections from a horse with common variable immunodeficiency. Bone marrow and mesenteric lymph node microsections from a horse with common variable immunodeficiency were stained using monoclonal antibodies against equine B-cell (CD19-like) and T-cell (CD3) markers, irrelevant control (negative), and 3-amino-9-ethylcarbazole (AEC) chromogen. Note the lack of germinal centers and paucity of lymphocytes in the lymph node. B cells are not detected in the bone marrow; numerous B cells are detected dispersed in the lymph node. T cells are present in the bone marrow and lymph nodes; however, the typical cortical-paracortical regions in the lymph node are lost with the lack of germinal centers.

Glucocorticoids in horses have been used for the treatment of a broad range of diseases that directly involve the immune system, including atopy or skin hypersensitivity reactions, contact dermatitis, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, immune-mediated myositis, uveitis, purpura hemorrhagica, vasculopathy, pemphigus foliaceus, inflammatory airway disease, recurrent airway obstruction, and lymphomas or lymphosarcomas, many times with limited efficacy.[11-23]

Glucocorticoids cause immunosuppression mainly by sequestration of $CD4^+$ T lymphocytes in the reticuloendothelial system and by inhibiting the transcription of cytokines.[3] A single IV dose (any of 0.05, 0.1, or 0.2 mg/kg body weight) of dexamethasone has shown to induce neutrophilia and lymphopenia, a decrease in the peripheral blood $CD4^+$ T-cell population with a concomitant increase in the $CD8^+$ T cells, and a consequent decrease of CD4:CD8 ratio; these effects are observed at 4 hours and 12 hours after the drug administration and gradually decrease over time in the first 48 hours.[24] Chronic treatment with glucocorticoids may lead to susceptibility to infection, hyperglycemia, hypokalemia (particularly isoflupredone), gastrointestinal ulceration, delayed wound healing, osteoporosis, growth suppression, myopathy, and hypertension.[3,22] Parenteral, oral, and aerosolized corticoids reversibly suppress adrenocortical function, while the response to ACTH stimulation remains intact.[22,25]

Aerosolized glucocorticoids have been used for the prevention and treatment of recurrent airway obstruction in the horse, and they were shown to decrease neutrophilic pulmonary inflammation and the expression of IL-1β and IL-8 in isolated alveolar macrophages.[18,19,22,23,26] Aerosolized fluticasone proprionate may be detected in plasma for a minimum of 72 hours post administration.[27] The treatment of heaves-affected horses with inhaled fluticasone at therapeutic dosages for 11 months had no significant or detectable effect on innate and adaptive (both humoral and cell-mediated) immune function assays, including response to vaccinations.[28]

Azathioprine inhibits the de novo pathway of purine synthesis, essential for DNA and RNA production and, consequently, lymphocyte activation and proliferation. Azathioprine has been used in horse patients for the treatment of immune-mediated anemia, immune-mediated thrombocytopenia, vasculopathy, and pemphigus foliaceus.[29] The use of azathioprine allows reduction in glucocorticoid dose when the two are combined in therapy. Because proliferation of many cell types can also be inhibited, adverse effects associated with azathioprine treatment include leukopenia, alopecia, and hepatotoxicity. A single IV dose (1.5 mg/kg) of azathioprine resulted in a rapid

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decrease in plasma drug concentration with a half-life of 1.8 minutes.[30] Oral bioavailability at 3 mg/kg was low and varied from 1% to 7%. When given daily for 30 days, and subsequently every other day for another 30 days, that oral dose did not cause clinical adverse effects or abnormal hemogram, leukogram, and serum biochemical analysis in most horses. Lymphopenia and immunosuppression were observed in one horse during the experiment.

Cyclosporine is a cyclic polypeptide that binds to the cytoplasmic receptor cyclophilin and, subsequently, to the catalytic domain of the cytoplasmic phosphatase calcineurin.[31] This binding results in the inhibition of dephosphorylation of transcription factors, most importantly the nuclear factor of activated T lymphocyte (NFAT), which prevents their translocation to the nucleus. Therefore, the production of key elements of T-cell activation and proliferation (IL-2, IL-4, CD40L, TNF-α, IFN-γ, c-myc) is suppressed. Cyclosporine has been used in the horse for intravitreal treatment of recurrent uveitis and immune-mediated keratitis.[32] Potential adverse effects of cyclosporine include vasoconstriction, hypertension, nephrotoxicity, hepatotoxicity, and potential susceptibility to infectious organisms that require cell-mediated protection.

Rapamycin and tacrolimus are macrolide antibiotics that bind to the cytoplasmic FK-binding protein (FK-BP), and the resultant protein complex inhibits calcineurin. The effect includes cell-cycle arrest and decrease in the expression of inflammatory cytokines. Rapamycin ocular toxicity and distribution have been studied for potential clinical use in the horse.[33]

Cyclophosphamide (phosphoramide and acrolein) and chlorambucil (phenylacetic acid mustard) metabolizes alkylate DNA bases, resulting in mutagenic, cytotoxic, antiproliferative, and chemotherapeutic effects. Cyclophosphamide's effect on B cells promotes its application for the treatment of autoantibody-mediated diseases. In horses, these drugs have been used for the treatment of lymphosarcoma.[34] Adverse effects associated with cyclophosphamide and chlorambucil therapies include anemia, leukopenia, alopecia, and secondary malignancies.

Vincristine is a vinca alkaloid that binds to tubulin in the mitotic spindle and prevents purine synthesis. Consequently, it inhibits cell proliferation, resulting in antitumor and immunosuppressive effects. In horses, vincristine has been used for the treatment of immune-mediated thrombocytopenia, pemphigus foliaceus, and lymphosarcoma.[35] Mild neurologic adverse effects (proprioceptive deficits) and ileus may occur in the horse.

The development of species-specific monoclonal antibodies and the identification of appropriate antigenic targets have contributed to the advance of their use in medicine.[36] The great advantage of monoclonal antibodies is the specificity of response, which may minimize adverse effects. Examples of use include treatment of inflammation (targeting inflammatory cytokines) and cancer.[37]

Immunosuppression Associated with Leukoproliferative Disorders

Siddra Hines • Debra C. Sellon

Neoplastic disease can impair cell-mediated and humoral immune responses as a result of an abnormal bone marrow environment, altered patterns of cytokine production or release, or impaired proliferative responses (anergy). In horses, immunodeficiency has most often been described in association with lymphosarcoma or plasma cell myeloma.

Lymphosarcoma

Immunodeficiency has been identified in some horses with equine lymphosarcoma. The immunologic abnormality most often described is a decrease in the concentrations of serum immunoglobulins, especially IgM.[1-5] Recurrent or persistent infections may occur and complicate recognition of the underlying neoplastic disorder. Neoplastic cells were suggested to be T-suppressor cells in one horse, suggesting a possible mechanism for the IgM deficiency.[1] Diminished lymphocyte blastogenesis responses indicative of impaired T-cell function have been described in two horses with lymphosarcoma, one of which had concurrent IgM deficiency.[5] Some horses with lymphosarcoma have been diagnosed with concurrent bacterial infections, which may be related to immunosuppression.[4,5] A horse with myelomonocytic leukemia was found to have pulmonary aspergillosis.[6] Lymphosarcoma has been associated with bone marrow necrosis in people and horses, leading to pancytopenia and sepsis presumably due to profound neutropenia.[7] Similarly, myelophthisis (bone marrow suppression) secondary to tumor cell infiltration of bone marrow may lead to pancytopenia and immunosuppression in horses.[8,9]

Plasma Cell Myeloma

Plasma cell myeloma has been reported in horses of several breeds.[10] Although reports of the condition are limited, there appears to be no gender predilection. Horses have ranged in age from 3 months to 22 years (median, 11 years) at diagnosis. Common clinical signs include weight loss, anorexia, fever, pneumonia, and limb edema. Both equine and human patients with plasma cell myelomas have an increased susceptibility to bacterial infections, probably as a result of a secondary immunodeficiency.[10-12] Immune suppression in human patients with myeloma is well documented and can lead to severe infection.[13] Mechanisms include abnormal γ-globulin production, abnormal cytokine production, and dysfunctional natural killer and dendritic cell populations.[13] As a malignancy of plasma cells or lymphocytoid plasma cells, plasma cell myelomas typically produce large quantities of a homogeneous immunoglobulin or immunoglobulin fragment, resulting in a monoclonal gammopathy. In both equine and human cases of myeloma, the predominant serum globulins are generally subclasses of IgG.[10,11] Hyperglobulinemia is a characteristic but not invariable finding. Monoclonal gammopathies in the horse have also been reported with lymphoma and benign disorders.[14,15] The concentrations of normal polyclonal immunoglobulins are generally decreased in myeloma patients as a result of several mechanisms, including decreased synthesis and accelerated catabolism of antibody and suppressed clonal expansion of B cells.[10-12] Decreased numbers of neutrophils, which may also be dysfunctional, and defective complement activation may also contribute to the impaired immune function.

Other Leukoproliferative Disorders

A wide variety of other leukoproliferative disorders have been described in horses, including acute and chronic granulocytic leukemia,[16-18] myeloblastic leukemia,[19] myelomonocytic leukemia,[20,21] monocytic leukemia,[22] eosinophilic myeloproliferative disorder,[23] and malignant histiocytosis.[24] Regardless of the primary cell line of origin, the end result is often myelophthisis and pancytopenia with the potential for significant immunosuppression.

Immunosuppression Associated with Infectious Agents/Processes

Debra C. Sellon[‡]

The interrelationship between infectious agents and the host immune system is complicated. Infection, regardless of etiology, initiates a cascade of complex reactions intended to assist the host in control and elimination of the infectious agent. When the immune system is compromised, infectious agents have an increased opportunity to become established and cause significant disease in the host. This may happen because external factors suppress immune function in the host before encountering a pathogen or the pathogen suppresses immune responses in the host.

[‡]Contributions to previous editions by Jill R. Johnson, Melissa T. Hines, and Debra C. Sellon are acknowledged.

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Common Infections in the Immunocompromised Host

Immunocompromised horses are incapable of developing a normal immune response, usually as a result of an immunodeficiency disorder, immunosuppressive therapy, underlying disease, or malnutrition. When an equine host has impaired immune responses for any reason, infectious agents have an increased opportunity to establish persistent infection or cause significant harm to the host. For many immunocompromised horses, the result is persistent or unusually severe disease secondary to infection with common equine pathogens. In some situations, however, the immune capabilities of the horse are so impaired as to enable normally nonpathogenic infectious agents to cause disease. Identification of such pathogens or patterns of infection in an equine patient should lead the clinician to suspect underlying immunodeficiency.

Undoubtedly, primary immunodeficiency disorders (including SCID, agammaglobulinemia, FIS, selective IgM deficiency), described in detail earlier in this chapter, represent the principal cause of immunocompromise in horses.[1-8] The most commonly described pathogens in horses with severe primary immunodeficiency include adenoviruses, *Cryptosporidium parvum, Candida* spp., *Pneumocystic jiroveci* (formerly called *P. carinii*), and *Rhodococcus equi* (in adult horses). These are generally considered to be pathogens of the respiratory and gastrointestinal tracts, and most affected horses present with persistent or severe clinical signs associated with these body systems. Horses with less severe primary or secondary immune deficiency (e.g., selective IgM deficiency) may present with recurrent respiratory tract infections associated with a variety of bacterial pathogens.[4] The most common secondary immunodeficiency disorder of horses is failure of passive transfer (FPT) of immunity.[9] Affected foals commonly develop bacterial septicemia with or without localized bacterial infections.

Some foals with FTP or other forms of immunosuppression develop localized or systemic candidiasis.[10,11] This disorder appears to be most common in foals with FPT that have been treated with broad-spectrum antimicrobial therapy for treatment of bacterial septicemia. This syndrome has some similarities to mucocutaneous candidiasis in people, which has been associated with several different subtle T-cell defects. Oral lesions range from discrete, focal, white, plaquelike lesions on the margins of the tongue to a generalized, thick, white, pseudomembranous coating covering the tongue and gingival mucosa. Most foals exhibit bruxism, ptyalism, fever, and depression. Other significant clinical problems include pneumonia, septic arthritis, and diarrhea. This syndrome should be distinguished from the glossitis caused by *Candida* infection seen in inappetent or debilitated neonatal foals, which is fairly common and generally resolves with amelioration of the primary disease.[12] Regardless of cause or underlying nature of the immunodeficiency, the prognosis for foals with oral candidiasis and associated bacterial septicemia is guarded to poor.

Immunosuppression may also occur secondary to corticosteroid administration, which is discussed in detail earlier in this chapter. Corticosteroid effects are mediated through binding to intracytoplasmic steroid receptors. The steroid-receptor complexes are transported to the cell nucleus, where they bind cellular DNA regulatory sequences and alter gene expression to enhance or inhibit production of specific proteins. The net result is lymphopenia, suppression of macrophage phagocytic function, impaired killing of ingested organisms, impaired secretion of monokines, and inhibited antigen processing and presentation.[13,14] Cell-mediated immunity is impaired through T-cell lymphopenia, altered cytokine production, and decreased antigen presentation, and it is reflected in the suppression of mitogen stimulation responses. Humoral immunity is impaired indirectly through altered T-cell responses, enhanced immunoglobulin catabolism, and decreased antigen presentation.[13] Horses receiving high or prolonged therapy with corticosteroids have been reported to experience exacerbations of preexisting infections or decreased resistance to newly encountered pathogens.[15,16] This may manifest as bacterial pneumonia or pleuropneumonia, candidiasis, equine protozoal myeloencephalitis, or a variety of other infectious disorders.[11,16]

Infections That Cause Immune Suppression

Some infectious agents have developed strategies to elude host defenses in hosts with otherwise normal, functioning immune systems. These strategies may downregulate immune responses to the extent that the host becomes vulnerable to secondary infection. Many viral, fungal, and bacterial infections transiently suppress specific and nonspecific immune responses, predisposing animals to secondary bacterial infections.[17] Severe endotoxemia or septicemia may suppress neutrophil numbers and bactericidal function, predisposing to secondary infection.

EQUINE INFLUENZA. Although there has been little work done to specifically examine the effects of equine influenza viruses on the equine immune system, it is widely acknowledged that this viral infection predisposes horses to secondary bacterial infection.[18,19] Proposed mechanisms for increased susceptibility to bacterial infection after influenza infection include disruption of the barrier function of alveolar epithelium, exposing bacterial adhesion molecules; desensitization of alveolar macrophages to bacterial Toll-like receptor ligands; and alteration of immune functions in the alveolar microenvironment.[20,21]

PERINATAL EQUINE HERPESVIRUS TYPE 1 INFECTION. Infection of the fetus with equine herpesvirus type 1 (EHV-1, rhinopneumonitis) late in gestation has been associated with postnatal development of interstitial pneumonia, lymphopenia, marked necrosis and atrophy of the thymus and splenic lymphoid tissue, and increased susceptibility to bacterial infections.[22] Affected foals may be either weak or normal at birth. Despite apparently adequate passive transfer of maternal antibody, affected foals contract a variety of infectious bacterial diseases, including colibacillosis, streptococcal septicemia, salmonellosis, and Tyzzer disease. EHV-1 is isolated from nasal passages in about 30% of the cases. The spleen and thymus are grossly small at necropsy. Bilateral adrenocortical hyperplasia is noted in most foals. Histologically, splenic periarteriolar lymphocytic sheaths are depleted of lymphocytes, and no lymphoid follicles are detectable. Thymic alterations vary from extreme diminutions of thymocyte numbers to complete necrosis of thymic lymphocytes with disappearance of Hassall corpuscles and disruption of the epithelial matrix. Lymph nodes also show lymphoid necrosis. An immunodeficiency secondary to the marked lymphoid damage induced by the virus is credited with allowing secondary bacterial infections to become established. Immunization of broodmares against EHV-1 would seem to be the most appropriate approach to prevention.

EQUINE HERPESVIRUS TYPE 5 INFECTION. Equine herpesvirus type 5 (EHV-5) is an emerging pathogen linked to equine multinodular pulmonary fibrosis (EMPF).[23-26] This γ-herpesvirus has been found in bone marrow of infected horses, contributing to speculation that the virus may be immunosuppressive.[25,26] Many affected horses are lymphopenic for undetermined reasons, most are anemic and thrombocytopenic, and at least one affected horse was profoundly pancytopenic, leading to speculation that immune-mediated or direct viral destruction of mature cells and/or hematopoietic precursors in the bone marrow may play a role in diminished cell counts in peripheral blood.[23-25] Transient improvement in cell counts after initiation of corticosteroid therapy supports the possibility of immune-mediated mechanisms for destruction of hematopoietic cells.[25] One case of EMPF presented with primary lymphocytic leukemia, generalized lymphadenopathy, and infiltration of neoplastic lymphocytes in bone marrow, lymph nodes, and spleen.[26] Infiltrating cells were almost exclusively T lymphocytes, whereas B lymphocytes could not be detected. Depletion of B-cell lines was accompanied by hypogammaglobulinemia.[26] EHV-5 infection was demonstrated in

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lung, bone marrow, and lymph nodes.[26] A link between the T-cell leukemia and infection by EHV-5 was suggested.

Immunosuppression Associated with Immune-Mediated Disorders

Siddra Hines • Debra C. Sellon

Immune-mediated disorders can result in immunosuppression and increased risk of secondary infection through a variety of mechanisms, including direct damage to immune components with subsequent immune dysfunction.

Penetration of the skin barrier resulting in an increased susceptibility to infection can occur with immune-mediated diseases such as cutaneous vasculitis, most commonly seen as purpura hemorrhagica. Immune complexes are deposited in the walls of small blood vessels and the resultant inflammation is manifested as severe edema, tissue necrosis, and ulceration. Secondary bacterial infection, particularly cellulitis and pneumonia, may occur. Therefore prophylactic antimicrobial therapy is often warranted in the treatment of purpura hemorrhagica.[1]

Reported occasionally in horses,[2] immune-mediated thrombocytopenia (ITP) has the potential to negatively impact immune responses.[3] Platelets can play both indirect and direct roles in protecting an animal from infection. They promote antiviral cytotoxic T lymphocyte–mediated responses and contain important antibacterial proteins that when released promote rapid microbial killing.[4] Diminished levels of platelet-derived cytokines may affect Th polarization and have a negative impact on bone marrow function.[5] Importantly, red blood cells from thrombocytopenic mice have demonstrated an increased susceptibility to hemoparasite infection, indicating that thrombocytopenia can have an important in vivo effect on immunocompetency.[4]

Alloimmune neonatal neutropenia causes moderate to severe neutropenia in neonatal foals and has been reported in conjunction with ulcerative dermatitis and thrombocytopenia.[6,7] The pathogenesis is similar to neonatal isoerythrolysis, with opsonization of neonatal neutrophils by colostrally derived antibodies resulting in enhanced clearance from circulation. The impaired immunity associated with profound neutropenia places these foals at significant risk for sepsis and other serious infections and must be identified early to allow successful intervention. Administration of exogenous granulocyte colony-stimulating factor (G-CSF) is usually necessary because affected foals often do not produce adequate levels of endogenous G-CSF.[6] Adult immune-mediated neutropenia has been reported in the dog, generally occurring concurrently with ITP and/or immune-mediated hemolytic anemia, but there have been no similar reports described in the horse.[8]

Immunosuppression Associated with Autoimmune Disorders

Siddra Hines • Debra C. Sellon

The etiology of most autoimmune diseases is uncertain but appears to be related to exposure to an environmental trigger in an individual animal or human that is genetically susceptible. Autoimmune disorders may lead to immunosuppression and secondary infection through a variety of mechanisms, including loss of primary infection barriers, loss of critical immune cellular elements, hormonal imbalances, and dysregulation of complex immune responses. Although these types of immunosuppressive syndromes have been infrequently described in horses, they are well documented in other species.

Autoimmune skin disorders causing lesions that impair the skin barrier can predispose affected areas to secondary infection.[1] This is primarily a concern with the large bullae and ulceration occurring in pemphigus vulgaris or bullous pemphigoid, but the risk exists for any skin disease that breaches this important physical barrier to infection. Pemphigus foliaceus, paraneoplastic pemphigus, cutaneous (discoid) lupus erythematosus, and systemic lupus erythematosus (SLE) can all cause lesions that may predispose to secondary infection. This risk may be amplified if the lesions are painful or pruritic, leading to excoriation or self-mutilation.

Systemic lupus erythematosus, rarely reported in horses,[2] may impair cutaneous defense to infection and compromise the adaptive immune system. In humans, SLE causes dysregulation of apoptosis that leads to premature death of peripheral blood mononuclear cells (PBMCs), resulting in leukopenia, particularly lymphopenia.[3] The functionality of T cells in patients with SLE is impaired, with decreased IL-2 secretion and other factors leading to weakened antiviral immunity.[3]

Aplastic anemia and myelodysplastic syndrome, both associated with autoimmune syndromes in humans,[4] have been reported rarely in the horse.[5,6] Severe panleukopenia is seen peripherally, whereas significant bone marrow hypocellularity and myeloid maturation arrest are seen in aplastic anemia and myelodysplastic syndrome, respectively. Profound immunosuppression would be expected to occur with such pathology because immune cells involved in all aspects of innate and adaptive immunity are affected.

Most reports of diabetes mellitus (DM) in the horse have described type 2 (noninsulin-dependent) DM secondary to pituitary pars intermedia dysfunction or equine metabolic syndrome. However, type 1 diabetes mellitus resulting from autoimmune destruction of pancreatic β-cells and subsequent decreased insulin production has been reported.[7] In humans, DM is associated with an increased risk of lower respiratory infections, urinary tract infections, and infections of the skin or mucous membranes.[8] Abnormal function has been documented in neutrophils, monocytes, and lymphocytes, including decreased adherence, chemotaxis, and intracellular killing, as well as impaired phagocytosis and diminished lymphocyte proliferative response.[9] These negative effects have largely been attributed to the impact of poor glycemic control, and it is therefore likely that similar effects could occur with equine DM.

Immunosenescence in Horses

Dianne McFarlane

Definition Immunosenescence is the term describing a multitude of changes in the immune system associated with aging. Reported age-associated changes in the immune system in people include alterations in cell population composition, as well as inadequate or inappropriate immune responses.[1] Immunosenescence is considered to be an important risk factor for the infectious, neoplastic, and inflammatory diseases that accompany aging. Although there are minimal available data, evidence suggests that horses experience similar age-related changes to immune function as people.

An important consideration when investigating age-related changes of immune function is how to define "aged." A study population that is too old may cause one to miss age-related immune defects because the selected population may have survived to extreme old age due to exceptional immune function. It is likely that aging biomarkers may differ between very old horse populations (e.g., horses older than 30 years of age) and less old horse populations, such as horses around 20 years of age. Risk of certain diseases, frailty, or other impairments differ along the spectrum of aging. Finally, it is also important that the comparisons are made between fully mature horses and aged horses.

Clinical Findings There are several important factors that must be considered when evaluating age-induced changes in the immune system. First, it is important to separate age-associated functional changes from disease-induced changes. In an aged population this can be difficult due to the high prevalence of comorbidities that contribute to chronic, low-grade, or occult inflammatory disease. Ideally strict evaluation criteria should be employed. In human

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immunologic research a screening procedure known as the SENIEUR protocol has been developed.[2] This protocol combines a clinical examination, medical and lifestyle history, diagnostic blood analyses, and urinalysis to identify healthy aged individuals for study inclusion. No such standardized protocols have been adopted in veterinary gerontology. In aged horse studies, important additional factors to consider would include endoparasite load and hormone profiles. The high prevalence of pituitary pars intermedia dysfunction (PPID) in the aged equine population, and the immunosuppressive effects of pars intermedia–derived pituitary hormones, make it absolutely critical that endocrine status be reported when evaluating immunosenescence in horses and ponies.[3,4] Other important considerations when assessing immune function in aged horses include diet, medications, nutritional supplements, exercise, season, and environmental conditions of the study participants.

Clinical Pathology Hematologic changes associated with aging in horses and ponies include a lower total white blood count due to a lower total lymphocyte count compared with younger counterparts.[5-8] In addition, there is a decrease in total monocyte and eosinophil counts in aged ponies.[6] The implications of these hematologic changes remain unclear.

Immunologic Findings Age-associated alterations in lymphocyte subset populations have been documented in several species, including people, dogs, and rodents, although inconsistencies in outcomes exist among the various studies.[9-12] Aging has been associated with alterations in subsets of circulating lymphocytes (i.e., $CD4^+$, $CD8^+$, and B cells) in horses and ponies.[5-8,13] The consistent decrease in total circulating lymphocyte populations in aged horses is due to a decrease in total number of $CD4^+$ and $CD8^+$ T cells and B cells,[5-7] although another study reported an increase in the percentage of $CD4^+$ lymphocyte population.[13] The CD4:CD8 ratio is an indicator of whether lymphocyte populations favor an inflammatory or immunosuppressive bias. The CD4:CD8 ratio has been reported to increase, decrease, or remain unchanged in geriatric human populations.[14-16] CD4:CD8 ratio has been reported to be increased in aged horses, suggesting a proinflammatory state, known as *inflammaging*.[7] A robust decrease in peripheral naive T cells has been a consistent finding in numerous studies in people and rodents.[17-20] Thymic involution is considered a likely major contributor to the failure to maintain a naive T-cell pool. In addition, it has been suggested the loss of naive T cells may be the result of lifelong infection by viruses, especially cytomegalovirus or other chronic antigenic stimulants.[21,22] The effect of age on naive T-cell populations has not been explored in the horse.

Serum cytokine profiles in the aged are typically those of a proinflammatory phenotype.[23,24] Aged horses show similar cytokine profiles with increased gene expression of TNF-α, IL-6, IL-1β, IL-8, IFN-γ, IL-15, and IL-18.[7,13] In addition, there are increased proinflammatory-to-antiinflammatory cytokine ratios such as IL6:IL10 and TNF-α:IL10.[25] Serum cytokine concentration of TNF-α was found to be increased in aged horses in one study but not another.[13,25] Confounding factors that might affect serum TNF-α concentration in these and other studies include concurrent illness, inflammation, or season of sample collection.

One of the most consistent findings in immunosenescence is a decrease in the ability of lymphocytes to proliferate. Studies in rodents and people have shown impaired lymphocyte proliferation possibly involving a decrease in serum IL-2 concentration or IL-2 receptor expression.[18,26,27] However, a decrease in lymphocyte proliferation has also been reported independent of these two factors, suggesting defects in intracellular signal transduction may also be a consequence of aging.[28] Horses also experience an age-associated decrease in lymphocyte proliferation, which is not responsive to IL-2 supplementation and not associated with a change in lymphocyte IL-2 receptor expression.[6,13,29] This suggests that similar to what has been observed in people, the age-associated defect in lymphocyte division in horses may be in intracellular signaling.

Several studies have assessed the ability of peripheral blood mononuclear cells (PBMCs) to respond to immune stimulation. Inflammatory response after stimulation of whole blood or PBMCs from healthy aged people results in a greater release of proinflammatory cytokines than that observed in nonaged adults.[30-32] Similar studies in aged horses have revealed an increase in TNF-α and IFN-γ production from PBMCs following stimulation.[13,25]

Although immunosenescence affects primarily adaptive immunity, changes in the innate immunity occur as well. Innate immunity includes the response of neutrophils and macrophages as a first-line defense against pathogens. Age-associated changes in neutrophil function that have been reported in people and rodents include decreases in phagocytosis, oxidative burst, chemokinesis, and chemotaxis, whereas neutrophil numbers appear to be maintained.[33-36] In healthy aged horses, neutrophil adhesion, oxidative burst, and phagocytosis were all found to be unchanged, whereas chemotaxis was increased compared with that observed in healthy adult horses.[37]

One of the major health concerns regarding immunosenescence in people is a failure of the geriatric population to develop an adequate protective titer following vaccination, particularly after influenza virus immunization.[38] As a result, morbidity and mortality due to influenza infection is greatest in the very old. The response of aged horses to influenza vaccines has also been reported to be less robust than that of young or adult horses in several studies.[6,39] Muirhead and colleagues[39] reported a decrease in immunoglobulin subisotypes IgG2 (former IgGa) and IgG4 (former IgGb) in aged horses, although single radial hemolysis titers suggested both adults and aged horses had adequate response that was protective. Using a different vaccine, Horohov and colleagues[6] reported a 10-fold decrease in resultant titers in aged ponies compared with nonaged adults, but it is not clear if adequate titers were achieved in either group. Response to naive antigenic challenge has also been examined in horses older than 20 years of age. Contrary to what has been reported in primates, the magnitude of a primary antibody response did not decline with age.[39-42] When a rabies vaccine was administered to aged horses naive to rabies vaccine, the antibody titer after both the initial and second immunization did not differ from that of nonaged adult horses. However, in this study 80% of both the control and aged population had low serum selenium concentrations, which could result in a suboptimal vaccine response in both groups. Further studies are necessary to clarify the ability of aged horses to respond to naive and anamnestic vaccinations and challenges and to assist in the development of ideal vaccination protocols for geriatric horses.

Diseases Caused by Allogeneic Incompatibilities (Horses and Ruminants)

Jill R. Johnson

The surfaces of cells are covered with molecular structures, the presence or absence of which are determined by genes. Some of these molecules have limited heterogeneity within a species, and all members of the species share identical forms (monomorphic). In other cases a spectrum of minor structural variations or polymorphisms of a particular molecule occur within the population, so some members of the species will have one form of the molecule, whereas others will have another. If the structural variations are such that the immune system of one individual can recognize the differences in the molecules from another individual, these are known as alloantigens. Antibodies produced against these antigens are alloantibodies. Examples of alloantigens include red blood cell antigens and lymphocyte antigens.

In nature, because there are few situations in which tissues are exchanged, there are relatively few naturally occurring diseases that involve allogeneic incompatibilities. Neonatal isoerythrolysis (NI), neonatal alloimmune thrombocytopenia (NAIT), and alloimmune

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neonatal neutropenia (ANN) are three examples of such naturally occurring diseases. Blood transfusion reactions and organ transplant rejection are examples of iatrogenic diseases associated with allogeneic incompatibilities.

The same alloantibodies that mediate disease are also useful in vitro as reagents for the detection of the presence of alloantigens and serve as the basis for blood typing.

Blood Typing and DNA Profiling

The blood type of an individual is actually a composite list of genetic markers that have been detected in the blood of an individual. Several kinds of genetic markers have been used in blood typing, including red blood cell alloantigens, electrophoretic markers, and lymphocyte alloantigens. Polymorphisms of the DNA itself have emerged as useful genetic markers and have essentially replaced other genetic tests for parentage verification.

Red Blood Cell Antigens

Seven independent red blood cell groups or systems have been internationally defined in horses under the auspices of the International Society for Animal Genetics.[1-4] (Tables 53-9 and 53-10). These systems are named A, C, D, K, P, Q, and U. Additional systems are recognized by individual laboratories. Each system corresponds to a particular gene for which two or more alleles exist. Some blood groups are relatively simple and contain only two alleles, whereas other systems may have more than two dozen different alleles.

TABLE 53-9

Domestic Animal Blood Groups[1,3]

Species	Blood Group Systems
Equine	A, C, D, K, P, Q, U
Bovine	A, B, C, F, J,* L, M, R′, S, T, Z
Ovine	A, B, C, D, M, R,* X
Caprine	A, B, C, M, J*

From Suzuki Y. 1990. Stormont Laboratories, Inc., Woodland, California. Personal communication.

*Soluble antigens.

TABLE 53-10

Blood Group Systems, Factors, and Alleles of the Horse Recognized by the International Society for Animal Genetics

System	Factors	Recognized Alleles
A	a,* b†, c, d, e, f, g	Aa, Aadf, Aadg, Aabdf, Aabdg, Ab, Abc, Abce, Abe, Ac, Ace, Ae, A–
C	a	Ca, C–
D	a, b†, c†, d, e, f, g†, h, i, k, l, m, n, o, p, q, r	Dadl, Dadlnr, Dadlr, Dbcmq, Dcefgmq, Dcegimnq, Dcfgkm, Dcfmqr, Dcgm, Dcdmp, Dcgmq, Dcgmqr, Ddeklqr, DeIno, Ddeloq, Ddelq, Ddfkir, Ddghmp, Ddghmq, Ddghmqr, Ddki, Ddlnq, Ddlnqr, Ddlqr, Ddno, Dq,(D–)
K	a	Ka, K–
P	a†, b, c, d	Pa, Pac Pacd, Pad, Pb, Pbd, Pd, P–
Q	a*, b, c†	Qa, Qab, Qabc, Qac, Qb, Qbc, Qc, Q–
U	a†	Ua, U–

From Cothran G. 1996. University of Kentucky, Lexington, KY. Personal communication.

*Most common factors involved in neonatal isoerythrolysis (NI).

†Previously reported to cause NI in at least one case.

The blood group genes produce surface molecules that contain antigenic sites known as *factors.* More than 30 different factors have been identified. Each factor is associated with only one system, although the same factor may be associated with more than one allele within the system. The factors are named with an uppercase letter to denote the system and a lowercase letter to designate the factor within that system. Groups of factors that are produced by a single allele are called *phenogroups.*

The presence of red blood cell antigens is detected primarily by either agglutination or complement–mediated lysis of test cells by antibodies directed against specific red blood cell alloantigens. Antigens in some systems are detected with antiglobulin tests.

Eleven blood groups have been identified in cattle [5] (see Tables 53-9 and 53-11). In cattle, groups B and J have the greatest clinical relevance. The B group is a complex system with more than 60 different antigens.[6] This complexity has been used to advantage for individual animal identification and parentage studies in the past, but it makes it difficult to closely match donor and recipient blood for transfusions.

The J antigen, a lipid found in body fluid, is adsorbed to erythrocytes; thus it is not a true erythrocyte antigen. Newborn calves do not have this antigen but usually acquire it during the first 6 months of life. After acquiring it, some groups of cattle have high amounts of J antigen both in the serum and adsorbed to erythrocytes, whereas other groups have small amounts found only on erythrocytes. These latter groups, often referred to as *J negative,* may actually have anti–J antibodies and develop transfusion reactions when transfused with blood from J-positive donors.[1]

Seven blood groups have been identified in sheep (see Table 53-9). The B system is analogous to the B system in cattle and is extremely polymorphic, with more than 52 different alleles. The R system is similar to the J system in cattle in that the antigens are soluble and are passively adsorbed to erythrocytes.[5] The M-L system is involved in the genetically determined red blood cell potassium polymorphism found in sheep.[7]

Blood groups of goats appear to be similar to those of sheep, and many of the reagents used for typing sheep blood have been used to type goats' blood. Reagents used to detect antigens of the J system of cattle have been used to detect differences in a similar system in goats.[8]

The biologic function of red blood cell antigens is not known for any system in any species with the exception of the M-L blood group system in sheep, which is involved in active potassium transport across red blood cell membranes.

TABLE 53-11

Blood Group Factors of Cattle Recognized by the International Society for Animal Genetics

System	Factors
AA*	A1, A2, H, Z, a
F*	F, V
J	J, j
L	L, l
M	M, m
Z	Z, z
R″	R′, S′
B†	B, G1, G2, G3, l1, l2, K, O1, O3, OX, Pl, P2, Q, T, Y2, A′, B′, D′, E1′, E2′, E3′, G′, I1′ (I′), I2′, Jl′, J2′, K′, O′, P1′, P2′, Q′, Y′, A″, B″, G″, I″
C	C1, C2, R1, R2, W, X, X2, L′, E1, C′, C″, X′, Fl, F6, F10, Fl5
S	S1, S2, U, H′, U′, S″, U″
T	

*Cases of neonatal isoerythrolysis associated with production of anti-red blood cell antibodies against factors in response to anaplasmosis and *Babesia* vaccines.

†Additional factors are recognized by individual laboratories.

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TABLE 53-12

Examples of Polymorphic Proteins Used in Blood Typing

Protein	System	Source
AlB glycoprotein	AlB	Serum
Albumin	ALB	Serum
Transferrin	TF	Serum
Carboxylesterase	ES	Serum
Vitamin D–binding protein	GC	Serum
Protease inhibitor	PI	Serum
Peptidase A	PEPA	Serum
Plasminogen	PLG	Serum
Glucose phosphate isomerase	GPI	Red cells
6-Phosphogluconate dehydrogenase	PGD	Red cells
Phosphoglucomutase	PGM	Red cells
Catalase	CAT	Red cells
Carbonic anhydrase	CA	Red cells
Acid phosphatase	AP	Red cells
Hemoglobin-a	HBA	Red cells
NADH diaphorase	DIA	Red cells

NADH, Reduced nicotinamide adenine dinucleotide.

Electrophoretic Markers

Many plasma and intracellular proteins have polymorphic forms. These variants have subtle biochemical differences, which for the most part do not alter the major characteristics of the molecules but which can be detected using electrophoretic methods. These are not technically alloantigens because the differences are not detected immunologically. The various forms of the molecules are detected on the basis of their different rates of migration in electrophoresis. The specific form(s) of any particular protein that an individual possesses are determined genetically, and those used in blood typing are usually expressed codominantly. Currently no diseases are clearly associated with the presence or absence of particular alleles of polymorphic proteins; however, they are useful genetic markers for identification and parentage studies and were commonly included in the blood type (Table 53-12).[3,8-10] Electrophoretic markers were used extensively in horses because red blood cell antigens did not provide the same degree of discrimination among individuals in this species as they do, for example, in cattle. The current application is limited to legacy parentage verification when parental DNA is not available for testing.

Lymphocyte Antigens

Three systems of equine lymphocyte alloantigens have been described: ELA, ELY 1, and ELY 2.[11-15] ELA is the major histocompatibility complex (MHC) of the horse. ELA is a complex system that includes several genes, each of which is polymorphic (e.g., has many different alleles). Because the MHC regulates the interactions of many cells in the immune response, a potential for the association of disease susceptibility or resistance with ELA exists. An association between a particular ELA allele and equine sarcoid has been described.[16,17] ELY I and ELY 2 have limited polymorphism and appear to be two allele systems.

The MHC of cattle is called BoLA, for bovine lymphocyte antigen. In sheep the MHC is called OLA for ovine lymphocyte antigen and is also known as SH-LA. In goats the comparable system is GLA.[18]

DNA Polymorphisms

A wide variety of approaches has been developed for detecting genetic variation using deoxyribonucleic acid (DNA). Certainly DNA sequencing is the most sensitive approach; however, this remains too costly for routine testing outside of research laboratories. Other approaches have been developed to detect DNA variants. Genetic variation of DNA can be detected among individuals on the basis of differences in length for a section of DNA or even for differences in base composition at specific sites. DNA length variants are usually referred to as *minisatellite* or *microsatellite markers.* Minisatellite DNA markers are based on sequences, often 15 to 100 bases long, that may be repeated hundreds of times on a chromosome. The number of repetitions can vary dramatically among individuals and can be readily detectable in Southern blotting assay. These tests were originally referred to as *DNA fingerprinting.* Although they are powerful, these tests are costly and time consuming. More recently, another type of DNA length variant has been discovered. Microsatellite DNA markers are short repetitions of nucleotides, usually ranging from one to nine bases long, which may be repeated 15 to 40 times. As with minisatellites, the number of repetitions may vary among chromosomes. The development of the polymerase chain reaction (PCR) has opened the door to easy, cheap detection of microsatellite and other types of markers. PCR is a method for amplifying short (fewer than 3000 bases, optimally 300 to 1000 bases) pieces of DNA, making it possible to easily study a particular gene. The amplification products can be separated by electrophoresis and length variants readily detected. More than 100,000 of these markers are thought to exist in each species. These markers form an important core for development of genetic maps in diverse species. These markers currently form the basis for most parentage analysis.

Variation recognizable as a change in a single base of DNA is more subtle but can be detected through a variety of techniques. DNA sequence variation is often detectable using restriction enzymes. Restriction enzymes are isolated from bacteria and will cleave DNA when the sequence is specific for the enzyme. For example, the method to detect the gene defect causing hyperkalemic periodic paralysis (HYPP) in horses is based on PCR amplification of the gene and then detection of sequence differences that occur between the normal and mutant gene using restriction enzyme digestion of the DNA. Other approaches to identifying DNA sequence differences include single-stranded conformational polymorphism (SSCP), allele-specific PCR amplification, and ligase chain reaction.

DNA-based testing has essentially replaced blood typing for purposes of parentage analysis. Furthermore, these techniques are also being used to develop gene maps for many species of domestic animals. These gene maps can be used to identify genes that play a role in performance, production, and disease.

Blood Typing and DNA Genotyping Applications

To determine an animal's blood type or DNA genotype, a battery of different tests is run on the blood or tissue to check for the presence or absence of each recognized allele in each of several genetic systems. Each system is controlled by a separate autosomal gene. These genes are inherited independently of one another.[4,15] Most genetic markers used in blood typing are expressed codominantly, which means that the alleles on both chromosomes are expressed. This often allows determination of genotype (the actual genes present) from the phenotype (the antigens actually detected). Some systems have null alleles with no detectable products that do not directly allow inference of genotype (e.g., C, K, and U blood group systems in horses). An individual can have only two of the possible different alleles for any given gene (one on each chromosome of a pair).

Blood typing based on red blood cell antigens and electrophoretic markers has been used for animal identification and pedigree analysis, but currently red cell typing is used primarily for prediction of potential for NI and crossmatching for blood transfusion.

The use of genetic markers for parentage verification is based on exclusion (i.e., markers are tested until a discrepancy is found). If no discrepancy is observed after a statistically acceptable amount of testing, the probability of a match is determined.

Because genetic testing is a composite mosaic of a large number of different, largely independent genetic markers, the odds of two individuals sharing exactly the same pattern of markers, whether red blood cell antigens, electrophoretic markers, or DNA polymorphisms, is remote. Thus once an animal's genetic type is on record, it can be a powerful identifier of an individual animal. In this sense it

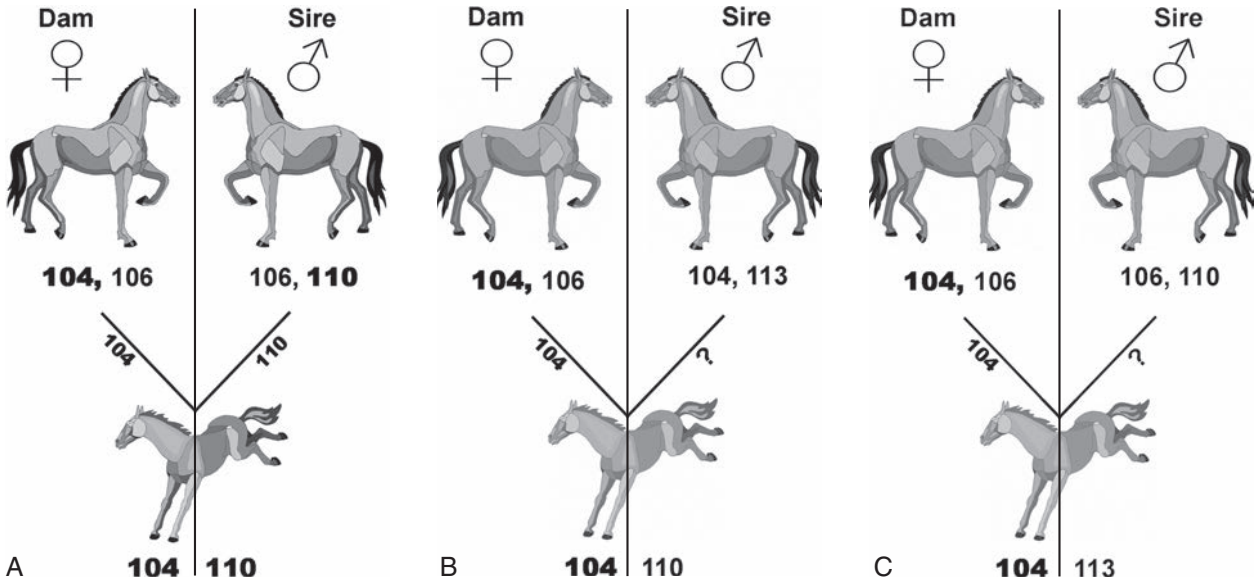


FIG. 53-7 **A,** The sire of this foal cannot be excluded as the sire of the foal on the basis of the results for the DNA marker VHL20. **B,** The sire of this foal is excluded by a type I exclusion. The foal possesses an allele for the DNA marker VHL20 not present on either parent. Assuming that the dam of the foal is known to be correct and therefore would have contributed the 104 allele to the foal, the sire must be incorrectly stated. **C,** The sire of this foal is excluded by both a type I and type II exclusion. The foal possesses an allele not present on either parent and also does not possess either allele expressed by the putative sire.

is an unalterable form of identification that is present from birth to death.

Because the presence or absence of markers is genetically determined and because the markers contributed by both parents are expressed in a codominant fashion (unless "blank" alleles exist), these markers can be used to support or refute parentage claims. Blood typing and DNA profiling cannot prove that one horse is the parent of another; however, in certain instances it can exclude with certainty a stated parent as the true parent. Two types of parentage exclusions can occur, type I and type II[19] (Fig. 53-7). With type I the foal possesses a dominant or codominant marker that is not present in either parent. This means that at least one of the stated parents is incorrect. If one parent (usually the dam) is known with certainty on the basis of circumstances other than genetic type, the error lies with the other stated parent. With type II exclusions, the foal does not possess either of the dominant or codominant markers of a stated parent. Because a foal must inherit one of the two markers expressed by each parent, exclusion can be made if neither of the two markers present on the stated parent is detected in the foal. In parentage cases, each genetic system is evaluated for type I and type II exclusions. A parent can be excluded on the basis of an inconsistency in even one system. For this reason, the more systems that are used the better genetic typing becomes as a tool for solution of parentage disputes. The calculated effectiveness of blood typing for detecting incorrect paternity using 20 internationally defined systems in horses is as high as 96%.[3,9,20] With DNA genotyping, effectiveness is as high as 99.998%.[21-23]

Laboratories that provide DNA genotyping in North America are listed in Box 53-1.

Neonatal Isoerythrolysis

Equine

Definition and Etiology Neonatal isoerythrolysis (NI) is a condition characterized by the destruction of red blood cells (RBCs) in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[2,24,25]

Production of alloantibodies can be stimulated in mares several ways, including transfusion, exposure to blood from the foal during parturition, or as a result of placental pathology during gestation. Incompatibilities of at least some blood groups between the dam and foal are the rule rather than the exception, and yet the incidence of sensitization of the dam and occurrence of NI is relatively low. In Thoroughbreds the prevalence is about 1%, and in Standardbreds the incidence is about 2%.[26] The prevalence in mules (donkey sire, horse dam) has been reported to be as high as 10%.[2] Most blood groups are not strongly antigenic under the conditions of exposure via previous parturition or placental leakage. Several blood group factors, however, are particularly immunogenic, and antibodies against these antigens have been reported to cause nearly all cases of NI. These include factor Aa in the A system and factor Qa in the Q system. In mules a unique donkey RBC antigen named donkey factor has been associated with NI.[27] Antibodies to these antigens develop after the exposure of the mare to RBCs and are not naturally occurring antibodies. In humans the absence of certain RBC antigens results in the production of natural antibodies against that antigen, presumably because of exposure to cross-reacting antigens in the diet. This does not occur in horses with a few exceptions and has not been associated with NI. Ca-negative (Ca–) horses frequently make anti-Ca antibody of low titer without known RBC exposure. However, anti-Ca antibody is generally not associated with NI, and in fact mares with anti-Ca antibody actually appear less likely to develop certain antibodies responsible for NI.

For NI to occur, several things must happen (Figs. 53-8 and 53-9). First, the dam must be negative for the antigen in question. Because most cases of NI in horses are associated with either anti-Aa or anti-Qa antibodies, mares that are Aa–, Qa–, or both are considered at risk. All horses appear to lack donkey factor; thus all mule pregnancies are considered at risk. Second, the mare must become sensitized and produce antibody to the offending antigen. Sensitization can be caused by exposure during a previous pregnancy, blood transfusion, or transplacental contamination with fetal RBCs earlier in the current pregnancy (rare). Third, the foal from the current pregnancy must have inherited from its sire the antigen(s) to which the mare has been sensitized. When these conditions are met, there is a significant potential that maternal antibody directed against the foal's RBC antigens will appear in the colostrum and, if subsequently ingested and absorbed by the foal, could cause loss of RBCs. The higher the anti-RBC titer is at foaling, the higher the risk. The highest titers are likely to be produced in a previously sensitized mare that is reexposed to the same RBC antigens shortly before parturition.

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BOX 53-1

Laboratories Providing DNA Genotyping Services in North America

Animal Genetic Testing and Research Laboratory
108 Gluck Equine Research Center
University of Kentucky
Lexington, KY 40546
(859) 218-1212
www.ca.uky.edu/gluck/AGTRL.asp
(Horses)

Animal Genetics, Inc.
1336 Timberline Road
Tallahassee, FL 32312-1766
(866) 922-6436
www.horsetesting.com
(Horses)

Maxxam Analytics
Animal DNA Laboratory
335 Laird Road, Unit 2
Guelph, Ontario
N1H 6J3
Canada
(519) 836-2400
http://maxxam.ca/services/dna-testing/animal-dna-testing
(Horses and cattle)

Zoetis Genetics
333 Portage Road, Building 300
Kalamazoo, MI 49007-9970
(269) 833-4744
www.zoetis.com/products-services/genetics
(Cattle)

Igenity
4665 Innovation Drive
Suite 120
Lincoln, NE 68521
(402) 435-0665
www.igenity.com
(Cattle)

Genetic Visions, Inc.
3220 Deming Way #160
Middleton, WI 33562
(608) 662-9170
www.geneticvisions.net
(Cattle)

Veterinary Genetics Laboratory
University of California, Davis
PO Box 1102
Davis, CA 95617-1102
(530) 752-2211
www.vgl.ucdavis.edu
(Multiple species)

Molecular Cytogenetics and Genomics Laboratory
Department of Veterinary Integrative Biosciences
Texas A&M University
Room 314B, Bldg. 1197 (VRB)
College Station, TX 77843
(979) 862-2879 or (979) 458-0520
http://vetmed.tamu.edu/vibs
http://vetmed.tamu.edu/labs/cytogenics-genomics
(Multiple species)

SRC Genserve Laboratories
125-15 Innovation Blvd.
Saskatoon, Saskatchewan S7N 2X8
Canada
(306) 933-7700
src.sk.ca
(Multiple species)

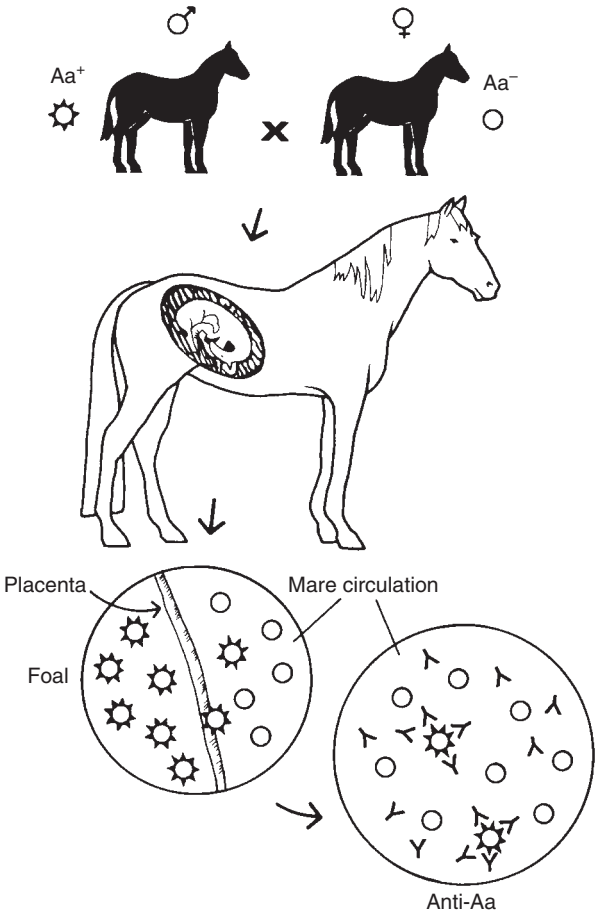


FIG. 53-8 Entrance of red blood cells of paternal antigen type into maternal circulation stimulates the production of alloantibody, and consequently the presence on alloantibodies in the mare's serum and in the colostrum.

Clinical Signs and Differential Diagnoses Foals are born healthy and usually begin to develop signs of NI at 24 to 36 hours of age, after suckling. Progressive lethargy and weakness are early signs. In acute cases, mucous membranes show initial pallor that is followed by icterus. In severe cases, hemoglobinemia and hemoglobinuria may be pronounced. In peracute cases, death may precede the development of icterus. Breathing becomes rapid and shallow, followed by labored breathing as the disease progresses. The foals may yawn repeatedly. Heart rate is elevated. Seizure-like activity may occur as the anemia becomes more severe.

Clinical Pathology Affected foals are anemic. All indicators of RBC concentration (packed cell volume [PCV] hemoglobin, RBC count) show significant decreases. PCV values often decline into the teens, and values as low as 5% have been observed. Hemoglobinemia and hemoglobinuria may be present. Bilirubin (mainly unconjugated) levels will be increased as a result of accelerated RBC destruction. Total bilirubin levels may be close to 20 mg/dL in severe cases. Affected foals, especially mule foals, may also be thrombocytopenic.[4]

Demonstration of significant amounts of alloantibodies in the colostrum (or serum from the mare) that are directed against the RBC antigens expressed by the foal provides a definitive diagnosis of NI. These antibodies are most commonly demonstrated by lytic and agglutinating tests. Lytic tests are believed to be more reliable indicators of the presence of offending antibody.[28] The presence of antibodies attached to the foal's RBCs can also be demonstrated with a direct antiglobulin test (Coombs test). The presence of antibodies in the mare's serum that attach to RBCs can be demonstrated with an indirect antiglobulin test.[2]

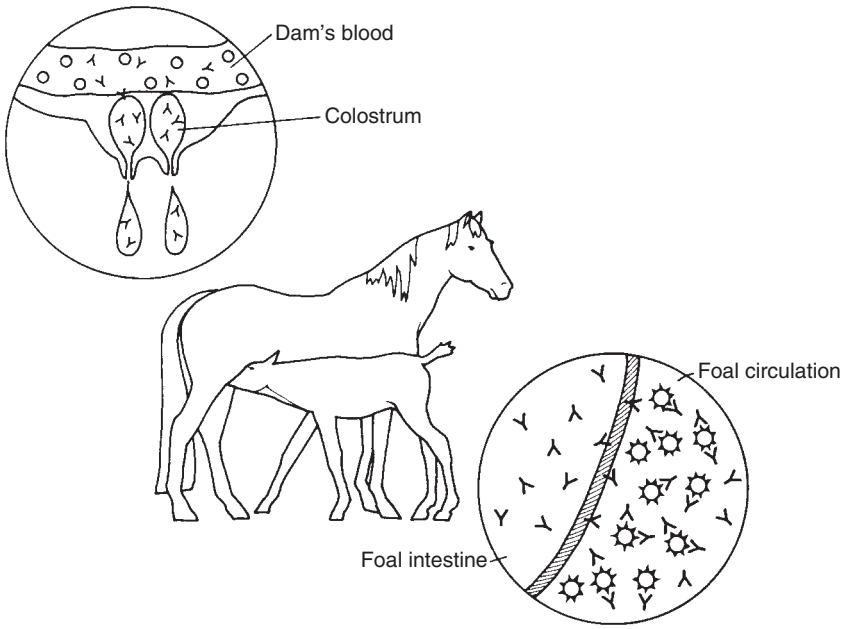


FIG. 53-9 Alloantibody in the mare's serum is concentrated in colostrum at the end of gestation. Through passive transfer, the foal absorbs immunoglobulins, including these alloantibodies. The antibodies attach to red blood cells and cause either premature removal from circulation or intravascular lysis.

Pathophysiology In mares sensitized to RBC antigens, most commonly Aa or Qa, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's RBCs carry the antigen that the antibody recognizes, the cells become antibody coated. Subsequently they are removed prematurely by the reticuloendothelial system or lysed intravascularly by complement. A distinction has been made between antibodies that are lysins as opposed to agglutinins; however, this distinction is based on in vitro testing and may be somewhat artificial. Under appropriate laboratory conditions, offending antibodies may exhibit both abilities.[26] However, with conventional agglutination tests some alloantibodies capable of producing NI may go undetected.[10]

Epidemiology The percentages of mares at risk for sensitization against the common offending antigens (Aa and Qa) vary among breeds, depending on the frequency in the population of each gene involved (Table 53-13). Increased numbers of mares at risk in a breed do not necessarily translate into higher numbers of NI cases. A corresponding number of stallions lack the factors in question and are therefore unable to sire foals with the offending antigen.[25] Virtually all mule pregnancies are incompatible with regard to donkey factor.[27]

Although the disease is more common in multiparous mares, NI can occur with the first pregnancy.

Necropsy Findings Liver failure, kernicterus, and complications related to bacterial sepsis are the most important causes of death in foals dying from NI.[29] Pale tissues with or without icterus and splenomegaly are characteristic necropsy findings. Lesions associated with RBC destruction and anemia, such as nephrosis and centrilobular hepatic necrosis, may also be present.

Treatment and Prognosis In most cases, by the time the problem is recognized clinically (e.g., when the foal is about 24 hours of age), the bulk of colostral antibody will have been depleted from the mare's milk and the absorptive ability of the foal's gut will have diminished. Withholding milk at this point is of questionable benefit.

Stress should be minimized and exercise restricted. Affected foals have decreased exercise tolerance and can collapse and die if forced to follow their dams. Generalized supportive care should be administered as indicated by clinical parameters. Intravenous fluids are frequently indicated to promote diuresis to minimize the effects of the large hemoglobin load presented to the kidneys. Acid-base balance should be monitored and corrected if indicated.

If the anemia becomes severe (e.g., PCV = 10% to 15%), transfusions that provide RBCs should be considered. Unless the PCV drops below this level, transfusion may not be necessary if rest is enforced. The object of transfusion is to provide the affected foal with RBCs that will not be destroyed by the maternal alloantibodies that were absorbed from colostrum. The foal is immunologically naive and will not have autologous alloantibody directed against any RBCs that would have an immediate effect on transfused RBCs. Thus the key is to select an RBC donor whose cells will not be destroyed by the maternal antibody derived from colostrum. Crossmatching, with particular attention to the reaction of mare sera, colostrum, and foal sera (all contain the same antibody), with the donor RBCs, is important for selecting a cell that will not be destroyed by the maternal antibody.

Washed RBCs from the dam are obviously the perfect choice in terms of cells that will not react with the alloantibodies present in the foal. However, to avoid administering additional harmful antibody to the foal, the mare's sera (containing antibody against the foal's cells) must be removed by washing before administration. Up to 6 to 8 L of blood can be collected from the mare and anticoagulated with acid-citrate-dextrose (ACD) or sodium citrate (3.8% NaCitrate solution; 1 part NaCitrate/9 parts blood), although 3 to 4 L usually

TABLE 53-13

Estimate of the Percentage of Mares in Selected Breeds That Are "At Risk" for Producing a Foal with Neonatal Isoerythrolysis*[26]

Breed	At Risk for Aa	At Risk for Qa
Thoroughbred	2%	16%
Standardbred—pacer	22%	†
Standardbred—trotter	3%	†
American Saddlebred	25%	88%
Quarter Horse	25%	68%
Arabian	3%	72%

*Based on the lack of all alleles that include factors Aa or Qa.

†Mares all lack factor Qa and are technically "at risk," but all Standardbred stallions also lack the factor.

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provide sufficient RBCs. The preparation of large volumes of washed cells is aided by a large-volume centrifuge, but the procedure can be accomplished by serial sedimentations. Anticoagulated blood from the mare is allowed to settle for 1 to 2 hours. The plasma is aseptically drawn off, a similar or greater volume of sterile isotonic saline (0.9% NaCl) is added to the RBCs and mixed, and the RBCs are again allowed to settle. The saline is then drawn off and discarded. At this point the RBCs can be resuspended in an equal volume of isotonic saline for administration, or the washing procedure can be repeated. The sedimentation method is less desirable than centrifugation because it is slower and does not remove as much of the offending antibody. The aim is to dilute any harmful antibody to insignificant levels.

If it is not possible to use the dam's RBCs, alternative donors can be selected. The donor should lack the antigen to which the alloantibody is directed. Because it is generally not possible to blood type donors on short notice, a previously identified horse that has been determined by blood typing to be Aa–, Qa–, and free of alloantibody is a good choice for a donor because most cases of NI are associated with these two antigens. The odds of randomly selecting a donor that lacks the offending type (e g., Aa–, Qa–, or both) and would therefore be a suitable donor vary significantly with the breed and would mirror the percentage of the population of mares at risk. For example, the odds of finding an Aa– Thoroughbred to serve as an RBC donor would be about 1 in 50 (2%), whereas in Quarter Horses the odds would be about 1 in 4 (25%) (see Table 53-13). The sire of the foal is not the donor of choice. He shares the same RBC antigens as the foal, and his cells will react with the maternal alloantibody present, adding more of a load to the foal's reticuloendothelial system as they are destroyed.

In the case of mules the same considerations in the use of washed cells would be necessary if the dam's cells were used. However, because the offending antibody is generally directed against a unique donkey antigen, it appears that RBCs from any horse would be satisfactory. Horses do not appear to make naturally occurring antibodies against donkey factor; therefore in most cases it is not necessary to wash the cells from horses that would not be likely to have been immunized by pregnancy against donkey factor.

Transfusion of RBCs that will not react with maternal alloantibody means introducing an obviously incompatible cell into the foal, a cell that will probably not survive for long periods of time in the circulation. Such transfusions should be considered temporary stopgap measures. Transfused cells may also sensitize the foal to future transfusions, causing reactions (perhaps not within hours or a few days, but potentially within a week). This must be considered when weighing the potential good versus potential harm of such transfusions.

To produce clinical improvement, 1 to 4 L of washed RBCs or whole blood are usually adequate, although some cases may require repeated transfusion if the anemia progresses. Exchange transfusions can be done whereby blood is administered via one jugular and withdrawn simultaneously from the opposite jugular and discarded, allowing administration of large volumes of blood without overloading the vascular system. There is no good evidence to suggest that this is more effective than simply providing a source of RBCs that are unaffected by the maternal antibody.

Limited transfusion studies in adult horses have suggested that transfused RBCs do not survive long in circulation (e.g., 2 to 4 days), whereas in foals, cells survived slightly longer (e.g., 4 to 6 days).[30-31] PCVs in foals with NI commonly increase following transfusion and then gradually decline. This decline is probably not great cause for concern if it is gradual because the PCV of the foal generally levels off as the offending maternal antibody is metabolized. However, even short-term survival of cells may be of benefit in severely affected foals and may allow them to survive until the titer of maternal anti-RBC immunoglobulin has declined in the circulation. Hepatic failure in foals administered blood transfusions may be the result of iron intoxication. Administration of drugs that increase iron excretion, such as deferoxamine mesylate, are of potential value.[32]

The prognosis varies, depending on the quantity of antibody ingested, the rapidity of onset of signs, and the degree of anemia. Peracute cases may die before the problem is recognized, with no chance for administration of therapy. Foals that develop the condition more slowly may respond to supportive care or transfusion if the PCV continues to fall.

Prevention and Control Several strategies are available for prevention of NI.[33,34] First, identify broodmares at risk for development of NI by testing them for the presence of Aa and Qa. Mares negative for either antigen, which means they could potentially make antibodies against them, should be considered at risk. One subsequent strategy would be to breed at-risk mares to Aa/Qa-negative stallions, thus eliminating the possibility of the foal inheriting the offending antigens. However, in breeds in which a relatively small part of the population is negative for these antigens, identifying a stallion that is negative for these antigens and suitable on the basis of other criteria may be difficult. The percentage of at-risk females based on the presence or absence of Aa or Qa is somewhat balanced by the numbers of males able to transmit the offending antigen. For example, all Standardbred mares would be considered at risk because of the absence of Qa; however, because the antigen Qa is not present in the Standardbred population, no stallions have the Qa antigen to pass on to foals.

In the circumstance of unknown or incompatible matings, sera from at-risk mares should be screened for the presence of anti-RBC antibodies within 30 days before foaling. This can be done by submitting a serum sample and an anticoagulated sample to a screening laboratory. A panel of 10 to 12 different RBCs selected to represent all major blood groups is adequate to screen for anti-RBC antibody in the absence of blood from the sire. If results of serum testing are equivocal (e.g., low but positive titer, especially if there is anti-Aa or anti-Qa activity), the test should be repeated closer to the time of parturition because the levels of offending antibody can rise quickly late in gestation.

If anti-RBC antibody is detected in the mare before parturition, the colostrum should be checked for reactivity against the foal's RBCs before allowing the foal to ingest colostrum. An alternative source of colostrum should be provided to the foal. Most field screening tests of colostrum have not proved to be satisfactory for practical use; however, the jaundiced foal agglutination (JFA) test described in Box 53-2 has been shown to correlate well with the standard hemolytic assay, and it may detect antibody that does not react on the standard agglutination tests.[7]

Horses negative for Ca frequently make anti-Ca antibody; however, this antibody is not known to produce adverse effects in the foal. It has clouded the issue of field screening tests for NI because it commonly causes positive reactions in most screening tests at low dilutions. Because these tests do not differentiate between antibody to Aa, Qa, Ca, or any other blood group, anti-Ca antibody, when present in low dilutions, is responsible for many false-positive reactions. This antibody actually appears to play a protective role in the prevention of sensitization of mares to NI through a mechanism of antibody-mediated immune suppression. Aa–/Qa– mares that are also Ca– (and thus often produce anti-Ca antibody) become sensitized to Aa and Qa at a significantly lower rate than mares that are Ca+.[35] This is attributed to the fact that anti-Ca antibody is produced by Ca– mares. The anti-Ca antibody may more rapidly remove potentially sensitizing cells from the circulation before they stimulate production of antibody against Aa or Qa.

Uncommonly, other antigens have been associated with NI in foals. These include factors Db, Dc, Dg, Ua, Pa, Qc, and Ab.[2,4,35-39] Two other factors, R and S, have been described to be associated with NI, but they are not detected by routine hemolytic or agglutinating methods and are only detected using an antiglobulin test (direct Coombs test).[24] Because of the difficulty in testing for these antigens, there has never been sufficient agreement among laboratories to allow international designation. These antigens may not be detected using the JFA screening test.[25] Estimates are that 1 in 2000

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BOX 53-2

Jaundiced Foal Agglutination Test (JFA Test)[44,45]

Materials

1. Centrifuge capable of spinning 300 to 600× gravity
2. Test tube rack
3. Test tubes: 13 × 100 mm disposable or blood collection tubes
4. Pasteur pipettes and rubber bulbs or other pipette system to deliver 1-mL volumes
5. Isotonic (0.9%) saline at room temperature
6. Serum or colostrum from the mare; RBCs from mare and foal, preferable in EDTA anticoagulant

Methods

1. Collect colostrum from the mare.
2. Collect an EDTA-anticoagulated blood sample from the foal before nursing.
3. Set up six tubes and add 1 mL of saline to each tube. Label the tubes Control, 1:2, 1:4, 1:8, 1:16, and 1:32.
4. Make serial dilutions of the colostrum at 1:2, 1:4, 1:8, 1:16, and 1:32 in five of the tubes. Add 1 mL of colostrum (or serum) to the tube labeled 1:2 and mix. Then take 1 mL from that tube and add it to the second tube labeled 1:4 and mix. Take 1 mL from that tube and add it to the third tube labeled 1:8, and so on until all five dilution tubes have been filled. Discard 1 mL from the last tube labeled 1:32.
5. Add 1 drop of the foal's whole blood to each of the six tubes and mix.
6. Centrifuge the tubes for 2 to 3 minutes at a medium speed (300 to 500× gravity).
7. Invert each tube, pouring out the liquid contents; observe the status of the button of RBCs at the bottom of the tube. Complete agglutination causes the cells to remain tightly packed in the button; strong agglutination causes the cells to remain in large clumps; for weaker agglutination the cells are in smaller clumps as they run down the side of the tube. When there is no agglutination, the cells easily flow down the side of the tube. This should be the case in the control tube. If the cells in the control tube are clumped, they may be autoagglutinating and the results will have questionable validity.

   If there is a positive reaction with the foal's cells, the test should be run with the dam's own RBCs to be certain that neither the conditions of the test nor the viscosity of the colostrum is causing the agglutination.

   Positive reactions at 1:16 or greater are considered significant. At levels of 1:16 or greater, this test correlates well with the standard hemolytic assay. At dilutions of less than 1:16 the correlation is not as good, and more false-positive results will be recorded. Also, other factors such as the viscosity of colostrum make less diluted samples more difficult to read.

EDTA, Ethylenediamine tetraacetic acid; *RBCs,* red blood cells.

pregnancies may result in sensitization against some other antigen besides Aa or Qa. Because these cases occur so infrequently, it is not practical to consider mares without these antigens to be at risk for NI. A blood-type evaluation of mares with a history of production of foals with NI should be done to identify the offending antibody/antigen.

A list of laboratories providing NI screening tests (e.g., Aa, Qa, and Ca typing and screening of sera for alloantibody) is given in Box 53-3. Routine agglutinating crossmatch tests using mare serum or colostrum and foal or sire cells can be performed by most veterinary or human hematology laboratories.

Ruminants

NI is not a naturally occurring disease in cattle, sheep, or goats. Its occurrence in cattle has been associated with administration of vaccines derived from blood origin, such as certain anaplasmosis and babesiosis vaccines.[2] When these vaccines are used on breeding females, they may sensitize the dam to certain blood groups, most commonly in the A and F systems. Under chance circumstances, if the blood types of the sire and offspring reflect these systems and the dam has produced alloantibodies, an isoimmune hemolytic crisis may appear in the calf associated with successful passive transfer. Hemolytic crises are rare in sheep and are even difficult to induce experimentally.[2]

BOX 53-3

Laboratories Providing Equine Neonatal Isoerythrolysis Testing* in North America

Clinical Laboratory Services—Hematology
University of California, Davis
Veterinary Medical Teaching Hospital
Central Laboratory Receiving, Room 1033
One Garrod Drive
Davis, CA 95616-8747
(530) 752-8684
www.vetmed.ucdavis.edu/vmth

Animal Genetics Testing and Research Laboratory
108 Gluck Equine Research Center
University of Kentucky
Lexington, KY 40546-0099
(859) 218-1212
www.ca.uky.edu/gluck/AGTRL.asp

Rood and Riddle Veterinary Laboratory
Rood and Riddle Equine Hospital
2150 Georgetown Road
Lexington, KY 40511
(859) 233-0331
www.roodandriddle.com/laboratory.html

Hagyard Laboratory
Hagyard Equine Medical Institute
4250 Iron Works Pike
Lexington, KY 40511-8412
(859) 259-3685
www.hagyard.com/Hagyard-Laboratory.html

*Serum or colostrum from the suspect mare is required to screen for the presence of alloantibody. Acid-citrate-dextrose anticoagulated blood is generally preferred for screening for red blood cell antigens.

Neonatal Alloimmune Thrombocytopenia

Equine

Definition and Etiology Neonatal alloimmune thrombocytopenia (NAIT) is a condition characterized by the destruction of platelets in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[40] The syndrome has been observed in horse and mule foals.[27,40,41] The prevalence of this condition is unknown. Some cases may be asymptomatic, and the condition may be self-limiting as alloantibody is metabolized.

Clinical Signs and Differential Diagnoses Few clinical signs may appear unless foals are traumatized. Affected foals may have prolonged bleeding from venipuncture sites. Petechial hemorrhages may not be present. Other conditions often associated with thrombocytopenia in neonates include sepsis, disseminated intravascular coagulation, equine infectious anemia, drug-induced thrombocytopenias, and angiopathies. The challenge is to determine whether the thrombocytopenia is primarily due to allogeneic antibodies or secondary to some other disease process.

Clinical Pathology Profound thrombocytopenia in the absence of other hematologic changes typifies uncomplicated NAIT. Evidence of successful passive transfer is present on the basis of quantification of serum IgG. Affected foals are thrombocytopenic. Thrombocyte counts less than 10,000/μL have been observed. Prolonged bleeding from venipunctures and petechia may be present.[40]

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Demonstration of significant amounts of antibody in the colostrum (or serum from the mare) that are directed against platelet antigens expressed by the foal provides a definitive diagnosis of NAIT; however, assays for equine platelet-bindable and platelet-associated immunoglobulins are not routinely available.

Pathophysiology The pathophysiology is believed to mirror that of NI. In mares sensitized to platelet antigens, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's platelets carry the antigen that the antibody recognizes, the platelets become antibody coated. Subsequently they are removed prematurely by the reticuloendothelial system. Platelet antigens have not been characterized in horses, although platelet-associated antibodies have been recognized in affected foals. Circulating antibody is removed by attachment to platelets and rapid clearance by the reticuloendothelial system.

Treatment and Prognosis Circulating antibody is removed relatively quickly, and treatment may not be necessary. Platelet-rich plasma may be indicated in cases of severe thrombocytopenia accompanied by clinical signs of bleeding problems; however, as offending antibody is removed, the problem will tend to be self-limiting.

Prevention and Control Currently there are no screening tests to predict NAIT. Following production of an affected foal by a mare, it would be prudent to provide an alternate source of colostrum to foals born in subsequent pregnancies.

Alloimmune Neonatal Neutropenia

Equine

Definition and Etiology Alloimmune neonatal neutropenia (ANN) is a condition characterized by the destruction of neutrophils in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[42,43]

Clinical Signs and Differential Diagnoses In the absence of secondary bacterial infections, no clinical signs were observed. Diagnosis depends on the presence of persistent neutropenia in the absence of evidence of increased consumption or decreased production of neutrophils.

Clinical Pathology Persistent neutropenia in the face of normal clinical conditions has characterized reported cases.

Pathophysiology The pathophysiology is believed to mirror that of NI. In mares sensitized to granulocyte antigens, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's neutrophils carry the antigen that the antibody recognizes, the neutrophils become antibody coated. Subsequently they are removed prematurely by the reticuloendothelial system. Neutrophil antigens have not been characterized in horses, but neutrophil-associated antibodies have been recognized in affected foals. Circulating antibody is removed by attachment to neutrophils and rapid clearance by the reticuloendothelial system.

Treatment and Prognosis ANN is self-limiting in infants and typically resolves over several weeks as maternal antibodies diminish. Administration of antimicrobial drugs may provide protection against bacterial infections. Corticosteroids are not currently recommended for treatment of the condition in human infants and have not been used in equine cases. Administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was associated with increases in neutrophil counts in one affected foal.[42]

Prevention and Control Demonstration of agglutinating neutrophil antibodies or immunoglobulin coating of neutrophils from the foal may be used to confirm a diagnosis.[42] Following production of an affected foal by a mare, it would be prudent to provide an alternate source of colostrum to foals born in subsequent pregnancies.

Ruminant Immunodeficiency Diseases

George M. Barrington, *Consulting Editor*

Failure of Colostral Passive Immunity

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Definition and Etiology The process of ingesting and absorbing colostral immune components (immunoglobulins, immunoactive substances, and immune reactive cells) is termed *passive transfer of colostral immunity.* Such transfer is necessitated due to the structure of the domestic ruminant placenta, which largely restricts the transfer of immune components from the dam to the fetus.[1] Ruminants have a synepitheliochorial placenta possessing eight distinct membrane components separating fetal blood from maternal circulation, allowing low concentration of colostral components to cross the placenta.[2] Thus it is essential for ruminants to ingest and absorb colostral components to acquire passive immunity. Failure to acquire sufficient colostral components that confer passive immunity is termed *failure of passive immunity* (FPI).

Colostral Constituents and Synthesis Colostrum contains protein, fat, carbohydrates, water- and fat-soluble vitamins, growth factors, nucleotides,[3] cytokines,[4] complement,[5] and immunoreactive cells.[6-8] The major proteins in colostrum include immunoglobulins, lactoferrin, transferrin, α-lactalbumin, β-lactoglobulin, and albumin.[9] Immunoglobulins constitute approximately 95% of the total whey proteins in colostrum, and the major class (85% to 90%) of immunoglobulin in bovine colostrum is IgG.[10,11] While bovine IgG can be broadly separated onto two subclasses, IgG1 and IgG2, the predominant subclass in bovine colostrum is IgG1, constituting approximately 80% of total immunoglobulin.[12] Immunoglobulin G1 can fix complement, whereas IgG2 cannot.[13] Other immunoglobulins present in colostrum include IgM and IgA, which only make up approximately 7% and 3% of colostral immunoglobulin, respectively.[10]

The majority of studies in neonatal domestic ruminants concerning passive immunity have concentrated on immunoglobulins as the major component, whereas passively acquired cell-mediated immunity is poorly understood.[14] Clearly, assessment of immunoglobulins after ingestion of colostrum is technically much easier to quantitatively and qualitatively assess compared with assessment of colostral-derived cells.

Maternal cells found in mammary secretions include lymphocytes, neutrophils, macrophages, and epithelial cells.[15] The role of colostral lymphocytes is hypothesized to provide the neonate with transient local and systemic cell-mediated immunity that reflects antigenic exposure of the dam.[7] Studies reveal that transfer of live maternal cells from colostrum to the neonate enhances the neonate's response to antigens to which the dam has been previously exposed.[16] Other suggested roles of the cellular components from mammary secretions include development of local immunity and modulation of the active immunization of the neonatal intestine.[17] In calves, colostral-derived cells have been demonstrated to provide protective effects against enterotoxigenic *Escherichia coli* infections.[15]

Mechanism of Passive Immunity of Colostral Components The process of acquiring passive immunity involves two distinct processes. The first is colostral synthesis (colostrogenesis) whereby IgG1 is transferred into colostrum from maternal blood via

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an active, selective, receptor-mediated process.[18-22] Transfer of IgG1 begins approximately 5 to 6 weeks before parturition and ceases 1 to 3 days prior.[21,23] Colostrogenesis is largely controlled by lactogenic hormones.[24-26] Receptors responsible for the transfer of IgG1 into colostrum are located on the basilateral surface of mammary secretory epithelial cells. Colostral IgM and IgA are largely derived from local synthesis by plasmocytes in the mammary gland.[27]

The second process related to passive immunity involves absorption of colostral immunoglobulin and other colostral components by the calf. Absorption of colostral components occurs primarily in the small intestine during the first 24 to 36 hours of life via a nonselective, non-receptor-mediated, saturable process involving pinocytosis.[28] Intestinal absorption of colostral components steadily declines from the time of birth, terminating (termed "closure") at approximately 24 hours of age.[29] Absorption of colostral components may be extended to approximately 30 hours of age if feeding is delayed.[28] The efficiency of absorption of immunoglobulins decreases with increasing immunoglobulin concentration of the colostrum being fed.[30] As a result of all macromolecules competing for the same absorptive process, the mass of immunoglobulin absorbed by the calf is inversely proportional to the concentration of nonimmunoglobulin macromolecules present in the gut.

Epidemiology of Failure of Passive Immunity

Over the years, numerous studies have reported a wide variation in the prevalence of FPI in dairy and beef calves.[31,32] Recently, prevalence in U.S. dairy heifer calves has been estimated to be 19.2%.[33] In beef calves, prevalence rates range from 11% to 31%.[34-36] Regardless of use group (beef or dairy), the success or failure of passive immunity is largely a function of three general factors, including formation of colostrum with an adequate immunoglobulin concentration, ingestion of an adequate mass of immunoglobulin, and absorption of immunoglobulin in a timely manner.

FORMATION OF COLOSTRUM WITH ADEQUATE IgG1 CONCENTRATION. The mass of immunoglobulin presented to the neonate for absorption is dependent on the colostral immunoglobulin concentration and volume of colostrum available. The volume of colostrum produced by the cow is usually not a limiting factor.[37] However, large variations exist between colostrum with regard to immunoglobulin concentration. A tremendous difference in IgG1 concentration exists between beef and dairy cow colostrum. On average, the concentration of IgG1 in beef cow colostrum is approximately two to three times greater than that of dairy cow colostrum.[38-41] Significant differences exist not only between different breeds of cattle but between cattle within a specific breed.[42] Lactation number also influences the concentration of IgG1 in colostrum, though this variation is less than between individuals or breeds.

Low immunoglobulin concentration colostrum and the resultant ingestion of an inadequate mass of immunoglobulin are the primary causes of FPI in dairy calves.[40] In contrast, FPI in beef calves is unlikely to be due to low colostral IgG1 concentration.

INGESTION OF AN ADEQUATE MASS OF IgG1 (IgG). Depending on the environment and pathogen load to which they are exposed, calves must ingest an adequate mass of IgG1 to obtain protective immunity. Clearly, the mass of immunoglobulin needed for optimal protection is dependent on many factors. Older studies suggested that an average, 45-kg calf needed to consume approximately 100 g of IgG1 in the first hours of life to attain a serum IgG1 concentration greater than 10 mg/mL.[43] More recent studies suggest a total mass of 150 to 200 g IgG1 be fed for adequate transfer of colostral immunity.[44]

If one considers average dairy cow colostrum to contain approximately 35 mg/mL IgG1, volumes of 3 and 6 L of colostrum would be necessary to provide 100 g and 200 g, respectively. The recommendation to feed 3 to 4 L of dairy colostrum as soon as possible in the first hours of life is consistent with both older and newer studies.[43,45,46]

As previously mentioned, low IgG1 concentration colostrum is rarely a significant factor causing FPI in beef calves. Instead, factors such as mismothering, poor udder conformation, or environmental stresses are the more typical causes of beef calves failing to ingest adequate colostrum. Other factors that may affect passive transfer in beef calves have been reviewed.[36] Little evidence exists to suggest a direct effect on passive transfer when beef cows are fed protein- or energy-restricted diets. Dystocia does not appear to affect passive transfer of immunoglobulins as long as the calf receives an appropriate mass of immunoglobulin in a timely manner. Finally, young age of the dam is a risk factor for failure of passive immunity. This could be due to either lower colostral immunoglobulin concentration in heifer colostrum (beef and dairy), poorer mothering ability, or both.

TIMELY ABSORPTION OF IgG1 BY THE GUT. Cessation of absorption of colostral immunoglobulins (closure) occurs at approximately 24 hours of age.[47,48] If colostrum is completely withheld, closure will still occur by approximately 30 hours of age at the latest.[28,49] Closure is minimally affected by stresses such as dystocia or cold environmental temperatures, but the effect of extremely high environmental temperatures has been associated with reduced immunoglobulin absorption in calves.[50,51] In a study comparing three different feeding methods of colostrum to dairy calves, a higher prevalence of FPI was associated with sucking when compared with artificial feeding methods.[43] The higher prevalence of FPI in suckled dairy calves was thought to be due to an inadequate colostrum volume ingested. That is, dairy calves suckling low IgG1 concentration colostrum are less likely to consume an adequate volume of colostrum to obtain an appropriate mass of IgG1 in a timely manner. When artificial feeding methods are used, inadequate colostral immunoglobulin concentration is the most important factor resulting in FPI, even when calves are fed in a timely manner.

Finally, an effect of mothering has been associated with increased efficiency of absorption of colostral immunoglobulins. This may simply entail the presence of the dam or may be related to the effect of the neonate physically suckling the dam.[47]

PASTEURIZATION OF COLOSTRUM. Pasteurization of colostrum is used to prevent transmission of infectious pathogens through contaminated colostrum. Currently only 0.8% of dairy producers pasteurize colostrum before feeding it to calves.[52] Variable study results have been reported on the negative effects of pasteurization on colostral IgG concentration.[53,54] Practically, on-farm pasteurization most likely has minimal negative effect on colostral IgG concentration but is likely to destroy the colostral cellular components.

COLOSTRUM SUPPLEMENTS AND REPLACERS (see also Chapter 21). Colostrum supplements and replacers derived from bovine serum or colostrum have been formulated for use in calves. Effects of colostrum replacers on serum IgG concentration following ingestion indicate varying results depending on the type of product used and the differences in IgG concentration (or mass).[55-58] Fortunately, the quality of colostrum replacers has improved when considering their IgG concentration. However, processing during production largely destroys any cellular components from which the replacer or supplement was derived. For this reason, it is unlikely that colostrum replacers or supplements can provide cellular immunity to the newborn.

ECONOMIC IMPORTANCE OF FPI. Failure of passive immunity is responsible for approximately 50% of calf death losses on U.S. dairy farms.[59] Calves with FPI have increased mortality due to *E. coli* septicemia.[15] Inadequate ingestion of colostral immunoglobulins affects calf health and survival beyond the neonatal period; calves with FPI have increased rates of mortality until at least 10 weeks of age.[60] The effects of FPI on health and production can extend long beyond the neonatal period. Calves with FPI have been shown to possess double the odds of developing pneumonia when compared with calves with

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adequate passive immunity during the first 3 months of life.[61] Higher serum IgG concentrations (>1200 mg/dL) at 24 to 48 hours of age in heifer calves are associated with increased daily weight gain up to 180 days of life and higher weaning weights compared with calves with low serum IgG concentration.[62] Calves with FPI have lower milk production in their first lactation and are more likely to be culled for low production.[63]

ASSESSMENT OF IMMUNOGLOBULIN CONCENTRATION IN BOVINE COLOSTRUM. Differentiating between low IgG concentration and high IgG concentration colostrum is useful to ensure adequate passive transfer of colostral components. Several practical methods have been used to assess bovine colostral IgG concentration:

VISUAL APPEARANCE AND HYDROMETERS IN BOVINE COLOSTRUM. Visual appearance of colostrum and hydrometers are the two most commonly used methods to evaluate colostrum quality in the United States.[52] Although 41% of dairy operations in the United States use visual appearance to evaluate colostral quality,[52] studies have shown that visual evaluation of colostral characteristics are of little to no value in predicting colostral immunoglobulin concentration.[64]

A hydrometer (colostrometer) measures colostral-specific gravity as an estimation of protein concentration, and thus colostral IgG concentration.[65-67] Measurement of colostral-specific gravity can be affected by several factors, including colostral temperature, month of calving, and lactation number.[67-69] In the United States, 43.7% of dairy producers estimate colostral IgG concentrations using hydrometers. Although the hydrometer is a practical and inexpensive method of estimating colostral IgG concentration, it also tends to overestimate the actual IgG concentration.

WEIGHT OF FIRST MILKING COLOSTRUM. Weight of first milking colostrum is inversely related to colostral IgG1 concentration.[40] In a study by Pritchett and colleagues,[40] first milking colostrum weighing less than 8.5 kg was shown to have higher IgG concentration than first milking colostrum weighing greater than 8.5 kg. In a later study, colostral IgG1 concentration was found to be only weakly correlated with colostral volume.[70] The sensitivity of the weight of first milking colostrum was low (0.42) in detecting colostral samples with low IgG concentration (<50 g IgG/L).[71] In summary, weight of first milking colostrum as a screening test to identify low IgG concentration colostrum is less predictive compared with using it as a screening test to help select colostrum with a higher IgG concentration.[40,71]

OPTICAL AND BRIX REFRACTOMETERS IN BOVINE COLOSTRUM. Refractometers have been evaluated as cow-side tests for estimating colostral IgG concentration. The sensitivity of both types of refractometers in identifying adequate IgG concentration colostrum was acceptable when using a cutoff point of 22% Brix score.[71,72]

RADIAL IMMUNODIFFUSION (RID) AND QUANTITATIVE ELISA IN BOVINE COLOSTRUM. Both radial immunodiffusion and ELISA tests specifically quantify colostral immunoglobulins. The commercial availability of these tests for use in calves is limited because they are primarily used in research.

Clinical Signs and Laboratory Findings in Ruminants with Failure of Passive Immunity

Failure of passive immunity of colostral immunoglobulins is not a disease but simply a risk factor for increased morbidity and mortality from various diseases and conditions that commonly affect neonates, particularly diarrhea and respiratory diseases.[15,61] High prevalence of diarrhea and respiratory disease in neonates may prompt investigation of passive transfer of immunity in neonatal ruminants in addition to the investigation of management, the environment, or pathogen load.

Abnormal laboratory findings on hemograms or serum biochemical analysis are commonly a result of secondary changes involving diarrhea, septicemia, arthritis, and meningitis.

Laboratory assessment of passive transfer of immunity is important for the treatment, prognosis, and management of colostral feeding practices on farms. Several methods are available for assessment of FPI in ruminants and are performed in calves aged 24 to 48 hours.

Qualitative Methods for Assessing Failure of Passive Immunity

SERUM TOTAL PROTEIN USING REFRACTOMETRY. Serum total protein measurement is an indirect estimate of serum IgG1 because immunoglobulins make up approximately 90% of serum proteins in the neonatal calf. A total serum concentration of 5.2 g/L is consistent with 1000 mg/dL serum IgG1 level in clinically normal calves.[73] In clinically ill calves, a serum total protein end point of greater than or equal to 5.5 g/L is used to indicate adequate passive transfer to account for dehydration.[74] Refractometric measurement of serum total protein is the test recommended for herd monitoring of calves for adequate transfer of colostral immunoglobulins.[75] A serum total protein of greater than or equal to 5.3 g/L has been shown to be consistent with adequate passive immunity of colostral immunoglobulins in goat kids.[76]

SODIUM SULFITE PRECIPITATION OF SERUM. A mixture of serum and a sodium sulfite solution causes precipitation of proteins of high molecular weight, including immunoglobulins, and the result is recorded visually.[75] Three concentrations of the sodium sulfite (14%, 16%, and 18%) are commercially available (Bova-S, VMRD, Pullman, Wash.; ICN Immunologicals, Lisle, Ill.; Bethly Laboratories, Montgomery, Tex.). Turbidity in only the 18% solution indicates transfer of less than 500 mg/dL, turbidity in both the 16% and 18% solution indicates 500 to 1500 mg/dL of transfer, and turbidity in all three solutions indicates greater than 1500 mg/dL of transfer. The preferred test end point appears to be the 1+ test result. A 1+ test result equates to observing turbidity in the 18% solution with no turbidity in either the 16% or 14% solutions. Tyler and colleagues[73] demonstrated that the lowest serum IgG1 concentration (as determined by RID) observed in calves with a 1+ test result was 645 mg/dL, indicating at least partial successful passive transfer of immunoglobulins. Therefore it is recommended that the sodium sulfite test be used as a single-dilution assay procedure whereby calves with 1+ test result (precipitation in only the 18% test solution) are classified as adequate passive transfer of colostral immunoglobulins. Serum refractometry and sodium sulfite tests are the most practicable, inexpensive, and on-farm–adaptable methods for assessing passive immunity in calves.

ZINC SULFATE TEST OF SERUM. Specific concentrations of zinc sulfate precipitate immunoglobulins.[77,78] A volume of serum (0.1 mL) is added to a zinc sulfate solution (6 mL) containing 208 mg of $ZnSO_4\,7H_2O$ per liter, and the solution is allowed to incubate at room temperature for 1 hour. The turbidity of the solution is then evaluated visually or with spectrophotometric methods.[77] The zinc sulfate turbidity test is no longer widely used for assessing passive immunity in calves because the test is less accurate than serum total protein refractometry or the sodium sulfite test.[73] Other limitations of the zinc sulfate turbidity test include misclassification of samples in the presence of hemolysis and the instability of the solution when exposed to atmospheric carbon dioxide.[73,79,80] However, a follow-up study suggests that higher zinc sulfate concentrations in the test solution can provide a more accurate assessment of passive immunity. When the zinc sulfate concentration is increased from 200 to 400 mg/dL, sensitivity decreases from 100 to 82.6 and specificity increases from 25.5 to 90.6, respectively. The concentrations of which zinc sulfate test solution to choose therefore depends on the goal of the test. Choosing a test solution with higher sensitivity (e.g., 250 mg/L zinc sulfate) is likely warranted when testing individual calves with high economic

value. In herd monitoring programs, however, the choice of a test solution with higher specificity (e.g., 350 to 400 mg/L zinc sulfate) can maximize the proportion of calves correctly classified.

GLUTARALDEHYDE COAGULATION TEST IN WHOLE BLOOD. A whole-blood glutaraldehyde coagulation test used to estimate γ-globulins in cattle has low sensitivity (0.00 to 0.41) and specificity ranging from 0.85 to 1.[81] The performance of the test using whole blood is insufficient for routine diagnostic use; however, when the test is performed on serum it can be an accurate predictor of passive transfer status in calves.[81,82]

γ-GLUTAMYL TRANSFERASE ACTIVITY IN THE SERUM. Increase in serum γ-glutamyl transferase (GGT) activity, an enzyme synthesized in the mammary gland, is observed after ingestion of colostrum in calves.[83] Although increased activity of GGT confirms ingestion of colostrum, the association between the activity of the enzyme and serum IgG concentration is low.[83] Although a study by Parish and colleagues[84] suggested predicting passive transfer status on the basis of age and serum GGT levels, a study by Wilson and colleagues[85] determined that serum GGT activity was of little value in predicting passive transfer in calves. In summary, the use of increased serum GGT activity in calves is strongly discouraged as a method to assess passive transfer in calves, but it is an acceptable test for assessing passive immunity in lambs.[75,86]

Quantitative Laboratory Methods for Assessing Failure of Passive Immunity

TURBIDIMETRIC ASSAY IN SERUM. Recently, a portable, quantitative, automated turbidimetric serum immunoassay called the MBC QTII Kit (Midlands BioProducts, Boone, Iowa), specific for bovine IgG, was reported to be reliable in determining IgG concentrations in dairy calves.[87] However, a limiting factor of this assay was the relatively high cost per test ($7).

RADIAL IMMUNODIFFUSION IN SERUM. The RID is considered the reference method and measures serum IgG concentration directly. Different serum IgG concentrations for the RID end points have been used to define adequacy of passive transfer in dairy calves.[§] In beef calves, higher IgG concentration (2600 mg/dL) end points have been recommended.[90] Currently IgG concentrations of 1000 mg/dL or greater are considered indicative of adequate transfer of passive immunity in dairy calves.

QUANTITATIVE ELISA. Due to cost and availability, these types of tests are primarily only used in research settings.

Management of Ruminants with Failure of Passive Immunity

Neonatal morbidity and mortality is a result of several factors. These include passive immune status, environment, hygiene, and nutrition.[91,92] Thus it is important to partition mortality attributable to each of the risk factors when investigating calf morbidity and mortality on farms.[59] Consequently, intervention strategies should be focused on areas with the greatest impact on calf health. Calves with FPI can survive if housing, nutrition, and hygiene are optimal.[75] Decisions to treat calves with FPI should be based on the calf age, value, and presence of other risk factors for morbidity and mortality.[75] Treatment of FPI in clinically normal calves includes transfusion with plasma,[93] serum,[94] or whole blood intravenously or intraperitoneally. Plasma administered at 20 to 40 mL/kg intravenously or intraperitoneally has been recommended. Although treatment is empirical and no controlled studies have evaluated the efficacy of plasma, serum, or whole blood on morbidity and mortality in calves with FPI, clinical impressions indicate increase in serum IgG concentration following transfusions with all of these products.

[§]References 43, 61, 62, 74, 88, 89.

Prevention of Failure of Passive Immunity

Prevention of FPI is based on managing the previously mentioned factors that affect intake and absorption of colostral components in calves. Low IgG concentration colostrum is one of the primary concerns with FPI in dairy calves. Thus efforts to estimate the colostral IgG concentration before feeding colostrum, as well as feeding an appropriate volume of colostrum, is the most important management practice that needs to be addressed in dairy calves. Low IgG1 concentration colostrum is not generally the main cause of FPI in beef calves; rather, it is the failure to ingest and absorb colostral components in a timely manner. Hence in beef cattle, efforts to reduce FPI should be focused on ensuring timely ingestion and absorption of colostrum.

Lethal Trait A46

Steven M. Parish

Lethal trait A46 is a primary immunodeficiency that is found in black pied Danish cattle of Friesian descent.[1] It is an autosomal-recessive trait in which the calves appear normal at birth but develop skin disease at 2 to 8 weeks of age. Skin lesions are characterized by exanthema, alopecia, and hyperparakeratosis, with initial lesions occurring around the head, neck, and flexor surfaces of the legs and later involving the entire animal. Death within 4 months is often associated with bronchopneumonia and diarrhea. These animals do respond normally to humoral antigens but show deficits in cellular immunity. At necropsy the calves show marked lymphoid regression involving the thymus, spleen, lymph nodes, and gut-associated lymphoid tissues in the thymic-dependent regions. The condition is responsive to oral zinc oxide therapy, which suggests an underlying problem in zinc metabolism. Daily oral dosages of up to 1 g of zinc oxide have been used to establish normal function.[1] The primary immunologic defect is found in T lymphocytes. It appears that, because of a defect in a recessive gene, these animals have an unusually high metabolic requirement for zinc ions needed to sustain normal T lymphocyte development and function.

Selective IgG2 Deficiency

A primary IgG2 deficiency has been described in the red Danish milk breed in which there is a primary partial to complete deficit in IgG2.[2,3] These animals appear to be more susceptible to gangrenous mastitis and pyogenic infections such as bronchopneumonia, peritonitis, and abomasoenteritis.[4] A transient IgG2 deficiency has also been reported in neonatal lambs.[3] In lambs that ingested colostrum, there was a delay in the onset of synthesis of IgG2 until 5 to 6 weeks of age without any adverse consequences.

Chediak-Higashi Syndrome

Chediak-Higashi syndrome is an inherited disorder that affects neutrophil and monocyte function in Hereford cattle, mink, cats, mice, killer whales, and humans.[5,6] Clinically these patients are recognized by partial albinism that affects the skin and eyes, coagulation difficulties, and an increased susceptibility to bacterial infections. Large cytoplasmic granules are seen within neutrophils. The increased susceptibility to pyogenic infections is related to decreased neutrophil killing of ingested organisms caused by a defect in the hexose monophosphate shunt activity and defective degranulation.

Bovine Leukocyte Adhesion Deficiency

Bovine leukocyte adhesion deficiency (BLAD) is an autosomal recessive disorder of Holstein calves characterized clinically by chronic bacterial infections and premature death.[7-9] Leukocytes of affected calves lack surface glycoproteins, termed *β-2 integrins.* A mutation of the gene encoding bovine CD18 causes this disorder. The gene defect is termed the *D128G allele mutation.*

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Heterozygous carriers are clinically normal; however, bulls and cows with this mutation may produce homozygous calves that manifest the deficiency. All calves with BLAD can be traced to a single male ancestor that must be present in both the sire and dam pedigree. In the United States, approximately 14% of sires and almost 6% of Holstein calves are affected with BLAD.

Homozygous calves have chronic, recurrent bacterial infections. Consistent clinical findings include fever, bronchopneumonia, stomatitis, gingivitis, recurrent or chronic diarrhea, peripheral lymphadenopathy, vasculitis, and dermatitis.[10,11] Calves appear normal at birth, but clinical signs are often present within the first few weeks of life. Affected calves usually die within the first year of life. Those surviving past 1 year of age have persistent ill-thrift. Hematologic abnormalities include mature neutrophilia (>40,000/L) without significant left shifts, lymphocytosis, and monocytosis. Abnormal serum biochemical findings include hypoalbuminemia; hyperglobulinemia; and low serum creatinine, urea nitrogen, and glucose concentrations.

Diagnostic tests are available to detect heterozygous carriers and identify homozygous clinically affected calves. Information regarding testing is available from the Holstein Association of America, Brattleboro, Vt.

Viral and Bacterial-Induced Immunodeficiency

Decreased B and T lymphocyte function has been reported associated with bovine virus diarrhea (BVD) infection in calves developing chronic BVD syndrome.[12] Depression of cellular, but not humoral, immunity is seen in cattle infected with Johne's disease *(Mycobacterium johnei),* with failure to develop, or DTH reactions in vivo and in vitro.[13] It is associated with a humoral-suppressive factor.

Combined Immunodeficiency

Genetic failure of development of both T- and B-cell lines results in a severely compromised immunodeficient animal. As passively acquired maternal antibody wanes, infections tend to develop. One possible case of combined immunodeficiency in a calf has been reported. It was recognized in a 6-week-old Angus that had an absence of serum IgM, low serum IgG, absolute lymphopenia, and an absence of lymphoid tissue at necropsy. The calf died of bronchopneumonia and disseminated fungal infection.[14]

Immunosuppression during Pregnancy and Postpartum Periods

James F. Evermann

Understanding

The immune response during pregnancy and immediately postpartum has been the focus of extensive research since the early reports by Hansen (1997) and Mallard and colleagues (1998).[1,2] There has been a remarkable surge in research reports over the past 5 years, which has allowed for increased knowledge regarding the mechanisms that affect the immune system during gestation.[3,4] With added data from the areas of reproductive immunology,[5,6] infectious disease ecology/epidemiology,[7] clinical medicine,[8,9] theriogenology,[10] and nutrition,[11] it has become apparent that what is observed clinically as outcomes of reproductive losses are indeed due to underlying immune suppressive states in the pregnant animal (Box 53-4). As the knowledge base expands, experts now recognize that, although transitory, the immunodeficient state extends into the postpartum period for at least 4 weeks.[12]

Mechanisms

T cells are an important population in the regulation and response of the immune system in general.[13] However, during pregnancy, the T cells are essential in the immunoregulation of the maternal immune system. Over the past 30 years it has become known that there is a maternal tolerance toward fetal alloantigens.[5] This has been partially explained by the interactions of the T-helper (Th) cells, which can be classified into various subgroups referred to as Th 1, Th 2, etc.[13] During pregnancy the Th 2–type (humoral) immunity overrules the Th 1–type (cell-mediated) immunity, therefore protecting the developing fetus from maternal Th 1–cell attack. In recent years, the Th-1/Th-2 paradigm has been expanded to include Th 17 and regulatory T cells (Treg).[3] The Th 17 cells produce the proinflammatory cytokine, IL-17, and play a vital role in the induction of inflammation. Treg cells are now recognized to inhibit proliferation and cytokine production in both $CD4^+$ (T helper) and $CD8^+$ (T cytotoxic) T cells, immunoglobulin production by B cells, cytotoxic activity of natural killers (NK) cells, and maturation of dendritic cells (DCs), resulting in the induction of tolerance, a form of immune regulation-suppression.[3] With the onset of pregnancy the hormonal factors cause macrophages to release predominately Th-2-stimulating cytokines that contribute to the overall dominance of humoral immunity during pregnancy and immediately postpartum.[12] The second key cell population affected during pregnancy and postpartum is the neutrophil.[14] The point of maximum immunosuppression occurs around the time when there is an acute elevation in glucocorticoids in the periparturient cow, as well as when there is a negative energy balance.[4,15]

BOX 53-4

Temporary Immune Suppression during Pregnancy Accounts for Both Direct and Indirect Effects on the Host Animal

Direct Effects

- Shift in T-cell population from Th 1 (CMI) to Th 2 (Humoral)
- Expansion of T-helper cells, such as Th 17, and T-regulatory cells
- Inhibition of T-cytotoxic cells
- Induction of maternal tolerance of the fetal alloantigens
- Inhibition of natural killer (NK) cells
- Inhibition of neutrophil function

Indirect Effects

- Increased risk of exacerbation of preexisting microbial infection
- Increased risk of systemic infections
- Increased susceptibility to environmental opportunistic pathogens
- Increased risk of metritis/endometritis
- Increased risk of mastitis

Outcome

The outcomes of the transitory immunodeficiency state that allow for fetal development also allow for exacerbation of preexisting microbial infections that were regulated by a potent Th 1–type immunity and for increased susceptibility to exterior environmental infections with bacteria, fungi, protozoa, and viruses.[12,13] The cell-mediated immune response relies primarily on the T-cytotoxic cells to control intracellular microbial infections, and when Th 1–type immunity is suppressed, these infections become systemic and affect the development of the fetus, by way of fetal loss, fetal congenital malformations, or birth of infected-weak neonates.[12] Concurrent with immunosuppression that accompanies pregnancy, there is an increase in shedding of infectious microorganisms (Fig. 53-10).[12] This is considered to be an extension of the impaired T-cytotoxic cell population, which follows systemic spread of the agents. Although the pregnant animal may appear clinically normal, her altered immune status results in the increased shedding of gastrointestinal viruses (coronavirus, rotavirus) and bacteria (*Mycobacterium paratuberculosis, Salmonella* spp., *Campylobacter* spp., etc.), usually during the periparturient period.[12]

The reduced neutrophil function and its association with periparturient immunosuppression has continued to be a major problem for dairy cattle, especially for the transition dairy cow.[10,14,15] This immune

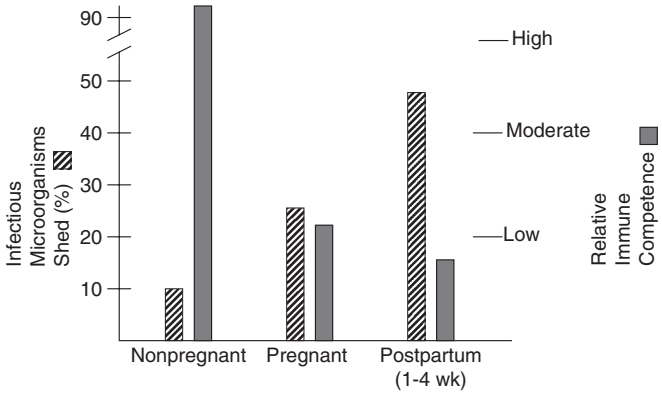


FIG. 53-10 Proposed relationships among shedding of infectious microorganisms during periods of nonpregnant, pregnant, postpartum, and relative immune competence. *(From Evermann JF. 2009. Pregnancy-associated immunodeficiency, pp 1681-1682. In Smith BP (ed), Large animal internal medicine, ed 4. Mosby, St Louis, MO.)*

suppression is directly related to increased cases of postpartum endometritis, metritis, and mastitis. As was noted with immune suppression during pregnancy, the periparturient period can be aggravated by preexisting subclinical infections, such as bovine herpesvirus type 4, and environmental bacterial pathogens, such as *Staphylococcus aureus* and *Klebsiella* spp.[12]

A more recent concern that accompanies the transitory immune suppression during pregnancy is the practice of using modified live-attenuated viral (MLV) vaccines during pregnancy. The controversy involves the ill effects of using MLV on naive animals and the potential effects on the pregnancy.[16] It has been a standard practice to vaccinate animals prebreeding and then booster during pregnancy to ensure fetal protection and enhance colostral immunity. The crucial data that are forthcoming are reporting ill effects in naive animals and should be interpreted with caution. As the report stated, "no conclusions can be made about adverse consequences (short-term or long-term) in using MLV vaccines at the appropriate time of breeding in vaccinated (prior immunity) animals."[16]

Management

Although the immunosuppressive periods during pregnancy and up to 4 weeks postpartum are well recognized, the exact mechanisms have not been fully revealed. However, one can proceed with control measures that accomplish two primary goals. These are to maximize reproductive performance and to ensure successful neonatal survival.[17,18] Over the years, the authors have emphasized the importance of effective vaccination programs prebreeding, use of licensed booster vaccine during pregnancy, clean birthing areas, and good hygiene for the lactating animals.[17,19] This, in conjunction with good colostral management, allows for us to compensate for the temporary immunosuppressive states encountered during pregnancy and immediately thereafter.

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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• CHAPTER 54

Disorders Caused by Toxicants

LYNN ROLLAND HOVDA, *Consulting Editor*

Poison cases in large animals occur less often than other species but are usually more time consuming and frustrating to manage. Generally, an animal is found dead in the stall or pasture or a sudden outbreak of illness occurs in a herd of animals. A rapid response is necessary, especially in herd cases, to eliminate the toxicant, treat affected animals appropriately, and prevent the development of further cases. The initial history is frequently limited, yet owners, trainers, barn managers, elevator owners, and others may demand an immediate answer. Emotions may run high, especially with the death of a beloved horse or when legal and media related issues arise. The veterinarian is left to provide answers to many complicated issues while attempting to undertake a diagnostic investigation.

Finding a toxicant does not necessarily mean it is the causative agent or that it is even related to the problem at hand. Concluding thus without further evidence could skew the investigation and result in an inaccurate diagnosis and further illness or death. A complete toxicologic investigation, including a thorough history, clinical signs, clinicopathologic testing (including necropsy if available), and analytic testing, should be undertaken in a careful and systemic manner. Internet websites can be used to provide accurate and rapid sources of toxicologic information to aid in the investigation and provide treatment options[1,2] (Table 54-1). An established working relationship with a diagnostic laboratory providing advanced testing and a board-certified toxicologist to help interpret results will increase the likelihood of a positive diagnosis.

History

An accurate history is the starting point of any toxicologic investigation and, done correctly, ensures that you have obtained the appropriate samples for further analysis. The investigation may vary from simple to complex but should always be done in a calm and ordered manner so that nothing is overlooked. The history should be used to provide information on circumstances surrounding the problem and may or may not identify the toxicant itself. Caution is advised in that the presence of a toxicant in the environment does not necessarily mean that it is the source of the problem. Finding a toxicant is simply a starting point. Many other factors, including the dose and degree of exposure, need to be considered because exposure to a nontoxic dose generally does not result in a worthwhile diagnosis.

Initial questions, however, often revolve around whether a known toxicant is present in the animals' environment. There are literally hundreds of toxicants, but many people, when questioned, often know which one may be playing a role. Common questions include whether or not medications, pesticides, herbicides, or fertilizers have recently been used or are present on the property. Is rodent control used in barns and outbuildings? Are there old junk piles on the property? What farm equipment/automotive products have been used recently? Have any old buildings been moved or torn down? Are there any known poisonous plants on the property?

Recent changes in animal management should be investigated in detail. Animal handlers should be questioned about the introduction of any new feeds, either new bags or fresh batches from a feed mill, or a complete change in feed. Feed should be examined closely for mold and the presence of any foreign bodies. Samples of feed, both as purchased and as fed, should be obtained and stored for further analysis. Hay and pasture should be examined for the presence of blister beetles, clippings from plants such as yew or oleander, other poisonous plants and weeds, foreign bodies, and mold. Again, samples should be taken and saved for analysis. Water samples from the original source and at the trough or stock tank should be taken and conserved in preserving jars for analysis if needed.

Species, breed, age, sex, body weight, and body condition are important pieces of information to be collected for all involved animals. Current and past medications used, vaccination history, reproductive status, and illnesses in other animals are other pieces of data that may be useful. Species identification is particularly important because some toxins are species specific or exhibit different toxicologic profiles. In addition, absorption of some toxins in ruminants, horses, and swine varies due to their specific gastrointestinal tracts. Some individual breeds may have different metabolic pathways resulting in delayed metabolism and excretion. The presence of a P-glycoprotein transporter in the *MRD-1* gene was recently identified in horses and in the future may play a role in the development of breed-related toxicosis.[3,4] Very young and very old animals are often at increased risk for developing signs of poisoning at much lower doses. Neonatal animals absorb some metals and chemicals more readily than adults, and nursing animals may receive toxic substances in the milk. Geriatric animals often have underlying deficiencies in liver metabolism and renal excretion that affect their ability to clear potential toxicants in a timely manner.

Clinical Signs

Live animals should have a complete physical examination performed and be closely examined for the presence of any unusual clinical signs. Ultimately, the conclusion of the physical examination may help narrow the list of toxicants. Both the nature of the signs and sequence of events should be documented. Specific abnormalities such as the color and consistency of mucous membranes, mouth lesions, blistering on pink skin areas, loss of hair around the eyes or tail, horizontal lines on hoof walls, and other abnormal findings may help determine whether the process is specific to an organ system or more generalized in nature. It is important to remember that in some instances this may not be an intoxication because other diseases and/or illnesses may result in similar generalized, nonspecific clinical signs.

The time frame from when the animal(s) was last noted to be normal to the onset of signs should be determined, as well as cessation, continuation, and/or duration of signs. Much of this

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TABLE 54-1

Common Internet Websites

Type	Organization	Web Address
Animal poison control centers	ASPCA Poison Center Pet Poison Helpline	www.aspca.org/pet-care/animal-poison-control www.petpoisonhelpline.com
Diagnostic laboratories	American Association of Veterinary Laboratory Diagnosticians	www.aavld.org
General information	Google Scholar Veterinary Information Network	www.scholar.google.com www.vin.com
Literature search sites	International Veterinary Information Service Medline National Agriculture Library Pub Med	www.ivis.org http://medlineplus.gov/ http://agricola.nal.usda.gov www.ncbi.nlm.nih.gov/pubmed/medline.html
Toxicology information	Extoxnet InChem MSDS Search Site Toxnet	http://extoxnet.orst.edu www.inchem.org http://www.msdssearch.com/ http://www.toxnet.nlm.nih.gov/

Refer to references 1 and 2 for a more complete listing of various forms of toxicology information resources.

information may need to be obtained in a historical manner from the animal caregiver because the veterinarian is often examining the animal at a single time point in the progression of signs and may otherwise miss valuable information.

Clinicopathologic Testing

The results of clinicopathologic tests often shorten the list of potential toxicants and may point toward a specific organ system and/or toxicant. It is invaluable to obtain and either perform or store appropriate samples at the time of the physical examination or postmortem. Blood should be examined for electrolytes, complete blood cell count (CBC), liver enzymes, blood urine nitrogen, and creatinine. Urine should be examined for specific gravity and the presence of crystals, casts, red blood cells, hemoglobin, and methemoglobin. Other body fluids (ocular, cerebrospinal, etc.), hair, and ingesta should be obtained as needed. All samples except the blood and central nervous system (CNS) fluid can be frozen.[5,6] Blood should be centrifuged, the clot removed, and the sample stored in the refrigerator. It is important to remember that zinc and many of the trace minerals must be collected in a special tube for analysis.[5]

If at all possible, animals should be referred to the appropriate diagnostic laboratory for a postmortem completed by a board-certified pathologist. This is especially important if the animal is insured or legal issues are looming on the horizon. Animals sent to the diagnostic laboratory should be identified by tattoo, microchip, ear tag, or other means. Digital pictures taken before shipment can be used as a further source of identification. If a field necropsy is performed, extra samples should be taken because it is far wiser to take more samples than needed and discard them later rather than not have them at all. Often necropsy results will show specific lesions that may confirm a working diagnosis or point the veterinarian in another direction. Sometimes, the postmortem shows only generalized lesions or no lesions at all.

Analytic Testing

Analytic testing can be used to provide a definitive answer, but it must be used correctly and the results analyzed judiciously. Samples should not be sent to an analytic laboratory without some knowledge and forethought. The analytic laboratory will need guidance in terms of what they are testing for, as well as a history including the time since intoxication, dose of toxicant, and postmortem changes. Urine is the gold standard, especially for drug identification, but serum and plasma can also be used for analysis. Different forms of instrumentation/analyses are used for specific substances. For example, metals such as lead, zinc, arsenic, and others are analyzed with atomic absorption and spectrometry.[5] Enzyme-linked immunosorbent assay screens are generally sensitive, but the risk of cross-reaction with other substances may be large.[6] Drugs, many pesticides, and plant toxins are analyzed using gas or liquid chromatography/mass spectrometry, but unless specifically requested, the results are generally not quantitated and only demonstrate the presence of a toxicant.[5,6]

In summary, poisoning cases can vary from simple and direct to highly complex. It is important to investigate each one using a systematic approach, including history, clinical signs, clinicopathologic findings, and the results of analytic testing. As the veterinarian works through the investigation, each step may narrow the list of toxicants until a final answer is found. Alternatively, some investigations do not come to a final conclusion and the veterinarian is left to wonder what actually occurred. In many of these cases, environmental and management changes eliminated the toxicant before the investigation, leaving only the aftereffects.

Poisonous Plants

Julia H. Wilson

Poisonous plants pose significant dangers to all large animal species and should be weighted more highly on a differential list when the animal's or herd's history and location suggest potential access. A search for an incentive to have consumed a toxic plant should also occur, unless the toxic plant is palatable, was inadvertently harvested in hay, or its seeds contaminated grain stores. Observation that multiple animals on the premises are affected points to a common source for illness such as a toxicity, feed error, or infectious disease. Plant poisonings are most common in hungry animals at pasture that are driven to consume plants that are normally avoided. The need for forage and therefore risk of toxicosis in both ruminants and equidae is well established. Significant economic losses have been attributed to poisonous plants in regions and countries that rely on grasslands for raising livestock. Studies in the western United States suggest

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that plant poisonings adversely impact 3% to 5% of rangeland cattle, sheep, goats, and horses.[1] In China, poisonous grassland species of plants are responsible for an estimated $12.3 million of all livestock losses, including loss of performance and mortality from 2000-2006.[2] The estimated price of plant poisonings in Australia is $100 million (Australian) per year.[3] Deaths attributed to toxic plants are estimated to constitute 10% to 14% of all cattle mortality in the major cattle-raising region of Brazil.[4] Swine raised in confinement are least likely to be affected by plant poisoning; however, free-roaming swine may consume both garden and pasture species with known toxic potentials.

Circumstances that should stimulate investigation of possible plant poisoning on the affected premises include limited availability of forage as evidenced by animal observation and body condition scores; drought affecting plant growth, availability, and potentially high concentrations of toxins such as nitrates; recent storms that may have downed trees or fences; feed changes; inappropriate disposal of garden, shrub, or tree trimmings; and administration of herbal products for medicinal value. The level of toxins within a given plant species is often variable, even in samples from within the same pasture. Toxicity may be more pronounced in specific growth phases of the plant species, during times of stress or rapid growth, or after drying. Endophyte or fungal infections of the plant may be important as well, either as the sole or additional source of toxicity. These factors can be important in the timing and choice of plant specimens to identify, as well as assay for toxicity.

The distribution of clinical signs due to plant poisonings may be more difficult to decipher within a group of animals because individual factors play a role in both quantity consumed and expression of clinical signs. More than one type of toxic plant may have been ingested, which may lead to a wider variety of clinical signs. An individual animal may develop a taste for a plant that is avoided by others in their herd or flock or be forced to eat it due to feed competition and low social order. Herbicide application may also enhance the palatability of plant species such as water hemlock.[5] Recent fertilizer application may increase nitrate concentrations in both plants and water supplies. Some plants can create a wide range of clinical signs depending on the amount consumed acutely or chronically. Research done on specific toxins and plants, and applied to feeding trials, has demonstrated that differences in metabolism, gastrointestinal flora, and genetics may have a role in disease expression. Yet another variable is interaction between plant toxins and medications. Consumption of hay with two species of nightshade (*Solanum* spp.) has recently been identified as a factor in the development of clinical signs of ivermectin toxicosis in horses.[6]

Any suspicion of plant poisoning in an individual or group of individuals in a herd or flock should trigger a methodical investigation. The first step is a complete history of the affected individual(s), herd or flock, and farm. In addition to routine health questions, focus must be placed on current feed and any changes that have been instituted, weather factors that may have affected feed and water access or quality, fertilizer use on forage sources, differences between management of affected and unaffected animals, and the potential for any feeding errors or inadvertent exposure to garden refuse.[7] If the history yields evidence to strengthen the suspicion of plant poisoning, immediate removal of access to the suspected source of clinical problems should ensue. If multiple animals have been affected over time, establishment of a time line of events and cases may be a useful way to evaluate the history and determine the cause.

The second step in the investigation should be thorough examination of affected animals to identify and characterize clinical abnormalities and lesions. Low body condition scores, particularly if accompanied by a strong appetite, should raise clinical suspicion of consumption of normally unpalatable plants. Pregnant animals should be evaluated for signs of potential abortion. Quick access to an animal poison control center or available online database where clinical signs are entered to yield potential diagnoses may help veterinarians quickly sort through potential differential diagnoses for the animal(s).[8] Symptomatic treatment is often the first line of medical response if the etiology has not been determined or a specific antidote is not available or approved for use in that species. Stress of treatment, particularly for ruminants, must be weighed against the benefits. Activated charcoal administration remains advisable for most acute toxicoses if the animal can withstand the stress of administration. In ruminants, rumenotomy for evacuation of contents and instillation of activated charcoal should be considered. In monogastrics, stomach lavage followed by instillation of a slurry of activated charcoal in water may be the best option for acute cases. A limited number of specific antidotes are described for a few plant poisonings, but their use may be restricted by cost and the need to avoid food residues. Enhanced excretion of toxins through the use of laxatives or manipulation of urine or rumen pH may be applicable in specific situations where the toxic plant or principle has been confirmed.

Postmortem examination of affected animals should take place as soon after death as possible to maximize the opportunities to identify lesions and an etiology. In some plant poisonings, a specific odor may be noted, such as a bitter almond smell in cyanide poisoning (e.g., *Prunus* spp.), acetone smell with white snakeroot poisoning, and a mousy aroma due to poison hemlock ingestion.[5] Samples should be taken of rumen or stomach contents to look grossly and microscopically for recognizable plant leaf fragments or seeds. An aliquot of the ingesta should be labeled and frozen as soon as possible if toxicologic analysis is anticipated. Depending on the history time line, more ingesta samples may be warranted from other segments of the digestive tract. Intact seeds may be identifiable in the distal intestinal tract or manure. Samples of aqueous humor, amniotic fluid, and fetal stomach fluid for nitrate concentrations should be considered if clinical signs are compatible with that etiology (see later). If the animal has died within a few hours, blood samples for hematologic, chemistry, and toxin profiling can be rewarding. Tissue samples are important for characterizing histologic lesions to confirm a plant toxicity or alternative etiology. All grossly affected tissues should be sampled and a piece of liver frozen for toxicologic analysis. If neurologic signs were observed, the brain should be removed with proper barrier precautions.[7]

Identification of the plants, feedstuffs, or water responsible for clinical signs or death(s) is important for guiding treatment and further control. This may entail feed inspection or walking the pastures and fence lines to look for not only feasible plants that fit the clinical signs but also evidence that it has been consumed. If blue-green algae poisoning is a potential etiology, this tour must include inspection of water sources, where a bloom of blue-green algae may be found to be responsible for sudden death (see next section on Blue-Green Algae). The veterinarian, farm manager, or owner should visually inspect feedstuffs, looking for not only noxious plant or seed contaminants but also for mycotoxins (see section on Mycotoxins). Unknown plants should be photographed and placed in plastic bags for later identification and potential toxin determination. If identification will be delayed, plant samples should be pressed between leaves of brown paper and weighted down with heavy books for several days; an aliquot should be frozen for later analysis if indicated. For identified plants known to have variable toxicity, such as larkspur (Color Plate 54-1) or selenium-accumulating plants, multiple samples should be taken of the same species, concentrating on areas where the plants have been visibly browsed or grazed.[9] Resources for plant identification include toxicology texts, the U.S. Department of Agriculture (USDA) plant identification website, the USDA Poisonous Plant Research Laboratory website and its publications, other country-specific websites, and university or extension service plant experts.[10-16] In the United States, plant samples can be sent to the USDA Poisonous Plant Research Laboratory or Texas A&M's Veterinary Diagnostic Laboratory.

Common plant poisonings often trigger a recognizable pattern of clinical signs and disease progression. These are reviewed below in more detail, with emphasis on diagnostic features, treatment options, and preventive measures. Less frequent causes of livestock morbidity and mortality are listed in tables, grouped by predominant

clinical signs. Highlights of newly described toxicities that have the potential to harm multiple animals are also presented in this chapter section.

Sudden Death

Poisonous plants, chemical toxins, lightning strikes, and infectious diseases are causes of sudden death that should be considered when investigating sudden death in multiple animals. Numerous plant species have the potential to kill multiple animals within minutes to hours (Table 54-2).

Several groups of plants warrant greater discussion because of the frequency with which they are incriminated in the death of livestock and horses. All produce a range of clinical signs, not just sudden death, because the spectrum is influenced by the amount consumed, time period of consumption, concentration of toxin(s), animal species, and in some instances, accommodation of ruminal microbes.

Larkspur (*Delphinium* spp.)

Larkspur is considered one of the most important plant poisonings of range animals in the United States, second only to locoweed in its impact.[10] Cattle are most susceptible but sheep and horses can also be affected. The toxicity varies with the specific plant, stage of growth, amount eaten, and the time period over which it is consumed. Numerous toxic diterpenoid alkaloids have been identified in the nine *Delphinium* spp. that most often cause poisoning in cattle. Tall larkspur *(Delphinium barbeyi)* is considered the most problematic.[1] The alkaloids cause a curare-like blockade of neuromuscular junctions, by reversibly binding to nicotinic acetylcholine receptors. Larkspur consumption may also enhance the toxicity of another range plant, death camas (*Zigadenus* spp.).[17]

Death may result in as little as 3 hours after consuming larkspur. Clinical signs include excitability, muscle tremors, stiffness, staggering, and a basewide stance.[10] Cattle may assume a kneeling position before collapsing. Bloat, regurgitation (ruminants), and constipation may also be seen. There are no pathognomonic postmortem changes. Mild gastrointestinal (GI) irritation, venous congestion, bloat, and aspiration pneumonia may be observed. A definitive diagnosis is usually reached by identifying pieces of larkspur in the upper GI tract.

If treatment is possible, bloat should be immediately addressed to relieve thoracic compression and reduce the chances of aspiration; however, the stress of treatment may hasten death. Intravenous physostigmine has been advocated at dosages of 0.04 to 0.08 mg/kg, repeated as needed over several hours.[10] Neostigmine at 0.04 mg/kg is slightly less effective. Neither drug is approved for use in food animals. An affected animal may be mistaken for a grass tetany case; however, treatment with magnesium exacerbates the effect of larkspur's toxins at the neuromuscular junction and should be avoided.

Prevention of larkspur toxicity in range cattle is challenging and requires knowledge of when the plants are most toxic and most palatable, particularly if other forage is limited. For example, early spring grazing of cattle in pastures with tall larkspur should be curtailed as soon as the flower stalks begin to elongate. Sheep are more tolerant and can be used to reduce the plant's density. Aversion to eating

TABLE 54-2

Plants with Potential to Cause Sudden Death in Large Animals*

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Cyanogenic plants[1,10]	Many	O, B, C, E, P	Hydrogen cyanide	Worldwide	Cyanosis, dyspnea, muscle twitching, staggering, convulsions, coma	Sodium thiosulfate, sodium nitrite
Nitrate-accumulating plants[10]	Many	B, O, C, E	Nitrates	Worldwide	Weakness, drowsiness, chocolate mucous membranes, muscle tremors, tachycardia, tachypnea, staggering gait	Methylene blue
Copperweed[10]	*Oxytenia acerosa*	B, O	Unknown	SW U.S.	Appetite loss, weakness, coma, death in 1-3 days (longer in sheep)	
Death camas[10,17]	*Zigadenus* spp.	O, B, E	Zygacine	U.S., Canada	Salivation, bloody frothing, vomiting, muscle weakness, staggering, tachycardia, coma	Atropine
Dogbane[1]	*Apocynum* spp.	O, B, E	Cymarin	North America	Blue mucous membranes, tachycardia, mydriasis, progressive weakness, coma	
Easter (Atamasco) lily[10]	*Zephyranthes atamasco*	B, E	Unknown	Southern U.S., Mexico	Staggering, diarrhea, collapse	
Erva de rato[18]	*Palicourea*	B, O, C	Monofluoroacetate	Brazil	Depression, incoordination, seizures	
False hellebore, skunk cabbage[10]	*Veratrum* spp.	O, C, B	Cyclopamine, cyclopasine, jervine	U.S.	Salivation with frothing, weakness, vomiting, tachyarrhythmias, muscle tremors, coma, congenital defects	
Fitweed[10]	*Corydalis* spp.	B, E	Isoquinolone alkaloid	U.S., Canada	Tachypnea, seizures, staggering, snapping at objects, muscle tremors, depression	
Foxglove[10]	*Digitalis purpurea*	B. E	Digitoxin, digitalin, digoxin, saponins, alkaloids	U.S., Canada, Europe	Colic, melena, anorexia, polyuria, arrhythmias, seizures	

Continued

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TABLE 54-2

Plants with Potential to Cause Sudden Death in Large Animals*—cont'd

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Goat's rue[19]	*Galega officinalis*	O, C, B	Galegin, hydroxygalegin	France	Asphyxia, hydrothorax	
Greasewood[1]	*Sarcobatus vermiculatus*	O, B	Oxalates	Western U.S.	Drooling, coma, crystalluria	
Jimsonweed, thornapple[20]	*Datura stramonium*	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Larkspur[1]	*Delphinium* spp.	B,O, E	Alkaloids (methyllycaconitine)	Western U.S.	Weakness, staggering gait, muscle twitching, bloat, tachyarrhythmias, salivation, vomiting	Neostigmine
Locoweed[1,10]	*Astragalus* and *Oxytropis*	E, B, O, C	Swainsonine and other alkaloids	Worldwide	Depression, irregular gait, abnormal behavior, abortion, congestive heart failure	
Milkvetches[1]	*Astragalus* spp.	B, O, E	Miserotoxin	Worldwide	Acute signs of respiratory distress, muscle weakness, emphysema. Chronic signs of goose stepping, knuckling, wheezing, drooling, collapse	
Milkweed[1]	*Asclepias* spp.	E, B, O, C	Cardenolides	North America	Depression, weakness, dyspnea, mydriasis, tachycardia, fever, spasms, bloat, respiratory paralysis	
Mistletoe[10]	*Phoradendron villosum*	E	Amines, toxic proteins	North America	Colic, diarrhea, bradycardia, hypotension	
Monkshood[10]	*Aconitum napellus*	E	Aconitine, mesaconitine, napelline, hypaconitine	U.S., Canada	Weakness, arrhythmias, salivation, bloat	
Nightshade[1]	*Solanum* spp.	E, B, P, O	Solanine and other glycoalkaloids	North America	Dypsnea with expiratory grunt, salivation, progressive weakness, trembling, paralysis	
Perilla mint[10]	*Perilla frutescens*	E, B, O, C	Perilla ketone, egomaketone, isoegomaketone	Eastern, southern U.S., Asia	Acute respiratory distress	
Poison hemlock[1,10]	*Conium maculatum*	O, B, P, E, C	Coniine, γ-coniceine, cyanapine	North America, Europe	Trembling, ataxia, salivation, incoordination, mydriasis, tachycardia, respiratory paralysis, coma, convulsions, abortion, birth defects	Atropine
Rayless goldenrod[1]	*Isocoma* spp.	E, B, O, C	Tremetol	SW U.S.	Muscle trembling (legs and nose), stiff gait, depression, constipation, urine dribbling, acetone odor on breath, coma	
Sweet clover[1]	*Melilotus* spp.	B, O	Coumarin converted to dicoumarol by molds	North America	Massive hemorrhages or sudden death, occasional bloat	
Tobacco[10]	*Nicotiana* spp.	E, B	Nicotine, anabasine	Southern U.S., Mexico	Muscle tremors, tachycardia, colic, dyspnea, diarrhea, congenital defects	
Water hemlock[21]	*Cicuta maculata*	B, E	Cicutoxin	U.S.	Salivation, frothing, muscle tremors, mydriasis, convulsions, coma	
White cedar, arbor vitae[19]	*Thuja occidentalis*	B, O, C	Thujone	Europe, NE U.S., Canada	Hypersalivation, colic, bloat, bloody diarrhea	
White snakeroot[1,10]	*Eupatorium rugosum*	B, E, O, C, P	Tremetol	U.S., Canada	Sluggish behavior, muscle tremors, anorexia, acetone breath odor, melena, constipation, dysphagia, tachyarrhythmias, congestive heart failure, myoglobinuria	
Yew[1]	*Taxus* spp.	B, E, O, C, P	Taxine alkaloids	Worldwide	Tremors, dyspnea, mydriasis, vomiting, diarrhea, weakness, convulsions, coma	

*Plant names in bold are discussed in more detail in the text.

†Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine, *P,* porcine.

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larkspur has been created with lithium chloride administration, a strategy that may be worthwhile on some ranches.[22] Larkspur reduction may not be cost effective with herbicides, leading investigators to use insect control with the larkspur myrid *(Hoplomachus affiguratus)*.[10]

Cyanogenic Plants

Toxicity induced by consumption of cyanogenic plants is one of the most readily recognized syndromes in all species producing sudden death, along with the characteristic signs of cyanotic mucous membranes and bright red blood. Cyanide blocks molecular oxygen transfer in cytochrome oxidase systems in mitochondria, causing tissue anoxia.[23] Other signs include obvious respiratory distress, rapid breathing, bloat, salivation, muscle twitching, staggering, mydriasis, cardiac arrhythmias, and convulsions.[10] Ruminants are more susceptible than monogastrics because rumen microorganisms readily release cyanide from the cyanogenic glycosides. Acute, sublethal cases generally recover within an hour. In one report in cattle, however, the onset of signs was delayed until later in the day when cattle in an arid environment drank water, rehydrating the rumen. Toxicities have also been reported in alpacas.[24] Chronic cyanide toxicity has been associated with sorghum consumption in pregnant horses and cattle. The foals and calves are born with arthrogryposis. Animals may also develop neurologic damage to the brain and spinal cord resulting in weakness, ataxia, and urinary incontinence. Low doses of cyanogenic glycosides can be goitrogenic.[10]

Cherry red venous blood may be observed in fresh postmortem examinations. In ruminants, a bitter almond odor may be detected in rumen contents.[10] Tracheal, pulmonary, and muscle congestion may be observed, along with hemorrhages in multiple organs. Cyanide ion content may be measured in refrigerated samples of heart, brain, or skeletal muscle or rumen contents. Blood samples for analysis should be kept in airtight containers at 4° C until analyzed. A sensitive field test for use on forage samples or rumen content has been developed using alkaline picrate-treated filter paper strips.[11]

A number of plants have varying levels of cyanogenic glycosides, including trees, shrubs, crops, and grasses: acacia, African star grass, apple, arrow grass, Bahia grass, bamboo, Bermuda grass, birdsfoot trefoil, bracken fern (Color Plate 54-2), cassava, chokecherry, Christmas berry vetch, corn, elderberry, eucalyptus, flax, flowering quince, hydrangea, Indian grass, Johnson grass, lima bean, mountain mahogany, poison suckleya, reed canary grass, service berry, sorghum, South African daisy, star grass, Sudan grass, tall manna grass, Texas queen's delight, and white clover.[10,23] Seeds of apples and crabapples (*Malus* spp.) and the seeds, as well as leaves of the *Prunus* spp. (bitter almond, cherry, chokecherry, apricot, peach, nectarine, plum, mock orange), may have large amounts of cyanide. Drying as hay or incorporation into silage generally decreases the toxic potential of the forage plants; most are not routinely grazed or browsed. Early growth phases of the plants are the most toxic. Poisoning is most likely if animals eat a large quantity in a short period of time. Wilting, frost, or other damage to the plant enhances toxicity.[1] Toxicity is measured as cyanogenic potential. Plant material containing more than 20 mg per 100 g (200 ppm) cyanide potential is reason for concern, but this varies between species.[23] Cyanogenic potential is significantly reduced by properly curing forages for hay or ensilage.

If the diagnosis is rapidly made, some cattle and sheep may be saved by intravenous or intraperitoneal injection of 20 mL of a 10% solution of sodium thiosulfate mixed with 10 mL of a 10% solution of sodium nitrite.[1] This treatment, however, is not approved for use in food animals. An alternative treatment for ruminants with thiosulfate alone using a 30% to 40% solution intravenously (IV) at a dose of 25 to 50 g/100 kg of body weight has also been described.[11] Administration of a gallon of vinegar diluted in 3 to 5 gallons of water administered by stomach tube to help acidify the rumen has also been recommended.[10] Preventive measures are largely focused on limiting access to highly cyanogenic plants and trees, particularly during rapid early-growth phases, and planting varieties with lower cyanogenic potential.

Nitrate Toxicity

Many plants in addition to some water sources contain harmful concentrations of nitrates, which can cause a wide range of clinical signs from sudden death to congenital defects in ruminants, camelids, and monogastrics. Examples of plants known to accumulate nitrates are listed in Table 54-3. When photosynthesis is impaired by shade or prolonged cloudiness or excessive nitrogen is applied to plants (e.g., fertilizer), nitrate accumulation may reach dangerous levels. Other triggers for nitrate accumulation include drought, frost, hail, and herbicide application. Nitrates are water soluble and can leach from harvested forages, occasionally causing toxicosis by elevating concentrations in the lowest bales of a rained-on haystack.[25]

In ruminants, ingested nitrates are converted to nitrites and ammonium in the forestomachs. Nitrates can also cross the placenta. If excessive nitrates are ingested, absorbed nitrites can trigger oxidation of the ferrous iron in hemoglobin, producing methemoglobin. Chocolate brown mucous membranes and blood are characteristic findings. Vasodilation and hypotension may result, leading to hypoxia, dyspnea, exercise intolerance, death, fetal stress and subsequent abortion, stillbirths, and/or weak neonates.[27] In bulls, sperm abnormalities and degenerative changes within the testes have been reported.[28] If the animals are anemic or hypoxic for any other reason, methemoglobinemia will have even greater consequences. At

TABLE 54-3

Plants with Potential to Accumulate Nitrates

Type	Common Name	Scientific Name	Reference(s)
Crops	Barley	*Hordecum* spp.	25
	Beets	*Beta vulgaris*	10
	Corn	*Zea mays*	10, 25
	Flax	*Linum* spp.	10
	Kale	*Brassica oleracea*	10
	Oats	*Avena* spp.	24, 25
	Pearl millet	*Pennisetum typhoides*	10, 25
	Rape	*Brassica napus*	10
	Rye	*Secale cereale*	10, 25
	Soybeans	*Glycine max*	10, 25
	Sunflower	*Helianthus annuus*	10
	Turnips	*Brassica rapa*	10
	Wheat	*Triticum aestivum*	10, 25
Forages	Alfalfa	*Medicago sativa*	10, 25
	Barnyard grass	*Echinochloa* spp.	10
	Button grass	*Dactyloctenium radulans*	26
	Johnson grass	*Sorghum halepense*	10, 25
	Sudan grass	*Sorghum vulgare*	10, 25
	Sweet clover	*Melilotus* spp.	10
	Tall fescue	*Lolium arundinaceum*	25
Weeds	Canada thistle	*Cirsium arvense*	10
	Cheese weed, mallow	*Malva* spp.	10
	Dock	*Rumex* spp.	10, 25
	Field bindweed	*Convolvulus arvense*	10
	Fireweed	*Kochia* spp.	25
	Goldenrod	*Solidago* spp.	10
	Jimsonweed	*Datura stramonium*	10
	Kochia (summer cypress)	*Kochia scoparia*	10, 25
	Lambsquarters	*Chenopodium* spp.	10, 25
	Nightshades	*Solanum* spp.	10, 25
	Pigweed	*Amaranthus* spp.	10, 25
	Ragweed	*Ambrosia* spp.	10
	Russian thistle	*Salsola kali*	10
	Smart weed	*Polygonum* spp.	10

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postmortem examination, a brownish cast of the tissues due to the methemoglobinemia may be apparent.

Congenital hypothyroidism in equine neonates is most often caused by insufficient iodine intake by the broodmare but can also be caused by excessive nitrate intake. Multiple animals in the herd may be affected.[29,30] Signs of high nitrate intake may not be observed in the broodmare. Abortion may result, or more commonly, a dysmature foal is produced after prolonged gestation. The affected neonates have varying degrees of signs but classically include mandibular prognathism, flexural deformities of the forelimbs, secondary rupture of the common digital extensor tendon just above the carpus, poorly ossified cuboidal bones, and poor immune function. If recognized at birth, these foals can survive to be useful animals if treated intensively with splints to address the flexural deformity, very limited weight bearing until the cuboidal bones ossify, and measures to reduce the likelihood of infection. If an affected foal is allowed to bear weight before full ossification of the cuboidal bones in the hocks and carpi, angular limb deformities will likely result. The syndrome can be prevented by avoiding high nitrate forage or water sources and ensuring that there is adequate iodine in the mare's diet. Confirmation of nitrate toxicity is based on demonstration of elevated levels in forages, weeds, water, or body fluids such as aqueous humor, fetal stomach fluid, and amniotic fluid.[1,10] In ruminants, plants containing more than 1.5% nitrates (measured as KNO3) dry weight may be lethal. Sublethal effects are seen from feed containing 0.5% to 1.5% nitrates. Seeds are usually unaffected by high nitrates in other plant parts. Ruminants can adapt to higher nitrate feeds if their introduction is gradual. Reproductive effects in ruminants are linked to forage concentrations greater than 5000 ppm on a dry matter basis.[27] In adult ruminants, signs of methemoglobinemia are seen with forages containing 2000 to 10,000 ppm nitrates on a dry matter basis. Water with greater than 200 ppm is excessive for pregnant ruminants, with 30 ppm the recommended limit for broodmares.[10,29,30] In nonpregnant animals, ranges from 445 to 1000 ppm in water are considered dangerous for livestock.[10,26]

Treatment of nitrate toxicity in ruminants is restricted by the paucity of approved drugs. Methylene blue administration is prohibited in food animals in the United States for at least 180 days before slaughter but, if permitted in other areas, may be given IV at a rate of 4 to 15 mg/kg body weight as a 2% to 4% solution.[10] Adjunct therapies that have been suggested in acute ruminant cases are administration of either cold water or vinegar to slow nitrate reduction, as well as mineral oil to hasten passage of the ingested source if the stress of intubation is warranted.[10] Identification of the nitrate source and prevention of animal access are the most effective management tools.

Forages known to have high nitrate potential should be tested before feeding them to livestock, particularly if fertilizer has been used. High nitrate forages can potentially be ensiled to reduce the nitrate content by as much as 30%.[26] Nitrate levels are highest at night and early morning, and this knowledge can be applied to the timing of pasture access and hay cutting. Gradual introduction of high nitrate forage into the ruminants' diet will permit rumen microflora to adapt, but this should preferentially begin with nonpregnant adult animals to minimize the reproductive effects. Monensin in the diet may lower the threshold for toxicity,[31] and probiotics containing *Propionibacteria* spp. reduce nitrates, which may also be useful.[10]

Neurologic Signs

Many plant ingestions result in neurologic signs exclusively or as part of an array of signs. Plants linked to neurologic deficits are listed in Table 54-4. Many other plants found in Australia and New Zealand are also capable of producing neurologic signs.[3] Abnormal behavior, seizures, coma, ataxia, weakness, and muscle tremors may be associated with ingestion of poisonous plants or other medical conditions such as rabies, encephalitis, and electrolyte disorders. Perennial ryegrass infected with an endophyte, *Neotyphodium lolii,* causes perennial ryegrass staggers in all herbivores. The syndrome, caused by lolitrem B, was recently reproduced in horses that demonstrated varying degrees of muscle fasciculations, tremors, truncal swaying, basewide stance, and limb edema.[35] Signs abate when the forage is changed.

Locoweed and Milkvetch

Locoweed and milkvetch (*Astragalus* spp. and *Oxytropis* spp.) (Color Plate 54-3) are the most important plant-related toxicoses in the western United States and significantly affect animals in other areas of the world.[10] A review of poisonous plants affecting livestock in China suggested locoweeds were responsible for an estimated 80% of all livestock losses due to plant toxicoses.[2] Many species in these genera can cause four different toxic syndromes: sudden death from methemoglobinemia due to nitro compounds in cattle and sheep (milkvetch [*Astragalus* spp.]); respiratory syndrome with emphysema-like signs, most often seen in sheep (milkvetch [*Astragalus* spp.]); neurologic signs (*Astragalus* spp. and *Oxytropis* spp.); and selenium toxicosis (*Astragalus* spp.). Recent investigations have shown that the toxin swainsonine, responsible for the signs of nervous system dysfunction, is produced by an endophyte *(Undilum oxytropis)* in the plant seeds rather than the plants themselves.[39] Swainsonine triggers clinical signs after chronic locoweed ingestion in horses and ruminants. This same toxin poisons horses and cattle that consume swainsona or darling pea (*Swainsona* spp.) in Australia.[3] The toxin creates a lysosomal storage disease in which α-mannosidase is inhibited, resulting in swelling of axonal hillocks and growth of new dendrites and synapses in severe locoweed cases, a nonreversible change.[36]

Clinical neurologic signs of locoweed intoxication begin with depression and incoordination, progressing to aberrant behavior including incoordination, aggression, circling, weight loss, and eventually death if locoweed consumption continues. In affected horses, this also leads to unpredictable behavior, endangering riders, so these animals are often euthanized or salvaged for breeding. Similar signs may be seen in horses forced to eat sagebrush.[10] Pregnant animals may abort or give birth to neonates with neurologic signs. In cattle and sheep, swainsonine-induced damage to the lungs and hearts may contribute to high mountain disease, characterized by right-sided heart failure.[10]

Nitro-toxins are the most common toxins found in the milkvetch species of *Astragalus* and are responsible for the greatest ruminant herd and flock problems. The toxic principles are β-D-glycosides converted to 3-nitro-1-propanol (miserotoxin) in the rumen and subsequently changed to the toxic compound 3-nitropropionic acid in the liver.[36] Signs of acute toxicosis include weakness, tachycardia, respiratory distress, coma, and death. Chronic consumption results in neurologic signs beginning with weakness, incoordination, fetlock knuckling, and goose stepping, progressing to paralysis and death. Respiratory emphysema, as well as incoordination and weakness, may be observed in both acute and chronic cases, particularly in sheep.

Chronic ill thrift is attributed to chronic locoweed consumption. Research in food animals has demonstrated a number of effects attributed to swainsonine, including reduced production of growth hormone and thyroxine, decreased intestinal absorption of nutrients, and reduced immune response to vaccinations. These can lead to poor weight gain and increased frequency of infections.[10]

Diagnosis of locoism is based on clinical signs and can be confirmed by measurement of swainsonine and/or α-mannosidase in serum. Vacuolation of peripheral lymphocytes may be evident in some cases. Vacuolation of many tissues, particularly brain and liver, may be seen histologically after finding little gross change at necropsy. Treatment is removal from locoweed forage.[10]

Locoweed is usually not palatable but will be eaten if more enticing forage is not available. For example, many locoweed species start growth early in the spring, attracting livestock less interested in dormant grasses. This period of preference is influenced by rainfall, so the impact of locoweed and milkvetch species will vary from year to year even within a region. Prevention is challenging if alternative forages are not available in the spring. One innovative approach is a

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TABLE 54-4

Plants Associated with Neurologic Signs*

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Blown grass, Pacific bent grass[3]	*Agrostis avenacea*	B, O	Corynetoxins in nematode	Australia, NZ, SW U.S.	Incoordination, weakness, muscle weakness, rocking stance, high stepping, collapse, seizures, abortion	
Bracken fern[10]	*Pteridium aquilinum*	E, P, B, O	Ptaquiloside	Worldwide	Weight loss, progressive incoordination, depression, tremors, crouching stance with arched neck (equine), blindness (sheep), aplastic anemia (ruminants), thrombocytopenia, bladder and gastrointestinal cancer	Thiamine
Buttercup[10]	*Ranunculus* spp.	B, E	Ranunculin	North America, Europe	Salivation, depression, blindness, hematuria, oral ulcers, diarrhea, colic	
Caltrop or carpetweed[10]	*Kallstroemia* spp.	B, O, C	Unknown	SW U.S.	Hindlimb weakness, knuckling, seizures, posterior paralysis	
Castor bean[19]	*Ricinus communis*	E, B, O, C, P	Ricin	Worldwide	Bloody diarrhea, tenesmus, colic, trembling, incoordination, seizures	
Coyotillo[10]	*Karwinskia humboldtiana*	B, O, C, E, P	Unknown	SW U.S.	Hypersensitivity, muscle tremors, abnormal high stepping gait, diminished reflexes, progressive paralysis	
Fitweed[10]	*Corydalis* spp.	B, E	Isoquinolone alkaloid	U.S., Canada	Tachypnea, seizures, staggering, snapping at objects, muscle tremors, depression	
Golden chain tree[10]	*Laburnum anagyroides*	E, B	Cystisine	Southern U.S.	Incoordination, muscle tremors, mydriasis, excitement, seizures, coma, vomiting, diarrhea, paralysis	
Hairy cat's ear, flatweed[32]	*Hypochaeris radicata*	E	Unknown	U.S., Europe, Australia	Bilateral stringhalt, depression, aggression	Phenytoin
Hairy vetch[10]	*Vicia villosa*	B, E	Unknown	U.S., Europe	Excitement, slobbering, oral ulcers, nasal discharge, cough, stiffness, anorexia, weakness, seizures, swelling of the head and neck, pruritic dermatitis, diarrhea, abortion, myocardial necrosis	
Halimium[33]	*Halimium brasiliense*	O	Unknown	Brazil, Uruguay	Transient seizures when excited, muscle tremors, ventroflexion of neck or opisthotonus, nystagmus, tetanic spasms, postictal ataxia	
Horse chestnut, buckeye[10]	*Aesculus hippocastanum*	B, O, C, E	Aesculin, fraxin, alkaloids	U.S., Europe	Muscle tremors, incoordination, depression or excitability, hopping gait, dorsomedial strabismus (ruminants), gastroenteritis (monogastrics)	
Horse nettle[10]	*Solanum carolinense*	B, E	Solanine	U.S., Canada	Falling when excited, incoordination, anorexia, emaciation, rough coat, constipation, mouth inflammation	Physostigmine
Horsetail or scouring rush[10]	*Equisetum* spp.	E, B, O	Aconitic acid, palustrine, thiaminase	Worldwide	Weight loss, staggering, muscle tremors or rigidity, paraparesis, tachycardia, diarrhea, coma	Thiamine
Jamaican nettle tree[34]	*Trema micrantha*	B, C, E	Trema toxin, ammonia	Americas	Apathy, blindness, recumbency, paddling, coma (hepatic encephalopathy)	
Jimmyweed[10]	*Haplopappus heterophyllus*	B, E	Tremetol	Western U.S., Mexico	Depression, trembling, weakness, knuckling, seizures, paralysis, congestive heart failure, acetone breath smell	
Jimsonweed, thornapple[35]	*Datura* spp.	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Johnson grass[10]	*Sorghum halepense*	B, O, E	Hydrocyanide	Worldwide	Posterior ataxia, urinary incontinence, cystitis, weight loss	
Kochia[1]	*Kochia scoparia*	B, O E	Thiaminase, nitrates, oxalates	Worldwide	Ataxia, muscle spasms, depression, blindness, photosensitization	Thiamine

Continued

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TABLE 54-4

Plants Associated with Neurologic Signs*—cont'd

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Locoweed[36]	*Astragalus* and *Oxytropis* spp.	E, B, O, C	Swainsonine (endophyte produced)	Worldwide	Abnormal behavior, abortion, reduced fertility, skeletal malformations, weight loss	
Locust trees[19]	*Robinia* spp.	E, B, O, C	Robinin, robitin	North America, Europe	Diarrhea, anorexia, weakness, posterior paralysis, mydriasis, dyspnea, arrhythmias	
Lupines[1]	*Lupinus* spp.	O, B	Piperidine, quinolizidine	U.S., Canada	Salivation, frothing, depression, dyspnea, loss of muscle control, convulsions, coma, birth defects	
Mescal bean, Eve's necklace	*Sophora* spp.	B, O, C, E	Cystisine	SW U.S., Mexico	Incoordination, violent muscle tremors, falling, stiffness, respiratory paralysis	
Milkvetches[10,36]	*Astragalus* spp.	B, O, E	Miserotoxin	North America	Acute and chronic—acute: respiratory distress, muscle weakness, emphysema; chronic: goose stepping, knuckling, wheezing, drooling, posterior paresis, collapse	
Milkweed[36]	*Asclepias* spp.	E, C, O, C	Glycosidic cardenolides	North America	Depression, weakness, dyspnea, ataxia, seizures, arrhythmias	
Morning glory[3]	*Ipomoea* spp.	B, O, C, E	Calystegines	Worldwide	Ataxia of hindlimbs, staggering	
Nightshade[10]	*Solanum* spp.	B, O, C, E	Solanine	Worldwide	Fatigue, muscle tremors, head tremors, seizures, bloat, congestion of lungs, heart, spleen	Physostigmine
Oak[10]	*Quercus* spp.	B, E, O, P	Gallotannins	North America, Europe	Incoordination in horses along with weakness, ileus, mouth ulcers, mucosal discoloration, patchy sweating, abnormal feces, colic, dark urine	
Paspalum grasses[37]	*Paspalum* spp.	B, E	Ergot alkaloids	Worldwide	Staggers, muscle tremors, seizures, abortion, gangrene	
Poison hemlock[1]	*Conium maculatum*	O, B, P, E	Coniine, γ-coniceine	North America, Europe	Trembling, ataxia, salivation, incoordination, mydriasis, tachycardia, respiratory paralysis, coma, convulsions, birth defects	Atropine
Russian knapweed[1]	*Centaurea repens*	E	Sesquiterpene lactones	Western U.S.	Twitching of lips, tongue flicking, involuntary chewing, weight loss, emaciation, poor prehension, incoordination, muscle tremors, facial paralysis	
Ryegrass[38]	*Lolium perenne*	B, O, E	Lolitrem B	Worldwide	Muscle tremors, fasciculations, truncal swaying, basewide stance, slowed movement, limb edema	
Sagebrush[10]	*Artemesia* spp.	E	Unknown	Western U.S., Mexico	Abnormal behavior, ataxia, sage aroma in breath and manure	
Sneezeweed[1]	*Hymenoxys* spp.	O, B, E	Sesquiterpene lactones	North America	Equine: weakness, incoordination, foaming at the mouth, seizures; ruminants: chronic vomiting, emaciation, stiffness	
Squirrel corn, Dutchman's breeches[10]	*Dicentra* spp.	B, E	Isoquinoline alkaloid	North America	Muscle tremors, seizures, extensor rigidity, dyspnea, pain	
Sudan grass[10]	*Sorghum sudanense*	B, O	Hydrocyanide, nitrates	Worldwide	Posterior ataxia, urinary incontinence, cystitis, weight loss	
Yellow jessamine[10]	*Gelsemium sempervirens*	E, B, O, C, P	Gelsemine, gelseminine	Eastern U.S., Mexico	Weakness, hypothermia, mydriasis, seizures, extensor rigidity, coma	
Yellow star thistle[1]	*Centaurea solstitialis*	E	Sesquiterpene lactones	U.S., Argentina, Australia	Twitching of lips, tongue flicking, involuntary chewing, weight loss, emaciation, poor prehension, incoordination, muscle tremors, facial paralysis	

*Plant names in bold are discussed in more detail in the text.

†Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine, *P,* porcine.

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conditioned food aversion model that combines feeding fresh-picked locoweed to naive animals with lithium chloride administration by stomach tube. The treated animals form a strong and lasting (>3 years) aversion to locoweed following a single dose but must be pastured separate from nonaverted animals on locoweed areas to prevent social facilitation from extinguishing the aversion.[22]

Musculoskeletal Disease Attributed to Plant Poisoning

Plant poisonings may affect the skeletal system, resulting in abnormal bone growth or remodeling. Day-blooming jasmine *(Cestrum diurnum)* induces calcinosis in horses and cattle by means of calcinogenic glycosides that may be converted to vitamin D–like compounds.[10,40] This plant is found in the southeastern United States and tropical countries. Other plants with this potential include *Solanum malacoxylon, S. sodomeum, S. linnaeanum, Trisetum flavescens,* and *Nierembergia veitchii*.[10] Those that affect the fetus are discussed in the reproductive section.

Signs of muscle dysfunction in livestock and horses have been attributed to ingestion of a number of plants, often as part of a larger panoply of signs. Muscle tremors may be manifestations of muscle or nervous system dysfunction, as well as electrolyte disturbances or pain. The toxin tremetol (tremetone and other compounds) affects all species of livestock and horses that consume it. The effects of the toxin are cumulative and affect both skeletal and cardiac muscle. Plants of importance include white snakeroot *(Eupatorium rugosum),* rayless goldenrod *(Haplopappus heterophyllus),* and burrow weed *(Isocoma pluriflora).*[10] Adult cattle are relatively unaffected by consumption of white snakeroot but pass the toxin through the milk, causing clinical signs in milk-fed calves. Rayless goldenrod produces myonecrosis and cardiomyopathy at higher doses in goats.[41] Horses, cattle, and pigs may also be affected by this plant. The effect of tremetol on myocardial tissue may lead to arrhythmias and congestive heart failure. Tremorgenic mycotoxins should also be considered in cases with muscle tremors, particularly in livestock grazing perennial ryegrass or paspalum species such as Dallisgrass or Bahiagrass.[42]

Cassia (Senna) species such as coffee weed (Color Plate 54-4) and sickle pod are an important source of skeletal and cardiac muscle degeneration and gastroenteritis in cattle, sheep, goats, horses, and pigs.[10] In severe cases, hepatic and renal failure may also be observed. Gossypol poisoning attributed to feeding cottonseed meal is a source of muscle degeneration and significant morbidity and mortality in livestock.[10]

Summer Pasture-Associated Myositis and Equine Atypical Myopathy

Recent research has defined ingestion of box elder seeds from female trees *(Acer negundo)* (Color Plate 54-5) as a cause of acute, nonexertional, severe, often fatal rhabdomyolysis in pastured horses and a donkey in the United States and Canada.[43] The syndrome of atypical myopathy seen in horses, donkeys, and zebras in Europe may also have this underlying cause because outbreaks have been linked to ingestion of maple leaves *(Acer pseudoplantanus)* covered with European tar spot *(Rhytisma acerinum).*[44] Box elder trees are also found in Europe. Additionally, European researchers have demonstrated a link between atypical myopathy and *Clostridium sordellii* toxin.[45] In both syndromes, one or multiple animals may be affected, typically on a premises that houses the equids for at least part of the day on a pasture surrounded by or with trees, sparse grass, and often after a storm or high winds in spring or autumn brings down tree branches or seeds.[43,46] The toxic principle identified in box elder seeds is hypoglycin A, a branched chain amino acid, which is metabolized to methylene cyclopropyl acetic acid (MCPA), a potent inhibitor of multiple acyl-CoA dehydrogenases (MADD). Lack of these enzymes damages mitochondria and impairs lipid metabolism within muscle cells, leading to lipid accumulation, thus limiting the muscle cell's energy supply and causing cell death.[43]

Clinical signs include muscle weakness, recumbency, and myoglobinuria.[43] Other signs that are reported include dysphagia, esophageal obstruction, or colic-like signs. In atypical myopathy, myocardial damage may be detected with electrocardiography (ventricular premature depolarizations, prolonged QT intervals); echocardiography (abnormal ventricular wall motion); and elevated serum troponin concentrations.[47] Histologically, the change in both diseases is marked myofibril degeneration with intramyofiber lipid accumulation in skeletal, respiratory, and cardiac muscles. Additional confirmation of this etiology for rhabdomyolysis can be obtained at specialized laboratories by demonstration of increased urinary organic acids (specifically ethylmalonic and methyl succinic acids and glycine conjugates) and abnormal patterns of serum acylcarnitines.[48] Other toxic etiologies for muscle disease to be considered are white snakeroot, rayless larkspur, and monensin toxicity.

Treatment of affected cases is symptomatic but should also include attention to establishing a positive energy balance. Case fatality rate is high despite treatment.[43] Preventive measures should focus on provision of sufficient forage to deter horses from consuming box elder seeds, rapid removal of downed box elder branches after high winds, and planting less toxic trees as windbreaks.

Cardiovascular and Hematologic Plant Toxicities

Ingestion of plants that contain toxins affecting myocardial function may result in a wide variety of signs including sudden death. Plants most noted for producing myocardial effects when consumed are those that contain cardiac glycosides; cattle are most frequently affected. These include the pasture plants milkweed (*Asclepias* spp.), dogbane or Indian hemp *(Apocynum cannabinum),* blue-eyed grasses (*Sisyrinchium* spp.), and a number of plants more likely to be found in gardens than pastures: foxglove (*Digitalis* spp.), hellebores (*Helleborus* spp.), hyacinth (*Hyacinthium* spp.), kalanchoe (*Bryophyllum* spp.), lily of the valley *(Convallaria majalis),* oleander (*Nerium* spp.), periwinkle *(Vinca major),* pheasant's eye *(Adonis microcarpa),* spindle tree (*Euonymus* spp.), squill (*Drimia* or *Urginea* spp.), and star of Bethlehem (*Ornithogalum* spp.). Digestive signs of hemorrhagic enteritis with colic may also be seen.[10] Gousiekte is a syndrome of heart failure and sudden death affecting sheep and cattle in South Africa 4 to 6 weeks after ingestion of Rubiaceae (coffee) family plants containing pavetamine. Six plants in the genera *Fadogia, Pavetta,* and *Vangueria* have been implicated in significant losses. New research suggests that toxin production in the plants may be linked to their infection by *Burkholderia* spp. of endophytic bacteria.[49] The toxin inhibits myocardial protein synthesis, resulting terminally in dilated cardiomyopathy and congestive heart failure.[50]

Four important plants with toxins that damage the myocardium and cause mortality in large animals are yew (*Taxus* spp.), avocado *(Persea americana),* death camas (*Zigodenus* spp.), and summer pheasant eye (*Adonis* spp.). Avocado poisoning in horses produces edematous swelling of the head and neck and subsequent respiratory distress, which may progress to congestive heart failure. Goats may also develop signs of heart failure. The udder is affected by avocados in female horses, cattle, and goats, creating a noninfectious mastitis.[10] Summer pheasant eye consumed in hay caused signs of colic and death in horses, and pigs have died after consuming a diet containing *Adonis* seeds.[51]

Signs of anemia and hemorrhage are linked to ingestion of several groups of plants that may cause methemoglobinemia, erythrolysis, or thrombocytopenia. Ingestion of wilted maple leaves or bark (*Acer* spp.) (Color Plate 54-6), most often red maple, results in oxidative damage to erythrocytes and acute Heinz body anemia with methemoglobinemia in horses and zebras. Weakness, tachycardia, tachypnea, icterus, and hemoglobinuria may occur. In severe cases, laminitis, colic, or abortion may result.[52] In ruminants, nitrate-accumulating plants that cause methemoglobinemia should be considered (see Table 54-3). Wild onions and garlic can also cause

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hemolytic anemia, most often observed as a clinical problem in cattle.[10]

Plants that contain coumarin, such as sweet clover (*Melilotus* spp.), have the potential for endogenous coumarin to be converted to dicoumarol if cut plants become moldy. Signs ranging from subtle to death may be observed, particularly in cattle, depending on the amount of dicoumarol ingested and trauma to the animal that may cause bleeding. Transfusion and vitamin K_1 administration may be necessary in moderate to severe cases.[10]

Thiaminase enzymes in bracken fern *(Pteridium aquilinum)* and horsetail (*Equisetum* spp.) produce thiamine deficiency most often in horses and pigs, resulting in anemia and hemoglobinuria. Other signs associated with bracken fern ingestion are due to alternate toxins, particularly ptaquiloside, a sesquiterpene glycoside responsible for detrimental effects on the bone marrow and neoplastic changes in the bladder and upper gastrointestinal tract. The cancerous changes in the urinary tract may be manifest as enzootic hematuria in cattle. Retinal changes resulting in blindness are reported in sheep. The toxins are transmitted through milk. Protamine sulfate administration may counteract the effects on blood coagulation. In horses, bracken fern may also produce neurologic signs and colic.[10,36]

Digestive and Hepatic Plant Poisonings

A plethora of plants have the potential to induce pathology in the digestive tract and liver. Plants that cause significant impact in large animals are listed in Table 54-5. The effects of a plant may be mechanical or chemical irritation, altered motility, or altered cell function. Depending on the toxin, plant species, animal species, and stage of intoxication, a single species of plant may produce a wide range of signs, even within the same animal. Clinical signs may include excessive salivation or slobbering, anorexia, dysphagia, colic, vomiting or regurgitation in ruminants, bloat, constipation, diarrhea, and melena. Excessive salivation may result from injury due to plant awns, irritant substances in the plant, mold infection of the plant (e.g., red clover and slaframine production), and inability to swallow. Sources of plant awns include grasses (e.g., foxtail, needle, squirrel tail, bristle, sandbur, medusahead rye, prairie three-awn, tanglehead, tickle grass); cacti (e.g., prickly pear); nettles; and many seed pods.[10,55] Substances irritating to mucous membranes are found in a number of plants and may also produce signs of diarrhea in the more distal digestive tract.

Bracken fern *(Pteridium aquilinum)* has long been recognized as a cause of enzootic hematuria and bladder cancer but more recently has been linked to upper digestive tract squamous cell carcinoma in cattle grazing pastures with high bracken content in conjunction with bovine papillomavirus type 4. In a study that reviewed 40 tumors in cattle, metastasis was common (56%), predominately to regional lymph nodes.[56]

Hepatic Disease

Absorption of toxins from the digestive tract results in subsequent exposure of liver tissue where further pathologic changes may be induced. Depending on the toxin and disease syndrome, signs of liver disease may be only subtle weight loss or failure to grow, but more often include icterus, photosensitization, and/or hepatic encephalopathy. For example, alsike clover in horses can produce two syndromes, either hepatic encephalopathy or photosensitization. (Plants causing primary photosensitization are listed in the later discussion of plant-induced skin lesions.) A variety of plants damage biliary cells leading to secondary photosensitization as the primary clinical sign, including agave *(Agave lecheguilla),* bear grass or sacahuista *(Nolina texana),* bog asphodel *(Narthecium ossifragum),* kleingrass and switchgrass (*Panicum* spp.), and puncture vine *(Tribulus terrestris).*[10] Mycotoxins can also produce biliary damage leading to photosensitization. Photosensitization is one of many systemic signs that may be seen with consumption of plants, such as black sage *(Artemesia nova)* consumed concurrently with horsebrush (*Tetradymia* spp.), *Brassica* spp., Dutchman's breeches *(Thamnosma texana),* hairy vetch *(Vicia villosa),* inkweed *(Phytolacca octandra), Kochia* spp., *Lantana* spp. (Color Plate 54-7), and yellow wood *(Terminalia oblongata).*[3,10,36,57] Plants containing pyrrolizidine alkaloids also produce photosensitization and are the most important source of widespread liver problems to both livestock and horses (see later).

Severe hepatic disease may lead to signs of liver failure, including hepatic encephalopathy and sudden death. The pyrrolizidine alkaloid

TABLE 54-5

Plants Producing Gastrointestinal Clinical Signs*

Common Name	Scientific Name	Species Affected*	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Pyrrolizidine alkaloid plants[10]	See Table 54-6	P, B, E, C, O	Pyrrolizidine alkaloids	Worldwide	Loss of appetite, lethargy, diarrhea, constipation, icterus, photosensitization	
Autumn crocus[10,16]	*Colchicum autumnale*	B, E, P	Colchicine, colchiceine	Europe	Salivation, dysphagia, colic, abdominal pain, diarrhea, tenesmus, melena, cardiorespiratory failure, congenital defects	
Bitterweed[1]	*Hymenoxys odorata*	O, B	Sesquiterpene lactone	SW U.S.	Weight loss, poor appetite, vomiting, bloat, abdominal pain, stiff gait (lambs)	
Box or boxwood[10]	*Buxus sempervirens*	E, B, O,	Alkaloids	Worldwide	Colic, melena, respiratory failure	
Broomweed, snakeweed[1]	*Gutierrezia* spp.	O, C, E, B	Saponins	Western U.S., Mexico	Diarrhea, constipation, rough hair coat, anorexia, abortion, photosensitization	
Buffalo bur[10]	*Solanum rostratum*	E, B, O, C	Solanine alkaloids and glycoalkaloids	U.S.	Trauma to mucosal surfaces, tiredness, muscle tremors, bloat, congestion of lungs, heart, liver, spleen	Physostigmine
Buttercup[10]	*Ranunculus* spp.	B, E	Ranunculin	North America, Europe	Salivation, depression, blindness, hematuria, oral ulcers, diarrhea, melena, colic	

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TABLE 54-5

Plants Producing Gastrointestinal Clinical Signs*—cont'd

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Castor bean[10]	*Ricinus communis*	E, B	Ricin	Worldwide	Bloody diarrhea, tenesmus, colic, trembling, incoordination, seizures	
Chinaberry[10]	*Melia azedarach*	P, B, O, C, E	Alkaloids, saponin	China, SE U.S.	Colic, vomiting, constipation, hemorrhagic diarrhea or muscle tremors, ataxia, seizures, tetraparesis	
Coffeeweed[10]	*Cassia* spp.	B, O, C, E, P	N-methylmorpholin and anthraquinone glycoside	Eastern, southern U.S.	Diarrhea, anorexia, staggering gait, myoglobinuria, renal failure, liver failure (horse)	
Colorado rubberweed (Pingue)[1]	*Hymenoxys richardsoni* var. *floribunda*	O, B	Sesquiterpene lactone	Western U.S.	Weight loss, poor appetite, vomiting, salivation, GI stasis, bloat, abdominal pain, weakness, depression, stiff gait	
Corn cockle[10]	*Agrostemma githago*	B, O, P, E	Githagenin	U.S., Europe	Colic, diarrhea	
False hellebore, skunk cabbage[10]	*Veratrum* spp.	O, B. C	Steroids	U.S., Canada	Salivation, colic, diarrhea, respiratory failure, abortion, malformed neonates	
Foxtail grass[10]	*Hordeum jubatum*	E	None	U.S., Canada	Foreign body–induced ulceration in ears, eyes, neck, face, mouth, colic, impaction	
Hairy vetch[10]	*Vicia villosa*	B, E	Unknown	U.S., Europe	Excitement, slobbering, nasal discharge, cough, stiffness, anorexia, weakness, seizures, swelling of the head and neck, pruritic dermatitis, hair loss, diarrhea, abortion, photosensitivity	
Horse nettle[10]	*Solanum carolinense*	B, E	Solanine	U.S., Canada	Anorexia, emaciation, rough coat, constipation, mouth inflammation, falling when excited	Physostigmine
Jimsonweed, thornapple[35,53]	*Datura* spp.	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Kentucky coffee tree[10]	*Gymnocladus dioica*	B, O, E	Cystisine	Eastern U.S., Canada	Vomiting, colic, diarrhea, hypotension, bradycardia, seizures, muscle paralysis	
Lantana[10]	*Lantana camara*	B, O, C, E	Lantadene A & B	Worldwide	Photosensitization, anorexia, constipation, gastroenteritis	
Laurel[10]	*Kalmia* spp.	E, O, B, C	Andromedotoxin	Northern U.S., Canada	Colic, nasal discharge, salivation, odontoprisis, bloat, bradyarrhythmias, collapse, coma	
Leafy spurge[10]	*Euphorbia* spp.	B, E	Unknown	North America	Blistering of lips, tongue, skin, gastrointestinal irritation, photosensitization	
Lobelia[10]	*Lobelia* spp.	B, O, C	Lobeline	U.S., Mexico	Excessive salivation, vomiting, diarrhea, mydriasis, coma, ± oral and corneal ulcers	
Locust trees[36]	*Robinia* spp.	E, B, O, C	Robinin, robitin	North America, Europe	Diarrhea, anorexia, weakness, posterior paralysis, mydriasis, dyspnea, arrhythmias	
Marsh marigold[10]	*Caltha palustris*	B, O, E	Anemonin	Northern U.S., Canada	Ulceration of skin, oral cavity, salivation, diarrhea, colic, nervousness	
Mesquite[10]	*Prosopis glandulosa*	E, B	Arabinose	Western U.S.	Colic, salivation, rumen or intestinal obstruction (phytobezoars), tremors, anemia, emaciation	

Continued

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TABLE 54-5

Plants Producing Gastrointestinal Clinical Signs*—cont'd

Common Name	Scientific Name	Species Affected†	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Nightshade[10]	*Solanum* spp.	B, O, C, E, P	Solanine	U.S.	Fatigue, muscle tremors, mydrasis, bloat, colic, watery diarrhea, congestion of lungs, heart, spleen	Physostigmine
Oak[10]	*Quercus* spp.	B, E, O, P	Gallotannins	North America, Europe	Incoordination in horses along with weakness, ileus, mouth ulcers, mucosal discoloration, patchy sweating, abnormal feces, colic, dark urine	
Oleander[10]	*Nerium oleander*	B, E	Oleandrin, neriine	Southern U.S., Mexico, Mediterranean	Tachycardia, severe gastroenteritis, diarrhea, abdominal pain, sweating, weakness	
Persimmon[10]	*Diospyros virginiana*	E	Tannins	Southern U.S.	Obstruction due to phytobezoars, colic, weight loss	
Pokeweed[10]	*Phytolacca americana*	B, O, C, P, E	Saponins, oxalates, alkaloids	Eastern U.S.	Oral irritation, excessive salivation, vomiting, colic, bloody diarrhea, depression	
Privet[10]	*Ligustrum vulgare*	E, B	Ligustrin, ligustron	U.S., Canada	Diarrhea, severe colic, hypotension, renal failure	
Rape[10]	*Brassica napus*	B, E	Glucosinolates	North America	Colic, bloat, diarrhea, pulmonary emphysema (cattle), icterus, anemia, goiter	
Red clover[10]	*Trifolium pratense*		Slaframine from mold infection	U.S.	Slobbers, bloat, stiffness, diarrhea, blindness, abortion, laminitis	
Rhododendron[10]	*Rhododendron maximum*	B, O, C, E	Andromedotoxin	U.S., Canada	Colic, nasal discharge, salivation, odontoprisis, bloat, bradyarrhythmias, collapse, coma	
Rosary pea[10]	*Abrus precatorius*	E, C	Abrin	SE U.S.	Anorexia, abnormal temperature, ulcers, incoordination, lung congestion, liver and urinary damage	
Sesbania or bladderpod[10]	*Sesbania* spp.	B, O, C	Saponins	North America	Severe hemorrhagic diarrhea, abomasitis, renal and hepatic necrosis	
Sneezeweed[1]	*Hymenoxys hoopesii*	O, B, E	Sesquiterpene lactone	North America	Vomiting, stiff gait, poor appetite, weakness, coughing ± aspiration, pneumonia, emaciation, ascites	
Tobacco[10]	*Nicotiana* spp.	E, B	Nicotine	Southern U.S., Mexico	Muscle tremors, tachyarrhythmias, colic, dyspnea, diarrhea, congenital defects (blindness, staggering, forelimb collapse, coma at high doses)	
Tung or candle nut tree[10]	*Aleurites* spp.	B	Saponins	China, SE U.S.	Anorexia, atonic rumen, watery diarrhea, emaciation	
Yellow wood[3]	*Terminalia oblongata*	B, O	Tannins	Australia	Nervous signs (sheep). Colic, photosensitization, icterus, dark urine, stiffness, nephrosis (cattle)	
Yellow bristle grass[10]	*Setaria lutescens*	E	None	U.S., Canada	Ulcers in mouth, digestive tract	
Yerba de pasmo[54]	*Baccharis pteronioides*	B, O, E	Trichothecenes	SW U.S., South America	Anorexia, hemorrhagic enteritis	

*Plant names in bold are discussed in more detail in the text.

†Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine; *P,* porcine.

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TABLE 54-6

Plants Containing Pyrrolizidine Alkaloids

Common Name	Scientific Name	Plant Habitat	Reference(s)
Groundsel	*Senecio* spp.	Western U.S., Australia	1, 3
Heliotrope	*Heliotropium* spp.	Worldwide	3
Houndstongue	*Cynoglossum officinale*	SW U.S.	1
Kochia	*Kochia scoparia*	Western U.S.	1
Paterson's curse	*Echium plantagineum*	Australia	3
Rattlebox, rattlepod	*Crotolaria* spp.	U.S., Australia	1, 3
Tansy ragwort	*Senecio jacobaea*	North America, Europe	10, 19
Tarweed, fiddleneck	*Amsinckia* spp.	U.S., Mexico, Australia	10
Viper's bugloss	*Echium vulgaris*	Australia, California	3

plants are the foremost plants associated with this. *Cassia* spp., in particular the seeds, are very toxic to multiple species. Sixty percent of a herd of broodmares died with signs of hepatic encephalopathy with histologic lesions of pericentrolobular necrosis after ingesting seeds of *Cassia occidentalis* in ground corn.[58] Cocklebur (*Xanthium* spp.) and blue-green algae should also be considered. Cocklebur most often produces signs in calves and cattle, but pigs and horses have also been affected.[10]

Pyrrolizidine Alkaloids

This large group of plants is a common source of adverse effects in livestock in many areas of the world, particularly in the southern United States. Plants in this category of toxins are listed in Table 54-6. Most often the clinical syndromes are chronic, with recognition of clinical signs of liver damage months after the plant is eaten. Cattle and horses are most susceptible. Poisoning typically occurs in overgrazed pastures but may also develop when plants such as houndstongue *(Cynoglosum officinale),* tansy ragwort *(Senecio jacobaea),* or rattlebox (*Crotolaria* spp.) (Color Plate 54-8) are incorporated in hay or accidentally harvested with small grains.[1] In cattle, chronic consumption usually occurs for an extended time before the onset of signs. Consumption of mature pyrrolizidine alkaloid forage at a rate of 5% or more of their total daily diet for more than 15 days usually results in death in 1 to 6 months.[1] Young plant growth tends to be even more toxic. Those animals that consume less may become chronic poor doers. Young animals are more easily affected. In horses, consumption of *Crotolaria* spp. causes liver failure and fibrosing pulmonary alveolitis.[10] There is some evidence that pyrrolizidine alkaloids pass through the placental membranes to affect the fetus. In humans, carcinogenicity is reported.[1] The pyrroles are powerful alkylating agents that react with cellular proteins, cross-link DNA, and cause cell necrosis and abnormal mitosis. Pigs are most prone to development of extrahepatic lesions.[36]

Clinical signs are variable but emanate from hepatic damage induced by the ingested pyrrolizidine alkaloids. Other stressors may trigger expression of clinical signs. Photosensitization of areas of white skin, particularly on the animal's dorsum and face, may be the first sign of illness. Crusting around the muzzle and eyes may be observed. In cattle, an unpleasant sweetish odor may be noted. Lethargy, loss of appetite, and weight loss are common. Weakness is observed when the animal tries to walk. In the terminal stages, signs of hepatic encephalopathy such as blindness and belligerent or compulsive behavior may be reported. Mucous membranes and sclera can be markedly icteric. Ascites, diarrhea, or constipation may be present as well.[1] Serum chemistry analysis confirms hepatocellular and biliary cell damage. The characteristic lesion on postmortem examination or biopsy is liver cirrhosis with necrosis and fibrosis, accompanied by bile duct proliferation. Varying degrees of hepatic megalocystosis may be observed in liver tissue.[36] Gastroenteritis may also be evident.

There is no specific treatment for pyrrolizidine alkaloid poisoning. Livestock may frequently graze these plants with seeming impunity if there is abundant high-quality forage available. If pastures with these plants are unavoidable, the use of herbicides should be considered. Biological control measures have been developed for some plants, such as tansy ragwort, and may also be considered as preventive measures.

Reproductive and Neonatal Effect of Poisonous Plants

Poisonous plants that affect fertility, pregnancy, fetal development, and lactation can have a large economic impact, as can plants infected with ergot or endophytes. Livestock at pasture or on a range are frequently affected, creating significant management challenges. The effects may be as subtle as reduced conception rates or as apparent as abortion storms and multiple neonates with congenital defects. Any severe plant poisoning in a pregnant animal has the potential to precipitate an abortion. Toxins from a few plants may pass into the udder in an active form, harming the neonate or human who drinks the milk.

Ponderosa pine *(Pinus ponderosa)* needles and bark, when consumed in the last trimester, are a significant cause of abortion and premature delivery in cattle in the western United States and Canada.[1] Junipers, lodgepole pine, and Monterey cypress evergreens may produce similar syndromes. A few cows or even the whole herd may be affected. Isocupressic acid, the abortifacient compound, is rapidly metabolized to agathic acid in the rumen, a process that is accelerated by conditioning of the cattle to pine needle consumption and thereby reducing its effect.[59] Other toxic compounds such as diterpene abietane acids are also present. A vasoconstrictive effect on uterine vessels leads to uterine inertia, abortion, and frequently, dystocia and/or retained placenta. Edematous swelling of the udder and vulva may be observed before abortion. Calves are typically weak, and lactation may be impaired.[1,10] Many other plants have been identified as sources of significant abortion in other parts of the world.[3,25,60]

Phytoestrogens may accumulate in a number of commonly consumed forages, adversely affecting reproductive performance. Examples include alfalfa and some types of clovers, which can produce coumestrol, and soybeans, which may contain isoflavones. Phytoestrogen concentrations may increase in stressed or diseased legumes. Fungal infections of feed may provide an additional source of xenoestrogens such as zearalenone. These phytoestrogens interact with endogenous estrogen receptors. In ruminants, this can create a syndrome of hyperestrogenism characterized by precocious sexual development in females and preputial swelling and testicular atrophy in immature males. Goats and sheep may be more susceptible than cattle. Disruption of cyclic estrogen changes in older animals has more subtle effects, with the end result of reducing fertility.[25]

A number of plants with significant reproductive effects are discussed earlier in this chapter, including locoweed and those that accumulate nitrate. Locoweed is particularly dangerous to range animals because it may contain excessive selenium and endophyte infection. Reduced fertility, abortion, fetal defects, abnormal placentas, hydrops, and weak neonates may be observed. Sperm quality is also affected.[10] Nitrate-accumulating plants (see Table 54-3) can be responsible for sudden death, abortions, stillbirths, congenital defects, and weak neonates.

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Congenital defects resulting from ingestion of specific plants during pregnancy may trigger abortion or result in nonviable neonates. Skeletal deformities such as arthryogryposis, kyphosis, scoliosis, torticollis, and cleft palate can be the result of lupine ingestion during early to midgestation in ruminants, a syndrome called "crooked calf disease," a significant problem in range cattle. The two specific teratogens that have been identified and studied are anagyrine, a quinolizidine alkaloid, and ammodendrine, a piperadine alkaloid, both of which reduce uterine motility. Toxin absorption and the likelihood of ingestion are affected by body condition score.[61] Anagyrine is also present in mountain thermopsis. Other plants with similar effects include locoweed, poison hemlock, and tobacco. The teratogenic effects of poison hemlock are greatest in cattle and pigs. In sheep, false hellebore and skunk cabbage (*Veratrum* spp.) ingestion in early gestation may result in abortion or birth of cyclopic lambs.[10] Cattle, goats, and llamas are also susceptible.

Congenital hypothyroidism in equine neonates can be caused by ingestion of high nitrate forages or plants with goitrogenic effect. Goitrogenic effects may be observed from plants that provide excessive iodine (e.g., seaweed) or compounds such as thiocyanates (white clover) or glucosinolates (*Brassica* spp., kale, turnips, and canola seeds) that interfere with iodine utilization. Horses are particularly susceptible to iodine excess, as well as iodine deficiency. Excessive iodine consumption in a seaweed-based supplement led to abortion in 27 of 39 mares, goiters, and signs of congenital hypothyroidism in many of the neonates, including pathologic changes in the long bones.[62] Diagnosis is most readily based on histologic evaluation of the thyroid gland or characteristic changes of the skeletal system characteristic of congenital hypothyroidism. More commonly, this syndrome is attributable to iodine deficiency or excessive nitrate in forages or water.

Milk-fed neonates may be affected by poisonous plants ingested by their dam, who may or may not show signs of toxicity, depending on the chemistry of the toxin and/or its metabolites. If plant poisoning is suspected in a sick dam, an alternative milk source for the neonate should be considered, particularly if the toxin is an alkaloid. Plants that affect milk flavor, such as onions, may diminish neonatal consumption. More significant toxic plants to consider in this category include those with pyrrolizidine alkaloids (see Table 54-6), white snakeroot, rayless goldenrod, locoweed, lupines, mountain thermopsis, poison hemlock, tobacco, *Cassia* spp., and lobelia. A number of plants in the Brassica family (mustards, kale, rape, turnips, horseradish, radish, and watercress) can adversely affect thyroid function, as well as impart a bitter flavor to the milk.[10]

Ergot Alkaloids and Endophytes

Clinical syndromes ascribed to plant infection with ergot and endophytes are often included in veterinarians' thought processes when considering poisonous plant etiologies. For this reason, plants with this potential are included in the charts of predominant clinical signs. Two categories primarily affecting reproductive functions are discussed here: ergot alkaloids (ergopeptines) from ergot and from endophyte infections. Neurologic signs and other syndromes associated with endophyte-infected locoweed are discussed in the neurologic section.

Ergot-infected forages and grains have much higher concentrations of ergot alkaloids than are found in endophyte-infected forages.[25] Ergot infection (*Claviceps* spp.) of many grasses and cereal grains produces dark fungal sclerotia (ergot bodies) shaped like seeds that are readily visible in the plant's seed head in pasture, hay, or contaminated grains.[63] Similarly, many grass species can be infected with endophytes, the most economically important of which is fescue (*Lolium* spp.) infected with *Neotyphodium coenophialum.* Ergovaline is the most prevalent ergopeptine in endophyte-infected tall fescue and considered responsible for the majority of signs associated with fescue toxicosis.[64] Infection provides fescue the advantages of increased resistance to drought, insects, parasitic nematodes, and herbivores. In contrast to ergot infections, endophyte infections are not visible to the naked eye and require microscopy for confirmation. The endophyte also infects the plant's seed, ensuring its survival to germination in subsequent seasons.[64] Tall fescue can be infected with both *Claviceps* spp. and the endophyte simultaneously.[25]

Ergot alkaloids affect all livestock and horses. Species susceptibility is highest in horses, followed by cattle, then sheep, goats, and finally camelids. Different disease syndromes may be seen, depending on the affected species and type of ergot alkaloids ingested. In ruminants and horses, ergot alkaloids, particularly ergovaline, have vasoconstrictive effects (α_2 adrenergic agonist) and/or depress secretion of prolactin via effects on lactotropic D_2-dopamine receptors in the adenohypophysis of the pituitary. There is a reduction in steroid genesis, including progesterone production by corpora lutea, and relaxin. Diminished relaxin production has less impact on readiness for parturition in ruminants because it is also produced by the placenta. Thermoregulatory centers are affected by diminutions in prolactin and dopamine receptor perturbation, leading to clinical problems in extreme temperatures.[64] *Claviceps cyperi* has produced signs of severe ergotism in dairy cows in the heat of South Africa.[65] In contrast, infection of grasses with another form of ergot, *Claviceps paspali,* produces predominately neurologic signs associated with γ-aminobutyric acid inhibition.[25]

Clinical abnormalities attributable to ergot and endophyte infections of grasses are most often detected in regions with warm, wet climates conducive to fungal infections, such as found in the southern portions of the United States (endophytes) and the cool wet springs of the northwestern United States (ergot).[66] Prevalence of toxicosis will vary by season and from year to year. Deciphering toxicity attributable to these fungal infections is complicated by the fact that some species of grasses can be simultaneously infected with both, as well as have dangerous levels of nitrates.[25] Additionally, concurrent copper deficiency may augment at least reproductive system clinical signs, as ergopeptine alkaloids impair copper homeostasis. Heavy parasitic loads may have a similar effect.[25]

Depending on environmental conditions, the vasoconstrictive effects of the ergot alkaloids can be costly to livestock. Cold weather can result in gangrene of the distal extremities and lameness. The tongue may also be affected in sheep. Lameness can lead to reduced feed consumption and diminished natural mating. In ruminants undergoing heat stress, hyperthermia can occur due to failure of heat dissipation through the skin. Sheep with full fleeces are particularly susceptible to this syndrome. Other signs include dull, rough hair coat and unthrifty condition. Nervousness, increased salivation, tachypnea, and delayed puberty may also be seen. In some regions, this condition is referred to as "summer slump." Ergot alkaloids should also be considered in alpacas and llamas that develop heat stroke.[64] Fat necrosis or lipomatosis in cattle and goats is associated with consumption of ergot alkaloids in fescue grasses. Masses of necrotic fat in the pelvic canal can lead to dystocia.[25] Because the ruminant placenta can produce a placental lactogen during pregnancy, the suppression of prolactin and hence milk production is minor in comparison with horses. Bulls grazing endophyte-infected pastures during the summer may have altered sperm motility parameters. Cows may have changes in ovarian follicular dynamics, as well as diminished embryo quality. Reduced fertility in both unshorn ewes and rams has been reported during the summer.[25] Diminished immune function may make animals more susceptible to infectious diseases and cases with dry gangrene more susceptible to wound infections. In swine, agalactia and abortion have been reported in association with ergot consumption.[63]

Ergot *(Claviceps purpurea)* and endophytes of forages such as fescue (*Lolium* infested with *Neotyphodium coenophialum*) have been extensively studied in horses. Broodmares eating ergot or endophyte-infected tall fescue pasture or hay may exhibit failure of udder development, agalactia, prolonged gestation, placental abnormalities, dystocia, decreased milk production, and subfertility.[66] Foals may show signs of dysmaturity despite prolonged gestation and frequently suffer failure of passive transfer and secondary septicemia due to the failure of udder and colostrum development. Early embryonic death and abortion are also possible, with a higher risk of abortion

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associated with ergot infections rather than endophyte.[67] Ergot alkaloids may stimulate the myometrium and probably impair placental circulation.[66] Gangrene of the extremities has been seen in horses exposed to ergot, as has a syndrome characterized by staggering following consumption of *Paspalum* grass seeds infected with *Claviceps paspali*.[68] A slightly different syndrome characterized by peripheral edema has been described in horses grazing Mediterranean tall fescue intentionally infected with a genetically modified, nontoxigenic form of endophyte, suggesting that other factors may also be involved and considered if reseeding of pastures is desired.[69]

Diagnosis of ergot alkaloid or endophyte-induced toxicity is based on recognition of clinical signs and consumption of infected feed. Diagnostic testing of suspect forages, hay, grain, or processed forages is based on observation of *Claviceps purpurea* sclerotia or intercellular endophyte infection via feed microscopy and testing of the forages. High-performance liquid chromatography (HPLC) can confirm the presence of ergopeptine alkaloid toxins: ergovaline, ergotamine, ergocristine, ergosine, ergocornine, and/or ergocryptine.[25,64] Adverse effects are linked to total dietary concentrations greater than 100 to 200 ppb. In affected broodmares, calcium concentrations in mammary secretions rarely exceed 50 ppm at parturition.[70]

Treatment is most effective if signs are recognized in the early stages and access to the implicated feed is removed. If pasture is the source, and alternative grazing is not available, mowing to remove seed heads and possible ergot bodies may be helpful. Foaling should be attended due to the risk of dystocia, placental problems, and likely dysmaturity of the neonate. Domperidone (1.1 mg/kg orally [PO] q24h) can be used successfully in pregnant mares suspected of ergot alkaloid toxicosis if use is begun 10 to 14 days before expected foaling. Reserpine (2.5 to 5 mg/450 kg PO q24h) may be helpful to induce lactation if administered postpartum.[66]

Prevention is focused on replacing contaminated feed sources with safer alternatives such as legumes or endophyte-free fescue grass. Ammoniation to degrade ergovaline in contaminated hay may be economically feasible on large cattle operations.[71] Pregnant broodmares should be removed from fescue pastures no later than day 300 of gestation. Domperidone can be used as described earlier in broodmares. Attention to mineral nutrition and other additive stressors is also advised.[66]

Respiratory Syndromes Following Poisonous Plant Ingestion

Few plants are associated with the development of predominately respiratory signs in large animals. Perilla mint *(Perilla frutescens)* (Color Plate 54-9) causes significant morbidity and mortality in ruminants. Perilla contains ketones and related furan compounds that are bioactivated in the lung and cause atypical interstitial pneumonia and acute respiratory distress. A similar syndrome may be seen in cattle following ingestion of sweet potatoes *(Ipomoea batatas)* damaged by *Fusarium* spp. molds.[72] Acute bovine pulmonary emphysema and edema may occur following ingestion of forages high in tryptophan, typically immature summer grasses. Rumen bacteria convert tryptophan to 3 methyl indole, a furan that is further metabolized to a lung toxicant. This syndrome can be prevented by gradually introducing cattle to these grasses or using monensin or tetracycline in the feed for a week before and 2 weeks after turnout on pasture. Peanut hay *(Arachis hypogaea)* has been linked to acute respiratory distress in beef cattle.[72]

Poisonous Plants Affecting Skin and Hooves

Skin and hooves may be adversely affected by plants causing physical trauma or those containing toxins or excessive selenium. Plants with awns or barbs that damage skin may also damage the digestive tract and adjacent tissues if migration occurs.

Photosensitization and laminitis are chief complaints that warrant further investigation. Photosensitization may be a primary effect of the ingested toxin or secondary to liver damage. Sunlight triggers an oxidative reaction with photoreactive, polyphenolic compounds absorbed from the digestive tract in areas of unpigmented skin, leading to inflammation, cellular necrosis, and sloughing of affected skin, particularly in horses and cattle. Lesions are typically most severe on the face and dorsum of the animal. Common plant sources of primary photosensitization are St. John's wort *(Hypericum perforatum),* buckwheat *(Fagopyrum esculentum),* Dutchman's breeches *(Thamnosma texana),* bishop's weed *(Ammi majus),* rain lily *(Cooperia pedunculata),* spring parsley *(Cymopterus watsonii),* giant hog weed *(Heracleum mentegazzianum),* and cow parsnip (*Heracleum* spp.).[10] Wild parsnips *(Pastinaca sativa)* contain furanocoumarins, which can result in contact blisters and photosensitization following ingestion.[55]

Hoary alyssum *(Berteroa incana)* (Color Plate 54-10) ingestion and black walnut *(Juglans nigra)* shavings used for bedding are known triggers of laminitis in horses.[10] Hoary alyssum, a weed often growing on the periphery of hayfields in Europe and North America, is usually avoided at pasture but remains toxic in hay for months. Clinical signs of toxicosis include limb edema, fever, and laminitis. In severe cases, intravascular hemolysis, endotoxemia, hypovolemic shock, diarrhea, abortion, and death may occur.[73,74] Black walnut shavings need not be ingested to cause limb swelling and laminitis in horses. Black walnut extracts containing the tree's heartwood and administered by nasogastric tube have been used to create a model for studying laminitis in horses. These studies suggest that oxidative stress to laminar tissues with subsequent inflammation is responsible for the predominant clinical sign, as well as a systemic inflammatory response.[75]

Selenium Toxicosis

Chronic excessive selenium ingestion produces skin and hoof abnormalities, known as "alkali disease." It is problematic for livestock in areas with seleniferous soils, such as the Great Plains of the United States and Canada, as well as many areas in Russia, Israel, and China.[76] Common seleniferous plant species with this potential include primary selenium accumulator plants, such as milkvetch (*Astragalus* spp.), woody aster *(Machaeranthera,* section *Xylorrhiza),* goldenweed *(Haplopappus*, section *Conopsis),* and prince's plume *(Stanleya pinnata).*[1,10] Selenium can reach levels of approximately 3000 ppm, remaining water soluble and not incorporated into plant protein. Secondary selenium accumulator plants may contain up to several hundred ppm and, rarely, several thousand ppm selenium. This group includes acacia, other asters (*Aster* spp.), beard tongue (*Penstemon* spp.), gumweed *(Grindelia),* Indian paintbrush *(Castilleja),* some milkvetch (*Astragulus* spp.), sage (*Artemesia* spp.), saltbush *(Atriplex patula),* snakeweed *(Gutierrezia),* stickleaf *(Mentselia),* and toadflax *(Comandra).*[1,10] A third group of plants that may endanger livestock do not accumulate selenium compounds but do incorporate it into readily absorbed plant proteins, rarely presenting with more than 50 ppm. This latter group is the most problematic because it includes grasses (e.g., Western wheat grass), small grains, and alfalfa.[1]

Toxicity is difficult to predict because palatability and tolerance vary with animal species, individual genotype, the form of selenium in the plant, duration of consumption, and amount consumed. Ruminants tend to be more tolerant of high selenium in the forage than horses. Water sources in seleniferous areas may also contribute to excessive selenium intake.[77]

Three syndromes are ascribed to excessive selenium intake: acute toxicosis, blind staggers, and chronic alkali disease. Signs of acute selenium toxicosis are most often described after iatrogenic overdosage of selenium and rarely occur from plant ingestion. In horses, the first signs of selenium toxicity may be vesicles on oral and nasal mucosa and a straw-colored exudate at mucocutaneous junctions, followed by coronary band separation from the hooves and hair loss in the mane and tail. In the tail, the hairs tend to break at the same level, leaving a "bob" tail.[10] In cattle, abnormal posture, unsteady gait, diarrhea, abdominal pain, and elevated pulse and respiratory rate are

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seen. Sheep do not show the typical signs of poisoning; rather, depression, increased respiration, and sudden death are observed.[10] At necropsy, in acute cases, endocardial petechial hemorrhage, acute congestion and hemorrhage of the lungs, enteritis, and passive congestion of the liver are reported.

Animals that chronically ingest high selenium forages show signs of emaciation, rough hair coat, lack of vitality, and lameness. Reproductive efficiency diminishes. Hooves may become overgrown or cracked (including swine), and long hair may fall out. At postmortem, cardiac atrophy, hepatic cirrhosis, anemia, and erosion of the long bones may be noted.[1,78]

Serum selenium provides an accurate reflection of the body's current selenium pool, whereas whole blood selenium (glutathione peroxidase) reflects a longer time period of selenium intake. Both can be useful in antemortem diagnosis. Hair and liver selenium are other options, particularly for more chronic cases and postmortem determination. Laboratories used for selenium determinations should provide ranges for normal values by species, and sample type, because these vary. Investigation of a herd or flock problem should ideally include samples from multiple animals to reduce the risk of misinterpretation on the basis of values of one or two individuals.

Once a selenium toxicosis is identified, producers and owners need to find alternative grazing and water sources for their animals, particularly breeding horses and cows. Consultation of soil maps may be useful, as well as looking for primary selenium accumulator species that serve as indicators. Animals that are relocated from high-selenium areas often recover when fed lower selenium rations. Producers should additionally check that diets contain sufficient copper and protein to avoid enhancement of selenium's toxic effects.[10]

Plant Toxicity in the Urinary System

Urinary system damage may be the result of direct toxin damage or secondary to the toxin's effects on other systems that lead to dehydration, pigmenturia, or hypoxia. Renal damage is an important determinant of case outcome for many intoxications, a fact that should focus clinical attention on hydration, urinary output, and other measures of renal function. Among common plant toxicities, renal dysfunction can be significant following consumption of bracken fern *(Pteridium aquilinum),* cocklebur (*Xanthium* spp.), inkweed *(Phytolacca octandra),* oak (*Quercus* spp.), pigweed *(Amaranthus retroflexus)* (Color Plate 54-11), jimsonweed (Color Plate 54-12), and all plants rich in oxalates.[36,57,72,79] Bracken fern's toxin, ptaquiloside, is carcinogenic to bladder epithelium and responsible for the syndrome of enzootic hematuria in cattle.[36] In oak poisoning, nephritis with necrosis and renal tubular casts is observed, which may lead to acute renal failure. Goats are relatively resistant to oak poisoning due to tannin-binding proteins in their saliva. Inkweed has caused acute renal tubular necrosis in calves, along with signs of photosensitization and cholangiohepatopathy.[57]

Oxalate Toxicity

Consumption of plants with high concentrations of sodium oxalate and/or potassium oxalate damages renal tissue if a large amount of plant is consumed over a short period. Additionally, some contain insoluble oxalate crystals in the form of complexes called *raphides,* which cause direct damage and irritation to the mucosal surfaces of the mouth and pharynx.[80]

Clinical manifestations of oxalate poisoning are variable and depend on factors such as the form of oxalate in the consumed plant, the animal species, and the rate of consumption. Plants that can cause oxalate toxicity are listed in Table 54-7. The balance between soluble (oxalic acid) and insoluble forms of oxalate in plants varies and is affected by gastrointestinal tract pH after ingestion. Binding of calcium can occur in the lumen. Once absorbed from the gastrointestinal tract, oxalates precipitate calcium from the blood, producing hypocalcemia, which may be most notable in lactating animals.[81] Oxalate crystals damage the microvasculature of the gastrointestinal tract and may also precipitate out on the wall of the rumen. Poorly soluble calcium oxalate crystals precipitate out in the renal tubules, causing acute nephrosis, tubular obstruction, and acute renal failure. At a cellular level, citric acid cycle of energy metabolism is inhibited,

TABLE 54-7

Plants That May Contain Oxalates

Type	Common Name	Scientific Name	Reference(s)
Crop	Agave	*Agave americana*	80
	Beets	*Beta vulgaris*	10
	Prickly pear	*Opuntia echios*	80
	Quinoa	*Chenopodium quinoa*	10
	Rhubarb	*Rheum* spp.	10
	Soybean	*Glycine max*	80
	Spinach	*Spinacia oleracea*	80
Grass	Beardgrass	*Brachiaria brizantha*	80
	Birdwoodgrass	*Cenchrus setigerus*	80
	Buffel grass	*Cenchrus ciliaris*	10
	Bristlegrass	*Setaria* spp.	10, 80
	Elephant grass	*Panicum* spp.	10
	Kikuyu grass	*Pennisetum clandestinum*	10
	Napier grass	*Pennisetum purpureum*	80
	Pangolagrass	*Digitaria decumbens*	80
Weed	Dock	*Rumex acetosa*	10
	Greasewood	*Sarcobatus vermiculatus*	10
	Halogeton	*Halogeton* spp.	10
	Kochia	*Kochia scoparia*	10
	Lambsquarters	*Chenopodium* spp.	10
	Nettleleaf	*Tragia urticifolia*	80
	Noseburn	*Tragia ramosa*	80
	Pigweed	*Amaranthus retroflexus*	10
	Pokeweed, pokeberry	*Phytolacca americana*	10
	Russian thistle	*Salsola* spp.	10
	Slenderleaf ice plant	*Mesembryanthemum nodiflorum*	80
	Sorrel	*Oxalis* spp.	10

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leading to cell death. In renal tubular cells, other pathways have been suggested, such as the production of phosphatidylserine, which promotes attachment of oxalates to the cell membrane, and phospholipase A_2 with subsequent mitochondrial damage and cell death.[82]

Oxalate poisoning in multiple animals is most often reported in sheep. Acute toxicosis is usually evident within 24 hours. The largest outbreaks are attributed to *Halogeton* spp. consumption. Other plants blamed for multiple deaths include slenderleaf ice plant *(Mesembryanthemum nodiflorum)* and golden bristlegrass *(Setaria sphacelata)* in Australia.[80] Muscle tetany or flaccid paralysis may be observed. These clinical signs pertain to hypocalcemia and hypomagnesemia, which result from sequestration of calcium and magnesium ions. Other reported signs include anorexia, ruminal stasis, mouth froth, weakness, stiffness, tachypnea, ataxia with jerky extensor rigidity, coma, and death. At necropsy, severe rumenitis may be evident. Kidneys are pale, edematous, and enlarged. Calcium oxalate crystals are readily identified in the rumen wall and kidneys. Less commonly, chronic toxicity has been reported with signs typical of chronic renal damage: anemia, weight loss, and poor appetite. Clinical signs of oxalate poisoning in cattle are similar to sheep but typically less acute and attributable to hypocalcemia. These include incoordination, belligerence, excessive salivation, bloat, recumbency, coma, and death. In calves, hypersensitivity to stimulation and seizures is possible.[11]

In horses, secondary nutritional hyperparathyroidism has been attributed to chronic high oxalate consumption, resulting in calcium binding in the hindgut and therefore deficiency. This leads to signs of osteodystrophia fibrosa.[80] Acute toxicosis with oxalate nephrosis failure is less common but associated with grass species with high oxalate content.

Treatment should be symptomatic with attention to electrolyte balance and renal function, but it may be insufficient in severely affected animals. Activated charcoal may help bind oxalates remaining in the gastrointestinal tract. Prevention requires recognition of the toxic potential of oxalate-bearing plants and management of livestock to avoid consumption of large amounts in a short period. Gradual introduction to the plants, ample alternative forage, and water are necessary to avoid deaths. In sheep, slow introduction (≈10 days) of sheep to grazing areas with high proportions of oxalate-bearing plants can result in better tolerance to the toxic effects. In contrast, a sheep acclimated to grazing other forage can be killed with as little as 12 oz (340 g) of halogeton.[1]

Blue-Green Algae

Birgit Puschner

Microcystis spp., *Nostoc* spp., *Anabaena* spp., *Planktothrix* spp.: cyanobacteria that produces hepatotoxic microcystins

Anabaena spp., *Oscillatoria* spp., *Phormidium* spp., *Planktothrix* spp.: cyanobacteria that produces neurotoxic anatoxin-a

Anabaena spp.: cyanobacteria that produces neurotoxic anatoxin-a_s

Aphanizomenon spp., *Anabaena* spp., *Lyngbya* spp., *Cylindrospermopsis* spp.: cyanobacteria that produces neurotoxic saxitoxins (paralytic shellfish poisoning toxins)

Blue-green algae blooms typically occur during warm months when water temperatures exceed 20° C and water is stagnant. High nutrient concentrations, especially phosphorus and nitrogen, increase the presence of cyanobacteria and cyanotoxins.[1] Algae can be suspended in the water column and easily visible, or attached to the surfaces of stones and sediments along the bottom of lakes or rivers.[2] Currently, of the 2000 species identified worldwide, more than 80 are categorized as toxigenic. It is well known that toxigenic and nontoxigenic species and strains coexist in water; thus, the potential toxicity of a given water source must be carefully evaluated not only by identification of the actual cyanobacteria population but also by measuring toxin concentrations.[3,4] George Francis first reported in *Nature* in 1878 a toxigenic bloom of a "poisonous Australian lake" with "a thick scum like green oil paint" and vividly described acute intoxications of sheep, horses, dogs, and pigs.[5] Since Francis's publication in 1878, numerous case reports describing animal morbidity and mortality exposed to cyanotoxins have been published.[6-12]



FIG. 54-1 Pond with *Microcystis* bloom in Petaluma, California. Pond water contained microcystin-LR and resulted in acute deaths and photosensitization of Holstein heifers.

The most commonly reported cyanotoxin poisoning in large animals is acute hepatotoxicosis subsequent to microcystin exposure. Microcystins are produced by multiple cyanobacteria and have been detected in fresh and coastal waters worldwide.[13] They present a realistic threat to pastured animals because of their presence in ponds and streams, and because animals readily consume algal-contaminated water (Fig. 54-1). Acute neurotoxicosis as a result of anatoxin-a or anatoxin-a_s can occur in large animals, but reports are rare.

The frequency of cyanotoxin poisoning in animals is likely underreported due to absent diagnostic workup of large animal mortalities and the current lack of well-established confirmatory methods in biological specimens. Diagnostic confirmation of suspect blue-green algae poisoning cases of humans and animals requires extensive efforts from both toxicologists and clinicians, and resources are often not readily available. New algal toxins are being discovered continuously, and oral bioavailability and toxicity data are often unavailable. It is probable that blue-green algae poisonings are more common in animals than humans due to increased dependence and contact with surface waters.

Hepatotoxic Microcystins

Microcystin-poisoned animals typically die within a few hours after exposure to contaminated water. Severe destruction of the hepatocytes leads to hypovolemia and shock secondary to blood loss into the disintegrated liver lobules and embolism of hepatocytes into the lung. Acutely poisoned animals develop signs of nervousness, reluctance to move, recumbency, diarrhea, and pale mucous membranes within 30 minutes to several hours of exposure.[14,15] Many die within hours to days, but animals exposed to nonlethal doses may survive and develop hepatogenous photosensitization (Fig. 54-2).

Clinical chemistry changes of animals with microcystin toxicosis include elevated serum gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), bile acids, alkaline phosphatase (ALP), hypoglycemia, and hyperkalemia. Acute hepatic damage results in a grossly enlarged and friable liver from intrahepatic hemorrhage and, histopathologically, in hepatocyte dissociation, degeneration, and necrosis. Pathologic findings should quickly lead to an environmental assessment for possible microcystin-contaminated water.[16] Necrotic hepatocytes can also be seen in the pulmonary vasculature.

Microcystis, Anabaena, Planktothrix, Nostoc, Oscillatoria, and *Anabaenopsis* genera are among the known microcystin producers.[17] Toxins are retained inside the cyanobacteria and only released upon cell damage, lysis, and death; of note, destruction of algal mats (either naturally or through the application of herbicides) may result in a pulse of microcystin release following destruction of the individual cell walls. Microcystins are cyclic heptapeptides that inhibit protein

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FIG. 54-2 Holstein heifer with hepatogenous photosensitization from microcystin-LR toxicosis; Central Valley of California.

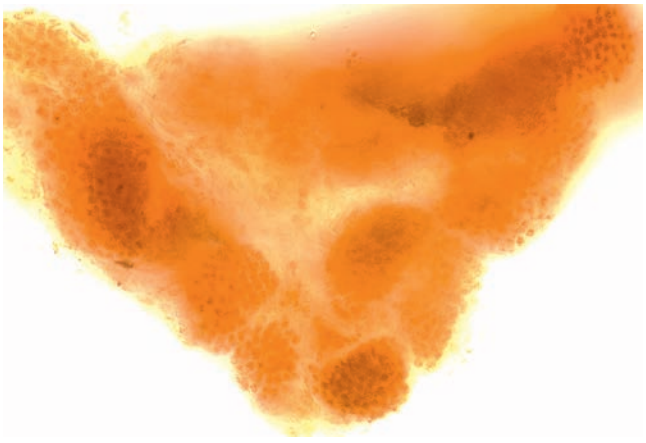


FIG. 54-3 Characteristic algal cell aggregates in rumen content of a heifer formed by *Microcystis* spp. Direct microscopic examination of rumen content in formalin (1 : 1; v/v). 60×. Rumen content was confirmed to contain microcystin-LR.

phosphatases; currently, more than 80 different structural variants have been identified. The most extensively studied congener, microcystin-LR, has been found worldwide and has caused acute, lethal hepatotoxicoses in farm animals.[2,15,18] Most natural outbreaks are a result of oral exposure through drinking water; microcystin-containing algae release microcystins in the acidic environment of the stomach. Recently, the risk of inhalation exposure to microcystins has been documented in humans recreationally using certain waters.[19,20] All animal species, including fish and reptiles, and humans are considered susceptible to the toxic effects.

Animals with acute microcystin poisoning may have algal material in the gastrointestinal tract (Fig. 54-3) or on the skin, especially the legs. Although identification of algae material in water and gastric contents is an important component of the diagnostic workup, it does not confirm intoxication. As mentioned previously, the toxicity of cyanobacteria is strain specific, and morphologic observations alone cannot predict the hazard level. Detection of microcystins in gastric contents is confirmatory, but these tests are not routinely available at diagnostic laboratories and are limited to a few structural variants.[21-23] Detection methods for microcystins in liver and other tissues are yet to be developed. Consumption of milk, meat, or liver is unlikely to pose a significant health risk to humans.[24,25] However, as a tumor promoter, microcystins may pose a cumulative health risk as they become more ubiquitous.

Neurotoxic Anatoxins

Anatoxins are produced by many cyanobacteria genera, such as *Anabaena, Aphanizomenon, Planktothrix, Oscillatoria, Microcystis, Cylindorspermum,* and *Phormidium.* Reports of anatoxin-a poisoning in livestock are extremely rare; most cases are documented in dogs. But all animals are considered susceptible. Anatoxin-a poisoning leads to muscle tremor, rigidity, respiratory failure, collapse, and death within minutes to a few hours.[26-28] This is a result of anatoxin-a being a potent cholinergic agonist at nicotinic receptors.[29] Animals poisoned with anatoxin-a_s develop acute signs of excessive salivation, lacrimation, diarrhea, and urination (SLUD) because anatoxin-a_s is a naturally occurring irreversible acetylcholinesterase inhibitor.[30] Animals often die of respiratory arrest within 30 minutes.

Because of the acute onset, CBC and chemistry profiles of animals with anatoxin poisoning are generally unremarkable. Furthermore, other than the possible presence of algae material in gastrointestinal contents, there are no specific gross or microscopic lesions. Confirmation of anatoxin-a poisoning is by analytic detection of the toxin in urine, bile, or gastrointestinal contents.[28] Diagnosis of anatoxin-a_s toxicosis is aided by the determination of blood acetylcholinesterase activity. In any suspect cases, environmental samples should undergo a toxicologic and phycological analysis.

Other Cyanotoxins

Other freshwater cyanotoxins of concern to livestock include neurotoxic saxitoxins, hepatotoxic nodularins, and cylindrospermopsin, which targets multiple organs (liver, kidneys, lung, heart, gastrointestinal tract).

Treatment for blue-green algae poisoning is supportive and often unsuccessful. No specific therapy has proven effective in laboratory animals, including decontamination with activated charcoal, and no data exist for adsorptive capacity in other animals.[31] Symptomatic and supportive care to treat hypovolemia and electrolyte imbalances, as well as antioxidants such as vitamin E and selenium, should be included in the therapeutic regimen for large animals poisoned with microcystins. Animals that develop photosensitization must be protected from sun exposure. Because of the rapid onset of clinical signs in animal with anatoxin-a poisoning, therapeutic options are often not possible, but artificial respiration may be of benefit along with general supportive care. Administration of activated charcoal has been recommended, but scientific evidence on its adsorptive capacity for anatoxin-a is lacking. Atropine should be considered in the treatment of animals poisoned with anatoxin-a_s. It is important to note that pralidoxime (2-PAM) is not recommended.[32]

The frequency and extent of harmful cyanobacterial blooms appears to increase with the addition of nutrients to surface fresh water ecosystems around the world. Steps must be taken to reduce fertilizer runoff and applications in fields surrounding ponds used for drinking water. Prevention of blooms is key to protecting animal and human health.

Mycotoxins

Timothy J. Evans • George E. Rottinghaus

Importance of Mycotoxins

Mycotoxins are secondary fungal metabolites, which, if consumed in sufficient amounts, cause adverse health effects in animal species including humans.[1] They can be detected in various matrices, including cereal grains and forage, and are a major concern to international agricultural production and a threat to food safety worldwide.[1-3] Individuals working within the United States swine and poultry industries are particularly cognizant of the potential for mycotoxin exposures, given the dietary dependency of those monogastric species on cultivated cereal grains. However, the globalization of agricultural commodities, climate change–related weather conditions favoring fungal growth and/or mycotoxin production,

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subsequent reductions in the availability of feedstuffs not contaminated by mycotoxins, and economic pressures from higher costs of better-quality feedstuffs all underscore the need for individuals participating in other aspects of animal agriculture in the United States to have a greater awareness of the potential for mycotoxin contamination.

Additionally, the increasing risk to human and animal health posed by mycotoxins means the veterinary profession must be vigilant in the surveillance of domesticated large animal populations as sentinels for mycotoxin contamination of agricultural products. Veterinary practitioners, regardless of whether their practices involve small companion animals or livestock, will need to be familiar with the "major" mycotoxins and the wide range of clinical signs, including subtle reductions in livestock production and food residues associated with these fungal toxins.[4] It is only through an increased awareness of these toxins that mycotoxin-related illness in food animals can be minimized, and companion animal and human exposure to mycotoxins limited or prevented.

General Principles of Mycotoxin Production and Detection

Many fungi are capable of producing toxins (i.e., are toxigenic), and a given mycotoxin could be synthesized by more than one fungal species.[3] Some fungi produce more than one toxin or even multiple classes of toxins.[1,3] Although many relatively common mycotoxins have already been identified, it is likely that several more potentially toxic, secondary fungal metabolites, such as those suspected in moldy hays, have yet to be isolated and characterized.[2,3,5] Fungal colonization does not necessarily mean that a given mycotoxin is being produced.[1,3] The substrate, moisture content, pH, ambient temperature, relative humidity, and other requirements for toxin synthesis are often more stringent than those for fungal growth.[1,2] The "ideal" toxigenic conditions for the production of specific mycotoxins have been characterized, and some mycotoxins are more likely to be produced in a "field" or "storage" setting.[1-3] The mere presence of fungal growth does not necessarily correlate with toxin production, and some mycotoxin-contaminated feedstuffs might not even be visibly moldy.[3]

From a clinical perspective, the inability to accurately predict whether mycotoxins will be present in a specific feedstuff means that fungal identification and spore counts are not adequate for identifying livestock diets contaminated with mycotoxins.[1-3] High-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS/MS), and/or enzyme-linked immunosorbent assays (ELISA) are some of the more common analytic techniques used to directly measure mycotoxin concentrations in grains or processed feedstuffs. The use of an ultraviolet light to detect fluorescence associated with kojic acid, as an indirect indicator of aflatoxins, is outdated as the sole means of detection of these toxins.[1,6] Likewise, utilization of semiquantitative methods, such as thin layer chromatography (TLC), as stand-alone evidence of fungal toxin contamination, is also less than optimal. The consistent use of appropriate sampling techniques ensures the detection of suspected mycotoxins and guarantees that detected mycotoxin concentrations are representative of actual livestock exposure.[3,7,8] Grain "screenings" or "fines" are the grain by-products most likely to contain the highest concentrations of mycotoxins.[1,3]

One of the biggest challenges pertaining to mycotoxin contamination in livestock rations is the accurate interpretation of analytic results, especially now, when low concentrations of mycotoxins are detected by increasingly sensitive laboratory methods.[4] Table 54-8 shows "action levels" established by the U. S. Food and Drug Administration (FDA) for some mycotoxin-contaminated commodities fed to different species of livestock. These action levels were originally intended to be guidelines for "acceptable" concentrations of individual mycotoxins in common substrates being transported between states.[6,9] The mycotoxin concentrations have often been interpreted as the highest dietary concentrations of these mycotoxins considered "safe" in the denoted species. However, the definition of "safe" is a relative term that is dependent on the end point being measured. Some concern has recently been expressed as to whether these action levels are low enough to prevent adverse health effects, especially with respect to carcinogenesis in humans.[10]

Mycotoxicoses

In discussing mycotoxin-related diseases it is important to differentiate "mycosis" from "mycotoxicoses." The term "mycosis" refers to a disease caused by fungal growth, rather than by the adverse effects of any toxins produced by that fungi.[3] "Mycotoxicoses," on the other hand, are diseases caused by the adverse health effects of mycotoxins, which, in most cases, have been ingested.[1-3] For a specific mycotoxicosis to occur, growth conditions in substrates colonized by the appropriate fungal species must favor production of a specific toxin and sufficient amounts of that toxin-contaminated substrate must be consumed by a susceptible animal species.

The higher the dietary concentration of a given mycotoxin, the more likely and severe are the observed adverse effects.[1-3] Similarly, the duration of exposure to a mycotoxin impacts the likelihood and severity of the observed clinical signs, with longer exposures increasing the probability of more severe intoxications.[2,3] Peracute and acute intoxications generally occur over a short period of time (usually days) and involve one or several "large" doses (orders of magnitude greater than "allowable" quantities) of a specific mycotoxin. In these instances, the diagnosis is often fairly straightforward because contaminated feed is more than likely available for testing. However, clinically recognized mycotoxicoses, more often than not, involve subacute (weeks) to chronic (months) dietary exposures to fungal toxins.[1] Depending on the dietary concentration of a given mycotoxin, clinical signs in these types of exposures might be "classic" for a mycotoxin's typical target organ (e.g., moderate to severe hepatocellular damage with sufficient amounts of aflatoxins) or more subtle in nature (e.g., immunosuppression, suboptimal growth, reproductive inefficiency, and/or carcinogenesis), reflecting impaired hepatic function.[3,4] In subacute to chronic mycotoxin exposures, affected animals could still be ingesting specific toxins, with contaminated feedstuffs readily available for testing, or the consumption of specific mycotoxins might have already ceased, especially if the observed clinical signs are more subtle in nature and/or took some time to develop. Under these circumstances, analyses of representative samples of grains or forages harvested at the same time as the suspect feedstuffs or analyses of samples of prepared rations retained by the supplier or manufacturer might be the only way to establish the definitive cause of a suspected mycotoxicosis.

Another aspect of a potential mycotoxicosis, as illustrated in Fig. 54-4, using reproduction as an example of monitored animal performance, is the role that mycotoxins might play in diminished livestock performance, such as decreased feed consumption, growth rates, and fertility, where there is no single "cause" but, rather, an etiology that is multifactorial in nature. The mention of this type of diagnostic conundrum has the potential to increase the overdiagnosis or misdiagnosis of a mycotoxicosis and should not be misconstrued as an effort to indict trace amounts of some mycotoxins as the primary cause of clinical abnormalities in livestock.[4,6] However, although it is not practical or even possible to eliminate all measurable fungal toxins from livestock diets, one should recognize that there is no nutritional requirement or benefit related to dietary mycotoxins. It is important, therefore, when no clear-cut, single cause of diminished performance is evident, to take an integrated approach and objectively evaluate the relative contributions of a wide variety of enzootic variables or "stressors" to the clinical problems being observed.[4]

Major Mycotoxins of Veterinary Importance

AFLATOXINS. Aflatoxins arguably pose the most clinically relevant, mycotoxin-related threat to the worldwide health and well-being of humans and domestic animals. A number of fungal species, in particular *Aspergillus flavus* (*A+fla+* toxin) and *Aspergillus parasiticus,* can produce aflatoxins under appropriate growth conditions

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TABLE 54-8

Summary of Important Mycotoxins of Importance to Livestock

Mycotoxins	Fungal Sources Substrates	Primary Toxic Effects	Dietary U.S. Food and Drug Administration Action Levels
Aflatoxins B_1, B_2, G_1, G_2	*Aspergillus flavus* and *parasiticus* Corn, nuts, cottonseed+	Macromolecular binding enzymatic inhibition DNA adducts formed→ hepatic insult/failure cancer (1° hepatic) All species	Total aflatoxins* Immature 20 ppb Dairy/horse 20 ppb 100+ lb pigs 200 ppb Feedlot beef 300 ppb Breeding 100 ppb
Deoxynivalenol (DON/Vomitoxin)	*Fusarium graminearum* (formerly *F. roseum*) Corn, wheat, barley+	↓Protein synthesis, GI irritation, ↑vomiting→ feed refusal, ↓nutrient absorption, ↓immunity 1° Swine Dairy cattle?	DON† Swine 1 ppm Horses/other 2 ppm Cattle 5 ppm
Zearalenone	*Fusarium graminearum* (formerly *F. roseum*) Corn, wheat, barley+	Hyperestrogenism→ reproductive tract Δs Pseudopregnancy Early embryonic death 1° Swine ↑Subfertility/ovary Δs Dairy cattle?	No action level determined Clinical signs Young gilts 1-3 ppm Mature sows > 3 ppm Bred sows > 15 ppm Heifers > 10 ppm Cows > 25 ppm
Fumonisins 1° B_1 and B_2	*Fusarium verticillioides* (formerly *F. monilforme*) 1° Corn	Sphingolipid Δs→ leukoencephalomalacia Horses Pulmonary edema Swine Hepatic disease in both	Total fumonisins† Horses 1 ppm Swine 10 ppm Ruminants 30 ppm *or* Repro/dairy 15 ppm
Ergot alkaloids Ergopeptine alkaloids *Ergovaline* Lysergic acid+ *Ergonovine/Lysergol* Ergopeptine alkaloids *Ergotamine*+	*Neotyphodium coenophialum* (genus formerly *Acremonium*) Tall fescue grass *Neotyphodium lolii* Perennial ryegrass *Claviceps purpurea* Small grains and grasses	1° Vasoconstriction→dry gangrene/↑temp ↓Feed intake Ruminants/camelids? 1° Hypoprolactinemia→ agalactia/long gestation Horses	Ergot bodies 0.1% by weight % Ergot bodies versus ergopeptine alkaloid concentrations

From references 1, 3, 6, 8, 9, 25, 33, 37, 46, 47.

*Based on corn action levels.

†Based on highest allowable grain level and percent of diet.

GI, Gastrointestinal.

in a variety of nuts and grains, including cottonseed, peanuts, and, especially, corn.[1-3] The major aflatoxins found in contaminated grains include aflatoxins B_1, B_2, G_1, and G_2 (B or G = fluorescence color), with aflatoxin B_1 (AB_1) generally being present in the highest concentrations.[3] Although aflatoxins are sometimes described as "storage" mycotoxins, there are certainly instances when they are produced under "field" conditions.[1,6] Drought and/or insect damage to corn or other susceptible plants, followed by warm (>25° C), humid (>70% humidity) ambient weather conditions, is the "classic" scenario that facilitates initial fungal invasion of compromised kernels/seeds and subsequent fungal growth with aflatoxin production.[1-3,6] In fact, drought conditions are often associated with increased scrutiny on the part of grain elevator operators, livestock producers, and regulators, with respect to possible aflatoxin contamination, particularly in corn and corn by-products.

Ingested AB_1 is metabolized by multiple cytochrome P_{450} subfamilies in the liver to produce several metabolites, including AB_1-8,9-epoxide and AB_1-dihydrodiol, which are toxic, and aflatoxin M_1 (AM_1), which can be found in meat as well as in milk.[1] AB_1-8,9-epoxide and other toxic metabolites bind to biologically important molecules, such as essential proteins, including enzymes involved in carbohydrate and lipid metabolism and protein synthesis.[1,3] These AB_1 metabolites also bind to macromolecular nucleic acids, inhibiting transcription and forming DNA adducts, which can be associated with carcinogenesis, especially hepatic tumors.[1-3,8] Additionally, toxic metabolites of AB_1 can also bind to subcellular organelles, such as mitochondria and ribosomes.[1]

Although excretion of violative AM_1 residues (>0.5 ppb or 0.0005 ppm) in the milk is the first observed "abnormality" associated with AB_1 exposure in lactating dairy animals, the liver is considered the major target organ of toxic AB_1 metabolites in all species.[1-3,6] Clinical signs of aflatoxicosis range from prolonged prothrombin time (PT), hemorrhage, bloody diarrhea, and rapid death in peracute and acute intoxication to anorexia, slow rumen motility, weakness, tremors, ataxia, reproductive failure (abortion), to hepatic failure with icterus, coma, and death in subacute aflatoxicoses.[1-3,6,8,11-16] Aflatoxin-induced hepatic insult and failure are usually accompanied by many of the typical clinical pathologic abnormalities expected with hepatocellular necrosis and/or hepatic failure, and elevations in the detected activities of liver-specific enzymes in serum often precede other clinical signs.[6] Suppression of immune function, particularly those aspects related to cell-mediated immunity, have also been reported in animals following repeated exposure to moderately high dietary concentrations of AB_1.[1,6,8,15] Chronic exposure to dietary aflatoxins can be associated with decreased growth rates and feed efficiency, roughened hair coats and ill thrift, impaired resistance to infectious disease, and hepatic fibrosis with regenerative nodules.[1,3,6,] Spermatogenesis can also be adversely

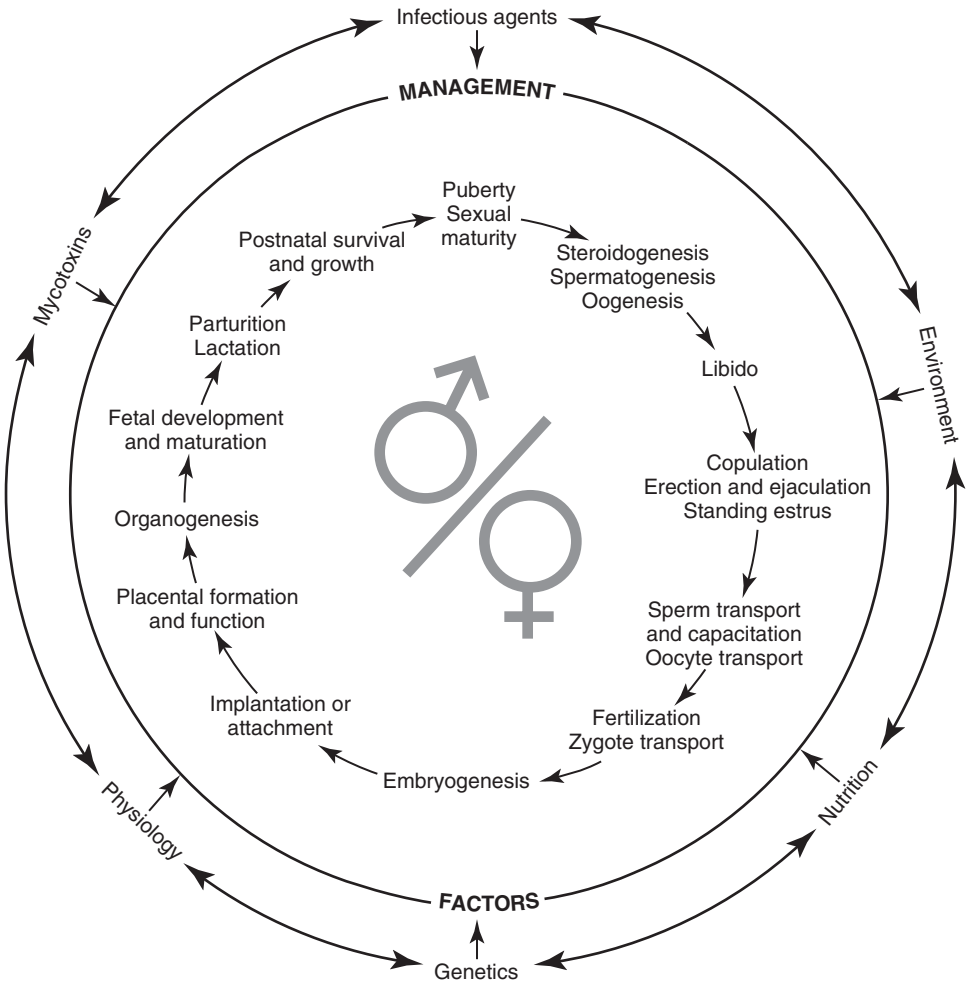


FIG. 54-4 The continuum of developmental stages and reproductive functions taking place in males and/or females, as well the embryo and fetus, are shown schematically and illustrate the complexity of reproduction in ruminant species. The possible influences of genetic and physiologic predispositions, as well as nutritional, environmental, infectious, and, especially, mycotoxin stressors, on decreased reproductive performance are also represented in Fig. 54-4, along with the role "management" can play in modulating those influences on reproductive function. *(Modified with permission from Evans TJ. 2011. Diminished reproductive performance and selected toxicants in forages and grains. Vet Clin North Am Food Anim Pract 27:345. Modifications and artwork courtesy Don Connor and Howard Wilson.)*

affected by chronic exposures of male animals to AB_1.[17] Low-level subacute to chronic exposures to AB_1 and its toxic metabolites also have the potential to be associated with teratogenesis, mutagenesis, and/or carcinogenesis, and, experimentally, AB_1 in grain dusts can be present in sufficient enough quantities to be converted to carcinogens by pulmonary cytochromes.[3,18]

Attempts to estimate the dosages or dietary concentrations of total aflatoxins likely to be "safe" or, conversely, those concentrations that will probably be associated with clinical disease can be challenging. Anecdotal evidence and reports of clinical cases of aflatoxicosis, which provide some dose-related data, might require additional scrutiny because some of the factors known to influence the toxicity of aflatoxins might be unaccounted for or unknown.[6] However, such reports are still of value because they represent "real" clinical situations. An animal's plane of nutrition, rate of hepatic metabolism, age, and species, as well as the level and duration of aflatoxin exposure, are all important determinants as to whether and what signs of aflatoxicosis are likely to be observed.[1,3,6,8] Animals fed a diet deficient in protein, selenium, and/or vitamin E and those with enhanced rates of hepatic metabolism are more likely to experience hepatic insult associated with dietary aflatoxin contamination.[6,8] Immature animals, particularly young swine, are the livestock populations considered most susceptible to adverse health effects associated with aflatoxins.[3,6] Weeks of exposure to total dietary aflatoxin concentrations of 200 ppb (0.2 ppm) have been associated with mild hepatic insult and suboptimal growth of piglets and decreased performance in calves.[3,6,8] Horses and more mature cattle and swine have experienced toxic insult to the liver following weeks to months of exposure to aflatoxin concentrations exceeding 400 and 600 ppb (0.4 and 0.6 ppm), respectively, and hepatic failure and death are possible in animals consuming feedstuffs that contain a flatoxin concentration exceeding 1000 ppb or 1 ppm.*

The "threshold" AB_1-induced "abnormality" usually first observed at the lowest dietary concentrations in livestock species is an actionable level of AM_1 detected in milk obtained from exposed lactating dairy animals.[3,6] The concentrations of AB_1 causing violative AM_1 residues in milk are much lower than those likely to cause liver-related adverse health effects, especially in ruminants.[3,6,8,11-16,19] The ratio of the concentration of AB_1 in the diet to the AM_1 concentration detected in the milk varies widely from less than 50:1 to almost 2000:1 (average of 300:1), and the proportion of dietary AB_1 excreted as AM_1 can range between 0% and 4% (average of 1%).[6] Excretion of AM_1 in the milk generally continues for 2 to 7 days following withdrawal from an AB_1-contaminated diet.[3,6]

The accurate diagnosis of clinical aflatoxicosis usually involves the detection of high AB_1 concentrations in the feed or, less optimally, the gastric contents of animals exhibiting appropriate clinical signs.[3,6,8]

*References 3, 6, 8, 11, 12, 14, 15, 19.

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The detection of AB_1 and/or AM_1 in the liver and kidney, in particular, can also be indicative of recent AB_1 exposure (usually within 7 days) and might help establish the consumption of dietary AB_1 by a deceased animal, when feedstuffs are unavailable for analyses.[3,8]

Treatment of aflatoxicosis in large animals is often cost prohibitive, especially in food-producing animals, and limited to therapy for hepatic insult and/or failure; provision of a balanced, AB_1-free diet; possible supplementation with trace minerals and vitamins (selenium and vitamin E); and, most importantly, prevention of further exposure.[3,6,8] Growth conditions are not conducive to AB_1 production in *Aspergillus*-infected stored grains when the moisture content is reduced to less than 15%.[8] Ammoniation has been reported to prevent fungal colonization and growth and to facilitate detoxification of aflatoxins.[1,3,8] In "emergency" situations where it is difficult to find affordable, alternative feedstuffs free of AB_1 contamination, producers may consider dilution of feeds to "safe" concentrations of AB_1.[3] However, this approach has some attendant risk, including the species of animal involved, exposure to enzootic stressors other than aflatoxins (e.g., infectious disease, poor nutrition), level of animal management and husbandry skills, willingness of the producer to thoroughly "blend" the feeds and collect frequent representative samples for AB_1 analyses, and the targeted "safe" concentration of AB_1.[3,4] One approach to the dilemma of which targeted AB_1 concentrations are actually likely to be "safe" might be for producers to aim for total aflatoxin concentrations approximately one half of that shown in Table 54-8 for total dietary aflatoxin action levels, particularly in diets intended for lactating dairy cows, immature livestock, or animals used for breeding purposes.[4,9] This approach can also be used for other mycotoxins for which there are action levels.[4] Another, added consideration, especially for aflatoxins, might be the incorporation of clay binders in rations to prevent the absorption of fungal toxins.[3,4,6,8] Hydrated sodium calcium aluminosilicates (HSCAS) have been shown to effectively prevent violative AM_1 residues in milk and meat and reduce livestock production indices, especially those parameters (e.g., growth and reproductive performance) likely to be impacted by low-level chronic exposure to dietary aflatoxins.[3,4,6,8,20-24] Before using a given binder, there should be in vivo evidence that the binder in question is effective at reducing AB_1 absorption in live animals.[1,3,4,6]

DEOXYNIVALENOL (DON OR VOMITOXIN). Deoxynivalenol (DON or vomitoxin) is classified as a trichothecene mycotoxin and is produced in grains such as corn, wheat, and barley by toxigenic *Fusarium* species, especially *Fusarium graminearum* (formerly *roseum*). This species is also the conidial stage of *Gibberella zeae* and associated with "head blight" and "scab" in wheat and "Gibberella ear rot" in corn.[1-3,25] Although growth of this toxigenic fungal species occurs in the field when temperatures are warmer (20° to 25° C), DON production is favored under storage conditions when it is cooler (0° to 15° C).[1,3] Rising and falling (undulating) temperatures, especially when associated with a cool, wet fall and delayed harvest, facilitate production of DON.[1,3,26] Trichothecenes are stable compounds that persist much longer than the fungi producing them.[1] Deoxynivalenol can also be found in forages (such as corn stover and wheat straw) associated with the grains most frequently contaminated by this mycotoxin.[1,27] In addition, grains contaminated with vomitoxin are often contaminated with zearalenone (see later), which is also produced by *Fusarium graminearum* (see Table 54-8) under similar fungal growth conditions.[1,3,25]

Deoxynivalenol is an extremely important trichothecene mycotoxin, from an agricultural perspective, because of its impact on indices of animal performance and the frequency with which it is detected in livestock diets, especially those intended for consumption by swine and dairy cattle.[1-3,8,26] This particular fungal toxin inhibits protein synthesis and induces emesis by direct stimulation of the chemoreceptor trigger zone in the medulla oblongata, hence the alternative name of "vomitoxin."[3,25] Immunosuppression has been reported in some animal species, but feed refusal and gastroenteritis are the most common clinical signs, particularly in swine.[1-3,25] Clinical pathologic abnormalities include those associated with decreased feed intake, impaired absorption of nutrients, vomiting, and diarrhea.[8,25]

Table 54-8 shows the action levels for DON in various species of livestock. Clinical signs of dietary exposure to DON, such as feed refusal, generally begin within 1 day of ingestion.[3,25] Dietary concentrations of DON associated with clinical disease range from 1 ppm (feed refusal) to 5 to 10 ppm (vomiting and possible gastroenteritis) in swine; ruminants have been reported to refuse eating contaminated feedstuffs containing more than 10 to 20 ppm of DON.[8,25] One of the dilemmas often associated with DON occurs because of the low concentration frequently found in grains and their related forages. It is difficult to differentiate the direct adverse effects of the mycotoxin itself from clinical signs related primarily to reduced palatability and/or the decreased nutritional value of poorer quality feedstuffs, particularly when feed refusal and abnormalities arising from reduced feed intake are the only observed clinical signs.[4] Similarly, any deviations from optimal dairy cattle performance should not necessarily be attributed solely to low-level mycotoxin contamination (<0.5 ppm) without taking into account the reduced palatability and nutritional value of contaminated grains and forages. Evaluation of overall diet quality, rather than just the presence or absence of low concentrations of mycotoxins such as DON, remains an important aspect of the management of livestock production systems, even when experimental data indicate improvement following the addition of "binders."[28,29] Such products might have benefits related to nutrient uptake, which are completely independent of interactions with DON or any other mycotoxins.[30]

As with AB_1, appropriate clinical signs and analyses of feedstuffs and, less desirably, gastric contents can be used to determine whether there has been dietary exposure to DON.[3,8,25] However, unlike AB_1, consumption of DON is not associated with residues in milk or meat.[3,25] Treatment of DON intoxication is limited to supportive care and prevention of further exposure to feedstuffs contaminated by DON and related mycotoxins. There has been limited in vivo success in developing binders that are effective in preventing the absorption of DON in experiments involving susceptible species.[31,32]

ZEARALENONE. Like DON, zearalenone (ZEA) is produced in corn and other grains and their corresponding forages by *Fusarium graminearum* (formerly *roseum*), as well as other *Fusarium* species.[1-3,8,33] The synthesis of ZEA is facilitated by a drop in temperature to 12° to 14° C with greater than 23% relative humidity.[1,3,8,33] Under certain growth conditions, both DON and ZEA can be detected in some contaminated feedstuffs, and the diagnosis, treatment, and prevention of dietary exposures to ZEA is essentially the same as outlined for DON.[1,3,25,33]

Zearalenone is a naturally occurring xenoestrogen that binds to both the α and β estrogen receptors (ERα and ERβ). Swine, especially sexually immature, prepubertal gilts, and dairy heifers, at about the time they are being bred to produce their first calf and to enter their first lactation, represent the livestock populations most susceptible to the effects. Swine are more sensitive to ZEA because of its slow detoxification and enterohepatic recirculation in this species.[1,3,33] Unlike other livestock, dairy cattle are reported to metabolize ZEA to the more potent estrogenic metabolite, β-zearalenol, rather than α-zearalenol, which has less estrogenic activity than ZEA.[1,4]

Within a few days to a week after exposure to dietary concentrations of ZEA as low as 1 ppm, classic hyperestrogenism, as evidenced by vulvar swelling (one of the earliest and most dramatic signs), enlarged mammary glands, possibly prolapsed rectum, and increased size and weight of the tubular portions of the female reproductive tract, can be observed in prepubertal gilts.[1,3,8,33] Nymphomania in females and feminization and decreased testicular weights in males can also be observed, especially in gilts and young boars.[33] Dietary concentrations of 3 to 10 ppm of ZEA can be associated with anestrus and pseudopregnancy in postpubertal gilts and sexually mature sows, due to the unique luteotrophic effect of estrogens in swine.[8,34] Exposure of recently bred sows (7 to 10 days after breeding

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or insemination) to concentrations of ZEA, exceeding 15 ppm, can result in early embryonic death and prolonged interestrous intervals.[8,33]

Although it is clear that postpubertal dairy heifers are more susceptible than mature dairy cows (>10 ppm vs. >25 ppm ZEA, respectively) to adverse reproductive effects associated with ZEA, there still remains doubt as to how often ZEA-related problems are observed in dairy cattle in "real-world" situations.[4,8,33] There are reports that cattle are insensitive to ZEA, while others report a 25% lower pregnancy rate in postpubertal heifers fed 12.5 ppm of ZEA.[4,33,35,36] The disparity between these reports attests to the significance of the stage of sexual maturity, concurrent exposure to other enzootic stressors, and sensitivity of the criteria used to evaluate impaired reproductive performance in determining how ZEA affects dairy cattle fertility.[4]

FUMONISINS. Fumonisins, especially fumonisin B_1 and B_2 (FB_1 and FB_2), are produced primarily by the ubiquitous fungal species *Fusarium verticillioides* (formerly *moniliforme*).[1-3] *Fusarium verticillioides* grows primarily on corn, and the highest concentrations of FB_1, which is the most common and clinically important fumonisin, are most often found in association with corn "screenings" or "fines."[8,37,38] Although growth conditions facilitating FB_1 production are not as well defined as those for AB_1, DON, and ZEA, drought conditions during the growing season and subsequent cool, wet weather during ear development seem to correspond to higher FB_1 concentrations.[8,37]

Fumonisins structurally resemble sphingolipids, which are found in highest concentrations in the brain and liver, and are essential for cell growth and differentiation, as well as vascular integrity.[1,3,8,37] One primary toxic mechanism of action proposed for fumonisins, in particular FB_1, is inhibition of the conversion of sphinganine to sphingosine, resulting in a disruption of sphingolipid biosynthesis.[3,8,37,39] Horses and swine are the two livestock species most susceptible to fumonisin intoxication.[1,3,37] The brain is generally considered the major target organ in horses, especially following more chronic, low-level exposures, but centrilobular hepatocellular necrosis, with clinical pathologic changes in the serum typical of toxic hepatic insult, can be observed in the absence of brain lesions when horses are acutely exposed to high FB_1 concentrations.[1,3,37] Subacute to chronic consumption of dietary concentrations of FB_1 exceeding 8 to 10 ppm have been associated with the sudden onset of the clinical syndrome referred to as *equine leukoencephalomalacia* (ELEM) or "moldy corn poisoning."[1,3,8,37,40-42] Horses affected by ELEM (also see Chapter 35) exhibit altered mentation, ranging from depression to neuroexcitation, sometimes accompanied by head pressing; incoordination and apparent blindness; and, finally, recumbency and death, often within 5 to 7 days of the onset of clinical signs.[1,3,37,40-42] The pathognomonic lesion of ELEM is *leukoencephalomalacia* or degeneration of the white matter of the brain, which can be grossly visible involving one or both cerebral hemispheres, or subtle and difficult to detect in stained sections of brain.[1,3,37,40-42] Hepatosis of varying severity can also be observed in cases of ELEM, and transient increases in the activities of enzymes specific for hepatocellular damage might be observed under those circumstances.[37,41]

The primary clinical abnormalities associated with FB_1 exposure in swine include porcine pulmonary edema (PPE), which is thought to be secondary to left-sided heart failure, and toxic insult to the liver.[1,3,8,37] However, unlike ELEM, it is difficult to pinpoint any consistent "threshold" dietary concentrations of FB_1 likely to cause heart failure and the resulting PPE in swine or, alternatively, histopathologic changes restricted to only the liver.[8,37,38,43,44] Some authors have suggested that FB_1 concentrations in contaminated corn or especially in contaminated corn screenings, ranging from the dietary action level of 10 ppm of FB_1 (see Table 54-8), should be considered actionable. Conversely, it is interesting to note that swine have been chronically exposed to dietary FB_1 concentrations in excess of 100 ppm, without the development of signs consistent with PPE and with hepatic fibrosis being the only observed histopathologic finding.[44] It appears that if PPE is going to develop, it will almost certainly do so within the first week of consumption of FB_1-contaminated diets.[37,43] This consistent observation suggests a role of various stressors, such as recent transport, excessive animal handling, and/or the presence of respiratory pathogens.[44,45]

The diagnosis of ELEM and PPE involves the observation of the appropriate, species-specific clinical syndromes, as well as the detection of sufficiently high enough concentrations of FB_1 in corn-based rations, especially those diets prepared using screenings from homegrown corn.[3,37] An elevated sphinganine-to-sphingosine ratio (SA : SO ratio) in the serum, urine, or tissues of animals suspected of being exposed to FB_1 can also be an accurate indication of recent (<7 days) exposure to FB_1.[3,8,37] As with DON and ZEA, treatment of fumonisin intoxication is limited to stabilization and supportive care, withdrawal from FB_1-contaminated rations, and, most importantly, prevention.[47] Unless absolutely unavoidable and only if there is concurrent and vigilant FB_1 surveillance to ensure that FB_1 concentrations remain below 1 ppm (see Table 54-8), horses should not be fed diets containing homegrown corn and/or, especially, corn screenings. A similar approach could also be used to prevent FB_1-related PPE and hepatic disease in swine.[3]

ERGOT ALKALOIDS. Ergot alkaloids (EAs) are a complex class of mycotoxins that play a role in several financially devastating livestock diseases (i.e., "fescue toxicosis," "perennial ryegrass staggers," and "ergotism").[1,46,47] However, unlike the other "major" mycotoxins discussed in this chapter, EAs are not found in corn and the most commonly occurring intoxications involving EAs are restricted to forages (i.e., fescue toxicosis and perennial ryegrass staggers). Unfortunately, the economic impact of these two mycotoxicoses is thought by many to be restricted to certain geographic regions.[46,47] Ergotism, on the other hand, which can be associated with the ingestion of contaminated forages or grains, has mistakenly been relegated to history because of its sporadic occurrence and is almost exclusively limited to livestock species.[46-48] Although there are several separate systems of nomenclature for EA, an easy way to view these compounds is to divide them into clavine alkaloids; ergopeptine alkaloids (ergopeptines, ergopeptides, or EPs); and lysergic acid and its derivatives (LA+).[46,47] The LA+ have also been referred to as "ergoline alkaloids"; however, this terminology has the potential to be confused with the ergoline ring structure present in all EAs.[46-48,50,51] The most clinically relevant EA to livestock species are EPs, which include ergovaline, ergotamine, ergocristine, ergosine, ergocryptine, and ergocornine and LA+, such as lysergol, lysergic acid amide, and ergonovine (see Table 54-8).[46,47,51,52]

Most of the naturally occurring EAs have been isolated from fungal species within the *Neotyphodium* and *Claviceps* genera.[46-51] *Neotyphodium coenophialum* (formerly *Acremonium coenophialum* or *Epichlöe typhina*) is the endophyte that can grow, as part of a symbiotic grass/endophyte relationship, within the intercellular spaces of tall fescue grass, a long-lived perennial, cool-season grass most simply referred to as *Festuca arundinacea* or, more recently, *Lolium arundinaceum*. Toxigenic endophyte-infected (E+) tall fescue grass grows in humid temperate areas worldwide, including the upper southeastern and lower midwestern United States.[1,48-51] The EP present in highest concentrations in E+ tall fescue is ergovaline (≈0.2 to 0.6 ppm of ergovaline in the vegetative parts of the plant and >1 ppm ergovaline in the seed heads), and LA+ are also present in this grass.[50,51-53] The livestock species most likely to consume E+ forages are ruminants, especially cattle, and horses. The primary sources of the EP compounds, ergotamine, ergocristine, ergosine, ergocornine, and ergocryptine, are the dark-colored ergot bodies or sclerotia of *Claviceps purpurea*. Ergot sclerotia, unlike endophytic mycelia, are externally visible and replace the individual seeds of many common pasture grasses, including E+ tall fescue and small cereal grains, such as oats, barley, wheat, and especially rye and triticale, but NOT corn.[47,48,50] The cool, wet springs in the northwestern United States and the northern Great Plains facilitate the germination and growth of *Claviceps purpurea*.[47,48,50] Those animal species likely to consume E+ tall fescue will also be exposed to the EAs produced

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by *Claviceps purpurea*, if the E+ tall fescue or other nearby grasses are infected by this fungal species ("ergotized"). On the other hand, when small cereal grains are contaminated by ergot bodies, not only ruminants and horses but also swine, poultry, and even humans are likely to be exposed to EAs. The total concentration of EPs in *Claviceps purpurea* sclerotia are extremely high, generally ranging from 2000 to 10,000 ppm, with LA+ also likely to be present.[47,48,50,54-57]

Although there is some overlap, the pathogenesis of clinical signs associated with dietary exposures to EA can be explained in terms of vasoconstriction and/or hypoprolactinemia. Vasoconstriction involving interactions with dopaminergic, adrenergic, and serotonergic receptors is responsible for many of the clinical signs observed in ruminants, especially cattle, and possibly in South American camelids.[46,47,51] Hypoprolactinemia-induced agalactia in late gestational mares is the most sensitive indicator of dietary exposure to EA.[47,50,51] The stimulation of D_2-dopamine receptors by EAs dramatically reduces prolactin secretion by lactotropes in the adenohypophysis.[8,46-51,58] Abdominal fat necrosis in cattle is associated with chronic exposure to EAs in E+ tall fescue and arises from both vasoconstriction and the effects of hypoprolactinemia on lipid metabolism.[46,51] The higher the dietary concentrations of EA, the more likely horses are to exhibit vasoconstrictive effects and the more likely agalactia will be observed in ruminants, in which a placental lactogen helps prevent abnormal lactation from the amounts of EAs often present in E+ tall fescue.[1,34,47,51] Swine exhibit vasoconstrictive effects and suboptimal reproductive performance, including agalactia, when exposed to sufficient concentrations of EAs.[1,47]

When trying to define levels of exposure to EAs, the most readily available data pertain to concentrations of EPs measured using HPLC. If animals ingest total dietary concentrations of EPs between 0.1 and 1 ppm, regardless of the sources, this is equivalent to low-level exposures involving only E+ tall fescue without seed heads, plus or minus other grasses.[50,51,53] Low to moderately high total dietary concentrations of EPs between 1 and 5 ppm correspond to what would be expected in pastures consisting entirely of E+ tall fescue in the seed head stage.[51,53] Moderately high dietary concentrations of total EP ranging between 5 and 10 ppm and very high dietary EP concentrations, exceeding 10 ppm, would involve contamination of feedstuffs by ergotized grains.[47,54-57,59]

Due to vasoconstriction, the toxicity of EAs can be extremely dependent on ambient weather conditions (see Table 54-8), especially with lower dietary concentrations of EAs (0.1 to 1 ppm total concentration of EP), which are typical of E+ tall fescue.[51] When it is hot, a syndrome referred to as "summer slump" or "summer syndrome" is observed in ruminants, in particular cattle, grazing E+ tall fescue.[1,51] This condition is thought to arise from the limited peripheral dissipation of heat associated with vasoconstriction.[1,3,48,49,51] Regardless of the source of toxins, EA-related "heat stress" is characterized by hyperthermia, rapid breathing, lethargy, an unthrifty appearance, and reductions in feed intake and average daily gain, as well as suboptimal male and female reproductive performance.[†] When it is colder, peripheral vasoconstriction in ruminants impairs the circulation to the distal extremities, resulting in cow discomfort, lameness, and, eventually, dry gangrene with sloughing of ear tips, switches, and hooves referred to as "fescue foot" or "gangrenous ergotism," depending on the source of EA.[‡] Controlled experiments indicated that dietary concentrations of ergovaline between 0.4 and 0.8 ppm produced gangrenous effects in ruminants.[64] However, ambient temperatures in those experiments were not below freezing, so, with the impact of ambient temperature on the vasoconstrictive effects of EA, lower ergovaline concentrations would be expected to cause "fescue foot" at temperatures below freezing.[47,51,64] Given "average" ergovaline concentrations in E+ tall fescue and clinical signs in cattle eating other forages "free" of EA, along with E+ tall fescue, it appears that adverse effects on production parameters can be observed in cattle, when total dietary concentrations of EP exceed 0.1 to 0.2 ppm, especially under extreme weather conditions.[47,51,53,54]

Exposure to EAs during the last month of pregnancy is the most common cause of agalactia in mares.[47,50,51,58] Hypoprolactinemia, with minimal udder development, was consistently induced in pregnant ponies treated with a semisynthetic EP, and lactational abnormalities will invariably be the first signs observed in late gestational mares consuming EAs.[50,58] Anecdotal reports suggest that dietary concentrations of ergovaline as low as 0.05 ppm can cause agalactia in some susceptible late gestational mares.[50] Prolonged gestation, dystocia, and abortion, as well as fetal and placental abnormalities, are additional adverse effects observed in pregnant mares consuming higher dietary ergovaline concentrations (generally ≥0.1 ppm).[47,50,51] Pellets containing screenings of ergotized grains or grasses can also be associated with EA intoxication in pregnant mares.[50] The absence of normal changes in udder development ("waxing"), on which horse breeders and veterinarians are dependent to predict imminent parturition, results in unexpected and unsupervised parturition.[58]

The diagnosis of intoxications involving EA requires the observation of appropriate clinical signs, identification of a source of EA, and determination of EA concentrations in that source, as well as in the total diet.[1,3,46] The accurate interpretation of those analytic results necessitates a thorough understanding of the analyses being performed and the pathogenesis of EA intoxications in different species.[1,46] Using reproductive performance as an example of a monitored parameter, management factors and the stressors shown in Fig. 54-4, particularly those related to environment, should be considered when interpreting analytic results.[3]

The basic principles for the treatment and prevention of intoxications related to EA are no different than those outlined for other mycotoxicoses (i.e., removal from the source, stabilization, and supportive care). Incorporation of pasture management practices, including frequent mowing with removal of seed heads, careful use of nitrogen-containing fertilizers, dilution with legumes, and pasture replacement with genetically modified varieties of continental tall fescue free from EAs, can provide added benefits to cattle producers and horse breeders living in enzootic areas.[47,51] Drying and ammoniation of E+ tall fescue hay, manipulation of stocking rates, use of stockpiled E+ tall fescue during winter, and copper supplementation can also help to further minimize EA-induced effects and maximize performance parameters in cattle.[3,48,65,66] Veterinarians should be aware of "fescue-associated edema syndrome" recently observed in horses consuming a genetically modified Mediterranean tall fescue in Australia.[67]

Provision of ample shade (also, possibly pond access) and plenty of potable water to cattle consuming low concentrations of EAs during the summer can help prevent "summer slump" or clinical signs resembling this condition, when the source of EA is not E+ tall fescue.[47,49] Knowledge of mare breeding dates, confirmation of pregnancy, and withdrawal from any dietary sources of EAs at least 30 days before the anticipated foaling date are critical for the prevention of agalactia in pregnant mares.[3,47,49-51] Frequent evaluation of mammary development and, if deemed necessary, daily administration of the D_2-dopamine antagonist domperidone (1.1 mg/kg body weight; watch for leaking colostrum) are additional ways to facilitate adequate lactation and prevent failure of passive transfer in foals.[47,49-51] Domperidone can also be used to mitigate prolonged gestation, along with the attendant risk of dystocia.[47,50,51]

Grain or grass screenings or "fines," in general, and/or any grains containing visible ergot bodies should NOT be incorporated into feeds intended for consumption by pregnant mares or cattle maintained under extreme weather conditions.[47,50,51] The only current FDA action level pertaining to EA is expressed in terms of the percentage of ergot bodies (see Table 54-8), rather than concentrations of EPs.[9] On the basis of the average EP content of ergot sclerotia in barley, 0.1% ergot bodies translates into approximately 2.5 ppm, which, depending on the proportion of the diet represented by this ergotized grain, might not be very protective in many clinical instances.[47,53-57]

[†]References 1, 3, 4, 46, 47-49, 60-63.

[‡]References 1, 3, 8, 46, 47, 51.

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FIG. 54-5 Photo of horse with swelling in muzzle and throatlatch area. *(Courtesy Dr. Skip Aaroe, Trinidad, Colo.)*



FIG. 54-6 Photo of horse with bilateral epistaxis and swollen muzzle. *(Courtesy Dr. Skip Aaroe, Trinidad, Colo.)*

Rattlesnake Bites

C. Langdon Fielding

The majority of snakebites reported in horses and other large animal species are associated with rattlesnakes, which belong to a group of venomous snakes, the pit vipers. There are approximately 30 different species of rattlesnakes found globally and their venom contains various enzymes, proteins, and peptides. Mortality rates for horses envenomated by rattlesnakes may be as high as 10% to 20%, but this depends on the severity of the bite and the response to treatment.[1-3] Rattlesnake bites typically occur during the spring and summer and should only be suspected in regions where the snakes are known to exist.[2]

The muzzle is the most commonly described location for rattlesnake bites in horses, and rapid, severe swelling is common (Fig. 54-5).[2] As the nostrils become swollen and the airways narrowed, respiratory distress is common. In more severe cases, swelling may continue to spread up the head and down the neck. Epistaxis is observed in many horses following rattlesnake bite, and bleeding from the ocular tissues can be seen as the effects of the venom progress (Fig. 54-6). Arrhythmias have been described in horses following rattlesnake envenomation both acutely and chronically.[1,3,4] Diagnosis of rattlesnake bite is based on the characteristic swelling in a horse from an appropriate region during the typical time of year (spring and summer). The presence of fang marks, which are difficult to find in some cases, supports the diagnosis and helps to differentiate from other causes of acute head swelling.

Thrombocytopenia and prolongation of clotting times are described hematologic abnormalities but have not been consistent across various studies in horses.[1-3] Anemia can also be observed and is suspected to be due to both hemolysis and blood loss. Increases in cardiac troponin I (cTnI) have been described in a recent study, confirming myocardial damage in horses with envenomation.[1]

Treatment of horses with rattlesnake envenomation is largely dependent on the severity of clinical signs with many animals requiring only careful monitoring for respiratory distress. Maintenance of a patent airway is the single most important aspect of treatment, and a tracheostomy may be necessary in up to 50% of animals presented for veterinary care.[2] A nasal stent (plastic tubing placed up one or both nostrils) can be used but may be challenging to place and maintain in a distressed and painful horse.

Antivenin has recently been described for the treatment of horses with rattlesnake envenomation.[2] Although clinical trials in other species have suggested efficacy, the use in horses has only been retrospectively reported.[5,6] Polyvalent antivenin (Antivenin, Fort Dodge Animal Health, Fort Dodge, Iowa) was rehydrated according to the label directions, diluted in saline, and administered slowly to horses over 30 minutes.[2] Horses typically required 1 to 2 vials and beneficial effects were anecdotally observed even when given 24 hours after envenomation.[2] A newer polyvalent antivenin (Crofab, BTG International [formerly Protherics], West Conshohocken, Penn.) is used in other species, but the use has not been reported in horses.[5]

Wound care, particularly cleaning of the bite site, and tetanus prophylaxis are important components of treatment. Intravenous fluids are often necessary if the horse is unable to drink, but catheter placement should be performed carefully because affected animals may be prone to bleeding. Many horses may not be able to eat well immediately following a bite, but soaked pellets or mashes can often be hand fed as the swelling subsides. The use of broad-spectrum antibiotics is controversial and not recommended in other species but has been advocated by some authors due to concerns of aspiration pneumonia and infection at the bite site. Nonsteroidal antiinflammatory medications are frequently administered to horses and may help to decrease pain and inflammation. There is no evidence to support the use of corticosteroids or antihistamines for rattlesnake envenomation.

Blister Beetle

Cantharidin toxicosis in horses occurs following ingestion of alfalfa hay that is contaminated with blister beetles.[7] Affected animals are typically found in the midwestern United States due to the swarming of beetles in this region and subsequent incorporation into cut hay. In one study, cases were most likely to occur during the late summer and early fall.[8] Cantharidin causes irritation to the mucous membranes and interferes with a family of enzymes called the phosphoprotein phosphatases.[9]

Horses with cantharidin toxicosis develop signs of gastrointestinal disease (colic, diarrhea); urinary system disease (renal failures, cystitis); and cardiac disease (arrhythmias).[7,10] Affected horses may also exhibit a stiff gait.[10] With increased severity, horses may exhibit synchronous diaphragmatic flutter, hypovolemic shock, and death.[7,10] Laboratory data reflect abnormal renal function (azotemia), as well as hypocalcemia, hypomagnesemia, and hypoproteinemia.[7] Myocardial damage may be reflected in changes in myocardial enzymes; however, this has not been evaluated in horses.

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Presumptive diagnosis of cantharidin toxicosis in horses can be made following the identification of the beetles present in ingested hay. Testing of stomach contents and urine for cantharidin levels has been suggested as a common means for definitive diagnosis.[8,11] It has been shown that 450 µg/kg body weight of ingested cantharadin can cause clinical signs and even mortality.[10]

Treatment of cantharidin toxicosis is primarily supportive. Administration of activated charcoal to animals with recent exposure may be appropriate. Intravenous fluid therapy is important to correct hypovolemia and dehydration. If renal failure is present, therapy should be directed toward maintaining urine production. A balanced isotonic intravenous fluid can be used for resuscitation. Electrolyte and acid-base abnormalities should be corrected using additional supplements to intravenous fluids (e.g., calcium gluconate, magnesium sulfate). Gastrointestinal protectants are indicated, as well as pain medications to provide relief for the ulceration of the gastrointestinal and urinary systems. Hay that is suspected of contamination should be removed and not fed to animals.

Metals and Other Inorganic Compounds

Gary Osweiler

Metals have properties common to the science of toxicology. They are persistent in and move within the environment, change valence, or can be converted in nature or commerce to more or less toxic forms. Metals can accumulate in organs, milk, bone, or muscle and thus present a public health issue. Some metals are both essential and toxic (e.g., copper, iron), so diagnosis depends not only on presence of the metal but also on their concentration in organs or hair.

Arsenic

Forms and sources are widely variable. Arsenic occurs naturally in plants and soil at low levels (2 to 6 ppm), generally in a pentavalent form, but also as sulfides and less common forms.[1-4] These various forms of arsenic can undergo environmental change due to different plant bioavailabilities and solubilities, as well as methylation by microorganisms. Most poisoning, however, occurs from exposure to commercial products where the valence and solubility have been changed for pesticidal or other uses.[1] Poisoning has become less frequent in recent years due to replacement of arsenicals by other products with a lower toxicity and less environmental persistence.[5]

Inorganic arsenic compounds are more toxic[6] and more likely to cause toxicosis than the organic arsenic compounds used as feed additives.[1] Inorganic arsenic products for commercial use may be in a trivalent (arsenite) or pentavalent (arsenate) form. Arsenites are more soluble and 5 to 10 times more toxic than arsenates.[1,5-7] Past use of inorganic arsenic included rodenticides, insecticides, herbicides, fungicides, crop desiccants, antifouling paints, wood preservatives, and fire salts.[4-6] Present use of arsenicals is much reduced due to regulatory restrictions and the development of newer, more effective substitutes. A continuing risk occurs when livestock ingest ashes left from the burning of older arsenic-treated wood as the arsenic becomes concentrated and more available.[2]

Organic arsenic compounds can be either aliphatic or aromatic. *Aliphatic* arsenic compounds have been used as herbicides and tonics. *Aromatic* organic arsenic chemicals are trivalent (used for canine heartworm therapy) or pentavalent (phenylarsonic compounds occasionally used as feed additives for poultry and swine).[6,8,9]

The mechanism of action varies for different forms of arsenic. *Pentavalent* inorganic arsenicals (e.g., arsenates) replace phosphate in glycolysis, which uncouples oxidative phosphorylation and reduces available metabolic energy. These may be factors in the neural damage that follows excessive and prolonged exposure to pentavalent arsenicals.[3,6] *Trivalent* arsenicals block the citric acid cycle,[4,6] resulting in reduced energy metabolism, affecting metabolically active organs (e.g., liver, kidney, gastrointestinal [GI] epithelium, heart). Blocking of metabolic energy by inorganic and aliphatic organic compounds directly affects capillaries, resulting in transudation of plasma, diarrhea, decreased blood volume, dehydration, and shock. Phenylarsonic feed additives cause degeneration of myelin sheaths and axons in monogastric animals, causing neural degeneration, ataxia, paralysis, and blindness.[1,6]

Different forms of arsenicals exhibit different toxicities. Acute arsenite toxicity ranges from 1 to 25 mg/kg body weight (bw), while toxicity of arsenates is 30 to 100 mg/kg bw. Methanearsonate herbicides are toxic at 10 to 25 mg/kg bw over several days. The organic phenylarsonic feed additives are toxic on the basis of exposure concentration in feeds. Seven to 10 days' consumption of arsanilic acid at 500 mg/kg (ppm) of diet or 3 nitro, 4 hydroxy-phenylarsonic acid (roxarsone) at 250 mg/kg of diet will cause nonfatal but prolonged to permanent neurologic signs in swine.[8,9]

The clinical signs and lesions are similar for the trivalent inorganic arsenicals, while the organic phenylarsonic compounds used as feed additives cause peripheral nerve degeneration in monogastric animals. The inorganic arsenic compounds (arsenites, arsenates) cause dosage-related peracute, acute, or subacute toxicosis with cardiovascular collapse, sometimes presenting as sudden death.[1,5-7] Acute poisoning occurs 3 to 12 hours after ingestion. Clinical signs include ataxia, diarrhea ± blood, recumbency, and death with the most prominent clinical sign in acute and subacute cases being diarrhea that is frequently hemorrhagic.[5,7-9] Other clinical signs include anorexia, dehydration, weakness, colic, and agalactia.[1,6,8,10,11] Consistent necropsy lesions are present in the GI tract and may be hemorrhagic, edematous, necrotic, or eroded. The lesions may be confined to one region or spread throughout the GI tract.[1, 2,4-11] In ruminants, the abomasum is often the most severely affected area. The gut lumen is sometimes filled with necrotic material from the sloughed lining of the GI tract. Other lesions include pulmonary edema and hemorrhage of the cardiac serosa and peritoneum.[1,6,7] Histopathologic examinations may reveal multifocal necrosis of the liver and proximal tubules of the kidney.[4,10] Renal lesions are likely in animals that survive a subacute toxicosis. Peracute cases often have no abnormal gross findings.

The diagnosis of acute arsenic toxicosis is confirmed by elevated levels of arsenic in the liver, kidney, and GI contents.[4,6,8,11] In peracute death, the tissues may have normal concentrations of arsenic, but GI contents will have increased levels. In chronic toxicosis, arsenic deposition in hair begins 2 weeks after exposure, and hair or skin can be used as a retrospective diagnostic tool.[5,7-10] Gastrointestinal contents, urine, and whole blood are the best samples to collect from live animals for diagnostics.[7-10] Arsenic elevations in the GI tract may persist for only 1 to 2 days in surviving animals, and because arsenic is rapidly excreted from blood and urine, any delay in sampling may reduce the chances of confirmation.

Environmental exposure to livestock has been documented but is not consistent. Cattle tissues examined from areas with elevated arsenic in drinking water showed accumulation of arsenic in milk, feces, urine, and hair as compared with those from control areas. Straw from soil-contaminated sites has accumulated up to 10-fold higher residues than the soil.[12] In contrast, data in the United States showed little potential for low levels of arsenic to accumulate in milk of dairy cattle.[13] In the United States, areas of high environmental contamination have included mining waste, industrial contamination, and residue from livestock dipping vats.[14] Roxarsone arsenical feed additive that is present in swine waste effluent degrades to either organoarsenicals or pentavalent arsenic and several unidentified metabolites. The return of organic arsenicals as a source of pentavalent arsenic to the environment could pose issues for swine producers using such products.[15]

Treatment is dictated by the type and severity of clinical signs. Dimercaprol, also known as BAL (British antilewisite), can be used as a specific antidote for trivalent inorganic or an aliphatic organic arsenic. Recommendations vary, but a rigorous protocol is a loading dose of 3 mg/kg intramuscularly (IM) q4h for the first 2 days, q6h on the third day, and q12h for another 10 days.[16,17] Dimercaprol side

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effects inhibit metallic coenzymes needed for cellular respiration, and adverse side effects include hypertension, tremors, convulsions, and coma.[16] Early experimental work showed lipoic acid (LA) to be a superior chelating agent to dimercaprol when administered to calves in a 20% solution at 50 mg/kg IM (two or three injection sites) q8h. A combination of BAL with LA was most effective.[18] Sodium thiosulfate is a safe and readily available chelator in large animals but effective only if given before the onset of clinical signs. Dosage is 30 to 40 mg/kg IV or 60 to 80 mg/kg PO two or three times daily for 3 to 4 days.[9] Newer chelators, including 2, 3-dimercaptosuccinic acid (DMSA, succimer), have the benefit of chelating toxic metals such as arsenic, lead, and mercury while sparing iron, magnesium, and calcium.[16,17] DMSA is likely cost prohibitive for most large animals. D-Penicillamine is an effective arsenic chelator in humans but also may be too expensive in livestock.[16,17] Ethylenediamine tetraacetic acid (EDTA) is not effective for arsenic toxicosis.[2] Treatment plans should include supportive therapy for dehydration, shock, reduced renal function, and hemorrhage.[16,17]

Copper

Sources of copper used in livestock are widely available as sulfates, chlorides, and oxides. Concentrates of copper are found in feed premixes, fertilizers, copper footbaths, aquacides, and fungicides (Bordeaux mixture). Acute copper toxicosis has occurred in cattle given injections of copper disodium edetate as a therapy for copper deficiency.[19-21] Sheep are very susceptible to poisoning by chronic copper accumulation in feeds formulated with excessive copper and inadequate molybdenum and sulfur.

Copper poisoning can be acute or chronic. Acute toxicosis results from ingestion or administration of soluble copper salts in one of the sources listed earlier, usually from one to several large doses of copper regardless of sulfur or molybdenum status. Chronic copper toxicosis can be categorized as simple, hepatogenous, or phytogenous. *Simple* chronic toxicosis is caused by ingestion of excessive copper relative to molybdenum and/or sulfate in the diet. Sheep fed diets with a copper-to-molybdenum ratio greater than 10:1 are at high risk for developing clinical copper poisoning. Molybdenum and sulfate bind to dietary copper in the rumen and also form a copper-molybdenum complex post absorption, which decreases absorption and eventual accumulation of copper in the liver.[22] In addition, there is increased excretion of copper in bile and urine. Copper accumulates in sheep liver when the dietary copper-to-molybdenum ratio is greater than 10:1.[22] For cattle, dietary copper-to-molybdenum ratios above approximately 40:1 will allow chronic copper accumulation, and most clinical cases in cattle involve dietary copper in excess of 40 mg/kg of diet. Modest increases of dietary molybdenum in cattle can actually cause copper deficiency.[22,23]

Sheep are often poisoned when fed rations intended for cattle or horses,[24] and llamas have developed copper toxicosis when fed cattle feed.[25] Sheep have developed toxicosis on pastures fertilized with manure from swine or poultry fed copper.[26] Cattle develop copper toxicosis when supplemented with excessive copper,[27] when fields are contaminated by copper smelting,[26,28,29] or when they are fed litter from chickens supplemented with copper.[30] Excessive copper in calf milk replacers has been a source of toxicosis in both calves[31,32] and goat kids.[33] Copper-poisoned dairy cattle have elevated copper concentrations in blood, liver, and diet, but little information has been available about the relative amounts of molybdenum, sulfur, or zinc in the ration.[34-37]

Some cattle breeds display differences in their ability to concentrate copper in the liver. Angus steers had higher plasma copper concentrations than Simmentals on identical rations.[38] Jersey cows have maintained higher hepatic copper concentrations than Holsteins, but the toxicologic significance of these differences has not been determined.[39] Holsteins fed high dietary copper (40 mg/kg dry matter [DM]) had liver copper values twice that of cows fed 10 mg/kg DM, but the high copper group did not have overt signs of copper toxicosis.[40]

Hepatogenous copper toxicosis occurs when *Senecio* species and *Heliotropium europaeum* damage the liver and cause copper retention.[22] *Phytogenous* copper poisoning occurs from prolonged grazing on plants (e.g., subterranean clover *[Trifolium subterraneum]*) with elevated copper/molybdenum ratios. In general, mature pastures have lower copper/molybdenum ratios than young, rapidly growing plants.[41]

The pathogenesis of copper toxicosis involves absorption, binding to albumin and transcuprein proteins, and transport to the liver, where it binds with ceruloplasmin, a hepatic metalloprotein. Absorption in monogastric and young ruminants with a nonfunctional rumen is 75%, but only 1% to 10% in cattle and sheep with normal rumen function.[41]Dietary molybdenum at 2 to 5 mg/kg diet and dietary sulfur at 0.4% of diet substantially reduce ruminant copper accumulation. High dietary zinc (>200 mg/kg diet) and iron also limit copper absorption in ruminants.[23,41]

The concentration of copper in hepatic lysosomes increases over several weeks to months, leading to excess accumulation. When this occurs, there is necrosis of liver parenchymal cells and swelling of Kupffer cells, followed by sudden spontaneous or stress-related release of copper into the bloodstream.[22,23,41] This acute phase includes reduced blood glutathione, increased erythrocyte fragility, hemoglobin oxidation, and methemoglobin formation. The resulting *intravascular* hemolysis leads to anemia, icterus, and hemoglobinuric nephrosis.[22,23,41]

The clinical signs of copper poisoning are most prominent in sheep and include an abrupt onset of depression, anorexia, and weakness. Feces may be watery, dark, or blood tinged, especially in cattle. Evidence of a hemolytic crisis is apparent and signs include anemia, methemoglobinemia, and hemoglobinuria. Mucous membranes are icteric, muddy brown, or a combination of both.[22,23,34-37] Cattle with copper toxicosis after injection of copper disodium edetate have dyspnea, head pressing, ataxia, and circling.[19,21]

Gross lesions are present in the liver, kidneys, and spleen. The liver is yellow and friable and may be larger or smaller than normal. Hemoglobin casts in tubules cause the kidneys to appear dark red or blue-black. The spleen is enlarged and congested. Histopathologic changes in the liver include centrilobular necrosis, pigment-laden Kupffer cells, hepatic fibrosis, and bile duct hyperplasia.[22,23,27,30] Granules in the liver are positive for copper when stained with copper-specific rhodamine or rubeanic acid.[31]

The diagnosis of chronic copper toxicosis relies on measuring copper levels in serum, liver, and kidney as well as in serum hepatic enzymes.[22,23,27] Serum copper is not elevated until just before or during the hemolytic crisis. Animals with toxic copper levels in the liver may have normal or low serum copper values, so serum copper levels alone are not useful for judging copper status. For sheep and cattle there is typically a substantial increase in serum aspartate amino transferase (AST) and gamma glutamyl transpeptidase (GGT) released from damaged liver before the hemolytic crisis occurs and while the animals are still clinically normal.[41] Controlled studies of serum activities for AST and GGT are excellent predictive indicators of hepatic copper accumulation in sheep or cattle that are clinically normal.[42]

For dead animals, copper should be measured in *both* fresh liver and kidney; after the liver has released copper into the bloodstream, liver copper values may fall into a nontoxic range, but kidney copper values will remain in a toxic diagnostic range. The diagnosis should correlate with histopathologic lesions in formalin-fixed liver and kidney.[22,23] Acute toxicosis from copper disodium edetate does not consistently cause elevated copper levels in the liver or kidney.[19]

Several treatment options are currently available but are often unsuccessful once an animal is in acute hemolytic crisis. Ammonium molybdate (50 to 500 mg PO once daily) and sodium thiosulfate (300 to 1000 mg PO once daily) for 3 weeks have been used for many years as a treatment.[22,23,41] Liver copper levels begin to decrease within 4 days of beginning therapy.[22] A newer, but currently unapproved, treatment is ammonium tetrathiomolybdate at 3.4 mg/kg subcutaneously (SC) on alternate days for three treatments.[43] Either route of

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administration significantly decreases liver copper levels within 6 days. This change is accompanied by an increase of copper in the blood, bile, feces, and urine.[22] Most of this copper is bound with tetrathiomolybdate and albumin in an inert complex.[22,23] Xylazine given with tetrathiomolybdate is reported to double the amount of copper excreted in the urine as compared with tetrathiomolybdate alone.[44] D-Penicillamine (26 mg/kg PO twice daily for 6 days) results in a 10- to 20-fold increase in urinary copper excretion in sheep,[45] but this option is expensive and may not be cost effective for many livestock. Animals in the acute hemolytic phase of poisoning should be treated as needed for serious hemolytic anemia and potential methemoglobinemia from copper's oxidant effect.

Iodine

Iodine is used to prevent some infectious diseases and as a treatment for foot rot. Common sources of iodine include potassium iodide, sodium iodide, kelp, Chilean saltpeter nitrate deposits, and ethylenediamine dihydriodide (EDDI). Oilseed proteins or their concentrates incorporated into foodstuffs contain 0.1 to 0.3 mg iodine/kg. Estimated iodine requirements as mg/kg diet are beef cattle, 0.5; dairy cattle (lactating), 0.8 to 1; sheep, 0.2 to 0.5; swine, 0.3 to 2; and horses, 0.1 to 0.2.[46] Over-supplementation can result in toxicosis.

The toxicity of iodine in which large doses of iodine inhibit organic iodide formation and reduce active transport of iodine by the thyroid leading to goitrogenic effects has been documented. Iodine concentrations greater than 50 mg/kg of diet for calves caused reduced growth rate, and greater than 100 mg/kg resulted in coughing and nasal discharge, as well as reduced hemoglobin and serum calcium concentrations. Previous use of EDDI as an expectorant in feedlot cattle (400 to 500 mg/head/day) or swine (250 to 500 mg/head/day) sometimes resulted in signs of excessive expectorant activity.[47]

Elevated iodine intake (50 mg/day) in dairy cows will raise milk iodine to concentrations that may be unacceptable for public health reasons. One report of abortions in dairy cows was associated with excessive iodine consumption. Maximum tolerable levels (mg/kg diet) based on available literature are cattle, 50; sheep, 50; and swine, 400.[48]

The clinical signs of toxicosis include a nonproductive cough, lacrimation, serous nasal discharge, scaly hair coats, and hyperthermia. Other reported signs include decreased milk production, decreased gain and feed conversion, exopthalmia, nervousness, dermatitis, alopecia, and tachycardia. Young animals appear more susceptible than other age groups. Adults may not develop toxicosis unless stress, disease, or nutritional imbalances are also present.[49] Excess supplementation in mares is associated with goiter in foals.

Serum biochemical changes are inconclusive for iodine toxicosis. A diagnosis can be confirmed only with serum or milk analysis. Iodine concentrations in milk are directly related to levels of iodine in the diet.[49] Elevated serum iodine concentrations (1600 µg/mL) may be associated with mild clinical signs. Nonlactating cows have higher serum iodine concentrations than lactating cows that are eliminating iodine in milk.

Treatment is restricted to removal of the dietary source of iodine. Clinical signs associated with the respiratory tract disappear 1 to 4 weeks after the iodine source is removed.[46]

Iron

Iron toxicosis associated with excess oral or parenteral iron supplementation is distinguished from hemochromatosis (iron deposition in liver).[50,51] Normally, physiological mechanisms limit excessive iron absorption, but very high dietary concentrations or dosing with tonics or concentrates can impair the intestinal barrier to absorption and result in liver accumulation and possible toxicosis. Excess iron is stored in the liver as ferritin and hemosiderin.[50,52] When iron binding capacity is exceeded, free iron release can cause peroxidative damage to cell membranes, especially in the liver.

Toxicosis from iron overload has occurred in neonatal foals (normally born with high iron absorption and high serum iron levels) and adult horses given ferrous fumarate orally; calves injected with ferrous gluconate and ferric ammonium citrate; neonatal swine dosed with parenteral iron; pigs born from vitamin E– and selenium-deficient sows; and young bulls injected with ferric ammonium citrate.[53-57]

The clinical signs of iron toxicosis in neonatal foals include depression, icterus, head pressing, and disorientation.[53] Adult horses develop anorexia, icterus, and sometimes petechial hemorrhages.[52] Calves with iron toxicosis exhibit trembling, vocalizing, bruxism, colic, and convulsions.[54]

Clinicopathologic findings are related to cholestatic liver failure. Animals often have elevated serum levels of γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), bile acids, and unconjugated bilirubin. Coagulopathies include abnormal coagulation profiles, thrombocytopenia, and elevated fibrinogen.[52-54]

The gross lesions are variable. The liver is discolored, pale tan, or mottled red-brown, and most are friable and swollen or shrunken. Hemorrhages may be present in the gastric mucosa, intestines, and urinary bladder. Microscopic lesions include perioral bile ductile proliferation, periportal necrosis, lobular necrosis, and fibrosis.[52-56]

Iron toxicosis is diagnosed on the basis of clinical signs and a history of recent iron exposure. When serum iron and total iron binding capacity (TIBC) are evaluated, serum iron often exceeds the TIBC. In dead animals, the liver iron is elevated to varying degrees in different species; iron may be above normal if the animal had hemolysis or blood congestion occurred within the liver.

The treatment of iron toxicosis is usually limited to supportive care. Repeated phlebotomy or chelation therapy with deferoxamine (40 mg/kg IM q4-8h) has been used to treat iron overload in humans and small animals.[57] The success rate and cost of these treatments in large animals has not been well documented.

Mercury

Mercury toxicosis has been caused by application or ingestion of an inorganic mercurial product used as a counterirritant or from ingestion of seeds treated with organic mercurial fungicides, which are no longer used in most of the world.[58] If blistering agents are used with dimethyl sulfoxide (DMSO), mercury absorption is enhanced.[59,60] The kidney is the primary target and storage organ of inorganic mercury, but mercury also localizes in the GI mucosa and is eventually excreted by the kidneys.[58-61]

Mercury causes two clinical syndromes: acute poisoning from inorganic mercury salts and chronic neurologic damage from organomercurials. Acute inorganic mercury causes ulceration of the mouth, esophagus, and the remainder of the GI tract followed by diarrhea and anorexia. If the animal survives, acute nephrosis develops. Anorexia, gastroenteritis, weight loss, nephritis, and alopecia occur in animals exposed to prolonged low doses of inorganic mercury.[60] Organic mercury fungicides cause brain damage, blindness, incoordination, and proprioceptive deficits. Most neurologic signs are long term or permanent.

The diagnosis of mercury toxicosis is supported by elevated serum creatinine and blood urea nitrogen levels, as well as proteinuria, glucosuria, and isosthenuria. Necropsy findings may include an ulcerated, necrotic, edematous, and hemorrhagic GI tract and pale, swollen kidneys. Confirmatory mercury concentrations may be found in liver, kidney, brain, whole blood, and urine.[58]

Therapy should include detoxification (oral sodium thiosulfate) for recent exposure and the appropriate antidotes. Sodium thiosulfate or BAL can be used for chelation therapy (refer to Arsenic earlier). Residual topical mercurial products (e.g., blisters) should be washed well from the animal's skin.[58-61] Supportive care should be provided for severe gastroenteritis and kidney failure. The success rate is low when poisoning is severe or progressive; the presence of oliguria indicates a poor prognosis.[58-61] Surviving food animals should be

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monitored closely for potential mercury residues, which may persist for extended periods in organs or muscle.[58]

Other Toxicants

Additional toxicants are covered in other chapters as follows:
Fluoride, Chapter 38
Lead, Chapter 35
Molybdenum, discussed under copper deficiency in Chapter 32
Selenium (see Toxic Plants, Chapter 54)
Sodium, discussed under salt poisoning in Chapter 35
Sulfate, discussed under copper deficiency in Chapter 32 and under polioencephalomalacia in Chapter 35
Zinc, discussed under osteochondrosis in Chapter 38

Medications and Therapeutic Agents

Lynn Rolland Hovda

Toxic and adverse drug reactions in large animals occur with some frequency but are not as routinely reported as small animal occurrences. Blurring of the lines between toxicity and adverse reactions exists in the literature and practice. Strictly speaking, toxic effects are dose related and do not occur at normal doses, whereas adverse reactions occur at normal, as well as elevated, doses.[1,2] The definition of an adverse drug reaction has not changed for 30 years and technically is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease, or for modification of physiological function."[2]

Adverse drug reactions can be classified in a variety of ways with six different presentations of the normal scheme.[2,3] A more simplified approach uses only two different types of reactions: dose related and idiosyncratic.[4] In dose-related reactions the signs move from physiologic to pharmacologic to toxic as the dose is increased. Often, simply stopping the medication and allowing the drug to clear the system results in cessation of the clinical signs. Anaphylactoid reactions are included in this group because they are not immune mediated and depend on mast cell degranulation to manifest effects. Idiosyncratic reactions are generally not related to a specific dose or concentration of the medication administered. Immune-mediated reactions are included in the group.

Finding accurate information on adverse or toxic medication reactions in large animals is difficult. Preclinical studies are generally small and include a limited number of animals when, in fact, the medication will be used to treat thousands of animals and reactions may not show up until these numbers are reached.[5] Clinical trials are often helpful, but again small numbers of animals may be involved. Useful information including preapproval medication data can often be found on the FDA's website. (http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm).

Treatment of adverse or toxic reactions varies for each medication and route of exposure. Few antidotes exist for large animal medications, and for the most part treatment is symptomatic and supportive.[6] The use of an offending medication should be discontinued as soon as a reaction is recognized. Bathing for topical exposures, gastric lavage followed by activated charcoal for most recent oral exposures, mineral oil, and intravenous fluids are all useful tools for dealing with the clinical signs.

The most commonly reported adverse or toxic drug reactions in horses include antimicrobials (procaine benzylpenicillin), nonsteroidal antiinflammatory drugs, anesthetic agents, sedatives, and antiparasitic drugs.[7] Reports in cattle and swine primarily implicate antimicrobials.[7] Some of these drugs are covered in separate chapters (see the equine section on nonsteroidal antiinflammatory drug toxicity, in Chapter 32) or discussed more generally throughout the textbook.

Antimicrobial Drugs

It is not possible in the scope of this chapter to begin to review all the antimicrobial drug adverse or toxic reactions. Two antimicrobials, however, have specific known risk factors for large animals and are covered here.

Doxycycline

Doxycycline is a tetracycline used in large animal medicine to treat a variety of illnesses. The IV use of doxycycline in horses is not recommended and has been associated with supraventricular tachycardia, systemic arterial hypertension, discomfort, collapse, and death.[8] The cause is unknown but may be concentration or infusion-rate dependent. Treatment is symptomatic and supportive.

Sudden death has been reported in calves accidentally receiving 3 to 10 times the recommended daily dose (5 mg/kg bid) of doxycycline.[9,10] There is no known breed or genetic predisposition. Clinical signs included lethargy, dullness, loss of appetite, cough, dysphagia from paresis or paralysis of tongue, tachycardia, and tachypnea. Major problems included myopathies and necrosis (tongue, myocardial, other striated muscle), acute tubular necrosis, and hepatic fatty degeneration or congestion.[9] The tongue is affected before the myocardium. The cause of acute tubular necrosis remains unknown but may be a combination of a decreased cardiac output from myocardial issues and an increase in myoglobin from muscle necrosis. Death was reported to be from myocardial necrosis, although a recent clinical study in healthy calves dosed at 5 times the recommended daily dose for 5 days failed to support this.[10]

Enrofloxacin

Enrofloxacin is a second-generation quinolone metabolized in the liver to ciprofloxacin, an active metabolite. Ciprofloxacin, itself a quinolone antimicrobial, should not be used orally in horses because it causes mild diarrhea to severe colitis, laminitis, and endotoxemia.[11]

The most common adverse reactions in horses include mild diarrhea, neurologic signs, and orthopedic disorders in young animals. The neurologic signs are generally dose related (i.e., high dose, bolus route) and transient, resolving in 10 to 15 minutes after administration.[12] Diluting the drug and administering it at a slower rate prevents the development of neurologic signs. Juvenile arthropathies with associated cartilage damage have been reported in neonatal foals and other species.[13]

Several other adverse or toxic reactions have been reported. Intrauterine infusion in mares resulted in acute endometrial ulceration, necrosis, and hemorrhage, as well as fibrosis with inflammation.[14] Oral ulcers developed in animals treated with a gel compounded from the injectable cattle product.[15] Finally, in order to prevent toxicosis, the dose in neonatal calves needs to be lowered to accommodate their lower amounts of body fat and different metabolic capacities.[16]

β_2-Adrenergic Receptor Agonists (Clenbuterol, Ractopamine, Zilpaterol)

All three of these agents have been abused in horses for their known anabolic effects.[17,18] The use of clenbuterol in food-producing animals, once similarly abused, is now completely banned due to accumulation in meat.[19] Ractopamine and zilpaterol are still allowed as feed additives and discussed later in this chapter.

Clenbuterol is labeled for the management of acute and chronic respiratory disorders in horses. The normal dosage range is 0.8 to 1.6 µg/kg bid with a maximum recommended dosage of 3.2 µg/kg bid for 3 days.[19] The dose needed for muscle partitioning in food-producing animals is estimated to be 5 to 10 times the therapeutic dose, while the dosage needed for repartitioning in horses is much lower at 2.4 µg/kg bid.[20]

At normal doses clenbuterol is a moderately selective β_2-adrenergic receptor agonist; at high doses all beta adrenergic

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receptors are stimulated, and a wide variety of signs occur. Clinical signs are dose dependent with nervousness and mild agitation, sweating, and increased heart rate occurring in some horses 5 to 10 minutes after a therapeutic dose of 1.6 µg/kg.[19] Far larger overdoses, 10 µg/kg and 100 µg/kg, were used in three Quarter Horses treated with compounded, bootlegged products.[17] The horses showed excitation, profuse sweating, tachycardia, whole body muscle tremors, hypothermia, recumbency, and in two cases, death. Laboratory abnormalities associated with these large overdoses included azotemia, elevated creatine kinase, hypocalcemia, hypochloremia, hyperbilirubinemia, hyperphosphatemia, and severe hyperglycemia. Treatment included, among other things, multiple sedatives and analgesics, gastrointestinal protectants, intravenous fluids, propranolol (0.01 mg/kg IV diluted in 150 mL over 30 minutes), and insulin (0.22 U/kg IM).[17] It is important to note that propranolol is effective in treating tachycardia but will do little for other signs and that hyperglycemia, in these horses, did not resolve spontaneously and required multiple doses of insulin.

Long-Acting Tranquilizers

Fluphenazine Decanoate

Fluphenazine decanoate is a phenothiazine neuroleptic agent used as a powerful antipsychotic medication in human beings.[21,22] Although not approved or marketed for use in horses, it has been used for years off label to provide long-term sedation for anxious or nervous show and race horses and for uncontrollable horses needing stall rest for surgical procedures.[22]

The suggested equine dose is 0.05 to 0.08 mg/kg IM, but clinical signs have occurred in horses 12 to 36 hours after doses of 25 mg to 125 mg (roughly 0.06 to 0.26 mg/kg).[22,23] Signs are consistent with development of an extrapyramidal syndrome and include extreme agitation followed by a brief quiet period, hypermetria, profuse sweating, circling, rhythmic head tossing and neck arching, violent pawing, and self-mutilation.[22,23] These signs are nonresponsive to normal means of control. Hepatitis and urticaria (multiple, raised nodules; nonpruritic) occurred in one horse but may be due to other factors.[24]

Short-term sedation with xylazine, detomidine, or romifidine may control the animal long enough to perform a physical examination and place an intravenous catheter. Often they are ineffective and a barbiturate is necessary. Diphenhydramine (0.67 mg/kg to 1.5 mg/kg IV q12-24h) or benztropine mesylate (0.018 to 0.035 mg/kg PO q12h) has been used to control the extrapyramidal signs.[22,23] They are not always effective and a barbiturate (pentobarbital or phenobarbital) may need to be used for several days until the signs resolve.

Reserpine

Reserpine, a medication infrequently used in humans to control blood pressure, is used off label in horses to provide long-term sedation.[25] Clinical signs of an adverse reaction include profuse sweating, trembling, shaking, flatulence, watery diarrhea, marked miosis, upper eyelid ptosis, and paraphimosis ranging from mild to almost irreversible.[25-27] Treatment is similar to fluphenazine decanoate, although diphenhydramine and benztropine mesylate are not effective because reserpine's mechanism of action is different.

Blood-Doping Agents—Erythropoietin/Darbepoetin

Blood-doping agents such as erythropoietin (EPO) and darbepoetin have been abused in horses, in particular those horses in endurance events such as horse racing.[28] They increase aerobic capacity and endurance by increasing red blood cell (RBC) production and therefore oxygen transport.[29,30] The danger in using human products is the potential for an immune response with antibody development.[31] Clinical signs including depression, lethargy, and anemia can occur after a single dose or may not occur until many doses have been administered.[28,31,32] Two Standardbred racehorses developed severe anemia, elevated serum irons, and bone marrow specific hypoplasia after receiving at least two doses of EPO (4000 IU).[28] Treatment for these horses included stopping the EPO and administering oral dexamethasone (0.05 mg/kg once daily) with tapering of the dose as anemia resolved.

Miscellaneous Medications

Isopropyl Alcohol

Isopropyl alcohol is not a problem when used topically, but toxicosis has occurred when inadvertently given orally. A horse accidentally received 2 L via nasogastric tube instead of mineral oil. Shortly thereafter it became dull, depressed, and collapsed with no menace response and slow pupillary light reflexes.[33] Treatment included gastric lavage, activated charcoal, and IV fluids with recovery complicated by surgical correction of a cecal impaction.

Dimethyl Sulfoxide

Dimethyl sulfoxide (DMSO) when administered intravenously in concentrations greater than 50% results in severe hemolysis.[34] Few issues occur with topical and oral use of DMSO without additives. DMSO-associated toxicosis occurs when it is used in combination with other products, carrying them across membranes including the skin and the blood-brain barrier. In two instances, the application of a DMSO and mercury blister to limbs resulted in the development of mercury toxicosis.[35]

Dioctyl Sodium Succinate (or Docusate)

Dioctyl sodium succinate (DSS) is frequently used as a stool softener in horses with impactions. Single doses of 0.65 to 1 g/kg have resulted in agitation, abdominal pain, dehydration, watery diarrhea, intestinal mucosal damage, collapse, and death with signs occurring within 1 to 2 hours of administration.[36] Treatment is supportive and includes GI protectants, IV fluids, correction of electrolyte abnormalities, and pain relief.

Lidocaine

Lidocaine, when used as a continuous IV infusion for ileus, has caused muscle fasciculations, anxiety, sedation, and visual dysfunction. The targeted serum level associated with this use of lidocaine is 1 µg/mL (0.98 µg/mL) with signs occurring at levels of 1.85 to 4.53 µg/mL.[37,38] Geriatric and neonatal horses, as well as those with hypoproteinemia, may develop signs at much lower doses and serum levels. Treatment consists of stopping the infusion and waiting a short time for the signs to resolve.[38]

Menadione Sodium Bisulfide (Vitamin K3)

Menadione sodium bisulfide (vitamin K3) is an ineffective anticoagulant in large animal species and toxic in normal doses to horses.[39] When administered to horses, weakness, stiffness, colic, laminitis, and a depressed appetite occur within 4 to 48 hours.[39,40] Acute tubular necrosis with azotemia, proteinuria, hematuria, hyperkalemia, hypochloremia, and hyponatremia develop.[39] Treatment is focused primarily on the renal system with IV fluids and diuretics such as furosemide or mannitol recommended.

Propylene Glycol

Propylene glycol is used as antifreeze, a drug vehicle, and a treatment for bovine ketosis. A mature horse inadvertently received a gallon of propylene glycol instead of mineral oil and developed depression, ataxia, sweating, pain, and salivation in 10 to 25 minutes; some signs resolved. Cyanosis, respiratory distress, and sudden death occurred 24 hours later.[41] Although not effective in this case, sodium bicarbonate may be used to treat developing lactic acidosis. Cows receiving an overdose (median toxic dose of 2.6 g/kg BW) become ataxic, depressed, and recumbent 2 to 4 hours after administration; signs resolve in 24 hours with supportive care.[42]

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Feed Additives

Robert H. Poppenga

Inclusion of a variety of chemicals in livestock feed is an efficient and cost-effective mechanism to improve animal performance and prevent disease. Livestock feed additives include growth promotants such as ionophores, partitioning agents such as ractopamine, antiparasiticides and larvicides such as tetrachlorvinphos, antibiotics, hormones such as melengesterol acetate, buffers, probiotics, nutritional agents, dietary supplements, and adsorbents such as sodium bentonite. Fortunately, the majority of feed additives are safe when used appropriately. The following discussion is limited to those feed additives that are most commonly associated with adverse effects.

Urea and Other Nonprotein Nitrogen Sources

Nonprotein nitrogen (NPN) is converted by ruminal bacteria to ammonia by the enzyme urease. Ammonia is subsequently used by the bacteria to form amino acids and, ultimately, protein. Utilization of ammonia for bacteria protein synthesis is dependent on the availability of a highly fermentable carbohydrate source.

NPN can replace a portion of more expensive natural protein in ruminant rations, providing up to 40% of their nitrogen requirement. Rumen bacteria can effectively utilize ammonia nitrogen in limited quantities. However, when ammonia is produced beyond the capacity of the bacteria to use it, it will accumulate in the rumen at potentially toxic concentrations. NPN is available in a granular form that is either incorporated into concentrates or range blocks or as a liquid that is incorporated into palatable vehicles such as molasses. The most commonly used form of NPN is urea, although other forms such as ammonium salts or ammoniated feed are also used.

Urea is typically recommended at a maximum rate of 3% of the grain ration or 1% of the total ration.[1]

The toxicity of NPN for ruminants is dependent to a certain extent on the adaptation of rumen bacteria to NPN; properly adapted animals can tolerate higher concentrations of NPN than naive individuals. Acclimation to NPN can be lost within 1 to 3 days, so maintaining a constant intake is important to prevent potential intoxication. In unacclimated cattle, a toxic dose of urea is approximately 0.45 g/kg body weight. In comparison, a lethal dose for acclimated cattle is approximately 1 to 1.5 g/kg body weight. Younger ruminants are more susceptible than older animals to intoxication.[1,2]

Ammonia not used by rumen bacteria is absorbed systemically and can result in hyperammonemia within ½ hour to 2 hours if it is not detoxified to urea by the liver for excretion. The amount of ammonia absorbed is dependent on the pH of the rumen. Normally, when rumen pH is below 7, the majority of ammonia is in the form of the charged ammonium ion (NH4+ vs. the uncharged NH3). As more ammonia is produced in the rumen, the pH of the rumen becomes more alkaline with a resultant dramatic shift in the relative amounts of NH4+ and NH3 in the rumen. Unionized NH3 readily crosses the rumen wall; in blood, ammonia is primarily in the form of ammonium ion.

NPN-induced ammonia toxicosis usually results from one of the following situations: (1) inadequate or improper feed mixing, (2) error in calculating the amount for inclusion in feed, (3) inadequate adaptation to NPN, (4) inclusion in carbohydrate-deficient rations, or (5) unrestricted consumption of palatable liquid NPN formulations.[2]

Clinical signs of ammonia toxicosis can occur within 30 minutes to several hours after consumption of excessive NPN. Signs include weakness; dyspnea; salivation; bruxism; bloat; excitation; belligerence; vocalizations; muscle tremors beginning with eyelids, lips, and neck and progressing posteriorly; and convulsions. Due to the rapid onset of clinical signs, it is common to find animals dead without signs being noted. There are no characteristic postmortem findings associated with intoxication. Gross or histopathologic lesions most often involve the lungs and brain and include generalized congestion, hemorrhages, and pulmonary and brain edema.

As evidenced by typical clinical signs, the central nervous system (CNS) is a primary target of NPN intoxication. Mechanistically, ammonium ion causes a number of changes in the CNS including amino acid disturbances, alterations in neurotransmission, cerebral energy deficits, and alteration of nitric oxide synthesis. Brain edema due to hyperammonemia is thought to occur through astrocyte swelling.[3]

A diagnosis of intoxication relies on a history of NPN supplementation, consistent clinical signs, and, ideally, measurement of elevated ammonia concentrations in rumen contents, whole blood, or ocular fluid. Unfortunately, ammonia is volatile, so appropriate sample handling and storage are critical for ammonia measurement. If urea is the NPN source, it can be measured in feed or, less usefully, in rumen contents. An antemortem rumen pH value greater than 8 is consistent with NPN intoxication. Postmortem pH values can be misleading depending on the time lag between death and necropsy.

Treatment is designed to decrease the amount of unionized ammonia absorbed from the rumen. Adult cattle should be given 20 to 30 L of cold water PO to reduce the ability of rumen bacteria to convert urea to ammonia by inhibiting and diluting urease. In addition, decreasing rumen pH shifts the form of ammonia to the unabsorbable ammonium ion; this is accomplished by administering 2 to 6 L vinegar.

A number of strategies can minimize the risk of intoxication. These include a gradual adaptation to NPN, feeding readily fermentable carbohydrate sources, ensuring uniform feed mixing, maintaining a regular feeding schedule, feeding liquid supplements with phosphoric acid to maintain an acidic rumen, coating urea with fat and extruding urea with concentrates such as grain, using urease inhibitors to decrease its hydrolysis, and ensuring that mineral nutrition is adequate.[2]

Ammoniated Feed

Ammoniated feed intoxication is a hyperexcitability syndrome called "bovine bonkers" and is reported in cattle and calves fed ammoniated molasses, hay, straw, and silage.[1] The ammoniation process improves the palatability and digestibility of otherwise poor-quality roughages. Ammoniation of high-quality roughages such as wheat, Sudan grass, alfalfa, orchard grass, Bermuda grass, fescue, and sorghum containing high concentrations of soluble sugars is most often associated with the syndrome. The putative toxicants are the imidazoles, 2- and 4-methylimidazole, which are formed during the ammoniation process. The mechanism causing CNS excitation is unknown.

Hyperexcitability, either spontaneous or induced, is a hallmark of the syndrome. Affected animals will suddenly stampede and run in circles or a straight line until they collide with other animals or buildings or fences. Other clinical signs include ear twitching, mydriasis, trembling, salivation, increased urination and defecation, and bellowing. The only postmortem lesions noted are secondary to trauma. The imidazoles can be excreted via milk, so nursing animals are at risk of intoxication.[4]

A diagnosis of intoxication depends on a history of feeding ammoniated forages and consistent clinical signs. Treatment is nonspecific and typically limited by difficulties in handling affected animals. Sedation can be tried; acepromazine has been suggested.[4] Animals often recover once exposure is halted.

Prevention involves restricting ammoniation to poor-quality roughages that contain low concentrations of soluble sugars. The amount of ammonia used should not exceed 3% of the dry weight of the forage. In addition, the processing temperature of the forage should not exceed 70° C (158° F).[1]

Ionophores

Ionophores are commonly added to cattle and poultry feed for their growth promotant and anticoccidial properties. A number of ionophores are commercially available including narasin, salinomycin, lasalocid, monensin, maduramycin, laidlomycin, and maduramycin.

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In cattle, ionophores result in more propionic acid production in the rumen, which improves feed efficiency. They are also used to prevent rumen acidosis and emphysema. Intoxication most often occurs due to errors in feed mixing that result in overdosing of target species (cattle and poultry) or accidental inclusion in feed of nontarget species (e.g., horses, camelids).

Ionophores are potentially toxic to a variety of mammalian and avian species, although sensitivities vary between species and among different ionophores.[5,6] Intoxications have been documented for horses, cattle, goats, pigs, camelids, chickens, turkeys, and quail. Ionophores bind and transport ions across cell and organelle membranes; the direction of movement depends on the concentration gradient of a particular ion. This results in disruption of multiple ion gradients as one or more ions move into or out of cells. Monovalent ionophores such as monensin, salinomycin, and narasin preferentially complex with either sodium (monensin) or potassium (salinomycin and narasin) ions. Divalent ionophores such as lasalocid and laidlomycin are capable of binding and transporting divalent cations such as calcium and magnesium across membranes. At a cellular level ionophores affect mitochondrial function and result in loss of aerobic energy production.

Horses Horses are the most sensitive livestock species with reported LD50s of 0.6 mg/kg for salinomycin, 2 to 3 mg/kg for monensin, and 21.5 mg/kg for lasalocid.[5]

Clinical signs in horses are similar irrespective of the ionophore ingested, although signs can vary among individuals within an affected group. Signs most commonly occur with 24 hours of exposure, but delayed onset can occur in some cases. Acute clinical signs are primarily due to effects on muscle cells and the nervous and digestive systems. Feed refusal is one of the earliest signs noted in horses. Other signs include weakness, ataxia or incoordination, tremors, stumbling, exaggerated stepping, hesitance to move or turn, tachycardia, congested mucous membranes, hypotension, dyspnea, hyperpnea, sweating, and recumbency. Death can occur without signs being observed. In individuals surviving acute intoxication, longer-term clinical signs result from myocardial damage and decreased cardiovascular function and include unthriftiness, poor performance, poor exercise tolerance, arrhythmias, pitting edema, and hyperpnea. Delayed sudden death can occur long after exposure.

A variety of clinicopathologic changes can occur including elevated ALP, AST, LDH, CPK, creatinine, indirect bilirubin, BUN, glucose, hematocrit, serum osmolality, and phosphorus. Decreased concentrations of serum Ca++ and K+ and urine osmolality occur. Myoglobinuria is often noted. Unfortunately, the usefulness of such changes is limited by significant variation among affected individuals and the timing of their occurrence. Measurement of serum cardiac troponin I has been suggested to help with the early identification of horses with cardiac damage.[7]

The most significant necropsy findings are due to direct or indirect myocardial damage. Acutely affected horses develop degeneration and necrosis of cardiac muscle, while horses dying later have marked cardiac myopathy and fibrosis. Lesions can be absent in horses dying peracutely.

A diagnosis of intoxication relies on a combination of consistent clinical signs, necropsy findings where death occurs, and analytic proof of ionophore exposure. Because medicolegal considerations are often encountered in cases involving horses, it is critical to try to quantify ionophore feed concentrations.[5] This is sometimes difficult if representative feed samples are not available or obtained. Testing several feed samples can be important to confirm nonuniform feed mixing. In the absence of feed testing, stomach contents and/or tissue testing can be done to confirm exposure, but not intoxication.

There is no specific treatment for ionophore poisoning.[8,9] It is critical to quickly remove access to suspect feed and initiate decontamination (e.g., gastric lavage and/or activated charcoal) as soon as possible. The efficacy of decontamination in most cases is questionable.

Supportive therapy is directed toward restoration and maintenance of cardiac output and tissue perfusion, stabilization of cell membranes, and treatment with antiarrhythmics if unstable, life-threatening arrhythmias are present.[8] Affected horses should be rested for up to 3 months after exposure, and echocardiograms (ECGs) and exercising ECGs performed to identify evidence of chronic cardiomyopathy. Reported mortality is 60% or greater.[8]

Cattle Cattle are less sensitive to ionophores than horses. At prescribed use levels, ionophores are safe. The LD50 for monensin in cattle is reported to be 26.4 mg/kg, and lethal doses of lasalocid range from 50 to 100 mg/kg.[6]

In cattle, signs of acute intoxication include early anorexia, rumen atony, CNS depression, muscle tremors, watery diarrhea, tachycardia, ataxia, recumbency, and death. Animals can be found dead without clinical signs being noted. Animals surviving acute intoxication can subsequently develop congestive heart failure characterized by brisket edema, prominent jugular pulses, ascites, fluid feces, dyspnea, and tachycardia. Deaths can occur weeks to months after exposure and be precipitated by exertion such as calving. In dairy cattle, decreases in milk production are likely with production requiring several days to a week to return to previous levels.

Clinical pathologic changes are similar to those described for horses. On necropsy, lesions include myocardiopathy, pulmonary edema, enlargement of the heart and liver, hydropericardium and hydrothorax, and ascites.

Elements necessary for a diagnosis in cattle are similar to those for horses. However, in contrast to cases involving horses in which confirming exposure is likely to be significant, in cattle it is important to confirm exposure to feed concentrations higher than expected concentrations. Treatment is similar to that for horses, although it is less likely to be as extensive in cases involving cattle.

Turkeys Both salinomycin and monensin intoxication have been reported in turkeys.[10] Sensitivity to salinomycin is age dependent with younger birds being less sensitive. Clinical signs in affected birds include dyspnea, drowsiness, sternal recumbency with rear legs extended posteriorly, inability to stand, stiffness, and weakness. Extensive fragmentation and necrosis of skeletal muscle fibers occurs and myocardial damage can also be noted.

β_2-Adrenergic Agonists

In livestock, β_2-agonists have been used as repartitioning agents (i.e., repartitioning nutrients away from fat in favor of muscle). This results in increased carcass weight and ratio of muscle to fat and improved feed efficiency. β_2-agonists approved in one or more countries for use in livestock feed include ractopamine (finishing beef cattle, swine, and turkeys) and zilpaterol (finishing beef cattle). Clenbuterol is approved for treating recurrent airway obstruction in horses but is not approved for use in food animals.[11] Due to the anabolic effects of β_2-agonists, there is the potential for their use as doping agents in racehorses. Horses appear to be more sensitive to adverse effects than cattle following exposure to zilpaterol. In a limited number of horses, adverse effects were noted soon after a single zilpaterol dosage of 0.17 mg/kg body weight PO; this is the recommended dosage for cattle.[12] Signs included nervous behavior, profuse sweating, muscle tremors, and tachycardia within 20 to 60 minutes post dosing. Clinical pathologic changes were consistent with muscle damage and included increased serum activity of LDH, CK, and AST. Myoglobin-induced nephropathy is possible in some individuals. The duration and severity of adverse effects were unanticipated, with some signs persisting for up to 2 weeks. Affected horses recovered completely without treatment.

On the basis of human data, clenbuterol is approximately 19 times more potent than zilpaterol and zilpaterol is approximately 125 times more potent than ractopamine. Dosages of ractopamine of up to 10 times the dose of zilpaterol given to horses have not been associated with adverse effects.[13]

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Antibiotics

The erroneous addition of antibiotics to feed is of particular concern in horses. Antibiotics such as lincomycin, clindamycin, tetracycline, and erythromycin have been associated with lethal colitis in horses.[5] Adverse effects are believed to be due to disruption of the normal microbial flora, resulting in overgrowth of pathogenic bacteria such as *Clostridium* spp., *Salmonella* spp., or *Escherichia coli*. Subsequent production of endotoxins or enterotoxins causes digestive tract damage and systemic clinical effects. Treatment primarily involves intravenous fluid therapy and correction of acid-base and electrolyte abnormalities.

Pesticides

Tetrachlorvinphos (TCVP) is an organophosphorus (OP) insecticide fed to horses, cattle, and swine as a pass-through fly larvicide. It is a cholinesterase inhibitor and intoxication is associated with overstimulation of muscarinic and nicotinic cholinergic receptors. Tetrachlorvinphos has low mammalian toxicity with an LD50 in laboratory animals of greater than 1 g/kg body weight. However, anecdotal evidence suggested that horses receiving TCVP at recommended levels were more likely to exhibit gastrointestinal problems and increased reactivity, leading to handling difficulties. In one study, six horses given the recommended dose of TCVP for 30 days were noted to have heightened reactivity to an external stimulus that correlated with a reduction in whole blood cholinesterase activity.[14] Another study demonstrated that TCVP at the recommended dose depressed plasma butyrylcholinesterase activity in horses but did not disrupt cholinergic neurotransmission in target tissues.[15] Although TCVP, at recommended doses, does not cause typical signs associated with OP overexposure, some clinicians have suggested that alternative methods for fly control be used for horses due to potential adverse effects on behavior.

Pesticides and Rodenticides

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Pesticides

Pesticides comprise a wide variety of chemicals used to control insects and parasites in agriculture, animals, and public health, as well as to control weeds, fungi, and rodents or other animals determined as unwanted by man. The toxicology of pesticides covers a number of different chemical classes. This section focuses primarily on insecticides and rodenticides that are more commonly associated with toxicoses in large animals. Poisoning or toxicosis in large animals generally occurs due to misuse or overdosage with a pesticide, malicious use of pesticides or baits, or occasionally from accidental exposure (e.g., drift from aerial spraying, cleanup of buildings with old stored products).

All pesticides sold and distributed in the United States must be registered by the U.S. Environmental Protection Agency (EPA). Registration is based on scientific data demonstrating that the chemicals can be used without posing unreasonable risks to people or the environment. With advancement of science, all pesticides that were first registered before November 1, 1984 were required to be reregistered to meet the more stringent standards. The U.S. Code of Federal regulations established four acute toxicity categories for acute hazards of pesticide products (with Category I the most toxic and Category IV the least toxic or irritating) based on five types of exposure: oral, dermal, inhalation, ocular irritation, and skin irritation.[1] These categories can be used for regulatory purposes, precautionary statements, human hazards, and personal protection equipment statements. General scientific data on the toxicity of pesticides can be located on the Internet for the EPA (www.epa.gov) and in numerous databases supported by the U.S. National Library of Medicine such as ToxNet (http://toxnet.nlm.nih.gov) using search terms for the chemical, CAS number, trade name, or clinical sign. The product label can also provide data on potential toxicosis.

Unfortunately for large animals, there is a limited number of antidotes available for treatment of pesticide and rodenticide toxicoses.[2] For example, atropine sulfate, epinephrine, and vitamin K_1 do not have New Animal Drug Approval and are not formally approved by the Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM), but the labels are reviewed and on file with the FDA/CVM.[3] These drugs may be used as antidotes in food animals, but the veterinarian should contact the Food Animal Residue Avoidance Databank (FARAD, www.farad.org or 888-873-2723) regarding withdrawal times if animals or milk will be put into the food chain. Regulatory considerations and information needed when using drugs not formally approved by the FDA in a toxicosis have been recently summarized for food practitioners and are not discussed here.[4] Because these toxicoses generally involve pesticides in nontarget species or at high concentrations, withdrawal intervals for these chemicals in food animals are often not readily available. A reasonable place to start locating this information is through contact with your state veterinarian, the District Office for the FDA in your region, and the U.S. Department of Agriculture Food Safety and Inspection Service (USDA FSIS, www.fsis.usda.gov). The state veterinarian may also assist with recommendations for proper disposal of chemically contaminated carcasses.

Organophosphates and Carbamates

Historically, inappropriate use or overdosage with these compounds was associated with a large number of toxicoses, particularly in herd situations. With the introduction of newer types of external parasiticides and chemical products, the incidence of these toxicoses has diminished significantly. Both organophosphate (OP) and carbamate insecticides inhibit acetylcholinesterase (AChE) at cholinergic nerve synapses and at neuromuscular junctions. They also inhibit other cholinesterases in the body (e.g., red blood cells, serum, liver, pancreas, nervous tissue). These insecticides lack species selectivity and may pose a hazard to domestic and companion animals, wildlife, and aquatic species. The anticholinesterase compounds may adversely affect the cardiovascular, respiratory, ocular, reproductive, endocrine, dermal, and immune systems but primarily act on the nervous system and skeletal muscles.[5] Death is usually the result of respiratory failure, often with cardiovascular involvement.

Approximately 200 OPs and several dozen carbamate compounds have been synthesized for numerous purposes. They are incorporated into a number of products including baits, dips, dusting powders, sprays, pour-ons, and oral anthelmintics. The OPs used as defoliants and herbicides, such as glyphosate and gluphosinate, have low acute mammalian toxicity but could induce delayed polyneuropathy.[5] Aldicarb, sold under the trade name Temik, was synthesized to mimic acetylcholine and is considered to have maximum potential for mammalian toxicity.[5]

Both OPs and carbamates inhibit the metabolism of acetylcholine at cholinergic sites. Acetylcholine is a neurotransmitter at postganglionic parasympathetic neurons in smooth muscles, cardiac muscles, or exocrine glands; at neuromuscular junctions of the somatic nervous system; at cholinergic synapses in the central nervous system (CNS); and between preganglionic and postganglionic neurons of the autonomic nervous system. The enzyme acetylcholinesterase (AChE) normally breaks down acetylcholine at these cholinergic sites, but when bound by OPs or carbamates it is inactive. During toxicity, acetylcholine maintains depolarization of the postsynaptic membrane, which is initially stimulatory but may progress to paralysis. The OPs have high affinity for the cholinesterase enzyme and are considered irreversible inhibitors of AChE. Organophosphates can undergo an "aging" process, which stabilizes the OP-acetylcholinesterase bond and cannot be broken. Carbamates do not undergo "aging" and can be dislodged from AChE, resulting in spontaneous enzyme regeneration. These insecticides also induce toxic effects through noncholinergic mechanisms that may involve glutamate release and activation of *N*-methyl-*D*-aspartate receptors

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and the γ-aminobutergic, adenosinergic, and monoaminergic systems that are involved in seizures, which are reviewed by Gupta and Milatovic.[5]

The toxicity of OPs and carbamates varies widely, from highly toxic compounds (OP nerve gases such as Sarin, Soman, VX, and carbamates such as aldicarb and carbofuran) to minimally toxic (e.g., malathion, tetrachlorvinphos). The very young, very old, and weakened animals are more susceptible to poisoning from these compounds. Following exposure, OPs and carbamates are rapidly distributed throughout the body and can undergo oxidation, hydrolysis, and conjugation. They are excreted in the urine and feces. The OPs tend to be more lipophilic than carbamates and are more likely to cross the blood-brain barrier; however, carbamates may cause marked CNS signs. Clinical signs can occur within minutes to hours of exposure depending on the dose, route of exposure, and toxicity of the insecticide. Death can occur within minutes with highly toxic chemicals or when large amounts are ingested. Repeated exposures can be clinically important. The insecticides may be metabolized and excreted within days of exposure, but the regeneration of AChE may require 2 weeks.[6] Clinical signs of acute toxicity due to OP and carbamate exposures result from overstimulation of muscarinic and nicotinic acetylcholine receptors because of the buildup of acetylcholine from inactivation of AChE. The clinical effect is excessive synaptic neurotransmitter activity and depolarization of effector organs.[7] Muscarinic signs include pytalism, excessive tracheobronchial secretions and sweating, bronchospasms and laryngospasms, lacrimation, nausea, diarrhea, miosis, and bradycardia. The muscarinic clinical signs are frequently described by the term "SLUD" or salivation, lacrimation, urination, and defecation. Nicotinic clinical signs include muscle fasciculations, tremors, weakness, ataxia, flaccid paralysis, vomiting, and paralysis of respiratory muscles. Muscarinic signs generally appear first, followed by nicotinic signs, and finally CNS effects (hyperactivity and seizures).

Not all clinical signs are observed in an OP or carbamate toxicosis. The clinical appearance of an anticholinesterase toxicosis may vary with the species exposed, toxic compound, dose, route of exposure, and time line in exposure-response. For example, the use of methiocarb as a snail bait in Australia uncommonly causes problems in horses but can result in AChE inhibition, clinical signs, and death. A 400-kg gelding developed clinical signs of profuse sweating, hypersalivation, lateral recumbency, paralysis of a distal hindlimb, and generalized muscle tremors within a few hours after consuming almost 20 g of methiocarb in bait form (1 kg of 2% weight/volume).[8] The horse had signs of colic, ileus, and a significant amount of nasogastric reflux (total reflux volume after presentation at a veterinary clinic was 55 L) but never developed diarrhea. Because of the large volume of nasogastric reflux, activated charcoal was not given nor was atropine administered due to the lack of gastrointestinal borborygmi. Gastric lavage had been performed about 6 hours post ingestion but was probably ineffective to recover ingested bait; the authors speculated that the worsening clinical signs were due to continued absorption of methiocarb, and the horse was euthanized about 54 hours post ingestion of the bait.

Delayed toxicosis has occurred with the use of chlorpyrifos, a chlorinated OP, as a pour-on in bulls and some exotic breeds of cattle. The toxicity appeared to be related to testosterone levels in cattle, with larger and older bulls affected. Clinical signs appeared 2 to 7 days post exposure and included weakness, muscle fasciculation, anorexia, rumen stasis and distention, and depression.[9] Decontamination of the skin and rumen, activated charcoal, and symptomatic treatment are recommended for treatment of chlorpyrifos poisoning in bulls.

Diagnosis of OP or carbamate toxicosis includes (1) history and clinical signs consistent with the toxicosis; (2) determining cholinesterase inhibition (whole blood, retina, brain), corresponding with adverse clinical effects; and (3) detection of the insecticide in biological tissues (gastrointestinal contents or tissues). The diagnosis can be challenging. Clinical pathologic changes are not consistent and postmortem lesions are nonspecific. Often pulmonary edema is evident on postmortem, along with tracheal fluid and diarrhea, but these changes are not unique to AChE toxicosis.

Measurement of cholinesterase activity in whole blood and brain is commonly used to establish an OP or carbamate diagnosis. Generally, AChE activity less than 50% of normal indicates exposure, and less than 25% of normal in an animal with compatible clinical signs indicates toxicosis from an OP and/or carbamate. Use of AChE activity alone is not always diagnostic. The use of OP anthelmintics in horses at therapeutic doses decreased AChE activity to less than 25% of normal, while no horses displayed clinical signs.[10] Interpretation of AChE activity is difficult in a carbamate toxicosis. Carbamates can spontaneously dislodge from the cholinesterase enzyme before or after sample collection; therefore, AChE activity may be in the normal range even though the animal is experiencing toxicity from a carbamate compound.

Check with your diagnostic laboratory for proper collection of specimens (whole blood, brain, plasma, serum, retina) for AChE activity. With an OP exposure, AChE activity in whole blood is fairly stable for about 7 days after collection if the blood is stored under refrigeration.[10] For determination of AChE activity in the brain, submit a chilled whole or half brain because cholinesterase activity varies with different regions of the brain and the laboratory may have a preference for the brain region tested.

Identification of the insecticide can often be made on postmortem specimens including rumen, gastrointestinal contents, liver, fat, brain, and perhaps kidney. Samples should also be taken of the suspect source (e.g., bait, feed, water) for identification and concentration. It is not unheard of to have acute death losses in animals, finding depression of AChE in brain, whole blood, and retina, detecting the insecticide in rumen contents, but locating no source of insecticide on the farm.[11] With suspect insecticide toxicosis, check with the diagnostic laboratory for proper collection and shipment of samples. Generally, the samples are kept chilled or frozen before analysis. Management of OP or carbamate toxicosis is dependent on the clinical signs and time from exposure. Treatment should be initiated quickly. If the animal is having seizures, stabilize the animal and attempt to control the seizures with diazepam, which may also need to be supplemented with methocarbamol, barbiturates, or general anesthesia. Oxygen therapy and ventilatory support may help with severe dyspnea. The noncompetitive antagonist for OPs and carbamate is atropine, which blocks excessive acetylcholine at synapses. It can control muscarinic signs and some CNS signs, but not nicotinic signs (e.g., muscle fasciculations, weakness, paralysis). The therapeutic range for atropine sulfate is between 0.25 and 1 mg/kg, with one quarter of the dose given intravenously and the remainder administered IM or SC.[6,7] It may be necessary to use the high end of the range in toxic situations. The dose should be repeated as needed (usually a lower dose and every 2 to 4 hours) to control bradycardia and secretions into the lungs. Avoid overtreatment with atropine, especially during prolonged treatment. Note that atropine has a low margin of safety in horses and causes gastrointestinal stasis, which should be carefully monitored during use. It is recommended not to exceed a total dose of 65 mg of atropine in the average horse.[6] When atropine is used in multiple doses as an antidote for a toxicosis, a 6-day milk withdrawal and a 28-day meat withdrawal have been recommended.[3] Note that veterinarians must also consider the residue/withdrawal interval for the insecticide in tissues.

Acetylcholinesterases can be reactivated with oximes, such as pralidoxime chloride (2-PAM), if aging has not occurred. The oxime attaches to the OP insecticide and dissociates the OP-cholinesterase bond. Response to oxime therapy is better when oximes are used within 24 hours after exposure to OP insecticides. Oximes ameliorate to some degree muscarinic, nicotinic, and CNS signs and work best with atropine. The dose, frequency, and route of administration of 2-PAM vary in the literature. A dose of 20 mg/kg IV q4-12h has been recommended in ruminants; the use should be stopped if no response occurs within 36 hours.[12] Excessive doses of oximes have the capability to inhibit cholinesterase.[5] The use of 2-PAM in treatment for a large animal OP toxicosis would be very expensive; in

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addition, 2-PAM is not approved for use in large animals and should be used with oversight under FDA/CVM guidance. Generally, 2-PAM is not used in carbamate toxicosis because the inhibition of AChE is spontaneously reversible by hydrolysis. In some cases the use of 2-PAM in carbaryl (carbamate) toxicity has been considered detrimental. However, in a murine model dosed with a lethal concentration of carbaryl, the use of a low dose of 2-PAM (25 mg/kg) with atropine improved survival to 24 hours.[13] The authors cautioned that the beneficial results of low-dose 2-PAM in a carbaryl toxicosis are based on a murine model (same sex, same age, same strain) using one carbamate with a small sample size.

Once the animal is stabilized, decontamination should be considered. Oral dosage of activated charcoal (1 to 2 lb/500 kg in a slurry) can bind the insecticides in the gastrointestinal tract and prevent absorption; this treatment may also be helpful with topical application of some insecticides. The use of activated charcoal is particularly recommended for ruminants, which have the capacity for large retention of gastrointestinal contents. With topical exposure to insecticides, animals should be washed with a liquid dishwashing detergent and rinsed off to reduce absorption. Gastric lavage with water may be indicated in high-dose exposures where only a few hours have passed since ingestion. Additional therapy may include fluids to treat dehydration and electrolyte imbalances.

Several drugs are contraindicated in OP and carbamate toxicosis (with cholinesterase inhibition) including opiates, physostigmine, phenothiazine tranquilizers, neostigmine, succinylcholine, levamisole, antihistamines, aminoglycoside antibiotics, and theophylline.

Pyrethroids

Pyrethroids are active synthetic derivatives of natural toxins in the plant *Chrysanthemum cinerariaefolium* and *Chrysanthemum cineum*. These chemicals are important insecticides used in crop protection, for controlling insect vectors carrying infectious diseases of animals and humans, and for controlling insects on premises. They are available as wettable powders, granules, and emulsifiable concentrates in sprays, dusts, dips, foggers, ear tags, pour-ons, and back rubbers. Pyrethrins are the naturally active insecticidal compounds from the plants; pyrethroids are synthetic analogs of the pyrethrin esters and tend to have more potent insecticidal activity, tend to be more stable in the environment, and tend to be more toxic. The pyrethroids are categorized as type I pyrethroids (a cyano group is absent) or type II pyrethroids (an alpha-cyano group is present that increases the insecticidal potency). Allethrin, bifenthrin, permethrin, resmethrin, and tefluthrin are examples of type I pyrethroids. Cyfluthin, cypermethrin, deltamethrin, and flumethrin are examples of type II pyrethroids. Often, synergists such as piperonyl butoxide, propyl ethers, and sesamin are combined with pyrethroids to inhibit mixed-function oxidase and esterase enzymes in the target species and reduce detoxification of the insecticide and prolong its action in insects. Synergists may also enhance toxicity in animals. Pyrethroids interfere with conductance of nerve membranes by binding to the membrane and prolonging the sodium current. The pyrethroids act on axons in the central and peripheral nervous systems. Gamma-aminobutyric acid-gated chloride channels may also be affected by high doses of type II pyrethroids. Compared with insect sodium channels, mammalian sodium channels are much less sensitive to pyrethroids and recover more quickly from depolarization.

Most pyrethroids are applied dermally, and there is limited absorption through this route. Pyrethroids are absorbed more efficiently across gastrointestinal and pulmonary membranes. Pyrethroids are lipophilic in nature and distribute into fat, central and peripheral nervous systems, milk, and other organs. Once absorbed, pyrethroids can undergo metabolism by nonspecific esterases and microsomal mixed-function oxidases. Pyrethroids and their metabolites are excreted in feces and urine, with a majority of pyrethroids excreted within 12 to 48 hours.[14]

Following application of pyrethroid pour-on products, cattle can exhibit a paresthesia-like syndrome, thought to result from direct action of pyrethroids on sensory nerve endings.[14] Cattle may be restless and uncomfortable, and twitch the skin on their backs. Young animals are more susceptible due to a lack of metabolism of pyrethroids; death can occur due to respiratory failure and convulsions leading to paralysis. No specific clinical pathologic or histopathologic changes have been reported with pyrethroid applications. In a toxicosis, check with the veterinary diagnostic laboratory regarding analytic testing on appropriate tissues. Pyrethroids concentrate more in nervous tissue than serum or plasma.

Pyrethroids have been implicated with disruption of the endocrine system, adversely affecting reproduction and sexual development, and interfering with the immune system. Pyrethroid treatment of laboratory animals and in vitro samples have induced a decrease in epididymal sperm count and sperm motility, as well as an increase in abnormal spermatozoa.[15,16] Pyrethroid treatments of mice and rats disrupt testosterone synthesis and downregulate 17 β-hydroxysteroid dehydrogenase (converts androstenedione to testosterone) and biosynthetic enzymes that have a critical role in the synthesis of testosterone in Leydig cells.[17,18] In addition, pyrethroid exposure has been shown to disrupt luteinizing hormone-responsible ovulatory genes in rats and prostaglandin synthesis in granulosa cells in vitro.[19]

Exposure of bulls in a bull stud to bifenthrin was associated with poor semen quality, including (1) decreased motility, (2) reduced ejaculate volume, and (3) spermatozoa abnormalities with a high percent of distal midpiece reflexes.[20] At 64 days post exposure, semen quality recovered to levels observed preexposure in these bulls. In this case, the use of bifenthin was apparently an excessive use of product in a building (bull stud) with the animals present so that excessive exposure was dermal, inhalation, and oral; additionally, these animals were being continually monitored for semen quality for cryopreservation and, therefore, clinical abnormalities in semen were easily detected.[21] Field cases of bulls exposed to pyrethroids and subsequently developing poor sperm quality and motility, with gradual recovery to normal after about 2 to 4 weeks, have been reported.[22,23] There is little scientific data, however, with controlled studies to support observations that use of pyrethroids will alter sperm quality in bulls.

Accidental pyrethroid exposure in bulls may result in inadequate semen quality (particularly for cryopreservation) but may not impair bull fertility when bulls are used in natural settings, such as pasture breeding where a number of males are available to breed female cows during a breeding season. The important considerations when using pyrethroids on pastured cattle are to exactly follow the application recommendations on the label, to use a product that the cattle producer has experience with for insect control, and to avoid using close to breeding if possible.[21] Another recommendation is to use only one method of insect control with pyrethroids on breeding cattle at a time (e.g., only spraying or only ear tags).[23]

With dermal exposure, wash and scrub the exposed area using liquid dishwashing soap and rinse well. Avoid using power washers because they may cause dermal trauma.[14] If seizures occur, the use of diazepam, methocarbamol, and barbiturates may be effective.

Neonicotiniamides

A relatively new and emerging class of insecticides are the neonicotinoids, which are heterocyclic nitromethylenes used primarily in crop protection against sucking and certain chewing pests. The neonicotinoids include imidacloprid, acetamiprid, dinotefuran, thiamethoxam, and clothianidin.

The neonicotinoids act on postsynaptic nicotinic receptors located in the CNS of insects. These insecticides initially increase the frequency of spontaneous discharge, which is followed by a complete block of nerve propagation. Neonicotinoids are considered relatively low risk for nontarget organisms and the environment.[24] The activity in vertebrates is much lower due to different binding properties to the nicotinic receptors, and they primarily act on the α_7 nicotinic receptor subtype.

Imidacloprid is used as an insecticide for dermal application on animals, as well as an insecticide for crop protection. Neonicotinoids do not readily pass the blood-brain barrier. Imidacloprid is primarily

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metabolized in the liver.[24] Metabolism of imidacloprid in mammals is by two routes: (1) oxidative cleavage and glutathione conjugation and (2) hydroxylation. Most of the imidacloprid is rapidly excreted in the urine. It is not carcinogenic nor a reproductive toxicant.

Adverse effects noted in laboratory animals dosed with imidacloprid were decreased activity and tremors, impaired pupillary function (dilated or pin point), and uncoordinated gait; higher doses were associated with hypothermia. The no observed effective level (NOEL) for chronic imidacloprid exposure in dogs was 15 mg/kg PO.[25]

Treatment for overdoses of imidacloprid is symptomatic. With dermal exposure wash the animal with soap and water, and with oral exposure use activated charcoal for adsorption and a cathartic. Generally, imidacloprid absorption and elimination are rapid and supportive care should provide recovery.

Organochlorines

Organochlorines are chlorinated hydrocarbons. These compounds include lindane, mirex, kepone, dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, heptachlor, chlordane, toxaphene, and endosulfan. The persistence of some organochlorines in the environment and concern for neurotoxicity and endocrine disruption have terminated the use of most organochlorines. These compounds have limited to no distribution in the United States but may occasionally cause toxicoses when stored chemicals contaminate feed or premises. Organochlorines are available in other countries.

The organochlorines have several mechanisms of action. The DDT-type organochlorines affect the brain and peripheral nerves by slowing sodium influx and inhibiting potassium outflow, partially depolarizing the cell and increasing firing of the neuron.[26] Several organochlorines may act by inhibiting attachment of γ-aminobutyric acid to its receptor, which stimulates the neuron. The organochlorines are absorbed orally and dermally. These compounds are highly lipid soluble and distribute to adipose tissue, brain, liver, kidney, and milk. Metabolism of organochlorines can be through dechlorination and oxidation, glucuronidation, and sulfation. More toxic epoxides can be formed by the mixed-function oxidases. The organochlorines are excreted into bile and the gastrointestinal tract. They can undergo enterohepatic recycling, prolonging exposure for weeks. These compounds bioaccumulate in fatty tissue and persist in the environment. Organochlorines can act as endocrine disruptors.

Acute clinical signs include salivation, vomiting, and nervous system signs of agitation, hyperexcitability, incoordination, apprehension, nervousness, and tremors. As clinical signs progress, animals may display clonic-tonic seizures, opisthotonus, paddling, and clamping of the jaw. Cattle may walk backward, lick excessively, or have abnormal postures.[26] Seizures can persist for several days. Between seizures the animals may be depressed or normal in appearance. Clinical pathologic changes and histopathology are nonspecific.

Diagnosis is based on history, clinical signs, and analytic determination of organochlorines in blood, fat, liver, brain, or milk. Contact the veterinary diagnostic laboratory for sample submission instructions. Generally, samples for organochlorine analysis should not be submitted in plastic but wrapped in aluminum foil and/or placed in clean glass containers. Note that tissue levels of organochlorines do not correlate well with severity of clinical signs or prognosis.

Detoxification is an important step in treatment. Animals with topical exposure need to be washed with soap and water; animals with long hair should be clipped to reduce organochlorine exposure. Treating personnel should wear gloves and aprons to reduce exposure. With oral exposure, activated charcoal (1 to 2 g/kg body weight in a slurry) should be administered orally. Feeding activated charcoal, at 500 to 1000 g/day for a limited time, to large animals will reduce enterohepatic cycling.[26] General supportive care, such as the use of diazepam or barbiturates to control seizures, and placing the animal(s) in an environment to prevent trauma and keep comfortable are important. Organochlorines typically have a prolonged residue time in body tissue. Animals that are lactating or losing weight generally eliminate more organochlorines due to loss of milk fat or body fat, respectively.

The state veterinarian should be contacted regarding exposure of animals to organochlorines and proper disposal of contaminated tissue or materials. The long persistence of organochlorines in tissue prevents immediate placement of food animals or milk into the food chain; proper state or federal agencies will need to be contacted for withdrawal intervals.

Paraquat

Paraquat is a bipyridyl herbicide used as a desiccant on crops. Most questions regarding paraquat exposure in large animals deal with aerial spray drift onto animals and/or their pasture and application to forages that will be used for livestock. Paraquat absorbed onto soil particles is biologically inactive. Animals that have access to concentrated paraquat formulations or to wet forages following paraquat application are at risk for developing clinical signs.

Paraquat is poorly absorbed (5% to 10%) from the intestinal tract but has prolonged residual time in the digestive tract. Emulsifiers or other chemicals in paraquat formulations may enhance absorption and toxicity. Paraquat is concentrated in renal tissue and is eliminated in the urine.

Paraquat forms free radicals in the body and has special affinity for the lung. The production of superoxide radicals and hydrogen peroxide results in damaged cellular membranes and tissue necrosis.

Following ingestion, the initial signs reflect the irritating action of paraquat resulting in abdominal pain, vomiting, anorexia, and depression. By the second to third day post exposure, the onset of renal failure appears along with liver damage (hepatocellular necrosis), which is followed by delayed development of pulmonary fibrosis, respiratory dyspnea, cyanosis, and pneumomediastinum.[27] Death may occur several weeks after exposure. With topical exposure to paraquat, erythema, blistering of skin, and corneal irritation can occur and may resolve without additional complications.

Histopathologic changes from paraquat toxicosis include apoptosis or necrosis of alveolar epithelial cells, denuded alveolar basement membranes, and with a chronic response, hyperplasia of type II alveolar epithelial cells and pulmonary fibrosis.[28] Hepatic and renal lesions may be present. The diagnosis is based on history of exposure to paraquat and chemical analysis of paraquat in urine, plasma (up to 30 hours post exposure), and lung tissue (after 30 hours post exposure).

Treatment should be initiated as soon as possible (within 24 hours) using activated charcoal, bentonite, or fuller's earth. Supportive care includes monitoring vital signs frequently, using fluids to maintain renal perfusion, treating secondary infections, and employing pain management. If treatment is delayed, the prognosis is extremely poor.

Rodenticides

Zinc and Aluminum Phosphide

Zinc phosphide is a rodenticide used since the 1930s. Zinc phosphide is a gray, crystalline powder, which is relatively stable under dry conditions. Rodent formulations contain 2% to 5% zinc phosphide mixed with grains; therefore, the baits are attractive to most species. Under wet or acidic conditions, zinc phosphide degrades to phosphine gas. Phosphine gas has the odor of acetylene or rotten fish, and poisoning can occur in people at detectable concentrations of 2 ppm. Acute, oral lethal doses of zinc phosphide were recently reviewed in various species.[29] The lethal dose of zinc phosphide in ruminants was approximately 60 mg/kg body weight.

Aluminum phosphide is a fumigant used in stored agricultural products to control rodents and insects. It is classified in Category I by the EPA with high potential of acute toxicity with inhalation exposure.[1] After application of aluminum phosphide tablets to grain, phosphine gas is released for up to 5 days. A general recommendation

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is that grain treated with aluminum phosphide should not be handled or fed for at least 10 days after treatment.

Phosphine gas is readily released in acidic environments and can block cytochrome C oxidase, resulting in disruption of oxidative phosphorylation within mitochondria of cells.[30] Blocking energy-producing pathways leads to cell death and eventual multiple-organ failure. Brain, heart, liver, and kidney are most affected by phosphine gas due to high metabolic rates and high demands for oxygen. Because of the higher pH of the rumen, as compared with an acidic monogastric stomach, ruminants should be more resistant to phosphide toxicants.

The onset of clinical signs occurs within 15 minutes up to 12 to 18 hours, depending on the dose and stomach contents (the more acidic, the quicker release of phosphine gas). Death can occur within several hours after appearance of clinical signs. Ruminants show tympany and bloat, while horses can display signs of colic and abdominal pain. Horses fed a pelleted ration recently treated (within 14 hours) with aluminum phosphide showed rapidly developing clinical signs of profuse sweating, tachycardia, tachypnea, pyrexia, ataxia, seizures, and widespread tremors.[31] Clinicopathologic changes include hypoglycemia, high serum lactate and ammonia concentrations, and elevated activity of γ-glutamyl transpeptidase, aspartate aminotransferase, and alkaline phosphatase. Several horses in this case developed clinical signs consistent with hepatic encephalopathy, and eventually 27 out of 28 clinically affected horses died within 2 days after exposure. Postmortem changes were petechial and ecchymotic hemorrhages in numerous organs, widespread vascular congestion, hepatic lipidosis, pulmonary edema, and neuronal necrosis in the cerebral cortex.

Phosphine gas can be detected in gastric contents, vomitus, and possibly liver and kidney. The samples need to be packed in air-tight containers and frozen immediately to prevent phosphine gas dissipation. Check with the veterinary diagnostic laboratory for analytical capability to detect phosphine gas.

The progression of clinical signs often limits treatment options. Early decontamination of the animal by emesis (if the animal vomits), gastric lavage (especially with 5% sodium bicarbonate), and products to increase gastric pH for zinc phosphide exposure is critical. Activated charcoal may be beneficial when mixed with an antacid and a cathartic (e.g., aluminum or magnesium hydroxide). No specific antidote is available for phosphine gas. Supportive therapy should be aimed at correcting acidosis, treating shock and liver failure, and controlling seizures. Horses developing clinical signs after phosphine gas exposure were treated by gastric lavage followed by di-tri-octahedral smectite, atropine, fluids, 10% dextrose, flunixin meglumine, and sedatives.[31]

Metaldehyde

Metaldehyde is a molluscicide, usually sold in less than 5% concentrations as pelleted baits, granules, liquids, and wettable powders. Feed ingredients such as apples, molasses, rice, oats, and soybeans have been added to the baits to increase palatability to nontarget species. Most toxicoses occur in the coastal areas of the United States, where snail and slug populations can be high.

The mechanism of action of metaldehyde is unclear but may be related to alterations of neurotransmitters in the brain. Metaldehyde is toxic to all known animals. Oral ingestion is the most likely route of exposure. Acute, oral lethal doses of metaldehyde were recently reviewed in various species.[32] The lethal dose ranges for metaldehyde were from 200 to 300 mg/kg body weight in ruminants and 60 to 360 mg/kg body weight in horses. Young animals appear to be more susceptible than adults.

Clinical signs of toxicosis usually occur within several hours of exposure and include salivation, restlessness, anxiety, hyperpnea, tremors, colic, ataxia, nystagmus, and convulsions. Blindness and loss of a menace reflex have been reported in cattle with metaldehyde toxicosis.[33] No specific changes in clinical pathology or histologic lesions occurred in animals poisoned with metaldehyde. Gross lesions have included congestion in renal, hepatic, pulmonary, and gastrointestinal tissues and petechial and ecchymotic hemorrhages throughout the body. Demonstration of metaldehyde in gastrointestinal contents (possibly serum/plasma and urine) confirms exposure. Samples should be submitted frozen to the diagnostic laboratory.

Initial therapy may involve control of seizures and tremors with diazepam and barbiturates; xylazine and acepromazine have been used in horses.[32] Decontamination by gastric lavage and activated charcoal, orally at 1 to 2 g/kg body weight, followed by mineral oil has also been recommended. Supportive care with intravenous fluids and a quiet environment may be beneficial.

Anticoagulant Rodenticides

Cases of hemorrhagic disorders reported in cattle generally involve repeated exposure to moldy sweet clover hay or sweet vernal hay (dicoumarol) over a prolonged period of time. Accidental ingestion of anticoagulant baits over a short time period may result in potential toxicosis in large animals. The anticoagulant rodenticides are divided into first-generation coumarin derivatives (e.g., coumachlor, coumatetralyl, warfarin); second-generation coumarin derivatives (e.g., brodifacoum, bromadiolone, difenacoum, flocoumafen); and the indanedione derivatives (e.g., chlorophacinone, diphacinone, pindone). Generally, the second-generation coumarin compounds are more toxic than the first-generation products and can poison with one feeding.

All of the anticoagulant rodenticides interfere with vitamin-K epoxide reductase, which converts inactive vitamin K to the active vitamin. A depletion of active vitamin K may impact vitamin K-dependent clotting factors in the intrinsic, extrinsic, and common coagulation pathways. Anticoagulant rodenticides are well absorbed on oral exposure and are highly bound to plasma proteins. Oral availability of warfarin, chlorophacinone, and bromadiolone in sheep was estimated to be more than 79%.[34] Anticoagulants are metabolized in the liver, and some compounds may undergo enterohepatic recirculation. The half-life of anticoagulant rodenticides varies greatly with the compound and the species. The half-life of brodifacoum in horses was given as 1.22 ± 0.22 days, as compared with that of warfarin in horses at 16 hours.[34,35] The half-life of bromadiolone in cattle was reported to be approximately 20 hours.[34] As a general observation, the duration of action of anticoagulant rodenticides in large animals is about 14 days for warfarin, 21 days for bromadialone, and 30 days for brodifacoum and other second-generation coumarin derivatives. Ruminants are thought to have lower susceptibility to anticoagulants; however, a study in anticoagulant-dosed sheep revealed that the compounds were not degraded in the rumen and their bioavailabilities remained high after oral dosing.[34] The authors speculated that several factors may lower ruminant susceptibility, including the presence of a large forestomach (diluting the compound) and ruminal production of vitamin K_1, which may partially counteract the toxic effects.

Clinical signs may become apparent 2 to 10 days post exposure. Affected animals may display melena, epistaxis, hematuria, or excessive bleeding from a wound. If bleeding occurs within a body cavity, the animal may exhibit pallor, weakness, dyspnea, fever, and depression. Animals may die suddenly from excessive hemorrhage and shock. Generally, gross and histologic lesions are consistent with hemorrhage. Diagnosis is based on history, clinical signs, prolonged clotting times and anemia, and response to the antidote, which is vitamin K_1. Analytic detection of the anticoagulant rodenticide in whole blood, liver, and perhaps gastrointestinal contents can confirm exposure.

Vitamin K_1 is the antidote for anticoagulant rodenticides; the duration of therapy will vary with the specific compound causing the toxicosis and may vary from several days to several weeks. The dose of vitamin K_1 in the adult horse has been recommended at 300 to 500 mg SC q4-6h.[36] The prothrombin time should return to normal within 24 hours. Vitamin K_3, although less expensive to use, is not as effective as K_1, will cause renal disease in horses,[27] and is not recommended.

Packed cell volumes should be closely monitored during clinical signs, and whole blood transfusions may be required if the animal is

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anemic. Decontamination of the gastrointestinal tract with activated charcoal may lower absorption of the anticoagulant. After the animal has stabilized and the appropriate time has passed, vitamin K_1 should be discontinued for 48 hours and prothrombin time retested.

1080

Sodium monofluoroacetate, fluoroacetate, or 1080 is a nonselective rodenticide toxic to animals and humans. The compound 1080 has been available in the United States since the 1940s but now is restricted for use as a predacide in the United States. It is used in Australia and New Zealand to kill invasive, unwanted species. Fluoroacetate naturally occurs in several plants in Africa, Australia, South America, and perhaps southern Florida. Sodium monofluoroacetate also appears to be available over-the-counter in the United States as foreign rodenticides or "herbal" pesticides. This compound is colorless, odorless, and water soluble.

The mechanism of action of 1080 involves a critical cycle, the Krebs or tricarboxylic acid cycle, in cellular metabolism. Many of the effects of 1080 toxicosis result from impaired oxidative metabolism and reduced energy production.[37] The oral LD_{50} for monofluoroacetate in ruminants and equines ranges from 0.22 to 0.55 mg/kg body weight.[38] Sodium monofluoroacetate is quickly absorbed from the gastrointestinal and respiratory tracts and through mucous membranes but slowly absorbed through intact skin.

In general, herbivores have cardiotoxic effects, omnivores have cardiac and CNS effects, and carnivores have CNS effects. Clinical signs occur within 30 minutes to several hours post ingestion. Cattle may stagger, tremble, sweat, and display signs of gastrointestinal irritation; they may even die of heart failure.[39] Horses may display hyperesthesia to external stimuli and have marked cardiac arrhythmias and ventricular fibrillation. Sheep and pigs may show a combination of cardiac and CNS signs. Animals may have decreased ruminal movements, salivation, restlessness, apparent blindness, ataxia, frequent urination, muscular tremors, polypnea, and tachycardia. Pigs may have intermittent vomiting. Clinical pathology changes may include hyperglycemia, increased serum citrate, hypocalcemia (ionized), and acidosis. Electrocardiograms on 1080-poisoned sheep revealed S-T segment elevation and a marked increase in T-wave amplitude, suggesting cardiac ischemia.[40] Severely affected animals generally die within a few days post exposure. Postmortem lesions in ruminants may involve endocardial and epicardial petechiae, edema of the brain, and lymphocytic infiltration of perivascular tissue. A diagnosis of 1080 toxicosis is based on clinical signs, history of exposure, and detection of 1080 in the bait, vomitus/gastric contents, kidney, and liver. Few veterinary diagnostic laboratories in the United States analyze for 1080 in tissues. Generally the assay is by gas chromatography/mass spectrometry with a detection limit of 10 µg/kg (or parts per billion).

A recent case of 1080 toxicosis involved high, acute death loss in ewes and lambs following transfer of the flock to a new pasture over a municipal landfill site.[41] Clinical signs observed in affected animals were disoriented running and breaking through fences, apparent blindness, weakness, and ataxia. Gross lesions included pulmonary congestion and edema and epicardial petechiae and ecchymotic hemorrhages on the ventricles. Histologic changes were acute to subacute myocardial degeneration and necrosis with neutrophilic and lymphohistiocytic myocarditis. Compound 1080 was detected in several kidney samples, but the source of 1080 was not determined. No long-term effects on health or reproductive performance were observed in ewes that survived experimental dosing with a single, near-lethal amount of 1080.[40]

Compound 1080 has no known antidote, and the rapid onset of clinical signs may prevent effective, quick decontamination of the gastrointestinal tract with activated charcoal. A treatment protocol for 1080 toxicosis in dogs involves gastric lavage followed by activated charcoal, control of seizure and convulsions with barbiturates or gas anesthesia, fluid therapy including sodium bicarbonate, monitoring serum calcium and potassium, and use of acetamide if available.[42] The prognosis for most cases of 1080 toxicosis is poor.

Strychnine

Strychnine is a rodenticide often sold at 0.5% to 1% concentrations in a powder, pellets, or with grain bait for below-ground application. Strychnine-treated seeds are often dyed red or green. In several states, the use of strychnine is restricted. Storage of old containers of strychnine-laced grains can be sources of accidental toxicoses. Accidental and malicious toxicoses continue to occur fairly regularly.

Strychine is an alkaloid from the seeds of *Strychnos nux-vomica* and *ignatii*. Strychnine blocks inhibitory action of glycine at the inhibitory neurons, Renshaw cells, spinal cord, and medulla. The lack of inhibition leads to rigidity and tetanic convulsions. Strychnine is quickly absorbed from the gastrointestinal tract and widely distributed in the body. A small portion of the dose is excreted into urine. Hepatic enzymes can readily metabolize strychnine.

Clinical signs can appear within a few minutes to a few hours and include sweating, nervousness, incoordination, recumbency, and tonic-clonic seizures. The seizures can be induced by stimuli such as bright light, loud noises, and touch. No specific clinical pathology or histologic changes occur in strychnine toxicoses. Analytic determination of strychnine in gastric contents (and to a lesser extent in urine, serum/plasma, liver, and kidney) confirms a strychnine toxicosis.

Decontamination by gastric lavage followed by oral administration of activated charcoal (binds strychnine) is important; however, the degree of sensory stimulation may require initial treatment to control seizures and support respiration. The use of barbiturates along with diazepam and methocarbamol may control seizures. Severe respiratory dyspnea may require mechanical ventilation. Additionally, intravenous fluid therapy and a quiet environment may be beneficial. Prognosis for treatment of large animals with strychnine toxicosis is poor because of the difficulty of treating animals in the field. In one case report, several horses had access to an old bag of strychnine-contaminated barley. Clinical signs of CNS stimulation were observed in five out of six horses, with two horses dying. Treatment in the field consisted of activated charcoal and mineral oil to assist decontamination of the gut and xylazine, diazepam, and pentobarbital for CNS signs.[43]

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The reference list can be found on the companion website at www.largeanimalinternalmedicine.com.

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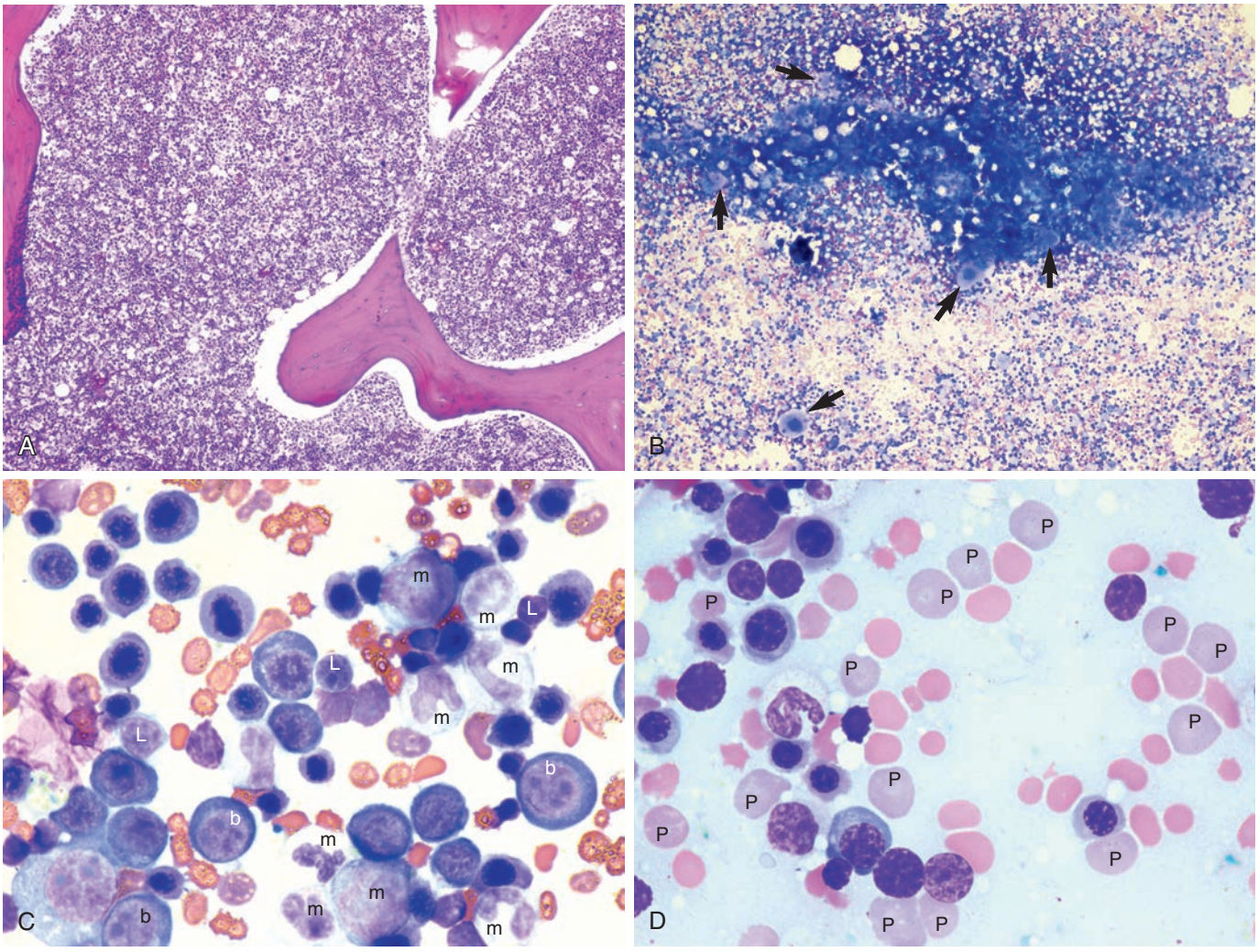


PLATE 28-1 Bone marrow biopsy and aspirate from a 5-year-old female Quarter Horse with marked anemia (PCV = 9%; 31% to 47%) and thrombocytopenia (42,000 platelets/µL; 125,000 to 300,000/µL). The bone marrow is highly cellular as seen in **A** (H&E) and **B** (Wright-Giemsa); arrows point to megakaryocytes, 10× objectives. The M:E ratio is decreased at 0.3, and polychromatophils comprise 30% of RBCs. **C** shows a large erythroid population (unmarked cells and b = erythroblast) with fewer myeloid cells (m) and lymphocytes (L); many polychromatophils (P) can be seen in **D** (Wright-Giemsa, 100× objective). This is representative of regeneration and consistent with either chronic blood loss or immune-mediated destruction of erythrocytes, which could both be occurring in this horse. The horse was diagnosed with intramuscular hemangiosarcoma.

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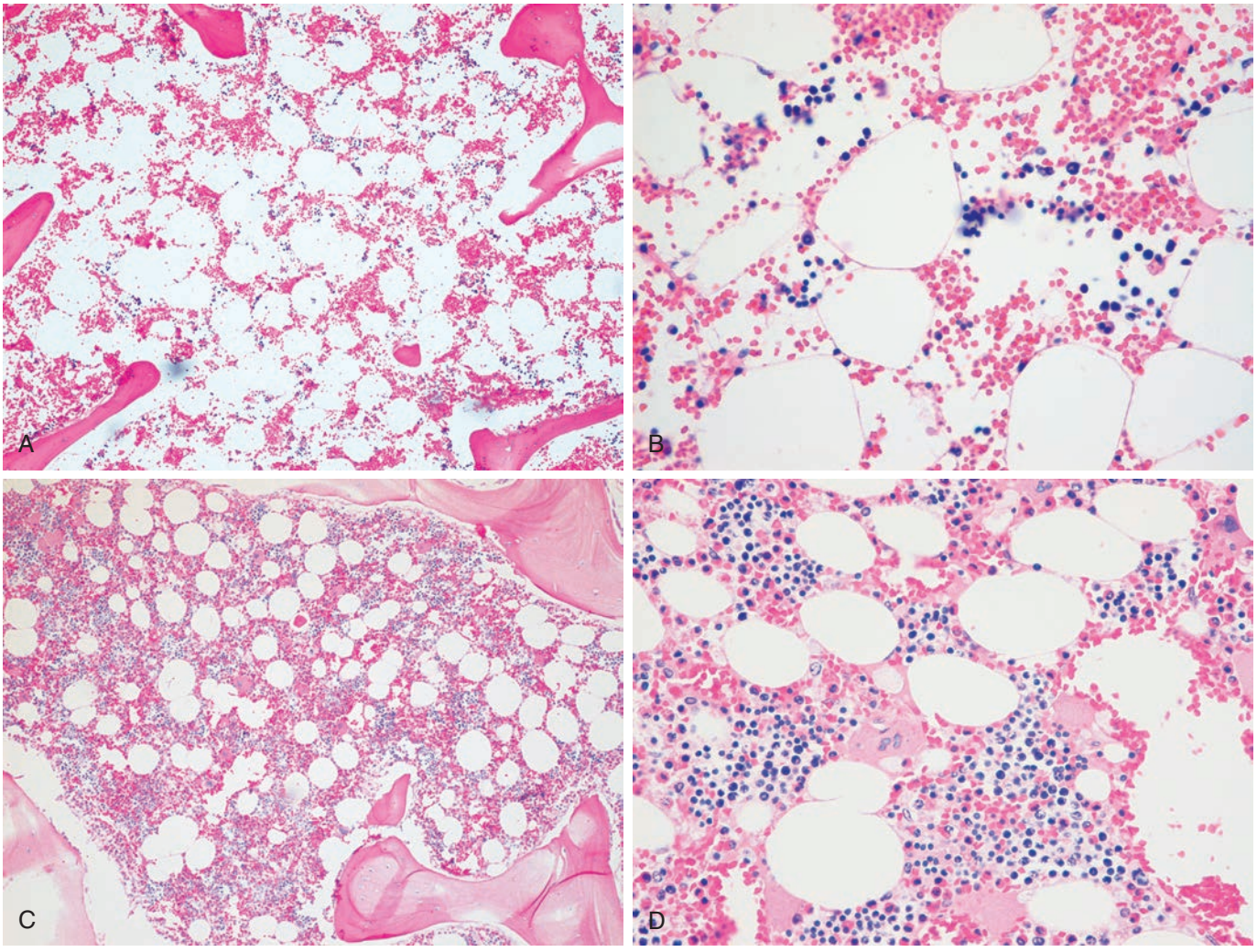


PLATE 28-2 Bone marrow biopsy from a 2-year-old mixed breed steer with mild anemia (PCV = 23%; 24% to 46%) and severe neutropenia (0/µL; 600 to 4000/µL) and thrombocytopenia (3000 platelets/µL; 100,000 to 800,000/µL) **(A, B),** compared with a normal age-matched control **(C, D).** Severe generalized bone marrow hypoplasia is apparent. The marked bone marrow suppression in this case is due to bracken fern toxicity. H&E; 10× **(A, C)** and 40× **(B, D)** objectives.

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PLATE 31-1 Postmortem photograph of tracheal edema syndrome. Note severe mucosal and submucosal thickening, which has obstructed the trachea by approximately 50%. *(Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.)*

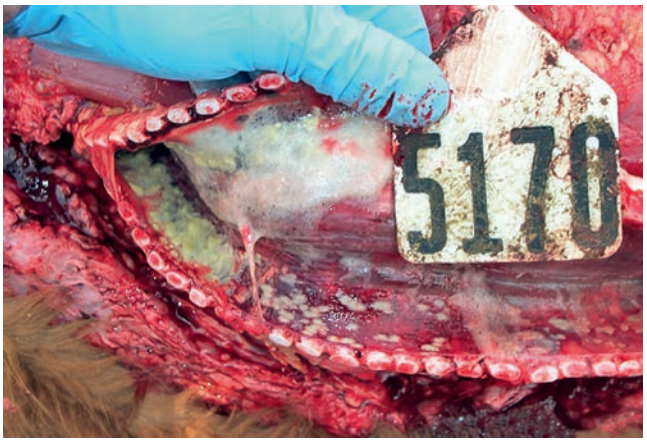


PLATE 31-2 Postmortem photograph of opened trachea from animal infected with bovine herpesvirus type 1 (BHV-1). Note multiple white fibrinonecrotic plaques and, distal to plaques, yellow fibrinopurulent material on dark red tracheal mucosa. *(Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.)*

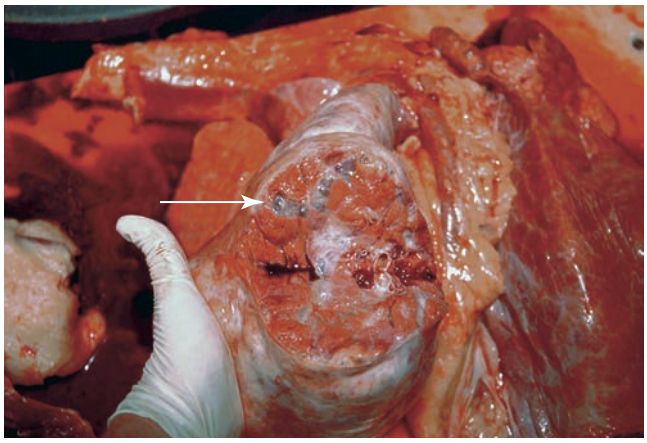


PLATE 31-3 Postmortem photograph of bovine lung with interstitial emphysema *(arrow)* often seen in severe bovine respiratory syncytial virus (BRSV) infection, as well as other causes of acute interstitial pneumonia (AIP). *(Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.)*

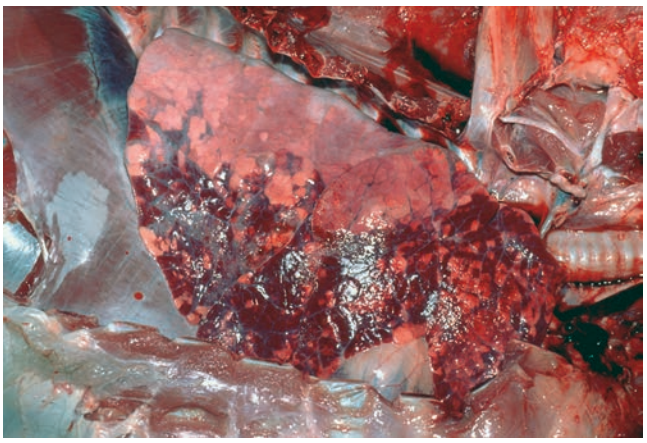


PLATE 31-4 Postmortem photograph of lungs from calf with severe BRSV infection. *(Photograph contributed by Dr. Laurel Gershwin, University of California, Davis, Calif.)*



PLATE 31-5 Postmortem photograph of fibrinopurulent pleuropneumonia caused by *Mannheimia haemolytica.* Note extensive dark red consolidated ventral lung, white fibrin on lung pleural surface, and red-tinged fluid in pleural space. *(Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.)*

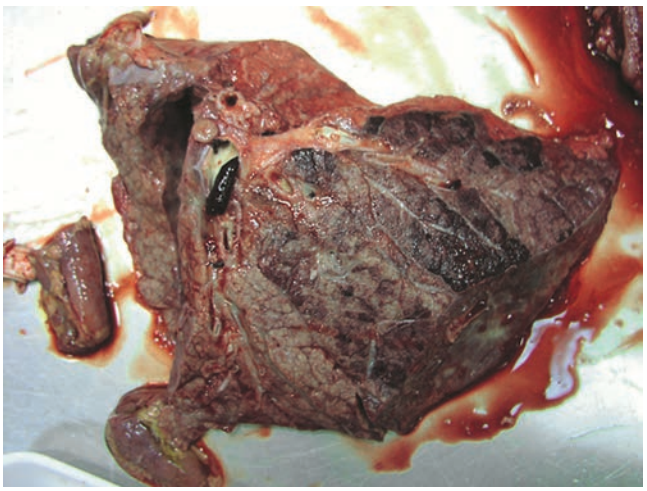


PLATE 31-6 Postmortem photograph of necrotizing bronchopneumonia caused by *Mannheimia haemolytica.* Abnormal lung is dark red to gray-brown in color. *(Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.)*

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PLATE 31-7 Postmortem photograph of cross-section of lung tissue from feedlot steer with bronchopneumonia caused by *Histophilus somni.* Note interlobular space is expanded with fibrin and edema *(arrow). (Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.)*



PLATE 31-8 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis.* Note extensive nodular abscessation of cranioventral lung. *(Photograph contributed by Dr. Tom Mullaney, Michigan State University, East Lansing, Mich.)*

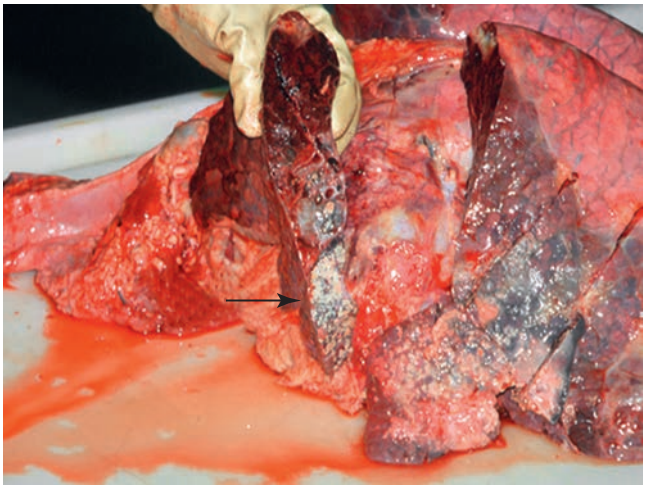


PLATE 31-9 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis.* Note dark red consolidated ventral lung with white caseous material visible on cut surface *(arrow). (Photograph contributed by Dr. Ricardo Rosenbusch, Iowa State University, Ames, Iowa.)*



PLATE 31-10 Postmortem photograph of lung lesions typical of enzootic calf pneumonia. Note scattered collapsed, dark red lobules in the cranioventral lung. This type of lesion could be caused by bovine respiratory syncytial virus (BRSV), parainfluenza virus type 3 (PIV-3), *Pasteurella multocida,* or various mycoplasmas. *(Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.)*



PLATE 31-11 Postmortem photograph of lungs from heifer with acute respiratory distress syndrome (ARDS) caused by feedlot acute interstitial pneumonia (AIP). Note expanded dorsocaudal lung and dark, collapsed lobules interspersed with pale, hyperinflated lobules. *(Photograph contributed by Dr. Amelia Woolums, University of Georgia, Athens, Ga.)*

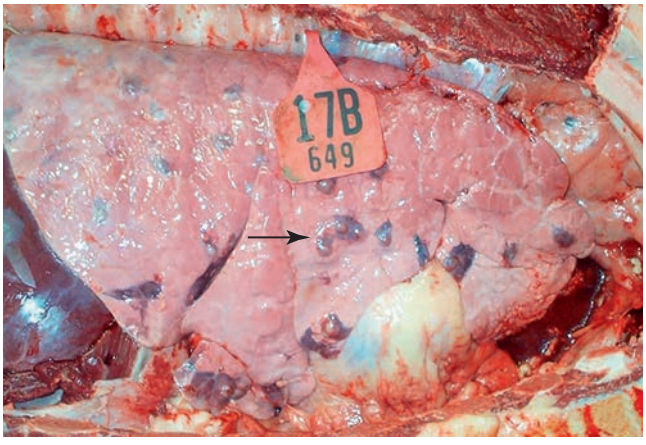


PLATE 31-12 Postmortem photograph of lung from feedlot steer with embolic pneumonia caused by caudal vena caval thrombosis. Note multiple dark red emboli *(arrow)* with raised abscesses scattered throughout lung. *(Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.)*

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PLATE 32-1 Endoscopic view of the esophagus of a 20-year-old gelding that presented with a history of 3 days of esophageal obstruction. The horse had recently been "rescued," and its previous history was unknown. After an obstruction consisting of grass was forcefully relieved by flushing water through a nasogastric tube, endoscopy revealed ulceration of the esophageal mucosa just orad to a stricture of the esophageal lumen. *(Courtesy Dr. M.J. Murray.)*

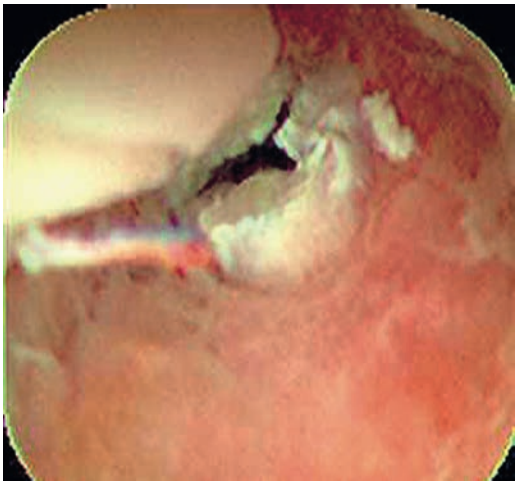


PLATE 32-2 Same horse as in Plate 32-1, 14 days later. The mucosa adjacent to the stricture remained ulcerated, and the diameter of the esophageal lumen had progressively diminished. At this point, it was not possible to advance the 10-mm-diameter endoscope through the stricture. *(Courtesy Dr. M.J. Murray.)*

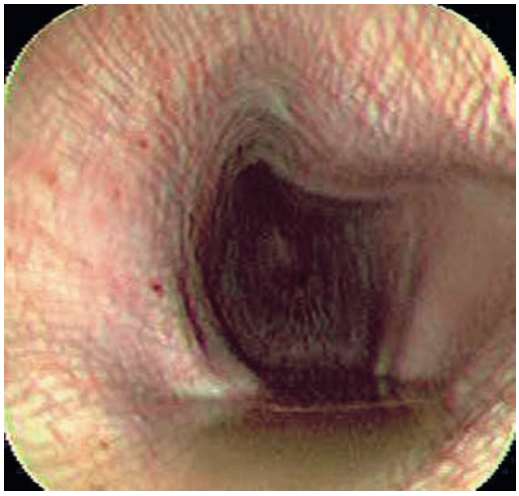


PLATE 32-3 Endoscopic view of megaesophagus in a 10-month-old foal, also shown in Fig. 32-45. The esophageal lumen is greatly distended, and the mucosa has multifocal erosion. *(Courtesy Dr. M.J. Murray.)*

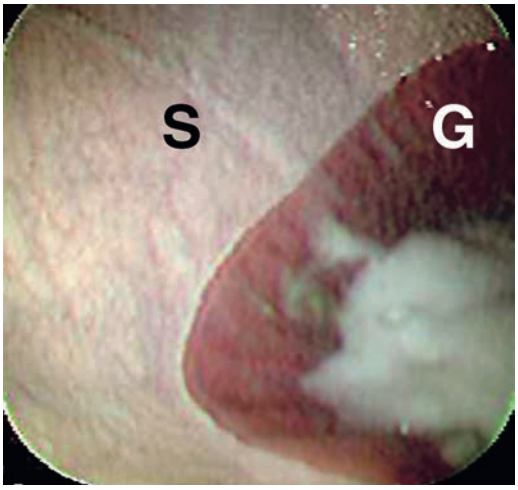


PLATE 32-4 Endoscopic view of the right side of a normal stomach, showing the pale squamous mucosa *(S)* and the red glandular mucosa *(G)*.

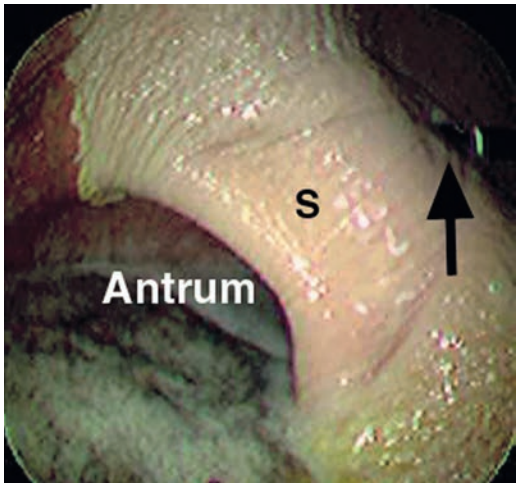


PLATE 32-5 Endoscopic view of the lesser curvature of a normal stomach, showing the pale squamous mucosa *(S)*. The antrum lies ventral to a fold formed by the squamous mucosa along the lesser curvature, and the pylorus is immediately ventral to the cardia, through which the endoscope *(arrow)* can be seen entering the stomach.

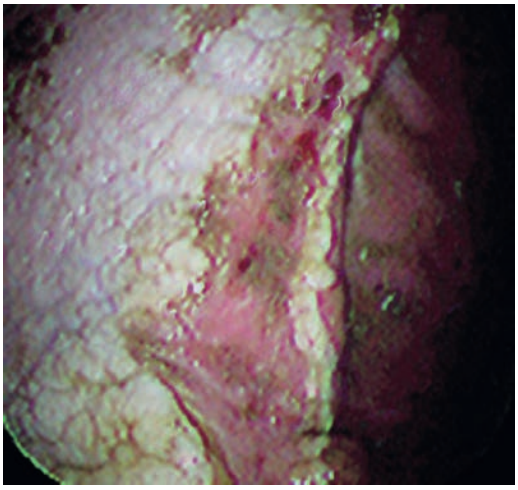


PLATE 32-6 Endoscopic view of a large area of ulceration of the squamous mucosa adjacent to the margo plicatus along the right side of the stomach.

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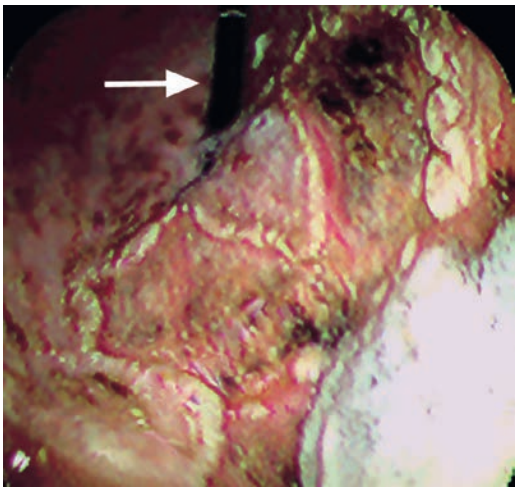


PLATE 32-7 Endoscopic view of a large area of ulceration of the squamous mucosa along the lesser curvature of the stomach. The ulceration has a "bufferfly" pattern, which is typical of ulcers at this site, and this pattern may reflect protection of the mucosa immediately ventral to the cardia by saliva entering the stomach from the esophagus. The *arrow* points at the endoscope entering the stomach through the cardia.



PLATE 32-8 Endoscopic view of an ulcer in the gastric glandular mucosa. The ulcer is in a rugal fold, which is a typical site of ulcers in the glandular portion of the stomach.

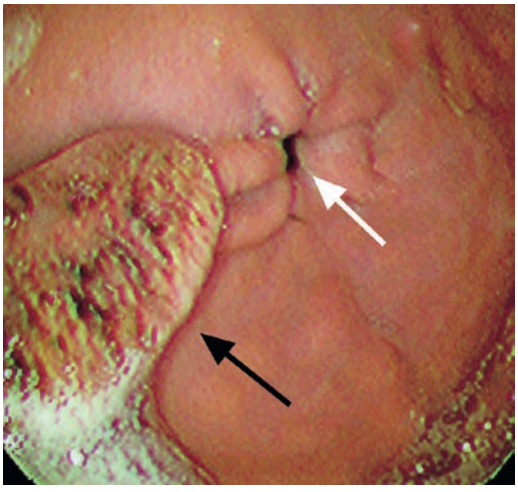


PLATE 32-9 Endoscopic view of the antrum of the stomach. The *white arrow* points at the pylorus. The *black arrow* points at an area of ulceration and thickening of a rugal fold leading to the pylorus. This is a severe example of a frequent finding in the stomach of adult horses: thickening of a rugal fold in the antrum with associated erosion or ulceration of the mucosa. The cause of these lesions is undetermined.

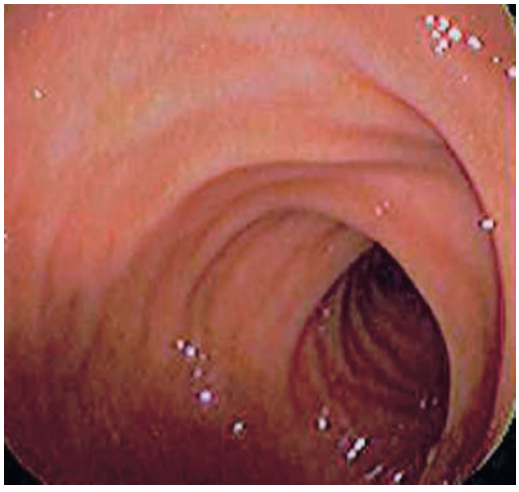


PLATE 32-10 Endoscopic view of normal duodenal mucosa. In this photograph, the endoscope has advanced aborad to the major duodenal papilla, which in most foals and horses is difficult and unusual to accomplish because of the anatomic configuration of duodenum with respect to the stomach.

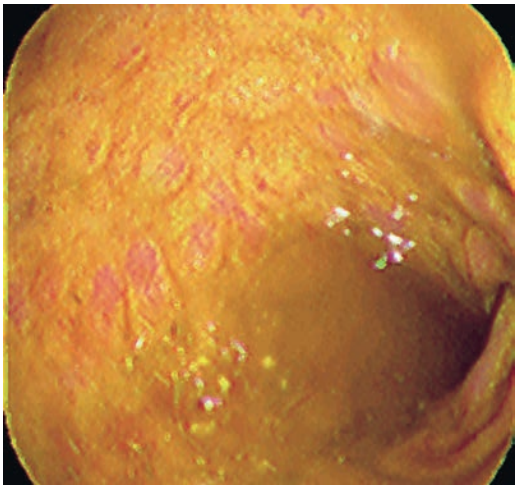


PLATE 32-11 Duodenum of a foal that presented with fever, depression, leukocytosis, and hyperfibrinogenemia. This endoscopic view is orad to the major duodenal papilla. The mucosa is inflamed and there is a yellow-orange fibrinous exudate adhered to the mucosal surface.

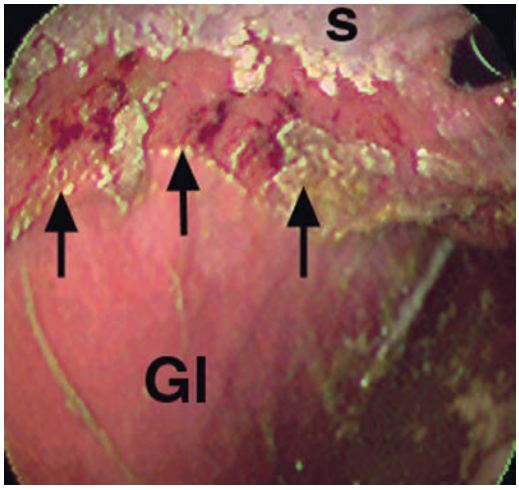


PLATE 32-12 Endoscopic view of the stomach of the foal in Plate 32-11. There is severe ulceration of the squamous mucosa *(S)* adjacent to the margo plicatus *(arrows),* because of delayed gastric emptying secondary to the severe duodenitis. Many foals with duodenitis present with classic gastric ulcer signs, because of delayed stomach emptying, accumulation of acidic peptic secretions in the stomach and often gastroesophageal reflux. *GI,* Glandular mucosa.

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PLATE 39-1 Marked asymmetry present when standing in front of this equine patient. Left eye is buphthalmic, with elevated lashes and diffuse corneal edema secondary to glaucoma. Right eye is developing phthisis bulbi, evident by increased scleral show and decreased lash height secondary to reduced orbital tissue volume.



PLATE 39-2 Entropion in a bovine patient; note the trichiasis present. Patient presented with blepharospasm and epiphora.



PLATE 39-3 Large third eyelid mass resulting in marked mucopurulent ocular discharge and enophthalmos.



PLATE 39-4 Caseous material obstructing the inferior puncta in a horse presented for epiphora. *(Photo courtesy Dr. Eric Storey.)*

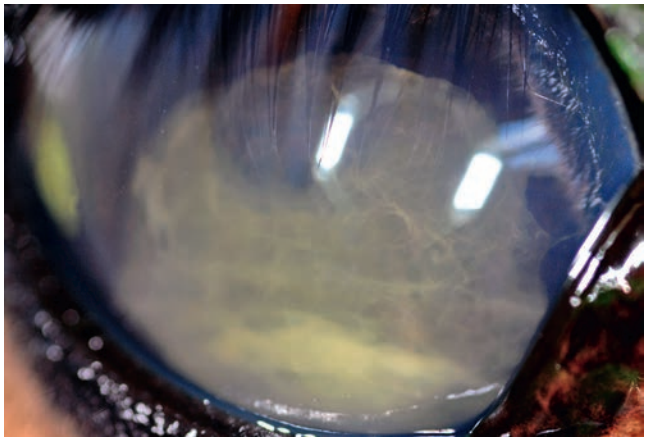


PLATE 39-5 Fibrin in the anterior chamber of a patient with anterior uveitis. Opacity is blocking the fundic reflex. Opacities in the cornea or anterior chamber will also obscure visualization of iris.



PLATE 39-6 Diffuse corneal edema in an equine patient. Diffuse patterns of edema, which are fluorescein negative, indicate endothelial dysfunction. *(Photo courtesy Dr. Lais Costa.)*

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PLATE 39-7 Corneal stromal abscess presenting as an area of off-white corneal infiltrate with secondary hypopyon and dense corneal vascularization (ciliary flush).



PLATE 39-8 Haab's striae in an equine patient with glaucoma.



PLATE 39-9 Light directed across the eye at a 45-degree angle is used to highlight anterior chamber abnormalities in this equine patient, including dyscoria secondary to synechia and a hypermature cataract.



PLATE 39-10 Iris atrophy in an equine patient.



PLATE 39-11 Dyscoric pupil secondary to posterior synechia and corneal scarring with a hypermature cataract in an equine patient with equine recurrent uveitis.

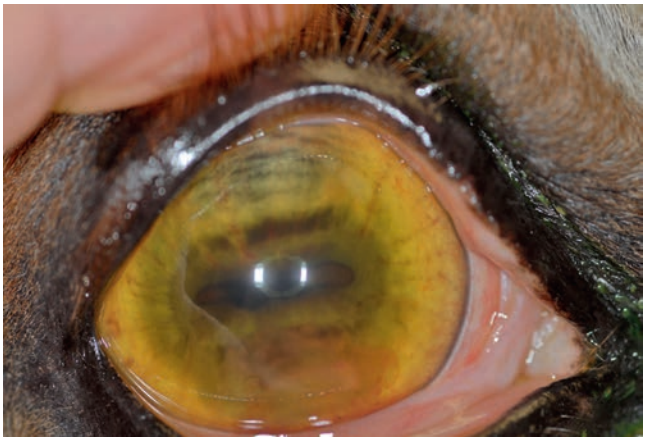


PLATE 39-12 Iridal color change, swelling, and miosis with blood (hyphema) and fibrin in the anterior chamber of a patient with anterior uveitis.

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PLATE 39-13 Phthisis bulbi secondary to chronic equine recurrent uveitis.



PLATE 39-14 Congenital cataract in a Thoroughbred colt.

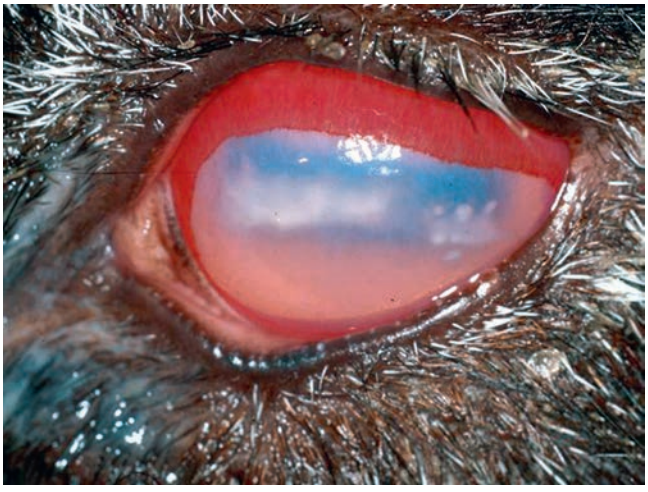


PLATE 39-15 Mycoplasmal keratoconjunctivitis in a goat. Note 360-degree superficial corneal vessels, diffuse corneal edema, a linear accumulation of white cellular infiltrates of the axial cornea, and miosis.

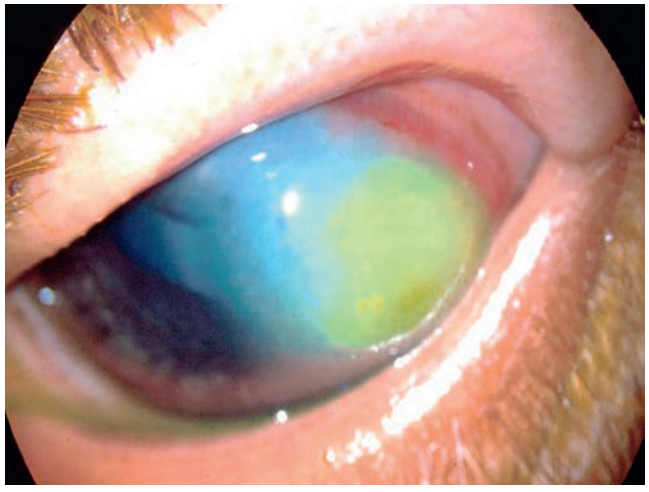


PLATE 39-16 Mycoplasmal keratoconjunctivitis in a sheep. Note miosis, focal corneal edema, and superonasal corneal vessels extending to the margins of a superficial corneal ulcer that has been stained with fluorescein dye.

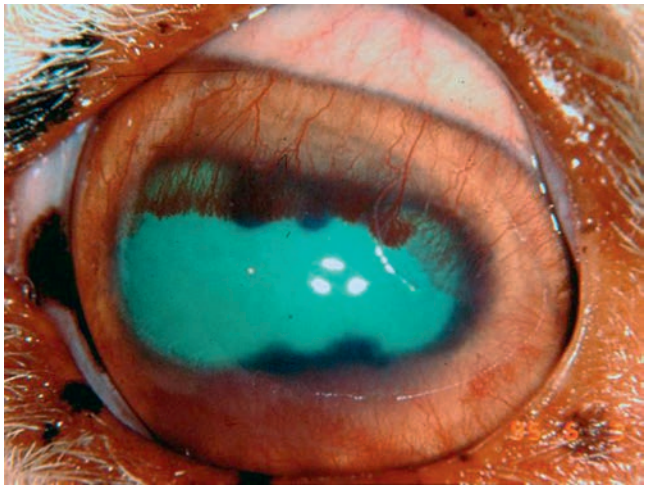


PLATE 39-17 *Chlamydophila* keratoconjunctivitis in a sheep. Note mild diffuse corneal edema, miosis, and 360-degree superficial branching corneal vessels.

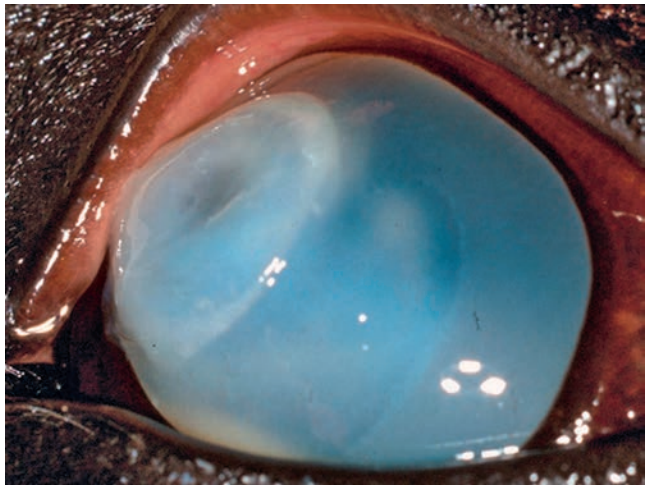


PLATE 39-18 Melting corneal ulcer, *Pseudomonas* infection. Note diffuse corneal edema, hypopyon, and a large superonasal ulcer with cellular infiltrate around margins and malacic corneal tissue protruding from surface.

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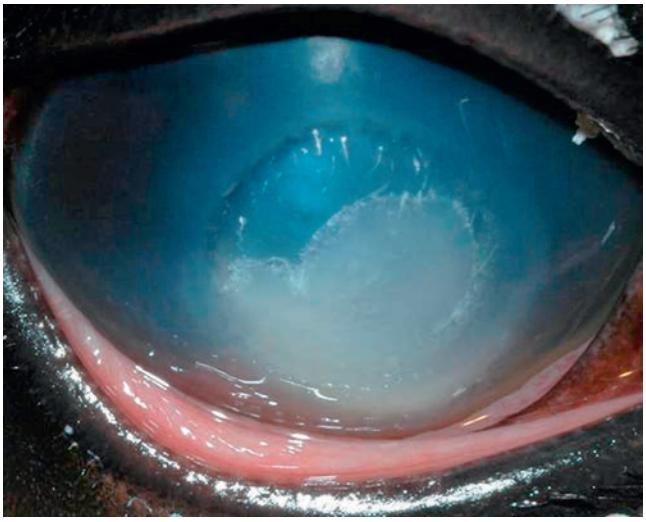


PLATE 39-19 Fungal keratitis with a granular white cellular infiltrate and a surrounding groove or gutter. Note corneal vascularization inferiorly.

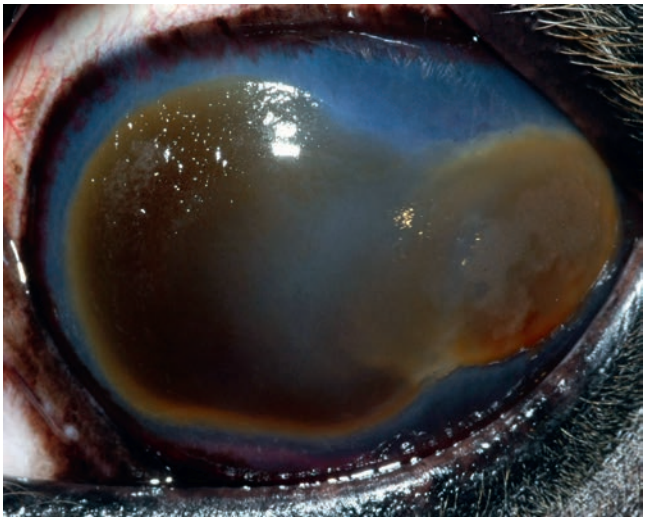


PLATE 39-20 Fungal keratitis with a pigmented necrotic axial plaque surrounded by active dense corneal vascularization.

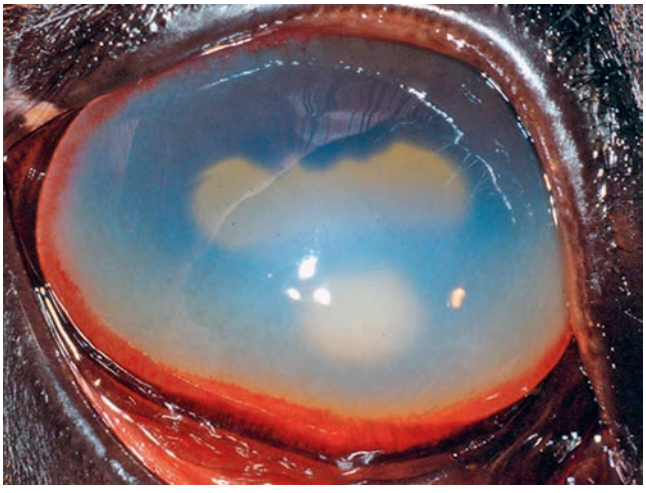


PLATE 39-21 Fungal corneal stromal abscess. Note 360-degree deep stromal corneal vessels, diffuse corneal edema, yellow cellular infiltrate of the inferior cornea, a paracentral foci of white deep stromal cellular infiltrate, and miosis.



PLATE 39-22 Bovine squamous cell carcinoma of lower eyelid and medial canthus, with secondary corneal ulcer.



PLATE 39-23 Large equine limbal (corneoscleral junction) squamous cell carcinoma extending into cornea.

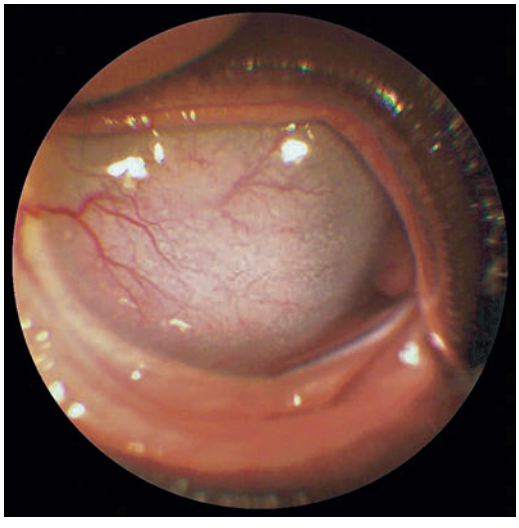


PLATE 39-24 Equine corneal stromal invasive squamous cell carcinoma. Note the vascularized infiltrative mass with smooth epithelial surface.

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PLATE 40-1 Pemphigus foliaceus in a goat.



PLATE 40-2 Alopecia areata on a horse's face.



PLATE 40-3 Vasculitis with ulceration on a horse's leg.



PLATE 40-4 Dermatophilosis on a goat's face.



PLATE 40-5 Dermatophilosis on a calf's head.



PLATE 40-6 *Corynebacterium pseudotuberculosis* abscess on a horse's neck.

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PLATE 40-7 Dermatophytosis on trunk of a Holstein cow. Lesions occurred after abdominal surgery.



PLATE 40-8 Scale and crust on a sheep's ear from biting flies, leading to eosinophilic dermatitis.



PLATE 40-9 Widespread squamous cell carcinoma on a goat's dorsum.



PLATE 40-10 Linear keratosis in a horse's jugular furrow.



PLATE 40-11 Vitiligo in a 5-year-old Quarter Horse.



PLATE 40-12 Chronic progressive lymphedema in a Gypsy Vanner horse.

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PLATE 54-1 Tall larkspur *(Delphinium barbeyi). (From Plumlee KH. 2004. Clinical veterinary toxicology. Mosby, St Louis, MO, pp 337-338.)*



PLATE 54-2 Bracken fern *(Pteridium aquilinum).* (*Source:* https://gobotany.newenglandwild.org/genus/pteridium/)



PLATE 54-3 Lambert's locoweed *(Oxytropis lambertii).* (*Source:* www.opsu.edu)



PLATE 54-4 Coffee weed *(Cassia). (From Schilcher, Heinz. 2010. Leitfaden phytotherapie. Elsevier, Urban & Fischer, München.)*



PLATE 54-5 Box elder *(Acer negundo). (Courtesy T. A. Turner, Stillwater, Minn.)*



PLATE 54-6 Maples (*Acer* spp.). *(Courtesy T. A. Turner, Stillwater, Minn.)*

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PLATE 54-7 Lantana *(Lantana camara). (From Knottenbelt DC, Pascoe RR. 2003. Diseases and disorders of the horse. Saunders, St louis, MO.)*



PLATE 54-8 Rattlebox (*Crotolaria* spp.). (*Source:* http://goldhillplantfarm-crystal.blogspot.com/2012/11/crotalaria.html)



PLATE 54-9 Perilla mint *(Perilla frutescens).* (*Source:* http://www.geolocation.ws/v/W/File:Perilla%20frutescens%20002.JPG/-/en)



PLATE 54-10 Hoary alyssum *(Berteroa incana).* (*Source:* http://www.luontoportti.com/suomi/en/kukkakasvit/hoary-alison)



PLATE 54-11 Pigweed *(Amaranthus retroflexus).* (*Source:* http://swbiodiversity.org/imglib/seinet/Amaranthaceae/photos/Amaranthus_retroflexus_020207_1.jpg)



PLATE 54-12 Jimsonweed *(Datura stramonium).* (*Source:* http://en.wikipedia.org/wiki/Datura_stramonium)

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Reference Intervals for Ruminants and Horses

	Cattle*	Sheep†	Goats†	Horses (Hot-Blooded Breeds)†	Horses (Cold-Blooded Breeds)†
PCV/HCT (%)	22-33	27-45	22-38	32-53	24-44
Erythrocytes ($\times 10^6/\mu L$)	5.1-7.6	9-15	8-18	6.8-12.9	5.5-9.5
Hemoglobin (g/dL)	8.5-12.2	9-15	8-12	11-19	8-14
MCV (fL)	38-50	28-40	16-25	37-58.5	—
MCHC (g/dL)	36-39	31-34	30-36	31-38.6	—
Reticulocytes	—	0	0	—	—

*From George JW, Snipes J, Lane M. 2010. Comparison of bovine hematology reference intervals from 1957-2006. Vet Clin Pathol 39:138.

†From Jain NC. 1986. Schalm's veterinary hematology, ed 4. Lea & Febiger, Philadelphia, PA.

Normal Values for Leukogram Data (Adult Animals)

	Cattle	Sheep	Goats	Horses
White blood cells ($\times 10^3/\mu L$)	4.9-12	4-12	4-13	5.4-14.3
Neutrophils ($\times 10^3/\mu L$)	1.8-6.3	0.7-6	1.2-7.2	2.3-8.6
Bands ($\times 10^3/\mu L$)	Rare	Rare	Rare	0-1
Lymphocytes ($\times 10^3/\mu L$)	1.6-5.6	2-9	2-9	1.5-7.7
Monocytes ($\times 10^3/\mu L$)	0-0.8	0-0.75	0-0.55	0-1
Eosinophils ($\times 10^3/\mu L$)	0-0.9	0-1	0.05-0.65	0-1
Basophils ($\times 10^3/\mu L$)	0-0.3	0-0.3	0-0.12	0-0.29
Neutrophil/lymphocyte (N/L) ratio	0.4-2.34	0.3-0.7	0.6-3.6	0.8-2.8

Normal Serum Protein Values for Horses, Cows, Sheep, and Goats

	Value	Horse	Cow	Sheep	Goat
Total	g/dL	5.2-7.9	6.74-7.46	6-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Fibrinogen	g/dL	200-400	200-700	200-500	200-300

From Appendix VIII: Blood analyte reference values in large animals. 1997. In Kaneko JJ, Harvey JW, Bruss ML (eds), Clinical biochemistry of domestic animals, ed 5. Academic Press, San Diego, CA.

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Clinical Chemistry: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Chemistry					
Total bilirubin	mg/dL	1.0-2.0	0.01-0.5	0.1-0.5	0-0.1
Direct	mg/dL	0-0.4	0.04-0.44	0-0.27	0-0.1
Indirect	mg/dL	0.2-2.0	0-0.3	0-0.12	0-0.1
Cholesterol	mg/dL	75-150	80-120	52-76	80-130
Creatinine	mg/dL	1.2-1.9	1.0-2.0	1.2-1.9	1.0-1.8
Glucose	mg/dL	75-115	45-75	50-80	50-75
Fibrinogen	mg/dL	100-400	300-700	100-500	100-400
Haptoglobin	mg/dL	0.01-0.17	0.0-0.05	NA	NA
Serum amyloid A	mg/dL	0-2.0	NA	NA	NA
Protein (total serum)	g/dL	5.2-7.9	6.7-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Urea nitrogen	mg/dL	10-24	20-30	8-20	10-20
Enzyme					
ALP	IU/L	143-395	0-488	68-387	93-387
AST	IU/L	226-366	78-132	60-280	167-513
CK	IU/L	108-430	44-211	64-158	104-219
GGT	IU/L	7-54	15-39	40-79	20-56
LDH	IU/L	162-412	697-1445	238-440	123-392
LDH-1	%	6.3-18.5	39.8-63.5	45.7-63.6	29.3-51.8
LDH-2	%	8.4-20.5	19.7-34.8	0-3.0	0-5.4
LDH-3	%	41-65.9	11.7-18.1	16.4-29.9	24.2-39.9
LDH-4	%	9.5-20.9	0-8.8	4.3-7.3	0-5.5
LDH-5	%	1.7-16.5	0-12.4	10.5-29.1	14.1-36.8
SDH	IU/L	1.9-5.8	4.3-15.3	5.8-27.9	14-23.6
Electrolyte					
Sodium	mEq/L	132-146	132-152	139-152	142-155
Potassium	mEq/L	2.4-4.7	3.9-5.8	3.9-5.4	3.5-6.7
Chloride	mEq/L	99-109	97-111	95-103	99-110
Calcium	mEq/L	11.2-13.6	9.7-12.4	11.5-12.8	8.9-11.7
Phosphorus	mEq/L	3.1-5.6	5.6-6.5	5.0-7.3	6.5
Magnesium	mEq/L	2.2-2.8	1.8-2.3	2.2-2.8	2.8-3.6
Osmolality	mOsm/kg	270-300	270-300	NA	NA
Anion gap	mEq/L	6-15	14-20	NA	NA
Acid-Base (Venous Blood)					
pH		7.32-7.44	7.31-7.53	7.32-7.54	NA
P_{CO_2}	mm Hg	38-46	35-44	37-46	NA
Bicarbonate	mEq/L	20-28	17-29	20-25	NA
T_{CO_2}	mEq/L	24-32	21-32	21-28	26-30
Special					
Red blood cell acetylcholinesterase	IU/L	450-790	1270-2430	640	270
Ammonia	µg/dL	13-108	NA	NA	NA
BSP ($t_{1/2}$)	min	2.0-3.7	2.5-4.0	1.6-2.7	2.1
Serum iron	µg/dL	73-140	57-162	166-222	NA
TIBC	µg/dL	200-262	63-186	NA	NA
Lactic acid	mmol/L	1.11-1.78	0.56-2.22	1.00-1.33	NA
Ketones					
Acetone	mg/dL	NA	0-10	0-10	NA
Acetoacetate	mg/dL	NA	0-1.1	NA	NA
BHB	mg/dL	NA	0-10	NA	NA

Data from Kaneko JJ, Harvey JW, Bruss ML, eds. 2008. Clinical biochemistry of domestic animals, ed 6. Academic Press, Burlington, MA; and the Normal Values Clinical Pathology Ontario Veterinary College and Animal Health Lab-Guelph, 2012.

ALP, Alkaline phosphatase; *AST,* aspartate aminotransferase; *BHB,* β-hydroxybutyrate; *BSP ($t_{1/2}$),* bromsulphalein clearance halftime; *CK,* creatine kinase; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *NA,* not applicable; *P_{CO_2},* partial pressure of carbon dioxide; *SDH,* sorbitol dehydrogenase; *T_{CO_2},* total carbon dioxide; *TIBC,* total iron-binding capacity.